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Review

What drives osteoarthritis?—synovial *versus* subchondral bone pathology

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Abstract

Subchondral bone and the synovium play an important role in the initiation and progression of OA. MRI often permits an early detection of synovial hypertrophy and bone marrow lesions, both of which can precede cartilage damage. Newer imaging modalities including CT osteoabsorptiometry and hybrid SPECT-CT have underlined the importance of bone in OA pathogenesis. The subchondral bone in OA undergoes an uncoupled remodelling process, which is notably characterized by macrophage infiltration and osteoclast formation. Concomitant increased osteoblast activity leads to spatial remineralization and osteosclerosis in end-stage disease. A plethora of metabolic and mechanical factors can lead to synovitis in OA. Synovial tissue is highly vascularized and thus exposed to systemic influences such as hypercholesterolaemia or low grade inflammation. This review aims to describe the current understanding of synovitis and subchondral bone pathology and their connection in OA.

Key words: osteoarthritis, OA, synovitis, subchondral bone, inflammation, bone, osteophyte, crystal, bone marrow lesion, osteoimmunology

Rheumatology key messages

- Both synovitis and subchondral bone remodelling are actively involved in OA and often precede cartilage damage.
- In OA, synovitis triggers osteoclastogenesis, pannus formation and increases adherence of synovial tissue to cartilage.
- Chronic mechanical impairment in combination with metabolic dysregulation is a common trigger of subchondral bone changes and osteophytosis.

Introduction

OA is a major socioeconomic health burden leading to chronic pain and disability. Arthroplasty has been a major breakthrough in the treatment of advanced OA, yet a non-invasive disease-modifying treatment notably for early or intermediate OA stages is lacking [1]. One reason for this is the heterogeneity of OA and its complex pathogenesis. Due to substantial anatomical and biomechanical differences, OA is a highly joint-specific disorder. While mechanical overload, malalignment or joint instability frequently underlie OA in the lower extremity, metabolic factors such as hypercholesterolaemia and genetic predisposition seem to play a larger role in hand or facet joint OA [2]. Instead of being a pure cartilage disorder, OA is now considered as a whole-joint disease that affects various anatomical structures in and around the joint capsule. These include muscle, ligaments, entheses, synovial tissue and the subchondral bone [3]. Inflammatory symptoms such as joint effusion or articular stiffness are common in OA and synovial inflammation detected by sonography occurs in more than half of the patients with early OA [4]. The advent of MRI has underlined the pathogenic role of both synovitis and the subchondral bone tissue in OA. A substantial volume of synovitis in suprapatellar, infrapatellar and intercondylar regions considerably increases the risk for incident radiographic knee OA [5]. A nested case–control longitudinal MRI study identified the presence of effusion and Hoffa synovitis at baseline as major risk factors for development of radiographic OA [6]. Bone marrow lesions (BMLs) are regularly encountered, for example, in early knee OA, as a sign of mechanical overload. BMLs are increasingly recognized as a reliable marker for OA as they develop and reverse earlier than cartilage damage. Osteosclerosis

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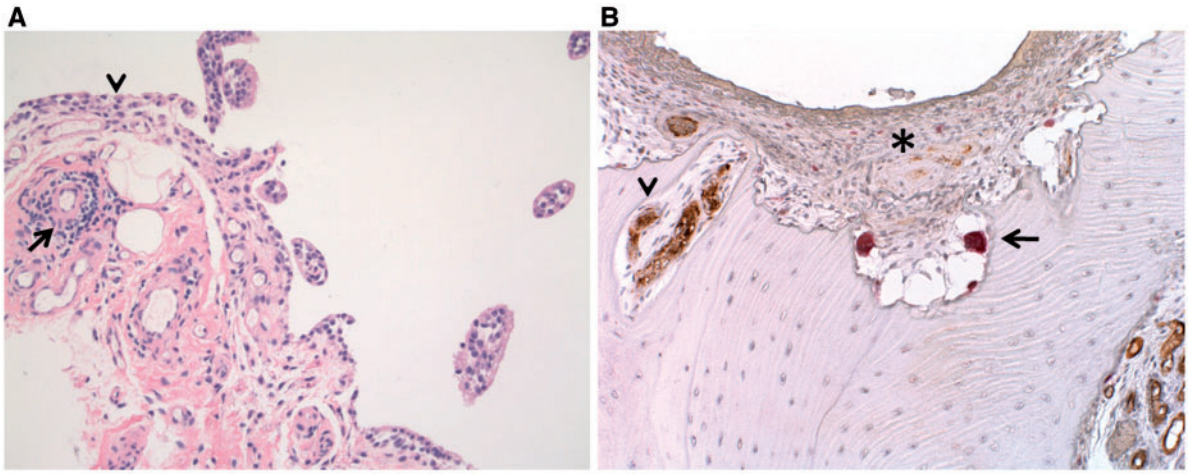
Fig. 1 Synovitis and pannus formation in OA



