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Review

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Metabolic Reprogramming of Macrophages in Atherosclerosis: Is It All about Cholesterol?

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ABSTRACT

Hypercholesterolemia contributes to the chronic inflammatory response during the progression of atherosclerosis, in part by favoring cholesterol loading in macrophages and other immune cells. However, macrophages encounter a substantial amount of other lipids and nutrients after ingesting atherogenic lipoprotein particles or clearing apoptotic cells, increasing their metabolic load and impacting their behavior during atherosclerosis plaque progression. This review examines whether and how fatty acids and glucose shape the cellular metabolic reprogramming of macrophages in atherosclerosis to modulate the onset phase of inflammation and the later resolution stage, in which the balance is tipped toward tissue repair.

Keywords: Hematology; Metabolism; Atherosclerosis; Macrophage; Cholesterol

INTRODUCTION

Atherosclerosis is the predominant cause of cardiovascular disease (CVD), which is the top cause of death in developed countries. The build-up of fat and cholesterol on the inner walls of arteries is strongly associated with their narrowing or blockage, a scenario that can be induced by a high-cholesterol diet in animals.[1] Macrophages present within atherosclerotic plaques play a central role in the initiation, development, and complications of arterial plaques and rely on tightly integrated metabolic rewiring to maintain vessel wall integrity and continuously clear neighboring cells.[2,3] In particular, when macrophages ingest atherogenic lipoprotein particles or clear apoptotic cells, their metabolic load is increased, promoting their metabolic rewiring.[4] Thus, it is not surprising that an excess of cellular cholesterol or cholesterol crystals trigger macrophage expansion, foam cell formation, and impaired effector functions, all of which contribute to disease progression.[5-7] However, despite the benefits of statins for lowering plasma cholesterol,[8,9] the number of individuals at risk of developing CVD is still growing and there is a crucial need to identify residual risk factors.[10] A Western lifestyle, especially a high-fat diet, was recently shown to induce meta-inflammation in mice, highlighting the need for a better understanding of the interplay between fatty acids, inflammation, and atherosclerosis.[11] In humans, dyslipidemia, which is characterized by higher levels of proatherogenic triglyceride-rich lipoproteins and lower

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levels of antiatherogenic high-density lipoprotein (HDL), and hyperglycemia have been identified as independent cardiovascular risk factors. In this review, we will explore the nodes linking metabolism and inflammation, a new emerging field termed 'immunometabolism,' in cardiovascular atherosclerotic disease.

IMMUNOMETABOLIC REGULATION OF MACROPHAGES IN ATHEROSCLEROSIS

1. Up-to-date knowledge on macrophage cholesterol metabolism

The atherogenic low-density lipoprotein (LDL), also known as "bad cholesterol," travels through the bloodstream and delivers cholesterol to the artery wall, promoting a local inflammatory response that is a major culprit of atherosclerosis development. Cholesterol plays a central role in macrophage biology and can be generated by cellular cholesterol biosynthesis or be internalized by receptor-mediated cholesterol endocytosis. The interplay between these pathways is extremely well balanced under homeostatic conditions by several regulatory systems.[5-7] Although macrophage foam cell formation could activate the synthesis of endogenous sterol derivatives that are liver X receptor ligands to suppress inflammation, the presence of additional extrinsic pro-inflammatory signals, such as modified LDL or cholesterol crystals, is thought to amplify inflammatory toll-like receptor signaling and the NLRP3 inflammasome. In a pioneer work, transplantation of wild-type bone marrow (BM) into hypercholesterolemic apolipoprotein (ApoE)-deficient mice was sufficient to prevent atherosclerosis, highlighting the crucial role of the immune system in promoting inflammation under hypercholesterolemic conditions.[12] Conversely, part of the role of LDL-cholesterol lowering therapy in preventing atherosclerosis progression has been attributed to anti-inflammatory properties.[13] Nevertheless, a recent single-cell RNA sequencing analysis revealed that non-foamy macrophages are proinflammatory *in vivo* in atherosclerotic plaques of experimental models.[14] Moreover, a similar approach in human atherosclerotic plaques also confirmed the presence of heterogeneous populations of macrophages within asymptomatic atherosclerotic plaques. Of interest, one of the macrophage subsets with a foam cell appearance showed pro-inflammatory properties.[15] These findings highlight the need of a better understanding of macrophage biology in their native tissue environment. In that context, the retention of LDL in the intima of arteries can become atherogenic after various modifications such as oxidation.[16] The aggregation and retention of cholesterol in specific depots can initiate the formation of cholesterol crystals, which are also pro-inflammatory in nature.[4,17]

