Discovery Immunology, 2026, **5**, kyag014
https://doi.org/10.1093/discim/kyag014
Published: 2 July 2026
Research article

Distinct lipid transport proteins are regulated by innate immune stimuli

Lydia P. Tsamouri[†], Najd M. Aljadeed, Antoni Olona[‡] and Paras K. Anand [*]

Department of Infectious Disease, Faculty of Medicine, Imperial College London, London UK
*Corresponding author. Paras K. Anand, Department of Infectious Disease, Imperial College London, The Commonwealth Building, Du Cane Road, London W12 0NN, UK. E-mail: paras.anand@imperial.ac.uk
[†]Current address: Pharmacology Program of the Weill Cornell Graduate School of Medical Sciences, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
[‡]Current address: Programme in Cardiovascular and Metabolic Disorders, Duke-NUS Medical School, Singapore.

Abstract

Introduction **Lipid transport plays a critical role in the distribution of lipids across subcellular compartments. This is pivotal during infection and other stress stimuli that increase metabolic demands. While lipid biosynthesis is regulated by immune stimuli, whether immune signalling also influences lipid transport mechanisms remains unexplored.**

Methods **We examined the effect of TLR and IFN-γ signalling on the gene expression of lipid transport proteins in human monocytic THP-1 cell line and compared these responses with those in primary bone marrow-derived mouse macrophages.**

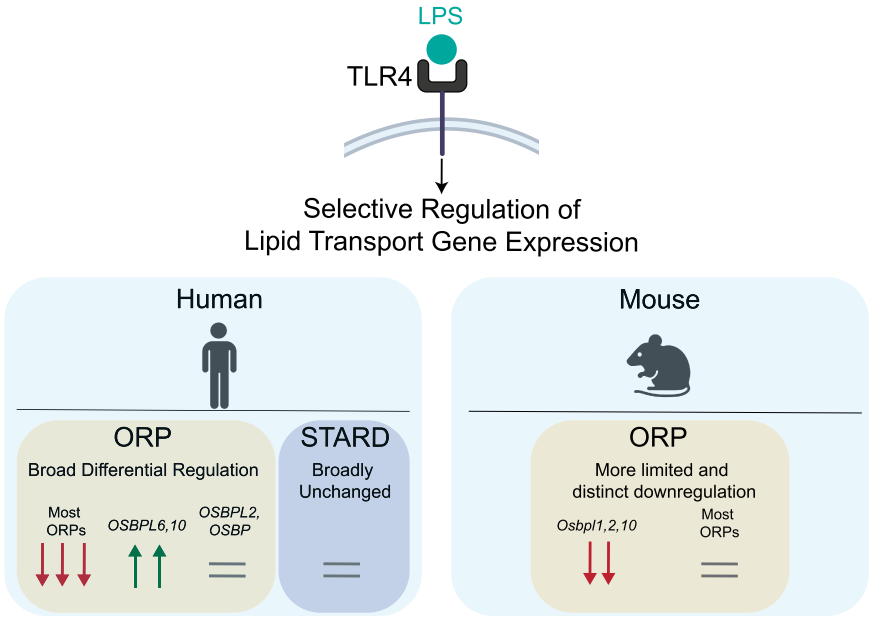
Results **Our data demonstrate that TLR4 signalling selectively modulates the expression of oxysterol-binding protein-related proteins (ORPs), a key family of proteins that transport lipids between organelles. Remarkably, TLR4 activation led to the downregulation of several ORP family members in human THP-1-derived macrophages. However, this response was less profound in mouse macrophages. In contrast, the expression of steroidogenic acute regulatory domain (STARD) proteins, many of which transport lipids between mitochondria and other compartments, exhibited no statistical difference. Moreover, IFN-γ, a cytokine that plays a key role in the immune response, did not considerably impact human ORP or STARD expression levels, either alone or in combination with LPS.**

Conclusion **Together, these results reveal that TLR signalling exerts selective and critical control over lipid trafficking pathways with important biological differences. These findings provide new insights into the crosstalk between immune signalling and lipid metabolism, which may offer novel targets to treat diseases characterized by dysregulated lipid pathways.**

Keywords lipids, lipid transport proteins, ORP, STARD, immune signalling

Received: 23 October 2025. **Revised:** 15 May 2026. **Accepted:** 19 June 2026

Graphical Abstract



Introduction

Lipids play a fundamental role in diverse cellular functions supporting the structural and energy needs of all cells [1, 2]. Additionally, lipids are critical to intracellular signalling and serve as second messengers. In particular, lipid metabolism in immune cells is dynamically rewired in response to cues sensed during infection and other stress stimuli [1, 3]. For example, cytokines like IFN-γ, a key modulator in immune responses, have been shown to influence lipid metabolism by decreasing cholesterol efflux and modulating lipid availability, thereby shaping immune cell activation and function [4, 5]. These shifts in metabolic pathways allow immune cells to meet the increased demands for effective defence [6]. They also help counter homeostatic imbalances during infection and stress. Consequently, lipids not only support cellular signalling but also reprogramme in response to immune cues to enhance host defence, drive inflammatory signalling, and maintain homeostasis.

While the impact of TLR signalling on lipid metabolism has been explored, it remains unclear whether immune signalling directly influences the mechanisms governing lipid trafficking, particularly through lipid transport proteins. Given their essential roles in cellular function, lipid transport mechanisms are integral to immune cell activity. These pathways maintain lipid distribution across compartments, enabling quick metabolic adjustments when required. Moreover, lipid metabolism is being increasingly recognized as a key target influenced by immune signalling, including through the TLR pathway [7]. TLR recognition of pathogen-associated molecular patterns initiates cascades leading to the activation of NFKB and MAP-kinase transcription factors, which in turn regulate the expression of a variety of genes [8]. Published research indicates that TLR signalling influences lipid metabolism in varied ways [9–11]. TLR ligation modulates pathways that activate SREBPs and LXRs, key transcription factors involved in lipid metabolism [12–15]. These transcription factors govern lipid biosynthesis and efflux, orchestrating the size of the cholesterol pool based on cellular demand. This is particularly evident in the case of TLR4 ligation by bacterial LPS, resulting in increased cholesterol biosynthesis to support the high lipid demands of immune cells under stress [16, 17]. Thus, there is a significant association between lipid metabolism and immune pathways. This crosstalk underlies the pathogenesis of several infectious and metabolic diseases. However, it remains unclear if immune signalling has a direct impact on the mechanisms that facilitate lipid movement between cellular compartments.

Here, we wanted to investigate whether TLR signalling differentially regulates lipid transport proteins under widely accepted and standard activation conditions used in the literature. Our objective here was not pharmacodynamic characterization, but rather to compare transcriptional modulation of these gene sets under relevant and well-established inflammatory conditions. We particularly focused on two families of lipid transport proteins, the oxysterol-binding protein-related proteins (ORPs) and steroidogenic acute regulatory domain (STARD) proteins. Understanding these regulatory mechanisms may reveal novel therapeutic targets for immune and metabolic diseases. The transfer of lipids across membranes is predominantly dependent on vesicular transport, lipoprotein-mediated transport, and lipid transfer proteins [18, 19]. Lipid transport proteins, in particular, are essential for the movement of lipids at membrane contact sites where organelles come close together but may not physically fuse. The major lipid transport protein families include oxysterol-binding protein-related proteins (ORPs), steroidogenic acute regulatory domain (STARD) proteins, and GRAMD proteins [18]. The ORP proteins are a key family of 12 members that mediate the non-vesicular transport of sterols and phospholipids between organelles, such as the ER and the plasma membrane [20][19, 20]. ORPs are classified into six subfamilies (I-VI) based on structural similarities and domain architecture (Supplementary Figure S1). Each ORP features a conserved oxysterol-binding protein-related domain (ORD), responsible for their lipid transport function, and additional accessory domains that mediate localization and specificity. For example, pleckstrin

homology (PH) domains enable ORPs to tether to specific lipid pools within membranes by recognizing phosphoinositide lipids. Several ORPs contain FFAT (two phenylalanines in an acidic tract) motifs, which facilitate interactions with the ER membrane. Additionally, ORP5 and ORP8 contain transmembrane (TM) domains that anchor them to specific organelles, enhancing their functional versatility. The diversity in lipid-binding preferences and the presence of accessory motifs confer unique roles in cellular lipid homeostasis [21, 22]. The STARD protein family, in contrast, primarily facilitates intracellular cholesterol movement to mitochondria, supporting synthesis and energy metabolism [23, 24]. The concerted effort of lipid transport proteins ensures precise distribution of lipids across cellular compartments, enabling cellular adaptability to metabolic demands and external stimuli.

