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REVIEW

Macrophage/Foam Cell Is an Attribute of Inflammation: Mechanisms of Formation and Functional Role

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Abstract—Transformation of macrophages into foam cells is traditionally considered in the context of atherogenesis, because lipid accumulation is believed to be a consequence of uptake of oxidized low density lipoproteins (oxLDL) through scavenger receptors (SR) of macrophages. However, an excessive uptake of oxLDL is recently shown to trigger compensatory mechanisms of cholesterol elimination from macrophages. Maintaining the lipid homeostasis in macrophages is mediated by regulation of a system of lipid sensors, which is reprogrammed under conditions of inflammation leading to formation of foam cell phenotype without involvement of SR. The increase in the inflammatory potential on macrophage polarization into the M1 phenotype is associated with suppression of LXR and PPAR, their target genes, induction of expression of genes responsible for fatty acid and cholesterol metabolism controlled by SREBP1c and SREBP2, proteins associated with lipid inclusions, macropinocytosis activation, secretion of LXR and PPAR endogenous ligands, and development of apoptosis. In this review the role of foam cells in development and resolution of acute inflammation, mechanisms of their formation from macrophages infected by some bacterial and virus pathogens causing chronic inflammation, and the significance of LXR and PPAR as therapeutic targets in chronic infectious and inflammatory diseases are also discussed.

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Key words: macrophage/foam cell, inflammation, lipid sensors, endogenous ligands PPAR and LXR, macrophage infections

Foam cells (FC) were first detected in atherosclerotic patches of vascular wall. At the end of the XX century a hypothesis appeared that FC could be produced in subendothelial space of blood vessels, mainly from macrophages (MP) as a result of uptake by scavenger receptors (SR) of oxidized low density lipoproteins (oxLDL) [1]. Independently of these studies, we found on a model of *in vivo* zymosan-induced peritonitis in mice that MP isolated from the inflammatory exudate accumulated neutral lipids as a result of a dramatic (20-fold!) increase in the rate of synthesis of triglycerides (TG) and of 10-fold increase in synthesis of cholesterol esters

Abbreviations: ABCA1 and ABCG1, ATP-bound A1 and G1 cholesterol cassette carriers; AEBP1, adipocytic enhancer-binding protein 1; aP2, fatty acid-binding protein; apoE, apolipoprotein E; ChE, cholesterol esters; COX-2, cyclooxygenase; 15-d-PGJ_2, 15-dioxy-delta-12,14-prostaglandin J_2; ER, endoplasmic reticulum; ERK1/2, kinase regulated by extracellular 1/2 signals; FC, foam cells; GM-CSF, granulocyte-macrophage colony-stimulating factor; 27- and 25-HC, 27- and 25-hydroxycholesterol; 15-HETE, 15-hydroxyeicosatetraenoic acid; HMGR, 3-hydroxy-3-methylglutaryl-CoA reductase; 13-HODE, 13-hydroxyoctadecadienoic acid; IκB, κB inhibitor; IL, interleukin; IFN-γ, interferon γ; iNOS, inducible NO-synthase; INSIG, insulin-induced gene product; IRF3, interferon-regulated factor 3; LDLR, LDL receptor; LO, lipoxygenase; LPS, bacterial lipopolysaccharide; LXR, liver X-receptors; MAPK, mitogen-activated protein kinase; MCP-1, monocytic chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MP, macrophages; MyD88, myeloid differentiation early response protein; Nef, negative factor; NF-κB, nuclear factor κB; NPC1 and 2, Niemann–Pick 1 and 2 proteins; Nrf2, NF-E2-related factor 2; OSBP, oxysterol-binding protein; oxLDL and nLDL, oxidized and native low density lipoproteins; PPAR, peroxisome proliferator-activated receptors; RhoA, Ras homolog gene family, member A; ROS, reactive oxygen species; SCAP, SREBP splitting-activating protein; SR, scavenger receptors; SREBP2 and 1c, sterol regulatory element-binding proteins 2 and 1c; StAR, steroidogenic acute regulatory protein; STAT1, Signal Transducers and Activators of Transcription family, member 1; TG, triglycerides; TGF-β1, transforming growth factor-β1; TLR, Toll-like receptors; TNFα, tumor necrosis factor α; TRIF, TIR-domain-containing adapter-inducing interferon-β.

(ChE) [2]. Addition of acetylated LDL or of native LDL (nLDL) into the incubation medium of MP induced an additional activation of ChE synthesis. Later, the production of FC was demonstrated on transplanted lines of MP cultivated in the presence of bacterial lipopolysaccharides (LPS) and other agonists of Toll-like receptors (TLR) [3-5] including zymosan [6]. Moreover, the transformation of MP into FC was found in different tissues in various inflammatory diseases: in synovial fluid in rheumatoid arthritis [7], in fatty tissue in diabetes [8], in kidneys in patients with glomerulonephritis [9], in microglia on LPS delivery into the brain [10]. Data of experiments on MP infected with the bacteria *Chlamydia pneumoniae* and *Mycobacterium tuberculosis*, human immunodeficiency viruses (HIV), and cytomegaloviruses also confirmed the infection- and inflammation-related origin of FC.

The transcriptional integration of lipid metabolism and immune functions of MP is mediated by lipid sensors, which under physiological conditions control in MP lipid homeostasis concurrently with the immune response [11]. During early stages of inflammation, the system of regulation of lipid sensors in MP is reprogrammed, and this is a prerequisite of their classic activation (polarization into the M1 phenotype) and of lipid accumulation in MP. However, the functional role of MP/FC generation under conditions of inflammation is still enigmatic. In addition to their phagocytic, antigen-presenting, and cytokine-producing functions during early stages of inflammation, macrophages are known to be involved in its resolution. Therefore, MP/FC actively secreting lipid mediators are likely to play an important role in preparing the terminating scenario of inflammation.

In this review, mechanisms of FC production upon the activation of MP by inflammatory stimuli and infection with some pathogens are considered, as well as a possible role of MP/FC in the development and resolution of inflammation.

