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Role of Atypical Chemokines and Chemokine Receptors Pathways In the Pathogenesis of Copd

Francesco Nucera¹, Federica Lo Bello¹, Sj S. Shen², Paolo Ruggeri¹, Irene Coppolino¹, Antonino Di Stefano³, Cristiana Stellato⁴, Vincenzo Casolaro⁴, Phil M. Hansbro³, Ian M. Adcock⁵, Gaetano Caramori¹

¹*Pneumologia, Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali (BIOMORF), Università di Messina, Messina, Italy;* ²*Centre for Inflammation, Centenary Institute, Sydney, and University of Technology Sydney, Faculty of Science, Ultimo, NSW, Australia;* ³*Divisione di Pneumologia e Laboratorio di Citoimmunopatologia dell'Apparato Cardio Respiratorio, Istituti Clinici Scientifici Maugeri, IRCCS, Veruno (NO), Italy;* ⁴*Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy;* ⁵*Airway Disease Section, National Heart and Lung Institute, Imperial College, London, UK*

Abstract: Chronic obstructive pulmonary disease (COPD) represents a heightened inflammatory response in the lung resulting generally from tobacco smoking-induced recruitment and activation of inflammatory cells and/or activation of lower airway structural cells. Several mediators can modulate activation and recruitment of these cells, particularly those belonging to the chemokines (conventional and atypical) family. There is emerging evidence for complex roles of atypical chemokines and their receptors [such as high mobility group box 1 (HMGB1), antimicrobial peptides, receptor for advanced glycosylation end product (RAGE) or toll-like receptors (TLRs)] in the pathogenesis of COPD, both in the stable disease and during exacerbations. Modulators of these pathways represent potential novel therapies for COPD and many are now in pre-clinical development. Inhibition of only a single atypical chemokine or receptor may not block inflammatory processes, because there is redundancy in this network. However, there are many animal studies that encourage studies for modulating the atypical chemokine network in COPD. Thus, few pharmaceutical companies maintain a significant interest in developing agents that target these molecules as potential anti-inflammatory drugs. Antibody-based (biological) and small molecule drug (SMD)-based therapies targeting atypical chemokines and/or their receptors are mostly at the preclinical stage and their progression to clinical trials is eagerly awaited. These agents will most likely enhance our knowledge about the role of atypical chemokines in COPD pathophysiology and thereby improve COPD management.

Keywords: Airway inflammation, alveolar macrophages, atypical chemokines, atypical chemokine receptors, chronic obstructive pulmonary disease, lymphocytes, small airways.

AIM OF THE REVIEW

In this review we will consider the role of the atypical chemokines and their receptors in the pathogenesis of COPD and how these can induce its exacerbations. In addition, we will review here the clinical efficacy of new compounds in preclinical and/or clinical development that modulate the release of these molecules and/or the activity of their complex network.

*Address correspondence to this author at the Dipartimento di Scienze Biomediche, Odontoiatriche e delle Immagini Morfologiche e Funzionali (BIOMORF), Università degli Studi di Messina, Piazza Pugliatti 1, 98122 Messina, Italy; Tel: +39-090-2212000; E-mail: gcaramori@unime.it

1. INTRODUCTION

The immunopathology of COPD is characterized on activation of both innate and adaptive immune responses due to the chronic inhalation of cigarette smoking [1]. In recent years, several studies have analysed lung specimens from COPD patients compared with those from smokers with normal lung function. The results have suggested (i) potential pathogenic roles of several cell types involved in both the innate and adaptive immune system and (ii) the activation of resultant pro/anti-inflammatory mediators and intracellular signalling pathways potentially causative in COPD [2]. These studies have contributed to improved knowledge of stable COPD immunopathology and of changes seen during exacerbations to provide a scientific rationale for research into new lung-specific drugs [2].

The main risk factor for COPD in developed countries is chronic inhalation of cigarette smoking [2]. As a result, the development of cigarette smoke-exposed animal models that mimic human COPD have provided key insights into the immunopathology of COPD and the opportunity to assess and develop new therapeutic agents. Many animal models of COPD have been developed, including the use of different causative agents (cigarette smoke or air pollution) and different animals (such as guinea pigs, rats, and mice) [1,3]. However, recent studies have primarily shifted to mouse models given our knowledge of their genomics, their relatively low maintenance costs, and the multitude of genetic modifications that are available. Indeed, transgenic mice with alterations in genes such as matrix metalloproteinase-1 (MMP-1), interleukin-13 (IL-13), transforming growth factor- β (TGF β) and interferon- γ (IFN γ) have shown the importance of these factors in the pathogenesis of COPD [1]. Importantly, these models, especially those involving nose-only cigarette smoke induction, reflect human COPD, with cigarette smoke as a major risk factor, and inflammation, mucous hypersecretion, emphysema, and impaired lung function as some of the crucial readouts of both human and experimental COPD [3]. In fact, commonalities appear in both human and experimental COPD, such as increases in macrophages, neutrophils, and mast cells, and increases in chemokines and cytokines such as CC-chemokine receptor-5 (CCR5), CCR6, CXC-chemokine ligand-13 (CXCL13), IL-1 β , IL-22 and IFN γ in addition to oxidative stress and epigenetic pathways [1,3-6]. Furthermore, infectious agents associated with COPD, such as *Streptococcus pneumoniae*, *Haemophilus Influenzae*, and *Moraxella catarrhalis* [7], can be administered in animal models to elucidate its link with the pathogenesis of COPD. Together, these models recapitulate important aspects of COPD that allow investigational studies to elucidate the immunopathology and efficacy of novel therapies [8].

2. ATYPICAL CHEMOKINES AND CHEMOKINE RECEPTORS GENERAL CHARACTERISTICS

In addition to their classic activities, the chemotactic activity of these molecules has been more recently recognized.

Conventional chemokines modulate the migration of the leukocytes into several sites of the body under inflammatory conditions, but also during physiological/homeostatic conditions [9], whilst atypical (previously called non-conventional) chemokines are classically part of the innate immune system.

In addition to their classical functions, these atypical chemokines also have chemotactic and chemokine-like properties towards many cells (Table 1) (Figure 1).

Table 1. Atypical chemokines and their role in COPD pathogenesis

Atypical chemokines (see their receptors in Table 2)	Evidence for their role in COPD	
	Stable phase	Exacerbation
High-mobility group protein B1	Serum + [78,81,85] and = [80] Spontaneous sputum + [78] Lung tissue + [79] BAL + [86-87] and - [88]	Serum + [82-83]
Cathelicidin (LL-37)	Serum = [152,178] and - [183] Spontaneous sputum + [152,178] Lung tissue + [185] BAL + in mild disease [179] and - in severe disease [179]	Serum + [181] Spontaneous sputum + [182] Induced sputum + [181]
Histatins		
Lactoferrin	Spontaneous sputum + [219]	Spontaneous sputum - [182]
α -defensins	BAL + [274]	Serum = [276] and - [279] Spontaneous sputum + [180,276]
β -defensins	Spontaneous sputum - [273] Lung tissue + [269-270]	Spontaneous sputum = [180] BAL + [277]
Hepcidin	Serum - [288]	
Lysozyme		Spontaneous sputum - [182]

Chemerins	Serum + [320-321]	
<i>RNases:</i>		
1		
2 (EDN)		Serum + [350]
3 (ECP)	Serum + [371-372] Induced sputum + [367-368, 370,372] BAL + [367]	Serum + [350]
4		
5 (angiogenin)		
6		
7		
8		
<i>Neuropeptides:</i>		
NPY		
SP		
CGRP		
VIP	Lung tissue + [427-428]	Serum + [426]
AM	Serum + [433-435,437]	Serum + [436]
α -MSH		
Macrophage migration inhibitory factor	Serum - [464-465] Induced sputum + [447] Lung tissue + [481] BAL + [447]	Serum + [463]

Atypical chemokines and chemokine receptors potentially involved in the pathogenesis of COPD are in bold.

α -MSH: α -melanocyte stimulating hormone; AM: adrenomedullin; CGRP: calcitonin-gene related peptide; ECP: eosinophil cationic protein; EDN: eosinophil-derived neurotoxin; NPY: neuropeptide Y; SP: substance P; VIP: vasoactive intestinal peptide.

Obtained with the data from [47-49,141,143,186,197,290-291,306,323,337,374,404,453].

Atypical chemokines	Lower airways	Gastrointestinal	Blood	Genital organs		Kidney and Urinary tract	Brain	Liver and Gall bladder	Adipose, soft tissue and skin	Pancreas	Bone marrow and lymphoid tissues
	Smooth muscle, alveolar epithelial, fibroblast, endothelial cells			Female	Male						
HMGB1											
LL-37											
Histatin											
Lactoferrin											
Lactoferricin											
Defensins											
Hepcidin											
Lysozyme											
Chemerins											
RNases											
Neuropeptides											
MIF											

HMGB1: high mobility group box 1; MIF: migration inhibitory factor.

Figure 1. Physiological human tissue atypical chemokines expression (Expression of atypical chemokines in the lower airways are indicated by a darker shade than other tissues).

Likewise, a family of atypical (also termed non-conventional or non-canonical, decoy, scavenger, or silent) chemokine receptors has also been described (Table 2) (Figure 2).

Table 2. Atypical chemokine receptors and their role in the COPD pathogenesis

Atypical chemokine receptors	Evidence for their role in COPD	
	Stable phase	Exacerbation
Large spectrum ACKRs:		
ACKR1 previously called (DARC)		
ACKR2 [previously called (CCbp2) and (D6)]	Lung tissue + [481] BAL + [481]	
Narrow spectrum ACKRs:		
ACKR3 [previously called (RDC1) and (CXCR7)]		
ACKR4 [previously called (CCRL1) and (CCXCRK)]	BAL in mice + [322]	
Atypical chemokine receptors still awaiting for their functional confirmation:		
Ackr5 [previously called (CCRL2) and (CRAM)]		
Ackr6 previously called (PITPNM3)		
Receptor for advanced glycosylation end product	Serum (sRAGE) - [80,127-128,130,137] Lung tissue + [87,134]	Serum (sRAGE) + [83]
Toll-like receptors:		
TLR2	Induced sputum + [528]	
TLR4	Lung tissue + [533]	
TLR9	Lung tissue + [536]	
CRTH2	Blood ILC2 + [546] Lung tissue + [548]	Blood ILC2+ [547]

Atypical chemokines and chemokine receptors potentially involved in the pathogenesis of COPD are in bold.

ACKRs: atypical chemokine receptors; CCbp2: chemokine binding protein 2; CCRL1: chemokine receptor like 1; CCRL2: chemokine CC motif receptor-like protein 2. CCRL2 is expressed on mast cells; CRTH2: prostaglandin P2 receptor; CXCR7: chemokine (C-X-C motif) receptor 7; CCXCRK: C-C chemokine receptor type 11; CRAM: chemokine receptor on activated macrophages; D6: cysteine-cysteine (C-C) chemokine receptor; DARC: duffy antigen receptor for chemokines. DARC is expressed on erythrocytes; TLRs: Toll-like receptors; sRAGE: soluble receptor for advanced glycosylation end product; PITPNM3: membrane-associated phosphatidylinositol transfer 3; RDC1: chemokine orphan receptor 1. Obtained with the data from [13-16,156,345,453,510-511,537-538].

Chemokine receptors	Lower airways	Gastrointestinal	Blood	Genital organs		Kidney and Urinary tract	Brain	Liver and Gall bladder	Adipose, soft tissue and skin	Pancreas	Bone marrow and lymphoid tissues
	Smooth muscle, alveolar epithelial, fibroblast, endothelial cells			Female	Male						
ACKR1											
ACKR2											
ACKR3											
ACKR4											
Ackr5											
Ackr6											
TLRs											
RAGE											
CRTH2											

ACKR: atypical chemokine receptor; CRTH2: Prostaglandin D2 receptor 2; RAGE: receptor for advanced glycation end products; TLR: toll-like receptor.

Figure 2. Physiological human tissue atypical chemokine receptors expression (Expression of atypical chemokine receptors in the lower airways are indicated by a darker shade than other tissues).

2.1. The structure of atypical chemokine receptors

A classification of atypical chemokine receptors (ACKRs) has been proposed, based on the number of ligands. However, several of these receptors are still awaiting functional confirmation of their role as atypical chemokine receptors. Moreover, several receptors that are conventionally part of innate immune system are being reconsidered as atypical chemokine receptors [10-16].

Although their structures are similar to those of the conventional chemokine receptors, atypical chemokine receptors are often unable to signal through the same pathways, or perform the same or similar functions, as conventional chemokine receptors (Figure 3).

ACKR: atypical chemokine receptor; CCL: CC chemokine ligand; CCR: CC chemokine receptor; CCRL1: chemokine receptor like 1; CXCL: CXC chemokine ligand; CXCR: CXC chemokine receptor; D6: cysteine-cysteine (C-C) chemokine receptor; DARC: duffy antigen receptor for chemokines.

Figure 3. Chemokine Binding Profiles of ACKRs.

Indeed, they are not coupled to G proteins and fail to induce typical intracellular signalling. However, they can regulate cell activation or migration by modulation of the chemo-attractant gradient, through concentrating or removing/scavenging chemokines for subsequent lysosomal degradation [10-12].

ACKR subfamily can be classified, according to their number of ligands [13-15], as:

- 1) Large spectrum ACKRs:
 - a) ACKR1 [previously named Duffy antigen receptor for chemokines (DARC)]
 - b) ACKR2 [previously named Chemokine binding protein 2 (CCbp2), and identified in the mouse as cysteine-cysteine (C-C) chemokine receptor D6]
- 2) Narrow spectrum ACKRs:
 - a) ACKR3 [previously named chemokine orphan receptor 1 (RDC1) and chemokine (C-X-C motif) receptor 7 (CXCR7)],
 - b) ACKR4 [previously named chemokine receptor like 1 (CCRL1) and Chemocentryx chemokine receptor (CCXCRK)],
 - c) Ackr5 [also termed chemokine CC motif receptor-like protein 2 (CCRL2) or chemokine receptor on activated macrophages CRAM] and ackr6 [membrane-associated phosphatidylinositol transfer 3 (PITPNM3)]. However, they are

still awaiting functional confirmation as to their role as atypical chemokine receptors [13-14] and for this reason they are indicated with lowercase characters.

ACKR2 and ackr5 are specific to CC- chemokines, ACKR3 binds only to CXC- chemokines, while ACKR1 and ACKR4 bind both CC- and CXC- subfamilies. None of the ACKRs bind XC- or CX3C- chemokines [14,16].

A functional classification of these receptors has been also proposed, whereby wide spectrum ACKRs mainly recruit leukocytes during inflammatory conditions, whilst narrow-spectrum ACKRs mainly act to control constitutive leukocyte trafficking and development [16].

In addition to atypical chemokines, several receptor families such as receptor for advanced glycosylation end product (RAGE) and toll-like receptors (TLRs) that are classically part of the innate immune system, have been recognized as possessing chemotactic properties and they are also considered atypical chemokine receptors.

2.2. Intracellular signalling by atypical chemokine receptors

Chemokine receptor are located on cell surface and coupled with G protein. These can induce variety of biological effects such as cell proliferation, chemotaxis and survival mediated by several intracellular pathways. However, a negative feedback system (desensitization) mediated by β -arrestin exists that induces chemokine receptor endocytosis [10,17-19].

“Typical” or “conventional” chemokine receptors are localized in the cell membrane and coupled with members of heterotrimeric G proteins family and in particular with the G inhibitory (G_i) type [17]. When a chemokine receptor recognizes its ligand there is a change in the conformation of its 7-transmembrane (7TM) helix domain. This results in different signalling events depending on whether it is mediated by β -arrestins or heterotrimeric G proteins [10,18-19].

Recognition by a chemokine receptor of its ligand causes GDP/GTP exchange of the associated heterotrimeric G_i proteins of the same receptor and the consequent dissociation of their β/γ subunits. This leads to the activation of several intracellular pathways, such as the phosphoinositide-specific phospholipase C (PLC) β , proto-oncogene tyrosine-protein (Src) family kinases and phosphoinositide 3-kinase (PI3K). This in turn causes inositol triphosphate (IP3)-mediated calcium mobilization and protein kinase C (PKC) activation [10-11,17-18].

Several downstream signalling pathways, such as the Janus kinase (JAK)/signalling transducer and activator of transcription (STAT) pathway, the PI3K/protein kinase B (Akt) pathway, the mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (Erk) signalling pathway and the RhoA pathway, may also be activated. The precise pathway(s) activated depend upon the type of chemokine receptor, its density on the cell surface, and the cellular context, such as inflammatory and/or homeostatic conditions [19-20]. This results in a variety of biological effects, such as cell proliferation, migration (chemotaxis) and survival [18-20].

Decreased G protein activity is induced by a negative feedback system, called “desensitization”, that causes endocytosis of β -arrestin [18-19]. β -arrestins are members of the “arrestin” protein family, which are classified into four subtypes. Arrestin-1 (also called visual arrestin) and arrestin-4 (also called cone arrestin) are specifically located only in retinal rods and cones. Arrestin-2 and arrestin-3 (also called β -arrestin 2 and -3) are classified as “non-visual” arrestins and are expressed in many cell types [19]. The affinity of β -arrestins for inactive (non-phosphorylated) chemokine receptors is low, which decreases cell basal activity. If β -arrestin displaces the G protein before the receptor recognizes its agonist, this gives rise to G protein-independent β -arrestin signalling [19].

In contrast, if β -arrestin competes with the G protein after chemokine receptor activation, G protein-dependent β -arrestin signalling occurs [19]. This process is well described and involves Erk phosphorylation, receptor internalization, and finally desensitization [19,21]. In comparison, G protein-independent β -arrestin-mediated signalling is less well characterized, but it has been discovered using G protein-coupled receptor (GPCR) mutants that are still able to signal through the Erk phosphorylation pathway even though they cannot bind to G proteins [19,22].

3. CHEMOKINE INTERNALISATION BY ACKRS

Unlike conventional chemokine receptors, ACKRs mainly mediate chemokines internalization. Some ACKRs can modulate this process by specific ligand-dependent signalling pathways, while others ACKRs do not require a specific ligand. This difference would seem to be related to changes in an amino acid sequence called “DRYLA-IV”. However, further studies are necessary to clarify this point [12].

Several *in vitro* studies have shown that the ability to internalize chemokines is a common feature among ACKRs. These results have led researchers to consider ACKRs as chemokine scavengers, decoy receptors or chemokine transporters [12]. Some ACKRs can internalize chemokines by specific ligand-dependent signalling pathways, while other ACKRs internalize chemokines in the absence of specific ligand binding [12]. This may modulate ACKRs trafficking that is necessary for their scavenging/decoy activity. However, ACKRs can control cellular functions both by direct activation of several signalling

pathways or indirectly by modulating responses through co-expressed 7TM receptors [12]. Furthermore, only a few ligands have been tested using *in vitro* studies for ACKR1, ACKR2 and ACKR4, and chemokines may differ in their capacity to stimulate signalling pathways or to be internalized in *in vivo* settings [12,23]. Moreover, inflammatory and homeostatic conditions will influence ACKR function, potentially weakening the value of the results obtained from *in vitro* studies on cells expressing ACKRs [12].

There is currently no known explanation for the unconventional properties of ACKRs, however marked alterations in the canonical amino acid sequence “DRYLA-IV” motif (Asp-Arg-Tyr-Leu-Ala-Ile-Val) may be a contributing factor to their function. It is known that in conventional chemokine receptors, this sequence is located in the junction between the third TM domain and the second intracellular loop. This region has a key role in coupling chemokine receptors with intracellular signal transduction pathways after ligand binding [12].

In ACKR1 this sequence is totally absent, while ACKR2, ACKR3 and ACKR4 possess two or three amino acid sequence differences which may alter the activation of intracellular signalling pathways [12]. Moreover, ACKR2, ACKR3 and ACKR4 have many more amino acid differences in other regions compared to conventional chemokine receptors, for example in the intracellular C-terminus. Indeed, ACKR1 has an almost completely different amino acid sequence than conventional chemokine receptors. Further studies and experiments are needed to better understand the signal transmission properties of ACKRs [12].

4. CHEMOKINE INTERNALISATION BY ACKR1 AND ACKR2

ACKR1 and ACKR2 can both internalize chemokines [12].

ACKR1 can mediate transcytosis, present internalized chemokines to leukocytes, while ACKR2 can degrade chemokines by arrestin-mediated endocytosis [12].

ACKR1 is able to internalize chemokines. However, *in vitro*, chemokines previously internalized by ACKR1 can move across cells (this mechanism is called transcytosis) and subsequently be presented to leukocytes and modulate transmigration [12, 24-25]. ACKR2 and ACKR3 cannot do this, however it is possible that cell-specific trafficking behaviour may lead to different several fates for internalized chemokines, depending upon which ACKRs have mediated their internalization [12, 26-27].

In contrast, ACKR2 is able to degrade chemokines by arrestin-mediated endocytosis [12]. Chemokines recognized by ACKR2 are rapidly internalized into cellular endosomes, where the low pH inside the lysosome causes their dissociation from the receptor and their subsequent degradation. After chemokine degradation, ACKR2 can migrate back to the cell surface to recognize another ligand. As a result, ACKR2 depletes extracellular chemokines through continued cycles of degradation [12, 26, 28-29]. The ACKR2 carboxyl terminus shows many differences in structure and in amino acid sequence compared to conventional chemokine receptors as aforementioned, which is the main contributor to the scavenging activity of this receptor [12,28,30]. In addition, it can modulate β -arrestin redistribution from cytosol to cell surface in a chemokine-independent manner [12, 28,30]. β -arrestins may regulate 7TM receptors and this is significantly influenced by their intracellular localization. Thus, an altered distribution of β -arrestins may change the functionality of co-expressed 7TM receptors [10,12, 30].

It is still unknown which region of the C-terminus of ACKR2 modulates β -arrestin re-localization and to what extent β -arrestin can affect the activity of ACKR2 [12]. In addition, whilst some studies indicate that β -arrestin mediates ACKR2 internalization and chemokine scavenging, other studies suggest that β -arrestins is not essential for these functions, but rather modulate receptor stability and intracellular trafficking [12, 28, 30].

When ACKR2 binds chemokines, there are no significant effects on β -arrestin distribution nor on the activation of signalling pathways induced by conventional chemokine receptors. However, chemokine binding causes increased cell surface levels of ACKR2 resulting in enhanced scavenging through the β -arrestin-dependent activation of the actin-binding protein via the Ras-related C3 botulinum toxin substrate1 (RAC1)-p21-activated kinase and 1-LIM domain kinase 1 cascade [12, 31].

5. CHEMOKINE INTERNALISATION BY ACKR3 AND ACKR4

ACKR3 and ACKR4 can both internalize chemokines [12].

In particular, ACKR3 activity is modulated by CXCL12, a conventional chemokine that can induce the downregulation of ACKR3 on the cell surface. Moreover, ACKR3 can induce several biological effects through activation of intracellular pathways such as MAPKs [12].

