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Inflammation Resolution: Implications for Atherosclerosis

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Abstract

Resolution is an active and highly coordinated process that occurs in response to inflammation in order to limit tissue damage and promote repair. When the resolution program fails, inflammation persists. It is now understood that failed resolution is a major underlying cause of many chronic inflammatory diseases. Here, we will review the major failures of resolution in atherosclerosis, including the imbalance of pro-inflammatory to pro-resolving mediator production, impaired clearance of dead cells, and functional changes in immune cells that favor ongoing inflammation. In addition, we will briefly discuss new concepts that are emerging as possible regulators of resolution and highlight the translational significance for the field.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability worldwide.[1] The rising prevalence of obesity and diabetes, two major risk factors for ASCVD, have exacerbated this further in the past decade, setting off a race to develop new therapies. Recent years have seen major advances in both the scientific understanding and clinical treatment of atherosclerosis. Conventional therapy focuses on lowering low-density lipoprotein (LDL) levels, yet many patients suffer recurrent clinical events despite having achieved “goal” LDL levels.[2, 3] This continued cardiovascular risk after optimal pharmacotherapy is referred to as “residual risk”. Clinical studies have now confirmed decades of pre-clinical research demonstrating that this enhanced risk is largely due to inflammation. The landmark CANTOS trial showed that in patients with already well-controlled LDL levels, blocking interleukin (IL)-1β led to reduced cardiovascular events independent of cholesterol lowering.[3] Subsequently, the COLCOT and LoDoCo 2 trials showed that treatment with colchicine, an anti-inflammatory medication that targets multiple inflammatory pathways, also leads to fewer cardiac events in patients with known ASCVD.[4, 5] While these studies mark a turning point in the treatment of ASCVD, they have simultaneously highlighted new challenges. Inhibition of the immune response compromises host defense, leaving patients susceptible to infectious complications. This was confirmed by both COLCOT, which reported a higher rate of pneumonia in patients receiving colchicine, and CANTOS, which observed a higher rate of fatal infection in

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Disclosures

None.

patients receiving anti-IL-1β therapy.[4, 6] Therefore, while targeting chronic inflammation in ASCVD is a priority, it is crucial to identify a way to do so without impairing the ability to mount an acute inflammatory response. A growing body of recent work suggests that the chronic inflammation associated with atherosclerosis results not only from excessive inflammation, but also from the failure of inflammation to resolve. Inflammation resolution is an active process that involves production of specific pro-resolving proteins and lipids that terminate the acute inflammatory response and guide tissue repair. This review will discuss recent advances in the study of inflammation resolution and how these concepts can be applied to our understanding of atherosclerosis in order to develop novel therapeutics.

Atherosclerosis is an Inflammatory Disease.

Atherogenesis arises in medium and large-sized arteries and typically begins at sites of perturbed or non-laminar flow. At these sites, endothelial cells are dysfunctional and permissive to the passage of circulating lipoproteins into the intimal space. Once there, lipoproteins become trapped in the subendothelial layer where they undergo enzymatic and oxidative modifications. Both native LDL and oxidized LDL (oxLDL) play an important role in atherogenesis. Oligopeptides derived from the apoplipoprotein B of native LDL drive T cell responses, while oxLDL elicits a robust innate inflammatory response.[7] In addition, trapped lipoproteins activate endothelial cells and vascular smooth muscle cells (VSMCs) to increase their expression of adhesion molecules and production of chemokines. In turn, this leads to recruitment of leukocytes into the vessel wall. Monocytes, in particular inflammatory Ly6c^{high} monocytes in mice, make up the majority of the infiltrating cells and differentiate into macrophages (Mϕs). Mϕs take up lipoproteins, producing the cholesterol ester-laden “foam cells” that are characteristic of early lesions.[8] The interaction of Mϕs with modified lipoproteins triggers pro-inflammatory cascades that augment leukocyte recruitment. As plaques become more advanced, lymphocytes, dendritic cells, and neutrophils accumulate alongside Mϕs. The pro-inflammatory milieu within the growing lesion, together with excess intracellular cholesterol, activates ER stress pathways leading to apoptotic cell death. Apoptotic cells that are not cleared in a timely fashion progress to necrosis by activating self-hydrolytic enzymes, which leads to swelling of the cell, irreparable damage to the cytoplasmic membrane, and cell disruption in a process known as “secondary necrosis”.[9] These necrotic cells coalesce to form a nidus of debris and lipid that becomes the necrotic core within the plaque. VSMCs migrate from the media to the intima where they elaborate extracellular matrix that forms the collagen cap overlying the lesion. This matrix also contributes to further entrapment of lipoproteins. Growing evidence suggests that VSMCs within the intima also undergo metaplasia to become Mϕs, contributing to foam cell formation. The fate of the plaque is ultimately determined by its growth and stability. Some plaques will suffer from continued leukocyte recruitment, ongoing proliferation of Mϕs, and excessive apoptosis. This then leads to heightened inflammation, expanding necrotic cores, thinning fibrous caps, and endothelial erosion, rendering the lesion more prone to cause clinical events. While the pro-inflammatory mechanisms associated with atherosclerosis have been long appreciated (and recently elegantly reviewed[8, 10-13]), it is now clear that failures of resolution are an equally important contributor to chronic inflammation.

Atherosclerosis Results from Failures of Resolution.

Inflammation is a physiologic process aimed at protecting the host, however the protective nature of the process relies on an adequate resolution phase. If resolution fails, the inflammatory phase persists, leading to tissue damage and development of chronic disease. In recent years, it has become evident that several aspects of the resolution program fail in advanced atherosclerosis.[14-16]

Specialized Pro-Resolving Mediators.

The specialized pro-resolving mediators (SPMs) comprise a family of ligands that function in a receptor-dependent fashion on a wide range of target cells. They are derived from arachidonic acid (AA), docosahexaenoic acid (DHA), or eicosapentaenoic acid (EPA) by the action of cyclooxygenases (COX) or lipoxygenases (LOX). This generates multiple classes of SPMs including the lipoxins (LX), resolvins (Rv), protectins, and maresins (Figure 1). SPMs can be produced by a wide variety of cell types including macrophages, neutrophils, and lymphocytes. In addition, transcellular synthesis has been observed between leukocytes, platelets, and epithelial cells, with intermediates being formed in one cell type and then synthesized to SPMs by the other.[17]

The ability of SPMs to influence plaque progression in mice has been demonstrated by a variety of studies in which the administration of exogenous SPMs to mice with established atherosclerosis led to reduced overall lesion area, smaller necrotic cores, reduced immune cell infiltration, enhanced lesional efferocytosis, and thicker collagen caps (Table 1). In humans, low levels of circulating SPMs correlate with the presence of atherosclerosis.[18] Further, plasma from symptomatic patients suffering from stroke showed significantly lower RvD1 levels compared with asymptomatic patients.[19] Recent work has identified an imbalance of pro-inflammatory and pro-resolving lipid mediators within lesions as a key feature of advanced atherosclerosis. In human carotid arteries, regions of advanced disease were shown to have a high LTB_4:SPM ratio compared with early plaque regions.[20] *Apoe*$^{-/-}$ mice fed a Western diet for 4, 8, or 16 weeks showed a steady increase in prostaglandin and LTB_4 content within the aortas. Simultaneously, there was a decrease in RvD2 and maresin 1.[21] Similarly, atheroprone *Ldlr*$^{-/-}$ mice fed a Western diet for 17 weeks had higher LTB_4:SPM ratios within the aorta compared to *Ldlr*$^{-/-}$ mice fed for only 8 weeks. Administration of RvD1 to *Ldlr*$^{-/-}$ mice with established plaque led to smaller necrotic cores, increased lesional efferocytosis, and thicker collagen caps during progression of disease. RvD1 treatment also led to an increase in overall SPM content, suggesting that RvD1 can trigger a local feed-forward mechanism within the vessel wall.[20] Together, these data suggest that the local balance of pro-resolving to pro-inflammatory mediators plays a pathogenic role in disease.

Several studies have shown that SPM production is dependent on the cellular milieu. Under inflammatory conditions, 5-LOX in Mϕs is phosphorylated, leading to its translocation to the nuclear membrane where it interacts with 5-LOX activating protein (FLAP) and promotes the synthesis of LTB_4. Under non-inflammatory conditions or in response to RvD1, 5-LOX remains unphosphorylated and instead is localized to the cytoplasm. There, in sequence with 12/15-LOX, it favors production of LXA_4.[22] Signaling through the

MER proto-oncogene tyrosine kinase (MerTK) receptor, an efferocytosis receptor, limits phosphorylation of 5-LOX and increases LXA_4 production.[22, 23] Examination of human carotid atherosclerotic lesions showed that in regions of advanced plaque, 5-LOX had a predominantly nuclear localization compared to healthy regions of arteries.[24] In addition, high-mobility group box 1 (HMGB1) signals through the receptor for advanced glycation end products (RAGE) to phosphorylate 5-LOX, increase 5-LOX nuclear localization, and increase LTB_4 production. Alternatively, when C1q is present, HMGB1 and C1q form a tetramolecular complex that links RAGE and the leukocyte-associated Ig-like receptor-1 (LAIR-1). This prevents phosphorylation of 5-LOX and increases production of LXA_4, RvD1, and RvD2 (Figure 2).[25]

SPM Receptors.

