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Regulation of macrophage functions by FABP-mediated inflammatory and metabolic pathways

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Abstract

Macrophages are almost everywhere in the body, where they serve pivotal functions in maintaining tissue homeostasis, remodeling, and immunoregulation. Macrophages are traditionally thought to differentiate from bone marrow-derived hematopoietic stem cells (HSCs). Emerging studies suggest that some tissue macrophages at steady state originate from embryonic precursors in the yolk sac or fetal liver and are maintained *in situ* by self-renewal, but bone marrow-derived monocytes can give rise to tissue macrophages in pathogenic settings, such as inflammatory injuries and cancer. Macrophages are popularly classified as Th1 cytokine (*e.g.* IFNγ)-activated M1 macrophages (the classical activation) or Th2 cytokine (*e.g.* IL-4)-activated M2 macrophages (the alternative activation). However, given the myriad arrays of stimuli macrophages may encounter from local environment, macrophages exhibit notorious heterogeneity in their phenotypes and functions. Determining the underlying metabolic pathways engaged during macrophage activation is critical for understanding macrophage phenotypic and functional adaptivity under different disease settings. Fatty acid binding proteins (FABPs) represent a family of evolutionarily conserved proteins facilitating lipid transport, metabolism and responses inside cells. More specifically, adipose-FABP (A-FABP) and epidermal-FABP (E-FABP) are highly expressed in macrophages and play a central role in integrating metabolic and inflammatory pathways. In this review we highlight how A-FABP and E-FABP are respectively upregulated in different subsets of activated macrophages and provide a unique perspective in defining macrophage phenotypic and functional heterogeneity through FABP-regulated lipid metabolic and inflammatory pathways.

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Declaration of Interest Statement

There is no conflict of interests for all listed authors.

1. Introduction

Fatty acid binding proteins (FABPs) comprise a family of 14–15 kDa cytoplasmic lipid chaperones that coordinate lipid distribution and responses inside cells [1–3]. Composed of 10 anti-parallel β stands and capped by a helix-turn-helix motif, FABP members are highly homologous with a similar tertiary structure. FABPs are capable of binding a variety of fatty acids (FAs) and other hydrophobic ligands in the cavity of their β barrel structure with different specificity and affinity. FABP members display tightly-regulated patterns of tissue distribution, such as liver FABP (L-FABP, also known FABP1), intestinal FABP (I-FABP, FABP2) and heart FABP (H-FABP, FABP3), which are mainly expressed in liver, intestine and heart, respectively [4]. However, accumulating studies demonstrated that some FABP members exhibit expression beyond the tissues where they were originally cloned (Table 1). For example, adipose FABP (A-FABP or FABP4) is expressed in endothelial cells and macrophages besides adipocytes [5, 6]. Epidermal FABP (E-FABP or FABP5) exhibits a more ubiquitous expression profile, including skin, adipose tissue and multiple immune populations [7–9], suggesting a critical role of E-FABP in maintaining basic cellular energy metabolism and functions. In our studies focusing on immune cell lipid metabolism and function, we found that A-FABP and E-FABP display unique expression patterns in tissue macrophages which regulate their metabolic and inflammatory signaling pathways [4, 9–11]. Given the phenotypic diversity and functional versatility of macrophages, this review provides a unique perspective by focusing on defining macrophage functions through FABP-mediated lipid responses in different disease settings.

2. Macrophage phenotypic and functional heterogeneity

2.1 Origin of macrophages

Macrophages are present in all tissues in the body, in which they play a central role in maintaining tissue homeostasis, repair, and immunomodulation. Colony-stimulating factor 1 (CSF1, also known as macrophage CSF, M-CSF) is essential to the development and survival of monocytes/macrophages. Genetic depletion of the functional receptor for CSF1 (CSF1R or CD115) is lethal in mice [12, 13], suggesting that the congenital presence of the macrophage lineage is essential for murine survival.

Macrophages are generally believed to come from bone marrow-derived monocytes, which sequentially differentiate through the hematopoietic stem cells (HSCs)/macrophage and dendritic cell precursor (MDP)/common monocyte progenitor (cMoP) axis. The mononuclear phagocyte system (MPS) proposes that homeostasis of tissue macrophages rely on constant recruitment of circulating monocytes [14]. However, emerging genetic fate mapping studies reveal that steady state tissue macrophages (*e.g.* brain microglia, liver Kupffer cells) are mainly derived from embryonic precursors in the yolk sac or fetal liver and maintained *in situ* by self-renewal [15]. Of note, circulating monocytes are able to give rise to tissue macrophages in certain pathogenic settings, such as inflammatory injuries and cancer [16, 17]. Thus, depending on the local microenvironment [18], both embryonic- and bone marrow-derived macrophages may dynamically and coordinately control tissue homeostasis, infection and inflammation.

2.2 Macrophage phenotypic heterogeneity

Originally developed from bone marrow MDPs and cMoPs, blood monocytes are phenotypically heterogeneous, which are usually defined by specific surface proteins. In mice, monocytes ($CD115^+$) are usually divided into two main subsets based on the expression of Ly6C: $Ly6C^+$ and $Ly6C^-$ monocytes [19]. Ly6C belongs to the family of Ly6 proteins which are widely used as lineage-specific markers in leukocyte subset identification [20]. As a GPI (glycosylphosphatidylinositol)-anchor membrane protein, Ly6C has been shown to mediate the migration of different leukocyte subsets [21, 22], suggesting that Ly6C expression is critical to monocyte migration. In line with this perspective, Ly6C is highly expressed on bone marrow monocytes, which can easily migrate to the peripheral blood and to sites of infection and inflammation to engage inflammatory responses. By contrast, $Ly6C^-$ monocytes normally patrol the endothelial surface of blood vessels and are recruited to inflamed sites at a late phase for tissue repair [23]. $Ly6C^+$ and $Ly6C^-$ macrophages also exist in lymphoid (*e.g.* draining lymph nodes and spleen) and nonlymphoid tissues (*e.g.* skin, intestine). During tissue injuries, blood $Ly6C^+$ monocytes can rapidly migrate to the injury sites and differentiate into tissue inflammatory macrophages, TNFα/iNOS produced dendritic cells (TipDCs) or tumor associated myeloid-derived suppress cells (MDSCs), whereas $Ly6C^-$ monocytes can give rise to alveolar macrophages [24]. In humans, based on surface expression of CD14 and CD16 glycoproteins, human blood monocytes can be divided into $CD14^{high}CD16^{negative}$ and $CD14^{low}CD16^{positive}$ subsets. Analysis of gene expression arrays suggests that human $CD14^{high}$ and $CD14^{low}$ monocytes functionally resemble murine $Ly6C^+$ and $Ly6C^-$ monocytes, respectively [25]. It is of great interest to understand which factors contribute to the phenotypic heterogeneity of monocytes/macrophages in mice and humans.

