Review
Mast cells in inflammatory arthritis

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Abstract

Mast cells are present in limited numbers in normal human synovium, but in rheumatoid arthritis and other inflammatory joint diseases this population can expand to constitute 5% or more of all synovial cells. Recent investigations in a murine model have demonstrated that mast cells can have a critical role in the generation of inflammation within the joint. This finding highlights the results of more than 20 years of research indicating that mast cells are frequent participants in non-allergic immune responses as well as in allergy. Equipped with a diversity of surface receptors and effector capabilities, mast cells are sentinels of the immune system, detecting and delivering a first response to invading bacteria and other insults. Accumulating within inflamed tissues, mast cells produce cytokines and other mediators that may contribute vitally to ongoing inflammation. Here we review some of the non-allergic functions of mast cells and focus on the potential role of these cells in murine and human inflammatory arthritis.

Keywords: inflammation, mast cells, rheumatoid arthritis, synovitis, synovium

Introduction

The mast cell has long been known to mediate important manifestations of allergic disease. Crosslinking of surface-bound IgE results in the immediate release of granule contents, including histamine, and the more gradual elaboration of other proinflammatory mediators. Clinical manifestations can range from seasonal allergic rhinitis to life-threatening anaphylaxis.

However, research over the past two decades has revealed that the role of mast cells is not limited to IgE-mediated immune responses. Mast cells express surface receptors for IgG, complement, and specific pathogen-associated molecular patterns. Mast cells are capable of phagocytosis, intracellular killing, and antigen presentation. Correspondingly, mice deficient in mast cells have been found to exhibit striking susceptibility to death from certain types of bacterial infection. Beyond the acute phase of the immune response, mast cells may participate in the response of tissue to injury by means of mediators that promote angiogenesis and fibrosis.

Recently, several laboratories have established that mast cells have a critical role in the pathogenesis of synovitis in a murine system with considerable similarity to rheumatoid arthritis (RA) [1,2]. This finding has renewed interest in older histological data documenting prominent mast cell infiltrates in the rheumatoid synovium. We review here the functions of mast cells as a prelude to the discussion of the current state of knowledge about the role of mast cells in murine and human inflammatory arthritis.

Basic biology of mast cells

Mast cells are found principally in mucosae and in connective tissue, generally clustered at epithelial surfaces and around nerves and blood vessels [3]. They originate in bone marrow and circulate as CD34+ committed progenitor cells, differentiating into mature mast cells only after entry into the tissue [4,5]. These mature cells may divide further. Tissue mast cells are highly heterogeneous, with great variability in size, granule contents, cytokine production and receptor expression; both *in vitro* experience and *in vivo* data suggest that this

GPI = glucose-6-phosphate isomerase; IL = interleukin; ITAM = immunoreceptor tyrosine-based activation motif; MHC = major histocompatibility complex; MIP = macrophage inflammatory protein; OA = osteoarthritis; RA = rheumatoid arthritis; SCF = stem cell factor; TGF-β = transforming growth factor-β; TLR = Toll-like receptor; TNF = tumor necrosis factor.

heterogeneity represents an exquisite developmental sensitivity to local signals [3]. Similarly, the maintenance of mast cells within tissues is controlled by the local environment, in particular the production of stem cell factor (SCF, c-kit ligand) by stromal cells [6]. Mature mast cells are also capable of trafficking, as shown by their recruitment to chemotactic stimuli such as RANTES and their efflux from tissue through lymphatic channels and possibly blood vessels [7–9].

Functions of mast cells

IgE-mediated activation
Mast cells express the high-affinity IgE receptor FcεR1, a tetrameric complex of an α chain (to which IgE binds), a β chain and a dimer of γ chains [10]. The γ chain is shared with other stimulatory receptors, including the high-affinity IgG receptor FcγR1 and the low-affinity immune complex receptor FcγR3a. On crosslinking of the IgE receptor by multivalent antigen, the immunoreceptor tyrosine-based activation motifs (ITAMs) on the β and γ chains become phosphorylated and initiate a signaling cascade, resulting in three distinct pathways of mediator production: explosive release of preformed mediators, elaboration of eicosanoids, and de novo synthesis of cytokines and chemokines.

Explosive release of preformed mediators
Within seconds to minutes of IgE crosslinking, granules in the cytoplasm of the mast cell fuse with each other and with the cell surface membrane, ejecting their contents into the extracellular milieu. The contents of the granules depend on the conditions under which the mast cell has matured, but include histamine, proteoglycans (for example heparin), and a series of neutral proteases broadly grouped into tryptases, chymases, and carboxy-peptidases. Histamine promotes vascular permeability; proteoglycans provide a scaffold within the granule that allows the packaging of proteases; and the neutral proteases cleave proteins from matrix and plasma in addition to activating propeptides such as the precursors for interleukin-1β (IL-1β) and angiotensin II. The tryptase mMCP6 (murine mast cell protease 6) also contributes potently to neutrophil chemotaxis [11]. Certain subsets of mast cells store tumor necrosis factor (TNF) within the granules as well, representing the body's only source of TNF available for immediate release [12].