(**A**) Low grade synovitis with moderate hyperplasia of the lining cells (arrowhead) and perivascular inflammatory cell infiltration (arrow) in knee OA. (**B**) Pannus in the form of infiltrating connective tissue in facet joint OA. Inflammatory cell infiltration (asterisks), CD34 positive neoangiogenesis (arrowhead) and TRAP-positive osteoclast formation with a bone lacuna (arrow).

and osteophyte formation in conventional radiography are considered as features of advanced OA. However, newer imaging modalities such as CT osteoabsorptiometry (CT-OAM) and hybrid SPECT-CT demonstrate that a constant and potentially reversible bone remodelling already takes place in early OA [7]. Owing to this, osteoclast inhibition by bisphosphonates or strontrium ranelate has been shown to be an effective treatment for OA in controlled clinical trials [8, 9]. Despite both synovial and subchondral bone pathology seeming to play a pivotal role in OA progression, it is still unclear if and how they are associated with each other and how they trigger cartilage damage. The focus of this translational review therefore is on histopathological changes of the synovium and subchondral bone along with the consequences, notably in cartilage damage.

Functional anatomy of the synovium

Synovial tissue separates the joint capsule from the joint cavity. Apart from cartilage nutrition and lubrication, the main function of synovial tissue is to prevent adherence of the capsule with cartilage. By the production of hyaluronan and plasminogen activator, the synovium preserves articular mobility [10]. Hyaluronan is also responsible for ensuring constant SF volume during exercise [11]. The inner layer of synovial tissue is called the intima and consists of a lining of cells, the type A and type B synoviocytes. Type A cells resemble macrophages and phagocytes whilst type B cells are fibroblasts secreting hyaluronan and other proteins. Synoviocytes do not possess a basal layer and lack cell–cell junctions, which facilitate the exchange between SF *with* blood or lymphatic vessels. Depending on the joint-specific biomechanics, the subintima can be composed of different types of connective tissue: fibrous, fatty or areolar. Areolar synovial tissue is a loose and highly viscoelastic connective tissue that permits stretching or folding. Villi increase the synovial surface further and allow adaption of the shape of the capsule during movement. The subintimal layer has a complex vascular network of lymphatic and blood vessels.

Synovial histopathology in OA

The histologic hallmark of OA-induced synovitis is proliferation and hyperplasia of the lining cells along with moderate inflammatory cell infiltration and neoangiogenesis (Fig. 1A). In knee OA, synovitis is predominantly located posterior to the crucial ligament and in the suprapatellar region [12]. Synovial tissue thickness and the extent of inflammatory cell infiltration are clearly correlated [13]. In end-stage OA, synovitis displaying high infiltration of $CD68^+$ macrophages is present in up to 90% of the patients [12, 14]. Some observations indicate that the grade of macrophage infiltration can be more pronounced in early stages of OA [15]. Vascular endothelial growth factor production by synovial macrophages has been postulated as a possible mechanism that exacerbates synovial angiogenesis and inflammation in OA [16]. Lymphoid cell aggregates are rarely seen in early OA but do occur in up to one-third of synovial samples from patients with severe OA [17]. Unlike in RA, germinal centre formation is usually absent in OA-induced synovitis [16]. Thus, innate immune activation seems to be an important driver of synovitis in OA. T cell polarization shows significantly more Th1 cells than Th2 or Th17 cells [18] with a subsequent release of Th1 cytokines such as IFNγ and TNF, which subsequently induce osteoclastogenesis in the bone by the stimulation of macrophages [19]. This

inflammatory osteopenia could explain the initial subchondral thinning in OA or cyst formation in its later stage.