2.3 Macrophage functional versatility

Besides phenotypic differences, macrophages exhibit functional versatility *in vivo*. Under homeostatic conditions, macrophages maintain normal physiologic functioning of organisms by shaping their architecture (*e.g.* brain, bone and mammary glands) and regulating diverse activities (*e.g.* metabolism, damage control and tissue repair). However, under pathological conditions, continuous insults from infection or chronic inflammation can subvert the trophic and regulatory roles of macrophages, thereby contributing to the progression of many diseases (*e.g.* cardiovascular disease and tumor) [26]. Given the myriad of possible environmental stimuli, macrophages are believed to exist in a vast array of functional states or “a functional spectrum” [27, 28]. To understand their functional complexity, macrophages are simply classified as M1/M2 dichotomy based on the widely accepted concept of Th1/Th2 polarization. During adaptive immune responses, Th1 lymphocytes mainly produce IFNγ while Th2 cells mainly produce IL-4, IL-13, *etc.* Accordingly, macrophages activated by Th1 or Th2 cytokines are called M1 or M2 macrophages, respectively [29, 30]. The classification of M1/M2 has been widely accepted and data generated based on this classification have provided insights into understanding macrophage functionality in different disease settings. Generally, the classical activation of M1 macrophages is characterized by pro-inflammatory and anti-tumor activities whereas the alternative activation of M2 macrophages increases angiogenesis and exhibits tumor-promoting functions [31, 32]. However, given the spectrum of functional states of macrophages *in vivo*

[33], these two extreme classifications are apparently oversimplified, especially in the tumor microenvironment. Recent studies demonstrate that pro-tumor macrophages in either the peritoneum or in tumor stroma do not follow the M1/M2 classification [6, 34]. Thus, the concept of functional adaptivity has been proposed that macrophages can change their functional phenotype in response to an array of microenvironmental stimuli [35, 36]. Emerging evidence suggests that macrophage metabolism determines their functional outcome [37, 38]. Dissecting the underlying metabolic pathways engaged during macrophage activation is critical to understanding their phenotypic and functional adaptivity in the progression of different diseases.

2.4 Macrophage metabolic pathways

As sentinels of the immune system, macrophages sense and respond to early signs of infection and inflammation [39]. In response to microbial invaders, monocytes/macrophages activated by IFNγ and LPS exhibit an increase of aerobic glycolysis and a decrease in fatty acid oxidation (FAO). Accordingly, this classical activation of M1 macrophages is considered as pro-inflammatory macrophages with high phagocytic potential in clearance of bacteria and tumor cells [26]. By contrast, macrophages can be alternatively activated by other environmental stimuli, such as parasitic infections. It is well known that alternative activation of M2 macrophages by IL-4 or IL-13 relies on FAO to fuel macrophage functions in anti-parasitic infection as well as in angiogenesis, tissue remodeling, and tumor progression [30]. Despite these two well-characterized metabolic pathways, macrophages can be metabolically activated by many other local tissue inputs. For example, obesity is associated with elevated levels of low density of lipoprotein (LDL) [40], which can be taken up by macrophages and induce alternative activation of macrophages through lysosomal acid lipase-mediated lipolysis pathway [41]. Given the alarming rate of obesity, it is intriguing to understand how lipid metabolism regulates macrophage functions in obesity and obesity-associated maladies.

3. FABP expression profile in macrophages

FABP family members facilitate lipid trafficking, metabolism and responses inside cells, circumventing low lipid solubility. Macrophages have been shown to mainly express A-FABP and E-FABP, which provides a unique perspective to dissect how A-FABP and E-FABP regulate FA metabolism and inflammatory pathways, thus shaping macrophage functional output.

Developed from HSCs and precursors, murine bone marrow monocytes ($CD115^+Ly6C^+$) express neither A-FABP nor E-FABP. Resting human monocytes also do not express detectable FABPs. Interestingly, *in vitro* activation of human monocytes with PMA (phorbol 13-myristate 12-acetate) upregulates the expression of both A-FABP and E-FABP [42]. These data demonstrate that FABPs are not essential to monocyte development in the bone marrow, but can be upregulated in monocytes activated by external stimuli, suggesting an important role of FABPs in activated monocytes/macrophages. Considering the heterogeneous subsets of monocytes/macrophages *in vivo*, we postulated that FABP expression in these cells is not uniform. Indeed, when we analyzed FABP expression in

