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Review

Osteoarthritis, angiogenesis and inflammation

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Angiogenesis and inflammation are closely integrated processes in osteoarthritis (OA) and may affect disease progression and pain. Inflammation can stimulate angiogenesis, and angiogenesis can facilitate inflammation. Angiogenesis can also promote chondrocyte hypertrophy and endochondral ossification, contributing to radiographic changes in the joint. Inflammation sensitizes nerves, leading to increased pain. Innervation can also accompany vascularization of the articular cartilage, where compressive forces and hypoxia may stimulate these new nerves, causing pain even after inflammation has subsided. Inhibition of inflammation and angiogenesis may provide effective therapeutics for the treatment of OA by improving symptoms and retarding joint damage. This review aims to summarize (i) the evidence that angiogenesis and inflammation play an important role in the pathophysiology of OA and (ii) possible directions for future research into therapeutics that could effectively treat this disease.

KEY WORDS: Osteoarthritis, Synovitis, Angiogenesis, Innervation, Osteophyte, Macrophage, Chondrocalcinosis.

Osteoarthritis (OA) is a group of chronic, painful, disabling conditions affecting synovial joints. The phenomenon of OA may be defined clinically, radiologically or pathologically; however, its aetiology remains poorly understood. As with other complex clinical syndromes, there is often a lack of concordance between the various components that we recognize as OA; for example, there is usually only a weak association between radiological features and pain. OA may be classified according to presumed aetiological factors, as in post-traumatic OA. It can be classified according to the distribution of joints affected; for example, into nodal, knee or hip joint arthritis. Furthermore, OA can be classified according to the presence or absence of associated features, such as chondrocalcinosis. Recent genetic and epidemiological analyses provide further support for these classifications, whilst further emphasizing heterogeneity within the diagnosis.

OA is commonly described as a non-inflammatory disease in order to distinguish it from 'inflammatory arthritis', such as rheumatoid arthritis (RA) or the seronegative spondyloarthropathies. Despite this, inflammation is increasingly recognized as contributing to the symptoms and progression of OA [1, 2]. Morning and inactivity stiffness are common symptoms in patients with the disease, and acute inflammatory flares, characterized by local warmth, tenderness and effusion, are not uncommon. Non-steroidal anti-inflammatory drugs alleviate symptoms of OA and may be more effective than simple analgesics, such as paracetamol [3]. Intra-articular injection of corticosteroids similarly may alleviate both pain and stiffness, not only during acute flares but also as maintenance therapy. Serological or histological evidence of synovitis is commonly found in OA, even though OA has not been consistently associated with specific immune responses.

Pain, the predominant symptom in OA, is multidimensional in its nature and mediated through a variety of factors. The presence or absence of synovitis may be an independent predictor of OA symptoms. The pain experience results from interactions between inflammation and other features of disease, including radiological severity [4], innervation of articular structures [5, 6], central and peripheral sensitization [7] and psychological factors [8]. The precise contribution of inflammation to pain in OA may vary from time to time and from patient to patient. It is currently unclear whether inflammation is a feature of all patients with OA at some stage of their disease, or whether synovitis itself defines one or more disease subgroups.

Inflammation may be both a primary event in OA and secondary to other aspects of the disease, such as biochemical changes within the cartilage. Recent studies indicate that histological and serological evidence of synovitis is an early feature in OA and not restricted to patients with end-stage disease undergoing joint replacement surgery [2, 9, 10]. Synovial inflammation may be detected in the presence of mild or severe cartilage changes in OA [9]. Even when inflammation is secondary to other processes within the osteoarthritic joint, synovitis may yet make an important contribution to the symptoms and pathology of disease. Clinically detectable joint inflammation may predict a worse radiological outcome in OA [11]. Furthermore, in a lapine model of arthritis, joint damage was exacerbated after induction of inflammation in rabbit knees following meniscal tear [12]. Synovitis, therefore, although not a prerequisite for OA, may lead to a poor clinical outcome.

Mechanisms by which synovitis exacerbates structural damage in OA are likely to be complex. Hypotheses have included alterations in chondrocyte function, enhanced angiogenesis and changes in bone turnover [13, 14]. Novel therapeutic interventions aiming to inhibit synovitis in OA may not only improve short-term symptoms but also reduce pain and disability in the long term.

