The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis

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Abstract | Osteoarthritis (OA), one of the most common rheumatic disorders, is characterized by cartilage breakdown and by synovial inflammation that is directly linked to clinical symptoms such as joint swelling, synovitis and inflammatory pain. The gold-standard method for detecting synovitis is histological analysis of samples obtained by biopsy, but the noninvasive imaging techniques MRI and ultrasonography might also perform well. The inflammation of the synovial membrane that occurs in both the early and late phases of OA is associated with alterations in the adjacent cartilage that are similar to those seen in rheumatoid arthritis. Catabolic and proinflammatory mediators such as cytokines, nitric oxide, prostaglandin E_2 and neuropeptides are produced by the inflamed synovium and alter the balance of cartilage matrix degradation and repair, leading to excess production of the proteolytic enzymes responsible for cartilage breakdown. Cartilage alteration in turn amplifies synovial inflammation, creating a vicious circle. As synovitis is associated with clinical symptoms and also reflects joint degradation in OA, synovium-targeted therapy could help alleviate the symptoms of the disease and perhaps also prevent structural progression.

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Introduction

Osteoarthritis (OA) is a degenerative joint disease characterized by cartilage breakdown, the formation of bony outgrowths at the joint margin (osteophytes), subchondral bone sclerosis, alterations to the joint capsule and inflammation of the synovial membrane.[1,2] The synovial membrane, which contains metabolically highly active cells (synoviocytes), is physiologically important as it both nourishes chondrocytes via the synovial fluid and joint space, and removes metabolites and products of matrix degradation. The inflammation of the synovium that occurs in OA results in synovitis that is detectable by imaging, arthroscopy or histology. Despite this synovial inflammation, however, OA is usually classified as a noninflammatory disorder, since the leukocyte count in OA synovial fluid is typically below the threshold that defines an 'inflammatory' disorder (2,000 cells per mm^3).[3]

Synovitis is directly responsible for several clinical symptoms and reflects the structural progression of the disease; it is a key factor in OA pathophysiology because of the action of several soluble mediators (Figure 1). Hence, treatments that specifically target this previously neglected component of OA could be beneficial for both the symptoms and structural changes that occur in OA.[4] In this Review, we present the role of synovitis in OA symptomatology, the methods used for its assessment, its involvement in the disease pathophysiology and the possibility of therapeutically targeting synovitis in clinical practice.

Competing interests
The authors declare no competing interests.

The clinical relevance of synovitis

Although it is not always easy to detect synovitis clinically, several clinical features are attributable to the inflammatory component of OA and reflect the presence of synovitis (Table 1). An 'inflamed' synovium is considered to be indicated by palpable joint swelling, which can arise from thickening of the synovium (through the development of pannus) or from synovial fluid effusion.[5] Typical signs of inflammation such as redness, swelling, pain or heat can occur, especially in the distal and proximal interphalangeal joints of the hand. Arthroscopy has been used to show that knee effusion is associated with the presence of synovitis.[6,7] Studies using ultrasonography and MRI have demonstrated synovitis in OA with relatively few symptoms or with limited alterations to the cartilage and subchondral bone, even in joints where synovitis was not detected clinically.[8–10]

Inflammatory OA pain is indicated when patients experience a sudden increase in pain, night pain and morning stiffness that lasts for at least 30 minutes.[11] Severe inflammatory flares associated with substantial synovial inflammation are seen in rapidly destructive OA, or in erosive hand OA .[12] The detection of these inflammatory flares is crucial since they could be caused by synovitis and they may have deleterious structural effects in post-traumatic patellofemoral chondropathy.[6] However, the correlation between synovitis assessed by arthroscopy and the degree of pain or functional impairment remains controversial. The strength of the relationship seems to depend on which compartment of the knee is studied (femoropatellar or medial femorotibial) and on the nature of the underlying disease (post-traumatic chondropathy or OA).[6,13] Finally, the clinical indicators

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Key points

- Substantial synovial inflammation can occur in early-stage osteoarthritis (OA), end-stage OA, or both
- Synovitis triggers several symptoms and clinical signs of OA
- OA synovitis can be assessed by MRI, ultrasonography and arthroscopy; however, the gold-standard method for detecting OA synovitis is histological analysis of biopsy-obtained samples
- Synovial inflammation can predict cartilage breakdown in OA
- OA synovitis perpetuates the processes of cartilage degradation
- The OA synovium releases several soluble mediators that could hold promise as biomarkers or therapeutic targets

of knee synovitis, such as effusion and heat, can be associated with the radiological progression of OA.[14]

Assessment of synovitis by imaging

MRI

MRI is a useful tool for the assessment of OA since it can be used to evaluate the whole joint (Table 1). Several studies that used MRI and arthroscopy simultaneously have demonstrated a correlation between the findings derived from gadolinium-enhanced MRI of the synovium and from histopathological observations of microscopic inflammation, notably in early OA.[15] An increase in synovial volume correlates with increased severity of knee OA, according to the Kellgren–Lawrence score, as well as with narrowing of the joint space.[5] Furthermore, synovial volume determined by MRI correlates with synovial inflammation seen on histological analysis of samples obtained by biopsy.[9,16] This correlation between MRI and histopathological observations has been documented at the onset of OA.[9] However, despite the detection by MRI of early synovial thickening (present in 73% of patients with disease duration of 4 years or less),[15] as yet there is no evidence of the involvement of synovitis independently of cartilage disturbance in OA pathogenesis.