monocytes/macrophages separated from different tissues, we found that FABP exhibited unique expression profiles in different macrophage subsets. For example, splenic macrophages ($CD11b^+F4/80^+$) can be divided into four subsets based on the surface expression of Ly6C and MHCII. While E-FABP is highly expressed in the $MHCII^+$ Q2 and Q3 subsets, A-FABP is only expressed in the $MHCII^-$ Q4 subsets [6, 9, 11]. Neither FABPs is expressed in the Q1 subset (Figure 1). The unique expression pattern of A-FABP and E-FABP in distinct macrophage subsets has been confirmed in other peripheral lymphoid tissues. For example, bone marrow monocytes are all located in Q1 subset, thus no/low FABP expression. Peripheral blood monocytes are mainly located in the Q1 and Q4 subsets, and A-FABP is only upregulated in the Q4 monocyte subset. Macrophages in draining lymph nodes are located in the Q2 and Q3 subsets, thus expressing E-FABP, but not A-FABP. Of note, $E\text{-}FABP^+$ macrophage subsets also highly express MHCII, a professional antigen-presenting molecule, whereas $A\text{-}FABP^+$ Q4 subset do not express MHCII molecules. Instead, $A\text{-}FABP^+$ macrophages highly express CD36, a membrane scavenger receptor for lipid uptake and bacterial phagocytosis [43–45]. These distinct characteristics suggest that $E\text{-}FABP^+$ macrophages are involved in accessory functions through antigen presentation and bridging innate and adaptive immunity. By contrast, $A\text{-}FABP^+MHCII^-CD36^+$ macrophages appear to be engaged in direct pathogen clearance, lipid processing and other patrolling function along the lumen of blood vessels[46–48].

4. Regulation of macrophage functions by FABPs in different diseases

As discussed above, heterogeneous murine blood monocytes contain $Ly6C^+$ and $Ly6C^-$ two main subsets. Numerous studies have reported that $Ly6C^+$ monocytes express chemokine receptors (*e.g.* CCR2) and are rapidly recruited to sites of injury, where they are activated to become either inflammatory macrophages/DCs ($MHCII^+$) or other subsets ($MHCII^-$) depending on local environmental cues [49–51]. By contrast, $Ly6C^-$ monocytes patrol the endothelium of blood vessel to scavenge pathogens, oxidized lipids or other debris. $Ly6C^-$ monocytes ($MHCII^-$) can also be recruited to injury sites at a late phase to mediate tissue remodeling and immunomodulatory functions [52–54]. Due to the distinct FABP expression profile in activated macrophages, we hypothesized that E-FABP expression in $MHCII^+$ macrophages and A-FABP expression in $MHCII^-$ $CD36^+$ macrophages contribute to the functional versatility of macrophages in different diseases.

4.1 Tumors

As the most abundant myeloid cells in the tumor stroma, tumor associated macrophages (TAMs) are known to exhibit phenotypic and functional heterogeneity [32, 55, 56]. Although it has been proposed that IFNγ-activated M1 macrophages exert antitumor activities by producing abundant pro-inflammatory cytokines whereas IL-4-activated M2 macrophages enhance angiogenesis and exhibit pro-tumor functions [29], it is difficult to identify which macrophage subsets exert anti-tumor or pro-tumor functions due to the lack of specific phenotypic and functional markers. Studies have shown that in the tumor stroma, TAM progenitors are originally come from $Ly6C^+$ monocytes, which gradually differentiate into either anti-tumor M1 or pro-tumor M2 TAMs depending on their locations in the tumor stroma [57, 58]. In line with these studies, we found that TAMs ($CD11b^+F4/80^+$) in

syngeneic mammary tumor models exhibited a dynamic alteration in their phenotype and function (Figure 2). Right after tumor implantation (0–3 days), TAMs were mainly Ly6C $^{+}$MHCII^{-} monocytes (Q1 subset), whereas 1–2 weeks later, the major TAM population exhibited M1-like phenotype (Ly6C^{+}MHCII^{+}CD11c^{+}) (Q2 subset). Three weeks later, the predominant TAM subset exhibited the M2-like phenotype (Ly6C^{-}MHCII^{-}) (Q4 subset)[6, 9]. Importantly, anti-tumor M1-like TAMs highly express E-FABP while pro-tumor M2-like TAMs highly express A-FABP. Using genetic knockout mouse models, we demonstrated that E-FABP expression in M1-like TAMs promotes their anti-tumor function by enhancing type I IFNβ responses through enhancing lipid droplet/viperin signaling [9]. Moreover, A-FABP expression in M2-like TAMs is critical to their pro-tumor function by promoting IL-6/STAT3 signaling through regulation of the NFκB/miR-29 pathway [6]. Of note, anti-tumor E-FABP^{+} macrophages differentiate early in tumor development [9]. If tumor cells are not eliminated at this stage, A-FABP^{+} TAMs gradually become dominant in the tumor stroma to promote tumor growth and progression [6] (Figure 2). Thus, E-FABP and A-FABP can be considered functional markers for anti-tumor and pro-tumor TAMs, respectively.

4.2 Inflammatory diseases

Buildup of lipid-laden macrophages (foam cells) is the most characteristic feature of atherosclerosis [59]. As such, atherosclerosis represents a good model to determine the contribution of macrophages to the pathogenesis of inflammatory diseases. A-FABP expression in macrophages was first reported to contribute to foam cell accumulation and atherosclerotic lesions using the ApoE$^{-/-}$ A-FABP$^{-/-}$ mouse model in a normal chow diet [42]. The critical atherogenic role of A-FABP expression in macrophages was further demonstrated in ApoE$^{-/-}$ mice fed a high fat Western diet that developed advanced atherosclerosis [60, 61]. E-FABP expression in macrophages also promotes atherosclerotic lesions by enhancing CCR2-mediated recruitment [62]. The conclusion that A-FABP and E-FABP contribute to atherosclerosis is mainly based on two observations: (1) macrophages express both E-FABP and A-FABP, and 2) A-FABP and E-FABP have a similar tertiary structure and ligand binding affinity [63]. Thus, it is assumed that A-FABP and E-FABP might have similar or redundant roles in macrophage-mediated atherogenesis. However, the observations that A-FABP deficiency is not compensated by E-FABP overexpression, nor does E-FABP deficiency result in A-FABP overexpression, do not support their functional redundancy in macrophages. Given that A-FABP and E-FABP have distinct expression profiles in different subsets of bone marrow-derived monocytes/macrophages, we proposed that A-FABP^{+} Ly6C^{-} CD36^{+} patrolling monocytes mainly contribute to oxidized lipid uptake and foam cell formation. Hyperlipidemia (*e.g.* oxLDL) in either ApoE$^{-/-}$ or LDLR $^{-/-}$ mice induces A-FABP-dependent lipotoxicity and macrophage death along the vascular endothelium, initiating local inflammation, and then recruits inflammatory E-FABP^{+} Ly6C^{+} CCR2^{+} monocytes, exacerbating atherosclerotic lesions already present (Figure 3). Thus, A-FABP and E-FABP each contribute to atherogenesis through the regulation of different subsets of macrophages.