Angiogenesis is the growth of new capillary blood vessels from pre-existing vasculature. It occurs during essential physiological processes, such as embryogenesis, wound repair and the female menstrual cycle. Angiogenesis can also contribute to a variety of pathological conditions, including the unwanted vessel growth in chronic inflammatory diseases, and the growth

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TABLE 1. Angiogenesis regulators localized to or released within osteoarthritic human synovium, synovial fluid and articular chondrocytes

Stimulators		Inhibitors	
Synovial fluid/synovium	Articular chondrocytes	Synovial fluid/synovium	Articular chondrocytes
Bradykinin*	SP [36]	Thrombospondin*	Thrombospondin [57]
SP*	PGE_2 [37]	Interferon-γ*	Leukaemia inhibitory factor [58]
CGRP*	Nitric oxide [38]	Leukaemia inhibitory factor*	Tissue inhibitors of MMP-1 and -2 [59]
Angiotensin II*	Histamine [39]	Tissue inhibitors of MMP-1 and -2 [49]*	TGF-β [44]
PGE_2*	$VEGF_{121/189}$ [15]	TGF-β [19]*	TNF-α [45]
Nitric oxide*	Endoglin [40]	TNF-α [20]*	Chondrocyte inhibitor of angiogenesis [60]
Histamine*	Hepatocyte growth factor [41]	Angiopoietin-2 [16]*	Chondromodulin-1 [61, 62]
$VEGF_{121/189}$ [15]*	IL-1 [42]	Endostatin*	
Angiopoietin-1 [16]*	IL-8 [43]	Hyaluronic acid (high molecular weight)*	
bFGF*	TGF-$\beta_{1/2/3}$ [44]	Platelet factor-4 [50, 51]	
Endoglin*	TNF-α [45]	Somatostatin [52, 53]	
Hepatocyte growth factor*	IL-18 [46]	Bactericidal/permeability-increasing protein [54, 55]	
Epidermal growth factor*	Connective tissue growth factor [47, 48]	IL-4 [35, 36]	
IL-1 [17]*			
IL-8 [18]*			
Angiogenin*			
TGF-β [19]*			
TNF-α [20]*			
Platelet-derived endothelial cell growth factor*			
Endothelial cell-stimulating angiogenesis factor*			
Hyaluronic acid (low molecular weight)*			
IL-18 [21, 22]			
Stem cell-derived factor-1 [23, 24]			
Fractalkine [25, 26]			
Platelet-derived growth factor [27, 28]			
Pleiotrophin [29, 30]			
Soluble E-selectin [31, 32]			
Vascular cell adhesion molecule-1 [31, 33]			
IL-4 [34, 35]			

*Primary references can be found in reference 63.

and metastasis of tumours. The process is regulated by numerous activating and inhibitory factors (Table 1), which may vary from tissue to tissue, between disease and normal physiology, and during different phases of a continuous disease process.

Angiogenesis is a complex multistep process controlled by a wide range of positive and negative regulatory factors (Table 1). Detailed reviews have been published on the angiogenesis process [14, 64–66]. Activated endothelial cells detach from their neighbouring cells, through disruption of vascular endothelial cadherin junctions, resulting in increased vascular permeability. The endothelial basement membrane is degraded by proteolytic enzymes such as matrix metalloproteinases (MMPs), releasing matrix-bound angiogenic factors that, in turn, stimulate endothelial cell migration and proliferation. Capillary tube formation, deposition of a new basement membrane and anastomosis lead to blood flow. Factors produced by endothelial cells, such as platelet-derived growth factor, attract supporting cells such as pericytes, whilst vascular endothelial growth factor (VEGF) and the angiopoietins ensure the stability of the new vessel. The new vessels differentiate into arterioles, capillaries and venules whilst redundant vessels regress, a process that requires endothelial cell apoptosis. Finally, vasoregulatory systems are developed and a fully functional microvasculature is formed.

Synovitis in osteoarthritis

Signs of acute synovitis may be apparent in patients with OA from time to time. However, the extent of subclinical inflammation in OA is now increasingly being recognized. Symptoms differ between acute and chronic inflammation and patients with OA may experience both: acute flares may occur either on the background of chronic synovitis or in an otherwise non-inflamed joint.

Acute inflammation usually has a sudden onset, becoming apparent over minutes or hours with the classic symptoms of heat, pain, redness and swelling. Chronic inflammation develops over a longer period of time and may persist for days, weeks or months. Neutrophils are the most abundant inflammatory cells in acute synovitis, whereas in chronic synovitis in OA, macrophages are most abundant, often with lymphocytic infiltrates [67].