MRI-detected synovitis and the level of pain associated with OA do not seem to correlate cross-sectionally.[17] Some longitudinal studies have shown an association between synovitis and cartilage loss on MRI, but others have not found this association, which suggests that the prognostic value of MRI-detected synovitis remains controversial.[17,18] Recently, MRI performed without the use of a contrast agent has been successfully used to evaluate OA synovitis, thus avoiding the risk attributable to the toxicity of gadolinium.[19]

Ultrasonography

Ultrasonography, which can use a gray scale or power Doppler,[20,21] is a valid and reliable method of assessing synovial disease. In this setting, ultrasonographic findings are quite similar to those obtained with MRI or arthroscopy, or both (Table 1).[22,23] Ultrasonographic findings are also in good agreement with radiographs in detecting the central joint erosions that are characteristic

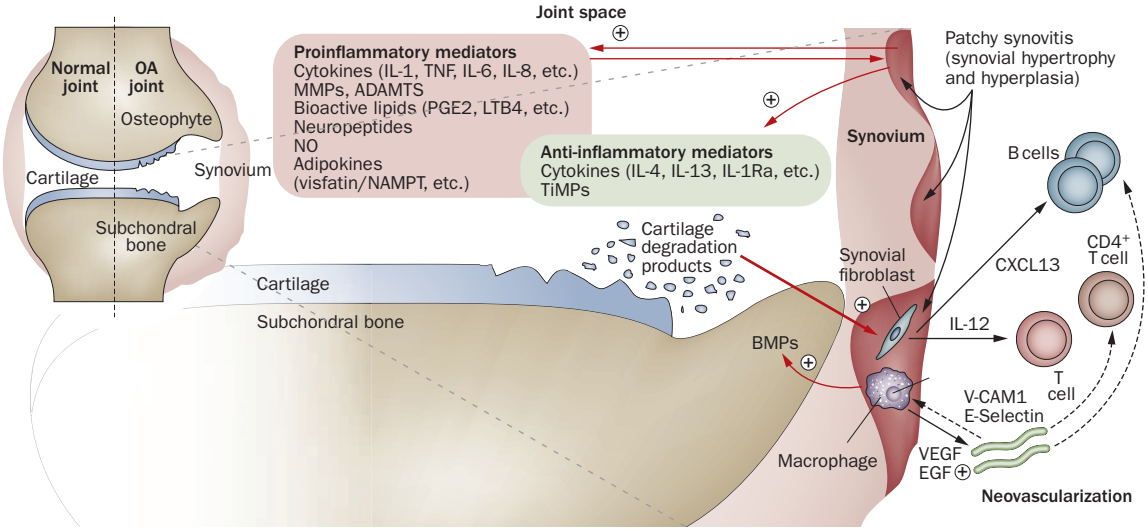

Figure 1 | Involvement of the synovium in OA pathophysiology. Products of cartilage breakdown that are released into the synovial fluid are phagocytosed by synovial cells, amplifying synovial inflammation. In turn, activated synovial cells in the inflamed synovium produce catabolic and proinflammatory mediators that lead to excess production of the proteolytic enzymes responsible for cartilage breakdown, creating a positive feedback loop. The inflammatory response is amplified by activated synovial T cells, B cells and infiltrating macrophages. To counteract this inflammatory response, the synovium and cartilage may produce anti-inflammatory cytokines. In addition to these effects on cartilage inflammation and breakdown, the inflamed synovium contributes to the formation of osteophytes via BMPs. Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BMP, bone morphogenetic protein; CCL2, CC-chemokine ligand 2; CXCL13, CXC-chemokine ligand 13; EGF, endothelial growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IL-1Ra, IL-1 receptor antagonist; LIF, leukemia inhibitory factor; LTB4, leukotriene B4; MMP, matrix metalloproteinase; NAMPT, nicotinamide phosphoribosyl transferase (also called visfatin); NO, nitric oxide; NGF, nerve growth factor; OA, osteoarthritis; PGE2, prostaglandin E2; TIMP, tissue inhibitor of metalloproteinase; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

