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Subchondral bone morphological and biochemical alterations in osteoarthritis

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Although major progress has been made in the last few years, there is still much to learn about the etiology, pathogenesis and progression of osteoarthritis (OA). This disease can be described as the degradation and loss of articular cartilage accompanied by hypertrophic bone changes with osteophyte formation and subchondral plate thickening.

Subchondral bone sclerosis is a well-recognized manifestation of human OA; however, the mechanisms responsible are unknown. Two theories are currently proposed. The mechanical stress on weight-bearing joints may contribute to increase in microfractures in the bone plate and overlaying cartilage. As articular cartilage slowly erodes, sclerosis of the subchondral bone plate also progresses and bone stiffness increases in this tissue, possibly contributing to further mechanical disturbances of the cartilage. On the other hand, changes in the subchondral bone such as sclerosis may precede cartilage damage in OA. A steep stiffness gradient in the underlying subchondral bone may therefore be an initiation mechanism of OA as the integrity of the overlying articular cartilage depends on the mechanical properties of its bony bed.

The mechanisms responsible for subchondral bone sclerosis in OA have not yet been elucidated, and whether these mechanisms reflect a cellular defect of osteoblasts or an adaptation to local and/or systemic factors is undetermined. We therefore undertook a study [1] in which we initially evaluated the phenotypic behavior of subchondral bone osteoblasts from OA and normal individuals by examining specific biomarkers. Data showed (Fig. 1) a phenotypic change in the cyclic adenosine monophosphate (cAMP) production of OA subchondral bone osteoblasts in response to parathyroid hormone (PTH) and prostaglandin (PGE_2), and an alteration of alkaline phosphatase and osteocalcin when these diseased cells were treated with vitamin D ($1,25(OH)_2D_3$).

Local, systemic and/or mechanical factors may also contribute to the modulation of bone density in this disease. We hypothesized that the abnormal osteoblasts from subchondral bone in human OA occurs due to an increased activity of growth factors and proteases present locally. More precisely, we postulated that two major systems are involved in this process, the insulin-like growth factor (IGF)-1 and plasminogen activator (PA)/plasmin systems as both can promote osteoblast cell growth directly or indirectly.

Our general hypothesis is as follows. At the onset or during the OA process, a thickening of the underlying subchondral bone is noted. This could result from repetitive loading, microfracture and/or the activity of the IGF/IGF binding protein (IGFBP) system leading to an abnormal response of the subchondral bone. This in turn creates local

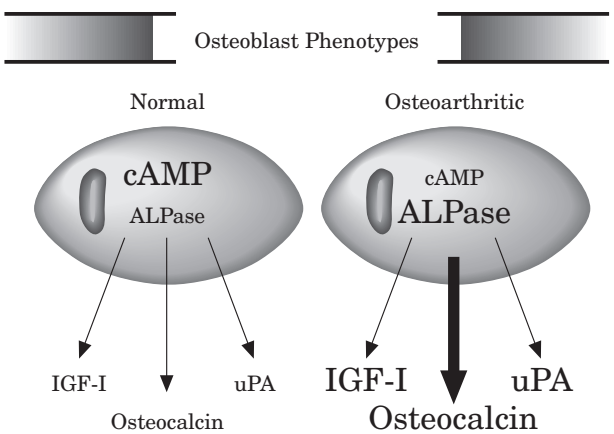

Fig. 1. Schematic representation of normal and osteoarthritic subchondral bone osteoblasts. Compared to normal, osteoarthritic cells showed a decreased cAMP response to PTH and PGE_2, and increased $1,25(OH)_2D_3$ response levels of alkaline phosphatase (ALPase) and osteocalcin; basal IGF-1 and urokinase (uPA) were also enhanced.

microfractures in the cartilage inducing cartilage matrix damage. This cartilage damage is normally repaired by either local synthesis or the release of IGF/IGFBP that stimulates matrix formation in the cartilage. At the same time, the IGF system promotes bone cell growth and bone matrix deposition. The anabolic activity of the IGF-1 system which can be locally regulated by the PA/plasmin system is enhanced in subchondral bone, while the local activation of the PA/plasmin system in cartilage promotes local cartilage alteration. Thus, the local induction in bone and cartilage of IGF-1 and its protease regulatory system promotes both cartilage damage and subchondral bone plate thickening, this last pathway leading to further cartilage damage. This imbalance in the repair capacity and damage of cartilage due to subchondral plate thickening subsequently leads to a progressively altered cartilage matrix and eventually to OA, hence, explaining the slow progression of the disease.

Indeed, results showed (1) that OA subchondral bone osteoblasts produce elevated levels of both IGF-1 and urokinase plasminogen activator (uPA), and that the level of the specific uPA inhibitor plasminogen activator inhibitor (PAI)-1 does not significantly differ between OA and normal subchondral bone osteoblasts. Moreover, preliminary experiments suggest that IGF-1 may stimulate the basal uPA activity. According to our theory, this causes an increase in bone formation thereby promoting a greater bone stiffness.

Data from our study strongly support the concept that a bone defect may contribute to the onset and/or progression of cartilage degradation in OA.

Reference

1. Hilal G, Martel-Pelletier J, Pelletier JP, Ranger P, Lajeunesse D. Osteoblast-like cells from human subchondral bone demonstrate an altered phenotype *in vitro*: Possible role in subchondral bone sclerosis. Arthritis Rheum 1998;41:981–99.