Unlike chronic inflammation, in which inflammation and repair occur concurrently, the host response in acute inflammation leads to elimination of the irritant followed by resolution of the tissue to its original state. During chronic inflammation the joint remains abnormal even after inflammation subsides. Histological evidence of chronic synovitis may be present in the absence of overt clinical signs, and the contribution of chronic synovitis to symptoms of pain and stiffness may be overlooked [9, 68].

The causes of acute inflammatory flares of OA are multiple and incompletely understood. Patients will often attribute flares to particular activities, indicating that physical trauma may play a role. Acute inflammatory flares in OA may also be associated with the presence of calcium pyrophosphate dihydrate (CPPD) or hydroxyapatite crystals within the joint. CPPD crystal deposition is associated with OA of the knee, and manifests as radiological chondrocalcinosis or intermittent acute synovitis (pseudogout). Up to 25% of patients undergoing knee joint replacement surgery for OA have radiological evidence of

chondrocalcinosis on preoperative radiographs (our unpublished observations). Nearly half of patients with chondrocalcinosis who present to a rheumatologist have associated generalized OA [69].

Pain is one of the classic symptoms of acute inflammation. This is mainly due to the sensitization of fine unmyelinated sensory nerves present in the osteoarthritic joint. However, this is not restricted to acute inflammation and chronic inflammation could also be a source of pain in OA.

Chronic synovitis

Evidence and cause of inflammation in OA

There is now much evidence that subclinical inflammation is common in OA, even in the absence of acute inflammatory flares. Circulating markers of inflammation, such as C-reactive protein (CRP), may be elevated in OA compared with control populations without disease [1, 2, 70, 71]. Histological examination of synovium frequently indicates inflammatory cell infiltration, involving macrophages and T cells, increased cell turnover and angiogenesis [9, 72–75]. The recent use of magnetic resonance imaging to study patients with OA of the knee has demonstrated synovial thickening in 73% of patients with relatively early OA [76]. This synovial thickening was found to correspond to mild chronic synovitis [77]. Raised serum CRP may reflect subclinical inflammation in affected joints, mediated by cytokines entering the circulation. IL-6 is up-regulated during synovial inflammation, and can augment inflammatory angiogenesis [78–80]. IL-6 is thought to be the chief stimulator of CRP production [81]. IL-6 is produced by synovial cells, osteoblasts and chondrocytes, and is detectable by immunoassay in synovial fluid samples that have been harvested from joints affected by OA [82–84].

The causes of chronic synovitis in OA remain poorly understood. Fragments of cartilage (often referred to as 'debris') may be found within the synovium associated with giant cells typical of foreign body type reactions. Haemosiderin deposition suggests a possible role for recurrent minor haemarthrosis in some patients. Histological synovitis has also been described in patients with chondrocalcinosis, even in the absence of an acute flare [85], and it is likely that histological synovitis is more common in OA with chondrocalcinosis than in OA alone. CPPD crystals can be identified in synovial tissue and fluid from patients with chondrocalcinosis between attacks of acute synovitis, when they may be associated with histological evidence of chronic synovitis [85, 86]. In addition to their acute effects on neutrophils, CPPD crystals can induce the expression of inflammatory, angiogenic factors such as TNF-α, IL-6 and IL-8, by monocytes and macrophages, and they can also stimulate cell proliferation [87–90]. CPPD crystal types with a low propensity to induce acute inflammation may therefore contribute to chronic synovitis and angiogenesis in chondrocalcinosis.

Inflammation, pain and joint damage

The symptoms of chronic synovitis are less well understood than those of acute inflammation. Features of inflammation, such as minor elevations of CRP and infiltration of macrophages into the synovium and even lymphoid aggregates, are not necessarily associated in OA with the classic signs of inflammation; heat, redness, soft tissue swelling or effusion. Chronic synovitis is associated with marked changes in the central connections of sensory nerves, and changes in their synthesis and release of neurotransmitters and neuromodulators [7]. Furthermore, there is increased turnover of cells within the inflamed synovium: fibroblasts and blood vessels proliferate, macrophages are recruited, and there is increased cellular apoptosis [14]. Turnover within the synovial tissue is accompanied by retraction and growth of sensory nerve terminals [91, 92]. Peripheral nerve growth and injury are closely associated with enhanced pain sensation [93].

