Estrogen receptor-associated receptor α and peroxisome proliferator-activated receptor γ in metabolism and disease (Review)

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Abstract. Estrogen receptor-associated receptor α (ERRα) is an orphan nuclear receptor that lacks corresponding ligands. ERRα recruits co-regulators to regulate gene transcription and plays an important role in human physiological functions. Peroxisome proliferator-activated receptor γ (PPARγ) is also a nuclear receptor that regulates the expression of target genes via a ligand-dependent mechanism, thereby participating in a series of physiological processes. Both ERRα and PPARγ are involved in the process of energy metabolism and tumorigenesis. In the present review, a concise overview of the important roles governed by ERRα and PPARγ in metabolism and their association with various disease are provided.

Contents

1. Introduction

Estrogen receptor-associated receptor (ERR) is an orphan nuclear receptor that exerts its biological function without binding to a ligand. In 1988, Giguère *et al* (1) identified a nuclear receptor that was highly homologous with ERα in nucleotide and amino acid sequences using cDNA for the DNA-binding domain of estrogen receptor α (ERα) as the probe. Both ERR and ER are type III nuclear receptors. To date, the following three subtypes have been found, ERRα (NR3B1), ERRβ (NR3B2) and ERRγ (NR3B3), in which ERRα is widely distributed in various adult tissues and participates in a variety of physiological processes, including mitochondrial biogenesis (2), gluconeogenesis, oxidative phosphorylation (3), fatty acid metabolism (4) and brown adipose tissue thermogenesis (5). It was also identified as an important regulator of the mammalian circadian clock, and its output pathways at both transcriptional and physiological levels regulated the expression of transcription factors involved in metabolic homeostasis (6). The ERRα-encoding gene is located at site 11q13 of the human chromosome and primarily consists of the following three functional domains: N terminal domain (NTD), DNA-binding domain (DBD) and ligand binding domain (LBD). Activation function 1 (AF1) is located at the NTD, while AF2 is located at the LBD (7). The DBD of ERRα contains two zinc fingers, which are used for identification and binding of special sequences at the regulatory region in the DNA of the target gene (8). AF2 regulates the transcriptional activity of nuclear receptors, primarily through functional interactions with coactivators, such as peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1), or corepressors, such as nuclear factor RIP140 (8).

Peroxisome proliferator-activated receptor (PPAR) is a novel steroid hormone receptor discovered by Issemann and Green (9) in 1990, which can be activated by fatty acid-like peroxisome proliferator. PPARs are nuclear transcription factors activated by ligands and members of the type II nuclear hormone receptor superfamily. There are three subtypes of PPARs: PPARα, β/δ and γ (10). Typically, PPARs and retinoid X receptors (RXR) form a heterodimer and recruit a co-inhibitory protein complex to inhibit the transcription of target genes (10). When PPARs are combined with ligands and activated, this heterodimer may release co-inhibitor proteins and bind to coactivator proteins, and subsequently combine with the promoter of the target gene, upstream peroxisome proliferator response element (PPRE), to regulate its transcription and activate its biological function (10). The PPARγ gene is located in the p25 region of chromosome 3 and contains six regions known as regions A-F, which are divided into four functional domains: Amino terminal domain, DNA binding domain, transcriptional activity regulatory domain and ligand

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binding domain (11). PPARγ regulates gene transcription through binding of the DNA binding domain to PPRE, and a number of nuclear factors, such as protein kinase C, protein kinase A and 5'AMP-activated protein kinase can affect the activity of PPARγ after binding to this domain (12,13).