The SPMs effect their cellular functions through their actions on G-protein coupled receptors in mice and humans, including *N*-formyl peptide receptor 2 (ALX/FPR2), LTB_4 receptor-1 (BLT1), Chemerin receptor 23 (ChemR23), and G protein-coupled receptor 18 (GPR18). In addition, humans express GPR32 for which there is currently no known ortholog in mice. *In vitro* and *in vivo*, a variety of athero-relevant functions have been attributed to SPM receptor signaling, including modulation of efferocytosis, leukocyte recruitment, and cytokine production (Table 2).

ALX/FPR2—ALX/FPR2 can promote either pro-inflammatory or pro-resolving signaling, dependent on the ligand. When activated by serum amyloid A (SAA), ALX/FPR2 promotes inflammatory cytokine signaling.[26, 27] In contrast, when activated by LXA_4 or RvD1, ALX/FPR2 promotes Mϕ skewing toward a pro-reparative phenotype and increases efferocytosis.[28] This suggests that in advanced plaques, where levels of pro-resolving ligands are low, pro-inflammatory ALX/FPR2 signaling predominates. Genetic deletion of *Fpr2* in $Ldlr^{-/-}$ or $Apoe^{-/-}$ mice led to reduced atherosclerotic lesion area compared with control mice early in the course of plaque development.[27, 29] As lesions progressed with longer lengths of feeding, the difference between the $Fpr^{+/+}$ and $Fpr^{-/-}$ groups was lost.[27, 29] In other studies, the authors utilized a bone marrow transplantation model to generate chimeric $Fpr2^{-/-} \rightarrow Ldlr^{-/-}$ mice. Interestingly, in this model, the mice receiving $Fpr2^{-/-}$ marrow developed significantly less plaque than those receiving wild type marrow despite long lengths of Western diet feeding.[27, 30] This suggests that there may be a role for FPR2 on non-hematopoietic cells in advanced atherosclerosis. Recently, a series of novel ALX/FPR2 agonists were developed that specifically target the pro-resolving properties of the receptor and decreased the number of adherent human neutrophils in an *in vitro* assay. While not yet used *in vivo*, this study suggests that it is possible to target the SPM receptors with small molecule agonists.[31]

BLT1—The role of BLT1 in atherosclerosis also appears to be dependent on stage of lesion development. Similar to ALX/FPR2, the BLT1 receptor has multiple ligands with opposing functions. These include LTB_4 which acts an agonist, as well as RvE1 and RvE2 that act as antagonists. In $Blt1^{-/-}$ $Apoe^{-/-}$ mice fed a Western diet, there was a decrease in aortic lesion size after 4 or 8 weeks of feeding compared to $Apoe^{-/-}$ mice. However, after 19 weeks of Western diet, there was no difference in lesion size.[32] A subsequent study confirmed these

findings, showing that *Blt1*$^{-/-}$ *Apoe*$^{-/-}$ mice fed a Western diet for 6 or 12 weeks had a reduction in lesion area.[33] Interestingly, these authors also found a markedly diminished number of SMCs, Mϕs, and T cells in the vessel wall of *Blt1*$^{-/-}$ *Apoe*$^{-/-}$ mice. They found that BLT1 is upregulated in human atherosclerotic lesions, and frequently co-localized with SMCs and Mϕs, suggesting that SPMs may also regulate vascular cells in ways that are not yet fully understood.[32]

ChemR23—Deletion of the ChemR23 receptor led to increased atherosclerotic lesion area in *Apoe*$^{-/-}$ or *Ldlr*$^{-/-}$ mice versus controls.[34] This increase in atherosclerosis was also associated with increased lesional Mϕ content, heightened pro-atherogenic signaling in Mϕs, enhanced foam cell formation, and reduced efferocytosis *in vitro* as well as increased necrotic core size *in vivo*. This stands in contrast to another study that utilized *Apoe*$^{-/-}$ mice in which the ChemR23 gene was replaced with eGFP (*ChemR23*$^{eGFP/eGFP}$ *Apoe*$^{-/-}$). In this study, *ChemR23*$^{eGFP/eGFP}$ *Apoe*$^{-/-}$ mice fed a western diet for either 4 or 12 weeks had smaller plaques and less lesional Mϕ accumulation than control mice.[35] While the explanation for this is not known, it is possible that the stage of lesion development influences the availability of ligands in the local microenvironment. Since ChemR23 can be stimulated by the inflammatory ligand, chemerin, as well as the resolving ligands, RvE1 and RvE2, it is interesting to hypothesize that the balance of pro-inflammatory:pro-resolving ligands may influence receptor function in a paradigm similar to that described for LTB4:SPMs above. In human atherosclerotic lesions from coronary and carotid arteries, ChemR23 expression was found primarily in Mϕs surrounding the necrotic core. Interestingly, ChemR23 expression was increased in plaques from patients on lipid-lowering therapy with statins, suggesting that receptor expression in addition to mediator abundance is dynamic. [34]

GPR32—Recently, the role of the GPR32 receptor was investigated *in vivo*. Because there is no murine homolog of GPR32, the authors created a transgenic mouse model expressing human GPR32 on an *Fpr2*$^{-/-}$ *Apoe*$^{-/-}$ background (*hGPR32*$_{myc}$*Tg Fpr2*$^{-/-}$ *Apoe*$^{-/-}$ mice). After 12 weeks of Western diet, these mice had reduced lesion area and smaller necrotic cores compared to *Fpr2*$^{-/-}$ *Apoe*$^{-/-}$ mice. Using zymosan-elicited Mϕs in a peritonitis model of sterile inflammation, the authors showed that expression of hGPR32 led to enhanced efferocytosis and increased expression of 12/15-LOX. Administration of the GPR32 agonist, AT-RvD1, further enhanced these phenotypes.[36]

Non-Lipid Pro-Resolving Mediators.

Pro-resolving proteins—The pro-resolving cytokine, IL-10, has been detected in human and murine atherosclerotic plaques, where it is produced primarily by Mϕs.[37] Through inhibition of nuclear factor (NF)-κB, IL-10 impedes the release of multiple pro-inflammatory mediators including intracellular adhesion molecule 1 (ICAM-1), IL-1β, monocyte chemotactic protein 1 (MCP-1), and tumor necrosis factor-α (TNF-α). IL-10 upregulates cholesterol efflux receptors and downregulates scavenger receptors, which limits foam cell formation.[38] Upregulation of IL-10 expression in Mϕs leads to increased Rac activity, which promotes efferocytosis.[39] In addition, it can inhibit the secretion of matrix metalloproteinase-9 (MMP-9) to prevent degradation of the fibrous caps in advanced

atherosclerosis.[40] Deletion of *Il10* from *Apoe*$^{-/-}$ mice led to dramatically increased lesion area and heightened MMP activity.[41] Overexpression of IL-10 in Mϕs of *Ldlr*$^{-/-}$ mice led to reduced atherosclerotic lesion area compared to control mice.[42, 43] Delivery of IL-10 to established atherosclerotic plaques using lesion-targeting nanoparticles led to decreased necrotic core area, increased collagen cap thickness, and a trend toward increased lesional efferocytosis (Table 1).[44] Notably, many of the SPMs, including LXA_4, RvD1 and RvE1, lead to increased expression of IL-10 in Mϕs, linking these two important arms of the resolution program.[17]

Annexin A1 (AnxA1), is also important in atherosclerosis and has been associated with a variety of pro-resolving functions, including inhibiting leukocyte recruitment, boosting efferocytosis, and reprogramming Mϕs toward a pro-reparative phenotype.[45] Deletion of AnxA1 in *Apoe*$^{-/-}$ mice led to increased atherosclerotic lesion area.[46] Administration of recombinant AnxA1 to *Ldlr*$^{-/-}$ mice with established lesions led to a reduction in overall lesion area and decreased necrotic core size.[47] Similarly, treatment of *Apoe*$^{-/-}$ mice with a bioactive peptide derived from AnxA1, Ac2-26, led to a reduction in lesion area and macrophage content by blocking chemokine-dependent integrin activation.[46] When delivered directly to plaques of *Ldlr*$^{-/-}$mice using a lesion-targeting nanoparticle, Ac2-26 decreased plaque necrosis, reduced lesional oxidative stress, thickened collagen caps, and increased intraplaque IL-10 expression (Table 1).[30]

