Mod Rheumatol (2003) 13:7–14

REVIEW ARTICLE

Daniel Lajeunesse · Frédéric Massicotte
Jean-Pierre Pelletier · Johanne Martel-Pelletier

Subchondral bone sclerosis in osteoarthritis: not just an innocent bystander

Abstract Osteoarthritis (OA) is considered to be a complex illness in which the tissues of the joint play a significant role in the initiation and/or progression of the pathophysiology. We still do not completely understand what initiates the degradation and loss of cartilage. However, it has been suggested that increased catabolism due to elevated cytokines and growth factors in OA joints plays a significant role. Recent evidence suggests a key role for the subchondral bone tissue in the progression and/or initiation of OA. Indeed, the subchondral bone tissue produces a number of similar proinflammatory cytokines, and growth factors are involved in cartilage tissue remodeling. Interestingly, studies have shown the presence of clefts or channels in the tidemark that appears early in OA, indicating a possible way to traffic cytokines and growth factors from the subchondral compartment to the overlying cartilage. Therefore, it is possible that certain bone-derived products drive cartilage metabolism. Potential candidates include insulin-like growth factor-1 (IGF-1), transforming growth factor-β (TGF-β) interleukin 1β (IL-1β), and interleukin-6 (IL-6). Demonstrating that the subchondral bone plays a role in the initiation of OA would greatly contribute to furthering our knowledge of this pathology and provide new insights for therapeutic approaches.

Key words Cytokines · Insulin-like growth factor-1 (IGF-1) · Osteoarthritis (OA) · Subchondral bone sclerosis · Transforming growth factor-β (TGF-β)

D. Lajeunesse (✉) · F. Massicotte · J.-P. Pelletier · J. Martel-Pelletier
Unité de recherche en Arthrose, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, 1560 rue Sherbrooke Est, Montréal, Québec H2L 4M1, Canada
Tel. +1-514-890-8000 (ext. 28914); Fax +1-514-412-7583
e-mail: lajeunda@jonction.net.

Introduction

Osteoarthritis (OA) is a chronic disorder of the skeleton involving joint structural changes in the cartilage, synovial membrane, and subchondral bone. Although OA is a complex disease of multifactorial origin involving many tissues of the joint, a subgroup of OA patients shows a genetic predisposition to the disease.[1–3] Numerous studies have focused on determining whether an abnormal metabolism of OA chondrocytes could play a role in the deterioration and loss of cartilage in this disease. Several processes are altered in OA cartilage, but no single mechanism is presently considered as the initiating event. In contrast, recent data indicate that subchondral bone may possibly play a role in the onset and/or progression of this disease.[4–9] Some, but not all, bone parameters, such as abnormal bone mineral density, osteoid volume, and bone mechanical parameters or indicators of bone turnover are altered in OA patients compared with normal individuals or osteoporotic patients. Moreover, patients with knee OA are associated with a specific type of vitamin D receptor[10] and collagen type II genotype.[11] Increased bone mineral density is always observed in OA subchondral bone tissue, yet this tissue is undermineralized,[7,12,13] 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 as to whether products (growth factors, degradative enzymes, cytokines) from the subchondral bone may seep through clefts or channels present in the tidemark[14–17] to invade the overlying cartilage and promote its degradation.

Pathophysiology of osteoarthritis

Osteoarthritis is characterized by progressive articular cartilage loss, appositional new bone formation and sclerosis of the subchondral trabeculae and growth plate, the formation of osteophytes, and an imbalance between loss of cartilage

(due to matrix degradation) and an attempt to repair this matrix.[18–20] Synovitis is often observed, and is considered to be secondary to the changes in hard tissues within the joint. However, despite major progress in the last few years, we still have a great deal to learn about the etiology, pathogenesis, and progression of this disease.[21–23] The slowly progressive loss of cartilage, the multifactorial nature of the disease, and the cyclical course with periods of active disease, possibly due to flares of inflammation followed by remission, have limited our comprehension of OA. Risks factors for this disease in humans include age, gender, genetic predisposition, mechanical stress and/or joint trauma, and obesity.[22,24–26] Dieppe et al.[27] reported that increased subchondral bone activity, as judged by enhanced uptake of technetium-labelled diphosphonate, predicts cartilage loss, while cartilage lesions do not progress in the absence of significant subchondral activity. Moreover, alterations of the bony bed precede cartilage changes in the *Macaca fascicularis* primate model of OA,[28,29] as in the Dunkin–Hartley guinea pig model.[30] Evidence for and against this hypothesis from both animal model studies[31–37] and clinical trials[38–44] has been obtained. However, trabecular thickening of the subchondral bone reflects osteoid volume increases and not always increased bone mineralization.[38,43] This alteration in bone tissue is an indication of abnormal mineralization and/or remodeling.[45] About 40 years ago, Johnson[46] suggested that changes in bone remodeling might be responsible for the loss of cartilage. Moreover, Sokoloff[47] proposed that bony changes in the human hip could not be dissociated from cartilage fibrillation, even in early disease. Likewise, stiffening of the subchondral bone, attributed to the healing of microfractures, preceded cartilage damage in guinea pigs.[48] The healing of microfractures due to increased subchondral bone stiffness was also reported to be the primary cause of OA in humans. Together, these data would support the concept that a bone cell defect in this disease may be a more generalized bone metabolic disease, as suggested by Dequeker's group.[49,50]

What are the possible causes of subchondral bone sclerosis?

The progression of joint cartilage degeneration is associated with intensified remodeling of the subchondral bone and increased bone stiffness.[40] The healing of trabecular microfractures in OA subchondral bone could generate a stiffer bone, which is no longer an effective shock absorber.[51,52] Conversely, subchondral bone stiffness may be part of a more generalized bone alteration leading to an apparent increased bone mineral density/volume. OA patients have a better-preserved bone mass,[53–56] independently of body weight,[57–60] and primary OA and osteoporosis rarely coexist.[61–63] The association between osteophytes and femoral bone mineral density indicates that a primary attribute of bone formation may underlie the pathophysiology of OA.[64] In animal models of spontaneous OA, increased bone density and osteoid volume are often more severe than cartilage changes.[28,29,32–36] Moreover, Carlson et al.[29] clearly demonstrated that thickening of the subchondral bone occurred prior to fibrillation of the articular cartilage in cynomolgus macaques. Bone remodeling is a tightly controlled mechanism that involves coupling between a mineralized collagen type I bone matrix, layed down by osteoblasts, and osteoclasts chewing up this matrix. Although OA is associated with a thickening of subchondral bone, explants of the femoral head of OA patients at autopsy showed a low mineralization pattern compared with normal.[7,12,44] Indicators of bone remodeling are also increased in OA patients.[13,65,66] The increase in indices of both bone formation and resorption in OA patients could explain abnormal remodeling and low mineralization. This apparent increase in bone mineral density in OA may be due to an increase in material density and not to an increased osteoid collagen matrix that is undermineralized.[6,7,67] Such a situation would retard normal remodeling by uncoupling bone formation and resorption. Abnormal mineralization in OA may then be viewed as an osteoblast problem.

