UTU Publishing Group

Bulletin of Biomedical Science

Journal Homepage: www.utu.com.sg

REVIEW

The Interaction between Polyunsaturated Fatty Acid Metabolites and Nuclear Receptors in Metabolic Diseases

Wenjing Xiu[1#], Jinjie Duan[2#], Guangyan Wang[1], Chunjiong Wang[1]

[1]Department of Physiology and Pathophysiology; NHC Key Laboratory of Hormones and Development, Chu Hsien-I Memorial Hospital and Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin 300070, China.
[2]School of Public Health, Tianjin Medical University, Tianjin 3000070, China.
[#]These authors equally contributed to this article

ARTICLE INFO

Received 20 December 2023
Accepted 6 January 2024
Online 26 January 2024

KEY WORDS:
Polyunsaturated fatty acids;
Bioactive lipids;
Nuclear receptors;
Metabolic diseases

Abstract

Polyunsaturated fatty acids (PUFAs), such as arachidonic acid, linoleic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), can be metabolized into a large number of bioactive lipids. These PUFA derivates play an important role in signal transduction by binding with nuclear or membrane receptors. A variety of PUFA metabolites have been reported to be involved in the regulation of glucose and lipid metabolism and participate in the development of metabolic disorders such as obesity, insulin resistance, nonalcoholic fatty liver disease and atherosclerosis. In addition to G protein-coupled receptors, nuclear receptors are important for mediating the effects of PUFA metabolites. On the other hand, nuclear receptors also act as upstream of PUFA derivates by regulating the expression of enzymes involved in PUFA metabolism. In the current review, we focused on the effects of PUFA metabolites on metabolic diseases by interacting with nuclear receptors.

Introduction

Nuclear receptors (NRs) belong to the ligand-dependent transcription factor superfamily. Endocrine hormones, lipid metabolites, exogenous biological agents, and drugs can serve as ligands of nuclear receptors to regulate their activities. Currently, the human NR superfamily includes 48 transcription factors (De Bosscher et al., 2020). NRs bind with DNA response elements in the form of monomers, homodimers or heterodimers or bind with other transcription factors to regulate gene expression (Marciano et al., 2014). NRs play important roles in metabolic diseases such as diabetes,

Corresponding author: Chunjiong Wang, MD, Department of Physiology and Pathophysiology, Tianjin Medical University, Tianjin, 300070, China. wangchunjiong@tmu.edu.cn
Guangyan Wang, MD, Department of Physiology and Pathophysiology, Tianjin Medical University, Tianjin, 300070, China. guangyan2016@tmu.edu.cn

obesity, nonalcoholic fatty liver disease, atherosclerosis, and hypertension (Marciano et al., 2014).

Arachidonic acid (ARA), linoleic acid (LA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are important bioactive lipid precursors that can be metabolized into a large number of bioactive lipids by cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450s (CYPs) (Gabbs et al., 2015; Zhang et al., 2015). LA can be metabolized into hydroxy-octadecadienoic acid (HODE) mainly through the LOX pathway, including 9-HODE and 13-HODE, and into epoxyoctadecenoic acid (EpOME) through the CYP and COX pathways. ARA can be metabolized into prostaglandins (PGs) and thromboxanes (TXs) by COX. It also generates hydroperoxy-eicosatetraenoic acid, which is metabolized into leukotrienes (LTs) via the LOX pathway and generates hydroxy-eicosatetraenoic acids (HETEs) via the CYP pathway. EPA can be metabolized into 3-series PG and TXs through the COX pathway and resolvins (RvE; RvE1-E3) and hydroxyeicosapentaenoic acids (HEPEs) via the LOX pathway. Epoxyeicosatetraenoic acids (EEQs) and dihydroxyeicosatetraenoic acids (diHETEs) are derived from EPA through CYPs. DHA is catalyzed to produce D-series resolvins (RvD), maresins, protectins (PD), and hydroxydocosahexaenoic acids (HDoHEs) by the LOX pathway and into epoxydocosapentaenoic acids (EDPs) and dihydroxydocosapentaenoic acids (DiHDPAs) by the CYP pathway (Schmitz et al., 2008; Gabbs et al., 2015).

These bioactive lipids derived from PUFAs have various biological functions. They play important roles in the occurrence and development of metabolic diseases. The mechanisms underlying the regulation of tissue homeostasis and pathology by PUFA metabolites are complex. These PUFA derivatives play important roles in signal transduction by binding with nuclear or membrane receptors. Many of them have been reported to act on G protein-coupled receptors (GPCRs). Eicosanoids derived from arachidonic acid exerting their biological functions through membrane receptors have been well summarized (Calder, 2020). In addition, several PUFA metabolites have been identified as endogenous ligands of nuclear receptors that directly regulate their activities. Moreover, some eicosanoids can regulate cell function by indirectly regulating nuclear receptor activity. Nuclear receptors can also affect eicosanoid production by regulating the expression of enzymes related to eicosanoid metabolism. This article will mainly focus on the roles of the interaction between eicosanoid and nuclear receptors in metabolic diseases.

The Roles of ARA or LA-derived Metabolites in Metabolic Diseases through Nuclear Receptors

Various metabolites of ARA or LA are reported to be endogenous ligands of peroxisome proliferator-activated receptors (PPARs). In addition to PPARs, the bioactivities of testicular orphan nuclear receptor 4 (TR4), farnesoid X receptor (FXR), and liver X receptor (LXR) can also be affected by ARA, LA or their metabolites.

1. ARA or LA-derived Metabolites and PPARs

The PPAR nuclear receptor superfamily includes three subtypes, PPARα, PPARδ (also known as PPARβ) and PPARγ. PPARs play an important role in regulating glucose and lipid metabolism. PPARα promotes the uptake and utilization of fatty acids, and its agonist fibrate is used clinically to treat hyperlipidemia. PPARδ exerts beneficial effects on reducing weight gain, increasing the skeletal muscle metabolic rate and reducing atherogenic inflammation. PPARγ can promote glucose metabolism and lipid storage. Its agonist thiazolidinediones (TZDs) are used as insulin sensitizers in the treatment of type 2 diabetes (Marciano et al., 2014). Several metabolites derived from ARA or LA have been identified as endogenous ligands of PPARs, with 15d-PGJ2 being the earliest discovered endogenous ligand of PPARγ (Kliewer et al., 1995; Behl et al., 2016).