2. Distribution and function of ERRα and PPARγ

ERRα is expressed in a variety of tissues from embryonic development to adulthood. The expression of ERRα can be detected in the heart, brain, kidney, brown adipose tissue (BAT), intestines, bones and uterus (Table I) (14). The expression of ERRα is higher in metabolically active tissues, including the heart, white adipose tissue, BAT and macrophages, while it is relatively lower in the liver, lung and vagina (15,16). Studies have demonstrated that ERRs play an important role in the regulation of eukaryotic gene expression, embryonic development, cell proliferation, bone cell production and angiogenesis (17-19). ERRα is an orphan nuclear receptor that does not have corresponding ligands, but may interact with and have a bypass effect on the classical oestrogen signalling pathway through competitive binding to the same target genes, transcription factors and coactivator proteins with ERα (7,20,21). Earlier studies reported the important role of ERRα in energy metabolism of the body via the regulation of its target genes. The metabolic processes that ERRα plays a role in include glucose metabolism (22,23), lipid metabolism (24) and mitochondrial oxidation metabolism (25-27). ERRα regulates the process of glucose metabolism mainly by affecting the gluconeogenic pathway and the derivatization of mitochondria (28,29). ERRα influences the lipid metabolism process through targeting and regulating genes of the fatty acid β oxidation pathway, such as acetyl-coenzyme A dehydrogenase and malonyl coenzyme A decarboxylase (30). ERRα regulates mitochondrial oxidation metabolism by upregulating gene expression related to oxidative phosphorylation through combined action with PGC-1α as the coactivator (31). When the body is affected by changes in the external environment, such as hunger and cold temperatures, the upregulation of ERRα expression may promote energy generation and the utilization of body energy, achieving an optimal adaptive state (32).

The mRNA of PPARγ is made up of ~4,000 nucleotides. A total of four subtypes of mRNA can be produced by different promoters and alternative splicing: PPARγl, PPARγ2, PPARγ3 and PPARγ4 (33). The isomers of these four mRNA subtypes have different promoters, expression modes, ligand affinity and tissue distribution. PPARγ1 is the main subtype of PPARγ and is relatively widely distributed (34). It is primarily distributed in adipose tissue, liver, heart, pancreas, intestines, kidney and skeletal muscle. The expression levels of PPARγ2 are the highest in adipose tissue, and lowest in skeletal muscle (35). PPARγ3 is expressed only in macrophages and the large intestine (36). However, little is known concerning PPARγ4 expression. PPARγ is differently expressed in a variety of tissues (Table I) (14). PPARγ regulates the expression of target genes through ligand-dependent mechanisms, thereby participating in a series of physiological processes. There are two types of PPARγ ligands: Endogenous and exogenous (37). The exogenous ligands contain insulin sensitizers used in the treatment of clinical diabetes, tyrosine-containing drugs, such as GW1929, and phenylacetic acid derivatives, such as ibuprofen (38). The endogenous ligands are mainly prostaglandin-derived metabolites (39). PPARγ forms a heterodimer with RXRα, and then binds to a specific DNA sequence of the PPRE to activate target genes (40). Based on previous studies, PPARγ exerts various biological effects and plays important roles in lipid metabolism (41), glucose metabolism (42), atherosclerosis formation (43) and inflammatory response (44). In addition, as a nuclear hormone receptor, PPARγ can affect the function of fatty acids and its derivatives at the transcriptional level to regulate cell survival and control the occurrence and development of cancer in different tissues (45).