4.3 Obesity and other diseases

In the past three decades, the prevalence of obesity has increased at an alarming rate [64–66]. Obesity is associated with chronic inflammation and many of mankind’s most common

diseases, including type II diabetes, cardiovascular disease, and at least 13 types of cancer [67, 68]. The underlying molecular mechanisms linking obesity and obesity-associated diseases are under active investigation. We used high fat diet (HFD)-induce murine obese models to demonstrate that obesity increases the risk of mammary tumor incidence and growth through at least two mechanisms: 1) Consumption of a HFD rich in saturated fat enhances differentiation of the A-FABP$^+$ Q4 subset in obese mice, thus increasing obesity-associated tumor risk [69]; 2) An HFD rich in saturated fat increases circulating levels of A-FABP, which directly target mammary tumor cells by enhancing tumor stemness for tumor progression [70]. Unlike A-FABP, circulating levels of E-FABP are similar in obese mice compared to lean mice, suggesting that A-FABP is an important link increasing the risk of obesity-associated cancer [71].

In several murine models we observed that HFDs, particular high saturated fat diets, induce chronic skin inflammation, which is associated with increased accumulation of MHCII$^+$ CD11c$^+$ macrophages in the lesion skin. E-FABP is highly expressed in these macrophages and promotes inflammatory IL-1β signaling, which leads to adaptive T cell responses. Importantly, E-FABP deficiency reduces IL-1β responses and completely prevents the HFD-induced skin lesion. Thus, E-FABP expression in MHCII$^+$CD11c$^+$ macrophages is critical in mediating IL-1β-induced inflammatory diseases in obesity. In addition, FABPs play a central role in other disease models. For instance, LPS injection induces infiltration of E-FABP$^+$ macrophages in the liver, which contributes to LPS-induced liver inflammation and injury [72]. IL-4 stimulation promotes macrophage polarization by upregulation of A-FABP through the IL-4/STAT6/PPARγ signaling axis [73–75]. A-FABP overexpression in liver Kupffer cells positively correlates with the poor outcomes of decompensated cirrhosis [76]. Recently studies demonstrate that A-FABP expression in alveolar macrophages is required for neutrophil recruitment and infection clearance [77, 78]. It is of great interest to determine whether severe symptoms often observed in obese COVID-19 patients are associated with dysregulation of A-FABP expression and neutrophil hyperinflammation. infection may patients. These mounting lines of evidence further suggest that E-FABP and A-FABP promote inflammatory diseases through regulating different macrophages *in vivo*.

5. Regulation of lipid-metabolic pathways by FABPs in macrophages

To further understand how A-FABP and E-FABP respectively regulate macrophage functions, we noticed that while both FABPs bind various dietary FAs with similar affinity [63, 79], they are unique in channeling different FAs to specific cellular organelles and in regulating their metabolic pathways in macrophages.

5.1 A-FABP regulates FA-mediated pathways in macrophages

Protein-ligand analysis demonstrated that A-FABP selectively transports specific FAs into the nucleus for transcriptional activation of nuclear receptor PPARγ [80]. Although A-FABP is able to bind multiple FAs with similar affinity, including palmitic acid, stearic acid, oleic acid, linoleic acid, arachidonic acid, *etc.*, A-FABP only delivers certain ligands (*e.g.* linoleic acid, troglitazone) to the nucleus. Structural analysis indicated that linoleic acid binding to A-FABP alters its tertiary structure to form a nuclear localization signal (NLS) whereas

binding of non-activating ligands (*e.g.* saturated FAs) masks the NLS, thus preventing their nuclear transport by A-FABP. Of note, ligand activation of PPARγ controls expression of multiple PPARγ-target genes, among which CD36 is well known to mediate oxLDL uptake and promote the formation of macrophage-derived foam cells [81] (Figure 4). A-FABP is also a direct PPARγ transcriptional activation gene, and oxLDL-induced PPARγ activation in turn promoted A-FABP expression and monocyte/macrophage differentiation [82, 83]. Thus, once egressed from bone marrow, $Ly6C^+$ monocytes can differentiate into $Ly6C^-$ patrolling monocytes through activation of the PPARγ/CD36/A-FABP pathway in response to external stimuli in the blood (*e.g.* oxLDL).

Besides channeling linoleic acids into the nucleus for PPARγ activation, A-FABP mediates other unsaturated FA (*e.g.* omega-3 FAs)-induced mitochondrial oxygen consumption and production of reactive oxygen species (ROS) in macrophages [69]. Macrophages deficient in A-FABP exhibit increased intracellular levels of unsaturated FAs and upregulation of UCP2 [84], further supporting a critical role of A-FABP in mediating unsaturated FA oxidation in macrophages. A-FABP also plays a critical role in coordinating saturated FA-mediated responses in macrophages, including palmitic acid-induced endoplasmic reticulum (ER) stress [85]. Our recent studies demonstrate that A-FABP is pivotal in mediating saturated FA-induced ceramide production and macrophage cell death [11, 86]. Thus, depending on the FA ligands, A-FABP transports them to different cellular compartments to coordinate unique metabolic pathways in macrophages (Figure 4).

