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INVITED REVIEW

The role of efferocytosis-fueled macrophage metabolism in the resolution of inflammation

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Summary

The phagocytosis of dying cells by macrophages, termed efferocytosis, is a tightly regulated process that involves the sensing, binding, engulfment, and digestion of apoptotic cells. Efferocytosis not only prevents tissue necrosis and inflammation caused by secondary necrosis of dying cells, but it also promotes pro-resolving signaling in macrophages, which is essential for tissue resolution and repair following injury or inflammation. An important factor that contributes to this pro-resolving reprogramming is the cargo that is released from apoptotic cells after their engulfment and phagolysosomal digestion by macrophages. The apoptotic cell cargo contains amino acids, nucleotides, fatty acids, and cholesterol that function as metabolites and signaling molecules to bring about this re-programming. Here, we review efferocytosis-induced changes in macrophage metabolism that mediate the pro-resolving functions of macrophages. We also discuss various strategies, challenges, and future perspectives related to drugging efferocytosis-fueled macrophage metabolism as strategy to dampen inflammation and promote resolution in chronic inflammatory diseases.

KEYWORDS
cell metabolism, efferocytosis, inflammation resolution, macrophages

1 | INTRODUCTION

Efferocytosis, the process by which phagocytic cells engulf and clear apoptotic cells from the body, is an integral part of tissue homeostasis.[1] Although non-professional phagocytes such as epithelial cells and mesenchymal cells can partake in efferocytosis,[2,3] the majority of apoptotic cells are cleared by macrophages. In healthy tissue, efficient efferocytosis is followed by a resolution response that involves the secretion of a variety of mediators, including transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), that dampen inflammation and promote tissue repair.[4,5] However, when apoptotic cells are not effectively cleared, they undergo secondary necrosis and release damage-associated nuclear molecular patterns (DAMPs) that elicit a pro-inflammatory response that can damage the surrounding tissue.[6] As such, defective efferocytosis contributes to the risk of various autoimmune and chronic inflammatory diseases,[7,8] including atherosclerotic cardiovascular disease, which is the leading causes of death worldwide. In advanced atherosclerosis, impaired efferocytosis leads to the formation of necrotic plaques with thin fibrous caps.[9–11] These so-called "unstable" plaques are prone to rupture, which can trigger occlusive luminal thrombosis and thereby cause a heart attack or stroke. On the other hand, "reawakening" of the macrophage-mediated resolution response promotes regression of atherosclerosis when hypercholesterolemia is reversed,[12] which is associated with an increased plaque stability and a lower risk of coronary artery disease in humans.[13,14] Strategies that promote efferocytosis and inflammation resolution could therefore have a

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major therapeutic benefit in atherosclerotic cardiovascular disease as well as the plethora of other diseases associated with defective efferocytosis, such as systemic lupus erythematosus (SLE)-type autoimmune diseases, metabolic disorders, respiratory diseases, and neurodegenerative disorders.[7,8]

Efferocytosis is a tightly regulated process that involves three sequential steps, which has been studied mostly in macrophages, the most efficient type of efferocyte.[15,16] First, the macrophages need to detect apoptotic cells, which is mediated by the release of so-called "find me" signals by dying cells. Examples of these signals include CX3CL1 (fractalkine), lipid-derived molecules such as sphingosine-1-phosphate (S1P) and lysophosphatidylcholine (LPC), and the nucleotides ATP and ADP.[17–19] These molecules bind to their cognate receptors on the macrophage surface, which allows the macrophage to follow a chemotactic gradient of find-me signals and migrate toward the dying cell. After localizing apoptotic cells, the macrophages undergo the second step of the efferocytic process, which involves the binding of macrophages to apoptotic cells. This binding is mediated by the expression of "eat-me" signals on the surface of dying cells interacting with receptors on macrophages, with or without intermediary bridging molecules such as growth arrest-specific factor 6 (Gas6), protein S, and milk fat globule-epidermal growth factor 8 (MFG-E8).[20–22] The most well-studied eat-me signal on apoptotic cells is phosphatidylserine (PtdSer). PtdSer is normally enriched on the inner leaflet of the plasma membrane, but it is translocated to the outer leaflet of the plasma membrane in a caspase-3-dependent manner in apoptotic cells.[23–25] Macrophages can bind to PtdSer and other molecules expressed on the surface of dying cells via a variety of receptors, including MER proto-oncogene tyrosine kinase (MERTK), the scavenger receptor CD36, and low-density lipoprotein receptor-related protein 1 (LRP1).[26–28] Eat-me signals are counterbalanced by "do not-eat-me" signals, such as CD47 that binds to macrophage signal regulatory protein alpha (SIRPα) to inhibit phagocytosis.[29] While the low expression of CD47 on healthy cells prevents their engulfment by macrophages, the CD47-SIRPα axis can also mediate immune evasion of tumor cells as well as defective efferocytosis of necrotic cells that have been shown to overexpress CD47.[30–32] The binding of apoptotic cells to macrophages sets in motion the third step of efferocytosis—apoptotic cell engulfment. Signaling through efferocytosis receptors promotes the polymerization and reorganization of the actin cytoskeleton to form a phagocytic cup, followed by internalization of the apoptotic cells.[33] Internalized apoptotic cells are subsequently degraded in the phagolysosome, which is followed by membrane recycling from the engulfed phagosome to restore the cell surface area and recycle efferocytosis receptors.[34–36] This recycling process is essential to internalize multiple apoptotic cells over a relatively short period of time, referred to as continual efferocytosis. Continual efferocytosis is particularly important in chronic inflammatory diseases such as atherosclerosis, where apoptotic cells far outnumber macrophages.[34,37]

Aside from membrane recycling, there are other processes initiated by the sensing, binding, engulfment, and degradation of apoptotic cells that promote continual efferocytosis. Signaling through efferocytosis receptors as well as the release of metabolites by the degradation of apoptotic cells can reprogram macrophage metabolism to facilitate continual efferocytosis and macrophage-mediated inflammation resolution, which are essential in regaining tissue homeostasis following an inflammatory insult. These efferocytosis-induced adaptations in macrophage metabolism are the subject of this review.

2 | MACROPHAGE METABOLISM IN EFFEROCYTOSIS AND RESOLUTION

2.1 | Amino acid metabolism

Amino acids are not only building blocks for protein synthesis but also play central roles in the regulation of macrophage polarization and function.[38] Macrophages are classified as pro-inflammatory or pro-resolving based, in part, on high expression levels of inducible nitric oxide synthase (iNOS) or arginase 1 (ARG1), respectively. Both of these enzymes use the amino acid L-arginine as their substrate, but they generate different products. While iNOS in pro-inflammatory macrophages converts arginine and NADPH into nitric oxide (NO) for immune defense, ARG1 in pro-resolving macrophages generates the polyamine precursor ornithine, which is essential for continual efferocytosis. Efferocytic macrophages use arginine and ornithine derived from apoptotic cell degradation to synthesize the polyamine putrescine, which promotes Rac1 activation required for actin-mediated internalization of subsequent apoptotic cells.[37] As such, mice lacking myeloid ARG1 or ornithine decarboxylase (ODC), the enzyme that converts ornithine into putrescine, have defects in efferocytosis and atherosclerosis regression, whereas treatment with putrescine promoted atherosclerosis resolution.[37] Putrescine can be further converted into spermidine and spermine, which both accumulate in macrophages during efferocytosis.[37,39] Interestingly, these polyamines were shown derive from Rac1-dependent polyamine import that occurs with efferocytosis[39] rather than from degraded apoptotic cells. While spermidine and spermine do not seem to enhance continual efferocytosis,[37] they suppress the production of pro-inflammatory IL-1β and IL-6.[39] Spermidine, by inducing mitochondrial oxidative phosphorylation through hypusination,[40] may also promote pre-resolving mediator production in efferocytosing macrophages, as explained in Section 2.2 below.

