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Commentary

Subchondral bone as a key target for osteoarthritis treatment

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ABSTRACT

Osteoarthritis (OA), the most common form of arthritis, is a debilitating and progressive disease that has become a major cause of disability and impaired quality of life in the elderly. OA is considered an organ disease that affects the whole joint, where the subchondral bone (SB) plays a crucial role. Regardless of whether SB alterations precede cartilage damage or appear during the evolution of the disease, SB is currently recognised as a key target in OA treatment. In fact, bone abnormalities, especially increased bone turnover, have been detected in the early evolution of some forms of OA. Systemic osteoporosis (OP) and OA share a paradoxical relationship in which both high and low bone mass conditions may result in induction and/or OA progression. Recent findings suggest that some drugs may be useful in treating both processes simultaneously, at least in a subgroup of patients with OA and OP. This review focuses on the role of SB in OA pathogenesis, describing relevant underlying mechanisms involved in the process and examining the potential activity as disease-modifying anti-osteoarthritic drugs (DMOADs) of certain SB-targeting agents currently under study.

1. Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by uneven and gradual loss of articular cartilage, osteophyte formation, subchondral sclerosis and a variety of associated abnormalities of the synovial membrane and periarticular structures. OA is a multifactorial disease characterized by pain, stiffness and functional impairment ultimately resulting in chronic disability and significant economic burden, especially in people 65 years and older [1]. Although repetitive trauma plays a crucial role in the pathogenesis of primary OA, there are other important factors that must be considered. These include genetic factors, menopause-related estrogen deficiency and aging [2].

OA has traditionally been seen as a primary articular cartilage disorder; however, the role of subchondral bone (SB) is currently believed to be of particular importance in the pathogenesis of the disease [1,3–8]. Nevertheless, it remains controversial whether SB alterations precede cartilage degradation or follow the damage caused by loss of cartilage during the evolution of the disease. Recent data from animal models demonstrate that microstructural SB alterations may occur before, during or after cartilage damage [5–8].

In humans, the relationship between systemic bone mineral density (BMD), local subchondral BMD and OA is not clearly defined. Bone alterations may not be uniform and are dependent on the status of overlying cartilage, whether healthy or damaged, and the stage of the disease [4,9]. Recently, data from the Multicenter OA Study (MOST) indicate that high systemic BMD increases the risk of incident knee OA, but not radiographic progression of knee OA [10]. On the contrary, experimental studies show that systemic or local OP worsens OA progression [11]. Hence, different and opposite disturbances of SB mineral density may induce incident OA or aggravate previous disease. Furthermore, the presence of low bone mass in SB does not have the same influence on healthy and diseased cartilage [9].

Thus, SB may be a potentially interesting target for OA treatment, and therefore, bone-acting agents may have favorable consequences on cartilage structure, and subsequently on OA progression.

In this review, we discuss the role of SB in OA pathogenesis and analyze the main effects of various antiresorptive and bone-forming agents on SB remodeling and their potential suitability for treating OA.

2. Definition and functions of the subchondral bone

SB is the zone of epiphyseal bone just beneath the articular cartilage, and includes the SB plate and the underlying trabecular and subarticular bone. The SB plate comprises the deepest area of the articular cartilage, which is the calcified cartilage, and a thin

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cortical bone layer [12]. The calcified cartilage is separated from the overlying hyaline cartilage by a line of demarcation called the tidemark. There is an absence of clear anatomical boundaries between SB regions when examined by current imaging techniques, which impedes a thorough study of their properties.

Nevertheless, SB is recognised as a key factor in normal joint protection. In fact, SB has been shown to exert important shock-absorbing and supportive functions in normal joints. SB can attenuate about 30% of the joint load, providing a mechanical base for joint cartilage [13]. Moreover, SB supplies nutrients to cartilage and facilitates the removal of metabolic waste products.

Currently, there is clear evidence for biological crosstalk between SB and joint cartilage. In fact, there is a considerable amount of information indicating the presence of channels between these two tissues, providing a route for the active interplay of biochemical signals throughout both compartments [13]. Many authors therefore consider that SB and articular cartilage represent an authentic functional unit [12–14].

3. Role of subchondral bone in OA pathogenesis

During the OA process, SB undergoes structural changes including increased bone turnover, microfractures, the appearance of new vessels (angiogenesis) and bone sclerosis in later stages. Furthermore, in terms of histopathology, the tidemark is duplicated, the hyaline cartilage is thinned, new blood vessels penetrate the calcified cartilage from SB and there is a subsequent increase in SB thickness [4,12]. These changes affect the biomechanical properties of the overlying joint cartilage and their intertwined biological relationship [12]. In addition, it may be possible that each SB anatomical region may respond differently during the OA process. Thus, SB alterations become a crucial contributor to OA pathogenesis.

The potential role of SB in the initiation and progression of OA was proposed by Radin and Rose [15]. The presence of SB stiffness may decrease its viscoelastic properties and produce a loss of SB shock absorbing capacity, which in turn causes significant extra mechanical load and subsequent breakdown of the overlying cartilage [15]. These same findings were also demonstrated in aged cynomolgus monkeys, where sclerosis of the tibial plateau was directly related to cartilage damage in the medial compartment of the knee [16]. In light of current knowledge on their close relationship, cartilage damage may in turn negatively influence subjacent SB, thus perpetuating a pathogenic circle in the OA joint.

