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Estrogen-related receptor alpha: A novel perspective on skeletal, muscular, and vascular systems

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Abstract: Estrogen-related receptor alpha can significantly affect cell metabolism and play key regulatory roles in healthy and diseased organisms. ERRα is also related to the onset and progression of various cancer types. ERRα is primarily expressed in metabolically active tissues and regulates the transcription of metabolic genes in such tissues. It coordinates metabolism and energy demand, affects osteoblasts, osteoclasts, and chondrocytes, promotes muscle regeneration, participates in angiogenesis, and regulates cell aging. In this study, the literature related to the identification of ERRα in skeletal, muscular, and vascular systems was reviewed to further elucidate this receptor.

Introduction

Nuclear receptors (NRs) are transcription factors that contain ligand-dependent molecules and orphan NRs. Natural ligands of NRs have not been identified. The earliest orphan NR identified was the estrogen-related receptor (ERR), which comprises three members (ERRα, ERRβ, and ERRγ, also known as Estrogen-related receptor alpha, ESRRA, NR3B1; ESRRB, NR3B2; and ESRRG, NR3B3, respectively) [1]. Although ERR is highly similar to ER, ERR does not bind to estrogen. Nevertheless, ERRα is involved in the estrogen regulatory pathway [2].

ERRα has numerous physiological functions with several different downstream effects (Fig. 1). Gene transcription analysis in mice revealed that ERRα was expressed in various organs [3]. Currently, ERRα is reported to critically affect cellular metabolism, general growth and development, and skeletal homeostasis [4]. ERRα is involved in tumor cell-associated metabolic processes. The function of ERRα in tumorigenesis has been elucidated through prior reports; furthermore, ERRα expression in tumorigenesis has a close relationship with tumor prognosis [5,6]. Reportedly, ERRα exerts certain regulatory effects on normal physiology and bone development [7,8]. It is involved in the regulation of osteocytes, osteoclasts (OCs), and chondrocytes, and consequently promotes the onset and progression of various diseases, including osteoporosis and osteoarthritis (OA). The involvement of ERRα in muscle differentiation has been reported previously [9–11]. The adult skeletal muscle is a relatively plastic tissue that may undergo changes under physical conditions. NR is an important regulator of skeletal muscle function, which is achieved through transcription factors. Previously, studies have investigated the physiological and metabolic functions of ERRα. However, these functions require further elucidation. Because ERRα has not been specifically reported in muscle, blood vessels, and bone, recent insights were summarized in this study to provide valuable guidance for further research.

Structure and function of ERRα

Structurally, ERRα appears to be similar to human ERR DNA-binding region sequence. based on this characteristic, novel steroid receptors have been identified via a cDNA library method [2]. An unknown protein, ERRα, with conserved steroid receptors, was identified in cDNA libraries of the kidney and heart. Notably, certain synthetic compounds can regulate the transcriptional activity of ERR [12–14], with a large proportion of these compounds inhibiting ERRα transcriptional activity.

Although DNA-binding regions of ERR and ER were reportedly similar (68%), other proteins—including the ligand and E region—only appeared to have a moderate similarity degree (36%). Thus, it is evident that ERRα cannot bind to estrogen [15]. However, ERRα is reported to have a certain effect on the estrogen pathway [16,17].

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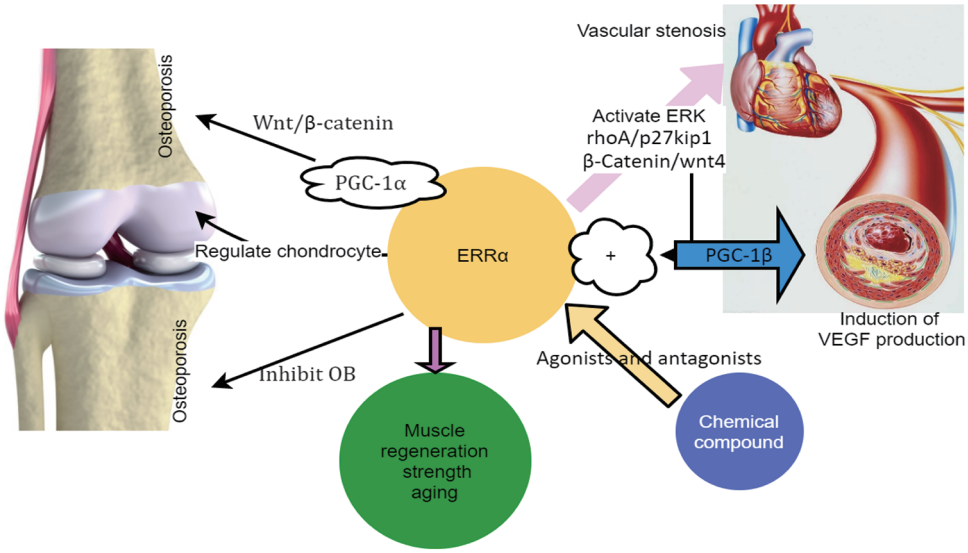

FIGURE 1. ERRα regulates the abnormal proliferation of VSMC and causes vascular stenosis. ERRα regulates muscle strength and the aging and regeneration of skeletal muscles. ERRα regulates osteoporosis and chondrocytes. Some agonists and antagonists of ERRα.

