LA MUERTE DE LOS OSTEOCITOS: UNA SEÑAL PARA LA REMODELACIÓN DIRIGIDA

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Resumen
Desde hace largo tiempo se piensa que la red de osteocitos compara continuamente las deformaciones mecánicas actuales con los niveles usuales de las mismas, y dispara señales a osteoclastos y osteoblastos que resultan en ganancia o pérdida ósea, según se necesite. Mientras que los niveles fisiológicos de estimulación mecánica mantienen la masa ósea, niveles demasiado bajos o demasiado altos de deformación inducen resorción ósea. Un mecanismo por el cual los osteocitos pueden gatillar la resorción ósea es entrando en apoptosis. Niveles altos o bajos de carga mecánica llevan a una mayor prevalencia de apoptosis osteocitaria, que temporalmente precede y está espacialmente asociada con el reclutamiento de osteoclastos y subsiguiente aumento de la resorción ósea. Además, recientemente se ha demostrado una relación causa-efecto entre muerte de los osteocitos y resorción ósea. Usando un modelo de ablación osteocítica inducible en ratón transgénico, Tatsumi y col. demuestran que la apoptosis de osteocitos es suficiente para gatillar reclutamiento de osteoclastos y resorción ósea. Más aún, la respuesta osteoclastogénica a la falta de carga está ausente en los huesos de ratones depletados de osteocitos, confirmando que estas células son indispensables para la adaptación esquelética a la ingravidez. Debido a que la apoptosis de los osteocitos es inhibida no sólo por la estimulación mecánica sino también por los estrógenos y los bifosfonatos, estos hallazgos plantean la posibilidad de que la preservación de osteocitos viables contribuya a las propiedades anti-resortivas de dichos agentes.

Palabras clave: osteocitos - apoptosis - remodelación

Summary
OSTEOCYTE DEATH: A BEACON FOR TARGETED REMODELING
It has been long proposed that the osteocyte network continually compares present mechanical strains to usual levels of strain, and triggers signals to osteoclasts or osteoblasts resulting in bone loss or gain, as needed. Whereas physiological levels of mechanical stimulation maintain bone mass, too low or too high levels of strain induce bone resorption. One mechanism by which osteocytes may trigger bone resorption is by undergoing apoptosis. Either low or high levels of mechanical loading lead to increased prevalence of osteocyte apoptosis, which temporally precedes and is spatially associated with osteoclast recruitment and the subsequent increase in bone resorption. Moreover, a cause and effect relationship between osteocyte death and bone resorption has been recently demonstrated. Using a transgenic mouse model of inducible osteocyte ablation, Tatsumi et al. show that osteocyte apoptosis is sufficient to trigger osteoclast recruitment and bone resorption. Moreover, the normal osteoclastogenic response to unloading is missing in bones from osteocyte-depleted mice, confirming that osteocytes are indispensable for the skeletal adaptation to weightlessness. Because osteocyte apoptosis is inhibited not only by mechanical stimulation but also by estrogens and bisphosphonates, these
findings raise the intriguing possibility that preservation of osteocyte viability contributes to the anti-remodeling properties of these agents.  

Key words: osteocytes - apoptosis - remodeling

Regulation of the executive cells of bone remodeling by osteocytes – the sclerostin paradigm

Osteocytes are ideally positioned to be the means by which bone adapts in response to mechanical stimuli. Osteoblasts and osteoclasts that are present on bone only transiently, in low number, and in variable locations. Osteocytes, on the other hand, constitute more than 90 percent of cells in bone and are strategically distributed throughout the entire bone volume. In addition, osteocytes form a syncytium among themselves and with cells on the bone surface via cytoplasmic processes that radiate from their bodies and travel along canaliculi excavated in the mineralized matrix. This network is perfectly suited to sense and respond to both mechanical and systemic stimuli by generating signals that affect osteoblasts, osteoclasts, and their progenitors in the bone marrow. In spite of significant progress in our knowledge about osteocytes in recent years, the mechanisms by which these cells control the function of osteoblasts and osteoclasts are just starting to emerge. Sclerostin is the first, undisputable mediator of the communication between osteocytes and the executive cells of bone remodeling. Osteocytes but not other cells in bone express sclerostin – the product of the Sost gene that antagonizes the action of Wnts and BMPs. Evidence from human diseases and experimental animals indicates that sclerostin acts in a paracrine fashion to inhibit bone formation. Recently, it was shown that sclerostin expression is potently inhibited by two recognized stimuli that increase osteoblast number: parathyroid hormone and mechanical loading, thereby representing a novel mechanism of regulation of bone formation mediated by osteocytes.

Osteocyte apoptosis: regulation and consequences

That osteocytes perceive changes in the level of both physical stimuli as well as circulating factors is evidenced by studies on the regulation of their life span. Osteocytes are long-lived cells. However, like osteoblasts and osteoclasts, they die by apoptosis; and decreased osteocyte viability accompanies the bone fragility syndrome that characterizes glucocorticoid excess and estrogen withdrawal. Conversely, preservation of osteocyte viability might explain at least part of the anti-fracture effects of bisphosphonates, which cannot be completely accounted for by changes in bone mineral density.

Osteocyte apoptosis is also regulated by mechanical forces. Thus, mechanical stimulation of osteocytes protects them from the pro-apoptotic action of glucocorticoids, etoposide and other death inducers. Mechanistic studies indicate that the transduction of mechanical forces into intracellular signals is accomplished by molecular complexes assembled at caveolin-rich domains of the plasma membrane and composed of integrins, cytoskeletal proteins and kinases including the focal adhesion kinase FAK and Src, resulting in activation of the ERK pathway and osteocyte survival. In vivo mechanical stimulation also regulates osteocyte life span. Thus, increased prevalence of apoptotic osteocytes is found in unloaded bones or in bones exposed to high levels of mechanical strain. In both cases, increased apoptosis of osteocytes was observed before any evidence of increased osteoclast resorption. Moreover, apoptotic osteocytes in unloaded bones accumulated in areas that were subsequently removed by osteoclasts. Taken together with the in vitro evidence, these findings had suggested that diminished mechanical forces eliminate signals that maintain viability, thereby leading to osteocyte apoptosis; and that dying osteocytes in turn become the beacons for osteoclast recruitment to the vicinity and the resulting increase in bone resorption (Figure).
Recent work provides direct evidence that death of osteocytes is sufficient to recruit osteoclasts and to increase resorption. Tatsumi et al. generated transgenic (TG) mice expressing the diphtheria toxin receptor (DTR) under the control of the dentin matrix protein 1 (DMP1) promoter that is only active in osteocytes. DTR is normally not expressed in murine cells; therefore, osteocytes are the only cells sensitive to the toxin in these TG animals. A single injection of DT resulted in rapid induction of apoptosis of 70-80% of osteocytes; and this was followed by increased osteoclasts and loss of bone. These findings demonstrate that osteocyte apoptosis is sufficient to trigger osteoclast recruitment and the resulting increase in bone resorption and bone loss.

In conclusion, the osteocyte ablation model revealed that osteocyte apoptosis is sufficient to initiate an osteoclastogenic response and that osteocytes are required for the skeletal adaptation to reduced mechanical forces. Whether living osteocytes continually produce molecules that restrain osteoclast recruitment or whether in the process of undergoing apoptosis osteocytes produce pro-osteoclastogenic signals remains to be determined. It is expected that intense investigations will take place in the near future attempting to identify the molecular mediators involved in the communication between osteocytes and osteoclasts.

References
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