Given the central role of lipid transport proteins in maintaining cellular lipid homeostasis, understanding how TLR signalling modulates these proteins is critical to uncovering the broader impact of immune signalling on lipid metabolism and its implications for disease. There is evidence suggesting that the interaction of TLR signalling with lipid transport is relevant to immune cell function [9]. For example, ORP proteins have been shown to modulate key proteins involved in cholesterol efflux from cells [25]. Despite these preliminary suggestions, whether TLR signalling regulates lipid transfer proteins remains unexplored. In this study, we demonstrate that TLR signalling specifically regulates the gene expression of ORP proteins. By contrast, the regulation of STARD family members remains unaffected. Furthermore, we identify differences in the magnitude of lipid transport gene regulation between human and mouse macrophage cell types. Our findings expand our understanding of immune-regulated lipid metabolism, which has the potential to identify therapeutic targets for lipid-related disorders and metabolic diseases.

Materials and methods

Ethical statement

All procedures on animals were performed under appropriate personal and project licenses (PPL number: PP4111881). The procedures were carried out in accordance with the Animals (Scientific Procedures) Act 1986 and were approved by the Imperial College Animal Welfare and Ethical Review Body (AWERB) and the UK Home Office.

Macrophage cell culture

WT C57BL/6J mice were obtained from Charles River, UK. The *in vitro* experiments used male and female mice in similar proportions, ranging in age from 8 to 12 weeks old. Bone marrow cells were obtained from the femurs and tibias from the mice and allowed to differentiate into bone marrow-derived macrophages as described previously [26, 27]. THP-1 monocytic cell line (ATCC, Catalog #: TIB-202; RRID: CVCL_0006) was maintained in RPMI-1640 medium containing 10% FBS, 2 mM L-glutamine, 1% penicillin-streptomycin, 4.5 g/L glucose, 1% HEPES, and 0.1% 2-mercaptoethanol. THP-1 cells were differentiated into macrophages by culturing them in RPMI-1640 medium supplemented with 20 nM phorbol-12-myristate-13-acetate (PMA) for 24 h.

Peripheral blood mononuclear cells (PBMC) were isolated from single-donor leukocyte cones purchased from the National Blood Transfusion Service (Colindale, UK) by density gradient centrifugation using Histopaque gradient separation (Sigma-Aldrich, Catalog #: H8889). The obtained peripheral blood mononuclear cells were resuspended in RPMI-1640 medium, and monocytes were obtained by adhesion purification after 2 h at 37°C and 5% CO_2. The monolayer of the adherent peripheral blood mononuclear cells was washed 2x with HBSS to remove non-adherent cells. The cells were subsequently differentiated into human monocyte-derived macrophages (hMDMs) using 100 ng/ml macrophage colony-stimulating factor (PeproTech, catalog #:315-02) supplemented with 10% FBS, for 5 days. The macrophage purity was confirmed by immunohistochemical assessment of CD68.

Cell stimulations

BMDMs were seeded in 24-well or 12-well plates at densities of 0.5×10^6 and 1×10^6 cells per well, respectively. THP-1 cells were seeded in 24-well or 12-well plates at densities of 1×10^6 and 2×10^6 cells per well, respectively. Following macrophage differentiation with PMA (20 nM, 24 h), THP-1 macrophages were washed and maintained in fresh PMA-free medium for an additional 24 h prior to any treatment. The concentrations of the stimuli used were selected based on prior studies demonstrating their ability to induce TLR signalling. For certain experiments (Figs 3 and 4a, and 4b), BMDMs and THP-1 macrophages were treated overnight with either recombinant mouse IFN-γ (50 ng/ml; Sigma-Aldrich) or human IFN-γ (50 ng/ml; Sigma-Aldrich), respectively [4, 28]. BMDMs and THP-1 macrophages were treated with 'ultrapure' LPS (500 ng/ml; Invivogen, Cat # tlrl-pb5lps) for 6 h. THP-1 macrophages were stimulated with various TLR ligands; PAM3 (500 ng/ml; Invivogen), poly I:C (1 μg/ml; Invivogen), and imiquimod (3 μg/ml; Invivogen) [29–32]. Poly I:C was administered extracellularly without the use of transfection reagents. Experiments with LPS were independently repeated and are included as a reference control in Fig. 2 and 4.

Real-time quantitative PCR

Cells were lysed and RNA was isolated using TRIzol (T9424; Sigma-Aldrich) according to the manufacturer's instructions. A total of 500 ng of RNA was then reverse transcribed in a Bio-Rad thermocycler using the High-Capacity cDNA Reverse Transcription Kit (4368814; Applied Biosystems), according to the manufacturer's instructions. Real-time PCR was then performed using gene-specific primers (Table 1) and PowerUp SYBR Green Master Mix (A25741; Applied Biosystems). Real-time PCR was performed in a ViiA 7 Real-Time PCR System (Applied Biosystems).

RT-qPCR data analysis

The ΔΔCt algorithm [33] was used in order to relatively quantify the data obtained from the RT-qPCR experiments. GAPDH was used as a housekeeping gene for all experiments, as it was uniformly and constantly expressed in all samples, across all treatments. When comparing gene expression between hMDMs and THP-1 macrophages in Fig. 1, no normalization methods were employed. This approach allowed us to directly compare gene

Table 1 Primers used for RT-qPCR.

Gene	Accession number	Primers (5′ to 3′)	
		Forward	Reverse
OSBPL1A	NM_080597	AGAGCAGTCTCTGGTGAAAGGC	TCAAAGGAGCGTGCTGTCACTG
OSBPL2	NM_144498	AGAGGTGACCACCTGAGAAAGG	GTTGATCCTCCAGAGCAGCTTG
OSBPL3	NM_015550	GTGGAAAAGCGGTTCATCGGCT	CTCGTAGCCTTTCGGCATAGGA
OSBP2	NM_030758.4	CAGCCTTAACCTCTGGAGCATC	TGGTACTCCAGGTCCTCTGTCA
OSBPL5	NM_020896	CAGACTGACAGCCGCACATTCT	ACCTGGACTTGGCTGTGATGCT
OSBPL6	NM_032523	CACCTCACTGACCCTCTGGAAA	CTCGGAAACCATCTGCTTCAGC
OSBPL7	NM_145798	CACACGGAGTTCTTCGATGCCT	AGGTCCAGCATCTCCTCAGACA
OSBPL8	NM_020841	GAGCCATGAAGAACTTGGAGAGG	AGGCAGAACCACCTTGGATAGG
OSBPL9	NM_148909	AGTCAGAGCAGCGTCCATCTTC	AGTGAGACTGCTACTCGGTGGT
OSBPL10	NM_017784	AGAAGCCAGGAGCCTCGGAAAA	GGTTATGTTGGCACTGGCTGATG
OSBPL11	NM_022776	AGACCTCTGGAGAAGCAGGATC	CGATGCCTTTCTTCAGTCCTCTG
OSBP	NM_002556	CTGGACCGATTAGAGGAGAATGG	TTTCCTGACGCAATGTCCAGCC
STAR	NM_000349	TACGTGGCTACTCAGCATCGAC	TCAACACCTGGCTTCAGAGGCA
PCTP	NM_021213	GATCGAGAGTGACGGCAAGAAG	GTTCTGACAGGCTCTTGCCATG
STARD3	NM_006804	CTTCATCTCCCTGCTCTGGATC	AGCAGTCCAGAGAAGCGGAAGA
STARD4	NM_139164	CGTTACACTACTGCTGGTCAGC	GGTCTCTTTTCATCCCAGTCAAG
STARD5	NM_181900	CGAAGCCAGGTTTTGTGAGAGG	TTCTGTGGGAGGTAACCGCTGA
STARD6	NM_139171	TTCCTCTACCAAACTGGAGACAG	GGAAATGGAGCCCACGGCAAAA
STARD7	NM_020151	ACAGATGTGACACCTCGGCAGT	CACATCCCTCTCAATCACCTCC
STARD8	NM_001142503	GCCGAGGAAAACCAGATGACAG	TGCCAATGAGGCTGCGTTTGCT
STARD10	NM_006645	ATGGATCGGACGCTGCACAAGA	ACGTCAGCGTTGACTGTCAAGC
CERT1	NM_005713	TTGGTAAGCCCACCAGAGGGAA	GGATACTCTCGCTTTGCCACTG
DLC1	NM_182643	GGACAGAGATGCCATTGAGGCT	CACAAGGCTCATCCTCGTCTGA
STARD13	NM_052851	GCTGTCTTTGGCGTTCCTCTCA	CGAGACTTCACTCCTGATTTGCG
ACOT11	NM_015547	TCTGGTGCTCAAAGCCATCGTG	TCATCTGCGTCCAGGACCACAA
ACOT12	NM_130767	GGAGGTTACCAGCACTGTGGAA	GCCAAATGTGCTGGACTTCCCA

expression differences while avoiding any potential biases introduced by data normalization methods. To maintain consistency in data acquisition, the PCR conditions were kept identical across species and throughout the study. The expression of all ORPs and STARDs was expressed in arbitrary units as stated in figure legends with or without $\log_{10}$ fold change (FC).