Table 1 | Evidence of the role of synovitis in OA

Level of evidence	Observation	References
Clinical	Effusion, joint swelling, or palpable synovitis Local signs of inflammation Sudden increase in pain Night pain and morning stiffness	Krasnokutsky *et al.* (2008)[5], Ayral (1999)[28]
Imaging	Gadolinium-enhanced synovium and increased synovial volume detected by MRI Correlation between MRI and histological observations Synovitis seen using ultrasonography of symptomatic joints Association between ultrasound-detected synovitis and clinical symptoms of synovitis Macroscopic synovial changes detected by arthroscopy in about half of patients with knee OA Arthroscopic synovitis associated with progression of knee OA	Loeuille *et al.* (2005)[9], Fernandez-Madrid *et al.* (1995)[15], Ostergaard *et al.* (1997)[16], D'Agostino *et al.* (2005)[25], Keen *et al.* (2008)[116], Ayral *et al.* (1999)[6], Ayral *et al.* (2005)[13]
Histological	Synovial hypertrophy and hyperplasia Infiltration of mononuclear cells (monocytes/macrophages, activated B cells and T cells) Adaptative immune T-cell and B-cell responses to fragments of extracellular matrix Increased angiogenesis Synovitis in the vicinity of degenerative cartilage	Ayral *et al.* (2005)[13], Myers *et al.* (1990)[42], Walsh *et al.* (2007)[45], Shibakawa *et al.* (2003)[48], Nakamura *et al.* (1999)[52], Alsalameh *et al.* (1990)[58]
Molecular	Production and/or release of proinflammatory cytokines (TNF, IL-1β, IL-6, IL-8, IL-15, IL-17, IL-21) Increased production of PGE2 and nitric oxide Increased expression of adhesion molecules (ICAM-1, VCAM-1) in the synovium Increased activity of MMPs (MMP-1, MMP-3, MMP-9, MMP-13) and ADAMTS Production of adipokines (visfatin, leptin, adiponectin) Release of EGF and VEGF Involvement of macrophages in osteophyte formation via BMPs Insufficient release of anti-inflammatory cytokines (IL-4, IL-10, IL-13, IL-1Ra) Release of proinflammatory and pain neurotransmitters (substance P, NGF)	Benito *et al.* (2005)[8], Smith *et al.* (1997)[43], Shibakawa *et al.* (2003)[48], Yuan *et al.* (2004)[51], Farahat *et al.* (1993)[73], Furuzawa-Carballeda & Alcocer-Varela (1999)[74], Scanzello *et al.* (2009)[81], Brentano *et al.* (2007)[82], Presle *et al.* (2006)[83], Nissalo *et al.* (2002)[86], Raychaudhuri & Raychaudhuri (2009)[95]
Biological markers	Increased levels of CRP (detected by ultrasensitive assay) Increased levels of MMP-3 and MMP-9 in synovial cells of patients with rapidly destructive hip arthropathy Other potential surrogate biomarkers of inflammation include CGP-39 and fragments of type II collagen and aggrecan	Pearle *et al.* (2007)[31], Conrozier *et al.* (2000)[39], Masuhara *et al.* (2002)[41]

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; BMP, bone morphogenetic protein; CGP-39, cartilage glycoprotein-39 (also known as chitinase-3-like protein 1 and YKL-40); CRP, C-reactive protein; EGF, endothelial growth factor; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; IL-1Ra, interleukin 1 receptor antagonist; MMP, matrix metalloproteinase; NGF, nerve growth factor; PGE2, prostaglandin E2; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

of erosive hand OA. Ultrasonography can differentiate between erosive and non-erosive OA.[24] Synovial inflammation, as defined by ultrasound-detected synovial enlargement and effusion, is present in 47% of cases of painful knee OA.[25] In hand OA, ultrasound-detected gray-scale synovitis has a prevalence similar to that of other classical signs of OA (such as joint space narrowing and osteophytes) whereas the power Doppler signal is detected less frequently.[26] In hand OA, symptomatic joints demonstrate gray-scale synovitis, power Doppler signal and osteophytes more frequently than asymptomatic joints, but these findings do not correlate with synovitis score or the quantitative evaluation of pain in individual patients.[26] In the knee, the synovitis and effusion visible with ultrasonography are usually observed in cases of advanced radiographic disease and are correlated with the presence of these features on clinical examination or with sudden aggravation of knee pain that evokes an inflammatory 'flare'.[25]

Together with Kellgren–Lawrence grading, knee pain intensity and disease duration, the presence of knee effusion predicts the need for joint replacement.[27] However, the prognostic utility of synovitis assessed by ultrasonography needs further investigation.[27]

Assessment of synovitis by arthroscopy

Arthroscopic studies suggest that localized proliferative changes (thickening) and inflammatory changes of the synovium occur in 50% of patients with OA.[13] In addition, the presence of synovitis detected by arthroscopy is associated with more-severe chondropathy.[13,28]

Macroscopic arthroscopy of the synovium seems to be a more sensitive method of detecting disease progression than weight-bearing radiographs of fully extended knees, and could more accurately predict structural and clinical changes.[29] A longitudinal arthroscopic study by Ayral *et al.*[6] showed that the severity of synovitis indicates how patellofemoral chondropathy will progress.

Box 1 | Arthroscopic features of synovial tissue*

Normal synovium

- Few translucent, slender villi with a fine vascular network can be clearly seen
- Proliferation of opaque villi

Reactive synovium

- Villi have normal morphology or somewhat thicker and squat ('cut grass') appearance
- Vascular network not seen due to loss of translucence

Inflammatory synovium

- Hypervascularization of synovial membrane and/or proliferation of hypertrophic and hyperemic villi are apparent

*Standardized macroscopic description established by Ayral *et al*.[13,30] for the arthroscopic evaluation of the medial perimeniscal synovium.

Using the same standardized macroscopic description of synovial appearance to study cases of medial tibiofemoral OA, the same authors were able to distinguish normal synovium from reactive and inflammatory synovium (Box 1).[13,30] They found that worsening of medial meniscal chondropathy and pain seemed to be more severe in patients with an inflammatory perimeniscal synovial membrane than in those with a normal or reactive one on arthroscopic assessment,[13] which suggests that synovial inflammation has a direct effect on adjacent cartilage. The correlation between the arthroscopic picture of synovitis and that produced by use of MRI or ultrasonography indicates that these latter noninvasive imaging techniques are valid methods for assessing the OA synovium (Table 1).