5.2 E-FABP-mediated FA pathways in macrophages

Although E-FABP has a high degree of homology with A-FABP, it exhibits a distinct expression profile in bone-marrow derived monocytes/macrophages, implying unique features in mediating lipid metabolic pathways. A-FABP is highly expressed in $Ly6C^-MHCII^-CD36^+$ monocytes/macrophages, whereas E-FABP is highly expressed in $Ly6C^+MHCII^+CD36^-$ macrophages. $E\text{-}FABP^+$ macrophages are lower in PPARγ, but higher in PPARβ/δ expression, suggesting a specific E-FABP/PPARβ/δ interaction. Mounting evidence indicates that E-FABP channels ligands from the cytoplasm to the nucleus for transcriptional activation of PPARβ/δ, and PPARβ/δ activation can directly induce E-FABP expression, thus forming a positive feedback loop [87–89]. Structural analysis indicated that E-FABP can bind a wide array of FAs and other hydrophobic ligands (*e.g. trans*-retinoic acid, N-acylethanolamine), but only certain ligands alter E-FABP conformation and tertiary NLS formation, leading to ligand-driven nuclear translocation [90]. It is clear now that E-FABP can transport unsaturated FAs, especially these with a U-shape conformation (*e.g.* linoleic acid, arachidonic acid) to the nucleus for PPARβ/δ transactivation. Besides nuclear transportation, E-FABP expression in TAMs facilitates unsaturated FA-induced lipid droplet (LD) formation in macrophages [9]. As LDs are essential in mediating IFNβ signaling [91, 92], we demonstrated that E-FABP expression in TAMs plays a critical role to promote anti-tumor type I IFNβ responses in mammary tumor models. Thus, E-FABP can also channel unsaturated FAs for LD formation, which provides a platform for unsaturated FA-mediated IFNβ responses in macrophages (Figure 5).

As E-FABP does not appear to channel saturated FAs (*e.g.* palmitic acid) to the nucleus for PPARβ/δ activation or formation of LDs in the cytosol, it is intriguing to know whether and how E-FABP regulates saturated FA-mediated responses inside macrophages. In an obese mouse model induced by a diet high in lard, we observed that the HFD-induced skin lesions were associated with $CD11c^+$ macrophage accumulation. Further analysis of the skin indicated that IL-1β signaling was significantly upregulated in $CD11c^+$ macrophages. Interestingly, saturated, but not unsaturated, FAs promote CD11c expression and induce IL-1β secretion in an E-FABP-dependent manner, suggesting that E-FABP enhances saturated FAs-mediated $CD11c^+$ macrophage differentiation and IL-1β signaling pathways [10, 93]. Recent studies demonstrate that saturated FAs are transported to lysosomes to form crystals for inflammasome activation and IL-1β release [94], suggesting that E-FABP may deliver saturated FAs to lysosomes in macrophages (Figure 5).

Of note, E-FABP expression is more ubiquitous than A-FABP and other FABP members. Besides expressed in macrophage subsets, E-FABP is also expressed in other immune cells and tissues (*e.g.* T cells, mammary gland, brain, lung) [95, 96], suggesting that E-FABP serves as a ubiquitous lipid carrier. Dysregulation of lipid metabolism links ER stress[97–99], exhaustion and ferroptosis[100, 101], which have been suggested to regulate immune cell activation and survival. Thus, FABP-mediated ER stress and other lipid signaling pathways can affect immune cell fate and disease progress. Further study is warranted to determine how FABPs regulate lipid metabolism and tissue/cell specific responses in obesity, tumor and other inflammatory diseases.

6. Summary

The family of FABP members is widely expressed in different tissue/organs, facilitating lipid uptake, transport, and coordinating lipid-mediated responses. Among FABP members, A-FABP and E-FABP are highly upregulated in activated macrophages, regulating different functions of macrophages in multiple disease settings. A-FABP and E-FABP are thought to be equally expressed in macrophages at similar levels [42]. Due to the similarity of their amino-acid sequences, protein structure and binding ligands, A-FABP and E-FABP are generally believed to function redundantly in macrophages [62]. Studies using A-FABP and E-FABP double knockout mice have generated striking phenotypes in preventing insulin resistance, chronic inflammation and other metabolic diseases [102–104]. However, macrophages exhibit heterogeneous phenotypes and functions *in vivo*. Depending on their origin, tissue distribution and wide arrays of stimuli received from the local environment, macrophages exhibit diverse activation status when engaged with different metabolic and inflammatory pathways. As such, emerging evidence indicates that A-FABP and E-FABP can be upregulated in different subsets of activated macrophages to coordinate lipid-mediated responses. For bone marrow-derived macrophages, A-FABP is highly expressed in $Ly6C^-$ $MHCII^-CD36^+$ patrolling monocyte/macrophages to facilitate oxidative lipid uptake, foam cell formation, angiogenesis, tissue remodeling and pro-tumor functions. By contrast, E-FABP is highly expressed in $MHCII^+CD11c^+$ macrophages and promotes inflammatory responses (*e.g.* IL-1 signaling), antigen presentation and anti-tumor immunity (*e.g.* IFNβ response). A-FABP and E-FABP are also upregulated with obesity to handle dysregulated levels of FAs and channel them to specific cellular organelles inducing different metabolic

and inflammatory signaling in macrophages. Thus, A-FABP and E-FABP represent a new line of functional markers defining macrophage functions to maintain homeostasis in health and engaging pathogenesis under various disease conditions.

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Highlights

1. Macrophages exhibit phenotypic, metabolic and functional heterogeneity.
2. FABPs, in particularly A-FABP and E-FABP, are expressed in different subsets of macrophages.
3. A-FABP and E-FABP regulate lipid metabolism by coordinating different FA-mediated pathways in macrophages.
4. A-FABP and E-FABP may serve as new metabolic/functional markers defining macrophage heterogeneity.

