Endocrinology & Metabolic Syndrome

Bonnelye, Endocrinol Metab Syndr 2016, 5:4
DOI:10.4172/2161-1017.1000244

Short Communication Open Access

Estrogen Receptor Related Receptor Alpha (ERRα) in Skeletal Tissues

E. Bonnelye*

INSERM-UMR1033, Faculty of Medicine, Lyon East, Université Claude Bernard 1, Lyon, France

***Corresponding author:** Edith Bonnelye, INSERM-UMR1033, Faculty of Medicine Lyon East, Université Claude Bernard 1, Rue Guillaume Paradin, 69 372 Lyon cedex 08, France, Tel: 33-4-787 857 38; Fax: 33-4-787-787-72; E-mail: edith.bonnelye@inserm.fr

Received date: June 21, 2016; **Accepted date: July 7, 2016**; **Published date: July 14, 2016**

Abstract

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

Keywords: ERRα; Cartilage; Osteoclasts; Cholesterol; Aging

Short Communication

Estrogen receptor related receptor alpha (ERRα) was the oldest orphan nuclear receptor with sequence identity to the estrogen receptors, ERα/β [1]. The sequence alignment of the ERRα 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 ERRα 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, ERRα 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 ERRα in osteoclasts differentiation and function [2]. In osteoclastogenesis, ERRa was already known to act as a pro-osteoclastic factor *in vivo*, the ERRα 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, ERRα 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, ERRα 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 predicator 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 1α (IL1α) secretion by macrophages and of RANKL (receptor activator of the NF-κB ligand) that are both strong pro-osteoclastic factors [9-11]. ERRα has also been link to osteoporosis. Indeed, ERRαexpression is stimulated by estrogen in proliferative osteoblasts *in vitro* and inhibited in bone *in vivo* in ovariectomized adult rats [12]. Similarly to estrogens/ERs, ERRα may also regulate vascularisation and VEGF expression which is also known to impact osteoblasts and osteoclasts [13-17]. Moreover, the conditional knock-out of ERRα in female mice in pre-osteoblasts and the global ERRα deletion confer resistance to bone loss induced by estrogen-deficiency which suggest that ERRα may contribute to bone loss in osteoporosis [18,19]. It seems that ERRα may also mediate the pharmacological effects of bisphosphonates, the most prescribed anti-resorptive drugs for fracture prevention in postmenopausal women [2].

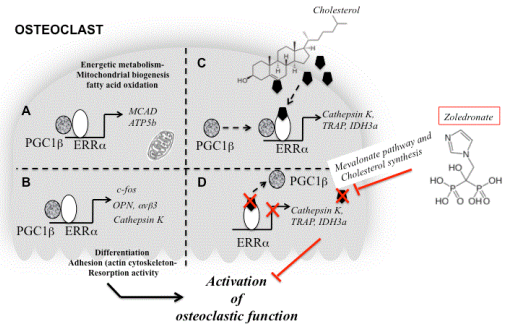

Figure 1: ERRα as a regulator of osteoclastogenesis through its function in both mitochondrial biogenesis (A) and actin organization and resorption capacity (B). Recently, ERRα was shown to mediate the effect of cholesterol on bone resorption (C), and its transcriptional activity was decreased by the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

Cholesterol also has the ability to recruit coactivators PGC1β to ERRα in osteoclasts [2] (Figure 1C). PGC1β is upregulated during the transition from bone marrow macrophages to pre-osteoclasts, and PGC1β knockout mice exhibited osteopetrosis [5]. It is also downregulated in mice that were deleted in NF-κB proteins in

osteoclast precursors [20]. Moreover, similarly to osteoclasts deleted in ERRα, PGC1β-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 ERRα-PGC1β through synthetic molecules like the inverse agonist XCT-790 that was designed to block ERRα activity by preventing its interaction with the PGC1 coactivators, can block the ERRα activation by cholesterol. Consequently, ERRα 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 ERRα transcriptional activity suggesting that ERRα 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 ERRα 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 ERRα [17,27]. Statins (Lovastatin) can also inhibit osteoclasts formation and a defect in ERRα in osteoclasts blocks the effect of Lovastatin [2].

In aging, cholesterol is strongly linked to age-related disorders [28]. ERRα 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 ERRα in skeletal aging [30,31]. The bone phenotype in ERRα 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, ERRα-PGC1β 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 ERRα-PGC1β 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 ERRα, combined with PGC1 family members, regulates ROS production. Indeed, dysregulation of ERRα with the inverse agonist XCT-790 enhanced ROS production in differentiated adipocytes, muscles and breast cancer [37-39] (Figure 2).