General functions of macrophages. Macrophages and monocytes are polypotent cells that display striking plasticity depending of external stimuli, and they can change their phenotype and transcriptional program. It is believed that under physiological conditions growth factors of MP play a decisive role in the differentiation and functions of MP. Thus, a deficiency of the macrophage colony-stimulating factor (M-CSF) is accompanied by a decrease in the osteoclast function and development of osteopetrosis (marble disease). In turn, a deficiency of granulocyte-macrophage colony-stimulating factor (GM-CSF) causes a decrease in the activity of the sensor of oxidized fatty acids PPARγ1 (peroxisome proliferator-activated receptor-γ1) and in the expression of ATP-binding cholesterol cassette carrier G1 (ABCG1) in pulmonary MP and also disorders in pulmonary surfactant clearance and development of alveolar proteinosis. However, despite the tissue heterogeneity of mature macrophages, they all have in common the origin from a hematogenous stem cell of the bone marrow and two of the most important functions: involvement in immune response and control of metabolism in the body. Disorders in these functions observed, in particular, on a selective deficiency of PPARγ1 in MP, lead to systemic disorders in lipid and carbohydrate metabolism in the body [12]. Significant changes in the functional conditions of MP occur during inflammation under the influence of cytokines, hormones, and microorganisms and cause a classic (M1) and alternative (M2) activation. The classic activation (M1) of macrophages is induced by IFN-γ, bacterial LPS, or by cytokines such as TNFα. The M1 phenotype macrophages are characterized by production of proinflammatory cytokines, which activate the Th1 response [13]. The alternative activation (M2) of macrophages is caused by IL-4, IL-13, immune complexes, IL-10, vitamin D_3, and glucocorticoids [13].

Comparative study on transcriptional profiles of M1 and M2 phenotypes of human MP [14] has revealed significant differences in the expression of genes associated with apoptosis, surface receptors, cytokines and chemokines, enzymes, extracellular mediators, and nuclear factors. In particular, the M1 phenotype is characterized by a significant decrease in expression of the mannose receptor, SR-A and CD36, the transforming growth factor-β (TGF-β), PPAR, and sensors of liver X-receptors (LXR). Classification of the alternative activation (M2) of MP is supplemented by additional subtypes: M2a induced by IL-4 or IL-13, M2b induced by immune complexes, and M2c induced by IL-10 and glucocorticoids [15]. Under normal conditions, MP are characterized by a high expression of lipid sensors of three isoforms of PPAR and LXR and of some SR, such as SR-A and CD36 (fatty acid translocases). In some works an insufficiently correct opinion is expressed that SR-mediated (mainly CD36-mediated) uptake of oxLDL [11] resulting in disorders in the back transport of cholesterol and an increase in the inflammatory potential of MP is the leading mechanism of lipid accumulation in MP. This opinion seems to be based on specific features of *in vitro* conditions of MP incubation in the presence of oxLDL and in the absence of cholesterol acceptors – high density lipoproteins (HDL). By now oxLDL are convincingly proved to stimulate under normal conditions compensatory reactions in MP promoting an increase in cholesterol export from cells and development of tolerance to inflammatory stimuli.

Lipid sensors in maintaining lipid homeostasis of MP. In the absence of inflammatory stimuli, in the center of signaling pathways involved in maintaining homeostasis in MP taking up oxLDL or nLDL there are transcription factors, such as nuclear receptors PPAR and LXR, and oxysterol and cholesterol sensors, or sterol-regulating element binding proteins (SREBP), which control expression of ~80 genes associated with lipid metabolism. The homeostatic signalization is mediated by interaction of endogenous ligands with the sensors that results in activa-

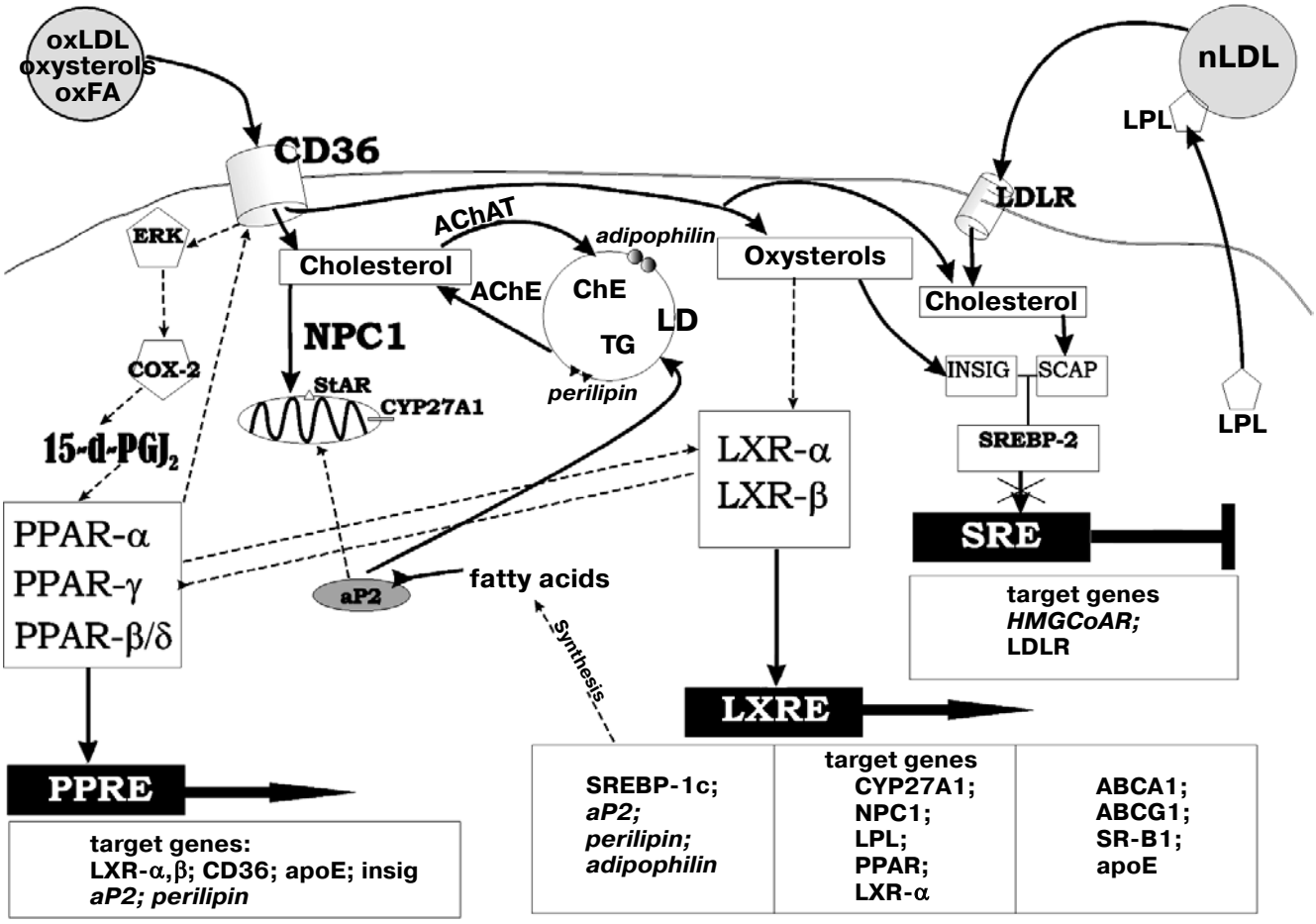
tion or inactivation of expression of products of gene cascades which are involved in maintaining lipid homeostasis. On the interaction of oxLDL with CD36 in MP, 15-dioxy-delta-12,14-prostaglandin (PG) J_2 (15-d-PGJ_2) is synthesized, and oxidized fatty acids are released, such as 15-hydroxyeicosatetraenoic acid (15-HETE) and 13-hydroxyoctadecadienoic acid (13-HODE), which are endogenous agonists of PPARγ1 and PPARα stimulating their expression [16]. Interaction of PPAR with hormone-responsive elements of PPAR (PPRE) in the promoter of the *LXRα* and *LXRβ* genes and interaction of LXR with hormone-responsive elements of LXR (LXRE) in the promoter of the *PPARγ1* and *PPARα* genes provides for the mutual coordination of expression of these transcriptional factors. Cholesterol entering into the cells binds with the Niemann–Pick C1 protein (NPC1), which transfers it into membranes of the endoplasmic reticulum (ER) and exchanges it with the mitochondrial steroidogenic acute regulatory protein (StAR). StAR transfers cholesterol onto the inner mitochondrial membrane where 27-cholesterol hydroxylase is located. Synthesis of the LXR endogenous agonist 27-hydroxycholesterol (27HC) in mitochondria also stimulates the expression of this nuclear receptor [17]. The activation of PPARγ1, PPARα, and LXR induces expression of target genes and of their products. The increase in expression and in protein products of cholesterol carriers ABCA1, ABCG1, the scavenger receptor B1 (SR-B1), and apolipoprotein E (apoE) promotes an accelerated export of cholesterol from MP [16]. Concurrently the expression is induced of genes and of synthesis of cholesterol carriers NPC1 and NPC2 proteins, of the fatty acid carrier aP2, of proteins perilipins and adipophilin stabilizing lipid inclusions, and also of the scavenger receptor CD36. Cholesterol and oxysterols in turn downregulate the activities of SREBP-2 and SREBP-1c involved in the activation of expression of genes associated, respectively, with metabolism of cholesterol and fatty acids. This regulation is realized on the interaction of sterol with transmembrane chaperon protein SCAP (the splitting-activating protein (SREBP)) and insulin-induced gene product (INSIG) that delays the SREBP2 transport into the Golgi apparatus, termination of its proteolytic processing, and suppression of expression of the LDLR family receptors limiting the enzyme of biosynthesis of cholesterol 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and other enzymes of its biosynthesis [18]. Thus, lipid accumulation in MP caused by oxLDL is compensated by induction of their elimination from the cell and suppression of their synthesis in cells (Scheme 1). It should be emphasized that maintaining the balance between cholesterol accumulation and back transport with involvement of LDL significantly depends on the immune reactivity of macrophages.