While spermidine and spermine were shown to suppress production of IL-1β (above), the amino acid serine has been shown to drive inflammation-induced IL-1β synthesis.[41,42] Multiple mechanisms may be involved in serine-dependent IL-1β production, including serine-driven synthesis of reduced glutathione to maintain cellular redox balance,[41] and serine-fueled generation of S-adenosylmethionine (SAM) to facilitate histone methylation and regulate inflammatory gene expression.[42] Although much less is known about serine in the context of efferocytosis, apoptotic cell-derived methionine has been shown to contribute to efferocytosis-induced resolution through SAM-dependent epigenetic regulation of a TGF-β resolution-repair

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program.[43] More specifically, DNA-methyltransferase-3A (DNMT3A) uses SAM to methylate Dusp4, a repressor of ERK signaling, to promote apoptotic cell-induced activation of ERK and induction of a pro-resolving Ptgs2-PGE2-TGF-β pathway in macrophages. Accordingly, bone marrow-specific deletion of DNMT3A was shown to blunt efferocytosis-induced TGF-β secretion and prevent atherosclerotic plaque resolution in mice, providing in vivo evidence for this DNMT3A-regulated TGF-β pathway. Thus, while SAM-dependent DNA methylation induces the expression of inflammatory cytokines in pro-inflammatory macrophages, it promotes the expression of resolving-repair genes in efferocytic macrophages. This suggests dynamic and context-dependent regulation of DNA methylation signatures in macrophages, potentially dependent on differential expression or activity of DNA-methyltransferases. This topic may be of particular interest to understanding how age-related loss-of-function somatic mutations in DNMT3A drive cardiovascular disease in clonal hematopoiesis.[44]

The essential amino acid tryptophan fuels the synthesis of kynurenine, serotonin, and indoles.[45] The kynurenine pathway is the most active pathway of tryptophan metabolism, and, beginning with the upstream enzyme indoleamine 2,3 dioxygenase 1 (IDO1), produces kynurenic acid, kynurenine, NAD^+, and other metabolites.[46] A role for IDO1 in efferocytosing macrophages was first brought to light by the work of McGaha and colleagues, who found that injection of apoptotic cells into mice led to the induction of IDO1 in splenic macrophages.[47] When these mice were treated with an IDO1 inhibitor, they developed a T-cell-mediated inflammatory response against the apoptotic cells, suggesting links between efferocytosis, IDO1, and tolerance to apoptotic cells. Using IDO1-overexpressing macrophages and the above mouse model, the group subsequently provided evidence that activation of an integrated stress response kinase called general control nonderepressible 2 (GCN2) by IDO1-mediated tryptophan depletion increased IL-10 and limited the expression of inflammatory cytokines in macrophages exposed to apoptotic cells.[48] However, unpublished in vitro and in vivo studies from our laboratory suggest that IDO1 mediates resolution in efferocytosing macrophages by catalyzing the conversion of tryptophan to kynurenine. Kynurenine promotes the expression of IL-10 and TGF-β and enhances continual efferocytosis by activating the macrophage aryl hydrocarbon receptor (AhR) in an autocrine/paracrine manner. These findings are consistent with other studies showing tryptophan/IDO1-derived kynurenine, in certain settings, can mediate immunosuppressive effects by activating AhR.[49] Although future work will be needed to sort out the different in vivo settings in which different mechanisms of IDO1 come into play, these combined studies suggest that IDO1-mediated tryptophan metabolism is an important mediator of tolerance and resolution in efferocytosing macrophages.

In addition to arginine, methionine, and tryptophan, which have well-characterized roles in the macrophage-mediated resolution response, an increasing number of amino acids are being identified as important immunometabolites. For example, it was recently shown that glutamine and spermidine are important regulators of energy metabolism in the context of efferocytosis, as highlighted in the next section.

2.2 | Oxidative phosphorylation

Macrophages polarized toward a pro-resolving $ARG1^+$ phenotype, which are more efficient efferocytes compared with pro-inflammatory macrophages,[37] rely mainly on oxidative phosphorylation (OXPHOS) for energy production.[50] Moreover, the process of efferocytosis further promotes OXPHOS in macrophages,[51,52] which facilitates certain aspects of the macrophage-mediated resolution program. The tricarboxylic acid (TCA cycle) oxidizes substrates from glycolysis, glutaminolysis, and fatty acid oxidation to generate NADH and $FADH_2$ required by the electron transport chain to generate usable energy in the form of ATP through OXPHOS. ATP generated through OXPHOS has been suggested to support efferocytosis by facilitating the energy-demanding process of actin cytoskeleton reorganization required for engulfment of apoptotic cells.[53] Nonetheless, in efferocytic macrophages, OXPHOS may not be fully coupled to ATP production. The uncoupling protein 2 (UCP2) is upregulated in phagocytes engulfing apoptotic cells,[51] creating a proton leak across the inner mitochondrial membrane that depolarizes the mitochondria and uncouples OXPHOS from ATP synthesis. Macrophages from mice lacking UCP2 exhibit impaired efferocytosis in vitro as well as in vivo,[51] suggesting that an excessive increase in the mitochondrial membrane potential affects the ability of macrophages to effectively clear apoptotic cells, although the exact mechanism remains unknown. Aside from its effects on efferocytosis itself, OXPHOS is also involved in efferocytosis-induced expression of the anti-inflammatory, pro-resolving cytokine, IL-10. Inhibition of fatty acid oxidation by etomoxir as well as disruption of a gene encoding the Rieske iron–sulfur protein (RISP) involved in electron transport blunts efferocytosis-induced production of IL-10.[52] Mechanistically, OXPHOS was shown to promote activation of the NAD^+-dependent enzyme sirtuin 1 (SIRT1) by elevating the NAD^+/NADH ratio, which subsequently promotes transcription if the IL-10 gene. Thus, lipid metabolism and OXPHOS are not only important for efferocytosis itself but also for the inflammation resolution response that is triggered by efferocytosis.