ERR presents the typical structural features of NR (Fig. 2) [18]. These include the AF-1 domain, DNA-binding domain (DBD), ligand binding domain (LBD), and AF-2 domain. The N-terminal contains the AF-1 domain, which enables weak transcriptional activation in a ligand-independent manner. NR proteins have several conserved regions, including a centrally located DBD and a C-terminal ligand-binding region. The latter is known to interact with transcriptional coregulators. ERR is localized primarily in the nucleus, which can facilitate the identification of the ERR response factors on or beyond the target gene promoter and the regulation of downstream target genes.

A recent study has reported extensive crosstalk between peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and ERRα, and the two proteins can influence the transcriptional activities of one another [18]. ERRα regulates the inflammatory response of macrophages. As part of its action mechanism, ERRα directly acts on the promoter region of the deoxygenase Tnfaip3 on the Toll-like receptor (TLR) signaling pathway. Furthermore, ERRα regulates TLR-induced inflammatory response [19]. The transcriptional coactivator family of PGC-1 integrates multiple pathways involving numerous NRs and non-NRs to activate fatty acid oxidation, mitochondria, glucose uptake, and gluconeogenesis in various tissues [20]. Reportedly, PGC-1α is considered a highly efficient ERRα coactivator, which regulates a variety of metabolic genes through synergy [21,22]. Similarly, thyroid hormone (TH) increases the expression of PGC-1α in the liver, which consequently upregulated ERRα expression, thereby promoting the TH-induced mitochondrial activity. ERRα expression can be regulated by estrogen receptor (ER) agonists or antagonists. ERRα can bind to multiple ER response units and recruit ERs similar to those recruited by coregulators, thereby mimicking ER-mediated gene expression [23].

ERRα plays regulatory roles at transcriptional levels, and the effect of microRNA (miR) on ERRα mRNA has been reported. ERRα expression decreased as a result of the action of miR-125a in the 3′ UTR sequence [24]. Additionally, ERRα has an inhibitory effect [25]. MiR-125a is reported to affect ERRα expression. Other microRNAs (miR-137, miR-497, and miR-135a) can target conserved

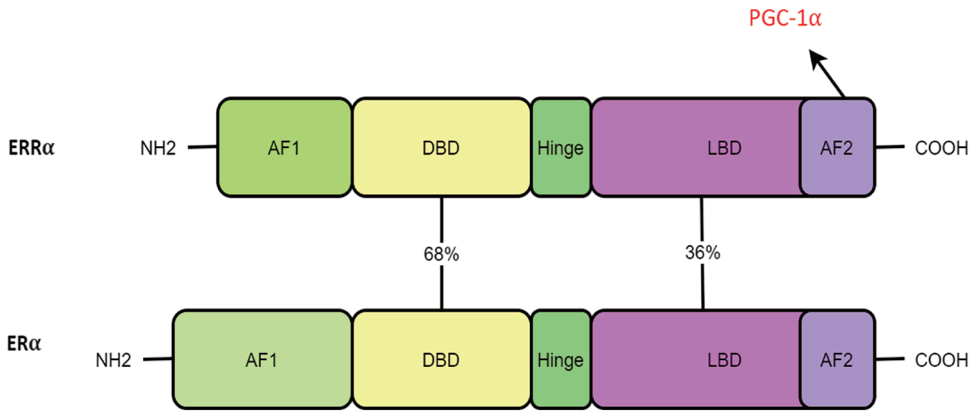

FIGURE 2. ERRα and ERα have the same structural features and domain homology, including the AF-1 domain, DNA-binding domain (DBD), ligand binding domain (LBD), and AF-2 domain.

sequences in the 3′ UTR [26–28]. In addition, miRs can inhibit tumor cell proliferation, cell migration, and extracellular matrix invasion.

Additionally, post-translational modifications can regulate ERRα activity. Protein stability is maintained through proteasome-dependent processes and ubiquitination. Parkin enables the expression of the ERR receptor in dopaminergic neurons and ERRα degradation in vascular endothelial cells [29,30]. Physically, ERRα interacts with the histone demethylase lysine-specific demethylase1 (LSD1), which consequently transforms the receptor's function from transcriptional repression to transcriptional activation [31]. LSD1 protects the receptor from ubiquitination and proteasome-dependent degradation, regardless of its enzymatic activity [32]. Although the mechanism of this protective effect requires further clarification, this mechanism may facilitate the efficient activation of the target of ERR-LSD1. ERRα can be phosphorylated via the following two pathways: the cAMP/PKA-dependent pathway in lung cells [33] and the EGF/MEK pathway in colorectal cancer cells [34]. Moreover, this synergistic effect upregulates ERRα expression, thereby increasing the activity of the surfactant A promoter and accelerating tumor growth. The involvement of these signaling pathways in ERRα mRNA is currently unclear. Thus, ERRα phosphorylation is assumed to be responsible for the stabilization of these pathways.

