European Journal of Pharmacology 886 (2020) 173529

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

MiRNAs in tuberculosis: Their decisive role in the fate of TB

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ARTICLE INFO

Keywords:
Tuberculosis
miRNA
Apoptosis
Autophagy

ABSTRACT

Tuberculosis (TB) is one of the most lethal global infectious diseases. Despite the availability of much higher levels of technology in health and medicine, tuberculosis still remains a serious global health problem. *Mycobacterium tuberculosis* has the capacity for prolonged survival inside macrophages by exploiting host metabolic and energy pathways and perturbing autophagy and apoptosis of infected cells. The mechanism(s) underlying this process are not completely understood but evidence suggests that mycobacteria subvert the host miRNA network to enable mycobacterial survival. We present here a comprehensive review on the role of miRNAs in TB immune escape mechanisms and the potential for miRNA-based TB therapeutics. Further validation studies are required to (i) elucidate the precise effect of TB on host miRNAs, (ii) determine the inhibition of mycobacterial burden using miRNA-based therapies and (iii) identify novel miRNA biomarkers that may prove useful in TB diagnosis and treatment monitoring.

Contribution to the field

TB is a significant global health concern and its diagnosis remains challenging due to the limitations in the specificity and sensitivity of the current diagnostic tests. *Mycobacterium tuberculosis* has the capacity for prolonged survival inside macrophages by exploiting host metabolic and energy pathways and perturbing autophagy and apoptosis of infected host cells. The mechanism(s) underlying this process are not completely understood but evidence suggests that mycobacteria subvert the host miRNA network to maintain its survival. Since miRNA profiles change with Mtb infection, the impact of miRNAs in TB infection is evident. However, how the bacterial virulence factors influence host miRNA expression to favor mycobacterial survival is not understood. This review offers new insight into the role of miRNAs in mycobacterium pathogenicity due to dysregulation of host metabolic and immune mechanisms. This knowledge opens windows for designing new therapies and diagnostic approaches for controlling tuberculosis based on miRNA technology.

1. Introduction

Tuberculosis (TB) is an infectious respiratory disease and the most common cause of death from infectious diseases across the globe. Despite substantial advances in TB diagnosis and treatment, controlling the disease still remains challenging. Based on epidemiological data from the World Health Organization (WHO), 9.0–11.1 million people around the world became infected with TB and there were 1.2 million TB-related deaths in 2018 (Organization, 2019).

Tuberculosis is caused by an intracellular pathogen, *Mycobacterium tuberculosis* (Mtb), which mainly infects macrophages. The immune response to Mtb is intricate and bacteria utilize highly complex mechanisms for immune escape. The critical problem with Mtb infection is the bacteria ability for intracellular survival and long-lasting infection (Dorhoi and Kaufmann, 2016). For this purpose; the bacteria triggers several host physiological responses which lead to host immune and metabolic re-patterning.

Mtb make these changes to support their nutritional needs and energy requirements and to maintain intracellular survival (Alipoor et al., 2017). The mechanisms underlying this process remain unclear but evidence suggests that Mtb triggers host microRNA (miRNA) networks

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https://doi.org/10.1016/j.ejphar.2020.173529
Received 4 June 2020; Received in revised form 28 August 2020; Accepted 28 August 2020
Available online 10 September 2020
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that are associated with carbon, nitrogen, and lipid metabolism in the infected cells (Ahluwalia et al., 2017; Alipoor et al., 2017).

miRNAs are small noncoding RNAs that generally regulate gene expression post-transcriptionally although transcriptional effects occur. miRNAs are known as the key element in several biological functions and their dysregulation are commonly accompanied with pathological outcomes (). Infection has a profound impact on miRNA expression implicating a key role in for miRNAs in mediating immune reactions (Kim et al., 2017). Furthermore, miRNAs are involved in immune response to Mtb infection (Mehta and Liu, 2014). In this review we summarized the role of miRNAs in the mechanisms that Mtb uses to escape from immune system and further discussing the importance of miRNAs in novel approaches for the treatment of Mtb.

2. General biology of miRNAs

In this section we provide an overview of miRNA biology: how they are generated and how they act to control cellular processes. miRNAs are small RNA molecules of 18–25 nucleotides in length that do not participate in the encoding of the proteins but rather act as critical controllers of gene expression in most cellular processes including cell proliferation, differentiation; signaling pathways as well as immune function. They do not generally act as on-off switches but they fine-tune the gene expression levels of central regulatory proteins to impact upon cellular phenotypes (Alipoor et al., 2016b). Each individual miRNA can regulate up to hundreds of mRNAs in parallel and each mRNA in turn may be affected by multiple miRNAs. As such, mutations or alterations in the structure of miRNAs or any change in their level of their expression may result in a profound effect on biological processes and could lead to pathological conditions (Alipoor et al., 2016b).

Alterations in miRNA-target gene expression may be a result, therefore, from acquired silencing by the native miRNA or from changes in miRNA structure. For example, a heterozygous C < G transition within miRNA-146a gene leads to the miRNA loss of function and increase individual susceptibility to cancers (Bodal et al., 2017). Furthermore, there are many reports associating the alteration in miRNA expression levels with a broad range of cancers (Alipoor et al., 2018a; Häusler et al., 2010; Leidinger et al., 2011; Lu et al., 2005). In addition to their predominant intracellular role, miRNAs may also be secreted into the extracellular space packaged inside exosomes or extracellular vesicles; which can be taken up by the other cells either locally or at a distance to affect their function (Alipoor et al., 2016). Thus, miRNAs are not only important modulators of cellular processes but are also involved in cellular communication.

2.1. miRNA biogenesis

miRNA genes are transcribed by RNA polymerase II in the nucleolus and generate a long primary miRNA (pri-miRNA) with a hairpin-loop structure (Fig. 1). A processor complex consisting of DiGeorge