Possible relationship between bone sclerosis and cartilage degradation

High body mass index and increased bone density suggest that new bone synthesis exceeds degradation in OA. In support of this hypothesis, osteocalcin (a marker of bone formation) in synovial fluid and serum osteopontin (a bone-specific matrix protein) were significantly higher in patients with knee-scan abnormalities.[68] Since serum osteopontin levels increase quickly following trauma, this implies that alterations in bone cell activity may occur quite early in the disease. Gevers and Dequeker[69] showed elevated serum osteocalcin levels in women with hand osteoarthritis, and elevated osteocalcin in cortical bone explants. An imbalance between collagen and noncollagen protein synthesis, such as osteocalcin by OA osteoblasts, could lead to an increase in bone volume, due to an increase in the extracellular matrix, without a concomitant increase in the bone mineralization pattern. An abnormal collagen content may also lead to abnormal mineralization, as only native collagen type I fibrils can mineralize. This is intriguing, since collagen type I is elevated in trabecular bone of femoral heads of OA patients, which in theory should lead to an increase in mineralization.[6,7] Collagen type I is composed of a heterotrimer of $\alpha 1$ and $\alpha 2$ chains at an average ratio of 2.4:1 in normal bone; however, this ratio varied between 4:1 and 17:1 in OA bone tissue.[67] Such an increase in $\alpha 1$ homotrimers caused a 50% reduction in bone strength in $\alpha 2$ knockout mice.[70] In fact, a reduction in $\alpha 2$ chains may lead to a tighter packing of collagen fibers and, coupled with the reduction in cross-links observed in OA bone tissue[7] and the overhydroxylation of lysine in collagen fibrils,[67] may explain the reduction in bone mineralization. As OA subchondral osteoblasts show increased osteocalcin and alkaline phosphatase levels in vitro[4,5,71] and in bone in vivo,[69] this implies that the in vivo alterations are due to abnormal

cellular metabolism and not to alterations in systemic regulation. Both calcitriol ($1,25(OH)_2D_3$) and parathyroid hormone (PTH) levels are normal in OA patients,[10,72] and they both inhibit collagen synthesis in vivo in bone.[73–75] However, OA subchondral osteoblasts are partially resistant to PTH stimulation in vitro[4] due to a decreased expression of PTH receptors,[76] a situation that could favor collagen synthesis.

Role of abnormal subchondral bone metabolism in osteoarthritis

Elevated bone density may be due to an increased activity of growth factors present locally in bone, to a generalized elevation of their production by bone cells or release of latent forms via enhanced remodeling, or both. That IGF-I and -II and TGF-β levels are higher in samples of iliac crest bone of patients with OA,[77] and hence at a site distant from weight-bearing joints, also suggests a generalized bone metabolic dysfunction. IGFs are among the most important growth factors regulating bone formation.[78] IGF-I is important in the changes observed in subchondral bone and cartilage in OA. OA subchondral osteoblasts produce variable total IGF-1 levels and less IGFBPs compared with normal,[4,79] leading to enhanced free-IGF-1 levels. Enhanced free IGF-I in OA subchondral bone could promote bone remodeling,[4,80] possibly increasing bone stiffness, a situation that exacerbates cartilage matrix degradation.[81] TGF-β and IGF-1 are also involved in matrix deposition and turnover. TGF-β stimulates matrix synthesis[82] and collagenase activity, while IGF-1 inhibits some matrix metalloproteases (MMPs) in bone cells.[83] Therefore, the increase in both growth factors could favor matrix deposition in bone and overall limit degradation. However, TGF-β addition to joints more directly mimics OA progression,[84] and we showed that all OA subchondral osteoblasts produced elevated levels of TGF-β1 regardless of the group of patients from which they were isolated.[85]

This elevation of TGF-β1 may be linked to abnormal metalloprotease (MMP) activity, as observed in OA cartilage. Indeed, two main metalloproteases, MMP-1 and MMP-13, are produced in OA cartilage and are preferentially distributed within the articular cartilage. Collagenase-1 (MMP-1) is preferentially localized in the superficial and upper intermediate layers of OA cartilage, whereas collagenase-3 (MMP-13) is found in the lower intermediate and deep layers.[86,87] Interestingly, TGF-β, but not IL-1β, upregulates collagenase-3 in normal cartilage, as found in OA cartilage.[88] Whereas TGF-β and its receptor levels are increased in the low intermediate and deep zone of OA cartilage,[87,88] we also found an important increase in the synthesis of TGF-β1 in OA subchondral osteoblasts.[85] This particular distribution of TGF-β and its receptors therefore suggests that bone-derived TGF-β could be responsible, at least in part, for collagenase-3 upregulation in OA cartilage. This also applies to hepatocyte growth factor (HGF). Indeed, HGF also stimulates collageanse-3 expression in chondrocytes,[89] and this factor is more elevated in OA than in normal cartilage.[90,91]

Insulin-like growth factors, or somatomedins, are families of growth stimulatory peptides that have important biological activities in bone.[92] They are single-chain polypeptides containing three intrachain disulfide bridges. IGF-I and IGF-II consist of 70 and 67 amino acid residues with molecular weights of 7649 and 7471 Da,[93,94] respectively. IGFs are among the most important growth factors regulating bone formation, an effect only partially dependent on cell replication.[78] A 12-year follow-up clinical study of patients with radiological OA of the knee showed a positive correlation between circulating IGF-I levels and osteophyte growth and overall progression of their condition, whereas no clear evidence could be found for a preventive effect of IGF-I on cartilage loss.[95] In this respect, the observation of elevated IGF-1 levels in the cortical bone from the iliac crest of OA patients[77] and in osteoblast cell cultures[4] suggests that IGF-1 may promote the formation of osteophytes. IGF-I initially produced by abnormal subchondral bone cells could infiltrate the cartilage via the vascular channels present in subchondral bone, which reach the deeper zones of articular cartilage.[14–17] It could also promote the PA/plasmin system and initiate cartilage breakdown, while stimulating other protease systems such as MMPs. As in the cartilage, in subchondral bone IGF-I may stimulate the plasminogen activator (PA)/plasmin system and promote IGFBPs turnover, increasing further bone formation/mineralization in this area, i.e., promoting an increase in bone stiffness. We showed an altered regulation of uPA in OA osteoblasts by IGF-1,[5] a situation that could lead to abnormal bone turnover via reduced local availability of other growth factors, such as TGF-β, that are derived from latent propeptides. Mechanical stresses may amplify this first local biochemical stress, with the thickening of the underlying subchondral bone reducing the shock-absorbing qualities of this tissue. The initial cartilage breakdown could stimulate local production of IGF-I by chondrocytes to limit degradation and promote matrix formation. This increase in IGF-I could then further activate the PA/plasmin system in the cartilage, causing progressive degradation. Concurrently, the increase in IGF-I and its stimulation of IGFBPs turnover would create an imbalance between IGF and IGFBPs, which would be enhanced by abnormal PA/plasmin activity in the cartilage, and prevent an adequate response to IGF-I. Secondarily, this would trigger the synthesis of more IGF-receptors in chondrocytes to translate IGF signals; hence a resistance to IGF-I could be in place at this stage of disease progression.