1.1 15d-PGJ2 and PPARγ

As early as 1995, 15d-PGJ2 was found to bind to and activate PPARγ to promote adipocyte differentiation, making it the first discovered endogenous ligand of PPARγ (Kliewer et al., 1995). Then, it is reported to affect physiological and pathophysiological processes such as lipogenesis, energy metabolism, and inflammation by activating PPARγ. Recent studies have demonstrated that a large number of mast cells are present in adipose tissue, which is further increased in the adipose tissue of obese mice. The conditioned medium of mast cells promotes 3T3-L1 cells to differentiate into adipocytes. Mechanistic studies show that 15d-PGJ2 secreted by mast cells acts on preadipocytes to activate PPARγ, thereby promoting adipocyte differentiation (Tanaka et al., 2011). In addition, 15d-PGJ2 improves insulin sensitivity in adipose tissue by mediating the interaction between G protein-coupled receptor 120 (GPR120) and PPARγ (Paschoal et al., 2020). GPR120 activation inhibited the metabolism of ARA into proinflammatory eicosanoids and promoted the production of 15d-PGJ2 by adipose tissue. 15d-PGJ2 can then activate PPARγ. Moreover, GPR120 is also a downstream target gene of PPARγ, which can then be activated after PPARγ activation (Paschoal et al., 2020). GPR120 is a membrane receptor of fatty acids, and PPARγ is a nuclear receptor of fatty acids. This study shows the key role of fatty acids in the metabolic regulatory network.

The interaction between adipose tissue and the central nervous system (CNS) plays important roles in regulating energy balance. Leptin secreted by adipose tissue can suppress appetite by acting on the hypothalamus. Meanwhile,

the occurrence of leptin resistance is indispensable in the pathogenesis of obesity. PPARγ activation in the central nervous system can inhibit leptin sensitivity and thus increase food intake (Ryan et al., 2011). 15d-PGJ2 is reported to inhibit leptin signal transduction by activating PPARγ, suggesting that it may act in the central nervous system to promote the development of leptin resistance (Hosoi et al., 2015).

Nonalcoholic fatty liver disease (NAFLD) is an important metabolic disease, and the activation of hepatic stellate cells (HSCs) promotes NAFLD-related liver fibrosis (Diehl et al., 2017). PPARγ improved liver fibrosis by inhibiting HSC activation (Tsuchida et al., 2017). 15d-PGJ2 was also found to inhibit the proliferation of HSCs and promote their apoptosis through activating PPARγ and inhibiting the expression of connective tissue growth factor mediated by TGF-β1 (Sun et al., 2006). In addition, activation of PPARγ by 15d-PGJ2 induces HSC senescence by upregulating P53 expression (Jin et al., 2016). These studies suggest that 15d-PGJ2 may have a protective effect against liver fibrosis.

In addition, a number of studies have shown that 15d-PGJ2 can suppress inflammation by activating PPARγ, thereby exerting a cardiovascular protective effect. 15d-PGJ2 can inhibit macrophage activation (Ricote et al., 1998), endothelial cell inflammation (Marcone et al., 2016), and adhesion of monocytes and neutrophils to endothelial cells (Jackson et al., 1999). Moreover, 15d-PGJ2 also inhibits the migration of vascular smooth muscle by activating PPARγ (Marx et al., 1998). 15d-PGJ2 reduces the formation of atherosclerotic lesions in apolipoprotein E knockout mice (Seno et al., 2011).

1.2 15-HETE, 9-HODE, 13-HODE and PPARγ

In addition to 15d-PGJ2, 15-HETE derived from ARA through LOX, and 9-HODE and 13-HODE derived from LA through LOX can also activate PPARγ. ARA can promote glucose uptake in 3T3-L1 adipocytes. Mechanistic studies showed that LOX inhibitors, but not COX1 and COX2 inhibitors, significantly inhibited the promoting effect of ARA on glucose uptake in adipocytes. Overexpression of the dominant negative PPARγ mutant plasmid had the same effect. This study suggests that the LOX metabolites of ARA may affect glucose uptake in adipose tissue by activating PPARγ (Nugent et al., 2001).

At a concentration of 30 μM, 15-HETE and 13-HODE increased the transcriptional activity of the PPARγ reporter genes (Huang et al., 1999). Studies have shown that interleukin (IL)-4 can promote the expression of the PPARγ target gene CD36 in macrophages, which can be abolished by a 15-LOX inhibitor (Huang et al., 1999). This study suggested that ARA-derived 15-HETE and LA-derived 13-HODE may be involved in IL-4-induced CD36 expression through activation of PPARγ.

The levels of 9-HODE and 13-HODE in plasma increased with the progression of NASH, indicating their potential as molecular markers of NASH (Maciejewska et al., 2020). Oxidized low-density lipoprotein (oxLDL) promotes monocyte maturation, PPARγ activity and CD36 expression. Through screening the lipids contained in oxLDL particles, 9-HODE and 13-HODE were found to promote monocyte maturation and CD36 expression as ligands for PPARγ (Nagy et al., 1998). Circulating levels of fatty-acid-binding protein 4 (FABP4) are increased in individuals with metabolic syndrome. HODEs increase the expression of FABP4 in THP-1 cells. 9-HODE was reported to act on the membrane receptor GPR132 and the nuclear receptor PPARγ. This study further found that the effects of 9-HODE and 13-HODE on the expression of FABP4 were mediated via PPARγ rather than GPR132 (Vangaveti et al., 2018). Structural biology studies further confirmed the direct binding of HODEs to PPARγ. This study showed that two molecules of 9-HODE are present in the ligand binding pocket of PPARγ and that one molecule of 13-HODE is in the ligand binding cavity (Itoh et al., 2008).

1.3 LOX-mediated ARA Metabolites and PPARα

Leukotriene B4 (LTB4) and 8-HETE are derived from ARA through LOX, and they are both reported to be endogenous ligands of PPARα. LTB4 interacts with leukotriene B4 receptors (BLTs) or the nuclear receptor PPARα. BLT1 and BLT2 are membrane receptors for LTB4. In HeLa cells lacking BLT1 and BLT2 receptors, LTB4 can still activate PPARα, indicating that its effect on PPARα is not caused by BLT1 and BLT2 receptors (Narala et al., 2010). Activation of BLTs has proinflammatory effects, while activation of PPARα has anti-inflammatory effects, indicating that LTB4 acts on different receptors to exert different effects.

