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Review article

Macrophage fatty acid metabolism and atherosclerosis: The rise of PUFAs

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HIGHLIGHTS

- The metabolism of polyunsaturated fatty acids (PUFAs) is central in the regulation of macrophage functions.
- Macrophages autonomously regulate the synthesis of PUFAs and their incorporation in phospholipids and other cellular lipids.
- Genetic alteration of unsaturated FA metabolism influences atherosclerosis, by modulating macrophage functions.

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ABSTRACT

Among the pathways involved in the regulation of macrophage functions, the metabolism of unsaturated fatty acids is central. Indeed, unsaturated fatty acids act as precursors of bioactive molecules such as prostaglandins, leukotrienes, resolvins and related compounds. As components of phospholipids, they have a pivotal role in cell biology by regulating membrane fluidity and membrane-associated cellular processes. Finally, polyunsaturated fatty acids (PUFAs) are also endowed with ligand properties for numerous membrane or nuclear receptors. Although myeloid cells are dependent on the metabolic context for the uptake of essential FAs, recent studies showed that these cells autonomously handle the synthesis of n-3 and n-6 long chain PUFAs such as arachidonic acid and eicosapentaenoic acid. Moreover, targeting PUFA metabolism in macrophages influences pathological processes, including atherosclerosis, by modulating macrophage functions. Omics evidence also supports a role for macrophage PUFA metabolism in the development of cardiometabolic diseases in humans.

Currently, there is a renewed interest in the role of n-3/n-6 PUFAs and their oxygenated derivatives in the onset of atherosclerosis and plaque rupture. Purified n-3 FA supplementation appears as a potential strategy in the treatment and prevention of cardiovascular diseases. In this context, the ability of immune cells to handle and to synthesize very long chain PUFA must absolutely be integrated and better understood.

1. Introduction

Monocytes and macrophages play a pivotal role in the initiation and progression of atherosclerosis [1]. Macrophages are plastic cells that sense internal or external signals such as cytokines, alarmins or Pathogens Associated Molecular Patterns (PAMPs) and subsequently adapt their activation status. Recent evidence suggests that macrophage activation/polarization requires dynamic changes in major cellular metabolic pathways. These changes allow the energy needs of immune cells to be met and to trigger the synthesis of molecules involved in the innate immune response (Reactive Oxygen Species, Nitric Oxide, and Eicosanoids) [2]. Among other pathways, the metabolism of unsaturated fatty acids (FAs) is central. Indeed, polyunsaturated FAs (PUFAs) act as precursors of bioactive molecules such as eicosanoids. As components of phospholipids, they have a pivotal role in cell membrane biology. Finally, PUFAs are also endowed with ligand properties for numerous nuclear or membrane associated receptors. Now, it clearly appears that myeloid cells autonomously regulate the synthesis of PUFAs and monounsaturated FAs (MUFAS) as well as their incorporation in phospholipids and other cellular lipids [3]. While most of the genes involved in PUFA metabolism in macrophages are now identified, the consequences of their modulation are still largely unexplored concerning quality and intracellular distribution of FAs, regulation of cell functions and finally their implication in pathophysiological processes. Beyond the quantitative accumulation of FAs in the cells, it is likely that qualitative alterations of FA profile and distribution affect the biological functions of the macrophages either through the production of bioactive lipid mediators or changes of cell membrane properties. Accordingly, recent studies have shown that genetic alteration of unsaturated FA metabolism even though restricted to myeloid cells

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Table 1
Genetic alteration of PUFA pathways in macrophages and experimental atherosclerosis.

Pathways	Genes	Models	Phenotype	Proposed mechanisms	Ref.
FA uptake	*Fatp1*	*Fatp1* $^{-/-}$ BM transplantation in *Ldlr* $^{-/-}$	Increased atherosclerosis	Increase of oxidative stress and inflammation in atherosclerotic plaques Potential metabolic shift of macrophages from FA oxidation toward glycolysis	Zhao et al. [18]
	Cd36	*Cd36* $^{-/-}$*/ApoE* $^{-/-}$ BM transplantation *in ApoE*$^{-/-}$	Decreased atherosclerosis	Decrease lipoprotein uptake Decrease foam cell formation	Febbraio et al. [16]
		Cd36 $^{-/-}$*/ApoE* $^{-/-}$	No effect	No difference in foam cell formation and accumulation in aortic lesions No difference in lipoprotein uptake	Moore et al. [17]
	Lpl	*Lpl*$^{-/-}$ fetal liver cells transplantation in *Ldlr* $^{-/-}$	Decreased atherosclerosis	Decrease CD36 expression and lipoprotein uptake	Babaev et al. [12]
		Lpl^{KOMAC} (LysMCre)*/ApoE* $^{-/-}$	Decreased atherosclerosis	Decreased cholesteryl ester and triglyceride accumulation Decreased PPAR activity and CD36 expression	Takahashi et al. [13]
Intracellular FA binding and trafficking	*Fabp4*	*Fabp4* $^{-/-}$ BM transplantation in *ApoE* $^{-/-}$	Decreased atherosclerosis	Decreased cholesteryl ester accumulation Macrophages display an anti-inflammatory phenotype	Makowski et al. [22]
	Fabp5	*Fabp5* $^{-/-}$ BM transplantation in *Ldlr* $^{-/-}$	Decreased atherosclerosis	Increased PPARγ activity Decreased CCR2 expression and inflammatory response	Babaev et al. [27]
Unsaturated FA activation	*Acsl1*	*Acsl1*^{KOMAC}(LysMCre) BM transplantation in diabetic *Ldlr* $^{-/-}$	Decreased atherosclerosis	Decreased arachidonoylCoA levels and eicosanoid synthesis in macrophages	Kanter et al. [28]
PUFA desaturation	*Fads1*	*Fads1* $^{-/-}$*/ApoE* $^{-/-}$	Decreased atherosclerosis	Decrease in the production of AA-derived pro-inflammatory mediators	Powell et al. [38]
		Fads1 ASO in *Ldlr* $^{-/-}$	Increased atherosclerosis	Increase in circulating monocytes and increased macrophage M1 activation Unbalanced secretion of pro- and anti-inflammatory PUFA-derived lipid mediators	Gromovsky et al. [37]
FA elongation	*Elovl6*	*Elovl6* $^{-/-}$ BM transplantation in *Ldlr* $^{-/-}$	Decreased atherosclerosis	Decrease in n-6 PUFA levels in cholesteryl esters Increased expression of cholesterol efflux transporters	Saito et al. [48]
PUFA incorporation into cellular lipids	*Lpcat3*	*Lpcat3*$^{-/-}$ fetal liver cells transplantation in *Ldlr* $^{-/-}$	Increased atherosclerosis	Decrease in cholesterol efflux and cholesterol transporters expression Alteration of LXR activity	Thomaset al. [10]
		Lpcat3^{KOMAC} (LysMCre) BM transplantation in *Ldlr* $^{-/-}$	No impact	Macrophages display a pro-inflammatory phenotype in link with increase TLR4 signaling	Jiang et al. [52]
Non-essential FA metabolism	*Fasn*	*Fasn*^{KOMAC}(LysMCre)*/ApoE* $^{-/-}$	Decreased atherosclerosis	Activation of LXR-dependent pathways involved in cholesterol efflux Decreased PPAR activity and CD36 expression	Schneider et al. [57]
	Scd1	*Scd1* $^{-/-}$ BM transplantation in *Ldlr* $^{-/-}$	No impact	No changes in cholesterol efflux No changes in inflammatory response	MacDonald et al. [60]