The presented simplified scheme does not include literature data about the proinflammatory effect of minimally oxidized LDL and oxLDL, which is mediated through signaling pathways of TLR and plays an important role in development of atherosclerosis.

Lipid sensors and their target genes in the regulation of immune reactivity of MP. Both 15-HETE and 13-HODE present in oxLDL activate a redox-sensitive transcriptional factor Nrf2 via suppression of the MP response to inflammatory stimuli [19]. However, induction of expression of PPAR and LXR and of their target genes observed under conditions of oxLDL uptake is also important for control of the functional state of MP because its disorders can result in a dangerous syndrome of MP activation associated with lesions of many organs. The expression of "inflammatory" genes upon induction of PPAR and LXR is suppressed through transrepression of transcriptional factors AP1 and NF-κB located on promoter regions of "inflammatory" genes by sumoylation of PPARγ1 and LXR. The sumoylation is a covalent addition of small (~20 kDa) ubiquitin-like modifiers (SUMO) to lysine residues of proteins under the influence of SUMO ligases. According to the mechanism proposed by Glass and colleagues, the addition of SUMO increases the affinity of PPARγ1 and LXR for corepressor complexes, such as NCoR and HDAC3 (E3-ligase) and prevents the detachment of the complex from the promoter regions of "inflammatory" genes [20]. Some products of the target genes PPAR and LXR also have an antiinflammatory potential. Thus, removal of cholesterol with involvement of ABCA1 and ABCG1 from cholesterol-enriched regions (the so-called rafts where ~23% of cholesterol is accumulated) makes difficult the transport and formation of TLR functional complexes [21]. Therefore, the deficiency of ABCA1 in mouse MP leads not only to an increase in the intracellular level of cholesterol, but also to an increased expression of "inflammatory" genes in response to the action of TLR ligands [22]. ApoE also performs various antiinflammatory functions inhibiting c-Jun N and c-Jun activation [23], regulating the balance between apoptosis and uptake of apoptotic cells, and preventing the cell necrosis [24]. Recently the increase in expression of NCP1 [25] and StAR [26] was shown to decrease MP reactivity. However, similarly to aP2 [27], perilipin [28] and adipophilin [29] can induce the inflammatory potential of MP.

Obviously, to provide for the classic activation of MP under conditions of inflammation, the lipid signalization must be reprogrammed to suppress antiinflammatory factors and activate factors increasing the inflammatory potential.

Transformation of MP into FC on classic activation. Formation of MP/FC during inflammation is caused by changes in the functional activity of lipid sensors of MP. The acute phase of inflammation begins from differentiation of monocytes under the influence of the macrophage colony-stimulating factor (M-CSF). Human MP respond to M-CSF by a decrease in the LXR-controlled expression of ABCG1 and apoE, an increase in the