ERRα and skeletal muscle diseases

ERRα regulates bone and muscle growth. The expression of ERRα in humans is critical for the body's metabolism and physiology [35]. Additionally, ERRα expression in bones and cartilage of limbs and the trunk may be critical for the regulation of the bone metabolism balance [36,37].

Skeletal muscle, the largest tissue in the human body, plays a pivotal role in the body's metabolism and exercise. Many mitochondrial function genes related to skeletal muscle aging were expressed based on the results of a public gene database analysis [38]. Polymerase chain reaction (PCR) results showed a significant decrease in the expression level of ERRα in the skeletal muscle of aged rats. In addition, the gastrocnemius muscle of rats showed significant differences between age groups in terms of ERRα expression, and the expression showed a tendency to decrease with increasing age [39]. ERR is an important transcription factor related to mitochondrial energy metabolism in the skeletal muscle aging process, and it is expected to become a new drug for muscle atrophy in older adults in the future. ERRα plays a key role in the regulation of oxidation and oxidative stress. The basic metabolic oxidative capacity of the ERRα deletion group was reported to be significantly decreased. Moreover, a significant decrease in its activity was observed [40]. Ahn et al. [41] reported that the body mass of the rats in the administration group did not change significantly. However, their endurance and grasping abilities were increased, which was attributed to the expression of myocyte enhancer-binding factor 2 (MEF2) transcription factors, such as PGC-1α and ERRα, thereby improving the effect of oxidative muscle fibers. The results showed that ERRα played a role in enhancing muscle strength. In adult muscle tissues, ERRα expression increases with exercise, consequently promoting mitochondria-driven oxidative remodeling [42].

Skeletal muscle aging in older adults considerably affects their quality of life. A previous study has reported that long-term accumulation of reactive oxygen species may cause damage to the structure and function of skeletal muscle mitochondria, thereby leading to mitochondrial damage [43]. In recent years, however, some scholars have opposed this concept [44]. Currently, the imbalance between mitochondrial energy metabolism and calcium balance has garnered increasing attention [45–47]. ERRα regulates the expression of more than 100 genes in mitochondrial electron transport [48]. ERRα is one of the key factors that affect the aging of skeletal muscle cells and plays a key role in ATP synthesis [49–51].

Mature skeletal muscles can independently recover after exposure to injury from daily activities and external stress. Regeneration of skeletal muscle is a necessary process for the human body to maintain the normal quality and function of the muscle, thereby meeting various diastolic and operational needs. ERRα regulates mitochondrial synthesis, glucose, and fatty acid oxidation in skeletal muscle cells. Controlling the oxidative capacity of mitochondria is an important step in maintaining normal muscle fiber regeneration during muscle regeneration [52]. LaBarge et al. [53] observed that muscle cell regeneration was impaired by constructing a muscle-specific ERRα−/−(M-ERRα−/−) mouse model. This mouse model showed that muscle fibers are shrunk and that cells clump together. Additionally, the decrease in mitochondrial biogenesis factors was associated with mitochondrial oxidative repair damage in M-ERR. The AMPK pathway is involved in the regeneration of normal muscle and the expression of ERRα. However, increased expression of AMPK during early regeneration may affect muscle fiber growth. Therefore, the delayed recovery of myofibers in the M-ERRα−/− muscle may be caused by increased AMPK activation. In summary, AMPK can regulate mitochondria by activating the ERRα pathway and promoting muscle regeneration. In contrast, in patients with facioscapulohumeral muscular dystrophy (FSHD), PGC-1α is an important cofactor of ERRα. Banerji et al. [54] reported the morphological and associated transcriptional changes of FSHD myogenesis. They reported that the inhibition of PGC-1α can inhibit the expression of ERRα in FSHD, which affects muscle differentiation and thus causes muscle atrophy. Furthermore, Sjögren et al. [55] reported that the regulatory effect of PGC-1α on the Branched-chain amino acid (BCAA) gene in human muscle tubes is related to ERRα. The PGC-1α-ERRα pathway may rescue myogenically differentiated cell lines from FSHD by adjusting nutrients—such as streptomycin A, flavonols, and genistein—to increase muscle diameter. The novel research results discussed above indicated that regulating the PGC1-α-ERR pathway can improve muscle strength in patients with FSHD and accelerate its repair and regeneration. PGC-1 is an important coactivator of ERRα, which cooperates with numerous metabolic genes. ERRα, as an important transcriptional activator, plays an important role in the oxidative process of the heart and skeletal muscles, which is consistent with the role of PGC-1α. Additionally, this observation was consistent

with the functional interaction of ERRα with PGC-1α, which is co-expressed with ERRα in these tissues.