Several *in vitro* studies have also shown that ACKR3 and ACKR4 can act as chemokine scavengers [12,32,33]. ACKR3 internalization can be both chemokine-dependent or independent, and interestingly CXCL12 modulates sustained or transient ACKR3 downregulation on the cell surface. However, the ACKR3 pool can be quickly recovered from intracellular stocks [12,27]. Several cellular factors change both the internalization capability of ACKR3 and its intracellular distribution and, similar to ACKR2, the C-terminus of ACKR3 has a major role in chemokine internalization [12,27,33-35].

In addition, constitutive ubiquitylation of the ACKR3 C-terminus is associated with receptor stability and modulation of the trafficking of this receptor. However, when ACKR3 recognizes CXCL12, the C-terminus is deubiquitylated [12, 35-37]. Finally, β -arrestins cannot be constitutively relocated by ACKR3 and ACKR4, although chemokine binding modulates β -arrestin movement from the cytosol to the cell surface [12,37-38].

Several *in vitro* studies show that ACKR3 alone induces biological effects such as cell survival, growth and adhesiveness in the absence of chemokine binding. These actions require the activation of intracellular pathways such as MAPKs [12,34,36-39].

6. CROSSTALK BETWEEN ACRKS

The activity of ACKRs can be regulated by dimerization processes. Indeed, similarly to conventional chemokine receptors, ACKRs can heterodimerize with each other or with other conventional chemokine receptors to mediate different biological effects [12].

Similar to the situation with conventional chemokine receptors, a full knowledge of the intracellular signalling mechanisms and cellular biological effects is lacking as these receptors often dimerise with each other [12]. For example, ACKR1 and CCR5 can be co-expressed on activated endothelial cells, and can heterodimerize to alter CCR5-mediated intracellular signalling and chemotaxis [12, 40]. ACKR3 can form homodimers and also heterodimerize with CXCR4, with these heterodimers modulating CXCR4 and β -arrestin expression and regulate CXCL12-mediated effects [12, 34, 41].

In addition, *in vitro* experiments indicate that ACKR2 decreases CCR4-mediated migration of transfected cells and of CXCL13-driven B cell migratory responses [12,42]. In addition, neutrophils with decreased ACKR2 expression show enhanced responses to the CCR1 ligand CCL3, resulting in altered neutrophil migratory capacity during cutaneous inflammation [12]. The mechanisms that mediate these alterations in chemokine receptor responsiveness by ACKR2 are not yet defined [12].

7. ATYPICAL CHEMOKINES AND CHEMOKINES RECEPTORS IN THE PATHOGENESIS OF COPD

Many studies have shown that expression of atypical chemokines and/or atypical chemokines receptors are impaired in the lower airway of COPD patients (both in stable and during acute exacerbation) compared to control subjects such as smokers with normal lung function or non-smokers subjects [43-44].

Many inflammatory and structural cells in the lower airway such as epithelial and endothelial cells, fibroblasts and smooth muscle cells express chemokines and chemokine receptors both during a state of health and in inflammatory diseases such as COPD (Figures 4-7) [43-44].

α -MSH: α -melanocyte-stimulating hormone; ECP: eosinophil cationic protein; EDN: eosinophil-derived neurotoxin; HMGB1: high mobility group box 1; MIF: migration inhibitory factor

Figure 4. Atypical chemokines involved in the pathogenesis of COPD (inflammatory cells).

HMGB1: high mobility group box 1; MIF: migration inhibitory factor.

Figure 5. Atypical chemokines involved in the pathogenesis of COPD (structural cells).

ACKR: atypical chemokine receptor; CRTH2: Prostaglandin D2 receptor 2; RAGE: receptor for advanced glycation endproducts; TLR: toll-like receptor.

Figure 6. Atypical chemokine receptors involved in the pathogenesis of COPD (inflammatory cells).

ACKR: atypical chemokine receptor; RAGE: receptor for advanced glycation endproducts; TLR: toll-like receptor.

Figure 7. Atypical chemokine receptors involved in the pathogenesis of COPD (structural cells).

The expression of both chemokines and their receptors are modified across lower airway compartments of patients with stable COPD disease and during exacerbations when compared to smokers with normal lung function and/or to non-smoker subjects (control subjects) [43]. Studies have usually been performed on BAL or central airways specimens sampled from COPD patients and control subjects (these could be volunteers or patients with clinical indication for bronchoscopy). In contrast, small airway samples are obtained from patients undergoing lung resection (mostly for peripheral lung carcinomas), from selected patients with pulmonary emphysema eligible for lung volume reduction surgery (LVRS) or from patients undergoing lung transplantation. As a result, the analysis of parenchyma and/or airways inflammation may be influenced by the selection criteria of the lung tissue specimens used [43].

Significant changes in the lower airway expression of atypical chemokines and/or atypical chemokine receptor in COPD patients compared with control subjects (such as smokers with normal lung function and non-smoker subjects) can be found only when mean age and smoking habit are very similar between analysed groups. In fact, the expression of atypical chemokines and/or atypical chemokine receptors often changes with aging in control subjects and by smoking habit, but is not related to a specific disease [43].

There is no defined minimum number of patients with COPD and of control subjects required to account for biological variability [43]. However, studies performed on bronchial biopsies can be considered sufficiently trustworthy for a reliable comparative analysis when each group has a minimum of 12 subjects and analysis is performed on similar airway tree level specimens (for example subsegmental or segmental) [43,45]. Using a standardised approach (e.g. 100 μ m beneath the reticular basement membrane) from all subjects decreases patient-to-patient variability and improves quantification of inflammatory cells [43]. In addition, to enable the comparison of different pharmacologic treatments between groups requires large numbers of subjects to achieve reliable results [43,46]. Discrepancies between the studies illustrated below may result from one or more of these factors in addition to the existence of distinct sub-phenotypes of COPD patients.

8. HIGH-MOBILITY GROUP PROTEIN B IN THE PATHOGENESIS OF COPD

HMGB1 is the most highly expressed member of the high-mobility group protein B (HMGB) protein family. It is a member of damage associated molecular pattern (DAMPs) and assists in the binding of DNA nuclear protein to several immune cells. HMGB1 can be also released extracellularly in response to inflammatory stimuli and is recognized by several transmembrane receptors such as RAGE and TLR4 to mediate an inflammatory response induced by nuclear factor (NF)- κ B and release of pro-inflammatory mediators [47-52].

Currently, literature data on HMGB1 expression in lower airway of COPD patients (both during stable phase or acute exacerbation) compared to control subjects are discordant.

The high-mobility group protein B (HMGB) protein family (Table 1) has four members (HMGB1-4) which are passively released by necrotic cells or actively secreted by many cells (Figures 4-7) [47-49]. HMGB1 is the most highly expressed member and has 3 isoforms: fully reduced (also called all-thiol) HMGB1, disulphide HMGB1 and oxidized HMGB1 [47-49].

HMGB1 has three redox-sensitive cysteines (C23, C45, and C106) and acts as a chemoattractant factor only if all three cysteines are reduced. This fully reduced (all-thiol) HMGB1 released by necrotic cells shows chemotactic activity through formation of a heterocomplex with CXCL12 to initiate the inflammatory process. This heterocomplex can only bind CXCR4, modulating its ability to promote neutrophil chemotaxis [50-52]. In contrast, the disulphide form is the only one that mimics cytokine-stimulation and exhibits a pro-inflammatory activity. Indeed, the disulphide link between C23 and C45 plays a key role in HMGB1-mediated leucocyte activation [47-48]. The oxidized HMGB1 form has no functional activity [47-48].

HMGB1, which can be considered as a damage associated molecular pattern (DAMPs), is a DNA-binding nuclear protein expressed in many cell types, including monocytes, neutrophils and in the lungs in epithelial, endothelial cells and alveolar macrophages [53-54]. Within the nucleus, HMGB1 binds the DNA helices ensuring its structural stability and thereby contributes to prevent genomic mutations, DNA repair and transcriptional regulation [48, 55]. As a consequence, HMGB1 deficiency causes genome instability [56], leading to shortening of telomeres [52].

Intracellular HMGB1 directly interacts with the autophagy protein Beclin1 and displacing B-cell lymphoma 2 (Bcl-2) to promote autophagy as a defence mechanism during cellular stress and thereby enhance cell survival and decrease apoptotic cell death [57-59]. Oxidative stress due to reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^\cdot$) or the loss of superoxide dismutase 1 (SOD1) increases mitochondrial HMGB1 expression and promotes its translocation into the cytosol and its subsequent extracellular release [57-59]. Reduced HMGB1 release decreases the number of autolysosomes and inhibits autophagic flux in stressed cells during oxidative stress condition [57-59].

HMGB1 can also be released extracellularly during cell injury and death, or actively secreted following an inflammatory stimulus such as lipopolysaccharide (LPS), Cytosine-Guanosine (CpG) DNA and pro-inflammatory mediators including IL-1 β and tumour necrosis factor- α (TNF α) [49,60]. HMGB1 can induce immune tolerance if passively released, whilst active secretion has pro-inflammatory effects such as activating nuclear factor (NF)- κ B and promoting the release of TNF α and IL-6 by alveolar macrophages [52].

Increased mitochondrial RAGE expression is induced by extracellular HMGB1, enhancing the mitochondrial HMGB1/RAGE axis activity and ATP production [61]. In addition, HMGB1 intracellular signalling is also activated when it is recognized by transmembrane receptors, such as TLR4 and RAGE [49].

Activation of TLR4 and NF- κ B signalling by HMGB1 results in chemoattraction of regulatory T (Treg) cells and activates their suppressive functions [62, 63]. Indeed, Treg cells from human blood treated with anti-TLR4 antibody and incubated with HMGB1 expressed increased mRNA and proteins levels of pro-inflammatory mediators such as IL-1 β , IL-10, IFN γ , and TGF β , compared with untreated Treg cells [63].

Just like LPS, the disulphide form of HMGB1 can be recognized only by the extracellular TLR4 adaptor myeloid differentiation factor-2 (MD-2) to trigger the expression of several chemokines such as CCL3 and CCL5 and cytokines such as TNF α and IL-6 [64-65]. Activated leucocytes secrete HMGB1 that consequently stimulates the inflammasome and NF- κ B pathways to induce increased expression of pro-inflammatory mediators such as TNF α and IL-1 β and enhance inflammatory responses [60,66]. Secreted HMGB1 can also induce activation of other pro-inflammatory signalling pathways, such as IFN γ regulatory factor-3 (IRF3) and PI3K [60].

Activation of the NF- κ B pathway by the HMGB1/RAGE axis also induces the release of vascular endothelial growth factor (VEGF) which is involved in tumor angiogenesis [67]. Indeed, inhibition of RAGE/HMGB1 axis suppresses tumour cell growth, migration and tissue invasion [68]. Similarly, HMGB1 has suppressive effects on the host's anti-cancer immunity, inducing apoptosis in macrophage-derived dendritic cells (DCs) in a mouse model of colon cancer [69]. Therefore, HMGB1 may also have a key role in the pathogenesis of lung cancer [48].

Several studies suggest that extracellular HMGB1 is involved in infection and may act as a late factor in the pathogenesis of sepsis [70-71].

In vivo administration of disulphide HMGB1 induces a systemic inflammatory response with anorexia, fever, anaemia, cognitive dysfunction, endothelial cell activation, acute lung injury, epithelial barrier dysfunction, arthritis and death in animal models [66]. Indeed, HMGB1 expression is considered a biomarker of mortality during severe pneumonia (in particular viral pneumonia) or during acute respiratory distress syndrome (ARDS) [72], and may discriminate between viral and bacterial pneumonia [73].

In mice infected with *Mycobacterium tuberculosis*, BAL levels of total HMGB1 protein peak one day after the infection following its release from alveolar macrophages and the bronchial epithelium. From day 7 to 21 after infection, oxidized HMGB1 levels are increased, whereas fully reduced HMGB1 is detected during the later stages [74].

Overall, patients with active pulmonary tuberculosis show increased serum and spontaneous sputum HMGB1 levels compared to healthy control subjects [75].

Patients with pulmonary fibrosis also demonstrate increased serum, spontaneous sputum and BAL HMGB1 levels, which correlated with an increased risk of disease progression [76-77].

Furthermore, serum and spontaneous sputum HMGB1 levels are increased in stable COPD patients (n=47, mean age 60 years) compared with smokers with normal lung function (n=34, mean age 44 years) [78]. Serum HMGB1 levels are negatively correlated with lung function (post-BD FEV₁/FVC ratio) in stable COPD patients (n=11, mean age 75 years) and in smokers with normal lung function (n=8, mean age 67 years), but not in non-smokers subjects (n=9, mean age 58 years). In addition, in the same study cohort, increased HMGB1 mRNA expression are found in surgically obtained lung tissue from COPD patients compared with smokers with normal lung function and with non-smokers subjects [79]. However, a separate study reported no significant difference in serum HMGB1 levels between stable COPD patients (n=51, mean age 59 years), smokers with normal lung function (n=212, mean age 52 years) and non-smokers (n=32, mean age 56 years). Moreover, there was no correlation between serum HMGB1 levels and lung function (FEV₁%) [80].

Serum HMGB1 levels are increased in stable COPD patients (n=37, mean age 71 years) and in stable idiopathic pulmonary fibrosis (IPF) patients (n=76, mean age 67 years) compared to smokers with normal lung function (n=74, mean age 54 years), however there are no significantly differences in serum HMGB1 levels between COPD and IPF groups [81]. Conversely, increased serum HMGB1 levels are reported in COPD patients during exacerbation (n=40, mean age 64 years), compared with the same patients during the stable phase. However, there are no significantly difference in HMGB1 protein levels between exacerbation and stable phase in the induced sputum from 35/40 of these COPD patients [82].

In another study serum HMGB1 levels were increased during exacerbation in COPD patients (n=44, mean age 68 years) compared to the stable phase (in the same COPD patient cohort) with a direct correlation between serum HMGB1 and serum soluble (s)RAGE levels, and their ratio (HMGB1/sRAGE) correlated with COPD severity [83]. Serum HMGB1 levels are also raised in COPD patients with co-morbid type 2 diabetes mellitus (n=112, mean age 65 years) compared with subjects with diabetes mellitus type 2 alone (n=126, mean age 66 years, not reported if smokers with normal lung function). In addition, serum HMGB1 levels were positively correlated with metabolic parameters such as homeostatic model assessment for insulin resistance (HOMA-IR), glycated haemoglobin (HbA1c), and smoking habits, and negatively correlated with lung function (FEV₁% and FEV₁/FVC ratio%) [84].

Similarly, serum HMGB1 levels are also increased in COPD patients with pulmonary hypertension (PH) (n=14, mean age 61 years) and in patients with idiopathic pulmonary hypertension (IPAH) (n=14, mean age 64 years, not reported if current or former smokers) compared with control subjects (n=14, mean age 64 years, not reported if smokers with normal lung function). HMGB1⁺ cells are present around remodelled vessels within the lung both in COPD patients with co-morbid pulmonary hypertension and also in IPAH patient. Moreover, *in vitro* exposure to HMGB1 induces a proliferative effect on pulmonary arterial smooth muscle cells and arterial endothelial cells [85]. BAL levels of HMGB1 are increased in stable COPD patients when compared to smokers with normal lung function and non-smokers [86], confirming previous data showing elevated BAL HMGB1 levels in COPD patients (n=30, mean age 58 years) when compared with smokers with normal lung function (n=20, mean age 56 years) and non-smokers (n=20, mean age 55 years) [87].

In contrast to these studies, Di Stefano and colleagues [88] reported significantly decreased BAL HMGB1 protein levels in patients with stable COPD (n=26, mean age 68 years) when compared with smokers with normal lung function (n=18, mean age 64 years). However, this difference was lost after removal of the outliers (for age and smoking habits) [88].

Increased HMGB1 protein and mRNA levels were found in the lung tissue of a mouse model of COPD involving 14 days LPS (200 µg) exposure together to 6 weeks cigarette smoke exposure in mice and following in mouse models concurrently exposed to hypoxia (18% O₂), compared to control mice. HMGB1 expression positively correlated with NF-κB protein and mRNA lung levels and the elevated levels of HMGB1 were attenuated by intraperitoneally injected of a NF-κB inhibitor in these animals [89]. Similarly, the elevated levels of lung HMGB1 protein and mRNA seen in LPS-exposed rats and cigarette smoke-exposed mice was attenuated by ulinastatin (100000 UI intravenously twice daily for 7 days), although the levels were not reduced to those seen in control animals [90].

Although current literature data on HMGB1 are discordant, it appears that HMGB1 is involved in the pathogenesis of COPD. Increased HMGB1 expression in lower airways (both immune and structural cells) of COPD patients can sustain inflammation by recruiting and activating several immune cells such as macrophages and T cells. These cells subsequently release others pro-inflammatory mediators such as TNF-α and IL-1β that can consequently induce airways remodelling [79,82-83,87]. In addition, data on animal models have shown that blocking of HMGB1 and of its intracellular pathways has a protective role in

mouse models lungs, although further studies are necessary to clarify this mechanistic pathway [90].

9. RECEPTOR FOR ADVANCED GLYCOSYLATION END PRODUCT IN THE PATHOGENESIS OF COPD

RAGE is a pattern recognition receptors (PRR) expressed in various types of cells and it is constitutively expressed in the lungs. RAGE can recognize several ligands and in particular AGEs and HMGB1 to induce an inflammatory response through NF- κ B activation [91]. 3 different RAGE isoforms exist [91], and literature data show that serum soluble RAGE levels are decreased in COPD patients while lung RAGE expression is increased in COPD patients. This suggests that RAGE may have a key role in maintaining a chronic inflammatory response during COPD pathogenesis.

RAGE is a transmembrane protein within the immunoglobulin (Ig) superfamily [91]. There are several alternatively spliced forms of RAGE resulting in isoforms with different levels of functionality despite being produced from a single gene (Table 2) [91]. The full-length receptor structure contains three Ig domains (V-type, C1-type and C2-type), a transmembrane domain, and an intracellular cytoplasmic domain [49, 91]. The N-truncated isoform that lacks advanced glycosylation end product (AGE) does not transduce intracellular signalling when it recognizes a ligand and acts as a dominant negative RAGE isoform serving as scavenger/decoy receptor [91]. This isoform does not possess a cytosolic domain and cannot transduce intracellular signalling whereas soluble RAGE (sRAGE) contains the complete extracellular domain, is produced through an alternative splicing and is secreted [91]. sRAGE can also be produced by cleavage of full-length RAGE by extracellular proteases, and this is the form that is mainly detected in the serum [91]. RAGE is a pattern recognition receptor (PRR) with many different ligands [49].

When compared with embryonic development, RAGE expression in adults is decreased in all tissues except in the lungs [92], where it remains constitutively expressed [93]. In particular, RAGE is expressed in type 1 alveolar epithelial (AT1) cells, for which it is considered a specific marker [94-95]. However, type 2 alveolar epithelial (AT2) cells can also express RAGE [96]. In addition, RAGE is also expressed in several cells such as neurons, vascular smooth muscle cells, endothelial cells, airway smooth muscle cells, DCs, macrophages, eosinophils, T and B cells (Figures 6-7) [93,97]. Interestingly, human T cells express RAGE intracellularly within endosomes, though the reason for this is unknown [93]. Lung expression of RAGE is increased during several inflammatory diseases, such as diabetes mellitus, amyloidosis, cystic fibrosis and rheumatoid arthritis [98], and decreased in lung cancer and pulmonary fibrosis [95,99].

Ligand recognition by RAGE results in increased receptor expression and activation of a positive-feedback loop that promotes multiple signalling pathways such as stress-activated protein kinase/c-jun-NH2-terminal kinase (SAPK/JNK), Cdc42/Rac, p38 MAPK, and ERK1/2. These, in turn, cause TNF α and IL-1 β secretion from blood monocytes, increase the expression of adhesion receptors on endothelial cells and MMPs on several cells such as human synoviocytes through NF- κ B activation [100-101].

RAGE was initially defined as a receptor for AGEs, but was also found to interact with HMGB1 and many calcium binding S100 protein, such as S100A4 released from smooth muscle cells of pulmonary artery, S100A12 from airway epithelium and eosinophils [102- 103], and S100A9 from keratinocytes [93,97]. All S100 proteins can form non-covalent homodimers both *in vitro* and *in vivo*. However, some of these such as S100A8 and S100A9 can also form heterodimers. Activated phagocytes can release both S100A8 and S100A9 as a heterodimer and in this complex, S100A8 has an active role while S100A9 is the modulator component [104]. S100A8 and S100A9 are both highly expressed by monocytes, neutrophils and macrophages. The myeloid cells that express S100A8/A9 complexes promote inflammatory process, whilst the S100A8/A9 complexes mediate further leukocyte recruitment [104-105]. Expression of S100A8/A9 complexes on the cell surfaces of leukocytes regulate their adhesion capacity [104]. S100A12, another member of the S100 family, is a potent monocyte chemoattractant [103]. In addition, S100A12 enhances neutrophil adhesion and their mobilization from bone marrow to inflammatory sites [103].

Chronic oxidative stress can lead to the “carbonyl stress”, a condition characterized by oxidants that can damage the surrounding tissues forming highly reactive organic molecules that are responsible for denaturation of proteins [106]. These modifications occur through a non-enzymatic pathway, forming carbonyl adducts on surface proteins, that are known as AGEs [107]. Historically, these AGEs have been shown to occur as a result of non-enzymatic glycation (called the Maillard reaction) between amino groups on proteins and the carbonyl group on an aldose reducing sugar (such as glucose and ribose) following prolonged hyperglycemia in diabetes mellitus [108]. Since ribose is over 20 times more reactive than glucose in forming these adducts [109], this may have significant consequences in COPD. This is because there is an altered metabolic profile in COPD due to mitochondrial dysfunction that results in increased pentose phosphate pathway activity and a consequent rise in ribose levels [110].

A recently identified enzyme, fructosamine-3-kinase (FN3K) and its homologue FN3K-RP, can reduce the levels of fructosamine-modified proteins and thereby limit progression to AGEs. It does this by phosphorylating the Amadori adduct of glycated proteins, making the modification unstable and liberating the native unmodified protein [111]. However, it is unclear whether this reaction can also impact on other forms of AGE adducts that target free amino groups on proteins [93].

Aging also elevates serum AGEs levels [112] and RAGE regulates various aspects of biology associated with ageing, including inflammation, innate immune responses, apoptosis, autophagy and cell proliferation [97].

Activation of RAGE enhances NF- κ B activation, which causes a steady pool of newly synthesized NF- κ B p65 protein and mRNA [113].

RAGE also enhances inflammatory cell recruitment and adhesion through inducing the expression of vascular cell adhesion protein 1 (VCAM-1) on endothelial and mesothelial cells [93]. RAGE signalling is also crucial for DC maturation and Th1 cell polarization, priming and proliferation [93].