Statistical analysis was performed using GraphPad Prism, by unpaired, two-tailed *t*-test or ANOVA (Figs 2 and 3, and 4). The level of significance was set at $P \leq 0.05$ and where *, $P \leq 0.01$; **, $P \leq 0.001$; ***, $P \leq 0.0001$; ****, $P \leq 0.0001$. The number of replicates of each experiment is indicated in the figure legends ($n = x$). Values are given as mean ± standard error of the mean (SEM), from *x* independent experiments, as indicated.

Data and code availability

All raw data reported in this paper will be shared by the lead contact upon request. This paper does not report original code. Any additional information required to reanalyse the data reported in this paper is available from the lead contact upon request.

Results

ORP proteins are constitutively expressed and are modulated in response to TLR ligation

Lipids participate in various cellular functions and have been associated with inflammatory signalling. The distribution of lipids across cellular organelles is a key determinant of organelle function and signalling emanating from subcellular compartments. However, whether lipid transport proteins are regulated by immune signalling remains ambiguous. To investigate whether the individual members of the ORP family of proteins are constitutively expressed, we measured their expression in primary human monocyte-derived macrophages (hMDMs) by RT-qPCR. All ORP family members showed detectable expression levels (Fig. 1a). Correspondingly, THP-1 differentiated macrophages showed a similar expression pattern of ORP members, compared to that observed in hMDMs (Fig. 1a). However, when comparing the two cell types, hMDMs displayed significantly higher expression levels for most ORPs, except *OSBP2, OSBPL5*, and *OSBPL7*, which showed comparable expression between hMDMs and THP-1 macrophages (Fig. 1a). A correlation analysis confirmed a strong positive relationship in the expression of ORP family members between the two cell types ($r^2 = 0.7414$, $P = 0.0003$), validating THP-1 macrophages as a suitable model for subsequent experiments (Fig. 1b).

Next, we investigated whether TLR4 signalling regulates the expression of ORP family members. We aimed to investigate these changes under relevant and well-established inflammatory conditions used in the literature to compare transcriptional modulation of these gene sets. THP-1 macrophages treated with LPS (500 ng/ml), a TLR4 agonist, for 6 hours demonstrated significant upregulation of the downstream NF-kB-dependent genes in the pathway, such as *TNFA* and *IL6* (Fig. 1c, d). LPS stimulation exhibited significant downregulation of most ORP family members compared to untreated controls (Fig. 1e). Notably, the expression of *OSBP2* and *OSBP* was not altered (not shown) while the relative expression of *OSBPL6* and *OSBPL10* was significantly upregulated (Fig. 1e). These results indicate that TLR4 signalling selectively and differentially regulates the expression of ORP family members.

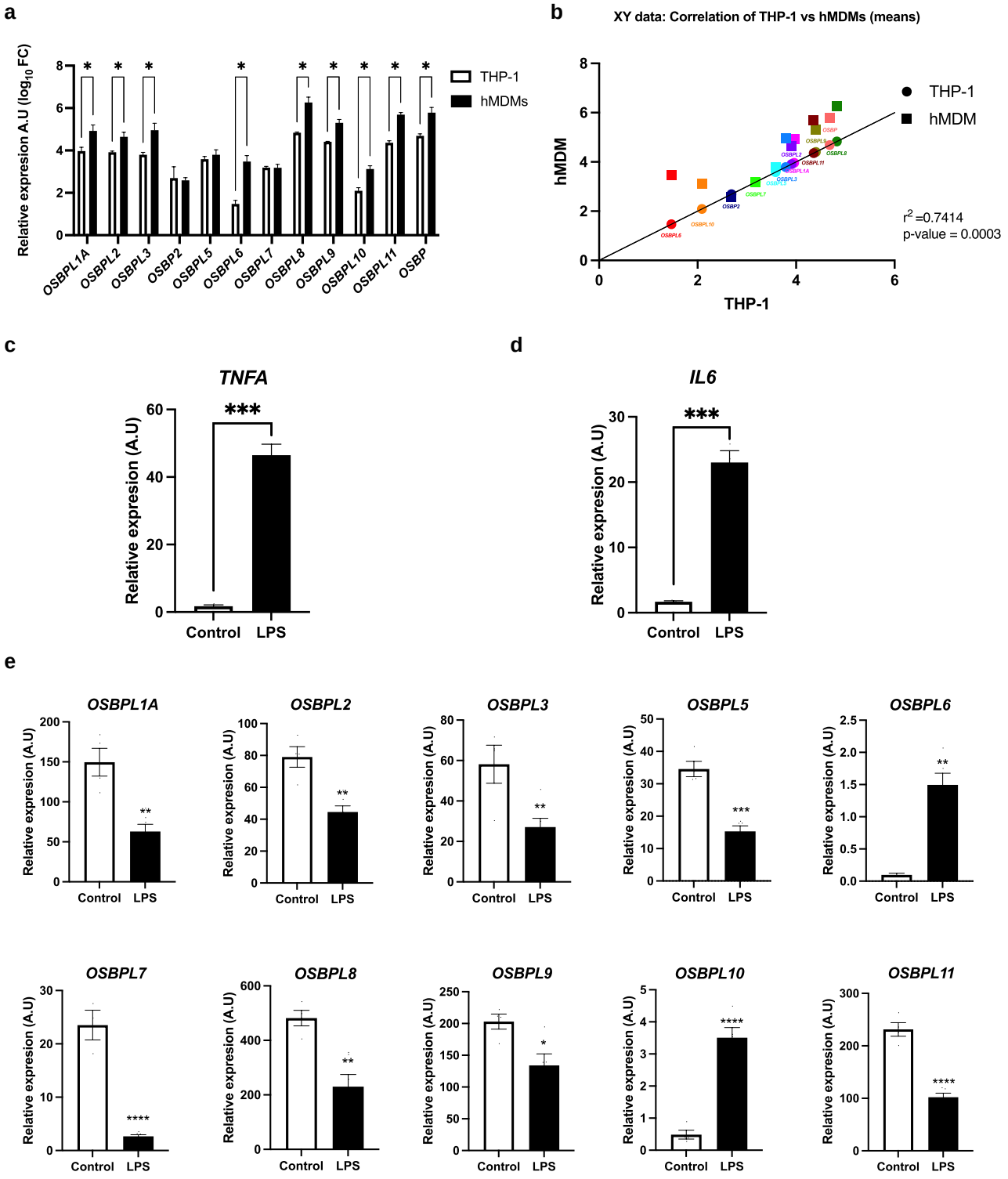


Figure 1 ORP proteins are constitutively expressed and are modulated in response to TLR ligation. (a) Gene expression of all 12 ORP family members as determined by real-time qPCR in hMDMs and THP-1 macrophages. (b) Correlation analysis of ORP family members between hMDMs and THP-1-differentiated macrophages. (c,d) *TNFA* and *IL6* expression in THP-1 macrophages either left untreated or treated with LPS (500 ng/ml) for 6 h. (e) THP-1 differentiated macrophages were either left untreated or treated with LPS (500 ng/ml) for 6 h. RNA was extracted and converted to cDNA. Gene expression of all 12 ORP family members was determined by real-time qPCR and is shown as arbitrary units. Error bars represent SEM. The statistical analysis of the data was performed using the Student's *t*-test where *, $P \leq 0.01$; **, $P \leq 0.001$; ***, $P \leq 0.0001$; ****, $P \leq 0.0001$. In panel d, each ORP is denoted by a different color. In panel b, significance was calculated between each gene in the two cell types, and in panel e, significance was calculated against the control, untreated group.