Large amounts of lipid deposition can lead to cardiovascular diseases, and exposure of the liver and pancreas to large amounts of lipid causes lipid accumulation. In muscles, fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) are key steps in fatty acid depletion. ERRα regulates the genes for FAO and OXPHOS in muscle. Kitamura et al. [56] treated the C2C12 mouse muscle cell line with 50 μM daidzein. FAO and OXPHOS genes were reported to be significantly upregulated, whereas ERRα may have been partially blocked. This indicated that soybean sapogenins regulate FAO and OXPHOS genes at least partially through the ERRα pathway, thereby reducing lipid deposition in muscle cells. Daidzein is reported to be involved in regulating ERRα, which consequently prevents various muscle lipotoxicity-caused diseases. Recently, resveratrol, a natural polyphenol contained in red wine, was shown to ameliorate high-fat diet-induced cardiomyopathy in an ERRα-dependent manner [57].

In summary, ERRα showed positive effects on skeletal muscle regeneration, angiogenesis, muscle strength, and improvement in aging status (Fig. 3).

ERRα and vascular-related diseases

To the best of our knowledge, effective treatments for peripheral arterial disease (PAD) and critical limb ischemia (CLI) are currently unavailable. Furthermore, mechanisms underlying intramuscular angiogenesis remain poorly understood. Sopariwala et al. [58] used a skeletal muscle-specific ERRα transgenic mouse model and reported that ERRα is a hypoxia-stimulating factor. Additionally, ERRα overexpression activates the angiogenic gene program in skeletal muscle, increases the distribution of blood vessels in skeletal muscles, promotes ischemic angiogenesis and vascular regeneration in skeletal muscles, and restores the blood supply of ischemic muscle. Therefore, in skeletal muscles, ERRα may be involved in muscle angiogenesis and can alleviate vascular complications caused by ischemic diseases including diabetes.

Metabolically active tissues such as skeletal muscles can regulate vascular density, thereby satisfying metabolic demands. However, the molecular mechanisms that coordinate these processes remain poorly understood. Oxygen and carbon sources reach the tissues via the vascular system as part of aerobic metabolism. According to the findings reported by a new study, ERRα overexpression in skeletal muscle promoted revascularization, characterized by increased capillary staining and muscle perfusion in diet-induced obese (DIO) mice after hindlimb ischemic injury. ERRα activation can promote ischemic revascularization and muscle recovery in obesity [59]. Transcriptional coactivator 1β (PGC-1β) reportedly induces vascular endothelial growth factor (VEGF) production, a process that requires the involvement of ERRα [60]. Baicalein is involved in angiogenesis through the baicalin-induced VEGF expression via activation of the ERRα pathway [61]. In addition, ERRα is involved in the regulation of vascular development during sinus follicle formation and affects angiogenesis [62].

Physical activity has a variety of beneficial effects on the human body through the metabolic, musculoskeletal, and nervous systems [63]. Furthermore, exercise increases serum levels of beta-aminoisobutyric acid (BAIBA), a compound that reduces insulin resistance and inflammation in skeletal muscle, induces the browning of white adipose tissues, and promotes fatty acid oxidation in the liver. *In vitro* experiments revealed that BAIBA has a significant

