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Estrogen-Dependent Regulation of Skeletal Muscle Mitochondria: Mechanisms and Implications

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ABSTRACT

Objective: *Estrogen is a fundamental sex steroid hormone that not only governs female reproductive physiology but also exerts wide-ranging effects on multiple organ systems, including the cardiovascular, nervous, immune, and musculoskeletal systems.* ***Methods:*** *The fall of estrogen, characteristic of postmenopausal women, has been believed to be one of the strongest players for developing all these problems associated with aging, including cardiovascular disease, neurodegenerative disorder, metabolic syndrome, osteoporosis, sarcopenia, and frailty [4, 5].* ***Results:*** *Estrogen exerts its biological actions through its receptors, called estrogen receptors (ERs). Estrogen-related receptors (ERRs: α, β, and γ), orphan nuclear receptors with high structural homology and overlapping transcriptional targets to ERs, have also been implicated in estrogen action [64], [65]. New emerging evidence emphasizes the pivotal involvement of both ERs and ERRs in skeletal muscle biology, such as the regulation of muscle mass, adaptation to exercise, and regeneration.* ***Novelty:*** *This review is highlighted on the the putative regulatory roles of ERs and ERRs exert on skeletal muscle physiology, with special attention in mediating mitochondrial function and metabolic homeostasis.*

INTRODUCTION

Estrogen belongs to the family of steroid hormones and is mainly produced and released by the ovaries in mammals. It plays a central role in the differentiation of sexual organs and in the development and maintenance of the reproductive system [1][2][3][4][5]. Beyond reproduction, estrogen exerts diverse physiological effects on multiple non-reproductive tissues, including the cardiovascular, nervous, immune, and musculoskeletal systems. In women, the decline of estrogen levels associated with menopause has been linked to the onset and progression of several pathological conditions, such as atherosclerosis, cognitive decline, lipid disorders, obesity, metabolic syndrome, type 2 diabetes, osteoporosis, sarcopenia, and frailty [6][7][8][9]. This review highlights the roles of estrogen and its receptors, together with estrogen-related receptors, in regulating skeletal muscle physiology.

Estrogen Actions in Muscle

Clinical evidence suggests that estrogen deficiency contributes to the development of sarcopenia, a condition characterized by the decline of skeletal muscle mass and strength [10][11][12][13]. This decline is typically more pronounced in postmenopausal women compared to age-matched men [14]. Since muscle mass is closely linked to muscle function, preventing muscle atrophy is essential for maintaining quality of life in aging women [12],[15]. Especially in the sarcopenia associated with menopause, muscle

strength often declines more severely than muscle mass [11],[12],[16], highlighting the necessity of decreasing muscle quality [11]. Multiple studies have shown that HRT with estrogen can prevent decreases in muscle mass and strength in menopausal women [9],[17][18][19]. For example, one meta-analysis demonstrated that HRT including estrogen increases muscle strength [20], and the benefits of muscle size and quality may be maintained post-therapy [19]. The efficacy of HRT, seems to be affected by a variety of factors such as dose, age and menopausal status [21]. In conclusion, the available literature suggests that estrogen has a protective effect against muscle loss associated with menopause [17].

Estrogen could have the impact on aging, but it may also have an influence on the performance of female athletes and on taking part in sports. Fluctuations in hormone levels through the menstrual cycle and the reductions due to athletic amenorrhea have been associated with alterations in physical performance, but further studies of larger sample sizes are necessary [22],[23].

Studies on animal models have also contributed to our understanding of the role of estrogen in muscle physiology. BackgroundOvariectomized (OVX) rodents, which cause estrogen deficiency, are often used to analyze muscle mass and strength during estrogen supplementation [24]. The OVX model permits the investigation of estrogen-specific actions, which is important because clinical HRT generally includes other hormones (e.g., progesterone) along with estrogen. Estrogen treatment in ovariectomized mice induced to be ovary-senescent by 4-vinylcyclohexene diepoxide (VCD) increased soleus strength and decreased fatigue without an increase in muscle size [25]. Consistent with this, we also demonstrated that OVX mice supplemented with estrogen had enhanced treadmill endurance relative to their OVX counterparts not receiving treatment, indicating that estrogen improves muscle quality as opposed to mass [26]. Concise transcriptomic profiling of soleus muscles showed that Ucp3 (uncoupling protein 3), a proton leak-promoting and mitochondrial inefficiency-inducing mitochondrial protein that we previously reported that estrogen suppresses, the estrogen-induced mechanism via which estrogen may maximally promote energy production as well.