Another theory is that synovially derived macrophages differentiate into functional osteoclasts, which then contribute to subchondral bone remodelling [20]. The mechanism of how those cells migrate from the SF into the subchondral bone, however, remains unclear. Ogawa *et al.* [21] have shown that mature osteoclast also occur in the synovial membrane, at least in aggressive forms of OA.

Mast cell numbers in the synovial tissue are higher in OA than RA samples, despite a lower synovitis score. A trend towards correlation between mast cells and radiographic OA severity, independent of synovitis, has been postulated [22]. Mast cells are a substantial source of preformed cytokines such as TNF. Interestingly, mechanical loading promotes mast cell degranulation [23]. Therefore synovial mast cells are potentially involved in mechanoinflammation in OA. Formation of a highly vascularized infiltrating connective tissue or pannus occurs not only in RA but also in OA. Pannus-like tissue has, for example, been described in medial knee OA, displaying increased expression of IL-1 or metalloproteinases [24]. Figure 1B shows an osteoarthritic lumbar facet joint with an erosive pannus tissue that is rich in multinucleated tartrate-resistant acid phosphatase positive osteoclasts forming a bone lacuna. Multinucleated osteoclasts as described above were not observed. Synovial surface fibrin deposition is commonly observed in endstage OA [25].

Causes of synovitis in OA

Overuse of the synovial tissue and joint capsule is a well-known mechanical cause of joint pain and effusion. Joint effusion physiologically prevents adherence of the mechanically damaged synovium to cartilage. MRI performed directly after a marathon race shows joint effusion, but not bone marrow oedema or cartilage damage [26]. Local irritation of the well-innervated capsule by osteophytes can also provoke pain and synovial damage [27]. In knee OA, synovitis is strongly associated with cartilage damage and BMLs [28, 29]. This may be related to the release of cartilage or subchondral bone breakdown products such as hyaluronan [30], cytokine expression by bone marrow macrophages or innate immunity activation, for example, by damage-associated molecular patterns (DAMPs) [31]. Direct contact of SF and bone marrow through osteochondral lesions *a priori* leads to macrophage infiltration and release of IL-1 or TNF. Even small BMLs can trigger synovitis with a large joint effusion, as seen in Fig. 2. Trauma such as meniscal tears or cruciate ligament ruptures is commonly accompanied by an inflammatory synovial reaction [32]. Instead of being mere bystanders, crystals in the form of calcium pyrophosphate in calcium pyrophosphate deposition disease, basic calcium phosphate or uric acid can be independent drivers of synovitis. They activate the inflammasome and thus IL-1 production in the synovium [33]. Basic calcium crystals can be detected in nearly all OA SF samples [34] and calcium pyrophosphate deposition disease crystals may occur in over 90% of patients with severe OA [35]. Notwithstanding, primary causes of crystal deposition such as hyperparathyroidism and gout along with other deposition disorders such as haemochromatosis should be excluded notably in the absence of biomechanical risk factors. Underlying autoimmune or autoinflammatory causes of synovitis such as spondyloarthritis or PsA are likely underdiagnosed in OA patients, especially in those with severe pain and low-grade and moderate radiographic disease. A deep Koebner effect has been postulated as a reason for synovitis due to mechanical injury in patients with (occult) psoriatic arthritis and might mimic OA [36]. The synovio-entheseal complex can be the interface between mechanical stress and synovitis both in rheumatological and in degenerative disorders. Figure 2 summarizes factors that might trigger synovitis in OA.

Synovitis-induced cartilage damage

The influence of the synovium on chondrocytes is thought to play a key part in the pathophysiology of OA [17, 37, 38]. This is mainly triggered by the release of cytokines and growth factors such as IL-1, IL-6 and TNF [39]. These factors are produced by the synovial membrane and diffuse into the cartilage via the SF and, among other mechanisms, lead to increased apoptosis of chondrocytes [38]. By inducing experimental OA in an MMP3-knockout mouse, Blom and coworkers [40] demonstrated that synovial macrophage activation plays a crucial role in establishing cartilage damage, suggesting that synovitis may be pivotal for OA development. Fibrin-triggered attachment of the synovial tissue to the cartilage could explain morning stiffness and opposing macular chondropathy in either endstage OA or secondary OA (Fig. 3). As described above, pannus as infiltrating connective tissue also occurs in OA and induces bone and cartilage damage (Fig. 1B).

