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COMMENTARIES

Is Estrogen Receptor α an Osteoblastic Mechanosensor?

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Commentary on:

- Armstrong VJ, Muzylak M, Sunters A, Zaman G, Saxon LK, Price JS, Lanyon LE. Wnt/beta-catenin signaling is a component of osteoblastic bone cell early responses to load-bearing and requires estrogen receptor alpha. *J Biol Chem*. 2007 July 13;282(28): 20715-27.
- Aguirre JI, Plotkin LI, Gortazar AR, Millan MM, O'Brien CA, Manolagas SC, Bellido T. A novel ligand-independent function of the estrogen receptor is essential for osteocyte and osteoblast mechanotransduction. *J Biol Chem*. 2007 Aug 31;282(35):25501-8.

Bone strength is maintained by proper loading upon bone tissue, and it is evident that bone senses and adapts to mechanical stress. However, the molecular basis of such mechanotransduction in bone cells is largely unknown. Two recent papers (1;2) suggest that estrogen receptor α (ERα) mediates intercellular mechanotransduction in osteoblastic cells. Armstrong *et al*. show that ERα depletion in cultured osteoblasts abolishes activation of canonical Wnt signaling by a dynamic mechanical stress (1). Moreover, in ERα(-/-) mice, the response to mechanical loading was impaired at the expression level of the Wnt signaling target genes. Aguirre *et al*. also reveal that activation of extracellular signal regulated kinases (ERKs) by mechanical stress was undetectable in osteocytes and osteoblasts deficient in ERα (2). Thus, two reports highlight the impact of ERα on osteoblastic mechanotransduction.

Mechanotransduction

In studies on the osteoblastic response to mechanical stress, such as fluid shear and gravity, a number of factors and signaling pathways have been implicated to support mechanotransduction at distinct stages of osteoblastic cytodifferentiation and different bone tissue sites (3;4). A very rapid response to mechanical stress in osteoblasts has been observed as an increase of intracellular calcium, followed by activation of calcium-induced intracellular signaling, including mitogen-activated protein kinase (MAPK)-mediated pathways (5). A significant role for the extracellular matrix and integrins in early mechanotransduction has been also documented. The impact of canonical Wnt signaling (see Fig. 1) on the response to mechanical stimuli became evident from experimental observations on human and rodent cells with mutated LRP5, one of the Wnt ligand receptors (6;7). Besides autocrine and paracrine cytokines, some endocrine hormones (IGF-I and PTH) also appear to support mechanotransduction. The importance of ERα in the bone mechanotransduction response was recently suggested (8). However, despite recent findings, the molecular basis of mechanotransduction remains unclear, particularly regarding the signaling network that is involved and how all these regulators coordinate the integral cellular response in osteoblasts.

Estrogen Receptors

ERs (α and β) are members of the nuclear steroid hormone receptor gene

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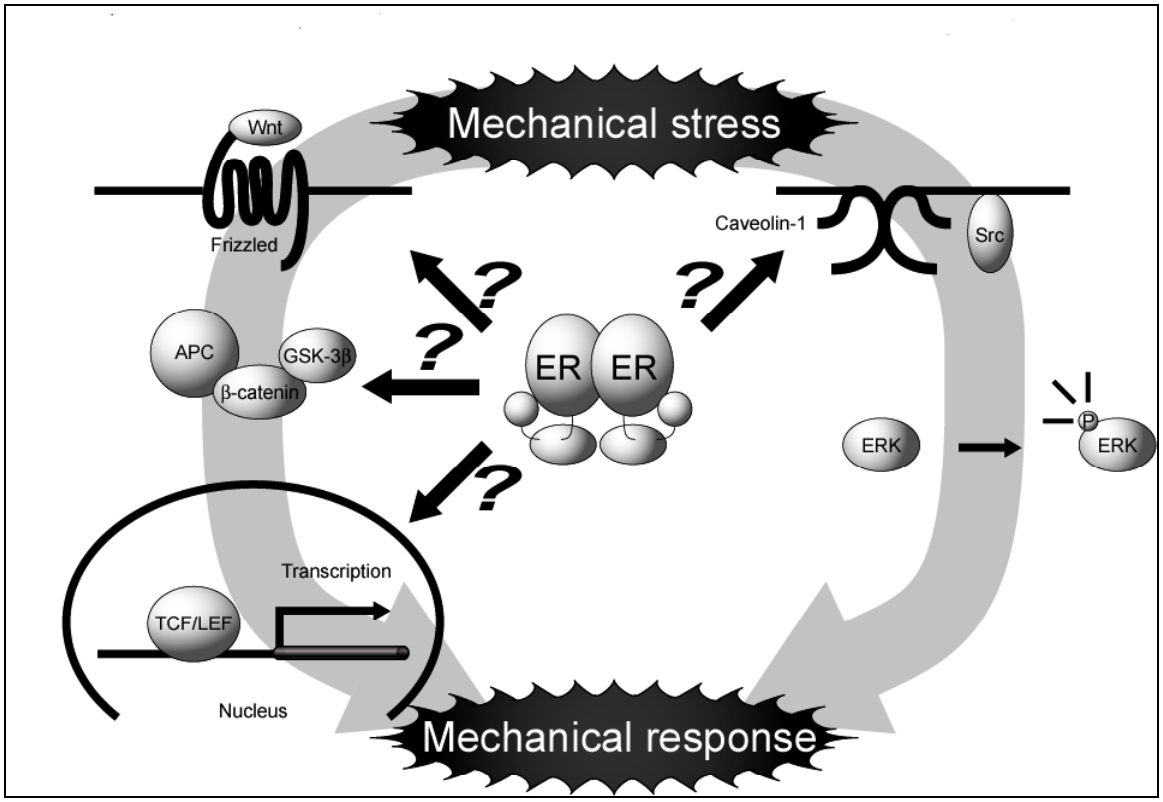