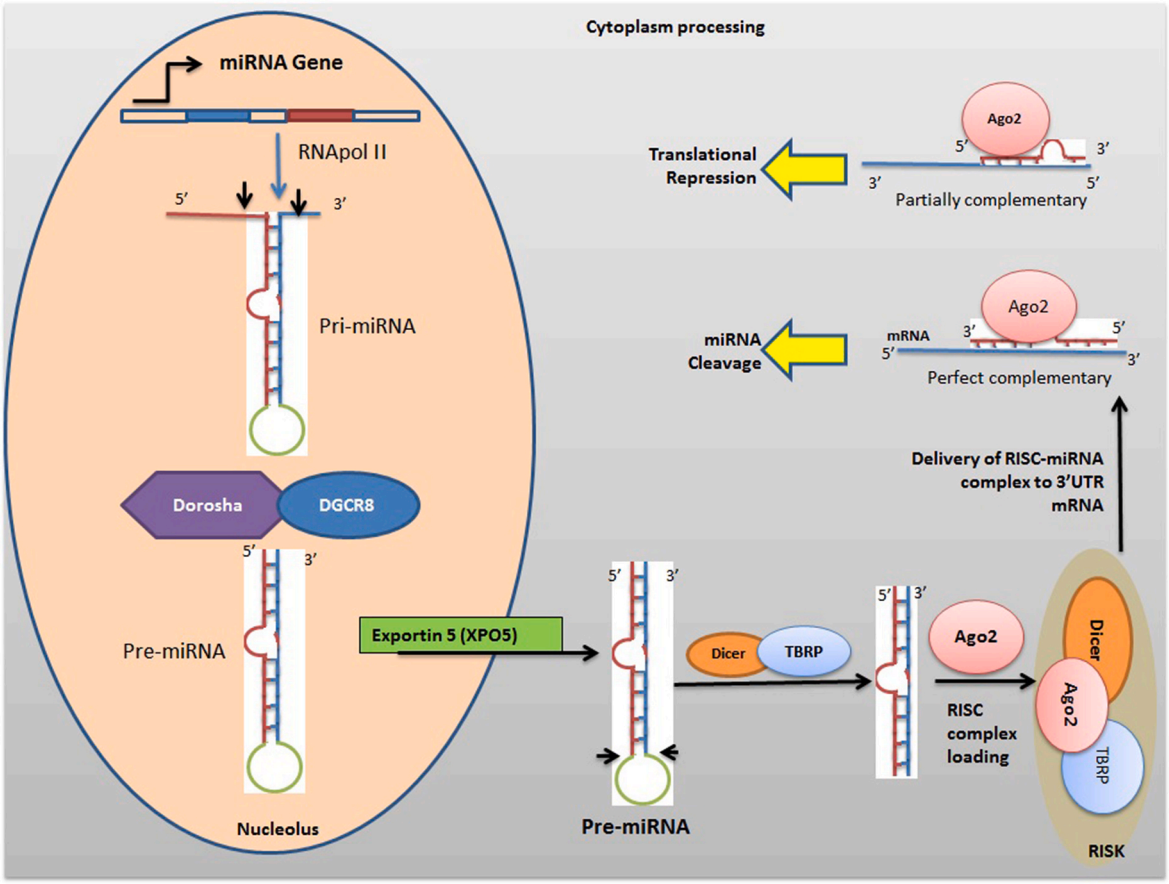

Fig. 1. miRNA biogenesis and mechanism of action. miRNA genes are transcribed by *Pol II*. primary miRNA transcripts (pri-miRNAs) are cleavage by the *Drosha/DGCR8* in the nucleus generating a stem-loop pre-miRNAs. Pre-miRNA is exported from the nucleus to the cytoplasm by the *nuclear export factor exportin 5* (EXPO5). In the cytoplasm the pre-miRNA is cleaved by *RNase III enzyme Dicer* generating a miRNA duplex of 18–22 nt. *Dicer*, *TRBP* and *Argonaute (AGO)* continue the processing of miRNA duplexe and assembly of *RISC* (RNA induced silencing complex). One of the two pre-miRNA strands, known as the guide strand forms the mature miR strand and remains on the Ago protein while the other one is degraded. Mature miRNA along with the RISC complex recognize and target seed sequences on the mRNA 3′-UTR. The degree of complementarity between these paired sites determines the impact on gene regulation; perfectly complementary base pairing gives rise to degradation of the mRNA whilst translational repression occurs when the complementarity levels are lower.

syndrome critical region gene 8 (DGCR8) in collaboration with another protein Drosha recognizes the hairpin-loop structure and cleaves the pri-miRNA to produce a precursor-miRNA (pre-miRNA) (MacFarlane and R Murphy, 2010).

Pre-miRNAs have a hairpin structure consisting of a short stem of 2–3 nucleotides with a 3′ overhang and is transported to the cytoplasm by exportin 5 (EXPO5). In the cytoplasm, pre-miRNA is processed to a two strand mature miRNA by the enzyme Dicer (Ha and Kim, 2014; MacFarlane and R Murphy, 2010). One of the two pre-miRNA strands, known as the guide strand (or miRNA), is integrated into the RNA-induced silencing complex (RISC), while the other one, known as the passenger or complementary (miRNA*) strand, is degraded, although this strand may occasionally also be functional (Alipoor et al., 2016b) (Fig. 1).

2.2. miRNA mechanism of action

miRNAs mainly regulate the expression of mRNA molecules through base-pairing with target mRNA which caused the mRNA molecules to be silenced through either cleavage and destabilization of the molecule or reduced efficiency of mRNA translation.

miRNAs use different mechanisms for fine-tuning of gene expression but mainly function by post transcriptional down regulation. The main miRNA mechanism is through miRNA-mRNA hybridization (Fig. 1). Six to 8-nucleotides in the 5′ region of miRNA, known as the “seed” sequence, is responsible for binding to mRNA targets in mRNA residue elements (MREs) mainly in the 3′ untranslated regions (3′ UTRs) of mRNA. The seed sequence is highly conserved among species and any change in this region may affect the function (MacFarlane and R Murphy, 2010).

miRNAs interact with mRNA using Watson-Crick pairing and the degree of complementarity between these paired sites determines the impact on gene regulation and may result in (i) translational suppression, (ii) mRNA cleavage or (iii) deadenylation (Davis-Dusenbery and Hata, 2010). Overall, perfectly complementary base pairing gives rise to degradation of the mRNA whilst translational repression occurs when the complementarity levels are lower (Fig. 1). However, RNA secondary structures and the flanking sequence of the miRNA target site do also influence the accessibility of the paired sites and the degree of hybridization (Valinezhad Orang et al., 2014).

2.3. Regulation of miRNAs

Similar to other RNAs, the expression of microRNAs is regulated by the mechanisms such as transcriptional elements or epigenetic events (Ha and Kim, 2014). miRNAs can be classified into intragenic and intergenic miRNAs based on their genomic position. More than half of identified miRNAs are intergenic and located between genes. These miRNAs generally have their own promoter and regulation elements and are transcribed independently of a host gene (Davis-Dusenbery and Hata, 2010). On the other hand, intragenic miRNAs, located within the introns or exons of coding genes, are co-regulated with their host genes (Davis-Dusenbery and Hata, 2010). miRNAs may also regulate their transcription by creating feedback loops such as reported with miR-200c. Zinc finger E-box-binding homeobox 1 (ZEB1) functions as repressor of the miR-200c gene but is also a target of this miRNA (Sundararajan et al., 2015).

Finally, processing of miRNAs within the nucleolus and cytoplasm is dependent upon the loops and secondary structures of each microRNA which may subsequently affect its processing efficiency and the expression level of the mature miRNA (Davis-Dusenbery and Hata, 2010). Therefore, the mechanisms underlying the regulation of miRNA expression may impact their expression profiles in pathological conditions and should be investigated further.

3. The virulence factors and mechanisms of immune escape of mycobacterium tuberculosis

This section summarizes our knowledge as to how Mtb virulence factors act within host cells to enable escape of the pathogen from immune surveillance. During TB infections, bacilli typically enter the body through the mouth or nose and subsequently reach the alveolar space via the airway (Philips and Ernst, 2012). Within the alveolar space the bacteria interact with and infect pulmonary epithelial cells, alveolar macrophages (AM) and other immune cells (Getahun et al., 2015). However AMs are the most favored target of Mtb (Mortaz et al., 2017). Mtb has two main routes for entering into AMs: via complement receptors (CRs) and via cell surface mannose receptors (MR) which recognize bacterial mannose residues (Gupta et al., 2012). AM demonstrate high MR activity after Mtb infection despite low levels of serum opsonins within the alveolar space (Gupta et al., 2012; Stokes et al., 2004). This suggests that MR-mediated phagocytosis is the major route of AM infection in the early stages of primary infection (Stokes et al., 2004).

Unlike some other bacterial pathogens that produce specific virulence factors, Mtb contains a complex combination of virulence determinants (Prozorov et al., 2014). A large number of different virulence factors have been identified in Mtb that may trigger host immune reactions (Forrellad et al., 2013) (Table 1). The unique type VII secretion systems and various complex lipids of the cell envelope have been identified as the most attractive factors in this regard (Raghavan et al., 2008). Comparative analysis of the genome sequences of virulent Mtb and the avirulent Mycobacterium bovis BCG enabled the delineation of Mtb virulence genes. This revealed a locus called the region of difference (RD)1 that was absent in all vaccine strains of M. bovis BCG and highlighted genes related to mycobacterium pathogenicity (Lewis et al., 2003). However, virulent Mtb has developed strategies to modulate the host immune response to favor the survival and proliferation of the pathogen.

