



OPEN ACCESS

EDITED BY

Geert Van Den Bogaart,
University of Groningen, Netherlands

REVIEWED BY

Fabrizia Bonacina,
University of Milan, Italy
Saeedeh Asgarbeik,
Universitätsmedizin Greifswald, Germany

*CORRESPONDENCE

Liang Chen

✉ lchen1@shu.edu.cn

Yan-wei Wu

✉ wuyanwei@shu.edu.cn

RECEIVED 20 October 2025

REVISED 05 January 2026

ACCEPTED 05 January 2026

PUBLISHED 27 January 2026

CITATION

Zhang X, Luo L-j, Wu Y-w and Chen L (2026)
The role of CD36 in immune function:
bridging innate and adaptive responses.
Front. Immunol. 17:1728509.
doi: 10.3389/fimmu.2026.1728509

COPYRIGHT

© 2026 Zhang, Luo, Wu and Chen. This is an open-access article distributed under the terms of the [Creative Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

The role of CD36 in immune function: bridging innate and adaptive responses

Xiang Zhang^{1,2,3,4}, Ling-jie Luo^{1,2,3,4}, Yan-wei Wu^{1,2,3,4*} and Liang Chen^{1,2,3,4*}

¹School of Medicine, Shanghai University, Shanghai, China, ²State Key Laboratory of New Targets Discovery and Drug Development for Major Disease, Xi'an, China, ³Shanghai Tenth People's Hospital, Shanghai, China, ⁴Institute of Artificial Intelligence and Biomanufacturing, School of Medicine, Shanghai University, Shanghai, China

CD36 is a multifunctional glycoprotein essential in fatty acid metabolism, angiogenesis, and atherogenesis, playing a critical role in immunological processes. This comprehensive review synthesizes current research to elucidate CD36's integral functions within the immune system, including its involvement in phagocytosis, inflammation, and the crucial interplay between innate and adaptive immune responses. We highlight novel insights into CD36 as a therapeutic target, presenting recent advances in targeting strategies for a spectrum of conditions such as inflammatory diseases, infections, metabolic disorders and cardiovascular diseases. By evaluating emerging research and clinical trials, this review proposes innovative approaches for exploiting CD36's therapeutic potential, aiming to inspire further research and development in disease treatment.

KEYWORDS

adaptive immunity, CD36, immune modulation, inflammation, innate immunity, phagocytosis

1 Introduction

The immune system is a highly coordinated network of cells, receptors, and signaling pathways that preserves physiological homeostasis and defends the host against pathogens. Central to its effectiveness is the interplay between innate and adaptive immunity, which relies on a wide range of receptors capable of recognizing lipids, metabolites, pathogens, and cellular debris (1). Among these, scavenger receptors have emerged as key mediators, bridging lipid metabolism, immune surveillance, and inflammatory regulation (2).

CD36, a multifunctional glycoprotein initially identified in the 1980s as a receptor for oxidized low-density lipoprotein (oxLDL) in atherosclerosis (3), has since been recognized as far more than a lipid scavenger. It exerts pleiotropic functions in angiogenesis (4), adipocyte lipid storage (5), taste perception (6), and immune regulation (7). Unlike other scavenger receptors such as SR-A (Scavenger Receptor Class A), which mainly clears cellular debris (8), or LOX-1 (Lectin-like Oxidized LDL Receptor 1), which is primarily associated with cardiovascular pathology (9), CD36 demonstrates remarkable ligand

promiscuity and signaling versatility. These features enable it to govern diverse immune processes, including the phagocytosis of apoptotic cells and pathogens (10), the activation of antigen-presenting cells (11), and modulation of inflammatory cascades. Through these mechanisms, CD36 functions as a critical molecular bridge between innate and adaptive immune responses.

Importantly, CD36 plays a paradoxical role in immunity: it can either amplify inflammation, contributing to tissue damage and chronic disease, or promote resolution and homeostasis depending on context. This duality has attracted growing interest in CD36 as a therapeutic target in inflammatory disorders, infectious diseases, metabolic syndromes, and cardiovascular conditions. In this review, we synthesize current evidence on the immunological functions of CD36, highlight its role at the intersection of innate and adaptive immunity, and discuss the translational potential of targeting this receptor for therapeutic intervention.

2 CD36: structure, expression, and ligand diversity

2.1 Protein structure and family background

CD36 belongs to the class B scavenger receptor family, which also includes SR-BI (SCARB1) and SR-BII. It is a heavily glycosylated transmembrane glycoprotein of ~88 kDa, encoded by the CD36 gene on chromosome 7q21.11 (12). Structurally, CD36 is characterized by two short cytoplasmic tails (N- and C-terminus) connected by two transmembrane domains, which flank a large extracellular loop of ~400 amino acids. This extracellular domain contains multiple N-linked glycosylation sites and hydrophobic pockets that confer broad ligand-binding specificity (13). Palmitoylation of the cytoplasmic tails contributes to receptor trafficking, membrane localization, and signal transduction. Functionally, CD36 serves as a pattern recognition receptor (PRR), linking lipid metabolism and immune surveillance, and its structural versatility underlies its ability to interact with diverse ligands ranging from lipoproteins to microbial components (14, 15).

2.2 Cellular and tissue distribution

CD36 is widely expressed in metabolically active and immune-relevant tissues. High expression is found in adipocytes, macrophages, dendritic cells, platelets, endothelial cells, cardiomyocytes, and hepatocytes, among others (16). This broad distribution reflects its multifaceted functions: in parenchymal cells such as hepatocytes, adipocytes, and cardiomyocytes, CD36 acts as a fatty acid translocase that supports long-chain fatty acid uptake and energy metabolism; in endothelial cells it regulates angiogenesis and vascular integrity; and in immune cells it couples lipid sensing/uptake to functions such as pathogen recognition, phagocytosis, antigen presentation, and metabolic reprogramming (17). Notably,

tissue-specific expression is tightly regulated by transcription factors such as PPAR γ , LXR, and nf-K β , allowing CD36 to adapt its function according to metabolic and inflammatory contexts (18). A detailed summary of cell type-specific expression, ligands, and functions is presented in Table 1.

2.3 Ligand repertoire and recognition mechanisms

A defining feature of CD36 is its promiscuous ligand-binding capacity. It recognizes a wide spectrum of endogenous and exogenous molecules, enabling it to act at the intersection of lipid metabolism, immunity, and inflammation. Endogenous ligands include long-chain fatty acids, oxLDL, high-density lipoproteins (HDL), thrombospondin-1, and advanced glycation end products (AGEs). Exogenous ligands encompass pathogen-associated molecular patterns (PAMPs), such as components of bacterial cell

TABLE 1 CD36 expression, ligands, and functions across cell types.

Cell type	Major ligands	Primary functions	Disease relevance
Macrophages	oxLDL, apoptotic cells, PAMPs, AGEs, TSP-1	Foam cell formation, phagocytosis, inflammasome activation, cytokine production	Atherosclerosis, diabetes, chronic inflammation (19)
Dendritic cells (DCs)	Apoptotic cells, microbial ligands	Antigen uptake and presentation, T-cell priming, immune tolerance	Autoimmunity, infection (20)
Neutrophils	oxLDL, microbial components, phospholipids	Phagocytosis, NETosis, ROS production, cytokine secretion	Cancer progression (21)
Adipocytes	Long-chain fatty acids, lipoproteins	Fatty acid uptake, lipid storage, metabolic regulation	Obesity, metabolic syndrome (22)
Endothelial cells	oxLDL, thrombospondin-1	Angiogenesis regulation, vascular inflammation, apoptosis control	Cardiovascular disease, cancer angiogenesis (23)
Platelets	oxLDL, TSP-1	Platelet activation, thrombosis, vascular remodeling	Thrombosis, cardiovascular events (24)
Cardiomyocytes	Long-chain fatty acids	Energy supply via fatty acid oxidation, metabolic stress response	Heart failure, ischemic heart disease (25)
Taste receptor cells	Long-chain fatty acids	Fatty acid sensing, taste perception	Obesity, dietary preference, metabolic disorders (26)
Hepatocytes	Long-chain fatty acids, oxLDL	Hepatic fatty acid uptake and lipid handling; regulation of lipid storage/oxidation	NAFLD/NASH, insulin resistance (27)

walls and parasitic molecules. Recognition of apoptotic cells is mediated through exposure of phosphatidylserine and oxidized phospholipids on dying cell membranes (28).

Mechanistically, ligand binding triggers conformational changes in CD36 that recruit intracellular signaling adaptors, such as Src family kinases, JNK, and MAPKs, thereby initiating downstream pathways that regulate phagocytosis, cytokine production, and metabolic reprogramming (29). Importantly, CD36 often cooperates with Toll-like receptors (e.g., TLR2/6) to amplify inflammatory signaling, while in other contexts it promotes anti-inflammatory and homeostatic responses (30). This ligand diversity and context dependence explain the dualistic roles of CD36 in disease progression and resolution.

3 Historical and functional evolution of CD36

The scientific understanding of CD36 has undergone remarkable evolution over the past five decades, transitioning from its initial identification as a platelet surface protein to its recognition as a multifunctional receptor with broad physiological and pathological relevance.

3.1 1970s–1980s: platelet glycoprotein, oxLDL uptake, and atherosclerosis

CD36 was first identified in the late 1970s as a glycoprotein on the surface of platelets, later named glycoprotein IV (31). By the early 1980s, it was established that CD36 played a critical role in the uptake of oxLDL, linking it to the development of foam cells and atherosclerosis (32). This discovery positioned CD36 as a key factor in lipid metabolism and cardiovascular diseases.

3.2 1980s–1990s: angiogenesis, adipogenesis, and immune modulation

In the following decades, CD36 research expanded beyond lipid handling to encompass diverse biological processes. Studies in the 1990s identified its function in angiogenesis through interactions with thrombospondin-1, whereby CD36 mediated anti-angiogenic signaling in endothelial cells (33). Concurrently, CD36 was shown to regulate fatty acid uptake and lipid storage in adipose tissue, highlighting its role in adipogenesis and energy homeostasis (34). Additionally, CD36 emerged as a key immune modulator, mediating phagocytosis of apoptotic cells, recognizing microbial ligands, and interacting with Toll-like receptors in innate immunity (35).

3.3 1990s–2000s: expanding roles in metabolism and inflammatory disease

During the 1990s and 2000s, CD36's functions in metabolism and immune modulation further expanded. It was shown to regulate

fatty acid uptake in tissues like muscle and liver, emphasizing its role in metabolic disorders (36). CD36's involvement in immune responses was clarified, particularly in phagocytosis and receptor interactions, enhancing both innate and adaptive immunity. The receptor was increasingly linked to chronic inflammatory diseases like atherosclerosis and osteoarthritis, where its interaction with oxidized lipids contributed to disease progression (37). Its association with metabolic disorders such as obesity and insulin resistance highlighted its potential as a therapeutic target.

3.4 2000s–present: sensory perception, metabolic disease, cancer, and immunity

Since the 2000s, CD36's functional repertoire has expanded further. Notably, it was found to mediate the oral detection of long-chain fatty acids, linking it to taste perception. Its dysregulation has been implicated in metabolic disorders like obesity and non-alcoholic fatty liver disease (38, 39). CD36 also plays a significant role in cancer biology, contributing to tumor angiogenesis, lipid-driven metabolic adaptation, and metastatic potential. Additionally, it remains a versatile immune receptor, bridging innate and adaptive responses, making it a key target for therapeutic interventions across various diseases (40–42).

