

## Estrogen Receptor Related Receptor Alpha (ERR $\alpha$ ) in Skeletal Tissues

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### Abstract

Estrogen receptor related receptor alpha (ERR $\alpha$ ) was the oldest orphan nuclear receptor with sequence identity to the estrogen receptors, ER $\alpha/\beta$ . Recently, cholesterol had been identified as a potential agonist of ERR $\alpha$  which brings new insights for ERR $\alpha$  in bone biology and aging.

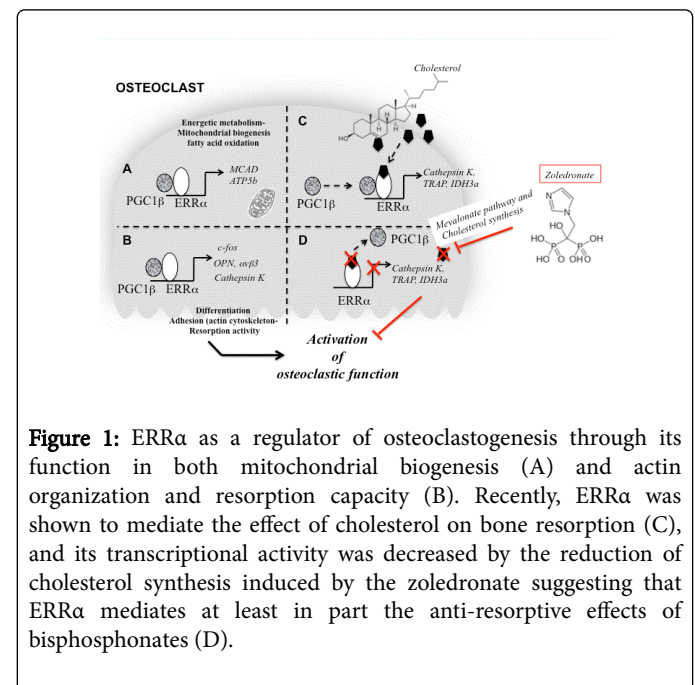
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### Short Communication

Estrogen receptor related receptor alpha (ERR $\alpha$ ) was the oldest orphan nuclear receptor with sequence identity to the estrogen receptors, ER $\alpha/\beta$  [1]. The sequence alignment of the ERR $\alpha$  and the ERs reveals a high similarity (68%) in the DNA-binding domain and a moderate similarity (36%) in other parts of the proteins such as the ligand-binding E domain [1]. If ERR $\alpha$  does not bind estrogen, cholesterol had been recently described as a potential agonist of the receptor [2]. Bone maintenance depends on a balance between bone resorption and bone formation that implicates bone-resorbing cells (osteoclasts), bone-forming cells (osteoblasts) and the osteocytes that modulate response of bone mechanical stress [3]. In skeletal tissues, ERR $\alpha$  plays mainly a functional role in osteoclasts (bone resorbing cells) but also has a role in osteoblasts (bone-forming cells) and chondrocytes [4].

A recent study has reinforced the role for ERR $\alpha$  in osteoclasts differentiation and function [2]. In osteoclastogenesis, ERR $\alpha$  was already known to act as a pro-osteoclastic factor *in vivo*, the ERR $\alpha$  knockout mice exhibiting osteopetrosis (excess of bone formation) [5]. Concomitantly, osteoclastogenesis was dramatically disturbed *in vitro* and genes implicated in mitochondrial biogenesis were down regulated (Figure 1A). Moreover, ERR $\alpha$  was also implicated in osteoclasts mobility and actin cytoskeletal organization by regulating the osteopontin (OPN)-integrin b3 chain-activated c-src (phosphorylated at the Tyr416) pathway causing the disruption of the specific actin structure (podosome belt) implicated in osteoclast adhesion, migration and invasion [6] (Figure 1B). Recently, ERR $\alpha$  was shown to mediate the effect of cholesterol on bone resorption and skeletal remodeling [2] (Figure 1C). Many studies have suggested a link between dyslipidemia (such as hypercholesterolemia) and low bone mineral density (a strong predictor of osteoporosis) for postmenopausal women [7]. Interestingly, osteoporosis is mainly due to an excess of osteoclasts since the amount of bone resorbed by the osteoclasts is not restored with the new bone deposited by the osteoblasts, suggesting that cholesterol may directly act through osteoclasts to induce bone loss in postmenopausal women [8]. Moreover, cholesterol had been described as a stimulator of Interleukin 1 $\alpha$  (IL1 $\alpha$ ) secretion by macrophages and of RANKL (receptor activator of the NF- $\kappa$ B ligand) that are both strong pro-osteoclastic factors [9-11]. ERR $\alpha$  has also been link to