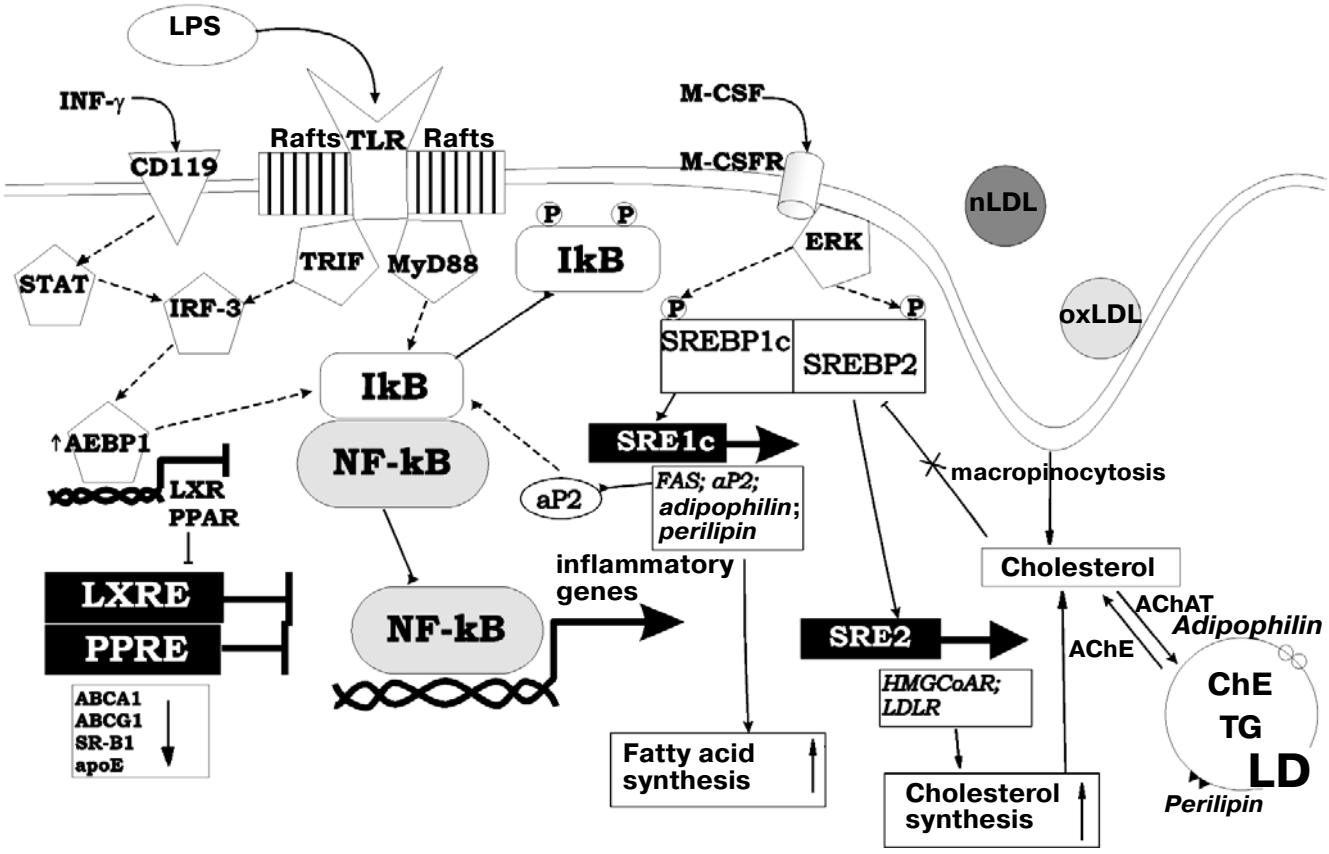
Homeostatic regulation of lipid metabolism in macrophages on their taking up of oxidized LDL in the absence of inflammatory stimuli. Target genes with antiinflammatory features are printed in normal type; target genes with proinflammatory features are italicized. Designations: 15-d-PGJ_2, 15-deoxy-delta-12,14-prostaglandin J_2; ABCA1 and ABCG1, ATP-binding cassette cholesterol carriers; SR-B1, scavenger receptor B1; ERK, kinases regulated by extracellular signals; COX-2, cyclooxygenase 2; LXR, liver X-receptor; LXRE, LXR-responsive element; PPAR, peroxisome proliferator-activated receptor; PPRE, PPAR-responsive element; aP2, adipocytic fatty acid-binding protein; CYP27A1, mitochondrial sterol-27-hydroxylase; LDLR, receptor; NPC1, Niemann–Pick disease C1 type protein; SREBP1c and 2, sterol regulatory element-binding protein 1c and 2; SRE, SREBP-responsive element; SCAP, SREBP splitting-activating protein; INSIG, insulin-induced gene product; StAR, steroidogenic acute regulatory protein; apoE, apolipoprotein E; AChAT, acyl coenzyme A:cholesterol acyltransferase; LD, lipid drop; LDLR, low density lipoprotein receptor; oxLDL and nLDL, oxidized and native low density lipoproteins; oxFA, oxidized fatty acids; AChE, alkaline cholesterol esterase; ChE, cholesterol esters; TG, triglycerides; LPL, lipoprotein lipase

Scheme 1

SREBP2-mediated expression of cholesterol enzyme synthesis that results in the increase in cholesterol concentration in the cells [30]. The influence of M-CSF also leads to an increase in transcription of the SREBP1c-regulated genes and to activation of biosynthesis of fatty acids and phospholipids necessary for phagocytosis by MP [31]. Under these conditions, cholesterol and oxysterols lose their ability to downregulate the transcriptional activity of SREBP2 (Scheme 2). In particular, SREBP is activated through phosphorylation of their nuclear forms by protein kinases ERK1/2 that leads to suppression of their sumoylation, release of the corepressor complex including histone deacetylase 3, and induction of expression of their target genes [32].

Suppression of antiinflammatory functions of nuclear hormonal receptors is the most important prerequisite of the classic activation of MP. There are many data that LPS and IFN-γ suppress the expression of PPARγ1 [33], LXRα, and their target genes [34] (Scheme 2). On the action of LPS *in vitro*, the decrease in the expression of nuclear receptors in MP is most pronounced already after 4 h, which coincides with the maximum expression of proinflammatory cytokines, whereas changes caused by IFN-γ are delayed (their maximum can be observed 16 h later) [35].

In an *in vivo* model of mouse peritonitis, we found a sharp decrease in the protein product and in the DNA-binding activity of PPARγ1, PPARα, LXRα, and RXR



Reprogramming lipid metabolism regulation on classic activation (M1) of macrophages. Designations: TLR, Toll-like receptor; LPS, lipopolysaccharide of *E. coli*; CD119, receptor of interferon-γ1; M-CSF, macrophage colony-stimulating factor; MyD88, myeloid differentiation early response protein; NF-κB, nuclear factor κB; IκB, inhibitor of κB; TRIF, TIR-domain-containing adapter-inducing interferon-β; IRF-3, interferon-regulating factor 3; STAT, protein of Signal Transducers and Activators of Transcription family; P, phosphoric acid residue; AEBP1, adipocytic enhancer-binding protein 1; IFN-γ, interferon γ

Scheme 2

along with a concurrent increase in lipid synthesis in peritoneal MP 18 h after the injection of zymosan [36-38]. LPS from *E. coli* had a similar but the less pronounced effect. Injection of synthetic agonists PPARγ, PPARα, LXR, and RXR prevented the zymosan-induced production of FC [36, 37]. As mentioned above, under normal conditions the uptake of LDL by cells inhibits the ability of SREBP2 to activate LDLR expression (Scheme 1). However, the action of LPS is associated with increased expression of LDLR even under conditions of cell incubation with nLDL [39] (Scheme 2). Moreover, incubation of M1 macrophages with nLDL leads to formation of FC and concurrent induced HMGR expression in MP accompanied by an increase in intermediate products of the mevalonate pathway involved in inflammation. Thus, an increase in the intracellular level of geranyl pyrophosphate promotes inhibition of ABCA1 expression in MP due to an increase in the geranyl-geranylation of RhoA (Ras homolog A of the family of small GTPases).