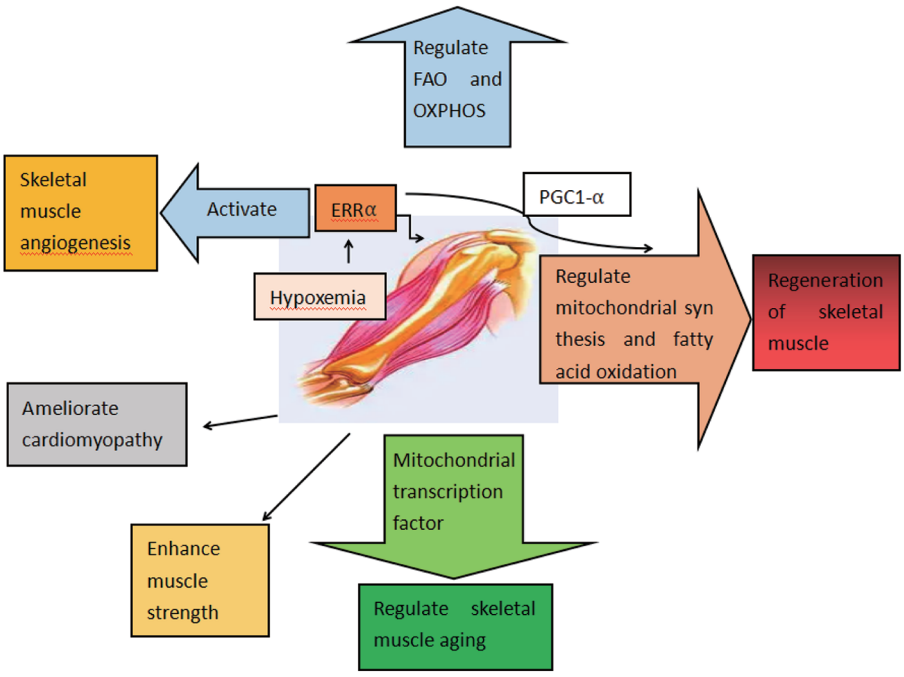

FIGURE 3. Functions of ERRα in skeletal muscle diseases. ERRα regulates FAO and OXPHOS. ERRα regulates the regeneration of skeletal muscle. ERRα enhances muscle strength and regulates skeletal muscle aging. ERRα regulates lipid deposition. ERRα ameliorates cardiomyopathy. ERRα activates skeletal muscle angiogenesis.

promoting effect on vascular endothelium and vascular endothelial cells, increases the expression of transcription factors including ERRα, and plays a role via PGC-1β-ERRα/PPAR-δ and PPAR-γ pathways [64].

Oxidative stress is reported to be a key contributor to vascular endothelial dysfunction and may result from an imbalance between antioxidant capacity and active substances [65]. Expression of ERRα was detectable in vascular endothelial cells (EC). However, the other two ERR isoforms—i.e., ERRβ and ERRγ—were nearly undetectable [66]. Notably, 17β-estradiol (E2)-induced ERRα expression enhanced fatty acid uptake/oxidation, increased mitochondrial replication and ATP production, and reduced formation of reactive oxygen species (ROS). Furthermore, E2-induced ERRα expression regulated fatty acid metabolism and reduced circulating lipids via endothelial cells. In mice on a high-fat diet, overexpression of ERRα in the vessel wall normalized the increase in plasma lipids induced by E2 deficiency, thereby ameliorating vascular injury [67].

The abnormal proliferation of vascular smooth muscle cells (VSMCs) was closely associated with the onset and progression of cardiovascular diseases. Abnormal migration and proliferation of vascular smooth muscle cells may lead to vascular restenosis [68]. Therefore, inhibiting the proliferation and migration of vascular smooth muscle cells is an effective strategy to help prevent cardiovascular diseases. The results revealed that XCT790 could reduce the expression of the ERRα gene, consequently inhibiting the ERK signaling pathway, thereby inhibiting VSMC proliferation [69]. The signal transduction of RhoA/p27Kip1 and β-Catenin/Wnt4 is related to the proliferation and migration of VSMCs. XCT790 significantly inhibited the proliferation, phenotypic transformation, and migration of rat RASMCs, whereas the reduction in ERRα inhibited the formation of RASMCs, cyclin transcription, and Rb hyperphosphorylation. Finally, ERRα exerts a significant inhibitory effect on the neovascularization of rat angiogenesis [70]. Therefore, ERRα has the potential to act as a new therapy.

In conclusion, ERRα can promote angiogenesis and improve vascular damage through various pathways, making it a new therapy.

ERRα and osteoporosis

Owing to the progressively aging population worldwide, osteoporosis has become a major public health concern, particularly in postmenopausal women. Osteoblasts (OBs) and OCs are the two main types of bone cells that coordinate with each other to maintain bone homeostasis. Bone formation in OB is impaired with aging due to a decrease in the number and activity of OB. Conversely, in OC, bone resorption increases and osteoporosis develops when bone resorption exceeds bone formation. Osteoporosis is a metabolic disease, and inhibition of OC differentiation may be a viable treatment direction for osteoporosis.

Notably, the expression levels of ERRα are particularly high in bone cells at all developmental stages, i.e., from the earliest precursor cells to the most mature OB in mineralized nodules. Additionally, the 23-bp nucleotide repeat polymorphism of the ERRα gene may be associated with bone mineral density [71]. Additionally, ERRα is reported to inhibit OB development and bone formation [72,73]. Inhibition of ERRα in primary rat cranial (RC) cells prevents differentiation of RC cells into mature OB and significantly reduces the number of mineralized bone nodules, whereas ERRα overexpression enhances differentiation, thereby affecting multiple stages of OB development [73].

ERRα can activate or inhibit Wnt signaling depending on the presence or absence of PGC-1α; furthermore, coactivators, including ERRα and PGC-1α, are novel regulators of the Wnt signaling pathway during OB differentiation [74]. Wnt pathway regulation is cell-intrinsic and does not affect β-linked protein nuclear translocation. However, the regulation of this pathway is dependent on the DNA binding of ERRα. Both knockdown and activation of ERRα in C3H10T1/2 cells regulate osteogenic differentiation via a DNA binding-dependent mechanism, and expression of active ERRα correlates with the effects of OB differentiation in the Wnt pathway. Female ERRα knockout mice are reportedly resistant to bone loss, suggesting that ERRα is an inhibitor of OB differentiation *in vivo* [75]. ERRα has also been reported to exert a certain induction effect on mesenchymal stem cells derived from periodontal tissue *in vitro* [73]. OBs are differentiated from mesenchymal stem cells (MSCs) [76,77]. In these cells, ERRα and Glutaminase (Gls) levels are elevated during the osteogenic induction of human MSCs [78]. The signal transduction pathway of ERRα/Gls plays a key role in this process. Therefore, the increase in ERRα in rat bone marrow mesenchymal stem cells can remarkably promote the expression of Gls, increase the consumption of glutamine (Gln), and rescue the osteogenic ability. ERRα knockout can counteract oophorectomy-caused bone loss. However, it cannot regulate natural aging-caused bone loss [79].