8-HETE and 8-HEPE (derived from EPA) are considered ligands of PPARα based on their effects on PPARα activation and PPARα-RXR heterodimer formation (Forman et al., 1997). 8-HETE activates PPARα in a ligand-dependent manner and competes with GW2331 (an agonist of PPARα) to bind with PPARα. These data indicate that 8-HETE is an endogenous agonist of PPARα (Kliewer et al., 1997).

In addition, the LOX metabolites of PUFAs may also play a role by affecting the expression of PPARα. The study showed that 5-LOX knockout or inhibition had a protective effect on acetaminophen-induced liver injury in mice and increased and activated PPARα expression but had no effect on the expression of PPARγ or its target genes (Pu et al., 2016).

1.4 Prostacyclin (PGI2) and PPARs

PGI2 produced from ARA through COX is a potential endogenous ligand of PPARα and PPARδ (Forman et al., 1997). ARA increases the expression of uncoupling protein 2 (UCP2) in skeletal muscle cells. This effect is blocked by COX but not LOX inhibitors. Both cPGI2 (an analogue of PGI2) and a PPARδ agonist induced a robust increase in UCP-2 expression

in skeletal muscle cells (Chevillotte et al., 2001). This study suggests that cPGI2 may promote the expression of UCP2 in skeletal muscle cells by activating PPARδ. In myocytes, cPGI2 promotes the expression of carnitine palmitoyltransferase 1, a key protein involved in fatty acid oxidation in myocardial cells. Mechanistic studies found that cPGI2 exerts this effect by activating PPARδ rather than its membrane receptor IP prostanoid receptor (Kuroda et al., 2007).

In addition, PGI2 released from endothelial cells participates in the regulation of smooth muscle cell function by blood flow (Tsai et al., 2009). Endothelial cells secrete PGI2 under the stimulation of laminar flow, which then promotes the expression of SM22-α through PPARα and δ activation to maintain the contraction phenotype of vascular smooth muscle cells (Tsai et al., 2009). cPGI2 is also reported to promote 14-3-3 expression by activating PPARδ, which protects endothelial cells from H_2O_2-induced apoptosis (Liou et al., 2006).

1.5 Epoxyeicosatrienoic Acids (EETs) and PPARs

ARA can be metabolized by CYP2C and CYP2J to produce four EETs: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. EETs can be further hydrolyzed by soluble epioxide hydrolase (sEH) (He et al., 2016). By increasing the levels of EETs, sEH inhibitors can significantly improve high-fat diet- and hyperhomocysteinemia-induced liver steatosis (Wang et al., 2019; Yao et al., 2019). EETs are reported to exert their effects through PPARs. The luciferase reporter gene system shows that 8,9-EET or 11,12-EET treatment and overexpression of CYP2J2 activates PPARα (Wray et al., 2009). Homocysteine can reduce the levels of 11,12-EET in the liver. Inhibition of sEH can increase the levels of 11,12-EET and activate PPARα in a ligand-dependent manner, which ameliorates liver steatosis by promoting oxidation of fatty acids (Yao et al., 2019). The sEH inhibitor TPPU increased PPARα expression in the livers of methionine-choline deficient diet-fed mice (Wang et al., 2019). In addition, cardiomyocyte-specific expression of CYP2J2 increased 11,12-EET levels and prevented Ang-II-induced cardiac remodeling through PPARγ activation (He et al., 2015). Moreover, 14,15-EET activates PPARγ to disrupt TGF-β1-Smad2/3 signaling in murine fibroblasts. Decreasing the level of 14,15-EET by blocking sEH can alleviate bleomycin-induced pulmonary fibrosis (Tao et al., 2022). Although a number of studies have reported the activation of PPARs by EETs, it is still unclear whether EETs directly bind to PPARs.

2. ARA or LA-derived Metabolites and TR4

TR4 is an orphan nuclear receptor. TR4 and PPARγ share 20.2% identity in overall structure, with 54.2% homology in their DNA-binding domain and 21.2% homology in their LBD (Liu et al., 2014). Although TR4 has high homology to the PPARγ protein, its effects on glucose and lipid metabolism are different from those of PPARγ in many ways. For example, TR4 activation causes insulin resistance and promotes the development of atherosclerosis, which is opposite to the effect of PPARγ (Lin et al., 2017). TR4 deficiency protects mice from obesity-induced liver lipid deposition and insulin resistance (Kang et al., 2011). ARA-derived 15-HETE and LA-derived 13-HODE are endogenous ligands of TR4 (Xie et al., 2009). 15-HETE and 13-HODE bind to TR4 to promote the expression of CD36 (Xie et al., 2009). However, it is unknown whether 15-HETE and 13-HODE can participate in glucose and lipid metabolism by activating TR4.

3. ARA and LXRs

The LXR family is composed of two members: LXRα and LXRβ. LXR plays an important role in the regulation of lipid metabolism. Its agonists have therapeutic effects, such as anti-atherosclerosis and anti-diabetes, but cause side effects of fatty liver and hyperlipidemia (Wang et al., 2018). Although the effects of ARA metabolites on LXR are unknown, ARA has been reported to exert biological functions by inhibiting LXR. PUFAs have been reported to inhibit the promoter activity of sterol regulatory element binding protein-1c (SREBP-1c) in an LXR-dependent manner. The inhibitory effect of ARA on the SREBP-1c promoter is greater than that of EPA, DHA, and LA (Yoshikawa et al., 2002). Further studies showed that ARA inhibited LXR activity by competing with endogenous LXR ligands (Ou et al., 2001; Yoshikawa et al., 2002). ARA inhibits insulin induced SREBP-1c expression by inhibiting LXR activity (Chen et al., 2004). In addition, deficiency of lipoprotein receptor-related protein 1 increases the release of ARA by promoting the activity of cytosolic phospholipase A2. ARA in turn inhibits the expression of ATP-binding cassette transporter A1 through the inhibition of LXR activity, which leads to an increase in cholesterol levels in smooth muscle cells (Zhou et al., 2009).

4. The Effects of ARA and Its Metabolites on Farnesyl Ester X Receptor (FXR)

FXR plays an important role in bile acid metabolism and glucose and lipid metabolism, and bile acids are its main endogenous ligands (Lu et al., 2020). PUFAs have also been reported to bind to FXR (Zhao et al., 2004). Further studies found that PUFAs act as FXR antagonists to inhibit the expression of FXR target genes (Zhao et al., 2004). Among ARA-derived eicosanoids, 15d-PGJ2 was reported to inhibit FXR in addition to activating PPARγ. Moreover, the inhibitory effects of 15d-PGJ2 on FXR promote the conversion of cholesterol to bile acids in HepG2 cells (Xu et al., 2013).