osteoporosis. Indeed, ERR $\alpha$  expression is stimulated by estrogen in proliferative osteoblasts *in vitro* and inhibited in bone *in vivo* in ovariectomized adult rats [12]. Similarly to estrogens/ERs, ERR $\alpha$  may also regulate vascularisation and VEGF expression which is also known to impact osteoblasts and osteoclasts [13-17]. Moreover, the conditional knock-out of ERR $\alpha$  in female mice in pre-osteoblasts and the global ERR $\alpha$  deletion confer resistance to bone loss induced by estrogen-deficiency which suggest that ERR $\alpha$  may contribute to bone loss in osteoporosis [18,19]. It seems that ERR $\alpha$  may also mediate the pharmacological effects of bisphosphonates, the most prescribed anti-resorptive drugs for fracture prevention in postmenopausal women [2].



**Figure 1:** ERR $\alpha$  as a regulator of osteoclastogenesis through its function in both mitochondrial biogenesis (A) and actin organization and resorption capacity (B). Recently, ERR $\alpha$  was shown to mediate the effect of cholesterol on bone resorption (C), and its transcriptional activity was decreased by the reduction of cholesterol synthesis induced by the zoledronate suggesting that ERR $\alpha$  mediates at least in part the anti-resorptive effects of bisphosphonates (D).

Cholesterol also has the ability to recruit coactivators PGC1 $\beta$  to ERR $\alpha$  in osteoclasts [2] (Figure 1C). PGC1 $\beta$  is upregulated during the transition from bone marrow macrophages to pre-osteoclasts, and PGC1 $\beta$  knockout mice exhibited osteopetrosis [5]. It is also downregulated in mice that were deleted in NF- $\kappa$ B proteins in

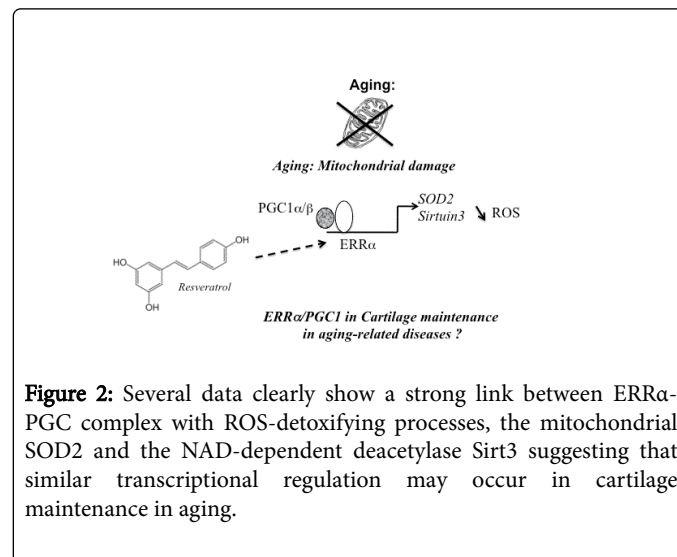
osteoclast precursors [20]. Moreover, similarly to osteoclasts deleted in ERR $\alpha$ , PGC1 $\beta$ -deficient osteoclasts displayed abnormal morphology and their bone resorbing activity was significantly impaired due to a reduction in phosphorylation of c-src at Tyr416 and a decrease in actin ring formation [5,6]. Taken together, these data suggest that targeting ERR $\alpha$ -PGC1 $\beta$  through synthetic molecules like the inverse agonist XCT-790 that was designed to block ERR $\alpha$  activity by preventing its interaction with the PGC1 coactivators, can block the ERR $\alpha$  activation by cholesterol. Consequently, ERR $\alpha$  regulation of the mitochondrial biogenesis and of the actin cytoskeletal organization that are required for osteoclasts formation, migration and resorption capacity could be altered [21].

1. In clinic, treatments that are generally recommended for postmenopausal women are bisphosphonates that bind to bone surfaces, target osteoclasts and decrease bone resorption [22]. Interestingly, the nitrogen-containing-bisphosphonates such as zoledronate inhibits the mevalonate pathway and therefore the production of cholesterol which results in osteoclasts apoptosis [23] (Figure 1D). In mice, Wei, et al. show that the reduction of cholesterol synthesis by the zoledronate decrease ERR $\alpha$  transcriptional activity suggesting that ERR $\alpha$  mediates at least in part the anti-resorptive effects of bisphosphonates [2] (Figure 1D). They also show that the statins that are the most prescribed cholesterol-lowering drugs can also regulate ERR $\alpha$  activity in muscle. In contrast to bisphosphonates, that only target bone matrix surfaces, statins have pleiotropic effects [24]. Indeed beside their cardio-protective properties, statins have also been described to act as pro-osteogenic molecules by increasing the bone mineral density in post-menopausal women [25,26]. Moreover, statins (Simvastatin, atorvastatin) are able to stimulate growth factors secretions such as VEGF in osteoblasts which is also a direct target gene of ERR $\alpha$  [17,27]. Statins (Lovastatin) can also inhibit osteoclasts formation and a defect in ERR $\alpha$  in osteoclasts blocks the effect of Lovastatin [2].