In the majority of the cases, bacteria escape immune detection and elimination mechanisms result in a latent infection (Maertzdorf et al., 2018). The most well-known mechanisms are inhibition of phagosome-lysosome fusion and phagosome maturation (Philips and Ernst, 2012). Routinely during the macrophage phagocytosis process, engulfed bacteria enter plasma membrane vesicles known as phagosomes. Phagosomes then mature through a series of steps including acquiring degradative hydrolases and reactive oxygen/nitrogen intermediates to eventually become acidic phagolysosomes. The small GTPase Rab 5 is recruited to the phagosome and is exchanged with another GTPase, Rab 7, which precipitate PI(3)P-phosphatidylinositol 3-phosphate generation on the cytosolic face of the phagosome through a process involving the autophagy class III PI3-kinase VPS34 protein. PI(3)P is a ligand for EEA1 (early autosomal antigen-1), and modulates phagosome fusion with early endosomes (Jeschke and Haas, 2016). Mtb inhibits the maturation of phagosomes and their fusion with lysosomes (von Both et al., 2018). The mechanism underlining this process remains poorly understood. It is suggested that phagosomes containing Mtb fail to undergo Rab5-Rab7 exchange and thereby restrict lysosomal fusion (Seto et al., 2011). Mtb also prevents the function of reactive oxygen and reactive nitrogen intermediates, inhibits oxidative stress function and interferes with MHC class II antigen-presentation.

Mtb also attenuates apoptosis and autophagy of infected macrophages. Apoptosis is an important aspect of the host immune defense against Mtb during the early phases of infection. Apoptotic cells can deliver antigen to antigen presenting cells and subsequently enhance immunity against Mtb (Poirier et al., 2014). Interestingly, the apoptosis of infected macrophages is associated with Mtb virulence. Highly virulent Mtb strains prevent infected AM apoptosis whilst Mtb with a low virulence promote AM apoptosis (Zhai et al., 2019). Thus, inhibition of apoptosis allows survival of highly virulent Mtb strains and triggers latent infection (Poirier et al., 2014). This will be addressed in more

Table 1
Key *Mycobacterium tuberculosis* virulence factors and their targets.

Category	Gen Name	Description	Ref.
Lipids and Fatty Acid Metabolism	kasB	3-oxoacyl-[acyl-carrier protein] synthase 2 kasb	Bhatt et al. (2007)
Lipids Synthesis	fadD26	Fatty-acid-Coa synthase	Sirakova et al. (2003)
	mmpL7	Conserved transmembrane transport protein	Sirakova et al. (2003)
Cholesterol Catabolism	choD	Putative cholesterol oxidase	Chang et al. (2009)
	fadE 28/29	Acyl coenzyme A dehydrogenases	Chang et al. (2009)
	ltp2	Probable lipid carrier protein	Chang et al. (2009)
Cell Envelope Proteins	erp	Exported repetitive protein	Berthet et al. (1998)
Cell wall proteins	fbpA	Fibronectin binding protein, mycolyltransferese	Armitige et al. (2000)
	mce1	Mammalian cell entry proteins. Possible lipids ABC-transporters	Gioffré et al. (2005)
	ompATb	Pore-forming protein	Raynaud et al. (2002)
	hbhA	Heparin binding hemaglutinin protein (Adhesine)	Pethe et al. (2001)
	oppABCD	Oligopeptide ABC-transporter	Flores-Valdez et al. (2009)
Lipoproteins	lppX	Carrier of DIM and antigen	Sulzenbacher et al. (2006)
	lprG	Cell wall assembly/TLR2 agonist	Bigi et al. (2004)
	lprG-p55	Antibiotic efflux pump (P55)	Bianco et al. (2011)
Secretion system	esxA	Esx-1 component or substrate (C or S)	Wards et al. (2000)
	RD1	Esx-1 C or S	Lewis et al. (2003)
Proteins Inhibiting antimicrobial effectors of the Macrophage	acr 1 (hspX)	Dormancy-associated protein	Yuan et al. (1998)
	acr 2	Alpha-crystallin (Acr) family of molecular chaperones	Stewart et al. (2005)
Phagosome arresting	nuoG	Subunit of the type I NADH dehydrogenase, NADH-1	Velmurugan et al. (2007)
	pe_pgrs30	Member of the PE family	Iantomasi et al. (2012)
Inhibition of apoptosis	pknD	Protein kinase D	Nicholas et al. (2012)
	pknE	Serine/threonine kinase E	Nicholas et al. (2012)

detail latter in section 4.3.

Autophagy is an intracellular degradation process by which cells remove unnecessary and dysfunctional materials through a series of self-digesting mechanisms and deliver them to the lysosomes (Deretic, 2011). Mtb takes advantage of this process and exploits the host degradation processes to convert cellular macromolecules into simpler ones to ensure its favored nutrient supply (Steele et al., 2015). Mtb products such as galactomannan (LAM), phosphatidylinositol mannoside (PIM) and phosphatidylinositol 3-phosphate (PI3P) phosphatase suppress phosphoinositide 3-kinases (PI3K) signaling and thereby inhibit host cell autophagy (Ramachandra et al., 2005).

Overall; the mechanisms underlying TB immune escape remain unclear but recent evidence suggests that manipulation of the host miRNA profile enables Mtb survival and escape from the host immune system (Yang and Ge, 2018). We now review the role of host miRNA in the evasion strategies by mycobacterium.

4. Mtb and host miRNA modulation

miRNAs are essential mediators in immunity function and have determinate role in host–pathogen interactions in multiple infection disease. The miRNA profile of the bacterial infected cells showed different miRNA expression profiles compared with healthy controls. These observations indicated the important role of miRNAs in immune surveillance and control of infection (Zhai et al., 2019), (Sabir et al., 2018; Yang and Ge, 2018). Intracellular pathogens utilize host miRNAs to create an immune tolerant environment to promote their survival and latency. For example, the Hepatitis C virus (HCV) highjacks liver miR-122 to replicate inside hepatocytes (Henke et al., 2008). Mtb subverts host cell miRNAs to modulate host immune responses; metabolic; autophagy and apoptosis pathways in the host cells (Alipoor et al., 2017). Some of the significant altered miRNAs such as miR-155 and miR-33 are involved in all of these pathways and promote Mtb survival via different mechanisms (Fig. 2). In the next sections we discuss how the host miRNA network is re-patterned following Mtb infection to provide a favorable environment for Mtb survival (Alipoor et al., 2017) (Fig. 2).

4.1. Modulation of host metabolic and energy pathways

The nutrients required for Mtb growth and proliferation inside the host cell are restricted and so the bacterium relies upon the host's cell metabolism to provide its nutrient supply (Mehrotra et al., 2014). For example; Mtb utilizes lipids as its central carbon source during infection (Gago et al., 2018) and the host lipid metabolism is targeted for this reason (Alipoor et al., 2017).

In this regard; Mtb sequesters the host cell metabolic and energy pathways which may trigger regulatory miRNA networks that control cellular carbon and nitrogen metabolism (Eisenreich et al., 2013)

Mtb infection results in the generation of lipid droplets (LDs) that accumulate in the form of cholesterol esters and fatty acids converting macrophages into foam cells (Guerrini et al., 2018). The mechanisms underlying this process not well understood but may involve Mtb-mediated repatterning of host miRNA networks (Ahluwalia et al., 2017; Alipoor et al., 2017).