Recent data show a fundamental role of the PA/plasmin system in the local regulation of IGF bioavailability in bone.[96] Hormones and local growth factors, including IGFs and IGFBPs,[97–100] closely regulate bone formation and resorption, the two major processes in bone remodeling. Bone resorption involves a well-characterized protease system; this comprises PA and their inhibitors, the equilibrium of which controls the formation of plasmin.[101,102] Plasmin is one of the factors capable of activating the latent form of TGF-β.[103,104] The PA/plasmin system can also produce

variable proteolysis at different sites on the IGF-I–IGFBP complex, resulting in peptides of variable sizes, and promoting the dissociation of IGFs bound to IGFBPs.[96,105,106] This generates free IGF-1, which is then available to exert its biological function(s). PA/plasmin-dependent proteolysis of IGFBPs has also been observed in the human osteosarcoma cell line MG-63,[107,108] a situation somewhat similar to that which takes place in human primary bone cell cultures,[109] while local regulation of the PA/plasmin system is slightly different in osteosarcoma cells. Moreover, TGF-β can reduce IGFBP-4 mRNA expression and enhance IGFBP-4 proteolysis in human primary bone cell cultures,[110] thus increasing free IGF-1 levels. Lastly, urokinase (uPA), and more specifically its amino-terminal fragment, stimulates mitogenic activity and proliferation in a human osteoblast-like cell line and in rat primary calvaria osteoblast-like cells.[111] Therefore, this suggest that, at least in bone cells, uPA could stimulate cell proliferation via proteolytic activation of local growth factor as well as directly. In this manner, this alteration in uPA could also contribute to couple bone resorption and formation (remodeling) by the PA/plasmin system.[112]

Conflicting reports exist on the local regulation of the PA/plasmin system in osteoblasts. In normal osteoblast-like cells, TGF-β1 stimulates, whereas IL-1β does not change, PA activity. In contrast, in the human MG-63 osteosarcoma cell line, TGF-β1 inhibits, while IL-1β stimulates, PA activity.[109] Moreover, in MG-63 cells, IGF-I stimulates IGFBPs synthesis, while it inhibits PA/plasmin activity.[108] Our own data indicate an increase of uPA abundance and activity (hydrolysis of a specific substrate coupled to p-nitroanilide), but not of its inhibitor PAI-1, in OA subchondral bone explants and in primary osteoblast cell cultures.[5] IGF-1 directly stimulated the PA/plasmin system in OA primary osteoblast cell cultures under basal conditions in vitro, whereas the addition of plasminogen to the system, to reproduce the in vivo situation, led to an inhibition of uPA activity.[5] In contrast, IGF-I does not modify PA activity in fetal rat osteoblast-enriched calvarial cells.[113] Regardless of this diversity, IGF-I can regulate its own activity via IGFBPs production in human normal and osteosarcoma bone cells.[108,109] IGF-I under these conditions can regulate its own bioavailability by regulating both IGFBPs production and the PA/PAI system, which regulates IGFBPs proteolysis. In addition, plasmin activates latent TGF-β1 in bone, and frees IGF-I from IGFBPs.[107] This suggests that autocontrol of PA/plasmin activity due to TGF-β1 produced locally by bone cells is plausible, while IGF-I availability could also be controlled via this loop. Recent data indicate that TGF-β is a chemoattractant for osteoblasts and for osteoblast precursors,[114] which means that it may draw mesenchymal cells to sites of new bone formation after local release and activation of matrix-bound TGF-β that could occur during resorption[115] or in the course of fracture healing. TGF-β could also act in addition to other cytokines/growth factors to promote IGF-1 synthesis in osteoblasts. PGE_2 alone also stimulates IGF-1 synthesis in osteoblasts.[85,116–118] Since PGE_2 levels are elevated in OA subchondral bone osteoblasts,[85] this could therefore lead to an upregulation of IGF-1 levels in bone tissue in OA patients.

The PA/plasmin protease system promotes the activation of MMPs such as collagenase-1, and thereby participates in cartilage breakdown. Its increase in OA osteoblast cell cultures,[4,5] if it reflects the in vivo situation, would then promote cartilage breakdown. The action of the PA/plasmin system might be limited, as some studies have indicated that other proteases, such as stromelysin (MMP-3), might be needed to promote cartilage breakdown fully.[119] The PA/plasmin system is stimulated by IL-1,[120] which is increased locally in the synovial fluid bathing OA cartilage. IL-1 also increases the synthesis of MMPs directly,[121] hence offering a converging pathway for cartilage degradation together with the PA/plasmin system. In contrast, TGF-β may contribute to stop the progression of cartilage degradation by promoting PAI-1 synthesis and mRNA increases in culture fluid and chondrocyte extracts, while IL-1α inhibits this activity.[122]

Phenotypic alterations of the subchondral bone compartment in osteoarthritis

Changes in OA subchondral bone may be due to alterations in bone collagen production and/or deterioration, noncollagenous protein production, alkaline phosphatase (ALPase) activity, and osteoblast metabolism.[4–7] OA osteoblasts from subchondral bone display a unique metabolic behavior in vitro[4,5] and in vivo.[6,7] These cells are characterized by high alkaline phosphatase and uPA activities,[4,5] elevated collagen production,[6,7] increased release of osteocalcin, and production of IGF-1[4] compared with normal cells. All these factors are involved in bone remodeling, suggesting that OA osteoblasts could have a very high metabolism. These factors are regulated in bone tissue by cytokines produced locally, and it is now well recognized that proinflammatory cytokines such as IL-1β and TNF-α, as well as prostaglandins, and especially PGE_2, are involved in the inflammatory process of OA.

Abnormal collagen production or content in OA subchondral bone may be related to altered collagen synthesis or reduced degradation.[7] Collagen production, collagen breakdown via collagenase production, and IGF-1/IGFBPs synthesis are regulated by parathyroid hormone (PTH) in osteoblasts.[123–125] As these effects of PTH are driven by protein kinase A (PKA), the observed reduction in cyclic AMP (cAMP) formation by OA osteoblasts in response to PTH stimulation (while OA osteoblasts are totally resistant to PGE_2 stimulation[4]) would suggest a specific inhibition of the PKA pathway in OA osteoblasts, and of downstream events. Since bone remodeling involves a tight coupling between bone resorption and bone formation, abnormal PTH signaling may lead to an imbalance in bone remodeling favoring bone formation.