Potential biological markers of OA synovitis

In OA, inflammation occurs mainly in a restricted area of a particular joint at any one time; however, some biomarkers of inflammation can be detected in the circulation, especially in cases of generalized OA. Inflamed OA synovial tissue might release synovial molecules or the damaged cartilage might trigger a systemic inflammatory response, leading to the release of inflammatory mediators by the synovium (Table 1).

An increased concentration of C-reactive protein measured using a high-sensitivity assay (hsCRP) is associated with an increasing degree of inflammatory cell infiltration of the synovial tissue and also with increasing levels of interleukin (IL)-6 (a cytokine released mainly by synovial tissue) in synovial fluid.[31] In OA, the concentration of IL-6 in synovial fluid is positively correlated with the total leukocyte count.[32] A high concentration of hsCRP is predictive of rapid disease progression in early knee OA.[33,34] In OA, hsCRP level is also associated with clinical severity, disability, number of involved joints and pain level.[35,36] From this evidence, hsCRP level could be a surrogate biomarker of synovial inflammation in OA patients, as it correlates with relevant features of OA including clinical inflammatory symptoms and structural alterations. Other studies have shown, however, that CRP concentration is also positively correlated with body mass index (BMI),[31] and that its ability to predict OA progression disappears when other factors, such as age, BMI and serum concentration of IL-6, are taken into account.[37,38] Thus, hsCRP level seems to be regulated mainly by proinflammatory cytokines and obesity, and to have no specific effect on OA progression.[37,38]

Cartilage glycoprotein-39 (CGP-39, also known as chitinase-3-like protein 1 and as YKL-40) is a 40 kDa glycoprotein secreted by chondrocytes and synoviocytes. Conrozier *et al.*[39] suggested that CGP-39 could be used as a surrogate marker of joint inflammation in OA, as they found a positive correlation between levels of CGP-39 and CRP in patients with OA.

Fragments of type II collagen or aggrecan are potential biochemical markers of the synthesis and degradation of these proteins, which are largely present in the cartilage matrix, in OA. A combination of these markers is probably required for the monitoring of cartilage turnover, however, since cartilage degradation is a complex process.[40] As well, some obstacles, such as the diurnal variation in the concentrations of these protein fragments, remain to be overcome before these markers can be used in clinical practice.

Finally, the synovial cells of patients with rapidly destructive hip OA, a typical form of inflammatory OA, contain increased concentrations of matrix metalloproteases (MMPs; MMP-3 and MMP-9). Work by Masuhara *et al.*[41] showed that concentrations of these enzymes are also elevated in the synovial fluid, plasma and sera of these patients.

Histopathological features of OA synovitis

Synovium

The histological changes that occur in the OA synovium include hypertrophy and hyperplasia with an increase in the number of synovial lining cells. These changes are often accompanied by infiltration of the sub-lining tissue with scattered foci of mononuclear cells (lymphocytes and macrophages). The infiltration of mononuclear cells into the synovium and the thickness of the synovial lining cell layer seem to be closely correlated.[42] Patients with OA of all grades experience thickening of the synovial lining cell layer, increased vascularity and inflammatory cell infiltration of the synovial membranes, with the most marked changes occurring in advanced OA.[43] Studies of the changes in the synovium that occur at various stages of OA have found that the amount of fibrin deposited in the synovial membrane and the degree of leukocyte infiltration are correlated with disease severity.[9] Although fibrin deposition seems to occur mainly in chronic OA, synovial inflammation is observable from the beginning of the disease process and might exacerbate cartilage damage.[9]

In contrast to the synovial inflammation observed in rheumatoid arthritis (RA), synovial inflammation in OA is not a diffuse process: its distribution is patchy and confined to areas adjacent to sites of chondropathy.[13] Microscopically, however, its appearance can be indistinguishable from that observed in RA,[7] especially in cases of late OA that involve neovascularization and infiltration by fibroblasts and macrophages. The

deposition of calcium pyrophosphate dihydrate (CDDP) crystals is directly linked to radiographically more-severe secondary OA; furthermore, CDDP crystal deposition is known to be acutely proinflammatory. However, a correlation between the presence of CDDP crystals and histological synovitis has not been proven.[44–46] The histopathological changes in the synovium can vary according to the location of the affected joint; in knee OA, for example, fibrosis is more frequently observed in the patellofemoral compartment than in the medial tibiofemoral compartment, where there are a greater number of inflammatory cells and increased pigmentation, vascularity, fragment deposition and synovial hyperplasia.[47,48]

Although these pathological features of the synovium are patent in advanced OA, they are also found in early-stage OA when cartilage damage is less extensive, which suggests that the synovium is involved early in the disease process. Nevertheless, it remains unclear whether the morphological changes that occur in the OA synovial membrane are primary or whether they are the result of joint inflammation, cartilage degradation and lesions of the subchondral bone.[49] Synovitis was found only at sites adjacent to degenerative cartilage in OA patients,[13] but degenerative cartilage is not always completely linked to synovitis. This finding suggests that inflammation is brought about by cartilage-breakdown products.[7] In advanced OA, synovial inflammation is particularly severe in the marginal zone (defined by Shibakawa *et al.*[48] as the region within 5 mm of the joint margin).[48] Surprisingly, the degree of synovial proliferation in OA is sometimes similar to that seen in RA synovitis.[50] In such cases of OA, cells isolated from this synovial tissue share to some extent properties of mesenchymal cells and chondrocytes and express MMPs.[51]