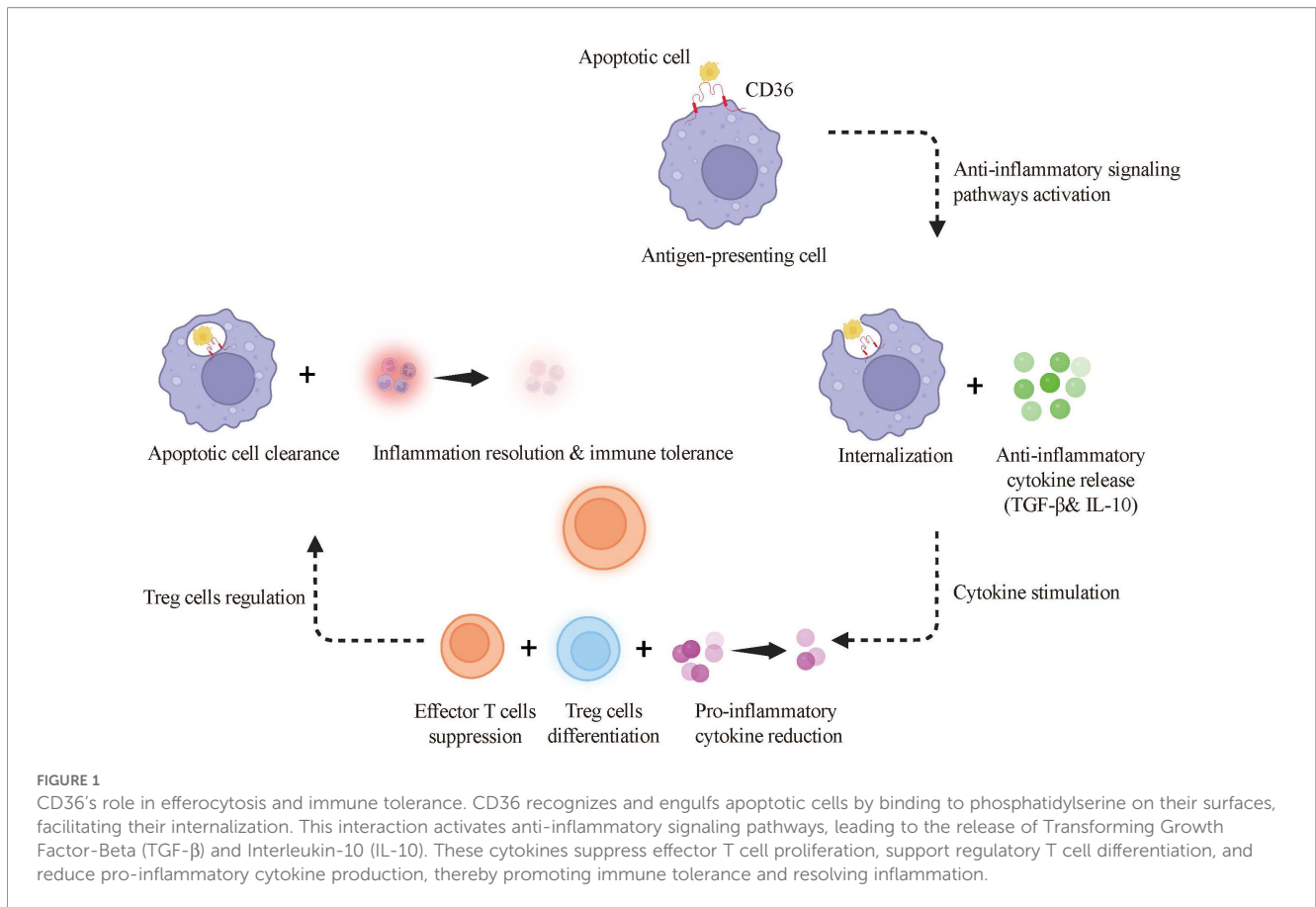
4 CD36 in innate immunity

4.1 Phagocytosis and efferocytosis: mechanisms and signaling

Phagocytosis and efferocytosis enable macrophages and DCs to remove pathogens, apoptotic cells, and debris, thereby supporting host defense and tissue homeostasis. CD36 contributes to both processes by recognizing apoptotic cell-associated ligands and microbial-associated patterns, promoting cargo clearance (43). Efficient efferocytosis is particularly important for preventing secondary necrosis, limiting inappropriate immune activation to self-antigens, and reducing autoimmune risk (44–46) (Figure 1).

CD36 rarely acts alone. Upon ligand engagement, it cooperates with other surface receptors—most notably TLR2/6—to enhance particle binding and coordinate intracellular signaling that drives actin remodeling and engulfment (Figure 2). In macrophages, CD36–TLR2 cooperation has been linked to improved bacterial uptake and clearance in several infection models (47), supporting a role for CD36 as an amplifier of innate immune responses.

At the molecular level, CD36 ligation (e.g., by oxLDL, anionic phospholipids, or thrombospondin-1) promotes assembly of signaling complexes at the phagocytic synapse. This includes recruitment of Src-family kinases (e.g., Lyn, Fyn) and downstream activation of Syk, which together support phagocytic cup formation, cytoskeletal rearrangement, and inflammatory gene regulation (48–51). CD36 signaling also engages PI3K/Akt to support phagocyte survival and phagosome maturation, facilitating efficient digestion of internalized cargo (25, 52, 53).



Small GTPases (e.g., Rac, Cdc42), along with PLC/PKC and MAPK pathways, further coordinate actin dynamics and phagosomal processing (54–56). In select contexts, CD36-dependent signaling has also been associated with caspase activation, which may contribute to clearance programs during responses to infected or transformed targets (57, 58). Collectively, these pathways position CD36 as a multifunctional regulator linking recognition to uptake, processing, and inflammatory tone.

4.1.1 Reconciling discrepant findings in CD36-dependent phagocytosis and efferocytosis

Although many studies support a facilitating role for CD36, its quantitative importance varies across systems. In injury settings enriched for oxidized lipids and apoptotic parenchymal cells (e.g., chronic kidney injury), CD36 deficiency has been associated with impaired corpse clearance and downstream fibrogenic signaling, consistent with a non-redundant contribution under high cargo-load and inflammatory stress (59). In contrast, in tissues where multiple efferocytosis receptors are co-expressed, CD36 loss can be partially compensated by alternative recognition pathways, preserving overall clearance despite changes in phagocyte composition or activation state (60, 61).

Methodological differences likely explain some of the conflicting results. Studies use different apoptotic targets (e.g., neutrophils vs epithelial cells), vary in whether serum-derived opsonins/bridging molecules are present, and measure different

endpoints (binding/tethering, internalization, or phagolysosomal degradation). Because CD36 may mainly affect specific steps in this sequence, its “requirement” can appear stronger or weaker depending on the assay used.

A similar context dependence applies to microbial phagocytosis. CD36 can enhance bacterial uptake and inflammatory responsiveness in certain infections (62), consistent with cooperation with TLR2/6 (63). However, when pathogens are strongly opsonized or when redundant pattern-recognition receptors dominate, host defense may rely more heavily on other PRR pathways, minimizing observable CD36 dependency (64). Together, these data support viewing CD36 as a context-sensitive amplifier—most impactful when its ligands are abundant and redundancy is limited, and less apparent when parallel clearance pathways or strong opsonization can substitute.

4.2 Innate immune cell activation and function modulation via CD36

4.2.1 Neutrophil activation: NETosis and pathogen clearance

Neutrophils are frontline innate immune cells that rapidly eliminate pathogens through phagocytosis, oxidative burst, and release of granule enzymes. CD36 expression on neutrophils enhances pathogen recognition and uptake, thereby strengthening early antimicrobial defenses and accelerating pathogen clearance

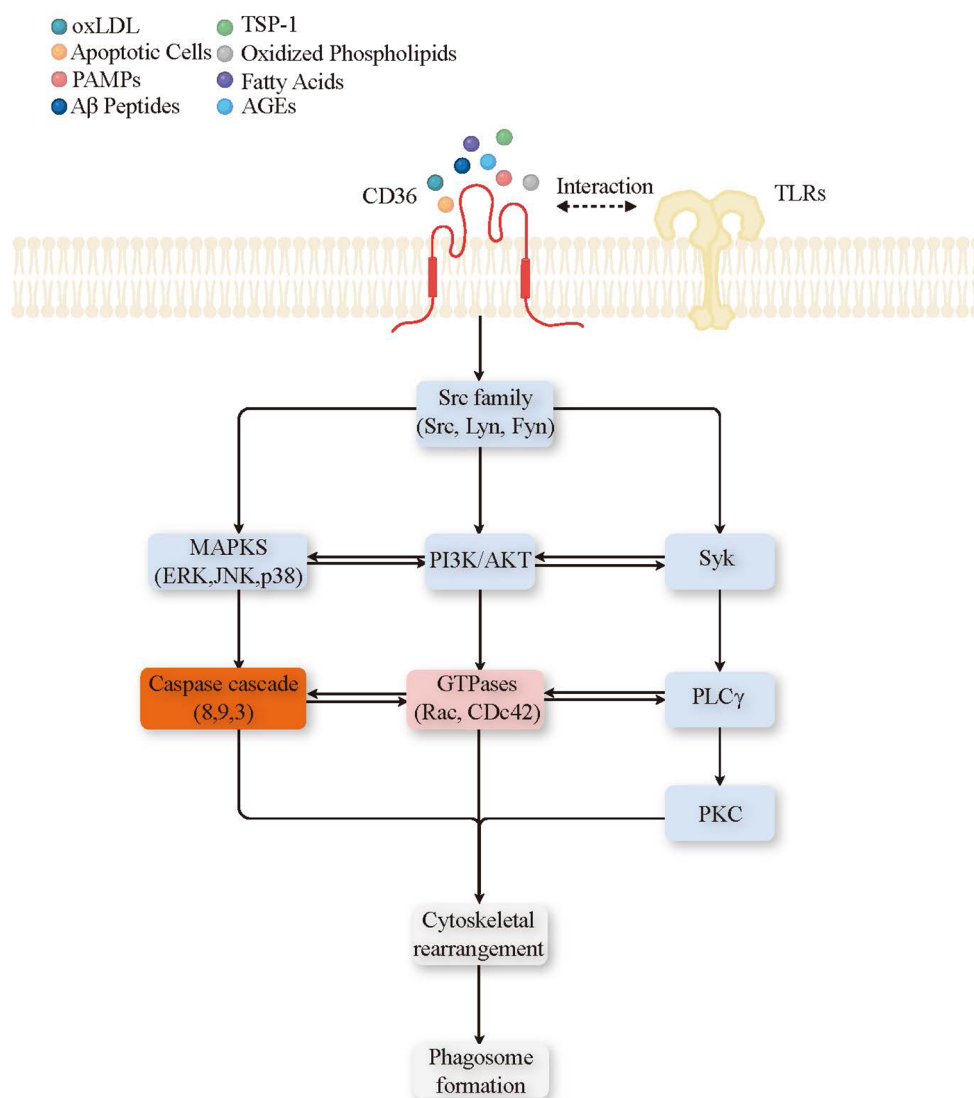


FIGURE 2
 CD36 ligand and signal transduction pathways leading to phagocytosis. Binding of various ligands (oxLDL, TSP-1, PAMPs, Aβ peptides, apoptotic cells, oxidized phospholipids, fatty acids, AGEs) to CD36 on the plasma membrane triggers the recruitment of TLRs, forming a complex that initiates several downstream signaling pathways. Key signaling components include kinases and signaling enzymes such as the Src family (Src, Lyn, Fyn), PI3K/AKT, MAPKs, Syk, PLCγ, and PKC (blue); second messengers and reactive molecules like GTPases (Rac, Cdc42) (pink); inflammatory mediators including the caspase cascade (3, 8, 9) (orange). These pathways converge to facilitate cytoskeletal rearrangement and phagosome formation, thereby promoting phagocytosis. Oxidized Low-Density Lipoprotein (oxLDL), Thrombospondin-1 (TSP-1), Pathogen-Associated Molecular Patterns (PAMPs), Amyloid-Beta (Aβ), Advanced Glycation End-products (AGEs), Non-receptor Tyrosine Kinases (Src family), Proto-Oncogene Tyrosine-Protein Kinase Src (Src), Tyrosine-Protein Kinase Lyn (Lyn), Proto-Oncogene Tyrosine-Protein Kinase Fyn (Fyn), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), Mitogen-Activated Protein Kinases (MAPKs), Spleen Tyrosine Kinase (Syk), Phospholipase C Gamma (PLCγ), Protein Kinase C (PKC), and Guanosine Triphosphatases (GTPases) including Ras-related C3 Botulinum Toxin Substrate (Rac) and Cell Division Control Protein 42 (Cdc42).

(65). Beyond direct killing, neutrophils shape the inflammatory milieu by producing cytokines and chemokines (e.g., IL-8, TNF-α, MIP-1α) that recruit and activate additional immune cells; CD36 engagement can modulate this secretory program, supporting coordinated amplification of the immune response (66, 67).

CD36 has also been linked to neutrophil extracellular trap (NET) formation, a defense mechanism in which chromatin fibers decorated with histones and antimicrobial proteins immobilize and neutralize microbes (68, 69). In several settings, CD36–ligand interactions promote NETosis by driving NADPH

oxidase–dependent ROS generation and activating inflammatory signaling pathways such as MAPKs and nf-Kb (70–72), potentially in part through broader effects on cytokine output (73, 74). However, NET release is not uniformly CD36-dependent: robust NETosis can be triggered by stimuli such as PMA or immune complexes via pathways that bypass CD36 (e.g., PKC activation or Fc receptor signaling), reducing the apparent requirement for CD36 (75). Discrepant conclusions across studies likely reflect both stimulus dependence (receptor-proximal vs bypass signaling) and measurement differences, as NETosis is quantified using distinct

endpoints (extracellular DNA, citrullinated histone H3, MPO–DNA complexes, or functional microbial trapping) that capture different stages of the process. Using the same stimuli and NET assays in human and mouse experiments will clarify whether CD36 is required for NET formation or mainly affects its magnitude.