Osteoblasts and stromal cells synthesize a number of cytokines that play crucial roles in skeletal cells via autocrine or paracrine pathways.[126] These include IL-1, -4,

-6, and -11, macrophage and granulocyte/macrophage colony-stimulating factors, and TNFs. All of these cytokines have important effects on bone remodeling, and they stimulate bone resorption via the recruitment/activation of osteoclasts. Two studies have reported data for cytokine production by osteoblasts prepared from femoral heads[127] or by subchondral trabecular bone from either hip or knee joints.[8] However, no clear trend has been established in these studies. This absence of a consensus may be linked to the cell culture conditions, time in culture, assay conditions, or the comparison between different bone sites. It is becoming recognized that bone cells from different locations show variable behavior, at least in in vitro culture.[128,129] Among cytokines and eicosanoids produced by bone cells, IL-1β, IL-6, PGE_2 and leukotriene B_4 (LTB_4) are the most important regulators of the extracellular matrix. IL-1β and IL-6 can directly promote matrix degradation in both subchondral bone and cartilage owing to their action on selective MMPs in these tissues.[130] Our own studies have shown variations for IL-6, PGE_2, TGF-β, and LTB_4 in OA subchondral osteoblasts.[85,131] However, the variable and opposite PGE_2 and LTB_4 levels detected in OA subchondral osteoblasts compared with normal[85,131] could promote bone formation in OA and the deposition of a new matrix,[132,133] although this matrix may be undermineralized. Indeed, PGE_2 stimulates bone formation at low concentrations, but it may be inhibitory at high concentrations.[134–136] PGE_2 stimulates collagen synthesis and can promote the proliferation of osteoblasts. Conversely, leukotrienes stimulate osteoclast differentiation and bone resorption.[137]

Role of bone-derived factors on cartilage degradation in osteoarthritis

The integrity of the overlying cartilage is maintained, at least in part, by a fine balance between anabolic/catabolic factors produced locally. As osteoblasts produce a number of cytokines/growth factors involved in tissue remodeling and OA subchondral bone is sclerotic, this could be explained by abnormal remodeling. The subchondral bone plate is of particular interest as it is in direct contact with the cartilage and could influence its degradation. Interestingly, osteoblasts with differing behavior in in vitro culture were obtained from either hip or knee joints of OA patients, and these cells showed a different capacity to degrade glycosaminoglycans.[8] Indeed, cocultures of OA osteoblasts with normal cartilage explants could initiate cartilage degradation, suggesting that OA osteoblasts may be releasing product(s) initiating the degradation of cartilage.[8,9] However, only about half of the conditioned media from OA osteoblast cell cultures could promote the degradation of glycosaminoglycans, and no key pathways or factors responsible for this process could be clearly identified at that time.[8] Potential players in this process, namely PGE_2 and IL-6,[85,129] and possibly IGF-1 and uPA,[4,5] are increased in OA osteoblasts. Interestingly, PGE_2 and IL-6 show very wide distribution levels in OA osteoblasts compatible with different catabolic activities, and could be used to classify patients in one of two groups that otherwise showed no significant phenotypic features or metabolic capacities.[85] Interestingly, Tardif et al.[138] showed that chondrocytes from OA patients can also be classified in two groups, low or high, according to their basal levels of one metalloprotease, collagenase-3. These two groups of cells responded differently to cytokine/growth factor stimulation,[85] yet phenotypic characteristics were similar between the cells.

The sum of these results would therefore indicate that OA patients undergoing surgery, although clinically similar, may be showing different patterns of expression of MMP, growth factors, and cytokines in both cartilage and subchondral bone tissues. However, as animal models are now showing that subchondral bone changes may be preceding cartilage degradation/loss, it is become increasingly evident that subchondral bone changes in OA are not merely secondary manifestations of the disease, but may be part of a more active component of the initiation and/or progression of OA. Subchondral bone tissue in OA could provide growth factors, cytokines, and prostaglandins to the overlying cartilage and promote its abnormal remodeling/metabolism, leading to degradation and loss. Therefore, even though the initiating event/effector has still not been clearly identified, research can now focus on potential candidates.

Acknowledgments The Arthritis Society of Canada grant No. 98043 and the Fonds De la Recherche en Santé du Québec (FRSQ) "Équipe Prioritaire" supported this research.

References

1. Knowlton RG, Katzenstein PL, Moskowitz RW, Weaver EJ, Malemud CJ, Pathria MN, et al. Genetic linkage of a polymorphism in the type II procollagen gene (COL2A1) to primary osteoarthritis associated with mild chondrodysplasia. N Engl J Med 1990;322:526–30.
2. Pun YL, Moskowitz RW, Lie S, Sundstrom WR, Block SR, McEwen C, et al. Clinical correlations of osteoarthritis associated with a single-base mutation (arginine519 to cysteine) in the type II procollagen gene. A newly defined pathogenesis. Arthritis Rheum 1994;37:264–9.
3. Vikkula M, Mariman EC, Lui VC, Zhidkova NI, Tiller GE, Goldring MB, et al. Autosomal dominant and recessive osteochondrodysplasias associated with the COL11A2 locus. Cell 1995;80:431–7.
4. Hilal G, Martel-Pelletier J, Pelletier JP, Ranger P, Lajeunesse D. Osteoblast-like cells from human subchondral osteoarthritic bone demonstrate an altered phenotype in vitro: Possible role in subchondral bone sclerosis. Arthritis Rheum 1998;41:891–9.
5. Hilal G, Martel-Pelletier J, Pelletier JP, Duval N, Lajeunesse D. Abnormal regulation of urokinase plasminogen activator by insulin-like growth factor 1 in human osteoarthritic subchondral osteoblasts. Arthritis Rheum 1999;42:2112–2.
6. Mansell JP, Tarlton JF, Bailey AJ. Biochemical evidence for altered subchondral bone collagen metabolism in osteoarthritis of the hip. Br J Rheumatol 1997;36:16–9.
7. Mansell JP, Bailey AJ. Abnormal cancellous bone collagen metabolism in osteoarthritis. J Clin Invest 1998;101:1596–603.
8. Westacott CI, Webb GR, Warnock MG, Sims JV, Elson CJ. Alteration of cartilage metabolism by cells from osteoarthritic bone. Arthritis Rheum 1997;40:1282–91.
9. Westacott CI, Webb GR, Elson CJ. Cells from osteoarthritic bone produce enzymes which degrade cartilage. Trans Orthop Res Soc 1998;23:919.