Elaboration of eicosanoids
Within minutes of IgE-mediated activation, mast cells begin to generate eicosanoids derived from cleavage of arachidonic acid from membrane phospholipids [13]. Important arachidonic acid metabolites include the leukotrienes (leukotriene B_4 and the cysteinyl leuko-trienes), which increase vascular permeability, induce vasoconstriction and recruit leukocytes, and prosta-glandins including the neutrophil chemoattractant and vasoactive mediator prostaglandin D_2.

De novo synthesis of cytokines and chemokines
Within hours, a later phase of mast cell activation through IgE becomes evident with the induction of new gene transcription and translation, generating a host of cyto-kines and chemokines (Table 1). The mix of cytokines generated by a particular mast cell depends on its individual state of differentiation.

The importance of IgE-mediated mast cell activation to the health of the organism is still incompletely defined. The preservation of this system under evolutionary pressure, despite allergic diseases and anaphylaxis, is strong suggestive evidence that there is benefit to the host. One likely candidate function is resistance to parasitic disease, because mice deficient in IgE exhibit impaired defense against the helminths *Schistosoma mansoni* and *Trichinella spiralis* [14,15].

IgE-independent functions of mast cells
Mast cells cluster at sites of contact with the external world, such as mucosal and epithelial surfaces. Similarly, they are found near blood vessels and in the linings of potential spaces such as the peritoneum, pleural space, and synovial cavity. This localization suggests a role in surveillance, and indeed mast cells are capable of detecting pathogens and initiating an inflammatory response, earning this cell the appellation of immune sentinel [16]. Further, mast cells accumulate in chronically inflamed tissue, suggesting that their role might not be limited to the initiation phase of the immune response.

Mast cells in bacterial infection
The physiological importance of mast cells in defense against bacteria has been clearly demonstrated. Mast-cell-deficient W/W^v mice have impaired clearance of bacterial infection in the peritoneum [17,18] and lung [18], accompanied by markedly higher mortality after experimental infection. This vulnerability was found to be associated with decreased infiltration of neutrophils to the site of infection and could be corrected by reconstitution with wild-type mast cells. Within an hour of peritoneal infection, lavage fluid shows a striking increase in TNF levels in the presence of mast cells. Anti-TNF treatment largely abrogates the effect of mast cell reconstitution, whereas injection of TNF concurrent with infection substantially mimics the benefits of reconstitution in mast-cell-deficient mice. Although mast cells can phagocytose and kill bacteria [19], the results imply that the critical role of mast cells in these models is not direct anti-bacterial action but the generation of TNF and other mediators (such as leukotrienes [20]) that recruit neutrophils and possibly other cells to contain the infection.

Mast cells possess multiple mechanisms to detect bacterial invasion. These include Toll-like receptors (TLRs) 1, 2, 4, and 6, CD48 (a receptor for a Gram-negative

Table 1

Selected mast cell mediators and their potential roles in arthritis

Mediator	Some relevant functions
Granules	
Histamine	Vascular permeability, leukocyte recruitment, fibroblast/chondrocyte activation
Heparin	Angiogenesis, osteoclast differentiation and activation
Neutral proteases	Matrix degradation, leukocyte recruitment, fibroblast activation
TNF	Leukocyte recruitment, fibroblast/chondrocyte activation
Eicosanoid mediators	
PGD_2	Vascular permeability, neutrophil recruitment
LTB_4	Vascular permeability, leukocyte recruitment and activation
Cysteinyl leukotrienes	Vascular permeability, immunomodulatory (LTC_4)
Cytokines/chemokines	
IL-1	Leukocyte recruitment, fibroblast/chondrocyte activation, angiogenesis
IL-2	Lymphocyte stimulation
IL-3	Leukocyte growth factor
IL-4	Immunomodulatory, profibrotic
IL-6	Activation of leukocytes and fibroblasts
IL-8	Neutrophil recruitment
IL-10	Immunomodulatory
IL-13	Immunomodulatory, B cell stimulation
IL-18	Angiogenesis, lymphocyte stimulation
TNF	Leukocyte recruitment, fibroblast/chondrocyte activation, angiogenesis
IFN-γ	Activation of synovial macrophages
TGF-β	Immunomodulatory, fibroblast mitogen, angiogenesis
PDGF	Fibroblast mitogen
VEGF	Fibroblast mitogen, angiogenesis
bFGF	Fibroblast mitogen
NGF	Fibroblast mitogen
MCP-1	Leukocyte recruitment
MIP-1α, MIP-1β	Leukocyte recruitment, osteoclast differentiation
RANTES	Leukocyte recruitment

bFGF, basic fibroblast growth factor; IFN, interferon; IL, interleukin; LTB_4, leukotriene B_4; LTC_4, leukotriene C_4; MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein; NGF, nerve growth factor; PDGF, platelet-derived growth factor; PGD_2, prostaglandin D_2; RANTES, regulated upon activation, normal T-cell expressed and secreted; TGF-β, transforming growth factor-β; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. See text for references.