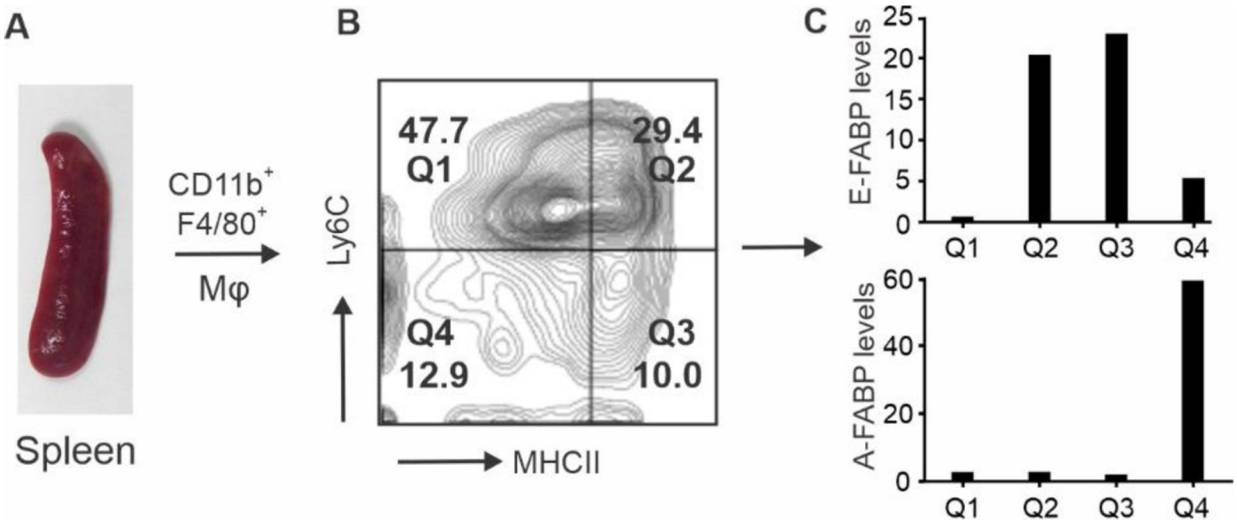

Figure 1. A-FABP and E-FABP expression pattern in splenic macrophages.

Splenic macrophages ($CD11b^{+}F4/80^{+}$) (A) are divided into four subsets (Q1-Q4) by the surface markers Ly6C and MHCII (B). Individual subsets were separated by a flow sorter and relative levels of A-FABP and E-FABP in each subset were assessed by real-time PCR (C).

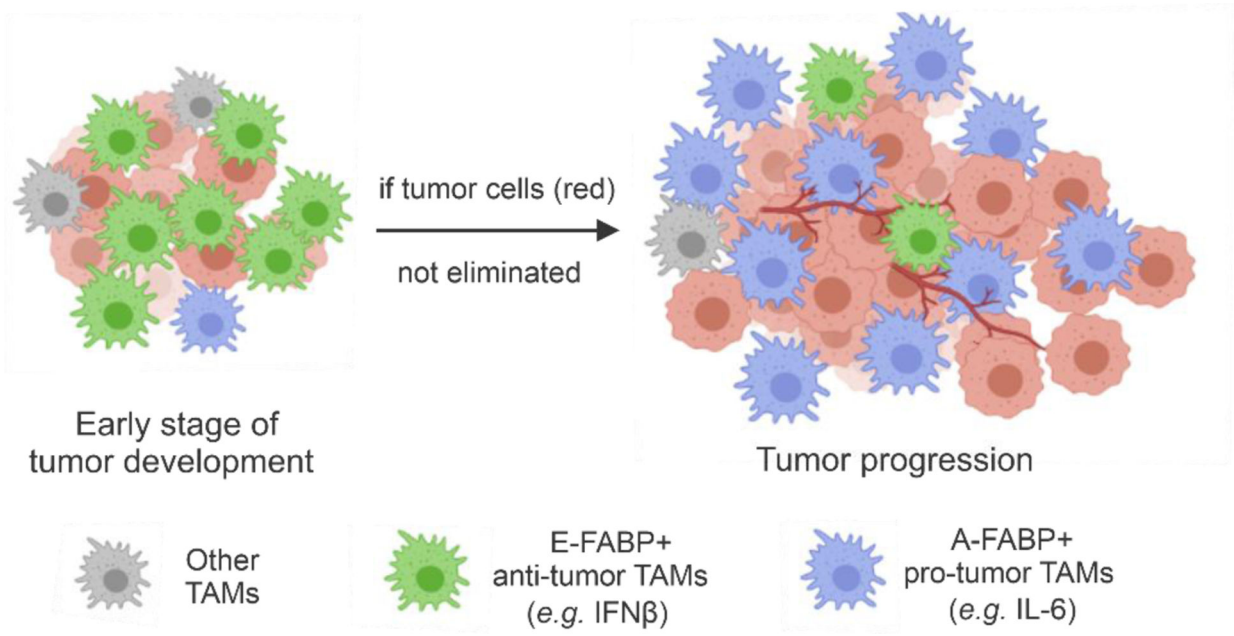

Figure 2. Expression of E-FABP and A-FABP in different subsets of TAMs.

E-FABP expression in TAMs exerts anti-tumor effects by promoting type I IFNβ signaling and adaptive immune responses, while TAM expression of A-FABP promotes tumor progression by enhancing pro-tumor IL-6/STAT3 signaling.

