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Editorial
Mast cells in inflammation and allergy

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The role of mast cells in inflammation and allergy was discussed in a meeting sponsored by the Inflammation Research Association and the Pulmonary Discussion Group held on 19 March 1985 at the New York Academy of Sciences. Mast cells are found predominantly in the skin, respiratory tract and gastrointestinal tract and may be triggering elements in allergic disease. Increased numbers of mast cells have been identified in inflammed tissue and, recently, reports have appeared to suggest they may participate in inflammatory synovitis (Arthritis Rheum. *27*, 852–856, 857–863, 1984).

Dr Steven I. Wasserman (Univ. California, San Diego) reviewed the role of mast cells as effectors of allergic disease. The activation of mast cells and subsequent synthesis and release of unstored mediators as well as preformed granule constituents is believed to be central to the expression of disorders such as allergic rhinitis, asthma and anaphylaxis. Although activation of mast cells has been most extensively studied using immunologic secretagogues involving IgE and IgG_4, numerous nonimmunologic activators (e.g., gastrin, substance P, opiates, basic drugs) exist that may play important roles in disease. The mast cell mediators can be subdivided into those with vasoactive properties (histamine, PAF, arachidonic acid metabolites such as LTC_4, LTD_4, LE_4 and PGD_2), those with chemotactic properties (ECF-A, ECF oligo-peptides, LTB_4, HETE, histamine), enzymes (tryptase, lysosomal hydrolases) and proteoglycans (heparin, chondroitin sulfates D and E) which are structural components of mast cell granules.

Cutaneous IgE-mediated mast cell activation has been well studied and has greatly assisted in elucidating the role of these mediators in both disease and homeostasis. The early phase, pruritis, wheal and flare, occurs within 15 to 60 min and is followed by an indurated lesion that persists for 4 to 24 h.

Mast cell activation begins within seconds of antigen challenge to be followed by dermal edema, endothelial cell activation and further mast cell degranulation. The late reaction is accompanied by fibrin deposition, tissue infiltration by neutrophils, eosinophils, basophils, lymphocytes and monocytes. The late phase response is inhibited by glucocorticoids, whereas the early response is sensitive to antihistamines. A sequence of early and late events follow antigen-induced bronchospasm although histologic events of early and late pulmonary responses have not yet been as fully elucidated. The early bronchospastic phase (5 to 60 min) is cromoglycate and β-adrenoceptor agonist inhibitable whereas the late (2 to 8 h) phase is inhibitable with glucocorticoids and also cromoglycate.

Dr R. F. Lemanske, Jr. (Univ. of Wisconsin, Madison) presented data suggesting that the early phase reactions were mast cell dependent and the late phase reactions (LPR) were a result of more general inflammatory events. He has studied a cutaneous model in the rat whereby compound 48/80 or anti-IgE is injected into the skin. These secretagogues elicit cutaneous mast cell degranulation 10 to 15 min later followed by a deep inflammatory infiltrate (mainly neutrophils) at 4 to 8 h. Mononuclear cells are present at 24 h. Intact mast cell granules also produce a neutrophil infiltration when injected into rat skin.

Further fractionation of the granules has yielded both high molecular weight (HMW) and low molecular weight (LMW) inflammatory factors of anaphylaxis (IF-A), both capable of inducing cutaneous inflammatory responses. The LMW is a small peptide (estimated mol. wt. 1407) consisting of 12 amino acids and provokes inflammation in submicrogram amounts. The HMW (mol. wt. > 10,000) fraction is currently under investigation.

The cutaneous LPR differs from cutaneous Arthus reaction in numerous ways; for example, the time of maximum onset of the Arthus in 4 h vs 12 to 24 h for LPR. The Arthus reaction is complement dependent and results from antigen-antibody complex formation whereas the LPR is complement independent and primarily involves IgE.

A LPR can also be elicited in the lung of animals whereby ovalbumin challenge via the trachea to actively immunized rats. It results in a neutrophil rich inflammation of the airways 2 to 4 h after antigen challenge.

