ABSTRACT

Allergic diseases, such as atopic rhinitis, bronchial asthma and urticaria, are prevalent and increasing in frequency. Mast cells are known to play a central role in the immediate phase reaction of allergic diseases through the IgE-mediated release of a variety of chemical mediators, such as histamine, leukotrienes and prostaglandins. In contrast, T lymphocytes, basophils and eosinophils are thought to be responsible for inducing the late phase response. However, whether the mast cell can be simplistically assigned a role in the immediate phase allergic response and whether mast cells are necessary for the ongoing allergic response, including the development of hyperresponsiveness, remains to be completely studied. In the present article, the author will discuss the integrated roles of mast cells in IgE-mediated allergic inflammation, with specific emphasis on the roles of mast cell-derived cytokines in the late phase allergic response and chronic allergic inflammation.

Key words: allergy, FcεRI, local IgE synthesis, mast cell.

INTRODUCTION

The chain of events that leads to a type I allergic reaction includes the recognition of allergen by the antigen-presenting cells (APC), antigen presentation to T cells, activation of T cells resulting in the production and release of cytokines, such as interleukin (IL)-4 and IL-13, class switching of IgM+ B cells to IgE+ plasma cells, the production of IgE, binding of IgE to the high-affinity IgE receptor (FcεRI) on the surface of mast cells and the cross-linking of the bound IgE–FcεRI complex with multivalent allergen on subsequent exposure to the allergen, resulting in the release of inflammatory mediators, such as histamine, leukotrienes (LT) and prostaglandins. However, the allergic reaction in a type I allergic disease, such as allergic rhinitis or atopic asthma, is comprised of two phases, an immediate phase reaction and a late phase allergic reaction. The immediate phase allergic reaction occurs as a result of cross-linking of the allergen-specific IgE, bound to the IgE receptor on the surface of mast cells, to allergen, resulting in the release of chemical mediators, such as histamine, LT and prostaglandin. By contrast, the late phase allergic reaction is largely inflammatory, occurring as a result of the inflammatory mediators released by the infiltrated cells. Thus, it is well known that mast cells play a central role in the immediate phase allergic reaction, whereas other cells, such as T cells, eosinophils and basophils, have been considered to play important roles in the late phase allergic reaction.

However, the question now is not just which of these effector cells have more important roles in allergic inflammation, but what exactly each of these cells do to perpetuate allergic inflammation and, in situations where their functions overlap, what the relative contribution of each cell type is to allergic inflammatory responses. Still, after decades of extensive study on the biology of these effector cell types, the complete spectrum of their roles in allergic inflammation remains to be defined. This is especially true with regard to the mast cell, where, despite important observations on the biology of mast cells and a variety of interesting hypotheses, the complete role of the mast cell in allergic inflammation is not yet well defined.

The purpose of the present review is not to discuss all of the roles of each effector cell in allergic disease. Instead, taking perennial allergic rhinitis (PAR) as a prototype of a type I allergic disease, I will discuss some of the shock organ-specific characteristics and roles of mast cells in allergic inflammation, thereby drawing a link between the
biology of these cells and the clinical expression of allergic disease.

Clinically, PAR is characterized by repeated attacks of sneezing, runny nose (rhinorrhea) and blockage of the nose (nasal obstruction). These typical symptoms are observed throughout the year and the most common cause of PAR is the house dust mite. This disease is observed even in childhood and is more common in those with a family history of atopic disease. These patients are diagnosed on the basis of the above-mentioned typical symptoms, anterior rhinoscopic findings of a pale, boggy nasal mucosa, often with hypertrophy of the turbinates and a watery nasal discharge, a positive radioallergosorbent test (RAST), positive skin and nasal provocation tests, as well as nasal eosinophilia (by nasal smear examination).