Based on the microarray analysis in clinical samples and in vitro studies miR-155, miR-33 and miR-1224 are the metabolic related miRNAs that increased in Mtb-infected macrophages. These miRNAs have critical roles in macrophage metabolism and foam cell production (Ahluwalia et al., 2017) (Fig. 2).We next discuss the mechanism of action in these miRNAs in the context of metabolic pathways.

miR-155 is overexpressed in Mtb-infected macrophages (Table 1) and has a conserved binding site for the ATP-binding cassette transporter ABCA1 (Du et al., 2014). ABCA1, also known as cholesterol efflux regulatory protein, is a cellular transporter that regulates the efflux of cholesterol (Du et al., 2014). Mtb depends on the cholesterol metabolism for its long-term persistence (Ahluwalia et al., 2017; Miner et al., 2009) and ABCA1 knockdown increases cholesterol uptake (Ahluwalia et al., 2017; Galkina and Ley, 2009).

miR-33a/b targets lipid metabolism and fatty acid oxidation genes including ABCA1, CROT, CPT1, HADHB and PRKAA1 and subsequently increases lipid levels in infected cells (Davalos et al., 2011; Najafi-Shoushtari et al., 2010; Rayner et al., 2010; Rottiers et al., 2011). Mtb induces host miR-33 expression to reprogram host lipid metabolism and promotes macrophage lipid stores through the inhibition of cellular fatty acid oxidation. Silencing of miR-33 and miR-33* enhances lipid catabolism and Mtb xenophagy (Ouimet et al., 2016). miR-33 also impairs the efflux of cholesterol from infected cells (Du et al., 2014). Additionally; miR-33 is located in the intronic region of the SREBP gene. SREBP is a transcription factor that up-regulates fatty acid and cholesterol metabolism associated genes (Behrouzi et al., 2019; Najafi-Shoushtari et al., 2010). Increased SREBP expression during Mtb infection serves a dual purpose for Mtb by up-regulating fatty acid metabolism genes and

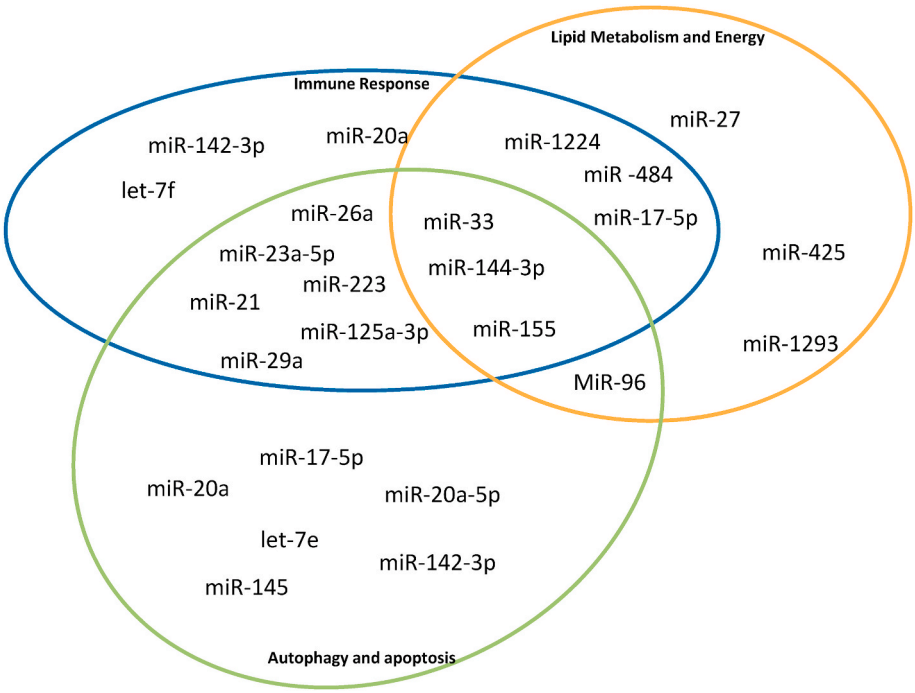

Fig 2. miRNAs involved in *Mycobacterium tuberculosis* (Mtb) immune escape mechanisms. Mtb modulates host immune responses, autophagy process as well as cell metabolism in the host cells by modulating the expression of many host cell miRNAs that target specific genes involved in these pathways.

enhancing the lipolysis machinery and preventing cholesterol efflux following miR-33 over expression (Ahluwalia et al., 2017; Najafi-Shoushtari et al., 2010).

miR-1224, a main regulator of lipid metabolism, is also up-regulated after Mtb infection in human macrophages (Alipoor et al., 2017, (Alipoor et al., 2018b). miR-1224 regulates the expression of lipid-related genes that are directly regulated by transcription factors such as SP1 (Niu et al., 2011).

Some of the other metabolic miRNAs also are reported to be influenced by Mtb infection (Fig. 2).

Infection of human monocyte derived macrophages (MDMs) with Mtb led to the release of a different subset of exosomal miRNAs including miR-1293, -425, −484, and −96 all of which were predicted to target metabolism and energy production-related pathways (Alipoor et al., 2017). miR-484 and miR-425 are the important regulators of metabolic pathway. miR-484 targets the mitochondrial fission protein 1 (Fis1) while mirR-425 has been associated with metabolic disorders (Wang et al., 2012) and its altered expression profile is linked to insulin resistance (Barwari et al., 2016). This cluster of dysregulated miRNAs modulates the central carbon metabolism (CCM) pathways. CCM converts carbon to energy via a complex of enzymatic steps (Alipoor et al., 2017) and has a determinant role in the pathogen adaptation to the intercellular milieu of the macrophages (Eisenreich et al., 2013). mir-96 is predicted to regulate peroxisome proliferator-activated receptors (PPARs) (Ahluwalia et al., 2017). PPARs are a group of transcription factors that play an essential role in glucose and lipid metabolism (Bouhlel et al., 2007). Mtb infection induces PPARγ in human macrophages (Arnett et al., 2018) probably via the regulation of miR-96.

Mtb also alters ketone body synthesis in host cells resulting in the accumulation of lipid bodies within macrophages (Singh et al., 2012). The cluster of dysregulated miRNAs released into exosomes from BCG-infected macrophages target genes involved in ketone body and amino acid synthesis, glycosaminoglycan biosynthesis and heparan sulfate/keratin sulfate metabolism pathways (Alipoor et al., 2017). Thus, Mtb may perturb the host miRNA network for the production of foam cells.

In summary, Mtb tolerates the hostile microenvironment inside the cells by re-pattering of the host metabolism to provide a lipid-rich niche. Understanding the host-pathogen interactions and cellular function is essential to provide greater understanding of Mtb pathogenesis.

4.2. Modulation of autophagy in host infected cells

Autophagy is a highly regulated process by which unnecessary and dysfunctional cellular components are degraded (Puleston and Simon, 2014). Autophagy is triggered by a variety of extra- and intracellular stimuli, such as nutrient starvation or oxidative stress and plays a central role in maintenance of cellular energy levels and nutrient supply during starvation (Jang et al., 2019). Furthermore, autophagy is used by cells to remove invading intracellular pathogens (also known as xenophagy) and is an essential innate immune mechanism to restrict intracellular growth of bacteria (Deretic, 2011). However, intracellular pathogens such as Mtb have developed mechanisms to inhibit or modulate the host autophagy response.