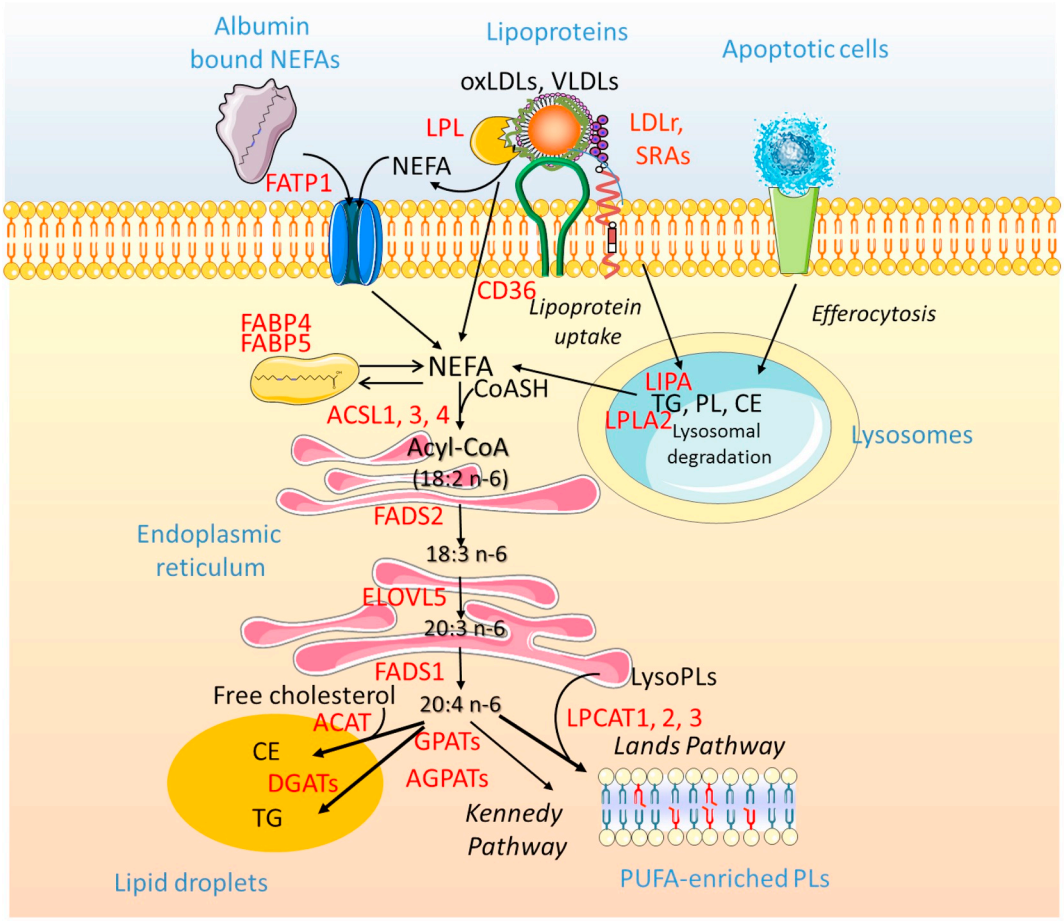

Fig. 1. PUFAs anabolic pathways in macrophages.
Macrophages acquire essential fatty acids (FAs) through different pathways: (1) uptake of albumin-bound non-esterified fatty acids (NEFAs) by the fatty acid transport protein 1 (FATP1); (2) release of NEFA from triglyceride-rich lipoproteins by the action of the lipoprotein lipase (LPL); (3) uptake of lipoproteins such as oxidized low density lipoproteins (OxLDL) or very low density lipoproteins (VLDL) by membrane receptors such as CD36, low density lipoprotein receptor (LDLr) or scavenger receptors type A (SRAs); (4) phagocytosis of apoptotic cells (efferocytosis).
Lysosomal enzymes such as the lysosomal acid lipase (LIPA) or lysosomal phospholipase A2 (LPLA2) hydrolyze lipids from lipoproteins or apoptotic cells including cholesteryl esters (CE), triglycerides (TG) and phospholipids (PLs) and release NEFAs. In the cell, NEFAs bind to fatty acid binding proteins (FABP), which act as chaperons and control the distribution of NEFA in different cellular compartments.
Activation of NEFA into acylCoA is mediated by long chain fatty acylCoA synthetase (ACSL) or FATP1. AcylCoA are used as substrates for long chain polyunsaturated fatty acid (PUFA) synthesis. This involves the successive actions of fatty acid desaturase (FADS2), elongation of very long chain fatty acids protein 5 (ELOVL5) and FADS1. Using C18:2 n-6 as substrate leads to the synthesis of an arachidonoyl-CoA molecule (C20:4 n-6).
Long chain PUFAs can be incorporated into cellular lipids. AcylCoA-cholesterol-acyl transferase (ACAT) leads to the synthesis of CE. Through the Kennedy pathway, PUFA are incorporated in PL and TG by the action of glycerol-3-phosphate acyltransferases (GPATs), 1-acylglycerol-3-phosphate-*O*-acyltransferase (AGPAT) and diacylglycerol-acyl-transferases (DGATs). Finally, PUFAs are used as preferential substrates by lysphosphatidylcholine
-acyl-transferases (LPCATs) and incorporated at the *sn*-2 position of phospholipids.