2. Fatty acid metabolism and macrophage effector functions

Despite the success of statins, significant cardiovascular risk remains.[8,9] In particular, dyslipidemia, which is characterized by higher levels of triglyceride-rich lipoproteins and lower levels of HDL, has been identified as a residual cardiovascular risk.[13] In addition to cholesterol, fatty acid metabolism is a central regulator of macrophage function. Two major sources of fatty acids have been described: 1) lipolysis of circulating triglyceride-rich lipoproteins during the postprandial phase following the ingestion of a meal and 2) release of free fatty acids from stored lipids through intrinsic lipolysis (i.e., lipophagy) or peripheral adipose tissue lipolysis in the fasting state (**Fig. 1**). Additionally, these pathways can be exquisitely balanced through feedback inflammatory pathways, as illustrated by the key role of interleukin (IL)-18 production via the NLRP1 inflammasome in controlling lipolysis.[18] Two recent studies elegantly showed that while dietary intake of lipids regulates the pool of

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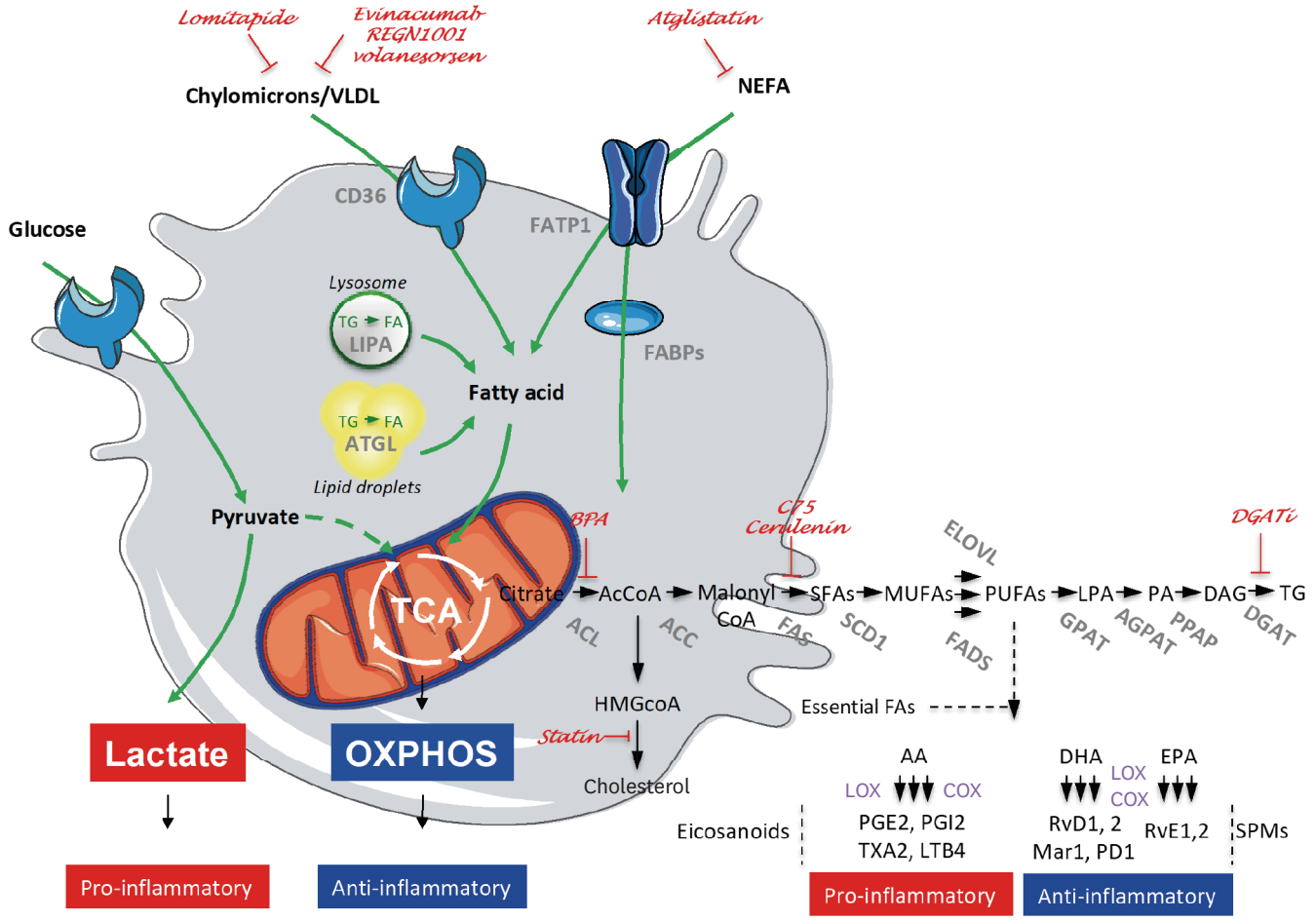

