Effector and potential immunoregulatory roles of mast cells in IgE-associated acquired immune responses

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Mast cells are best known as critical effector cells in anaphylaxis and other examples of IgE-associated immediate hypersensitivity reactions. However, mast cells also can contribute to the development of the late-phase responses that occur in some sensitized subjects hours after initial exposure to specific antigen, and can promote many of the features of chronic allergic inflammation, including tissue remodeling and functional changes in the affected organs. In addition to such effector cell functions in IgE-associated immune responses, recent evidence indicates that mast cells can importantly influence the sensitization phase of at least some acquired immune responses, and can contribute to the pathology of autoimmune disorders and to the expression of peripheral tolerance.

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Introduction

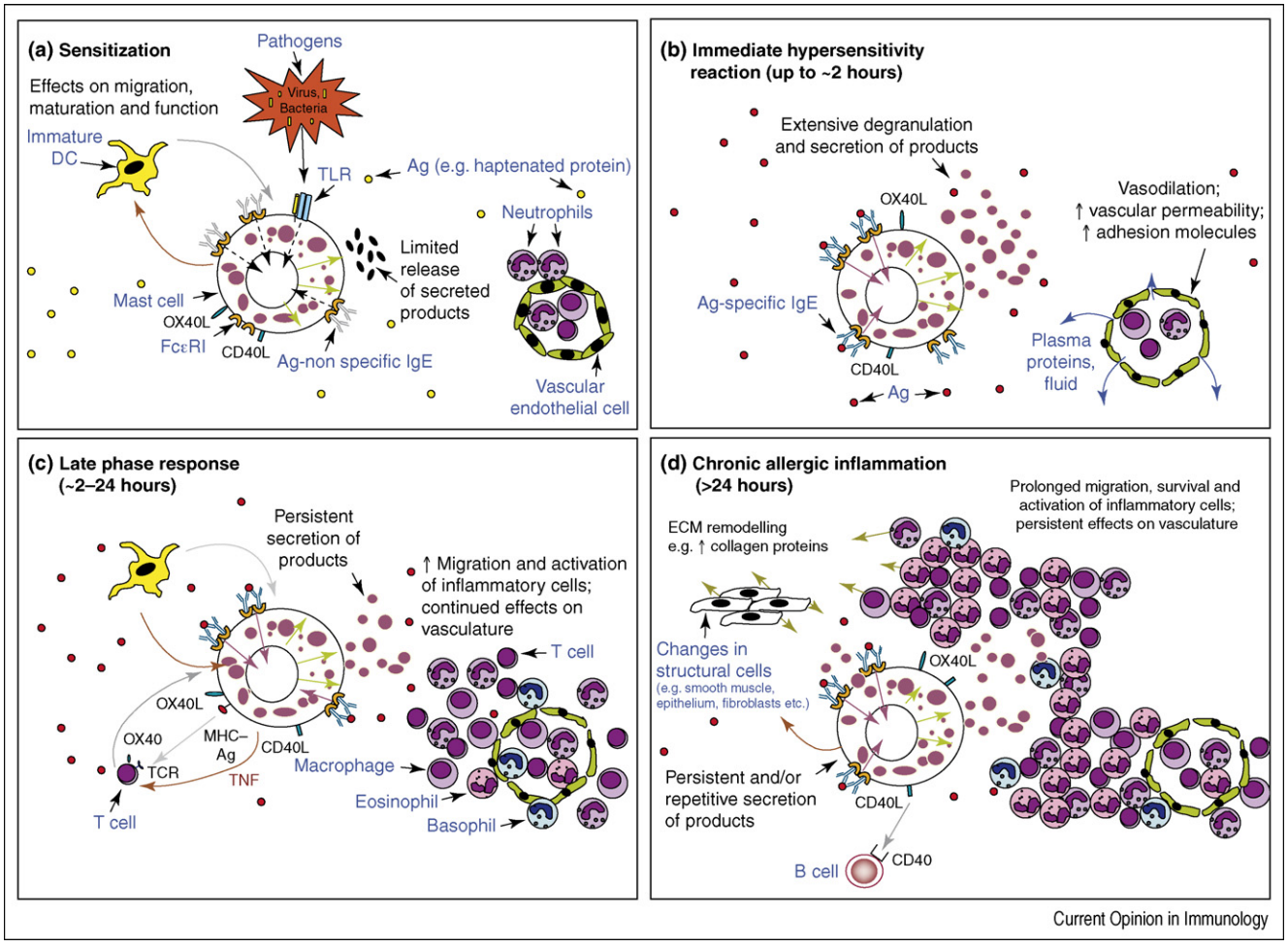
Mast cells are important effector cells in anaphylaxis and in IgE-associated allergic diseases such as atopic asthma, allergic rhinitis (hayfever) and atopic dermatitis (eczema) [1–3]. In such subjects, mast cells bear on their surface, bound to high affinity receptors for IgE (i.e. FcεRI), IgE antibodies that have specificity for the antigen(s) to which the subject is sensitive [1–3]. In such antigen-sensitized individuals, subsequent exposure to bi- or multi-valent antigen that is recognized by the mast cell-bound IgE initiates crosslinking of FcεRI-bound IgE on the mast cell surface, aggregation of the FcεRI, and the subsequent activation of mast cells to secrete preformed mediators stored in the cells' granules (in a process called 'degranulation') and to synthesize *de novo* several cytokines, chemokines and lipid mediators [1–3]. This IgE-dependent mast cell activation, in some settings together with similar antigen-, IgE- and FcεRI-dependent activation of basophilic granulocytes ('basophils', which also express FcεRI), in turn contributes to the acute manifestations of IgE-dependent reactions to antigen, including anaphylaxis, bronchoconstriction (in subjects with asthma), and sneezing and rhinitis (in subjects with allergic rhinitis) [1–3].