Ras-proteins of the GTPase superfamily stimulate processes involved in activation of macropinocytosis, in particular, they organize cytoskeleton rearrangement and formation of endosomes. Farnesol induces stress of ER, the NF-κB signaling pathways, and stimulates generation of reactive oxygen species (ROS) [40]. The activation of TLR4 promotes an increase in sphingomyelin synthesis in MP that results in "anchoring" of cholesterol on the plasma membrane and stimulation of autophagy [41].

The ligand interaction not only with TLR4 but also with other types of TLR initiates lipid accumulation in MP. The yeast polysaccharide zymosan (a TLR2 ligand) has high ability to increase the intracellular content of lipids, to stimulate lipid inclusions of protein adipophilin and of a protein binding fatty acids Mal1 in two strains of mouse MP and in transformed human monocytes [6, 42].

LPS of *E. coli* (a TLR4 ligand), double-strand RNA, poly I:C (TLR3 ligands), nonmethylated regions of CpG DNA (a TLR9 ligand), and imidazoquinoline (a TLR7 ligand) have a lower potential for inducing formation of

lipid inclusions. Note that the M1 phenotype is in particular characterized by a high expression of many forms of TLR (except TLR5), which has the bacterial flagellar protein flagellin as an antagonist [14]. However, the influence of TLR5 ligands on the generation of MP/FC is poorly studied.

TLR-dependent mechanisms of repression of PPAR and LXR functions. To realize the transcription of TLR-dependent "inflammatory" genes, it is necessary to release the nuclear receptor corepressor (NCoA) anchored in the promoter by a sumoylated LXR. The activation of the TLR leads to phosphorylation of LXR with involvement of calcium/calmodulin-dependent protein kinase IIγ that results in SUMO detachment from LXR by protease SENP3 and in releasing the complex NCoA component coronene 2A, which interacts with the oligomeric nuclear actin in MP [43]. The repression of the *LXR* and *PPARγ1* genes on activation of the TLR3- and TLR4-signaling pathways occurs independently of MyD88 and NF-κB but is due to an alternative pathway via a transcriptional interferon regulatory factor 3 (IRF3); suppression of this factor prevents a decrease in the expression of LXR-dependent genes [34]. Under conditions of TLR4 activation, an important role in the inhibition of PPARγ1 and LXR signalization is played by adipocytic enhancer-binding protein 1 (AEBP1) [44, 45]. An increase in AEBP1 expression in MP under the influence of LPS is directly associated with the downregulation of expression of genes, protein products, and transcriptional activities of *PPARγ1* and *LXR* and leads to a decrease in the levels of *ABCA1*, *ABCG1*, *apoE*, and *CD36* mRNAs. Concurrently, an additional activation of NF-κB occurs, expression of proinflammatory factors is induced, and TG are accumulated in the cytoplasm [46] (Scheme 2). Mutation analysis has revealed that the *C*-terminal mutant of *AEBP1* is unable to bind with DNA and inhibit the PPARγ1 and LXR expression but retains the ability to induce the inflammatory response. On the contrary, the *N*-terminal mutant of this protein inhibits PPARγ1 and LXR but loses the ability to activate NF-κB. Under the influence of LPS, TNFα, and IL-6 other mechanisms of inhibiting the PPARγ1 expression are realized in MP, thus miRNA-27b is induced, which destabilizes mRNA of *PPARγ1* [47]. TLR4 ligands and cytokines TNFα and IL-1β are shown to suppress the activity of cholesterol-27-hydroxylase (CYP27), to decrease the level of *StAR* mRNA, and also to inhibit synthesis of PPAR coactivators (PPC-1α and SRC-2) [48].

As mentioned above, the M1 phenotype formation in MP is associated with a pronounced increase in the synthesis of fatty acids and TG and in the expression of fatty acid carriers (aP2) and also of lipid inclusion proteins. Inflammatory stimuli concurrently inhibit β-oxidation of fatty acids in mitochondria due to a decrease in the PPARα expression. Under conditions of suppressed mitochondrial oxidation, fatty acids carried by aP2 can induce the signaling pathway NF-κB (Scheme 2) through activation of c-Jun-*N* kinases and kinases of the κB inhibitor (IκB) and acceleration of IκB ubiquitinylation and degradation in proteasomes. Therefore, the inhibition of fatty acid binding with aP2 occurs concurrently with inhibition of cytokine production in MP activated by LPS [49], whereas an increase in the expression of the protein product adipophilin in M1 macrophages is associated with an increase in production of TNFα, the macrophage chemoattractant protein 1 (MCP-1), and IL-6 [29]. Expression of the protein perilipin 3 also associated with lipid inclusions and possessing proinflammatory potential is increased on the incubation of MP with the TLR9 ligand [28].

Thus, reprogramming of lipid metabolism during the classic activation of MP promotes the enhancement of proinflammatory signals, which finally results in formation of the FC phenotype (Scheme 2).

A possible role of MP/FC in development and resolution of inflammatory response. Although experimental data allow us to consider MP/FC as an attribute of inflammation, functions of these cells in the development of inflammation remain unclear. However, during inflammation FC act rather as active producers of lipid mediators than passive lipid reservoirs. Note also that the accumulation of cholesterol, oxysterols, and fatty acids in MP is a trigger of FC apoptosis. Considering these intriguing data, it was suggested that generation of FC could be a part of a program of development and resolution of acute inflammation.

Endogenous ligands of lipid sensors in the development of inflammation. At early stages of inflammation, endogenous ligands of lipid sensors can stimulate immunity acting through mechanisms independent of lipid sensors. At the later stages lipid mediators are synthesized that limit development of inflammation and stimulate its resolution. Thus, the LXR ligand 25-hydroxycholesterol (25HC) secreted by MP in response to LPS can synchronously stimulate the functions of inborn immunity and regulate the adaptive immune response. The rapid expression and activation of cholesterol-25-hydroxylase (CH25H) in MP under the influence of LPS causes an increase in the 25HC level in the incubation medium. Nevertheless, expression of the *CYP7b1* gene encoding the enzyme responsible for the elimination of 25HC does not change [50]. The expression of CH25H increases independently of MyD88 but is inhibited with deficiency of TLR4. In healthy subjects the 25HC concentration in blood increases twofold 4 h after an intravenous injection of LPS. Studies performed in our laboratory have shown that the intracellular concentration of 25HC in peritoneal mouse MP can increase after two injections of LPS later (after 3 days) [51]. The expression and activity of CH25H also increase on STAT1 activation in dendritic cells and in lung macrophages under the influence of IFN-α and IFN-β [52]. Macrophages cultured with 25HC respond