In asthma patients, a single nucleotide polymorphism (SNP) (rs2070600) identifies a RAGE isoform that is associated with increased FEV₁ decline [114-115]. S100A8/A9 is implicated in asthma airway remodelling and inflammation [104] whilst eosinophil-derived S100A12 stimulates IgE-mediated responses and mast cell degranulation in the lung, and is involved in the pathogenesis of rheumatoid arthritis, inflammatory bowel diseases and vascular complications of diabetes as well as having a key role in parasite defences [103]. Furthermore, RAGE^{-/-} mice are completely protected against asthma-like allergic airway inflammation and in these models, RAGE has a key role in the release of IL-5, IL-13 and eotaxins, but not of IL-4 [116]. RAGE also promotes IL-33 expression in the lung [93].

In mouse models of acute lung injury (ALI) and in patients with ALI/ARDS, sRAGE BAL levels are increased and associated with the severity of lung disease [95]. In addition, RAGE signalling pathway enhances lung inflammation during ALI, indeed RAGE^{-/-} mice are protected from hyperoxia-induced ALI with decreased mortality [117]. RAGE^{-/-} mice show decreased lung injury following inoculation with Gram-negative (such as *Escherichia coli*) [118] or Gram-positive (such as *Streptococcus pneumoniae*) [119] bacterial challenges. However, there are no significant differences in LPS-induced ALI between wild-type and RAGE^{-/-} mice, likely because RAGE-mediated inflammation is promoted by different PAMPs other than LPS [118].

RAGE expression is decreased in non-small cell lung cancer (NSCLC) [93], whereas its ligands are increased [120-123] and are predictors of poor prognosis [124]. Conversely, *in vitro* overexpression of RAGE in lung cancer cells decreased proliferation and tumour growth [99,125]. Thus, the role of RAGE ligands in promoting lung cancer tumorigenic mechanisms are similar to that seen in other kinds of tumours [93].

The RAGE axis may have a key role in the pathogenesis of COPD. Several studies have shown that serum sRAGE levels are decreased in COPD [126-130] and generally correlates with severity whilst limited information on RAGE levels in the lungs tissue of COPD patients [78, 87,117,127,131-135,137] suggests that RAGE signalling can maintain the chronic inflammatory activity in COPD. Activation of RAGE signalling due to chronic cigarette smoke exposure is likely the initiating step which evolved as a protective mechanism against inhaled pollutants that induces an inflammatory response; chronic cigarette smoke exposure develops a “tipping point,” when this response becomes unmodulated, probably due to genetic susceptibility factors [86,136].

RAGE levels are increased in surgically obtained epithelial cells and smooth muscle cells from stable COPD patients (n=20, mean age 62 years) compared with smokers with normal lung function (n=14, mean age 61 years) and non-smoker subjects (n=10, mean age 61 years) [87]. In addition, serum levels of sRAGE are decreased in COPD patients (n=51, mean age 59 years) and smokers with normal lung function (n=212, mean age 52 years) compared to non-smoker subjects (n=32, mean age 56 years) and sRAGE levels correlate with decline lung function and negatively with smoking habits [80]. In another study, serum sRAGE levels were decreased in COPD patients (n=200, mean age 66 years) compared with smokers with normal lung function (n=201, mean age 65 years), and these levels also negatively correlated with pulmonary emphysema severity assessed by thorax CT [137].

Decreased serum sRAGE levels was validated in another COPD cohort (n=146, mean age 60 years) compared with smokers with normal lung function (n=81, mean age 59 years), in this COPD cohort, sRAGE serum levels were more decreased in patients with long term oxygen therapy (LTOT) (n=36, mean age 59 years) compared to COPD patients without LTOT (n=104, mean age 63 years) [128]. In a follow-up study, the same authors confirmed that serum sRAGE levels are decreased in stable COPD patients (n=88, mean age 63 years) compared to smokers with normal lung function (n=44, mean age 61 years) and non-smokers (n=11, mean age 58 years) and that levels did not correlate with lung function decline [127].

Moreover, there were no differences in serum sRAGE levels between smokers with normal lung function (n=37, mean age 42 years) and non-smoker subjects (n=40, mean age 38 years), despite decreased expression of the gene encoding RAGE (AGER) in the bronchial mucosa of smokers with normal lung function compared to never smokers [138]. Serum sRAGE levels were also decreased in stable COPD patients (n=61, mean age 70 years) compared with smokers with normal lung function (n=42, mean age 62 years). This decreased even further in 24 COPD subjects during an acute exacerbation requiring hospitalisation, though levels returned to those seen in the stable phase during convalescence [130].

In contrast, another study has shown that sRAGE serum levels are increased in COPD patients (n=44, mean age 68 years) during exacerbation compared to the stable phase in the same cohort. In addition, sRAGE levels were directly correlated with serum HMGB1 levels, while the serum HMGB1/sRAGE ratio was correlated with COPD severity [83].

Few studies have reported RAGE levels in lung tissue of COPD patients. One study reported increased RAGE expression in surgically obtained lung tissue from 29 COPD patients compared to non-smoker subjects despite a significant reduction in serum sRAGE levels [139]. Murine models of COPD suggest a critical role for RAGE in COPD/emphysema. Intratracheal instillation of porcine pancreatic elastase induces emphysema and this is reduced in RAGE^{-/-} mice along with decreased expression of IL-1 β protein and BAL neutrophils [134]. Similar results were seen in a 6 months cigarette smoke-exposed RAGE^{-/-} mice whereby they were protected from the development and progression of pulmonary emphysema compared to wild-type (WT) mice [133]. Short term cigarette smoking (4 weeks) in RAGE^{-/-} mice also resulted in reduced BAL levels of IL-1 β , IL-6 and TNF α proteins compared to WT mice. In addition, the lung tissue of RAGE^{-/-} mice have decreased S100A8 and S100A9 gene expression compared to WT mice [140].

Furthermore, in both 6 months cigarette smoking and porcine pancreatic elastase mice models of COPD, an intraperitoneal injection of the RAGE-specific antagonist FPS-ZM1 decreased BAL levels of cytokines such as IL-6 and TNF α , macrophages, neutrophils and lymphocytes. In addition, there were decreased levels of sRAGE and reduced development and progression of pulmonary emphysema in FPS-ZM1-treated mice when compared to untreated mice [139].

10. ANTIMICROBIAL PEPTIDES IN THE PATHOGENESIS OF COPD

Antimicrobial peptides (AMPs), are a large family of peptides that are known for their direct antimicrobial activity against several pathogens and more recently for their modulatory effects on inflammatory process and innate and adaptive responses in response to infections. These are classified in based to their structure in α -helical and β -sheet, however these are secreted as precursors that subsequently undergo a cleavage process before reaching the mature form [141-144].

Antimicrobial peptides (AMPs), also called host defence peptides (HDPs), show several immunomodulatory properties such as modulating the inflammatory and innate and adaptive immune responses causing an increased recruitment of leukocytes to the site of infection [141-144] and are produced by all organisms in theory (Table 1). So far, more than 2500 peptides have been identified, of which 134 are produced in the human species [145].

Although AMPs display diverse primary and secondary structures, they show several common features, such as their many Arginine and Lysine residues that generate their overall positive charge, and in addition an amino acids sequence with at least ~50% hydrophobic amino acids. These hydrophobic amino acids promote their interaction with cell surfaces and also translocation into cells [141].

AMPs vary considerably in length and are classified based on their secondary structure into α -helical (such as LL-37, human lactoferrin, lactoferricin and histatins) and β -sheet (such as defensins) peptide groups [143,146-148]. The major characteristic of AMPs is that they are released as large polypeptide precursors and, after a proteolytic processing (during or post-translationally), these are released as active peptide segments that can either be arranged in single or multiple copies [141]. Processed functional peptides in human are classified into many groups, including cathelicidins, defensins, transferrin, hepcidin, lysozyme and antimicrobial neuropeptides [141].

AMPs have antimicrobial action against viral, bacterial, fungal and protozoan infections [141, 144] and may potentially inhibit microbial biofilms [149-150].

AMPs can act directly and rapidly against pathogens (direct mechanism) either by disrupting the microbial cell membrane integrity and/or by translocating into bacteria cytoplasm targeting intracellular components [143,151]. Membrane permeabilization by AMPs causes extracellularly exit of ions and metabolites, inducing a transmembrane potential depolarization and thus membrane dysfunction due to altered osmotic regulation mechanisms and inhibition of cellular respiration. This leads to cellular membrane destruction and lysis of microbial cells [143].

11. CATHELICIDIN IN THE PATHOGENESIS OF COPD

LL-37 is the only human cathelicidin, and is expressed by several innate immune cells, but also by lung epithelial cells [152-155].

LL-37 shows a direct antimicrobial activity; additionally, it can recruit several immune cells, such as monocytes, neutrophils, eosinophils, dendritic cells and T cells, to the site of infection either directly or indirectly through the release of several pro-inflammatory mediators, and activate them [152-155].

Several studies have shown that LL-37 expression is increased in lower airway of COPD patients compared with control subjects, suggesting an important role in the pathogenesis of COPD.

LL-37 (the only human cathelicidin) is a small active of 37 amino acids peptide released from the C-terminal end of the cathelicidin antimicrobial peptide [(CAMP) also termed human cationic antimicrobial protein-18, CAP18] (Table 1) following cleavage by the neutrophil granule-derived proteinase 3 [152].

Lung LL-37 is released by neutrophils, alveolar macrophages and also by epithelial cells (Figures 4-5) [153] and possesses

several pleiotropic effects, such as chemotaxis of blood monocytes, neutrophils, eosinophils, dendritic cells and T cells [154], in addition to its antimicrobial and immunomodulatory functions [155].

LL-37 can directly recruit these immune cells to the site of infection, but also it promotes immune cell chemotaxis indirectly by inducing the release of chemokines such as CXCL1, CXCL8, CCL2, CCL4, CCL5 and CCL20 from both structural cells such as epithelial cells and from immune cells [156]. In addition, LL-37 increases the expression of conventional chemokine receptors such as CXCR4 and CCR2 in alveolar macrophages [156]. LL-37 also acts directly through binding to CXCR2, the formyl peptide receptor 2 (FPR2) and mycobacterial glyceraldehyde 3-phosphate dehydrogenase (GAPDH) [155,157]. BAL levels of LL-37 range from 2-5 µg/ml (0.4-1µM) in healthy individuals up to 20 µg/mL (2.2µM) during infection disease. In nasal secretions, LL-37 levels can vary from 1.2-80 µg/mL [158].

LL-37 “stabilizes” or “modulates” TLRs signalling [159], consequently regulating secretion of cytokines such as TNFα [160], apoptosis [161], inflammasome activation [162] and phagocytosis [163].

LL-37 inhibits TLR2-mediated lipoteichoic acid (LTA)-induced and TLR4 (LPS-induced) production of IL-1β, IL-6, IL-8 and TNFα from blood monocytes [164-165]. Overall, the anti-inflammatory activity of LL-37 appears to target key inflammatory pathways such as the TLRs and NF-κB activated by exogenous stimuli such as LPS, thereby decreasing the release of pro-inflammatory mediators including TNFα and IL-1β [156,165].

LL-37 has a high affinity for nucleic acids, can bind both RNA and DNA and may act as a transmembrane transporter for intracellular nucleic acid release [166]. Indeed, neutrophil AMPs are present in circulating DNA-containing immune complexes in patients with systemic lupus erythematosus developing both anti-DNA and anti-neutrophil AMPs autoantibodies [167]. Moreover, activated neutrophils release DNA-antimicrobial peptide complexes called neutrophil extracellular traps (NETs) that can be recognized by TLR9 on plasmacytoid DCs [167]. NETs are important in the pathophysiology of ARDS and sepsis [168] and interestingly, LL-37 expression is decreased in neutrophils isolated from patients with septic shock [169].

In several infection diseases and sepsis animal models, LL-37 can regulate host immune responses by reducing pathogen-induced inflammation [156]. LL-37 has a role in the innate immune responses against influenza type A virus (IAV) infection in mice [141,158,170]. Indeed, mice infected with IAV and treated with either LL-37 or the anti-flu drug zanamivir both show a 60% increase in survival compared to untreated animals [171]. In addition, LL-37 inhibits IAV replication prior to viral RNA or protein synthesis [158,170]. LL-37 shows also antiviral activity against respiratory syncytial virus (RSV) *in vitro* [172] and children with decreased serum cathelicidin levels show increased susceptibility to RSV infection with increased risk of severe RSV-associated bronchitis [173].

In vitro stimulation of blood monocytes with the vitamin D3 analogue calcitriol increases LL-37 mRNA expression in both healthy subjects and active pulmonary tuberculosis patients. However, the increase in LL-37 is greater in patients with active pulmonary tuberculosis and in particular in these without pulmonary tubercular cavities compared with patients with pulmonary tubercular cavities [174].

LL-37 has known anti-fungal activity *in vitro* and can directly bind to the surface of *A. fumigatus* at high concentration (20 µM) to disrupt the integrity of the cell wall, and at lower concentrations (4µM) to significantly attenuate mycelial adhesion and prevent the invasion and destruction of epithelial cells [175-177]. LL-37 has anti-fungal activity, as it can inhibit *A. fumigatus*-induced pro-inflammatory mediators *in vitro*, such as IL-6 and TNFα [175]. In a murine model of intratracheal *A. fumigatus* infection, LL-37 decreased fungal burdens and decreased IL-6 and TNFα protein levels in the lungs compared to untreated infected mice. This suggests that LL-37 enhances clearance of *A. fumigatus* and controls the hyphae invasion to alleviate pathological damage [175]. Moreover, transgenic LL-37^{+/+} mice are protected against *A. fumigatus* infection. In addition, lung tissues from LL37^{+/+} mice have reduced levels of TNFα and IL-6 levels compared to WT mice [175]. Similar results are shown in an *A. fumigatus*-infected immunosuppressed (induced by treatment with high dosage of glucocorticoids) mouse model [175].

In COPD, increased LL-37 protein levels in sputum are correlated with increased severity of the disease [152,178]. For example, sputum LL-37 levels are increased in patients with mild/moderate stable COPD (n=13, mean age 62 years) and are further elevated in severe/very severe disease (n=15, mean age 63 years) compared to both smokers with normal lung function (n=14, mean age 60 years) and non-smokers subjects (n=18, mean age 63 years); however, blood levels of LL-37 are similar between subject groups [178]. Interestingly, BAL LL-37 protein levels are increased in stable COPD patients with mild/moderate disease, but these are decreased in severe/very severe disease, compared with control subjects [179]. Human experimental infection with rhinovirus (RV) causes increased LL-37 sputum levels only in COPD patients (n=20, mean age 60 years) but not in smokers with normal lung function (n=21, mean age 51 years) and non-smokers subjects (n=10, mean age 62 years) [180].

However, some studies show that serum and induced sputum LL-37 protein levels are increased in stable COPD patients (n=215, mean age 63 years) compared with smokers with normal lung function (n=45, mean age 54 years), and a further increase is observed in COPD patients during exacerbation (n=56, mean age 63 years). In addition, serum and induced sputum LL-37 levels are positively correlated with the risk of acute exacerbations in COPD patients and with *Haemophilus Influenzae*

colonisation [181]. A large study has shown that LL-37 protein levels in COPD spontaneous sputum sampled over 6 years (n=11, mean age 66 years, n samples=153) are increased during exacerbation due to *Haemophilus Influenzae* and *Moraxella catarrhalis* compared with culture-negative samples COPD patients [182].

In contrast, serum LL-37 levels have also been reported to be decreased in stable COPD patients (n=138, mean age 63 years) compared to healthy subjects (n=33, mean age 58 years, not reported if smokers with normal lung function). This decrease is more pronounced in COPD patients with very severe disease (n= 34, mean age 69 years) compared to COPD patients with mild (n= 34, mean age 58 years) or moderate (n= 35, mean age 60 years) disease [183]. In addition, decreased serum LL-37 levels correlated with a more rapid decline in lung function in smokers with normal lung function (n= 308, mean age 49 years), moreover, there was not difference between current and former smokers [184].

Increased LL-37 protein levels are also seen in surgically obtained lung tissue from stable COPD patients (n=18, mean age 62 years) compared to smokers with normal lung function (n=18, mean age 61 years). In addition, *in vitro* treatment of lung tissue of COPD patients with LL-37 causes increased MUC5AC expression in a dose-dependent manner [185].

These data suggest that LL-37 has a key role in the pathogenesis of COPD. Indeed, several studies have shown increased LL-37 expression in the lower airways of COPD patients,

even in the absence of a known infection [152,178-180,182]. Increased levels of LL-37 can maintain inflammatory processes inducing release of pro-inflammatory mediators such as IL-1 β , IL-8 and TNF- α and recruitment and activation of immune cells with subsequent airway remodelling and apoptosis of bronchial epithelial cell and alveolar epithelial cell [152,178-180,182]. Thus, blocking LL-37 axis represents a possible novel therapeutic target in COPD [179].

12. HISTATINS IN THE PATHOGENESIS OF COPD

Histatins are a large family of AMPs. There are many members of this AMPs family, but all of these derive by 2 precursor members. These shows antimicrobial activity mediated by their cationicity against several pathogens, in particular against fungi. They are secreted by salivary and lacrimal glands showing a key anti-microbial role in the oral cavity and eyes [186-187]. Currently, there are no studies on histatins expression in COPD.

Histatins are a family of AMPs characterized by cationic, histidine-rich low-molecular weight peptides (Table 1) [186]. Histatin-1 (38 amino acids) and histatin-3 (32 amino acids), are full-length products and from these 2 members derive the other histatin members (histatin-2, -4, -5, -6, -7, -8, -9, -10, -11, and -12) through proteolytic cleavage [186]. The most prevalent forms of human histatins are histatin-1, -3 and -5 which each contribute 20-30% to the total histatin pool [187]. Histatins are synthesized and released by submandibular, sublingual, parotid and von Ebner glands [186], but they are detected also in many other tissues. Histatin-1 is found in human lacrimal glands but also in melanoma cell lines and metastatic lesions from melanoma where it is indicated as a potential prognostic marker for malignancy, whilst histatin-5 is reported on the human ocular surface [186].

Histatin peptides have several functions such as creating the protective pellicle of teeth, inhibiting microbial interactions such as hemagglutination and coaggregation between bacterial species [188]. Histatins also inhibit protease activity and neutralise endotoxins deriving from Gram-negative bacteria [188]. In addition, histatin-1 and -3 are released from oral keratinocytes where they induce increased cell adhesion and migration, and are present in non-oral epithelial cells, endothelial cells and in gingival and dermal fibroblasts [186]. Furthermore, histatin-2 enhances the migratory capacity of human primary gingival and dermal fibroblasts and promote primary skin keratinocyte migration and re-epithelialization [186]. However, histatin-5, does not show these activities *in vitro* [186]. Finally, histatin-1 is implicated in the regulation of endothelial barrier function, induction of angiogenesis and promotion of endothelial cell adhesion [186].

Histatins have an important anti-microbial role in the oral cavity (their concentration in the saliva is 50-425 mg/mL) [189] by enhancing extracellular ATP-induced death of many pathogenic microorganisms [190]. They can inhibit and kill *Candida* organisms, *ballistoconidia* and germinated cells. In this respect, histatin-5 is the most active, histatin-3 shows moderate activity and histatin-1 is the least active [188]. For example, *in vitro* histatin-5 has the highest anti-fungal activity against *Candida albicans* [191], *Cryptococcus neoformans*, *Candida glabrata*, *Candida krusei*, and *A. fumigatus* [192]. In addition, histatin-5 has also antibacterial against *Staphylococcus aureus* [193].

Histatin-5 recognizes the cell wall proteins (Ssa1/2) and several glycans of *C. albicans* and is taken up by the cells using fungal polyamine transporters involving an energy-dependent mechanism [194]. Once histatin 5 is inside fungal cells, it can alter mitochondrial function, increase oxidative stress and ion imbalance resulting in cell death [194]. Histatin-5 inhibits the bacterial proteases released from *Porphyromonas gingivalis* and *Clostridium histolyticum* [195]. Currently, there are no studies on the role of histatins in the pathogenesis of COPD although lower levels of histatin-5 are found in the saliva of human immunodeficiency virus (HIV)-positive patients and this correlates with an increased prevalence of *Candida albicans* [196].

13. HUMAN LACTOFERRIN AND LACTOFERRICIN IN THE PATHOGENESIS OF COPD

Lactoferrin, a non-heme iron-binding glycoprotein, is expressed in many exocrine secretions, including bronchial secretions. It is also an important component of secondary granules of neutrophils. Lactoferrin shows anti-microbial activity including

inhibition of bacterial adhesion to host cell and colonization of bronchial epithelial. In addition, it shows an important anti-inflammatory activity in several chronic inflammatory diseases including COPD [197-214].

Lactoferricin, derived by lactoferrin, shows important anti-microbial activity, especially against viruses, but also antitumor activity [197]. However, there are no studies on lactoferricin expression in COPD.

Lactoferrin, a non-heme iron-binding glycoprotein, is abundant in exocrine secretions such as bronchial secretions, but also sweat, tears, saliva, semen, vaginal fluids, nasal fluids, bile, urine, gastrointestinal fluids, milk and colostrum (Table 1) [197]. Lactoferrin is an 80 kDa glycoprotein that binds two ferric ions per molecule [198] composed of a single 691 amino acids single polypeptide chain [199]. This forms a bi-lobed structure, with an N-lobe and a C-lobe, each of which can reversibly bind a ferric ion with high affinity ($K_d \sim 10^{-20}$ M) [200]. The iron binding site in each lobe is identical and contains two tyrosines, one aspartic acid and one histidine residue [200-201]. Lactoferrin has an open iron-free (unsaturated) and a closed iron-bound (saturated) conformational state. The closed forms are more resistant to term denaturation and protease actions compared to the open conformation [199, 202-203].

Lactoferrin is an anti-inflammatory mediator capable of suppressing pro-inflammatory cytokines such as IL-6, which has a key role in iron homeostasis disorders. Meanwhile, Lactoferrin appears to be an important mediator of iron and inflammatory homeostasis [202]. *In vitro*, Lactoferrin modulates the phenotypic shift of macrophages from M1 to M2 following treatment with LPS, further supporting the role of IL-6 in the characterisation of the M1 phenotype [202,204]. In these experiments, Lactoferrin was internalized and translocated into the nucleus of macrophages where it inhibited IL-6 production [202].

Interestingly, intranasal Lactoferrin decreases β -amyloid deposition in the brain and attenuated cognitive deterioration in mouse models of Alzheimer's Disease. This correlated with a marked decrease in neuronal ROS production and reductions in both TNF α and IL-6 mRNA levels in the brain [205]. A clinical trial of oral Lactoferrin (250 mg/day for three months) decreased IL-6 serum levels and increased IL-10 serum levels in Alzheimer's Disease, showing a protective effect in the development disease [206]. In addition, Lactoferrin (250 mg/day) given for 3 months to children with type 2 diabetes decreased diabetes-associated inflammation due to inhibition of the TLR4/NF- κ B axis which correlated with a reduction in pro-inflammatory mediators in the serum including TNF α , IL-1 β and IL-6. There was a subsequent significant increase in insulin synthesis and decreased glycemia was observed [207].