The role of mast cells in cartilage degradation was discussed by Dr D. E. Wooley (University Hospital of South Manchester, UK). In spite of the large number of PMN in the synovial fluid of many RA patients, there was relatively little degradation of cartilage where synovial fluid was in contact with the cartilage surface. Instead, over 90% of all erosions were found at the cartilage-pannus junction. In agreement, immunohistological staining for collagenase showed it to be predominantly localized at the cartilage-pannus junction at sites of erosion and as halos around nearby chondrocytes. To gain insight into the cellular mechanisms of cartilage erosions, the cellular compositions at sites of erosion were determined histologically. They were found to vary markedly from specimen to specimen and also between different sites of erosion at the same cartilage-pannus junction. Macrophages (11 out of 27 specimens) and fibroblasts (10/27) were the dominant cell types in most specimens but others showed mast cells (3/27), PMN (2/27), dendritic (1/27) and plasma cells (1/27).

Histologically, over 40% of rheumatoid synovia showed evidence of subchondral erosion of the cartilage. These specimens were presumably infiltrated with bone derived cells including macrophages and chondroblasts. The chondroblasts were often enlarged, multinucleated and showed ruffled borders where they contacted hyaline cartilage. A hypothesis suggested by some of these findings is that factors produced by the invading cells lead to activation of the chondrocyte in the local environment and subsequent cartilage breakdown. For examples, there appears to be local accumulation of mast cells at newly formed sites of cartilage erosion and adjacent chondrocytes showed enlarged lacunae. Thus, crude preparations of mast cell products (MCP) prepared from sonicated dog mast cells, i.e., from canine mastocytomas, were examined for effects in several systems. These preparations contained good proteoglycan, but poor collagen degrading activity. When added to monocytes in the presence of lymphocytes, it induced the formation of IL-1. When added directly to cultures of human rheumatoid synovial fibroblast, it induced a 50–400 fold increase in PGE synthesis and 10–50 fold increase in collagenase release. Neither histamine, heparin nor PGE had MCP activity. Thus both MCP and MCP-induced IL-1 production might play a role in enhancing synovial fibroblast or chondrocyte synthesis of PGE and collagenase in the rheumatoid synovium.

The rat mast cell typically contains around 500 granules and each granule is a reservoir of biologically active materials. They contain histamine and heparin, hydrolases, oxidative enzymes which can cleave fibronectin, type IV collagen and proteoglycans. Dr Dean D. Metcalfe (National Institute of Allergy and Infectious Disease, Bethesda) discussed the fate of released mast cell granules. Soluble granule constituents such as histamine are quickly lost, but other substances such as chymotrypsin and superoxide dismutase remain active and adherent to the heparin matrix of the granule. Phagocytosis of granules by macrophages, eosinophils or PMN can terminate their biological activity. In skin, however, it appears that the mast cell granules are phagocytized by fibroblasts. Dr Metcalfe demonstrated granule uptake and interalization by fibroblasts which are not considered a phagocytic cell.

The fibroblast was shown to digest the granule as determined by loss of granule staining after ingestion. Thus at 24 h the fibroblasts were loaded with mast cell granules, whereas by 72 h, granules were almost undetectable within the fibroblast. Ingestion of mast cell granules led to the release of β-hexosaminidase and collagenase

24 and 48 h after phagocytosis of granules. No increase in lactic dehydrogenase (a measure of cell viability) or superoxide dismutase (a granule associated enzyme) was observed. Thus one can speculate that the role of the fibroblast is in part to quench the biological activities of the mast cell granule. This also recruits the fibroblast to become part of the inflammatory process as judged by the induced secretion of collagenase and β-hexosaminidase.

The precise role of mast cells in the pathogenesis of allergic disease and rheumatoid arthritis remains to be defined. However, the presence of numerous inflammatory mediators within these pluripotential cells and their interactions with other cell types involved in the inflammatory process suggests they have a crucially important role in these diseases.