10. Uitterlinden AG, Burger H, Huang Q, Odding E, Duijn CM, Hofman A, et al. Vitamin D receptor genotype is associated with radiographic osteoarthritis at the knee. J Clin Invest 1997;100: 259–63.
11. Vikkula M, Palotie A, Ritvaniemi P, Ott J, Ala-Kokko L, Sievers U, et al. Early-onset osteoarthritis linked to the type II procollagen gene. Detailed clinical phenotype and further analyses of the gene. Arthritis Rheum 1993;36:401–9.
12. Li B, Aspden RM. Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J Bone Miner Res 1997;12:641–51.
13. Li B, Marshall D, Roe M, Aspden RM. The electron microscope appearance of the subchondral bone plate in the human femoral head in osteoarthritis and osteoporosis. J Anat 1999;195(Pt 1): 101–10.
14. Sokoloff L. Microcracks in the calcified layer of articular cartilage. Arch Pathol Lab Med 1993;117:191–5.
15. McKibben B, Holdsworth FW. The nutrition of immature joint cartilage in the lamb. J Bone Joint Surg 1966;48-B:793–803.
16. Imhof H, Breitenseher M, Kainberger F, Rand T, Trattnig S. Importance of subchondral bone to articular cartilage in health and disease. Top Magn Reson Imaging 1999;10:180–92.
17. Malinin T, Ouellette EA. Articular cartilage nutrition is mediated by subchondral bone: a long-term autograft study in baboons. Osteoarthritis Cartilage 2000;8:483–91.
18. Poole AR. Cartilage in health and disease. In: McCarty DJ, Koopman WJ, editors. Arthritis and allied conditions: a textbook of rheumatology. Philadelphia: Lea and Febiger; 1993. p. 279–335.
19. Lohmander LS. Articular cartilage and osteoarthrosis. The role of molecular markers to monitor breakdown, repair and disease. J Anat 1994;184:477–92.
20. Hamerman D. The biology of osteoarthritis. N Engl J Med 1989;320:1322–30.
21. Dieppe P. Osteoarthritis: clinical and research perspective. Br J Rheumatol 1991;30 Suppl 1:1–4.
22. Davis MA. Epidemiology of osteoarthritis. Clin Geriatr Med 1988;4:241–55.
23. Hardingham TE, Venn G, Bayliss MT. Chondrocyte responses in cartilage and in experimental osteoarthritis. Br J Rheumatol 1991;30:32–7.
24. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. Ann Intern Med 1988;109:18–24.
25. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham osteoarthritis study. Semin Arthritis Rheum 1990;20:42–50.
26. Hochberg MC. Epidemiology of osteoarthritis: current concepts and new insights. J Rheumatol Suppl 1991;27:4–6.
27. Dieppe P, Cushnaghan J, Young P, Kirwan J. Prediction of the progression of joint space narrowing in osteoarthritis of the knee by bone scintigraphy. Ann Rheum Dis 1993;52:557–63.
28. Carlson CS, Loeser RF, Jayo MJ, Weaver DS, Adams MR, Jerome CP. Osteoarthritis in cynomolgus macaques: a primate model of naturally occurring disease. J Orthop Res 1994;12:331–9.
29. Carlson CS, Loeser RF, Purser CB, Gardin JF, Jerome CP. Osteoarthritis in cynomolgus macaques. III. Effects of age, gender, and subchondral bone thickness on the severity of disease. J Bone Miner Res 1996;11:1209–17.
30. Billingham MEJ, Meijers MHM, Mahwinney B, Malcolm A. Spontaneous osteoarthritis in guinea pigs: cartilage degeneration is preceded by loss of subchondral trabecular bone [abstract]. J Rheum 1996;Suppl 1:104.
31. Armstrong S, Read R, Ghosh P. The effects of intraarticular hyaluronan on cartilage and subchondral bone changes in an ovine model of early osteoarthritis. J Rheumatol 1994;21:680–8.
32. Dedrick DK, Goldstein SA, Brandt KD, O'Connor BL, Goulet RW, Albrecht M. A longitudinal study of subchondral plate and trabecular bone in cruciate-deficient dogs with osteoarthritis followed up for 54 months. Arthritis Rheum 1993;36:1460–7.
33. Yang C, Wolf E, Roser K, Delling G, Muller PK. Selenium deficiency and fulvic acid supplementation induces fibrosis of cartilage and disturbs subchondral ossification in knee joints of mice: an animal model study of Kashin–Beck disease. Virchows Arch 1993;423:483–91.
34. Vener MJ, Thompson RC Jr, Lewis JL, Oegema TR Jr. Subchondral damage after acute transarticular loading: an in vitro model of joint injury. J Orthop Res 1992;10:759–65.
35. Oettmeier R, Arokoski J, Roth AJ, Helminen HJ, Tammi M, Abendroth K. Quantitative study of articular cartilage and subchondral bone remodeling in the knee joint of dogs after strenuous training. J Bone Miner Res 1992;7 Suppl 2:S419–S424.
36. Brandt KD, Myers SL, Burr D, Albrecht M. Osteoarthritic changes in canine articular cartilage, subchondral bone, and synovium 54 months after transection of the anterior cruciate ligament. Arthritis Rheum 1991;34:1560–70.
37. Matsui H, Shimizu M, Tsuji H. Cartilage and subchondral bone interaction in osteoarthrosis of human knee joint: a histological and histomorphometric study. Microsc Res Tech 1997;37:333–42.
38. Zysset PK, Sonny M, Hayes WC. Morphology–mechanical property relations in trabecular bone of the osteoarthritic proximal tibia. J Arthroplasty 1994;9:203–16.
39. Hulth A. Does osteoarthrosis depend on growth of the mineralized layer of cartilage? Clin Orthop 1993;287:19–24.
40. Burr DB, Schaffler MB. The involvement of subchondral mineralized tissues in osteoarthrosis: quantitative microscopic evidence. Microsc Res Tech 1997;37:343–57.
41. Eckstein F, Putz R, Muller-Gerbl M, Steinlechner M, Benedetto KP. Cartilage degeneration in the human patellae and its relationship to the mineralisation of the underlying bone: a key to the understanding of chondromalacia patellae and femoropatellar arthrosis? Surg Radiol Anat 1993;15:279–86.
42. Chai BF. Scanning electron microscopic study of subchondral bone tissues in the osteoarthritic femoral head. Chung Hua Wai Ko Tsa Chih 1991;29:573–6, 590–1.
43. Grynpas MD, Alpert B, Katz I, Lieberman I, Pritzker KPH. Subchondral bone in osteoarthritis. Calcif Tissue Int 1991;49:20–6.
44. Sowers M, Lachance L, Jamadar D, Hochberg MC, Hollis B, Crutchfield M, et al. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. Arthritis Rheum 1999;42:483–9.
45. Puzas JE. Primer on the metabolic bone diseases and disorders of mineral metabolism. New York: Raven Press; 1993.
46. Johnson LC. Joint remodelling as a basis for osteoarthritis. J Am Vet Med Assoc 1962;141:1237–41.
47. Sokoloff L. The biology of degenerative joint disease. Chicago: University of Chicago Press; 1969.
48. Simon SR, Radin EL, Paul IL, Rose RM. The response of joints to impact loading. II. In vivo behaviour of subchondral bone. J Biomech 1972;5:267–72.
49. Gevers G, Dequeker J, Martens M, Van Audekercke R, Nyssen-Behets C, Dhem A. Biomechanical characteristics of iliac crest bone in elderly women, according to osteoarthritis grade at the hand joints. J Rheumatol 1989;16:660–3.
50. Gevers G, Dequeker J, Geusens P, Nyssen-Behets C, Dhem A. Physical and histomorphological characteristics of iliac crest bone differ according to the grade of osteoarthritis at the hand. Bone 1989;10:173–7.
51. Fernandes JC, Martel-Pelletier J, Jovanovic D, Tardif G, Di Battista JA, Lascau-Coman V, et al. Effects of tenidap on canine experimental osteoarthritis. II. Study of the expression of collagenase-1 and IL1β by in situ hybridization. J Rheumatol 1998;25: 951–8.
52. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop 1986;213:34–40.
53. Foss MVL, Byers PD. Bone density, osteoarthrosis of the hip and fracture of the upper end of the femur. Ann Rheum Dis 1972; 31:259–64.
54. Roh YS, Dequeker J, Muiler JC. Bone mass is osteoarthrosis, measured in vivo by photon absorption. J Bone Joint Surg Am 1974;54A:587–91.
55. Carlsson A, Nillson BE, Westlin NE. Bone mass in primary coxarthrosis. Acta Orthop Scand 1979;50:187–9.
56. Moore RJ, Fazzalari NL, Manthey BA, Vernon-Roberts B. The relationship between head–neck-shaft angle, calcar width, articular cartilage thickness and bone volume in arthrosis of the hip. Br J Rheumatol 1994;33:432–6.
57. Gotfriedsen A, Riis BJ, Christiansen C, Rodbro P. Does a single local absorptiometric measurement indicate the overall skeletal