4.2.2 Macrophage polarization: metabolic and inflammatory switching

As a fatty acid translocase and scavenger receptor, CD36 links macrophage lipid uptake to immunometabolic remodeling. Uptake of long-chain fatty acids and oxidized lipids via CD36 promotes lipid droplet accumulation and can fuel mitochondrial β -oxidation or ROS generation, thereby shaping inflammatory signaling and foam-cell biology in lipid-rich tissues such as atherosclerotic plaques (76). In addition to lipid uptake, CD36 modulates macrophage polarization. Engagement of CD36 by oxLDL, fatty acids, or AGEs promotes M1-like pro-inflammatory polarization, driving secretion of IL-1 β , IL-6, and TNF- α (77). Conversely, CD36-mediated clearance of apoptotic cells favors an M2-like phenotype, characterized by anti-inflammatory cytokine production and tissue repair (78). This context-dependent regulation highlights CD36 as a molecular switch influencing macrophage function in metabolic and inflammatory settings.

4.2.3 Dendritic cell surveillance

CD36 also supports the uptake and clearance of apoptotic cells and microbial ligands by DCs, reinforcing their role in innate immune surveillance. Through this activity, CD36 helps maintain tissue homeostasis and prepares antigens for subsequent presentation to the adaptive immune system (7).

5 CD36 in adaptive immunity

While CD36 is known for its critical contributions to innate immunity, it also plays a vital role in shaping adaptive immune responses. By influencing antigen processing, cytokine production, and the activation of antigen-presenting cells (APCs), CD36 bridges the innate immune system to adaptive immunity, influencing T and B cell responses.

5.1 Antigen presentation by dendritic cells and macrophages

CD36 on dendritic cells and macrophages promotes uptake of apoptotic cells and microbial ligands, thereby supporting antigen processing and presentation. CD36 enhances both MHC class I cross-presentation and MHC class II presentation, expanding the antigen repertoire available for T-cell priming. Engagement of CD36 (e.g., by oxLDL) activates MAPK (ERK, JNK, p38) and nf-Kb pathways, which drive APC maturation and increase expression of MHC molecules and co-stimulatory receptors (CD80/CD86), enabling effective CD28-dependent T-cell activation (79). Functionally, ERK supports antigen-processing capacity, whereas JNK and p38 modulate antigen-presentation programs; in chronic

inflammatory settings, p38 can also favor regulatory outputs, including IL-10 production (80, 81). nf-Kb signaling sustains inflammatory cytokine release (e.g., TNF- α , IL-6), reinforcing APC activation and T-cell survival (82). Collectively, CD36-dependent APC activation shapes the cytokine milieu (including IL-12, IL-6, and TNF- α) to guide T-cell differentiation and coordinate adaptive immunity (82–84) (Figure 3).

5.2 T cell priming, polarization, and tolerance

CD36 shapes T-cell fate through both antigen-presenting cell (APC)–extrinsic effects (antigen uptake, processing, and costimulatory programming) and T-cell–intrinsic effects (lipid uptake and metabolic reprogramming). Consequently, its impact on T-cell priming and polarization is strongly context dependent.

In lipid-rich or pathogen-associated settings—for example, in the presence of oxLDL or microbial lipids—CD36 engagement on APCs often coincides with inflammatory cues (including Toll-like receptor signaling) that promote APC maturation and costimulation. Under these conditions, CD36-dependent antigen handling is frequently associated with enhanced effector polarization, particularly toward Th1 and Th17 programs (85).

By contrast, during efferocytosis under non-inflammatory or resolving conditions, CD36 preferentially supports a tolerogenic APC phenotype, favoring the induction of FoxP3⁺ regulatory T cells (Tregs) and the maintenance of peripheral tolerance (86). Mechanistically, CD36-mediated recognition of apoptotic cells activates anti-inflammatory pathways that increase TGF- β and IL-10 production (87). These cytokines suppress effector T-cell expansion and inflammatory cytokine output while promoting Treg differentiation and function (88, 89).

Beyond its effects mediated through APCs, CD36 also exerts T cell–intrinsic metabolic control. CD36 is expressed on multiple T-cell subsets, including CD8⁺ effector T cells and Tregs, particularly in lipid-rich microenvironments such as tumors and chronically inflamed tissues. As a high-affinity transporter for long-chain fatty acids and oxidized lipids, CD36 directly influences intracellular lipid availability, redox balance, and mitochondrial function (90). In CD8⁺ T cells, excessive CD36-mediated lipid uptake promotes lipid peroxidation and ferroptosis, resulting in impaired cytokine production and reduced cytotoxic capacity, where CD36 functions as an immunometabolic checkpoint that dampens antitumor immunity (85). In contrast, Tregs preferentially exploit CD36-dependent fatty-acid uptake and β -oxidation to sustain mitochondrial fitness, FoxP3 stability, and suppressive function (91).

Seemingly contradictory observations regarding CD36 function can therefore be reconciled by distinguishing where CD36 is expressed and which signals dominate the microenvironment. CD36 on APCs can facilitate effector T-cell priming when coupled to strong inflammatory and costimulatory signals, whereas CD36 on T cells directly modulates metabolic fitness and survival. In lipid-rich environments, CD36-driven lipid uptake may suppress CD8⁺ effector responses through oxidative stress and

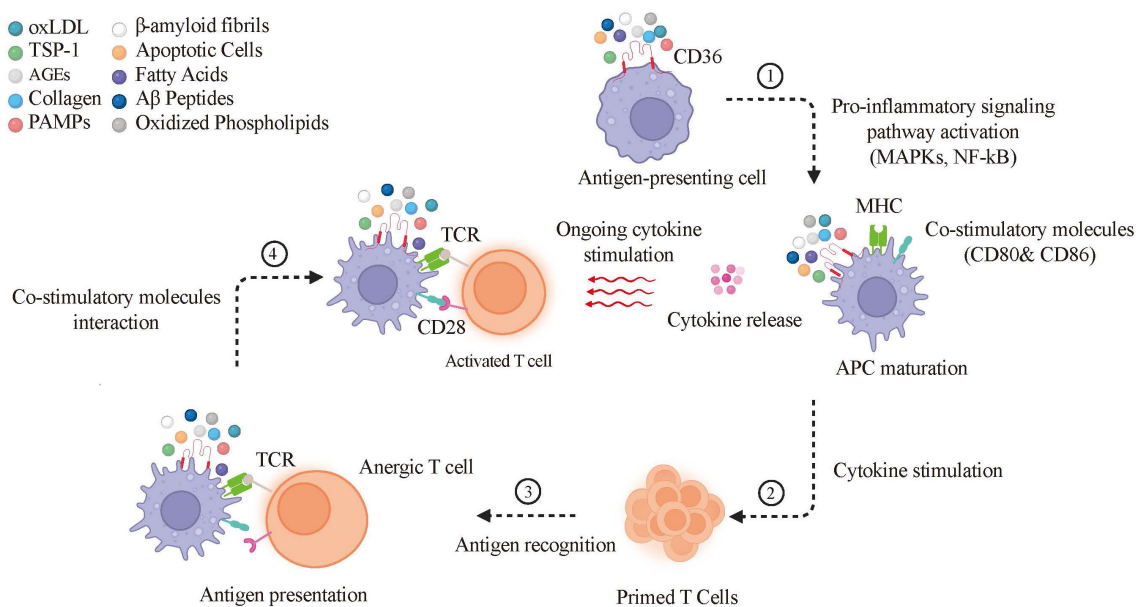


FIGURE 3

CD36's role in maturation of dendritic cells and macrophages and subsequent T-cell activation. CD36 interaction with diverse ligands on APCs (such as oxLDL, TSP-1, AGEs, and apoptotic cells) activates MAPKs (ERK, JNK, p38) and the nf-kb pathway, leading to the upregulation of MHC and co-stimulatory molecules like CD80 and CD86. This interaction also triggers cytokine release, which stimulates primed T cells. The TCR on these primed T cells recognizes antigens presented by the MHC; however, without the additional co-stimulatory signal from molecules like CD28 on the APCs, the T cell remains anergic. Full activation of the T cell is achieved when it receives both MHC-mediated antigen presentation and co-stimulatory signals, along with ongoing cytokine stimulation. Oxidized Low-Density Lipoprotein (oxLDL), Thrombospondin-1 (TSP-1), Advanced Glycation End-products (AGEs), Pathogen-Associated Molecular Patterns (PAMPs), Amyloid-Beta Peptides (Aβ Peptides), Antigen-Presenting Cells (APCs), Mitogen-Activated Protein Kinases (MAPKs) which includes ERK, JNK, p38, Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (nf-kb), Major Histocompatibility Complex (MHC), Cluster of Differentiation 80 and 86 (CD80 and CD86), T-Cell Receptor (TCR), and Cluster of Differentiation 28 (CD28).

ferroptosis (92), while simultaneously reinforcing Treg-mediated immune regulation or tolerogenic antigen repertoires when antigen encounter occurs in the absence of robust danger signals (93).

5.3 Interaction with B cells and antibody responses

Although less extensively characterized, CD36 also plays an indirect role in shaping humoral immunity. By influencing antigen clearance and modulating cytokine production in APCs, CD36 can impact B cell activation and the dynamics of germinal centers, which are critical for the production of antibodies (94). There has been proposed cross-talk between CD36-mediated antigen uptake and Fc receptor (FcR) signaling, suggesting that CD36 may influence antibody class switching and potentially contribute to autoantibody generation (95). These interactions highlight the potential role of CD36 in autoimmunity as well as in protective antibody responses.

6 CD36 in inflammation: a double-edged sword

The dual role of CD36 in inflammation is dictated by its ability to engage various signaling pathways, yielding distinct outcomes

based on the cellular context and the specific ligands involved. This section delineates how CD36's signaling pathways diverge to promote both pro-inflammatory and anti-inflammatory responses, reinforcing the receptor's versatile role in immune modulation.

6.1 Pro-inflammatory pathways triggered by CD36

Upon binding to ligands such as oxLDL, anionic phospholipids, and advanced glycation end products (AGEs), CD36 activates multiple signaling cascades. The proinflammatory signaling pathway triggered by CD36 and its ligand has been shown (Figure 4). Key among these is the MAPK pathway, involving ERK, JNK, and p38 MAPK, which facilitates the nuclear translocation of transcription factors such as nf-kb and AP-1 (96). This translocation upregulates inflammatory genes like TNF- α , IL-6, and IL-1 β (97), which are crucial in inflammatory disorders such as rheumatoid arthritis where CD36-mediated MAPK activation exacerbates tissue damage (98).

Further, CD36's interaction with oxLDL and lipopolysaccharide (LPS) robustly stimulates the PI3K/AKT pathway, enhancing cellular responses that perpetuate inflammation, as observed in chronic conditions like COPD (99). Similarly, activation of the JAK/

STAT pathway by CD36, especially in the context of systemic lupus erythematosus (SLE), exacerbates chronic inflammation through enhanced cytokine production (100). Additionally, the interaction of CD36 with TSP-1 initiates the recruitment of adaptor proteins like MyD88 and TRIF (101), leading to the activation of kinase TAK1 and NADPH oxidase, which results in the production of reactive oxygen species (ROS) (102, 103). NADPH oxidase generates ROS, which further activates MAPK pathways and nf-Kb, intensifying the inflammatory signaling cascades and contributing to neuroinflammatory processes in diseases like Alzheimer's (104).

Moreover, CD36 activation can lead to the formation of the NLRP3 inflammasome, a multiprotein complex that plays a pivotal role in innate immunity (105). This inflammasome activates caspase-1, an enzyme critical for the maturation and release of pro-inflammatory cytokines such as IL-1 β and IL-18 (106, 107). The activation of NLRP3 and caspase-1 contributes significantly to the inflammatory response, linking CD36 signaling to the exacerbation of inflammation in various chronic conditions such as type 2 diabetes (108).

6.2 Anti-inflammatory pathways triggered by CD36

Conversely, CD36's engagement with anti-inflammatory ligands such as omega-3 fatty acids activates nuclear receptors like Liver X Receptors (LXRs) (109) and Peroxisome Proliferator-Activated Receptor gamma (PPAR γ) (110). These receptors facilitate the transcription of genes that not only enhance cholesterol efflux but also diminish the expression of pro-inflammatory genes, supporting the resolution of inflammation and aiding tissue recovery (111). The anti-inflammatory signaling pathway triggered by CD36 and its ligand has been shown (Figure 5).

Activation of AMP-activated protein kinase (AMPK) by CD36, in response to its interaction with ligands, downregulates nf-Kb signaling, thereby reducing the production of pro-inflammatory cytokines (112, 113). This modulation is particularly advantageous in inflammatory bowel disease (IBD), where it helps mitigate intestinal inflammation and promotes mucosal healing (114). Additionally, CD36-mediated activation of the cAMP Response Element-Binding Protein (CREB) pathway increases the production of anti-inflammatory cytokines such as IL-10, crucial for suppressing inflammation in conditions like psoriasis (115).

Furthermore, engagement of CD36 with its ligands also triggers the Nrf2 pathway, a critical regulator of cellular defense mechanisms against oxidative stress (116), which is particularly significant in conditions where inflammation results in tissue damage, such as multiple sclerosis (MS) (117). Enhancing this pathway through CD36 activation can substantially mitigate disease progression and severity by boosting cellular resilience against oxidative stress (118).