Pro-resolving gases—Nitric oxide (NO) is known to have both pro-apoptotic and anti-apoptotic properties depending on the local concentration. In atherosclerosis, high levels of inducible nitric oxide synthase (iNOS) lead to high concentrations of NO, which favor apoptosis and clearance of leukocytes.[48] In addition, NO can nitrosylate the NLRP3 inflammasome in order to prevent its assembly in Mϕs.[49] Hydrogen sulfide (H_2S) is also a potent inhibitor of the inflammasome[50]. *In vitro* and in an *in vivo* murine peritonitis model, H_2S led to enhanced efferocytosis and reduced pro-inflammatory cytokine expression.[51] Enhancing H_2S activity in *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice led to reduced plaque formation, lower expression of ICAM-1, and reduced aortic expression of pro-inflammatory cytokines.[52, 53] Conversely, genetic targeting of the H_2S synthetic enzyme, cystathionine γ-lyase led to exacerbated atherosclerosis in *Apoe*$^{-/-}$ mice.[54] Carbon monoxide (CO) may also play a role in resolution in atherosclerosis. Heme oxygenase (HO-1) is an enzyme induced by oxidative stress, inflammation, and oxidized lipoproteins that produces CO as a byproduct of heme degradation.[55] It is expressed at low levels in endothelial cells and VSMCs but is highly upregulated in pro-resolving Mϕs.[56] CO and HO-1 are known to suppress pro-inflammatory cytokine production and block leukocyte infiltration into tissue. In a murine peritonitis model, inhaled CO led to lower levels of leukocyte infiltration to the peritoneum and increased efferocytosis by Mϕs.[57] Induction of HO-1 expression and activity in *Ldlr*$^{-/-}$ mice inhibited the formation of atherosclerotic lesions.[58] Importantly, CO has been shown to increase levels of the SPMs, again indicating that these arms of the resolution program are closely linked.[57]

Tissue hypoxia is a contributor to the development of atherosclerosis. Recently, it was shown that ventilating atheroprone mice with carbogen gas (95% O_2 and 5% CO_2) led to reduced plaque hypoxia. This was associated with increased lesional efferocytosis, and

smaller necrotic cores. *In vitro*, hypoxia led to decreased expression of MerTK by Mϕs, which may be the mechanism by which this occurs.[59]

Efferocytosis and the Clearance of Dead Cells.

Cell death is a quintessential part of the resolution process and a crucial mechanism by which the immune cell burden within developing lesions is reduced. Cells within plaques undergo cell death in a variety of ways including necroptosis, pyroptosis, ferroptosis, and apoptosis.[60-63] The engulfment of dead cells by professional phagocytes is called efferocytosis. This process is mechanistically distinct from classical phagocytosis in that it requires phagocyte expression of receptors that recognize ligands on dead cells. It is a highly regulated and efficient process that rapidly allows the phagocyte to reorganize its cytoskeleton and upregulate metabolism to process the large amount of nutritional cargo represented by the ingested apoptotic cell (AC). When efferocytosis is properly executed, it leads to the downregulation of pro-inflammatory signaling and upregulation of pro-resolving pathways, including SPM production. It is now well appreciated that efferocytosis is impaired in chronic inflammatory diseases, including atherosclerosis.[62, 64] Emerging data from GWAS studies have identified SNPs in genes related to efferocytosis pathways. One example is phosphatase and actin regulator 1 (*PHACTR1*), in which rs9349379 was associated with early-onset myocardial infarction.[65] Subsequent studies showed that the risk allele (rs9349379-G) was associated with lower levels of PHACTR1 expression in Mϕs and impaired efferocytosis in human monocyte-derived Mϕs as well as human lesional Mϕs compared to the common allele.[66] *In vitro,* the loss of PHACTR1 from human or murine Mϕs led reduced ability to engulf ACs and therefore inhibited efferocytosis. Mice lacking hematopoietic expression of PHACTR1 (*Phactr1*$^{-/-}$ marrow transplanted to *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice) had increased atherosclerotic lesion area, larger necrotic cores, and thinning collagen caps.[66, 67]

Compromise of efferocytosis receptors—Impaired efferocytosis occurs during atherogenesis for several reasons (Figure 3). Efferocytosis receptors, including LDL Receptor Related Protein 1 (LRP1) and MerTK, can be proteolytically cleaved or degraded during advanced atherosclerosis.[68, 69] In response to oxLDL, LRP1 is ubiquitinated and then bound by epsins 1 and 2, leading to its internalization and degradation. Mϕs in which epsins are genetically deleted had increased total and surface levels of LRP1. *Apoe*$^{-/-}$ mice in which epsins 1 and 2 were deleted from myeloid cells had smaller atherosclerotic lesions, smaller necrotic cores, and diminished inflammatory cell content within the aortas after Western feeding.[70] Deletion of LRP1 from hematopoietic cells or macrophages in atheroprone mice also led to increased overall plaque area and necrotic core size.[71-73] MerTK and LRP1 are targets of a disintegrin and metalloproteinase 17 (ADAM17), which can cleave the extracellular domain from the receptors, rendering the remaining receptor incapable of signaling.[69] In the case of MerTK, it also generates a soluble fragment, known as soluble Mer (solMer), which can compete for binding to the bridging molecule Gas6, decreasing its availability and further impairing efferocytosis.[74] Levels of MerTK decrease with progression of atherosclerosis while ADAM17 and solMer accumulate within plaques from both mice and humans.[75-77] Loss of MerTK in atheroprone mice (*Mertk*$^{-/-}$ *Ldlr*$^{-/-}$) leads to increased lesion size, larger necrotic core area, and reduced lesional

SPMs.[22, 69, 75, 76] In a mouse model in which MerTK was replaced by a cleavage-resistant mutant (*Mertk*^{CR} *Ldlr*$^{-/-}$ mice), there were significantly smaller necrotic cores, enhanced lesional efferocytosis, and higher levels of SPMs compared with control mice.[75] This suggests that cleavage of the MerTK receptor plays a causative role in atheroprogression.

It is worth noting that the role of ADAM17 is not completely straightforward. Despite the atherogenic role of ADAM17 suggested by the above studies, low levels of ADAM17 in *Ldlr*$^{-/-}$ mice (hypomorphic *Adam17*$^{ex/ex}$ mice that express low residual ADAM17 expression) led to larger atherosclerotic lesions, with more lesional macrophages compared to littermate controls.[78] In a subsequent study, myeloid-specific *Adam17*$^{-/-}$ mice (*Adam17*$^{flox/flox}$ *Lyz2*^{Cre} *Apoe*$^{-/-}$) fed a western diet for 12 weeks developed significantly more atherosclerotic lesion area but reduced lesional macrophage area and increased collagen content while the endothelial-specific loss of Adam17 (*Adam17*$^{flox/flox}$ *Bmx*^{Cre} *Apoe*$^{-/-}$) led to significantly smaller lesions. This made clear that the effects of ADAM17 on atherosclerosis are cell type specific and will require further investigation.[79]

Several pathways have been elucidated that play into the regulation of MerTK in atherosclerosis. For example, calcium/calmodulin-dependent kinase 2 gamma (CaMK2γ) activity is heightened in Mϕs within advanced atherosclerotic plaques of humans and mice.[80] *In vitro*, this was shown to prevent signaling of an ATF6/LXRα pathway that drives MerTK expression. Genetic deletion of CaMK2γ (*Camk2g*$^{-/-}$ *Ldlr*$^{-/-}$ mice) or delivery of nanoparticles carrying CaMK2γ siRNA to *Ldlr*$^{-/-}$ mice restored signaling of this pathway, leading to increased MerTK expression, reduced necrotic core size, and enhanced lesional efferocytosis.[80, 81]

Loss of bridging moleculesx—In addition to efferocytosis receptors, bridging molecules that allow for the indirect binding of ACs can be compromised in advanced atherosclerosis. For example, milk fat globule-EGF factor 8 (MFGE8) is a bridging molecule that interacts with integrin αvβ3 whose lesional expression declines during atheroprogression in mice.[82] *Ldlr*$^{-/-}$ mice lacking MFGE8 (bone marrow transfer of *Mfge8*$^{-/-}$ marrow into *Ldlr*$^{-/-}$ mice) have increased atherosclerotic lesion area and increased plaque necrosis.[82] Similarly, Transglutaminase 2 (TG2) acts as a bridging molecule for integrin β_3.[83] When marrow from *Tg2*$^{-/-}$ mice is transplanted into *Ldlr*$^{-/-}$ mice, the resulting lesions are larger, contain more Mϕs, and have larger necrotic cores.[84] The complement component, C1q, is another bridging molecule whose loss in *Ldlr*$^{-/-}$ mice leads to increased atherosclerotic lesion area and heightened accumulation of lesional ACs.[85] While C1q serves multiple functions in inflammation, it is known to promote resolution and efferocytosis through its ability to interact with HMBG1 to influence 5-LOX localization and enhance SPM production in Mϕs (Figure 2).[25]