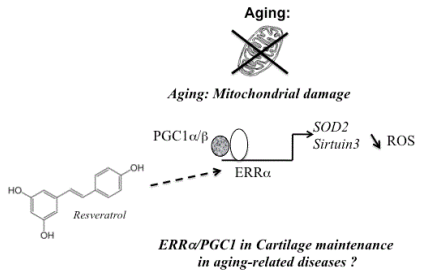

Figure 2: Several data clearly show a strong link between ERRα-PGC complex with ROS-detoxifying processes, the mitochondrial SOD2 and the NAD-dependent deacetylase Sirt3 suggesting that similar transcriptional regulation may occur in cartilage maintenance in aging.

Moreover, in DAergic neuronal cells, ERRα was involved in Sirt3 neuroprotective functions by regulating Sirt3 expression via ERRα-PGC1α 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 ERRα 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 ERRα-PGCα 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 ERRα in regulation of osteoclasts differentiation and function. Together, the data suggest that ERRα mainly act as a regulator of bone resorption. They also bring new insights into ERRα function and suggest that ERRα 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 ERRα function in mitochondria and in oxidative stress as a regulator of ROS production, suggest that ERRα may also act as a regulator of the aging process in skeletal tissues.

References

1. Giguère V, Yang N, Segui P, Evans RM (1988) Identification of a new class of steroid hormone receptors. Nature 331: 91-94.
2. Wei W, Schwaid AG, Wang X, Wang X, Chen S, et al. (2016) Ligand Activation of ERRα by Cholesterol Mediates Statin and Bisphosphonate Effects. Cell Metab 23: 479-491.
3. Plotkin LI, Bellido T (2016) Osteocytic signalling pathways as therapeutic targets for bone fragility. Nat Rev Endocrinol.