The important role of OXPHOS in the context of efferocytosis raises the question of how this metabolic pathway is regulated by macrophages. Apoptotic cell stimulation of primary macrophages promotes expression of genes involved in fatty acid oxidation, the electron transport chain, and OXPHOS, indicating transcriptional regulation of lipid utilization.[52] This may be in part due to the polyamine spermidine, whose levels are increased in macrophages upon efferocytosis.[37] Spermidine enables hypusination, a polyamine-dependent post-translational modification, of eukaryotic translation initiation factor 5A (eIF5A), which can subsequently promote the expression of mitochondrial proteins that promote TCA flux and OXPHOS.[40] Furthermore, the gene encoding glutaminase 1 (GLS1), an enzyme that breaks down glutamine into the TCA cycle

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intermediate α-ketoglutarate, was recently shown to be upregulated in macrophages by apoptotic cell ingestion.[53] By generating more substrate to fuel OXPHOS, glutaminolysis was found to meet the demand for high-energy actin polymerization required for efferocytosis. Whether the glutamine in this pathway is taken up from the extracellular environment or is derived from the apoptotic cells that are engulfed and degraded by macrophages is remains unknown. Besides fatty acids and glutamine, glucose can fuel the TCA cycle by generating acetyl-CoA. We elaborate on the role of glucose in efferocytosis and macrophage-mediated resolution in the following section.

2.3 | Aerobic glycolysis and lactate

In contrast to OXPHOS, glycolysis is generally associated with a pro-inflammatory macrophage phenotype. Inflammatory molecules and cytokines such as bacteria-derived lipopolysaccharides (LPS) and interferon-gamma (IFN-γ), which are employed in vitro to promote pro-inflammatory macrophage polarization, upregulate the transcription factor hypoxia-inducible factor 1-alpha (HIF1α).[54] HIF1α shifts the cell toward a more glycolytic phenotype by upregulating key enzymes and proteins in glycolysis, including hexokinases, pyruvate kinases, and the glucose transporter GLUT1.[55] At the same time, several key TCA cycle enzymes are downregulated in inflammatory macrophages, resulting in a broken TCA cycle and accumulation of the TCA cycle intermediate succinate.[56,57] Succinate further stimulates glycolysis by promoting HIF1α stability, which drives the production of the inflammatory cytokine IL-1β and supports the inflammatory macrophage phenotype.[58,59]

Recent work has challenged the idea that glycolysis is linked exclusively to inflammatory macrophage metabolism by showing that glycolysis is increased in efferocytic macrophages.[60] Nonetheless, the mechanisms involved in glycolysis in inflammatory vs. efferocytic macrophages are distinct. The transition to glycolysis in inflammatory macrophages is irreversible and depends on genetic reprogramming and rewiring of the TCA cycle.[61,62] In contrast, the increased glycolysis in efferocytic macrophages is transient and depends on rapid, Akt-mediated post-translational mechanisms that increase cell surface localization of the glucose transporter GLUT1, via phosphorylation of the GLUT1 adaptor thioredoxin-interacting protein (TXNIP), and activation of the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFBF2).[63] These processes could theoretically enable glucose to be shunted into the TCA cycle via acetyl-CoA to generate more available energy required for apoptotic cell engulfment. However, efferocytosis was rather shown to promote the breakdown of glucose into lactate,[60] which serves several purposes. First, intracellular lactate promotes calcium-dependent recycling of the efferocytosis receptors MerTK and LRP1 required for continual efferocytosis.[63] Second, lactate released from the cell can act as a paracrine mediator of inflammation resolution by skewing neighboring macrophages toward an anti-inflammatory and pro-resolving phenotype.[60] Third, lactate availability drives lysine lactylation, a newly identified post-translational modification of histones and non-histone proteins.[64] While the role of lactylation of non-histone proteins in macrophages remains to be elucidated, histone lactylation has been associated with a more pro-resolving macrophage phenotype, specifically, increased expression of Arg1, suggesting lactate-dependent epigenetic regulation of inflammation resolution.[64] Lactate has also been shown to enhance histone acetylation to promote polarization to a more pro-resolving phenotype in the context of tumor-induced immunosuppression.[65] While these epigenetic changes may be more sustained, glycolysis in efferocytic macrophages is relatively short-lived (<24 h). Thus, efferocytosis induces glycolysis in a rapid manner to produce a burst of lactate for pro-resolving processes, followed by a transition to OXPHOS to maintain the macrophages' resolving-repair phenotype. Lactate itself can be converted to pyruvate to feed into the TCA cycle and OXPHOS, which may be the mechanism by which this metabolic switching occurs in efferocytic macrophages. Indeed, lactate has been identified as a key input to fuel the TCA cycle in many tissues under physiological conditions.[66] Furthermore, silencing the lactate transporter MCT1 blunts oxidative phosphorylation in macrophages,[67] suggesting that macrophages use lactate as a source for OXPHOS.

In addition to lactate affecting macrophage function by feeding into the TCA cycle, lactate can signal via cell surface receptors such as the G-protein coupled receptors GPR81 and GPR132.[68] Both receptors have been identified previously to respond to lactate by dampening inflammation and promoting phenotypic switching of macrophages to a resolving-repair phenotype.[68] Given that GPR81 and GPR132 are cell surface receptors that respond to extracellular lactate, lactate secreted by efferocytic macrophages may spread pro-resolution signaling to neighboring, non-efferocytic macrophages and other cell types. Consistent with this idea, genetic targeting of the lactate exporter MCT1 in macrophages has been shown to impair tissue repair in the context of peripheral nerve injury.[67] Moreover, treating naïve macrophages with conditioned media collected from efferocytic macrophages increased mRNA expression of pro-resolving mediators such as *Tgfb* and *Il10*, which was blocked when the efferocytic macrophages could not export lactate.[60] Interestingly, GPR132 is downregulated upon LPS stimulation, which may function to sustain inflammation and blunt lactate signaling.[69] In a study under review from our group, we have also identified that lactate is critical to sustaining efferocytosis-induced macrophage proliferation (EIMP) through the lactate receptor GPR132. EIMP, which is discussed in Section 2.5 below, is a process that increases the pool of macrophages competent in continual efferocytosis to boost the resolution-efferocytosis cycle. The central driver of EIMP is upregulation of Myc protein, and lactate was found to stabilize Myc through GPR132-mediated activation of an AMPK-NAD^+-SIRT1 pathway. Both AMPK and SIRT1 have been implicated previously in macrophage polarization toward a pro-resolving phenotype[52,70,71] and play a role in promoting efferocytosis.[72,73] As discussed above, NAD^+-SIRT1 signaling was found to enhance efferocytosis-induced IL-10 expression in efferocytosing macrophages.[52]

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Efferocytosis is a non-inflammatory form of phagocytosis despite the uptake of large quantities of potentially pro-inflammatory molecules released directly from the apoptotic cell or from the phagolysosomal degradation of engulfed apoptotic cells.[7,74,75] Furthermore, molecules released from apoptotic cells or derived from apoptotic cell degradation in macrophages and then secreted could cause paracrine effects in neighboring macrophages.[75] For example, ATP, a "find-me signal,"[17] is released through pannexin channels by apoptotic cells, and, conversely, high levels of extracellular ATP can trigger a strong inflammatory response.[76] Additional pathways are activated during efferocytosis to promote a tolerogenic response. One such pathway involves the upregulation of the chloride transporter SLC12A2, which was reported to prevent pro-inflammatory sensing of apoptotic cells.[74] Another key mechanism of immunosuppression in macrophages may involve lactate production, as *Slc16a1*, which encodes the lactate transporter MCT1, is upregulated during efferocytosis,[60] and, as noted above, lactate can play important roles in local immunosuppression, including in tumor-mediated immunosuppression.[77]