During the pathogenesis of Mtb, phagosomal maturation is arrested and the host immune defense pathways, particularly those engaged in autophagy and lysosomal function, are usurped (Kim et al., 2017). Secretion of the macromolecules protein-tyrosine phosphatase A (PtpA) and secreted acid phosphatase M (SapM) by Mtb, enables the bacteria to arrest autophagy by blocking phagosome maturation in infected macrophages (Bach et al., 2008).

It is unclearly how virulence factors of Mtb offset autophagy in infected cells, however, miRNAs have an important role in this process.

miR-30a; miR-33/33*; miR-17; miR-27a and miR-155 are the TB related dysregulated miRNAs that are involved in autophagy regulation. In continue we discuss the role of these miRNAs in the context of autophagy related pathways.

miR-30a regulates autophagy by inhibiting Beclin and autophagy related (ATG)5 expression and Mtb can induce miR-30a to escape intracellular elimination in macrophages (Wei et al., 2012).

miR-33/33* target autophagy-related genes and regulate autophagy (Ouimet et al., 2017). Silencing of miR-33/miR-33* promotes autophagy flux through modulation of key effectors including ATG5, ATG12, LC3 and lysosomal-associated membrane protein 1 (LAMP1) and the

transcription factor EB (TFEB) (Pastore et al., 2016). TFEB has crucial role in the transcriptional regulation of autophagy-related genes and activating innate immune responses (Ouimet et al., 2016). Interestingly; similar to miR 33; the Mtb mannose-capped LAM (ManLAM) suppress autophagy by reduction of the LC3 in phagosomal membranes. This suggests that ManLAM may tune miR-33 to control the autophagy in infected macrophages (Liang et al., 2017; Shui et al., 2012). This fits with the previously described role of miR-33/miR-33* in regulating lipid accumulation as autophagy delivers lipid droplets and cholesterol esters to lysosomes and promotes lipid catabolism (Ouimet et al., 2011). Together, this indicates that Mtb utilizes the host regulatory circuit to simultaneously impair xenophagy, increase fatty acid stores in lipid bodies and guarantee nutrient supply during macrophage infection (Ouimet et al., 2016).

miR-17 targets genes Mcl-1 and STAT3. Mtb infection inhibits the expression of this miRNA and so increases the expression of these target genes; thereby further perturbing autophagy (Kumar et al., 2016).

Another recent study demonstrated a role for miR-17 in targeting ULK1, an initial autophagy-related gene, resulting in the inhibition of auto-phagosome formation and host defenses against BCG (Duan et al., 2015).

miR-27a regulates calcium-associated autophagy by targeting ER-located Ca2+ transporter CACNA2D3 (La Rovere et al., 2016). miR-27a is highly expressed in Mtb-infected macrophages (Wang et al., 2017). Targeting of this transporter leads to the down-regulation of Ca^{2+}signaling, and inhibition of auto-phagosomes formation (La Rovere et al., 2016). Mice lacking of miR-27a are more resistant to Mtb infection suggesting that Mtb-induction of mir-27a may enhance intracellular survival through this strategy (Liu et al., 2018) (Fig. 3).

Mtb enhances the expression of **miR-155** in an ESAT6 (6 kDa early secretory antigenic target)-dependent manner which targets ATG3 and hijacks the autophagy process, promoting bacterial intracellular survival (Etna et al., 2018). In addition; Mtb infection attenuates IFNγ-induced autophagy in macrophages via an mTOR-responsive epigenetic process involving miR-155 induction (Fig. 3) (Holla et al., 2014). There are also other Mtb related disregulated miRNAs that have role in autophagy regulation (Fig. 2; 3).

Overall; autophagy is critical for the regulation of immune responses and macrophage defenses in Mtb infection. Regarding the importance of autophagy mechanism in the maintaining of intracellular homeostasis and immune defense, autophagy modulator agents offers host-based therapeutic opportunities for control of TB infection and represent promising candidates in the fighting against TB.

4.3. Modulation of host cell apoptosis following infection

Cellular apoptosis is one of the important defense mechanisms of macrophages against Mtb infection. The ability of Mtb to induce apoptosis by highjacking the host cell miRNA network has been the focus of much research. MPT64 secretion by Mtb inhibits the apoptosis of Mtb-infected macrophages. MPT64 induces bcl-2 expression by regulation of miRNA-21 and of the transcription factor nuclear factor kappaB (NF-κB) (Wang et al., 2014). MiR-223 and Mir-155 are the dis-regulated miRNAs with roles in apoptosis regulation.

miR-223 inhibits macrophage apoptosis by targeting FOXO3 (Xi et al., 2015). This miRNA that is up-regulated in active TB patients. Deletion of miR-223 increased susceptibility to lung infection in Mtb-resistant mice. In contrast, transfection of human macrophages (TDMs and MDMs) with a miR-223 antagomir inhibited apoptosis of these cells (Xi et al., 2015). Moreover, miR-21 overexpression triggers apoptosis in infected DCs by targeting Bcl-2 (Sims et al., 2017).

miR-155 inhibits monocyte apoptosis by targeting the transcription factor forkhead box O3 (FOXO3) (Huang et al., 2015; Yang et al., 2015). miR-155 is repeatedly reported to be increased in the serum of active TB patients (Ahluwalia et al., 2017; Etna et al., 2018; Ghorpade et al., 2012; Wang et al., 2011; Wu et al., 2012) (Supplementary Table 1). Additionally; there is a negatively association between the serum miR-155 level and NK cell toxicity against TB (Zhang et al., 2015a). Increased levels of miR-155 are seen in Mtb-infected macrophages and associated with decreased NO synthesis and increased mycobacterium load (Qin et al., 2016). In addition, lipomannan Mtb (TB-LM) treatment destabilizes TNF mRNA transcripts by enhancement of miR-125 expression and modulating the PI3K/Akt pathway (Rajaram et al., 2011).

Overall, Mtb prevents apoptosis of infected cells by dysregulation of miRNAs involved in regulating the apoptosis pathway. Understanding the role of miRNAs involved in the regulation of Mtb infection is important for host-directed therapies designed to control autophagy and apoptosis.