In aging, cholesterol is strongly linked to age-related disorders [28]. ERR $\alpha$  in association with the PGC1 family of coactivators play a main role in the transcriptional control of mitochondrial biogenesis and respiratory function [29]. Deregulation of mitochondrial function is a common feature in multiple aspects of bone loss and cartilage destruction suggesting the involvement of ERR $\alpha$  in skeletal aging [30,31]. The bone phenotype in ERR $\alpha$  knock-out mice is more prevalent in aged mice (10 to 12 month) compared with 4 to 5 month-old mice and mainly due to osteoclasts defects and downregulation of genes implicated in mitochondrial function and biogenesis [5]. Very recently, ERR $\alpha$ -PGC1 $\beta$  had been linked to Sirtuin 3, a major mitochondrial deacetylase (nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase) that regulates oxidative stress resistance, in bone homeostasis [32,33]. Indeed, mice deficient in SIRT3 exhibit osteopenia due to increased numbers of osteoclasts. Huh et al show that in response to the pro-osteoclastic cytokine RANKL, the osteoclasts progenitors Sirt3 $^{-/-}$  undergo increased osteoclastogenesis due to the stimulation of the ERR $\alpha$ -PGC1 $\beta$  at the transcriptional level.

Mitochondria also play a key role in chondrocytes function, survival and oxidative stress [34]. Chondrocytes from osteoarthritis cartilage, the most common chronic joint disease in the elderly population, showed a significant decrease of mitochondrial electron transport chain activity leading to mitochondrial damage of the outer membrane [30,35]. Proteomics study from osteoarthritic (OA) chondrocytes

described a decrease in mitochondrial superoxide dismutase (SOD) levels and an increase in intracellular reactive oxygen species (ROS) in OA chondrocytes [36]. Considerable data now support the idea that ERR $\alpha$ , combined with PGC1 family members, regulates ROS production. Indeed, dysregulation of ERR $\alpha$  with the inverse agonist XCT-790 enhanced ROS production in differentiated adipocytes, muscles and breast cancer [37-39] (Figure 2).



**Figure 2:** Several data clearly show a strong link between ERR $\alpha$ -PGC complex with ROS-detoxifying processes, the mitochondrial SOD2 and the NAD-dependent deacetylase Sirt3 suggesting that similar transcriptional regulation may occur in cartilage maintenance in aging.

Moreover, in DAergic neuronal cells, ERR $\alpha$  was involved in Sirt3 neuroprotective functions by regulating Sirt3 expression via ERR $\alpha$ -PGC1 $\alpha$  interaction and binding on Sirt3 promoter. Increase of Sirt3 expression led to interaction with SOD2 that prevented ROS production and DAergic neurons death observed in Parkinson's disease [40]. Also, the anti-oxidant effect of resveratrol was recently linked to the transcriptional regulation of SOD2 by ERR $\alpha$  in cells deficient in mitochondria Complex I [41] (Figure 2). Currently, no similar data are yet available in osteoarthritic chondrocytes, but these results clearly show a strong link between ERR $\alpha$ -PGC $\alpha$  complex with ROS-detoxifying processes, the mitochondrial SOD2 and the NAD-dependent deacetylase Sirt3 suggesting that similar transcriptional regulation may occur in cartilage in aging.

In conclusion, we have reviewed the increasing data supporting a role for ERR $\alpha$  in regulation of osteoclasts differentiation and function. Together, the data suggest that ERR $\alpha$  mainly act as a regulator of bone resorption. They also bring new insights into ERR $\alpha$  function and suggest that ERR $\alpha$  may mediate the pharmacological effects of anti-resorptive drugs such as bisphosphonates and statins that are both targeting cholesterol metabolism. The fact that cholesterol is also linked to age-related disorders combined with ERR $\alpha$  function in mitochondria and in oxidative stress as a regulator of ROS production, suggest that ERR $\alpha$  may also act as a regulator of the aging process in skeletal tissues.

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