4. Bonnelye E, Aubin JE (2013) An energetic orphan in an endocrine tissue: a revised perspective of the function of estrogen receptor-related receptor alpha in bone and cartilage. J Bone Miner Res 28: 225-233.
5. Wei W, Wang X, Yang M, Smith LC, Dechow PC, et al. (2010) PGC1beta mediates PPARgamma activation of osteoclastogenesis and rosiglitazone-induced bone loss. Cell Metab 11: 503-516.
6. Bonnelye E, Saltel F, Chabadel A, Zirngibl RA, Aubin JE, et al. (2010) Involvement of the orphan nuclear estrogen receptor-related receptor alpha in osteoclast adhesion and transmigration. J Mol Endocrinol 45: 365-377.
7. Makovey J, Chen JS, Hayward C, Williams FM, Sambrook PN (2009) Association between serum cholesterol and bone mineral density. Bone 44: 208-213.
8. Geusens P (2015) New insights into treatment of osteoporosis in postmenopausal women. RMD Open 1: e000051.
9. Boyle WJ, Simonet WS, Lacey DL (2003) Osteoclast differentiation and activation. Nature 423: 337-342.
10. Sjögren U, Mukohyama H, Roth C, Sundqvist G, Lerner UH (2002) Bone-resorbing activity from cholesterol-exposed macrophages due to enhanced expression of interleukin-1alpha. J Dent Res 81: 11-16.
11. Luegmayr E, Glantschnig H, Wesolowski G, Gentile M, Fisher J, et al. (2004) Osteoclast formation, survival and morphology are highly dependent on exogenous cholesterol/lipoproteins. Cell death Differ 11: 108-118.
12. Bonnelye E, Kung V, Laplace C, Galson DL, Aubin JE (2002) Estrogen receptor-related receptor alpha impinges on the estrogen axis in bone: potential function in osteoporosis. Endocrinology 143: 3658-3670.
13. Hu K, Olsen BR (2016) Osteoblast-derived VEGF regulates osteoblast differentiation and bone formation during bone repair. J Clin Invest 126: 509-526.
14. Kusumbe AP, Ramasamy SK, Adams RH2 (2014) Coupling of angiogenesis and osteogenesis by a specific vessel subtype in bone. Nature 507: 323-328.
15. Ciccone MM, Scicchitano P, Cortese F, Gesualdo M, Zito A, et al. (2013) Modulation of vascular tone control under isometric muscular stress: role of estrogen receptors. Vascul Pharmacol 58: 127-133.
16. Ciccone MM, Scicchitano P, Gesualdo M, Fornarelli F, Pinto V, et al. (2013) Systemic vascular hemodynamic changes due to 17-β-estradiol intranasal administration. J Cardiovasc Pharmacol Ther 18: 354-358.
17. Stein RA, Gaillard S, McDonnell DP (2009) Estrogen-related receptor alpha induces the expression of vascular endothelial growth factor in breast cancer cells. J Steroid Biochem Mol Biol 114: 106-112.
18. Teyssier C, Gallet M, Rabier B, Monfoulet L, Dine J, et al. (2009) Absence of ERRalpha in female mice confers resistance to bone loss induced by age or estrogen-deficiency. PLoS One 4: e7942.
19. Gallet M, Saïdi S, Haÿ E, Photsavang J, Marty C, et al. (2013) Repression of osteoblast maturation by ERRα accounts for bone loss induced by estrogen deficiency. PLoS One 8: e54837.
20. Zeng R, Faccio R, Novack D (2015) Alternative NF-κB Regulates RANKL-Induced Osteoclast Differentiation and Mitochondrial Biogenesis via Independent Mechanisms. J Bone Miner Res. 30: 2287-2299.
21. Busch BB, Stevens WC, Martin R, Ordentlich P, Zhou S, et al. (2004) Identification of a selective inverse agonist for the orphan nuclear receptor estrogen-related receptor alpha. J Med Chem 47: 5593-5596.
22. Black DM, Rosen CJ (2016) Postmenopausal Osteoporosis. N Engl J Med 374: 2096-2097.
23. Drake MT, Clarke BL, Khosla S (2008) Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 83: 1032-1045.
24. Shah S, Werlang C, Kasper F, Mikos A (2015) Novel applications of statins for bone regeneration. Natl Sci Rev 2: 85-99.
25. Edwards CJ, Hart DJ, Spector TD (2000) Oral statins and increased bone-mineral density in postmenopausal women. Lancet 355: 2218-2219.
26. Rejnmark L, Buus NH, Vestergaard P, Andreasen F, Larsen ML, et al. (2002) Statins decrease bone turnover in postmenopausal women: a cross-sectional study. Eur J Clin Invest 32: 581-589.
27. Maeda T, Kawane T, Horiuchi N (2003) Statins augment vascular endothelial growth factor expression in osteoblastic cells via inhibition of protein prenylation. Endocrinology 144: 681-692.
28. Liu HH, Li JJ (2015) Aging and dyslipidemia: a review of potential mechanisms. Ageing Res Rev 19: 43-52.
29. Audet-Walsh É, Giguére V (2015) The multiple universes of estrogen-related receptor α and γ in metabolic control and related diseases. Acta Pharmacol Sin 36: 51-61.
30. Hwang HS, Kim HA (2015) Chondrocyte Apoptosis in the Pathogenesis of Osteoarthritis. Int J Mol Sci 16: 26035-26054.
31. Almeida M (2012) Aging mechanisms in bone. Bonekey Rep 1.
32. Huh JE, Shin JH, Jang ES, Park SJ, Park DR, et al. (2016) Sirtuin 3 (SIRT3) maintains bone homeostasis by regulating AMPK-PGC-1Î² axis in mice. Sci Rep 6: 22511.
33. Santos L, Escande C, Denicola A (2016) Potential Modulation of Sirtuins by Oxidative Stress. Oxid Med Cell Longev 2016: 9831825.
34. Blanco FJ, Rego I, Ruiz-Romero C (2011) The role of mitochondria in osteoarthritis. Nat Rev Rheumatol 7: 161-169.
35. Maneiro E, Martín MA, de Andres MC, López-Armada MJ, Fernández-Sueiro JL, et al. (2003) Mitochondrial respiratory activity is altered in osteoarthritic human articular chondrocytes. Arthritis Rheum 48: 700-708.
36. Ruiz-Romero C, Blanco FJ (2010) Proteomics role in the search for improved diagnosis, prognosis and treatment of osteoarthritis. Osteoarthritis Cartilage 18: 500-509.
37. Mootha VK, Handschin C, Arlow D, Xie X, St Pierre J, et al. (2004) Erralpha and Gabpa/b specify PGC-1alpha-dependent oxidative phosphorylation gene expression that is altered in diabetic muscle. Proc Natl Acad Sci USA 101: 6570-6575.
38. Chen L, Wong C (2009) Estrogen-related receptor alpha inverse agonist enhances basal glucose uptake in myotubes through reactive oxygen species. Biol Pharm Bull 32: 1199-1203.
39. Wu Y, Chen Z, Jiang G, Zhang K, Liu Q, Liang S, et al. (2016) Inverse agonist of estrogen-related receptor α suppresses the growth of triple negative breast cancer cells through ROS generation and interaction with multiple cell signaling pathways. Oncotarget. 2016 Mar;7(11): 12568-12581.
40. Zhang X, Ren X, Zhang Q, Li Z, Ma S, et al. (2016) PGC-1α/ERRα-Sirt3 Pathway Regulates DAergic Neuronal Death by Directly Deacetylating SOD2 and ATP Synthase b. Antioxid Redox Signal 24: 312-328.
41. Mathieu L, Costa AL, Le Bachelier C, Slama A, Lebre AS, et al. (2016) Resveratrol attenuates oxidative stress in mitochondrial Complex I deficiency: Involvement of SIRT3. Free Radic Biol Med 96: 190-198.