The ability of inflammation to cause pain depends upon the sensory innervation of the joint. Fine unmyelinated sensory nerves containing neuropeptides such as substance P (SP) and calcitonin gene-related peptide (CGRP) have been localized to the synovium, ligaments, tendons, menisci and the osteochondral junction in normal and osteoarthritic joints [92, 94, 95]. Such nerves may mediate slow, burning pain, as described by many patients with OA. Myelinated nerve fibres in the joint capsule and intra-articular structures may mediate the sudden pain on movement or pressure.

During inflammation, chemicals such as adenosine, prostaglandin (PG) E_1 and $PGF_{2\alpha}$, leukotriene B_4 and (8R-15S)-dihydroxyeicosa-(5E-9,11,132)-tetraenoic acid (8R-15S-diHETE) are released within the joint, where they sensitize nerves, resulting in increased firing to a given stimulus [96]. At the same time, inflammatory mediators such as bradykinin, histamine, 5-HT, PGE_2, prostacyclin and acidosis stimulate nerves even in the absence of mechanical stimulation [95, 97]. Over a period of hours or days, recruitment of inflammatory cells and up-regulation of genes within the synovium generates cytokines such as IL-1, IL-6, IL-8 and TNF-α, in addition to nerve growth factor [97]. These factors further enhance peripheral sensitization, whilst neuronal plasticity contributes to central sensitization.

Inflammation may exacerbate cartilage degradation in osteoarthritis (Fig. 1). Patients with OA in whom radiological scores progress rapidly tend to have higher serum concentrations of CRP at baseline than do those whose disease progresses slowly [1, 2]. TNF-α and IL-1 stimulate chondrocytes to produce MMPs and plasminogen activator, which degrade matrix proteoglycans and collagen [98, 99]. Chondrocytes also produce further IL-1 that acts in an autocrine manner and further stimulates MMP and plasminogen activator production [42]. As discussed below, stimulation of angiogenesis by synovitis may also contribute to progressive joint damage in OA.

Angiogenesis and inflammation

Angiogenesis and chronic inflammation are closely integrated processes. Inflammation can stimulate angiogenesis, and angiogenesis can facilitate inflammation (Fig. 1). However, although chronic inflammation is almost always accompanied by angiogenesis, angiogenesis can occur in the absence of inflammation.

Inflammatory angiogenesis

Inflammatory mediators can either directly or indirectly stimulate angiogenesis. Inflammatory cells that produce these factors include the macrophages and mast cells that are present in abundance in chronically inflamed osteoarthritic synovium. There are some general mechanisms by which macrophages can induce angiogenesis. New vessel growth can be stimulated directly by factors secreted from macrophages [100]. Macrophages can be found in most sites where abnormal angiogenesis is occurring, for example in synovitis and in tumours. Many of the inflammatory mediators produced by these macrophages induce angiogenesis *in vivo* (Table 1). Macrophages can also secrete factors that stimulate other cells, such as endothelial cells and fibroblasts, to produce angiogenic factors such as VEGF [67, 78, 101].

Although not as well defined, neutrophils and lymphocytes have also been implicated in the induction of angiogenesis. Angiogenic factors such as basic fibroblast growth factor

