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• EDITORIAL •

Mechanisms for amplified mediator release from colonic mast cells: Implications for interstinal inflammatory diseases

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The mast cell is an enigmatic cell type whose physiological function has preoccupied large numbers of investigators for decades[1]. Some have concluded that the absence of mast cells is incompatible with life, at least in humans, because no human conditions have been documented where these cells are absent from the body. On the other hand, mice harboring specific mutations in certain growth factors, or their receptors, that lead to apparently an almost total ablation of the mast cell lineage, are viable, although they do have several documented abnormalities and may exhibit altered inflammatory responses in a variety of tissues[2]. The viability of such animals may reflect redundancy in the murine system for specific mast cell functions, and/or that other cell types adapt to become repositories of characteristic mast cell mediators. But in any event, mast cells have long been considered to play specific roles in pathophysiology, particularly in disease states that are characterized by allergic inflammation[1-5]. In the setting of the gastrointestinal tract, release of mast cell mediators has been thought to contribute to tissue injury and inflammation, as well as alterations in epithelial and smooth muscle function, in conditions such as food allergy, systemic anaphylaxis, ulcer disease and inflammatory bowel diseases, as well as, more controversially, irritable bowel syndrome[3,5-13]. The spectrum of mast cell involvement has also been expanded by recognition that they can participate in biological events not classically related to allergic responses, such as innate immunity, the phagocytosis of bacteria and cross-talk with the peripheral and enteric nervous systems[14-16].

Mast cells are activated classically by cross-linking of membrane IgE receptors[17]. *In vivo*, this occurs when a genetically susceptible individual mounts an IgE antibody response to a foreign protein that would be seen as innocuous by the immune system of those who are not allergic. The IgE antibodies bind with great avidity to the mast cell IgE receptors. Thus, because mast cells in the tissues are also long-lived, the allergic individual becomes chronically sensitized, with mast cell IgE receptors occupied by allergen-specific IgE, priming the cell to be activated by a subsequent exposure to the allergen. Binding of allergen to adjacent IgE molecules on such primed cells results, in turn, in apposition of the IgE receptors, thereby initiating a signal transduction cascade, involving, among other steps, mobilization of intracellular calcium and activation of protein kinases, that leads ultimately to release of mast cell mediators[17,18]. The mediators that account for the biological effects of mast cell activation may be stored in cytoplasmic granules, such as histamine and a protease known as tryptase that were studied by He and co-workers in work reported in the *Journal*[19-24]. Other potent mediators, including various cytokines and leukotrienes, are synthesized *de novo*, with delayed or rapid kinetics depending on whether gene transcription is or is not required, respectively[19]. The process of mast cell activation can be mimicked *in vitro* by artificially stimulating aspects of the signaling cascade. He and co-workers accomplished this by using antibodies directed against the IgE molecule itself, which cause allergen-independent IgE receptor cross-linking, or a calcium ionophore, which causes an increase in the levels of cytoplasmic calcium.

In addition to the immunological activation of mast cells, it has been known for many years that various other substances can initiate or potentiate mast cell mediator release[25]. These include neuropeptides, highly basic compounds, peptides from bee venom, and adenosine. The work from He *et al.*, conducted with mast cells isolated from human colonic specimens, extends this list to include histamine and proteases, including trypsin and mast cell tryptase itself[20-24]. While these and other investigators had shown that proteases can activate some mast cell populations to release histamine, it was important to demonstrate directly that they were active against human intestinal mast cells due to the known existence of substantial functional and biochemical heterogeneity among mast cells isolated from different tissue sites and from different species[26-29]. Moreover, the ability of histamine to activate tryptase release from intestinal mast cells had not previously been demonstrated; rather, in other mast cell populations, histamine has been shown to inhibit mediator release, although others have shown that histamine H_1 receptor antagonists can block mediator secretion from basophils, consistent with the findings of He *et al.*[30,31]. The work from He and co-workers also implies important autoregulatory mechanisms that almost certainly contribute to the overall level of mediator release from mast cells *in vivo*. Thus, not only are histamine and tryptase released from mast cells, but they also likely stimulate further mediator release once present in the extracellular space. The concentrations of histamine capable of activating mediator release are well within the range that might be expected in the vicinity of activated mast cells[20]. Likewise, the biological significance of the inferred effect of tryptase on mediator release is illustrated by the fact that inhibitors of the proteolytic activity of this enzyme significantly reduce mast cell mediator release evoked by IgE cross-linking[23]. Overall, these findings suggest that mast cells participate in a self perpetuating amplification mechanism that would be capable of sustaining mediator release, at least from the granule-associated pool, until released mediators had been cleared from the area by diffusion or metabolism. However, there also appear to be some "brakes" to the system that would preclude wholly uncontrolled release of the panoply of potent mast cell mediators. For histamine in