2.4 | The pentose phosphate pathway

The pentose phosphate pathway (PPP) branches from glucose-6-phosphate in the glycolytic pathway and has both an oxidative and a non-oxidative phase.[78] The oxidative phase of the PPP generates NADPH, which can be used by NADPH oxidases to generate reactive oxygen species (ROS) required for the defense against pathogens. In addition, this phase can be used to generate ROS-scavenging antioxidants, such as reduced glutathione, to protect the cell from oxidative stress-induced damage. The non-oxidative phase of the PPP produces ribose-6-phosphate, which is used for the synthesis of nucleotides required for cell proliferation. Pro-inflammatory macrophages exhibit increased oxidative PPP activity,[56] in line with the important role they play in host defense. Non-oxidative PPP activity is suppressed in pro-inflammatory macrophages as a result of downregulation of the sedoheptulose kinase CARKL, which bridges glycolysis and non-oxidative PPP by shifting glucose-3-phosphate toward sedoheptulose-7-phosphate.[79] In contrast, pro-resolving macrophages express higher levels of CARKL, thereby enhancing the non-oxidative branch of the PPP while decreasing overall PPP flux.[79] The role of the PPP in efferocytosis is controversial. While the oxidative phase of PPP was shown to support efferocytosis by generating NADPH in the setting of physiological hypoxia,[80] another study found that efferocytosis decreases PPP flux under normoxic conditions as a result of reduced expression of PPP-related genes. In this latter setting, restoration of PPP activity in efferocytic macrophages blunted engulfment of apoptotic cells and stimulated pro-inflammatory cytokine production.[81] Consistent with these findings, a third study, that showed that PPP agonism reduced efferocytosis in vitro and aggravated autoimmune disease in a mouse model of SLE.[82]

These findings suggest that PPP flux could be an important regulator of continual efferocytosis or the inflammatory response, depending on oxygen availability within the tissue microenvironment. Although the underlying mechanisms are largely unknown, a decreased PPP flux could be coupled to an increased glycolytic flux in efferocytic macrophages, thereby promoting lactate-mediated continual efferocytosis and resolution. However, blunted oxidative phosphorylation under hypoxic conditions may deplete intracellular NADPH, resulting in a compensatory increase in PPP as well as glycolysis to maintain NADPH levels and redox homeostasis. Whether flux through the PPP is indeed coupled to glycolysis in efferocytic macrophages, and whether this could (in part) underly the association between PPP activity and efferocytosis, remains to be investigated. Moreover, further research is needed to elucidate how oxygen availability regulates macrophage metabolism in the context of efferocytosis and inflammation resolution, particularly given that tissue hypoxia is a hallmark of chronic inflammatory diseases.

2.5 | Nucleotide metabolism

Nucleotide metabolism supports RNA synthesis and DNA replication required for cell growth and proliferation. Although local proliferation of inflammatory macrophages exacerbates chronic inflammatory diseases such as atherosclerosis,[83] proliferation of pro-resolving macrophages can be beneficial by expanding the pool of pro-resolving, pro-efferocytic macrophages. In the setting of type 2 immunity and would healing, the anti-inflammatory cytokine interleukin-4 (IL-4) has been shown to promote the proliferation of tissue-resident macrophages to facilitate tissue repair.[84–86] This proliferation response was not directly linked to efferocytosis, but it was blunted in mice in which the PtdSer-dependent receptors MerTK and Axl were genetically ablated.[84] This role of efferocytosis was addressed in a subsequent study showing that efferocytosis selectively induces the proliferation of pro-resolving macrophages and that this process, termed efferocytosis-induced macrophage proliferation (EIMP), facilitates inflammation resolution and atherosclerosis regression in vivo.[87] This pathway begins with the release into the macrophages of nucleotides derived from the phagolysosomal hydrolysis of apoptotic cell-DNA by DNase2a. The major function of the nucleotides is to trigger a DNA-dependent protein kinase (DNA-PK)-mTORC2 pathway that, together with MerTK signaling via ERK, drives expression of *Myc* mRNA and protein to stimulate cell cycling. Secondarily, the macrophages recycle the apoptotic cell-derived nucleotides to support DNA synthesis in this setting. As mentioned in Section 2.3 above, another key component of EIMP related to Myc is that lactate production through efferocytosis-induced glycolysis is necessary to stabilize Myc protein expression and sustain EIMP. Finally, studies in the field of cancer have shown that Myc, which is a proto-oncogene, promotes expression of the gene encoding ODC.[88,89] Thus, it is possible that apoptotic cell-induced Myc, by promoting ODC-mediated putrescine synthesis (above), may also enhance the pro-resolving

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properties of macrophages undergoing EIMP. Consistent with this idea, EIMP macrophages are better at continual efferocytosis than naïve macrophages,[87] which may be attributable to increased putrescine production via ODC.[37] Thus, not unlike macrophage glycolysis as discussed above, macrophage proliferation has distinct mechanistic underpinnings in the setting of efferocytosis, which opens up therapeutic avenues to specifically target these processes to promote the resolution in chronic inflammatory diseases.

2.6 | Cholesterol metabolism

Cholesterol plays a crucial role in regulating cell function and is an important structural component of the cell membrane. However, cellular cholesterol homeostasis must be tightly regulated to prevent free cholesterol-induced cytotoxicity.[90] Accordingly, the substantial increase in cellular cholesterol that occurs when macrophages engulf apoptotic cells is coupled to protective mechanisms to prevent cholesterol-induced cell death.[91] Key among these mechanisms is the activation of survival pathways involving NF-κB and PI-3 kinase/Akt, which protect phagocytes from apoptosis when free cholesterol levels become elevated.[91] Moreover, the increase in free cholesterol itself is limited in efferocytosing macrophages by several mechanisms. For example, free cholesterol is esterified to fatty acids by acyl-CoA cholesterol acyltransferase (ACAT), followed by storage of the resulting cholesterol esters within intracellular neutral lipid droplets. In addition, cholesterol is excreted from the cell via ATP-binding cassette transporter A1 (ABCA1)- and ABCG1-mediated cholesterol efflux. Transcription of ABCA1 and ABCG1 is induced by the nuclear hormone receptor LXR, which was shown to be upregulated in macrophages undergoing efferocytosis.[92] Aside from protecting the macrophages from free cholesterol overload, the LXR pathway induces expression of the efferocytosis receptor MerTK and dampens expression of pro-inflammatory mediators including IL-1β, suggesting a more tolerogenic macrophage phenotype.[92] Indeed, mice lacking LXR were shown to develop autoimmune characteristics, while administration of an LXR agonist ameliorated SLE-like autoimmune disease.[92] Other targets of LXR include the sterol-regulatory element-binding proteins (SREBPs), which are transcription factors that regulate the expression of genes involved in the biosynthesis of fatty acids and cholesterol. On the one hand, inflammatory signaling through toll-like receptors such as TLR4 has been shown to promote SREBP1 expression, resulting in lipid synthesis, production of inflammatory cytokines, and downregulation of the efferocytosis receptor LRP1 in human macrophages.[93] However, SREBP1 has also been shown to contribute to the resolution of pro-inflammatory TLR4 signaling through the synthesis of anti-inflammatory fatty acids.[94] LXR and SREBPs function in a coordinated manner, and transcription of LXR target genes depends on co-activation by SREBP, which facilitates context-specific regulation of lipid metabolism.[94] The complexity of macrophage LXR-SREBP signaling and its role in efferocytosis and resolution require further investigation.

