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SIGNALING FUNCTIONS OF FATTY ACIDS IN THE PLACENTA

This review summarizes the current understanding of FA-activated signal transduction systems in the placenta. Their effect on membrane and nuclear receptors, as well as their participation in the processes of decidualization and modulation of inflammation in the placenta, associated with G-protein-coupled receptors, has been shown. The effects of peroxisome proliferator-activated receptors mediated FAs in the placenta are described. Particular attention is paid to the Toll-mediated inflammatory signaling pathways of the FAs in the placenta. Research data on the effect of FAs on the expression of genes involved in placenta angiogenesis are summarized.

These data demonstrate that FAs and their derivatives are signaling molecules that regulate the metabolic and inflammatory processes in the placenta through a family of trans-membrane receptors associated with G-protein and Toll-like receptors that activate pro-inflammatory transcription factors: activating protein-1, nuclear factor kappa B and anti-inflammatory nuclear transcription factors - PPAR. Saturated FAs and unsaturated FAs in the placenta activate inflammation and apoptosis via TLR2/TLR4, while ω-3 polyunsaturated FAs inhibit their expression and further pathways of inflammation, which is associated with their anti-inflammatory effect.

In this review, FAs are considered as signaling molecules involved in the regulation of implantation, placentation, trophoblast differentiation, angiogenesis, modulation of inflammation and apoptosis in the placenta, and the pathogenesis of pregnancy complications.

Keywords: lipids, fatty acids, receptors, signal transduction, pregnancy, placenta.

Introduction. It has now been established that FAs are not only structural components of cell membranes and energy substrates, but also act as signaling molecules that regulate cell function. FAs modify the activity of phospholipases, protein kinases, G-proteins, adenylate and guanylate cyclases, as well as ion channels and other biochemical events involved in stimulus-response interaction mechanisms.

The effect of FAs on the signal transmission pathway can be direct and / or indirect (by the catabolic conversion of arachidonic acid-AA to eicosanoids). However, studies clearly show that FAs themselves are molecules of the messenger and modulator of several signal transduction pathways [14, 25, 34].

FAs can function as signaling molecules, acting through receptors in the cytosol or on the cell surface. Most of the effects of FAs in the placenta are mediated by their nuclear receptors that regulate transcription. The interaction of nuclear receptors with the FAs ligand leads to the formation of a ligand-receptor complex with subsequent translocation into the nucleus and activation of the expression of specific genes.

Depending on the structure of the carbon chain, FAs can act as inhibitors or activators of gene expression by directly regulating the activity of nuclear receptors (PPAR, X-receptor of the liver, nuclear factor of hepatocytes 4α) and transcription factors (sterol regulatory element-binding protein (SREBPs), protein binding elements sensitive to carbohydrates and NF-kB) or indirectly, through physicochemical changes in the properties of the membrane and activation of signal transmission paths [26].The study of the signal functions of FAs and their derivatives for a long time remains an important scope of an inquiry in medicine and biology due to the diversity and importance of the functions performed by these compounds. Despite the observed progress in this research area, comprehensive reviews, including new data on the mechanisms of signal transduction of FA in the placenta, have not yet been conducted.

The search for scientific publications in PubMed, Google Scholar databases was conducted. Information search was about the signal function of the FAs in the placenta. Notice has been focused on studies of FAs signaling pathways mediated by G-protein receptors (G-protein receptors 120, 41, 43), PPAR γ, Toll-like receptors (TLR2 and TLR4). Articles were searched in English and Russian using keywords in various combinations. All abstracts and full-text articles have been considered, and the most relevant are included in this review. The literature review used an analytical research method.