fimbrial protein), and receptors for anaphylatoxins C3a and C5a and the complement opsonin iC3b [21–25]. Interestingly, mast cells triggered by means of these mechanisms seem capable of responses that are substantially more differentiated than those unleashed through IgE/FcεR1. In contrast to the wholesale 'anaphylactic' degranulation that characterizes maximal IgE-mediated stimulation, bacteria can trigger a gradual and partial (so-called 'piecemeal') degranulation proportional to the stimulus [19,26]. The production of lipid mediators and cytokines/chemokines seems also to be tailored to the event, and can even be entirely decoupled from the release of granule contents (reviewed in [27]).

An important consequence of mast cell activation may be the mobilization of adaptive immunity. Mast cell leukotriene B4 recruits memory CD4^{+} and CD8^{+} T cells, which can then be activated locally by mast cells presenting

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phagocytosed peptides via both MHC class II and MHC class I molecules [28–31]. Mast cells might also potentiate *de novo* antigen-specific responses by promoting the migration of dendritic cells to lymph nodes and recruiting circulating naive T cells to these nodes by means of TNF and macrophage inflammatory protein-1β (MIP-1β) [8,32,33]. Although the ultimate physiological importance of each of these defensive capabilities remains to be established, it seems probable that antimicrobial efficacy accounts at least in part for the remarkable evolutionary conservation of the mast cell.

Mast cells in antibody-mediated disease
As noted, mast cells express receptors for IgG as well as IgE. These include FcγR2b and FcγR3a, low-affinity IgG receptors involved principally in the response to immune complexes and other constellations of colocalized IgG molecules. Under certain conditions, mast cells can also express the high-affinity receptor FcγR1 [34]. These receptors permit mast cells to participate in humoral defense, but they also enable a role for mast cells in antibody-induced pathology. Thus, in a mouse model of peritonitis induced by intraperitoneal injection of antibody against an antigen injected intravenously (the reverse passive Arthus reaction), peritoneal mast cells exposed to immune complexes release a burst of preformed TNF and recruit neutrophils [35]. Similarly, in an analogous skin model, mast cells have been shown to potentiate the response to antibody administered subcutaneously against an antigen delivered systemically [36]. Optimal mast cell participation in this reaction requires a functional complement system, suggesting that complement fixation by immune complexes provides an important auxiliary signal to mast cells, in particular via C5a [37]. A related phenomenon is observed in a model of bullous pemphigoid: subcutaneous administration of an antibody against the hemidesmosomal antigen BP180 induces inflammatory attack, resulting in lysis of the dermal–epidermal junction. In the absence of mast cells or complement, inflammation is markedly attenuated [38,39]. As in bacterial peritonitis, the key function of mast cells in these models of antibody-mediated pathology seems to be the mobilization of neutrophils, because the wild-type phenotype can largely be rescued in mast-cell-deficient animals with injection of neutrophils or neutrophil chemotactic factors.

Mast cells: a role in chronic inflammation?
In the models discussed so far, the principal function of mast cells seems to be to 'jump start' the immune response, in particular to initiate the rapid recruitment of inflammatory cells. Structurally, the mast cell is uniquely equipped for this task, with its capacity for the immediate release of preformed mediators and the rapid elaboration of lipid mediators. However, the mast cell's activity does not end with this initial response. Mast cells continue to elaborate cytokines for hours after a single stimulus, and a degranulated mast cell can recharge and fire again [40,41]. Some mast cell mediators have effects such as the promotion of angiogenesis, whose relevance is more evident after the acute inflammatory response [42]. Further, mast cells accumulate at sites of chronic inflammation, *prima facie* evidence that their role is not restricted to the initiation of immune responses; examples include the gut in inflammatory bowel disease or helminthic infection, the asthmatic airway, sclerodermatous skin, and lung in interstitial pulmonary fibrosis [43–46]. Though no pathogenic role has yet been definitively assigned to the mast cell in these conditions, potential functions include ongoing recruitment of inflammatory cells, stimulatory effects on stromal cells resulting in fibrosis, and the development of new blood vessels. It is also conceivable that mast cells might in some cases limit or otherwise modulate local inflammation, although no data to this effect are available. Particular proinflammatory mechanisms are discussed below in detail as they pertain to the potential role of the synovial mast cell in arthritis.

