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Perspective Article

Hylonome

Altered subchondral osteoblast cellular metabolism in osteoarthritis: cytokines, eicosanoids, and growth factors

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Although major progress has been made in the last few years, we still have a lot to learn about the etiology, pathogenesis and progression of osteoarthritis (OA)[1-3]. Limiting factors such as the slowly progressive nature of the disease and the multifactorial nature of this disease has limited our comprehension of OA. Osteoarthritis can be described as the degradation and loss of articular cartilage, due to an imbalance between matrix degradation and an attempt to repair this matrix, accompanied by hypertrophic bone changes with osteophyte formation and subchondral plate thickening[4-6]. OA is increasingly considered as a complex illness in which all tissues of the joint play significant roles in the initiation and/or progression of the pathophysiologic manifestations. The specific interaction between bone and cartilage is still not clearly defined, nor why chondrocytes can not adequately repair the cartilage matrix. Risk factors for this disease in humans include age, gender, genetic predisposition, mechanical stress and/or joint trauma, and obesity[2,7,8]. Increased bone density may also be viewed as a risk factor for this disease. However, we are still far from a complete understanding of what goes on to initiate the degradation and loss of cartilage.

Some, but not all, bone parameters are altered in OA individuals, such as abnormal bone mineral density, osteoid volume, bone mechanical parameters or indicators of bone turnover, compared to normal individuals or osteoporotic patients[9-12]. Moreover, some patients with knee OA are associated with a specific type of vitamin D receptor[13] and collagen type II genotype[14]. An increased bone mineral density of the subchondral bone tissue is always observed in OA yet this tissue is undermineralized[15,16], indicating that bone remodeling could be altered in these patients. As the loss of cartilage in OA can be attributed to a deficient repair/remodeling mechanism(s), the question arises whether degradative products from the subchondral bone tissue may reach the overlying cartilage and promote its degradation. Such an interaction between OA osteoblasts and normal cartilage has been previously suggested by Westacott et al.[17], however no single effector responsible for this link has been identified.

Recent evidence suggests a key role for the subchondral bone tissue in the progression and/or initiation of OA[11,12,18] possibly via the production of cytokines and growth factors. Indeed, bone tissues produce a number of pro-inflammatory cytokines and growth factors involved in tissue remodeling, the same factors involved in cartilage catabolism. As early pathological studies have shown the presence of clefts or channels in the tidemark that appear early on in OA[19,20], this indicates a possible way to traffic cytokines and growth factors from the subchondral compartment to the overlying cartilage. Hence, it is feasible that bone-derived products could drive cartilage metabolism. Potential candidates could include insulin-like growth factor-1 (IGF-1), transforming growth factor-beta (TGF-β) and interleukin 1β and 6 (IL-1β, IL-6). The demonstration of a role of the subchondral bone tissue in the initiation of OA would greatly contribute to further our knowledge of this pathology and give new insights to clinical approaches to treat osteoarthritis.

Roentgenographic changes in the subchondral cancellous bone, such as sclerosis and cyst formation, are observed in patients with OA, yet have been considered secondary. However, one of the mechanisms of initiation of OA may be a steep stiffness gradient in the underlying subchondral bone[21,22]. Indeed, the integrity of the overlying articular cartilage depends on the mechanical properties of its bony bed. Evidence from a primate animal model (*Macaca fascicularis*) of OA is now indicating that alterations of the bony bed may be preceding the cartilage changes[23,24]. Evidence for and against this hypothesis has recently emerged both from animal model studies and clinical trials. However, trabecular

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thickening in subchondral bone is not always accompanied by increased bone mineralization, but by osteoid volume increases[9,10]. This is an indication of abnormal mineralization[25] and indeed recent studies have indicated hypomineralization in OA bone tissues[15,16], hence suggesting that a disregulation of bone remodeling may be part of OA. This would support the concept of a bone cell defect in this disease which indeed may be a more generalized bone metabolic disease as suggested by the group of Dequeker[26,27].

