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Life cycle of macrophages in atherosclerotic inflammation progression and resolution: mediators and interventions (narrative review)

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Abstract

As one of the pathological causes of coronary heart disease, atherosclerosis poses a major threat to human health. Macrophages play an important role in regulating atherosclerotic disease progression. Specifically, atherosclerotic inflammation is initiated when low-density lipoproteins infiltrate the subcutaneous area and are phagocytosed by macrophages, leading to foam cell formation. The subsequent inflammation progression or resolution depends on the delicate balance between proinflammatory and anti-inflammatory mediators. In cases where proinflammatory factors dominate, macrophages tend to activate the pyroptosis and necrosis pathways, resulting in the release of intracellular damage-associated molecular patterns and promoting necrotic core formation and plaque progression. Conversely, when anti-inflammatory factors prevail, macrophages engage in autophagy-mediated intracellular lipid metabolism while inhibiting inflammation progression through the efferocytosis of apoptotic cells. The regulatory function of macrophages in atherosclerosis can also be understood from the perspective of their life cycles. Lipid retention within the arterial intima and its subsequent uptake by macrophages are the characteristic pathological hallmarks of atherosclerosis. As pivotal effector cells in this process, macrophages with their distinctive performances decisively determine the progression and resolution of atherosclerotic inflammation. The complete life cycle of macrophages in atherosclerotic plaques encompasses chemotaxis, infiltration, polarization, uptake of lipoproteins for metabolic efflux, foam cell formation, lipid overload, and various forms of programmed necrosis, including autophagy, pyroptosis, apoptosis, necrosis, and efferocytosis, to facilitate the removal of apoptotic macrophages and limit inflammation progression. The behavior of macrophages in atherosclerosis has rarely been comprehensively addressed in previous review articles. This article provides an extensive overview of the entire life cycle of macrophages following their response to atherosclerotic inflammation and the impact of regulatory factors on inflammation progression and resolution. Considering that macrophages play a pivotal role in the inflammatory response associated with atherosclerosis, targeting the regulation of their life cycle holds promise for therapeutic interventions against atherosclerosis-related cardiovascular diseases.

Keywords: Atherosclerosis, Autophagy, Efferocytosis, Macrophage, Pyroptosis

Introduction

With disturbed blood flow, vascular endothelial cells and their tight junctions become permeable, facilitating the uptake of plasma low-density lipoprotein (LDL) and triglyceride (TG)–rich lipoproteins through transepithelial transport or diffusion across cell-cell junctions. Consequently, endothelial cells are activated due to the oxidative reactions of lipoproteins and other inflammatory mediators, resulting in the expression of P-selectin, E-selectin, vascular cell adhesion molecule-1 (VCAM1), and intercellular cell adhesion molecule-1 (ICAM1). This promotes the adhesion of monocytes, other leukocytes, and chemokines, such as CCR2 and CCR5. Monocytes are recruited to the vessel wall by endothelia cells and express adhesion molecules and chemotactic proteins. Upon entering the intimal region, these cells differentiate into macrophages owing to the local production of Macrophage colony-stimulating factor and other cytokines.[1]

Fatty acid–derived bioactive lipids act as anti-inflammatory mediators

Macrophages form foam cells after the phagocytosis of oxidized LDL (oxLDL), thereby exacerbating atherosclerotic inflammation progression. Conversely, fatty acid metabolism generates a class of bioactive lipids known as specialized pro-resolving mediators (SPMs), that promote inflammation resolution.

The anti-inflammatory effects of SPMs are mediated through the activation of receptors involved in diverse signaling pathways, leading to NLRP3 inflammasome activation downregulation, mitochondrial oxidative stress mitigation, reducing oxLDL uptake, inhibition of nuclear membrane localization of 5-lipoxygenase (5-LOX), and subsequent production of inflammatory mediators, while enhancing efferocytosis.[2,3]

Macrophages polarize to different phenotypes under epigenetic modification

Stimulation with proinflammatory factors and SPMs induces macrophage polarization into divergent phenotypes, thereby eliciting contradictory responses to inflammation and influencing the course of inflammatory progression. According to the proinflammatory and anti-inflammatory functions, macrophages can be classified

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into M1 and M2 phenotypes. M1 cells secrete high levels of proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, and IL-12, while exhibiting low production of anti-inflammatory cytokines and chemokines such as IL-10 and CXCL-9. In contrast, M2-activated macrophages play a crucial role in atherosclerotic lesions by contributing to the reduction in inflammation, clearance of apoptotic cell debris, and tissue repair.[4]

Macrophage polarization toward proinflammatory phenotypes (M1)

Cathepsin B (CTSB) protein upregulation may contribute to the development of atherosclerosis and other cardiovascular diseases (CVDs) through inflammasome activation and pyroptosis induction.[5] Mettl14 enhances atherosclerotic inflammation progression by upregulating Myd88 expression and promoting IL-6 transcription through m6A methylation modification of Myd88 mRNA.[6] Additionally, it can increase VCAM-1/ICAM-1 levels by modifying mRNA via m6A methylation for the transcription factor FOXOI.[7] METTL3 enhances Braf expression through N6-methyladenosine modification of its mRNA, thereby promoting extracellular regulated protein kinases (ERK)–mediated production of downstream proinflammatory factors IL-1β, IL-6, and tumor necrosis factor-α (TNF-α).[8] Upon recognition of pathogenic microorganisms, the nodal protein TAB2 in macrophages binds and activates the protein kinase TAK1, thereby facilitating downstream production of inflammatory factors. TAB2 ubiquitylation by the E3 ubiquitin ligase RNF99 leads to TAB2 degradation, which subsequently inhibits the aforementioned process.[9]