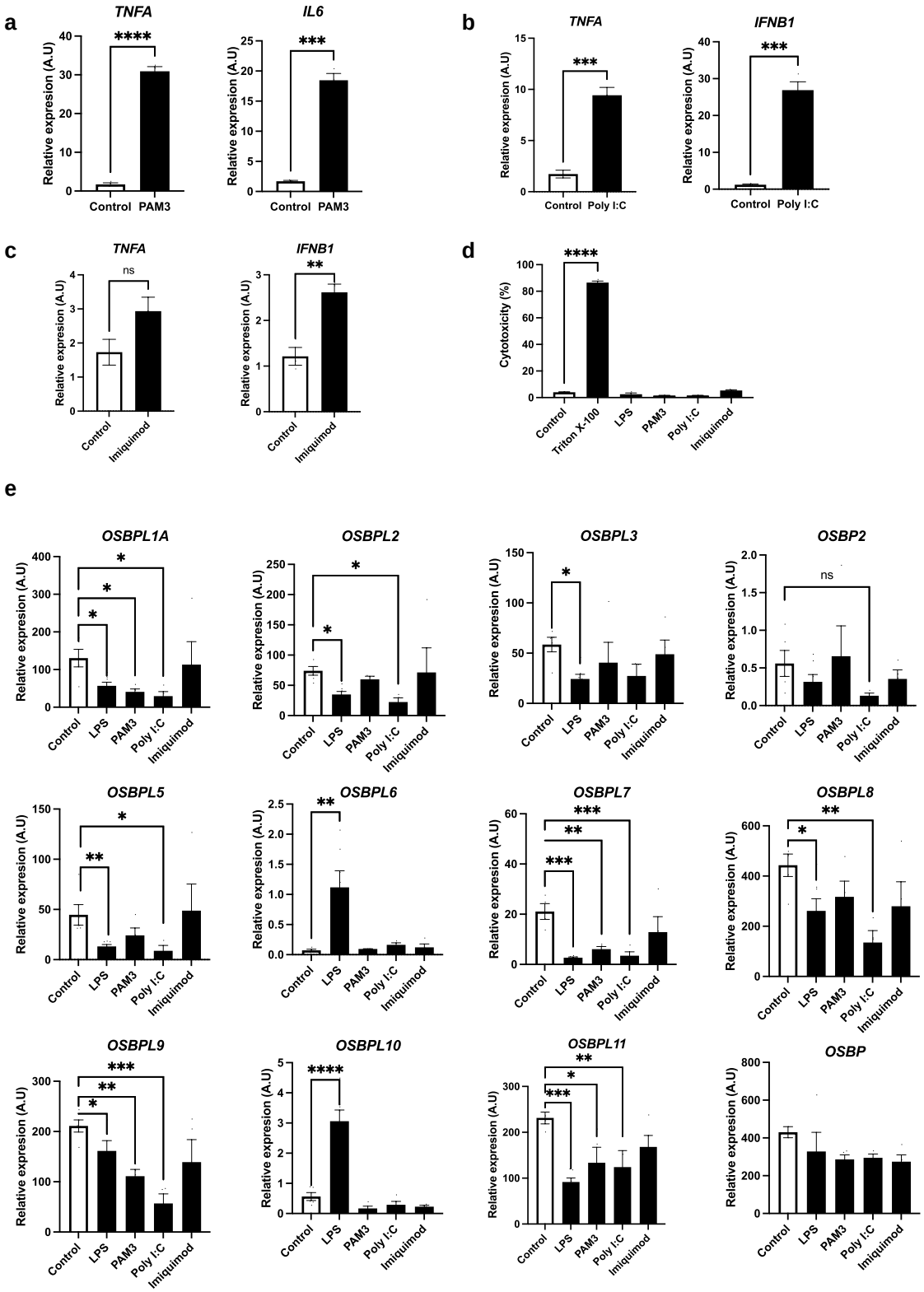


Figure 2 ORP expression is differentially regulated by TLR stimuli. THP-1 differentiated macrophages were either left untreated or treated with LPS (500 ng/ml), PAM3 (500 ng/ml), poly I:C (1 μg/ml), or imiquimod (3 μg/ml) for 6 h (a) Gene expression of *TNFA* and *IL6* following PAM3 stimulation. (b) Gene expression of *TNFA* and *IFNB1* following poly I:C stimulation. (c) Gene expression of *TNFA* and *IFNB1* following imiquimod stimulation. Panels A–C confirm successful TLR pathway activation at the concentrations used. (d) Cell viability assessed across all stimuli to confirm the selected concentrations were not cytotoxic. Triton X-100 was used as a positive control for cytotoxicity. (e) Gene expression of all 12 ORP family members determined by real-time qPCR, shown as arbitrary units, $n = 4$. Error bars represent SEM. The statistical analysis of the data was performed using one-way ANOVA where *, $P \leq 0.01$; **, $P \leq 0.001$; ***, $P \leq 0.0001$; ****, $P \leq 0.0001$. Significance was calculated against the control, untreated group.

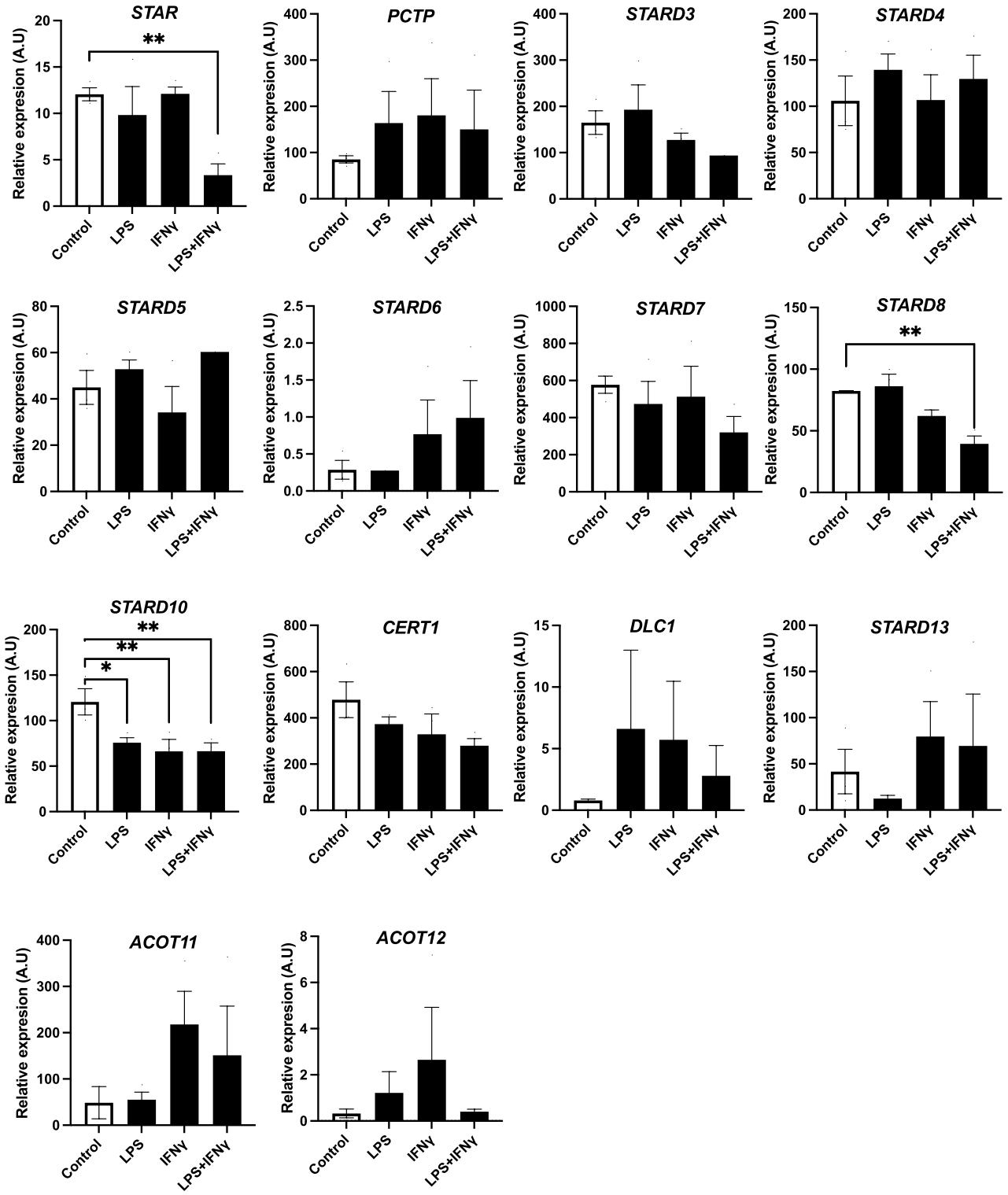


Figure 3 TLR signalling does not significantly regulate the expression of STARD family members. THP-1 differentiated macrophages were either left untreated or treated with LPS (500 ng/ml) for 6 h, human IFN-γ (50 ng/ml) overnight, or a combination of both. RNA was extracted and converted to cDNA. Gene expression of 14 STARD family members was determined by real-time qPCR. The expression of the STARD family members upon various treatments is shown as arbitrary units, $n = 4$. Error bars represent SEM. The statistical analysis of the data was performed using one-way ANOVA. Significance was calculated against the control, untreated group.