influences pathological processes, including atherosclerosis, by modulating macrophage functions. (see Table 1, Fig. 1)

Many studies have addressed the impact of dietary FAs or exogenous FA supplementation on macrophage functions or the biological roles of oxygenated fatty acid derivatives. The aim of this review is to focus on PUFA anabolic pathways in macrophages and to present the potential mechanisms by which alterations of these pathways may affect macrophage functions and atherosclerosis development.

2. An overview of PUFA anabolic pathways in myeloid cells and macrophages and their impact in experimental models of atherosclerosis

2.1. Essential FA uptake

Since FAs with double bonds at the n-3 or n-6 position cannot be synthetized in mammalian cells, they must be provided exogenously to macrophages either through lipoproteins or non-esterified FA (NEFA) uptake. Although these pathways are not specific to essential FAs, they are absolutely required to supply macrophages with n-3 and n-6 C18 FAs that can be used for the synthesis of downstream molecules such as arachidonic acid (AA) (C20:4 n-6) and eicosapentaenoic acid (EPA) (C20:5 n-3). Therefore, myeloid cells are dependent on the general metabolic/dietary context as well as the local lipid environment for essential FA uptake. As examples, dietary supplementation with essential FAs directly affect the FA composition of circulating mononuclear cells while macrophages within the atheroma plaque are exposed to atherogenic lipoproteins which contain large amounts of PUFAs notably linoleic acid (18:2 n-6) (LA) [4,5].

Depending on the delivery routes, different mechanisms are involved in FA uptake. Some pathways are preferentially used in macrophages as compared to other cells or tissues. Plasma NEFA, mainly bound to albumin, are efficiently taken up by most cell types, including macrophages. While diffusion and flip-flop mechanisms within the

phospholipid bilayer have been demonstrated, it now appears that facilitated transport mechanisms across the cell membrane contribute to the rapid uptake of FAs by cells, a pathway that involve members of the FA transport protein (FATP) family [6]. FATPs could directly promote the physical translocation of FA across the membrane. Alternatively, the acylCoA synthetase (ACS) activity of FATPs allow them trapping FA as acylCoA derivatives to promote diffusion processes. Regarding the macrophages, the function of the FATP1 transporter (*SLC27A1*) has been characterized by inactivation and overexpression experiments. These studies have shown that FATP1 is an important contributor to the overall FA uptake and plays a role in the metabolic reprogramming of macrophages during inflammation [7]. FATP1 inactivation enhances glucose metabolism and promotes an inflammatory macrophage phenotype while FATP1 overexpression stimulates FA metabolism at the expense of glucose metabolism and reduced LPS-stimulated inflammatory response [7]. Interestingly, FATP1 overexpression reduces free AA and eicosanoid synthesis in classically activated macrophages, suggesting an increased conversion of AA toward other cellular pathways.

Lipoprotein lipase (LPL) promotes the release of free FA from triglyceride-rich lipoproteins. LPL is highly expressed in macrophages and it contributes to FA accumulation in myeloid cells. LPL-mediated uptake of unsaturated FA such as linoleic acid (C18:2 n-6) may modulate PPAR (peroxisome proliferator-activated receptors) activity and signaling pathways involved in myelopoiesis. In a mouse model, *Lpl* deficiency in myeloid cells decreases circulating monocytes and impairs monocyte to macrophage differentiation [8].

The CD36 receptor is also a FA translocase. Nevertheless, its activity as a scavenger receptor that recognizes oxidized lipoproteins also contributes to the uptake of FAs by macrophages [9]. Indeed, besides molecular mechanisms that are common to many cell types, macrophages can also acquire essential FAs via specific pathways linked to their roles in innate immunity. Thus, the expression of scavenger receptors, notably scavenger receptor A1 (SRA1) and CD36, enables macrophages to capture large amount of modified/oxidized lipoproteins in bypassing negative feedback mechanisms. Although the impact of these pathways is well documented regarding cholesterol accumulation, it is important to integrate that lipoproteins also represent an abundant source of essential FAs for the macrophages, especially linoleic acid (LA). Consequently, low density lipoprotein (LDL) uptake by macrophages results in an enrichment of LA in cellular glycerolipids and cholesteryl esters [5,10]. Finally, phagocytosis and efferocytosis processes also represent a significant source of essential FAs which play a role in the metabolic reprogramming of macrophages toward an anti-inflammatory, post-efferocytosis, phenotype as recently demonstrated by an extensive metabolomic analysis [11].

Although many studies have found a significant impact of the pathways involved in FA uptake by macrophages on atherosclerosis development, the potential mechanisms involved largely extend beyond the framework of unsaturated FA metabolism. Therefore, these studies will only be discussed briefly. Loss of function experiments in different mouse models have consistently shown that LPL deficiency in macrophages reduces atherosclerosis without affecting plasma lipid levels, probably by reducing macrophage lipid uptake and cholesterol ester formation [12,13]. LPL may also affect atherosclerosis by promoting myelopoiesis and macrophage differentiation which could be related to LPL-mediated PUFA uptake and subsequent modulation of M-CSF signaling [8]. However, in a recent study, myeloid *Lpl* deficiency did not affect lipid accumulation in tissue macrophages or the polarity of plaque macrophages. Moreover, it had no impact on atherosclerosis regression. These findings are in striking contrast to the phenotypic changes observed *in vitro* in LPL deficient macrophages, indicating the importance of *in vivo* validation [14].