ERRα is dynamically regulated during OC differentiation, and MYC (a broadly acting transcription factor) regulates OC production [80] and consequently bone remodeling through ERRα modulation. In addition, ERRα is associated with OC adhesion, migration, and invasion [81,82]. ERRα deficiency reportedly disrupts OC differentiation and inhibits bone resorption [83]. *In vivo* studies have reported that bone mineral density in ERRα knockout female mice does not experience an age-related decrease [73,84], which is associated with increased bone formation. However, bone resorption is unaltered, and the amount and activity of OC remain unchanged [85], highlighting that the effect is mediated by OB rather than OC [86].

ERRα is involved in regulating OC differentiation and the response to rosiglitazone, a synthetic PPAR γ agonist, thereby causing bone loss [87]. PPAR γ can activate OC formation and inhibit OB formation, indicating that rosiglitazone can reduce bone formation while maintaining or increasing bone resorption. Notably, PPARγ induces the expression of ERRα. After the ERRα-mediated release of PGC1β, the dependent mechanism induces mitochondrial gene expression to promote OC formation. Furthermore, a polymorphic autoregulatory hormone response element on

the human ERRα promoter was associated with bone mineral density. These findings not only identify ERRα as a critical regulator of skeletal and mineral homeostasis but also highlight a functional association between the PPARγ and ERRα pathways, converging at the transcriptional coactivator PGC1β. Therefore, rosiglitazone stimulates the formation of OCs and bone resorption via a transcriptional network comprised of ERRα, PPARγ, and PGC1β.

ERRα-knockout cells and mice cannot respond to statins, bisphosphonates, and cholesterol [88]. Thus, ERRα is involved in the regulation of the cholesterol pathway. Statins are reported to reduce osteoporosis by lowering cholesterol. Cholesterol oxidation products (COPs) are important compounds that maintain bone metabolism homeostasis. COPs participate in many vital biological processes, such as the differentiation of MSCs, bone formation in OB, and bone absorption in OC. Recent research confirmed that the effect of specific COPs on MSCs the promotion of OB production and inhibition of adipocyte production [89]. Cholesterol is known to affect ERRα, and the evidence of this activity was derived from the investigation of the bone calcium production process. Additionally, the luciferase report proved that cholesterol can regulate the transcriptional activity of ERRα [90]. ERRα-knockout mice exhibited a decrease in bone resorption and an increase in bone mass, highlighting that ERRα can promote OC differentiation. OC function inhibition is achieved through the administration of statins and nitrogen-containing bisphosphonates. These drugs can inhibit cholesterol biosynthesis and reduce cholesterol accumulation by blocking HMG-CoA reductase and farnesyl diphosphate synthesis (FPPS), respectively [91,92]. However, in the absence of ERRα, OC differentiation is not inhibited by statins or enhanced by cholesterol. These observations highlighted the role of cholesterol as an ERRα agonist involved in OC formation. Cholesterol can also enhance ERR α in OCs and PGC1β. Their interaction subsequently promotes OC formation and bone absorption. Bisphosphonates can negatively regulate OC-mediated bone absorption in patients with cancer. Thus the application of bisphosphonates to protect the bones of patients with cancer is particularly widespread [93].

Sterol regulatory factor-2 (SREBP2) is a vital class of transcription factors that can regulate cholesterol synthesis and OC differentiation [94,95]. Yao et al. [96] applied carnosic acid (CA) to a murine monocyte line and revealed that CA inhibited SREBP2 activity and OC formation, directly bound to ERRα, and promoted its degradation. These findings demonstrated the excellent anti-osteoporotic effects of CA. In addition, Huang et al. found that andrographolide interfered with OC differentiation as an ERRα inverse agonist and could be used to prevent physiological and pathological bone loss [97].

The abovementioned point highlights the critical involvement of ERRα in regulating the function of OB and OC to maintain bone homeostasis. Researchers have speculated that ERRα may be regulated to treat bone metabolic diseases such as osteoporosis and osteosclerosis. Furthermore, CA and andrographolide exhibited favorable anti-osteoporosis effects through ERRα.