The immediate phase allergic reaction or the early phase response occurs within several seconds of encounter with antigen and occurs as a result of cross-linking of the bound allergen-specific IgE by allergen, resulting in the release of histamine, LT and prostaglandin and is clinically characterized by sneezing, rhinorrhea and nasal obstruction. Sneezing results from the action of histamine on H1 receptors, present on the sensory nerve endings of the trigeminal nerve in the subepithelium of the nasal mucosa. Of particular importance is the action of histamine on the subepithelial blood vessels, causing vasodilatation, hyperemia and mucosal edema (Fig. 1). These facts provide definite evidence that the mast cell is the central cell involved in the type I allergic reaction.

In contrast, the late phase allergic reaction occurs several hours after the early phase response (4–6 h), with a recurrence of symptoms that lasts for about 18–24 h. The late phase response is characterized by prolongation of symptoms, such as occasional sneezing, rhinorrhea and, most predominantly, sustained nasal blockage. Several in vivo studies have shown that the late phase allergic reaction occurs as a result of cytokines released from T lymphocytes, which induce the up-regulation of adhesion molecules like vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 on endothelial cells. This results in the infiltration of
eosinophils, basophils and T cells and the subsequent release of a number of soluble products, such as prostaglandins (PG), LT, platelet-activating factor (PAF), eosinophil cationic protein (ECP), major basic protein (MBP) and so on (Fig. 1).8–10 The physiological effects of the newly synthesized LT, which may include LTC4, LTD4 and LTE4, are mediated by increasing vascular permeability, vasodilatation and inducing mucus secretion. Moreover, studies on the levels of mediators, such as histamine, PGD2 and tryptase, in nasal lavage fluid after allergen challenge have implicated basophils, but not mast cells, as the main histamine-containing cells involved in the late phase (based on results that the levels of histamine, but not PGD2, increase in late phase reaction (LPR), because only mast cells and not basophils contain PGD2).9,10 However, recent studies have demonstrated that mast cells are a source of multifunctional cytokines, suggesting that these cells may also play important roles in the cell infiltration associated with the late phase allergic reaction.11–13

Since the discovery of the granule-laden mast cell (Mastzellen) in 1879 by Paul Ehrlich,14 and the description by Riley et al. about the presence of the preformed mediator, histamine, in the mast cell,15 much has been learnt about its biochemical characteristics and functional properties. In 1966, Enerback first classified mast cells (in rats) based on the morphology, size and density of granules as well as their staining properties.16 Subsequently, Irani et al. classified human mast cells into two phenotypically distinct subpopulations, based on the type of neutral proteases they express. Specifically, MC (T) mast cells contain only tryptase and the MC (TC) mast cells contain chymase, cathepsin G and carboxypeptidase in addition to tryptase.17 Tryptase is known to exert different functions, such as: (i) cleavage of the bronchodilator peptides, factor VII, peptide histidine-methionine and vasodilator calcitonin gene-related peptide; (ii) sensitization of bronchial smooth muscle to contractile agents; (iii) a kallikrein-like activity; (iv) cleavage of matrix; (v) a mitogenic activity for fibroblasts and epithelial cells; (vi) stimulation of release of the granulocyte chemoattractant IL-8; and (vii) up-regulation of ICAM-1 expression on epithelial cells. Chymase is involved in the degradation of the neuropeptide neurtensin and IL-4 and stimulation of secretion from gland cells. Thus, it is now well known that mast cells have phenotypically distinct subpopulations and exhibit not only species-specific but also site-specific heterogeneity.