Fig. 1. Schematic representation of immunometabolic pathways in macrophages linking glucose and fatty acid metabolism to pro- and anti- inflammatory responses. Pro-inflammatory macrophages are more glycolytic, reflecting their need to rapidly meet the energy requirements of acute inflammation in the form of ATP. Upon aerobic glycolysis, a large amount of glucose is converted to lactate, which serves as an intermediate for anabolic reactions that have been linked to a pro-inflammatory response. Pro-inflammatory macrophages also produce eicosanoid inflammatory mediators by the oxidation of AA. By contrast, anti-inflammatory macrophages utilize fatty acid OXPHOS to slowly but efficiently generate ATP to support the resolution of inflammation. Fatty acids originate from 1) circulating NEFAs, which are generated during peripheral lipolysis or intracellular lipophagy; 2) hydrolysis of triglyceride-rich lipoproteins and extracellular uptake; 3) lysosomal hydrolysis; or 4) endogenous synthesis. In this context, SPMs are produced.
AA, arachidonic acid; ACC, acetyl-CoA carboxylase; AcCoA, acetyl-coenzyme A; ACL, ATP citrate lyase; AGPAT, acylglycerolphosphate acyltransferase; ATGL, adipose triglyceride lipase; ATP, adenosine triphosphate; BPA, bempedoic acid; COX, cyclooxygenase; DAG, diacylglycerol; DGAT, diacylglycerol acyltransferase; DHA, docosahexaenoic acid; ELOVL, elongation of very long chain fatty acids protein; EPA, eicosapentaenoic acid; FA, fatty acid; FABP, fatty acid binding protein; FADS, fatty acid desaturase; FAS, fatty acid synthase; FATP, fatty acid transport protein; GPAT, glycerol-3-phosphate acyltransferase; LIPA, lysosomal acid lipase; LOX, lipoxygenase; LPA, lysophosphatidic acid; LTB4, leukotriene B4; Mar1, maresin 1; MUFA, monounsaturated fatty acid; NEFA, non-esterified fatty acid; OXPHOS, oxidation and subsequent oxidative phosphorylation; PA, palmitic acid; PD1, protectin D1; PGE1, prostaglandin E1; PGI1, prostaglandin I2; PPAP, phosphatidic acid phosphatase; PUFA, polyunsaturated fatty acid; RvD, D-series resolvins; RvE, E-series resolvins; SCD, stearoyl-CoA desaturase; SFA, saturated fatty acid; SPM, specialized pro-resolving mediator; TG, triglyceride; TXA2, thromboxane A2; VLDL, very low-density lipoprotein.

circulating inflammatory monocytes that infiltrate tissues,[19] a lipase-independent pathway of lipid release from adipose tissue via lipid-filled vesicles has an impact on local macrophage behavior.[20] These findings raise the question how different fatty acid delivery routes influence macrophage effector functions.