The role of CD36 has been extensively studied and macrophage CD36 has been shown to be an important modulator of atherosclerosis in mice, notably by promoting lipoprotein uptake and foam cell formation, although the overall impact may depend on the stage of atherosclerosis development [15–17].

Interestingly, while these works suggest that excessive FA uptake may be detrimental, an opposite observation has been made with FATP1. Indeed hematopoietic *Fatp1* deficiency significantly increases atherosclerotic lesion size as well as inflammation possibly related to a metabolic shift of macrophages from FA oxidation toward glycolysis and a pro-inflammatory phenotype [18].

2.2. Intracellular FA binding and trafficking

Once taken up by the cells, intracellular FAs bind to lipid chaperones that belong to the class of FA binding proteins (FABPs). FABPs are small intracellular proteins (approx. 15 kDa) that are expressed at high levels in cells and reversibly bind various hydrophobic ligands including PUFAs. FABPs control the intracellular shuttling of FA between cellular compartments and their availability for metabolic or signaling pathways. FABPs appear therefore as major determinants of FA biological functions. Two members of the family are expressed at significant levels in macrophages: FABP4 (aP2) and FABP5 (Mal1) [19]. Interestingly, the impact of FABPs on macrophage functions is driven in part by a modulation of PUFA metabolism. Thus, FABPs are able to bind and to deliver PUFAs from the cytoplasm to the nucleus, thereby modulating the transcriptional activity of FA-sensitive nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) [20,21]. The role of FABP4 in macrophages has been extensively investigated, and its pro-inflammatory actions as well as its role in promoting lipid-induced endoplasmic reticulum (ER) stress have been demonstrated by several studies [22–25]. FABP4 deficiency in macrophages increases PPARγ activity which stimulates cholesterol efflux through the Liver X Receptor α (LXRα)-ABCA1 (ATP binding cassette transporter A1) pathway and reduces intracellular cholesterol ester accumulation. *Fabp4*-deficient macrophages also display reduced NF-κB activity and impaired production of inflammatory cytokines in response to LPS stimulation. Interestingly, the impact of FABP4 on atherosclerosis is almost totally related to its expression in macrophages. Thus, $ApoE^{-/-}$ mice with hematopoietic *Fabp4* deficiency show a similar reduction in atherosclerotic lesions as compared with $ApoE^{-/-}$ presenting a constitutive *Fabp4* deficiency [25]. Potential protective mechanisms involve a decreased cholesterol accumulation, an anti-inflammatory macrophage phenotype and a reduction of macrophage ER stress [24,25]

Similarly, FABP5 deficiency in macrophages is associated with an anti-inflammatory phenotype [26,27]. Macrophages from *Fabp5*-deficient mice display an up-regulation of PPARγ-dependent pathways involved in cholesterol trafficking. $Fabp5^{-/-}$ macrophages also showed decreased expression of pro-inflammatory genes such as *Cox2* or *Il6* in response to LPS stimulation [27]. Hematopoietic *Fabp5* deficiency is also atheroprotective in $Ldlr^{-/-}$ mice in link with increased PPARγ activity and a decreased monocyte recrutement in atherosclerosis lesions [27].

2.3. Unsaturated FA activation

As discussed above, one important limiting step for the uptake of FAs is their activation into acylCoA via a thioesterification reaction. The newly synthetized acylCoA can be subsequently used in various metabolic pathways, including biosynthesis or catabolism reactions, and in particular for the incorporation of FAs into glycerophospholipids and cholesteryl esters. As mentioned previously, while members of the FATP family possess significant ACS activity, another family of enzymes, called long-chain-fatty-acid-CoA ligases (ACSLs), has been characterized. Several enzymes from this class with different specificities towards saturated and unsaturated FAs are present in macrophages including ACSL1, ACSL3 and ACSL4. Different studies indicate that the activity of ACSLs in myeloid cells and macrophages is critical for the synthesis of active lipid mediators derived from n-3 and n-6 FAs.

Moreover, ACSL activity is altered in specific metabolic contexts. Thus, an increase in the expression of ACSL1 has been found in monocytes from diabetic mice and from patients with type 1 diabetes and was associated with high levels of arachidonoylCoA, increased secretion of prostaglandin E2 (PGE2) [28]. Myeloid *Acsl1* deficiency reduces the development of atherosclerosis in diabetic *Ldlr*$^{-/-}$ mice while it has no impact in non-diabetic mice. In a diabetic context, *Acsl1* deficiency corrected the increased release of PGE2 and inflammatory cytokines by macrophages [28]. In myeloid cells, it seems that ACLS1 modulates the AA content of phospholipids and thus the AA pool available for eicosanoid synthesis [28]. ACSL1 is also required for the inhibitory action of linoleic acid on cholesterol efflux [29]. ACSL4 is also an arachidonoylCoA synthetase. Rosiglitazone-mediated inhibition of ACSL4 reduces the incorporation of FAs into glycerolipids [30]. Interestingly, macrophages from *Acsl4*-deficient mice display a marked reduction of the amount of long chain PUFAs in their phospholipids since *Acsl4*$^{-/-}$ macrophages fail to activate long chain PUFAs which accumulate as free FAs. These free FAs are used as substrates by cyclooxygenases and this leads to an enhanced release of eicosanoid following LPS stimulation [31]. ACSL3 also contributes to very long chain PUFA synthesis even though its specific role in macrophages remains to be investigated [32].

2.4. FA desaturation

The synthesis of very long chain PUFAs is a multi-step process requiring the initial activation of the substrate FA into an acyl-CoA and the successive actions of elongases and FA delta 5 and delta 6 desaturases. By this pathway, LA (C18:2 n-6) can be converted into AA. A similar pathway is used for n-3 FA and EPA synthesis, while docosahexaenoic acid (DHA) (22:6 n-3) synthesis requires additional specific reactions, including elongation, desaturation and peroxisomal beta-oxidation.