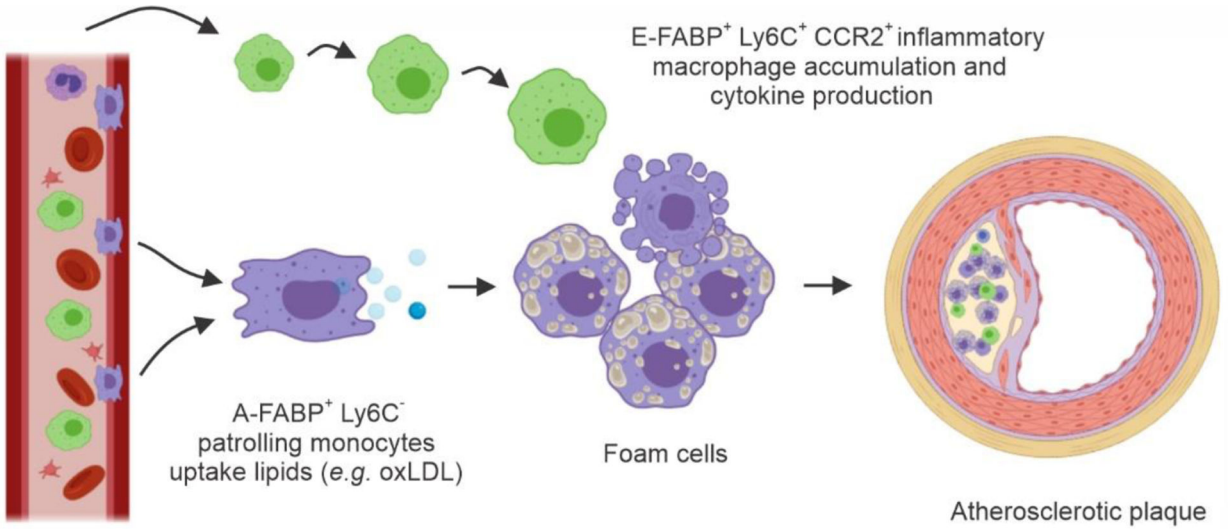

Figure 3. A-FABP and E-FABP contribute to atherosclerosis by regulating different subsets of monocytes/macrophages.

A-FABP^{+}Ly6C^{-}CD36^{+} patrolling monocytes uptake oxLDL and initiate atherosclerotic lesions while recruited Ly6C^{+} CCR2^{+} monocytes express E-FABP, contributing to local inflammation in the atherosclerotic plaque.

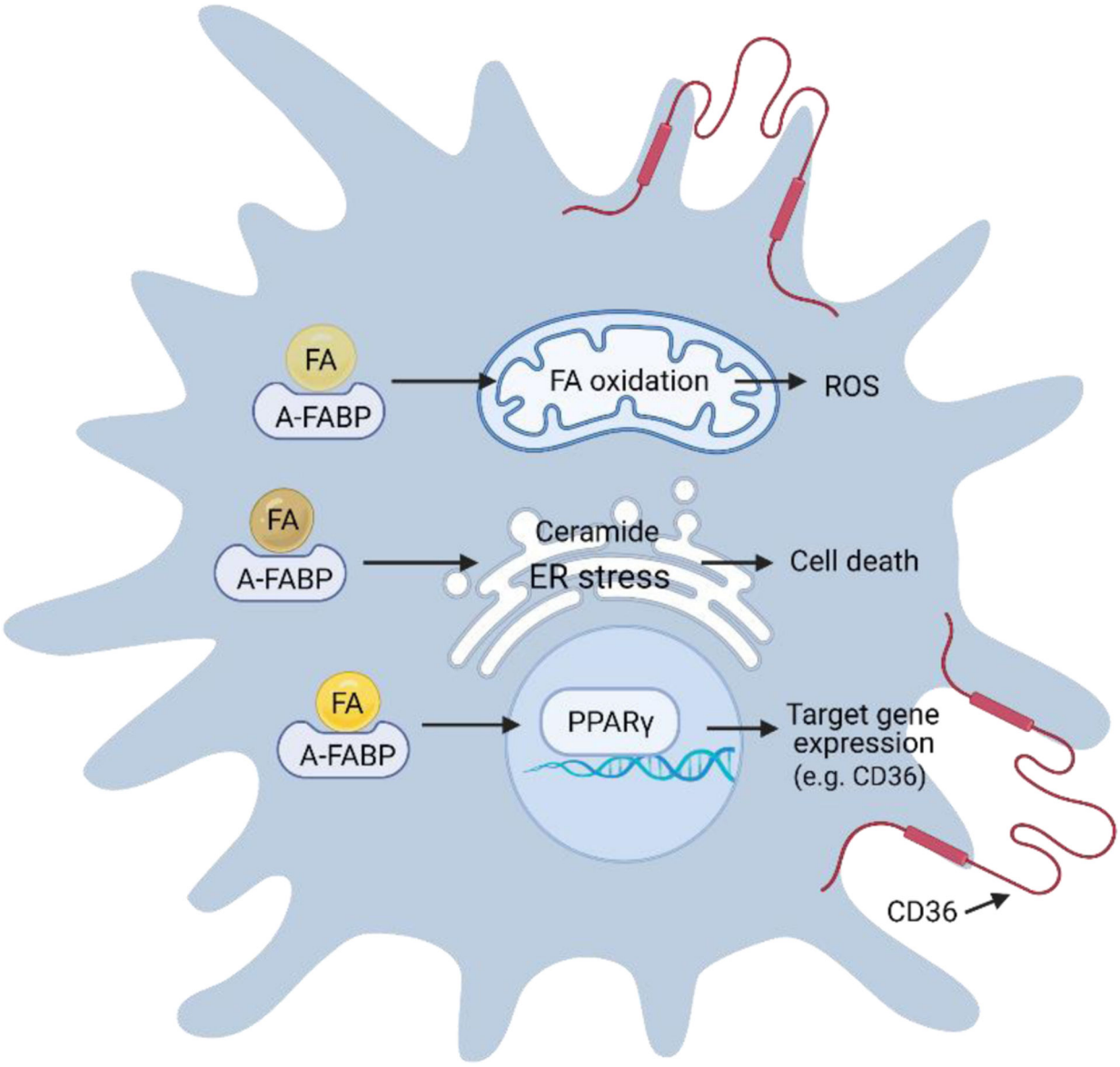

Figure 4. A-FABP coordinates FA responses in macrophages.

In A-FABP^{+} macrophages, A-FABP can facilitate multiple FA-mediated responses, which include FA oxidation and ROS production in mitochondria, ceramide production and ER stress, and activation of nuclear transcriptional factors (*e.g.* PPARγ) activation and regulation of gene expression (*e.g.* CD36).