The lipolysis of triglyceride-rich proteins in the postprandial phase, is mediated by various lipases, including *sn-1* lipases such as lipoprotein lipase (LPL), hepatic lipase, and endothelial lipase; the role of these enzymes in accelerating atherosclerosis has been extensively described elsewhere.[21] However, a link to innate immunity has only emerged with the generation of myeloid cell-specific LPL deficiency. Seminal works have revealed that

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transplantation of LPL-knockout BM into atherosclerotic Ldlr$^{-/-}$ mice and the generation of myeloid-specific LPL deficiency in ApoE$^{-/-}$ mice prevented foam cell formation and atherosclerosis.[22,23] Additionally, LPL-deficient mice exhibited a reduction in the level of circulating myeloid cells (i.e., neutrophils and monocytes) but these effects are probably not cell-intrinsic.[24,25] Several inhibitors have been developed as alternative targets for dyslipidemia, including a microsomal triglyceride transfer protein inhibitor (lomitapide) used in patients with familial hypercholesterolemia, human monoclonal antibodies against ANGPTL3 (evinacumab) or ANGPTL4 (REGN1001), an antisense oligonucleotide (ANGPTL3-LRx), and an antisense oligonucleotide against *APOC3* (volanesorsen), as previously summarized elsewhere.[13] The role of these inhibitors in modulating macrophage effector functions have not yet been investigated.

The hydrolysis of stored adipose tissue triglycerides to non-esterified fatty acids (NEFAs) and glycerol occurs in the fasting state. Adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase are sequentially required in adipocytes. Deficiency of ATGL, the rate-limiting enzyme that regulates the mobilization of NEFAs by hydrolyzing triglyceride species at the *sn-2* and *sn-1* positions, promotes massive ectopic lipid accumulation in various tissues, including adipose tissue, liver, smooth muscle, and heart.[26] However, ATGL-deficient mice exhibit reduced adipose tissue and liver immune cell infiltration[27] most likely due to limited recruitment signals released upon acute lipolytic stimulation[28] and potentially meta-inflammation.[29-31] Indeed, inflamed adipose tissue secretes more NEFAs during expansion.[32] In part, this results from local insulin resistance and the elevated generation and release of inflammatory molecules such as IL-6, and this is associated with cardiometabolic complications.[33] Chronic pharmacological ATGL inhibition with atglistatin consistently prevented adipose tissue inflammation and cardiometabolic complications upon high-fat feeding without inducing ectopic lipid deposition.[34] At least 3 cofactors have been identified as regulators of ATGL activity. Comparative gene identification-58 (CGI-58) binds and activates ATGL activity.[35] In contrast, the interactions of ATGL with G0/G1 switch gene 2 (G0S2) and hypoxia-inducible lipid droplet-associated protein (HILPDA) inhibit its activity.[36-38] Although adipose tissue-specific overexpression of G0S2 or CGI-58 and HILPDA deficiency recapitulated most of the phenotype of ATGL-deficient mice, their relevance to meta-inflammation and cardiometabolic diseases is still poorly understood.[39-41]