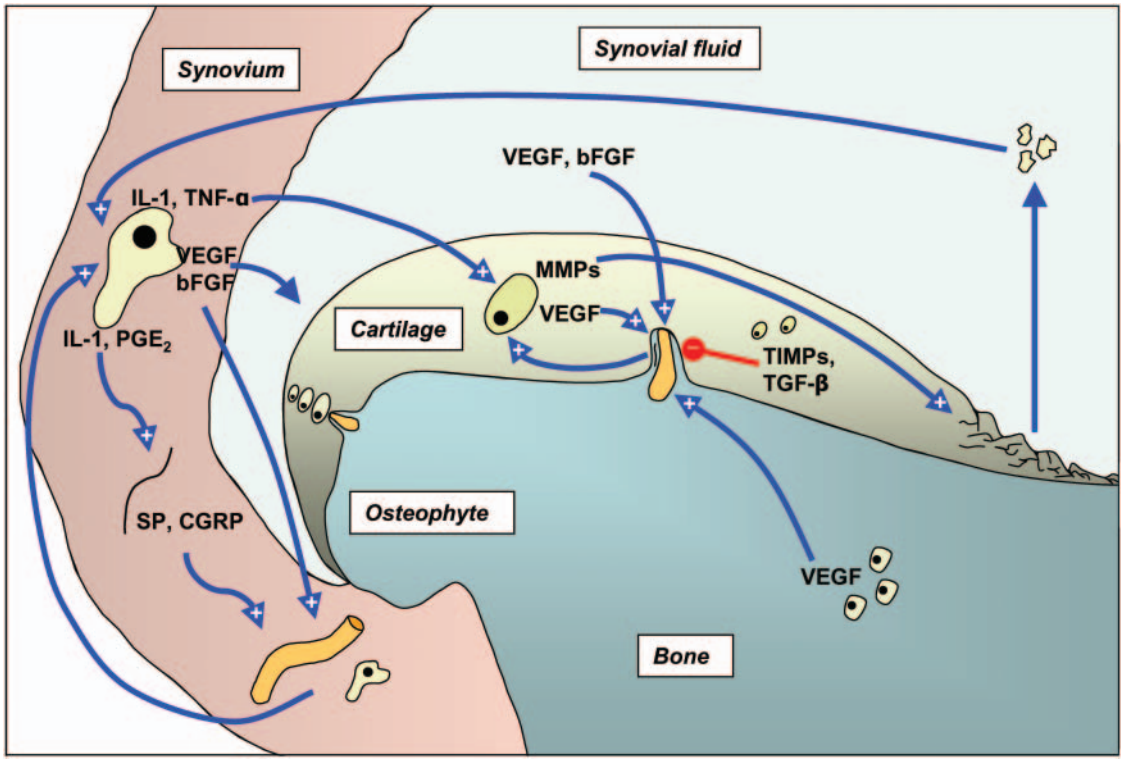

FIG. 1. Interactions between inflammation and angiogenesis in the osteoarthritic joint. Blood vessel growth is regulated by a balance between angiogenic and anti-angiogenic factors within the joint. Inflammation may facilitate angiogenesis directly through the release of growth factors from cells such as macrophages, and also by stimulation or sensitization of other cells, such as chondrocytes, nerves and osteoblasts, that in turn release additional angiogenic factors. Angiogenesis at the osteochondral junction leads to endochondral ossification and the formation of osteophytes. Angiogenesis and joint damage further exacerbate inflammation. New vessels, which breach the tidemark may later become innervated and could be a source of pain. Through these mechanisms, angiogenesis and inflammation can contribute to pain and joint damage in OA. bFGF, basic fibroblast growth factor; CGRP, calcitonin gene-related peptide; IL-1, interleukin-1; MMP, matrix metalloproteinase; PGE_2, prostaglandin E_2; SP, substance P; TIMP, tissue inhibitor of metalloproteinases; TGF-β, transforming growth factor-β; TNF-α, tumour necrosis factor-α; VEGF, vascular endothelial growth factor.

(bFGF) and VEGF may be produced by lymphocytes, and neutrophils may be involved in the early induction of angiogenesis [67, 102, 103].

As well as inflammatory cells, inflammatory conditions can also stimulate angiogenesis. Tissue hypoxia often occurs in inflamed tissue and is a potent stimulator of angiogenesis [104]. VEGF gene expression is up-regulated during hypoxia and it is thought that this stimulation of angiogenic factors is an attempt to relieve the low oxygen content of the tissue [104, 105]. Plasma extravasation and fibrin deposition also result in the generation of angiogenic factors such as kinins [106].

Angiogenesis is observed in the synovium of osteoarthritic joints, closely associated with chronic synovitis [63, 107]. The normal synovium is highly vascular in order to supply the normally avascular cartilage with nutrients and oxygen. In OA, increased endothelial cell proliferation is associated with new vessel formation [63]. Concurrent vascular regression results in little overall change in vascular density [73]. Instead, there is a redistribution of vessels within the synovium and a change towards a more immature phenotype [108]. Increased vascular turnover in the osteoarthritic synovium reflects a change in the balance between angiogenic and anti-angiogenic factors (Table 1). The extent of endothelial cell proliferation increases with increasing vascular density, increased macrophage infiltration and increased VEGF expression within the synovium, indicating that synovial neovascularization may be largely driven by synovitis [9]. Up-regulation of hypoxia inducible factor-1α in the osteoarthritic synovium is also associated with increased microvascular density and expression of angiogenic factors, indicating that hypoxia may play an additional mediating role [109].