Mast cells are derived from CD34+ hematopoietic progenitor cells,18–20 which migrate to and undergo maturation in the peripheral tissues. Interactions between the tyrosine kinase receptor c-kit, which is expressed on the surface of mast cells and their precursors, and the c-kit ligand, stem cell factor (SCF), are essential for normal mast cell development and survival.21 Stem cell factor is expressed on the plasma membrane of a variety of structural cells, such as fibroblasts and vascular endothelial cells, and the extracellular domain of SCF can be released from these cells by proteolytic cleavage.21 In fact, it is possible that the local levels of SCF may regulate not only the numbers, but also the phenotypes of mast cells in normal and inflammatory tissues and also contribute to the striking alterations in the proportion of mast cells observed in association with a variety of disease processes.21–28 However, it is also likely that a complex interplay of cytokines and growth factors other than SCF may regulate the development and phenotypic characteristics of human mast cells.
In humans and many other mammalian species, the numbers of mast cells in normal tissues exhibit considerable variation according to the anatomic site. Moreover, the numbers of mast cells vary in association with the underlying inflammatory or immunologic condition.\(^{21,23-28}\) For example, in the nasal epithelium of normal subjects, mast cells are undetected (although mast cells are detected in the lamina propria), but in patients with allergic rhinitis there is an increase in the numbers of MC (T) cells into the nasal epithelial compartment (Fig. 2).\(^{28}\) Whether these MC (T) cells are migrating mature mast cells that normally reside in the lamina propria, but have migrated under the influence of some specific stimuli, or are newly differentiated mast cells from precursors that reside in the nasal mucosa is not yet quite clear. Furthermore, the selective migration/increase of MC (T) cells is also of interest.

**MAST CELLS AS A SOURCE OF MULTIFUNCTIONAL CYTOKINES**

Cytokines are a highly potent, biologically active, diverse group of glycoproteins that are synthesized and secreted by many cell types in response to their activation and can modulate both specific immune responses and immunologically non-specific inflammation, through their ability to alter the function or gene expression of the responsive target cells. Allergic inflammation is characterized by many cytokine-dependent processes, including: (i) the induction of IgE synthesis (IL-4 and IL-13); (ii) eosinophil recruitment, development and survival (IL-3, IL-5, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-16 and certain C-C chemokines, such as regulated upon activation, normal T cell expressed and presumably secreted (RANTES)
and Eotaxin); (iii) recruitment of monocytes and T cells (IL-16 and certain C-C chemokines, such as RANTES); and (iv) basophil recruitment (tumor necrosis factor (TNF)-α, IL-4) or enhanced mediator production (IL-3, IL-4, the C-C chemokine macrophage inflammatory protein (MIP)-1α). Moreover, cytokines promote allergic inflammation by enhancing the recruitment of leukocytes through the up-regulation of adhesion molecules, such as P-selectin, E-selectin and VCAM-1, and on vascular endothelial cells. Finally, cytokines can also critically influence the development and perpetuation of chronic allergic inflammation.

 Mast cells represent a potential source of many cytokines that may influence allergic inflammation and the synthesis and release of these products can be induced via IgE-dependent mechanisms. When mouse mast cells are activated via the FceRI, they can express increased levels of mRNA for a range of cytokines (IL-1α, IL-3, IL-4, IL-5, IL-6, GM-CSF, MIP-1α, MIP-1β and several other C-C chemokines) and also secrete substances with corresponding activities. In humans too, recent studies have clearly shown that mast cells are a potential source of several cytokines, including IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, TNF-α and basic fibroblast growth factor. Bradding et al. first reported the expression of IL-4, IL-5 and IL-6 in bronchial mast cells of atopic asthmatics. It is well known now that bronchial and nasal mast cells from atopic asthmatics and allergic rhinitics are an important source of the T helper (Th)2-type cytokines IL-4, IL-5, IL-6, and IL-13 (Fig. 3). We have recently demonstrated that nasal mast cells from patients with PAR to house dust mite can release the IL-4, IL-6 and IL-13 proteins when stimulated by specific allergen (mite antigen) and that the levels of secreted IL-13 are 10-fold more than that of IL-4. However, it is also of interest that there is some heterogeneity in the cytokine expression between subsets of mast cells, in that MC (T) mast cells preferentially express IL-5, IL-6 and IL-7, whereas MC (TC) mast cells preferentially express IL-4. Isolated skin mast cells, which are nearly all MC (TC), express high levels of IL-4 immunoreactivity, but almost no immunoreactivity for IL-5 or IL-6. Such differences in the distribution of cytokine expression between subsets of mast cells, even within the same target tissue, suggest a difference in the capacity of mast cell subsets to produce various cytokines and therefore a difference in their specific roles in allergic inflammation.