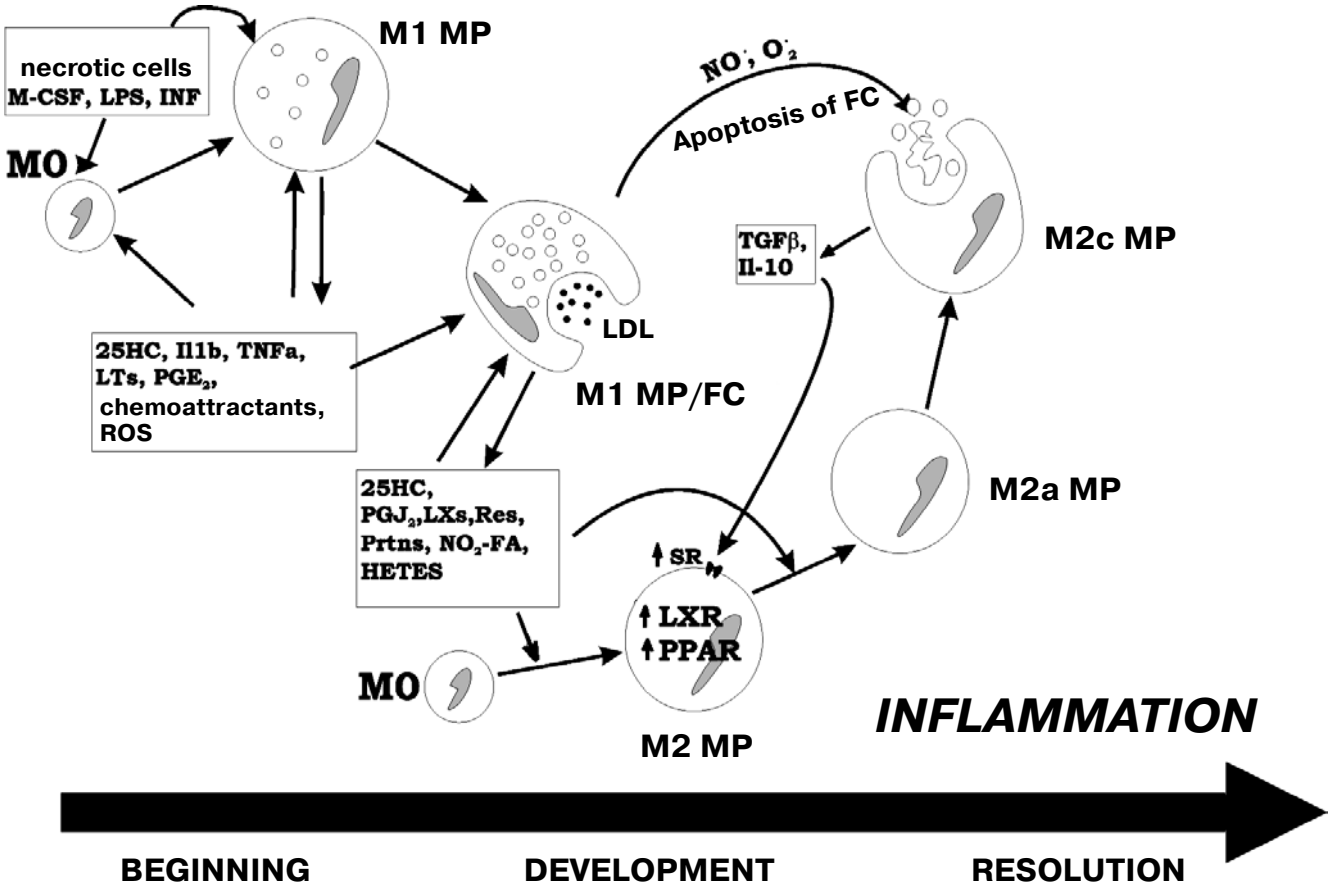
by production of chemokine CCL5, which is required for survival of MP under conditions of viral infection. However, nanomolar concentrations of 25HC inhibit proliferation of B-lymphocytes induced by IL-2, suppress the induction of cytidine deaminase, prevent production of IgA [53], and also inhibit proliferation of lymphocytes and expression of HLA-DR in human monocytes stimulated by lymphokines [54, 55]. In a culture of human MP, micromolar concentrations of 25HC induce a cascade of proinflammatory cytokines and generation of ROS through expression of NADPH oxidase. And the inhibition of MAP kinase and of NF-κB by lycopene prevents the oxysterol-induced expression of cytokines [56]. Moreover, oxysterols manifest themselves as regulators of markers of differentiation of dendritic cells CD80 and CD86 [57]. It seems that the proinflammatory activity of oxysterols manifests itself during the acute phase of inflammation under conditions of LXR suppression. This can explain the exacerbation of chronic inflammation caused by injection of LXR agonists in a model of rheumatoid arthritis [58]. Proteins binding oxysterols OSBP [59] and ORP8 [60] are known to downregulate ABCA1 due to location in atherosclerotic patches of human blood vessels in the same places as activated CD68(+)MP. It seems that OSBP can act as lipid sensors of 25HC in M1 macrophages, which respond to oxysterol signals due to additional decrease in ABCA1 function.

Thus, "elimination" of LXR during the first hours of an acute inflammation can cause a proinflammatory effect of some oxysterols, and this can help to explain contradictions of the data on their involvement in the realization of the inflammation program. However, PPARγ agonists can also enhance the inflammatory signal during the acute phase of the *in vivo* inflammatory response to LPS. Experiments on Vietnamese pigs have shown that injections of the PPARγ agonist rosiglitazone and of its antagonist bisphenol A potentiated and abolished, respectively, the inflammation-inducing effect of LPS [61]. These results can be explained by the known ability of PPARγ agonists to suppress the production and activity of the antiinflammatory factor TGF-β.