ERRα and OA

OA is a well-known arthritic disease that primarily involves chronic inflammation of the articular cartilage [98] and causes pathological alterations in the synovium, meniscus, and subpatellar fat pad with low-grade inflammation [99,100]. Research on OA has shifted from being considered a “wear and tear” disease to a “metabolic” disease [101,102]. Cellular senescence, inflammatory cytokines, metalloproteinases, estrogens, and biomechanical imbalances play a critical role in OA progression and may lead to a series of key pathological alterations [103,104], ERRα is expressed in human and murine articular chondrocytes and is dysregulated in inflammatory arthritis, which is more commonly observed in older populations [10]. Therefore, ERRα can be considered an important regulator of cellular senescence [105] and may be involved in chondrocyte senescence, thereby promoting OA progression [106].

The effect of ERRα on cartilage is primarily related to the regulation of Sox9. This gene is involved in the proliferation, differentiation, and maturation of chondrocytes; additionally, Sox9 is a key regulator of cartilage differentiation and cartilage formation [107–109]. Regulation of ERRα contributes to the maturation of proliferating chondrocytes to hypertrophy, which may be attributed to direct or indirect regulation of Sox9 by ERRα [110].

ERRα overexpression in C518 cells increased the expression of cytoskeletal transcription factor Sox9 in the SRY-type high mobility group, which is an important factor leading to chondrogenesis [111]. In addition, ERRα plays a vital role in the early proliferation and differentiation of mandibular condyle chondrocytes and exerts a certain regulatory effect on the Sox9 gene; additionally, ERRα exerts a certain promotion effect on the proliferation of mandibular condyle chondrocytes [112]. The ERRα inverse activator XCT790 can inhibit the Sox9 expression in human OA chondrocytes, thereby inhibiting its interaction with PGC-1α. This then leads to inhibition of the expression of Sox9 in cartilage tissue, which regulates Sox9 expression together with ERRα and PGC-1α, thereby confirming the presence of a synergistic effect of the two on cartilage formation and maintenance [112,113].

Interleukin-1β (IL-1β) is an inflammatory factor closely associated with OA pathogenesis [114,115], which may be related to the pathological process of OA. IL-1β can significantly increase the expression of ERRα in OA chondrocytes *in vitro*, whereas the ERRα-mediated degradation of cartilage is associated with IL-1β and matrix metalloproteinase-13 (MMP-13) [116].

XCT790 reduced the upregulation of ERRα by Sox9 and IL-1β and decreased the level of MMP-13 mRNA in a dose-dependent manner, highlighting that ERRα regulates itself through the IL-1β pathway and promotes cartilage formation [113]. Furthermore, the abovementioned report found that statins can inhibit IL-1β-induced articular chondrocyte senescence as well as MMP production [117]. They also increase mRNA levels of bone morphogenetic protein, aggregated proteoglycan, and type II collagen, maintain chondrocyte longevity, inhibit catabolic factor-induced matrix-degrading enzyme production, and prevent OA cartilage degeneration.

Agonists and antagonists of ERRα

Despite previously unavailable natural ligands for ERRα, recent studies have shown that endogenous cholesterol may be a potential ligand for ERRα [118,119]. However, it is inconclusive whether cholesterol and other related substances are natural endogenous ligands of ERRα [120]. In addition, statins enhanced hepatic gluconeogenesis by modulating PCK1, which was negatively regulated by ERRα [121,122]. Although statins can have excitatory effects *in vitro*, their actual effects in the body are much more complicated than ERRα. This complex mechanism warrants a considerable degree of research for verification.

In addition to several plant-derived compounds (apigenin, resveratrol, rutaecarpine, and flavone), genistein, forskolin, and phorbol 12-myristate13-acetate(3MA) are agonists of ERRα and ERRα-PPARGC1A dimers [123–126]. Certain signaling modulators, such as PMAs and herbal compounds, including apigenin, resveratrol, and rutin, are the most potent ERRα activators.

The expression of ERRα in breast cancer is associated with its poor prognosis. The potential applications of ERRα in breast cancer are evident. LingH2-10 is a novel selective ERRα inversion activator, and its action mechanism involves the reduction of pyruvate dehydrogenase kinase 4 (PDK4), osteopontin, and presenilin-2 (pS2), thereby inhibiting TNBC proliferation [127]. Compound 11 has a significant inhibitory effect on the transcriptional regulation of ERRα, and its action mechanism is to regulate the signaling pathway downstream of the receptor, thereby infiltrating and transferring the ER-negative MDA-MB-231 cell line. The results showed that compound 11 was a highly effective ERRα inverse activator [128].

XCT790 has been considered a specific inverse agonist of ERRα [129]. shRNA or XCT790 induces a remarkable degree of apoptosis in myeloma cell line MM. 1S cells by interfering with ERRα expression [130], inhibits pancreatic cancer (PC) progression by inhibiting ERRα and MEK/ERK signaling pathway [131], suppresses ERRα activity, and causes considerable accumulation of triglyceride present in rat hepatocytes, thereby reducing triglyceride secretion in the culture medium and regulating triglyceride metabolism [132]. Rotenone and aminopterin appear to be more effective than XCT790 in inhibiting ERR and PGC/ERR signaling pathways [124].