The action of fatty acids through membrane receptors. As pointed above, FAs can affect cells through several different mechanisms, including receptors on the surface of the cell. Recently, there is increasing evidence that FAs serve as natural ligands for a group of G-protein coupled receptor (GPCRs), which are called free FAs receptors, essentially intertwining metabolism and immunity in several ways, for example, by regulating inflammation and secretion of peptide hormones. Several receptors that are activated by free FAs with different chain lengths have been identified and characterized. So, A. Hirasawa et al. (2005) identified the G-protein receptor (GPR) 120 as a long chain polyunsaturated fatty acid (LC PUFA) receptor [15], which is involved in the regulation of various cellular and physiological functions, including during pregnancy, and mediates anti-inflammatory and insulin-sensitizing effects of docosahexaenoic acid (DHA) [10].

The data obtained in the study of the placenta in obese women showed that GPR120 is expressed mainly in the microvilli of human placenta and its expression level does not changes depending on the mother's body mass index. Thus, it was found that FAs in maternal circulation can affect the cellular transmission of trophoblast signals mediated by activation of the GPR120 receptor [13]. Other researchers have shown the involvement of GPR120 in the processes of decidualization during pregnancy. GPR120 stimulates decidualization processes by enhancing the absorption of glucose and the pentose phosphate pathway of human stromal endometrial cells. The

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enhancement of decidualization with GPR120, in researcher's opinion, can be mediated by the signaling pathway ERK1/2-MAPK-FOXO1 [29]. However, the functional significance and subsequent effects of GPR120 activation in the placenta have yet to be determined.

Other G-protein coupled receptors studied in the placenta are GPR41 and GPR43, which have been identified as short-chain FAs receptors (S-CFA). Studies conducted by C. Voltolini et al. (2012) showed the role of GPR43 expression in the tissues of the uterus and placenta, as well as the importance of S-CFAs themselves in modulating inflammatory reactions in the in fetuses born to women at term and in preterm delivery. At the same time, there was an increased expression of GPR41 and GPR43 in the myometrium and fetal membranes in women with preterm birth. The action of S-CFAs contributed to a decrease in lipopolysaccharide-induced expression of inflammatory genes, including IL-6, IL-8, COX-2, IL-1α, intracellular adhesion molecule-1, and platelet-endothelial cell adhesion molecule-1 [4]. Thus, while studying the interaction of GPR43 - S-CFAs, the authors showed new ways of regulating inflammatory processes during childbirth.

The action of fatty acids through nuclear receptors. Other mechanisms associated with the effects of FAs relate to their ability to bind to PPAR. There are three PPAR isotypes: PPAR*α*, PPAR*γ* and PPAR*β/δ.* Several studies have demonstrated the role of PPAR in implantation, placentation, trophoblast differentiation, and angiogenesis [35]. PPAR*γ*, like other nuclear receptors, binds lipophilic ligands and regulates transcription in the active state. Among endogenous PPAR*γ* ligands, unsaturated, oxidized, and nitroxylated FAs, AA metabolites were found: 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, 15-hydroxyeicosatetraenoic acid, 9-hydroxyoctadecadienoic acid, 13-oxo-octadecadienoic acid, phosphatasidinoic acid, components of oxidized low-density lipoproteins (LDL) [34]. Some studies show that PPAR*γ* are able to bind not one specific FA, but whole FAs patterns, including two FA molecules simultaneously. Such binding of the ligand, according to the researchers, indicates that PPAR*γ* is not a specific factor of FA alone, but a sensor of the intracellular mixture of FAs, the ratio of which may affect physiological processes. Moreover, FAs and their derivatives (eicosanoids) have been shown to regulate gene expression through direct interaction with PPAR*α* and PPAR*γ* [22].

Summarizing the results of studies about the role of PPAR*γ* in the processes of trophoblast invasion and the growth of human placenta, F. Wieser, L. Waite, C. Depoix, R.N. Taylor (2008) indicate that PPAR*γ* is expressed in the invasive trophoblast in the first trimester of pregnancy, while PPAR*γ* expression is shown in the syncytio and cytotrophoblast of the anchoring villi in the second trimester. In the third trimester, PPAR*γ* is localized mainly in the extravillous trophoblast and villus syncytiotrophoblast, where this transcription factor regulates the secretion of placental hormones [27].