Mast cells in inflammatory arthritis
Mast cells in normal and inflamed human synovium
The synovium of patients with RA is an archetypal example of a chronically inflamed tissue characterized by an expanded population of mast cells (Fig. 1). In the normal joint, the synovium consists of a thin lining layer of macrophages (macrophage-like synoviocytes, 'Type A' cells) and fibroblasts (fibroblast-like synoviocytes, 'Type B' cells) embedded in a connective tissue matrix and resting on a sublining of highly vascular loose connective tissue and adipose tissue. In the absence of inflammation, scattered mast cells are seen in the sublining, clustered around vessels and nerves and forming up to 3% of all cells within the synovium [47]. The role of mast cells in the normal synovium remains to be defined, although the importance of mouse peritoneal mast cells for defense against bacterial peritonitis suggests that one important function of synovial mast cells might be to monitor the vulnerable acellular joint cavity for early evidence of infection.

In RA, the synovial lining thickens from 1–3 cells to 10 cells or more, and the sublining becomes infiltrated with T cells, B cells, macrophages, and occasional neutrophils. Mast cells are commonly markedly increased in number and can make up 5% or more of the expanded population of total synovial cells. The number of accumulated mast cells differs substantially from patient to patient, in general varying directly with the intensity of joint inflammation [17,24,48–55]. Mast cells are present throughout the synovial sublining, with occasional microanatomic clustering in the pannus near sites of cartilage and bone erosion [53,54]. A relative mastocytosis may also be

Figure 1
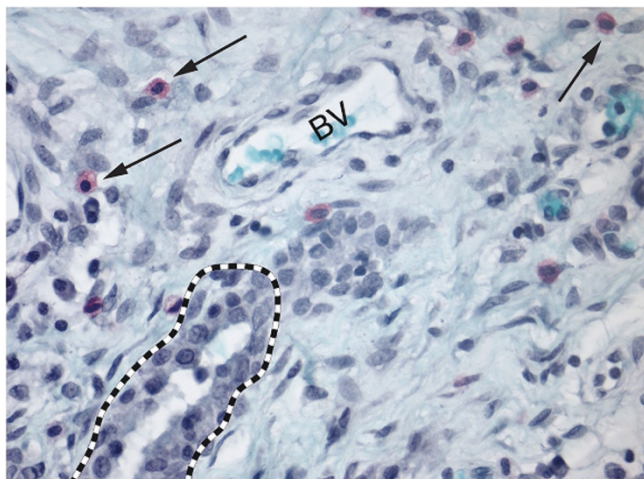
Mast cells within the rheumatoid synovium. Shown is fixed, paraffin-embedded synovial tissue obtained during arthroplasty from a patient with chronic rheumatoid arthritis. This tissue was stained with safranin-O, which labels mast cell granule proteoglycans red, and counterstained with hematoxylin. Note the frequent safranin-O-positive mast cells present within the synovial sublining (several indicated with arrows). A fold of thickened synovial lining is seen at the bottom left of the image (outlined with a dotted line) and a blood vessel (BV) is visible in the middle of the field, with erythrocytes staining blue. (Section 5 μm thick; original magnification ×400.)

observed in other arthritides, including juvenile rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, and some cases of osteoarthritis (OA) [49].

Accompanying the increased numbers of mast cells, mast cell mediators are also present at higher concentrations in the synovial fluid of inflamed human joints. These mediators include histamine and tryptase, both considered to be specific for mast cells [56–60]. Again, patient-to-patient variability is considerable. Although mast cells from RA and OA do not appear distinct histologically, and express a generally similar panel of surface receptors, RA but not OA mast cells have been noted to express the receptor for the anaphylatoxin complement fragment C5a [24]. Interestingly, whereas normal human synovium contains mainly mast cells of the so-called 'connective tissue' phenotype, expressing both tryptase and chymase in their granules (MC_{TC}), inflamed synovium also features mast cells that express only tryptase (MC_T), a phenotype more commonly associated with mast cells maturing under the influence of T cell cytokines at mucosal sites [24,55,61]. Although the significance of these subpopulations is uncertain, mast cells with similar phenotypes isolated from skin and lung exhibit divergent patterns of cytokine secretion, with IL-4 produced predominantly by MC_{TC} cells whereas MC_T cells elaborate IL-5 and IL-6 [62]. If this is true in the synovium, then these two types of mast cell might have different pathophysiological roles in inflammatory arthritis, because IL-4 has profibrotic effects whereas IL-6 may be stimulatory for T and B lymphocytes (reviewed in [63]). Correspondingly, MC_{TC} cells tend to be found in 'deeper,' more fibrotic areas of the inflamed synovium, whereas MC_T cells tend to be found more superficially and in association with lymphoid aggregates [24,61].

Mast cells in arthritis: insights from the K/BxN arthritis model

Synovial mast cell degranulation was previously noted in association with arthritis in several animal models, but a critical functional role in pathogenesis has recently been firmly established with the K/BxN mouse model [1,2,64,65]. This arthritis model, mediated by auto-antibodies against the ubiquitous enzyme glucose-6-phosphate isomerase (GPI), demonstrates important similarities to human RA including symmetric joint involvement, chronicity, a distal-to-proximal gradient of joint involvement, and histological features including synovial infiltrates, pannus, and erosions of cartilage and bone [66].