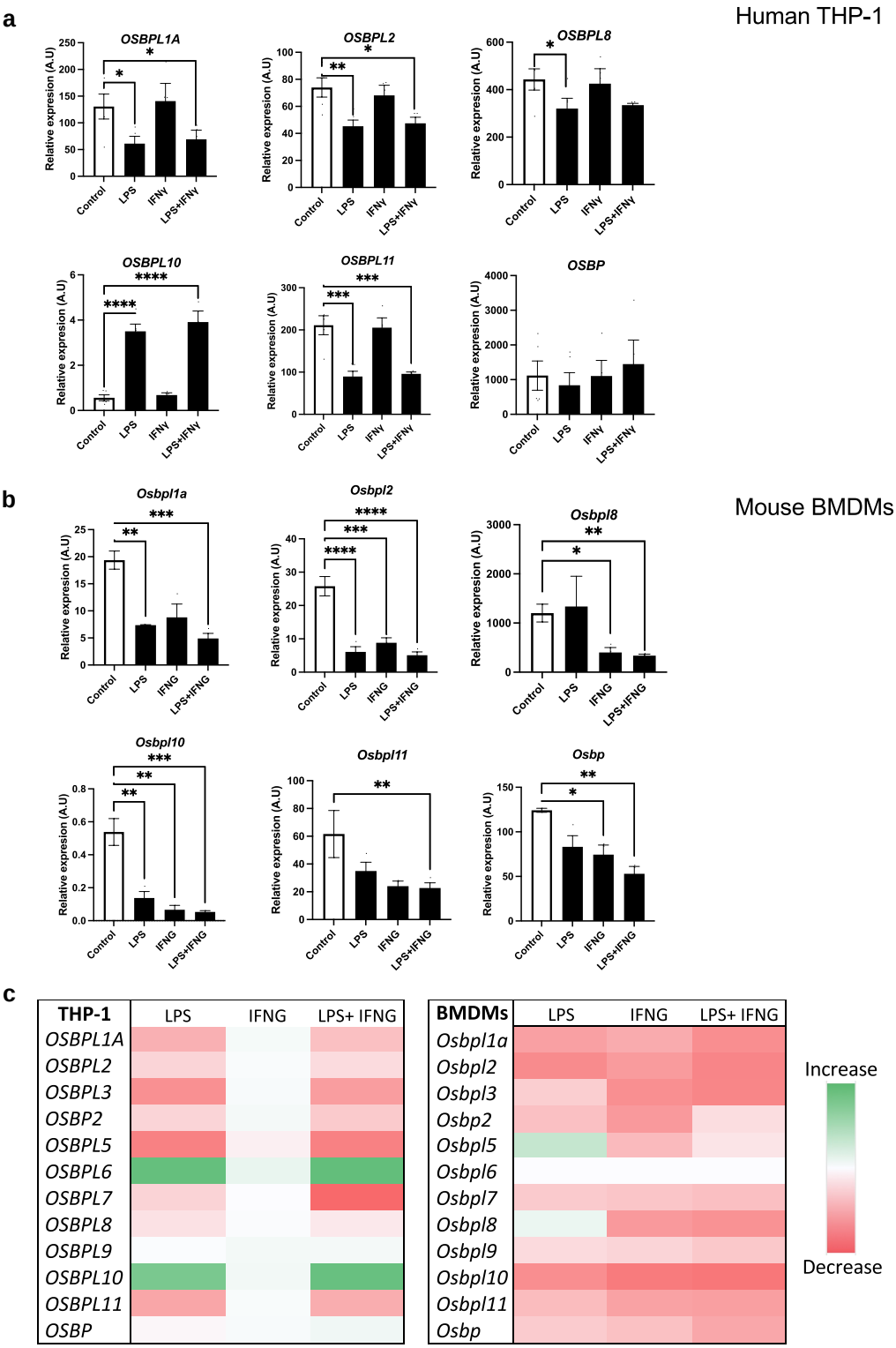


Figure 4 Differences in ORP regulation by LPS and IFN-γ between human and mouse macrophages. BMDMs and THP-1 differentiated macrophages were either left untreated or treated with LPS (500 ng/ml) for 6, human or mouse IFNγ (50 ng/ml) overnight, or a combination of both. RNA was extracted and converted to cDNA. Gene expression of all 12 ORP family members was determined by real-time qPCR. The relative expression of only the significant ORPs differentially regulated by IFNγ in (a) BMDMs was plotted alongside the expression of these ORPs in (b) THP-1 differentiated macrophages. Relative expression of ORPs is shown as arbitrary units. (c) Descriptive statistics were performed on the effect of each treatment against the control for each ORP member in BMDMs, and the results were plotted in a heat map. Red shading indicates a decrease, while green shading represents an increase. A darker shade of red or green colour signifies a greater decrease or increase, respectively. $n = 8$ for THP-1 cells and $n = 4$ for BMDMs. Error bars represent SEM. The statistical analysis of the data was performed using one-way ANOVA, where *, $P \leq 0.01$; **, $P \leq 0.001$; ***, $P \leq 0.0001$; ****, $P \leq 0.0001$. Significance was calculated against the control, untreated group.

ORP expression is differentially regulated by TLR stimuli

Humans express 10 TLR family members, which are involved in sensing a wide variety of pathogen-associated molecular patterns. These TLRs are predominantly localized at the plasma membrane, with the exception of TLRs 3, 7, 8, and 9, which are localized at the endosomal membrane. Distinct TLRs activate different signalling pathways via specific adaptor proteins, leading to unique gene expression profiles. For example, TLR4 predominantly signals through the MyD88 adaptor protein to activate NFKB and MAP-kinase pathways but can also signal via TRIF, under certain conditions [34–37]. In contrast, TLR3 exclusively signals through TRIF to induce the expression of type-I interferons [38].

To determine whether the observed regulation of ORPs is specific to TLR4 or also initiated by other TLRs, THP-1 macrophages were exposed to ligands for TLR2, TLR3, and TLR7, in addition to TLR4, which was used as a reference control and ensured experimental consistency across independent datasets. The concentrations used for these ligands (Pam3Cys: 500 ng/ml, poly(I:C): 1 μg/ml, imiquimod: 3 μg/ml) were chosen based on widely accepted and recommended concentrations for activation of these pathways in prior studies [39–42]. In agreement, stimulation of indicated TLRs in THP-1 macrophages resulted in increased elevation of their respective target genes (Fig. 2a-c) with no significant changes observed in cell viability (Fig. 2d). Since poly I:C was added extracellularly without transfection reagents, it is expected to signal predominantly through endosomal TLR3 under these conditions [30]. While cytosolic RIG-I and MDA5 can theoretically be engaged by poly I:C, such activation typically requires intracellular delivery and displays delayed kinetics beyond the 6 h timepoint used here, making a significant contribution from these pathways unlikely.

Consistent with our previous results (Fig. 1e), exposure to LPS resulted in a significant downregulation of the majority of the ORP family members, with the exception of *OSBP2* and *OSBP* (Fig. 2e). By contrast, *OSBPL6* and *OSBPL10* exhibited an increase in expression (Fig. 2e). Stimulation with the TLR2 ligand, Pam3CSK4, significantly downregulated *OSBPL1A, OSBPL7, OSBPL9,* and *OSBPL11* while other ORPs were unaffected (Fig. 2e). Poly(I:C), a TLR3 ligand, suppressed the expression of *OSBPL1A*, *OSBPL2*, *OSBPL5*, *OSBPL7*, *OSBPL8*, *OSBPL9,* and *OSBPL11,* while imiquimod, a TLR7 ligand, had no significant effects on any of the ORPs (Fig. 2e). These data summarizing changes in ORP gene expression by TLRs are presented in Table 2. These results suggest that ORP transcriptional responses do not correlate strictly with canonical adaptor usage for the examined TLR pathways. Moreover, the specific regulation of most ORPs by TLR4, but not TLR2, suggests the involvement of additional factors beyond the shared downstream pathways between the two receptors. This may involve TRIF-associated or downstream signalling pathways. It is worth noting that PMA-differentiated THP-1 cells have measurable TLR7 transcript levels and retain the capacity to respond to TLR7 stimulation, albeit at lower expression levels than specialized cell types such as plasmacytoid dendritic cells [43]. The absence of ORP regulation by imiquimod should therefore be interpreted in this context.

