The Roles of Osteocyte Signaling in Bone

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Osteocytes are the cells that reside within the bone matrix and make up 90% to 95% of the cellular component of the tissue. Until recently, they were thought to serve as little more than "space holders" in the tissue. However, significant advances have demonstrated that osteocytes are of the utmost importance in regulating the dynamic nature of bone; indeed, it may be that this is their major function. Specifically, osteocyte signaling in skeletal metabolism contributes to (1) regulation of local mineralization, (2) regulation of systemic mineralization, (3) bone formation by osteoblasts, and (4) bone resorption by osteoclasts.

Regulation of Local Mineralization

Because the osteocyte is, by definition, located within the dense, calcified matrix of bone, it is reasonable to suggest that some part of its repertoire is devoted to developing and maintaining that matrix. Three main proteins have been identified in the mineralization process: dentin matrix acidic phosphoprotein-1 (DMP1), phosphate-regulating neutral endopeptidase (PHEX), and matrix extracellular phosphoglycoprotein (MEPE). As a highly phosphorylated protein, DMP1 seems to be involved in the regulation of hydroxyapatite formation. PHEX is thought to play a similar role and likely interacts extensively with DMP1; indeed, deletion of either gene in mice results in a similar, if not identical, bone phenotype.[1] MEPE, along with DMP1, belongs to the SIBLING (small integrin-binding ligand, N-linked glycoprotein) family and is thought to be involved in the regulation of matrix mineralization.

Regulation of Systemic Mineralization

The transport of inorganic minerals within the skeleton necessarily requires interaction with other organs—particularly the kidneys. One factor that is central to the regulation of the bone-kidney axis is fibroblast growth factor-23 (FGF-23). Abnormal circulating levels of FGF-23, either increased or decreased, can cause a variety of disorders. A fascinating feature of this protein is its predominant production by osteocytes and its regulation by PHEX, DMP1, and MEPE.[2] It appears that osteocytes are capable of coordinating bone formation with renal regulation of systemic phosphate homeostasis through the regulated expression of sclerostin, FGF-23, and possibly other factors.

Osteocyte Signaling and Bone Formation by Osteoblasts

In addition to their role in local and systemic mineral homeostasis, osteocytes have a direct effect on the bone formation activities of osteoblasts. One product in particular that has this effect is sclerostin, which is encoded by the *SOST* gene. Highly expressed in osteocytes, this factor appears to directly inhibit bone formation.[3] By presenting the opportunity to tap directly into bone-building pathway, *SOST* could yield novel anabolic

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therapeutic agents to combat such diseases as osteoporosis.

Osteocyte Signaling and Bone Formation by Osteoclasts

Early discoveries of the relationship between osteocytes and osteoclast activity showed that isolated avian osteocytes could support osteoclast formation in the absence of any other osteotropic factors.[4] This fact confirmed that the necessary intracellular machinery exists in osteocytes to produce cytokines related to osteoclastogenesis. Of particular utility in probing the relationship between osteocytes and osteoclastogenesis is the study of their response to localized, noninflammatory microinjury. This response stems from the unique relationship between microdamage in bone and the intrinsic tissue-repair processes. Existing in vivo loading models have been developed, such that microdamage can be induced in localized regions of bone without causing an inflammatory response in the surrounding tissues. In early studies of this kind, fatigue-induced microdamage was shown to cause apoptosis (ie, regulated cell death) in osteocytes nearby, which would subsequently undergo resorption by osteoclasts. Extensive research has been performed since then on the characterization of this system.[5] Most recently, it has been shown that apoptotic osteocytes themselves do not upregulate pro-osteoclastogenic markers following fatigue.[6] A separate and discrete group of osteocytes surrounding them are the source of this cytokine signaling. This penumbra-like phenomenon of nonapoptotic cells surrounding those undergoing apoptosis has also been reported in other focal injury systems, such as those of the ischemic brain and heart.[7]

Our knowledge of the contribution of osteocytes to distinct aspects of skeletal metabolism is expanding at an unprecedented rate. The early belief that osteocytes were merely placeholders in the mineralized matrix has been displaced by exciting, and sometimes unexpected, discoveries that reveal this population of cells to be a highly sensitive, active, and responsive network. The recent discovery that apoptosis in osteocytes is essential for osteoclastogenesis, but that it is not those dying osteocytes but rather nearby neighbors that carry out that task, indicates a division of labor among osteocytes in response to damage paralleling that seen in ischemic injury. Such similarities suggest that common pathways and mechanisms probably exist in localized remodeling of many tissue types.

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