A key feature of this model is the ability to transfer the pathogenic autoantibodies passively to induce arthritis in recipient mice [67]. This passive transfer arthritis mechanistically 'disconnects' the afferent pathogenic events involving the adaptive immune response and affords an analytic focus on the efferent pathogenic mechanisms of synovial inflammation. Given the large and ever-increasing number of targeted genetic deletions in mice, it has been possible to apply the power of this genetic technique to dissect the molecular requirements for induction of arthritis. Transfer of serum into mice deficient in various participants in the inflammatory response has identified a critical role for cytokines (IL-1, TNF), IgG Fc receptors (especially FcγR3), complement (C3, C5) and the C5a complement receptor in arthritis pathogenesis [2,68,69]. Immune complexes are implicated in the pathogenesis by the observation that multiple anti-GPI antibodies with non-overlapping epitope specificities – as would be required to form an antigen–antibody lattice – are required for the initiation of arthritis [70].

At the cellular level, the concept of the mast cell as immune sentinel led to the hypothesis that this lineage might participate pathogenically in autoantibody-driven K/BxN serum transfer arthritis. Expressing receptors for both immune complexes and complement, synovial mast cells would be well positioned to initiate the tissue response to K/BxN serum. Consistent with this hypothesis is the observation that mice deficient in mast cells are highly resistant to arthritis, whereas reconstitution with normal mast cells restores the wild-type phenotype (Fig. 2). Furthermore, degranulation of mast cells in the

Figure 2
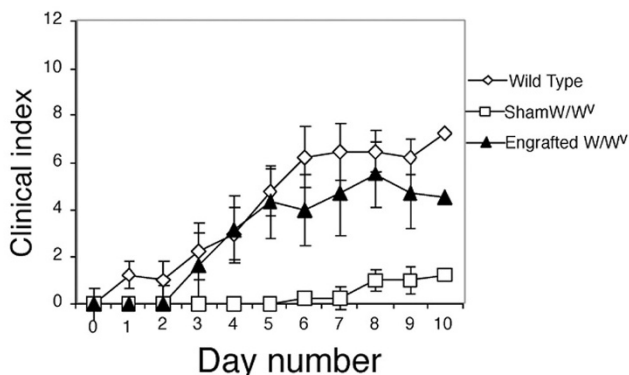
Mast cells constitute a critical pathogenic link in K/BxN serum transfer arthritis. Compared with wild-type controls, mast-cell-deficient W/W^v mice injected with K/BxN arthritogenic serum are resistant to the development of arthritis. After reconstitution with cultured wild-type mast cells, but not sham reconstitution, normal susceptibility is restored. Error bars = SEM. (Adapted from reference [1], with permission.)

synovium is the first event observed histologically, occurring within 1–2 hours of administration of K/BxN serum [1]. Thus, as in antibody-mediated peritonitis, synovial mast cells seem to act as early responders, mobilizing the inflammatory response against a perceived insult. In their absence, no other cell constitutively resident within the synovium or present in the circulation seems to have the capacity to initiate the recruitment of inflammatory cells to the joint that characterizes arthritis in the wild-type animal. However, details of the mechanisms of mast cell activation as well as the relevant mast cell effector functions in this model remain to be defined.

Mast cells and the initiation of human synovitis
The involvement of mast cells in the earliest phases of human synovitis remains a subject for conjecture. As described previously, mast cells can be triggered by IgG immune complexes, complement, TLR ligands, and microbial antigens. Each of these stimulatory pathways may be of relevance to human arthritis. Immune complexes are thought to cause the arthritis of serum sickness and cryoglobulinemia but have also been documented in the serum, synovial fluid, synovium, and cartilage of patients with RA and are once again a field of active investigation in the pathogenesis of RA [71–74]. Complement activation has similarly been well documented within rheumatoid synovium [75]. Infection with bacteria or viruses could trigger mast cell activation by means of TLRs and specific pathogen receptors. Even in the absence of infection, mast cells could be stimulated via TLRs by synovial constituents with TLR ligand activity, including heat shock protein 60 and breakdown products of hyaluronan, potentially amplifying any inflammatory

process within the joint [76]. Mast cell IgE receptors might also have a role in a small subset of patients, because IgE rheumatoid factors and IgE-containing immune complexes have been documented in some patients with RA [77,78].