The important role of PPAR*γ* in the differentiation of trophoblasts and the growth of placenta is also emphasized by studies using agonists. The main processes of placental growth were evaluated by V. Garnier et al. (2015) in the absence or presence of prokinetin receptor antagonists (PROKR) 1 and PROKR2. Both in human trophoblast cells and in placental explants, the researchers demonstrated that rosiglitazone, a PPAR*γ* agonist, increased secretion of EG-VEGF, expression of EG-VEGF mRNA and its receptors, and also increased the process of placental vascularization through PROKR1 and PROKR2; but at the same time inhibited trophoblast migration and invasion via PROKR2 [28].

J. Zhang et al. (2017) showed that PPARγ has a pro-angiogenic effect on the growth of animal placenta. This transcription factor mediates the vascularization process by modulating isoforms and receptors of vascular endothelial growth factor (VEGF): VEGF120/VEGFRs, VEGF188/VEGFRs and PlGF/VEGFRs by enhancing the expression of angiopoietin-1 mRNA. In addition, the authors suggest that PPARγ can interact with hypoxia-induced factor (HIF) and thereby activate VEGF transcription. Therefore, PPARγ can be involved in the process of angiogenesis by stimulating the adhesion, proliferation and migration of endothelial cells, as well as by enhancing the formation and stability of capillary-like tubules [25]. Thus, the researchers proved that different VEGF isoforms and VEGFR subtypes can be differently involved in different stages of the angiogenic process and differentially regulate vascularization processes.

PPARγ is also known for its role in promoting the accumulation of lipids in the placenta. An increase in PPARγ activity increases FAs absorption and accumulation in primary human trophoblast cells by regulating the expression of fatty acid binding proteins (FABP). In turn, it was shown that oxidized LDLs are able to activate PPARγ in primary cytotrophoblast cells and even inhibit trophoblast invasion [21]. Therefore, the authors conclude that PPARγ regulates and is itself regulated by lipid metabolites. At the same time, the potential role of PPARγ in the regulation of oxidative stress in the placenta across pregnancy is emphasized. PPARγ plays an important role in many metabolic pathways during placentation and across pregnancy. These include trophoblast differentiation, inflammatory and oxidative reactions, nutrient sensitivity, in particular FAs metabolism. Thus, one of the mechanisms of FAs signal transduction in the placenta is the regulation of gene expression by direct activation of the PPARγ nuclear receptor.

Toll-mediated signaling pathways of fatty acids in the placenta. FAs are able to stimulate an inflammatory response through the signaling pathway of Toll-like receptors (TLRs). TLRs refer to pattern-recognizing receptors that respond to the constituent elements of various pathogens, the so-called molecular patterns. In particular, they distinguish the molecular structures of various causative agents of infectious diseases, they are expressed on the surface of cells of the myelomonocytic line, endothelial and epithelial cells, as well as on the surface of placental cells, uterine and trophoblast epithelial cells [17]. The ligands of these receptors are both components of microorganisms and saturated fatty acids (SFA). SFAs are an important component of bacterial endotoxins. Lipid A lipopolysaccharide (LPS) contains 6 SFAs and 2 phosphate residues. The carbon chain length of these acids in lipid A varies from 12 to 16 carbon atoms. An interesting fact is that the replacement of SFA mono- or PUFA reduces the pro-inflammatory activity of LPSs. It was shown that SFAs acylated on lipid A of LPS or bacterial lipoproteins playing an important role in ligand recognition and activation of TLR4 and TLR2 [14]. A specific ligand for TLR4, which is a single chain transmembrane protein, is LPS from the wall of gram-negative bacteria. A specific ligand of TLR2 is a bacterial lipoprotein. In the process of binding TLRs to ligands, their coreceptors also have a role: CD14 (lacking an intracellular part) and MD-2, which increase the affinity and stability of the whole complex. The activated signaling transduction after binding of LPSs or bacterial lipoprotein is provided mainly by the adapter molecule MyD88 (myeloid differentiated factor 88). At the final stage of intracellular signal chains, there is a nuclear transcription factor NF-κB, which, moving from the cytosol to the cell nucleus, stimulates the expression of genes