Inappropriate signaling from apoptotic cells—In advanced atherosclerosis, ACs themselves can contribute to defective efferocytosis (Figure 3). For example, dead cells in lesions express lower amounts of the ‘eat me’ signal, calreticulin. GWAS showed that human carriers of the cardiovascular risk allele at chromosome 9p21 have lower intraplaque expression of *CDKN2B* and reduced lesional expression of calreticulin.[65, 86] Similarly, *Apoe*$^{-/-}$ mice lacking *Cdkn2b* have decreased levels of calreticulin and ACs from these

animals are resistant to engulfment. Fed a Western diet, *Cdknb*$^{-/-}$ *Apoe*$^{-/-}$ mice have increased plaque area and larger necrotic cores.[86] There can also be inappropriate expression of 'don't-eat-me' signals. One such signal is CD47, whose expression renders ACs inedible to efferocytes.[87] CD47 expression is significantly upregulated in human atherosclerotic plaques compared to healthy arteries.[87] Treating *Apoe*$^{-/-}$ mice with an anti-CD47 antibody led to smaller necrotic cores and enhanced lesional efferocytosis. It is not yet known what leads to increased CD47 on the ACs in advanced plaques, however, *in vitro* studies have suggested that signaling through the TNF receptor, TNFR1, and NF-κB may lead to its upregulation.[87] Another potential mechanism of CD47 regulation is via the microRNA, miR-149-5, which acts as a negative regulator of CD47. Recently, the long non-coding RNA, myocardial infarction-associated transcript (MIAT) was found to act as a 'sponge' for miR-149-5, thereby increasing CD47 expression. Of note, MIAT is highly expressed in symptomatic human plaques and advanced murine atherosclerosis, suggesting that in advanced disease, MIAT leads to upregulation of CD47.[88, 89] This was supported by studies showing that *Miat*$^{-/-}$ *Apoe*$^{-/-}$ mice had decreased CD47 expression, increased efferocytosis, and decreased plaque necrosis.[89] Interestingly, MIAT was also found to promote transdifferentiation of SMCs into inflammatory macrophage-like cells, suggesting another mechanism by which MIAT promotes atherosclerosis.[88]

Metabolic reprogramming by efferocytosis—When accomplished effectively, the outcome of efferocytosis is not only clearance of dead cells, but also a shift toward a pro-reparative Mϕ phenotype, which includes metabolic reprogramming. RNA sequencing of efferocytes actively engulfing ACs revealed a genetic signature associated with phagocytosis.[90] Subsequent studies have shown important roles for glycolysis, oxidative phosphorylation (OXPHOS), and their related metabolic pathways in efficient efferocytosis. Binding of ACs to Mϕs leads to upregulation of the glucose transporter SLC2A1 (GLUT1) and serum/glucocorticoid-regulated kinase 1 (SGK1) that enhance glucose uptake and activate aerobic glycolysis.[90] This pathway was shown to be critical for the successive clearance of ACs, known as 'continual efferocytosis', since blocking glucose uptake or glycolytic flux led to failures in actin polymerization that prevented further AC engulfment.[90] Deletion of *Slc2a1* from myeloid cells in atheroprone mice (*Slc2a1*$^{flox/flox}$ *Lyz2 Cre* marrow transplanted into *Ldlr*$^{-/-}$ mice) led to increased necrotic core size and decreased lesional collagen content.[91] Another solute transporter, SLC16A1, was found to be upregulated by Mϕs in response to AC internalization. SLC16A1 is responsible for the release of lactate, the end-product of glycolysis, from the cell. Interestingly, lactate acts in a paracrine fashion on neighboring cells to enhance their production of IL-10 and TGF-β, further linking glycolysis to the resolution program.[90]

OXPHOS also appears to promote resolution. Strategies that promote OXPHOS enhance the expression of resolution genes and inhibiting aspects of the OXPHOS pathways leads to impaired efferocytosis.[92] Fatty acid oxidation (FAO or β-oxidation) provides reducing equivalents to OXPHOS. Therefore, changes in FAO may contribute to OXPHOS phenotypes in Mϕs. One study showed that loss of Lipin-1, a phosphatase with transcriptional coregulator activity, is required for FAO and OXPHOS in pro-reparative macrophages.[93] While lipin-1 deficient Mϕs were able to ingest a single AC, they

had a specific impairment in their ability to take up subsequent cells.[94] Interestingly, these functions were attributable to the transcriptional role and not the enzymatic activity of lipin-1. The loss of lipin-1 from myeloid cells (*Lpin1*$^{flox/flox}$ *Lyz2*^{Cre}) in hypercholesterolemic mice led to increased lesion area and necrotic core size.[95] Another study showed that activation of FAO in response to efferocytosis stimulated the mitochondrial respiratory chain, leading to sirtuin-dependent activation of transcription factor PBX1 and IL-10 expression. Disruption of the electron transport chain led to decreased IL-10 and impaired resolution.[96] Recently, it was shown that glutaminolysis, which also feeds substrates into the OXPHOS pathway, promotes efficient efferocytosis. In response to ingestion of an AC, glutaminase-1 (GLS1) is upregulated to produce glutamate that is then metabolized via a non-canonical transaminase-dependent OXPHOS pathway. Loss of GLS1 from Mϕs impaired efferocytosis *in vitro* and genetic deletion of GLS1 from atheroprone mice fed a Western diet (*Gls1*$^{-/-}$ *Lyz2*^{Cre} *Apoe*$^{-/-}$ mice) led to augmented plaque size and an increased number of lesional ACs.[97] These authors also showed that *Gls1* expression is reduced in atheroprogression, suggesting that loss of GLS-1 during plaque development may contribute to failed efferocytosis *in vivo*. Glutamate can be further metabolized into ornithine, arginine, or polyamines. When ACs are degraded, Mϕs take up a load of arginine and ornithine that are further metabolized by arginase (Arg1) and ornithine decarboxylase (ODC) into putrescine. Putrescine promotes Rac1 activation to facilitate actin rearrangement and engulfment of ACs. Interestingly, the loss of Arg1 or ODC did not affect the ability of Mϕs to take up a single AC but led to a dramatic reduction in the ability of the Mϕ to carry out successive rounds of efferocytosis. This underscores that the upregulation of this pathway occurs in response to AC-derived arginine/ornithine rather than endogenously generated polyamines. Interestingly, genetic deletion of Arg1 or nanoparticle-mediated silencing of lesional ODC in *Ldlr*$^{-/-}$ mice did not reduce overall atherosclerotic burden in the progression of disease. However, in a model of atherosclerotic regression, loss of either Arg1 or ODC impaired plaque remodeling and led to persistently large necrotic cores and thinner collagen caps than observed in control mice.[98] The authors went on to show that ODC-dependent putrescine synthesis sustains MerTK expression *in vitro* and *in vivo*, leading to enhanced efferocytosis and increased IL-10 expression.[99]

Efferocytosis triggers a pro-resolving macrophage phenotype—As alluded to in prior sections, efficient efferocytosis increases the production of pro-resolving mediators. After ingesting ACs, Mϕs quickly upregulate lipoxins and the D-series resolvins.[100] The reciprocal relationship between efferocytosis and pro-resolving mediator production creates a positive feedback loop, in which treatment of Mϕs with IL-10 or SPMs enhances efferocytosis and increased efferocytosis then leads to heightened production of these pro-resolving mediators. This could be particularly important in diseases such as atherosclerosis where the burden of ACs is high and continual efferocytosis is important for maintaining homeostasis. Further, this may also be another mechanism by which the lower content of lesional SPMs in late-stage lesions contributes to impaired efferocytosis.