Lipid sensor ligands secreted by MP/FC polarize MP into the M2 phenotype. In the first stages of inflammation, the expression in MP of cyclooxygenase (COX), 15/12-lipooxygenase (15/12-LO), and 5-LO increases, which leads to a rapid biosynthesis and secretion of proinflammatory prostaglandins and leukotrienes such as PGE_2, thromboxane, and PGD_2. In the second stage these proinflammatory factors induce biosynthesis of antiinflammatory and repair mediators (lipoxins, resolvins, and protectins [62]) (Scheme 3). Lipid inclusions of MP are experimentally shown to be a place of synthesis and accumulation of arachidonate derivatives, which are active lipid mediators. Induction of generation and accumulation of esters of PGE_2 and 15(S)-HETE in lipid inclusions of MP/FC has been observed when MP are infected with mycobacteria [63] and also upon transfection of the exogenous 15-LO into FC [64]. As early as 12 h after the stimulation of MP with LPS, PGD_2 is found to be actively converted into the endogenous PPARγ ligand 15d-PGJ_2. Concurrently, the expression of inducible nitroxide synthase (iNOS) and the attack by NO radicals of unsaturated fatty acids result in formation of their nitrified derivatives, which in nanomolar concentrations activate PPARγ [65]. And a significant fraction of linoleate nitro-derivatives is located in lipid inclusions of MP as cholesterol esters (cholesterol nitrolinoleate) [66]. Lipid mediators secreted by MP in the late stages of inflammation limit its development and promote its resolution. Lipoxins inhibit the infiltration with neutrophils and eosinophils, activate phagocytosis of microorganisms and apoptotic cells, induce migration of phagocytes from lymph nodes, and realize the antimicrobial mechanisms of defense. The 15d-PGJ_2 manifests various antiinflammatory effects inhibiting the pathways of NF-κB activation and stimulating PPARγ [67]. Oleate nitrite is also known to inhibit adhesion molecules, inflammatory infiltration, and production of foam cells in blood vessels and thus to increase the levels of collagen and α-actin in smooth muscle cells [68]. The phenotype of monocytes recruited into the inflammation focus can be an important function of PPAR endogenous ligands. Synthetic ligands of PPARγ [68] and PPARβ/δ [69] are known to cause monocyte differentiation into M2 MP, which express SR required for a rapid phagocytosis and utilization of apoptotic cells and necrotic masses (Scheme 3). Such properties are demonstrated by lipoxins, which induce migration of macrophages and their polarization into the M2 phenotype of MP capable of active phagocytizing of apoptotic cells [62]. It seems that 15d-PGJ_2 and NO_2-derivatives of fatty acids can also stimulate an alternative activation of MP, but to confirm this hypothesis additional studies are necessary.

The role of PPARβ/δ in the resolution of inflammation is poorly studied. However, deletion of the *PPARβ/δ* gene is known to decrease opsonin expression and lower the clearance of apoptotic cells [70]. The clearance of apoptotic cells in the late stages of inflammation is also realized by LXR agonists, which activate expression of the key factor of phagocytosis transglutaminase through the retinoic acid receptor [71].

Apoptosis as a signal for resolution of inflammation. The classic activation of MP not only reprograms lipid metabolism in MP but can also trigger the "clockwork" of FC death through apoptosis. Studies on the *in vivo* model on zymosan-induced peritonitis have shown that apoptosis of MP can stimulate the resolution of inflammation by influencing its development in the exudate. Zymosan-induced peritonitis is a biphasic process, the second stage of which is associated with apoptosis of ~20% of MP [72], a recovery and increase in the levels of PPAR-γ and LXR-α, and a high secretion of TGF-β1 in MP [38]. The M1



Involvement of macrophage/foam cells in the development and resolution of an acute inflammatory response. Designations: 25HC, 25-hydroxycholesterol; HETEs, hydroxyeicosatetraenoic acids; IL-10, interleukin 10; IL-1β, interleukin 1β; IFN, interferon; LPS, lipopolysaccharide of *E. coli*; LTs, leukotrienes; LXs, lipoxins; NO_2-FA, NO_2-derivatives of fatty acids; PGE_2, prostaglandin E_2; PGJ_2, prostaglandin J_2; Prtns, protectins; Res, resolvins; SR, scavenger receptors; TGFβ, transforming growth factor β; TNFα, tumor necrosis factor α; ROS, reactive oxygen species; M0, non-stimulated monocyte of the M0 phenotype; LD, lipid drop

Scheme 3

MP apoptosis is thought to be a result of generation of NO radicals, which increase expression of the protein CHOP homologous to CCAA/enhancer-binding protein (C/EBP) and the development of ER stress [73] (Scheme 3). The induction of apoptosis can also be contributed by fatty acid nitroalkanes produced as a result of generation of NO radicals via stimulation of the caspase cascade [74] and oxysterols acting through protein kinases, the cytochrome *c* release from mitochondria and stimulation of death receptors, such as Fas. MP (with an apparent M2c phenotype) specialized for apoptotic cell uptake via interaction with the phosphatidylserine receptor [75] and induction of its signaling pathways actively secret the antiinflammatory factor TGF-β1 (Scheme 3), which stimulates synthesis of the lipoxin A4, 15-HETE, and expression of PPAR-γ, but inhibits biosynthesis of thromboxane and generation of NO radicals [76] and restores lipid metabolism regulation in MP due to stimulation of expression of apoE [77], PPARγ [78], ABCA1, ABCG1, and SR-B1 via LXR-mediated signaling pathways [79].

Thus, MP/FC can be considered as active contributors to the organization and resolution of acute inflammation (Scheme 3).

Bacteria use lipid sensors of the host. Some pathogens induce synchronization of inflammation using for their survival lipid sensors of MP and stimulating an alternative activation of MP with a low production of cytotoxic oxygen radicals. *Pseudomonas aeruginosa* [80] and *Toxoplasma gondii* [81] secrete their own LO that converts arachidonic acid into 15-HETE, which provides for PPAR-γ expression and switches on the immune response "stop-signal" in infected MP. *Tropheryma whipplei* activates SR, CD14, the receptor signal inhibitor of IL-1 (IL-1ra), and IL-10 polarizing MP into the M2 phenotype and thus creating favorable conditions for its reproduction [82]. Apoptosis is lethal for many pathogens. Therefore, *Listeria monocytogenes* induces CH25H activity and CD5l expression in infected mouse MP due to inhibition of caspase 1 and increase in cell survival [83]. The LXRα-deficient mice are resist-

ant to infection with *L. monocytogenes* that is associated with a high level of production of NO radicals and IL-1β in MP [84]. Some pathogens need cholesterol for supporting their activity. Thus, for growth of *T. gondii* cholesterol is necessary, and it is delivered into the infected cells through LDLR [85]. Mutation analysis of the *mce4* and *igr* loci of virulent forms of *M. tuberculosis* has revealed that *mce4* is required for active import of cholesterol into the mycobacteria and for its accumulation in the bacterial lipid-free wall [86]. In the bacterial membrane region of cholesterol accumulation it is degraded with involvement of the *igr* locus [87] containing the *CYP125A1* gene and genes of other enzymes of cholesterol metabolism. Mutations of these genes or deficiencies of these enzymes significantly decrease the persistence of bacteria due to toxic effect of cholesterol on the respiratory chain of the bacteria. It should be noted that monooxygenases encoded by the *CYP125A1* and *CYP142* genes of *M. tuberculosis* catalyze production of the LXR ligand 27HC, which is later metabolized to intermediate products: alcohols, carbonyl acids, and aldehydes. Deficiency of C27-monooxygenase in the mycobacteria prevents their growth in a cholesterol-containing medium.

Mice infected with *M. tuberculosis* demonstrate increased expression of LXR-β in lung cells. Deficiency of two LXR isoforms is associated with increased sensitivity to infection, increased production of FC, and decreased function of neutrophils [88]. Note that injection of a synthetic agonist of LXR can significantly suppress bacterial invasion of the lungs due to activating Th1/Th17 lymphocytes.