Table 2 Changes in ORP expression in response to different TLR ligands in THP-1 macrophages.

	LPS	Pam3	Poly I:C	Imiquimod	Exceptions
OSBPL1A	↓↓	↓	↓	–	
OSBPL2	↓↓	–	↓	–	
OSBPL3	↓↓	–	–	–	
OSBP2	–	–	–	–	
OSBPL5	↓↓↓	–	↓	–	
OSBPL6	↑↑	–	–	–	Increased expression compared to other *ORPs*.
OSBPL7	↓↓↓↓	↓↓	↓↓↓	–	
OSBPL8	↓↓	–	↓↓	–	
OSBPL9	↓	↓↓↓	↓↓↓	–	
OSBPL10	↑↑↑↑	↓	–	–	Increased expression compared to other *ORPs*.
OSBPL11	↓↓↓↓	↓	↓↓	–	
OSBP	–	↓	–	–	

Arrows indicate direction of change. Arrows pointing upwards show an increase while downward-facing arrows show a decrease in gene expression. The number of arrows correspond to the level of significance (e.g. ** for two arrows). A dash indicates no significant change in gene expression.

TLR signalling does not significantly regulate the expression of STARD family members

Lipid transport is essential to lipid metabolism, facilitating the movement of lipids between cellular compartments and enabling energy storage and cellular signalling. Beyond ORPs, STARD proteins also play key roles in intracellular lipid transport. Consisting of 15 family members, STARD proteins transport cholesterol and phospholipids across organelles, which is important to mitochondrial function and cellular homeostasis. To investigate whether TLR signalling regulates STARD proteins, we analysed their expression in THP-1 macrophages. Unlike ORPs, STARD gene expression remained unaltered, with the exception of *STARD10*, following TLR4 activation with LPS (Fig. 3). Although *STARD9* could not be assessed due to inefficient primers, the lack of regulation in other STARD family members suggests that TLR4 signalling specifically targets ORPs, with statistical changes limited to only a few STARD proteins.

IFN-γ is a crucial innate immune stimulus, which has previously been shown to modulate lipid metabolism and transport. Specifically, IFN-γ inhibits genes involved in cholesterol and fatty acid synthesis pathways. Moreover, when combined with LPS, IFN-γ has the ability to enhance lipid efflux and promote lipid catabolism [5]. Considering these roles, we next examined whether IFN-γ by itself or in combination with LPS has the ability to regulate *STARD* genes. To investigate this, THP-1 macrophages were exposed to IFN-γ overnight in the absence or presence of prior LPS stimulation for 6 hours. After overnight stimulation, purified RNA was subjected to RT-PCR. Among the STARD family members, STAR, STARD8, and STARD10 exhibited modest downregulation in response to the combined IFN-γ and LPS treatment, while other members showed no significant changes (Fig. 3). These findings suggest that compared to ORP family members,

only a minor set of STARD genes show any statistically significant regulation under the experimental conditions tested in this study. This indicates a distinct regulatory framework for these two protein families.

Differences in ORP regulation by LPS and IFN-γ between human and mouse macrophages

Our results so far indicate that ORP genes are selectively regulated by TLR signalling, while STARD genes are not affected by either TLR or IFN-γ signalling. To further investigate whether IFN-γ modulates ORP expression, we exposed human THP-1 macrophages to IFN-γ alone or in combination with LPS. Consistent with our previous findings, LPS alone resulted in significant downregulation of most ORPs. However, IFN-γ alone had no significant effect on ORP expression, and its combination with LPS produced a similar expression profile to LPS alone. These results suggest that IFN-γ does not play a role in modulating the expression of lipid transport genes in human macrophages.

Previous studies have highlighted specific differences in lipid transport and metabolism between humans and mice. For example, the expression of cholesteryl ester transfer protein, an enzyme that facilitates cholesterol transfer between lipoproteins, significantly differs between mice and humans [44, 45]. Similarly, the gene expression of *APOA1*, which is associated with HDL metabolism, differs between the species [46]. To explore differences in expression between human and mouse macrophages, we next examined ORP expression in mouse bone marrow-derived macrophages (BMDMs) under the same conditions (Fig. 4). Unlike in human cells, IFNγ alone significantly downregulated *Osbpl2*, *Osbpl8*, *Osbpl10*, and *Osbp* in mouse BMDMs (Fig. 4a, b). LPS treatment in BMDMs also regulated a more limited subset of ORPs, specifically downregulating *Osbpl1*, *Osbpl2*, and *Osbpl10*. Interestingly, human *OSBPL10* exhibited an increase in expression following LPS treatment (Fig. 2), underscoring distinct regulatory mechanisms between experimental models. When IFN-γ and LPS were combined in BMDMs, only a limited synergistic effect was observed, particularly for *Osbpl1* and *Osbpl10*. A descriptive heatmap summarizes these differences, highlighting the contrasting effects of LPS and IFNγ on ORP expression in human THP-1 macrophages and mouse BMDMs (Fig. 4c). These findings emphasize the importance of cellular and experimental context when investigating immune-regulated lipid metabolism and transport.

Discussion

Lipid transport proteins, such as the ORPs and STARDs families, are central to cellular lipid metabolism and contribute to lipid transport across organelles. In this study, we report that the lipid transporters are regulated by immune stimuli in human and mouse macrophage models. Our results underscore the complexity and specificity of immune regulation on lipid transporters, with distinct patterns observed between the ORP and STARD family members.

Our findings demonstrate that all 12 members of the ORP family are constitutively expressed and depict a positive correlation between hMDMs and THP-1 macrophages. However, their expression levels vary between the two cell types, with generally higher expression levels observed in hMDMs. TLR4 activation through LPS resulted in significant downregulation of most ORP members in THP-1 macrophages, except for *OSBPL6* and *OSBPL10*, which were upregulated. Notably, stimulation of TLR2, TLR3, and TLR7 also modulated specific ORPs, albeit to a lesser extent. For example, Pam3CSK4 (TLR2 ligand) reduced *OSBPL1A*, *OSBPL7, OSBPL9,* and *OSBPL11* expression, while poly(I:C) (TLR3 ligand) and imiquimod (TLR7 ligand) primarily affected *OSBPL7* and *OSBPL11*. These data suggest that TLR4 has a broader impact on ORP regulation compared to other TLRs but highlight the nuanced and context-dependent nature of ORP modulation by different immune pathways. These results are consistent with published findings showing that LPS alters the expression of genes involved in lipid metabolism [13, 15]. The upregulation of *OSBPL6* and *OSBPL10* suggests that these proteins may have compensatory or specialized roles in maintaining lipid homeostasis during immune activation. Future work could focus on elucidating their specific lipid substrates or roles in immune-metabolic interactions.

Despite the established role of TLRs in regulating lipid metabolism, the specificity of interactions between different TLRs and lipid transport proteins such as ORPs and STARDs remains largely unexplored. While our findings reveal distinct regulatory patterns for ORPs across TLR2, TLR3, TLR4, and TLR7 signalling, the molecular basis of these specificities remains unknown. Future studies are needed to investigate how different TLRs uniquely influence lipid transport proteins and how these pathways contribute to immune and metabolic homeostasis.

Interestingly, these responses were specific to TLR4 ligation, as none of the other TLR ligands tested such broadly altered ORP expression. This suggests that TLR4-mediated ORP regulation is not solely due to shared downstream pathways but may involve additional factors unique to TLR4 signalling.