Other studies showed decreased grip strength in OVX mice as well as decreased TA muscle cross-sectional areas, both of which were rescued with estrogen treatment [27]. In addition, they also showed that OVX mice had smaller fast-twitch fibers, further supporting an estrogen protective role against muscle atrophy, possibly through a fiber type shift towards faster phenotypes (274). Finally, estrogen deficiency was correlated with decreased satellite cell expansion, differentiation, and self-renewal, thereby contributing to the impairment of muscle regeneration.

Supporting this, Chaiyasing et al. demonstrated that estrogen administration increased the diameter of regenerated myotubes following cardiotoxin-induced injury in OVX mice, highlighting estrogen's essential role in muscle repair and regeneration [28].

Table 1. Effects of estrogen replacement on muscle function and phenotype in ovariectomized mouse models.

Mouse	Experimental condition	Phenotype	Other phenotype in muscle	References
Ovarian-senesce by chemical, 4-vinylcyclohexene diepoxide (VCD) treatment followed by estrogen treatment for 8 weeks	In vitro muscle contractility test	Estrogen replacement increases muscle strength compared with no estrogen treatment mice.	No difference in soleus muscle size	**[25]**
OVX followed by estrogen administration for 10 weeks	Treadmill endurance test	Endurance is increased by estrogen administration.	Mitochondrial uncoupling protein 3 (UCP3) is upregulated by ovariectomy and downregulated by estrogen administration	**[26]**
OVX for 24 weeks	Grip strength test	Grip force is decreased by OVX.	Increase in the proportion of fast twitch type fibers in the tibialis anterior muscle. This fiber-type shift was recovered by estradiol.	**[27]**
OVX followed by estrogen administration for 2 weeks	Treadmill endurance test	Endurance is increased by estrogen administration.	Satellite cells were impaired in OVX mice. Nitric oxide synthase activity is increased in females compared with males	**[29]**

RESEARCH METHOD

These results punctuate that counsellors in public secondary schools in the Federal Capital Territory, Abuja have an appreciable professional competence through counseling qualifications, certification status, membership of professional association, participation in conference and availability of demonstrating of counselling knowledge and skills. In addition, positive and significant correlations can be found between the professional competence of the counsellors and the outcome of guidance service in terms of lessening behavioural problems, better academic motivation, mental awareness, career and blended (online and offline) counselling readiness and, attaining the goal of the school. These results indicate that professional competence is a key factor of effective guidance service delivery and that continuous allocation of resources devoted to the training, supervision, and institutional support of guidance personnel is needed to enhance student developmental outcomes. Hence, it emphasizes the importance of ongoing professional development, developmental monitoring systems, and resource allocation in policy to sustain high standards of counselling practice in public secondary schools. Therefore, this study could benefit from future research using longitudinal designs, larger samples, and more advanced statistical modelling to explore actual causal relationships (and potential moderating variables such as school location, resource availability, and counsellor workload) within and outside of the FCT, but certain generalisation caution are warranted given the use of a descriptive survey design and the relatively small sample sizes.

RESULTS AND DISCUSSION

Estrogen Actions in Muscle

In the C57BL/6J mouse strain, female animals display a higher proportion of type I myosin heavy chains and a lower proportion of type II myosin heavy chains in soleus muscle fibers compared with males, which correlates with superior endurance capacity [29]. Interestingly, ovariectomy (OVX) eliminates this enhanced endurance in females, whereas estrogen supplementation restores exercise performance in males to levels comparable with intact females. Nitric oxide synthase, a downstream effector of estrogen signaling, has been proposed as a mediator of this improved exercise capacity.