2.7 | Metabolism of fatty acids into specialized pro-resolving mediators

An important component of inflammation resolution is the conversion of polyunsaturated fatty acids into various classes of specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins, and maresins, that together restrain inflammation and promote tissue repair to restore homeostasis. Lipoxygenase (LOX) enzymes catalyze the formation of lipoxins from the omega-6 fatty acid arachidonic acid (AA), while they use omega-3 fatty acids such as eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) to generate resolvins, protectins, and maresins. Efferocytosis has been reported to promote the production of these SPMs by macrophages in two ways: by increasing the availability of SPM precursors (e.g., AA, EPA, and DHA) through degradation of the metabolic content of apoptotic cells and by stimulating enzymatic conversion of these precursors into mature lipid mediators.[7] In particular, activation of MerTK by the binding of apoptotic cells promotes excursion of the enzyme 5-LOX from the nucleus into the cytoplasm.[95,96] This brings 5-LOX in close proximity with cytoplasmic 12/15-LOX, which together can promote the conversion of AA into the lipoxin LXA_4 and DHA into the resolvin RvD1. Moreover, efferocytosis promotes the expression of 12/15-LOX, which may further enhance SPM biosynthesis.[97] Conversely, LXA_4 and RvD1 promote efferocytosis, suggesting a positive feedback loop between efferocytosis and SPM production.[98,99] Loss of 12/15-LOX activity prevents clearance of apoptotic cells by tissue-resident macrophages and promotes the development of a lupus-like autoimmune disease in mice,[100] consistent with a role for LOX-dependent SPM biosynthesis for efferocytosis-mediated resolution.

In summary, as schematized in Figure 1, efferocytosis causes an array of metabolic adaptations in macrophages that facilitate tissue resolution, the continual clearance of apoptotic cells, and the protection of macrophages from the stresses of substantial apoptotic cell-cargo load.

3 | TARGETING MACROPHAGE METABOLISM IN CHRONIC INFLAMMATORY DISEASES

3.1 | The therapeutic potential of modulating macrophage immunometabolism

Various anti-inflammatory therapies have been developed for the treatment of chronic inflammatory diseases, including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying drugs.[101] NSAIDs and glucocorticoids are used mostly to relieve symptoms of these diseases, whereas disease-modifying drugs target specific pathogenic processes to prevent tissue damage and limit disease progression. A key example of a disease-modifying drug is anti-TNFα antibody, which is used for the treatment of inflammatory rheumatoid arthritis (RA) and other inflammatory

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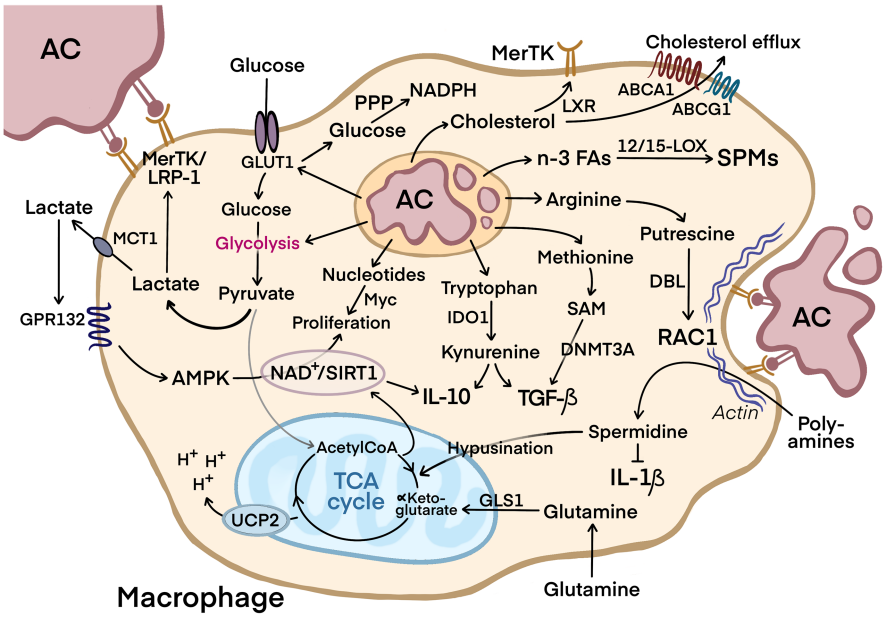

FIGURE 1 Process of efferocytosis and the release of metabolites by the degradation of apoptotic cells (AC) modulates metabolic signaling in macrophages to facilitate inflammation resolution, continual efferocytosis, and protection from excess AC-cargo load.

joint diseases. Although this therapy has proven to be very effective in reducing pro-inflammatory cytokines and halting progressive destruction of joints[102,103] and is also used as part of the treatment for ulcerative colitis and Crohn's disease,[104] its use in other inflammatory conditions is limited. A more broadly applicable anti-inflammatory drug is colchicine, which is indicated for the treatment of RA and pericarditis and has recently been shown to reduce the rate of recurrent cardiovascular events.[105] Cardioprotective actions were also found for canakinumab, a monoclonal antibody against IL-1β, which reduces the risk of atherosclerotic cardiovascular disease in patients with previous myocardial infarction.[106] However, these anti-inflammatory therapies are associated with adverse events related to impaired host defense, notably infection and sepsis. A promising strategy to limit chronic inflammation while minimizing loss of essential host defense mechanisms is through boosting inflammation resolution.[101] Resolution-repair processes are regulated by pro-resolving-type macrophages that possess distinct and dynamic metabolic signatures. This review has extensively discussed metabolic pathways that are upregulated in pro-resolving macrophages, particularly following efferocytosis. This section will focus on the clinical landscape and therapeutic potential of targeting these metabolic pathways.

3.2 | Targeting metabolic signaling pathways associated with pro-resolving macrophage function

The ARG1- and ODC-mediated synthesis of the polyamines putrescine, spermidine and spermine promote pro-resolving pathways in macrophages. Although supplementation of putrescine in the drinking water of mice was shown to restore inflammation resolution and features of plaque stability in atherosclerosis,[37] dietary intake of putrescine has not been associated with a decreased cardiovascular risk in humans.[107] In contrast, high intake of spermidine in humans is associated with a reduced risk of cardiovascular disease and a lower incidence of death after myocardial infarction.[107] The cardioprotective role of spermidine has been attributed to its antihypertensive effects, but it is unknown whether inflammation resolution is also involved. While dietary supplementation of polyamines could be beneficial to some extent, therapeutic efficacy could be enhanced by directly targeting ARG1/ODC in macrophages to promote their pro-resolving phenotype and to boost localized release of polyamines within the inflamed tissue. This could be particularly useful in chronic inflammatory diseases, which are dominated by the presence of pro-inflammatory macrophages that express relatively low levels of ARG1.[108] Promoting the ARG1-dependent conversion of arginine into pro-resolving polyamines instead of the iNOS-dependent conversion of arginine into NO could drive these macrophages toward a more pro-resolving phenotype and thereby contribute to inflammation resolution. Indeed, high macrophage ARG1 expression in rabbits confers resistance to atherosclerosis,[109] providing proof of concept that promoting ARG1 expression in macrophages could reduce the risk of chronic inflammatory disorders.