The Effects of DHA/EPA Metabolites on Metabolic Disease through Nuclear Receptors

DHA and EPA are important ω-3 PUFAs that have been reported to have protective effects on glucose and lipid metabolism. In recent years, an increasing number of studies

have focused on the function of metabolites derived from DHA and EPA. Several DHA and EPA metabolites have been reported to act on membrane receptors (GPCRs) and nuclear receptors (mainly PPARs) to exert their biological functions. By constructing the GAL4-PPARs system, researchers found that 5-, 8-, 9-, 12- and 18-HEPE produced by EPA metabolism could activate PPARα and PPARγ, while 5-, 8-, 9-, 12-HEPE also activated PPARβ (Yamada et al., 2014). That study also revealed that 8-HEPE promotes lipogenesis in preadipocytes by activating PPARγ and increases glucose uptake of myoblasts by activating PPARβ (Yamada et al., 2014). In addition, the EPA metabolite 15d-PGJ3 can promote 3T3-L1 cells to secrete adiponectin through PPARγ (Lefils-Lacourtablaise et al., 2013), but whether 15d-PGJ3 is a ligand of PPARγ remains to be studied. In obesity and NASH mouse models, 18-HEPE and 17-HDHA can upregulate PPARα and PPARγ to exert liver protective functions (Rodriguez-Echevarria et al., 2018).

Retinoid-related orphan receptor alpha (RORα) agonists show protective effects against nonalcoholic steatohepatitis (Chai et al., 2020). MaR1, derived from DHA through LOX catalysis, activates RORα to promote M2 polarization of macrophages and alleviate inflammation in the progression of NASH. Surface plasmon resonance and fluorescence resonance energy transfer assays confirmed that MaR1 could directly bind to RORα, indicating that MaR1 is an endogenous ligand of RORα. Activation of RORα in macrophages further promotes the expression of 12-LOX to increase the production of MaR1, thus forming a metabolic circuit (Han et al., 2019). In cardiomyocytes, MaR1 increases IGF-1 production by binding with RORα and then induces cardiomyocyte hypertrophy through the PI3K/Akt pathway (Wahyuni et al., 2021). Because MaR1 has no activation effect on other nuclear receptors, such as retinoic acid receptors β and PPARs, and other eicosanoids, such as DHA and RvD1, cannot activate RORα.Thus, the activation of RORα by MaR1 is relatively specific (Han et al., 2019).

PUFAs and Other Nuclear Receptors

In addition to the above-mentioned nuclear receptors closely associated with metabolism, PUFAs may also bind to other nuclear receptors. However, it is still unclear whether they have a relevant effect on metabolic diseases through these nuclear receptors. Nurr1 pull-down combined with high-resolution mass spectrometry suggested that DHA may bind to Nurr1. Solution NMR spectroscopy revealed that the binding epitope between DHA and Nurr1 was in its ligand binding domain (de Vera et al., 2016). However, which biological functions DHA can exert through binding to Nurr1 remains to be studied. The binding of DHA and ARA to the Nur77 ligand domain was also discovered using the pull-down method combined with high-resolution mass spectrometry (Vinayavekhin et al., 2011).

The Role of NRs in PUFA Metabolism

PUFA metabolites can act as endogenous ligands to affect the activity of nuclear receptors. Conversely, nuclear receptors can also regulate the production and metabolism of these bioactive PUFA metabolites, forming a complex regulatory network in energy metabolism homeostasis and metabolism. Nuclear receptors (PPARs, RORα and LXRs) can affect the production and metabolism of ω-6/ω-3 PUFA-derived bioactive metabolites by regulating the expression of related metabolic enzymes (Figure 1).

PPARγ knockout increases the expression of mPGES-1 and COX in adipose tissue to promote PGE2 production. PGE2 in turn represses the expression of PPARγ and blocks rosiglitazone-mediated preadipocyte differentiation (Garcia-Alonso et al., 2013). This indicates that PPARγ and PGE2 have a mutual regulatory network in adipose tissue, thus affecting adipose tissue function. In myocardial cells, PPARγ can also inhibit the expression of COX-2 and reduce the level of PGE2 (Mendez et al., 2003). The expression of CYP4A, as well as the ARA metabolites 19-HETE and 20-HETE, in the livers of diabetic rats and fasting rats is increased. Further study found that the increased expression of CYP4A was mediated by PPARα activation (Kroetz et al., 1998). CYP2C8 can metabolize ARA into EETs, and PPARα is reported to directly act on the promoter of CYP2C8 to promote its transcription

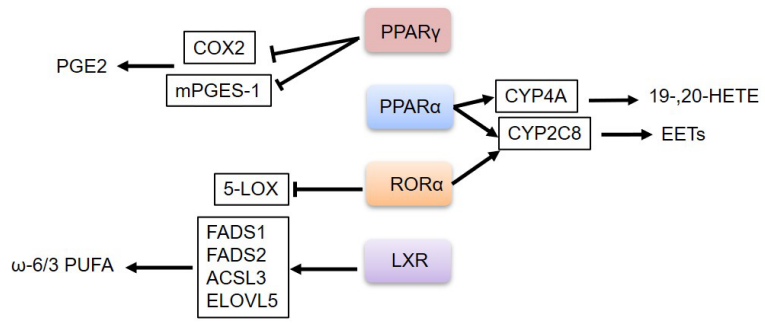

Figure 1. Summary of the effects of nuclear receptors on production of ω-6/ω-3 PUFA-derived bioactive metabolites

(Thomas et al., 2015).

RORα can inhibit the expression of 5-LOX in prostate cancer cells, thereby inhibiting the proliferation-promoting effect of ARA on prostate cancer cells (Moretti et al., 2004). Melatonin can act on RORα receptors to inhibit the expression of 5-LOX and inhibit the activation of hepatic stellate cells (Shajari et al., 2015). In addition, CYP2C8 is also a target gene of RORα; overexpression of RORα can increase its expression (Chen et al., 2009).

