Truly MASTerful cells: mast cells command B cell IgE synthesis.

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Editorial

The effector functions of mast cells in allergic inflammation through the inflammatory mediators and cytokines secreted by these cells have been extensively studied and well recognized. These cells are distributed throughout the connective tissue, where they are situated adjacent to blood and lymphatic vessels as well as beneath epithelial surfaces. When encountering allergens or other stimuli, mast cells rapidly release spasmogenic and vasoactive mediators, which act on smooth muscles and blood vessels. Concomitantly, these cells are responsible for recruiting other leukocytes to the inflammatory sites, which can contribute to the amplification and progression of the inflammatory reactions initiated by mast cells. However, the view that mast cells are simply potent effector cells is being challenged, and recent data suggest that these cells may have important regulatory functions in the immune system.

Previously, Gauchat et al. (1) reported that human mast cell and basophil lines as well as freshly purified lung mast cells and peripheral blood basophils can induce IgE synthesis by B cells. In the case of primary mast cells and mast cell lines, this activity is dependent on the presence of IL-4, whereas for basophils, no exogenous cytokines are required. In this issue of the *Journal*, Pawankar et al. (2) report an extension of these findings by using mast cells obtained from tissues which are clinically involved in allergic inflammation. They were able to purify nasal mast cells (NMC) from inferior turbinate mucosa acquired during surgery (conchotomy) and obtained cells of $> 99\%$ purity and $> 95\%$ viability. They found that NMC from patients with perennial allergic rhinitis contain high levels of IL-4 and IL-13 and secrete these cytokines when activated by allergens. They then showed that NMC are able to induce IgE synthesis by purified tonsillar B cells in the presence of a mite allergen, Der fII. In contrast, NMC from patients with chronic infective rhinitis fail to do so. The presence of the specific allergen is essential but exogenous cytokines are not required. Presumably, IL-4 and IL-13, secreted by the allergen-activated mast cells, contribute to the induction of IgE production. Indeed, NMC-induced IgE synthesis is partially blocked by neutralizing anti–IL-4 mAb and completely blocked by anti–IL-13 mAb.

This study also supports the significant observation made previously by Gauchat et al. (1) that activated mast cells express CD40L (ligand for CD40 on B cells), an important cell surface antigen expressed by T cells and critically involved in T/B cell interactions leading to immunogobulin production. It is noteworthy that CD40L appears to be induced on mast cells under allergic inflammatory conditions, as NMC from patients with allergic rhinitis express significantly elevated levels of this ligand as compared with those cells from patients with chronic infective rhinitis. The essential role of this molecule in mast cells' induction of IgE synthesis is substantiated by the finding that the IgE production is inhibited by anti-CD40L mAb. In addition to the upregulated expression of cytokines and CD40L, NMC from the allergic patients also contain significantly greater numbers of the high affinity IgE receptor (FcεRI). This finding is consistent with the previously reported correlation between the number of FcεRI on basophils and serum IgE levels (3 and references cited therein). Furthermore, the present study shows that FcεRI expression on NMC can be upregulated by IL-4.

Therefore, under inflammatory conditions, mast cells are induced to express higher levels of FcεRI, CD40L, as well as Th2-type cytokines, IL-4 and IL-13. As a result of heightened FcεRI expression, these cells can become more highly sensitized, because they are able to acquire greater amounts of allergen-specific IgE, captured by FcεRI. Upon further exposure to the allergens, the cells are triggered to secrete cytokines, as well as various mediators. In the mean time, with the acquisition of CD40L on the cell surface and the capability to produce cytokines, such as IL-4 and IL-13, these mast cells become suited for interacting with B cells and direct the latter to produce IgE. In this fashion, mast cells are in fact functioning as a surrogate T helper cell. Some similarities between mast cells and T cells, including the shared adhesion receptors, have been reported previously (4). The striking resemblance between these two cell types is further underscored by the presence of CD40L, the secretion of Th2-type cytokines, and especially the ability to induce B cell immunoglobulin production.

Based on existing data, mast cells may be able to exert influences on T cells, in addition to directing B cell function. Mast cells are a major source of cytokines (e.g., IL-4, IL-10, and IL-13) which can presumably signal naive and memory T cells to preferentially differentiate into the Th2 subset. Another exciting and potentially important development that has not yet received significant attention is the observation that mast cells are able to present antigen to T cells in a MHC class II-restricted and co-stimulatory molecule-dependent fashion (5, 6). It is possible that through presenting antigen to T cells, mast cells can direct T cells into becoming polarized Th2 populations. Therefore, mast cells appear to have diverse functions and potential to contribute to allergic inflammation through multiple pathways. First, because of the various inflammatory mediators they secrete, these cells can exert short-range effector functions. Second, through cytokines they produce and possibly through their antigen presentation capability, they can modulate T cell activation and differentiation; Th2 cells in turn would lead to heightened IgE production. Finally, as suggested by the studies of Pawankar et al. (2) and Gauchat et al. (1), these cells can directly act on B cells and induce IgE synthesis. The increase in allergen-specific IgE might result in greater mast cell sensitization and subsequent activation. Thus, processes described above can be perpetuated and the allergic inflammation can be amplified.

In summary, recent studies have suggested that mast cells can regulate allergic inflammation by directly controlling IgE production. Additional studies are obviously needed to determine the in vivo relevance of these findings. However, it is possible that in chronic inflammatory situations, mast cells, after being sufficiently activated, may be able to replace the func-

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tion of T helper cells, and this perhaps leads to a higher efficiency in terms of inflammatory responses that can be achieved locally and temporarily. If mast cells in fact contribute to allergic inflammation in a much broader and compelling fashion than previously conceived, one would believe that mast cell inhibitors may have profound effects in suppressing allergic inflammation and deserve to be more actively investigated. Moreover, the important role of mast cells in host defense against infection has been recently highlighted (7). It is conceivable that under inflammatory conditions that occur in infection, mast cells may be able to take control of the local immune response by directly signaling B cells to produce immunoglobulin. Therefore, these recent findings should have an impact on our view of mast cells in the immune response in general.

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