The desaturation reactions occur stereo specifically at positions 5 and 6 of the fatty acyl chain and are catalyzed by desaturases FADS1 and FADS2 respectively; strikingly, no other gene in the human or murine genomes is able to compensate for their activity. Mice deficient for *Fads1* or *Fads2* display a virtual absence of very long chain FAs such as AA, EPA or DHA with a severe phenotype including sterility and reduced lifespan [33–35]. While most attention has been paid towards organs with a high FA turnover such as the liver and the intestine, recent data show that this metabolic pathway is active within the immune cells including myeloid lineage. Interestingly, FADS1 and FADS2 are markedly induced during monocyte to macrophage differentiation [36]. Desaturases appear to contribute significantly to the diversity of lipid molecules found in myeloid cells, with an impact on the functions and activation of macrophages [37]. *Fads1* knockdown in macrophages induces the polarization of macrophages toward an inflammatory phenotype and potentiates the LPS response. *Fads1* inhibition also results in decreased levels of AA, EPA and DHA derived oxidized mediators and induces an overall shift toward a more pro-inflammatory and less pro-resolving lipid mediator profile [37]. *Fads2* deficient macrophages also failed to produce AA-derived mediators such as leukotriene B4 [34].

To the best of our knowledge, no study has yet evaluated the role of FADS1 and FADS2 on the development of atherosclerosis by using tissue specific strategies such as hematopoietic cell transplantation or conditional gene inactivation in myeloid cells.

Nevertheless, two recent studies have evaluated the impact of a global FADS1 inactivation on the development of atherosclerosis. Powell et al. observed a 40% decrease in atheromatous lesion in *Fads1*$^{-/-}$ mice as compared to control mice on a *ApoE*$^{-/-}$ background as well as a decreased inflammatory response in the arterial wall [38]. At the opposite, *Fads1* inhibition by using antisense oligonucleotides (ASO) was associated with a significant increase in atherosclerotic lesions in *Ldlr*$^{-/-}$ mice. Interestingly, the difference was mainly observed when the mice were fed an omega 3 enriched diet [37]. Although increased LDL cholesterol levels in mice treated with *Fads1* ASO certainly contributes to the increased development of atherosclerotic lesions, several observations highlight a cell autonomous effect of FADS1 in myeloid cells. Indeed, *Fads1* ASO treatment induced an increase in circulating monocytes as well as an exacerbation of the LPS response in the aortic arch in mice fed the omega 3 enriched diet. The discrepancies between these two works are certainly explained by the distinct models of atherosclerosis (*ApoE*$^{-/-}$ *vs.* *Ldlr*$^{-/-}$). Nevertheless, the molecular mechanisms proposed in these two studies provide the most interesting perspective. The first study suggests that the lack of AA synthesis due to *Fads1* deficiency could impair the production of AA-derived pro-inflammatory mediators by macrophages. Conversely, the second study proposes that a defect in the synthesis of pro-resolving lipid mediators contributes to the increased atherosclerosis. Interestingly the phenotype was mainly observed with an omega 3 enriched diet, a nutritional context promoting the production of anti-inflammatory mediators. Conversely, the former study used a western type diet containing mainly C18:2 n-6 as source of essential FA thus favoring the synthesis of AA-derived eicosanoids. It is therefore likely that the impact of the PUFA synthesis pathways on the macrophage phenotype is highly dependent on the overall metabolic/nutritional context and the balance between n-6 and n-3 FAs. Indeed, very recent studies suggest that the ratio between n-3 FAs derived pro-resolving mediators and n-6 FAs derived pro-inflammatory mediators is important for plaque stability and atherosclerosis progression. Decreased resolvin D1 to leukotriene B4 ratio was observed in vulnerable area of plaques [39]. An increase in leukotriene B4 and prostaglandin E2 levels associated with a concomitant decrease of resolving lipid mediators, resolvin D2 and maresin 1, during atherosclerosis progression was observed in *ApoE*$^{-/-}$ mice [40]. Further evidence suggests an atheroprotective role of n-3 derived pro-resolving mediators, notably resolvin E1 [41–43].

2.5. Unsaturated FA elongation

Several FA elongases are present in mammals with different specificities. These enzymes are required for the synthesis of very long chain FAs from C16 to C20 precursors that are the products of the fatty acid synthase (FASN) or provided by the diet. Elongation of very long chain FAs proteins (ELOVLs) performs the condensation of a malonylCoA to an acylCoA molecule, which is the first limiting step in the elongation cycle of FAs. ELOVLs 1, 3, 6 are mainly involved in monounsaturated and saturated FA synthesis while ELOVLs 2, 4 and 5 appeared to be preferentially involved in PUFA metabolism [44]. Coordinate action of elongases with FADS1 and FADS2 is required for production of very long chain PUFAs. However, as far as macrophages are concerned, ELOVL5 seems to play a prominent role in PUFA metabolism. Indeed, the very low level of ELOVL2 expression in myeloid cells certainly accounts for the inability of macrophages to produce significant amount of DHA via the Sprecher pathway [45]. Thus, while macrophages from *Elovl2*-deficient mice display an inflammatory phenotype, this is likely related to systemic DHA deficiency rather than cell-autonomous production [45,46]. Experimental data indicate that ELOVL5 is required and is a limiting factor for the synthesis of C20 and C22 n-3 and n-6 PUFAs. *Elovl5*$^{-/-}$ mice accumulate n-6 and n-3 C18 precursors in their tissues at the expense of the downstream products such AA and DHA. ELOVL5 is able to modulate the activity of two key lipogenic transcription factors i.e. sterol responsive element binding protein 1c (SREBP1c) and PPARγ by generating long chain PUFAs that are respectively antagonists of SREPB1c and agonists of PPARs [46].While the specific function of ELOVL5 in macrophages remains to be deciphered, recent studies suggest that it could play a critical role in myeloid cells. *ELOVL5* is a direct LXR target gene in human macrophages and is involved in promoting PUFA synthesis after LXR agonist treatment while NCoR deficiency in myeloid cells results in the derepression of ELOVL5 and activation of long chain n-3 FA synthesis through an LXR-dependent mechanism [32,47]. Finally, while ELOVL6

is mainly involved in saturated and monounsaturated FA elongation, macrophages from *Elovl6*$^{-/-}$ mice display reduced cholesterol accumulation and decreased n-6 PUFAs in the cholesteryl ester fraction. Accordingly, hematopoietic *Elovl6* deficiency reduced atherosclerosis in *Ldlr*$^{-/-}$ mice [48].