3. Macrophage fatty acid metabolism

At the cellular level, fatty acids can be translocated across the membrane by the fatty acid translocase CD36 receptor or fatty acid transport proteins (FATPs) such as FATP1 (SLC27A1). Intriguingly, CD36-deficient and FATP1-deficient macrophages exhibited opposite inflammatory phenotypes and were associated with protecting against or exacerbating atherosclerosis plaque development, respectively.[42,43] Although fatty acid uptake by CD36 can be coupled to mitochondrial oxidative phosphorylation to promote alternatively activated macrophage polarization,[44,45] recent evidence has suggested that in the context of atherosclerosis, the uptake of pro-atherogenic oxidized LDL by CD36 could induce an unexpected metabolic shift towards glycolysis, which is pro-inflammatory in nature.[46] Intriguingly, a lack of fatty acid uptake by FATP1-deficient macrophages was also associated with enhanced glycolytic activity and modulation of eicosanoid synthesis.[47] Nevertheless, knockdown of the 2 major fatty acid binding proteins (FABPs) that control intracellular fatty acid trafficking to the nucleus in macrophages—namely, FABP4 (aP2) and FABP5 (Mal1)—prevented atherosclerosis.[48-50] These FABPs could promote macrophage inflammation by

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inducing foam cell formation and by modulating fatty acid-sensitive nuclear receptors such as peroxisome proliferator-activated receptors (PPARs), endoplasmic reticulum stress, and toll like receptor-dependent nuclear factor kappa B activity, as discussed elsewhere.[51] Thus, limiting the uptake and trafficking of specific fatty acids in macrophages may have beneficial impacts in limiting atherosclerosis development.

The intrinsic degradation of triglycerides from macrophage lipid droplets has also emerged as a central regulator of macrophage effector functions. Indeed, ATGL-deficient macrophages showed defective PPAR-β/δ and small Rho GTPase activation, associated with impaired motility and efferocytosis.[52,53] In contrast, these cells manifested signs of increased alternative polarization, with increased expression of canonical markers such as mannose receptor 1 and arginase 1 and enhanced secretion of the anti-inflammatory cytokines IL-10 and transforming growth factor-β.[53] Atherogenic Ldlr$^{-/-}$ mice transplanted with ATGL$^{-/-}$ BM exhibited less systemic inflammation and tissue monocyte infiltration, attenuating the development of atherosclerotic lesions.[54] These findings contrast with HSL-deficient macrophages, which exhibit a pro-inflammatory phenotype with increased proteolytic activity[55] and accelerated atherosclerosis.[56] Currently, we lack a unifying hypothesis reconciliating these observations. One possibility would be the redundancy of several hydrolases in macrophages that play a dual role in hydrolyzing both cholesterol and triglycerides, as has been shown for HSL.[57,58] Lysosomal acid lipase (LIPA) also plays a dual role in hydrolyzing both triglycerides and cholesterol, and has been found by the Pearce laboratory to oppose the effect of ATGL on macrophage alternative polarization (**Fig. 1**). Indeed, fatty acid generation by LIPA supports the metabolic requirements of macrophage alternative polarization.[44] This process involves C36 receptor-mediated endocytosis or fusion of lipid droplets with lysosomes (i.e., lipophagy).[59-61] Additionally, while enhanced LIPA activity limited atherogenic lipid loading-induced inflammatory and apoptotic responses,[60] LIPA deficiency promoted cholesterol accumulation, lysosomal inflammation, and defective clearance of apoptotic cells.[62-64] An additional role of LIPA is its involvement in the generation of anti-inflammatory lipid mediators.[65] These findings have to been linked to pioneering research on LIPA-deficient mice, which are characterized by exacerbated myelopoiesis, liver abnormalities, and accelerated atherosclerosis.[66] These complications are rescued by myeloid cell-specific re-expression of LIPA.[67]