**The IgE Receptor and Regulation of its Expression in Mast Cells**

Ishizaka and Tomioka first described the presence of IgE receptors on mast cells and that these cells could be activated to degranulate when cell surface-bound IgE is cross-linked by allergen. Therefore, the expression of the high-affinity IgE receptor (FceRI) in mast cells and basophils is critical to the development of allergic diseases. The FceRI is a tetrameric structure, comprising an α-subunit, a β-subunit and two disulfide-linked γ-subunits. The extracellular portion of the FceRIα chain contains the entire IgE-binding site. The β-subunit is considered to be largely within the cell membrane, spanning it four times so that both the amino- and carboxy-termini are within the cytoplasm. The β- and γ- subunits are known to be involved in signal transduction. Studies in FceRIα chain-deficient mice have demonstrated the inability of these mice to exert allergen-induced anaphylaxis, even with normal numbers of mast cells. Several lines of evidence indicate that mast cells or basophils must display the high-affinity IgE receptors on their surface to be able to have significant IgE antigen-specific effector function.

Previously, two groups have independently demonstrated that the level of FceRI expression on circulating basophils of patients with atopic dermatitis exhibits a positive correlation with serum IgE. In our studies, we have found no significant difference in the total number of nasal mast cells between patients with atopic and non-atopic rhinitis. In contrast, nasal mast cells from PAR patients exhibit increased levels of FceRI expression and IgE binding ability compared with those from non-atopic rhinitics. Moreover, FceRI expression in the nasal mast cells (NMC) of PAR patients correlates well with the levels of serum IgE. This is of considerable interest, because Pastorello et al. have previously demonstrated a strong positive correlation between the level of serum IgE and clinical symptoms in symptomatic patients with allergic rhinoconjunctivitis. More recently, several researchers have shown that IgE itself can regulate FceRI expression in mast cells. In this context, it is also of great significance that nasal mast cells from PAR patients exhibit increased IgE-mediated mediator (histamine and cytokine) release, indicating the clinical relevance of the increased expression of FceRI in the most cells of atotics. These findings may explain our earlier observations that mast cells from allergic nasal polyps release significant amounts of histamine when stimulated with anti-IgE,
compared with those from non-allergic nasal polyps, which fail to exhibit any IgE-mediated histamine release, even after passive sensitization.\(^5^2\)

Again, little has been known until recently about the factors that regulate the expression of the IgE receptor in mast cells. Toru et al. first reported that IL-4 can up-regulate expression of Fc\(e\)RI in cord blood-derived cultured human mast cells (CBHCMC).\(^5^3\) Yamaguchi et al.\(^5^4\) and Saito et al.\(^5^5\) have reported that IgE can up-regulate Fc\(e\)RI expression in mouse mast cells and CBHCMC. However, there is species-specific heterogeneity in mast cells and also differences between cultured cells and primary cells. In this context, our observations that nasal mast cells exhibit increased levels of Fc\(e\)RI expression and increased IgE-mediated mediator release and that IL-4 up-regulates Fc\(e\)RI expression in nasal mast cells\(^3^6,^3^7\) suggest an important autocrine amplification mechanism involving the mast cell itself, because mast cells can produce IL-4.