Lactoferrin also has antimicrobial, anticancer, antioxidant, and anti-allergic activities [197]. In particular, Lactoferrin has an important innate immune role being secreted at mucosal surfaces [208]. Usually, the antimicrobial activity of lactoferrin is inversely associated with iron, since the addition of iron reverses the effects of lactoferrin [209-210].

However, Lactoferrin also exerts an iron-independent bactericidal action by interacting directly with LPS from the cellular membrane of Gram-negative bacteria or with lipoteichoic acid from Gram-positive bacteria [209,211]. The anti-microbial activity of Lactoferrin is mediated by its N-terminal region, as the pepsin-digested cationic peptide exhibits more potency against Gram-negative bacteria [209,212]. The bactericidal activity against both Gram-positive and -negative bacteria involves the same cationic residues [209,213].

Lactoferrin has an independent iron-binding activity that decreases bacterial adhesion to host cells through a competitive bond to host cells and/or to microbial surface components. In addition, lactoferrin can inhibit cellular entry of both Gram-negative and Gram-positive bacteria [209,213].

Bronchial epithelial cells secrete lactoferrin, which helps prevent microbial colonization and triggers the adaptive immune response [214]. Lactoferrin is also released from neutrophils [197] and is an important component of neutrophil secondary granules [215]. The release of lactoferrin by neutrophils at the sites of infection is important due to the acidic nature of the infected site resulting from pathogen activity. Acidic conditions promote the generation of free radicals (for example in the phagolysosome) against pathogens. However, under physiological pH conditions, lactoferrin-mediated production of radicals is decreased (Figures 4-5) [215-216]. Human blood neutrophils from healthy subjects exposed to hypoxia (0.8% oxygen, 3 kPa for 4 h) *in vitro* show increased lactoferrin protein release both at baseline and after an inflammatory insult with either platelet-activating factor, the synthetic chemotactic factor f-Met-Leu-Phe or granulocyte-macrophage colony stimulating factor (G-CSF) compared to that seen under normoxic conditions [217]. Lactoferrin reduces the inflammatory response seen at infected bronchial epithelium by down-regulating IL-1 β , IL-6 and IL-8 expression [218]. Intratracheal instillation of lactoferrin (100 or 200 μ g) significantly decreased BAL leukocytes and neutrophils in mice during a bronchial infection with several decreased expression of pro-inflammatory mediators such as IL-1 α , IL-1 β , IL-6, KC (analogous to human IL-8), CCL2, G-CSF and IL-12 mRNA [208].

H. Influenzae infection increases lactoferrin expression in spontaneous sputum from both COPD patients (n=10, mean age 63 years) and in smokers with normal lung function (n=10, mean age 52 years) [219]. In addition, spontaneous sputum lactoferrin protein levels in stable COPD patients over 6 years (n=11, mean age 66 years) are decreased both during exacerbations and during colonization with *Haemophilus Influenzae* and *Moraxella catarrhalis* [182]. A study has shown that, surgically obtained lung tissues from 2 stable COPD patients show increased expression of lactoferrin and other AMPs together with that of

osteopontin, an anionic, phosphorylated glycoprotein, that interestingly can bind lactoferrin to inhibit its anti-bacterial activity against *S. Pneumoniae* and *P. Aeruginosa* [220].

Both budesonide and beclomethasone dipropionate (10^{-6} mol/L) decrease constitutive lactoferrin production from surgically obtained bronchial epithelial cells (n=10, mean age 62 years) with the maximum suppression seen at day 3. In addition, methacholine-mediated (10^{-4} mol/L) induction of lactoferrin secretion was suppressed by budesonide [221]. Lactoferrin also exhibited antiviral activity against RSV-infected human epithelial cells [141] by directly binding to the RSV F protein (F1 subunit), which modulates virion entry into the cell [222-224]. A similar effect of lactoferrin was seen with influenza viruses where it inhibits cellular apoptosis through direct interaction with viral hemagglutination [225-228].

Lactoferricin, derived from lactoferrin by hydrolysis, is a short 25 amino acid peptide that possesses several functions [197]. It has powerful nutritional value, but it has also shown anticancer, antimicrobial, antiparasitic, antiviral and anti-inflammatory activities [197]. In addition, lactoferricin exerts antiviral activity against human cytomegalovirus (HCMV) [229], herpes simplex virus (HSV) [230], human papilloma virus (HPV) [231] and HIV [232]. The parent protein lactoferrin shows greater antiviral activity than lactoferricin *in vitro* although lactoferricin has potent antiviral efficacy *in vivo* in mice [233]. Lactoferricin also shows a high antitumor action on several cancer cell types, for example, by inducing human monocyte leukaemia cell (THP-1) apoptosis through intracellular ROS release [234].

Lactoferricin targets phosphatidylserines within tumour cell membranes and induces cytotoxicity through activation of several signalling pathways, altering their metabolism and possibly inducing programmed cell death [235-237]. Despite the roles of lactoferricin in nutritional intake, immunomodulation, antimicrobial activity [238], antiviral activity [233], antiparasitic activity [239-240] and antitumor activity, further research into lactoferricin as a therapeutic agent is required [197]. Currently, there are no studies on the role of lactoferricin in the pathogenesis of COPD.

14. DEFENSINS IN THE PATHOGENESIS OF COPD

Defensins are a large family of AMPs, produced and released by neutrophils. These are classified in based to their structure in α - and β - defensins. Defensins show a direct anti-microbial activity, but can also modulate innate immune response and release of pro-inflammatory mediators [141, 241-243]. There are several studies on the role of Defensins in the pathogenesis of COPD, but the findings are still unclear and further studies are necessary to clarify their role in the pathogenesis of COPD.

Defensins are members of an antimicrobial peptide family, are released by neutrophils and also by airway epithelial cells in response to pathogens, and represent a first line of defence by the innate immune system (Figures 4-5) (Table 1) [241-243]. Defensins are classed into six human α -defensins (DEFA1-6) and four human β -defensins (DEFB1-4) [141]. Human DEFAs are 29 to 34 amino acids in length with an overall positive charge. In contrast, DEFBs contain a short N-terminal pro-region but maintain antimicrobial activity only in the full-length form and therefore do not require N-terminal processing for their function [141]. As defensins were originally isolated from neutrophils, DEFA1 to DEFA4 are also known as “human neutrophil peptides” [141]. However, other immune cells such as macrophages, natural killer (NK) cells and some subtypes of B and T-cells can produce these defensins [141,244-245]. In contrast, DEFA5 and -6 are produced in epithelial cells in the small intestine [141,244-245]. The first 3 DEFBs (DEFB1, -2 and -3) are well known whereas DEFB4 has only recently been identified [141]. DEFBs are mainly produced by keratinocytes and epithelial cells, however they are also expressed by several immune cells such as macrophages, neutrophils, mast cells, DCs, NK cells, and B and T lymphocytes [141,244-247]. Recent data indicate that DEFA and DEFBs have similar antimicrobial activity and that there is a functional redundancy between these 2 classes. [248]. DEFB2 and -3 can induce chemotaxis for several leukocytes (DCs, monocytes/macrophages and neutrophils) via the involvement of the CCR6 and CCR2 axes [249]. There is another sub-family of defensins termed θ -defensins [141]. Although mRNA of θ -defensins are found in humans, there are no functional proteins known due to the presence of a premature stop codon [246].

Defensins (both α - and β -) confer protection against HIV, human adenovirus (HAdV), IAV, severe acute respiratory syndrome coronavirus (SARSC), RSV, HPV, and HSV [141]. Defensins inhibit viral infection both by directly inhibiting viral particles or by indirectly blocking the viral life cycle at several stages [247, 250]. The main antiviral activity is against the first steps of a viral infection, in particular against virus entry into cells. However, other antiviral actions are directed against viral trafficking within virus-infected cells [141,251]. Moreover, defensins regulate the innate immune response against viral infections, through modulating macrophage, T-cell and DC recruitment to sites of infection, inducing angiogenesis, maturation and differentiation of DCs, enhancing macrophage production of pro-inflammatory mediators such as IL-1 β and TNF α , and regulating cell death pathways [246]. The expression of DEFB1-3 is detected in several epithelial cell types and each DEFBs have shown different expression profile against IAV infection [252]. DEFB1-2 are also expressed in monocytes/macrophages and they can neutralize IAV strains [247,252].

Although DEFBs are poorly able to directly inhibit IAV virions, they may have a key role in modulating and limiting inflammation during IAV infection [252]. Deletion of the human DEFB1 orthologue in mice results in an increased inflammatory response to IAV infection [252-253]. In addition, DEFB3 has an anti-inflammatory action against LPS-stimulated

(50 ng/mL) cells along with the capacity to inhibit the expression of pro-inflammatory cytokines such as TNF α [254]. DEFA1 can modulate several phases of the replication cycle of HIV [243], such as inhibiting protein kinase C signalling, which has key role in integrating the HIV genome with that of the host cell and in viral transcription [255]. DEFA5 also inhibits HIV-1 replication in a dose-dependent manner (IC₅₀ = 400 μ M) by blocking viral entry into the cell. For example, DEFA5 competes with HIV for CD4 binding and thereby blocks HIV entry into target cells [256]. DEFA4 inhibits HIV replication more effectively than DEFA1-3 but it is unknown whether this is due to direct anti-viral activity or by indirectly altering viral replication within infected cells [247,257]. Viruses, bacteria, microbial derivatives such as endotoxins, but also pro-inflammatory mediators such as TNF α and IL-1 β enhance DEFB2-3 expression [252]. HIV induces the expression of DEFB2-3, but not DEFB1, mRNA in human oral epithelial cells [258]. Finally, DEFB2 blocks the production of HIV proteins, especially those induced at the early stages of infection, but doesn't modulate cell-cell fusion [247].

Defensins have shown a key role in fungal infection, through absorption and/or inactivation of melanin that is commonly found in many fungi and fundamental for their survival [259].

DEFA1, DEFA2 and, in particular, DEFA3 released from neutrophil-specific azurophilic granules have anti-fungal activity against *H. capsulatum*, inhibiting its growth in a dose dependent-manner [260]. Defensins can also block hyphae formation and eventually kill *C. albicans* after neutrophils-mediated phagocytosis [261].

The role of defensins in the pathogenesis of COPD is still unclear. Both DEFA and DEFB genes are localized in a part of chromosome 8p23 with highly polymorphic repeats [262]. Indeed, due to numerous polymorphisms, different copy numbers of the DEFA1 and DEFA3 genes can be inherited, whilst the DEFA3 gene is frequently absent [263]. A DEFB4 gene cluster is overexpressed in epithelial cells of stable COPD patients compared to smokers with normal lung function [262]. Interestingly, TNF α only increases defensin transcription when the gene cluster is also overexpressed [262]. These data suggest that this DEFB4 gene cluster is correlated with an increased risk of developing COPD. In contrast, expression of polymorphisms in the DEFA genes and SNPs in the DEFB1 gene are not correlated with an increased risk of COPD [263-264] but are associated with an increased risk for chronic bronchitis [265].

Cigarette smoke exposure increases lung expression of DEFB2 and DEFB3 but not of DEFB1 in animal model of COPD [266-267]. However, *in vitro* treatment with cigarette smoke extract decreases DEFB2 expression in bronchial epithelial cells [264]. This recapitulates the results seen in COPD, where decreased DEFB2 mRNA expression is found in bronchial epithelial cells from current smokers with stable COPD when compared to former smokers with stable COPD and control smokers with normal lung function [268]. However, both DEFB2 mRNA expression and protein levels are increased in the peripheral lung tissue from COPD patients (n= 25, mean age 65 years, former smokers, n=11, mean age 62 years, current smokers) compared to smokers with normal lung function (n=7, mean age 59 years) and non-smokers subjects (n=8, mean age 57 years) [269]. Furthermore, DEFB1 mRNA expression is increased in the bronchial epithelium from patients with COPD (n=34, mean age 62 years) compared to smokers with normal lung function (n=10, mean age 31 years) [270] and DEFA1-3 expression is increased in the areas of squamous metaplasia of smoking subjects without any significant difference between COPD patients (n=15) and smokers with normal lung function (n=13) [271].

Increased levels of DEFB3 and other AMPs are seen in surgically obtained lung tissue from 2 stable COPD patients. However, there was enhanced expression of osteopontin that may modulate the potential benefits of DEFB3 as osteopontin binding to DEFB3 inhibits its anti-bacterial activity against bacteria such as *S. Pneumoniae* or *P. Aeruginosa* [220]. *In vitro*, co-infection with RV-16 and *Pseudomonas Aeruginosa* increases DEFB2 protein and mRNA levels in primary human bronchial epithelial cells of non-smokers subjects (n=5, mean age 36 years). Pre-treatment with cigarette-smoke extract inhibits DEFB2 protein and mRNA production. In addition, there is reduced expression of human DEFB2 protein and mRNA from primary human bronchial epithelial cells of COPD patients (n=5, mean age 65 years) and smokers with normal lung function (n=5, mean age 58 years) following RV-16 and *Pseudomonas Aeruginosa* co-infection [272].

Unsurprisingly, DEFB2 is undetectable in the sputum of stable COPD patients (n=19), compared to smokers with normal lung function (n=21) and non-smoking subjects (n=10) [273]. A proteomic analysis of BAL demonstrated enhanced expression of DEFA1 and -2 in patients with stable COPD (no clinical data reported) compared to smokers with normal lung function (no clinical data reported) [274]. The expression of defensins is altered during COPD exacerbations and infection with RV increases sputum DEFA levels in COPD patients (n=20, mean age 60 years) but not in smokers with normal lung function (n=21, mean age 51 years) and non-smokers subjects (n=10, mean age 62 years). In contrast, RV infection in the same study cohort does not affect baseline sputum levels of DEFB2 in all groups [180]. This is despite RV inducing DEFB2 expression in airway epithelial cells *in vitro* [275].

DEFA1-3 levels in sputum are significantly increased during COPD exacerbations (n=30) compared to stable COPD patients (n=21), whereas serum levels of DEFA1-3 are not significantly increased in stable COPD or during COPD exacerbations [276]. Furthermore, DEFB2 expression is increased in the BAL of COPD patients during severe exacerbations (n= 15, mean age 77 years) requiring endotracheal intubation, compared to smokers with normal lung function (n=6, mean age 79 years) and non-smokers subjects (n=10, mean age 75 years) [277]. Experimental challenge with high doses of LPS in control smokers with

normal lung function (n=22, mean age 53 years) increases blood levels of DEFB2 [278]. In addition, blood DEFA3 mRNA is decreased during severe exacerbations requiring intensive care unit admission (n= 12, mean age 67 years) compared to exacerbations that do not require intensive care unit admission (n=12, mean age 73 years) [279]. *In vitro*, cigarette smoke exposure decreases the expression of the fatty acid binding protein 5 (FABP5), which stimulates the expression of DEFB2 in the airway epithelium [280]. The expression of FABP5 is decreased in the peripheral lung of patients with stable COPD compared to control smokers with normal lung function [281]. *In vitro*, prostaglandin E₂ increases DEFB2 production in primary bronchial epithelial cells from control smokers with normal lung function, but not from cells obtained from stable COPD patients [282].

15. HEPCIDIN IN THE PATHOGENESIS OF COPD

Hepcidin is an AMP mainly expressed by liver cells. It modulates hepatocyte iron homeostasis and increased hepcidin levels are found during inflammatory process, in particular during chronic viral hepatitis [141, 283-287]. Whereas in COPD, serum hepcidin levels are negatively correlated with the severity of disease.

Hepcidin is a 25-amino acid long AMP discovered in human blood. It is also known as human liver expressed antimicrobial peptide-1 (LEAP-1) because it is mainly produced by hepatocytes (Table 1) [141,283]. Mature and active Hepcidin is derived from an inactive pre-pro-peptide which undergoes two sequential cleavages. The first cleavage releases the N-terminal sequence into the endoplasmic reticulum whilst cleavage of the pro-peptide results in the mature hepcidin peptide [141]. Hepcidin has a key role in hepatocyte iron homeostasis, but this activity is also seen in several other cell types [141, 283-285]. Hepcidin modulates iron flux into the cell by directly targeting and destroying ferroportin, an iron transporter [141,284]. Consequently, increased hepcidin levels correlate with decreased cellular iron uptake whereas decreased hepcidin levels gives rise to accumulation of dietary iron within cells which causes toxicity. Moreover, hepcidin expression is induced by increased serum iron levels [141,284-285].

Hepcidin expression limits the infectivity of several iron-dependent pathogens by reducing iron uptake [141]. Conversely, viral infections and subsequent inflammatory responses, particularly IL-6, can induce hepcidin production [141].

Liver injury induced by hepatitis B (HBV) and C (HCV) increases Hepcidin production [286]. Hepcidin expression is increased in patients with chronic viral hepatitis (by HBV and HCV), but not during acute phase of these infections, and also shows a positive correlation with HBV DNA levels [286-287]. This may reflect that Hepcidin production is enhanced only when there are high iron levels, which is seen in the later stages of viral infection [287]. Hepcidin levels are increased in HIV positive patients during acute infection, which peaks together with viral load, leading to decreased iron levels [287]. In chronic infection, hepcidin levels remains increased even in patients undergo anti-retroviral therapy [287]. High hepcidin levels are correlated with a change of several inflammatory mediator expression such as IL-6, IL-10, IL-18, IL-22, INF γ , TNF α proteins [287]. However, hepcidin-mediated iron accumulation in several immune cells such as macrophages and lymphocytes can enhance HIV replication [141].

Serum hepcidin levels are decreased in patients with moderate (n=24; mean age 62 years) and severe COPD (n=25; mean age 61 years) but not in mild (n=25; mean age 62 years) COPD patients compared with smokers with normal lung function (n=35; mean age 69 years), showing a negative correlation with disease severity. In addition, there is a negative correlation between serum hepcidin levels and mean age or average pack-years, while there is a positive correlation with BMI, PaO₂, SO₂ and lung function, suggesting that serum hepcidin expression in COPD is mainly correlated to hypoxaemia rather inflammation process, representing a potential disease severity biomarker [288].

16. LYSOZYME IN THE PATHOGENESIS OF COPD

Human lysozyme is expressed in many cell types including innate immune cells and airways alveolar epithelial cells. It has an important antimicrobial activity mediated by its cationic features [289-291].

In addition, when recognized by PRR, it can modulate the pro-inflammatory response [291]. The role of lysozymes in the pathogenesis of COPD is still unclear and further studies are necessary to elucidate its role.

Three types of lysozymes exist and are classified according to amino acid sequence and biochemical activity: conventional type (c-type) also called “chicken”, goose type (g-type), and invertebrate type (i-type) [289-290].

The c-type lysozyme was the first to be discovered and is the major lysozyme species produced by most vertebrates, including humans [289].

Human lysozyme (also known as N-acetyl furamide glycanohydrolase) is a 130-amino acid cationic peptide that acts on the β -1,4 glycosidic bonds of N-acetyl-muramic acid within bacterial cell walls, damaging and destroying bacterial cells by lysis similar to that driven by defensins (Table 1) [290-291].

In mammals, lysozyme is detected in blood and liver, in several immune cells including DCs, macrophages and neutrophils, and also in secretions such as milk, tears, saliva and urine. Its concentration on mucosal surfaces is ~1 mg/mL [289-290].

Lysozyme is also expressed in lungs and in particular in the surface liquid of the airways and of alveolar epithelial cells (Figures 4-5), where its concentration is around 20-100 µg/mL. This level is sufficient to kill both Gram-positive bacteria such as *Staphylococcus aureus* and Gram-negative bacteria such as *Pseudomonas Aeruginosa* or *Klebsiella pneumoniae* [291].

However, lysozyme has greater efficacy against Gram-positive bacteria compared to Gram-negative bacteria. The reason of this difference may be due to the amount of teichoic acids within peptidoglycans, which vary among the species. Teichoic acid is negatively charged, enabling it to bind to lysozymes and prevent its hydrolytic action on the peptidoglycan [292].

Lysozyme antibacterial activity is mediated, as mentioned above, by hydrolysing the β-1,4 glycosidic bond that maintains the structure of peptidoglycan [290]. However, c-type lysozymes also possess cationic properties and form pores in negatively charged bacterial membranes. These cationic features together with the enzymatic activity are involved in its antibacterial activity [289-290,293].

Lysozyme also interacts with LPS; however, the details of this interaction have not been examined in detail. Lysozyme binds LPS mainly through non-specific hydrophobic interactions between lysozyme and LPS lipid A, a hydrophobic component that mediates toxic effects of LPS [291].

Bacteria have evolved several mechanisms to prevent lysozyme-mediated killing such as changing peptidoglycans, making them more resistant to lysozyme-mediated hydrolysis, modifying the bacterial envelope integrity and charge and producing lysozyme blockers [290]. The role of lysozyme in supporting the immune system response against pathogens have generally utilised mice lacking lysozyme M. This is homologous to human lysozyme and is produced by several myeloid cells particularly phagocytes [290,294]. Mice also express lysozyme P, another type of murine lysozyme mainly expressed by intestinal Paneth cells. In Lysozyme M^{-/-} mice, there are increased levels of lysozyme P in non-intestinal cells to compensate for the lack of lysozyme M [293,294].

Neutrophils and macrophages produce Lysozyme that is released into bacterium-containing phagosomes [289]. Bacteria that are more sensitive to lysozyme are more likely to be destroyed within the phagocyte phagosomes [295-297]. Lysozyme-mediated destruction of *N. gonorrhoeae*, in particular, is correlated with increased neutrophil phagosome activation, which suggests that lysozyme can regulate innate immune activation [290,296]. PRRs activated through lysozyme-mediated degradation include TLRs, the Nucleotide-binding oligomerization domain-containing protein (NOD)-1 and NOD2 receptors, and the inflammasome [291].

Although lysozyme can induce a pro-inflammatory response, lysozyme shows also decreases systemic inflammatory process [298,293].

Lysozyme^{-/-} mice infected with intratracheally injected *Klebsiella pneumoniae* show an increased bacterial burden but also decreased IL-10 levels (anti-inflammatory mediator), when compared to wild-type (WT) mice [294]. Similarly, lysozyme^{-/-} mice show increased inflammation compared with WT mice in an *S. pneumoniae*-mediated model of otitis media infection [299].

However, these studies have not dissected the relative contribution of lysozyme inhibitory functions on inflammation and bacterial outgrowth, which by itself is pro-inflammatory. Administration of exogenous lysozyme induces several immune-modulating effects, decreasing neutrophil chemotaxis and ROS production through still unknown mechanisms [300-301]. Lysozyme binds to and neutralizes extracellular pro-inflammatory AGEs [302]. However, inhibiting the bactericidal activity of lysozyme may induce other effects on immune responses during infection [302].