The LXR agonist promoted the transcription of lysophosphatidyltransferase 3 in macrophages and significantly increased the content of ARA in polar lipids, especially phosphatidylcholine. LXR agonist pretreatment increased the release of arachidonate-derived eicosanoids such as PGE2 and thromboxane after lipopolysaccharide stimulation (Ishibashi et al., 2013). Moreover, ARA redistributed into neutral lipids when lysophosphatidyltransferase 3 was Knocked down (Ishibashi et al., 2013). In addition, LXR also mediated the expression of multiple synthetic PUFA genes, including FADS1, FADS2, ACSL3, and ELOVL5. LXR agonists promoted the generation of ω-6 and ω-3 PUFAs derived from C18 substrates (Varin et al., 2015).

Conclusion

A large number of bioactive lipids are produced by the metabolism of PUFAs, and they can serve as signaling molecules to exert biological functions through corresponding receptors. Various PUFA metabolites can bind to GPCRs or NRs to regulate energy metabolism and participate in the development of related diseases. PPARs, LXR, FXR and TR4 can act as fatty acid receptors and thus become an important link between PUFA metabolism and cell function changes (Table 1). There are still numerous PUFA metabolites with complex functions, and their receptors are unknown. Compared with mechanistic studies of EPA- or DHA-derived metabolites, more studies have focused on ARA-

Table 1. The effects of ω-6/ω-3 PUFA-derived bioactive metabolites on metabolic disorders through nuclear receptors

Precursors	Metabolites	NRs	Function	References
ARA&LA	15d-PGJ2	PPARγ	Adipocyte differentiation↑	(Kliewer et al., 1995), (Tanaka et al., 2011)
			Adipose tissue insulin sensitivity↑	(Paschoal et al., 2020)
			Leptin sensitivity↓	(Hosoi et al., 2015)
			Hepatic stellate cell proliferation↓ apoptosis↑	(Sun et al., 2006)
			Hepatic stellate cell senescence↑	(Jin et al., 2016)
			Vascular smooth muscle cell migration↓	(Marx et al., 1998)
		FXR	Conversion of cholesterol to bile acids in HepG2 cells↑	(Xu et al., 2013)
	15-HETE	PPARγ	Expression of CD36↑	(Huang et al., 1999), (Nagy et al., 1998)
			Monocyte maturation↑	(Nagy et al., 1998)
		TR4	Expression of CD36↑	(Xie et al., 2009)
	9-HODE	PPARγ	Circulation level of FABP4↑	(Vangaveti et al., 2018)
	13-HODE	PPARγ	Expression of CD36↑	(Huang et al., 1999), (Nagy et al., 1998)
			Monocyte maturation↑	(Nagy et al., 1998)
			Circulation level of FABP4↑	(Vangaveti et al., 2018)
		TR4	Expression of CD36↑	(Xie et al., 2009)
	PGI2	PPARδ	Level of UCP2 in skeletal muscle cell ↑	(Chevillotte et al., 2001)
			Expression of 14-3-3↑ Endothelial cell apoptosis↓	(Liou et al., 2006)
		PPARα PPARδ	Synthetic-to-contractile phenotypic phenotype of vascular smooth muscle cell ↑	(Tsai et al., 2009)
	11,12-EET	PPARα	Hyperhomocysteinemia-induced hepatic steatosis↓	(Yao et al., 2019)
		PPARγ	Ang-II-induced cardiac remodeling↓	(He et al., 2015)
EPA & DHA	15d-PGJ3	PPARγ	Adiponectin secretion in 3T3-L1 cells ↑	(Lefils-Lacourtablaise et al., 2013)
	8-HEPE	PPARα PPARγ PPARδ	Lipogenesis in preadipocytes↑ Glucose uptake↑	(Yamada et al., 2014)
	18-HEPE 17-HDHA	PPARα PPARγ	Protective function in obesity or NASH mice liver	(Rodriguez-Echevarria et al., 2018)
	MaR1	RORα	M2 macrophages polarization ↑ NASH inflammation and fibrosis↓	(Han et al., 2019)

derived eicosanoids. However, in recent years, an increasing number of studies have focused on the underlying mechanism of ω-3 PUFA-derived metabolites. Direct or indirect regulation of nuclear receptors is one of the key mechanisms for their functions. The changes in nuclear receptor activity can, in turn, affect the production of PUFA metabolites by regulating the expression of related enzymes. Therefore, PUFA metabolites and nuclear receptors form a regulatory network and play an important role in metabolic diseases. Studies focused on eicosanoid metabolism, exploring their targets and downstream signaling pathways will contribute to exploring new therapeutic targets for metabolic diseases.

Conflict of Interest

The authors declare no competing interests.

Acknowledgements

This study was supported by National Natural Science Foundation of China (82170635; 82300679; 82370637).

References

[1] Behl T, Kaur I, Goel H, Kotwani A. Implications of the endogenous PPAR-gamma ligand, 15-deoxy-delta-12, 14-prostaglandin J2, in diabetic retinopathy. Life Sci. 2016;153:93-9.

[2] Calder PC. Eicosanoids. Essays Biochem. 2020;64(3):423-41.

[3] Chai C, Cox B, Yaish D, Gross D, Rosenberg N, Amblard F, Shemuelian Z, Gefen M, Korach A, Tirosh O, Lanton T, Link H, Tam J, Permikov A, Ozhan G, Citrin J, Liao H, Tannous M, Hahn M, Axelrod J, Arretxe E, Alonso C, Martinez-Arranz I, Betes PO, Safadi R, Salhab A, Amer J, Tber Z, Mengshetti S, Giladi H, Schinazi RF, Galun E. Agonist of RORA attenuates nonalcoholic fatty liver progression in mice via up-regulation of microRNA 122. Gastroenterology. 2020;159(3):999-1014.e9.

[4] Chen G, Liang G, Ou J, Goldstein JL, Brown MS. Central role for liver X receptor in insulin-mediated activation of Srebp-1c transcription and stimulation of fatty acid synthesis in liver. Proc Natl Acad Sci USA. 2004;101(31):11245-50.

[5] Chen Y, Coulter S, Jetten AM, Goldstein JA. Identification of human CYP2C8 as a retinoid-related orphan nuclear receptor target gene. J Pharmacol Exp Ther. 2009;329(1):192-201.

[6] Chevillotte E, Rieusset J, Roques M, Desage M, Vidal H. The regulation of uncoupling protein-2 gene expression by omega-6 polyunsaturated fatty acids in human skeletal muscle cells involves multiple pathways, including the nuclear receptor peroxisome proliferator-activated receptor beta. J Biol Chem. 2001;276(14):10853-60.