Figure 1. Does ERα mediate mechanotransduction in osteoblasts? Mechanical stress on osteoblasts is know to induce a number of intracelluar signals. Armstrong *et al*. (1) report the activation of Wnt signaling (left), while Aguirre *et al*. (2) report the activation of MAPK signaling (right), in response to mechanical stimulation. In both systems, ERα appears significant in transmitting these intracellular signals, though the detailed molecular mechanism remains unknown.

superfamily and mediate most biological effects of estrogen. Both ERs are able to recognize and specifically bind as homo- and hetero-dimers the same DNA response elements in target gene promoters. No clear difference in the binding of endogenous estrogens has been observed between ERα and β subtypes, but ERβ is inferior to ERα in the hormone-induced activation function. Reflecting the difference in receptor activity in transcriptional control, a greater physiological impact of ERα in estrogen target tissues has been confirmed by the receptor gene disruption approach in mice (9).

Osteoclastic ERα Mediates Osteoprotective Estrogen Action

Total ablation of ERα or ERβ in mice does not induce apparent bone loss, a finding supported by observations on estrogen-deficient humans and rodents (9). Recently, we have ablated osteoclastic ERα and observed clear bone loss in trabecular areas, suggesting that the major osteoprotective action of estrogen is exerted through the osteoclastic ERα in trabecular bone (10). However, these findings do not exclude the possibility that osteoblastic ERα does play a significant role in estrogen osteoprotective action, as well as in the response to mechanical stress.

Cellular Localization of ERs

Unlike the other steroid receptors, ERs are localized primarily in the nucleus in most estrogen target cell types irrespective of estrogen binding. For hormone-induced transcriptional control, ERs sequentially associate with distinct classes of transcriptional co-regulators and co-regulator complexes to exert genomic actions of estrogen (11). Besides transcriptional co-regulators, other signaling factors are thought to potentially interact with ERs in the nucleus (12). In the cytosol,

ERs are proposed to mediate a non-genomic rapid response to estrogen. ER localization in the plasma membrane has been detected, and ERα associated with caveolin-1 was suggested as a putative cell membrane estrogen receptor mediating non-genomic estrogen actions (13). As the cellular distribution of ERs is diverse and appears to depend on the type of cell tested, cellular localization of ERs in osteoblasts and osteoclasts during the stages of cell proliferation and differentiation remains an open question.

Is ERα a Component of the Canonical Wnt Signaling Pathway Mediating Mechanotransduction in Osteoblasts?

Several groups have demonstrated that Wnt signaling is activated in osteoblastic cells upon mechanical stimulation (14;15). Earlier, Lance Lanyon's group reported that ERα was indispensable for the estrogenic response to mechanical loading in intact bone (8). Expanding upon previous studies, this group has now shown that ERα supports mechanical stress-activated Wnt signaling in intact bone tissue, and further confirmed that ERα function is required for the activation of β-catenin-mediated Wnt signaling by mechanical stress in an osteoblastic cell line (ROS 17/2.8) and in primary cultured osteoblasts (1) (see Fig. 1). Though the molecular mechanism behind the co-regulatory function of ERα in Wnt signaling during mechanotransduction remains to be determined, it is not surprising, considering the reported association of nuclear receptors with β-catenin and the demonstration that ERα is a β-catenin co-regulator in transcriptional control by Wnt signaling (16). Even so, it is of great interest to define the mode of ERα co-regulatory function for Wnt signaling during osteoblastic mechanotransduction.

Is ERα a Component of MAPK-mediated Mechanotransduction?

Activation of MAPK by mechanical stress has been previously established (17;18). Aguirre *et al*. provide evidence that activation of one of the MAPKs, ERK, occurs upon mechanical stress in osteocytes and osteoblasts, and that this activity is associated with inhibition of cell death (2). Such a mechanical response was undetectable in osteoblastic cells deficient in either ERα or ERβ. Nuclear translocation of ERK required ERα or ERβ and, interestingly, the caveolin-interacting domain, but not the DNA binding domain, of ERα was indispensable for the stress-induced nuclear accumulation of ERK (2).

Is ERα an Osteoblastic Mechanosensor?

These two papers highlight the significance of ERα in osteoblastic mechanotransduction, and Aguirre *et al*. propose that the lifespan of osteocytes is prolonged by mechanical loading through ERα action, which is in accordance with the abundant expression of ERα in osteocytes. Though these findings clearly indicate the importance of ERα in mechanotransduction, the intracellular function of ERα still remains to be addressed. In this respect, it will be of great interest to understand how ERs functionally associate with regulators involved in osteoblastic mechanotransduction.

Conflict of Interest: The authors report that no conflict of interest exists.

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