Inflammatory cellular infiltrate

Activated T cells, B cells and macrophages are major components of the synovial infiltrate.[52] Benito *at al.*[8] showed that synovial tissue from patients with early OA contains considerably more $CD4^+$ lymphocytes and $CD68^+$ macrophages and increased levels of blood-vessel formation, intercellular adhesion molecule-1 and vascular endothelial growth factor than tissue from patients with advanced OA. These data suggest that inflammation is more intense during the early phase of OA and that angiogenesis occurs in the inflamed area of the synovium, suggesting crosstalk between vascular and synovial cells.[53]

The T cells that infiltrate the synovium are mainly $CD4^+$, but are accompanied by $CD8^+$ T cells and B cells.[15] The decreased expression of CD3ζ on these $CD4^+$ T cells indicates that they are activated, suggesting that local chronic T-cell stimulation is involved in OA.[54] The organization of T cells in the synovium becomes angiocentric, mainly in perivascular areas.[55] The T cells seem to be activated *in situ* in the synovial membrane after exposure to antigens and express leukocyte and endothelial adhesion molecules but less abundantly than in RA.[56] These infiltrating T cells exhibit a restricted repertoire in OA: the reported presence of similar T-cell receptor (TCR) Vβ rearrangements in different OA patients indicates oligoclonal expansion.[52] This finding was confirmed in other studies that showed the restricted expression of the TCR Vα and Vβ genes.[57] Thus, the T-cell response in OA seems to be directed against common antigenic targets that may be autoantigens in the cartilage or synovium, and to involve antigen-presenting cells. Clonally expanded T cells in the OA synovial membrane could initiate and/or amplify the inflammation process. A study highlighting the reactivity of T cells towards chondrocyte membranes suggests that the antigens could come from products of cartilage breakdown.[58] Two possible autoantigens in this process are chitinase-3-like protein 2 (also known as YKL-39), a protein derived from human cartilage, and type II collagen, but the data are somewhat conflicting.[55,59,60] Patients with OA also seem to express cellular immunity to proteoglycan link proteins.[61] $CD8^+$ T cells that are cytotoxic for common herpesviruses (such as Epstein–Barr virus and cytomegalovirus) have been reported in patients with OA, but the direct involvement of these cells in the disease process needs to be elucidated since they can accumulate nonspecifically in the OA synovium.[55,62]

B cells are rarely found in the OA synovial membranes but those that are present exhibit an activated state.[63,64] These activated B cells could be attracted by the presence of CXC-chemokine ligand (CXCL) 13, a potent chemoattractant of B cells, in OA synovial membrane lymphoid aggregates.[65] Antibodies against autoantigens such as the breakdown products of type II collagen have been identified in OA cartilage, suggesting that these antibodies are locally produced by synovium-infiltrating B cells.[63,66]

The presence of innate receptors that recognize pathogen motifs in the synovial membrane of patients with OA, such as Toll-like receptor (TLR) 2 and TLR4, implicate innate immunity in the pathogenesis of OA.[67] TLR2 and TLR4 might recognize the hyaluronan and fibronectin usually present in the cartilage OA matrix and thus be involved in synovial activation and inflammation. Although the role of innate immunity in RA has been extensively studied, these preliminary results need further investigation to delineate the involvement of innate immunity in the pathogenesis of OA.

Angiogenesis of the synovium

The normal synovium is highly vascularized as it supplies the physiologically avascular cartilage with nutrients and oxygen. In OA, endothelial cell proliferation is increased; the formation of new vessels is said to be attributable to an imbalance between antiangiogenic and proangiogenic factors.[68] Angiogenesis and inflammation are closely integrated processes and may affect disease progression and pain.[45] Endothelial cell proliferation, macrophage infiltration and inflammation occur to a greater extent in patients with OA than in healthy controls, and are all closely intercorrelated.[45] These processes may affect disease progression and pain. Inflammation can stimulate angiogenesis and, in turn, angiogenesis can facilitate inflammation. Angiogenesis in the synovium is closely associated with chronic synovitis and may occur at all stages of OA.[53] The production of proangiogenic vascular

endothelial growth factor (VEGF) is increased in the OA synovium, indicating neovascularization.[53] Hypoxia, acting through hypoxia inducible factor-1α , could also be involved because this factor is co-localized in the osteoarthritic synovium with increased microvascularity and the overproduction of proangiogenic factors. Indices of endothelial cell proliferation are lower in OA than in RA, although vascular densities are similar between the two diseases. However, the degree of angiogenesis is occasionally similar in the two diseases.[69] Although levels of VEGF are usually higher in RA synovial fluid than in OA synovial fluid, its concentration in synovial tissues seems to be similar in both diseases.[70,71]

Angiogenesis could contribute to the transition from acute to chronic inflammation[68] by potentiating and perpetuating, rather than initiating, inflammation.[45] Adhesion molecules in new vessels, such as E-selectin, may facilitate inflammatory cell infiltration.[72] In addition, the inflammatory response is maintained by the transportation by new vessels of inflammatory cells, nutrients and oxygen to the site of inflammation. Finally, angiogenesis promotes itself by increasing cell infiltration.[45]