[7] De Bosscher K, Desmet SJ, Clarisse D, Estebanez-Perpina E, Brunsveld L. Nuclear receptor crosstalk - defining the mechanisms for therapeutic innovation. Nat Rev Endocrinol. 2020;16(7):363-77.

[8] De Vera IM, Giri PK, Munoz-Tello P, Brust R, Fuhrmann J, Matta-Camacho E, Shang J, Campbell S, Wilson HD, Granados J, Gardner WJ, Jr., Creamer TP, Solt LA, Kojetin DJ. Identification of a binding site for unsaturated fatty acids in the orphan nuclear receptor Nurr1. ACS Chem Biol. 2016;11(7):1795-9.

[9] Diehl AM, Day C. Cause, Pathogenesis, and treatment of nonalcoholic steatohepatitis. N Engl J Med. 2017;377(21):2063-72.

[10] Forman BM, Chen J, Evans RM. Hypolipidemic drugs, polyunsaturated fatty acids, and eicosanoids are ligands for peroxisome proliferator-activated receptors alpha and delta. Proc Natl Acad Sci USA. 1997;94(9):4312-7.

[11] Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr. 2015;6(5):513-40.

[12] Garcia-Alonso V, Lopez-Vicario C, Titos E, Moran-Salvador E, Gonzalez-Periz A, Rius B, Parrizas M, Werz O, Arroyo V, Claria J. Coordinate functional regulation between microsomal prostaglandin E synthase-1 (mPGES-1) and peroxisome proliferator-activated receptor gamma (PPARgamma) in the conversion of white-to-brown adipocytes. J Biol Chem. 2013;288(39):28230-42.

[13] Han YH, Shin KO, Kim JY, Khadka DB, Kim HJ, Lee YM, Cho WJ, Cha JY, Lee BJ, Lee MO. A maresin 1/RORα/12-lipoxygenase autoregulatory circuit prevents inflammation and progression of nonalcoholic steatohepatitis. J Clin Invest. 2019;129(4):1684-98.

[14] He J, Wang C, Zhu Y, Ai D. Soluble epoxide hydrolase: A potential target for metabolic diseases. J Diabetes. 2016;8(3):305-13.

[15] He Z, Zhang X, Chen C, Wen Z, Hoopes SL, Zeldin DC, Wang DW. Cardiomyocyte-specific expression of CYP2J2 prevents development of cardiac remodelling induced by angiotensin II. Cardiovasc Res. 2015;105(3):304-17.

[16] Hosoi T, Matsuzaki S, Miyahara T, Shimizu K, Hasegawa Y, Ozawa K. Possible involvement of 15-deoxy-Delta(12,14) -prostaglandin J2 in the development of leptin resistance. J Neurochem. 2015;133(3):343-51.

[17] Huang JT, Welch JS, Ricote M, Binder CJ, Willson TM, Kelly C, Witztum JL, Funk CD, Conrad D, Glass CK. Interleukin-4-dependent production of PPAR-gamma ligands in macrophages by 12/15-lipoxygenase. Nature. 1999;400(6742):378-82.

[18] Ishibashi M, Varin A, Filomenko R, Lopez T, Athias A, Gambert P, Blache D, Thomas C, Gautier T, Lagrost L, Masson D. Liver x receptor regulates arachidonic acid distribution and eicosanoid release in human macrophages: a key role for lysophosphatidylcholine acyltransferase 3. Arterioscler Thromb Vasc Biol. 2013;33(6):1171-9.

[19] Itoh T, Fairall L, Amin K, Inaba Y, Szanto A, Balint BL, Nagy L, Yamamoto K, Schwabe JW. Structural basis for the activation of PPARgamma by oxidized fatty acids. Nat Struct Mol Biol. 2008;15(9):924-31.

[20] Jackson SM, Parhami F, Xi XP, Berliner JA, Hsueh WA, Law RE, Demer LL. Peroxisome proliferator-activated receptor activators target human endothelial cells to inhibit leukocyte-endothelial cell interaction. Arterioscler Thromb Vasc Biol. 1999;19(9):2094-104.

[21] Jin H, Lian N, Zhang F, Chen L, Chen Q, Lu C, Bian M, Shao J, Wu L, Zheng S. Activation of PPARγ/P53 signaling is required for curcumin to induce hepatic stellate cell senescence. Cell Death Dis. 2016;7(4):e2189.

[22] Kang HS, Okamoto K, Kim YS, Takeda Y, Bortner CD, Dang H, Wada T, Xie W, Yang XP, Liao G, Jetten AM. Nuclear orphan receptor TAK1/TR4-deficient mice are protected against obesity-linked inflammation, hepatic steatosis, and insulin resistance. Diabetes. 2011;60(1):177-88.

[23] Kliewer SA, Lenhard JM, Willson TM, Patel I, Morris DC, Lehmann

JM. A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor gamma and promotes adipocyte differentiation. Cell. 1995;83(5):813-9.

[24] Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, Devchand P, Wahli W, Willson TM, Lenhard JM, Lehmann JM. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc Natl Acad Sci U S A. 1997;94(9):4318-23.

[25] Kroetz DL, Yook P, Costet P, Bianchi P, Pineau T. Peroxisome proliferator-activated receptor alpha controls the hepatic CYP4A induction adaptive response to starvation and diabetes. J Biol Chem. 1998;273(47):31581-9.

[26] Kuroda T, Hirota H, Fujio Y, Sugiyama S, Masaki M, Hiramoto Y, Shioyama W, Okamoto K, Hori M, Yamauchi-Takihara K. Carbacyclin induces carnitine palmitoyltransferase-1 in cardiomyocytes via peroxisome proliferator-activated receptor (PPAR) delta independent of the IP receptor signaling pathway. J Mol Cell Cardiol. 2007;43(1):54-62.

[27] Lefils-Lacourtablaise J, Socorro M, Géloën A, Daira P, Debard C, Loizon E, Guichardant M, Dominguez Z, Vidal H, Lagarde M, Bernoud-Hubac N. The eicosapentaenoic acid metabolite 15-deoxy-δ(12,14)-prostaglandin J3 increases adiponectin secretion by adipocytes partly via a PPARγ-dependent mechanism. PLoS One. 2013;8(5):e63997.