Additionally, CD36 activation leads to the stimulation of SIRT1 (Sirtuin 1), a NAD⁺-dependent deacetylase that plays a key role in

cellular stress responses (119, 120). SIRT1 activation results in the deacetylation and inhibition of nf-Kb, further contributing to the reduction of pro-inflammatory cytokine production (121). This pathway also enhances mitochondrial function and promotes autophagy, aiding in the resolution of inflammation and the maintenance of cellular homeostasis (122, 123).

6.3 Underlying mechanisms of CD36 driving both pro-inflammatory and anti-inflammatory pathways

CD36 orchestrates diverse immune responses by activating both pro-inflammatory and anti-inflammatory pathways, reflecting its complex regulatory role. This section explores the mechanisms enabling these dual actions, focusing on cellular context, ligand specificity, signaling overlap, transcriptional regulation, and feedback loops.

6.3.1 Cellular context

The impact of CD36 signaling is highly dependent on the cellular environment, which varies based on cell type and activation state. This variability affects how ligands interact with CD36, influencing downstream signaling pathways. For instance, in macrophages, CD36 engagement with oxLDL typically promotes a pro-inflammatory response, facilitating the formation of foam cells, a key process in atherosclerosis development (124). In contrast, when endothelial cells engage CD36 with the same oxLDL under stress-free conditions, it triggers protective, anti-inflammatory pathways that help maintain vascular homeostasis (125). This difference can be attributed to the distinct sets of downstream signaling molecules and receptors expressed in macrophages versus endothelial cells, illustrating how the cellular context dictates the outcome of CD36-ligand interactions (126).

6.3.2 Ligand specificity and receptor crosstalk

Ligands may not be exclusively pro-inflammatory or anti-inflammatory. For example, phospholipids, commonly recognized for their role in membrane structure and pro-inflammatory signaling (127), can potentially activate anti-inflammatory pathways under certain conditions, such as low concentration exposure or in the presence of other modulating signals (128). This dual potential is often due to receptor crosstalk. Receptor crosstalk occurs when the binding of a ligand to CD36 influences the activity of other receptors or signaling pathways (90). For instance, binding of phospholipids to CD36 may modulate the function of TLRs or other scavenger receptors, leading to a combination of signaling responses (129). This interaction can result in the activation of anti-inflammatory pathways through receptors like LXRs or PPAR γ (130), while simultaneously influencing pro-inflammatory pathways through TLRs or nf-Kb (131). The complexity of these interactions results in a mixed response, where the final outcome depends on the balance and context of these signaling events.

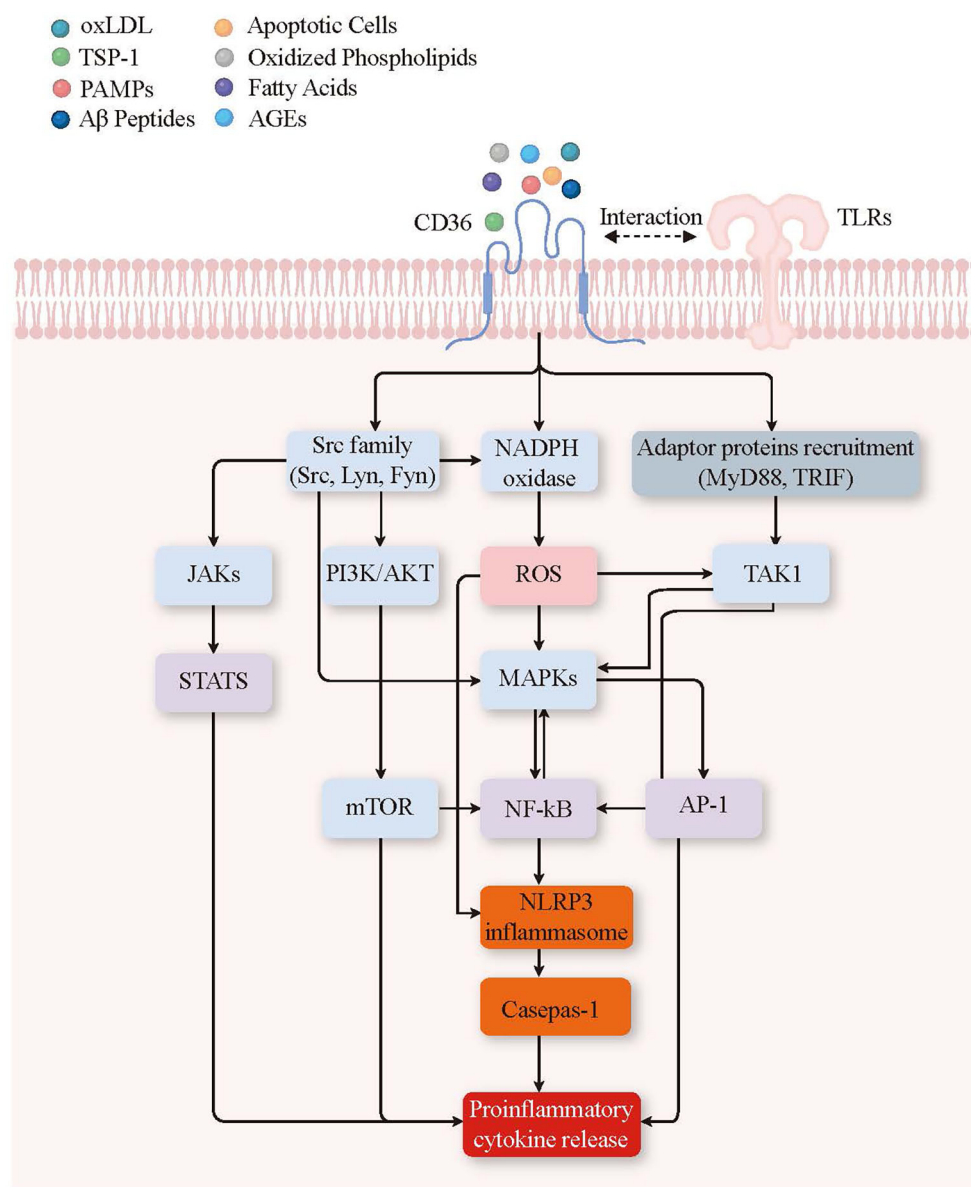


FIGURE 4
 CD36 ligand and signal transduction pathways leading to proinflammatory cytokine release. Binding of various ligands (oxLDL, TSP-1, PAMPs, Aβ peptides, apoptotic cells, oxidized phospholipids, fatty acids, AGEs) to CD36 on the plasma membrane triggers the recruitment of TLRs, forming a complex that initiates several downstream signaling pathways. Key signaling components include kinases and signaling enzymes such as the Src family (Src, Lyn, Fyn), NADPH oxidase, JAKs, PI3K/AKT, TAK1, mTOR, and MAPKs (blue); second messengers and reactive molecules like ROS (pink); transcription and nuclear factors such as STATs, nf-Kb, and AP-1 (purple); inflammatory mediators including the NLRP3 inflammasome and caspase-1 (orange); and adaptor proteins such as MyD88 and TRIF (grey). These pathways converge to activate the NLRP3 inflammasome and caspase-1, leading to the release of pro-inflammatory cytokines, thereby promoting inflammation. Oxidized Low-Density Lipoprotein (oxLDL), Thrombospondin-1 (TSP-1), Pathogen-Associated Molecular Patterns (PAMPs), Amyloid-Beta Peptides (Aβ Peptides), Advanced Glycation End-products (AGEs), Non-receptor Tyrosine Kinases (Src family), including Proto-Oncogene Tyrosine-Protein Kinase Src (Src), Tyrosine-Protein Kinase Lyn (Lyn), Proto-Oncogene Tyrosine-Protein Kinase Fyn (Fyn), Janus Kinases (JAKs), Signal Transducers and Activators of Transcription (STATs), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), Reactive Oxygen Species (ROS), Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH oxidase), Mitogen-Activated Protein Kinases (MAPKs), Mechanistic Target of Rapamycin (mTOR), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (nf-Kb), Activator Protein 1 (AP-1), NOD-like Receptor Family Pyrin Domain Containing 3 Inflammasome (NLRP3 inflammasome), Caspase-1, Transforming Growth Factor Beta-Activated Kinase 1 (TAK1), Myeloid Differentiation Primary Response 88 (MyD88), and TIR-Domain-Containing Adapter-Inducing Interferon-β (TRIF).

6.3.3 Signaling pathway overlap

The pathways leading to inflammatory responses often share common molecular components with those leading to anti-inflammatory outcomes. For instance, both pro-inflammatory and

anti-inflammatory pathways might involve MAPKs and PI3K/AKT (132) but diverge at a certain point where specific adapters or transcription factors such as nf-Kb (pro-inflammatory (133)) versus PPARγ and LXRs (anti-inflammatory (134)) are activated. The

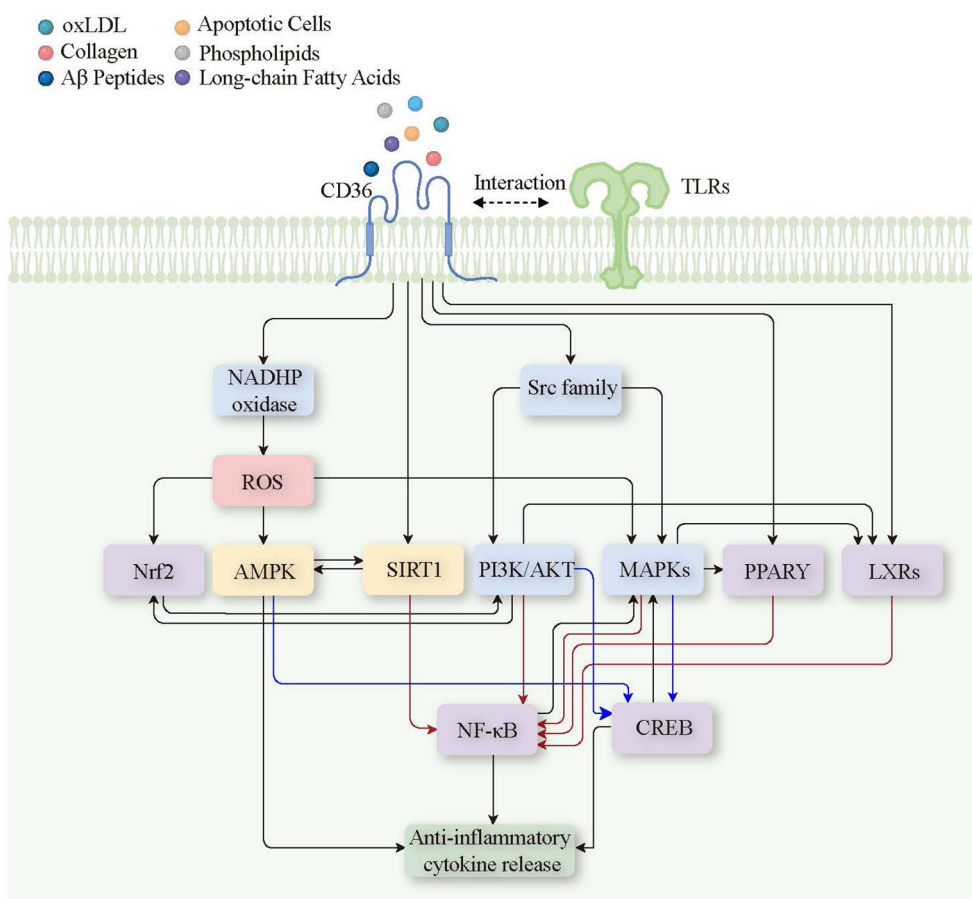


FIGURE 5
 CD36 ligand and signal transduction pathways leading to anti-inflammatory cytokine release. Binding of various ligands (oxLDL, collagen, Aβ peptides, apoptotic cells, phospholipids, long-chain fatty acids) to CD36 on the plasma membrane triggers the recruitment of TLRs, forming a complex that initiates several downstream signaling pathways. Key signaling components include kinases and signaling enzymes such as NADPH oxidase, Src family, PI3K/AKT, and MAPKs; second messengers and reactive molecules like ROS; metabolic and stress response regulators such as AMPK and SIRT1; transcription factors and nuclear receptors including Nrf2, PPARγ, LXR, nf-κB, and CREB. These pathways converge to activate anti-inflammatory responses, leading to the release of anti-inflammatory cytokines, thereby promoting inflammation resolution. Red lines indicate the inhibition of nf-κB, while blue lines indicate the activation of the CREB signaling pathway. Oxidized Low-Density Lipoprotein (oxLDL), Amyloid-Beta Peptides (Aβ Peptides), Toll-Like Receptors (TLRs), Nicotinamide Adenine Dinucleotide Phosphate Oxidase (NADPH oxidase), Reactive Oxygen Species (ROS), Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2), AMP-Activated Protein Kinase (AMPK), Sirtuin 1 (SIRT1), Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT), Mitogen-Activated Protein Kinases (MAPKs), Peroxisome Proliferator-Activated Receptor Gamma (PPARγ), Liver X Receptors (LXR), Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (nf-κB), and cAMP Response Element-Binding Protein (CREB).

initial segments of these pathways may be similar, which allows a ligand the potential to influence both pathways depending on the dynamics within the cell at the time of activation.