encoding the synthesis of inflammatory regulatory substances, including cytokines, chemokines, and other components of the immune system [20]. However, it has been shown that TLR4 can also transmit signals independently of MyD88. This signaling occurs through an adapter protein containing a Toll/IL-1 receptor domain that induces IFN-β (TRIF), which not only activates the NF-κB pathway, but also leads to phosphorylation of regulatory factor-3 IFN (IRF-3) [17].

In human placenta, mRNA expression of ten TLR, coreceptors, and auxiliary proteins was established. However, we focused on the TLR4 and TLR2-mediated FAs signaling pathways in the placenta.

Currently, it has been established that SFAs and PUFAs differently regulate placental viability, antioxidant ability, inflammation and the effects of gram-positive and gram-negative endotoxins [32].

The combination of many studies shows the activation of TLR4 SFAs and their inhibition of PUFAs caused by both SFAs and LPSs. However, data were obtained proving the mutual modulation of the activation of TLR4 SFA (lauric - LA) and PUFA - (DHA) by regulating the dimerization and recruitment of TLR4 to lipid rafts. In addition, it was found that the dimerization and recruitment of TLR4 to lipid rafts were associated events mediated by the generation of NADPH oxidase-dependent reactive oxygen species. These results provide a new understanding of the mechanism by which FAs differentially modulates the TLR4-mediated signaling pathway and subsequent inflammatory responses that are involved in the development and progression of many chronic diseases [14]. X. Yang et al. (2015) investigated the effect of FAs on the synthesis and secretion of cytokines in trophoblast cells isolated from human placenta. It has been demonstrated that SFAs (stearic - SA and palmitic - PA) stimulate the synthesis and release of TNFα, IL-6 and IL-8 by trophoblast cells, while HUFA (palmitoleic, oleic - OA, linoleic - LNA) do not significantly affect expression of pro-inflammatory cytokines. Moreover, the authors note that palmitate-induced inflammatory effects are mediated by activation of TLR4, phosphorylation, and nuclear translocation of NF-kB [31]. In animal experiments, it was also shown that a high concentration of PA in the uterine endometrium induces the development of oxidative stress and high secretion of pro-inflammatory cytokines (IL-6, IL-8, TNFα) by activating the NF-κB signaling pathway [24]. Therefore, activation of TLR4 in the placenta leads to the recruitment of the transcription factor NF-kB and an increase in the synthesis of proinflammatory cytokines, and the induction of TLR4 pathways under the influence of FAs largely depends on the length of their carbon chain and the number of double bonds.

Other authors have shown that SFAs (LA, PA, and SA) can induce the expression of cyclooxygenase-2 (COX-2) via NF-kB-dependent mechanisms in macrophage cell lines. It was noted that LA had the highest ability to activate COX-2 via TLR4. Unlike SFAs, monounsaturated and PUFAs did not contribute to TLR4 signal activation. In addition, it was indicated that pretreatment of in vitro cells with DHA and OA significantly reduced the pro-inflammatory effect caused by LA and contributed to the reduction of inflammation [30]. The obtain results indicate that the TLR4 signaling pathway can be modulated by PUFA.

There is evidence showing the involvement of TLR2 in the induction of COX-2 and prostaglandin E2 in trophoblast cells via the NF-kB and MAPK pathways [33]. Thus, SFA and bacterial products (LPS) induce pro-inflammatory reactions by binding to TLRs, activating JNK and p38 MAPK signaling and downstream transcription factors.