Subchondral bone anatomy

The articular cartilage and subchondral bone form a functional osteochondral unit in order to optimize shock absorption and load distribution. A mineralized or calcified cartilage layer forms a junction between bone and non-calcified cartilage tissues. The interface between calcified and non-calcified cartilage is called the tidemark. Osteoarthritic cartilage displays multiplication of the tidemark representing enhanced calcification of the deep cartilage zone [41] (Fig. 4). Remodelling and turnover of the subchondral bone plate in OA has a biphasic character and initially displays thinning of the plate. At a later stage, the calcified cartilage layer vanishes and the bone plate thickens substantially at the expense of fatty bone marrow [42]. The subchondral bone plate is highly vascularized and accounts for over 50% of the hyaline cartilage nutrition with glucose, oxygen or water [43]. The subchondral trabecular bone and fatty bone marrow connect to the lower end of the subchondral bone plate.

BMLs in OA

BMLs are commonly observed in osteoarthritic joints by MRI, where they appear as ill-defined hyperintensities on short T1 inversion recovery images and T2-weighted magnetic resonance images [5]. BMLs in the knee are associated with malalignment and meniscal damage [44, 45]. Thus, in knee OA, BMLs can be regarded as resulting from increased remodelling of subchondral bone and marrow in response to abnormal loading. A longitudinal MRI study in 217 patients with primary knee OA has demonstrated that BMLs, once present, rarely regress [46]. Instead, an increase in lesion size strongly associates with progressive cartilage loss and development of OA [46, 47]. Conversely, absence or regression over time of BMLs is associated with a decreased risk of cartilage loss [47] or favourable treatment response to a mechanical intervention [48]. Two-dimensional MRI analyses of tibiofemoral subregions have demonstrated that subchondral BMLs predict cartilage loss and subchondral bone attrition at the same subregion [49, 50]. A recent study using a three-dimensional quantitative MRI assessment of 88 knee joints with advanced OA confirmed a strong spatial relationship between BMLs and severe cartilage damage in tibiofemoral joint compartments [6]. Cartilage denudation, typical for end-stage OA, exclusively collocated with large BMLs covering >70% of the denuded area. Notably, the complex interaction between different joint tissues in the pathogenesis of OA becomes evident when assessing end-stage OA joints by whole-organ MRI scoring [29]. This method showed that BMLs, subchondral cysts and subchondral bone attrition are positively correlated with histological synovitis severity.

While the diagnostic and prognostic value of BMLs in OA have been firmly established, surprisingly little is known about the morphological and histological characteristics of BMLs. Hunter *et al.* performed a microcomputed tomography study of bone specimens containing BMLs. The results displayed increased bone volume but reduced tissue mineral density consistent with osteosclerosis. Subchondral trabecular bone had undergone extensive remodelling leading to a lower trabecular number and an increase in trabecular spacing and width [51]. Histological analysis of bone marrow hyperintense tissue in osteoarthritic knee joints displayed a number of non-characteristic abnormalities including marrow fibrosis, marrow necrosis and trabecular abnormalities [5]. It has been suggested that BMLs might correspond with newly formed osteoid islets in subchondral bone marrow spaces, which have been identified as a major pathological disease mechanism in a post-traumatic model of OA [52]. Excessive osteoblast activity and bone formation in subchondral marrow spaces comprise major histopathological features of facet joint OA and SPECT-positive lesions in ankle OA [53, 54]. SPECT-CT can also be applied for the detection of mechanically induced OA due to knee malalignment or hypercompression of the patella (Fig. 5). In a recent immunohistological study, we have identified increased inflammatory cells in sclerotic subchondral bone subjacent to areas of severe cartilage loss [55], which are known to contain abundant BMLs [6]. Sclerotic bone tissues showed fibrovascular tissue infiltration into otherwise predominantly adipose marrow tissues. Infiltrating tissues were macrophage- and osteoclast-rich and contained foci of B cells [55]. The presence of monocytes, macrophages and osteoclast progenitors in subchondral marrow spaces of osteoarthritic sclerotic bone tissues was corroborated by a flow cytometry study of isolated marrow cells [56]. Walsh and co-workers have established increased inflammatory infiltration and vascular invasion at the osteochondral junction as characteristic histopathological features of advanced OA [57].