[28] Lin SJ, Yang DR, Yang G, Lin CY, Chang HC, Li G, Chang C. TR2 and TR4 orphan nuclear receptors: an overview. Curr Top Dev Biol. 2017;125:357-73.

[29] Liou JY, Lee S, Ghelani D, Matijevic-Aleksic N, Wu KK. Protection of endothelial survival by peroxisome proliferator-activated receptor-delta mediated 14-3-3 upregulation. Arterioscler Thromb Vasc Biol. 2006;26(7):1481-7.

[30] Liu S, Lin SJ, Li G, Kim E, Chen YT, Yang DR, Tan MH, Yong EL, Chang C. Differential roles of PPARgamma vs TR4 in prostate cancer and metabolic diseases. Endocr Relat Cancer. 2014;21(3):R279-300.

[31] Lu Y, Shao M, Xiang H, Zheng P, Wu T, Ji G. Integrative transcriptomics and metabolomics explore the mechanism of kaempferol on improving nonalcoholic steatohepatitis. Food Function. 2020;11(11):10058-69.

[32] Maciejewska D, Drozd A, Skonieczna-Zydecka K, Skorka-Majewicz M, Dec K, Jakubczyk K, Pilutin A, Stachowska E. Eicosanoids in nonalcoholic fatty liver disease (NAFLD) progression. Do serum eicosanoids profile correspond with liver eicosanoids content during NAFLD development and progression? Molecules. 2020;25(9):2026.

[33] Marciano DP, Chang MR, Corzo CA, Goswami D, Lam VQ, Pascal BD, Griffin PR. The therapeutic potential of nuclear receptor modulators for treatment of metabolic disorders: PPARgamma, RORs, and Rev-erbs. Cell Metab. 2014;19(2):193-208.

[34] Marcone S, Evans P, Fitzgerald DJ. 15-deoxy-delta(12,14)-prostaglandin J2 modifies components of the proteasome and inhibits inflammatory responses in human endothelial cells. Front Immunol. 2016;7:459.

[35] Marx N, Schönbeck U, Lazar MA, Libby P, Plutzky J. Peroxisome proliferator-activated receptor gamma activators inhibit gene expression and migration in human vascular smooth muscle cells. Circ Res. 1998;83(11):1097-103.

[36] Mendez M, LaPointe MC. PPARgamma inhibition of cyclooxygenase-2, PGE2 synthase, and inducible nitric oxide synthase in cardiac myocytes. Hypertension. 2003;42(4):844-50.

[37] Moretti RM, Montagnani Marelli M, Sala A, Motta M, Limonta P. Activation of the orphan nuclear receptor RORalpha counteracts the proliferative effect of fatty acids on prostate cancer cells: crucial role of 5-lipoxygenase. Int J Cancer. 2004;112(1):87-93.

[38] Nagy L, Tontonoz P, Alvarez JG, Chen H, Evans RM. Oxidized LDL regulates macrophage gene expression through ligand activation of PPARgamma. Cell. 1998;93(2):229-40.

[39] Narala VR, Adapala RK, Suresh MV, Brock TG, Peters-Golden M, Reddy RC. Leukotriene B4 is a physiologically relevant endogenous peroxisome proliferator-activated receptor-alpha agonist. J Biol Chem. 2010;285(29):22067-74.

[40] Nugent C, Prins JB, Whitehead JP, Wentworth JM, Chatterjee VK, O'Rahilly S. Arachidonic acid stimulates glucose uptake in 3T3-L1 adipocytes by increasing GLUT1 and GLUT4 levels at the plasma membrane. Evidence for involvement of lipoxygenase metabolites and peroxisome proliferator-activated receptor gamma. J Biol Chem. 2001;276(12):9149-57.

[41] Ou J, Tu H, Shan B, Luk A, DeBose-Boyd RA, Bashmakov Y, Goldstein JL, Brown MS. Unsaturated fatty acids inhibit transcription of the sterol regulatory element-binding protein-1c (SREBP-1c) gene by antagonizing ligand-dependent activation of the LXR. Proc Natl Acad Sci USA. 2001;98(11):6027-32.

[42] Paschoal VA, Walenta E, Talukdar S, Pessentheiner AR, Osborn O, Hah N, Chi TJ, Tye GL, Armando AM, Evans RM, Chi NW, Quehenberger O, Olefsky JM, Oh DY. Positive reinforcing mechanisms between GPR120 and PPARγ modulate insulin sensitivity. Cell Metab. 2020;31(6):1173-88.e5.

[43] Pu S, Ren L, Liu Q, Kuang J, Shen J, Cheng S, Zhang Y, Jiang W, Zhang Z, Jiang C, He J. Loss of 5-lipoxygenase activity protects mice against paracetamol-induced liver toxicity. Br J Pharmacol. 2016;173(1):66-76.

[44] Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature. 1998;391(6662):79-82.

[45] Rodriguez-Echevarria R, Macias-Barragan J, Parra-Vargas M, Davila-Rodriguez JR, Amezcua-Galvez E, Armendariz-Borunda J. Diet switch and omega-3 hydroxy-fatty acids display differential hepatoprotective effects in an obesity/nonalcoholic fatty liver disease model in mice. World J Gastroenterol. 2018;24(4):461-74.

[46] Ryan KK, Li B, Grayson BE, Matter EK, Woods SC, Seeley RJ. A role for central nervous system PPAR-γ in the regulation of energy balance. Nat Med. 2011;17(5):623-6.

[47] Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. Prog Lipid Res. 2008;47(2):147-55.

[48] Seno T, Hamaguchi M, Ashihara E, Kohno M, Ishino H, Yamamoto A, Kadoya M, Nakamura K, Murakami K, Matoba S, Maekawa T, Kawahito Y. 15-Deoxy-Delta(1)(2),(1)(4) prostaglandin J(2) reduces the formation of atherosclerotic lesions in apolipoprotein E knockout mice. PLoS One. 2011;6(10):e25541.

[49] Shajari S, Laliena A, Heegsma J, Tunon MJ, Moshage H, Faber KN. Melatonin suppresses activation of hepatic stellate cells through RORalpha-mediated inhibition of 5-lipoxygenase. J Pineal Res. 2015;59(3):391-401.

[50] Sun K, Wang Q, Huang XH. PPAR gamma inhibits growth of rat hepatic stellate cells and TGF beta-induced connective tissue growth factor expression. Acta Pharmacol Sin. 2006;27(6):715-23.