status? Implications for osteoporosis and osteoarthritis of the hip. Clin Rheumatol 1990;9:193–203.
58. Vandermeersch S, Geusens P, Nijs J, Dequeker J. Total body mineral measurements in osteoarthritis, osteoporosis and normal controls. In: Ring EF, editor. Current research in osteoporosis and bone mineral measurement. London: British Institute of Radiology; 1990. p. 49.
59. Mokassa Bakumobatane L, Dequeker J, Raymaekers G, Aerssens J. Effects of osteoarthritis (OA) and body weight on subchondral cancellous bone quality of proximal tibia. Osteoarthritis Cartilage 1993;1:55–6.
60. Hordon LD, Stewart SP, Troughton PR, Wright V, Horsman A, Smith MA. Primary generalized osteoarthritis and bone mass. Br J Rheumatol 1993;32:1059–61.
61. Dequeker J, Goris P, Uytterhoeven R. Osteoporosis and osteoarthritis (osteoarthrosis). JAMA 1983;249:1448–51.
62. Raymaekers G, Aerssens J, Van den Eynde R, Peeters J, Geusens P, Devos P, et al. Alterations of the mineralization profile and osteocalcin concentrations in osteoarthritic cortical iliac crest bone. Calcif Tissue Int 1992;51:269–75.
63. Verstraeten A, van Ermen H, Haghebaert G, Mijs J, Geusens P, Dequeker J. Osteoarthrosis retards the development of osteoporosis. Clin Orthop 1991;264:169–77.
64. Hannan MT, Anderson JJ, Zhang Y, Levy D, Felson DT. Bone mineral density and knee osteoarthritis in elderly men and women. Arthritis Rheum 1993;36:1671–80.
65. Seibel MJ, Duncan A, Robins SP. Urinary hydroxy-pyridinium crosslinks provide indices of cartilage and bone involvement in arthritic diseases. J Rheumatol 1989;16:964–70.
66. Sowers M, Zobel D, Weissfeld L, Hawthorne VM, Carman W. Progression of osteoarthritis of the hand and metacarpal bone loss. A twenty-year follow-up of incident cases. Arthritis Rheum 1991;34:36–42.
67. Bailey AJ, Sims TJ, Knott L. Phenotypic expression of osteoblast collagen in osteoarthritic bone: production of type I homotrimer. Int J Biochem Cell Biol 2002;34:176–82.
68. Sharif M, George E, Dieppe PA. Correlation between synovial fluid markers of cartilage and bone turnover and scintigraphic scan abnormalities in osteoarthritis of the knee. Arthritis Rheum 1995;38:78–81.
69. Gevers G, Dequeker J. Collagen and non-collagenous protein content (osteocalcin, sialoprotein, proteoglycan) in the iliac crest bone and serum osteocalcin in women with and without hand osteoarthritis. Coll Relat Res 1987;7:435–42.
70. Misof K, Landis WJ, Klaushofer K, Fratzl P. Collagen from the osteogenesis imperfecta mouse model (oim) shows reduced resistance against tensile stress. J Clin Invest 1997;100:40–5.
71. Lajeunesse D, Hilal G, Pelletier JP, Martel-Pelletier J. Subchondral bone morphological and biochemical alterations in osteoarthritis [review]. Osteoarthritis Cartilage 1999;7:321–2.
72. Geusens P, Dequeker J, Bouillon R. Salmon calcitonin stimulates PTH (1–84) and 1,25-dihydroxyvitamin D_3 in osteoporosis and osteoarthritis. In: Christiansen C, Overgaard K, editors. Osteoporosis. Copenhagen: Osteopress, ApS; 1990. p. 368–9.
73. Canalis E, Lian JB. 1,25-Dihydroxyvitamin D_3 effects on collagen and DNA synthesis in periosteum and periosteum-free calvaria. Bone 1985;6:457–60.
74. Harrison JR, Clark NB. Avian medullary bone in organ culture: effects of vitamin D metabolites on collagen synthesis. Calcif Tissue Int 1986;39:35–43.
75. Kream BE, Rowe DW, Gworek SC, Raisz LG. Parathyroid hormone alters collagen synthesis and procollagen mRNA levels in fetal rat calvaria. Proc Natl Acad Sci USA 1980;77:5654–8.
76. Hilal G, Massicotte F, Martel-Pelletier J, Fernandes JC, Pelletier JP, Lajeunesse D. Endogenous prostaglandin E2 and insulin-like growth factor 1 can modulate the levels of parathyroid hormone receptor in human osteoarthritic osteoblasts. J Bone Miner Res 2001;16:713–21.
77. Dequeker J, Mohan R, Finkelman RD, Aerssens J, Baylink DJ. Generalized osteoarthritis associated with increased insulin-like growth factor types I and II and transforming growth factor beta in cortical bone from the iliac crest. Possible mechanism of increased bone density and protection against osteoporosis. Arthritis Rheum 1993;36:1702–8.