Owing to the synergistic relationship between ERRα and PGC-1α, Lynch et al. [133] performed an ERR/PGC antagonist assay to compare the ERR antagonist activity of each compound in the presence and absence of the cofactor PGC-1α. Artemisinin, carfilzomib, bortezomib, and showed antagonistic effects in the ERR/PGC assay, implying that these compounds inhibit ERR via PGC-1α. In addition, SAHA and etoposide showed antagonistic activity in the ERR assay but agonist activity in the ERR/PGC assay. Lynch et al. [133] also identified five antitumor drugs (artemisinin, methichlorophen, bortezomib, carfilzomib, and gimerticam) and nine pesticides (acriflavine, berberine, chlormidazole, fluoxastrobin, picoxystrobin, proflavin, pyridaben, rotenone, and trifloxystrobin) as ERRα antagonists. Additionally, these nine insecticides inhibit and/or control pests by adversely affecting the metabolism and mitochondrial function in multiple ways [134–136]. The activity of ERRα and PGC-1α decreased after exposure to these pesticides [133].

Recently, food products like genistein, apigenin, resveratrol, rutin, piceatannol, daidzein, flavonoids, and cholesterol are potential cholesterol-promoting substances [119,137,138]. In addition, certain pesticides (acriflavine, imidazole, pyridaben, and fluridone), antineoplastic drugs (artemisinin, bortezomib, etoposide, and vorinostat), and other compounds (rotenone, camptothecin, toxic carotene, papaverine, staurosporine, and progesterone) appear to be ERRα antagonists or ERRα/peroxisome proliferator-activated receptor gamma coactivator 1alpha (PPARGC1A) antagonists or an antagonist of both [123,139] Although the aforementioned compounds have been developed in clinical trials, information regarding their roles is lacking in normal physiological conditions and diseases [140–151]. Among the above compounds, the classification of ERRα will no longer be orphan NR. According to the impact of ERRα on pathogenesis, the use of ERR molecules to modulate the disease research provides a new biological basis for preventing and treating the disease (Tables 1 and 2).

TABLE 1

Some antagonists of ERRα

Antagonist	Action target	Possible mechanism of action	References
XCT190	ERRα	Unknown	[129,133]
LingH2-10	ERRα	Unknown	[140]
Thiazolidinediones	ERRα	Covalent interactions	[141,142]
Gimatecan	ERRα	Inhibition of cytochrome C	[139]
SAHA; Vorinostat	ERRα	Downregulation of ERRα activity/expression; the mechanism of PGC/ERR reporter gene activity remains unknown	[133,139]
Forkskolin	ERRα	Possible stimulation of PGC1α expression and activity in PGC/ERR cell lines	[133]
3'-Deoxyadenosine	ERRα	Inhibition of mitochondrial fusion and induction of mitochondrial fission	[143]

(Continued)

Table 1 (continued).

Antagonist	Action target	Possible mechanism of action	References
DES	ERRα, ERRβ, and ERRγ	Unknown	[144]
CA	ERRα	Inhibits SREBP2 activity and OC formation, binds directly to ERRα, and promotes its degradation	[92]
AM251 analog	ERRα	Binds to and destabilizes the ERRα protein	[143]
Andrographolide	ERRα	Interference with OC differentiation	[97]
PS-341	ERRα	Prediction affects the stability of ERRα and PGC-1α	[139]
Statins	ERRα	*In vivo* inhibition; *in vitro* reaction; may affect the expression or activity of the ERRα receptor itself; may affect coactivators other than PGC1 α.	[120,147]
Artemisinin	ERRα	Anticancer activity; apoptosis induction; and transcriptional level inhibition	[139,148]

TABLE 2

Some agonists of ERRα

Agonists	Action target	Possible mechanism of action	References
Cholesterol	ERRα	Unknown	[149,150]
Flavone and isoflavone	ERRα, ERRβ	Unknown	[151]
Etoposide	ERRα	Stimulation of PGC1α expression and increase in mitochondrial biosynthesis through AMPK activation	[139]
Daidzein	ERRα	Regulation of FAO and OXPHOS genes	[57]
Resveratrol	ERRα	Increase ERRα	[124]
Baicalin	ERRα	Induction of ERRα expression and regulation of reporter gene activity under the control of ERRα binding elements	[61]

Conclusion and Perspective

As a typical member of the orphan receptor, ERRα has the typical structural features of NR and is an important transcription factor. ERRα has numerous physiological functions,critically affect cellular metabolism, general growth and development, and skeletal homeostasis. The data reported in the present study suggest that ERRα plays a regulatory role in osteoporosis, OA, skeletal muscle diseases, vascular diseases, and other diseases. Previously, it was believed that ERRα has no natural ligand, but happily, Several ERRα receptor agonists and antagonists are already used in clinical trials, The ultimate goal could be to utilize the transcriptional advantages of ERRα to prevent and treat human diseases, such as vascular and skeletal, metabolic, and other disorders.

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