Inflammatory mediators

The inflammatory mediators detected in OA synovial fluid can come from the three tissues that undergo histological modification—cartilage, subchondral bone and the synovium. Two major cytokines involved in the pathogenesis of OA, IL-1β and tumor necrosis factor (TNF), are mainly produced by activated synoviocytes, mononuclear cells and articular cartilage. In OA, the equilibrium between IL-1β and its natural antagonist, the IL-1 receptor antagonist (IL-1Ra), could favor IL-1β because relatively little IL-1Ra is produced.[61] The synovium also contains supranormal amounts of IL-6, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF) and chemokines (IL-8, also known as CXCL8, and monocyte chemotactic protein-1, also called CC-chemokine ligand 2), as well as of vascular cell adhesion molecule-1 and intercellular adhesion cell molecule-1.[43,48,50] The supernatants of cultures of OA or RA synovium contain IL-1β, TNF and IL-8.[50] The synovial fluid of patients with early OA (that is, patients with knee pain, normal radiographs and arthroscopic manifestations of OA) has been shown to contain more IL-1β and TNF than that of patients with late OA (that is, patients needing joint arthroplasty).[8]

Whereas the RA synovium secretes more IL-1, IL-6, endothelial growth factor and IL-10 than does the OA synovium, concentrations of TNF, IL-8, tissue inhibitor of MMP-1 (TIMP-1) and prostaglandin E_2 (PGE_2) are similar in advanced OA and RA.[8,50,73,74] Consequently, some researchers consider the main difference between the OA and RA synovia to be the amounts of cytokine released.[50,73,74] The differences in the profiles of released cytokines and mediators according to the stage of the disease could be related to differences in mononuclear cell infiltration.[8]

IL-1β and TNF can stimulate their own production in an autocrine manner because synovial fibroblasts bear high concentrations of the IL-1β receptor and the TNF receptor TNF-R55.[75,76] These cytokines can also stimulate chondrocytes and synovial cells to produce other cytokines (IL-6, IL-8, leukocyte inhibitory factor) and PGE_2. All these proinflammatory cytokines are thought to diffuse into the synovial fluid and act on the cartilage matrix and chondrocytes from a distance.

Several of the cell types present in the OA synovium could be responsible for the observed synovial inflammation. Elegant studies on the depletion of synovial macrophages have shown that TNF and IL-1β in the OA synovium are produced mainly by $CD14^+$ synovial macrophages;[77] the depletion of these macrophages leads to decreased levels of IL-1β and TNF, which may in turn inhibit the release of IL-6, chemokines (IL-8, monocyte chemotactic protein-1) and MMPs (MMP-1 and MMP-3). Thus, macrophages seem to drive the inflammatory and destructive responses of the synovial fibroblasts by way of the combined effects of TNF and IL-1β.

Another proinflammatory cytokine, IL-17, also induces OA synovial fibroblasts to produce proangiogenic factors by acting alone and in cooperation with TNF.[78] IL-17 also contributes to cartilage inflammation by stimulating chondrocytes and synovial fibroblasts to release chemokines such as IL-8 and growth-regulated α protein (also known as GRO-α) that are involved in attracting mononuclear cells and in chondrocyte differentiation.[79] However, although the IL-17 receptor has been clearly identified in chondrocytes, this cytokine does not seem to be produced locally in most cases of OA.[80]

IL-15, a cytokine produced in innate immune responses, could be involved in early OA since higher concentrations of IL-15 are found in the synovial fluid of patients with early OA than in those with end-stage OA.[81] Its receptor (IL-15Ra) is present on the cells of the synovial lining layer and endothelium. IL-15 may stimulate MMP production and the recruitment or survival of $CD8^+$ T cells within the OA joint.[81] Another cytokine, IL-21, which shares a common γ-chain with IL-15, is also present at high concentration in the early-OA synovium.[81]

The OA synovium also contains adipokines that are classically released by adipose tissue, such as visfatin (also called nicotinamide phosphoribosyl transferase), adiponectin and leptin, but their synovial concentrations are usually lower in OA than in RA. These adipokines might also be involved in the pathogenesis of OA as mediators of inflammation and cartilage degradation.[82,83] Synovial tissue seems to be the main source of adipokines in the OA joint.[83]

Neuropeptides in the OA synovium

The responses of patients with symptomatic OA to everyday stimuli are exaggerated as a result of changes in the function of the joint nociceptive system. The source of pain in OA is not the cartilage, which contains no pain fibers. Nociceptive fibers have, however, been described in the joint capsule, synovium, meniscus, bone marrow, periosteum and subchondral bone, and in the marrow cavities of osteophytes.[84,85]

Chronic synovitis is associated with marked changes in the central connections of sensory nerves, and with changes in the synthesis and release of neurotransmitters and neuromodulators.[86] Inflammatory mediators contribute to pain by activating high-threshold receptors or by sensitizing these receptors to other stimuli.[87] Proinflammatory cytokines such as TNF, IL-6 or IL-1β can cause hyperalgia indirectly (via increasing the release of prostaglandin) or directly (by acting on nociceptive neurons).[87] However, few data are available on the nociceptive actions of inflammatory mediators in the OA synovium. In addition to their role in pain, neuropeptides are involved in vasodilation, inflammation (by activating inflammatory infiltrating cells and by producing proinflammatory cytokines), osteoclast formation, and synoviocyte proliferation and activation.[49]