Both ERRα and PPARγ are members of the nuclear receptor superfamily, and as ligand-dependent transcription factors, they need to bind to co-factors to form heterodimers and participate in the regulation of their target genes. A genome-wide analysis of ERRα and ERRγ has confirmed their direct and overlapping binding at the promoter regions of a large number of mitochondrial genes, a number of which are PGC-1α targets (46). These genes cover various aspects of mitochondrial oxidative metabolism, ranging from glucose utilization, fatty acid oxidation, the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) (46). Using laser capture techniques, Teng *et al* (47) demonstrated that the expression of the selected ERRα target gene isocitrate dehydrogenase (IDH) was involved in the TCA cycle. PPARγ is a master regulator of macrophage polarization. Angajala *et al* (48) showed that macrophages control the first break of the TCA cycle that occurs in the enzymatic step involving IDH. Wei *et al* (49) demonstrated that rosiglitazone-activated PPARγ can induce ERRα expression. PGC-1α can target ERRα and transactivate nuclear factor erythroid 2-related factor (NRF)1/NRF2 target genes, which are the nuclear respiratory factors (50). In addition, research has revealed that the induction of NRF1 transcription factors is a prerequisite for the transcriptional activation of cytochrome *c* (cyt *c*), which is an important electron transporter in OXPHOS (51). ERRα was previously implicated in regulating the gene encoding medium-chain acyl-CoA dehydrogenase (MCAD), which catalyses the initial step in mitochondrial fatty acid oxidation (52). Additionally, MCAD was previously reported to be a target gene of PPARγ (53). Gandhi *et al* (54) demonstrated that increased PPARγ levels can regulate insulin-mediated glucose uptake through the translocation and activation of glucose transporter type 4 in the PI3K/phosphorylated-Akt signalling cascade. Therefore, both ERRα and PPARγ can regulate the amount of acetyl-CoA that will enter the TCA cycle by affecting fatty acid metabolism. The aforementioned findings indicated that PPARγ can also affect the production of pyruvates associated with the TCA cycle by affecting the glycolysis pathway. It was also suggested that ERRα expression can influence cyt *c* expression, which is closely associated with the OXPHOS process. Glycolysis, fatty acid metabolism, OXPHOS and the TCA cycle are all ubiquitous metabolic pathways in the body that provide the most direct energy source, ATP (Fig. 1).

3. Association of ERRα and PPARγ with disease

ERRα recruits co-regulators, is activated in a constitutive manner, regulates gene transcription, and serves an important

Table I. Expression levels of ERRα and PPARγ in various tissues.

Gene	Top ten tissues of gene expression in C57/Bl6J mouse, displayed from high to low (14)									
ERRα	Jejunum	Ileum	Olfactory bulb	Kidney	Heart	Gall bladder	Muscle	Preputial gland	BAT	Duodenum
PPARγ	WAT	BAT	Colon	Stomach	Preputial gland	Thyroid	Aorta	Skin	Ovary	Eye

ERRα, estrogen receptor-associated receptor α; PPARγ, peroxisome proliferator-activated receptor γ; WAT, white adipose tissue; BAT, brown adipose tissue.

Table II. ERRα-associated diseases and related tissues.

Tissue	Diseases (8)
Heart	Ventricular hypertrophy, myocardial infarction and heart failure
WAT	Obesity
Liver and muscle	Diabetes and non-alcoholic fatty liver disease
Bone	Osteoporosis
Human reproductive organs	Cancer

ERRα, estrogen receptor-associated receptor α; WAT, white adipose tissue.

role in cell physiological functions, as well as participates in the pathological processes of some diseases, such as diabetes, fatty liver and hepatocellular carcinoma (55). Research has demonstrated that the expression levels of OXPHOS-associated genes are downregulated early in the development of insulin resistance in human diabetes (56). ERRα is a target gene of PGC-1, and hence can regulate the expression of OXPHOS and fatty acid oxidation genes. Studies have reported that the expression levels of ERRα-regulated genes are decreased in patients with insulin resistance (57), and there is an association between insulin sensitivity and the expression of ERRα mRNA in human adipose tissue (58). Overaccumulation of triglycerides in liver cells leads to non-alcoholic fatty liver disease (NAFLD). Decreased expression of ERRα affects the intake of dietary fat, thus inhibiting NAFLD development (59). In addition, a previous study indicated that the absence of ERRα activity promoted the development of rapamycin-induced NAFLD (60). Furthermore, in a mouse model of pressure overload-induced left ventricular hypertrophy, ERRα expression was found to be significantly downregulated, which resulted in faster development of heart failure (61). In addition, several studies found that in rodent models of heart failure, including models of decompensated right ventricular hypertrophy and myocardial infarction, and genetic models that show accelerated heart failure, the expression of ERRα and its coactivator are reduced (62-64).