Macrophage polarization toward anti-inflammatory phenotype (M2)

Major vault protein binds to and inhibits ASK1 dimerization and phosphorylation, thereby suppressing downstream inflammatory factor–related pathways and promoting the stability of atherosclerotic plaques.[10] The proteins encoded by the Lcor and Ncor2 genes interact with nuclear receptors retinoid X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR), respectively, thereby exerting inhibitory effects on normal mitochondrial oxidative metabolism regulation. Conversely, miR-10a and let-7b bind to and downregulate the expression of Lcor and Ncor2, promoting normal oxidative metabolism in mitochondria. This process provides energy to cells and metabolizes fatty acids generated by intracellular uptake of oxLDL while inhibiting foam cell formation and inflammatory factor production.[11] The Treg immune cells can also engage with macrophages through the secretion of the anti-inflammatory factor IL-10, thereby facilitating the polarization of macrophages toward an anti-inflammatory M2 phenotype and promoting plaque repair.[12]

Relevant factors governing the process of foam cell formation by macrophages (including lipid uptake and efflux)

Macrophages uptake different types of lipids via distinct mechanisms. Macrophage internalization of fatty acids occurs via specific membrane transporters such as CD36 and FATP. LDL is recognized by receptors on the cell membrane, including SR-A, CD36, LDL receptor (LDLR), and LOX-1, and undergoes clathrin-dependent endocytosis for cellular uptake. Lipid degradation takes place in lysosomes through lipophagy, with important proteins like NPC1 and STARD3 mediating their lysosomal breakdown and exportation. Finally, free fatty acids (FFAs) are either expelled from the cells or used for intracellular oxidation to generate energy.[13]

Regulation of lipid uptake

Upon binding to oxLDL, the class A1 scavenger receptor (SR-A1) facilitates oxLDL internalization through its intracellular segment's K63-linked ubiquitinated long chain while activating inflammatory signaling pathways. The deubiquitinating enzyme USP9X attenuates SR-A1 internalization by removing the K63 polyubiquitinated chain, thereby inhibiting lipid uptake and foam cell formation in macrophages and shifting cells toward an anti-inflammatory phenotype.[14] The purinergic receptor P2Y6R in macrophages has been recently exhibited enhancing the SRA receptors expression on the macrophage surface by modulating the dissociation of phospholipase Cβ-mediated key molecules stimulator of interferon (IFN) genes (STIMI) and calreticulin (CALR), as well as CALR and SRA uncoupling. This mechanism facilitates lipid endocytosis by macrophages.[15] CD146, an adhesion receptor expressed on the surface of macrophages, attenuates the responsiveness of macrophages to chemokines CCL19 and CCL21, leading to impaired emigration of foam cells from plaques and atherosclerosis exacerbation. Targeting CD146 using inhibitors or antibodies effectively decelerates foam cell formation and retention, thus mitigating atherosclerosis.[16] Ubiquitin-binding epsins, a family of endocytic receptors, can also interact with differentiation 36 (CD36) conjugated with oxLDL on the macrophage membrane to facilitate its internalization and trafficking to the plasma membrane for recycling, thereby enhancing lipid uptake. Simultaneously, epsin promotes ABCG1 degradation while inhibiting cholesterol efflux and reverse transport.[17] PCSK9 upregulates CD36 and SRAI on the cell surface to enhance lipid internalization by macrophages and promote the production of inflammatory factors.[18] The utilization of PCSK9 antagonists, in contrast, can effectively impede foam cell formation and suppress VCAM1/ICAM1 and CCL2 expression, thereby inhibiting foam cells migration to subcutaneous regions and mitigating inflammatory responses.[19] After heart transplantation, the recipient hepatocyte-derived PCSK9 inhibits CD36 expression and fatty acid uptake on the surface of infiltrating macrophages from the donor heart. These macrophages exhibit a proinflammatory phenotype and secrete various cytokines that induce host rejection of the graft.[20]

Regulation of intracellular lipid metabolism, including lipophagy and lipid efflux mechanisms

Lipophagy is a selective process of autophagic degradation, wherein lipid droplets (LDs) are engulfed by cell, which requires the ubiquitination labeling of the LDs to be degraded, transport to the lysosome and degradation after interaction between lipophagy selectivity factors, and autophagy receptors on the autophagosome membrane. Within the lysosome, LDs are hydrolyzed by lysosomal acid lipase into free cholesterol and fatty acids, which is directed toward the mitochondria to participate in fatty acid oxidation (FAO) via oxidative phosphorylation to generate ATP or transported out of the cytosol through cholesterol efflux receptors for reverse cholesterol transport.[21,22]

The fatty acids generated through lipophagy metabolism are excreted from the cell via lysosomal exocytosis. The degradation products, FFAs, are transported to the cytosol and effluxed out of the cell through fusion between lysosomes and the plasma membrane, a process regulated by MCOLN1, a calcium-channel protein located in the lysosomes. Subsequently, the effluxed fatty acids are taken up by macrophages close to or within the same microenvironment, which transports them to the mitochondria for oxidation or re-esterification into TGs for storage in LDs.