This review focuses especially on the roles of mast cells in: the sensitization phase of acquired immune responses, when the host first encounters antigen; the immediate 'mast cell autonomous' phase of those immediate hypersensitivity reactions that are initiated when challenge with specific antigen induces activation of tissue mast cells via the FcεRI-bound antigen-specific IgE of the cells; the IgE-associated late phase response (LPR) that is characterized by recruitment of inflammatory cells to the site of antigen challenge; and IgE-associated chronic allergic inflammation that is associated with structural and related functional changes in the underlying tissue (Figure 1). But, before addressing these topics, we will briefly review certain important aspects of mast cell biology, as well as some mouse models that are currently being used to assess mast cell function *in vivo*.

Basic biology of mast cells

In mammals and other vertebrates, mast cells reside in virtually all vascularized tissues and can be especially numerous in anatomical sites that are directly exposed to the environment, including the skin, airways and gastrointestinal tract [1–4]. It has long been known that mast cells arise from hematopoietic progenitor cells and that mature mast cells ordinarily do not circulate in the blood; instead, mast cells acquire their mature phenotype locally in the tissues in which they will ultimately reside [5]. Two reports recently attempted to clarify the hematopoietic developmental pathway that leads to the generation of committed mast cell progenitors in adult mice, but arrived at rather different conclusions [6,7]. Although it will be important to resolve the differences between the results presented in those two reports, several lines of evidence indicate that changes in mast cell numbers, as well as local changes in the tissue distribution and/or phenotypic characteristics of the cells, can be finely controlled by growth factors such

Figure 1



Mechanisms by which mast cells (MCs) might **(a)** promote the transition from innate to acquired immune responses or contribute to the development of **(b)** immediate hypersensitivity reactions, **(c)** late phase responses and **(d)** chronic allergic inflammation. Some of the MC surface structures and secreted products that can influence various aspects of the biology of dendritic cells (DCs), T cells, B cells, granulocytes and other leukocytes, as well as vascular endothelial cells and other cells normally resident in the affected tissues such as smooth muscle cells, fibroblasts, epithelial cells, nerves, etc., are shown. (a) MCs can respond to local signals (e.g. certain haptenated non-microbial proteins or other antigens [Ags], or the products of pathogens). Such responses can include secretion of mediators or expression of other functions that can enhance the sensitization phase of acquired immune responses through effects on DC migration, maturation and/or function. For example, exposure to Ag-non specific IgE might 'prime' MCs to express higher levels of mRNA for some crucial mediators or cytokines (see main body of text for details). MC activation also can contribute to the development of the inflammation associated with certain innate immune responses. (b) In hosts sensitized to express an IgE-associated immune response, secondary exposure to bi- or multi-valent Ag initiates IgE + Ag-dependent MC activation. The clinical features of the ensuing 'immediate hypersensitivity' reactions primarily reflect the actions of cells normally resident at such sites (MCs, vascular endothelial cells and smooth muscle cells, nerves, etc.). (c) Sometimes, IgE-associated 'immediate' reactions are followed, hours later, by 'late phase responses' (LPRs). MCs can contribute to such reactions through effects of secreted mediators that promote the recruitment and/or functional activation of circulating leukocytes, as well as by persistent effects on cells resident at the site. IgE-dependent MC activation can also promote DC migration from sites of Ag challenge. Direct activation of effector T cells by Ag, and perhaps bi-directional interactions between MCs and T cells (see text), also can contribute to LPRs. (d) At sites of prolonged or repetitive exposure to specific Ag, MC activation can be prolonged and/or recurrent, MC numbers can increase, and MC phenotype and/or anatomical distribution can change. In such settings, MCs can contribute significantly to many of the features of chronic allergic inflammation, including functional changes in the affected organ (e.g. airway hyperresponsiveness to immunologically non-specific agonists of bronchoconstriction in the asthmatic lung). MCs also might have effects (including those mediated through interactions of MC CD40 ligand [CD40L] with B cell CD40 and/or effects of MC-derived histamine on T-cell polarization [see text]) that could promote local IgE production. However, in some circumstances (not shown), certain MC products or functions can serve to limit or to resolve aspects of these inflammatory responses. Arrows within MCs: black dashed arrow, signaling related to occupancy of FcεRI by IgE in the absence of known specific antigen; red arrow, strong FcεRI aggregation signal; green arrow, synthesis of newly formed mediators and products.