A recent paper identified a novel mechanism by which efferocytosis shifts the pool of murine Mϕs or human monocyte-derived Mϕs toward a pro-resolving phenotype. The authors found that nucleotides derived from the digestion of AC-derived DNA activate an

mTorc2-dependent pathway that upregulates the transcription factor, Myc. This promotes proliferation of the efferocytosing Mϕs, thereby expanding the pool of pro-resolving Mϕs. Silencing DNase2a, which is responsible for the degradation of AC-derived DNA, or Rictor, which is a key component of the mTorc2 pathway, blocked proliferation. Further, the authors found that in murine models of atherosclerotic regression, efferocytosis and Mϕ proliferation are necessary for the resolution of necrotic cores and when DNase2a or Rictor are silenced within lesional Mϕs of *Ldlr*$^{-/-}$ mice with established plaque, regression is impaired.[101]

Necroptosis—Until recently, it was thought that the necrotic cores of atherosclerotic plaques were solely the result of secondary necrosis due to failed efferocytosis, however, it is now appreciated that necroptosis contributes to this. Like apoptosis, necroptosis is a specific cell death program. When a death receptor is triggered, receptor-interacting protein kinase 1 (RIP1) and caspase-8 are activated to promote apoptosis. In situations where caspase-8 is inactive or overwhelmed, RIP1 instead interacts with RIP kinase 3 (RIP3) to form the 'necrosome'. The necrosome can then recruit mixed lineage-kinase domain-like (MLKL) and assemble the necrotic pore.[63] This leads to active disruption of the mitochondrial, lysosomal, and plasma membranes and results in leakage of cell contents that can act as DAMPs and augment inflammation.[102] Necroptotic cells (NCs) release high levels of the pro-inflammatory lipid mediators thromboxane B_2 and PGE_2, which likely contribute to their inflammatory nature in tissue.[103] NCs as well RIP1, RIP3, and MLK have been identified in advanced and symptomatic, but not early, human plaques, suggesting that necroptosis may contribute to the progression of disease.[104, 105] The mechanisms by which NCs are cleared from tissue are not yet well understood. A recent study showed that while Mϕs tend to wholly engulf ACs, they instead 'nibble' NCs. The authors found that NCs express high levels of the 'don't eat me' signal, CD47, that contributes to their inefficient uptake. When co-cultures of Mϕs and NCs were treated with an anti-CD47 antibody, there was a significant increase in their ingestion (Figure 3).[106] Whereas ACs activated CDC42 and provoked a wide 'mouth-like' phagocytic cup, NCs instead activated RhoA that led to a thin 'arm-like' structure that failed to encompass the dead cell. Anti-CD47 treatment produced the wider 'mouth-like' structure even in interacting with NCs. Similarly, treatment of *Apoe*$^{-/-}$ mice with anti-CD47 during atheroprogression led to fewer lesional NCs and less plaque necrosis.[106] Anti-CD47 treatment also led to reduced pro-inflammatory mediator production and upregulation of RvD1 production by NCs.[103, 106] Treatment of mice with RvD1 led to enhanced NC clearance through shifting the balance of RhoA:CDC42 and facilitating release of the 'eat me' signal, calreticulin.[103] Deletion of *Mlkl*$^{-/-}$ from hypercholesterolemic mice led to decreased Mϕ death, smaller necrotic cores, and increased collagen cap thickness compared to control mice.[103] In addition, the *Mlkl*$^{-/-}$ mice were found to have increased total plaque SPMs and an improved SPM:pro-inflammatory lipid mediator balance.[103] Together, this suggests that increased necroptosis in advanced plaques is another mechanism by which inflammation resolution is impaired in atherosclerosis.

Macrophage Egress vs Retention in Plaque

At the conclusion of an inflammatory response, it is crucial that immune cells be able to leave the site of tissue injury in order to return to homeostasis. In atherosclerosis, there is accumulating evidence that Mϕs are inappropriately retained within the vessel wall, adding

to the growth of the plaque. This is due to both the increased expression of molecules that promote retention and impairment of those that enhance movement. Cholesterol loading of Mϕs leads to upregulation of the Mϕ chemostasis factors, semaphorin 3E and netrin-1, which both promote Mϕ survival and decrease Mϕ emigration from tissue.[107-109] The loss of hematopoietic netrin-1 in $Ldlr^{-/-}$ mice led to reduced atherosclerotic plaque size and lower lesional Mϕ content.[107] New work has now shown that temporally silencing netrin-1 can also promote plaque regression. Using a model of tamoxifen-induced netrin-1 deletion in hyperlipidemic mice ($Ntn1^{flox/flox}Cx3cr1^{creERT2+}$), the authors showed that deletion of myeloid netrin-1 led to a dramatic reduction of plaque size and complexity. Netrin-$1^{-/-}$ Mϕs had a pro-resolving phenotype in plaque that favored increased IL-10 expression and enhanced lesional efferocytosis. Further, utilizing bead-labeling to track plaque Mϕs, the authors showed that loss of netrin-1 changed macrophage dynamics to favor egress from plaque. Through transcriptional profiling, they found that netrin-deleted Mϕs expressed higher levels of CCR7 which they hypothesized is the mechanism by which netrin-1 modulated Mϕ trafficking.[110] Studies have previously shown that CCR7 is expressed at low levels in plaque Mϕs and is upregulated in emigrating Mϕs during regression.[111, 112] Blocking CCR7 leads to retention of Mϕs within plaque.[112] Interestingly, a netrin-1 mutation has recently been identified in a family with premature atherosclerosis. *In vitro,* the product of this variant had a diminished ability to promote chemotaxis of Mϕs, suggesting that the role of netrin-1 is clinically relevant.[113]

T regulatory cells

In addition to Mϕs, T_{regs} have emerged as potent regulators of the immune response and important cellular mediators of resolution. These cells have been shown to be atheroprotective through their ability to elaborate IL-10 and TGF-β, limit excessive inflammation, foster skewing of Mϕs toward a pro-resolving phenotype, and to directly promote resolution themselves.[114-117] In humans, low levels of circulating T_{regs} are associated with an increased risk of acute coronary syndromes.[118] In addition, advanced or symptomatic atherosclerotic plaques contain fewer T_{regs} than early or asymptomatic plaques.[119, 120] In mouse models of atherosclerosis, T_{reg} numbers decline in the circulation as well as in aortic plaques and their function is impaired as atherosclerosis progresses.[121-123] Depletion of T_{regs} in hypercholesterolemic mouse models leads to increased atherosclerosis.[39, 117, 124] Either the adoptive transfer of T_{regs} or antibody-mediated expansion of T_{regs} also leads to decreased plaque progression.[39, 117, 125, 126] Together, these suggest that T_{regs} play an important role in the regulation of atherosclerosis.

We have previously shown that T_{regs} are able to specifically regulate resolution processes, including efferocytosis. Co-culture of Mϕs with T_{regs} led to enhanced AC uptake *in vitro*. Conversely, Mϕs isolated from mice in which T_{regs} had been depleted (either by an anti-CD25 antibody depleting strategy or using a Foxp3-diptheria toxin receptor mouse model) had reduced capacity for efferocytosis.[39] This was due to the ability of activated T_{regs} to elaborate IL-13 that led to upregulation of IL-10 in Mϕs in order to promote a STAT3/Vav1/Rac1 pathway that promoted actin rearrangement and facilitated AC engulfment.[39] In a recent study, co-culture of Mϕs and T_{regs} *in vitro* led to upregulation of SPMs including 15R-LXA_4, RvD1 and RvD6 as well as of the SPM receptors, Gpr18, ALX/FPR2, and

ChemR23, which may also explain the positive effect of T_{regs} on efferocytosis.[127] In a positive feedback look, efferocytosis also increases T_{reg} numbers *in vivo*, as infusion of ACs to mice led to a TGF-β-dependent expansion of T_{regs}.[128]

A fascinating study has recently identified a role for T_{regs} in conditioning lymphatic endothelial cells in order to regulate leukocyte trafficking in the resolution phase. In this study, the authors found that activation of T_{regs} led to their upregulation of lymphotoxin α1β2 (LTα1β2) that promoted their interaction with lymphatic endothelial cells and upregulated adhesion molecules on the endothelial cells. The net effect was movement of leukocytes out of inflamed tissue and into the lymphatic system, which promoted interaction of T_{regs} with effector T cells and dendritic cells within the draining lymph nodes in order to terminate immune responses.[129] Endothelial cells also secrete developmental endothelial locus-1 (DEL-1) during the resolution phase. DEL-1 has previously been shown to regulate leukocyte recruitment, promote efferocytosis, and increase SPM production.[130] Recently, it was found that DEL-1 can also promote induction of de novo T_{regs} in the periphery. Together, this may explain the observation that DEL-1 overexpression attenuated atherogenesis in mice fed a high-fat diet.[131, 132] In addition, this provides another example of endothelial cross talk with T_{regs} that promotes resolution and homeostasis.