Generation of MP/FC on mycobacterial infection. *Mycobacterium tuberculosis* is thought to activate MP through TLR2 [15] and this probably stimulates MP/FC generation by the above-described scenario of reprogramming of lipid metabolism (Scheme 2). However, MP/FC infected with *M. tuberculosis* are characterized by increased expression of PPARγ, which depends on the virulence of the strain under study [89, 90]. Virulent mycobacteria contain membranous lipoarabinomannan, which interacts with mannose receptors of MP and stimulates the MAPK-p38-caused increase in activity of phospholipase A_2 and release of arachidonate required for synthesis of PPARγ ligands. The deficiency of PPARγ in MP promotes an increase in TNF production and decelerates intracellular growth of bacteria. Attenuated BCG mycobacteria stimulate PPARγ less pronouncedly. And the expression of PPARγ is not induced on TLR2 deficiency in MP but depends on the TLR2-mediated increase in expression of IL-8 and COX2. Moreover, PPARγ antagonists inhibit the formation of lipid inclusions and synthesis of PGE_2 caused by the death of the BCG mycobacteria, whereas PPARγ agonists, on the contrary, promote the mycobacteria proliferation. Virulent and avirulent strains of *M. tuberculosis* are also different in their ability to stimulate apoptosis or necrosis of infected MP [91]. As differentiated from avirulent mycobacteria stimulating in MP synthesis of proapoptotic PGE_2, the virulent mycobacteria induce production of lipoxin A4 due to inhibition of PGE_2 synthesis [92]. Suppression of apoptosis by lipoxin A4 is closely related with its ability to inhibit iNOS activity and Ca^{2+} release into the cytoplasm that prevents the Ca^{2+}-dependent fusion of lysosomes with the plasma membrane, which is necessary for membrane repair in apoptosis. Damages of the inner mitochondrial membrane under these conditions lead to cell necrosis that significantly enhances chances for the bacteria to survive. Deficiency of PGE synthase in mouse macrophages is also favorable for proliferation of virulent forms of the mycobacteria.

Generation of MP/FC under conditions of "infectious" atherosclerosis. Bacteria stimulating the development of atherosclerosis demonstrate an increased ability to convert MP into FC. Under the influence of alive or inactivated *Chlamydia pneumoniae*, MP/FC are generated by the classic pathway of MP activation (Scheme 2) via TLR2, TLR4, the MyD88 adaptor, signaling proteins IRF3 and TRIF [93], including JNK activation [94] that results in a decrease in the PPARγ1 expression. Retinoic acid, which is a synthetic agonist of LXR and a ligand of the orphan receptor (relative to retinoid receptors) [95], prevents MP/FC formation. An essential role in pathogenesis of atherosclerosis caused in mice by *Ch. pneumoniae* belongs to IL-17. IL-17-deficient mice are resistant to atherosclerosis despite a high blood level of cholesterol. It should be emphasized that the T-lymphocyte subclass of $CD4^+$Th helpers producing IL-17 is involved in development of such autoimmune diseases as asthma, rheumatoid arthritis, Crohn's disease, multiple sclerosis; the blood level of IL-17 increases on exacerbation of these diseases. Moreover, three isoforms of PPAR and LXR are involved in the regulation of cell differentiation of Th17 lymphocytes. LXR agonists inhibit IL-17 expression in splenocytes in autoimmune encephalitis in mice, and therefore the possibility of their use in therapy of this disease is under consideration.

Generation of MP/FC is required for HIV replication. Some viruses induce reprogramming of the lipid metabolism in MP transforming them into FC. For entrance, assemblage, and exit many viruses (HIV, Ebola, Marburg, influenza) use as platforms rafts enriched with cholesterol and sphingomyelin [96]. Late stages of HIV replication in MP need cholesterol and its delivery into specialized rafts where the assemblage of the virus particles occurs. Moreover, for HIV transmission from dendritic cells into T-lymphocytes a high content of cholesterol in rafts is also required. The negative factor (Nef) expressed at the early stages of infection plays an important role in the HIV-caused rearrangement of the cholesterol metabolism in MP. The interac-

tion of Nef with cholesterol results in its transport into the rafts. In HIV-infected MP, LDLR expression and HMGR activity are increased, and this is characteristic for MP polarization into the M1 phenotype stimulated through TLR3 by double-strand RNA (Scheme 2). The transfection of Nef into mouse MP induces a decrease in ABCA1 activity and inhibits apoA1 internalization leading to increase in cholesterol ester synthesis and formation of typical MP/FC [97]. MP infected with cytomegaloviruses also display low activity of ABCA1 carriers as a result of their intracellular cleavage by the Ca^{2+}-dependent cysteine proteinase calpain. However, analysis of the *ABCA1* gene mutations has shown that a decrease in ABCA1 activity caused by the Nef protein of HIV is not associated with the calpain-caused ABCA1 proteolysis but occurs because of increased ABCA1 degradation in proteasomes [97]. Both *in vitro* and *in vivo* studies have shown that PPARγ and PPARα agonists inhibit the replication of the virus [98] and concurrently decrease the production of proinflammatory cytokines in MP. The endogenous PPARγ ligand 15d-PGJ_2 can inhibit HIV replication in the U937 line of human MF and covalently bind with the thiol group of cysteine of a transactivator of expression of the gene *Tat* (HIV protein) and suppress the replication of the virus independently of the negative influence on NF-κB-dependent pathways [99]. Synthetic LXR ligands inhibit HIV replication in dendritic cells more efficiently than PPARγ ligands and also prevent the transfection of virus into lymphocytes [100]. The inhibition of HIV replication by the LXR agonist TO-901317 in lymphocytes, macrophages, and lymphoid cells *ex vivo* and in infected mice of the RAG-hu line *in vivo* is associated with stimulation of the ABCA1 function [101]. Infection with HIV is often associated with development of atherosclerosis and tuberculosis. Therefore, using selective LXR ligands seems promising for treatment of these three diseases.

Thus, the data presented indicate that the M1 polarization of monocytes and MP includes the reprogramming of the lipid sensor regulation and formation of MP/FC, which are important attributes of inflammation and active components of its development and resolution. However, under conditions of an insufficient apoptosis of FC, a disturbed balance of secretion of pro- and antiinflammatory mediators in MP, or deficient clearance of apoptotic cells, FC can indicate and provoke the exacerbation of chronic inflammation.

It must be emphasized that the PPAR and LXR lipid sensors can be compared with key "levers" of management of lipid metabolism and immune functions of macrophages and considered as molecular pharmacologic targets not only in atherosclerosis, but also in various infectious and autoimmune diseases.

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