6.3.4 Differential regulation of transcription factors

Some transcription factors can have dual roles depending on the context, such as nf-κB, which is typically associated with inflammation but can also participate in the resolution phase under certain conditions (135). For instance, during the later stages of inflammation, nf-κB can induce the expression of anti-inflammatory genes like IL-10 and TGF-β in the presence of specific cofactors or signaling molecules (136). Additionally, in the context of chronic inflammation, such as in atherosclerosis, nf-κB activation in

regulatory T cells (Tregs) can promote the production of anti-inflammatory cytokines, aiding in the resolution of inflammation (137). The balance between different forms of the same transcription factor or its interaction with other cofactors can shift the response from pro-inflammatory to anti-inflammatory, illustrating the complexity and adaptability of immune responses.

6.3.5 Feedback mechanisms

Cells often have intrinsic feedback mechanisms that can alter the response to a stimulus. For example, prolonged exposure to an inflammatory stimulus might activate regulatory pathways aimed at suppressing overactive inflammatory responses to prevent tissue damage, thus engaging anti-inflammatory mechanisms even in the presence of a primarily pro-inflammatory ligand (138).

7 Therapeutic targeting of CD36

CD36 is a multifunctional scavenger receptor that integrates lipid uptake with inflammatory and immune signaling. Because it participates in diverse processes (e.g., fatty acid transport, oxLDL recognition, macrophage activation, and immune-cell metabolic programming), CD36-targeted interventions must be context-specific (cell type, ligand milieu, and disease stage). Therapeutic development is therefore evolving beyond broad CD36 inhibition toward modality- and tissue-tailored strategies that (i) reduce CD36 expression or activity in pathogenic compartments, (ii) block defined CD36-ligand axes driving disease, (iii) rewire CD36 trafficking/signaling to avoid systemic metabolic liabilities, and (iv) use targeted delivery or rational combinations to improve efficacy and safety.

7.1 Modulating CD36 expression and activity

To modulate CD36 pathways, researchers increasingly apply nucleic-acid based approaches that enable cell- or tissue-selective control of CD36 function. These include RNA interference (RNAi) and antisense strategies to reduce CD36 expression, as well as CRISPR/Cas9-based editing to generate durable loss-of-function in experimental models (139). Importantly, delivery technologies (e.g., lipid nanoparticles and ligand-directed carriers) are enabling *in vivo* editing or transcriptional silencing in disease-relevant tissues, which may mitigate systemic effects. Recent work also highlights that targeting upstream regulators (e.g., transcriptional programs that govern FA uptake and scavenger receptor expression) can indirectly tune CD36 activity while preserving basal homeostasis (13). Beyond direct receptor knockdown, emerging strategies include modulating downstream metabolic nodes (e.g., AMPK activation) or inflammatory programs to reduce CD36-driven lipid overload and sterile inflammation (140).

7.2 Inhibiting CD36-ligand interactions

Directly blocking pathogenic CD36–ligand interactions is a key therapeutic strategy. While small-molecule inhibitors such as sulfosuccinimidyl oleate (SSO) suppress CD36-mediated fatty acid uptake and signaling, their irreversible action and limited selectivity hinder translation (141), motivating efforts to develop reversible, more selective antagonists and define ligand-specific binding determinants. In parallel, biologics (peptides/antibodies) that target defined CD36 epitopes have advanced; the peptide EP80317 reduced atherosclerosis in ApoE-deficient mice (142). In oncology, CD36 is emerging as an immunometabolic checkpoint: the humanized IgG4 antibody PLT012 enhanced antitumor immunity in lipid-rich tumors (143).

7.3 Targeting CD36 trafficking and signaling bias

An emerging concept is that CD36 pathogenicity can be reduced without complete receptor ablation by controlling receptor localization, turnover, and signaling output. CD36 trafficking is dynamically regulated by post-translational modifications, including palmitoylation, which influences membrane residence and endocytosis (144). Modulating these processes can, in principle, reduce deleterious lipid uptake or inflammatory signaling in specific compartments while maintaining essential basal functions. For example, inhibition of CD36 palmitoylation was reported to promote mitochondrial localization, enhance fatty acid beta-oxidation, and alleviate lipid accumulation and inflammation in a NASH model (145). Such strategies point to a next generation of CD36-directed therapies that target receptor behavior (trafficking/signaling bias) rather than simply receptor abundance.

7.4 Precision delivery and rational combination strategies

Given CD36's broad expression, precision delivery has become central to improving therapeutic index. Nanocarrier-based systems and targeted nanoparticles can concentrate CD36 inhibitors within disease-relevant tissues such as atherosclerotic plaques, inflamed adipose depots, fibrotic liver, or the tumor microenvironment (146). Targeting ligands (antibodies, peptides, aptamers) and stimuli-responsive formulations (pH/enzymatic triggers) offer additional specificity. Combination regimens are also gaining traction: CD36 blockade can be paired with lipid-lowering agents or anti-inflammatory drugs in metabolic disease, and with immune checkpoint inhibitors or anti-angiogenic therapy in oncology, where preclinical data suggest CD36 targeting may restore responsiveness to PD-1/PD-L1 blockade in lipid-rich, immune-excluded settings (147).

7.5 Challenges and potential side effects of targeting CD36

7.5.1 Complex role in physiology and immunity

Targeting CD36 poses significant challenges due to its involvement in crucial physiological processes such as lipid metabolism, clearance of apoptotic cells, and immune response regulation. Because CD36 facilitates these essential functions, inhibiting it could disrupt normal cellular operations, potentially leading to unintended consequences (148). For instance, impaired clearance of apoptotic cells due to CD36 inhibition might result in the accumulation of cellular debris, provoking chronic inflammation (149).

7.5.2 Risk of exacerbating inflammatory conditions

Another major concern with targeting CD36 is the risk of exacerbating chronic inflammatory conditions. CD36 plays a critical role in balancing pro-inflammatory and anti-inflammatory signaling pathways. In conditions like atherosclerosis or metabolic syndrome, where inflammation is a central feature, indiscriminate inhibition of CD36 could shift the balance towards increased inflammation, potentially worsening the clinical outcomes (29).

7.5.3 Selective inhibition challenges

The broad expression of CD36 across various tissues and its interaction with multiple ligands complicates the development of targeted therapies. Selective inhibition of CD36 is essential to avoid interfering with its beneficial effects, such as its roles in clearing oxidized lipoproteins and apoptotic cells (150). Developing receptor-specific modulators that can selectively block pathological interactions without impeding the receptor's normal functions remains a crucial area of research.

7.5.4 Targeted delivery systems

To mitigate the potential side effects of systemic CD36 inhibition, research is focusing on targeted delivery systems. These systems aim to concentrate therapeutic agents at specific disease sites, such as atherosclerotic plaques or tumor tissues, minimizing systemic exposure and reducing adverse effects on healthy tissues. Advanced drug delivery technologies, including nanoparticle-based carriers and localized drug depots, offer promising methods to achieve this targeted approach (146).

8 Conclusion and perspectives

Throughout this review, we have detailed the multifunctional role of CD36, emphasizing its critical influence in both promoting and regulating immune responses. CD36's involvement in key processes such as phagocytosis, inflammation, and the integration of innate and adaptive immune systems underscores its potential as a valuable therapeutic target across a spectrum of diseases. By facilitating essential interactions within the immune system, CD36 plays a pivotal role in the progression of metabolic disorders and cardiovascular diseases.

The intricate role of CD36 in immune modulation is vital for developing innovative therapeutic strategies. Its impact on the functionality of APCs and T-cell responses presents strategic opportunities for enhancing immune effectiveness, which is particularly valuable in improving vaccine efficacy. Future research focusing on CD36 pathways holds promise for not only mitigating chronic inflammation but also for preventing the severe complications associated with inflammatory conditions. By expanding our understanding and targeting of CD36, we can potentially revolutionize treatment paradigms, improving outcomes across a broad range of immune-related disorders.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

XZ: Writing – original draft. L-jL: Writing – review & editing. Y-wW: Writing – review & editing. LC: Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by National Natural Science Foundation of China (82293635), the Key Program of National Natural Science Foundation of China (92169211), National Natural Science Foundation of China (82471823 and 82173823) and the National Key Research and Development Program of China (No. 2023YFC2306401).

Acknowledgments

We would like to sincerely acknowledge all persons and agencies that contributed in one way or another towards the compilation of this review. Furthermore, we acknowledge the Shanghai University School of Medicine for facilitating this research.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