A number of studies have demonstrated the close association between ERRα and the occurrence, development and clinical prognosis of various tumours. In hormone-dependent tumours, such as endometrial (65), ovarian (20), breast (66) and prostate cancer (67), ERRα may regulate tumour development through its effect on the ERα signalling pathway. In non-hormone-dependent tumours, including colorectal cancer, non-small cell lung cancer, nasopharyngeal carcinoma and glioma, ERRα may play a role by indirectly affecting gene transcription or proliferation of tumour cells. In endometrial cancer, a previous study revealed that upregulated expression of ERRα was significantly associated with tumour cell proliferation (68). Based on the findings of previous studies, it has been proposed that ERRs and ERs are co-expressed in ovarian cancer, and the interaction between these two families may be the molecular basis for the complex endocrine biological behaviour of ovarian cancer. Sun *et al* (20) showed that the ERRα was associated with the occurrence of ovarian cancer and the survival rate of patients, and could be used as a factor for poor prognosis of ovarian cancer. In addition, breast cancer is also a hormone-dependent tumour. Kraus *et al* (69) pointed out that ERRα could compete with ERα to bind to the oestrogen response element to regulate the transcription of target genes. Recent *in vitro* studies demonstrated that ERRα promoted triple-negative breast cancer (TNBC) cell migration and invasion, which was regulated by STAT3, providing a potential therapeutic option against TNBC metastasis (70). Previous studies on prostate cancer revealed that ERR protein was highly expressed in prostatic epithelial cells, whereas in prostate cancer cells expression was lower, and the increase of ERRα expression levels was significantly associated with prostate cancer development, disease prognosis and the survival rate of patients (67,71). ERRα-associated diseases and related tissues are shown in Table II (8).

The biological functions of PPARγ are complex and diverse, and studies have provided a number of novel approaches for the clinical prevention and treatment of diabetes (72), atherosclerosis, hypertension, NFLAD (73) and kidney disease (74). For the treatment of diabetes, thiazolidinedione (TZD) drugs can promote glucose utilization in skeletal muscle and inhibit glucose synthesis in the liver (75). When activated by TZD, PPARγ can promote the expression of the PI3K subunit p85, promote c-Cbl associated protein (CAP) transcription, promote insulin signalling and improve insulin resistance (76). In islet α cells, activated PPARγ improved insulin resistance by suppressing the activity of the transcription factor Pax6 and suppressing the expression of glucagon at the transcription level (77). Studies have reported that PPARγ ligands can induce CD36 expression, promote the phagocytosis of oxidized low-density lipoprotein by macrophages and cause