Subchondral bone remodelling

The spatial collocation of subchondral bone sclerosis and cartilage degeneration in human and experimental OA has been extensively studied [52, 58–66]. Subchondral bone sclerosis is characterized by an increase in bone volume

Fig. 2 Conditions triggering synovitis in OA

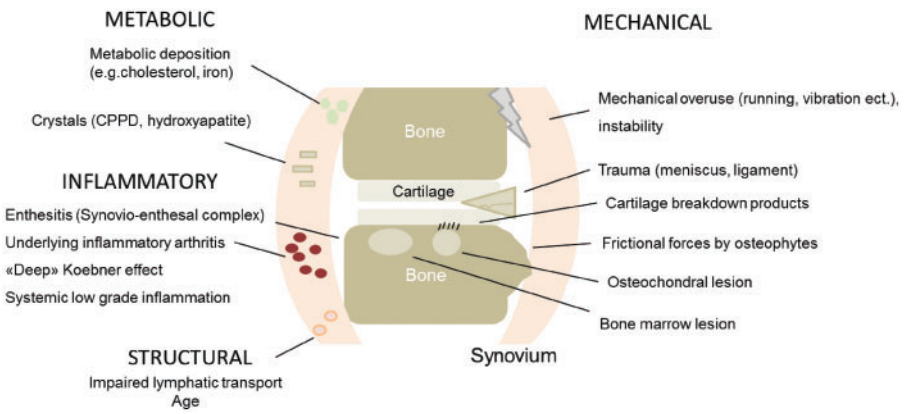
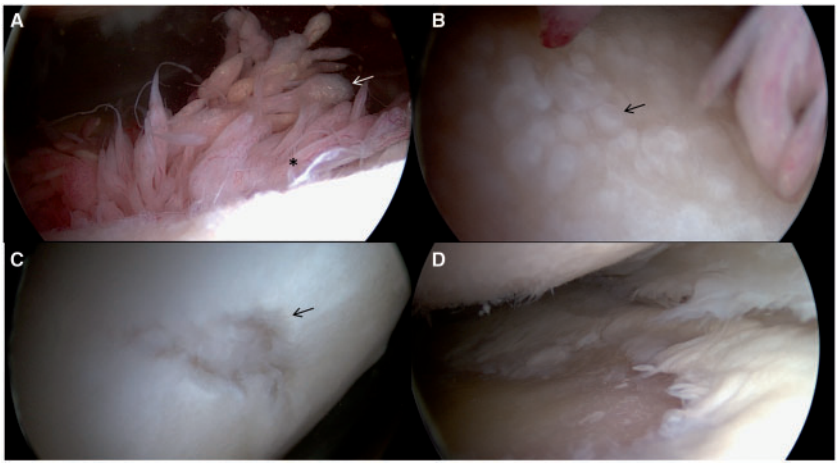
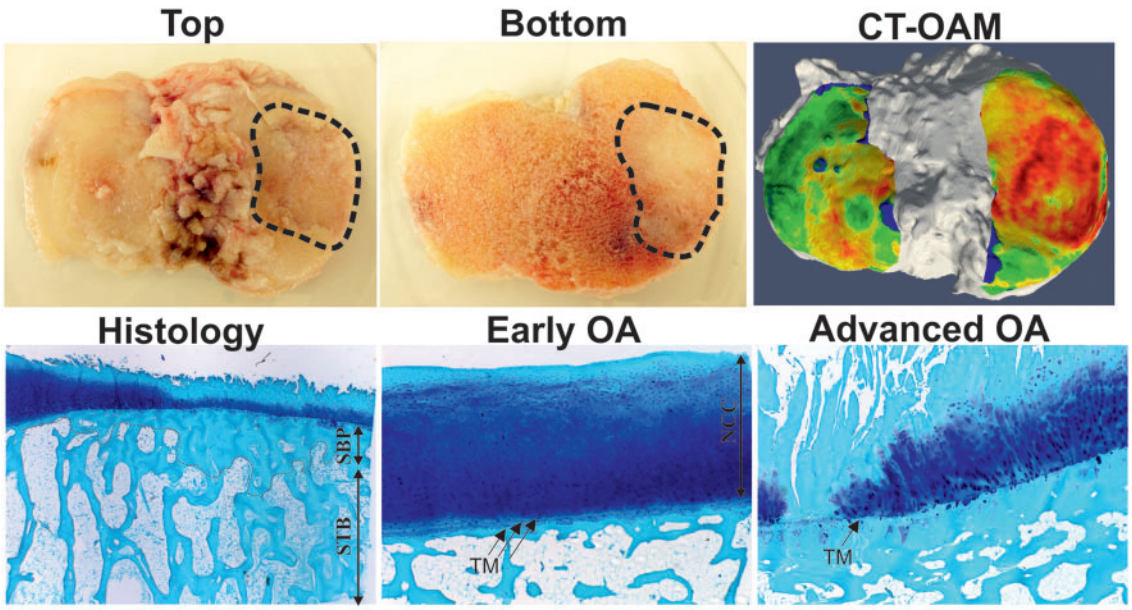