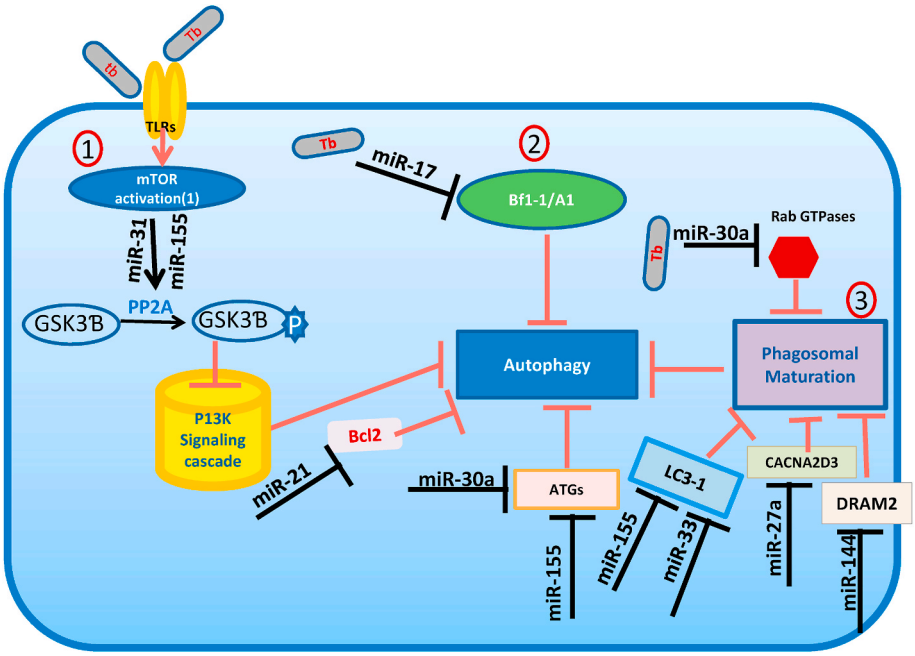

Fig. 3. Regulation of autophagy by *Mycobacterium tuberculosis* (Mtb)-mediated host cell miRNAs. (1)Mtb interacts with toll like receptors and induces mTOR activity through a series of downstream reactions. MTOR mediates epigenetic changes at Mir 155 and Mir 31 promoters and increase the expression of these miRNAs. miR-155 and miR-31 inhibit GSKB activity by targeting PP2A phosphatase and finally leads to suppression of autophagy. **2)** TB decreases the expression of miR-17 and up-regulates its target anti-autophagic factor, Bfl-1/A1 **3)**Mtb inhibits phagosome maturation by increase the level of several host miRNAs that impact autophagy-related genes and key effector proteins. MIR144 target autophagy protein DRAM2; miR-27a target ER-located Ca2+ transporter CACNA2D3 and suppress calcium-associated autophagy; mir-33 suppresses autophagy by reduction of the LC3 in phagosomal membranes.

4.4. Modulation of the host immunity response

The host immune response against mycobacteria invasion is mainly determined by host-pathogen interactions which play a crucial role in triggering the downstream signaling pathways (Wang et al., 2011). Exposure of the host immune system to Mtb leads to a complicated and multifaceted immune response that may result in latent infection, active disease or the complete clearance of the pathogen (Bettencourt et al., 2016). Pathogenic mycobacteria have evolved strategies to manipulate the host immune response to favor themselves by modulating host miRNAs involved in immune interactions. The cross-talk between human miRNAs and Mtb mRNAs may be important in determining the outcome of Mtb infection (Guo et al., 2010).

Mtb manipulates immune reactions by dysregulation of miRNAs involved in macrophage polarization or cytokine production. In this context miR-155; miR-26, mir-27, Mir-33, Mir −223, miR-1224 and let-7f have been shown with critical role. In continue we address the mechanism of these miRNAs in the context of immune pathways.

MiR-155 is involved in fine-tuning of immune responses by targeting several immune associated genes including SOCS1 and the TLR signaling adaptor TAB2 (Kim et al., 2017). miR-155 also play an important role in regulating T cell–dependent responses (Testa et al., 2017). Other miR-155 target genes include BTB and CNC homology 1 (Bach1) and SH2-containing inositol 5′-phosphatase (SHIP1). Bach1 represses the transcription of heme oxygenase-1 which is an activator of the Mtb dormancy regulon (Kumar et al., 2012) whilst SHIP1 inhibits Akt activation and thereby promotes intracellular Mtb survival within macrophages. In addition, miR-155-mediated inhibition of SHIP1 leads to the increased ROS production in BCG-infected macrophages (Wang et al., 2014a). Furthermore, miR-155 inhibits cyclooxygenase-2 and IL-6 expression, resulting in the suppression of the macrophage innate inflammatory responses (Kumar et al., 2012).

miR-155 also targets FOXO3 leading to inhibition of human macrophage apoptosis during Mtb infection (Huang et al., 2015). Moreover, miR-155-deficient mice show increased susceptibility and higher bacterial loads within the lungs compared with wild-type mice upon Mtb infection further illustrating the important role for miR-155 in host immune responses to Mtb (Iwai et al., 2015). In contrast, Mtb intracellular survival was decreased when mouse macrophages were transfected with miR-155 (Kumar et al., 2012).

miR-26a; **miR-27** and **miR-33** regulate macrophage polarization. M1 and M2 macrophages, extreme ends of macrophage polarization, are regulated by Kruppel-like factor 4 (KLF4) (Liao et al., 2011). During Mtb infection, down regulation of miR-26a promotes up-regulation of KLF4 and prevents trafficking of Mtb to lysosomes (Sahu et al., 2017). NOD2 and IRF4 are also important in macrophage polarization towards an M2 phenotype and the promotion of Mtb survival (Lawrence and Natoli, 2011) (Fig. 4). miR-33 has a putative binding site for the 3′-UTR of NOD2 whilst miR-27 targets the 3′-UTR of IRF4 (Ahluwalia et al., 2017) (see Fig. 5).

miR-223 controlled susceptibility to TB infection by targeting chemokine (C–C motif) ligand 3 (CCL3), chemoattractant chemokine (C-X-C motif) ligand 2 (CXCL2) and IL-6 in myeloid cells and thereby affecting their recruitment to lungs (Dorhoi et al., 2013).

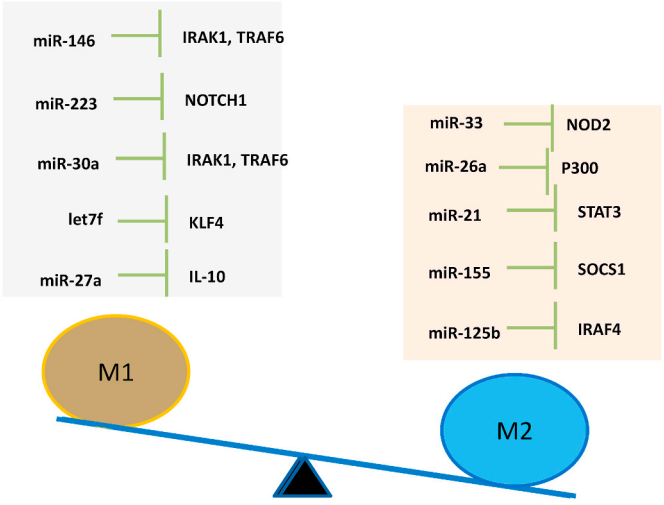

Fig. 5. The role of miRNAs in host macrophages polarization during *Mycobacterium tuberculosis* (Mtb) infection. M1 and M2 macrophages are the extreme ends of macrophage polarization, a process that is regulated by miRNAs. Modulation of host miRNAs by Mtb repattern host macrophages towards an immune-compromised M2 phenotype, supporting Mtb persistence.