**MAST CELLS AND IgE SYNTHESIS**

Gauchet et al. first reported that, when cultured human mast cells (HMC-1) were stimulated with PMA and Ca\(^{2+}\) ionophore and then co-cultured with purified B cells in the presence of IL-4 and anti-CD40 L, these cultured human mast cells could induce the synthesis of IgE in vitro.\(^5^6\) However, HMC-1 cells do not express the high-affinity IgE receptor and no evidence has existed as to whether or not allergen- and IgE-mediated activation of mast cells can induce IgE synthesis. Recently, we have demonstrated that nasal mast cells from PAR patients not only release sufficient amounts of IL-4 or IL-13 on stimulation with specific mite antigen, but also express the CD40 ligand (CD40L) and induce IgE synthesis in B cells.\(^3^6\) Interestingly, the mast cell-induced IgE synthesis was more IL-13 dependent,\(^3^6\) bringing us to our earlier observations of a strong correlation between levels of IL-13 expression in the nasal mucosa of PAR patients and levels of serum IgE.\(^1^2\) Again, while it is well known that allergen-activated Th2 cells can produce IL-4 and IL-13 and induce IgE synthesis in B cells, the finding that mast cells can induce IgE synthesis not only suggests novel roles for mast cells in perpetuating chronic allergic inflammation, but also suggests that IgE may be produced locally in the shock organ itself.

**LOCAL IgE SYNTHESIS**

As early as 1970, Tada and Ishizaka first reported the existence of a significant number of IgE-positive cells in the bronchial mucosa and nasal polyps of atopics.\(^5^7\)
These researchers then proposed the concept of local IgE synthesis in the relevant mucosa and attributed the lack of a good correlation between skin tests and clinical symptoms to the local synthesis of IgE, pointing out that the skin sensitivity did not, in reality, reflect the nasal/bronchial reactivity or the extent of local inflammation. Recently, the presence of mRNA for IgE in patients with seasonal allergic rhinitis has been reported after in vivo antigen challenge. However, it is possible these IgE mRNA+ B cells had infiltrated into the nasal mucosa after allergen challenge, in vivo. In this context, we have recently reported the up-regulation of mRNA expression for IgE C epsilon chain in nasal biopsies after in vitro challenge with mite antigen (Der fII), indicating that IgE class switch can occur locally in the nasal mucosa itself (Fig. 5). Then, the question of whether the nasal mucosa is provided with sufficient numbers of B cells that can synthesize IgE arises. In this context, one can refer to earlier studies on the proportion of lymphocyte subsets in the nasal mucosa that have shown B cells to comprise approximately 20% of the total lymphocyte population in the nasal mucosa of allergic rhinitics. Moreover, we and others have shown an increase in the numbers of IgE+ B cells in the nasal mucosa of allergic rhinitics (although few in number). Thus, one could speculate that the shock organ may play a crucial role in the synthesis of specific IgE, whereas the total IgE may also have a systemic contribution from the associated lymphoid follicles. This would explain why the cellular and molecular changes in the shock organ reflect the clinical expression of allergic disease. In fact, in the diagnosis of allergic rhinitis, nasal provocation tests are more reliable than the skin tests.

**Adhesion molecule expression in mast cells**

In addition to cytokines, a number of cell-surface molecules are involved in the recruitment of inflammatory cells into specific sites of inflammation. Lymphocytes and mast cells in the tissues are surrounded by other cells, such as fibroblasts and mucosal cells, as well as extracellular matrix (ECM) proteins (e.g. collagen, fibronectin and laminin). Therefore, the interaction of these inflammatory cells with fibroblasts and ECM may be important in the perpetuation of chronic inflammation. It has been reported that β1-integrins, such as very late antigen (VLA)-4, VLA-5 and the vitronectin receptor integrin, are involved in mast cell activation, up-regulation of cytokine expression in mast cells and mast cell survival. Recently, we have demonstrated an up-regulation of the expression of VLA-4 and VLA-5 in nasal mast cells from PAR patients and that IgE-mediated activation of mast cells induces the release of greater levels of IL-4, IL-13 and TNF-α, when cultured on fibronectin. Thus, mast cell–ECM interactions may contribute to the enhancement of mast cell activation, especially when the levels of IgE and antigen in the micro-environment are rather low. This may explain, in part, the phenomenon of hypersensitivity seen in patients with allergic rhinitis.