Spontaneous sputum lysozyme protein levels of stable COPD patients over 6 years (n=11, mean age 66 years) were decreased during both exacerbation and during colonization with *Haemophilus Influenzae* and *Moraxella catarrhalis* [182]. Stable COPD patients treated with oral lysozyme (270 mg/day) for 28 days (n=24, mean age 75 years) improved lung function and symptoms compared to an untreated control period [303]. In contrast, oral lysozyme (90 mg) administered 3/day for 52 weeks to COPD patients (n=202, mean age 69 years) in stable phase had no effect on exacerbations reduction or on lung function decline compared to untreated COPD patients (n=204, mean age 70 years). However, only a subgroup of lysozyme-treated COPD patients with a predominant airway disease phenotype (n=49) showed a statistically significant decrease in exacerbations [304].

17. CHEMERIN IN THE PATHOGENESIS OF COPD

Chemierins, also called retinoic acid receptor responder 2 (RARRES2), are produced by liver and adipose cells.

They can modulate several biological functions and show both pro- and anti-inflammatory activities in modulating immune cell recruitment depending on their interactions with different coupled receptors [305-308].

The role of chemierins in modulating tumour cells growth is well stabled, but their role in the pathogenesis of COPD is still unclear.

Chemierin [also known called retinoic acid receptor responder 2 (RARRES2) or tazarotene induced gene 2 (TIG2)] is a chemoattractant (Table 1) that modulates angiogenesis, adipogenesis, metabolic activity, skin function, and tumour-genesis

[305]. Human chemerin is 163 amino acids long and is produced by white adipose tissue and liver as precursor called pro-chemerin [305-306]. Cleavage of the 20 amino acid N-terminal signal sequence occurs by a specific set of serine proteases prior to secretion into blood but chemotactic activity is still seen after further C-terminal processing [305-307].

Serine and cysteine extracellular proteases act at distinct C-terminal sites to produce several chemerin isoforms. Of these, chemerin 157 is the most active isoform, while other isoforms have been characterized as highly active (chemerin 156 and 158), moderately active (chemerin 155), and inactive (chemerin 152 and 125) [305-307].

Depending on the cleavage site and the interaction with its coupled hepta-helical receptors, ACKR4, ackr5 and G protein-coupled receptor 1 (GPR1), chemerin exhibits both pro- or anti-inflammatory effects depending upon the biological context [305]. Chemerin shares high structural similarity with cathelicidins and may be considered as a distant member of this family. For this reason, an anti-microbial role has been suggested for chemerin [308].

Chemerin is mainly expressed in liver and adipose tissue but has been detected in most tissues (Figures 4-5) [306].

Chemerin induces NF- κ B activation, increases the expression of adhesion molecules on endothelial cells, which results in increased monocyte adhesion and the development of atherosclerosis [306,309]. In diabetic patients, chemerin also induces activation of the p38 MAPK pathway enhancing renal injury inflammation-mediated in diabetic nephropathic disease [306,310]. Chemerin can be both increased or reduced in cancer tissues showing a pro- or anti-cancer action depending upon the disease context [306].

Chemerin induces immune cell recruitment via ACKR4, ackr5 and GPR1 receptors to inhibit tumour growth [305-306,311]. When these receptors are activated, chemerin induces immune cell arrest and reduces diapedesis and infiltration into the tumour microenvironment to modulate the growth and survival of cancer cells. Thus, chemerin produces its anti-tumoral effect by recruiting immunostimulatory DC, NK cells and cytotoxic T cells [306,311].

In contrast, cancer cells may evade anti-tumoral immune responses by recruiting myeloid-derived suppressor cells (MDSC) or immunosuppressive regulatory T cells that can inhibit cytotoxic anti-tumour responses. Finally, the balance between these leukocytes-mediated pro- and anti-tumoral activities causes either tumour progression or tumour cell death [306, 311].

The anti-tumoral mechanisms of chemerins include inhibition of MAPK, β -catenin and AKT, where the latter is achieved by phosphatase and tensin homolog (PTEN) activation [306]. These mechanisms are induced in part by via the β -arrestin2 and RhoA/serum response factor-induced signalling. These pathways are activated when chemerins are recognized by GPR1 and ACKR4 [306]. Alternatively, the tumour-promoting effects of chemerin are induced when MMPs, p38 MAPK, and AKT pathways are activated in a β -arrestin1-mediated a manner [306]. Ackr5 is considered unable to transduce intracellular signalling activities, but can enhance the chemerin link to ACKR4 and potential link to GPR1 [32,306,312-313].

The ability to increase VEGF expression is another fundamental chemerin-mediated tumour promoting action [306]. Chemerin's potent angiogenic activity is mediated by binding to ackr5 on endothelial cells, and through induction of MMP-2 and MMP-9 [314]. Chemerin also promotes angiogenesis via phosphorylation and activation of Akt and p42/44 extracellular signal-regulated kinase (ERK) pathways [306,315]. Decreased ACKR4 levels, but not of ackr5, inhibit chemerin-induced migration and angiogenesis of human umbilical vein endothelium cells (HUVECs). This suggests that chemerins promote angiogenesis mainly via ACKR4 [306, 315].

Circulating chemerin levels are elevated in NSCLC patients and may exert detrimental effects. In NSCLC, increased chemerin expression correlated with increased tumours, inflammatory biomarkers, number of infiltrating tumours to lymph nodes, and more severe NSCLC disease stage [306,316]. These data were confirmed by several studies, which also indicated correlations with advanced TNM stage, increased lymph node metastasis and distant metastasis [306, 317]. Patients with increased serum chemerins had poor outcomes, such as overall survival and relapse-free survival, when compared with NSCLC patients with lower circulating levels. This indicates that serum chemerins can influence the prognosis of NSCLC patients and act as an independent risk factor [306,317]. A similar, but smaller, study reported increased serum chemerins levels, but no association with clinical or pathological parameters [306,318]. Currently, chemerins have been assessed for their involvement in asthma, diabetes mellitus and inflammation-based gastro-intestinal (GI) tract diseases, such as chronic pancreatitis or inflammatory bowel diseases (IBD) pathogenesis [319].

Serum chemerin levels are increased in stable COPD patients, and in particular when in combination with metabolic syndrome, suggesting that chemerins may have a role in maintaining chronic inflammatory processes. However, the role of chemerins in the pathogenesis of COPD is still unclear and further studies are needed [320-321].

Serum chemerin levels were significantly increased in stable COPD patients (n=43, mean age 61 years) compared with non-smoker subjects (n=38, not reported mean age), but levels were no different between current and former smoker COPD patients. In addition, serum chemerin levels positively correlated with serum total cholesterol [320].

Serum chemerin and low-density lipoproteins (LDL) levels are elevated in COPD patients (n=150) compared to non-smoker

subjects (n=30), but decreased in thin COPD patients (BMI<18.5, n=116) compared to normal weight COPD patients (BMI≥18.5, n=34). Moreover, serum chemerin levels in COPD patients were negatively correlated with plasma levels of total cholesterol, triglyceride and high-density lipoproteins (HDL), and positively correlated with plasma LDL levels. Overall, serum chemerin levels in COPD patients are correlated with lipid metabolites [321].

In a murine chronic cigarette smoke-induced model 4 times/day for 30 minutes, 5 days/week for 4 weeks for 24 weeks, chemerin protein levels were elevated in bronchial epithelium and associated with increased numbers of BAL neutrophils and monocytes [322].

18. RNASES IN THE PATHOGENESIS OF COPD

RNase A superfamily is a vertebrate-specific group of proteins. 7 members (RNases1-7) exist with the same motif signature (CKXXNTF) and the same three-dimensional conformation. These are produced by several immune cells and have known antimicrobial activities, especially against viruses [323-324]. However, only RNase 2 and -3 are been studied in COPD and their role in the pathogenesis of this disease is still unclear.

The RNase A superfamily is a vertebrate-specific group of proteins that have the characteristic traits of immune-related proteins (Table 1) [323]. Although each member shows low sequence homology, all RNases possess the motif signature (CKXXNTF) and are structured with the same three-dimensional conformation [323-324]. They are usually secreted extracellularly, have a low molecular weight (13-15 kDa) and a low amino acid length signal peptide (25-27 amino acid) [323-324]. The active peptide has an $\alpha+\beta$ kidney-shaped fold cross-linked by disulphide links [323-324]. Innate immune cells express several RNase A superfamily members that show antimicrobial activity and can modulate immune system activities. Moreover, these act as alarmins during infection and/or inflammation [323-324].

18.1. RNase 1

RNase1 is detected in most tissues [325] but is highly expressed by endothelial cells (Figures 4-5) [326-327]. RNase1 contains a ~150 amino acid long catalytic domain and an N-terminal mitochondrial targeting sequence (MTS) [328]. RNase1 is produced in two different isoforms depending on whether it is localized inside the nucleus or inside the mitochondria [328-329]. RNase1 catalyzes the hydrolysis of the phosphodiester bond of the single RNA strand within a double-stranded RNA/DNA duplex. Four consecutive ribonucleotides are required to mediate this hydrolytic cleavage [328,330]. The human enzyme is Mn^{2+} -dependent, but Ca^{2+} can inhibit its activity [328]. Although both human and bacterial RNases1 mainly bind RNA/DNA hybrids, they may also bind and cleave double-stranded RNA [328,331].

RNase1 can modulates extracellular RNA (ex-RNA) content [332-333] in blood, which is enhanced under hypoxic conditions. RNase1 administration provides cardiac protection in a mouse model of myocardial "ischaemia/reperfusion (I/R) injury" [334]. Administration of RNase1 *in vivo* also reduces the release of pro-inflammatory mediators such as IL-1 β and IL-6 and provides a multi-organ protection in mice [335]. There are currently no studies on the role of RNase1 in the pathogenesis of COPD.

18.2. RNase 2

Human RNase2 [also termed eosinophil-derived neurotoxin (EDN)], together with human RNase3 [eosinophil cationic protein (ECP)], is one of the main proteins produced and released by eosinophil secondary granules (Figure 4) [328,336-337].

RNase2 and RNase3 are highly cationic with cytotoxic activities [338-340]. They are secreted by activated eosinophils and have potent activity against viruses, parasites, and helminths [341]. Active RNase2 is composed of three proteins [328,342]: a catalytic subunit (called RNase2A) and two additional proteins (H2B and H2C) that modulate these catalytic reactions [328]. Despite low sequence homology, the catalytic subunit of RNase2 shows a very similar fold to RNase1 [328].

RNase2 expression is detected in other cells besides eosinophils, such as monocytes, basophils, neutrophils, and DCs [337]. Chemotactic eosinophil proteins such as CCL11 and CCL24 induce eosinophil RNases release activating the PI3K/MAPK pathway in both humans and mice [323, 343]. RNase2 has immune-regulatory effects that induce leukocyte activation and maturation and mediates chemotaxis [337]. In particular, RNase2 regulates host immunity by acting as a chemotactic agent for DCs [344-345] and stimulating DC maturation as evidenced by increased expression of human leucocyte antigen (HLA)-DR, CD83, and CD86. RNase2 may also promote Th1 cell polarization indirectly by enhancing IL-12p70 release from DCs [344]. RNase2 activates the myeloid differentiation primary response 88 (Myd88) pathway by stimulating TLR2 and can activate host immune responses by interacting with leukocytes, specifically with antigen-presenting DCs and enhancing INF γ -mediated T-cell responses [323, 344-346].

RNase2 is released from eosinophils when these come into contact with a pathogen [347-348], in particular pathogenic bacteria, such as *Clostridium difficile*, whereas contact with a probiotic strain, such as *Bifidobacteria*, do not activate eosinophils or induce RNase2 release [349]. Eosinophils also release RNase2 in response to other pathogens such as *Staphylococcus aureus*, but not against *Haemophilus* or *Prevotella* species. The reasons why eosinophils have different activation profiles based on the type of pathogen with which they come into contact with are still unknown [350].

RNase2 is also induced in response to viral infection [337,351-352], showing a potent antiviral activity, in particular against single strain RNA (ssRNA) viruses [337,353]. In particular, RNase2 can block the replication process of several viruses such as RSV, human HIV-1, and HBV [351,354]. RNase2 antiviral activity is aided by its unique protein structural features as well as its high catalytic activity [353, 355]. *In vitro*, it reduces the RSV infectivity of human epithelial cells [353].

RSV infection induces eosinophil activation, recruitment and degranulation [352], and RNase2 levels are a known biomarker for RSV bronchiolitis [356]. Viral infections of the lower airways mainly cause lung parenchyma inflammation and increased RNase2 release [323,343]. This is associated with local tissue damage, further eosinophilic degranulation and the release of more RNases that contribute to the tissue remodelling process [323,343]. RNase2 levels within eosinophils is negatively correlated with a specific aa-405 polymorphism. This causes an increased risk of acquiring visceral leishmaniasis [357].

There are very few data in the literature on the role of RNase2 in COPD. One study shows increased serum EDN levels in COPD patients during exacerbation irrespective of the presence (n=30, mean age 72 years) or absence (n=47, mean age 74 years) of pulmonary embolism when compared to healthy subjects (n=35, mean age 71 years, not reported if smokers with normal lung function) suggesting that recruitment and eosinophilic degranulation may have a key role in the pathogenesis of COPD exacerbations [358].

18.3. RNase 3

Human RNase3 (or ECP) is the other abundant RNase within the eosinophil secondary secretory granule and together with RNase2 represent about one-third of the total protein pool (Figure 4) [323, 359]. The catalytic site of RNase3 is composed by the typical RNase fold [328,360].

Both infection and inflammation can induce RNase3 release and their circulating levels are correlated with eosinophil degranulation. Thus, RNase3 represents a good biomarker for the diagnosis and monitoring of chronic inflammatory airway disorders, such as asthma [323,338,340]. Indeed, RNase3 release, eosinophil activation and degranulation with subsequent local tissue injury has been correlated with airway inflammation and with damaged airway epithelia [323,361-362]. RNase3 possesses several activities [323] including neurotoxic and antiviral activities which it shares with RNase2 [353] as well as its anti-bactericidal activity [363].

RNase3 shows *in vitro* antiviral activity and can participate in host defense against RSV. Its RNase activity is required for RNase3-mediated antiviral and neurotoxic activities, but not against bacteria and helminths [323,336].

RNase3 shows activity *in vitro* against both Gram-negative and Gram-positive bacteria as well as against fungi such as *C. albicans*. Its mechanism of toxicity involves targeting both the bacterial cell wall and the cytoplasmic membrane [336,364]. Moreover, its high cationic charge and aggregation region promotes RNase3 self-aggregation and mediates agglutination of bacterial cells [323,365]. Bacterial cell agglutination is increased by binding to LPS within the Gram-negative bacterial wall [323,366].

There are very few data in the literature on the role of RNase3 in COPD. RNase3 levels are increased in induced sputum, bronchial wash and BAL from stable COPD patients (n=18, mean age 62 years) compared with smokers with normal lung function (n=11, mean age 58 years), with highest RNase3 levels in induced sputum compared to bronchial wash and BAL [367]. Induced sputum RNase3 protein levels are also increased in stable COPD patients (n=68, mean age 69 years) compared to non-smokers subjects, and are further increased during exacerbation (n=34, mean age 69 years) [368]. In addition, RNase3 levels in induced sputum are increased in stable COPD patients (n=28, mean age 58 years) after mannitol challenge [369].

RNase3 mRNA expression is also enhanced in induced sputum cells of stable COPD patients (n=12, mean age 70 years) compared to asthma patients (n=13, mean age 53 years) and non-smoker subjects (n=13, mean age 42 years), and there is a negative correlation between RNase3 mRNA expression and macrophages counts [370]. Furthermore, serum RNase3 levels are increased in COPD patients during exacerbation irrespective of the presence (n=30, mean age 72 years) or absence (n=47, mean age 74 years) of pulmonary embolism compared to healthy controls (n=35, mean age 71 years, not reported if smokers with normal lung function) [358].

Serum RNase3 levels are also reported to be increased in both asthma patients (n=76) and stable COPD patients (n=136) compared to healthy subjects (n=33, not reported if smokers with normal lung function). However, there was no correlation between serum RNase3 and eosinophil counts [371]. In contrast, another study reported no differences in either serum or induced sputum RNase3 levels between stable COPD patients (n=33, mean age 68 years) and stable asthma patients (n=24, mean age 51 years) [372].

These data suggest that eosinophil recruitment and activation can have an important role in pathogenesis of COPD exacerbations and in their severity [358,367-370].

18.4. RNase 4

There is a controversy around the physiological role of RNase4 and there are few reports concerning its biological properties. Interestingly, both RNase4 and RNase5 have anti-HIV activity and are secreted by T cells [323,373]. RNase4 is expressed in

several human tissues [323,325,374], but mainly in the liver [325] and lungs [375]. Interestingly, monocytes also produce RNase4 [323,376].

BAL TGF1 β protein levels, total cell counts, macrophages, lymphocytes, and neutrophils are decreased in RNase4 knockout mice that were exposed to cigarette smoke and intranasal polynosinic-polycytidylic acid [poly(I:C)] when compared to WT exposed to cigarette smoke and poly(I:C) mice [377]. There are no studies on the role of RNase4 in the pathogenesis of COPD.

18.5. RNase 5

Human RNase5 is expressed both in many adult and embryonic somatic cells [323,378]. It is also expressed in several blood cell types and epithelial cells [323,379-382]. Furthermore, RNase5 expression is increased during inflammation [381,383], and can promote angiogenesis. As a result, it is also known as angiogenin [384]. The purified protein displays antimicrobial [379,385] and some immunomodulatory properties [385-386] in addition to promoting angiogenesis. In particular, this protein has anti-inflammatory effects, including its capacity to inhibit neutrophil activation and suppress immune responses [387-388]. In tumour-cell lines, the expression of RNase5 correlates with the promotion of cell proliferation and the development of malignant cancers [323,389]. Currently, there are no studies on the role of RNase5 in the pathogenesis of COPD.

18.6. RNase 6

The expression of human RNase6 is increased during genitourinary tract bacterial infections [323,390], and it has a potent antibacterial activity against both Gram-positive and Gram-negative species [323,390-391]. RNase6 antiviral activity has also been reported, and interestingly, decreased RNase6 protein expression in Th17 polarized cells was found upon HIV infection [323,392]. Currently, there are no studies on the role of RNase6 in the pathogenesis of COPD.

18.7. RNase 7

RNase7 is expressed by several tissues (epithelial cells, liver, kidney, muscles) and contribute mainly to epidermis protection and urinary tract sterility (Figures 4-5) [323,393-396]. Potent antimicrobial activity against several infective microorganisms [364,390,393,397-398] and some immune-modulatory properties have been reported [323]. Inflammatory cytokines such as IL-1 β and IFN γ [397] and activation of the PI3K/AKT pathway [399] also enhance RNase7 expression. PI3K/AKT signalling modulates innate immune cell activity during inflammation and prevents sepsis [400,401].

RNase7 expression is also enhanced in airway basal cells following damage, suggesting a possible protective role of RNase7 during tissue injury [402]. In addition, RNase7 directly stimulates plasmacytoid DCs following tissue damage and infection, and may act as an alarmin. Moreover, RNase7 regulates immune cell activities by binding to self-DNA and activating TLR9 receptors [403]. Currently, there are no studies on the role of RNase7 in the pathogenesis of COPD.

18.8. Antimicrobial neuropeptides in the pathogenesis of COPD

Neuropeptides are a large family of AMPs that are produced and released by neurons. They show a direct antimicrobial activity through their cationic features. In addition, neuropeptides have an indirect anti-microbial activity immunomodulatory effect, regulate Th1/Th2 cytokine secretion, mobilization of immature DC cells, and the cytotoxic capacity of CD8 $^{+}$ T lymphocytes. Neuropeptides are potent modulators of several pro-inflammatory cytokines that induce inflammatory responses [404-412].

In particular, a precursor of adrenomedullin (pro-adrenomedullin), has been shown to be a potential mortality biomarker in COPD patients.

Neuropeptides (NPs) are small peptides produced and released predominantly by neurons that act on neural substrates [404] (Table 1).

Currently, around 100 neuropeptides are known, but there are probably many more that are yet to be identified [404]. They have three common characteristics: they are derived from precursor proteins (called pro-peptides), are released from vesicles, and are recognized by cell-surface receptors over a relatively large distance to target cells that are often localized in the brain and the periphery [404].

They are cationic peptides of low molecular weight, and are classically known for their ability to transduce and modulate signalling pathways in the central and peripheral nervous systems, or to regulate the activity of other co-released neurotransmitters by increasing or decreasing the strength of synaptic signaling [404]. However, in the periphery, neuropeptides can act in a similar manner as peptide hormones to modulate most bodily functions as well have having antimicrobial activities [404-406]. The most widely studied NPs are neuropeptide Y (NPY), substance P (SP), calcitonin-gene related peptide (CGRP), adrenomedullin (AM), vasoactive intestinal peptide (VIP) and α -melanocyte-stimulating hormone (α -MSH) [404-405].

NPs possess an indirect antimicrobial activity through immunomodulatory effects on host cells mediated by a bi-directionally correlation between specific nerve fibers and primary or secondary lymphoid tissue and the appropriate G-protein coupled NP receptors on immune cells [405]. NPs also have direct antimicrobial activities that are exerted upon release at sites of microbial invasion, resulting in perturbation of the microbial membrane and leading to microbial death [405]. NPs show direct

antimicrobial and antiparasitic effects *in vitro* [405,407- 409].

NPs can regulate Th1/Th2 cytokine secretion, mobilization of immature DC cells, the cytotoxic capacity of CD8⁺ T lymphocytes [405,410-412], modulate the defense response mediated by subpopulations of T helper cells, and induce cellular mechanisms that cause T cell responses, antigen recognition and effector phases of adaptive cellular immunity (Figures 4-5) [405].

In particular, CGRP and NPY regulate integrin expression, which influences T cell adhesion to the extracellular matrix (ECM) ligand fibronectin through activation of β -1 integrins on the T-cell surface [405,410].

NPs generally act by activation of specific G-protein coupled receptors; however, mast cell degranulation and macrophage activation are mediated by receptor-independent pathways or by coupling with a “non-specific” receptor [405]. NPs are potent modulators of the inflammatory response. SP, CGRP and NPY cause increased secretion of pro-inflammatory cytokines such as TNF α , INF γ , TGF β , IL-1 β , and IL-6, chemokines such as CXCL8, and arachidonic acid metabolites from both immune and non-immune cells, while VIP, α -MSH and AM show the opposite effects [405,413-416].