2.6. Incorporation of PUFAs into cellular lipids

Incorporation of PUFAs into cellular lipids may be considered as the final step of their metabolism. To date, there is little understanding of how the addressing of specific PUFAs within the different classes of cellular lipids is achieved. However, it is clear that the enzymes involved in the synthesis of glycerolipids or cholesteryl esters display substrate specificities toward different FAs. Although neutral lipids present in macrophages such as triglycerides and cholesteryl esters contains PUFAs such AA, EPA or DHA, this represents mainly a form of storage. In contrast, glycerophospholipids are arguably the most dynamic reservoir of PUFAs in myeloid cells. Indeed, the high proportion of PUFAs in phospholipids (PLs) constitutes a pool for the synthesis of oxygenated lipid mediators such as eicosanoids. Moreover, the presence of PUFAs within the PLs directly contributes to the physicochemical properties of biological membranes such as their fluidity and secondarily affect numerous membrane-associated cellular processes.

Although *de novo* synthesis of PLs occurs via the Kennedy pathway, PLs are continuously remodeled in the cells through deacylation and reacylation reactions in the Lands cycle [49]. In this metabolic pathway, the turnover of FAs at the *sn*-2 position is mediated by the opposite actions of phospholipases A2 and lyso-PL acyltransferases (LPLAT) [50]. It is thought that saturated FAs at the *sn*-1 position of PLs mainly derived from *de novo* biosynthesis (Kennedy pathway), whereas the unsaturated FAs preferentially located at the *sn*-2 position are provided by the Lands cycle. LPLATs differ in their tissue distribution and in their substrate preferences for both acyl donors and lysosphopholipid acceptors. Therefore, they play a crucial role to maintain PUFA homeostasis within the PLs in different cell types or cellular compartments. Since LPLATs affect both the PUFA content of phospholipids and the availability of FAs such as AA used for eicosanoid synthesis, they are important factors to control the cellular response to inflammatory stimuli and in particular the eicosanoid cascade [51]. Lysophosphatidylcholine acyl transferase 3 (LPCAT3) seems to be the major LPCAT isoform in macrophages based on relative expression levels and enzymatic activities [52].

LPCAT3 uses PUFAs (mainly AA and EPA) and lysophosphatidylcholines (LPC) or lysophosphatidylethanolamines (LPE) as preferential substrates. LPCAT3 appears as a key determinant of AA distribution and availability in macrophages [53,54]. *Lpcat3*$^{-/-}$ macrophages display major reductions in the arachidonate content of diacyl phospholipids and plasmalogens. These changes are associated with an altered cholesterol homeostasis notably a decreased cholesterol efflux in *Lpcat3*$^{-/-}$ macrophages. Eicosanoid secretion (PGE2 and Thromboxane B2 (TxB2)) is also impaired in *Lpcat3*$^{-/-}$ macrophages following LPS stimulation [10,54]. Partial *Lpcat3* deficiency or *Lpcat3* inhibition in mouse macrophages was associated with increased LPS-induced inflammatory cytokine release through activation of TLR signaling [52,53]. It is suggested that the reduction of PUFA-containing phospholipids promotes a relocalization of TLR4 in the lipid rafts [52].

LPCAT1 and LPCAT2 are expressed at significant levels in macrophages, besides their roles in phospholipid remodeling they are also involved in production of platelet activating factor (PAF) a potent pro-inflammatory mediator through the incorporation of acetylCoA at the *sn*-2 position of Lyso PAF, thus they may have dual functions in membrane biogenesis and production of PAF in inflammatory cells [55].

Two recent studies have specifically targeted the incorporation of PUFAs into phospholipids by evaluating the role of LPCAT3 in hematopoietic cells and myeloid cells on the development of atherosclerosis. Using a fetal liver cell transplantation model, it was observed that *Lpcat3* deficiency in hematopoietic cells induces an increase in atherosclerotic lesions in *Ldlr*$^{-/-}$ mice. This phenotype was associated with alterations of cholesterol homeostasis and inhibition of efflux pathways in *Lpcat3*$^{-/-}$ macrophages [10]. Conversely, Jiang et al. using a conditional inactivation of LPCAT3 in myeloid cell did not observe significant differences in atherosclerotic lesions despite a pro-inflammatory phenotype of *Lpcat3*$^{-/-}$ macrophages [52]. These discrepancies could be explained in part by the LysMCre system, which induces only a partial inhibition of LPCAT3 with an approx. 20% residual expression. In addition, the transplantation of fetal liver cells used in the first study induces an *Lpcat3* deficiency in all hematopoietic cells, which may also play a role in the development of atherosclerosis. However, in both studies, *Lpcat3* deficiency promoted a pro-atherogenic macrophage phenotype.

2.7. Non-essential FA metabolism

In contrast to n-6 and n-3 FAs, macrophages are able to produce saturated and unsaturated FAs from n-9 and n-7 families. The pathway involves the synthesis of palmitic acid (C16:0) from acetyl-CoA by acetylCoA carboxylase and fatty acid synthase (ACC and FASN) and additional elongation and desaturation steps, involving stearylCoA desaturases (SCD1 and SCD2). Macrophage activation is associated with major metabolic switches; notably there is an increase in anaeraobic glycolysis at the expense of the TCA cycle and oxidative phosphorylation, similar to the Warburg effect. FA metabolism also seems to be dramatically affected as *de novo* FA synthesis is markedly increased during macrophage activation [3].