The vasodilator and inflammatory peptide bradykinin is generated in the OA synovium, which also expresses the bradykinin receptor. Bradykinin contributes to the initiation and maintenance of inflammation, and to the excitation and sensitization of sensory nerve fibers, acting synergistically to potentiate the effects of proinflammatory cytokines. The intra-articular administration of a specific bradykinin B2 receptor antagonist has been reported to produce a long-lasting analgesic effect in patients with knee OA.[88]

The neurotransmitter substance P mediates proinflammatory signals, vasodilatation and also contributes to pain.[89–91] Substance P is found in the subintimal portion of the synovial membrane and in areas containing osteophytes or cartilage erosions;[49] it is involved in joint inflammation, in inducing the production of PGE_2 and collagenases by synoviocytes, and in the proliferation of synoviocytes themselves.[92]

The β-endorphin met-encephalin is less abundant in OA joints than in RA joints; it is found in macrophages/monocytes (type A synoviocytes), lymphocytes and plasma cells, but little is found in fibroblast-like synoviocytes in the OA synovium. The opioid receptors (μ and δ) are also found on immune cells and on sensory nerve endings in both the RA and OA synovia.[93] Other neuropeptides, such as corticotropin-releasing factor, urocortin and vasoactive intestinal peptide, could also have a role in OA pain and in the perpetuation of synovial inflammation and cartilage degradation.[49] For example, nerve growth factor (NGF) is produced by the OA synovium, and its production is stimulated by proinflammatory factors such as IL-1β and TNF.[94] Synovial cells express the NGF receptor and are thus sensitive to NGF. In addition to its known roles in pain transmission and hyperalgesia,[95] stimulation of proinflammatory cytokines (IL-1, IL-2, IL-6, IL-8, TNF), and leukocyte activation or migration,[94] NGF can stimulate proliferation of the synovium. An antibody against NGF is being investigated as a potential treatment for improving pain and function in human OA.[96]

Pathogenic role of synovitis in OA

Low-grade synovitis may act via the proinflammatory cytokines discussed above and other soluble mediators (nitric oxide, PGE_2, leukotriene B_4) to accelerate the catabolism of articular cartilage and thus contribute to the progression of chondropathy.[49,97] Synovial cells and OA chondrocytes both produce large quantities of MMPs (MMP-1, MMP-3, MMP-9, and MMP-13).[48,51] The main endogenous inhibitor of these MMPs, TIMP-1, is also produced by the synovium. MMP-3 is predominantly synthesized on the border of hyaline cartilage, which suggests that MMP-3 is secreted by OA synovial tissue and acts directly to break down cartilage.[51] MMP-3 has been detected immunohistochemically; its staining (corresponding to its level of expression) is directly correlated with infiltration of the synovium by inflammatory cells.[98]

In addition, functional MMP-2 is produced by synovial fibroblasts in horses.[99] The production of the aggrecanase ADAMTS-4 (a disintegrin and metalloprotease with thrombospondin motifs 4) is mainly driven by TNF and thus is indirectly driven by synovial macrophages. Synovial macrophages seem to be crucial for the induction of synovial MMP-3 in an experimental model of OA cartilage,[100] where they lead to the generation of the MMP-neoepitopes that are responsible for perpetuating cartilage breakdown. MMP-mediated cartilage damage is not possible without macrophage activation.[100] These synovial macrophages also produce pro-MMP-9, which is activated to active MMP-9 via the MMP-3 or MMP-13 pathway.[101]

Synovial macrophages have extrainflammatory functions in OA pathogenesis. The depletion of synovial macrophages by intra-articular injection of clodronate-laden liposomes into knees inhibited the formation of transforming growth factor-β-induced osteophytes.[100,102,103] Thus, synovial macrophages are crucial intermediaries in transforming growth factor-β-induced formation of osteophytes, perhaps via the secretion of bone morphogenetic proteins (BMPs) such as BMP-2 and BMP-4, or via a chondrogenic signal that acts on mesenchymal stem cells, or in both ways.

The mediators that affect the activation of synovial macrophages have not been clearly identified. If they come from cartilage, this would suggest that the involvement of synovial macrophages in the pathophysiology of OA is a secondary process. Nevertheless, macrophages could be involved in the early stages of OA pathogenesis. Likewise, activated macrophages release IL-1β, which may stimulate the synovium in a paracrine–autocrine manner to produce MMPs and to generate the neoepitopes responsible for a synovial T-cell immune response, as illustrated by TCR-rearrangement studies.[53–57] The presence of activated T cells and of interferon-γ and IL-2 (cytokines associated with a type 1 helper T [T_H1] cell response) in chronic joint lesions of patients with OA suggests that T cells truly contribute to chronic inflammation, even though they are less abundant than in the RA synovium.[56] This T_H1-like cytokine pattern could be driven by IL-12 released by macrophages, which is a potent inducer of T_H1 cytokines and that is produced in the synovial membranes of patients with OA.[56]

Together these data indicate that, while synovitis could be affected in early OA, synovial inflammation can also be caused by the breakdown products of the extracellular matrix produced by mechanical stress and tissue-breakdown enzymes (Figure 1). Once cartilage degradation has begun, the synovial cells phagocytose the breakdown products released into the synovial fluid, resulting in the synovial membrane becoming hypertrophic and hyperplasic. These enzymes then activate synovial cells to cause the release of proinflammatory cytokines, collagenases and other hydrolytic enzymes. Consequently, a vicious positive-feedback loop involving cartilage breakdown and synovial inflammation occurs.