Innate immune agonists activate distinct but overlapping transcriptional programmes that provide a plausible framework for the stimulus-specific regulation we observe across lipid-transport gene families. Downstream of TLR ligands (including LPS/TLR4), MyD88- and TRIF-linked signalling rapidly engages canonical inflammatory transcription factors such as NFKB and AP-1, with additional involvement of IRF-family factors depending on the cellular context [47, 48]. In parallel, IFNγ signals through the JAK–STAT pathway to activate STAT1 and induce IRF1, and many IFNγ–responsive genes rely on combinatorial control (e.g. STAT1/IRF1 cooperation) encoded by promoter and enhancer *cis*-elements [49]. Notably, TLR4 signalling has been reported to engage IRF1 in macrophages and to promote the activation of IFN-stimulated loci, offering a mechanistic precedent for LPS-driven regulation of gene subsets that overlap with IFN-like transcriptional programmes [50]. Consistent with these observations, the endosomal TLR ligands tested in this study did not reproduce the broad ORP repression observed with LPS. Since TLR7 signals via MyD88, this suggests that MyD88 signalling alone is not sufficient to drive widespread ORP transcriptional changes in this context and instead points to TLR4-specific features (e.g. receptor compartmentalization and/or additional downstream signalling inputs) as contributors. These immune transcription factor pathways can also directly intersect with lipid metabolism

and reshape lipid-handling gene expression. For example, IFNγ can downregulate LXR-ABCA1-linked cholesterol efflux programmes in macrophage models via a JAK/STAT1-dependent mechanism [51]. Together, these precedents support a model in which differential responsiveness of ORP vs STARD genes reflects differences in immune-responsive *cis*-regulatory features and/or chromatin accessibility at these loci. The context-specific effects could potentially arise from divergence in transcription factor usage or regulatory elements. These possibilities can be tested in future work by targeted transcription factor occupancy assays or focused reporter approaches. We acknowledge that the absence of dose–response data limits the strength of our comparative conclusions, and that differences between the two cell systems may reflect experimental variables rather than true species-level divergence.

In contrast to the observed regulation of the ORP family, the STARD family, including well-studied lipid transporters like *STAR, PCTP*, and *STARD3*, was less responsive to immune stimuli. While most STARD members showed no statistically significant changes by LPS or IFNγ stimulation, combined treatment with LPS and IFNγ led to modest suppression of *STAR*, *STARD8*, and *STARD10* expression. This limited response contrasts with the broad regulation observed in the ORP family. A plausible hypothesis is that the STARD proteins are regulated by metabolic or homeostatic pathways rather than immune signalling, consistent with their basal roles in organelle-specific lipid shuttling [52]. These findings indicate a potential functional divergence between the ORP family members and the STARD family members, with the former more actively engaged in immune-related lipid transport and the latter more aligned with basal metabolic cellular processes.

When comparing human and mouse macrophages, we observed notable differences in the magnitude and pattern of ORP expression responses between the two cell types. Mouse BMDMs displayed a more limited response to LPS compared to human THP-1 macrophages, with only *Osbpl1a*, *Osbpl2*, and *Osbpl10* being downregulated. Conversely, human *OSBPL10* expression was increased following LPS stimulation, suggesting differences in regulatory mechanisms between human and mouse macrophages. Additionally, IFNγ alone downregulated *Osbpl2*, *Osbpl8*, *Osbpl10*, and *Osbp* in mouse BMDMs, a response that was not observed in human cells. These results are consistent with studies demonstrating variations in lipid metabolism between human and murine models [46, 53], and may reflect evolutionary adaptations in lipid metabolism and immune function. These differences underscore the complexity of context-specific regulation, complicate the extrapolation of murine data to human immunological studies, and emphasize the importance of validating findings from murine models in human systems. Further comparative studies across species are essential for identifying both conserved and differential regulatory mechanisms, providing critical insights that can guide translational applications in immunology and pharmacology. However, comparative studies pose challenges, such as differences in baseline gene expression, divergent immune adaptations, and variations in experimental protocols, which must be carefully addressed.

The regulation of lipid transport by immune signalling is critically relevant to several disease contexts, yet it remains inadequately studied. Dysregulated lipid metabolism contributes to the pathogenesis of diseases such as atherosclerosis, diabetes, and chronic inflammatory disorders, where the interaction between immune signalling and lipid transport mechanisms is poorly understood. Our findings suggest that ORPs, which are selectively regulated by TLR4 signalling, could represent novel therapeutic targets for such conditions. Integrating molecular mechanisms into disease contexts, particularly in metabolic and cardiovascular diseases, will enhance the translational impact of future research.

In conclusion, this study provides novel insights into the selective regulation of lipid transport proteins by immune signalling. The differential regulation of the ORP family members by TLR4 and the lack of modulation of the STARD family members suggest distinct roles for these protein families in immune and metabolic contexts. Furthermore, the observed differences in ORP regulation underscore the importance of considering biological context when interpreting immune-metabolic interactions. Future work should focus on elucidating the molecular mechanisms underlying these regulatory differences, including defining the transcription factor programmes and *cis*-regulatory features that drive the stimulus- and context-specific ORP and STARD regulation observed in this study.

Acknowledgements

The authors would like to thank the reviewers for their valuable comments and suggestions, which helped improve the quality of this manuscript. The Editor-in-Chief and handling editor, Simon Milling, would like to thank Vuk Cerovic and an anonymous reviewer for their contribution to the publication of this article.

Author contributions

Lydia P. Tsamouri (Conceptualization, Data curation, Investigation, Methodology, Writing—original draft, Writing—review & editing), Najd M. Aljadeed (Data curation, Formal analysis, Writing—review & editing), Antoni Olona (Investigation, Writing—review & editing), and Paras Anand (Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Software, Supervision, Visualization, Writing—original draft, Writing—review & editing)

Supplementary material

Supplementary material is available at *Discovery Immunology* online.

Conflicts of interest

The authors declare no competing interests.

Funding

This research was in part supported by funds from The UK Research and Innovation (MR/S00968X/1), and core funds from Imperial College London to P.K.A. Current research in the Anand lab is supported by The UK Research and Innovation (Grant number: UKRI1408).

Data availability

All data generated during this study are included in this published article. Further data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Experiments were performed under the regulations of the Home Office Scientific Procedures Act (1986) and were subject to local ethical review by the AWERB and followed ARRIVE 2.0 guidelines (https://arriveguidelines.org/arrive-guidelines).

Permission to reproduce

Not applicable.