T_{regs} have now also been shown to induce regression of atherosclerosis. In a murine model of regression, mice were rendered hypercholesterolemic by injection of a gain-of-function PCSK9 variant accompanied by Western diet-feeding to establish plaques and then subsequently treated with an apolipoprotein B antisense oligonucleotide (apoB-ASO) and a chow diet to rapidly lower cholesterol. The authors found that regressing plaques have significantly higher number of T_{regs} and that these were predominantly induced T_{regs} generated in the periphery.[127] In a subset of mice undergoing regression, they depleted T_{regs} using an anti-CD25 antibody. Strikingly, they found that the depletion of T_{regs} blocked regression overall. Whereas Mϕs in regressing lesions upregulated pro-reparative Mϕ markers such as Arg1 and CD206, those with T_{reg} depletion did not. T_{reg}-depleted plaques also showed evidence of Mϕ retention and blocked egress from the lesion and Mϕs in these lesions showed decreased efferocytosis and lower IL-10.[127] Together, these studies suggest that T_{regs} play an important role in atherosclerosis and that the loss of T_{regs} during atheroprogression may contribute to failed resolution and impede plaque regression.

Other Processes Contributing to Failed Resolution.

Aging and Senescence.

Aging contributes to a variety of diseases including neurodegenerative disease and ASCVD. The persistent inflammation associated with aging is becoming increasingly well characterized as a failure of resolution. Aging has been shown to impair efferocytosis *in vitro* and *in vivo*.[133] Intriguingly, the transfer of young peritoneal Mϕs to aged mice reproduced the poor efferocytosis observed in older mice, suggesting that there is an “aging milieu” that impairs Mϕ function.[134-137] Aging in mice also leads to an imbalance in pro-inflammatory and pro-resolving mediators, with an increase in LTs and prostaglandins but a decrease in D-series resolvins and lipoxins.[136, 138] Administration of RvD1 and RvD3 led to enhanced resolution and improved efferocytosis.[136] This is now supported by human

data that shows elderly patients have an imbalance of lipoxins:leukotrienes.[138] Cellular senescence, which is a process in which cells cease to divide yet survive and undergo distinctive phenotypic shifts, is also common in aging.[139] The senescence 'phenotype' exacerbates inflammation and also impairs clearance of dead cells.[138, 140] Senescent cells release factors that promote cleavage of MerTK, contributing to impaired efferocytosis. This was rescued by exogenous administration of RvD1.[140] In addition, Gas6, which facilitates binding of ACs to MerTK, was found to be downregulated in aged mice.[137] Together, these suggest a mechanism by which efferocytosis and inflammation resolution are impaired with advanced age.

Clonal Hematopoiesis.

A novel link between aging and inflammation, known as clonal hematopoiesis of indeterminate potential (CHIP) has recently been uncovered. This occurs when somatic mutations arise in a subset of genes in hematopoietic progenitor cells, conferring a proliferative advantage to them. To date, mutations in *JAK2*, *DNTM3A*, *TET2*, and *ASXL1* have been associated with CHIP. These are rare in young people but are found in >10% of those ≥ 70 years old.[141] Those who have these clones are at increased risk of hematological cancers as well as ASCVD. The mechanisms by which CHIP increases risk of these diseases is an active area of investigation, but data thus far suggests that the mutations associated with CHIP lead to pro-inflammatory changes in myeloid cells.[141] Recently, the potential role for the resolving program has begun to be explored. When marrow from mice expressing a gain of function mutation in the *Jak2* gene was transplanted to atheroprone mice ($Jak2^{V617F}$ marrow into $Ldlr^{-/-}$ mice), the authors observed increased lesion size with larger necrotic cores and defective lesional efferocytosis compared to controls. Mechanistically, this was attributed to lower surface levels of MerTK on Mϕs and increased MerTK receptor cleavage. Interestingly, lesions from the $Jak2^{V617F} \rightarrow Ldlr^{-/-}$ mice also demonstrated enhanced phagocytosis of erythrocytes due to lower levels of the 'don't eat me' signal CD47 on their surface. *In vitro*, the enhanced ingestion of erythrocytes led to competition for ingestion of ACs by Mϕs, suggesting that this may further contribute to impaired efferocytosis. In similar models, where Jak^{V617F} is specifically expressed in Mϕs or in chimeric mice that model CHIP by transplanting a 1:4 ratio of Jak^{V617F}:WT marrow to $Ldlr^{-/-}$ mice, the authors found similarly increased lesion area with larger necrotic cores compared to controls. Further, they found that deletion of essential inflammasome components including caspase 1, caspase 11, and Aim2 reversed these findings. In particular, *Aim2* was found to be overexpressed in Jak^{V617F} Mϕs and in lesions of Jak^{V617F} mutant mice. This suggests that CHIP mutations are linked to important resolving functions, including efferocytosis. This will be an exciting and important area of study in the coming years.

Therapeutic Possibilities and Future Directions

From the bench to the bedside, it is now clear that the immune system is a major driver of ASCVD and targeting inflammation in atherosclerosis can prevent major adverse cardiac events.[3-6] This strategy is unfortunately hampered by infectious complications that arise as a result of suppressing host immune defense. Approaches that instead promote resolution may therefore offer an attractive alternative. Administration of exogenous SPMs is currently

being studied as a therapeutic in several clinical trials for other inflammatory diseases, however, the short half-life of these mediators complicates their use in the treatment of chronic disease. While clinical trials that administered both EPA and DHA as a means of boosting production of endogenous production have yielded mixed results, the recent Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) treated patients with EPA alone and found a 25% reduction in cardiovascular events in patients with established ASCVD or major ASCVD risk factors.[142, 143]. While the trial was aimed at lowering triglyceride levels as an independent risk factor for ASCVD, pre-clinical studies suggest that treatment with EPA would boost production of the E-series resolvins and it is exciting to hypothesize that this could have contributed to the observed risk reduction.[144] While this has not yet been assessed in this patient population, this data is likely forthcoming, and would certainly lend support to the concept of pro-resolving therapy for ASCVD. Already, RvE1 analogs are actively being studied in clinical trials for the treatment of other inflammatory diseases (Thetis Pharmaceuticals). Further, the synthesis of small molecule agonists of the SPM receptor, FPR2, brings resolution-targeting therapeutics one step closer.[31]

Targeting efferocytosis in human ASCVD is also emerging as a promising therapeutic strategy. In a study of cancer patients being treated with a humanized anti-CD47 antibody (magrolimab), those receiving anti-CD47 therapy had a significant reduction in vascular inflammation as measured by ^{18}F-fluorodeoxyglucose positron-emission tomography and computed tomography (^{18}F-FDG PET CT).[145] Further studies will be necessary to determine whether this is sufficient to reduce cardiovascular events. Other recent studies have harnessed advances in nanotechnology to target atherosclerotic plaques. A number of studies have used atherosclerotic plaque-targeting nanoparticles to deliver pro-resolving proteins such as Annexin A1 or to silence components of pathways that negatively regulate pro-resolving pathways.[30, 81, 99, 101] While these have not yet been used in clinical trials, there is a precedent for the use of nanotechnology in treating human disease and the hope is that these pre-clinical studies will provide the base on which to build the next clinical trials.

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NONSTANDARD ABBREVIATIONS AND ACRONYMS:

AC	apoptotic cell
ADAM17	a disintegrin and metalloproteinase 17
AnxA1	annexin A1
apoB	apolipoprotein B
Arg1	arginase 1
ASCVD	atherosclerotic cardiovascular disease

BLT1	LTB4 receptor-1
CaMK2γ	calcium/calmodulin-dependent kinase 2 gamma
ChemR23	chemerin receptor 23
CHIP	clonal hematopoiesis of indeterminate potential
CO	carbon monoxide
DEL-1	developmental endothelial locus-1
FLAP	5-LOX activating protein
FPR2	N-formyl peptide receptor 2
GLS1	glutaminase-1
GLUT1	glucose transporter SLC2A1
GPR18	G-protein–coupled receptor 18
GPR32	G-protein–coupled receptor 32
H_2S	hydrogen sulfide
HMGB1	high-mobility group box 1
HO-1	heme oxygenase-1
ICAM-1	intracellular adhesion molecule 1
IL	interleukin
iNOS	inducible NO synthase
LAIR-1	leukocyte-associated Ig-like receptor-1
LDL	low-density lipoprotein
LOX	lipoxygenase
LRP1	low-density lipoprotein receptor-related protein 1
LTα1β2	lymphotoxin α1β2
LXA_4	lipoxin A4
Mϕ	macrophage
MCP-1	monocyte chemotactic protein 1
MerTK	MER proto-oncogene tyrosine kinase
MFGE8	milk fat globule-EGF factor 8
MIAT	myocardial infarction–associated transcript

MLKL	mixed lineage-kinase domain-like protein
MMP-9	matrix metalloproteinase-9
NC	necroptotic cell
NF-κB	nuclear factor kappa B
ODC	ornithine decarboxylase
oxLDL	oxidized low-density lipoprotein
OXPHOS	oxidative phosphorylation
PHACTR1	phosphatase and actin regulator 1
RAGE	receptor for advanced glycation end products
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial
RIP1	receptor-interacting protein kinase 1
RIP3	receptor-interacting protein kinase 3
RvD1	resolvin D1
SAA	serum amyloid A
SGK1	serum/glucocorticoid-regulated kinase 1
SPM	specialized pro-resolving mediator
TG2	transglutaminase 2
TNF-α	tumor necrosis factor-α

