Review

Fibroblast biology
Effector signals released by the synovial fibroblast in arthritis

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Abstract

There is mounting evidence indicating that the synovial fibroblast is a direct effector of tissue injury and matrix remodeling in inflammatory synovitis. Through the elaboration of effector signals including cytokines and chemokines, mesenchymal cells stimulate or suppress inflammation via autocrine and paracrine mechanisms. Synovial fibroblasts are the principal cells mediating joint destruction through secretion of metalloproteinases, and recent evidence suggests that they may also promote bone resorption by stimulating osteoclastogenesis. Moreover, they may play an integral role in the initial phases of synovitis by releasing chemokines that recruit leukocytes to the joint, and cytokines that trigger angiogenesis. Studies focusing on synoviocyte–leukocyte interactions mediated via the cytokine network and the role of cell–cell contact in driving synoviocyte activation will help define the complex interplay that leads to the initiation and perpetuation of synovial inflammation.

Keywords: chemokines, cytokines, effector cell, rheumatoid arthritis, synovial fibroblast, synovial membrane

Introduction

In rheumatoid arthritis, the normally delicate synovial membrane is transformed into a proliferating invasive cell mass or pannus that erodes the surrounding tissue and bone. Infiltrating T lymphocytes, monocytes and synoviocytes of monocyte (type A) and fibroblast (type B) lineage have been implicated in orchestrating and maintaining synovitis, although their relative contributions have been the subject of considerable debate [1••,2,3]. Recent clinical trials with anti-tumor necrosis factor therapies in rheumatoid arthritis have demonstrated that these agents significantly improve clinical measures and retard bone erosion [4–6]. This focused attention on the pivotal role of the monocyte in mediating the proximal events in inflammatory synovitis. However, enthusiasm for this pathway must be tempered by the observation that 25% of patients are resistant to these therapies and that remissions are rare, suggesting other mechanisms may also be important.

One of the most striking features of inflammatory arthritis is the hyperplasia of synovial fibroblasts (SF) in the lining layer [7•]. In serial culture, these fibroblasts exhibit several novel properties including high proliferative rates, loss of contact inhibition, constitutive expression of cytokine mRNA and protein, and anchorage-independent cell growth [8•,9•,10]. These observations challenged the

BMP = bone morphogenic protein; MCP = macrophage chemotactic protein; MIF = macrophage inhibitory factor; MIP = macrophage inflammatory protein; MMP = metalloproteinase; RA = rheumatoid arthritis; RT-PCR = reverse transcriptase polymerase chain reaction; SCID = severe combined immunodeficient; SF = synovial fibroblasts; TIMP = tissue inhibitors of metalloproteinases;TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

traditional view of fibroblasts as target cells that mediate tissue repair in response to signals provided by monocytes and lymphocytes. The aggressive potential of these cells was convincingly demonstrated when serially cultured human SF invaded co-implanted human cartilage engrafted into severe combined immunodeficient (SCID) mice [11••]. Subsequent studies support these initial observations. Sensitive molecular and immunologic techniques have been applied to better understand the mechanisms that lead to the altered phenotype of the fibroblasts. As a result of these efforts, there is now abundant evidence indicating that SF release effector molecules that act on a variety of cells (lymphocytes, monocytes, mesenchymal cells) to modulate joint inflammation and promote matrix degradation (Table 1).

Table 1

Effector molecules released by synovial fibroblasts

Signal function	Effector molecules
Angiogenesis	IL-8, TGF-β, PDGF, GM-CSF, G-CSF, FGF, VEGF, EGF
Chemoattractant	IL-8, IL-16, MCP-1, MIP-1α
Pro-Inflammatory	IL-1, IL-6, IL-7, IL-8, IL-11, IL-15, LIF, PDGF, MIF, GM-CSF, TRX
Anti-Inflammatory	p55 TNFR, p75 TNFR, IL-10
Matrix degradation	PGE_2, collagenase, stromelysin, 92 kD gelatinase, cathepsins B, L, and K
Inhibit matrix degradation	TIMP, TGF-β IL-11
Osteoclastogenesis	RANKL, VEGF
Bone formation	TGF-β, BMP-2

EGF, epidermal growth factor; FGF, fibroblast growth factor; G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; IL, interleukin; LIF, leukemia inhibitory factor; MIF, macrophage inhibitory factor; PDGF, platelet derived growth factor; RANKL, receptor activity of nuclear factor κB ligand; TGF, transforming growth factor; TIMP, tissue inhibitors of metalloproteinases; TNFR, tumor necrosis factor receptor; TRX, thioredoxin; VEGF, vascular endothelial growth factor.