4. Macrophage specialized pro-resolving mediator (SPMs) metabolism

Multiple mechanisms have been proposed to link fatty acid and inflammatory signaling pathways, including the modulation of plasma and organelle membrane fluidity, formation of crystalline structure, and histone acetylation, among others that have been reviewed elsewhere.[3,6] In this section, we will focus on growing evidence regarding the role of SPMs[68] which could have an impact on inflammation and the resolution of atherosclerosis.[69,70] Briefly, in response to an inflammatory stimulus, polyunsaturated fatty acids (PUFAs) including arachidonic acid, the essential fatty acid eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid are hydrolyzed by phospholipases, and following the action of several lipoxygenases, lipid mediators of inflammation and resolution can be produced (**Fig. 1**).[71] Leukotrienes are a family of eicosanoid inflammatory mediators produced by the oxidation of arachidonic acid and eicosapentaenoic acid in leukocytes. Leukotriene production is accompanied by the production of prostaglandins, which are crucial inflammatory mediators. These proinflammatory mediators act on G protein-coupled receptors (GPCRs) to promote the secretion of inflammatory cytokines.[69,70] SPMs can also activate their cognate GPCRs to facilitate resolution of inflammation.[71] Two recent studies have shown an imbalance between SPMs

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and leukotrienes in advanced atherosclerosis in human and murine plaques.[72,73] Interestingly, myeloid cell-specific deficiency of fatty acid synthesis upstream of PUFA generation, including long-chain-fatty-acid-CoA ligase 1,[74] fatty-acid synthase,[75] fatty acid desaturase 1[76] or fatty acid elongase 6,[77] led to reduced atherosclerosis development, along with the modulation of several SPM and leukotriene mediators. Thus, novel fatty acid synthesis inhibitors that are being currently tested in different diseases, such as bempedoic acid, an inhibitor of ATP citrate lyase, C75 or cerulenin, fatty synthase inhibitors, and diacylglycerol acyltransferase inhibitors, may provide novel anti-inflammatory therapeutic opportunities. Genetic evidence of a role of SPMs in atherosclerosis has also been extensively described elsewhere, with noteworthy findings regarding 5-lipoxygenase, 12/15-lipoxygenase, and SPM GPCRs such as N-formyl peptide receptor 2, leukotriene B4 receptor 1, and resolvin E1 receptor.[69]

5. Macrophage glucose metabolism

^{18}F-fluorodeoxyglucose positron emission tomography imaging has revealed enhanced incorporation of the glucose analogue in inflamed atherosclerotic plaques,[78-81] which was strongly correlated with its incorporation in peripheral hematopoietic tissues.[82-84] These findings highlight the link between high hematopoietic metabolic activity and CVD, most likely reflecting systemic inflammation and extramedullary hematopoiesis.[85] However, direct evidence for the role of hyperglycemia or enhanced glucose flux in CVD risk has long been lacking. It is only recently that randomized clinical trials have shown that reduced glycemia and hemoglobin A1c levels are key drivers of CVD risk reduction.[86] Genome-wide association studies have also identified single nucleotide polymorphisms linking plasma glucose levels to CVD events.[87,88] In a mouse model of atherosclerosis, we confirmed that disruption of the main glucose transporter in hematopoietic cells reduced the number of circulating monocytes and the development of atherosclerosis.[89] These findings highlight the causal role of enhanced hematopoietic glycolytic activity in CVD. However, 2 recent studies have raised concerns that blocking macrophage-specific glycolytic activity may have local adverse effects on atherosclerotic plaque complexity because it limits the energy requirements of efferocytosis.[90,91] Thus, there is a need to identify downstream glycolytic shunts that may prevent inflammation without impacting efferocytosis, such as downstream steps of lactate production (**Fig. 1**).[90] Interestingly, we and others have found that targeting 2 independent targets of the pentose phosphate pathway—namely, carbohydrate-responsive element-binding protein and sedoheptulose kinase—promoted macrophage inflammation[92] and atherosclerosis.[93]

CONCLUSION

Exploiting the metabolic plasticity of macrophages to limit chronic inflammation and improve inflammation resolution in atherosclerosis has emerged as a topic of major interest in the scientific community. Identifying links between currently known metabolic CVD risks and inflammation, beyond hypercholesterolemia, may provide novel therapeutic opportunities to improve the management of CVD.

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