Aside from IL-4, which is widely used to promote the pro-resolving ARG1 macrophage phenotype in vitro, signaling through the LXR is known to promote ARG1 expression.[110] This is accompanied by an increase in macrophage efferocytosis receptors and a dampened inflammatory response (see Section 2.6), suggesting that LXR agonists can be employed to promote ARG1-mediated inflammation resolution. In this regard, a recent study found that phytanic acid, a microbiota-associated metabolite, restores efferocytosis in female lupus-prone mice by activating PPARγ/LXR signaling.[111] However, systemic LXR activation promotes hepatic steatosis and hypertriglyceridemia by acting on the liver,[112] implying the need for targeted drug delivery. Macrophage-specific drug targeting could be achieved by using targeted nanoparticles, which can deliver a broad range of therapeutic agents to inflamed tissues.[113] This strategy has

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been employed to enhance delivery of the LXR agonist GW3965 to atherosclerotic plaque macrophages, which showed superior efficacy in mice as compared to untargeted treatment without adverse effects on the liver.[114] Thus, by increasing therapeutic efficacy while reducing adverse effects, nanoparticle-mediated drug delivery holds great therapeutic potential.

Another advantage of using nanoparticles is that they markedly improve the chemical stability of the loaded therapeutics, which is important for the delivery of small interfering RNAs (siRNAs) and microRNAs that are sensitive to degradation by serum nucleases. Nanoparticle-mediated delivery of siRNA targeting Ca^{2+}/calmodulin-dependent protein kinase γ (CaMKIIγ), an inhibitor of LXR signaling, restores MerTK-dependent efferocytosis in atherosclerotic lesional macrophages and promotes plaque stabilization.[115,116] MerTK-mediated efferocytosis may also be increased by palmitoylethanolamide (PEA), a lipid mediator that is generated by the enzyme N-acetylphosphatidylethanolamine-hydrolyzing phospholipase D (NAPE-PLD). PEA was shown to act via the orphan receptor GPR55 to promote the expression of MerTK,[117] whereas oleoylethanolamide (OEA), another product of NAPE-PLD, was found to drive the polarization of macrophages to a pro-resolving phenotype in an AMPK-PPARα-dependent manner.[118] Although the disadvantageous pharmacokinetic profile of PEA and OEA limit their clinical use, activation of NAPE-PLD has been suggested as a therapeutic strategy to treat cardiometabolic diseases, leading to the development of small molecule activators of NAPE-PLD that are effective in raising PEA and OEA levels and promoting efferocytosis in vitro.[119] Future studies that employ targeted delivery of NAPE-PLD activators are required to evaluate whether this strategy is effective in promoting efferocytosis and inflammation resolution in vivo.

A therapeutic approach that is garnering increased interest is to target pathogenic microRNAs (miRs), for example, by using anti-miRNA nucleotides or other strategies to neutralize disease-causing miRs packaged in nanoparticles.[120] In this context, it may be possible to promote pro-resolving efferocytosis-induced glycolysis by targeting miR-646, which inhibits PFKFB2, the enzyme that mediates the pro-resolving process of efferocytosis-induced glycolysis[121] (Section 2.3). A circular RNA termed circFLNA was shown to act as a sponge of miR-646, thereby promoting PFKFB2 expression. Although PFKFB2 is expressed in various cell types and tissues, macrophage-specific delivery of circFLNA using nanoparticles may promote efferocytosis and inflammation resolution while limiting risks and side effects of treatment. As illustrated below, another strategy uses nanoparticles to deliver siRNAs, and this could be employed to silence genes that inhibit efferocytosis and resolution.

Most nanoparticles are constructed from a lipid-polyethylene glycol (PEG) layer conjugated to peptides as targeting agents, such as a collagen IV-targeting peptide ligand for delivery to collagen-rich atherosclerotic lesions[114] or S2P that recognizes the macrophage receptor stabilin-2.[87,115,116] However, these nanoparticles may be taken up by multiple cell types or by macrophages not in the inflamed tissue of interest. To overcome this limitation, an approach was developed to specifically target synovial inflammatory macrophages in RA.[122] Nanoparticles were designed to consist of a drug-based core with an oxidative stress-responsive PtdSer-coated protein corona and an outer shell of low molecular weight heparin. Heparin binds to P-selectin on activated endothelium, which localizes the nanoparticles to the inflamed tissue, that is, the joint synovium in the case of RA. ROS within the inflamed microenvironment promotes shedding of the outer shell and exposes the PtdSer corona. Macrophages then bind to PtdSer and engulf the drug-based core of the nanoparticle in an efferocytosis-like manner. This strategy was shown to be effective in delivering siRNA against *Irf5*, a regulator of the inflammatory macrophage phenotype, to synovial macrophages and thereby reduce inflammation and restore joint function in a mouse model of RA.[122] In theory, this approach could be used to target tissue-resident macrophages in other chronic inflammatory diseases, including atherosclerotic lesional macrophages, to enable site- and cell-type specific delivery of drugs that promote pro-resolving macrophage metabolism while minimizing off-target effects.

3.3 | Supplementation of pro-resolving mediators to promote macrophage-mediated inflammation resolution

Besides targeting proteins and enzymes within metabolic pathways to promote the resolution program, their precursors and end-products can be administered directly to dampen inflammation and promote tissue repair. An imbalance between SPMs and pro-inflammatory leukotrienes have been found in human atherosclerotic plaques,[123] airway fluid of cystic fibrosis patients,[124] and in blood of individuals with asthma and inflammatory periodontal disease.[125,126] These findings not only show that SPMs may be valuable diagnostic biomarkers,[127] but also suggest that raising SPM levels could be beneficial for the treatment of a variety of inflammatory diseases.[128] In animal models, exogenously administered resolvins have been shown to attenuate vascular injury and inflammation-induced atherogenesis.[129,130] Moreover, targeted nanoparticles containing Ac2-26, a peptide that acts on the same receptor as RvD1, protects against advanced atherosclerosis in mice,[131] similar to IL-10-containing nanoparticles that were also shown to promote inflammation resolution and efferocytosis in atherosclerosis.[132] In addition, injection of SPMs into inflamed human skin promotes active resolution in the short term,[133] however, long-term studies with SPMs in humans with chronic inflammatory disease are lacking. These studies may be hampered by unfavorable pharmacokinetics of SPMs, such as their limited biological half-life, making it difficult to effectively raise SPM levels at the inflamed tissue site. However, synthetic analogues of SPMs with improved metabolic stability may provide therapeutic advantages. Another approach to promote local SPM generation is by administering PUFAs as precursors, which can be converted into SPMs within the target tissue. Indeed, omega-3 fatty acid supplementation is associated with increased SPM production in humans,[134–139] and low levels of SPMs in patients with coronary artery disease could be completely restored by a