18.9. Substance P and calcitonin-gene related peptide

SP enhances LPS-activated neutrophil adherence to lung epithelial cells and increase their secretion of pro-inflammatory cytokines, such as TNF α and IL-1 β [417]. Moreover, in combination with NPY, SP can indirectly enhance the production of several AMPs such as cathelicidins including LL-37 and DEFBs by lung epithelial cells [418]. *In vitro*, SP and CGRP (Table 1) synergistically cause a concentration-dependent increase in the secretion of TNF α , IL-1 β , and IL-6 proteins from cultured human peripheral blood mononuclear cells including T cells [413].

18.10. Neuropeptide Y

NPY has divergent effects on phagocytic function acting via specific receptors. Y5 receptors enhance ROS production while Y1 and Y2 receptors inhibit phagocytosis [405, 419]. In addition, the Y1 receptor negatively regulates T cell activation whilst activating APC function [420]. Increased NPY levels are expressed in the sympathetic ganglia and tissues with a high density of sympathetic innervation, such as the heart atrium, blood vessels, vas deferens and spleen, suggesting a key role in sympathetic neurotransmission [421].

NPY as well as CGRP can also modulate phagocytic activity depending on whether pathogen recognition is direct (without opsonins) or indirect (with opsonins) [405,407]. They induce opsonin-dependent ingestion of pathogens by neutrophils but not of opsonin-dependent ingestion [405]. NPY is expressed in airway smooth muscle and also in the nerves of human blood vessel adventitia. In particular, increased extractable NPY levels are found in upper trachea and major bronchi compared to lower trachea and middle lung airways [422].

18.11. Vasoactive intestinal peptide

VIP enhances the bactericidal effects of the cathelicidin LL-37 against *Streptococcus mutants*, *Staphylococcus aureus* *Escherichia coli* and *Pseudomonas aeruginosa* [423]. VIP can also act potently and directly against the protozoan parasite *Trypanosoma brucei*, that causes African sleeping sickness [405]. Indeed, in addition to causing direct membrane destruction as seen with many other AMPs, VIP is also endocytosed by the parasite, and accumulates intracellularly [405]. Intracellular VIP disrupts lysosomal glycolytic enzyme accumulation in the cytosol, leading to VIP-induced autophagic-like cell death due to energy metabolism failure [424-425].

Increased serum VIP levels are correlated with increased risk of an exacerbation in COPD patients [426]. Furthermore, increased serum VIP levels are found in COPD patients during exacerbation (n=120, mean age 67 years) compared to patients with stable COPD (n=167, mean age 66 years) [426].

Although it is unclear whether the increase in serum VIP levels is the cause or result of an exacerbation of COPD, VIP may represent a useful biomarker for the diagnosis of COPD exacerbation [426].

In vitro, lung mucus glands, but not lung smooth muscles of subjects with chronic bronchitis (n=12, mean age 63 years) defined as cough and sputum production on most days of the month for at least 3 months/year during the previous 2 years, have increased density of VIP-nerves compared to non-bronchitis specimens (n=7, mean age 68 years). In addition, there is a negative correlation between the density of VIP+ nerves in lung mucus glands and average pack-years, as well as mean age [427].

No significant differences are found in VIP mRNA levels in surgically obtained lung tissue between patients with mild/moderate stable COPD (n=8, mean age 66 years), patients with severe stable COPD (n=7, mean age 54 years), smokers with normal lung function (n=15, mean age 71 years) and patients with IPF (n=10, mean age 50 years). However, lung tissue mRNA VIP levels are negatively correlated with FEV₁/FVC ratio in all four groups [428].

Stimulation of mucous and serous cells from surgically obtained airway submucosal glands with VIP decreased in a dose-dependent manner lysozyme release. This decreased release is more pronounced in mucous and serous cells from healthy subjects (n=9) compared to patients with chronic bronchitis (n=5) [429].

VIP also decreases the activity of the transcription factor Nuclear Factor of Activated T-cells (NFAT) in murine airway smooth muscle cells, implicating VIP in the aetiology of vascular remodelling in hypoxic PH [428]. This may also explain the important relaxant effect of VIP on bovine and human pulmonary arteries [430].

18.12. Adrenomedullin

AM is a multifunctional regulatory peptide that enhances cyclic adenosine monophosphate (cAMP) formation in several tissues, and is mainly expressed in the lungs, particularly in airway epithelial basal cells and type II pneumocytes [431]. AM shows two distinct antibacterial mechanisms: direct cell-wall disruption of *E. coli*, and altering bacterial cell division to induce abnormal septum formation by *S. aureus* [405, 432].

Midrange-pro-adrenomedullin (MR-proAM) is a more stable precursor of AM and its expression is elevated in the serum of stable COPD patients (n=21, mean age 67 years) and asthma patients (n=28, mean age 61 years) compared to healthy subjects [433]. In addition, this increase in serum MR-proAM levels in stable COPD has been confirmed in another 2 cohorts (cohort 1: n=671, mean age 67 years; cohort 2: n=614, mean age 67 years), and levels were correlated to increased risk of mortality [434]. Although increased serum MR-proAM levels in stable COPD patients (n=490, mean age 67 years) were correlated with an increased risk of mortality, there was no correlation between serum MR-proAM levels and mortality in COPD patients during exacerbation (n=101, mean age 71 years) [435].

Furthermore, serum MR-proAM levels in hospitalized COPD patients during exacerbation (n=277, mean age 69 years) were not correlated with risk of death, ICU transfer or new hospitalization for COPD exacerbation within 30 days [436]. In contrast, increased serum MR-proAM levels in 2 stable COPD study cohorts (cohort 1: n=671, mean age 67 years; cohort 2: n=614, mean age 67 years) were positively correlated with risk of COPD exacerbation [437].

Literature data seems to indicate that MR-proAM may have a key role in the pathogenesis of COPD and their acute exacerbations correlated to release of several pro-inflammatory and pro-angiogenic mediators such as CXCL1 and CXCL5 MR-proAM mediated. In addition, MR-proAM can be represented as a useful potential biomarker of disease severity [433-437].

18.13. α -melanocyte stimulating hormone

α -MSH is widely expressed in many non-nervous cells including melanocytes, monocytes, dendritic cells, and T-lymphocytes [141]. α -MSH has antimicrobial activity against viruses such as HIV-1 [438], bacteria (such as *S. aureus*, and *E. coli*) and fungi (e.g. *C. albicans* and *Cryptococcus neoformans*) [439, 440]. α -MSH is the most effective NPs against *Staphylococcus aureus*. Importantly, α -MSH has activity against both methicillin-resistant (MRSA) and methicillin-sensitive (MSSA) strains [405]. In addition, α -MSH can also act against staphylococcal biofilms [405, 441].

The molecular mechanisms of α -MSH antibacterial activity are still unknown. However, similar to other AMPs, it has cationic properties that may electrostatically alter the bacterial membrane to cause membrane damage and induce cell death [405, 442]. α -MSH can also bind a fungal membrane receptor mediating increased production of cAMP [443]. α -MSH action against *Candida albicans* reduces its viability but also inhibits germ tube formation, which allows its transition to the virulent yeast-filamentous form [405, 444].

α -MSH reduces the concentration of pro-inflammatory mediators such as TNF α , INF γ , IL-1 β and IL-6 *in vivo* and *in vitro* through the induction of cAMP and inhibition of NF- κ B [405]. α -MSH may have a role in several chronic inflammatory diseases, such as allergic inflammation of skin, eyes, and lungs, arthritis (rheumatoid and gout), systemic inflammation (septic shock syndrome), inflammatory bowel disease (Crohn's disease and ulcerative colitis) and reperfusion injuries of the heart and gut [440, 445].

19. MACROPHAGE MIGRATION INHIBITORY FACTOR IN THE PATHOGENESIS OF COPD

Macrophage migration inhibitory factor was originally described due to its capacity to decrease the migration of macrophages and their activity. However, MIF can regulate recruitment and activation of several immune cells into the lung. MIF can be recognized by different chemokine receptors to activate macrophages and induce the release of several pro-inflammatory mediators [446-451]. It is increased in several acute and chronic inflammatory diseases. Literature on its expression in COPD are conflicting and its role in pathogenesis of COPD is not completely clear.

Macrophage migration inhibitory factor (MIF) was originally described as a T-cell derived factor that decreased the migration of macrophages and subsequently as a mediator that regulated macrophage host-defence activities (Table 1) [446-448]. MIF is produced by several inflammatory immune cells such as neutrophils, monocytes/macrophages, eosinophils, B and T lymphocytes, but also by non-immune-cells such as endocrine, endothelial, epithelial, and neuronal cells of different histogenetic origin [447-448]. Its expression is regulated in response to stress effectors [449-450], but its precise mechanism of

action in the suppression of migratory capacity of macrophages is still unclear. Despite this, it is clearly an important mediator that can regulate inflammatory and immune responses [451] (Figure 4).

MIF exhibits chemokine-like activities to regulate cell recruitment into the lungs [452]. MIF binds to CD74, a type II transmembrane protein, and promotes its phosphorylation and activation of CD44, which then promotes ERK1/2 MAPK phosphorylation [452]. This receptor link can also involve CXCR2 or CXCR4, which can both recognize MIF, to mediate several MIF-induced chemotactic activities, such as leukocyte rolling, endothelial wall adherence and macrophage endothelial transmigration [452-455]. In particular, CXCR2 together with its ligands CXCL1 and CXCL8, have a key role in the modulation of the mobilization and arrest of monocytes at the vessel wall [455]. Moreover, CXCR2 can also interact with other members of the CXC subfamily and also with MIF, despite its structural dissimilarity, allowing MIF to regulate the recruitment and arrest of monocytes at the vessel wall [455]. In contrast, MIF can also promote the production and release of pro-inflammatory mediators such as IL-1 β , IL-6, IL-8, IL-12 and TNF α from activated macrophages [455-456].

MIF expression and release are increased in several acute and chronic inflammatory diseases such as sepsis [457], arthritis [458], asthma [459-460] and in NSCLC patients with COPD [461]. MIF expression is increased in the peripheral lung from stable COPD patients compared to control subjects, but the clinical significance of these results is unknown [461-462]. MIF protein levels are elevated in induced sputum in stable COPD patients (n= 12, mean age 59 years) compared to non-smoker subjects (n=13, mean age 59 years), but not when compared to smokers with normal lung function (n=12, mean age 54 years). In addition, MIF protein levels in BAL from stable COPD patients (n=12, mean age 59 years) and smokers with normal lung function (n=12, mean age 54 years) are increased compared to non-smokers subjects (n=13, mean age 59 years). However, there are no differences in serum MIF levels between these groups [447].

In contrast, serum MIF levels were increased in stable COPD patients (n=424, mean age 64 years) compared to smokers with normal lung function (n=325, mean age 59 years). MIF levels were further elevated in the same COPD cohort during exacerbation (n=149) compared to the stable phase [463]. These results were the opposite to those reported in another study, which showed decreased serum MIF levels in stable COPD patients (n=32, mean age 69 years) compared to non-smokers subjects (n=18, mean age 50 years), and their levels were negatively correlated with COPD severity [464]. This may reflect the effect of aging on serum MIF levels since aging in stable COPD patients (n=32, mean age 74 years) is associated with decreased MIF-1 serum levels compared to age-matched smokers with normal lung function (n=40, mean age 73 years) [465].

It is not completely clear whether increased MIF levels in COPD and increased serum MIF levels is due to localized lung inflammation, systemic inflammation, or a combination [447].

In addition, there are several potential triggers of MIF release in COPD, such as increased levels of several proinflammatory mediators both in the lungs and in blood, and altered lung microbiome [447].

In an ozone-induced mouse model of COPD, (exposure of 3 ppm ozone 3 hours, twice a week for 6 weeks), there is increased BAL total cells, MIF, GM-CSF and TNF α protein and mRNA levels. In addition, intraperitoneal pre-treatment with a MIF-antagonist ISO-1 but not with dexamethasone reduced the inflammatory response [447]. However, cigarette smoke exposure in mice suppressed MIF mRNA and protein levels in lung tissue compared to untreated controls [464]. Whether this is merely due to the tissue examined or reflects important differences in the models used is unknown, but knockout mice lacking MIF or the MIF receptor (CD74) spontaneously develop emphysema after 6 months [465]. In addition, MIF^{-/-} mice chronically exposed to cigarette smoke showed enhanced lung tissue remodelling and increased susceptibility to developing key features of COPD [464-465].

20. ATYPICAL CHEMOKINE RECEPTORS IN THE PATHOGENESIS OF COPD

Unlike conventional chemokine receptors, ACKRs mainly act to scavenge chemokines and reduce increased levels of several pro-inflammatory mediators. For these reasons, their expression may be increased during inflammatory diseases including COPD [12]. However, only the role of ACKR2 has been currently evaluated in the pathogenesis of COPD.

20.1. ACKR1 in the pathogenesis of COPD

ACKR1 (Table 2) is expressed mainly on erythrocytes and endothelial cells [466], where it can recognize several CC- and CXC-ligand chemokines, leading to their immobilization on the cell surfaces [467]. ACKR1 acts as a chemokine “sink” on erythrocytes by absorbing excessive circulating chemokines, thereby preventing blood leukocytes from being exposed to increased levels of chemokines, inhibiting leukocyte desensitization and enhancing leukocyte emigration [467].

ACKR1 was originally identified as the receptor for the human malarial protozoa *Plasmodium vivax* and *Plasmodium knowlesi*. Indeed, subjects with decreased ACKR1 levels (Duffy negative) or with polymorphic variants show decreased susceptibility to these infections [468]. In addition, in an animal model of bone fracture, ACKR1^{-/-} mice show decreased levels of several pro-inflammatory mediators (IL-1 β , IL-6, and CCL2) and macrophages around their fractures [469].

In another animal model, ACKR1^{-/-} mice show partial protection from atheroma development in the aorta and have decreased levels of inflammatory chemokines (CCL2 and CXCL1) and T lymphocytes in aortic atheromatous plaques [470]. Currently, there are no reports of a potential role of ACKR1 in the pathogenesis of COPD.

20.2. ACKR2 in the pathogenesis of COPD

ACKR2 (Table 2) is expressed by alveolar macrophages, innate-like B cells and lymphatic endothelial cells (Figures 6-7) [24]. ACKR2 acts as a chemokine scavenger receptor, which mediates endocytosis and intracellular degradation of chemokines [26,29]. ACKR2 regulates lymphatic vessel density [471] and function [472] and may induce resolution of the inflammatory response by decreasing the release of several pro-inflammatory mediators such as TNF α , CCL3 or CCL5, and inhibiting excessive leukocyte recruitment and/or activation. For example, ACKR2 regulates macrophage efferocytosis and their secretion of pro-inflammatory mediators such as TNF α , IL-1 β and CCL5 [473].

ACKR2^{-/-} mice show accumulation of inflammatory cells due to a lack of chemokine clearance [474]. However, decreased ACKR2 expression cannot prevent priming of auto-reactive T-cells, but can enhance T-cell polarization towards Th17 cells in mouse models of arthritis and neuropathy [475]. In contrast, some studies show that ACKR2^{-/-} mice are resistant to developing experimental autoimmune encephalomyelitis [476] and show decreased renal inflammation in a model of diabetic nephropathy [477].

ACKR2 also regulates lung inflammation during *Mycobacterium tuberculosis* infection. ACKR2^{-/-} mice have increased *M. tuberculosis*-mediated mortality which is correlated with both local and systemic inflammation [478-479]. In the bleomycin-induced lung injury ACKR2^{-/-} mice have reduced body weight loss, lung collagen content and lethality compared with WT mice. In addition, the lung tissues of ACKR2^{-/-} mice expressed reduced levels of some pro-inflammatory mediators such as IL-1 β , IL-6, IL-13, TGF β 1, CCL2, CCL3, CCL11, CXCL2, and CXCL9 but increased expression of other pro-inflammatory mediators such as IFN γ , CCL5, CCL12 and CCL17 [480].

In the lungs, ACKR2 is mainly expressed on alveolar macrophages [15,481] and lymphatic vessels [15,472]. However, it can also be detected on both plasmacytoid and myeloid DCs and on some B lymphocytes [15]. ACKR2 works predominantly as a chemokine scavenger receptor decreasing inflammatory activity [467]. Interestingly, the number of alveolar macrophages expressing ACKR2 are increased in stable COPD patient lungs compared to control subjects [15,481], but the functional relevance of this condition is still unclear.

ACKR2 mRNA and protein expression is enhanced in alveolar macrophages obtained from the lung tissue of stable COPD patients (n=13, mean age 63 years), compared to smokers with normal lung function (n=9, mean age 66 years) and non-smoker subjects (n=5, mean age 6 years), but not in monocyte-derived macrophages within lymphatic vessels. In the same cohort, BAL ACKR2 mRNA levels were increased in COPD patients compared to smokers with normal lung function and non-smokers. In addition, ACKR2 levels are positively correlated with CD8⁺ T cell numbers and with pro-inflammatory mediators (IL-32, TNF α , phosphor-p38 MAPK) and are negatively correlated with lung function (FEV₁ %) [481].

This data suggests that in addition to its known scavenger activity in acute inflammation, ACKR2 may show additional functions in chronic inflammatory conditions, such as enhancing immune cells activation and consequently inducing the release of pro-inflammatory mediators [481]. Thus, ACKR2 can maintain inflammatory process inducing airways remodelling.

Increased numbers of ACKR2⁺ cells are found in the bronchiolar and alveolar parenchymal lymphatic vessels in patients with advanced GOLD stage IV COPD (COPD GOLD IV n=10, mean age 62 years) compared to non-smoking subjects (n=8, mean age 66 years) [482].

20.3. ACKR3 in the pathogenesis of COPD

ACKR3 (Table 2) is expressed by endothelial cells, mesenchymal cells, and neurons (Figure 7) [13,37]. ACKR3 decreases CXCL12 protein function through modulation of CXCR4 expression and signalling activity due to the formation of CXCR4:ACKR3 heterodimers [483]. ACKR3^{-/-} mice possess congenital defects such as disrupted radial glial scaffold and invasion of boundary cap cells into the brain, and malformation of the glomerular tuft and ballooning of glomerular capillaries in kidneys [484-485]. The expression of ACKR3 is enhanced on blood T cells and on endothelial cells in inflammatory bowel disease [486]. ACKR3 expression is also increased on M1 macrophages in atherosclerotic plaques [487] and in the rheumatoid arthritis synovium, where it increases angiogenesis through signaling via CXCL12 and IL-1 β proteins [488].

Lung carcinoma cells, including lung squamous cell carcinoma, express increased ACKR3 levels compared to healthy human lung [489]. In addition, there is a non-significant negative correlation between ACKR3 mRNA expression in these cells and patient survival [490]. In lung carcinoma cells, *in vitro*, TGF β 1 increase both ACKR3 mRNA and protein expression, which may regulate cancer cell motility and their epithelial-to-mesenchymal transition. *In vivo*, increased levels of both TGF β 1 and ACKR3 correlated with poor patient survival [491]. Currently, there are no studies on the role of ACKR3 in the pathogenesis of COPD.

20.4. ACKR4 in the pathogenesis of COPD

ACKR4 (Table 2) is expressed by bronchial epithelial cells, thymic epithelial cells and keratinocytes. ACKR4 binds homeostatic chemokines such as CCL19 (preventing signalling through CCR7), CCL21, CCL25, and CXCL13 (Figure 7)

[492]. ACKR4^{-/-} mice demonstrate an increased Th17 responses and serum CCL19 and CCL21 proteins levels compared to WT mice, which can lead to autoimmune encephalomyelitis [492].

ACKR4 can modulate the migration and recruitment of leukocytes through effects mediated by chemerin [313]. Moreover, localized production and release of active chemerin contributes to the activation of plasmacytoid DCs, which promote activities against several pathogen-mediated inflammatory events and may represent a potential therapeutic target in infectious diseases and cancers [319]. This suggests that ACKR4 directs migration of DCs during inflammatory condition [493].

In acute (4 times/day for 30 minutes, 5 days/week for 4 weeks) and chronic (4 times/day for 30 minutes, 5 days/week for 24 weeks) cigarette smoke-induced mouse models, ACKR4 expression in the bronchial epithelium is increased compared to mice without cigarette smoke exposure. This may drive a pro-inflammatory response with increased BAL neutrophils, monocytes and T cells levels. This pro-inflammatory response is attenuated in cigarette smoke-exposed ACKR4^{-/-} mice compare to WT mice [322].

Molecules acting as antagonists to ACKR4 are being designed, such as CA4910 and CA5183, that can recognize human ACKR4 with moderate affinity [319,494]. These are composed of a common binding site that is very similar to chemerin, the natural ligand of ACKR4, which would inhibit chemerin-induced increase in intracellular calcium levels [319]. There is partial inhibition of ACKR4 when chemerins are used as agonists and there is complete inhibition when the chemerin nonapeptide (amino-acids 149-157) is used as an agonist [319,494]. Another study has shown the potential beneficial effects of using nanobodies to neutralize endogenous chemerin *in vivo* [319,495]. In a murine dextran sulfate sodium (DSS)-induced colitis model, these nanobodies did not improve clinical symptoms but decreased the histological damage of colonic tissues when compared to the placebo group. The response correlated with decreased IFN γ and TNF α , but not IL-6, protein levels in colonic cells [319,495]. These nanobodies have therapeutic potential but can also be used to detect ACKR4 on cell membranes in several tissue compartments and thus enables further studies on chemerin distribution and pharmacological properties [319].

Preclinical trials in mice on the selective ACKR4 antagonist CCX832 have shown promising results. However, an open study of CCX832, an ACKR4 nanobody, in psoriasis has been halted and the results have not been published [319,496].

20.5. Akr5 and akr6 in the pathogenesis of COPD

Akr5 is expressed on many immune cells such as monocyte/macrophages, neutrophils, eosinophils dendritic cells, T and B cells, NK cells, mast cells, and CD34⁺ bone marrow precursors in humans (Table 2) (Figure 7) [312,497]. Akr5 expression is upregulated by LPS and TNF α in human neutrophils and dendritic cells [497-500]. *In vitro*, akr5 forms both homodimers and heterodimers with CXCR2 and thereby modulates the expression and activation of β 2-integrins on immune-cell-surface with CXCR2 [501].

Akr5 can recognize chemerin and promote chemerin presentation to its main receptor ACKR4 on adjacent cells [312]. However, the biochemical properties of akr5 are less well characterized than those of ACKR4 [502]. When chemerin is recognized from akr5, it can interact with ACKR4-expressing neighbour cells through its exposed C-terminal domain to further transduce intracellular signals [319,502]. Akr5 lacks signalling capability, but it increases local chemerin levels by presenting the ligand to ACKR4 expressed on the cell surface of leukocytes [319,503].

During inflammatory arthritis, akr5 expression is upregulated, enabling akr5 to modulate CXCR2-mediated neutrophil recruitment to the sites of inflammation [501]. Akr5 expression is also enhanced on the bronchial epithelium and lung macrophages in a mouse model of ovalbumin-induced allergic asthma [504] and akr5^{-/-} mice are partially protected from developing allergic asthma in this model. This is associated with a reduced ability of DCs to migrate to the mediastinal lymph nodes and prime Th2 responses [499]. Intranasal challenge of mice with LPS also induces akr5 expression on endothelial cells and enables recruitment of NK cells into the airways [505]. Akr6 is expressed in spleen, and at low levels in ovary and other tissues (Table 2) (Figure 2) [506].