Fig. 3 Fibrin deposition and opposite cartilage damage in secondary OA due to long standing RA



(**A**) Proliferative chronic synovitis with angiogenesis (asterisk) and fibrin depositis on villi (arrow). (**B**) Macular chondropathy opposite to fibrin-coated villi (seen on the right), likely as a result of repetitive adherence. (**C**) Cartilage fissure. (**D**) End-stage cartilage damage with meniscal impairment.

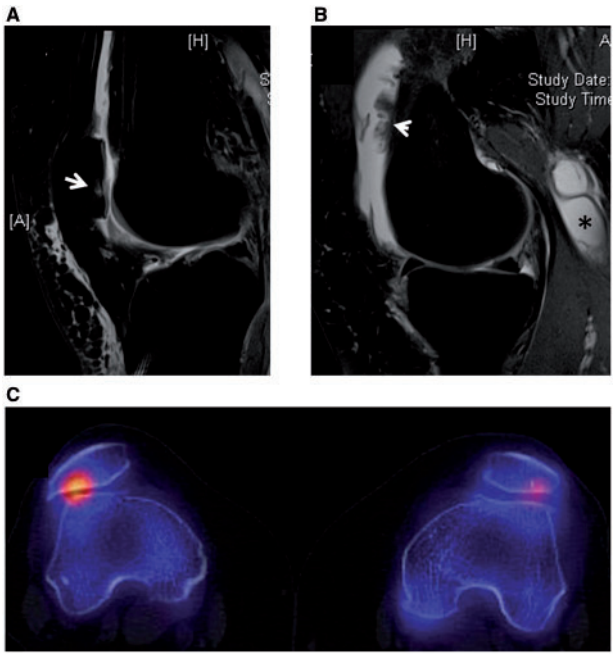
Fig. 4 Representative macroscopic, histological and CT-osteoabsorptiometry images of a knee tibial plateau with severe medial OA



Top and bottom views of a dissected plateau reveal co-localization (dashed line) of severe cartilage damage (top) with increased subchondral bone volume (bottom). CT-osteoabsorptiometry (CT-OAM) confirms an increase in bone mineral density distribution subjacent to the cartilage lesion. The histological image displays structural remodelling of the subchondral bone plate (SBP) and subchondral trabecular bone and marrow (STB) beneath a cartilage lesion. The SBP and trabeculae thicken and fatty marrow is replaced by a fibrovascular tissue. High magnification images of early and advanced OA demonstrate multiplication of tide marks (TM) below the non-calcified cartilage (NCC) in early disease. In advanced OA, calcified cartilage (dark blue) beneath the TM has disappeared.

due to enhanced bone turnover, but a decrease of tissue mineralization. This results in a lower tissue elastic modulus (material stiffness) but increased structural stiffness [67]. Cox *et al.* [68] have used computational modelling to demonstrate that decreased mineralization partially drives increase of bone volume. Lesser tissue

FIG. 5 Early OA as a consequence of lateral patellar compression syndrome



(**A**) MRI with cartilage defect and patellar bone marrow oedema (arrow). (**B**) Synovial proliferation (arrowhead) associated with joint effusion and a baker cyst (asterix). (**C**) SPECT-CT showing subchondral osteoblast activity along the lateral aspect of the patellar surface as a result of malalignment.

mineralization and subchondral bone sclerosis coincided with BMLs in osteoarthritic knee joints [51]. Cellular and molecular characterization of outgrowth osteoblasts from sclerotic subchondral cortical plate and trabecular bone tissues has demonstrated an aberrant hypomineralization phenotype *in vitro* [69–73]. Recently, Campbell and co-workers [74] as well as us have independently demonstrated that mesenchymal stem cells/osteoprogenitors from osteoarthritic sclerotic bone tissues also possess a hypomineralization phenotype [75]. Enhanced recruitment of mesenchymal stem cells in subchondral marrow spaces followed by formation of osteoid islets has been elucidated as a major pathological mechanism in experimental post-traumatic OA [52].