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pharmaceutical formulation consisting of a mixture of the omega-3 fatty acids EPA and DHA.[140] Most importantly, an omega-3 fatty acid-rich marine oil supplement not only increased SPM levels in individuals with peripheral artery disease, but also increased the phagocytic activity of peripheral blood monocytes and reduced their inflammatory phenotype.[141] Clinical trials are currently underway to test whether restoration of SPMs by various formulations of omega-3 fatty acids can also improve clinical outcomes in patients with chronic inflammatory diseases. Of note, such a therapy depends on the activity of 12/15-LOX, and it may be less effective in individuals with, for example, a reduced 12/15-LOX expression as a result of genetics[142–144] or a defect in efferocytosis, which might occur in settings of chronic inflammation.[11]

Lactate has many of the pro-resolving properties of SPMs, and thus boosting lactate production or administering exogenous lactate may be used as therapeutic strategies for chronic inflammatory diseases. Such strategies could also mimic the pro-resolving effects observed by our laboratory resulting from efferocytosis-induced lactate production to sustain the efferocytosis-resolution cycle by boosting continual efferocytosis and expanding the pool of pro-resolving macrophages. Some studies have begun to investigate such possibilities using animal models, ex vivo studies, or small-scale human trials. Direct injection of lactate into the circulation was found to be an effective method of delivery given the rapid transport of lactate through the circulation. This is a particularly effective method of lactate delivery to the brain, given that lactate readily crosses the blood–brain–barrier. In mice, both intracerebroventricular and intravenous injection of lactate were found to have a neuroprotective effect in ischemia–reperfusion injury of the brain,[145] which is likely explained by the anti-inflammatory and anti-oxidant properties of lactate.[69,146] Furthermore, injecting lactate is an effective method to activate SIRT1 in the hippocampus to boost the expression of brain-derived neurotrophic factor (BDNF), which is critical for memory and learning and has been associated with neurodegenerative diseases such as Alzheimer's and Parkinson's disease.[147,148] SIRT1 is also an important player in promoting efferocytosis,[73] as well as efferocytosis-associated macrophage proliferation and IL-10 production,[52] providing further evidence for lactate as a therapeutic tool to boost the efferocytosis-resolution cycle in vivo. One promising study found pro-resolving and tissue repair effects of lactate injection in dampening myocardial inflammation following acute myocardial infarction in humans.[149] Ischemic postconditioning, together with an injection of lactated Ringer's (sodium lactate) solution with each bout of brief reperfusion in myocardial infarction patients, resulted in dampened inflammation, reduced occurrence of arrhythmias, and attenuated tissue damage following full reperfusion by stenting.[149] Although the authors attribute these beneficial effects to a lactate-dependent prevention of hypercontraction, lactate could also contribute to tissue repair by promoting macrophage efferocytosis and dampening inflammation. The anti-inflammatory properties of lactate have also been observed in type 1 diabetes patients, where short infusions of lactate reduced LPS-stimulated secretion of pro-inflammatory cytokines by peripheral blood mononuclear cells ex vivo.[150]

Given that efferocytosis itself can trigger the acute production of pro-resolving lactate through glycolysis and also leads to the intracellular accumulation of other pro-resolving, pro-efferocytic metabolites derived from apoptotic cell degradation, such as nucleotides and amino acids,[37,43,60,63] potential therapies to boost efferocytosis itself are important to consider.[151] Direct injection of apoptotic cells was found to have clinically beneficial effects in acutely reducing inflammation, for example, by dampening cytokine storm during sepsis and attenuating arthritis-related inflammation.[152,153] The therapeutic potential of using apoptotic cells to stimulate efferocytosis is further illustrated by a recent study on mesenchymal stromal cell (MSC) infusion therapy, which showed that apoptosis of MSCs and subsequent efferocytosis contributes to the efficacy of this treatment.[154] However, strategies that involve administration of apoptotic cells are not as effective when macrophage efferocytosis is impaired, which is known to occur not only in chronic inflammatory diseases but also in aging.[7,155] Upregulation of the "do not-eat-me" signals CD24 and CD47 have been suggested to contribute to the accumulation of pathogenic senescent cells in aged tissues.[156] Similarly, hepatocytes dying from necroptosis upregulate CD47 in inflammation-mediated liver disease, or nonalcoholic steatohepatitis (NASH). This pathological process prevents macrophage-mediated clearance of necroptotic hepatocytes, which exacerbates NASH progression.[31] Blocking "do not-eat-me" signaling has therefore been suggested as a therapeutic approach to boost efferocytosis for the treatment of chronic inflammatory diseases. In mice, neutralizing antibodies that target CD47 were shown to boost efferocytosis and attenuate disease progression for both atherosclerosis and NASH.[31,157] A small retrospective study in patients with atherosclerotic disease showed attenuated vascular inflammation after treatment with anti-CD47 antibody.[158] Finally, an elegant approach involving the fusion of efferocytic receptors to a specific signaling domain within the cytoplasmic adaptor protein ELMO1 resulted in a chimeric receptor with an improved capacity for efferocytosis.[159] Introduction of this chimeric receptor genetically via either transgenesis or viral delivery in mice resulted in increased efferocytosis and attenuated inflammation and tissue injury in multiple pathologies, including colitis and drug-induced hepatotoxicity.[159] Importantly, introduction of the chimeric receptor also increased expression of glycolytic genes in phagocytes, suggesting increased production of pro-resolving lactate to boost the efferocytosis-resolution cycle.[159]

Aside from direct injection of lactate or boosting efferocytosis, lactate levels can be acutely raised through exercise. Exercise is well-known to generate lactate, promote anti-inflammatory signaling, and enhance tissue repair.[160–162] This exercise-induced resolution-repair program repairs skeletal muscle that becomes injured through exercise.[163] The process is initiated by the recruitment of pro-inflammatory Ly6c^{hi} monocytes by the chemokine CCL2. These monocytes develop into pro-inflammatory macrophages in an initial inflammatory phase before a local conversion to pro-resolving macrophages during the repair phase.[164] Moreover, efferocytosis is known to be critical for the proper repair of exercise-induced muscle damage.[165] Given that both inflammation and efferocytosis

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drive an increase in lactate production,[60,63] lactate may aid in the conversion of inflammatory macrophages to resolving-type macrophages. Consistent with this idea, lactate supplementation has been observed to promote tissue repair in mouse models of muscle damage. For example, oral lactate supplementation in mice with cardiotoxin-induced muscle damage stimulates skeletal muscle regeneration,[166] and implantation of a Matrigel plug containing lactate promotes the expression of pro-resolving macrophage markers in muscle and stimulates muscle perfusion, vascularization, and regeneration in an ischemia model of hind leg muscle injury.[167] Lactate has thus become recognized as a major myokine and exerkine (exercise-induced secreted signaling molecule) that promotes the systemic and local beneficial metabolic and anti-inflammatory effects of exercise.[168] Aside from the direct pro-resolving and tissue repair roles of lactate, a novel exercise-induced circulating metabolite *N*-lactoyl-phenylalanine (Lac-Phe), derived from lactate and phenylalanine, has been identified in mice and humans to suppress food intake, promote glucose balance, and prevent obesity.[169] We therefore think it would be interesting to examine whether Lac-Phe or other novel lactate-derived metabolites could also have pro-resolving and pro-efferocytosis effects in tissue repair and disease.