Angiogenesis and induction of inflammation

New blood vessel formation or angiogenesis is a characteristic feature of inflamed synovial membranes, and it is now appreciated that the endothelial cell is an active participant mediating both inflammatory and immunologic interactions [12]. The role of pro-angiogenic cytokines in arthritis is the subject of active investigation in many laboratories, and treatment strategies using anti-angiogenic molecules show promising results in animal models [12]. Several important pro-angiogenic cytokines and growth factors are released by SF including transforming growth factor-β, interleukin (IL)-8, platelet derived growth factor, granulocyte-macrophage colony stimulating factor, epidermal growth factor, vascular endothelial growth factor (VEGF) and fibroblast growth factor. VEGF, one of the most potent angiogenic factors, is expressed constitutively in SF, and secretion is augmented by IL-1 and hypoxia [13]. Further support for the inducibility of VEGF by cytokines was demonstrated by suppression of VEGF in dissociated synovial membrane cultures after combined neutralization of IL-1 and tumor necrosis factor (TNF)-α [14].

Synovial fibroblasts have the potential to induce synovitis by releasing mediators that attract leukocytes into the joint. This underscores the concept that resident mesenchymal cells can act as effector cells during the early stages of synovitis [15]. Following cytokine stimulation and/or engagement of the CD40 receptor, SF release chemoattractant molecules including the chemokines macrophage chemotactic protein (MCP)-1 and macrophage inflammatory protein (MIP)-1α that are primarily responsible for attracting monocytes into the synovium [16•,17]. SF can also secrete the chemokines IL-8, RANTES and MIP-1β. Recent data have shown that SF can attract CD4 cells into the synovium by antigen independent mechanisms through the release of IL-16 [18•].

The possibility that cells of mesenchymal origin may be instrumental in triggering the initial phases of inflammatory arthritis was recently raised by Zvaifler *et al* [19,20]. Mesenchymal stem cells were isolated from the peripheral blood and synovial fluid of patients with inflammatory synovitis. These cells displayed osteocyte and osteoclast morphology, and stained positive for tartrate resistant alkaline phosphatase, vimentin and collagen-1 but not vascular cell adhesion molecule-1. They also expressed receptors for bone morphogenic protein (BMP), a heterodimer expressed by mesenchymal stem cells. Cells of similar appearance were found in the joints of mice with collagen-induced arthritis before the onset of visible synovitis. The presence of these cells in the bare area of the joint suggests that these cells may migrate into the synovium via interconnecting channels from the bone marrow. Furthermore, these cells released the chemokine stromal-derived factor-1, which stimulated transmigration of T and B cells and enhanced their viability. These observations provide an alternative model of inflammation in which the mesenchymal cell is the key effector cell inducing synovitis by recruiting and retaining lymphocytes in the joint space.

Modulation of inflammation: pro- and anti-inflammatory cytokines

A common thread emerging from studies of the synovium is the presence of cytokine networks involving complex interactions between lymphocytes, synovial fibroblasts and macrophages. The release of IL-1 or TNF-α by monocytes/macrophages followed by activation of resident tissue cells (fibroblasts, endothelial cells, stromal cells) triggers the cascade, which can in turn amplify or suppress inflammation by releasing cytokines and/or growth factors. The SF

secrete a number of different cytokines that exert pleiotropic effects on monocyte/macrophages, T and B lymphocytes, mesenchymal cells and bone marrow cells [21].

Synovial fibroblasts release growth factors (granulocyte-macrophage colony stimulating factor and colony stimulating factor-1) that regulate the development and activation of hematopoietic cells and their precursors [21,22]. They can trigger the acute phase response through secretion of the IL-6-type cytokines (IL-6, IL-11 and Leukemia Inhibitory Factor) [23]. Release of IL-15 and, to a lesser extent, IL-7 promotes T-cell activation and expansion [24]. Unstimulated SF produce abundant quantities of macrophage inhibitory factor (MIF), a cytokine with a broad range of pro-inflammatory actions including induction of TNF-α secretion by macrophages, enhancement of macrophage phagocytosis and intracellular killing, and T-cell activation [25]. Low concentrations of dexamethasone stimulated release of macrophage inhibitory factor from SF, while IL-1β, TNF-α and interferon-gamma had no effect. Both β-fibroblast growth factor and platelet derived growth factor are mitogenic for SF and, as mentioned earlier, are important angiogenic factors. Platelet derived growth factor promotes anchorage-independent cell growth in synovial fibroblasts, a characteristic attributed to transformed cells. Immunolocalization of thioredoxin to SF and monocytes in the rheumatoid synovial lining unveils the presence of a pro-inflammatory pathway induced by oxidative stress [26]. Thioredoxin augments secretion of TNF-α and IL-1, and also blocks apoptosis.

The simultaneous production of endogenous anti-inflammatory cytokines highlights the presence of complex regulatory pathways in the inflamed joint. These inhibitory proteins can specifically block the biologic activity of the early-response cytokines IL-1 and TNF or exert more global suppressive actions on cytokine release. SF secrete both the p55 and p75 soluble TNF receptors that can bind and neutralize TNF-α. They also express mRNA for the IL-1 receptor antagonist, but the intracellular protein is not secreted, making it unlikely that it blocks IL-1 actions in the synovial tissue [1••].