- Holgate ST. Innate and adaptive immune responses in asthma. *Nat Med.* (2012) 18:673–83. doi: 10.1038/nm.2731
- Canton J, Neculai D, Grinstein S. Scavenger receptors in homeostasis and immunity. *Nat Rev Immunol.* (2013) 13:621–34. doi: 10.1038/nri3515
- Nozaki S, Kashiwagi H, Yamashita S, Nakagawa T, Kostner B, Tomiyama Y, et al. Reduced uptake of oxidized low density lipoproteins in monocyte-derived macrophages from cd36-deficient subjects. *J Clin Invest.* (1995) 96:1859–65. doi: 10.1172/JCI118231
- Simantov R, Silverstein RL. Cd36: A critical anti-angiogenic receptor. *Front Biosci.* (2003) 8:s874–82. doi: 10.2741/1168
- Christiaens V, Van Hul M, Lijnen HR, Scroyen I. Cd36 promotes adipocyte differentiation and adipogenesis. *Biochim Biophys Acta (BBA)-General Subj.* (2012) 1820:949–56. doi: 10.1016/j.bbagen.2012.04.001
- Sayed A, Šerý O, Plesnik J, Daoudi H, Rouabah A, Rouabah L, et al. Cd36 aa genotype is associated with decreased lipid taste perception in young obese, but not lean, children. *Int J Obes.* (2015) 39:920–4. doi: 10.1038/ijo.2015.20
- Urban BC, Willcox N, Roberts DJ. A role for cd36 in the regulation of dendritic cell function. *Proc Natl Acad Sci.* (2001) 98:8750–5. doi: 10.1073/pnas.151028698
- Westman J, Grinstein S, Marques PE. Phagocytosis of necrotic debris at sites of injury and inflammation. *Front Immunol.* (2020) 10:3030. doi: 10.3389/fimmu.2019.03030
- Barreto J, Karathanasis SK, Remaley A, Sposito AC. Role of lox-1 (Lectin-like oxidized low-density lipoprotein receptor 1) as a cardiovascular risk predictor: mechanistic insight and potential clinical use. *Arteriosclerosis thrombosis Vasc Biol.* (2021) 41:153–66. doi: 10.1161/ATVBAHA.120.315421
- Silverstein RL, Febbraio M. Cd36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior. *Sci Signaling.* (2009) 2:re3–re. doi: 10.1126/scisignal.272re3
- Gherardin NA, Redmond SJ, McWilliam HE, Almeida CF, Gourley KH, Seneviratna R, et al. Cd36 family members are tcr-independent ligands for cd1 antigen-presenting molecules. *Sci Immunol.* (2021) 6:eabg4176. doi: 10.1126/sciimmunol.abg4176
- Rač ME, Safranow K, Pencyljusz W. Molecular basis of human cd36 gene mutations. *Mol Med.* (2007) 13:288–96. doi: 10.2119/2006-00088.Rac
- Glatz JF, Heather LC, Luiken JJ. Cd36 as a gatekeeper of myocardial lipid metabolism and therapeutic target for metabolic disease. *Physiol Rev.* (2024) 104:727–64. doi: 10.1152/physrev.00011.2023
- Zeng S, Wu F, Chen M, Li Y, You M, Zhang Y, et al. Inhibition of fatty acid translocase (Fat/cd36) palmitoylation enhances hepatic fatty acid β -oxidation by increasing its localization to mitochondria and interaction with long-chain acyl-coa synthetase 1. *Antioxidants Redox Signaling.* (2022) 36:1081–100. doi: 10.1089/ars.2021.0157
- Hao J-W, Wang J, Guo H, Zhao Y-Y, Sun H-H, Li Y-F, et al. Cd36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis. *Nat Commun.* (2020) 11:4765. doi: 10.1038/s41467-020-18565-8
- Hoosdally SJ, Andress EJ, Wooding C, Martin CA, Linton KJ. The human scavenger receptor cd36: glycosylation status and its role in trafficking and function. *J Biol Chem.* (2009) 284:16277–88. doi: 10.1074/jbc.M109.007849
- Krieger M. Scavenger receptor class B type I is a multiligand hdl receptor that influences diverse physiologic systems. *J Clin Invest.* (2001) 108:793–7. doi: 10.1172/JCI14011
- Tontonoz P, Spiegelman BM. Fat and beyond: the diverse biology of ppar γ . *Annu Rev Biochem.* (2008) 77:289–312. doi: 10.1146/annurev.biochem.77.061307.091829
- Zhang J, Chang J, Beg MA, Zhao Y, Chen Y. Cd36 Facilitate Macrophage Phagocytosis through Mitochondrial Ros during Initiation of Atherosclerosis. *Circulation.* (2022) 146:A14406–A. doi: 10.1161/circ.146.suppl_1.14406
- Ma Y, Jiang T, Zhu X, Xu Y, Wan K, Zhang T, et al. Efferocytosis in dendritic cells: an overlooked immunoregulatory process. *Front Immunol.* (2024) 15:1415573. doi: 10.3389/fimmu.2024.1415573
- Ekstedt S, Cardenas EI, Piersiala K, Liljeström V, Petro M, Ezerskyte M, et al. Cd18 and cd36 expression in neutrophils from tumors and tumor-draining lymph nodes: implications for metastasis in oral squamous cell carcinoma. *Clin Exp Metastasis.* (2025) 42:37. doi: 10.1007/s10585-025-10356-z
- He N, Li Y, Liu F, Dong X, Ma D. Adipocytes regulate monocyte development through the ogt-nefa-cd36/fabp4 pathway in high-fat diet-induced obesity. *Cell Death Dis.* (2025) 16:401. doi: 10.1038/s41419-025-07721-x
- Cifarelli V, Appak-Baskoy S, Peche VS, Kluzak A, Shew T, Narendran R, et al. Visceral obesity and insulin resistance associate with cd36 deletion in lymphatic endothelial cells. *Nat Commun.* (2021) 12:3350. doi: 10.1038/s41467-021-23808-3
- Tang Z, Xu Y, Tan Y, Shi H, Jin P, Li Y, et al. Cd36 mediates sars-cov-2-envelope-protein-induced platelet activation and thrombosis. *Nat Commun.* (2023) 14:5077. doi: 10.1038/s41467-023-40824-7
- Shu H, Peng Y, Hang W, Nie J, Zhou N, Wang DW. The role of cd36 in cardiovascular disease. *Cardiovasc Res.* (2022) 118:115–29. doi: 10.1093/cvr/cvaa319
- Nagai Y, Tokita K, Yasumatsu K. Fatty acid taste quality information via gpr40 and cd36 in the posterior tongue of mice. *Acta Physiologica.* (2025) 241:e70071. doi: 10.1111/apha.70071
- Rada P, González-Rodríguez Á, García-Monzón C, Valverde ÁM. Understanding lipotoxicity in naflD pathogenesis: is cd36 a key driver? *Cell Death Dis.* (2020) 11:802.
- Wang J, Cao H, Yang H, Wang N, Weng Y, Luo H. The function of cd36 in mycobacterium tuberculosis infection. *Front Immunol.* (2024) 15:1413947. doi: 10.3389/fimmu.2024.1413947
- Karunakaran U, Elumalai S, Moon J-S, Won K-C. Cd36 signal transduction in metabolic diseases: novel insights and therapeutic targeting. *Cells.* (2021) 10:1833. doi: 10.3390/cells10071833
- Seimon TA, Nadolski MJ, Liao X, Magallon J, Nguyen M, Feric NT, et al. Atherogenic lipids and lipoproteins trigger cd36-tlr2-dependent apoptosis in macrophages undergoing endoplasmic reticulum stress. *Cell Metab.* (2010) 12:467–82. doi: 10.1016/j.cmet.2010.09.010
- Soucek O, Kacerovsky M, Kacerovska Musilova I, Stranik J, Kukla R, Bolehovska R, et al. Amniotic fluid cd36 in pregnancies complicated by spontaneous preterm delivery: A retrospective cohort study. *J Maternal-Fetal Neonatal Med.* (2023) 36:2214838. doi: 10.1080/14767058.2023.2214838
- Mallat Z, Tedgui A. Century of milestones and breakthroughs related to the immune mechanisms of atherosclerosis. *Arteriosclerosis Thrombosis Vasc Biol.* (2024) 44:1002–6. doi: 10.1161/ATVBAHA.124.319397
- Dawson DW, Pearce SFA, Zhong R, Silverstein RL, Frazier WA, Bouck NP. Cd36 mediates the *in vitro* inhibitory effects of thrombospondin-1 on endothelial cells. *J Cell Biol.* (1997) 138:707–17. doi: 10.1083/jcb.138.3.707
- Greenwald T, Scheck S, Rhinehart-Jones T. Heart cd36 expression is increased in murine models of diabetes and in mice fed a high fat diet. *J Clin Invest.* (1995) 96:1382–8. doi: 10.1172/JCI118173
- Frantz S, Kobzik L, Kim Y-D, Fukazawa R, Medzhitov R, Lee RT, et al. Tll4 (Tlr4) expression in cardiac myocytes in normal and failing myocardium. *J Clin Invest.* (1999) 104:271–80. doi: 10.1172/JCI6709
- Febbraio M, Hajjar DP, Silverstein RL. Cd36: A class B scavenger receptor involved in angiogenesis, atherosclerosis, inflammation, and lipid metabolism. *J Clin Invest.* (2001) 108:785–91. doi: 10.1172/JCI14006
- Pfander D, Cramer T, Deuerling D, Weseloh G, Swoboda B. Expression of thrombospondin-1 and its receptor cd36 in human osteoarthritic cartilage. *Ann Rheumatic Dis.* (2000) 59:448–54. doi: 10.1136/ard.59.6.448
- Laugerette F, Passilly-Degrace P, Patris B, Niot I, Febbraio M, Montmayeur J-P, et al. Cd36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. *J Clin Invest.* (2005) 115:3177–84. doi: 10.1172/JCI25299
- Yan W, Cui X, Guo T, Liu N, Wang Z, Sun Y, et al. Alox15 aggravates metabolic dysfunction-associated steatotic liver disease in mice with type 2 diabetes via activating the ppar γ /cd36 axis. *Antioxidants Redox Signaling.* (2025). doi: 10.1089/ars.2024.0670
- Perry JS, Russler-Germain EV, Zhou YW, Purtha W, Cooper ML, Choi J, et al. Cd36 mediates cell-surface antigens to promote thymic development of the regulatory T cell receptor repertoire and allo-tolerance. *Immunity.* (2018) 48:923–36. doi: 10.1016/j.immuni.2018.04.007
- Oh DS, Lee HK. Autophagy protein atg5 regulates cd36 expression and anti-tumor mhc class ii antigen presentation in dendritic cells. *Autophagy.* (2019) 15:2091–106. doi: 10.1080/15548627.2019.1596493
- Wang J, Li Y. Cd36 tango in cancer: signaling pathways and functions. *Theranostics.* (2019) 9:4893. doi: 10.7150/thno.36037
- Prasad G, Dhar V, Mukhopadhya A. Vibrio cholerae ompu mediates cd36-dependent reactive oxygen species generation triggering an additional pathway of mapk activation in macrophages. *J Immunol.* (2019) 202:2431–50. doi: 10.4049/jimmunol.1800389
- Kumar S, Calianese D, Birge RB. Efferocytosis of dying cells differentially modulate immunological outcomes in tumor microenvironment. *Immunol Rev.* (2017) 280:149–64. doi: 10.1111/imr.12587
- Kim KK, Dotson MR, Agarwal M, Yang J, Bradley PB, Subbotina N, et al. Efferocytosis of apoptotic alveolar epithelial cells is sufficient to initiate lung fibrosis. *Cell Death Dis.* (2018) 9:1056. doi: 10.1038/s41419-018-1074-z
- Canavati C, Siam A, Labes S, Trabelsi N, Regev E, Parnasa E, et al. Pathogenic variants of scavenger receptor cd36 lead to decreased efferocytosis and predispose to myocarditis following vaccination with pfizer-biontech bnt162b2 against coronavirus infection (Covid-19). *Circulation.* (2024) 149:270–3. doi: 10.1161/CIRCULATIONAHA.123.064884
- Woodworth KE, Callaghan NI, Davenport Huyer L. Biomaterial strategies for targeted intracellular delivery to phagocytes. *Advanced Funct Materials.* (2025):e08761.