The molecules VCAM-1 and ICAM-1 are the counter-receptors or ligands for β1- and β2-integrins, respectively. A striking feature in allergic inflammation is the selective accumulation of activated eosinophils and basophils, without increased numbers of neutrophils. In this context, one may refer to studies that demonstrated that ICAM-1 expression in the nasal mucosa of allergic rhinitics was not up-regulated after stimulation with antigen; however, VCAM-1 was up-regulated at 24 h after allergen challenge. Because VLA-4 is not expressed by neutrophils, the selective up-regulation of VCAM-1 in the nasal mucosa may result in the selective accumulation of activated eosinophils, basophils and lymphocytes, without increased numbers of neutrophils. It is known that IL-4 and IL-13 can up-regulate VCAM-1 expression in endothelial cells. This indicates that mast cells and lymphocytes may indirectly contribute to the recruitment of eosinophils and basophils, through the IL-4/IL-13-induced up-regulation of VCAM-1 expression in the nasal mucosa.

**Fig. 5** In vitro up-regulation of mRNA expression for interleukin (IL)-4, IL-13 and C epsilon chain of IgE in the nasal mucosa of a perennial allergic rhinitis patient after stimulation with mite antigen, examined by reverse transcriptase polymerase chain reaction. Lanes 1, 3, unstimulated (controls); lanes 2, 4, stimulated with Der fII.
INTEGRATED ROLES OF MAST CELLS IN MODULATING IgE-MEDIATED ALLERGY

Immediate phase response

The immediate hypersensitivity reaction is the pathophysiologic hallmark of allergic rhinitis, allergic asthma and anaphylaxis and the central role of the mast cell in the pathogenesis of these disorders is widely accepted (Fig. 6). It is conventionally believed that mast cells, when activated via the high-affinity IgE receptor, react by undergoing several morphologic changes, including swelling of the cytoplasmic granules and subsequent solubilization of their granule contents. Histamine, tryptase, PGD2 and LTC4 are among the mast cell products that can be detected immediately after exposure to allergens. Histamine induces vasodilatation, increased vascular permeability and increased glandular secretion in the ipsilateral as well as contralateral sides through neural reflexes. Prostaglandins, such as PGD2, also cause edema by vasodilatation and increased vascular permeability.

Late phase response

The late phase allergic reaction occurs as a result of the infiltration of a variety of inflammatory cells, such as eosinophils, basophils and T cells, and the subsequent release of a number of soluble products, such as PG, LT, PAF, ECP, MBP and so on. Tissue eosinophilia is therefore an important aspect of the late phase allergic reaction. Mast cells can induce the infiltration of eosinophils not only through the up-regulation of VCAM-1 (by TNF-α, IL-4 and IL-13) on endothelial cells, but also through release of eosinophil-chemotactic factors, such as PAF and LTB4. In addition, mast cells can also enhance eosinophil survival through the release of GM-CSF. Interestingly, strong correlations have been reported to exist between the numbers of IL-4+, IL-5+ and TNF-α+ mast cells and the number of tissue eosinophils in atopic asthma and allergic rhinitis.11 In this context, we refer to the hypothesis of Galli and others,21-23 who have proposed that a mast cell–leukocyte cytokine cascade critically contributes to the initiation and perpetuation of IgE-dependent allergic inflammation in the airways and other sites. In particular,

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**Fig. 6** Integrated roles of nasal mast cells modulating IgE-mediated allergy. APC, antigen-presenting cell; MHC, major histocompatibility complex; Ag, antigen; TCR, T cell receptor; IL, interleukin; Th, T helper cell; NMC, nasal mast cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VLA, very late antigen; FcεRI, high-affinity IgE receptor.
the activation of mast cells through FcεRI initiates the response (in part through the release of TNF-α, IL-4, IL-13 and other cytokines) that can influence the recruitment and function of additional effector cells (Fig. 6). These recruited cells then promote the further progression of the inflammatory response by providing additional sources of certain cytokines (that can also be produced by mast cells stimulated by ongoing exposure to allergen), as well as new sources of cytokines and other mediators that may not be produced by mast cells.