Other options that FAs can function as TLR signaling pathway modulators are studies by S. Lager, F. Gaccioli, V.I. Ramirez (2013), who showed that OA regulates cellular signaling and placental transport of amino acids via TLR4, by increasing the phosphorylation of the JNK signal protein and activator of transcription 3 (signal transducer and activator of transcription, STAT3) [18]. Later it was found that DHA, OA and PA FAs differentially regulate trophoblast amino acid transport. DHA promotes inhibition of cell trophoblast signaling (p38 MAPK, STAT3 and mechanical target of rapamycin (mTOR) and amino acid transport activity. On the contrary, OA increases amino acid transport and phosphorylation of ERK, mTOR, S6 kinase 1 and rpS6. The combination of DHA with OA increases the transport of amino acids and phosphorylation of rpS6. PA does not affect the transport of amino acids, but it contributes to a decrease in the expression of Iκ-Bα [19].

Thus, FAs mediate the inflammatory response in the placenta via the TLR signaling pathway. However, the exact molecular mechanisms regulating pro-inflammatory reactions in the placenta remain to be determined.

Recently, research of TLR-mediated trophoblast apoptosis has been of great interest. It was shown that some pathogenic microorganisms can cause apoptosis in the trophoblast, and TLR mediate this process. In trophoblast, apoptosis can be activated via TLR2 and TLR4 [3].

Three microRNAs (miRs) have been identified that regulate TLR2-mediated responses in human trophoblast cells: miR-329, miR-23a and let-7c. Activation of TLR2 by bacterial peptidoglycan (PDG) induces the expression of miR-329, which plays a key role in the regulation of trophoblast apoptosis and inhibition of IL-6 expression by targeting the p65, the NF-κB subunit. Other researchers indicate that overexpression of TLR6 blocks apoptosis, production of IL-6 and IL-8 by trophoblast cells [3].

The results obtained indicate that TLR10 is highly expressed in trophoblast cells in early pregnancy, as well as the important role of TLR10 in stimulating PDG-induced apoptosis.

There are publications that show that trophoblast cells respond to the viral ligand via the TLR3 system. TLR3 is able to recognize mRNA of viruses located in the genital tract of women - herpes simplex virus, human papilloma virus, hepatitis B and C virus, cytomegalovirus, HIV. Data are also presented on the role of TLR2 in the identification of herpes simplex virus type I and cytomegalovirus [3].

The trophoblast apoptosis associated with the infection attracts close attention as an alternative mechanism of placental pathology. To date, there is enough information about the role of FAs in the implementation of apoptosis in trophoblast cells. It was shown that FAs can act either as inducers of apoptosis, in the case of a high content in the extracellular space, or inhibit this process in the placenta [8]. We found a cytomegalovirus-dependent induction of oxidative stress and an imbalance of FAs triggering apoptosis of trophoblast cells [1]. However, it should be noted that the molecular mechanisms of the implementation of cell apoptosis are determined not only by the action of free radical molecules, but also by a signal-transmitting system of lipid nature, including AA and PA. The induction of placental apoptosis in viral infection, apparently, is the result of the action of PA on the membrane of the endoplasmic reticulum, which, as shown by studies, causes modulation of lipid components and creates an unfavorable environment for the correct conformation of the protein, both along the proteasome and non-proteasome pathways. According to T. Liu et al. [24], PA can cause endoplasmic reticulum stress associated with increased expression of the proapoptotic transcription factor CHOP and activation of Akt.

According to Y. Zhang et al. (2011), PA induces caspase-3 and apoptosis [12], which is also confirmed by our studies [2]. The mechanism by which PA induces endoplasmic reticulum stress can be associated with TNF-induced apoptosis realized through activation of the nuclear transcription factor NK-kB [23]. The data presented emphasize the need for further research to elucidate the detailed molecular mechanisms underlying the FAs signal transduction in the placenta.