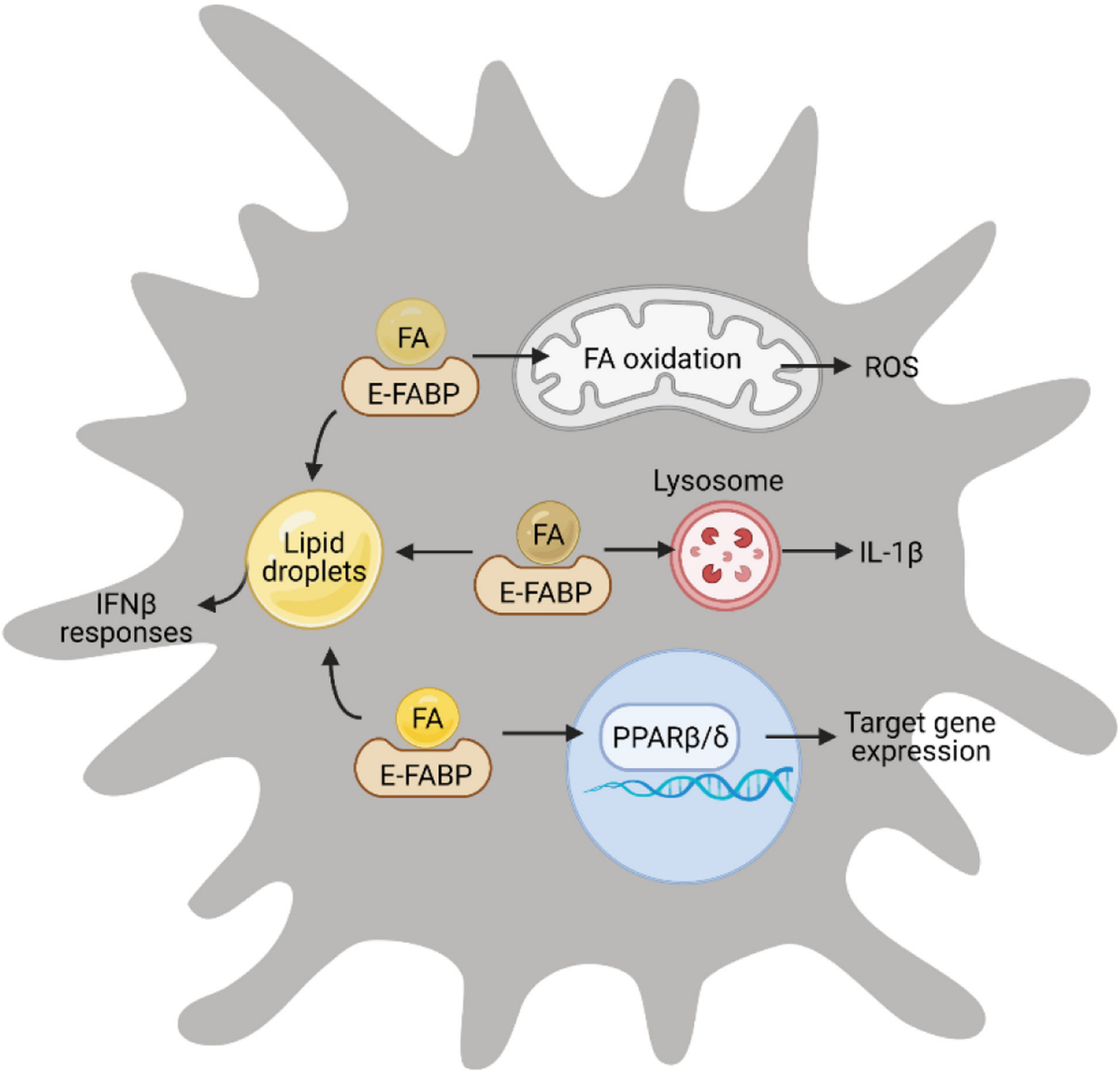

Figure 5. E-FABP coordinates FA responses in macrophages.

In E-FABP^{+} macrophages, E-FABP mediates multiple FA-induced responses, including FA oxidation and ROS production, inflammasome activation and IL-1β upregulation, lipid droplet formation and IFNβ responses, and nuclear transcriptional factor activation and gene regulation.

Table 1.

The distribution, binding ligands and functions of FABP family members

Gene	Protein	Alternative names	Predominant tissue localization	Major binding ligands	Pathological functions
FABP1	L-FABP	Liver FABP, heme-binding FABP	Liver, duodenum, small intestine, colon, rectum, kidney, appendix	Broad hydrophobic ligands, such as heme, bile acids, acyl-CoA, vitamins, xenobiotic drugs	Hepatic steatosis, nonalcoholic fatty liver disease
FABP2	I-FABP	Intestine FABP, gut FABP	Duodenum, small intestine	Long chain fatty acids (LCFA)	Metabolic syndromes, colorectal cancer
FABP3	H-FABP	Heart FABP, muscle FABP	Muscles (heart, skeletal)	LCFA, eicosanoids, retinoic acids	Biomarker for acute myocardial infarction
FABP4	A-FABP	Adipose FABP, aP2	Adipose tissue (adipocytes and macrophages), endothelium	LCFA, eicosanoids, retinoic acids	Metabolic diseases (such as type 2 diabetes, atherosclerosis, insulin resistance), cardiovascular disease, asthma, cancer
FABP5	E-FABP	Epidermal FABP, mal1, psoriasis-associated FABP, keratinocyte FABP	Skin, adipose tissue, lung, immune cells (macrophages, T cells,*etc*), esophagus, stomach, colon	LCFA, eicosanoids, retinoic acids, cannabinoids	Inflammatory skin diseases (such as psoriasis, dermatitis), atherosclerosis, autoimmune diseases, cancer
FABP6	IL-FABP	IIeal FABP, gastrotropin	Small intestine (distal)	Bile acids, cholate, LCFA	Type 2 diabetes, bile acid-associated gut diseases
FABP7	B-FABP	Brain FABP, brain lipid binding protein (BLBP)	Cerebellum, hippocampus	Polyunsaturated FAs, particulary DHA	Overexpression in Down's syndrome and Schizophrenia
FABP8	M-FABP	Myelin FABP	Cerebral cortex	LCFA, eicosanoids, retinoic acids, cholesterol	Guillain-Barre syndrome
FABP9	T-FABP	Testis FABP, testis lipid binding protein (TLBP)	Testis, esophagus	LCFA, eicosanoids, retinoic acids	Sperm head abnormalities