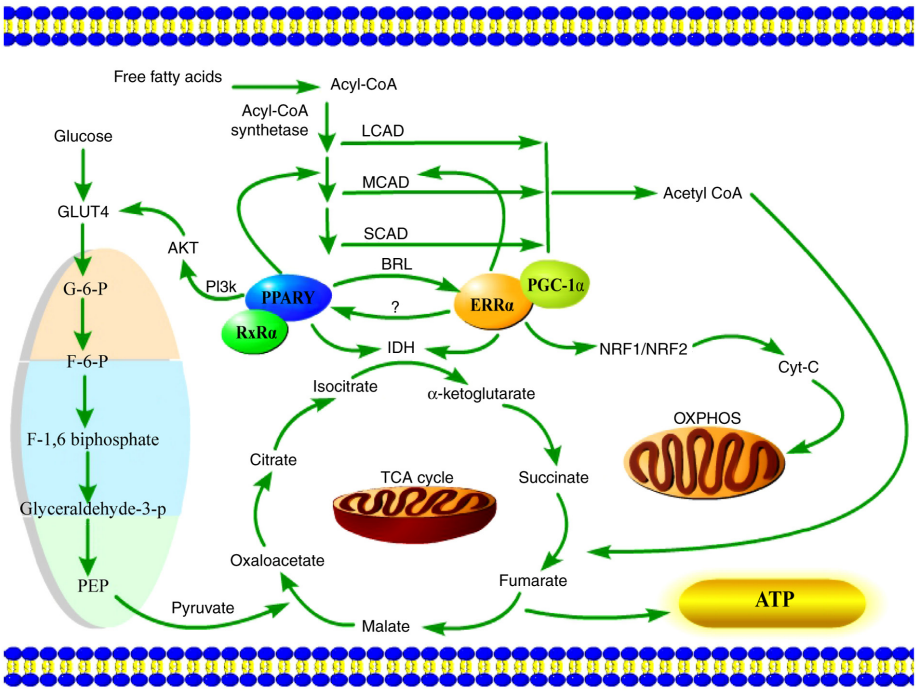

Figure 1. ERRα and PPARγ in energy metabolism. PPARγ affects glycolysis via the PI3K/p-Akt signaling pathway. Pyruvate produced by glycolysis enters the mitochondria to produce ATP via the TCA cycle. ERRα affects fatty acid oxidation via regulating MCAD and also affects OXPHOS via targeting NRF1/NRF2 genes. Acetyl CoA is produced through the β-oxidation of acyl-CoA and participates in the TCA cycle to produce ATP. The mitochondrial respiratory chain couples with ATP synthase to complete the process of OXPHOS and produce ATP. LCAD, long-chain acyl-CoA dehydrogenase; MCAD, medium-chain acyl-CoA; SCAD, short-chain acyl-CoA dehydrogenase; TCA, tricarboxylic acid cycle; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate; ERRα, estrogen receptor-associated receptor α; PPARγ, peroxisome proliferator-activated receptor γ; GLUT4, glucose transporter type 4; G-6-P, glucose 6-phosphate; F-6-P, fructose 6-phosphate; PEP, phosphoenolpyruvate; RXRα, retinoid X receptor α; PGC-1α, peroxisome proliferator-activated receptor γ coactivator-1α; NRF, nuclear factor erythroid 2-related factor; cyt c, cytochrome *c*; IDH, isocitrate dehydrogenase.

Table III. PPARγ-associated diseases and related tissues.

Tissue	Diseases (96)
WAT	Diabetes and atherosclerosis
CNS	Parkinson's disease, Alzheimer's disease, brain injury and ALS
Heart	Cardiomyopathies
Kidney	Kidney disease
Breast	Breast cancer

PPARγ, peroxisome proliferator-activated receptor γ; WAT, white adipose tissue; CNS, central nervous system; ALS, amyotrophic lateral sclerosis.

intracellular lipid accumulation (78,79). In addition to enabling lipids to be taken up by macrophages, PPARγ can also transfer excess intracellular cholesterol to the extracellular space via ATP-binding cassette transporter A1 protein (80). Intimal macrophages engulf cholesterol and form foam cells during the progression of atherosclerosis. PPARγ is expressed in the vascular endothelium, and PPARγ agonists can lower blood pressure (81). *In vitro* endothelial cell culture experiments found that TZD-like ligands can significantly promote the secretion of vasomotor factor C-type natriuretic peptide in bovine carotid artery endothelial cells and inhibit the secretion of the vasoconstrictor factor endothelin (82).

PPARγ is a nuclear hormone receptor and its transcriptional level may affect the oxidation of fatty acids and the mitochondrial biogenesis of BAT (83). Therefore, PPARγ is most likely involved in the development of cancer in different tissues by regulating cell proliferation and differentiation. The expression of PPARγ has been reported in various types of tumour cells, including breast (84), prostate (85) and lung cancer cells (86), and it has been found that the binding of PPARγ to its ligand could inhibit the growth of tumour cells (87). However, other studies found that the expression levels of PPARγ was significantly increased in endometrial (88) and epithelial ovarian cancer (89, 90). Dong (84) found that efatutazone, a PPARγ agonist, could promote the differentiation of tumour cells in breast cancer in a specific stage, and thus interfere with tumour occurrence and development. In a study on ovarian cancer, Luo *et al* (91) found that PPARγ could upregulate the expression levels of microRNA-125, and thereby inhibit the proliferation of ovarian cancer cells. In colon cancer, studies demonstrated that patients with high PPARγ expression were more likely to survive than those with low PPARγ expression (92). In lung cancer, PPAR activation may inhibit the metastasis of tumour cells by inhibiting the epithelium-mesenchymal transition (93). In pancreatic cancer, it was revealed that PPARγ was highly expressed in pancreatic cancer cells, and activation of PPARγ may inhibit the growth of PANC-1 cells (94). In gastric cancer, He *et al* (95) reported that rosiglitazone, a PPARγ agonist, could induce cell apoptosis, and thus inhibit the growth and invasion of tumour cells, and this effect could be reversed by GW9662, a PPARγ