Transcriptomic analyses further revealed that estrogen treatment in OVX mice upregulates pyruvate dehydrogenase kinase isoform 4 (Pdk4), a mitochondrial enzyme that inhibits pyruvate dehydrogenase activity in glycolysis [30]. This regulation promotes a metabolic shift toward fatty acid oxidation, enhancing oxidative metabolism in skeletal muscle. Since PDK4 facilitates the preferential use of fatty acids over glucose as an energy source, estrogen-induced activation of Pdk4 supports the concept that female skeletal muscles rely more heavily on fatty acid oxidation for energy production [31].

Types and Structure of Estrogen Receptors

Estrogen receptors (ERs) are members of the nuclear receptor superfamily, specifically classified within the NR3 group of nuclear steroid receptors [32]. There are two nuclear ER isoforms: ERα (NR3A1) and ERβ (NR3A2) that have similar structures

but with differences in tissue distribution and abundance [33]. In humans, the ESR1 and ESR2 genes respectively encode these receptors. This is the way that estrogen achieves its biological effects by binding these receptors [34].

Erα is a member of the nuclear receptor superfamily9 and structurally contains four major domains: the N-terminal domain (NTD), DNA-binding domain (DBD), hinge region, and ligand-binding domain (LBD). The NTD, the largest domain, has transcriptional activation function 1 (AF-1), which drives gene transcription in a ligand-independent manner [35],[36]. Such intrinsic disorder of this domain enables rapid allosteric regulation by ligands, DNA, and co-regulators.

The DBD, which has ~97% amino acid identity between ERα and ERβ, contains two zinc finger motifs. The proximal box (P-box) within the first zinc finger is essential for binding to the consensus sequence for the estrogen response element (ERE) (GGTCAnnnTGACC) [37]. Box-D is a receptor dimerization post, and part of the second zinc finger (13). Similar to the NTD [36], the hinge region is involved in nuclear localization and offers flexible structure for receptor contacts.

The LBD is a compact, globular domain that consists of 12 α-helices and contains a ligand-binding pocket. The eleven helices form the high-affinity binding site, and helix 12 plays a critical role in the transcriptional activation function 2 (AF-2) [38]. Helix 12 relocates upon ligand binding and activates the AF-2 by hydrogen bond from the bottom of the pocket AF-2 also plays a role in estrogen-dependent transcriptional activity by recruiting coactivators and regulating chromatin accessibility [36],[39]. AF-2 is a co-activator (which enhance) and suppressor (which suppression it) of AF-1 in the absence of ligand [40].

Beyond direct DNA binding, ERs can regulate transcription through protein–protein interactions with other transcription factors such as SP1, AP-1, and RUNX1. This indirect mechanism, known as **tethering**, allows ERs to influence gene expression without binding directly to DNA [41], [42].