Fatty acids and expression of genes involved in angiogenesis. A number of studies have been conducted to research the effect of FAs on the expression of genes involved in angiogenesis. G.M. Johnsen et al. (2011) investigated the effect of PUFAs (AA, eicosapentaenoic - EPA, DHA and OA) on tube formation (as a measure of angiogenesis) and on the expression of genes involved in angiogenesis (VEGF and angiopoietin-like protein 4 - ANGPTL4) on the trophoblast cell line HTR8/SVneo. It was shown that only DHA upregulated the expression level of VEGF mRNA, while the remaining PUFAs stimulated the expression of ANGPTL4 mRNA. This study demonstrated that PUFAs selectively affects the placentation process through pro-angiogenic action [11]. Evidence of the selective effect of various FAs on angiogenesis, expression of lipid metabolic genes in a cell model was the study of S. Basak, A.K. Duttaroy (2013), which shows the dependence of the angiogenic properties of FAs (AA, EPA, DHA, OA) on their level of saturation. It has been demonstrated that DHA has the highest angiogenic properties; further, the angiogenic effect of FAs decreases in the following order: EPA>AA>OA [7]. It was also confirmed that DHA and conjugated linoleic acid (LNK) mediate angiogenesis in placental cells in the first trimester through stimulation of gene expression not only of the main angiogenic factors (VEGF and ANGPTL4), but also by increasing the expression of intracellular proteins that bind FAs (FABP), FABP4 and FABP3, which are known to directly modulate angiogenesis [5].

Studies of S. Basak, A. Sarkar, S. Mathapati, A.K., Duttaroy (2018) are also indicate the pro-angiogenic role of FABP4 in the cells of the first trimester placental trophoblast. They showed the effects of exogenously added FABP4 (Exo-FABP4) and its inhibitor (BMS309403) on cell growth, proliferation, and tube formation (as a measure of in vitro angiogenesis) in HTR8/SVneo. The dose-dependent pro-angiogenic effect of FABP4 was noted. Exo-FABP4 stimulated gene expression of pro-angiogenic mediators, such as a tissue inhibitor of matrix metalloproteinase-1 (TIMP1), insulin-like growth factor (IGF1), and prokinetin 2 (PROK2) [9].

It should be noted that the expression of FABP4 in trophoblast cells increases under the action OA, and VEGF [63]. It was also shown that expression of FABP1, FABP3, FABP4, and FATP2 is regulated by HIF-1α and/or HIF-2α in placentas of women with preeclampsia [16]. In addition, it was found that the c9, t11-cisLNA isomer can regulate angiogenic processes during early placentation through increased expression and other pro-angiogenic factors such as COX-2 and adipose differentiation-related protein (ADRP), with a concomitant increase in DHA absorption in these cells [6]. Consequently, PUFAs stimulate placental angiogenesis through gene expression of both major angiogenic factors (VEGF, ANGPTL4) and other pro-angiogenic mediators (FABPs, eicosanoids, COX-2, ADRP).

Conclusion. Thus, scientists are currently paying much attention to the mechanisms of signal transduction of FAs in the placenta. Despite a sufficiently large number of studies, many regulatory mechanisms and components of signaling systems in the placenta, associated with FAs and their derivatives, remain unknown. However, despite outstanding issues, convincing evidence suggests that FAs are a separate class of lipid mediators acting on PPARγ, TLR1, TLR2, GPR120, GPR41, GPR43 receptors that activate various signal transduction systems and have a wide range of regulatory effects in the placenta. PPARγ, TLR, GPR and other FAs receptors were involved in the processes of implantation, placentation, differentiation of trophoblasts and angiogenesis, modulation of inflammatory responses, placental apoptosis, pathogenesis of the most common disorders across pregnancy. This fact provides a sustainable interest to the study of FAs receptors from both fundamental science and the pharmacological industry. The presented data expand the understanding of the mechanisms of FAs signal transduction and emphasize the need for further targeted study of the unique aspects of FAs signal functions in the placenta, which will allow us to move from fundamental research to practical aspects of the use of these substances in obstetrics and perinatology.

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