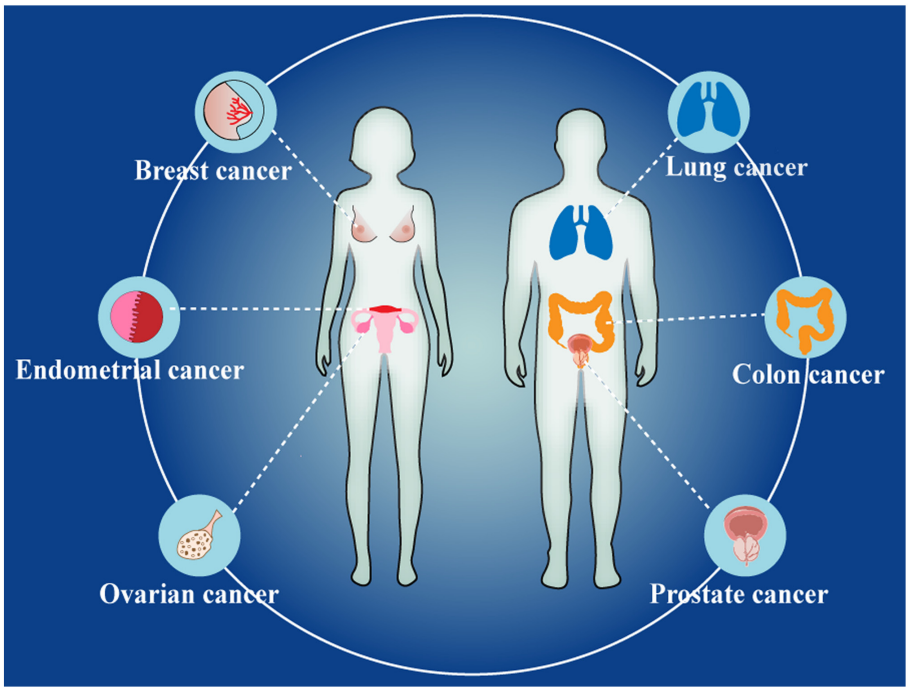

Figure 2. Types of cancer related to both ERRα and PPARγ. ERRα, estrogen receptor-associated receptor α; PPARγ, peroxisome proliferator-activated receptor γ.

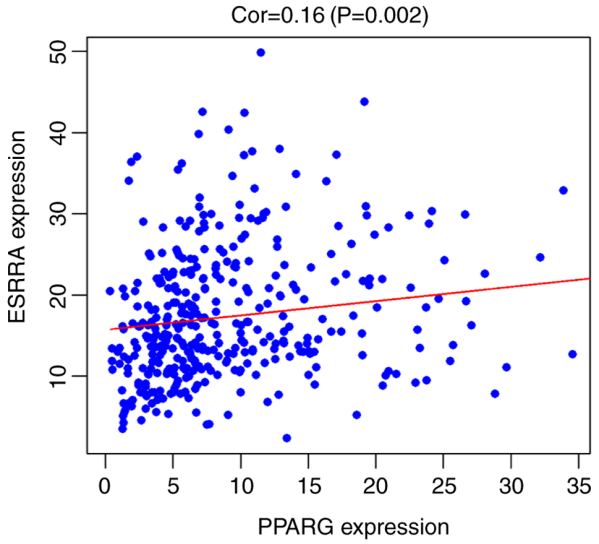

Figure 3. Pearson's correlation analysis. Pearson's correlation coefficient was performed to show the correlation between ERRα expression (ESRRA) and PPARγ expression (PPARG). ERRα, estrogen receptor-associated receptor α; PPARγ/PPARG, peroxisome proliferator-activated receptor γ; ESRRA, steroid hormone receptor ERR1.

antagonist. PPARγ-associated diseases and related tissues are shown in Table III (96).