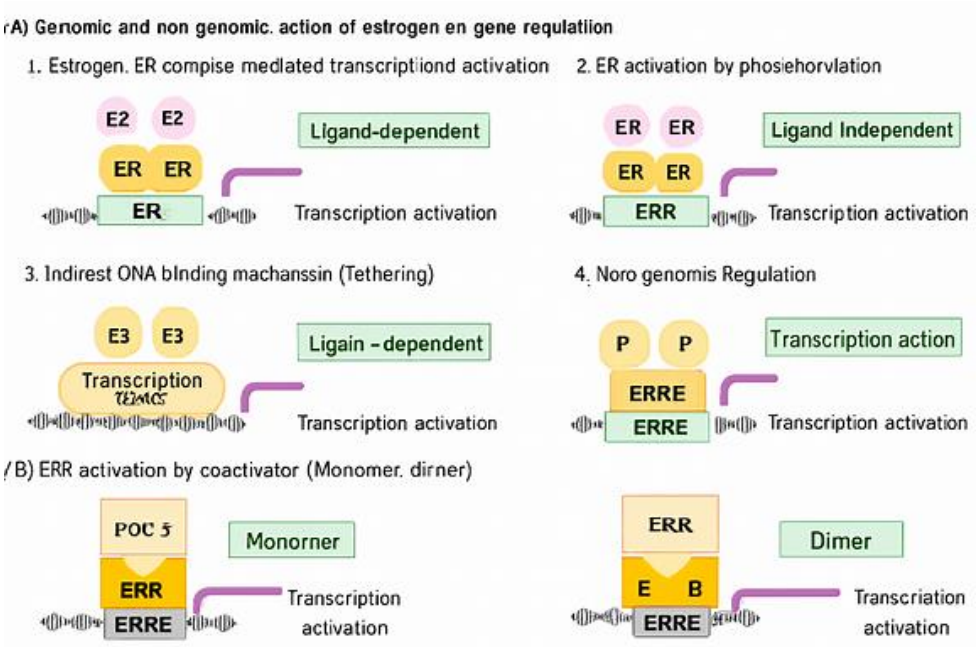

Figure 1. Upon ligand binding, the conformation of estrogen receptors (ERs) undergoes substantial changes. ERα is capable of initiating transcription not only through direct DNA binding but also via interactions with other transcription factors already bound to DNA [41]. In this indirect mechanism, ERα engages in protein–protein associations with factors such as SP1, AP-1, and RUNX1, thereby influencing gene expression without directly contacting DNA. This process of transcriptional regulation is referred to as tethering [42].

Estrogen-ER Signaling in the Regulation of Skeletal Muscle Function and Mitochondria

Estrogen has been widely recognized for its positive influence on mitochondrial activity and related clinical outcomes, including enhanced metabolic control in type 2 diabetes and protection against sarcopenia. Consequently, its mechanisms of action have been extensively studied in the context of disease prevention [10],[47][48][49]. Notably, skeletal muscle from estrogen-treated female rats demonstrates increased mitochondrial content, improved antioxidant defense, and elevated oxidative phosphorylation compared with male counterparts [50],[51]. In contrast, ovariectomized (OVX) females exhibit reduced oxygen consumption, diminished expression of genes involved in mitochondrial biogenesis and remodeling, and elevated hydrogen peroxide production [26],[52]. Supporting this, Torres et al. mice [53] suggests that estrogen deficiency reduces mitochondrial respiration complex I activity in muscle, which may be ameliorated by physiologic estrogen supplementation[53].

Due to its prominent oxidative pathways and the role of insulin-mediated glucose uptake, skeletal muscle is a major contributor to overall energy metabolism 54[56]. Association of estrogen with the regulation of muscle metabolism is supported by the transcript of its receptor (ER (ESR1)), which is shown to be lower in women with the metabolic syndrome, and correlating negatively with adiposity and fasting insulin concentrations [57].

Additional findings from the muscle-specific ER knockout (MERKO) mice emphasize the critical role of estrogen signaling. Muscle fibers isolated from MERKO animals fatigue more quickly compared to controls (Table 2). These mice also display glucose intolerance, insulin resistance, lipid accumulation in skeletal muscle, and increased inflammatory signaling with phosphorylation of c-Jun N-terminal kinase (JNK1/2) and IκB kinase (IKK) [57],[58]. Utilizing shRNA to knockdown Esr1 in muscle cells revealed further defects in fatty acid oxidation, and possibly explains the lipid accumulation in MERKO muscle [57].

Reduced basal and stimulated oxygen consumption, decreased mitochondrial DNA replication, and increased reactive oxygen species (ROS), all microarray indicative of mitochondrial dysfunction, in MERKO mice. Collectively, analyses of MERKO muscle and Esr1-silenced C2C12 myoblasts imply that downregulation of the mitochondrial DNA polymerase Polg1 underlies some of these defects [57]. In addition to functional changes, morphological changes are also apparent with mitochondria shaped elongated and highly contiguous due to repression of fission signaling. More directly, depletion of ER increases inhibitory phosphorylation of DRP1, a protein that is important for mitochondrial fission. Together, these data provide evidence that ER play a protective role in female skeletal muscle by preserving mitochondrial integrity and function.

Table 2. Phenotypes of transgenic or knockout mice for ERs on muscle performance.