The temporal sequence of subchondral bone remodelling and cartilage degeneration in the onset of OA remains a heavily discussed topic. However, due to the existence of distinct clinical OA subtypes with clear differences in structural degradation and symptoms [76], the relative importance of subchondral bone remodelling in pathogenesis is likely to vary. Increased subchondral bone remodelling has been identified as a crucial early event in several experimental OA models [52, 58, 66, 77–87]. Micro CT has demonstrated that temporal thinning and increased porosity of the subchondral bone plate occurs early after surgically or stability-induced OA [52, 78, 85, 87]. These results have implicated enhanced osteoclast-mediated bone resorption in the response to abnormal loading as a potential pathomechanism for OA [52, 66, 79]. In a seminal study, Zhen and co-workers demonstrated that surgical induction of OA led to uncoupled subchondral bone remodelling, characterized by enhanced osteoclast and osteoblast activities taking place at separate time points and locations (spatiotemporal uncoupling). This disease mechanism is also responsible for the onset of joint destruction in experimental RA in mice and spontaneous OA in guinea pigs [77, 88]. However, this is unlikely to be the sole mechanism in the onset of OA, since early subchondral bone thickening has been described as causative for cartilage degeneration in different experimental OA models [58, 77, 80]. Care has to be taken when interpreting data from experimental models, which are complicated by the fact that surgical induction might introduce confounding factors that affect downstream bone remodelling [78].

Corresponding with a crucial role of osteoclast-mediated bone resorption, treatment with anti-resorptive drugs including strontium ranelate [89, 90], zoledronate [91, 92] and cathepsin-K inhibitor [91] has demonstrated therapeutic efficacy in experimental OA. Data from the strontium ranelate efficacy in a knee OA trial have demonstrated a reduction of cartilage loss and BMLs [8] and a significant reduction in radiological disease progression and amelioration of clinical symptoms including pain and physical function [9]. Clinical efficacy of joint distraction in human ankle OA, which we have shown to be characterized by increased osteoblast-mediated bone formation [54], was associated with an overall decrease of subchondral bone density and resolution of subchondral cysts [94]. These results demonstrate that subchondral bone

sclerosis is principally reversible through pharmacological treatment or surgical restoration of joint biomechanics. Meanwhile, experimental OA models continue to reveal novel treatment targets in subchondral bone tissues including stimulation of ephrin signalling [95] and inhibition of SDF-1/CXCR4 and TGFb1 signalling [52, 96, 97].

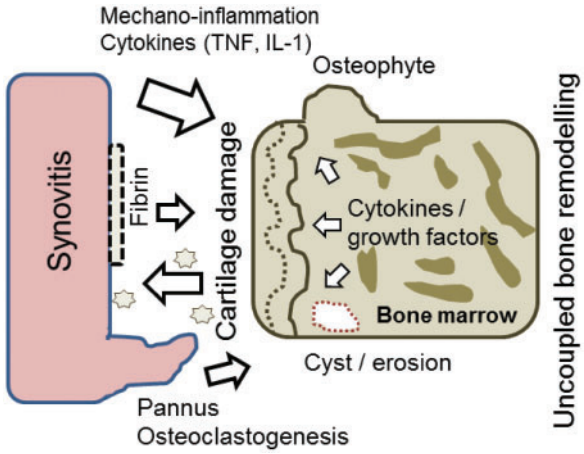
Interaction between subchondral bone and synovitis

In many ways the question whether and how bone marrow tissue and synovial lining might interact in OA is similar to the situation in inflammatory arthritis, where both synovium-to-marrow and marrow-to-synovium hypotheses for pathogenesis have been convincingly stated [98]. In fact, the metabolic environment of SF in OA is similar to that in inflammatory arthritis [99]. It has been unequivocally demonstrated that both synovitis and BMLs occur and coexist before the development of radiographic OA [100]. Yet BMLs typically develop subjacent to areas of cartilage loss [50], which in knee OA are frequently localized in the central region of the condyles or tibial plateau and relatively distant from synovial lining tissue. Therefore it might be postulated that BMLs in the first line are the consequence of mechanical stress (by increased bone-to-bone pressure or tendon traction) that ends in osteosclerosis. On the other hand, synovial tissue also detects mechanical impairment but at the same time acts as a local and systemic metabolic sensor. By fostering osteoclast formation, synovitis likely is involved in catabolic bone remodelling as observed in early stages of OA [20]. Penetration of cartilage and the subchondral bone by pannus-like tissue has been demonstrated in the medial compartment OA of the knee [24]. However, despite a similar inflammatory cytokine profile expression in RA and OA, pannus-like tissue in OA does invade the cartilage surface but causes less erosions as typically seen in RA [101].