As aforementioned, both ERRα and PPARγ are involved in tumour development. Specifically, they were reported in studies on hormone-dependent tumours (endometrial, ovarian, breast and prostate cancer) and hormone-independent tumours (lung and colon cancer) (Fig. 2). Using R programming language (version 3.6.3; https://www.r-project.org/), based on The Cancer Genome Atlas database (https://portal.gdc.cancer.gov/), Pearson's correlation analysis was performed. It was found that ERRα expression was weakly positively correlated with PPARγ expression (correlation, r=0.16, P<0.01; Fig. 3). Using bioinformatics analysis, based on the Search Tool for the Retrieval of Interacting Genes database (97), the co-expression analysis revealed that ERRα and PPARγ have a co-expression relationship (Fig. 4), suggesting that the two genes may have several similar functions. The protein-protein interaction network (http://string-db.org/cgi/input.pl) between ERRα and PPARγ showed that ERRα and PPARγ proteins interacted with nuclear receptor coactivator 1, histone acetyltransferase p300, CREB-binding protein, leptin, adiponectin receptor protein 1, CCAAT/enhancer-binding protein b and fatty acid-binding protein adipocyte. Searching UniProt database (https://www.uniprot.org/) and GeneCards database (https://www.genecards.org/), it was found that these interacting proteins are involved in the activation of gene transcription, the modification of transcription factors and cellular energy metabolism (Fig. 5).

4. Conclusions and perspectives

To date, there are very few studies involving both ERRα and PPARγ. A previous study demonstrated that ERRα knockout with small interfering RNA resulted in decreased PPARγ expression levels in 3T3-L1 pre-adipocytes (98). Studies have also reported that PPREs are present at the ERRα promoter, and PPRE was the PPAR response element (49). A previous study revealed that rosiglitazone, as a PPARγ agonist, could induce the expression of ERRα after activating the expression of PPARγ, thus enhancing mitochondrial biogenesis and osteoclast function (49). Therefore, it can be hypothesized that there is an association between ERRα and PPARγ expression. However, further studies are required to verify and clarify this association.

In previous years, studies on ERRα, PPARγ and tumorigenesis were gradually applied to clinical diagnosis and treatment.