Mouse	Experimental condition	Phenotype	Other phenotypes in muscle	References
Muscle-specific knockout of ER (MERKO)	In vitro muscular force and endurance test	Single muscle fibers from MERKO mice fatigued faster than fibers from control muscle.	Reduced oxygen consumption rates, excessive production of reactive oxygen species in mitochondria, and morphological abnormalities ofmitochondria, indicating an impairment of fission-fusion dynamics. Reduction in mitophagy.	[57]
Muscle-specific knockout of ER (skmER KO)	In vitro muscle contractile test	Greater fatigability and impaired recovery from fatigue in muscles from skmER_KO mice	Phosphorylation of myosin regulatory light chain (RLC) was decreased in muscles from skmER_KO compared with WT mice.	[59]
Muscle specific	Ex vivo or in vivo testing of	Smaller force and fatigability of		[60]

estrogen receptor knockout mice (skmER KO)	muscle contractility	soleus muscles. Less torque in in vivo plantar flexor muscle contractility		
Muscle-specific ER -knockout (mER KO)	Grip strength test	The absolute mean maximum strength was slightly decreased only in female KO mice compared with control mice.	Fast-type dominant muscle mass decreases in young female KO mice. There was no difference in running performance.	[61]
Muscle-specific constitutively active ER transgenic (Mck-caER)	Treadmill endurance test	Increased endurance	Genes related to lipid metabolism, insulin signaling, and growth factor signaling were upregulated	[62]

Skeletal Muscle-Specific ER Deficiency

A distinct line of skeletal muscle-specific ER-deficient mice (skmER KO) was developed, which displayed reduced strength and contractility across several muscle groups [59],[60]. In these mice, the extensor digitorum longus showed impaired eccentric contractions and diminished submaximal/maximal isometric force, while the soleus muscle fatigued rapidly with poor recovery. Furthermore, maximal torque and power generation in plantarflexors and dorsiflexors were reduced, accompanied by decreased phosphorylation of the myosin regulatory light chain. These findings highlight the role of ER in mediating estradiol's positive effects on muscle strength.

Recent work by Collins et al. demonstrated that estrogen preserves satellite cell populations in both female mice and humans [63]. Muscle stem cell-specific ER knockout models revealed that ER is essential for satellite cell maintenance, self-renewal, and protection against apoptosis—functions critical for muscle regeneration. Conditional ER deletion in skeletal muscle also led to osteopenia, suggesting that estrogen signaling influences myokine expression, which in turn regulates osteoclast differentiation and activity [64].

In muscle-specific ER knockout (mER KO) mice, treadmill performance was unchanged compared to controls, but grip strength was significantly reduced in females [61]. Young female mER KO mice also exhibited reduced fast-type muscle mass. Both muscle-specific and satellite cell-specific ER knockout models consistently showed declines in muscle mass and strength, along with reduced satellite cell proliferation [61].

Constitutively Active ER Models

Our group generated Mck-caER transgenic mice expressing a constitutively active mutant of human ER (caER, Y537S substitution) specifically in muscle [62],[65],[66]. These mice displayed normal muscle-to-body weight ratios but significantly prolonged

treadmill running times, indicating enhanced endurance capacity. Transcriptomic analysis of quadriceps femoris revealed enrichment of genes involved in:

1. **Fatty acid metabolism** (Acaca, Fasn, Elovl6, Scd1)
2. **Insulin sensitivity** (Adipoq, Pparg)
3. **Growth factor signaling** (Igf1, Igf2)

These results suggest that estrogen signaling enhances exercise endurance by modulating metabolic gene networks.

In C2C12 myoblasts overexpressing caER, mitochondrial uncoupling protein 3 (Ucp3) was downregulated, while intracellular ATP levels increased [26]. This indicates that estrogen promotes efficient ATP generation by reducing energy dissipation. Additionally, nuclear receptor NR4A1 was identified as an estrogen-responsive gene in caER-overexpressing cells [67]. Since NR4A1 stimulates mitochondrial respiration [68], it may serve as a mediator of estrogen's effects on muscle metabolism.

Estrogen and Mitochondrial Function

Estrogen is thought to enhance oxidative metabolism in muscle and support mitochondrial function, thereby contributing to disease prevention. Mitochondria, the central regulators of oxidative metabolism, contain their own maternally inherited genome—a circular, double-stranded DNA of 16,569 base pairs in humans [69]. While this genome encodes a limited set of RNAs and proteins for the electron transport chain, most mitochondrial genes are nuclear-encoded, requiring tight coordination between nuclear and mitochondrial transcriptional programs to maintain metabolic homeostasis [70].