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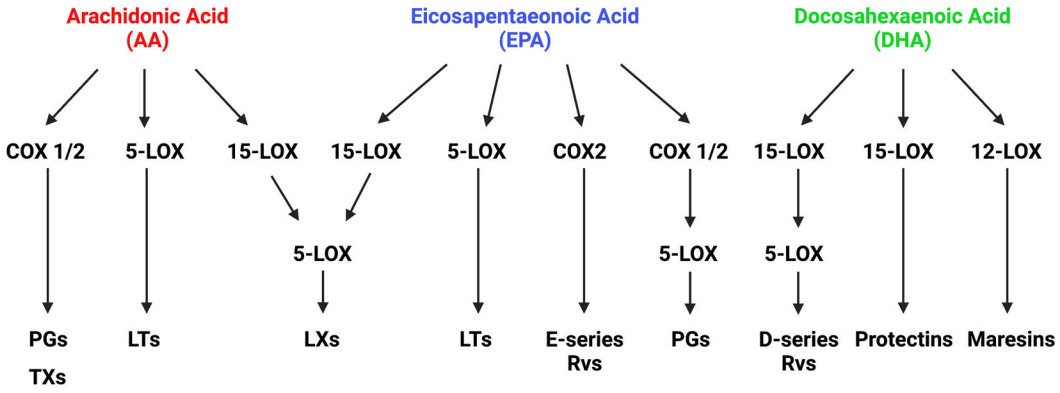

Figure 1. Simplified scheme of lipid mediator production.

The fatty acids, including arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are precursors for the generation of pro-inflammatory and pro-resolving lipid mediators. Through the action of enzymes including 5-lipoxygenase (5-LOX), 15-lipoxygenase (15-LOX), and cyclooxygenase (COX) 1 and 2, they give rise to multiple families. These include prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs), lipoxins (LXs), resolvins (Rvs), protectins, and maresins.

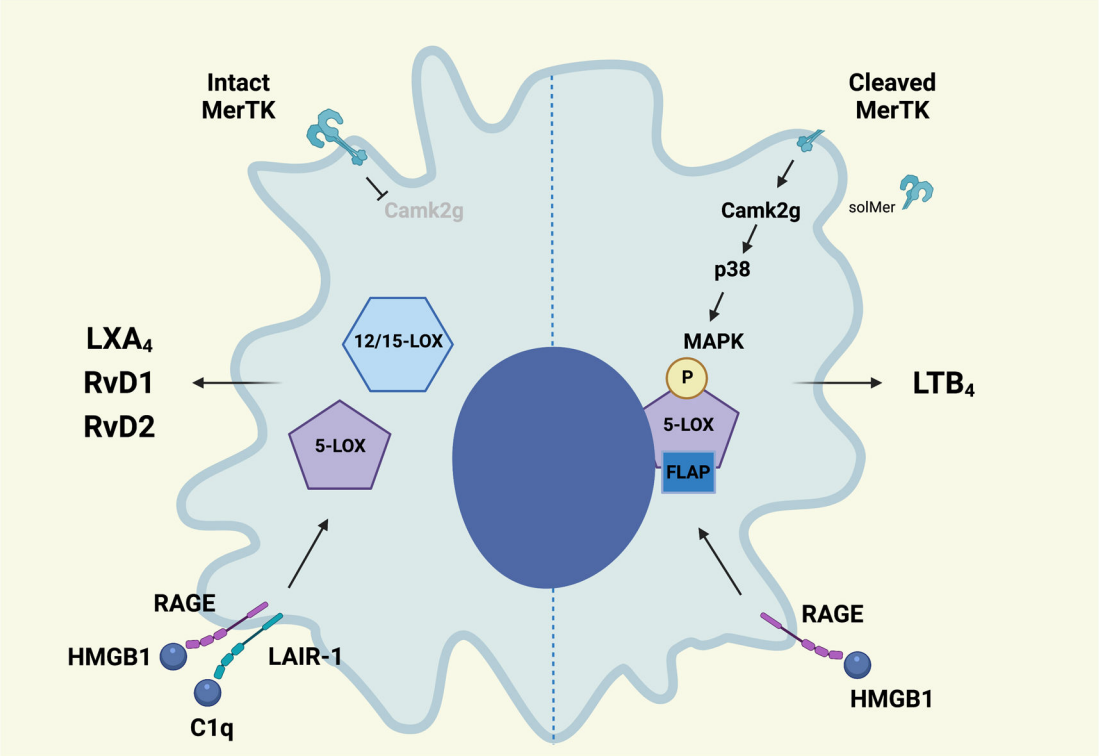

Figure 2. Nuclear localization of 5-lipoxygenase specifies lipid mediator production in response to receptor signaling.

Signaling by MerTK inhibits Calcium/calmodulin-dependent kinase 2γ (CaMK2g) activity and turns off a p38MAPK-MK2 cascade. This favors 5-LOX translocation to the cytoplasm where it is brought into proximity with 12/15-LOX and promotes lipoxin A_4 (LXA_4) production. Pro-inflammatory stimuli lead to MerTK cleavage and increased CaMK2g/p38MAPK-MK2 signaling that phosphorylates 5-LOX, enhancing its interaction with 5-LOX activating protein (FLAP). This promotes nuclear localization and leukotriene B4 (LTB_4) production. The interaction of high-mobility group box 1 (HMGB1) with the receptor for advanced glycation end products (RAGE) also promotes phosphorylation of 5-LOX and increased LTB_4 production. When complement 1q (C1q) is present, HMGB1 and C1q form a complex with RAGE and the leukocyte-associated Ig-like receptor-1 (LAIR-1). This tetramer favors cytoplasmic 5-LOX and increases SPM production. (Illustration credit: Ben Smith)

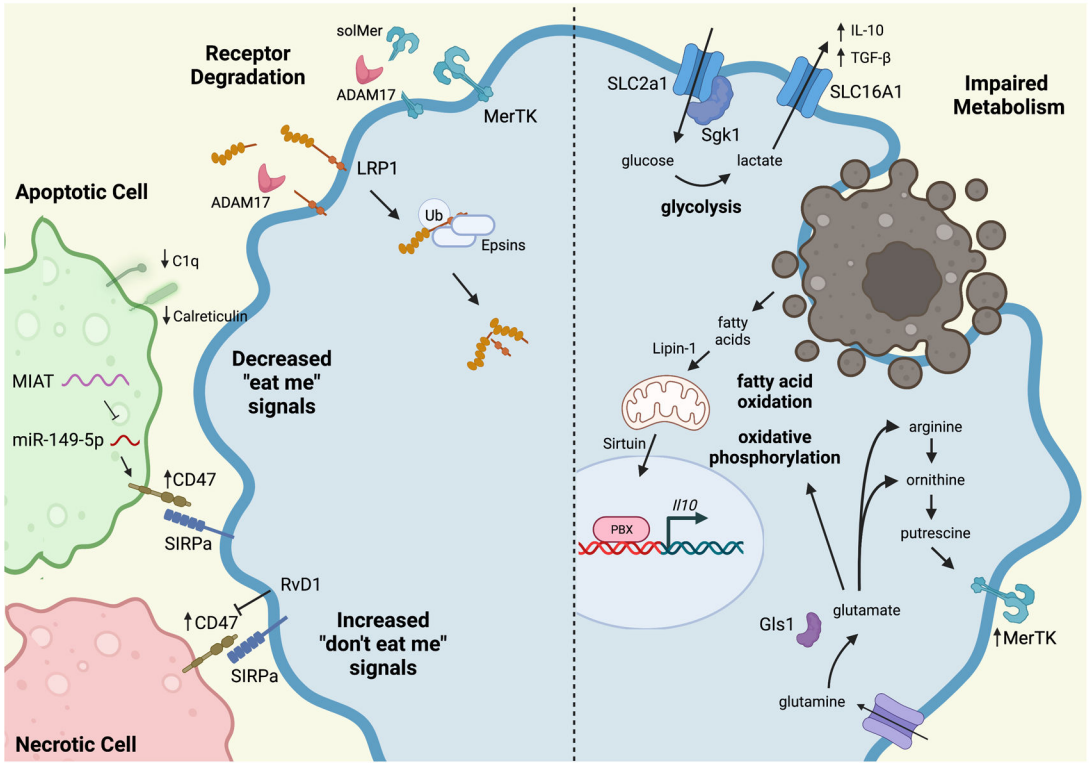

Figure 3. Mechanisms of Defective Efferocytosis in Atherosclerosis.