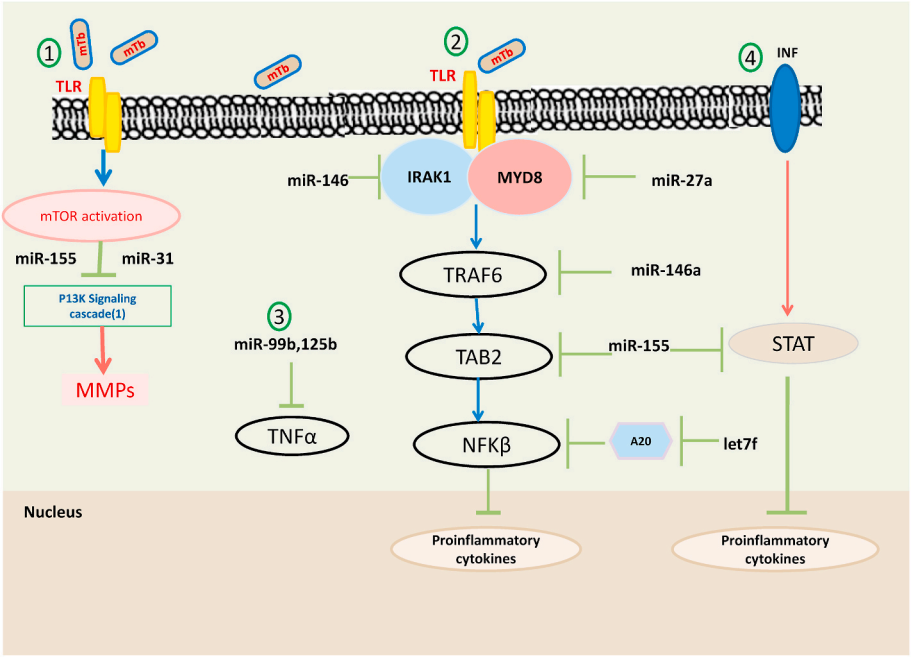

Fig. 4. *Mycobacterium tuberculosis* (Mtb) regulated miRNAs and the innate immune response. (1) Upon activation of TLRs; Mtb induces MTOR-dependent upregulation of miR-155 and miR-31; suppresses PI3K signaling cascade and increases the expression of MMPs. (2) TLR activation enhances the expression of miR-146a and miR-155 and miR-27a. These miRNAs negatively regulates signal transduction pathways leading to NF-κB activation and production of pro-inflammatory cytokines. In addition, miR-27a decreases production of inflammatory mediators by suppression of MyD88-dependent signaling pathway. (3)Mtb increases the expression of miR-99 and miR-125b and reduces TNF-α production. (4) INF binding to its receptor upon Mtb infection leads to STAT activation and its translocation into the nucleus to active the promoter of inflammatory cytokines. miR-155 inhibits STAT and suppress production of pro-inflammatory cytokine in this manner. All of these changes leads to a coordinated reduction in the production of various inflammatory cytokines and enhances bacterial survival.

let-7f is down-regulated in Mtb-infected macrophages. let-7f targets A20 which is a negative regulator of the NF-κB pathway (Kumar et al., 2015). Overexpression of let-7f in human macrophages reduces Mtb survival along with elevating levels of the inflammatory mediators TNF and IL-1β (Kumar et al., 2015).

miR-1224 has been involved in regulating inflammatory responses particularly by targeting tumor necrosis factor α (TNF-α) production. TNF-α plays an important role in promoting phagosome-lysosome maturation and thereby increasing T cell-dependent anti-mycobacterial response (Alipoor et al., 2018b). Other dysregulated miRNAs in the mycobacterium infection process may conflict immune responses. For example; miR-146a inhibits host innate responses and the production of iNOS and NO through targeting TRAF6 (Ghorpade et al., 2013) or miR-99 induced Mtb in DCs inhibits TNF-α production (Zhou et al., 2018) (Fig. 2; 3).

Interestingly; Mtb infection results in the release of membrane vesicles by macrophages. These vesicles induce the expression of GRAIL (a marker of T-cell anergy) in stimulated $CD4^+$ T-cells, reduced IL-2 production and consequently decreased the activation and proliferation of $CD4^+$ T-cells inducing anergy (Athman et al., 2017). This may reflect the transfer of miRNAs between cells by the microvesicles.

Mtb also is able to drive a tissue destructive phenotype to facilitate its transmission. In this regard, Mtb perturbs host regulatory and signaling pathways to increase matrix metalloproteinase-1 (MMP-1) by modulating the PI3K/AKT/mTORC1 pathway (Brace et al., 2017). Blockade of PI3Kδ (a subunit of the PI3K pathway) increases MMP-1 expression and importantly, the expression of PI3Kδ is not detected in granulomas from TB patients which may reflect TB accumulation inside granulomas (Brace et al., 2017). Interestingly, we have recently found a cluster of miRNAs including miR-1224, -1293, −425, −484 and −96 that are dysregulated upon Mtb infection in human macrophages (Alipoor et al., 2017). These dysregulated miRNAs are mostly involved in the regulation of MMP and P13K-associated pathways (Alipoor et al., 2017) emphasizing that Mtb may interfere with MMP inhibitory pathways in infected macrophages via modulating of host miRNA networks (Alipoor et al., 2017).

Furthermore; miRNAs are the important regulators of developing MDR –TB. Membrane transporter proteins which are responsible for uptake or efflux of drugs are regulated by miRNAs. miR-155 and miR-33 are the key miRNAs affected by Mtb infection; have critical role in the regulation of ATP-binding cassette (ABC) transporter family proteins (Gago et al., 2018; Xie et al., 2018). These family of proteins active drug resistance by pumping drugs out the cell and hydrolyzing of ATP. Thus; Mtb could influence the drug response mechanisms by altering the level of the host miRNAs. Additionally 26 Mt b genes may be targeted by human miRNAs expressed in the lung and by human macrophages. These include genes involved in drug-resistance and bacterial survival such as rpsL, hspR, grpE, dnaJ1 and sodC (Guo et al., 2010; Kurt and Acar, 2015).

Single nucleotide polymorphisms (SNPs) occurring in the miRNA gene region particularly within miRNA seed sequences could alter miRNA target selection or expression level resulting in functional changes (Moszyńska et al., 2017) and susceptibility to TB infection. rs2910164 (miR-146a G > C) and rs3746444 (miR 499 T > C) are involved in the regulation of TLR signaling pathway-associated genes and are associated with increased TB risk in some of Chinese populations (Li et al., 2011; Zhang et al., 2015b). Additionally, rs3742330 A > G within miR-632 was associated with a decreased susceptibility to TB in another Chinese cohort (Song et al., 2013). However, no association was observed between these SNPs and TB risk in Iranian subjects (Naderi et al., 2015; Wang et al., 2016).

5. The potential of miRNAs as biomarkers in TB diagnosis

The diagnosis of TB is hampered by the limited specificity and sensitivity of current diagnostic assays. The early detection of TB is the crucial step in controlling the disease and is essential to prevent the spread of infection. Thus, introducing novel biomarkers would be highly valuable in TB control. On the other hand; monitoring miRNA profiles in TB patients before and after therapy could be valuable. There is evidence of an association between changes in miRNA profiles and the response to therapy. Hence, the miRNA profile in serum may act as a potential biomarker for diagnosis as well as monitoring the therapy process in TB and MDR patients.

For example, serum levels of miR-125a-5p is up-regulated compared with down-regulation of miR-21–5p, miR-92a-3p and miR-148 b-3p in TB patients who respond optimally to therapy (Wang et al., 2018). Furthermore, miR-155 (Wagh et al., 2017) and miR-29a (Corral-Fernández et al., 2017) were up-regulated and miR-326 was down-regulated after directly observed treatment short-course (DOTS), and their expression correlated with diminished Th1 responses (Corral-Fernández et al., 2017). Additionally; the serum level of miR-16 was lowest in multi-drug resistant (MDR) TB patients who are resistant to treatment with at least two first-line anti-TB drugs, compared with treated patients, TB-treatment naïve and healthy subjects (Wagh et al., 2017).

Interestingly; the functional miRNAs may be packaged inside exosomes and shuttle to other cells and induce transcriptomic and functional changes in target cells (Alipoor et al., 2016d) and may act as potential biomarkers for TB (Kruh-Garcia et al., 2015). For example, the level of exosomal miR-484, miR-425, and miR-96 in the serum of TB patients correlated with infection status and demonstrated a measure of diagnostic potency (Alipoor et al., 2019).

Hence; the combination of miRNA measures along with conventional diagnostic markers may improve our ability to diagnose and monitoring of TB.