Although these pathways are not the primary focus of this review, it is important to mention recent studies that have shown that the biosynthesis of saturated and monounsaturated FAs in macrophages had a significant impact on macrophage functions and cardiometabolic diseases. *Fasn* deficiency in murine macrophages alters the composition and biophysical properties of cell membranes and impairs macrophage inflammatory response. In accordance with these *in vitro* observations, mice with myeloid *Fasn* deficiency are protected against insulin resistance and presented lower inflammation and reduced macrophage infiltration in adipose tissue [56]. *Fasn* deficiency in macrophages reduces atherosclerosis development and cholesterol accumulation in macrophages probably through the derepression of LXRα [57].

Generation of monounsaturated FAs in macrophages mediated by SCDs inhibits ABCA1 activity through the alteration of cell membrane properties and subsequently decreases cholesterol efflux [58,59]. In contrast SCD1 and SCD2 may also promote the synthesis of palmitoleic acid (C16:1 n-7) by macrophages, a lipokine with potential insulin-sensitizing and anti-inflammatory properties [47]. Nevertheless, *Scd1* deficiency when limited to hematopoietic cells does not affect atherosclerosis development in *Ldlr* $^{-/-}$ mice [60].

3. Regulation of PUFA metabolism in macrophages

Regulation of PUFA metabolism in macrophages is mediated by transcription factors involved in lipogenesis and FA metabolism such as LXRs and SREBP1c. One of the specificities in macrophages is the extremely dynamic regulation of this pathway during the acute phase response to inflammatory stimuli and during the resolution of inflammation. Thus, this temporal modulation of PUFA metabolism is likely to contribute to the plasticity of macrophages in particular by controlling the balance between pro-and anti-inflammatory mediators release.

3.1. Role of LXR and SREBP1c

Liver X receptors are oxysterol-activated nuclear receptors involved in the regulation of cholesterol homeostasis and they are also major regulator of lipogenesis. Initial studies have demonstrated that LXR

activation in macrophage increases the expression of lipogenic genes such as *SREBP1c* and *SCDs* in a similar way as other tissues. More recently it was shown that LXRs coordinately regulate the enzymes responsible for the synthesis of long chain PUFAs. Activation of LXRs in macrophages by synthetic agonists induces in a coordinated manner the expression of all of the key enzymes required for the synthesis of PUFAs, including activation (ACSL3), delta 6 and delta 5 desaturation (FADS1 and FADS2) and FA elongation (ELOVL5) enzymes [32]. While ACSL3 and ELOVL5 seem to be direct LXR targets, regulation of FADS1 and FADS2 by LXR is likely mediated though the induction of SREBP1c [32]. In accordance with these transcriptomic data, LXR activation increases the rate of PUFA synthesis either from n-6 or n-3 precursors as well as the amounts of n-3 and n-6 long chain PUFAs in mouse and human primary macrophages [32]. LXRs also promote the incorporation of PUFAs into glycerophospholipids through LPCAT3 and an enrichment of phospholipids with AA was observed in macrophages after LXR agonist treatment. *In vivo*, LXR activation also modulates the PUFA composition and mRNA levels of genes involved in PUFA synthesis in mouse atherosclerotic arteries [54]. Accordingly, Li et al. observed that specific deletion of NCoR in mouse macrophages resulted in the derepression of several enzymes involved in PUFA synthesis, such as ELOVL5, FADS1 and FADS2 in a LXR-dependent manner. This was associated with increased levels of n-3 long chain PUFAs such as EPA and DHA and an insulin-sensitive and hypoinflammatory phenotype in mice [47]. Interestingly, exogenous n-3 FAs have been shown to exert anti-inflammatory effect by stimulating cell membrane receptors such as GPR120 [61]. In contrast, the effects of endogenously synthetized n-3 FAs appear to be independent of GPR120. It seems that endogenous n-3 FAs directly inhibit expression of pro-inflammatory genes by decreasing histone methylation and reducing NF-kB complex activity [47].

These studies bring some support to the hypothesis that the anti-atherogenic and insulin-sensitizing activity of LXRs might be related, at least in part, to their lipogenic activity in myeloid cells.

3.2. Temporal changes in PUFA metabolism during the inflammatory response

Classical activation of macrophages is traditionally associated with an increased FA synthesis while lipolysis and FA oxidation are rather linked with alternative polarization [2]. Newly synthesized FAs could be required for cell membrane formation, in a context of increased phagocytic activity and endoplasmic reticulum enlargement. Unsaturated n-6 FAs may also be used for the synthesis of pro-inflammatory oxygenated derivatives such as PGE2 or leukotrienes. Accordingly, several genes involved in FA uptake and PUFA activation are increased by inflammatory stimuli including *CD36* and *ACSL1* [62]. ACSL1 is induced after LPS stimulation in macrophages and is involved in arachidonate-containing phospholipids turnover, thus controlling the release of AA-derived mediators such as PGE2 [28,63]

However, very recent studies suggest that PUFA metabolism in macrophages is subject to complex and subtle temporal changes during the inflammatory response [64,65]. Lipidomic analysis revealed that cellular content of n-3 and n-6 PUFA of mouse macrophages is rapidly decreased following TLR4 activation and this correlated with downregulation of genes involved in PUFA synthesis including *Fads1*, *Fads2* and *Elovl5*. This is followed by a second, late phase response (12–24 h after TLR4 stimulation), that is associated with increased intracellular n-3 and n-6 PUFA levels as well as induction of the corresponding genes [64,65]. The mechanisms responsible for downregulation of lipid biosynthetic genes during the early phase response remain to be established; however, it appears to be independent of LXR and could be mediated by an NF-κB dependent mechanism. Surprisingly, induction of PUFA synthesis in the second phase is also independent of LXR and appears to be mainly driven by SREBP1c. Accordingly, PUFA synthesis is impaired in *Srebf1*$^{-/-}$ macrophages that display a reduced FA biosynthetic gene expression as well as decreased PUFA levels during the late phase response to TLR activation. Moreover, SREBP1c expression appears to be required for resolution of the inflammatory response and *Srebf1*$^{-/-}$ macrophages display an LPS-hyper-responsive phenotype [65].