48. Agarwal S, Saha S, Ghosh R, Sarmadhikari D, Asthana S, Maiti TK, et al. Elevated glycosylation of cd36 in platelets is a risk factor for oxdlretstion. Platelet activation in type 2 diabetes. *FEBS J*. (2024) 291:376–91. doi: 10.1111/febs.16976
49. Kazerounian S, Duquette M, Reyes MA, Lawler JT, Song K, Perruzzi C, et al. Priming of the vascular endothelial growth factor signaling pathway by thrombospondin-1, cd36, and spleen tyrosine kinase. *Blood J Am Soc Hematol*. (2011) 117:4658–66. doi: 10.1182/blood-2010-09-305284
50. Yang Y, Liu X, Yang D, Li L, Li S, Lu S, et al. Interplay of cd36, autophagy, and lipid metabolism: insights into cancer progression. *Metabolism*. (2024), 155905. doi: 10.1016/j.metabol.2024.155905
51. Geahlen RL. Getting syk: spleen tyrosine kinase as a therapeutic target. *Trends Pharmacol Sci*. (2014) 35:414–22. doi: 10.1016/j.tips.2014.05.007
52. Yan Y, Zhou M, Meng K, Zhou C, Jia X, Li X, et al. Salvianolic acid B attenuates inflammation and prevent pathologic fibrosis by inhibiting cd36-mediated activation of the pi3k-akt signaling pathway in frozen shoulder. *Front Pharmacol*. (2023) 14:1230174. doi: 10.3389/fphar.2023.1230174
53. Chen S, Peng J, Sherchan P, Ma Y, Xiang S, Yan F, et al. Trem2 activation attenuates neuroinflammation and neuronal apoptosis via pi3k/akt pathway after intracerebral hemorrhage in mice. *J Neuroinflamm*. (2020) 17:1–16. doi: 10.1186/s12974-020-01853-x
54. Dorta-Estremera S, Torres A, Rivera-Robles M, Cruz-Collazo A, Borrero-Garcia L, Dharmawardhane S. Abstract B011: rac and cdc42 inhibition in the tumor microenvironment as a strategy to prevent metastasis. *Cancer Res*. (2023) 83:B011–B. doi: 10.1158/1538-7445.METASTASIS22-B011
55. Freeman SA, Grinstein S. Phagocytosis: receptors, signal integration, and the cytoskeleton. *Immunol Rev*. (2014) 262:193–215. doi: 10.1111/imr.12212
56. Baranova IN, Kurlander R, Bocharov AV, Vishnyakova TG, Chen Z, Remaley AT, et al. Role of human cd36 in bacterial recognition, phagocytosis, and pathogen-induced jnk-mediated signaling. *J Immunol*. (2008) 181:7147–56. doi: 10.4049/jimmunol.181.10.7147
57. Cai L, Wang Z, Ji A, Meyer JM, van der Westhuyzen DR. Scavenger receptor cd36 expression contributes to adipose tissue inflammation and cell death in diet-induced obesity. *PLoS One*. (2012) 7:e36785. doi: 10.1371/journal.pone.0036785
58. Sheedy FJ, Grebe A, Rayner KJ, Kalantari P, Ramkhalawon B, Carpenter SB, et al. Cd36 coordinates nlrp3 inflammasome activation by facilitating intracellular nucleation of soluble ligands into particulate ligands in sterile inflammation. *Nat Immunol*. (2013) 14:812–20. doi: 10.1038/ni.2639
59. Pennathur S, Pasichnyk K, Bahrami NM, Zeng L, Febbraio M, Yamaguchi I, et al. The macrophage phagocytic receptor cd36 promotes fibrogenic pathways on removal of apoptotic cells during chronic kidney injury. *Am J Pathol*. (2015) 185:2232–45. doi: 10.1016/j.ajpath.2015.04.016
60. A-Gonzalez N, Quintana JA, Garcia-Silva S, Mazariegos M, Gonzalez de la Aleja A, Nicolas-Avila JA, et al. Phagocytosis imprints heterogeneity in tissue-resident macrophages. *J Exp Med*. (2017) 214:1281–96. doi: 10.1084/jem.20161375
61. Shrimpton RE, Butler M, Morel A-S, Eren E, Hue SS, Ritter MA. Cd205 (Dec-205): A recognition receptor for apoptotic and necrotic self. *Mol Immunol*. (2009) 46:1229–39. doi: 10.1016/j.molimm.2008.11.016
62. Onlisakin TF, Li H, Xiong Z, Kochman EJ, Yu M, Qu Y, et al. Cd36 provides host protection against klebsiella pneumoniae intrapulmonary infection by enhancing lipopolysaccharide responsiveness and macrophage phagocytosis. *J Infect Dis*. (2016) 214:1865–75. doi: 10.1093/infdis/jiw451
63. Park YM. Cd36, a scavenger receptor implicated in atherosclerosis. *Exp Mol Med*. (2014) 46:e99–e. doi: 10.1038/emm.2014.38
64. Wieland CW, van Lieshout MH, Hoogendijk AJ, van der Poll T. Host defence during klebsiella pneumoniae relies on haematopoietic-expressed toll-like receptors 4 and 2. *Eur Respir J*. (2011) 37:848–57. doi: 10.1183/09031936.00076510
65. Garcia-Bonilla L, Racchumi G, Murphy M, Arnrather J, Iadecola C. Endothelial cd36 contributes to postischemic brain injury by promoting neutrophil activation via csf3. *J Neurosci*. (2015) 35:14783–93. doi: 10.1523/JNEUROSCI.2980-15.2015
66. Pérez-Figueroa E, Álvarez-Carrasco P, Ortega E. Crosslinking of membrane cd13 in human neutrophils mediates phagocytosis and production of reactive oxygen species, neutrophil extracellular traps and proinflammatory cytokines. *Front Immunol*. (2022) 13:994496. doi: 10.3389/fimmu.2022.994496
67. Montecucco F, Steffens S, Burger F, Da Costa A, Bianchi G, Bertolotto M, et al. Tumor Necrosis Factor-Alpha (Tnf- α) Induces Integrin Cd11b/Cd18 (Mac-1) up-Regulation and Migration to the Cc Chemokine Ccl3 (Mip-1 α) on Human Neutrophils through Defined Signalling Pathways. *Cell signalling*. (2008) 20:557–68. doi: 10.1016/j.cellsig.2007.11.008
68. Greenlee MC. Clearance of apoptotic neutrophils and resolution of inflammation. *Immunol Rev*. (2016) 273:357–70. doi: 10.1111/imr.12453
69. Song Y, Kadiyala U, Weerappuli P, Valdez JJ, Yalavarthi S, Louttit C, et al. Antimicrobial microwebs of DNA–histone inspired from neutrophil extracellular traps. *Advanced Materials*. (2019) 31:1807436. doi: 10.1002/adma.201807436
70. Jenne CN, Kubes P. Virus-induced nets—critical component of host defense or pathogenic mediator? *PLoS Pathog*. (2015) 11:e1004546.
71. Hu Y, Wang H, Liu Y. Netosis: sculpting tumor metastasis and immunotherapy. *Immunol Rev*. (2024) 321:263–79. doi: 10.1111/imr.13277
72. Chen J, Wang T, Li X, Gao L, Wang K, Cheng M, et al. DNA of neutrophil extracellular traps promote nf-Kb-dependent autoimmunity via cgas/thr9 in chronic obstructive pulmonary disease. *Signal Transduction Targeted Ther*. (2024) 9:163. doi: 10.1038/s41392-024-01881-6
73. Griffiths HR, Gao D, Pararasa C. Redox regulation in metabolic programming and inflammation. *Redox Biol*. (2017) 12:50–7. doi: 10.1016/j.redox.2017.01.023
74. Awasthi D, Nagarkoti S, Kumar A, Dubey M, Singh AK, Pathak P, et al. Oxidized ldl induced extracellular trap formation in human neutrophils via thr-pkc-irak-mapk and nadph-oxidase activation. *Free Radical Biol Med*. (2016) 93:190–203. doi: 10.1016/j.freeradbiomed.2016.01.004
75. Xanthis A, Hatzitolios A, Fidani S, Befani C, Giannakoulas G, Koliakos G. Receptor of advanced glycation end products (Rage) positively regulates cd36 expression and reactive oxygen species production in human monocytes in diabetes. *Angiology*. (2009) 60:772–9. doi: 10.1177/0003319708328569
76. Prendeville H, Lynch L. Diet, lipids, and antitumor immunity. *Cell Mol Immunol*. (2022) 19:432–44. doi: 10.1038/s41423-021-00781-x
77. Hung M-Y, Yeh C-T, Yadav VK, Fong I-H. The lipoprotein (a)-induced soluble cd36/interleukin-6/ras homolog family member a-gtp signaling axis promotes M1 macrophage polarization in coronary artery spasm. *Circulation*. (2023) 148:A13607–A. doi: 10.1161/circ.148.suppl_1.13607
78. Qin H, Xiao A, Lu Q, Li Y, Luo X, Zheng E, et al. The fatty acid receptor cd36 promotes macrophage infiltration via P110 γ Signaling to stimulate metastasis. *J Advanced Res*. (2025) 74:237–53. doi: 10.1016/j.jare.2024.10.006
79. Ashaq MS, Zhang S, Xu M, Li Y, Zhao B. The regulatory role of cd36 in hematopoiesis beyond fatty acid uptake. *Life Sci*. (2024), 122442. doi: 10.1016/j.lfs.2024.122442
80. Ryan MB, de la Cruz FF, Ahronian LG, Phat S, Myers DT, Shahzade HA, et al. Erk mapk inhibition enhances the immunogenicity of kras-mutant colorectal cancer. In: *MOLECULAR CANCER RESEARCH. AMER ASSOC CANCER RESEARCH 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA* (2020).
81. Lin F-Y, Tsao N-W, Shih C-M, Lin Y-W, Yeh J-S, Chen J-W, et al. The biphasic effects of oxidized-low density lipoprotein on the vasculogenic function of endothelial progenitor cells. *PLoS One*. (2015) 10:e0123971. doi: 10.1371/journal.pone.0123971
82. Butler MO, Lee J-S, Ansen S, Neuberger D, Hodi FS, Murray AP, et al. Long-lived antitumor cd8+ T lymphocytes for adoptive therapy generated using an artificial antigen-presenting cell. *Clin Cancer Res*. (2007) 13:1857–67. doi: 10.1158/1078-0432.CCR-06-1905
83. Li S, Wang N, Brodt P. Metastatic cells can escape the proapoptotic effects of tnf- α through increased autocrine il-6/stat3 signaling. *Cancer Res*. (2012) 72:865–75. doi: 10.1158/0008-5472.CAN-11-1357
84. Albert ML, Pearce SFA, Francisco LM, Sauter B, Roy P, Silverstein RL, et al. Immature dendritic cells phagocytose apoptotic cells via Av β 5 and cd36, and cross-present antigens to cytotoxic T lymphocytes. *J Exp Med*. (1998) 188:1359–68. doi: 10.1084/jem.188.7.1359
85. Ma X, Xiao L, Liu L, Ye L, Su P, Bi E, et al. Cd36-mediated ferroptosis dampens intratumoral cd8+ T cell effector function and impairs their antitumor ability. *Cell Metab*. (2021) 33:1001–12. doi: 10.1016/j.cmet.2021.02.015
86. Subramanian M, Marelli-Berg FM. Cd36 pumps fat to defang killer T cells in tumors. *Cell Metab*. (2021) 33:1509–11. doi: 10.1016/j.cmet.2021.07.004
87. Mikołajczyk TP, Skrzeczyńska-Moncznik JE, Zarębski MA, Marewicz EA, Wiśniewska AM, Dzięba M, et al. Interaction of human peripheral blood monocytes with apoptotic polymorphonuclear cells. *Immunology*. (2009) 128:103–13. doi: 10.1111/j.1365-2567.2009.03087.x
88. Stüber T, Monjezi R, Wallstabe L, Kühnemundt J, Nietzer SL, Dandekar G, et al. Inhibition of tgf- β -receptor signaling augments the antitumor function of ror1-specific car T-cells against triple-negative breast cancer. *J Immunotherapy Cancer*. (2020) 8.
89. Zhong H, Liu Y, Xu Z, Liang P, Yang H, Zhang X, et al. Tgf- β -induced cd8+ Cd103+ Regulatory T cells show potent therapeutic effect on chronic graft-versus-host disease lupus by suppressing B cells. *Front Immunol*. (2018) 9:35. doi: 10.3389/fimmu.2018.00035
90. Chen Y, Zhang J, Cui W, Silverstein RL. Cd36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate. *J Exp Med*. (2022) 219:e20211314. doi: 10.1084/jem.20211314
91. Zhang S, Lv K, Liu Z, Zhao R, Li F. Fatty acid metabolism of immune cells: A new target of tumour immunotherapy. *Cell Death Discov*. (2024) 10:39. doi: 10.1038/s41420-024-01807-9
92. Lee J, Cheu JW-S, Wong CC-L. The diverse roles of lipid metabolism reprogramming in shaping the tumor immune microenvironment. *Cancer Res*. (2025). doi: 10.1158/0008-5472.CAN-25-2568
93. Perry JS, Russler-Germain EV, Zhou YW, Purtha W, Cooper ML, Choi J, et al. Transfer of cell-surface antigens by scavenger receptor cd36 promotes thymic regulatory T cell receptor repertoire development and allo-tolerance. *Immunity*. (2018) 48:923–36. doi: 10.1016/j.immuni.2018.04.007
94. He C, Wang S, Zhou C, He M, Wang J, Ladds M, et al. Cd36 and lc3b initiated autophagy in B cells regulates the humoral immune response. *Autophagy*. (2021) 17:3577–91. doi: 10.1080/15548627.2021.1885183