The extent of angiogenesis and inflammation can vary widely between different patients with OA. Endothelial cell proliferation indices in synovia from groups of patients with OA are generally lower than those in RA, although vascular densities are similar [73]. However, angiogenesis in synovia from some patients with OA may reach levels comparable to some of the highest seen in RA [73]. Synovial fluid and serum levels of the angiogenic factor VEGF may be higher in groups of patients with RA compared with OA [110, 111]. However, VEGF levels in the synovial tissue of patients with OA have been found to be similar to those found in RA [112]. Also the formation of tubular networks that morphologically resemble capillaries have been induced to similar extents by synovial fluids from patients with OA or RA [113]. Some authors have, however, reported that synovial fluids from OA patients can display lower angiogenic potential than patients with RA [114]. The severity of histological inflammation in synovia from patients with OA can also reach similar levels to those observed in RA [9, 72]. Systemic markers of inflammation such as CRP are elevated in OA, but generally to a lesser extent than in RA [115].

Synovial inflammation and angiogenesis are enhanced in a substantial proportion of patients with OA. It remains unclear, however, whether this heterogeneity observed in cross-sectional studies reflects subgroups of patients with 'inflammatory OA', or inflammatory episodes that are common to all patients with OA. Synovial angiogenesis and inflammation are observed across the

full range of disease severity, indicating that they are not unique to early- or late-stage disease [2, 9, 72].

Contribution of angiogenesis to inflammation

Angiogenesis may be most important in potentiating or perpetuating inflammation rather than in initiating it. Increased permeability of newly formed blood vessels to macromolecules facilitates oedema formation [116]. Adhesion molecules such as E-selectin are highly expressed by new vessels, facilitating inflammatory cell infiltration [117, 118]. The inflammatory response can also be maintained by new vessels transporting inflammatory cells, nutrients and oxygen to the site of inflammation [119]. It is also thought that deficient neural and peptide regulatory factors in the neovasculature may impair the vascular regulation of inflammation [120]. Angiogenesis may indirectly promote itself by increasing inflammatory cell infiltration, thereby increasing the availability of angiogenic factors produced by these cells. It has been speculated that, during early synovitis, angiogenesis may contribute to the transition from acute to chronic inflammation [14].

Angiogenesis in the bone and cartilage of osteoarthritic joints

Angiogenesis occurs at the osteochondral junction as well as within the osteoarthritic synovium. Vascularization of the articular cartilage and osteophytes is characteristic of the pathology of OA [15]. The normal articular cartilage is avascular in the adult [60]. A deep layer of calcified cartilage lies between the tidemark and the osteochondral junction. Blood vessels may penetrate the calcified cartilage within fibrovascular channels originating from the subchondral bone [121]. With increasing severity of OA, these vascular channels breach the tidemark, and blood vessels may be found more superficially in the non-calcified articular cartilage. Blood vessels within the deep layers of the osteoarthritic articular cartilage are derived from the vasculature that is normally present in subchondral bone.

As in the synovium, vascularization of the articular cartilage may also be due to a change in the balance between angiogenic and anti-angiogenic factors (Table 1). Osteoarthritic articular cartilage displays reduced resistance to invasion by blood vessels in the chick embryo chorioallantoic membrane assay [122]. The sources of angiogenic signals to the subchondral bone remain poorly understood. Hypertrophic chondrocytes within the deeper layers of articular cartilage produce angiogenic factors [15] (Fig. 1). With disruption of the tidemark, angiogenic factors may also reach the osteochondral junction by mass transport and diffusion from the synovium through synovial fluid and the cartilage matrix [123]. Synovial fluids from patients with OA may stimulate endothelial tube formation *in vitro* [113], and synovial tissues and fluids from patients with OA contain a variety of angiogenic factors (Table 1 and Fig. 1). The subchondral bone may itself contribute or support angiogenic stimuli within the osteoarthritic joint, through expression of angiogenic factors by osteoblasts [124] (Fig. 1).

Endochondral ossification is the formation of calcified bone within a cartilage scaffold, and is the normal mechanism of growth at the epiphyses of long bones. Differentiated chondrocytes proceed through a series of late differentiation steps, resulting in mature hypertrophic chondrocytes that express alkaline phosphatase and secrete matrix proteins such as collagen X [125]. Hypertrophic chondrocytes then undergo apoptosis, leaving a cartilaginous matrix that is mineralized prior to the formation of new bone [126]. Where endochondral ossification is undesirable, for example in normal articular cartilage, this late chondrocyte differentiation is subject to negative regulation.