To counteract this inflammatory response, the synovium and cartilage may produce anti-inflammatory cytokines, including IL-13, IL-4, IL-1Ra and IL-10 (Figure 1). These cytokines have been shown to be spontaneously produced by the synovial membrane and are present in the synovial fluid of patients with OA.[61] They decrease the release of PGE_2, IL-1β, TNF and MMPs, and stimulate the production of IL-1Ra and TIMP.[104] Additionally, IL-4 and IL-13 can inhibit the apoptosis of synoviocytes, thus contributing to synovial hypertrophy.[49]

The synovium could—in addition to its effects on cartilage inflammation and breakdown in OA via MMPs and ADAMTS—be involved in bone matrix remodelling. Synovial macrophages can differentiate to form functional osteoclasts capable of bone formation and resorption.[105] Moreover, mature, activated osteoclasts have been found in rapidly destructive OA that are not found in common OA.[106] These data show that the synovium has a major role in the osteoclastogenesis of subchondral bone in OA.[106]

Synovitis as a target for new therapies

Non-targeted therapies

Classical non-targeted strategies for treating OA, such as the use of NSAIDs and local and systemic administration of steroids, can modulate synovial inflammation in OA and substantially affect pain and stiffness during both acute flares and chronic complaints. Chondroitin sulfate acts on chondrocytes and reduces the inflammatory activity of synovitis. Animals with collagen-induced arthritis given high doses of chondroitin sulfate for 9 weeks showed decreased inflammatory cell infiltration and synovial cell proliferation.[107] In addition, randomized controlled studies found that chondroitin sulfate had a beneficial effect on patients with moderate pain and signs of synovitis (joint swelling and effusion).[107] This drug may have an anti-inflammatory effect by acting directly on the synovium in OA, perhaps by reducing the nuclear translocation of the transcription factor NFκB in synoviocytes and macrophages and so reducing cell activation and decreasing synovitis.[107]

Targeted therapies in development

The synovial membrane is a promising target for novel strategies to prevent structural alterations and treat clinical symptoms.[108] Designed to interfere with specific targets, these novel therapies include antifibrotic agents, biologic molecules such as anti-TNF agents, anti-NGF antibodies, antiproteases (anti-MMPs and ADAMTS) and bradykinin-blocking agents.[108–112] Studies are underway to assess the effects of systemic TNF-blocking agents in OA, although local IL-1 blockade has not been markedly beneficial.[113] Data concerning the role of IL-6 in OA pathogenesis suggests that IL-6-targeted therapy could be an interesting approach to treating OA.[114,115]

Future directions for research

Many of the studies on the role of synovitis in OA cited in this Review are recent, but several issues remain to be elucidated by future research. With respect to imaging, the correlation between imaging data and clinical outcomes needs to be clarified, and a comparison of MRI and ultrasonography in terms of their relative sensitivity, specificity and prognostic value would also be worthwhile. The relative impact of each cytokine produced by synovial tissue on OA pathogenesis needs further study. More research is also needed to define the roles of the various cell types present in synovial tissue. The communication pathways between cartilage, subchondral bone and synovial tissue are not yet clearly understood, nor is the role of synovial neovascularization in the pathogenesis of OA. Finally, the influence of mechanical stress on synovial tissue remains to be fully appreciated.

Conclusions

Clinical symptoms of inflammation, the presence of histological inflammation in OA synovial tissue and early cartilage lesions at the border of the inflamed synovium are strong indicators that synovitis is a pivotal factor in the pathogenesis of OA (Box 1). The traditional view of OA as a cartilage-only disease is obsolete. OA should now be considered to be a whole-joint disease that includes the synovial tissue. Bone, cartilage and synovium communicate by way of cell–cell interactions, through the release of soluble mediators and via mechanical signals. Synovial inflammation, despite not being a prerequisite for the development of OA, is clearly involved in cartilage breakdown and thus in the progression of the disease. Targeting the inflammatory synovium should delay or prevent articular cartilage damage and the formation of osteophytes, especially in early OA. Preclinical and/or clinical studies of anti-cytokine molecules and inhibitors of signaling pathways will help to clarify the role of synovitis in OA.

Review criteria

A large number of potential references for this Review were collected from PubMed as well as from the authors' personal collections. We performed a systematic review of the literature by searching PubMed for papers published up to December 2009 using the following MeSH terms: "osteoarthritis" in combination with "synovitis" or "synovium". This search was completed by a manual search for relevant studies. The references for this Review were limited to papers published in English or French, and were selected according to their relevance to the topic and following critical discussion.

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Author contributions

J. Sellam and F. Berenbaum contributed equally to researching data for the article, discussion of content, writing and review/editing of the manuscript before submission.