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Leaders

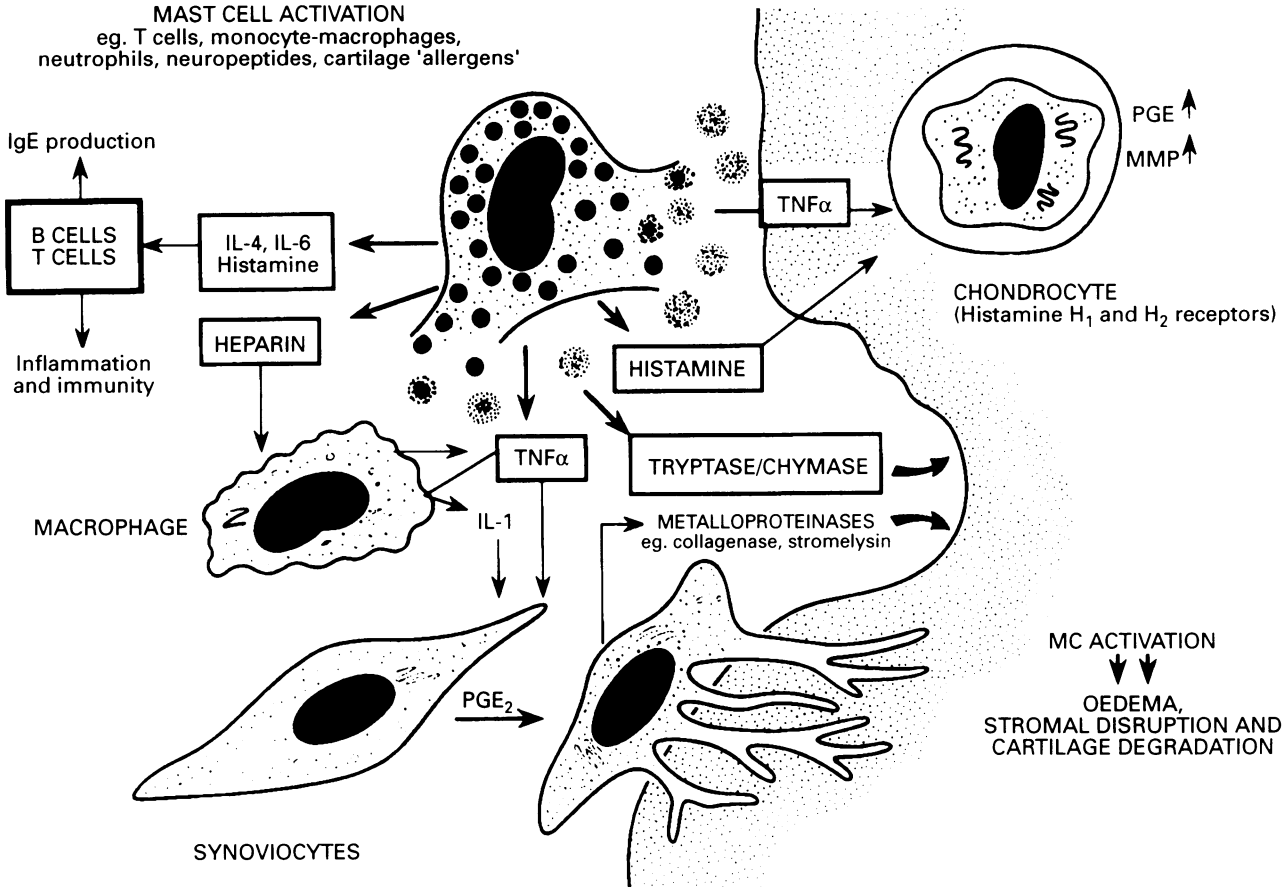
Mast cells in the rheumatoid lesion—ringleaders or innocent bystanders?

Over the past 10 years an increasing number of publications have drawn attention to the distribution and potential roles of mast cells (MCs) in rheumatoid disease.[1–5] The main reason for these cells having escaped attention for so long is undoubtedly the failure of traditional histological stains, such as haematoxylin and eosin, to identify them in rheumatoid tissues. Even the more usual MC staining procedures such as toluidine blue, Giemsa or Alcian blue have significantly underestimated MC numbers compared with the more sensitive and specific immunohistological techniques described in this issue of the *Annals*.[5] Observations of localised MC accumulations and evidence of MC degranulation at sites of cartilage erosion[1 5] have strongly suggested that MCs could play a leading role in the pathophysiological processes associated with cartilage destruction, chronic inflammation, and pannus formation. The questions currently being asked are: why do MCs aggregate at cartilage-pannus junctions; which factors are responsible for their activation in the rheumatoid lesion; and would pharmacological stabilisation of MCs ameliorate some of the destructive and inflammatory processes?