particular, the effect on mediator secretion was biphasic, with higher concentrations of the amine less effective than lower ones[20]. Thus, released histamine would amplify ongoing mediator release from the cell of origin or others in the neighborhood, but only up to a certain point. The biphasic effect of histamine may also explain differences between the findings of He *et al.* and those reported previously by others[20,30].

The authors also have begun to examine the specific receptors and other mechanisms that contribute to protease-activated mediator release from human colonic mast cells. The process is active rather than cytotoxic, and can be reproduced by peptide agonists specific for a member of a novel class of receptors, the proteinase-activated receptors, or PAR' s[32]. PAR' s are G-protein coupled receptors that are activated by proteolytic cleavage, revealing a tethered ligand. The prototypic member of this class is the thrombin receptor, or PAR-1[32]. In addition, PAR-2 has been shown to contribute to inflammatory reactions, including in the intestine, and is activated by both trypsin and tryptase, as well as by synthetic peptides that mimic the sequence of the tethered ligand[32-36]. He *et al.* developed evidence that mast cells are likely activated by PAR-2 ligation, such as would be stimulated by release of tryptase itself [21]. On the other hand, the receptor subtype mediating the effect of histamine on tryptase release from human colonic mast cells is not yet known.

Some minor caveats should be raised about the studies presented. First, the mast cells used for the experiments were studied as an unpurified preparation in which mast cells constituted only about 5% of the total cell number[20-24]. Thus, the effects of either histamine and proteases on mediator release could in fact be indirect, and mediated secondarily by another substance released from a contaminating cell type responsive to either agent. However, this scenario does not necessarily detract from the clinical relevance of the responses studied by He and co-workers, because mast cells are not activated in isolation *in vivo*. Likewise, the presence of PAR-2, although not histamine receptors, has been demonstrated directly on human mast cells in a variety of tissues using immunohistochemistry. Second, the authors speculate that mast cells in the gut wall might constantly be exposed to pancreatic trypsin during the normal process of digestion, and that this might evoke mediator release. However, even if a small proportion of luminal trypsin does leak across the small intestinal epithelium in intact form to encounter subepithelial mast cells, and at concentrations comparable to those needed to activate mast cells *in vitro* (which is unproven at the present time), this is unlikely to occur in the colon, and so the studies would need to be repeated using mast cells isolated from the small intestine to understand fully whether the findings have physiological or pathophysiological relevance. Finally, we know little about the persistence of mast cell mediators in the interstitium following their release. While the concentrations of both histamine and proteases capable of activating colonic mast cells are at least theoretically within the biological range immediately following degranulation, it is unknown whether these concentrations remain elevated for long enough to contribute significantly to amplifying subsequent mediator release.

The caveats notwithstanding, the studies of He *et al.* enhance our understanding of the possible roles of mast cells in initiating and/or perpetuating intestinal disorders, including inflammatory bowel diseases and peptic ulcer disease. Knowledge of the mechanisms that regulate mediator release from intestinal mast cells specifically should aid in our ability to modulate the activity of this cell type, with potential therapeutic benefits given the wide range of adverse effects of released mediators. Indeed, He and co-workers themselves suggest that proteinase inhibitors might be attractive targets for drug development, although the biological actions of such compounds would almost certainly extend beyond simply an effect on mast cell activation, given the wide distribution of PAR' s[23]. Further, the findings may shed light on pathogenic mechanisms in diseases not currently appreciated as being dependent on mast cells and their mediators. For example, colon cancer cells often release novel trypsins into their environment, and this in turn could conceivably account for the fact that mast cells are often observed at the margins of tumors examined histologically, based on the possibility that such cells are chronically activated by the tumor microenvironment[37-39]. Overall, progress in this field should be expected to improve the understanding and treatment of a whole host of digestive disorders.

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