78. Hock JM, Centrella M, Canalis E. Insulin-like growth factor I has independent effects on bone matrix formation and cell replication. Endocrinology 1988;122:254–60.
79. Massicotte F, Martel-Pelletier J, Pelletier J-P, Lajeunesse D. Abnormal modulation of insulin-like growth factor 1 levels in human osteoarthritic bone oesteoblasts [abstract]. Arthritis Rheum 2000;43:S206.
80. Martel-Pelletier J, Di Battista JA, Lajeunesse D, Pelletier JP. IGF/IGFBP axis in cartilage and bone in osteoarthritis pathogenesis [review]. Inflamm Res 1998;47:90–100.
81. Dequeker J, Mokassa L, Aerssens J. Bone density and osteoarthritis. J Rheumatol Suppl 1995;43:98–100.
82. Palcy S, Goltzman D. Protein kinase signalling pathways involved in the up-regulation of the rat alpha1(I) collagen gene by transforming growth factor beta1 and bone morphogenetic protein 2 in osteoblastic cells. Biochem J 1999;343(Pt 1):21–7.
83. Rydziel S, Delany AM, Canalis E. Insulin-like growth factor I inhibits the transcription of collagenase 3 in osteoblast cultures. J Cell Biochem 1997;67:176–83.
84. van den Berg WB. Osteophyte formation in osteoarthritis. Osteoarthritis Cartilage 1999;7:333.
85. Massicotte F, Lajeunesse D, Benderdour M, Pelletier J-P, Hilal G, Duval N, et al. Can altered production of interleukin 1β, interleukin-6, transforming growth factor-β and prostaglandin E2 by isolated human subchondral osteoblasts identify two subgroups of osteoarthritic patients. Osteoarthritis Cartilage 2002;10: 491–500.
86. Fernandes JC, Martel-Pelletier J, Lascau-Coman V, Moldovan F, Jovanovic D, Raynauld JP, et al. Collagenase-1 and collagenase-3 synthesis in early experimental osteoarthritic canine cartilage. An immunohistochemical study. J Rheumatol 1998;25:1585–94.
87. Moldovan F, Pelletier JP, Hambor J, Cloutier JM, Martel-Pelletier J. Collagenase-3 (matrix metalloprotease 13) is preferentially localized in the deep layer of human arthritic cartilage in situ: in vitro mimicking effect by transforming growth factor beta. Arthritis Rheum 1997;40:1653–61.
88. Moldovan F, Pelletier JP, Mineau F, Dupuis M, Cloutier JM, Martel-Pelletier J. Modulation of collagenase-3 in human osteoarthritic cartilage by activation of extracellular transforming growth factor beta: role of furin convertase. Arthritis Rheum 2000;43:2100–9.
89. Reboul P, Pelletier JP, Tardif G, Benderdour M, Ranger P, Bottaro DP, et al. Hepatocyte growth factor induction of collagenase 3 production in human osteoarthritic cartilage: involvement of the stress-activated protein kinase/c-Jun N-terminal kinase pathway and a sensitive p38 mitogen-activated protein kinase inhibitor cascade. Arthritis Rheum 2001;44:73–84.
90. Feuerherm AJ, Borset M, Seidel C, Sundan A, Leistad L, Ostensen M, et al. Elevated levels of osteoprotegerin (OPG) and hepatocyte growth factor (HGF) in rheumatoid arthritis. Scand J Rheumatol 2001;30:229–34.
91. Pfander D, Cramer T, Weseloh G, Pullig O, Schuppan D, Bauer M, et al. Hepatocyte growth factor in human osteoarthritic cartilage. Osteoarthritis Cartilage 1999;7:548–59.
92. Schmid C, Ernst M. Insulin-like growth factors. In: Gowen M, editor. Cytokines and bone metabolism. Boca Raton: CRC Press; 1992. p. 229–65.
93. Rinderknecht E, Humbel RE. The amino acid sequence of human insulin-like growth factor I and its structural homology with proinsulin. J Biol Chem 1978;253:2769–76.
94. Rinderknecht E, Humbel RE. Primary structure of human insulin-like growth factor II. FEBS Lett 1978;89:283–6.
95. Schouten JS, Van den Ouweland FA, Valkenburg HA, Lamberts SW. Insulin-like growth factor-1: a prognostic factor of knee osteoarthritis. Br J Rheumatol 1993;32:274–80.
96. Campbell PG, Novak JF, Yanosick TB, McMaster JH. Involvement of the plasmin system in dissociation of the insulin-like growth factor-binding protein complex. Endocrinology 1992; 130:1401–12.
97. Canalis E, McCarthy TL, Centrella M. The role of growth factors in skeletal remodeling. Endocrinol Metab Clin North Am 1989;18:903–18.
98. Mohan S, Baylink DJ. Bone growth factors. Clin Orthop 1991; 263:30–48.