Mast cells are considered to play a pivotal role in inflammation, tissue remodelling, angiogenesis and, especially, hypersensitivity reactions.[6 7] As they contain or express numerous potent mediators, including histamine, heparin, proteinases, leukotrienes, prostaglandin D_2, cytokines, and growth factors,[6 7] it seems likely that MC secretion, activation, or degranulation has the potential to bring about microenvironmental changes in both connective tissue architecture and the behaviour of all neighbouring cells. For example, histamine induces changes in vasopermeability and tissue oedema via its effects on endothelial cells, modulates complement production by monocyte-macrophages,[8] activates chondrocytes via both H_1 and H_2 histamine receptors, and stimulates synoviocytes through H_1 receptors.[9] MC heparin interacts with growth factors, has a purported role in angiogenesis, and stimulates interleukin-1 (IL-1) production by monocyte-macrophages.[10] Soluble MC products stimulate collagenase, stromelysin, and prostaglandin E production by synoviocytes and chondrocytes in vitro[9]—responses probably explained by recent reports that human MCs express a range of multifunctional cytokines including IL-3, IL-4, IL-5, IL-6, and especially tumour necrosis factor α (TNFα)[6 7]—a factor known to stimulate metalloproteinase and IL-1 expression by specific target cells.[11 12] Indeed, as MCs contain stored TNFα, a cytokine usually considered to be of macrophagic origin and recently recognised as a crucial factor in proinflammatory processes,[12 13] its production and release by activated MCs could represent a major source of this cytokine within the rheumatoid lesion. Alternatively, MCs may also express 'repair' cytokines such as transforming growth factor β, IL-3, and IL-4,[6 7] thereby providing a repertoire of cytokines, growth factors, and other potent mediators which opens up numerous possibilities for the functional importance of MCs in the pathophysiology of rheumatoid disease.

Much interest has recently been shown in stem cell factor (SCF) (also called c-kit ligand or mast cell growth factor)—a cytokine produced by mesenchymal cells such as fibroblasts and endothelial cells which has profound effects on mast cell biology.[14 15] SCF is reported to regulate the migration and survival of mast cell precursors, promote proliferation of both immature and mature mast cells, enhance mast cell maturation, and directly induce secretion of mast cell mediators. The SCF receptor is encoded by the c-kit proto-oncogene, belongs to the transmembrane tyrosine kinase family, and is expressed by all mast cells and their precursors.[14] Recent studies have indicated that SCF is one of the most important factors influencing the numbers, phenotype, and function of MCs in health and disease, yet its production and expression in the rheumatoid lesion have yet to be examined.

The traditional view of MC activation/degranulation is that induced by allergens via the IgE mediated type I hypersensitivity response which characterises various atopic conditions. The recent report that a proportion of rheumatoid patients produced serum IgE antibodies to cartilage collagens type II, IX, and XI indicated that an 'allergic' type activation of MCs would be possible in some patients who develop such IgE specificity.[16] However, MC activation/degranulation in vivo may also be induced by soluble factors derived from a variety of cell types including T cells, monocyte-macrophages, neutrophils, eosinophils, and platelets, in addition to neuropeptides and some drugs.[6 7] These various MC secretagogues all induce degranulation with a rapid release of histamine, resulting in localised tissue oedema. For comparative purposes the 'weal and flare' reaction observed during skin prick testing of allergens gives a good visual indication of the dramatic consequences of MC activation. Similar events appear to occur intermittently within the rheumatoid lesion,[5] thereby supporting the concept that MC activation promotes connective tissue disruption and facilitates numerous cellular interactions which may exacerbate and perpetuate cartilage erosion and chronic inflammation. Thus MCs in states of activation/degranulation may well be assigned a



Schematic illustration of potential cellular interactions which may result as a consequence of mast cell activation at the rheumatoid lesion. Mast cell (MC) stimulation of synoviocytes results in both morphological transformation and enhanced metalloproteinase and prostanoid production.[9] Moreover, the MC proteinases tryptase and chymase activate precursor forms of the metalloproteinases.[18] MC stimulation of chondrocytes via histamine and tumour necrosis factor α (TNFα) promotes prostanoid (PGE) and metalloproteinase (MMP) production;[9] MC stimulation of monocyte-macrophages mediated via heparin promotes IL-1 production;[9] MC stimulation of lymphocytes via histamine and IL-4 modulates antibody production and the inflammatory cycle.[8 19 20]

'ringleader' role, initiating microenvironmental catabolic activity, contributing to the inflammatory cycle, and modulating the behaviour of all surrounding cells. The figure illustrates just a few of these possible cellular interactions.

How often do synovial MCs become activated in vivo? At present this is impossible to assess; it may well vary from joint to joint and patient to patient. Many rheumatoid synovial specimens at times of sampling show little evidence of MC degranulation, their 'intact' appearance being compatible with their traditional 'surveillance' role. However, the observation that MC granules are not exocytosed does not in itself imply that MCs are inactive. Indeed, the controlled production and release of specific MC derived cytokines and growth factors may well have import for the maintenance of local tissue homeostasis,[10] and may even contribute to the fibrotic process[17] of pannus formation. Such a functional role perhaps comes closest to the description of 'innocent bystander', although it is most unlikely that the MC becomes totally redundant in the rheumatoid lesion. Whether or not MC activation/degranulation is a crucial factor in the pathophysiological processes of joint destruction awaits the availability of specific and effective MC stabilising compounds. At present, such MC 'anaesthetics' have yet to be applied to rheumatoid patients, and final judgment on the 'Jekyll and Hyde' nature of MCs has to be adjourned, even though the biochemical and histological evidence to date appear incriminating.

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