Previous clinical studies in OA patients and immunohistochemical studies with OA bone tissue have shown upregulation of alkaline phosphatase and osteocalcin levels[15,26], which are both produced by osteoblasts. However, these *in vivo* changes may be due to abnormal systemic regulation, or abnormal cell behavior. Our own studies have focused on the determination of whether primary human OA subchondral osteoblasts would show abnormal biomarkers, and abnormal response to hormonal challenge. *In vitro* alkaline phosphatase activity of human osteoblasts isolated from the subchondral bone plate of tibial plateaus is higher in cells from OA patients than from normal individuals, both in control or after $1,25(OH)_2D_3$ stimulation. However, the cells from OA patients respond normally to $1,25(OH)_2D_3$ stimulation[28,29]. Likewise, when osteocalcin release was evaluated at the protein or mRNA level, it was clearly elevated in OA osteoblasts, reminiscent of the findings by the group of Dequeker who showed elevated osteocalcin levels in OA bone explants. Hence, this would suggest an abnormal cell behavior, not an altered response to systemic factor(s) or local stimulation, since $1,25(OH)_2D_3$ levels are normal in OA patients. Actually, since we are using human primary bone cells in controlled *in vitro* culture conditions, devoid of any systemic or hormonal regulation that they would experience *in vivo*, those differences in osteocalcin and alkaline phosphatase would strongly indicate an abnormal bone cell behavior in OA osteoblasts.

As cartilage degradation can be driven by osteoblast-derived factors in about 50% of OA cases as shown by Westacott et al.[17], we attempted to determine which factors could be modified in OA osteoblasts. Our attention focused on cytokines, eicosanoids and growth factors. We found that the levels of certain cytokines and prostaglandin E2 can discriminate two groups of OA individuals[30]. Osteoblasts from one group of OA individuals produced low levels of PGE2 and IL-6, very similar to normal cells, whereas another group of OA individuals always showed an increase in PGE2 and IL-6 production. Individuals are restricted to one group, meaning that, within the same cells, if they are producing large amounts of PGE2, they are also producing higher amounts of IL-6. However, this does not extend to IL-1β and TGF-β production by OA osteoblasts. For IL-1β levels, there seems to be no significant difference compared to normal, whereas TGF-β levels were higher for all OA osteoblasts. In contrast, another eicosanoid, leukotriene B4 (LTB4) which is produced at relatively low levels by normal osteoblasts, also discriminate two groups of OA individuals, yet opposite to that observed by PGE2[31]. Hence cells producing high levels of PGE2 produce low levels of LTB4 and vice versa. This puzzling situation could be explained by the selective use of arachidonic acid via the cyclooxygenase (COX) pathway or the lipoxygenase pathway in OA osteoblasts, and indeed, the chronic inhibition of COX-2 leads to upregulation of LTB4 production[31].

The group of Dequeker also previously demonstrated increases in IGF-1, IGF-2, and TGF-β levels in bone explants from the iliac crest of OA patients[27]. Interestingly, our own studies have shown an increase in total IGF-1 levels in *ex vivo* OA subchondral bone explants and *in vitro* osteoblasts. This increase is due, to a large part, to an increase in the IGF-1 messenger RNA levels that we measured by RT-PCR in OA osteoblasts, and separating the patients between the low and high OA patients also clearly showed different *in vitro* production of IGF-1. In contrast, the levels measured for IGFBPs were lower in OA osteoblasts with IGFBP-3, -4 and -5 showing a 47 ± 3.6, 50.3 ± 11.4 and 22.6 ± 10.6% reduction, respectively, in OA osteoblasts compared to normal. So it would be difficult that these differences could explain the variations that we observed in total IGF-1 levels although it would translate into elevated free IGF-1 levels. Moreover, whereas under basal conditions the levels of IGFBP-3, 4, and 5 produced by OA osteoblasts are reduced compared to normal, the stimulation by PTH does not increase IGFBP-3 and 5 yet can stimulate IGFBP-4 production. Lastly, IGF-1 signaling is altered in OA osteoblasts, a situation that could also explain, at least in part, bone sclerosis.

In summary, OA osteoblasts show a number of metabolic alterations that may interfere with normal cell metabolism and signaling, possibly leading to altered extracellular matrix composition and function. In turn, such changes in cellular events may lead to abnormal cross-talk between cells from the subchondral bone plate and articular cartilage leading to altered cartilage repair, and ultimately cartilage loss.

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