Our group identified cytochrome c oxidase subunit 7a-related protein (COX7RP) as an estrogen-responsive gene [71]. Cox7rp-knockout mice exhibited reduced treadmill endurance, diminished mitochondrial respiratory complex activity, and impaired formation of respiratory supercomplexes. Conversely, COX7RP-transgenic mice showed enhanced endurance and increased complex IV activity. ATP synthesis was also reduced in Cox7rpKO mice. These findings suggest that COX7RP mediates estrogen-dependent activation of mitochondrial respiration, playing a critical role in energy metabolism [71],[72].

Similarities Between Estrogen-Related Receptors (ERRs) and ERs

Estrogen-related receptors (ERRα, ERRβ, ERRγ) are nuclear receptors with significant sequence similarity to ERs, and both belong to the NR3 subgroup of the nuclear receptor superfamily [32]. Unlike ERs, ERRs lack endogenous ligands such as estrogen and instead rely on transcriptional coactivators or protein ligands for activity [73].

Structurally, ERRs share the canonical features of nuclear receptors: a non-conserved N-terminal domain (NTD), a central DNA-binding domain (DBD), and a ligand-binding domain (LBD) that recruits coregulators [73]. The NTD contains AF-1 and is often post-translationally modified, while the DBD includes two zinc finger motifs that bind to the estrogen-related response element (ERRE, TCAAGGTCA) [75]. ERRs can bind ERRE as monomers or homodimers. The LBD contains AF-2 and can interact with both

ERRE and ERE, suggesting overlapping regulatory networks between ERs and ERRs [73],[76]. For example, the osteopontin promoter is activated by both ERRα and ER via ERRE sequences [77]. Estrogen also induces ERRα expression in mouse heart and uterus, with ER binding to multiple MHREs in the ERRα promoter. This crosstalk highlights shared regulatory targets between ER and ERR subgroups.

ERR Signaling in Skeletal Muscle and Mitochondria

ERRs were initially linked to mitochondrial regulation [78], and their role in muscle was investigated earlier than ERs (Table 3). Muscle-specific ERRα transgenic mice displayed markedly redder muscles, with hind limb muscles resembling the oxidative soleus [79]. These mice exhibited reduced muscle weight in glycolytic and mixed fiber types, but increased mitochondrial size and number. Endurance testing revealed significantly greater running distance and oxidative capacity compared to wild-type controls.

During exercise, transgenic mice showed a lower respiratory exchange ratio, indicating a metabolic preference for fatty acid oxidation over glucose utilization. Mitochondrial enzyme activities, including succinate dehydrogenase and aconitase, were strongly elevated. Gene expression analysis suggested a fiber type shift from fast type II to slow type I fibers. Conversely, ERRα heterozygous knockout mice demonstrated shorter treadmill endurance and reduced expression of fatty acid uptake and oxidation genes, consistent with impaired fatty acid utilization.

Table 3. Phenotypes of transgenic or knockout mice for ERRs on muscle performance.

Mouse	Experimental condition	Phenotypes	Other phenotypes in muscle	References
Muscle-specific ERR and VP16ERR transgenic [ERR (N-TG) and VP16ERR (TG)]	Treadmill endurance test	Increased endurance	Decrease in muscle weight of glycolytic and mixed fiber muscles, increase in numbers of large mitochondria, and improved oxidative capacity and mitochondrial enzymatic function.	**[79]**
Heterozygotes knockout of ERR (HET) Muscle-	Treadmill endurance test	Decreased endurance	Impaired mitochondrial oxidative metabolism.	**[79]**

specific ERR transgenic (ERRGO)	Treadmill endurance test	Increased endurance	Increase in mitochondrial respiration, type I fiber specification, and vascularization. miRNAs (miR-499 and miR-208b) and type I fiber-related genes were reduced	**[80]**
Muscle–specific ERR /ERR double knockout (ERR / dmKO)	Treadmill endurance test	Decreased endurance	suggesting that ERRs are required for type I fiber formation.	**[81]**
ERR knockout (ERR KO)	Treadmill endurance test	Decreased endurance	Decreased muscle mass and reduced expression of many genes involved in mitochondrial oxidative metabolism	**[82]**