The integrity of articular cartilage may depend not only on SB, which confers specific mechanical properties and influences cartilage remodeling, but also on subarticular bone beneath SB. More recent evidence has shown changes in the structure of bone beneath damaged cartilage in established OA in both humans and animals. This suggests that underlying bone and not just SB may contribute to the development of OA [8,17,18].

Several biological events confirming the presence of increased SB turnover have been described in OA using different study techniques (Table 1). First, several authors have demonstrated increased tracer uptake in subarticular bone scintigraphy [19,20], which has been found to be a good predictor of faster knee OA progression [19,20]. However, it is unclear in which SB region this increased turnover happens. Second, increased SB turnover and remodeling accompanied by specific structural changes in the subchondral trabecular bone have been identified in early stages of OA joints, while increased bone stiffness has been described as later finding [8,12]. Third, elevated levels of bone biomarkers have also been reported in patients with progressive knee OA [21,22]. Finally, magnetic resonance imaging (MRI) findings have indicated increased bone turnover, which are strong predictors of poor prognosis in knee OA [23]. Consequently, modulation of SB turnover may become an attractive approach to OA treatment.

Table 1
Main experimental methods to evaluate subchondral bone in OA.

SB evaluation method/technique	Parameters analyzed
Bone formation biomarkers	Bone alkaline phophatase, osteocalcin, PINP, PICP
Bone resorption biomarkers	TRAP, TRAP5b, pyridinolines (PYD) NTX-I, CTX-I
Bone isotopic scintigraphy	Isotopic tracer uptake
Image techniques: MRI, μCT	Bone microstructural variables Bone microarchitectural variables
Histomorphometry	Histomorphometric parameters

Abbreviations: MRI: magnetic resonance imaging; NTX-I/CTX-I: crosslinked C- (CTX) and N-terminal (NTX) telopeptides of type I collagen; PICP: C-terminal propeptide of type I collagen; PINP: N-terminal propeptide of type I collagen; PYD: pyridinolines; SB: subchondral bone; TRAP (5b): tartrate-resistant acid phosphatase (5b fraction); μCT: micro-computerized tomography.

Osteoblasts (OBs) and osteoclasts (OCs) are, respectively, the cellular effectors of anabolic and catabolic processes in SB and other skeletal regions [24], while chondrocytes preserve homeostasis in cartilage [25]. There is close biological communication between the osteoblasts and osteoclasts in SB and the chondrocytes in joint cartilage [5,26]. Various cytokines, growth factors, prostaglandins (PGs) and leukotrienes produced by SB cells, particularly OBs, seep through the SB-cartilage interface and promote cartilage breakdown [27]. It has therefore been proposed that OBs play a crucial role in this relationship. Indeed, some researchers characterize OA based on the subchondral OB phenotype and whether the OBs are low or high producers of endogenous PGE_2 and interleukin (IL)-6, which is related to the speed of OA progression [5,28].

Another interesting system that is clearly involved in cartilage and SB microarchitecture abnormalities in OA is the osteoprotegerin/receptor activator of nuclear factor (NF)-κB (RANK)/RANK-Ligand (OPG/RANK/RANKL) signaling pathway. The molecular triad OPG/RANK/RANKL is a common final regulator of bone remodeling, which has also been implicated in chondrocyte homeostasis [29–31]. In fact, RANKL expressed by subchondral OBs may be responsible for increased recruitment of active osteoclasts in osteoarthritic SB, thus leading to a rise in bone resorption observed in the early phase of experimental OA. Furthermore, human chondrocytes also express and produce each member of this molecular complex [32]. As a consequence, the RANKL/OPG system has a double mechanism of action in the pathogenesis of OA, through its effect on SB remodeling by stimulating osteoclastogenesis and by a direct effect on chondrocyte homeostasis. OPG has been proposed as a valid biomarker of hand OA [33], and high levels of synovial fluid OPG and increased serum RANKL/OPG ratio have correlated with disease severity in patients with primary knee OA [29]. These findings provide good evidence for the potential value of anti-RANKL therapy in OA.

In general, current data indicate that SB abnormalities are mainly resorptive in the initial phases of OA [8,34] and reparative (bone sclerosis, osteophyte formation) in later stages [35].

4. Osteoarthritis vs. osteoporosis

The paradoxical but unquestionable relationship between the two diseases, OA and OP, is another fascinating subject. Regardless of local communication between SB and joint cartilage and the influence of remodeling in subchondral and subarticular bone on the overlying cartilage, systemic OP may also be involved in OA pathogenesis. The current paradigm supports an inverse relationship between OA and OP [36,37]; however, the relationship has been shown to vary according to the location of BMD measurements and the type of OA (i.e., localized or generalized) [37,38]. As a point of fact, a direct relationship between both diseases has also been described [37,38], which has been used to show how