Time kinetics of cytokine secretion from purified lung mast cells have shown that on IgE-mediated stimulation, mRNA expression for IL-13 is up-regulated within 2–4 h and the protein secretion is detectable at 12 h and peaks at 24–48 h. In addition, nasal mast cells from allergic rhinitics release both IL-4 and IL-13 at 24–48 h. In fact, in the presence of SCF, the ligation of cell-bound IgE results in an increase in the transcription and production of these cytokines in mast cells. Immunelectron microscopy has shown that these cytokines are located in the mast cell secretory granules and are released on IgE-dependent stimulation along with other preformed mediators. Again, TNF-α is constitutively expressed in mast cells and can be released within 2 h of IgE-mediated stimulation. In fact, Klien et al. have shown that activation of mast cell products in fragments of human skin in vitro results in the up-regulation of E-selectin expression in adjacent vascular endothelial cells and this is attributed to the release of TNF-α. Moreover, interaction of mast cells with extracellular matrix further enhances the IgE-mediated cytokine release from mast cells. Taken together, these studies strongly suggest that the mast cell is a key effector cell in the late phase reaction. In this context, I would like to refer to the report that the late asthmatic response can be inhibited by disodium cromoglycate (DSCG) and also by β-agonists, such as salbutamol, all of which inhibit mast cell degranulation following IgE-dependent activation, indicating the important role of the mast cell in LPR.

**CHRONIC ALLERGIC INFLAMMATION**

Most recent studies suggest that the mast cell has the potential to regulate allergic inflammation by inducing IgE synthesis in B cells. Under allergic inflammatory conditions, ‘primed’ mast cells express high levels of the high-affinity receptor for IgE and the ligand for the surface antigen CD40, which is involved in T/B cell interactions leading to immunoglobulin production, as well as the Th2-type cytokines IL-4 and IL-13. The critical role of these cells in the induction of IgE synthesis is supported by the findings that anti-ligand for the surface antigen CD40, anti-IL-4 and anti-IL-13 monoclonal antibodies inhibit IgE production. Mast cells also have the potential to function as APC, with the ability to shift T cells into Th2 subtypes. These recent findings suggest that mast cells can modulate important regulatory functions of the allergic response by acting directly on B cells and inducing IgE. Because it is almost undoubtedly known now that IgE synthesis can occur locally in the nasal mucosa itself, it is quite likely that the locally produced IgE can thereafter up-regulate FcεRI expression in mast cells. The augmented FcεRI in mast cells may contribute to the binding of increased number of IgE–Ag complexes, which in turn can enhance the sensitivity of mast cells to allergen, resulting in the enhancement of the production of immunomodulatory cytokines and chemical mediators and forming an important positive-feedback amplification loop involving the IgE–IgE receptor mast cell cascade (Fig. 6).

Finally, mast cell activation may directly or indirectly promote the release of cytokines from other resident cells in the respiratory tract, such as macrophages, epithelial cells, vascular endothelial cells, fibroblasts, and nerves; cytokines released in these responses then contribute to the vascular and epithelial changes and to the angiogenesis that is so prominent. At certain points in the natural history of these complex processes, cytokines derived from mast cells (transforming growth factor (TGF)-β1), eosinophils or other recruited cells may also contribute to the down-regulation of the response.