By promoting lipophagy, we can mitigate lipid accumulation at plaques and foam cell formation while facilitating cholesterol exocytosis or metabolic degradation to alleviate atherosclerosis. Therefore, targeting the regulation of lipophagy holds clinical significance.[23]

Excessive intracellular cholesterol biosynthesis impacts the inflammatory response and phenotypic polarization of macrophages

Upon lipopolysaccharide (LPS) stimulation, mTOR receptors transmit signals to SREBP2 in the endoplasmic reticulum (ER), leading to cholesterol synthesis within the ER via SREBP2 nuclear translocation. Interferon on the cytomembrane upregulates intracellular cholesterol-25-hydroxylase, leading to the synthesis of 25-hydroxycholesterol and inhibition of SREBP2 nuclear translocation and cholesterol biosynthesis. Excessive intracellular cholesterol accumulation induces mitochondrial damage, releasing mitochondrial DNA (mtDNA) into the cytoplasm and activating the absent in melanoma 2 (AIM2) sensor within the inflammasome, ultimately triggering IL-1B production and inflammation induction. Therefore, intracellular cholesterol synthesis modulation represents a potential therapeutic target for regulating atherosclerotic inflammation.[24]

Diverse outcomes of foam cells, including apoptosis, autophagy, necrosis, and pyroptosis, exert distinct influences on the direction of inflammation progression

Foam cells derived from macrophages and smooth muscle cells ultimately undergo distinct forms of programmed necrosis, including apoptosis, autophagy, pyroptosis, and necroptosis, which collectively contribute to the formation of a necrotic core within the plaque.[2]

Autophagy

There are 3 types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA).

Overview and regulation of macroautophagy. Macroautophagy is initiated by various stressors, and the double-membrane phagophore surrounds misfolded proteins and damaged organelles, elongating over time to form double-membrane autophagosome vesicles. ThePI3K-AKT-mTORC1 pathway functions as a regulatory switch for autophagy, suppressing autophagy under normal conditions, and relieving the inhibitory effects of mTORC1 during stress. The vacuolar protein sorting 34 (VPS34) complex is involved in phagophore formation, whereas subsequent complexes, involving human microtubule-associated protein light chain 3II (LC3II) and autophagy protein (ATG) 5-ATG12-ATG16L, promote elongation of the phagophore to form an autophagosome. Intracellularly damaged organelles or other protein substrates requiring degradation are labeled with ubiquitinated multimeric chains, followed by recognition by LC3II-linked sequestosome 1 (P62). Subsequently, they are enclosed within an autophagosome for lysosome transportation, ultimately resulting in substrate degradation.[25]

The transcription factor EB (TFEB), which acts downstream of the PI3K-AKT-mTORC1 pathway, plays a crucial role in regulating autophagy. When the mTORC1-mediated TFEB inhibition is relieved, it undergoes nuclear translocation to promote autophagy. This process can be influenced by various drug molecules, pathways, and mechanisms.[26] Rosuvastatin administration can also induce autophagy by inhibiting the PI3K/Akt/mTOR pathway, while simultaneously promoting cholesterol efflux and macrophage polarization toward the M2 phenotype. This leads to a reduction in the secretion of inflammatory factors, thereby alleviating atherosclerosis.[27] Ox-LDL induces an upregulation of reactive oxygen species (ROS), leading to P300 activation. This enhances the binding affinity of BRD4 to the promoter regions of inflammatory genes. Curcumin exerts atherosclerosis-delaying effects by promoting nuclear translocation of TFEB, enhancing autophagy levels in foam cells, attenuating ROS production, and inhibiting the release of P300-BRD4 axis–mediated inflammatory factors.[28]

Furthermore, many molecules regulate autophagy by modulating various stages such as autophagosome formation and autolysosome maturation. The autophagosome membrane is equipped with the scavenger receptor BI (SRBI), which upregulates the transcription factor peroxisome proliferator-activated receptor α and promotes nuclear translocation of TFEB. This process subsequently enhanced autophagy protein 14 L (ATG14L) transcription within the VPS34 complex. Conversely, SRBI binds to ATG14L via its cholesterol domain and facilitates recruitment of the VPS34 complex onto the autophagosome, thereby promoting downstream autophagy.[29] ATG14L on autophagosomes recruits STX17, forms a complex with SNAP29, and binds to lysosomal SNARE-VAMP8. Additionally, the binding of ATG14 and STX17 to LC3 in lysosomes plays a crucial role in facilitating phagolysosome fusion.[30]

Besides ATG14, the macrophage-specific V-ATPase subunit ATP6V0D2 can also contribute to autophagosome-lysosome fusion by interacting with STX17 and VAMP8.[31] ATP6V0e2 is an important protein for maintaining autophagy and serves as a crucial effector in regulating atherosclerosis. LDLR binds to both AMP-activated protein kinase (AMPK) and acetaldehyde dehydrogenase 2 (ALDH2), inhibiting AMPK by phosphorylating ALDH2; loss of this inhibitory effect leads to the AMPK-mediated phosphorylation of ALDH2 and its subsequent translocation into the nucleus, resulting in ATP6V0E2 function inhibition and contributing to autophagy dysfunction and atherosclerosis development.[32]

Intracellular metabolic reprogramming regulates autophagy in macrophages. When damage-associated molecular patterns (DAMPs) stimulate macrophages, FLT4/VEGFR receptors on their cytosolic membranes are activated, leading to PRKAA1 phosphorylation and subsequent intracellular metabolic reprogramming regulation. Increased citrate/nicotinamide adenine dinucleotide phosphate (NADPH) production facilitates autophagy by promoting the fusion between MAP1LC3 on autophagosome membranes and LC3II in lysosomes.[33]

CMA regulation. CMA is a selective degradation pathway of intracellular proteins with a CMA-KFERQ-like motif. Motif-associated proteins are recognized and combined with the chaperone protein HSC70 to form a complex that binds to lysosome-associated membrane protein (LAMP-2A) on the lysosomal membrane for subsequent degradation. LAMP-2A serves as a rate-limiting CMA component, and higher expression levels on the lysosomal membrane result in faster CMA.