Angiogenesis is required for endochondral ossification [127]. In growing long bones, hypertrophic chondrocytes produce angiogenic factors, including VEGF [125]. New blood vessels grow from the underlying bone into channels created by the chondrocytes. In turn, arrest of late chondrocyte differentiation may be overcome by factors produced by vascular endothelial cells, including proteases and bone morphogenic proteins [125, 128, 129]. Vascular invasion of articular cartilage may, therefore, further stimulate chondrocyte differentiation with a switch to collagen I and X production [122]. Chondrocytes induce vascular invasion, and vascular invasion is a prerequisite for new bone formation. Inhibition of endogenous angiogenic factors, VEGF for example, impairs endochondral ossification, resulting in hypertrophy of the cartilaginous growth plate [130].

Fibrovascular channels within the articular cartilage are typically cuffed with bone, although their tips may be in direct contact with the cartilage. It is likely that this new bone formation at the osteochondral junction recapitulates, in some respects, endochondral ossification in the growth plate and that the new blood vessels contribute to bone formation [127]. The articular cartilage in OA becomes thinner, therefore, not only by loss of articular surface but also through an advancing wave of ossification at the osteochondral junction.

The growth of osteophytes at the joint margin also occurs through the process of endochondral ossification [131] (Fig. 1). Cartilaginous extensions of the articular surface become invaded by blood vessels, and bone extends from the subchondral structures. The bony core of the fully developed osteophyte contains trabeculae and marrow cavities that are continuous with the adjacent subarticular bone, with no clear boundary between the two [131].

Angiogenesis and the sensory nervous system

Angiogenesis and pain

Whereas a contribution of angiogenesis to inflammation is by now generally accepted, the role of angiogenesis in pain remains less well established. As discussed above, any facilitation of inflammation may itself contribute to the symptoms of pain. New vessel formation may, in addition, facilitate pain through structural reorganization of the joint.

Capillary growth can occur over a period of days and differentiation of blood vessels into arteries and veins occurs over days or weeks. Innervation is a more protracted process. Peripheral nerves do not proliferate, but rather grow by neurite extension or arborization. Growth of fine unmyelinated sensory nerves follows angiogenesis in a wide variety of tissues [94, 120]. Sensory nerves can be localized within polyether sponges approximately 2 weeks after subcutaneous implantation in rats [120]. Full-thickness skin grafts in man, however, may remain only partially innervated many years after grafting [132]. Growing and damaged peripheral nerves display sensitization, and are associated with increased pain sensation [93]. It is likely, therefore, that the neo-innervation that follows from angiogenesis may itself contribute to the pain experience during chronic synovitis.

Some articular structures are not normally innervated, for example articular cartilage and intervertebral discs [60]. In OA, the articular cartilage becomes vascularized, and these new vessels may be associated with new sensory nerves [133] (Fig. 1). Osteophytes are new bony structures that develop by endochondral ossification at the borders of the osteoarthritic joint [131]. Angiogenesis is an essential stage in endochondral ossification and sensory innervation of the osteophyte may in part explain the association between radiological osteophytosis and pain reporting. In so-called degenerative disc disease, intervertebral discs are invaded by blood vessels which themselves may be accompanied by sensory nerves [134, 135]. High compressive

forces, hypoxia and acidosis within the articular cartilage and intervertebral disc may stimulate these new nerves, thereby contributing to persistent pain even after inflammation has subsided.

Sensory nerves as mediators of angiogenesis and inflammation

Fine unmyelinated sensory nerves not only respond to inflammation; they may also initiate or facilitate inflammation through the release of vasoactive substances into the joint (Fig. 1). Neuropeptides such as SP and CGRP are released into peripheral tissues, where they act on specific cell surface receptors localized to blood vessels. SP enhances plasma extravasation through interaction with the neurokinin NK_1 class of G protein-coupled receptor, and CGRP is a potent vasodilator [136–138]. Activation of sensory nerves causes the classic wheal and flare responses of acute neurogenic inflammation [96]. More recently, evidence has accumulated that persistent activity in fine unmyelinated nerves is accompanied by cellular infiltration ('neurogenic chronic infiltration') [139]. Furthermore, SP and CGRP can enhance endothelial cell proliferation, migration and capillary tube formation *in vitro*, and angiogenesis *in vivo* [140–142]. Recent work with specific NK_1 receptor antagonists has revealed that endogenously released SP contributes to the early stages of angiogenesis in capsaicin- and carrageenan/kaolin-induced synovitis [143, 144]. Neuropeptides interact with other acute inflammogens such as bradykinin during the initiation of angiogenesis in acute inflammation [144].