We recently described the immunolocalization of IL-10 to both monocytic and fibroblastoid synoviocytes in the lining layer of inflamed synovial membranes (Ritchlin and Haas-Smith, submitted). Fibroblast synoviocytes constitutively produced IL-10 in serial culture that was enhanced by TNF-α and IL-1β. IL-10, a potent cytokine synthesis inhibitor, can block the release of monokines, lymphokines and class II MHC expression by monocytes. It is present in relatively high levels in inflamed joints, although addition of exogenous IL-10 to dispersed rheumatoid synovial membranes further suppressed IL-1 and TNF production, emphasizing a relative deficiency of anti-inflammatory cytokines in diseased joints [27].

Matrix degradation

A fundamental aspect of inflammatory synovitis is the erosion of articular cartilage and bone by the pannus. The seminal work of Gay *et al* illustrated that SF can promote cartilage degradation in the absence of T cells or monocytes in the SCID mouse [11••]. Subsequent *in vitro* studies have expanded on these initial observations and provide a framework to better understand the mechanisms that underlie the invasive properties of SF. Addition of purified macrophages and fibroblasts to radiolabeled cartilage discs resulted in cartilage degradation by osteoarthritis and RA SF but not fibroblasts derived from skin or bone marrow [28•]. Erosion of cartilage was augmented by addition of TNF-α, IL-1β and IL-6. Degradation occurred only when SF were in direct contact with cartilage and CD44 was involved in the fibroblast–cartilage interaction. The enhancing effect of IL-1 on cartilage destruction, and the requirement of β1, α4, α5 and αV integrin expression for fibroblast invasion, were noted using a similar *in vitro* model [29•]. Taken together, these studies demonstrate that SF can invade bone in the absence of other immune cells but this invasiveness can be dramatically increased by exposure to pro-inflammatory cytokines. Furthermore, expression of adhesion molecules and integrin receptor engagement is required for cartilage invasion.

Degradation of the extracellular matrix is mediated by a number of different enzymes including cathepsin B and cathepsin L, serine proteases and metalloproteinases (MMP). The MMPs collagenase (MMP-1) and stromelysin (MMP-3) are expressed by SF *in situ*, and production of these enzymes by cultured SF can markedly increase under direct contact with T cells or exposure to pro-inflammatory cytokines [30•]. The prostanoid PGE_2, another mediator of bone resorption, is similarly secreted in large quantities by these cells. The role of cathepsin B and cathepsin L in mediating bone erosion is of questionable relevance because these enzymes function optimally at a pH lower than that observed in the synovial microenvironment. The activity of MMPs is counterbalanced by tissue inhibitors of metalloproteinases (TIMP), also produced by lining cells of fibroblast lineage. Transforming growth factor-β, IL-6 and IL-11 enhance TIMP production, but in studies of rheumatoid synovial membranes MMPs are present in excess of their natural inhibitors favoring catabolism. Bone morphogenic protein-2 may also participate in this compensatory response by stimulating new bone formation [31].

Cells at the site of bone erosion in RA display phenotypic features of osteoclasts [32•]. A pathway leading to osteoclast differentiation and proliferation was recently described [32•]. It has been shown that bone resorption is stimulated through the upregulation of RANKL, a membrane-bound member of the TNF family. RANKL binds to its receptor RANK expressed by osteoclast precursors [33•]. Macrophage colony stimulating factor (M-CSF) and

RANKL are required for osteoclast differentiation from progenitor cells and subsequent activation, although VEGF can substitute for M-CSF [34]. RANKL mRNA was detected by reverse transcriptase polymerase chain reaction (RT-PCT) in rheumatoid arthritis (RA) synovium but not normal tissues [35•]. In addition, RANKL mRNA was expressed by synovial fibroblasts and activated T lymphocytes derived from RA synovium. These findings suggest that synovial fibroblasts can directly promote the formation and activation of osteoclasts at sites of bone erosion in RA.

Conclusions

The synovial fibroblast has emerged as a pivotal effector cell in the inflamed joint, based on its ability to degrade the extracellular matrix and to provide chemotactic and activation signals to resident parenchymal cells and infiltrating immunocytes. *In vitro* studies have demonstrated that cultured synovial fibroblasts display unique properties that set them apart from fibroblasts isolated from different anatomic sites. These cells, most importantly, release an impressive array of cytokines and growth factors, which have the capacity to stimulate and, in some cases, dampen the inflammatory response. However, the impact of these effector molecules on the pathobiology of synovitis must be viewed in the context of a cytokine network involving complex cellular interactions both locally and systemically. Exploring the interaction between monocytes and SF may yield valuable insights given the close apposition of these cells in the synovial lining and the key role of TNF in the early phases of synovitis. Moreover, therapeutic strategies that inhibit SF effector pathways responsible for angiogenesis, pro-inflammatory cytokine release and matrix degradation should significantly diminish joint inflammation and prevent bone resorption.

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