Once activated, mast cells in the synovium would be expected to initiate inflammation through several mechanisms; a limited number of candidate pathways are outlined in Fig. 3. Vasoactive mediators such as histamine, prostaglandin D$_2$, and the leukotrienes increase vascular permeability, whereas TNF, IL-1, and histamine promote the expression of the adhesion molecules P-selectin, E-selectin, ICAM-1, and VCAM-1 on the endothelial surface [79,80]. Circulating leukocytes bearing appropriate counter-receptors, such as leukocyte function-associated antigen-1 (LFA-1) (itself of heightened affinity under the influence of proinflammatory cytokines through 'inside-out' regulation), could then be recruited into the synovium along gradients of chemotactic mast cell products such as leukotriene B$_4$, monocyte chemoattractant protein-1, tryptases (for example mMCP6), and IL-8. Activation of resident synovial macrophages and arriving monocytes and neutrophils by means of interferon-γ, IL-6 and TNF would be expected to result in further amplification of leukocyte recruitment and an enhanced output of proinflammatory cytokines.

Beyond the 'jump start': a role for mast cells in chronic synovitis in mouse and humans?
In some murine models of bacterial and antibody-induced disease, the physiological role of mast cells can largely be replaced by a single administration of neutrophils or neutrophil chemoattractants [17,31,35,38]. This observation suggests that mast cells have no substantial continuing role in these pathologic states. In K/BxN arthritis, and potentially in human arthritis, is there a role for the synovial mast cells beyond the initiation of synovitis?

An initial observation applies. In K/BxN serum transfer arthritis, two serum injections are followed within 1–3 days by an intense synovitis. This reaction peaks over the course of 2 weeks but is ultimately self-limiting, resolving within 6 weeks. Although some human joint diseases run such a self-limited course (such as serum sickness and postviral arthritis), many human arthritides are chronic. In such chronic conditions, any factors inducing mast cell activation might well be persistent. This is so in K/BxN mice, which exhibit a progressive erosive arthritis in the setting of persistently high levels of autoantibodies in the serum. 'Chronicity' can be mimicked in wild-type mice by means of a repeated transfer of K/BxN serum. In this setting, synovial mast cells can undergo repetitive cycles of activation and thus participate in ongoing disease much more substantially than has been observed in models of peritonitis and skin disease. Indeed, degranulating synovial mast cells are readily observed in established K/BxN

Figure 3
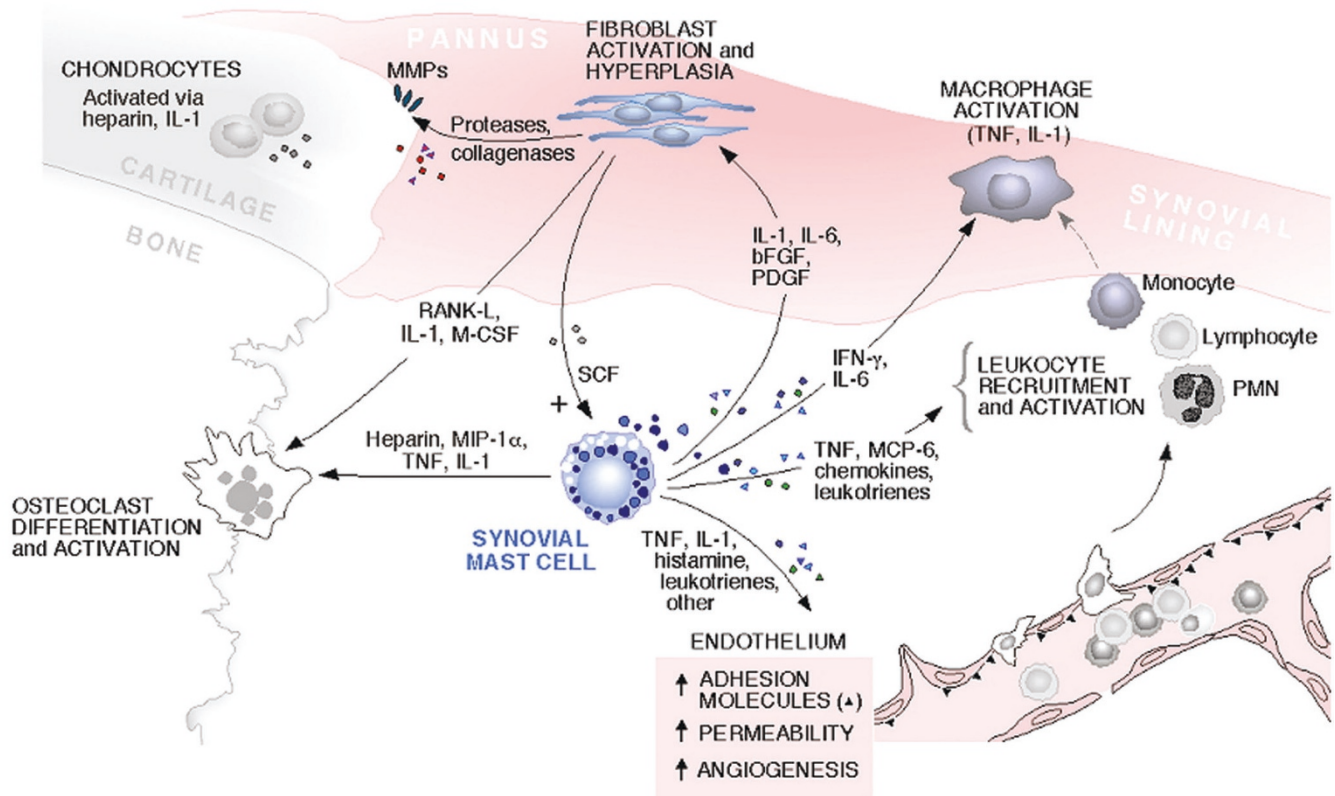
Candidate proinflammatory functions of mast cells in synovitis. Mast cell effector functions suggest their participation in diverse pathogenic pathways in inflammatory arthritis, including leukocyte recruitment and activation, synovial fibroblast activation and hyperplasia, angiogenesis, and cartilage and bone destruction. Activated mast cells elaborate mediators potently capable of enhancing vasopermeability, inducing endothelial expression of adhesion molecules, recruiting circulating leukocytes, and activating infiltrating leukocytes as well as resident macrophages, thereby contributing to the early phases of inflammatory arthritis. In chronic synovitis, mast cells synthesize mitogens and cytokines that activate synovial fibroblasts, recruit macrophages, and promote the growth of new blood vessels, implicating them in synovial lining hyperplasia and pannus formation. Further, mast cells may participate in joint destruction by the induction of matrix metalloproteinases (MMPs) from fibroblasts, by activation of chondrocytes, and by direct and indirect promotion of osteoclast differentiation and activation. Because activated synovial fibroblasts demonstrate enhanced stem cell factor (SCF) expression, a potentially important positive feedback loop is established in which SCF promotes mast cell survival and proliferation, leading to the mastocytosis described in inflamed synovium. Note that the importance of these candidate pathways *in vivo* remains to be established. See text for details and references. bFGF, basic fibroblast growth factor; IFN, interferon; IL, interleukin; MCP = monocyte chemoattractant protein; M-CSF, macrophage colony-stimulating factor; MIP, macrophage inflammatory protein; PDGF, platelet-derived growth factor; PMN, polymorphonuclear cell; RANK-L, receptor activator of NF-κB ligand; TNF, tumor necrosis factor. (Graphic design by Steve Moskowitz.)