Therapeutic implications

Pharmaceutical agents designed to modify the progress of inflammation in rheumatological conditions have largely been developed for RA. The intensive search for anti-angiogenic agents has been driven by therapeutic potential in oncology. The mechanisms of inflammation and angiogenesis may differ between OA, RA and cancer but this need not exclude the application of existing therapies to diseases that were previously thought of as 'degenerative'. Perhaps the greatest therapeutic potential, however, will come from finding mechanisms of inflammation and angiogenesis that are disease-specific. Drugs that broadly inhibit inflammation or angiogenesis may have limited applicability to OA because of the potential toxicity that follows the inhibition of such biologically important processes. Patients' desire to take medications is often determined by short-term gains, and targeting inflammation may be attractive in OA if, in addition to retarding disease progression, it relieves symptoms of pain and stiffness. Treatments that only improve long-term prognosis may yet be desirable to patients even in the absence of short-term symptomatic benefits. This is particularly the case when rapid determination of efficacy is possible, as with anti-hypertensive therapies and cholesterol lowering agents. Angiogenesis inhibitors could fall into this group for OA if biomarkers can be identified that predict long-term success in clinical trials.

The testing of potentially disease-modifying agents in OA requires large numbers of patients studied for years due to the normally slow progression of the disease and the relative insensitivity to change of existing radiological outcomes. It is understandable, therefore, if pharmaceutical companies are only willing to undertake such studies when there is good preclinical evidence of likely efficacy. Much has been learnt over the past few years on the characteristics of inflammation and angiogenesis in human OA. Animal models of OA, however, have often been developed with cartilage pathology in mind, and the roles of angiogenesis and inflammation in these models remains uncertain. Further studies over the next few years are likely to overcome many of these technological difficulties, raising the hope of therapeutic advance in the foreseeable future.

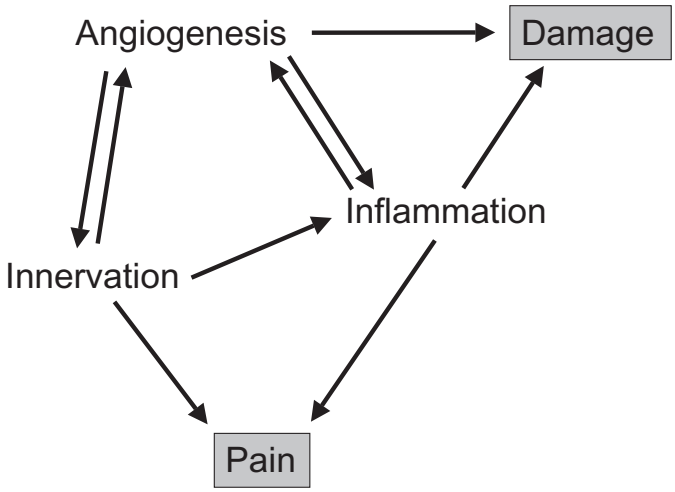

FIG. 2. Summary of the relationship between inflammation, neurovascular plasticity and the symptoms of osteoarthritis. Inflammation can stimulate angiogenesis, and angiogenesis can facilitate inflammation. These two processes can contribute to damage of the osteoarthritic joint through cartilage degradation and osteophyte formation. Angiogenesis can also lead to innervation of the articular cartilage that could be a source of pain in OA. The sensitization of sensory nerves by inflammatory mediators is also a source of pain, and sensitized nerves can cause neurogenic inflammation and initiate new vessel growth.

Conclusion

Osteoarthritis is a group of chronic, disabling conditions of complex aetiology that affect the synovial joints. It is a major public health issue with a substantial economic impact, and is expected to increase as the population ages. At present, treatment is centred on relief of pain through analgesic and anti-inflammatory agents, with total joint replacement surgery rescuing those in whom conservative management has failed. Angiogenesis and inflammation are important processes in the pathophysiology of osteoarthritis (Fig. 2). They can contribute to joint damage by stimulating MMP production and endochondral ossification. Pain, the major symptom of OA, can be caused or enhanced by inflammation and angiogenesis. Angiogenesis may introduce sensory nerves into the aneural cartilage, and inflammation can sensitize nerves present in the joint. Angiogenesis, inflammation and innervation are highly interconnected, and each may up-regulate the others. Inhibition of inflammation and angiogenesis may provide effective therapeutics for the treatment of OA by improving symptoms and retarding joint damage.

Rheumatology	Key messages
	• Angiogenesis and inflammation can contribute to disease progression and pain in OA. • Understanding the molecular mechanisms of angiogenesis and inflammation in OA should lead to the development of new therapeutic agents.

The authors have declared no conflicts of interest.

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