References

1. Anand PK. Lipids, inflammasomes, metabolism, and disease. *Immunol Rev* 2020, **297**, 108–22.
2. Anand PK. From fat to fire: the lipid–inflammasome connection. *Immunol Rev* 2025, **329**, e13403.
3. Ertunc ME, Hotamisligil GS. Lipid signaling and lipotoxicity in metaflammation: indications for metabolic disease pathogenesis and treatment. *J Lipid Res* 2016, **57**, 2099–114.
4. Panousis CG, Evans G, Zuckerman SH. TGF-β increases cholesterol efflux and ABC-1 expression in macrophage-derived foam cells: opposing the effects of IFN-γ. *J Lipid Res* 2001, **42**, 856–63.
5. Wang XQ, Panousis CG, Alfaro ML, Evans GF, Zuckerman SH. Interferon-gamma-mediated downregulation of cholesterol efflux and ABC1 expression is by the Stat1 pathway. *Arterioscler Thromb Vasc Biol* 2002, **22**, e5–9.
6. Olona A, Leishman S, Anand PK. The NLRP3 inflammasome: regulation by metabolic signals. *Trends Immunol* 2022, **43**, 978–89.
7. Creagh EM, O'Neill LAJ. TLRs, NLRs and RLRs: a Trinity of pathogen sensors that co-operate in innate immunity. *Trends Immunol* 2006, **27**, 352–7.
8. Everts B, Amiel E, Huang SCC, Smith AM, Chang CH, Lam WY, *et al.* TLR-driven early glycolytic reprogramming via the kinases TBK1-IKKε supports the anabolic demands of dendritic cell activation. *Nat Immunol* 2014, **15**, 323–32.
9. Köberlin MS, Heinz LX, Superti-Furga G. Functional crosstalk between membrane lipids and TLR biology. *Curr Opin Cell Biol* 2016, **39**, 28–36.
10. Meana C, Peña L, Lordén G, Esquinas E, Guijas C, Valdearcos M, *et al.* Lipin-1 integrates lipid synthesis with proinflammatory responses during TLR activation in macrophages. *J. Immunol* 2014, **193**, 4614–22.
11. Neyen CD, Gordon S. Macrophages in lipid and immune homeostasis. *Encyclopedia of Life Sciences* 2008. doi:10.1002/9780470015902.a0021029
12. DeBose-Boyd RA, Ye J. SREBPs in lipid metabolism, insulin signaling, and beyond. *Trends Biochem Sci* 2018, **43**, 358.
13. Oishi Y, Spann NJ, Link VM, Muse ED, Strid T, Edillor C, *et al.* SREBP1 contributes to resolution of pro-inflammatory TLR4 signaling by reprogramming fatty acid metabolism. *Cell Metab* 2017, **25**, 412–27.
14. Castrillo A, Joseph SB, Vaidya SA, Haberland M, Fogelman AM, Cheng G, *et al.* Crosstalk between LXR and toll-like receptor signaling mediates bacterial and viral antagonism of cholesterol metabolism. *Mol Cell* 2003, **12**, 805–16.
15. Park HY, Kang HS, Im SS. Recent insight into the correlation of SREBP-mediated lipid metabolism and innate immune response. *J Mol Endocrinol* 2018, **61**, R123–31.
16. Olona A, Hateley C, Muralidharan S, Wenk MR, Torta F, Behmoaras J. Sphingolipid metabolism during toll-like receptor 4 (TLR4)-mediated macrophage activation. *Br J Pharmacol* 2021, **178**, 4575–87.
17. Qi HY, Shelhamer JH. Toll-like receptor 4 signaling regulates cytosolic phospholipase A2 activation and lipid generation in lipopolysaccharide-stimulated macrophages. *J Biol Chem* 2005, **280**, 38969–75.
18. Luo J, Jiang LY, Yang H, Song BL. Intracellular cholesterol transport by sterol transfer proteins at membrane contact sites. *Trends Biochem Sci* 2019, **44**, 273–92.
19. Reinisch KM, Prinz WA. Mechanisms of nonvesicular lipid transport. *J Cell Biol* 2021, **220**, e202012058.
20. Jaworski CJ, Moreira E, Li A, Lee R, Rodriguez IR. A family of 12 human genes containing oxysterol-binding domains. *Genomics* 2001, **78**, 185–96.
21. Nakatsu F, Kawasaki A. Functions of oxysterol-binding proteins at membrane contact sites and their control by phosphoinositide metabolism. *Front Cell Dev Biol* 2021, **9**, 664788.
22. Kentala H, Weber-Boyvat M, Olkkonen VM. OSBP-Related Protein family: mediators of lipid transport and signaling at membrane contact sites. *Int Rev Cell Mol Biol* 2016, **321**, 299–340.
23. Soccio RE, Breslow JL. StAR-related lipid transfer (START) proteins: mediators of intracellular lipid metabolism. *J Biol Chem* 2003, **278**, 22183–6.
24. Clark BJ. The mammalian START domain protein family in lipid transport in health and disease. *J Endocrinol* 2012, **212**, 257–75.
25. Zhao K, Foster J, Ridgway ND. Oxysterol-binding protein-related protein 1 variants have opposing cholesterol transport activities from the endolysosomes. *Mol Biol Cell* 2020, **31**, 793–802.
26. Leishman S, Aljadeed NM, Qian L, Cockcroft S, Behmoaras J, Anand PK. Fatty acid synthesis promotes inflammasome activation through NLRP3 palmitoylation. *Cell Rep* 2024, **43**, 114516.
27. de la Roche M, Hamilton C, Mortensen R, Jeyaprakash AA, Ghosh S, Anand PK. Trafficking of cholesterol to the ER is required for NLRP3 inflammasome activation. *J Cell Biol* 2018, **217**, 3560–76.
28. Genin M, Clement F, Fattaccioli A, Raes M, Michiels C. M1 and M2 macrophages derived from THP-1 cells differentially modulate the response of cancer cells to etoposide. *BMC Cancer* 2015, **15**, 1–14.
29. Brandt KJ, Fickentscher C, Kruithof EKO, De Moerloose P. TLR2 ligands induce NF-κB activation from endosomal compartments of human monocytes. *PLoS One* 2013, **8**, e80743.

30. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-κB by toll-like receptor 3. *Nature* 2001, **413**, 732–8.
31. Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, *et al.* Small anti-viral compounds activate immune cells via the TLR7 MyD88–dependent signaling pathway. *Nat Immunol* 2002, **3**, 196–200.
32. Hamilton C, Olona A, Leishman S, MacDonald-Ramsahai K, Cockcroft S, Larrouy-Maumus G, *et al.* NLRP3 inflammasome priming and activation are regulated by a phosphatidylinositol-dependent mechanism. *Immunohorizons* 2022, **6**, 642–59.
33. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2−ΔΔCT method. *Methods* 2001, **25**, 402–8.
34. Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, *et al.* Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science* 2003, **301**, 640–3.
35. Muzio M, Natoli G, Saccani S, Levrero M, Mantovani A. The human toll signaling pathway: divergence of nuclear factor kappaB and JNK/SAPK activation upstream of tumor necrosis factor receptor-associated factor 6 (TRAF6). *J Exp Med* 1998, **187**, 2097–101.
36. Kawai T, Adachi O, Ogawa T, Takeda K, Akira S. Unresponsiveness of MyD88-deficient mice to endotoxin. *Immunity* 1999, **11**, 115–22.
37. Medzhitov R, Janeway CA. Innate immune recognition and control of adaptive immune responses. *Semin Immunol* 1998, **10**, 351–3.
38. Zhang SY, Herman M, Ciancanelli MJ, Pérez de Diego R, Sancho-Shimizu V, Abel L, *et al.* TLR3 immunity to infection in mice and humans. *Curr Opin Immunol* 2013, **25**, 19.
39. Cantelli BA, Segura GG, Bitencourt TA, de Abreu MH, Petrucelli MF, Peronni K, *et al.* Transcriptome analysis of co-cultures of THP-1 human macrophages with inactivated germinated *Trichophyton rubrum* conidia. *J Fungi* 2023, **9**, 563.
40. Zhang Q, Chao T, Patil VS, Qin Y, Tiwari SK, Chiou J, *et al.* The long noncoding RNA ROCKI regulates inflammatory gene expression. *EMBO J* 2019, **38**, e100041.
41. Jiang J, Wang S, Fang J, Xu Y, Tong L, Ye X, *et al.* Stable silencing of TIPE2 reduced the poly I:C-induced apoptosis in THP-1 cells. *Mol Med Rep* 2017, **16**, 6313–9.
42. Lee HJ, Kang SJ, Woo Y, Hahn TW, Ko HJ, Jung YJ. TLR7 stimulation with imiquimod induces selective autophagy and controls *Mycobacterium tuberculosis* growth in mouse macrophages. *Front Microbiol* 2020, **11**, 1684.
43. Odoardi N, Kourko O, Petes C, Basta S, Gee K. TLR7 ligation inhibits TLR8 responsiveness in IL-27-primed human THP-1 monocytes and macrophages. *J Innate Immun* 2021, **13**, 345–58.
44. Oestereich F, Yousefpour N, Yang E, Phénix J, Nezhad ZS, Nitu A, *et al.* The cholesteryl ester transfer protein (CETP) raises cholesterol levels in the brain. *J Lipid Res* 2022, **63**, 100260.
45. Tanigawa H, Billheimer JT, Tohyama JI, Zhang YZ, Rothblat G, Rader DJ. Expression of cholesteryl ester transfer protein in mice promotes macrophage reverse cholesterol transport. *Circulation* 2007, **116**, 1267–73.
46. Gordon SM, Li H, Zhu X, Shah AS, Lu LJ, Davidson WS. A comparison of the mouse and human lipoproteome: suitability of the mouse model for studies of human lipoproteins. *J Proteome Res* 2015, **14**, 2686–95.
47. Kawai T, Akira S. Signaling to NF-κB by toll-like receptors. *Trends Mol Med* 2007, **13**, 460–9.
48. Roy A, Srivastava M, Saqib U, Liu D, Faisal SM, Sugathan S, *et al.* Potential therapeutic targets for inflammation in toll-like receptor 4 (TLR4)-mediated signaling pathways. *Int Immunopharmacol* 2016, **40**, 79–89.
49. Hu X, li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. *Signal Transduct Target Ther* 2021, **6**, 402.
50. Song R, Gao Y, Dozmorov I, Malladi V, Saha I, McDaniel MM, *et al.* IRF1 governs the differential interferon-stimulated gene responses in human monocytes and macrophages by regulating chromatin accessibility. *Cell Rep* 2021, **34**, 108891.
51. Hao XR, Cao DL, Hu YW, Li XX, Liu XH, Xiao J, *et al.* IFN-γ down-regulates ABCA1 expression by inhibiting LXRα in a JAK/STAT signaling pathway-dependent manner. *Atherosclerosis* 2009, **203**, 417–28.
52. Clark BJ. The START-domain proteins in intracellular lipid transport and beyond. *Mol Cell Endocrinol* 2020, **504**, 110704.
53. Straniero S, Laskar A, Savva C, Härdfeldt J, Angelin B, Rudling M. Of mice and men: murine bile acids explain species differences in the regulation of bile acid and cholesterol metabolism. *J Lipid Res* 2020, **61**, 480–91.