The NLRP3 protein within the inflammasome can undergo degradation as a substrate for CMA, without affecting apoptosis-associated speck-like protein containing a CARD (ASC) and caspase 1. Both macroautophagy and CMA contributed to clearing the inflammasome; however, macroautophagy requires ubiquitin-dependent conditions and accounts for only a small portion of NLRP3 clearance. In contrast, CMA is the primary pathway for NLRP3 degradation in macrophages. By degrading the inflammasome, CMA effectively reduces downstream proinflammatory processes such as IL-1 family cytokine release and gasdermin D (GSDMD)–mediated pyroptosis.[34] The S-palmitoylation modification can function as a regulatory switch for NLRP3 degradation through CMA. Protein palmitoylation is a reversible lipid modification primarily catalyzed by the zinc finger-containing DHHC (zDHHC) family of palmitoyl S-acyltransferases. zDHHC2 facilitates NLRP3 palmitoylation, enabling its recognition by the HSC70 protein and promoting CMA-mediated degradation.[35]

Additionally, CMA can affect cellular metabolism by regulating lipid metabolism and the degradation of glycolysis-related enzymes,

thereby inhibiting atherosclerosis. CMA dysfunction results in reduced glucose utilization (hyperinsulinemia and insulin resistance), lipid accumulation (hyperlipidemia and hypercholesterolemia), increased fat supply, and decreased energy consumption, leading to obesity, all of which are significant risk factors for atherosclerosis development. The degradation of key intracellular metabolic regulatory enzymes through the CMA pathway may serve as a novel target for disease treatment. The histone acetylase Jmjd4 hydroxylates the K66 site of PKm2, enabling its recognition by HSP70 and subsequent degradation via the CMA pathway.[36]

CMA dysregulation not only impacts metabolism systemically but also influences cellular polarization and atherosclerosis development by modulating the metabolism of inflammation-associated proteins in macrophages and smooth muscle cells. CMA is responsible for the degradation of various proinflammatory proteins, including those involved in cell junctions, leukocyte recruitment and activation, and NOS and iNOS synthesis. CMA dysfunction enables vascular smooth muscle cells to differentiate into a proinflammatory/synthetic phenotype characterized by reduced lipid metabolism and secretion of proinflammatory factors upon intracellular lipid stimulation. This mechanism contributes to the formation of foam cells derived from smooth muscle cells and is accompanied by increased matrix deposition, promoting plaque development.[37] The lysosomal LAMP-2A stability decreases physiological (aging) and pathological states, such as chronic hyperlipidemia and intracellular lipid accumulation. Consequently, CMA dysfunction can occur. Therefore, enhancing the CMA function has emerged as a crucial strategy for treating atherosclerosis.[38]

Pyroptosis

The classic pyroptosis-related inflammasome is composed of a sensor nucleotide-binding oligomerization domain-like receptor (NLR) family, including NLRP3, NLRP1, NLRC4, AIM2, adaptor ASC, and effector pro-caspase 1. Classic pathways involve priming and inflammasome activation wherein extracellular stimuli such as IL-1 family, TNF-α, DAMPs/PAMs, oxLDL, and LPS act on cell surface pattern recognition receptors Toll-like receptor (TLR)/IL receptor/TNF receptor (TNFR), they activate downstream nuclear factor kappa-B (NF-κB) pathway to initiate transcription of inflammasome-related components including NLRP3, pro-caspase 1, ASC, pro–IL-1 family, and GSDMD. Next is the activation process, in which various activating factors such as K efflux, Ca influx, DAMPs crystallization-induced lysosomal rupture, increased ER stress, and mitochondrial ROS elevation lead to inflammasome assembly. Once NLRP3 is activated, it undergoes conformational changes to recruit ASC and pro–caspase-1. Pro–caspase-1 cleaves itself, thereby generating its catalytically active subunit, p20/10, within the center of the inflammasome. Activated caspase-1 cleaves GSDMD and pro–IL-1 families, resulting in the formation of N-terminal pore-forming GSDMD fragment (GSDMD-NT) and IL-1β and IL-18. GSDMD-NT perforates the cell membrane, promotes cellular pyroptosis, and promotes the release of inflammatory factors.[39] GSDME/caspase 3–mediated pyroptosis is more frequently observed in the nonclassic pathway inflammasome.[40,41]

The priming of the inflammasome is regulated by various epigenetic modifications, including NLRP3 deubiquitination, which mediates downstream pyroptosis processes.[42] Transcription of NLRP3 is regulated by epigenetic modifications of long noncoding RNA (lncRNAs). Specifically, the lncRNA NEAT1 undergoes m6A methylation mediated by the METTL14 enzyme. This modification site on NEAT1 is competitively recognized and bound by YTHDC1 in the nucleus, facilitating cleavage and clearance of the lncRNA. Upon oxLDL stimulation, downregulation of nuclear YTHDC1 impairs NEAT1 clearance, binding it to KLF4, which also binds to and represses NLRP3 transcription. Therefore, when NEAT1 binds to KLF4, it promotes NLRP3 transcription, thereby triggering pyroptosis. Exercise downregulates NEAT1 m6A methylation mediated by the METTL14 enzyme, thereby enhancing NEAT1 recognition and clearance through YTHDC1, ultimately reducing endothelial cell pyroptosis.[43]

Multiple drugs can target distinct components involved in inflammasome activation as well as downstream effector molecules. For example, MCC950 inhibits the assembly and activation of NLRP3 inflammasome, whereas chloroquine inhibits ASC multimerization.[44] VX765 inhibits the activity of caspase 1, thereby disrupting the mutually reinforcing vicious circle between mitochondrial autophagy dysfunction and NLRP3 inflammasome activation.[45] IL-1 inhibition suppresses atherosclerotic inflammation and mitigates adverse ventricular remodeling and heart failure resulting from myocardial cell pyroptosis following myocardial infarction.[46] Olfr2 receptors mediate mitochondrial and cytosolic ROS production to promote inflammasome activation and IL-1 release by binding to the lipid peroxide octanal in hyperlipidemia; therefore, inhibition of Olfr2 receptors could be a target for inflammasome activation reduction.[47] Olfr2 mediates the upregulation of ROS and consequently promotes inflammasome activation, whereas quercetin has recently been discovered to inhibit oxidative stress by generating antioxidants, thereby inhibiting inflammasome activation.[48] Histone deacetylase 11 binds to the transcription factor ERG, inducing its deacetylation and activating the NLRP3/caspase-1/GSDMD and caspase-3/GSDME pathways, thereby promoting pyroptosis.[49]