[51] Tanaka A, Nomura Y, Matsuda A, Ohmori K, Matsuda H. Mast cells function as an alternative modulator of adipogenesis through 15-deoxy-delta-12, 14-prostaglandin J2. Am J Physiol Cell Physiol.

2011;301(6):C1360-7.
[52] Tao JH, Liu T, Zhang CY, Zu C, Yang HH, Liu YB, Yang JT, Zhou Y, Guan CX. Epoxyeicosatrienoic acids inhibit the activation of murine fibroblasts by blocking the TGF-β1-Smad2/3 signaling in a PPARγ-dependent manner. Oxid Med Cell Longev. 2022;2022:7265486.
[53] Thomas M, Winter S, Klumpp B, Turpeinen M, Klein K, Schwab M, Zanger UM. Peroxisome proliferator-activated receptor alpha, PPARalpha, directly regulates transcription of cytochrome P450 CYP2C8. Front Pharmacol. 2015;6:261.
[54] Tsai MC, Chen L, Zhou J, Tang Z, Hsu TF, Wang Y, Shih YT, Peng HH, Wang N, Guan Y, Chien S, Chiu JJ. Shear stress induces synthetic-to-contractile phenotypic modulation in smooth muscle cells via peroxisome proliferator-activated receptor alpha/delta activations by prostacyclin released by sheared endothelial cells. Circ Res. 2009;105(5):471-80.
[55] Tsuchida T, Friedman SL. Mechanisms of hepatic stellate cell activation. Nat Rev Gastroenterol Hepatol. 2017;14(7):397-411.
[56] Vangaveti V, Shashidhar V, Collier F, Hodge J, Rush C, Malabu U, Baune B, Kennedy RL. 9- and 13-HODE regulate fatty acid binding protein-4 in human macrophages, but does not involve HODE/GPR132 axis in PPAR-γ regulation of FABP4. Ther Adv Endocrinol Metab. 2018;9(5):137-50.
[57] Varin A, Thomas C, Ishibashi M, Menegaut L, Gautier T, Trousson A, Bergas V, de Barros JP, Narce M, Lobaccaro JM, Lagrost L, Masson D. Liver X receptor activation promotes polyunsaturated fatty acid synthesis in macrophages: relevance in the context of atherosclerosis. Arterioscler Thromb Vasc Biol. 2015;35(6):1357-65.
[58] Vinayavekhin N, Saghatelian A. Discovery of a protein-metabolite interaction between unsaturated fatty acids and the nuclear receptor Nur77 using a metabolomics approach. J Am Chem Soc. 2011;133(43):17168-71.
[59] Wahyuni T, Kobayashi A, Tanaka S, Miyake Y, Yamamoto A, Bahtiar A, Mori S, Kametani Y, Tomimatsu M, Matsumoto K, Maeda M, Obana M, Fujio Y. Maresin-1 induces cardiomyocyte hypertrophy through IGF-1 paracrine pathway. Am J Physiol Cell Physiol. 2021;321(1):C82-c93.
[60] Wang B, Tontonoz P. Liver X receptors in lipid signalling and membrane homeostasis. Nat Rev Endocrinol. 2018;14(8):452-63.
[61] Wang X, Li L, Wang H, Xiao F, Ning Q. Epoxyeicosatrienoic acids alleviate methionine-choline-deficient diet-induced non-alcoholic steatohepatitis in mice. Scand J Immunol. 2019;90(3):e12791.
[62] Wray JA, Sugden MC, Zeldin DC, Greenwood GK, Samsuddin S, Miller-Degraff L, Bradbury JA, Holness MJ, Warner TD, Bishop-Bailey D. The epoxygenases CYP2J2 activates the nuclear receptor PPARalpha in vitro and in vivo. PLoS One. 2009;4(10):e7421.
[63] Xie S, Lee YF, Kim E, Chen LM, Ni J, Fang LY, Liu S, Lin SJ, Abe J, Berk B, Ho FM, Chang C. TR4 nuclear receptor functions as a fatty acid sensor to modulate CD36 expression and foam cell formation. Proc Natl Acad Sci USA. 2009;106(32):13353-8.
[64] Xu X, Lu Y, Chen L, Chen J, Luo X, Shen X. Identification of 15d-PGJ2 as an antagonist of farnesoid X receptor: molecular modeling with biological evaluation. Steroids. 2013;78(9):813-22.
[65] Yamada H, Oshiro E, Kikuchi S, Hakozaki M, Takahashi H, Kimura K. Hydroxyeicosapentaenoic acids from the Pacific krill show high ligand activities for PPARs. J Lipid Res. 2014;55(5):895-904.
[66] Yao L, Cao B, Cheng Q, Cai W, Ye C, Liang J, Liu W, Tan L, Yan M, Li B, He J, Hwang SH, Zhang X, Wang C, Ai D, Hammock BD, Zhu Y. Inhibition of soluble epoxide hydrolase ameliorates hyperhomocysteinemia-induced hepatic steatosis by enhancing β-oxidation of fatty acid in mice. Am J Physiol Gastrointest Liver Physiol. 2019;316(4):G527-g38.
[67] Yoshikawa T, Shimano H, Yahagi N, Ide T, Amemiya-Kudo M, Matsuzaka T, Nakakuki M, Tomita S, Okazaki H, Tamura Y, Iizuka Y, Ohashi K, Takahashi A, Sone H, Osuga Ji J, Gotoda T, Ishibashi S, Yamada N. Polyunsaturated fatty acids suppress sterol regulatory element-binding protein 1c promoter activity by inhibition of liver X receptor (LXR) binding to LXR response elements. J Biol Chem. 2002;277(3):1705-11.
[68] Zhang X, Yang N, Ai D, Zhu Y. Systematic metabolomic analysis of eicosanoids after omega-3 polyunsaturated fatty acid supplementation by a highly specific liquid chromatography-tandem mass spectrometry-based method. J Proteome Res. 2015;14(4):1843-53.
[69] Zhao A, Yu J, Lew JL, Huang L, Wright SD, Cui J. Polyunsaturated fatty acids are FXR ligands and differentially regulate expression of FXR targets. DNA Cell Biol. 2004;23(8):519-26.
[70] Zhou L, Choi HY, Li WP, Xu F, Herz J. LRP1 controls cPLA2 phosphorylation, ABCA1 expression and cellular cholesterol export. PLoS One. 2009;4(8):e6853.