A variety of impairments contribute to defective efferocytosis in atherosclerosis. Efferocytosis receptors, including MerTK and LRP1, can be cleaved by ADAM17. LRP can also be ubiquitinated and degraded by Epsins. Apoptotic cells express decreased levels of “eat me” signals, such as C1q and calreticulin. Apoptotic and necrotic cells inappropriately express the “don’t eat me” signal, CD47, that prevents their efficient uptake by macrophages. This can be overcome by treatment with resolvin D1 (RvD1). Metabolism also plays an important role in efficient efferocytosis, particular in continual efferocytosis where successive apoptotic cells must be consumed. Glycolysis produces lactate, which increases IL-10 production and enhances subsequent efferocytosis. Digestion of apoptotic cells provides fatty acids as a substrate for fatty acid oxidation and oxidative phosphorylation, which also increase production of IL-10. Apoptotic cell-derived arginine and ornithine are converted to putrescine, which leads to enhanced, persistent MerTK expression on the macrophage, further enhancing efferocytosis. Glutamine is converted to glutamate, which contributes to oxidative phosphorylation, but also produces arginine and ornithine to feed the polyamine synthesis pathway. (Illustration Credit: Ben Smith).

Table 1.

The effects of manipulating pro-resolving mediator pathways in animal models of atherosclerosis.

	Animal Model	Diet	Outcome	References
Lipoxygenases				
5-LOX knockout	*Alox5*$^{-/-}$/*Ldlr*$^{-/-}$	Western	↓ aortic plaque size	146
12/15 LOX overexpression	12/15-LOX-transgenic *Apoe*$^{-/-}$ mice	Chow	↓ aortic plaque size ↑ LXA4	147, 148
12/15 LOX overexpression	12/15-LOX transgenic *Apoe*$^{-/-}$ mice	Western	↔ aortic plaque size	148
15-LOX Mϕ overexpression	Human 15-LOX transgenic rabbit	Western	↓ aortic plaque size	149
SPMs				
AT-LXA$_4$ (osmotic pump)	*Apoe*$^{-/-}$ mice	Western	↓ aortic plaque size	29
RvD1 (*i.p.*)	*Ldlr*$^{-/-}$ mice	Western	↓ aortic plaque necrosis, ROS ↑ fibrous cap thickness, efferocytosis	20
RvD2 and MaR1 (*i.p.*)	*Apoe*$^{-/-}$ mice	Western	↓ aortic plaque necrosis, Mϕ content ↑ fibrous cap thickness	21
RvE1 (*p.o.* gavage)	*ApoE*3* Leiden transgenic mice	Western	↓ aortic plaque size, expression of pro-atherogenic genes	150
RvE1 (*p.o.* topical)	Rabbit	Western	↓ aortic plaque size, inflammatory cell infiltration	151
Receptors				
ALX/FPR2 knockout	*Fpr2*$^{-/-}$ *Apoe*$^{-/-}$ mice	Chow	↓ aortic plaque size (16 weeks diet)	29
		Western	↔ aortic plaque size (4 weeks diet)	29
	Fpr2$^{-/-}$ *Ldlr*$^{-/-}$ mice	Western	↓ aortic plaque size (12 weeks diet)	27
			↓Mϕ content, collagen content	
		Western	↔ aortic plaque size (16-20 weeks diet)	27
	Fpr2$^{-/-}$ marrow into *Ldlr*$^{-/-}$ mice	Western	↓ aortic plaque size (17-20 weeks diet)	27, 30
BLT1 knockout	*Blt1*$^{-/-}$ *Apoe*$^{-/-}$ mice	Western	↓ aortic plaque size (4-12 weeks diet)	32, 33
			↔ aortic plaque size (19 weeks diet)	32
ChemR23 knockout	*Chemr23*$^{-/-}$ *Apoe*$^{-/-}$ mice	Western	↑ aortic arch plaque area, ↑ aortic root plaque size, ↑ Mϕ content (8 weeks diet)	34
		Western	↑ aortic arch plaque area, ↔ aortic root plaque size, ↑ Mϕ content (12 weeks diet)	34
	Chemr23$^{GFP/GFP}$ *Apoe*$^{-/-}$ mice	Western	↓ aortic root plaque size, ↓ Mϕ content (4 and 12 weeks diet)	35
	Chemr23$^{-/-}$ marrow into *Ldlr*$^{-/-}$ mice	Western	↑ aortic plaque size, plaque necrosis, Mϕ content (12 weeks diet)	34
	Chemr23$^{GFP/GFP}$ marrow into *Apoe*$^{-/-}$ mice	Western	↓ aortic plaque size (6 weeks diet)	35
GPR32 overexpression	*hGPR32*$_{myc}$*Tg Fpr2*$^{-/-}$ *Apoe*$^{-/-}$		↓ aortic plaque size, plaque necrosis	36
Pro-resolving Proteins				
Annexin A1 knockout	*Anxa1*$^{-/-}$ *Apoe*$^{-/-}$ mice	Western	↑ aortic plaque size	46
Ac2-26 (*i.v.*)	*Apoe*$^{-/-}$ mice	Western	↓ aortic plaque size and Mϕ content	46
Ac2-26 (nanoparticles *i.v.*)	*Ldlr*$^{-/-}$ mice	Western	↓ aortic plaque size, plaque necrosis, ROS ↑ fibrous cap thickness	30
IL-10 knockout	*Il10*$^{-/-}$ *Apoe*$^{-/-}$ mice	Western	↑ aortic plaque size	41

	Animal Model	Diet	Outcome	References
IL-10 overexpression in Mϕs	*Ldlr*$^{-/-}$ mice	Western	↓ aortic plaque size	42, 43
IL-10 (nanoparticles *i.v.*)	*Ldlr*$^{--}$ mice	Western	↓ aortic plaque necrosis, ROS ↑ fibrous cap thickness	44

Modified from Kasikara, Doran, et al.[15]

Table 2.

Resolving mediators, receptors, and their athero-relevant downstream effects.

Receptor	Ligands	Athero-relevant downstream effects	References
ALX/FPR2	Annexin A1 (Ac2-26)	↑ efferocytosis, neutrophil apoptosis	30, 46, 152-156
		↓ PMN infiltration to tissue	
	AT-LXA_4	↑ efferocytosis	157
	LXA_4	↑ efferocytosis, anti-inflammatory cytokine production	158-161
		↓ PMN infiltration to tissue, pro-inflammatory cytokine production	
	RvD1	↑ efferocytosis, anti-inflammatory cytokine production	28, 162-165
		↓ PMN infiltration to tissue, pro-inflammatory cytokine production	
	RvD3	↓ PMN infiltration to tissue, pro-inflammatory cytokine production	166
	SAA	↑ leukocyte chemotaxis, pro-inflammatory cytokine production	26, 167
BLT1	LTB_4 (agonist)	↑ leukocyte chemotaxis, foam cell formation	32
	RvE1 (antagonist)	↓ PMN infiltration to tissue, NF-κB activation, platelet aggregation, LTB4-induced calcium mobilization	168-170
	RvE2 (antagonist)	↑ phagocytosis	168, 171
		↓ PMN chemotaxis/infiltration to tissue	
ChemR23/ERV	RvE1	↑ phagocytosis	168, 169, 172, 173
		↓ PMN chemotaxis/infiltration to tissue, pro-inflammatory cytokine production	
	RvE2 (partial agonist)	↑ phagocytosis	170, 171
		↓ PMN chemotaxis/infiltration to tissue	
	Chemerin	↑ adhesion and chemotaxis of leukocytes	
		↓ pro-inflammatory cytokines	174, 35
		↑ apoptosis	
FPR1	Annexin A1 (Ac2-26)	↓ PMN chemotaxis/infiltration to tissue, leukocyte:endothelial cell interaction	154, 175, 176
GPR18/DRV2	RvD2	↑ efferocytosis	165, 177-179
		↓ PMN infiltration to tissue, pro-inflammatory cytokine production, leukocyte:endothelial cell interaction, leukocyte activation	
GPR32/DRV1	AT-RvD1	↑ phagocytosis, 12/15-LOX expression	36
		↓ oxLDL uptake	
	LXA_4	↑ efferocytosis, anti-inflammatory cytokine production	158-161
		↓ PMN infiltration to tissue, pro-inflammatory cytokine production	
	RvD1	↑ efferocytosis, anti-inflammatory cytokine production	28, 162-164
		↓ PMN infiltration to tissue, pro-inflammatory cytokine production	
	RvD3	↑ efferocytosis	166
	RvD5	↑ phagocytosis, ↓ pro-inflammatory cytokine production	180

Modified from Kasikara, Doran, et al.[15]