99. Mohan S, Baylink DJ. Modern concepts of insulin-like growth factors. New York: Elsevier; 1991.
100. Mohan S, Jennings JC, Linkhart TA, Baylink DJ. Primary structure of human skeletal growth factor: homology with human insulin-like growth factor-II. Biochim Biophys Acta 1988;966:44–55.
101. Saksela O, Rifkin DB. Cell-associated plasminogen activation: regulation and physiological functions. Annu Rev Cell Biol 1988; 4:93–126.
102. Vassalli JD, Sappino AP, Belin D. The plasminogen activator/plasmin system. J Clin Invest 1991;88:1067–72.
103. Sato Y, Rifkin DB. Inhibition of endothelial cell movement by pericytes and smooth muscle cells: activation of a latent transforming growth factor-beta 1-like molecule by plasmin during co-culture. J Cell Biol 1989;109:309–15.
104. Lyons RM, Gentry LE, Purchio AF, Moses HL. Mechanism of activation of latent recombinant transforming growth factor beta 1 by plasmin. J Cell Biol 1990;110:1361–7.
105. Koutsilieris M, Frenette G, Lazure C, Lehoux JG, Govindan MV, Polychronakos C. Urokinase-type plasminogen activator: a paracrine factor regulating the bioavailability of IGFs in PA-III cell-induced osteoblastic metastases. Anticancer Res 1993;13:481–6.
106. Martin TJ, Allan EH, Fukumoto S. The plasminogen activator and inhibitor system in bone remodeling. Growth Regul 1993; 3:209–14.
107. Lalou C, Silve C, Segovia B, Binoux M. Interactions of insulin-like growth factors (IGF) and their binding proteins with the plasminogen/plasmin activator system in cultured osteoblasts. Ann Endocrinol (Paris) 1994;55:103–7.
108. Lalou C, Silve C, Rosato R, Segovia B, Binoux M. Interactions between insulin-like growth factor-I (IGF-I) and the system of plasminogen activators and their inhibitors in the control of IGF-binding protein-3 production and proteolysis in human osteosarcoma cells. Endocrinology 1994;135:2318–26.
109. Fawthrop FW, Oyajobi BO, Bunning RA, Russell RG. The effect of transforming growth factor beta on the plasminogen activator activity of normal human osteoblast-like cells and a human osteosarcoma cell line MG-63. J Bone Miner Res 1992;7:1363–71.
110. Durham SK, Riggs BL, Conover CA. The insulin-like growth factor-binding protein-4 (IGFBP-4)-IGFBP-4 protease system in normal human osteoblast-like cells: regulation by transforming growth factor-beta. J Clin Endocrinol Metab 1994;79:1752–8.
111. Rabbani SA, Desjardins J, Bell AW, Banville D, Mazar A, Henkin J, et al. An amino-terminal fragment of urokinase isolated from a prostate cancer cell line (PC-3) is mitogenic for osteoblast-like cells. Biochem Biophys Res Commun 1990;173: 1058–64.
112. Allan EH, Martin TJ. The plasminogen activator inhibitor system in bone cell function. Clin Orthop 1995;313:54–63.
113. Cheng SL, Shen V, Peck WA. Regulation of plasminogen activator and plasminogen activator inhibitor production by growth factors and cytokines in rat calvarial cells. Calcif Tissue Int 1991;49:321–7.
114. Hughes FJ, Aubin JE, Heersche JN. Differential chemotactic responses of different populations of fetal rat calvaria cells to platelet-derived growth factor and transforming growth factor beta. Bone Miner 1992;19:63–74.
115. Oreffo RO, Mundy GR, Seyedin SM, Bonewald LF. Activation of the bone-derived latent TGF beta complex by isolated osteoclasts. Biochem Biophys Res Commun 1989;158:817–23.
116. Bichell DP, Rotwein P, McCarthy TL. Prostaglandin E2 rapidly stimulates insulin-like growth factor-I gene expression in primary rat osteoblast cultures: evidence for transcriptional control. Endocrinology 1993;133:1020–8.
117. McCarthy TL, Centrella M, Raisz LG, Canalis E. Prostaglandin E2 stimulates insulin-like growth factor I synthesis in osteoblast-enriched cultures from fetal rat bone. Endocrinology 1991;128: 2895–900.
118. Pash JM, Delany AM, Adamo ML, Roberts CT Jr, LeRoith D, Canalis E. Regulation of insulin-like growth factor I transcription by prostaglandin E2 in osteoblast cells. Endocrinology 1995;136: 33–8.
119. Xie D, Hui F, Meyers R, Homandberg GA. Cartilage chondrolysis by fibronectin fragments is associated with release of several proteinases: stromelysin plays a major role in chondrolysis. Arch Biochem Biophys 1994;311:205–12.
120. Murphy G, Cockett MI, Stephens PE, Smith BJ, Docherty AJP. Stromelysin is an activator of procollagenase. A study with natural and recombinant enzymes. Biochem J 1987;248:265–8.
121. Pelletier JP, McCollum R, Cloutier JM, Martel-Pelletier J. Synthesis of metalloproteases and interleukin 6 (IL-6) in human osteoarthritic synovial membrane is an IL-1-mediated process. J Rheumatol 1995;22:109–14.
122. Campbell IK, Wojta J, Novak U, Hamilton JA. Cytokine modulation of plasminogen activator inhibitor-1 (PAI-1) production by human articular cartilage and chondrocytes. Down-regulation by tumor necrosis factor-α and up-regulation by transforming growth factor-β basic fibroblast growth factor. Biochim Biophys Acta 1994;1226:277–85.
123. Rosen CJ, Donahue LR, Hunter SJ. Insulin-like growth factors and bone: the osteoporosis connection. Proc Soc Exp Biol Med 1994;206:83–102.
124. Canalis E, Centrella M, Burch W, McCarthy TL. Insulin-like growth factor I mediates selective anabolic effects of parathyroid hormone in bone cultures. J Clin Invest 1989;83:60–5.
125. Linkhart TA, Mohan S. Parathyroid hormone stimulates release of insulin-like growth factor-I (IGF-I) and IGF-II from neonatal mouse calvaria in organ culture. Endocrinology 1989;125:1484–91.
126. Manolagas SC, Jilka RL. Bone marrow, cytokines, and bone remodeling. Emerging insights into the pathophysiology of osteoporosis. N Engl J Med 1995;332:305–11.
127. Lisignoli G, Toneguzzi S, Pozzi C, Piacentini A, Riccio M, Ferruzzi A, et al. Proinflammatory cytokines and chemokine production and expression by human osteoblasts isolated from patients with rheumatoid arthritis and osteoarthritis. J Rheumatol 1999;26:791–9.
128. Aubin JE. Advances in the osteoblast lineage. Biochem Cell Biol 1998;76:899–910.
129. Bonnelye E, Aubin JE. Differential expression of estrogen receptor-related receptor alpha and estrogen receptors alpha and beta in osteoblasts in vivo and in vitro. J Bone Miner Res 2002;17: 1392–400.
130. Kusano K, Miyaura C, Inada M, Tamura T, Ito A, Nagase H, et al. Regulation of matrix metalloproteinases (MMP-2, -3, -9, and -13) by interleukin-1 and interleukin-6 in mouse calvaria: association of MMP induction with bone resorption. Endocrinology 1998;139: 1338–45.
131. Paredes Y, Massicotte F, Pelletier JP, Martel-Pelletier J, Laufer S, Lajeunesse D. Study of role of leukotriene B4 in abnormal function of human subchondral osteoarthritis osteoblasts. Effects of cyclooxygenase and/or 5-lipoxygenase inhibition. Arthritis Rheum 2002;46:1804–12.
132. Kaneki H, Takasugi I, Fujieda M, Kiriu M, Mizuochi S, Ide H. Prostaglandin E2 stimulates the formation of mineralized bone nodules by a cAMP-independent mechanism in the culture of adult rat calvarial osteoblasts. J Cell Biochem 1999;73:36–48.
133. Franchimont N, Rydziel S, Delany AM, Canalis E. Interleukin-6 and its soluble receptor cause a marked induction of collagenase 3 expression in rat osteoblast cultures. J Biol Chem 1997;272: 12144–50.
134. Raisz LG, Fall PM. Biphasic effects of prostaglandin E2 on bone formation in cultured fetal rat calvariae: interaction with cortisol. Endocrinology 1990;126:1654–9.
135. Hakeda Y, Nakatani Y, Kurihara N, Ikeda E, Maeda N, Kumegawa M. Prostaglandin E2 stimulates collagen and non-collagen protein synthesis and prolyl hydroxylase activity in osteoblastic clone MC3T3-E1 cells. Biochem Biophys Res Commun 1985;126:340–5.
136. Igarashi K, Hirafuji M, Adachi H, Shinoda H, Mitani H. Role of endogenous PGE2 in osteoblastic functions of a clonal osteoblast-like cell, MC3T3-E1. Prostaglandins Leukot Essent Fatty Acids 1994;50:169–72.
137. Gallwitz WE, Mundy GR, Lee CH, Qiao M, Roodman GD, Raftery M, et al. 5-Lipoxygenase metabolites of arachidonic acid stimulate isolated osteoclasts to resorb calcified matrices. J Biol Chem 1993;268:10087–94.
138. Tardif G, Pelletier JP, Dupuis M, Geng C, Cloutier JM, Martel-Pelletier J. Collagenase 3 production by human osteoarthritic chondrocytes in response to growth factors and cytokines is a function of the physiological state of the cells. Arthritis Rheum 1999;42:1147–58.