The CCL18/akr6 axis may be involved in epithelial mesenchymal transition and the migration and invasion of pancreatic and hepatocellular carcinoma cells [507-508]. This axis also promotes angiogenesis and invasiveness of breast cancer cell lines [509] and a novel CCL18/akr6 blocker (SMC-21598) significantly inhibits CCL18-induced adherence, invasiveness and migration of breast cancer cells [509]. Currently, there are no studies on the role of akr5 and akr6 in the pathogenesis of COPD.

20.6. TLRs in the pathogenesis of COPD

TLRs are part of the PRR family. These are classified into transmembrane TLRs and intracellular TLRs. They are expressed by several immune cells and can recognize several PAMPs in response to infections mediated by bacteria, viruses and fungi [510-519], but also several DAMPs [511-515]. After recognition of their specific ligands, TLRs induce pro-inflammatory gene expression and consequent release of several pro-inflammatory mediators [520]. There are literature data to suggest an important role of some TLRs (TLR2, -4 and -9) in the pathogenesis of COPD, thus TLRs also represent potential therapeutic target in the treatment of this pathology.

TLRs (Table 2) are members of the PRR family that mediate responses against several pathogens or are activated by tissue injury (Figure 6-7) [510]. TLRs are widely expressed on lung epithelial cells, macrophages, neutrophils and DCs, and are divided into two categories based on plasma membrane (TLR1, 2, 4, 5, 6, and 11) or endolysosomal compartment expression (TLR3, 7, 8, and 9) [511]. Plasma membrane TLRs recognize extracellular PAMPs, while intracellular TLRs bind nucleic acid-based PAMPs [511]. In addition to their capacity to recognize their coupled ligands, in particular PAMPs, TLRs also form heteromeric dimers with other TLRs, increasing the range of PAMPs that can be recognised [511]. TLRs also recognize DAMPs, including heat shock proteins (HSPs), low molecular-weight hyaluronan, heparin sulphate, fibronectin, HMGB1 protein, and low-density lipoproteins [511-515].

Viral nucleic acids can be bound by endosomal TLRs in immune cells, which induces $\text{INF}\gamma$ release [516]. TLR2 recognises LTA from Gram-positive bacteria, but also several non-typical Gram-negative bacteria-derived LPSs [510,517], TLR4 can bind LPS and endogenous ligands whilst TLR9 mainly binds bacterial and viral DNA [510,518]. TLR9 is one of three major receptors that account for most of DNA-driven immune responses, together with cyclic GMP-AMP synthase (cGAS) and absent in melanoma 2 (AIM2) [519].

After recognition of their specific ligands, TLRs promote activation of signalling pathways downstream of MyD88 that activate several transcription factors, including NF- κ B, which induce the secretion of pro-inflammatory mediators such as IL-1 β and TNF α [520].

TLRs also have a key role in the recruitment of innate immune cells against fungal infections by recognition of fungal components such as chitin. Recognition of chitin through TLR9 activates inflammatory responses against *C. albicans* by enhancing secretion of IL-10 [521].

Genetic variation in the genes encoding TLRs have been suggested to explain different levels of susceptibility to fungal infective diseases between individuals [522]. The TLR4 variants rs4986790 (D299G) and rs4986791 (T399I) are two haplotypes that are associated with an increased risk of developing invasive pulmonary aspergillosis (IPA) and chronic aspergillosis due to a decreased capacity to recognize specific ligands [523-525].

Several studies have shown that there are TLR genetic variations other than those for TLR4 that are also correlated with an increased risk for fungal disease. Indeed, there are associations between the polymorphisms rs5743611 (R80T) and rs4833095 (N248S) in TLR1 and rs5743810 (S249P) in TLR6 with an increased risk for IPA [526], while the TLR9 genetic variant rs5743836 is correlated with an increased risk for allergic bronchopulmonary aspergillosis (ABPA) [524].

Evidence suggests that atypical innate immunity contributes to COPD pathogenesis. For example, TLRs such as TLR2, TLR4 and TLR9 are involved in cigarette smoke-induced inflammation and the development of COPD [527].

Thus, impaired innate immune system activity is correlated to lung tissue damage, cell necrosis and emphysema development [527].

The expression of extracellular TLR2 protein in induced sputum and of intracellular TLR2 mRNA levels in macrophages is decreased in COPD following ICS treatment (n=21, mean age 66 years) compared to COPD patients without ICS treatment (n=29, mean age 68 years) [528].

In vitro stimulation of alveolar macrophages isolated from stable COPD patients (n=19, mean age 66 years) and smokers with normal lung function (n=9, mean age 67 years) with the TLR2 agonist Pam3CSK4 increases secretion of TNF α , CCL5, CXCL8, IL-6 and IL-10. However, repeated challenge with LPS decreased production of these pro-inflammatory mediators except for CXCL8 and IL-6 [529].

TLR4 modulates oxidant/antioxidant balance by inhibiting NADPH oxidase 3 expression in several structural cells in the lung, including lung endothelial cells [527]. This is confirmed by studies that demonstrated an increase in oxidative stress in TLR4^{-/-} and MyD88^{-/-} mice, which is associated with features of age-related emphysema, such as enhanced elastolysis and tissue necrosis [527-530]. In addition, brief cigarette smoke exposure causes increased neutrophil-mediated airway inflammation that is dependent on TLR4, MyD88 and IL-1R1 [527,531-532].

Increased TLR4 protein levels are found in surgically obtained lung tissue from stable COPD patients (n=24, mean age 63 years) compared to lung tissue from smokers with normal lung function (n=24, mean age 63 years) [533]. Increased TLR4 protein expression in the lung tissue is seen in an *in vivo* cigarette smoke exposure model of COPD (1hour/day for 8 weeks and with intratracheal LPS 200 μ g) compared to controls. In addition, stimulation of pulmonary artery smooth muscle cells from these COPD mice with LPS enhanced the expression of TLR4 and IFN γ proteins, while the TLR4 inhibitor TAK significantly suppressed this response [534].

Acute *in vitro* stimulation of alveolar macrophages from stable COPD patients (n=19, mean age 66 years) and smokers with normal lung function (n=9, mean age 67 years) with the TLR4 agonist LPS increased the expression of TNF α , CCL5, CXCL8, IL-6 and IL-10 protein. In contrast, repetitive stimulation with LPS decreased the expression of these pro-inflammatory

mediators except for CXCL8 and IL-6 [529]. In addition, *in vitro* stimulation of blood neutrophils isolated from stable COPD patients (n=101, mean age 56 years) significantly increased CXCL8 protein and TLR2 and -4 mRNA expression compared to stimulated neutrophils isolated from smokers with normal lung function (n=101, mean age 53 years). Furthermore, the extent of smoking positively correlated with CXCL8 protein levels and negatively correlated with lung function [535].

In vivo cigarette smoke exposure in mice increased TLR9 mRNA and protein in the lung tissue. However, cigarette smoke exposure in TLR9^{-/-} mice did not result in pulmonary emphysema compared to WT mice [536]. Bronchial epithelial cells from stable COPD patients (n=6, mean age 50 years) and smokers with normal lung function (n=6, mean age 36 years) expressed increased TLR9 levels compared to non-smoker subjects (n=9, mean age 36 years). In addition, bronchial epithelial cells from stable COPD patients and smokers with normal lung function stimulated with TLR agonists showed enhanced secretion of G-CSF, IL-6, CXCL5 and IL-1 β compared to stimulated cells from non-smokers subjects [536].

20.7. CRTH2 in the pathogenesis of COPD

CRTH2 is the receptor for prostaglandin D₂. This axis is implicated in multiple inflammatory diseases. CRTH2 is expressed by several immune cells, such as innate lymphoid type 2 cells (ILC2), TH2 lymphocytes, eosinophils, basophils, and epithelial cells [537-542]. Recently Th2 inflammation and in particular CRTH2-expressing ILC2 have been implicated in the pathogenesis of COPD.

The receptor CRTH2, also known as prostaglandin D₂ receptor (DP₂), is a G-protein receptor that mediates the inflammatory effects of DP₂ (Table 2) [537-538]. CRTH2 and DP₂ are involved in eosinophil recruitment and allergic inflammation [537]. The interaction of DP₂ with CRTH2 results in increased intracellular calcium levels, decreased intracellular cAMP levels and activation of several signalling pathway intermediates such as PLC, PI3K, and p38-MAPK [538].

Several cells such as innate lymphoid type 2 cells (ILC2), TH2 lymphocytes, eosinophils, basophils, and epithelial cells (Figure 7) express CRTH2 [537,539-541]. However, mast cells only express CRTH2 intracellularly, and thus PGD₂ cannot alter Ca²⁺ levels in response to CRTH2, which suggests that this receptor activates other signalling pathways and functions in these cells [537,542].

The PGD₂/CRTH2 axis is strongly implicated in chronic inflammatory diseases such as asthma, COPD, allergic rhinitis and atopic dermatitis. Indeed, Th2 cells modulate the production of mediators such as IL-4, IL-5, and IL-13, which promote the recruitment and activation of allergic inflammatory cells [537-538,543]. As such, CRTH2 represents a potential target for the treatment of asthma. However, placebo-controlled clinical trials have failed to show benefits of drugs like Fevipiprant in uncontrolled moderate and severe atopic asthmatics [544-545], and development has been stopped.

Recent studies have also implicated Th2 inflammation and CRTH2 in COPD pathogenesis. Stable COPD patients (n=107, mean age 67 years) express greater levels of serum IL-5, IL-6, IL-13 and IL-33 levels compared to smokers with normal lung function (n=110, mean age 67 years), and have increased numbers of blood innate lymphoid cells (ILC2) with an increased density of surface CRTH2 when compared to smokers with normal lung function [546]. Increased blood Th2 cells, Th2:Th1 ratio, enhanced ILC2 and CRTH2 mRNA levels are also found in COPD patients during exacerbation (n=98, mean age 67 years) compared to stable COPD patients (n=112, mean age 67 years) and smokers with normal lung function (n=110, mean age 66 years) [547].

Blood ILC2 cells from stable COPD patients (n=107, mean age 67 years) exposed to IL-33 *in vitro* showed enhanced release of IL-5, IL-6 and IL-13 protein, and also increased CRTH2 mRNA expression. This effect of IL-33 is prevented by an anti-ST2 (IL-33 receptor) blocker [546]. Furthermore, blood ILC2 cells obtained from COPD patients during an acute exacerbation and co-cultured with CD4⁺ T cells *in vitro* showed a significant increase in the Th2:Th1 ratio associated with enhanced expression of IL-4, IL-5, and IL-13. However, this effect of ILC2s on Th2 cells was inhibited by an anti-MHC II blocking antibody [547].

These data suggest that IL-33, and consequently ILC2 cells expressing increased levels of CRTH2, may have a key role in the pathogenesis of COPD both in stable phase and during acute exacerbation. This is through ILC2 acting as antigen presenting cells to alter the Th2/Th1 balance, resulting in a Th2 shift [546-547]. Thus, this represents a potential new therapeutic target.

There were increased CRTH2 expression in surgically obtained lung epithelial cells from stable COPD patients (n= 12, not reported mean age) that showed hypertrophic and hyperplastic phenotypes (especially in apical surface of epithelial cells) compared to those cells showing metaplastic phenotype [548]. Clinical trials are underway in moderate-severe COPD patients with high blood eosinophilia (NCT03810183) and the results are awaited with interest.

21. NEW COMPOUNDS MODULATING THE SYNTHESIS/RELEASE OF CHEMOKINES AND/OR CHEMOKINE RECEPTORS FOR THE TREATMENT OF COPD

Several new compounds capable to target atypical chemokines and/or atypical chemokine receptors are under development for the treatment of several inflammatory diseases including COPD [43]. However, the redundancy in the chemokine network is a great obstacle in the potential use of these compounds [43], moreover cross-species reactivity can be a problem to studying, developing and testing these molecules [43]. In addition, many of these compounds are not currently studied for the treatment of COPD.

Drug development for COPD has been directed towards new anti-inflammatory compounds such as chemokine and/or chemokine receptors antagonists and blocking antibodies that attenuate activation of inflammatory cells and their recruitment into the airways (Tables 3 and 4) [43].

Table 3. Current status of atypical chemokines and atypical chemokine receptor blockers development for the treatment of COPD

	Pre-clinical	Phase I	Phase II	Development halted
Atypical chemokines				
HMGB1	√			
AMPs	√			Aprepitant
MIF	√			
Atypical chemokine receptors				
RAGE	√			
TLR2 antagonist	√			
TLR4 antagonist	√			NI-0101
TLR9 antagonist	√			
TLR9 agonist	√			
Multiple TRLs antagonist (7,8,9)	√			
CRTH2 antagonist	√			AZD1981

AMPs: antimicrobial peptides; CRTH2: prostaglandin P2 receptor; HMGB1: high-mobility group protein box 1; MIF: Macrophage migration inhibitory factor; RAGE: receptor for advanced glycosylation end product; TLR: Toll-like receptor.

Obtained with the data from clinical trials.gov (<http://clinicaltrials.gov/ct2/home>) and current controlled trials (<http://www.controlled-trials.com/>), Patent Lens (<http://www.patentlens.net/>) and the current pipeline in the websites of the pharmaceutical companies (see Table 4). √: indicates the current stage of development.

Table 4. websites of the pharmaceutical companies developing chemokines and/or chemokine receptors antagonist

Pharmaceutical company	web site
Amgen (including formerly Tularik compounds)	www.amgen.com
Astra-Zeneca (including compounds from Cambridge Antibody Technology, and Medimmune)	www.astrazeneca.com/Home
Biokine	www.biokine.com
Boehringer Ingelheim (including compounds from Funxional Therapeutics)	www.boehringer-ingelheim.it
Bristol-Meyers Squibb (including formerly Medarex compounds)	www.bms.com
Chemocentryx	www.chemocentryx.com
Chiesi Farmaceutici	www.chiesi.com
Dompè	www.dompe.com
GlaxoSmithKline (including formerly SmithKline Beecham and Human Genome Sciences compounds)	www.gsk.com
Incyte	www.incyte.com
Johnson and Johnson [including Janssen Biotech (including formerly Centocor Ortho Biotech and Respivot compounds) *]	www.jnj.com [www.janssenbiotech.com]
Kyowa-Hakko Kirin Pharma	www.kyowa-kirin-pharma.com

Merck Sharp and Dohme (including Schering-Plough compounds)	www.merck.com
Novartis	www.novartis.com
Pfizer	www.pfizer.com
Polyphor	www.polyphor.com
Progenics Pharmaceuticals	www.progenics.com
Sanofi (including formerly Aventis, Genzyme and Anor-MED compounds)	www.sanofi.com
Sobi (including Novimmune compounds)	www.sobi.com
Taigen Biotechnology	www.taigenbiotech.com
Takeda Pharmaceuticals (including formerly Nycomed, Altana, Byk Gulden and Millennium Pharmaceuticals compounds)	www.takeda.com
UCB (including compounds formerly from Celltech)	www.ucb.com
Vertex Pharmaceuticals (including formerly Virochem Pharma compounds)	www.vrtx.com

The following website of some former pharmaceutical companies are currently inactive: Archemix, Chemokine Therapeutics, ProtAffin, Tobira Therapeutics, VLST Corporation.

However, the redundancy in the chemokine network represents a major obstacle in the potential using of chemokines and their receptors as therapeutic targets for COPD [43]. Indeed, several chemokine receptors can recognize many ligands, and one small molecule that blocks a specific chemokine/chemokine receptor axis probably cannot block binding of other ligands [43]. Thus, inhibiting a single specific chemokine receptor may be insufficient to modulate the inflammatory response induced by this specific chemokine [43]. However, the results obtained from studies on knockout mice and/or the use of small molecule antagonists in animal models of COPD show encouraging data to suggest that inhibition of the chemokine network may represent a possible therapeutic strategy for COPD [43,549].

Cross-species reactivity may represent an obstacle to studying, developing and testing new chemokine antagonist compounds in animal models. However, the use of chimeric transgenic mice to replace murine chemokine/chemokine receptor with a human analogue, sometimes in conjunction with a genetic knockout model of COPD has sped up the drug screening process [43,550-551].

22. MODULATION OF HMGB1 AND RAGE IN COPD

Currently, several compounds that can target HMGB1 have shown encouraging results in many preclinical trials with inflammatory animal models [47,49, 552-561]. However, there are no clinical studies regarding modulation of HMGB1 in COPD.

While, a RAGE antagonist is currently in a phase 3 trial for Alzheimer's [562] disease treatment, but there are no studies on use of RAGE antagonist in the treatment of COPD.

HMGB1 is a potential therapeutic target for several diseases [49]. Compounds that target HMGB1 include monoclonal antibodies (mAb), HMGB1-specific antagonists, and pharmacological inhibitors [49]. Many preclinical trials with HMGB1-mediated inflammatory animal models (e.g. sepsis, trauma, epilepsy, acute liver injury, systemic lupus erythematosus and arthritis) have shown encouraging results [49]. However, although pre-clinical data is promising, the clinical benefit of HMGB1 neutralization needs to be assessed [47,49,66] (Table 3).

A humanized anti-HMGB1 monoclonal antibody (2G7) has been developed and tested in mouse models, where it attenuated inflammation in a model of drug-induced liver injury, and improved hind-limb grip strength but not survival in a mouse model of amyotrophic lateral sclerosis [552,553]. In a murine sepsis model, use of anti-HMGB1 antibodies regulated inflammation and decreased mortality but had no immunosuppressive effect [49,554]. Meanwhile, HMGB1 neutralization mainly through the use of anti-HMGB1 mAb showed a disease-modifying anti-epileptogenic effect in an experimental epileptic model [49]. Moreover, use of an anti-HMGB1 mAb decreased production and/or release of the inflammatory mediators CCL2, CXCL1, TLR4, and IL-6 in the cerebral cortex and hippocampus and improved cognitive function [49,555-556]. *In vitro* treatment of cultured macrophages using an anti-HMGB1 monoclonal antibody inhibited internalization of HMGB1 and HMGB1-LPS complexes and reduced their activation [49,557].

Affibodies are small molecules that mimic antibodies, and have shown a good distribution profile in tissues [47,558]. Currently, there is one HMGB1-neutralizing Affibody under development that has potential use for future clinical studies (<http://www.counterstroke.net/>) [47]. In several preclinical studies of inflammatory diseases such as infection, sepsis, ischemic brain damage, systemic lupus erythematosus and rheumatoid arthritis, use of a recombinant DNA-binding domain (sequence 2-89) in HMGB1 called box A protein has shown potent HMGB1 antagonistic activity. However, its mechanism of action is still unclear [47,50, 66,559,560]. Recent studies have discovered a tetramer (FSSE) that acts as a specific MD-2 antagonist, capable of preventing MD-2/HMGB1 binding and subsequent activation of TLR4, but it does not inhibit the MD-2/LPS axis [47]. This tetramer when administered in mice showed a protective role against influenza, sepsis and hepatic ischemia/reperfusion injury [47]. These results suggest strategies to inhibit the inflammatory response to DAMP-mediated infections without inducing immunosuppression [47,65,561]. However, there are no clinical studies regarding modulation of HMGB1 in COPD.

In vitro exposure of a human adenocarcinoma lung epithelial type 2 cell line to cigarette smoke extract increased levels of pro-inflammatory cytokines such as IL-6, TNF α proteins and RAGE expression, whilst decreasing sRAGE levels. Pre-treatment with a RAGE-specific antagonist FPS-ZM1 (500-1000 ng) attenuated the effects of cigarette smoke extract on these cell lines [563].

TTP488 (also known as PF-04494700 or azeliragon) is an oral small-molecule antagonist of RAGE that inhibits binding of multiple RAGE ligands, including AGEs, HMGB1, S100B, and A β into the brain. TTP488 was successful in phase 2 clinical studies for the treatment of Alzheimer's disease (AD) and a phase 3 trial (NCT02080364, the STEADFAST Study) is currently underway in a mild AD cohort of 800 subjects [562]. However, there are no studies regarding modulation of RAGE in COPD.

23. MODULATION OF ANTIMICROBIAL PEPTIDES IN TREATMENT OF COPD

Many AMPs are currently studied for the treatment of several infection diseases [143], however, clinical trials on use of AMPs in COPD have shown unsatisfactory results.

Several AMPs are potential therapeutic anti-microbial agents in COPD due to their rapid, potent and direct bactericidal activity [143]. Currently, there are very few AMPs that are used for clinical practice, and this includes polymyxins that have been used clinically since the 1950s [143,564-565]. Several AMPs are under clinical development as potential treatment against bacterial infection (Table 3) [143]. Pexiganan, a 22-amino-acid membrane that mediated microbial membrane cellular destruction, has been studied in two phase 3 clinical trials (NCT00563394, NCT00563433) and as a topical cream for the treatment of bacterial infection-related diabetic foot ulcers [143,566-567]. Omiganan, a derivative of indolicidin, was isolated for the first time from bovine neutrophils, and was evaluated in phase 3 clinical trials for the topical treatment of catheter infections (NCT00231153) and rosacea (NCT01784133) [143]. LTX-109, a synthetic AMP, was tested as a topical drug in phase 2 clinical trials for treatment of Gram-positive bacteria skin infections (NCT01223222) and for impetigo (NCT01803035) [143]. It was also evaluated in a phase 1-2 clinical trial in subjects with nasal colonization of *S. aureus* (NCT01158235) [143,568]. hLF1-11, a cationic fragment of amino acids 1-11 of human lactoferricin, was studied in a phase 1-2 clinical trial as an intravenous drug for the treatment of bacterial and fungal infections in immunocompromised stem cell transplant recipients (NCT00509938) [143,569].

In addition, other clinical trials are underway to test AMPs for clinical indications other than as antimicrobials or antifungal agents [143]. LL-37 is the best one known antimicrobial peptide and was studied as a topical drug in a phase 1-2 clinical trial for the treatment of venous leg ulcers [143,570]. LL-37 impacts several wound repair mechanisms such as re-epithelialization and angiogenesis as well as the inflammatory response. Re-epithelialisation is probably promoted by the chemotactic effect of LL-37 on epithelial cells [143,571-572] whereas vascularization is mediated by LL-37-induced production of angiogenic factors and enhanced endothelial tube formation [143, 573-574].

Use of an antagonist of SP (aprepitant, orally administered 125 mg daily) in a cohort of stable COPD patients (n=16, mean age 70 years) paradoxically increased serum SP levels compared to untreated stable COPD patients and no improvements in lung function and the perception of breathlessness were seen [575]. Another similar and more recent study confirmed these data (NCT01854177).