Interactions between the NLRP3 inflammasome and autophagy

Autophagy can regulate inflammasome activation by modulating its activators, such as mitochondrial dysfunction (increased mtROS and secretion of OXmtDNA from the mitochondria), calcium influx, potassium efflux, and lysosomal cleavage. Specifically, labeling damaged mitochondria through parkin-mediated ubiquitination enables their recognition by P62-LC3II in the autophagosome and subsequent clearance through autophagy. Autophagy degrades ROS, mtDNA, and damaged mitochondria, thereby inhibiting inflammasome activation, suppressing pyroptosis, and generating inflammatory factors. However, autophagy can degrade inflammasome components and impede their activation. TRIM 20 can bind to the components of the NLRP3 inflammasome to produce IL-1. It also provides a platform for assembling crucial complexes involved in autophagy to form autophagosomes, such as ULK1, beclin1, and ATG16. Consequently, TRIM 20 facilitates the transport of inflammasome components to autophagosomes and promotes efficient autophagic degradation. Following inflammasome inactivation, ASC undergoes K-63 polyubiquitination to form ubiquitinated long chains that are subsequently recognized by P62. This recognition leads to ASC-mediated NLRP3 inflammasome sequestration via autophagosomes. Autophagy also participates in the regulation of IL-1 release. Autophagosomes can directly degrade pro–IL-1 through autophagy. The double-layered vesicles can also encapsulate mature IL-1, facilitating its transportation to the cell membrane for extracellular release, which contradicts autophagy's anti-inflammatory effects. It remains unclear whether IL-1B phagocytosis promotes its degradation or secretion into the extracellular compartment, which may be determined by distinct inflammasome activators, autophagy inducers/inhibitors, and cell types.

The NLRP3 inflammasome exerts regulatory control over autophagy by directly binding to key autophagy-regulating proteins

such as beclin1. The direction of autophagy regulation is contingent on the specific type of activated inflammasome sensor. Caspase 1 can cleave the autophagy-regulating protein parkin, which impairs damaged mitochondrial autophagy, resulting in a detrimental cycle of continuous inflammasome activation caused by unclear mtROS and mtDNA. Caspase 1 also cleaves TIR-domain-containing adaptor inducing IFN-β (TRIF) and inhibits TRIF-mediated autophagy, removing the inflammasome components.[50]

Apoptosis and necrosis

During apoptosis, TNF- α binds to TNFR on the cytosolic membrane, forming complex I, which contains phosphorylated and ubiquitinated Receptor-interacting serine/threonine-protein kinase 1 (RIPK1). This complex regulates cell survival through the downstream MAPK and NF-KB signaling pathways. Upon dephosphorylation and deubiquitination, RIPK1 is released from complex I. In the presence of activated caspase 8, RIPK1 acts as a kinase activating caspase 8 and initiating the downstream caspase 3/7 cascade, which induces apoptosis. Caspase 8 inhibited by cellular FLICE (FADD-like IL-1β-converting enzyme)–inhibitory protein (c-FLIP), deubiquitinated RIPK1 activates downstream RIPK3 and MLKL proteins, thereby mediating cell necrosis. Both apoptosis and necrosis are forms of programmed cell death. In atherosclerotic plaques, apoptosis and necrosis can be detected through elevated expression of related molecules.[50]

Multiple mechanisms regulate apoptosis. HuR is an RNA-binding protein that exerts its regulatory function by translocating from the nucleus to the cytoplasm and binding to specific mRNA molecules. This interaction leads to the downregulation of proapoptotic markers, such as p53, p27, and caspase 3/8/9, while upregulating antiapoptotic factors like BCL 2 and Mcl1. Consequently, this molecular cascade inhibited apoptosis. In contrast, lncRNA MAARS can interact with nuclear HuR and impede its translocation to the cytoplasm. Therefore, apoptosis is upregulated while atherosclerotic plaque stability is inhibited.[51] The immune-related guanosine triphosphate (GTP) kinase family M protein (IRGM) promotes mitochondria-dependent caspase 9 mediated endogenous apoptosis by enhancing cellular ROS production, activating phosphorylation of the MAPK pathway JNK/p38/ERK and downregulating antiapoptotic BCL families. ROS also triggers caspase 8–mediated exogenous apoptosis. Both pathways ultimately converge to activate caspase 3, leading to DNA fragmentation and cellular morphological changes. Conversely, IRGM knockdown inhibits apoptosis and enhances the stability of atherosclerotic plaques.[52]