ERR Signaling in Skeletal Muscle

Studies on muscle-specific ERR transgenic mice have shown that ERR enhances the expression of oxidative metabolism genes (e.g., *Ucp3, Pdk4, Cycs, Cox5a*, and *Lpl*) as well as oxidative myofiber markers (*Mhc1a* and *Mhc2a*) [80]. ERR also promotes angiogenesis and vascularization within skeletal muscle, contributing to fatigue resistance in slow-twitch fibers. Transcriptomic analyses revealed increased expression of angiogenic genes such as *Vegfa*. ERR-overexpressing (ERRGO) mice display elevated oxygen consumption, enhanced oxidative metabolism, and improved blood supply to skeletal muscle. These mice also exhibit a lower respiratory exchange ratio (RER), favoring fatty acid oxidation over carbohydrate utilization, longer treadmill endurance, and reduced weight gain under a high-fat diet. Collectively, ERR appears to support oxidative metabolism, vascularization, and endurance capacity while protecting against diet-induced weight gain.

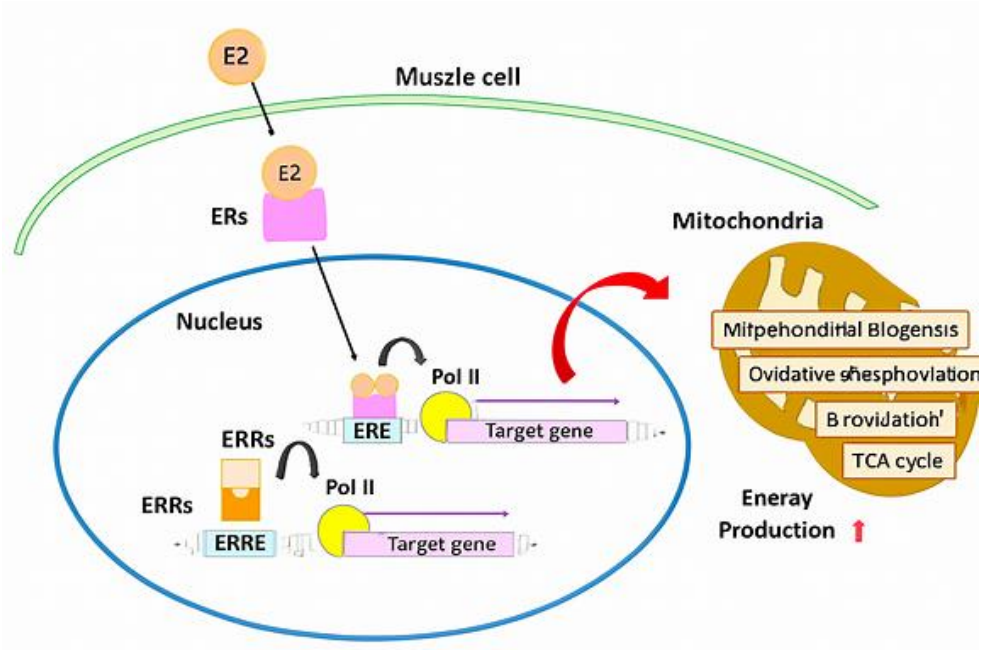

Figure 2. Estrogen signaling in muscle cells enhances mitochondrial function and energy production. Through genomic interactions with estrogen receptors (ERs) and estrogen-related receptors (ERRs), transcription of target genes is activated, promoting mitochondr biogenesis, oxidative phosphorylation, β-oxidation, and the TCA cycle.

ERR Double Knockout Models

To dissect the roles of ERR isoforms, skeletal muscle-specific double knockout mice lacking *Esrrg* and *Esrrb* (ERRγ/β dmKO) were generated [81]. These mice showed reduced expression of slow-twitch fiber-related genes and fewer type I myosin heavy chain-positive fibers in the gastrocnemius muscle. Endurance testing revealed shorter running distances compared to wild-type controls, consistent with altered fiber-type composition. Human muscle biopsies further demonstrated a strong correlation between *ESRRG* expression and endurance determinants such as type I fiber percentage, ATPmax, and VO_2max. Additionally, miRNA-499 expression correlated with endurance traits, suggesting that the ERRγ/miRNA-499 axis, under PPARδ regulation, contributes to type I fiber characteristics.