95. He C, Hua G, Liu Y, Li S. Unveiling the hidden role of the interaction between cd36 and fcγriib: implications for autoimmune disorders. *Cell Mol Biol Lett.* (2024) 29:76. doi: 10.1186/s11658-024-00593-7
96. Zhao T, Chen H, Cheng C, Zhang J, Yan Z, Kuang J, et al. Tiraglutide protects high-glucose-stimulated fibroblasts by activating the cd36-jnk-ap1 pathway to downregulate P4ha1. *Biomedicine Pharmacotherapy.* (2019) 118:109224. doi: 10.1016/j.biopha.2019.109224
97. Park J-Y, Chung T-W, Jeong Y-J, Kwak C-H, Ha S-H, Kwon K-M, et al. Ascofuranone inhibits lipopolysaccharide-induced inflammatory response via nf-kappab and ap-1, P-erk, tnf-α, il-6 and il-1β in raw 264.7 macrophages. *PLoS One.* (2017) 12:e0171322. doi: 10.1371/journal.pone.0171322
98. Alturaiki W, Alhamad A, Alturaiqi M, Mir SA, Iqbal D, Bin Dukhyil AA, et al. Assessment of il28s ilf6 and ccl 5 levels in newly diagnosed saudi patients with rheumatoid arthritis. *Int J Rheumatic Dis.* (2022) 25:1013–9. doi: 10.1111/1756-185X.14373
99. Zhou M, Zhi J, Zhi J, Xiong Z, Wu F, Lu Y, et al. Polysaccharide from *strongylocentrotus nudus* eggs regulates intestinal epithelial autophagy through cd36/pi3k-akt pathway to ameliorate inflammatory bowel disease. *Int J Biol Macromolecules.* (2023) 244:125373. doi: 10.1016/j.ijbiomac.2023.125373
100. Hashimoto R, Kakigi R, Miyamoto Y, Nakamura K, Itoh S, Daida H, et al. Jak-stat-dependent regulation of scavenger receptors in lps-activated murine macrophages. *Eur J Pharmacol.* (2020) 871:172940. doi: 10.1016/j.ejphar.2020.172940
101. Rao X, Zhao S, Braunstein Z, Mao H, Razavi M, Duan L, et al. Oxidized ldl upregulates macrophage dpp4 expression via thr4/trif/cd36 pathways. *EBioMedicine.* (2019) 41:50–61. doi: 10.1016/j.ebiom.2019.01.065
102. Cohen P, Strickson S. The role of hybrid ubiquitin chains in the myd88 and other innate immune signalling pathways. *Cell Death Differentiation.* (2017) 24:1153–9. doi: 10.1038/cdd.2017.17
103. Lee I-T, Shih R-H, Lin C-C, Chen J-T, Yang C-M. Role of thr4/nadph oxidase/ ros-activated P38 mapk in vcam-1 expression induced by lipopolysaccharide in human renal mesangial cells. *Cell Communication Signaling.* (2012) 10:1–15. doi: 10.1186/1478-811X-10-33
104. Zhen J, Chen X, Mao Y, Xie X, Chen X, Xu W, et al. Glx351322, a novel nadph oxidase 4 inhibitor, attenuates tmj osteoarthritis by inhibiting the ros/mapk/nftis signaling pathways. *Oxid Med Cell Longevity.* (2023) 2023:1952348. doi: 10.1155/2023/1952348
105. Hou Y, Wang Q, Han B, Chen Y, Qiao X, Wang L. Cd36 promotes nlrp3 inflammasome activation via the mtros pathway in renal tubular epithelial cells of diabetic kidneys. *Cell Death Dis.* (2021) 12:523. doi: 10.1038/s41419-021-03813-6
106. Guey B, Bodnar M, Manié SN, Tardivel A, Petrilli V. Caspase-1 autoproteolysis is differentially required for nlrp1b and nlrp3 inflammasome function. *Proc Natl Acad Sci.* (2014) 111:17254–9. doi: 10.1073/pnas.1415756111
107. Ataide MA, Andrade WA, Zamboni DS, Wang D, MdC S, BS F, et al. Malaria-induced nlrp12/nlrp3-dependent caspase-1 activation mediates inflammation and hypersensitivity to bacterial superinfection. *PLoS Pathog.* (2014) 10:e1003885. doi: 10.1371/journal.ppat.1003885
108. Chen X, Zhang D, Li Y, Wang W, Bei W, Guo J. Nlrp3 inflammasome and il-1β Pathway in type 2 diabetes and atherosclerosis: friend or foe? *Pharmacol Res.* (2021) 173:105885. doi: 10.1016/j.phrs.2021.105885
109. Ducheix S, Montagner A, Polizzi A, Lasserre F, Marmugi A, Bertrand-Michel J, et al. Essential fatty acids deficiency promotes lipogenic gene expression and hepatic steatosis through the liver X receptor. *J Hepatol.* (2013) 58:984–92. doi: 10.1016/j.jhep.2013.01.006
110. Zheng J-S, Chen J, Wang L, Yang H, Fang L, Yu Y, et al. Replication of a gene-diet interaction at cd36, nos3 and pparγ in response to omega-3 fatty acid supplements on blood lipids: A double-blind randomized controlled trial. *EBioMedicine.* (2018) 31:150–6. doi: 10.1016/j.ebiom.2018.04.012
111. Zhong Q, Zhao S, Yu B, Wang X, Matyal R, Li Y, et al. High-density lipoprotein increases the uptake of oxidized low density lipoprotein via pparγ/cd36 pathway in inflammatory adipocytes. *Int J Biol Sci.* (2015) 11:256. doi: 10.7150/ijbs.10258
112. Huang B-P, Lin C-H, Chen H-M, Lin J-T, Cheng Y-F, Kao S-H. Ampk activation inhibits expression of proinflammatory mediators through downregulation of pi3k/P38 mapk and nf-kb signaling in murine macrophages. *DNA Cell Biol.* (2015) 34:133–41. doi: 10.1089/dna.2014.2630
113. Li Y, Yang P, Zhao L, Chen Y, Zhang X, Zeng S, et al. Cd36 plays a negative role in the regulation of lipophagy in hepatocytes through an ampk-dependent pathway [S. *J Lipid Res.* (2019) 60:844–55. doi: 10.1194/jlr.M090969
114. Bassaganya-Riera J, Reynolds K, Martino-Catt S, Cui Y, Hennighausen L, Gonzalez F, et al. Activation of ppar γ and Δ by conjugated linoleic acid mediates protection from experimental inflammatory bowel disease. *Gastroenterology.* (2004) 127:777–91. doi: 10.1053/j.gastro.2004.06.049
115. Teague HL, Varghese NJ, Tsoi LC, Dey AK, Garshick MS, Silverman JL, et al. Neutrophil subsets, platelets, and vascular disease in psoriasis. *JACC: Basic Trans Sci.* (2019) 4:1–14. doi: 10.1016/j.jaccbts.2018.10.008
116. Li W, Febbraio M, Reddy SP, Yu D-Y, Yamamoto M, Silverstein RL. Cd36 participates in a signaling pathway that regulates ros formation in murine vsmcs. *J Clin Invest.* (2010) 120:3996–4006. doi: 10.1172/JCI42823
117. Gooijert M. The protective and pathogenic roles of cd36 in multiple sclerosis. (2023).
118. Brandes MS, Gray NE. Nrf2 as a therapeutic target in neurodegenerative diseases. *ASN Neuro.* (2020) 12:1759091419899782. doi: 10.1177/1759091419899782
119. Chen Y-P, Tsai C-W, Shen C-Y, Day C-H, Yeh Y-L, Chen R-J, et al. Palmitic acid interferes with energy metabolism balance by adversely switching the sirt1-cd36-fatty acid pathway to the pkc zeta-glut4-glucose pathway in cardiomyoblasts. *J Nutr Biochem.* (2016) 31:137–49. doi: 10.1016/j.jnutbio.2016.01.007
120. Cao Y, Xue Y, Xue L, Jiang X, Wang X, Zhang Z, et al. Hepatic menin recruits sirt1 to control liver steatosis through histone deacetylation. *J Hepatol.* (2013) 59:1299–306. doi: 10.1016/j.jhep.2013.07.011
121. Niu B, He K, Li P, Gong J, Zhu X, Ye S, et al. Sirt1 Upregulation Protects against Liver Injury Induced by a Hfd through Inhibiting Cd36 and the Nf-Kb Pathway in Mouse Kupffer Cells. *Mol Med Rep.* (2018) 18:1609–15. doi: 10.3892/mmr.2018.9088
122. Xu C, Wang L, Fozouni P, Evjen G, Chandra V, Jiang J, et al. Sirt1 is downregulated by autophagy in senescence and ageing. *Nat Cell Biol.* (2020) 22:1170–9. doi: 10.1038/s41556-020-00579-5
123. Dai S-H, Chen L-J, Qi W-H, Ye C-L, Zou G-W, Liu W-C, et al. MicroRNA-145 inhibition upregulates sirt1 and attenuates autophagy in a mouse model of lung ischemia/reperfusion injury via nf-kb-dependent beclin 1. *Transplantation.* (2021) 105:529–39. doi: 10.1097/TP.0000000000003435
124. Yang Z, Ming X-F. *Cd36: the common soil for inflammation in obesity and atherosclerosis.* United Kingdom: Oxford University Press (2011) p. 485–6.
125. Zhong T, Li Y, He X, Liu Y, Dong Y, Ma H, et al. Adaptation of endothelial cells to shear stress under atheroprone conditions by modulating internalization of vascular endothelial cadherin and vinculin. *Ann Trans Med.* (2020) 8. doi: 10.21037/atm-20-3426
126. Kalucka J, Bierhansl L, Wielockx B, Carmeliet P, Eelen G. Interaction of endothelial cells with macrophages—Linking molecular and metabolic signaling. *Pflügers Archiv-European J Physiol.* (2017) 469:473–83. doi: 10.1007/s00424-017-1946-6
127. Yaeger MJ, Shaikh SR, Gowdy KM. Making mountains out of mole hills: the role of cd36 in oxidized phospholipid-driven lung injury. *Am Thorac Soc.* (2024) . p:3–4. doi: 10.1165/rcmb.2023-0312ED
128. Rios FJ, Ferracini M, Pecenin M, Koga MM, Wang Y, Ketelhuth DF, et al. Uptake of oxldl and il-10 production by macrophages requires ppar and cd36 recruitment into the same lipid rafts. *PLoS One.* (2013) 8:e76893. doi: 10.1371/journal.pone.0076893
129. Huang W, Li R, Ramakrishnan DP, Silverstein RL. Interruption of protein-protein interaction of cd36 with other proteins alters cd36 biological functions. *Arteriosclerosis Thrombosis Vasc Biol.* (2014) 34:A260–A. doi: 10.1161/atvb.34.suppl_1.260
130. Rigamonti E, Chinetti-Gbaguidi G, Staels B. Regulation of macrophage functions by ppar-A, ppar-Γ, and lxr in mice and men. *Arteriosclerosis thrombosis Vasc Biol.* (2008) 28:1050–9. doi: 10.1161/ATVBAHA.107.158998
131. Chen Y, Huang W, Yang M, Xin G, Cui W, Xie Z, et al. Cardiotonic steroids stimulate macrophage inflammatory responses through a pathway involving cd36, thr4, and na/K-ATPase. *Arteriosclerosis thrombosis Vasc Biol.* (2017) 37:1462–9. doi: 10.1161/ATVBAHA.117.309444
132. Feng T, Zhou L, Gai S, Zhai Y, Gou N, Wang X, et al. Acacia catechu (Lf) willd and scutellaria baicalensis georgi extracts suppress lpspressis progressis9.sis responses through nf-κb and pi3k signaling pathways in alveolar epithelial type ii cells. *Phytotherapy Res.* (2019) 33:3251–60. doi: 10.1002/ptr.6499
133. Baeuerle PA. Pro-inflammatory signaling: last pieces in the nf-kb puzzle? *Curr Biol.* (1998) 8:R19–22.
134. Schmutz M, Moosbrugger-Martinez V, Blunder S, Dubrac S. Role of ppar, lxr, and pxx in epidermal homeostasis and inflammation. *Biochim Biophys Acta (BBA)-Molecular Cell Biol Lipids.* (2014) 1841:463–73. doi: 10.1016/j.bbalip.2013.11.012
135. Volcic M, Karl S, Baumann B, Salles D, Daniel P, Fulda S, et al. nf-kb regulates DNA double-strand break repair in conjunction with brca1-ctip complexes. *Nucleic Acids Res.* (2012) 40:181–95. doi: 10.1093/nar/gkr687
136. Pourhassan P, Khani M, Burke B, Ebrahimi M, Sotoodehnejadnematlahi F. The effects of hif-1 gene on the expression of il-10, tgf-β and versican genes in human bone marrow and adipose tissue mesenchymal stem. (2022).
137. Askari VR, Rahimi VB, Rezaee SA, Boskabady MH. Auroaptene regulates th1/th2/treg balances, nf-kb nuclear localization and nitric oxide production in normal and th2 provoked situations in human isolated lymphocytes. *Phytomedicine.* (2018) 43:1–10. doi: 10.1016/j.phymed.2018.03.049
138. Karunakaran D, Nguyen M-A, Geoffrion M, Vreeken D, Lister Z, Cheng HS, et al. Ripk1 expression associates with inflammation in early atherosclerosis in humans and can be therapeutically silenced to reduce nf-kb activation and atherogenesis in mice. *Circulation.* (2021) 143:163–77. doi: 10.1161/CIRCULATIONAHA.118.038379
139. Bai Y, Nan Y, Wu T, Zhu A, Xie X, Sun Y, et al. Lipid nanoparticle7.ymatata delivery of crisprpryic against rubicon ameliorates nafld by modulating cd36 along with glycerophospholipid metabolism. *Advanced Sci.* (2024) 11:2400493. doi: 10.1002/advs.202400493

140. Dutta P, Saha D, Giri A, Bhatnagar AR, Chakraborty A. Decoding the cd36-centric axis in gastric cancer: insights into lipid metabolism, obesity, and hypercholesterolemia. *Int J Trans Med.* (2025) 5:26. doi: 10.3390/ijtm5030026
141. Mansor LS, Sousa Fialho M, Yea G, Coumans WA, West JA, Kerr M, et al. Inhibition of sarcolemmal fat/cd36 by sulfo-N-succinimidyl oleate rapidly corrects metabolism and restores function in the diabetic heart following hypoxia/reoxygenation. *Cardiovasc Res.* (2017) 113:737–48. doi: 10.1093/cvr/cvx045
142. Bessi VL, Labbe SM, Huynh DN, Menard L, Jossart C, Febbraio M, et al. Ep 80317, a selective cd36 ligand, shows cardioprotective effects against post-ischaemic myocardial damage in mice. *Cardiovasc Res.* (2012) 96:99–108. doi: 10.1093/cvr/cvs225
143. Yu Y-R, Tzeng S-F, Hsiao H-W, Park J, Kandalaf L, Lin Y-H, et al. Revitalizing anti-tumor immunity through plt012 monoclonal antibody, targeting cd36 for metabolic rewiring in the tumor microenvironment. *Cancer Res.* (2024) 84:2370–. doi: 10.1158/1538-7445.AM2024-2370
144. Terry AR, Nogueira V, Rho H, Ramakrishnan G, Li J, Kang S, et al. Cd36 maintains lipid homeostasis via selective uptake of monounsaturated fatty acids during matrix detachment and tumor progression. *Cell Metab.* (2023) 35:2060–76. doi: 10.1016/j.cmet.2023.09.012
145. Zhao L, Zhang C, Luo X, Wang P, Zhou W, Zhong S, et al. Cd36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis. *J Hepatol.* (2018) 69:705–17. doi: 10.1016/j.jhep.2018.04.006
146. Majumder J, Taratula O, Minko T. Nanocarrier-based systems for targeted and site specific therapeutic delivery. *Advanced Drug delivery Rev.* (2019) 144:57–77. doi: 10.1016/j.addr.2019.07.010
147. Yu Y-R, Tzeng S-F, Hsiao H-W, Chen H-K, Y-h L, Tsai C-H, et al. 1205 Plt012, a humanized cd36-Blocking antibody, induces durable anti-Tumor immunity via immunometabolic reprogramming. *BMJ.* (2025). doi: 10.1136/jitc-2025-SITC2025.1205
148. Feng WW, Zuppe HT, Kurokawa M. The role of cd36 in cancer progression and its value as a therapeutic target. *Cells.* (2023) 12:1605. doi: 10.3390/cells12121605
149. Saas P, Bonnefoy F, Toussiro E, Perruche S. Harnessing apoptotic cell clearance to treat autoimmune arthritis. *Front Immunol.* (2017) 8:1191. doi: 10.3389/fimmu.2017.01191
150. Stewart CR, Stuart LM, Wilkinson K, Van Gils JM, Deng J, Halle A, et al. Cd36 ligands promote sterile inflammation through assembly of a toll-like receptor 4 and 6 heterodimer. *Nat Immunol.* (2010) 11:155–61. doi: 10.1038/ni.1836