4 | CURRENT LIMITATIONS AND FUTURE DIRECTIONS

Key gaps in our understanding of macrophage metabolism will need to be addressed to optimize the refinement and implementation of the aforementioned therapeutic strategies for the prevention and treatment of chronic inflammatory diseases in humans. For example, our knowledge on macrophage phenotypes and their metabolic profile in human tissue is relatively limited. The majority of studies on macrophage metabolism have been performed in murine peritoneal and bone marrow-derived macrophages. While these cell models have given us valuable insight into macrophage biology, they do not always share the same properties as human tissue-resident macrophages. In fact, even peritoneal and bone marrow-derived macrophages from mice, while from the same species, have distinct metabolic phenotypes. Peritoneal macrophages are often collected under elicited conditions that promote their metabolic activity and increase their dependency on glucose as an energy source,[170,171] whereas bone marrow-derived macrophages are differentiated ex vivo and show more distinct metabolic and functional phenotypes depending on the method of differentiation. The strong dependency of elicited peritoneal macrophages on glycolysis in the resting state may explain why efferocytosis results in a higher increase in oxidative phosphorylation compared to glycolysis in these cells.[52] Bone marrow-derived macrophages that undergo efferocytosis also upregulate all pathways of energy metabolism, but shift transiently toward glycolysis soon after engulfment of apoptotic cells.[63] Nevertheless, the current paradigm of pro-resolving macrophages expressing high levels of ARG1 and pro-inflammatory macrophages expressing high levels of iNOS holds true for both macrophage populations. This paradigm is challenged by human macrophages, which express very little or even undetectable levels of iNOS and ARG1 in vitro.[172,173] Although this has created a debate on whether these enzymes are relevant for the metabolism and function of human macrophages,[174] their expression has been detected in human tissue-resident macrophages in vivo.[175–178] Whether ARG1 expression is induced in tissue-resident human macrophages in settings that require (continual) efferocytosis and inflammation resolution, as occurs in tissue-resident murine macrophages,[37] remains to be investigated. Moreover, apoptotic cells release ornithine to human macrophages after efferocytosis, which can feed the pro-resolving putrescine pathway (Section 2.1) independently of ARG1.[37] Metabolic differences between mouse and human macrophages are further exemplified by studies utilizing LPS and IL-4 to promote a pro-inflammatory and pro-resolving macrophage phenotype, respectively. Activation of mouse bone marrow-derived macrophages by LPS promotes a shift in energy metabolism from oxidative phosphorylation to glycolysis, whereas human peripheral blood monocyte-derived macrophages fail to undergo metabolic reprogramming upon LPS stimulation.[179] Furthermore, stimulation toward a pro-resolving macrophage phenotype by IL-4 depends on oxidative phosphorylation in murine macrophages[180,181] but not in human macrophages.[182] These findings collectively argue for better models for studying human macrophage biology, that is, to better understand human-specific aspects of pro-resolving macrophage metabolism and to refine therapeutic strategies that have a better chance of become clinically useful.

Another factor that may complicate the implementation of macrophage-targeted therapeutics is that macrophage metabolism is highly context-dependent. The metabolic signature and functional response of macrophages is plastic and adapts to the tissue microenvironment,[183,184] which is difficult to mimic in an in vitro setting. A large variability in oxidative metabolism of macrophages within different tissues has already been observed under homeostatic conditions,[185] and this may be further increased in the context of disease. For example, in the chronic inflammatory setting of atherosclerosis, plaque macrophages are exposed to pro-inflammatory cytokines, apoptotic cells and their releasate, and high levels of (oxidized) lipids and cholesterol, which can all affect their functional phenotype.[186] As such, both peritoneal macrophages and bone marrow-derived macrophages were found to be phenotypically distinct from macrophages in atherosclerotic lesions of mice.[187] When comparing gene expression in macrophages isolated from these lesions, researchers found a gradual decrease in pro-resolving macrophage markers with increasing disease severity,[187] in line with the impaired efferocytosis and resolution that occurs as atherosclerosis progresses.[9–11] A contributing factor may be hypoxia, since chronically inflamed tissues are often poorly oxygenated which promotes hypoxia-driven inflammatory signaling through HIF1α. Mice with hematopoietic HIF1α-deficiency show less pro-inflammatory macrophages and reduced atherosclerosis,[188] while reversal of hypoxia in atherosclerotic plaques of mice through carbon oxygenation enhances macrophage efferocytosis and prevents plaque progression.[189] The majority of in

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vitro studies on macrophages are performed under normoxic conditions, which is another aspect that may limit translation to an in vivo inflammatory setting characterized by a low-oxygen availability.

Most chronic inflammatory diseases would benefit from a therapeutic strategy that promotes tissue resolution by shifting the balance from inflammatory to pro-resolving macrophages. In cancer, however, the situation is more complex. A persistent inflammatory stimulus can drive oncogenesis by inducing DNA damage, stimulating proliferation, and conferring resistance to apoptosis.[190] However, established tumors need to evade detection by the immune system in order to grow and metastasize. Many types of human tumors have developed ways of suppressing the immune system to enhance their survival, which is a major hurdle in the development of anti-cancer therapies. As mentioned in Section 2.3, an important mechanism of tumor-mediated immunosuppression involves the glycolytic end-product lactate. Lactate released by cancer cells drives the pro-resolving phenotype of tumor-associated macrophages. Macrophages that undergo efferocytosis promote a permissive tumor microenvironment through the production of anti-inflammatory cytokines and SPMs. Other contributors to tumor-mediated immunosuppression include PtdSer and PtdSer receptors such as MerTK,[191] major histocompatibility complex (MHC) class I,[192] CD24,[193] CD47-SIRP1 interaction,[194] and PD-1-PD-L1 signaling,[195] which are currently being investigated as therapeutic targets to increase the tumoricidal activity of the immune system. This situation raises the intriguing questions as to whether pro-efferocytic/pro-resolving therapy for chronic inflammatory diseases may run the risk of promoting nascent tumor growth and, conversely, if tumor growth can be prevented by blocking the immunosuppressive pathways of efferocytic macrophages, but at the risk of triggering of a systemic inflammatory response. Perhaps highly targeted therapy can overcome these potential problems, that is, by promoting efferocytosis in specific areas of inflammation, as has been demonstrated preclinically for atherosclerosis,[116,131] and by using tumor-targeted therapy for blocking efferocytosis-induced immunosuppression.[151]

5 | CONCLUDING REMARKS

Extensive work has shown that efferocytosis-induced signaling, including signaling triggered by the cargo of engulfed and degraded apoptotic cells, changes metabolic pathways within the efferocytosing macrophage to promote pro-resolving functions. These studies have provided insight into potentially new therapeutic strategies to promote inflammation resolution in chronic inflammatory diseases, or, conversely, to prevent tumor-mediated immunosuppression in cancer. Examples of pathways discussed in this review that may be amenable to therapeutic manipulation include ARG1/ODC-mediated polyamine metabolism, lactate signaling, and SPM biosynthesis. Although therapeutic translation of pre-clinical findings is hindered by the lack of good models that reflect human macrophage biology in vivo, there are a few hints that some of these strategies may hold promise in a clinical setting, such as anti-CD47 antibody to block "do not-eat-me" signaling and lactate supplementation to promote inflammation resolution. However, much more extensive clinical testing, supported by robust pre-clinical studies, will be needed to fully evaluate the potential disease-modifying benefits and safety profile of drugging efferocytosis-fueled macrophage metabolism.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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