ERR Knockout Phenotypes

ERR knockout mice exhibit reduced muscle mass in the heart, gastrocnemius, soleus, and quadriceps compared with wild-type animals [82]. These mice also show diminished treadmill endurance and higher RER values, indicating a greater reliance on carbohydrate metabolism. ERR target genes (*Cycs, Idh3g, Pdha1*) involved in mitochondrial energy metabolism are downregulated before and after exercise. Metabolomic analyses revealed accumulation of TCA cycle intermediates (citrate, cis-aconitate, α-ketoglutarate) after exercise, suggesting compensatory responses to impaired oxidative capacity. Conversely, succinate and malate levels decreased due to reduced α-ketoglutarate dehydrogenase activity. Together, these findings highlight ERR's role in sustaining mitochondrial oxidative metabolism and exercise tolerance.

ERRs and PGC-1 Coactivators

Although ERRs are orphan receptors without endogenous ligands, their transcriptional activity depends on coactivators, particularly PGC-1α and PGC-1β [90]. The ERR–PGC-1 axis regulates multiple aspects of mitochondrial function [90],[91]. Exercise stimulates mitochondrial turnover through mitophagy and biogenesis, processes coordinated by PGC-1 [92]. In PGC-1 knockout mice, both mitophagy and mitochondrial renewal are impaired, underscoring its regulatory role [93],[94]. With aging, PGC-1 and ERR expression decline in skeletal muscle, correlating with mitochondrial dysfunction and tissue deterioration [95]. Muscle-specific PGC-1 overexpression in aged mice improves endurance, while knockout accelerates age-related muscle decline [91]. Thus, the PGC-1/ERR axis represents a central molecular circuit orchestrating mitochondrial metabolism and muscle function [82].

Clinical Implications of ER and ERR in Muscle Disease and Tissue Engineering

Insights into ER and ERR signaling in skeletal muscle may inform novel therapeutic strategies, particularly in regenerative medicine. Satellite cells from OVX mice or ER-deficient models exhibit reduced self-renewal and differentiation [27],[61]. Estrogen enhances satellite cell proliferation in rats following exercise [96],[97] and promotes regeneration after injury, with ER playing a key role [98],[99]. Estrogen also improves the generation of functional myogenic cells from adipose-derived stem cells, which can be applied with scaffolds for treating conditions such as stress urinary incontinence [100].

ERR signaling likewise contributes to muscle differentiation. In C2C12 cells, ERR overexpression promotes myoblast differentiation, whereas inverse agonist XCT790 impairs myotube formation, reduces mitochondrial content, and disrupts sarcomeric assembly [101]. ERR agonists also enhance cardiac maturation in hiPSC-derived cardiomyocytes, including transverse tubule formation [102]. These findings suggest that ER and ERR pathways are valuable for muscle disease modeling and tissue engineering applications.

CONCLUSION

Fundamental Finding : Over the past century, increased female life expectancy has extended postmenopausal lifespan, during which sarcopenia, frailty, and strength loss are highly prevalent and closely associated with reduced estrogen secretion, while ERs and ERRs function as key regulators of skeletal muscle metabolism and mitochondrial activity within complex gene networks that sustain muscle integrity. **Implication :** Elucidating ER and ERR signaling pathways provides a conceptual basis for developing innovative diagnostic markers and targeted therapeutic strategies to address muscle disorders in aging women with estrogen deficiency and to enhance quality of life by mitigating muscle decline and frailty. **Limitation :** The current understanding of ER and ERR mechanisms in skeletal muscle remains incomplete, particularly regarding the integrated gene networks and their dynamic regulation in postmenopausal conditions. **Future Research :** Further investigations should focus on clarifying the molecular interactions of ER and ERR signaling in muscle metabolism and mitochondrial regulation

to support translational applications for prevention and treatment of estrogen-related muscle deterioration.

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