Ferroptosis

Polyunsaturated fatty acids in the phospholipid bilayer form lipid peroxides via ferrous ions, thereby damaging the cell membrane. In cases of cellular iron overload, ferritin releases ferrous ions that react with H_2O_2 produced by the mitochondria via the Fenton reaction, generating hydroxyl free radicals that further contribute to lipid peroxide formation. From a physiological perspective, cellular glutathione (GSH) peroxidase 4 (GPX4) eliminates ferroptosis by oxidizing GSH and reducing lipid peroxides to harmless alcohols. The Na(+)-independent glutamate/cystine exchanger (Xc-antiporter) reverse transport system facilitates the reciprocal transportation of glutamate (Glu) and cysteine (Cys), enabling Cys to participate in GSH synthesis and subsequent GPX4-mediated clearance of lipid peroxides within cells.[53] The rupture and hemorrhage of atherosclerotic plaques can induce ferroptosis following red blood cells phagocytosis, resulting in lipid peroxidation and endothelial damage, thereby exacerbating the inflammatory progression of atherosclerosis.[54] The active metabolite of parthenolide, micheliolide (MCL), exerts its inhibitory effect on macrophage ferroptosis by upregulating intracellular GPX4 and Xap5 circadian timekeeper levels, suppressing mitochondrial oxidative stress and lipid peroxidation. Simultaneously, MCL hinders the KEAP1/NRF2 complex formation and facilitates NRF2 nuclear translocation through binding to the Arg483 site of KEAP1, thereby impeding ferroptosis.[55] By contrast, the induction of macrophage ferroptosis through the NF-κB–activated hepcidin/FPN/SLC7A11 pathway facilitates atherosclerosis progression.[56]

Regulation of efferocytosis (engulfment and digestion of apoptotic cells as well as cytokine secretion) to impact inflammation progression

Efferocytosis involves the recognition of macrophages and AC through surface receptors, leading to the formation of a phagocytosis cup, where macrophages engulf AC. Subsequently, a phagosome is formed to enclose AC, which are then transported to lysosomes. Fusion occurs in the lysosomes, forming phagolysosomes for degradation. Therefore, the effective regulation of efferocytosis necessitates intervention in the molecular pathways governing these intricate processes.

Regulation of efferocytosis

Signaling molecules involved in efferocytosis encompass "Find me" signals released by AC to facilitate their recognition and uptake. Additionally, ACs are distinguished by "Eat me" signals, such as PtdSer, which interact with corresponding receptors on macrophages, like MerTK. Moreover, intracellular signaling activators and transmitters, including TLR4 and CD14, are cytoskeletal regulators that facilitate endocytic processes, such as Ca and Rac1. Finally, phagocytes further release anti-inflammatory factors such as transforming growth factor β (TGF-β), IL-10, and VEGF that activate efferocytosis.[57]

Regulation of engulfment

Regulation of efferocytosis. Recognition of surface receptors: LRP1 functions as a recognition receptor for efferocytosis on the surface of macrophages and interacts with the "Eat me" receptor calreticulin on AC to facilitate efferocytosis, whereas CD47 acts as a "Do not eat me" signal on apoptotic cell surfaces, inhibiting efferocytosis and exacerbating atherosclerosis.[57] Cyclophilin upregulates CD47 expression on apoptotic macrophage surfaces while downregulating calreticulin levels, inhibiting immunogenicity and degradation of AC through efferocytosis. Simultaneously, cyclophilin A upregulates the CD36 receptor for the uptake of oxLDL by macrophages while downregulating the ABCA1 receptor responsible for cholesterol efflux; these actions increase foam cell production and worsen atherosclerosis.[58] The inhibition of nuclear translocation of the pyruvate kinase PKM2 in macrophages leads to LRP1 receptor upregulation on the cytosolic membrane, thereby inducing enhanced efferocytosis and inhibiting foam cell formation as well as inflammatory factors expression.[59] The downregulation of LRP1 on the cytosolic membrane is accompanied by a decrease in efferocytosis.[60] Additionally, MerTK serves as a crucial receptor on the surface of phagocytes for transmitting efferocytosis signals.[61] The CaMKIIγ enzyme activation in macrophages within atherosclerotic plaques inhibits MerTK expression and efferocytosis.[62] Recently, the efferocytosis recognition process has become a target for drug developments, such as anti-CD47 utilization to enhance efferocytosis; however, LRP1 is essential for its effectiveness.[63] The delivery of anti-CD47 antibodies using platelet membrane-coated nanocarrier, platelet membrane-coated mesoporous

silicon nanoparticles, which specifically targets atherosclerotic plaques, facilitates efferocytosis for treating atherosclerosis.[64] However, using anti-CD47 may result in anemia; therefore, targeting the CD47 receptor SIRPα specifically is an alternative approach to hindering the antiefferocytosis effects exerted by CD47.[65] In addition, CD47 expression can be downregulated by miR-149-5p; however, the binding of LncRNA MIAT to miR-149-5p inhibits its interaction with target genes, leading to compromised efferocytosis and exacerbated atherosclerotic inflammation.[66]

Formation of phagosome: GTP kinases, such as members of the Rac family, facilitate the endocytosis of AC by promoting actin multimerization at the intracellular surface of the phagocytosis cup, leading to the cytosolic invagination of macrophages. Macrophage ALDH2 enhances Rac2-mediated cytosolic invagination and efferocytosis by competitively binding to the lysine 123 site on Rac2 with E3 ligase or other ubiquitinating enzymes, thereby inhibiting the formation of linked K48 multimeric ubiquitinated long chains and preventing Rac2 degradation. In contrast, individuals with ALDH2rs671 mutation do not show inhibited Rac2 degradation, resulting in reduced efferocytosis and increased susceptibility to CVD. Rac2 expression can be upregulated in individuals with ALDH2rs671 mutation to promote efferocytosis.[67] Rac: Rho balance plays a crucial role in regulating cytoskeletal rearrangement and phagosome formation. Statins can enhance efferocytosis by inhibiting the activation of the Rho family, leading to an upregulation of Rac1 within the GTPase family.[68] The myosin light chain (MLC) functions similarly to actin and is involved in phagosome formation and endocytosis of AC. Phosphorylated MLC (p-MLC) is the active form of efferocytosis. PHACTR1 regulates MLC phosphorylation, and a mutation in the intrinsic subunit rs9349379 of PHACTR1 prevents binding of the enhancer to the transcription factor MEF2, resulting in PHACTR1 expression downregulation. This facilitates the translocation of PP1α from the nucleus to the cytoplasm, enabling MLC dephosphorylation, and inhibiting p-MLC–mediated efferocytosis.[69]