24. MODULATION OF MIF IN TREATMENT OF COPD

MIF modulation is currently evaluated through several clinical trials for the treatment of oncological and haematological diseases [576-580]. However, MIF modulation has not yet been evaluated for COPD treatment.

Both imalumab (anti-MIF) and milatuzumab (anti-CD74/MIF receptor) show promising efficacy in several studies, such as increasing tumoral death during *in vitro* treatment on mantle cell lymphoma cell lines [576] or in the treatment of metastatic rectal-colon cancer, and have good safety profiles [577]. Milatuzumab was used as an orphan drug for multiple myeloma treatment, where the MIF/CD74 axis that induces cellular survival is extensively activated on malignant B cells. In a phase 1B clinical trial, it demonstrated good efficacy against lupus nephritis [578-580]. Ibudilast, originally developed as a phosphodiesterase inhibitor, is a small-molecule specific MIF antagonist and it is currently in an advanced phase of clinical development [579,581]. In a phase 2 clinical trial, Ibudilast demonstrated a good efficacy profile in multiple sclerosis, where

increased MIF expression is associated with enhanced risk of progressive disease [579,582-583].

Both MIF and the MIF receptor CD74 are overexpressed in most patients with NSCLC, suggesting that MIF could be used as an early biomarker of disease [584-585,586]. Furthermore, high expression of MIF is associated with poorer outcomes in NSCLC [584,587-588] and humanized anti-MIF and anti-CD74 antibodies are being evaluated in this disease as a priority [584,589].

In an animal model, a MIF neutralizing antibody (anti-CD74, intratracheally administered) significantly decreased LPS-induced neutrophils and macrophages numbers in BAL or in the lungs tissue [590]. However, currently there are no reports of agents targeting MIF for use as COPD treatment (Table 3).

25. MODULATION OF TOLL-LIKE RECEPTORS IN TREATMENT OF COPD

Several TLRs modulators (both antagonists and agonists) are been studied for the treatment of many inflammatory chronic disease including asthma [591]. However, none of these modulators have been evaluated in COPD.

Generally, TLR antagonists are synthesized or modified natural agonists that can specifically bind several TLRs, without activation of downstream signal transduction induced by structural rearrangement of the receptor [591] (Table 3). There are several ongoing studies of TLR2 antagonists [591]. Indeed, a humanized antibody against TLR2 (called OPN-305) has been developed by Opsona Therapeutics, showing reduced myocardial ischemia/reperfusion injury in pigs [591-592]. In a phase 1 study, OPN-305 prevented reperfusion injury associated with organ transplantation with a good safety profile at several dosages. Furthermore, OPN-305 prevented TLR2-induced increases in IL-6 release in blood monocytes [593]. This compound is undergoing a phase 2 clinical trial evaluating efficacy, safety, and tolerability profiles in delayed host-graft function (NCT01794663) and is in phase 1/2 clinical trial for its effect in the treatment of myelodysplastic syndromes (NCT02363491) [591-593].

An inhibitor of bacterial origin called staphylococcal superantigen-like 3 (SSL3), which binds TLR2 and blocks ligand binding, was tested as an immunomodulator [591,594]. In addition, it blocks TLR heterodimerization with TLR1 or TLR6 and decreased signalling from the TLR2-lipopeptide complex [594].

In addition, several studies have reported the development of small molecules and/or antibodies against TLR2 that inhibit heterodimerization with TLR1. These are effective in decreasing TNF α release from stimulated human blood monocytes. However, none of these molecules have been tested in human [595-596].

The best-known TLR4 antagonists are TAK-242 (Resatorvid) and Eritoran (E5564) that bind the intracellular TIR domain and the extracellular LPS binding pocket, respectively [591]. A phase 3 clinical trial of TAK242 (Resatorvid) was initiated for the treatment of septic shock and received Fast Track Designation by the FDA for the treatment of severe sepsis in July 2005. However, its use was terminated in 2009 (NCT00633477). A phase 2 clinical trial of E5564 for the treatment of diabetes mellitus improved glucose metabolism and decreased insulin resistance (NCT02267317), and E5564 is in a phase 3 clinical trial for severe sepsis (NCT00334828).

Another TLR4 antagonist, NI-0101, designed to decrease LPS-induced inflammation, has good safety, tolerability, distribution, and elimination profiles in phase 1 studies [597]. NI-0101 is in a phase 2 clinical trial for rheumatoid arthritis treatment (NCT03241108), but has never been studied in COPD or in other chronic lung diseases.

The use of cytidine-phosphate-guanosine oligodeoxynucleotide 2088 (CpG ODN 2088), an intratracheally administered TLR9 antagonist, reduced heat hypersensitivity injury-induced spinal cord injury *in vivo* [598] and increased protection against kainic acid (KA)-induced excitotoxic neuronal death [599]. In addition, CpG ODN 2088 reduced CXCL1 and CCL2 mRNA and protein expression and IL-6 protein but not mRNA expression in astrocytes *in vitro* [599].

Other TLR9 agonists are being investigated for the treatment of several malignancies. For example, lefitolimod (MGN1703) is in a phase 2 clinical trial for the SCLC [600] and GNKG168 is in phase 1 clinical trial for acute leukaemia in paediatric patients [601]. IMO-8400 (a TLR7, -8, and -9 antagonist, Idera Pharmaceuticals) has been tested in several phase 1/2 studies such as in Waldenstrom's macroglobulinemia (NCT02092909) and diffuse large B-cell lymphoma (NCT02252146) [591]. In addition, IMO-8400 is in a phase 2 clinical trial for treatment of dermatomyositis (NCT02612857) and plaque psoriasis [602].

AstraZeneca is developing an inhaled TLR9 agonist (AZD1419) for the treatment of asthma and it is currently in phase 2 to evaluate its safety and effectiveness (increased asthma control) in combination with an ICS/LABA versus placebo (NCT02898662). However, none of these TLRs antagonist have been studied in COPD.

26. MODULATION OF CRTH2 IN TREATMENT OF COPD

Several CRTH2 modulators have been studied for the treatment of asthma [537]. One of these was also valued for the treatment of COPD, however its development is currently interrupted [548].

Some small-molecule oral antagonists of CRTH2 have shown promising results in preclinical studies to warrant progression to clinical trials for asthma (Table 3) [537]. OC000459 has been evaluated in patients with asthma [537]. A 4-week, placebo-controlled parallel group clinical trial with OC000459 (200 mg administered twice daily) demonstrated a non-statistically significant improvements in FEV₁, but a significant improvement in quality of life and night-time symptoms compared with placebo. Active treatment, but not placebo, induced a significant reduction in eosinophil counts in induced sputum [537,603].

In another placebo-controlled study, OC000459 at lower doses (25 and 200 mg once daily, and 100 mg twice daily) produced similar improvements in FEV₁ at each dose and also resulted in improvements in the asthma quality of life questionnaire (AQLQ) and asthma control questionnaire (ACQ) scores when compared with placebo [537,604]. OC000459 showed increased efficacy and improvements in lung function in patients with atopy and those with higher blood eosinophil counts (>250 cells/ μ L) [537,604]. Furthermore, the CHTR2 antagonist, BI671800, produced improvements in FEV₁ when compared to placebo in asthmatic subjects but not to ICS or oral anti-leukotriene. The effects of BI671800 were also greater in subjects with increased blood eosinophil counts (>350 cells/mm³) [537,605].

In asthma patients using ICS, AMG853 which has a dual function as an antagonist of both prostaglandin D2 receptor 1 (DP₁) and CRTH2, failed to demonstrate any significant improvement in lung function, AQLQ, ACQ, or on symptom scores compared to placebo after 12 weeks of treatment [606]. In addition, in asthmatics with moderate-severe disease and sputum eosinophil counts >2% [537,607], Fevipiprant resulted in a significant decrease in sputum eosinophil percentage and eosinophil counts in the bronchial submucosa. However, this study could not adequately assess lung function and symptoms, and Fevipiprant has failed in phase 3 [607].

The CRTH2 antagonist AZD1981 causes lung function improvements after 4 weeks in atopic patients, with FEV₁ significantly increased by ~170-180 mL after 4 weeks in atopic asthma patients although no improvement in expiratory flow rate was observed compared to placebo [608]. A phase 2 study of AZD1981 (orally 1000 mg twice daily for 4 weeks) in stable COPD patients (n=61, mean age 64 years) did not increase lung function and showed no improvements in quality of life compared with placebo (n=56, mean age 62 years). Despite AZD1981 having a good safety profile [548], its development for the treatment of COPD is interrupted.

27. THE INTERPLAY BETWEEN MICROBIOME AND CHEMOKINES/RECEPTORS AS A THERAPEUTIC TARGET OF COPD

Altered gut and lung microbiome seems to be correlated with the pathogenesis of COPD and with the severity of disease [609-612]. In addition, microbiome can modulate chemokine release and consequently immune cell response representing a potential novel target for the treatment of COPD. However, further studies are necessary to clarify how microbiome can modulate chemokines release.

There is accumulating evidence to indicate both an important role of the microbiome in inflammatory diseases and the capacity for its modulation to alter the immune response and disease outcome. The microbiome is a collection of microorganisms that inhabit a host. However, the majority of studies have investigated only bacterial communities and as a result we focus on these in this section.

Indeed, the gut (and more recently, the lung) microbiome, and more specifically changes to the composition of the bacterial communities, termed dysbiosis, is correlated with respiratory conditions including COPD [609-612]. Unlike in other diseases, the lung microbiome in COPD doesn't appear to differ too much in composition, but rather in specific taxa. Notably, *Prevotella*, *Veillonella*, *Haemophilus* and *Moraxella* species are strongly associated with exacerbations and severity of COPD [613-615]. One mechanism involved in this host-microbiome interaction is the recruitment of leukocytes through chemokines. Certainly, the four microbial strains associated with COPD are able to modulate leukocyte recruitment. Exposure of non-typeable *H. influenzae* (NTHi) in the airways upregulates the expression of CCL20, CXCL1, CXCL2 and IL-17 and promotes the recruitment of leukocytes, especially neutrophils, to the lungs [616-617]. Similarly, *in vitro* incubation of lung cells with NTHi or *M. catarrhalis* also resulted in increased levels of CXCL2 and TNF α [617].

In other studies, mice deficient in Pellino-1 (involved in the TLR signalling pathway) have increased levels of CXCL1 in their BAL and airways neutrophilia following acute or chronic LPS exposure. Importantly, this was associated with increased clearance of NTHi [618]. Co-exposure of rhinovirus and NTHi resulted in increased CCL20 production from human bronchial epithelial cells *in vitro* [619]. Other studies show that *M. catarrhalis* induces CXCL8 production, oxidative burst, and degranulation in human granulocytes *in vitro* [620]. Although there are limited studies investigating the direct effect of microbiome on chemokines, it is clear that the microbiome, and indeed specific strains associated with COPD, affect chemokine responses and probably disease outcomes.

The capacity for the microbiome to modulate the severity of COPD provides an exciting opportunity whereby microbiome modulations can be a potential therapeutic strategy. There have been many reviews that highlight microbiome modulations as a potential therapy for inflammatory diseases, cancer, metabolic conditions, and mental disorders [621-624]. Indeed, with an increased consumption of a "Western" diet that is lacking in dietary fibre, and this diet associating with inflammatory diseases

such as COPD [625], researchers have investigated addition of fibre as a microbiome modulator [626]. Indeed, current or ex-smokers with low (less than 17.6 g daily) intake of fibre had 33-fold and 10-fold increase in risk of COPD, while high fibre intake (26.5 g or more) reduced the risk of COPD by 30% [627]. This reiterates results from a previous prospective study [628].

One mechanism in which dietary fibre exerts anti-inflammatory effects is through promoting the growth of bacterial that have anti-inflammatory effects. Thus, these and other beneficial bacteria have also been utilised as probiotic therapeutics for COPD. *In vitro*, the probiotic bacteria *L. rhamnosus* and *Bifidobacterium breve* suppressed cigarette smoke extract-induced increases in cytokines and chemokines, including CXCL8 and HMGB1, in a human monocytic cell line (THP-1) [629]. Furthermore, the use of antibiotics can shift the microbiome composition, especially during early life. Long term use in children is largely detrimental to health but has the potential to reduce bacterial burden and inflammation. However, the use of antibiotics is only recommended in patients with very severe COPD according to a recent systematic review [630].

Meanwhile, prophylactic antibiotics are efficacious in prolonging the time to the next COPD exacerbation, and reducing the severity of exacerbations, though this needs to be balanced with risks such as antibiotic resistance and associated costs [631]. Taken together, although researchers have identified four bacterial strains that are involved in COPD, potentially by modulation of chemokine production and recruitment of leukocytes, current treatments do not target these strains. Somewhat disconcerting is the fact that for current microbiome modulating therapies, especially with antibiotics, there is still controversy over its effectiveness and use in patients with COPD. Moreover, the mechanisms by which these therapies work is largely unknown and poorly explored in the context of COPD. Therefore, future research assessing how the microbiome can modulate immune responses through regulating the production of chemokines would benefit not only COPD research, but all respiratory and inflammatory disease research.

CONCLUSIONS

Currently, there are no cures for COPD, and conventional therapeutic approaches rely on palliative bronchodilators. Treatments based on drugs that reduce pulmonary inflammation in asthma, such as glucocorticoids, are ineffective in reducing airway inflammation and preventing the decline in lung function in most subjects [43,632-633]. Therefore, new therapies that can effectively reduce airway inflammation and mortality both in the stable phase of disease and during COPD exacerbations are necessary [43]. There remains a paucity of knowledge regarding the inflammatory components of COPD and the chemokine-related mechanism(s) that mediate inflammatory cell recruitment into COPD airways. Moreover, studies aimed at discovering these mechanisms should be performed in primary cells and/or in tissues from COPD patients rather than only in animal models to ensure better translation into successful clinical trials [43]. Future studies using lung or airway organoids or primary cell airway-on-a-chip cultures including immune cells should provide valuable information and a potentially better model to test drug efficacy as seen with cystic fibrosis organoids [634].

Currently, there is increased evidence on the key role of atypical chemokines and their receptors such as HMGB1, AMPs, RAGE or TLRs in the pathogenesis of COPD, both in the stable disease and during exacerbations. Thus, modulation of these inflammatory mediators may represent potential novel therapies for COPD and many are now in preclinical development.

However, compounds that antagonize chemokines and/or chemokine receptors are generally in early clinical development and phase 2 clinical trial results are awaited with great interest. These data will give us clinically useful evidence but also will provide proof-of-mechanism(s) [43]. Identifying specific target components that can induce/modulate leukocyte recruitment represents a significant therapeutic challenge, while use of chemokines as potential biomarkers to predict clinical phenotypes or progression of COPD or even to identify responders to particular therapies will probably be realized soon [43,635]. Clinical trials should include single cell RNA sequencing and proteomic (CyTOF) analysis of bronchoscopy or BAL samples to obtain greater insight into molecular characteristics between responders and non-responders.

Recent evidence implicating the microbiome in inflammatory diseases such as COPD makes it an exciting therapeutic target. There is evidence to suggest that the microbiome can regulate chemokine production and recruitment of leukocytes to the airways, thus influencing the outcomes of COPD. In addition, the gut microbiome is easily modifiable, and there is accumulating evidence that strategies such as a high fibre diet, probiotics, and antibiotics can alter the microbiome and chemokine responses. However, there is still an urgent need to understand how this occurs before these strategies can be tested and implemented into clinical practice.

LIST OF ABBREVIATIONS

7TM	=	7 transmembrane
α -MSH	=	α -melanocyte-stimulating hormone
ABPA	=	Allergic bronchopulmonary aspergillosis
ACKR	=	Atypical chemokine receptor
ACQ	=	Asthma control questionnaire

AD	=	Alzheimer's disease
AGE	=	Advanced glycosylation end product-specific receptor
AGER	=	Gene encoding RAGE
AIM2	=	Absent in melanoma 2
AKT	=	Protein kinase B
ALI	=	Acute lung injury
AM	=	Adrenomedullin
AMPs	=	Antimicrobial peptides
AQLQ	=	Asthma quality of life questionnaire
ARDS	=	Acute respiratory distress syndrome
AT1	=	Type 1 alveolar epithelial
AT2	=	Type 2 alveolar epithelial
BAL	=	Bronchoalveolar lavage
BMI	=	Body mass index
CAMP	=	Cationic antimicrobial peptide
CAP18	=	Cationic antimicrobial protein-18
CCL	=	CC chemokine ligand
CCbp2	=	Chemokine binding protein 2
CCR	=	CC chemokine receptor
CCRL	=	Chemokine CC motif receptor-like protein
CCX-CKR1	=	Chemocentryx chemokine receptor 1
cGAS	=	Cyclic GMP-AMP synthase
CGRP	=	Calcitonin-gene related peptide
CKXXNTF	=	Conserved motif signature
COPD	=	Chronic obstructive pulmonary disease
CRAM	=	Chemokine receptor on activated macrophages
CRTH2	=	Prostaglandin D2 receptor 2
CXCL	=	Cysteine-X-cysteine chemokine ligand
CXCR	=	CXC chemokine receptor
D6	=	Cysteine-cysteine (C-C) chemokine receptor
DAMPs	=	Damage-associated molecular patterns
DARC	=	Duffy antigen receptor for chemokines
DCs	=	Dendritic cells
DEFA	=	α -defensin
DEFB	=	β -defensin
DP1	=	Prostaglandin D2 receptor 1
DP2	=	Prostaglandin D2 receptor 2
DSS	=	Dextran sulfate sodium
ECM	=	Extracellular matrix

EDN	=	Eosinophil-derived neurotoxin
EPC	=	Eosinophil cationic protein
Erk	=	Extracellular signal-regulated kinase
Ex-RNA	=	Extracellular RNA
FABP5	=	Fatty acid binding protein 5 factor
FEV1	=	Forced expiratory volume in one second
FN3K	=	Fructosamine-3-kinase
FPR2	=	Formyl peptide receptor 2
FVC	=	Forced vital capacity
GAPDH	=	Glyceraldehyde 3-phosphate dehydrogenase
G-CSF	=	Granulocyte-macrophage colony stimulating
Gi	=	Inhibitor G protein
GI	=	Gastrointestinal
GPCR	=	G protein-coupled receptor
GPR1	=	G protein-coupled receptor 1
HAdV	=	Human adenovirus
HbA1c	=	Glycated haemoglobin
HBV	=	Hepatitis B
HCMV	=	Human cytomegalovirus
HCV	=	Hepatitis C
HDL	=	High-density lipoproteins
HDPs	=	Host defence peptides
HIV	=	human immunodeficiency virus
HLA	=	Human leukocyte antigen
HMGB1	=	High-mobility group protein B1
H ₂ O ₂	=	Hydrogen peroxide
HOMA-IR	=	Homeostatic model assessment for insulin resistance
HPV	=	Human papilloma virus
HSV	=	Herpes simplex virus
HUVECs	=	Human umbilical vein endothelium cells
IFN	=	Interferon
IAV	=	Influenza type A virus
IBD	=	Inflammatory bowel diseases
IL	=	Interleukin
ILC2	=	innate lymphoid type 2 cells
IP3	=	inositol triphosphate
IPAH	=	Idiopathic pulmonary hypertension
IPF	=	Idiopathic pulmonary fibrosis
I/R	=	Ischaemia/reperfusion

IRF3	=	IFN γ regulatory factor-3
JAK	=	Janus kinase
JNK	=	Jun N-terminal kinase
KA	=	Kainic acid
KC	=	Analogous to human IL-8
LDL	=	Low-density lipoproteins
LEAP-1	=	Liver expressed antimicrobial peptide-1
LPS	=	Lipopolysaccharide
LTA	=	Lipoteichoic acid
LTOT	=	Long term oxygen therapy
LVRs	=	Lung volume reduction surgery
mAb	=	Monoclonal antibody
MAPK	=	Mitogen activated protein kinase
MD-2	=	Myeloid differentiation factor 2
MDSC	=	Myeloid-derived suppressor cells
MIF	=	Macrophage migration inhibitory factor
MMP	=	Matrix metalloproteinase
MRSA	=	Methicillin-resistant
MSSA	=	Methicillin-sensitive <i>S. aureus</i>
MTS	=	Mitochondrial targeting sequence
MyD88	=	Myeloid differentiation primary response 88
NETs	=	Neutrophil extracellular traps
NFAT	=	Nuclear factor of activated T-cells
NF- κ B	=	Nuclear factor- κ B
NK	=	Natural killer
NOD	=	Nucleotide-binding oligomerization domain-containing protein
NP _s	=	Neuropeptides
NPY	=	Neuropeptide Y
NSCLS	=	Non-small cell lung cancer
NTHi	=	Non-typeable <i>H. influenzae</i>
O ₂ ⁻	=	Superoxide anion
OH ⁻	=	Hydroxyl radical
PH	=	Pulmonary hypertension
PI3K	=	phosphoinositide 3-kinase
PITPNM3	=	Membrane-associated phosphatidylinositol transfer 3
PKC	=	protein kinase C
PLC	=	Phosphoinositide-specific phospholipase C
Poly (I:C)	=	Polynosinic-polycytidylic acid
PRR	=	Pattern recognition receptor

PTEN	=	Phosphatase and tensin homolog
RAC1	=	Ras-related C3 botulinum toxin substrate 1
RAGE	=	Advanced glycosylation end product-specific receptor
RARRES2	=	Acid receptor responder 2
RDC1	=	Chemokine orphan receptor
ROS	=	Reactive oxygen species
RSV	=	Respiratory syncytial virus
RV	=	Rhinovirus
S100	=	Calcium binding protein
SAPK	=	Stress-activated protein kinase
SARSC	=	Severe acute respiratory syndrome coronavirus
SMD	=	Small molecule drug
SNP	=	Single nucleotide polymorphism
SOD1	=	Superoxide dismutase 1
SP	=	Substance P
sRAGE	=	Soluble RAGE
Src	=	Proto-oncogene tyrosine-protein kinase
SSL3	=	Staphylococcal superantigen-like 3
ST2	=	IL-33 receptor
STAT	=	Signalling transducer and activator of transcription
Tc	=	T cytotoxic
TGF	=	Transforming growth factor
Th	=	T helper
THP-1	=	Human monocyte leukaemia cell
TIG2	=	Tazarotene induced gene 2
TLR	=	Toll-like receptor
TNF	=	Tumour necrosis factor
VCAM-1	=	Vascular cell adhesion protein 1
VEGF	=	Vascular endothelial growth factor
VIP	=	Vasoactive intestinal peptide
WT	=	Wild type

CONFLICT OF INTEREST

Potential conflict of interests of Gaetano Caramori: Unrestricted educational/research grants and/or Lecture fees and/or grants for travel and accommodation to participate to scientific meetings from: Astra Zeneca, Alfasigma (Biofutura has merged inside it), Boehringer-Ingelheim, Chiesi Farmaceutici, Enfarma, GSK, Menarini Group.

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