**POTENTIAL THERAPIES THAT TARGET THE IGE–IGE RECEPTOR MAST CELL CASCADE**

Glucocorticoids and cyclosporine are known to inhibit cytokine production in many cell types. In mice, both glucocorticoids and cyclosporine can diminish mast cell cytokine production in vitro, and can also suppress mast cell- and TNF-α-dependent allergic inflammation in vivo. Immunotherapy has also been shown to reduce the number of intra-epithelial mast cells in patients with seasonal allergic rhinitis, in good correlation with the clinical symptoms. However, the identification of key cells and molecules involved in the initiation and maintenance of allergic inflammation is likely to become an important target in the treatment of allergic diseases. Although anti-IgE monoclonal antibodies (mAbs) have always been
used to trigger mediator release from basophils or mast cells, non-anaphylactogenic antihuman IgE Ab are now in clinical evaluation as a therapeutic agent against atopic disease. One type of these new mAbs, which is non-anaphylactogenic, recognizes receptor-bound IgE and prevents the association of IgE with its receptor if immune complexes are formed between IgE and anti-IgE mAb. This can explain the phenomenon that addition of anti-IgE Ab to receptor-bound IgE results in a decrease of receptor-bound IgE, because IgE dissociating from the receptor is complexed, altering the thermodynamic balance of receptor-bound and free IgE.

CGP 51901 is another non-anaphylactogenic mouse/human chimeric antihuman IgE antibody that binds to free IgE and surface IgE of IgE-expressing B cells, but not to IgE bound to high-affinity IgE receptors (FceRI) on mast cells and basophils or low-affinity IgE receptors (FceRII) on other cells. A phase 1 double-blind, placebo-controlled, single-dose study with doses of 3, 10, 30, and 100 mg CGP 51901 was conducted in 33 pollen-sensitive subjects who had raised levels of serum IgE and received either intravenous CGP 51901 or placebo. The administration of CGP 51901 was well tolerated and resulted in a decrease of serum-free IgE levels in a dose-dependent manner, with suppression after 100 mg of CGP 51901 reaching > 96%. The time of recovery to 50% of baseline IgE correlated with the dose of administered antibody.

Another group of researchers have recently studied the expression of IgE and FceRI on human basophils of 15 subjects receiving humanized anti-IgE mAb intravenously. Treatment with the anti-IgE mAb decreased free IgE levels to 1% of pretreatment levels and also resulted in a marked down-regulation of FceRI on basophils. The responsiveness of the cells to IgE-mediated stimulation using anti-IgE Ab was marginally decreased (approximately 40%), while the response of the same cells to stimulation with dust mite Ag, Dermatophagoides farinae, was reduced by approximately 90%. As also indicated in our studies and those of others, one possible explanation for these results is that FceRI density is directly regulated by plasma-free IgE levels. Thus, the increased level of FceRI expression in NMC from PAR patients that is associated with an increase in mediator release on cross-linking of the receptor may be very effectively down-regulated by the use of anti-IgE mAb.

**Conclusion**

It has been suggested that allergic airway inflammation results from a failure in the normal capacity to control otherwise harmful IgE-mediated immune responses. In the present review, it is suggested that an alternative pathogenetic mechanism is operating in atopic patients with asthma or rhinitis. In addition to a genetic predisposition towards an exaggerated defensive IgE response to inhaled allergens, there may be an up-regulated FceRI expression in mast cells. Indeed, while the present brief review has emphasized the roles of mast cells in modulating allergic inflammation, the redundancy in the effector mechanisms that potentially participate in allergic inflammation is considerable. Many cells express several cytokines, several mediators, the FceRI and/or CD23 and thus have overlapping functions. At the same time, the possibility that some of the cells and mediators that participate in the allergic responses may help to down-regulate the allergic response cannot be ruled out. Even cytokines that have pro-inflammatory effects may have anti-inflammatory effects at certain points in time. In this context, TGF-β from mast cells and eosinophils may play an important role in down-regulating the allergic response. Thus, the delicate balance in directing an effector cell to act in a particular direction (inflammatory or anti-inflammatory) is vital to the development of clinical disease. In conclusion, we have highlighted recent evidence that mast cells play more diverse and crucial roles as both effector and immunoregulatory cells in perpetuating allergic inflammation. Future management of allergic airway diseases should take into account mast cells as potential targets for anti-allergy therapy targeting the IgE–FceRI-mast cell cascade.

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