arthritis [1]. Yet a functional contribution of mast cells to continuing inflammation remains to be experimentally determined.

In humans, given the expanded numbers of mast cells within the joint and their enormous capacity for the production of cytokines and chemokines, it would be surprising indeed if they were of no consequence to the chronic inflammatory response. The broad range of mast cell effector functions includes the elaboration of mediators with bioactivity directed at marrow-derived leukocytes as well as mesenchymal tissue elements (Fig. 3). Because the pathogenic state of inflammatory arthritis displays prominent responses by both infiltrating

leukocytes and mesenchymal cells, in particular synovial fibroblasts, we will examine the potential influence of mast cells on both compartments in arthritis.

Mast cells and synovial leukocytes
The rheumatoid synovium is thick with infiltrating leukocytes. These include T lymphocytes, B lymphocytes, macrophages, mast cells and scattered neutrophils. Ongoing recruitment of these cells results from the upregulation of selectins and integrins on synovial endothelium, allowing migration up chemotactic gradients into the joint. The composition of inflammatory cells recruited in a continuing fashion by mast cells, including the degree of skewing of lymphocytes toward Th1 versus Th2 responses, might be an important

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determinant of the ultimate outcome of inflammation. The production of anti-inflammatory mediators by mast cells remains uncharacterized [81].

Prominent within the rheumatoid synovium is a greatly expanded population of synovial macrophages. These cells do not proliferate locally but instead are recruited from circulating monocytes [82]. Mast cells are potent sources of chemokines that mediate this recruitment, including IL-8, monocyte chemoattractant protein-1, MIP-1α, and RANTES [3]. Mast cells might also contribute to the activation of these macrophages through the production of interferon-γ and IL-6. Because macrophages are major sources of the proinflammatory cytokines TNF and IL-1 within the joint, mast cell effects on the size and activation state of the synovial macrophage population might functionally modulate the course of inflammatory arthritis.

Mast cells and the synovial mesenchyme
The synovial mesenchyme, consisting principally of synovial fibroblasts, is prominently involved in joint inflammation. Fibroblasts increase greatly in numbers and assume a histological appearance suggestive of increased synthetic activity, with expansion of the endoplasmic reticulum and increased numbers of granules in the cytoplasm [83]. Indeed, synovial fibroblasts make up the shroud-like pannus characteristic of the rheumatoid joint and are an important source of multiple mediators implicated in arthritis. These include degradative enzymes such as collagenase and stromelysin and proinflammatory molecules including IL-1, IL-6, and prostaglandin E_2 (reviewed in [84]). They contribute to the differentiation and activation of osteoclasts, the effector cell responsible for bone erosions, through the production of macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL) [85,86].