Conclusion

Rather than being separate and independent joint tissues, the articular cartilage, subchondral bone and bone marrow compartments as well as the synovium closely interact at mechanical and biological levels in health and OA (Fig. 6). Increased remodelling of each of these compartments has been demonstrated during the onset and progression of OA. The temporal sequence of tissue remodelling events can differ between human and experimental OA models and between OA clinical phenotypes. BMLs typically reflect mechanical impairment and can lead to osteosclerosis. Synovitis can induce cartilage damage by fibrin deposition, pannus formation or via inflammatory cytokine expression and triggers osteopenia, notably in early OA stages. Thus, besides mechanical impairment, metabolic or underlying systemic factors trigger bone remodelling and should always be taken into consideration in the treatment of OA.

Fig. 6 Schematic illustration of the interaction between synovial tissue, cartilage and subchondral bone in OA



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Clinical vignette

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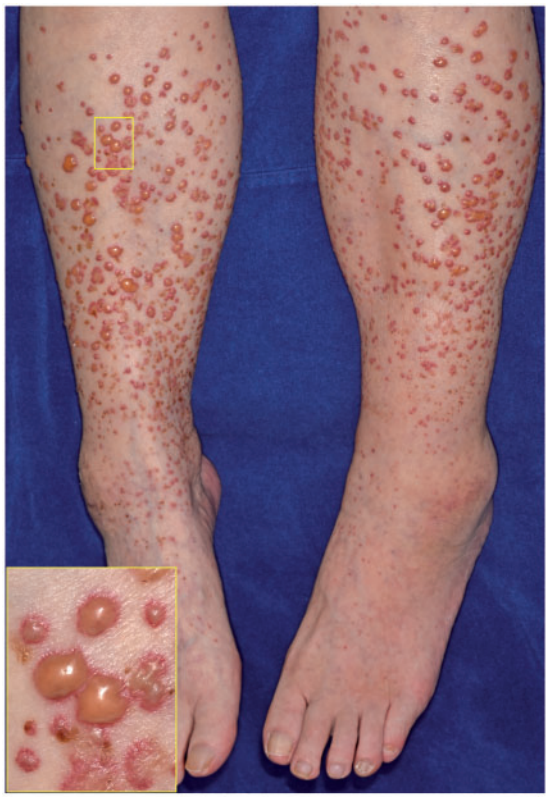
Unusual tense bullae on the legs of a woman with rheumatoid arthritis

A 78-year-old Japanese woman presented with symmetrically distributed, disseminated tense bullae and pustules up to 8 mm and petechiae without tenderness on the lower legs (Fig. 1). She had a 2 year history of RA that had been treated with a combination of prednisone (10 mg/day) and salazosulfapyridine; additionally, abatacept had been administered for the 4 weeks before her visit to us. Her 28-joint DAS with CRP score was 4.96 on presentation and no abnormalities were detected in other organs. Biopsy of a tense bulla revealed subepidermal blistering with numerous neutrophils in the dermis. No vasculitis was present. The diagnosis of bullous rheumatoid neutrophilic dermatosis (RND) was made and additional prednisone was administered (20 mg/day total).

RND, a condition occasionally observed in patients with RA, manifests as non-tender erythematous papules, plaques or nodules. Bullous RND is an extremely rare subtype of RND characterized by uniform eruptions of symmetrical tense bullae and petechiae on the lower legs, accompanied by no other organ abnormalities. The disease aetiology remains unknown, however, the appearance of skin lesions has been associated with severe cases of RA. Clinicians should be aware of the occurrence of these striking tense bullae in patients with RA [1, 2].

Fig. 1 Clinical image of the patient's legs



Symmetrically distributed tense bullae and pustules formed on preceding purpura on the legs.

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