However; these procedure faces challenges. The main challenge in this context; is the lack of reproducibility as well as poor diagnostic specificity of the identified miRNAs. Despite a large number of studies there is no consistency in the miRNA signatures reported (Supplementary Table 1) (Wallis et al., 2013). These differences may be due to differences between the source of samples e.g. serum or plasma (Backes et al., 2016). Several studies have shown that blood miRNAs may originate from different organs in both healthy subjects and patients and miRNAs from venous and arterial plasma have different expression profiles which are also different from that in tissues (Xu et al., 2017). Furthermore, the age of the patients studied and the presence of multiple comorbidities influence the expression of circulating miRNAs (Backes et al., 2016). In addition, the sampling method including the preservation and the processing of the samples can lead to inconsistency in the results (Lan et al., 2015), which demands that protocol standardization becomes established. The sample size in any biomarker discovery cohort is important and affects the variability in the reported results. The cohort size in a biomarker study should represent the population and so a large enough cohort size should to be chosen to be able to differentiate the healthy and diseased status (Moldovan et al., 2014).

6. miRNAs as potential treatments for controlling TB

Due to the clear role of miRNAs in determining the fate of TB infection, there is a growing interest in targeting specific miRNAs in TB. Thus, miRNAs delivered to lung may modulate lung immunity against microbial infections and offer an exciting avenue for the control and treatment of TB. However, a possible limitation is that delivery of exogenous miRNA may have off-target effects since each miRNA targets multiple mRNAs. Notwithstanding, nanoparticle-mediated delivery of miRNAs to macrophages and DCs and other techniques that can package miRNAs for cell delivery are being tested for TB (Zhou et al., 2013).

These novel therapeutic approaches will include delivery of miRNAs that are significant determinants of TB infection including miR-155, miR-146a, miR-27a, mir-20 or miR-33/33* (Kleinsteuber et al., 2013; Ouimet et al., 2017; Wang et al., 2017). MiR-155 is most reported

miRNA in TB and its biology is complex with many pathways implicated in the control of TB infection (Table 1). For example this miRNA suppress the activity of NK cells against Mtb (Zhang et al., 2017). On the other hand, miR-155 also targets Ras homolog enriched in brain (Rheb) and inhibits autophagy in infected macrophages (Wang et al., 2013).

Silencing miR-33/33* enhances autophagy activation (Ouimet et al., 2016, 2017). miR-23a targets TLR2/MyD88/NF-κB pathway-associated genes which modulate autophagy induction and promote Mtb survival suggesting this as a potential target in TB therapy (Gu et al., 2017). miRNAs involved in innate immunity or that target cytokine-associated genes could also be considered as miRNA-based therapies. For example, miR-99b inhibits the secretion of pro-inflammatory cytokines in Mtb infection (Singh et al., 2013) whilst miR-20b reduced the inflammatory response of TB in vivo by targeting the NLRP3/caspase-1/IL-1β pathway (Lou et al., 2017).

Anti-miR-mediated silencing of miRNAs is currently suggested as a powerful technology for the treatment of infectious diseases (Sethupathy, 2016). For example; miravirsen, a locked nucleic acid (LNA)--modified anti-miR-122 oligonucleotide, has been approved for HCV infection. (Gebert et al., 2014). However; there are several challenges need to be overcome for translation of the current research on miRNA drugs from the bench to the beside. First of all, due to their targeting of multiple genes, their inhibition could have systemic effects (Alipoor et al., 2016b). Secondly, despite a large number of differentially expression miRNAs, few of these are expressed at sufficiently high levels to make suitable targets for therapeutic purposes. Conversely, many of them belong to miRNA families with similar seed regions that may provide additional opportunities since anti-miRs are not able to differentiate between miRNAs with similar seed regions under the physiological conditions (Nauser and Stites, 2001). Thirdly, chemical modifications of oligonucleotides is necessary to increase their affinity and specificity which is known to induce dose dependent toxicity (Li and Rana, 2014). For example, miravirsen prolongs clotting time and triggers activation of the alternative complement pathway at high doses in monkeys (Hildebrandt-Eriksen et al., 2012).

In vivo delivery of miRNAs is also possible using lentiviral vectors, exosome-like small vesicles or lipid conjugates (Sabir et al., 2018). In a study by Rosas-Taraco, targeting TGF-β1 by delivery of siRNA to the lung, enhanced the antimicrobial capacity of Mtb-infected mice (Rosas-Taraco et al., 2011). However, these novel approaches for miRNA delivery require validation before the optimal conditions are determined for any future miRNA-based therapy of TB. Recent advances in gene delivery methods may open an exciting avenue for development of host directed therapies (HDT) based on specific miRNAs.

The local pulmonary delivery via inhalation route also can be more advantageous for TB treatment. Inhaled lung delivery of miRNAs warranties high delivery efficiency with a lower dose and minimal loss of drug and so is more cost-efficient. On the other hand; inhaled drugs are used routinely in the variety of pulmonary pathological conditions and several specified inhalation devices are currently used for this purpose (Ari and Fink, 2020). However this strategy faces challenges in the case of miRNAs delivery including choosing a suitable carrier to protect miRNAs from degradation during preparation process, potential systemic side effects, the determination of the precise pharmacokinetics of miRNAs after intrapulmonary administration as well as lung inflammatory and toxicological responses caused by the delivery vehicle. However; an inhaler dry powder formulation of nanoparticles loaded with siRNA has been shown promising results in invirto gene silencing **(**Jensen et al., 2012**).** These delivery technologies could provide us new avenues for translating lung delivery of miRNAs via inhaler drugs in clinical use.

7. Conclusion

TB is one of the most deadly infectious diseases worldwide. Despite the substantial advances in TB control, the diagnosis and treatment of the disease remains a challenge due to its prolonged survival inside macrophages. Macrophages are the main player in the host immune defense against Mtb infection and their function is highly regulated by miRNAs. A substantial number of studies have confirmed the key role of selective miRNAs such as miR-155 and miR-33/33* in the modulation of immune responses against Mtb and the miRNA expression pattern is associated with disease progression and latency.

miRNAs play important role in the pathogenesis of Mtb infection by regulation of autophagy or apoptosis in infected cells and by exploiting the host's energy and metabolic pathways. The modulation of the host cell miRNA profile upon infection with mycobacterium is driven by the pathogen. However, the mechanism(s) by which bacterial virulence factors influence the regulation of miRNA expression towards preventing immunodetection is unclear. Future studies on miRNA expression and function in TB may provide greater understanding of Mtb pathogenesis and direct towards better diagnostics and/or novel treatment modalities.

Abbreviations

ATG3	Autophagy Related 3
BACH1	BTB Domain And CNC Homolog 1
BCG	Bacillus Calmette–Guérin
Bcl-2	B-Cell CLL/Lymphoma 2
BMDM	Bone marrow-derived macrophages
DC	Dendritic cell
FOXO3	Forkhead box O3
IFN	Interferon
IL	Interleukin
IRAK-1	Interleukin-1 receptor-associated kinase 1
LTB	Latent tuberculosis
MDM	Monocyte-derived macrophage
Mtb	*Mycobacterium tuberculosis*
MyD88	Myeloid Differentiation Primary Response Gene 88
NF-κB	Nuclear factor kappaB
NO	Nitric oxide;
N-WASP	Neural Wiskott-Aldrich syndrome protein
PBMC	Peripheral blood mononuclear cells
PPD	Purified protein derivative of tuberculin
PTB	Pulmonary tuberculosis
Rheb	Ras Homolog Enriched In Brain 2
ROS	Reactive oxygen species
RT-qPCR	Reverse transcription – quantitative polymerase chain reaction
SHIP1	SH2 Domain-Containing Inositol Phosphatase 1
TB	Tuberculosis
Th17	Type 17 T-helper cell
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor alpha
TRAF6	Tumor necrosis factor receptor (TNFR)-associated factor 6
Th1	Type 1 T-helper cell

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejphar.2020.173529.

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