4. Human evidence

4.1. Genetic evidence

To date, no genome-wide association study (GWAS) has identified a link between genes specifically involved in unsaturated FA metabolism and the risk of coronary artery disease (CAD) or ischemic stroke [66,67]. Nevertheless, some GWAS highlight some relationships between several of these genes and the cardiometabolic risk. Genetic variation at the *FADS1-2* gene cluster has been associated with metabolic traits including glucose homeostasis, Body mass index, plasma liver enzymes and lipid parameters [68–70]. SNPs near the *FADS1-2* cluster have also been associated with leucocyte and monocyte counts supporting a potential role of these enzymes in the regulation of myelopoiesis [71]. By using gene candidate approaches, it has been shown that subjects carrying *FADS* haplotypes associated with higher desaturase activity presented higher C reactive protein levels and increased risk of CAD [72]. Reciprocally, FADS polymorphisms associated with lower arachidonate levels decrease the risk of CAD in a Korean population [73]. Several SNPs near the *ACSL1* locus are associated with fasting glucose and diabetes status in humans. Furthermore, one of these SNPs is also associated with subclinical atherosclerosis [74]. Finally, by using a gene candidate approach, a functional variant on the *FABP4* gene promoter was associated with decreased FABP4 levels, reduced risk of myocardial infarction and more stable, less inflammatory carotid plaques [75,76].

4.2. Monocytes and peripheral blood

Although plasma PUFA distribution has been associated with the cardiovascular risk by many studies, it is speculative to establish a direct relationship with myeloid cell metabolism. Nevertheless, changes in the expression of key genes of PUFA metabolism have been found in circulating monocytes and associated with cardiovascular risk. Human subjects with type 1 diabetes had significantly elevated *ACSL1* mRNA levels in monocytes and this was potentially related with inflammation and cardiovascular risk [29]. In human monocytes, increased FADS1 expression was identified as a component of a metabolic network that was significantly associated with T2 diabetes and coronary artery calcium [77]. Finally, FABP4 plasma levels were shown to predict atherosclerosis progression and incident cardiovascular events [78,79], while FABP5 plasma levels were associated with carotid atherosclerosis [80].

4.3. Lipidomic and transcriptomic profiling of human atheroma plaques

Transcriptomic analysis of symptomatic *versus* asymptomatic human carotid plaques revealed changes in some FA pathways, although not specific to PUFA metabolism, including an upregulation of LPL, CD36, FABP4 and FAPB5 in symptomatic plaques [81]. Accordingly, FABP4 expression was previously related to plaque inflammation and vulnerability [82].

Several lipidomic and metabolomic characterizations of human atheroma plaques have been published in recent years. While these studies do not discriminate between the different cell types in the atheroma plaque, they demonstrate that alterations in PUFA distribution within lipid molecules occur according to the stage of atherosclerosis development or to the vulnerability of plaques. Particularly, changes in arachidonate-containing lipid molecules seem to be associated with the stage of lesions or clinical patterns of patients. Thus, a decrease in arachidonate-containing plasmalogens has been observed in

maximally *versus* minimally diseased carotid plaque samples [83]. An increase in AA-containing phospholipid and LPC has also been observed in carotid plaques from diabetic patients as compared to non-diabetic patients [83,84]. Interestingly, it appears that the lipid distribution within the plaque correlates only weakly with plasma lipids, coming in support of an active local metabolism [85]. Nevertheless, dietary FA supplementation has a direct impact on the FA composition of atheroma plaques. Indeed omega 3 FA supplementation results in a significant increase of EPA and DHA in carotid plaque and decreased plaque inflammation [86,87]. Recently, the Reduced-it trial that included 8179 patients for 5 years, showed a 25% reduction of major acute cardiovascular events in individuals receiving high doses of EPA ethyl ester (Icosapent Ethyl 4 g daily) as compared with placebo [88]. It is unlikely that changes in plasma lipid profile could account totally for the beneficial impact of EPA. Indeed, the lower occurrence of major adverse cardiovascular events with icosapent ethyl appeared to be independent of the changes in plasma LDL cholesterol or triglyceride levels. Among other potential mechanisms, the reduction of high-sensitivity C reactive protein observed in the patient group receiving EPA may have contributed to the reduction in the cardiovascular events. Thus, it is tempting to speculate that the atheroprotective effects of EPA are related at least in in part to its ability to modulate macrophages and myeloid cells activation in the atheroma plaque. Accordingly, a recent experimental study suggests that the atheroprotective effects of EPA are related to the production of EPA-derived pro-resolving mediators such as resolvin E1 and subsequent modulation of macrophage functions including decreased oxidized LDL uptake and increased phagocytosis [41].

While it is too early to establish a direct relationship between changes in PUFA composition of the plaques and alterations in PUFA anabolic pathways in macrophages, studies combining immunology and mass spectrometry imaging open up very promising prospects. Using this approach, it was observed a concomitant decrease of LPCAT3 expression and arachidonoyl-PC enrichment in advanced human atherosclerotic lesion [89].

5. Conclusion and perspectives

There is growing evidence that n-3 and n-6 PUFAs as well as their pro- and anti-inflammatory oxygenated derivatives play a crucial role in the development of atherosclerosis and the vulnerability of plaques [39,41,90].Moreover, the positive results of recent clinical trials renew the interest of n-3 FA supplementation in the prevention of cardiovascular diseases [88] In this context, the ability of immune cells to handle and to synthesize very long chain PUFA must absolutely be integrated and better understood. One future challenge will be to characterize how myeloid cells modulate their PUFA metabolism to shift from the secretion of pro-inflammatory to anti-inflammatory lipid mediators. Generation of mouse model with conditional inactivation of PUFA genes such as *Fads1*, *Fads2* and *Elovl5* in myeloid cells will be of great interest. Additional studies are also needed to assess the impact of PUFA genes on atherosclerosis development in different metabolic contexts, i.e. omega 6 *versus* omega 3 enriched diets. Finally, development of single cell RNA sequencing approaches combined with mass spectrometry imaging will allow a very fine characterization of PUFA metabolism in different populations of immune cells within human atheroma plaques.

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Author contributions

L.M, A.J, C.T. and D.M. wrote and discussed the manuscript.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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