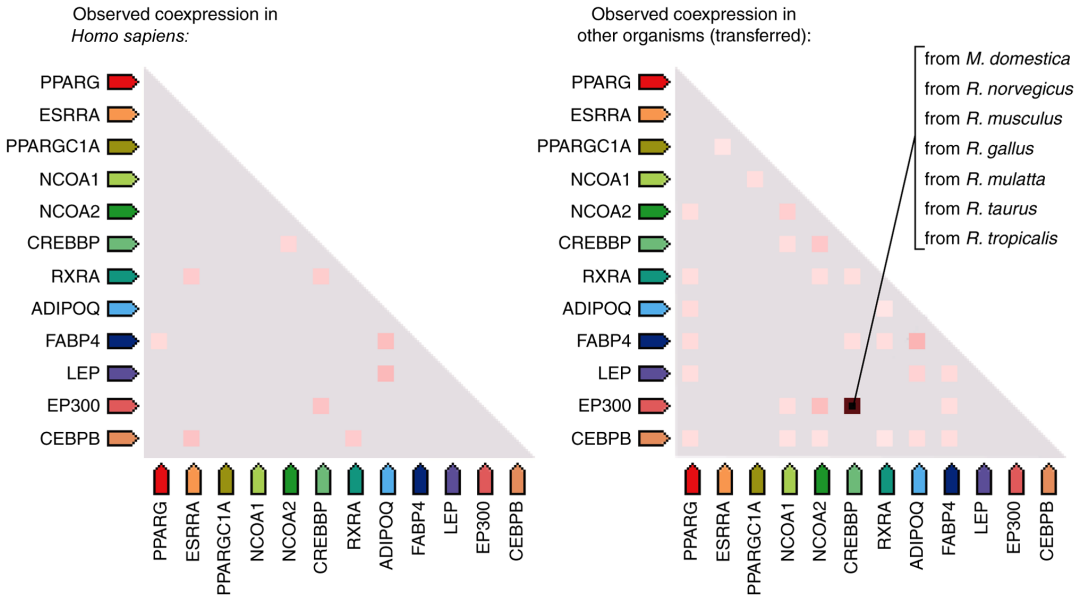

Figure 4. Co-expression network based on RNA expression patterns of ERRα (ESRRA) and PPARγ (PPARG). ERRα, estrogen receptor-associated receptor α; PPARγ/PPARG, peroxisome proliferator-activated receptor γ; ESRRA, steroid hormone receptor ERR1.

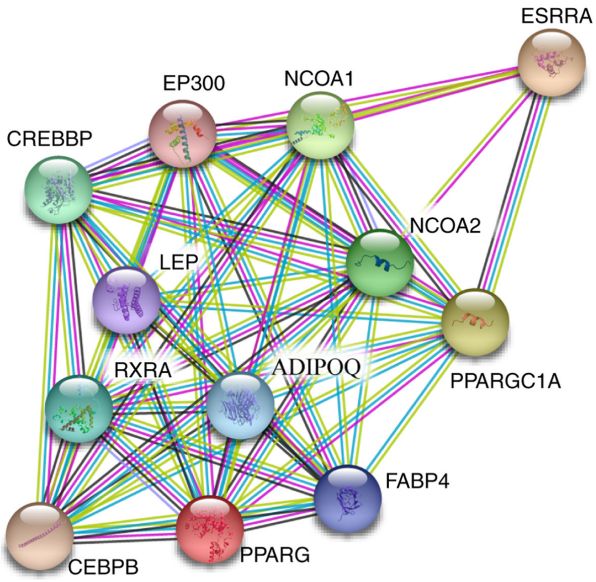

Figure 5. Protein-protein interaction network between ERRα and PPARγ. The protein-protein interaction maps revealed interactome networks related to known proteome properties. ERRα, estrogen receptor-associated receptor α; PPARγ/PPARG, peroxisome proliferator-activated receptor γ; NCOA1, nuclear receptor coactivator 1; EP300, histone acetyltransferase p300; CREBBP, CREB-binding protein; LEP, leptin; ADIPOQ, adiponectin receptor protein 1; CEBPB, CCAAT/enhancer-binding protein b; FABP4, fatty acid-binding protein adipocyte; ESRRA, steroid hormone receptor ERR1; NCOA2, nuclear receptor coactivator 2; PPARGC1A, peroxisome proliferator-activated receptor γ coactivator-1α; RXRA, retinoic acid receptor RXR-α.

In diseases that have been extensively studied, such as ovarian and breast cancer, ERRα is generally considered to be a factor closely related to the poor prognosis of tumours, and hence is also considered to be a potential target for tumour therapy. Meanwhile, PPARγ expression in tumours varies, and the relationship between PPARγ and tumour prognosis is yet to be determined. In metabolic diseases that have been comprehensively studied, such as diabetes, PPARγ has become an important therapeutic target (99). ERRα is also closely related to numerous metabolic diseases. Currently, thiazolidinediones, as PPARγ agonists, have been used in the clinical treatment of metabolic syndromes, and they are expected to play an important role in the treatment of inflammation and tumours (100-102).

However, there are few reports concerning the association between ERRα and PPARγ, the underlying mechanism of their interaction and their combined role in diseases. ERRα and PPARγ are related to a number of diseases, and both act as transcription factors that regulate cellular metabolic functions. Studying the relationship between ERRα and PPARγ could help to further understand the progress of certain diseases and will be useful for drug research. In addition, researches on new drugs for the ERRs have been reported (103), and thus it may be possible to develop ERRα and PPARγ dual-targeted drugs to provide further insight into the treatment of diseases.

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Availability of data and materials

The datasets analyzed during the current study are available in the TCGA database (https://portal.gdc.cancer.gov/) and STRING: functional protein association networks (http://string-db.org/cgi/input.pl).

Authors' contributions

WYH and PMS designed the study. WYH was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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