Mast cells may potently influence synovial fibroblast biology in RA. Consistent with a proposed role in wound healing and in multiple fibrotic disease states, mast cells produce a range of mediators with powerful effects on fibroblasts (Table 1) [87]. Further, synovial mast cells are often noted in close physical proximity to synovial fibroblasts [50]. Mast cell tryptase promotes chemotaxis and collagen synthesis in fibroblasts, and histamine stimulates fibroblast proliferation [88–90]. Other fibroblast mitogens produced by mast cells include nerve growth factor, basic fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β) [91]. The cytokine IL-4, produced predominantly by mast cells of a tryptase–chymase phenotype, induces proliferation and collagen production by fibroblasts [92], and indeed, as noted above, MC_{TC} cells tend to reside in more fibrotic areas of the inflamed joint. Because leukotriene C_4 seems

to have antifibrotic effects, it remains possible that mast cells can limit as well as promote fibrosis, although scattered foci of fibrosis associated with mast cell infiltrates in systemic mastocytosis suggest a net profibrotic effect [91,93,94].

Mast cells may also potentiate mediator production by synovial fibroblasts through the elaboration of cytokines such as TNF and IL-1. IL-1 induces the elaboration of collagenase and prostaglandin E_2, and TNF elicits similar responses while also inducing synovial fibroblasts to generate IL-1 [95–97]. Indeed, the production of collagenase and other inflammatory products of fibroblasts has been noted to localize to the immediate environment of activated mast cells [98].

This communication between mast cells and synovial fibroblasts is bidirectional. Mast cells require stimulation by SCF for differentiation *in situ* as well as activation [6]. Fibroblasts in inflamed or healing tissues express higher levels of SCF, and upregulation of SCF expression has been noted in synovial specimens exposed to TNF [99–101]. Indeed, such surface expression seems to be of particular importance to mast cell development, because Sl/Sl^d mice unable to display surface-bound SCF lack tissue mast cells despite an intact production of soluble SCF [102,103]. Further, transwell experiments demonstrate that physical contact is required for certain stimulatory effects of fibroblasts on mast cells [104,105]. Fibroblasts might also promote the survival of mast cells by means of SCF-independent pathways yet to be fully defined [106].

In addition to fibroblasts, the synovial mesenchyme also contains blood vessels. As would be expected, the expanded cellular population in the inflamed synovium requires an enhanced blood supply, and neoangiogenesis has an important pathophysiological function in RA. Mast cell mediators implicated in the promotion of angiogenesis include heparin, vascular endothelial growth factor, TGF-β, TNF, IL-1, and IL-18 [42,107]. Further, TNF can induce synovial fibroblast production of another pro-angiogenic factor, angiopoietin-1 [108]. Though the ultimate importance of mast cells in synovial angiogenesis remains unclear, the association of mast cells with blood vessels, including newly developing blood vessels, makes the promotion of angiogenesis a plausible role for mast cells *in vivo* (reviewed in [109]).

Finally, some data suggest that mast cell mediators might exert a direct effect on cartilage and bone. Thus, whereas the coculture of chondrocytes with inactive mast cells tends to promote the synthesis of proteoglycans, the activation of mast cells in this context favors proteoglycan degradation [110]. Further, the activation of chondrocytes via IL-1, TNF, and histamine might induce the production

of matrix metalloproteinases and prostaglandins [111,112]. Finally, mast cell mediators including histamine and MIP-1α might directly promote the differentiation and activation of osteoclasts, the final common pathway of bone destruction in inflammatory arthritis [113–115]. Corroboration *in vivo* will be required to establish the importance of these *in vitro* findings.

Conclusions

Mast cells are a normal cell population within the human synovium, and in line with their role as sentinels they likely have an important physiological role as an 'early warning system' for infection within the vulnerable joint cavity. Data from the K/BxN mouse model now show that mast cells also have a critical role in the pathogenesis of inflammatory arthritis, in particular in arthritis induced by autoantibody-containing immune complexes. Although a similar mechanism remains unproven for human joint inflammation, markers of mast cell activation are observed in joint fluid from patients with chronic arthritis and mast cell numbers are often greatly expanded within the inflamed synovium. Equipped with an impressive array of mediators, mast cells can promote synovitis by recruiting inflammatory cells from the blood, inducing synovial fibroblast hyperplasia and mediator production, and fostering angiogenesis. Although much remains to be learned about the role of the mast cell in arthritis, such a role now seems highly likely, offering a potential new target for therapeutic agents in the treatment of RA and other inflammatory diseases of the joints.

Competing interests

The author(s) declare that they have no competing interests.

Acknowledgements

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