Biological Functions of Mast Cells

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Mast cells (MCs) are myeloid cells derived from hematopoietic stem cells of the bone marrow. They circulate as immature progenitors in blood, from which they home to most tissues of the body and there develop into mature MCs by the influence of local growth factors such as stem cell factor and IL-3 (1,2).

The most clearly distinguishing feature of MCs is their remarkably high content of highly electron-dense secretory granules. The granules are filled with a number of preformed compounds ("mediators"), including bioactive amines (histamine, serotonin, dopamine, polyamines), preformed cytokines (e.g. TNF), proteoglycans of serglycin type and MC-restricted proteases (3). Serglycin is composed of a small protein "core", to which highly sulfated and thereby negatively charged glycosaminoglycans of either heparin or chondroitin sulfate type are attached (4), and previous studies have demonstrated a crucial role for serglycin in promoting the storage of histamine, serotonin and the MC-restricted proteases (5-7). The MC-restricted proteases encompass serine proteases of chymase and tryptase type, which both are endopeptidases, as well as carboxypeptidase A3, the latter an exopeptidase belonging to the metalloprotease family (6,8,9).

Studies imply that granule homeostasis is a result of a dynamic electrostatic balance between granule compounds of opposite electric charge. Hence, a reduction in negative charge (as imposed by the absence of serglycin or N-deacetylase/N-sulfotransferase-2) results in a decrease in the ability of granules to accommodate positively charged compounds. Conversely, a reduction of positively charged compounds (as imposed by the absence of proteases or histamine) results in a corresponding decrease in the ability of granules to accommodate negative charge. In addition to these electrostatic effects described above there are also indications of homeostatic mechanisms that are not necessarily of electrostatic nature.

During various pathological conditions, MCs are activated. A hallmark event during such circumstances is that MCs undergo degranulation, by which the preformed granule compounds are released to the exterior (2,10). MC activation can be induced by many mechanisms, of which binding of multivalent antigen (allergen) to IgE molecules bound to their high affinity cell surface receptor (FcεRI) represents the "classical" MC activation that is a hallmark event during allergic responses (10). However, MCs can be activated by numerous other mechanisms, including stimulation by anaphylatoxins, neuropeptides and various toxins, as well as through engagement of toll-like receptors (2).

Undoubtedly, MCs are mostly known for their detrimental impact on various allergic conditions including allergic asthma. However, MCs have during more recent years been recognized for having a detrimental impact on a panel of additional disorders, including cancer, atherosclerosis, arthritis, aneurysm formation, diabetes, fibrosis and obesity. Conversely, MCs have also been implicated to carry beneficial functions, most notably in the context of bacterial infection (11).

Having identified a role for MCs in a variety of pathological settings, a major focus for current research is to gain a deeper understanding of the molecular mechanisms by which MCs influence a given pathological condition. Recent studies have shown that, in many cases,

the effects of MCs on an immune reaction are closely associated with the biological actions of the released preformed granule compounds, as exemplified by the recent findings showing that MC granule amines and proteases account for many of the protective and detrimental effects of MCs in various inflammatory settings.

Based on these findings, another major focus for MC researchers is to find ways to intervene with MC-mediated pathological events, as exemplified by the use of histamine receptor antagonists and various inhibitors of MC-restricted proteases. A novel approach for this purpose is to selectively induce MC apoptosis by permeabilization of their secretory granules. We have recently developed this concept and have shown that this strategy is an effective means of selectively depleting MCs both in vitro and in vivo (12,13). Recently, we have also shown that one of the MC granule compounds, tryptase, in addition to being released to the exterior can be found in the nuclear compartment of MCs. Here, tryptase has been found to cause truncation of core histones, thereby removing sites for epigenetic histone modification (14).

In this presentation, novel aspects of MC granule function are discussed.

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