Regulation of intracellular vesicle transport and reutilization. The translocation and reutilization of phagocytic vesicles within the cell rely heavily on intracellular calcium levels. Specifically, when expressed in cardiac tissue-resident macrophages, legumain (LGMN) enhances intracellular calcium by cleaving protease-activated receptor 2, which facilitates the specific recognition of LC3II on phagosome to bind apoptotic cardiomyocytes and transports them to lysosomes for degradation. Therefore, the upregulation of intracellular LGMN expression in macrophages could be a potential target for regulating efferocytosis to effectively clear apoptotic cardiomyocytes.[70] The intracellular translocation of Ca from the ER to the mitochondria for storage occurs in macrophages when phagocytosis is absent. Following AC efferocytosis, activation of the Drp1 receptor on mitochondria (through specific mechanisms that potentially enhance posttranscriptional translation of Drp1 mRNA or inhibit Drp1 protein degradation) facilitates mitochondrial fragmentation. Consequently, binding between the mitochondria and the ER weakens, preventing the sequestration of ER-derived Ca by the mitochondria, releasing ER Ca into the cytoplasm, which fuels phagosome formation and lysosome fusion. Phagocytic vesicles are recycled and transported to form new vesicles within the cytosol, ensuring continuous efferocytosis. Disruption of mitochondrial division-mediated Ca release from the ER hinders this efferocytosis; conversely, silencing the mitochondrial Ca unidirectional transporter mitochondrial calcium uniporter (MCU) to upregulate intracellular Ca could serve as a potential therapeutic target.[71]

Metabolic reprogramming affects efferocytosis and cellular phenotypic polarization

Metabolites derived from AC engulfed by macrophages can specifically modulate cholesterol, glucose, amino acid, lipid, and nucleic acid metabolism, thereby influencing macrophage efferocytosis and inflammatory responses.[72]

Effects of AC-derived cholesterol on efferocytosis. The hydrolysis of cholesterol leads to the production of cholesteryl esters that can activate hepatic X receptors, which facilitate MerTK upregulation in the cytomembrane. Cholesterol hydrolysis inhibition by *Lipase A* (LIPA) induces mitochondrial oxidative stress, generating ROS, which activates NLRP3 and inhibits Rac1 activation and cytoskeletal rearrangements. Consequently, phagosome formation and translocation are inhibited.[72] Desmosterol, an intermediate product in cholesterol biosynthesis, can also activate LXR/RXR, leading to the upregulation of ABCA1 and ABCG1. This activation promoted lipid efflux and inhibited foam cell formation. In addition, desmosterol inhibited mitochondrial ROS production and NLRP3 inflammasome activation. Furthermore, LXR suppresses the expression of IFN-related genes, thereby mitigating the inflammatory phenotype and attenuating inflammatory development in atherosclerosis.[73]

Effects of glucose metabolism on macrophage efferocytosis. Mitochondrial dysfunction in macrophages leads to an increased mtROS production, which reduces cellular oxidative phosphorylation and elevates aerobic glycolysis. These metabolic changes provide the necessary energy and substrates for the rapid generation of inflammatory responses and clearance of ACs during hypoxic conditions caused by infarction. However, this metabolic reprogramming hinders macrophage efferocytosis, which affects the production of anti-inflammatory factors and transitions to an anti-inflammatory phenotype. Consequently, persistent myocardial inflammation occurs along with impaired tissue repair capabilities, ultimately leading to compromised cardiac function.[74] Macrophages can induce efferocytosis and cellular polarization toward an anti-inflammatory phenotype by upregulating the expression of the SLC gene family associated with cellular glucose metabolism. Small molecules released by ACs, such as adenosine triphosphate (ATP), stimulate SGK1 expression in ACs, which in turn promotes the phosphorylation and activation of macrophage SLC2A1. This facilitates glucose uptake into the cell for aerobic glycolysis while inhibiting oxidative phosphorylation. Aerobic glycolysis further enhances actin multimerization in phagocytic cups to facilitate the engulfment of ACs. Briefly, the upregulation of aerobic glycolysis provides energy for actin-mediated AC endocytosis. Following AC internalization by macrophages, SLC16A1 expression is upregulated, promoting the extracellular excretion of lactic acid produced through glycolysis. This lactic acid acts on other phagocytes within the microenvironment and triggers the secretion of anti-inflammatory factors, such as IL-10 and TGF-β, thereby establishing an anti-inflammatory microenvironment.[75] Unlike SLC2A1, PFKFB2-mediated lactate increase participates in the mutual recognition of ACs and phagocytes. After phagocytosis by AC, macrophages activate the GLUT1 adapter enzymes TXNIP and PFKFB2 through Akt phosphorylation. Phosphorylated TXNIP promotes the nondegradation of the GLUT1 transporter protein, thereby sustaining inward glucose transport across the cell membrane. PFKFB2 can mediate lactate production from glycolysis (unlike PKM2- and SLC2a1-mediated glycolysis in inflammatory cells, PFKFB2-induced glycolysis is transiently reversible and does not interfere with oxidative phosphorylation or the tricarboxylic acid cycle). Sustained lactate efferocytosis occurs via mitochondrial division-mediated cytoplasmic Ca upregulation, promoting an increase in MerTK and LRP1 receptors on the cytomembrane to facilitate AC and macrophage

recognition. PFKFB2-mediated glycolysis exerts an anti-inflammatory effect. PKM2- and SLC2a1-mediated glycolysis can inhibit macrophage efferocytosis by degrading efferocytosis-associated molecules, including decreased LRP1 expression in PKM2+ inflammatory cells. Therefore, targeting PFKFB could be a therapeutic approach for inhibiting inflammation by upregulating efferocytosis.[76]

Effects of amino acid metabolism on macrophage efferocytosis. Macrophages use amino acids derived from the AC to generate sustained efferocytosis and anti-inflammatory factors. Upon AC uptake, macrophages upregulate GLS1, which promotes the hydrolysis of glutamine into Glu. Glu participates in the tricarboxylic acid cycle to produce NADPH, which provides the reducing equivalent for GSH synthesis. GSH then participates in the mitochondrial electron transport chain and oxidative phosphorylation to generate ATP, which supplies energy for actin multimerization on the inner membrane of the phagocytosis cup and promotes efferocytosis.[77] Simultaneously, Glu is metabolized into arginine. Macrophage arginase 1 converts AC-derived arginine into ornithine, which is further converted into putrescine by ornithine decarboxylase (ODC). Putrescine enhanced the binding of HuR to Mcf2 mRNA, which encodes the GTP-exchange factor Db1, thereby stabilizing Mcf2 mRNA and promoting sustained Db1 expression. Rac1 activation by Db1 induces actin multimerization on the surface of the phagocytic cup and continues AC internalization. Consequently, the addition of putrescine to macrophages sustains efferocytosis, inhibiting the inflammatory response and atherosclerosis progression.[78] In addition, ODC-catalyzed putrescine production facilitates DNA methylation of the histone encoding MerTKd, leading to enhanced transcription of MerTKd and promotion of efferocytosis. Simultaneously, upon binding to AC, MerTKd activates the downstream ERK-mediated secretion of the anti-inflammatory factor IL-10.[79] Efferocytosis suppresses further generation of the inflammatory response, focusing on effective utilization of AC-derived amino acids to continuously stimulate macrophages for anti-inflammatory mediator production. Upon binding to AC, macrophage surface CD36 phosphorylates downstream ERK1/2, thereby activating the Ptgs2–PGE2–TGF-β1 pathway responsible for generating anti-inflammatory factors. However, DUSP4, which is produced downstream of P-ERK, negatively inhibits ERK phosphorylation and blocks this pathway. Intracellular AC-derived methionine is converted to s-adenosylmethionine, which methylates DNA methyltransferase 3a and downregulates Dusp4. This reduction in negative feedback inhibition by DUSP4 allows continued ERK phosphorylation and enables the ERK-ptgs2-PGE2-TGFB1 pathway to produce anti-inflammatory factors.[80]

Effects of fatty acid metabolism on macrophage efferocytosis. AC-derived fatty acids underwent β-oxidation in macrophage mitochondria, thereby activating the mitochondrial electron transport chain and generating the intermediate metabolite NAD^+. This leads to downstream SIRT1 activation, promoting an increase in the transcription factor, pbx1, of IL-10, ultimately upregulating IL-10 for inflammatory repair.[81] Additionally, the FAO process reduces equivalents for mitochondrial oxidative phosphorylation, thereby exerting anti-inflammatory effects.[61]

Effects of nucleic acid metabolism on macrophage efferocytosis. Efferocytosis and anti-inflammatory effects are augmented and amplified by sustained macrophage proliferation after the metabolism of AC-derived nucleic acids. In macrophage phagolysosomes, DNase2a degrades AC DNA into nucleotides that phosphorylate Akt via the DNA-PKcs/mTORC2/Rictor axis. This leads to an increase in Myc expression, which plays a crucial role in inducing efferocytosis-induced noninflammatory cell proliferation (EIMP) by upregulating Bhlhe40 and downregulating c-Maf. EIMP promotes the proliferation of non-inflammatory macrophages, exerts anti-inflammatory effects, and facilitates injury repair. Furthermore, AC bound to MertK mediates subsequent EIMP by promoting Erk1/2 phosphorylation and activating Myc expression. This further enhances the upregulation of anti-inflammatory factors such as TGF-β and IL-10.[82]

Conclusion

Macrophages can be activated into a proinflammatory phenotype upon the recognition of oxLDL, thereby promoting atherosclerotic inflammation progression. Assessment of M1 macrophage activation markers can serve as an indicator for predicting the progression and prognosis of atherosclerotic diseases. For instance, recent studies have revealed a close correlation between plasma levels of macrophage YKL-40 and clinical outcomes in CVD. By inhibiting proinflammatory factors and supplementing SPMs, macrophages can be polarized toward an anti-inflammatory phenotype, facilitating autophagy and efferocytosis, while suppressing pyroptosis and necrosis. Currently, numerous drugs target different methods of cell death in macrophages to regulate atherosclerotic inflammation, potentially leading to their future application in clinical treatment. Considering that atherosclerosis is a complex inflammatory process involving multiple cell types, the behavior of other immune, endothelial, and smooth muscle cells may influence inflammatory progression by affecting macrophages. Therefore, regulation of the interaction between macrophages and other cells is expected to become a therapeutic target for atherosclerotic CVD. Specific nanomaterials have been discovered to modulate the life cycle of macrophages in atherosclerosis by binding to receptors on these cells and inducing many functions such as macrophage recruitment, proliferation, foam cell formation, efferocytosis, and secretion of proinflammatory and anti-inflammatory mediators. In the future, along with lipid-lowering therapies, therapeutic strategies targeting macrophages are expected to emerge as crucial approaches for treating atherosclerosis.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Feng Y wrote and revised the paper. Wang Q and He B participated in the revising and editing of the paper. Hou X supervised and revised the paper.

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