increase c-*kit* expression with maturation. The SCF interaction with c-*kit* is an absolute requirement for the development of constitutive tissue mast cells residing in skin and connective tissue sites and for the accumulation of mast cells at mucosal surfaces during T_H2-type immune responses. Several T cell-derived cytokines (IL-3, IL-4, IL-5, and IL-9) can potentiate SCF-dependent mast cell proliferation and/or survival in vitro in mice and humans. Indeed, mast cells are absent from the intestinal mucosa in clinical T cell deficiencies, but are present in the submucosa. Based on the immunodetection of secretory granule neutral proteases, mast cells in the lung parenchyma and intestinal mucosa selectively express tryptase, and those in the intestinal and airway submucosa, perivascular spaces, skin, lymph nodes, and breast parenchyma express tryptase, chymase, and carboxypeptidase A (CPA). In the mucosal epithelium of severe asthmatics, mast cells can express tryptase and CPA without chymase. The secretory granules of mast cells selectively positive for tryptase exhibit closed scrolls with a periodicity suggestive of a crystalline structure by electron microscopy, whereas the secretory granules of mast cells with multiple proteases are scroll-poor, with an amorphous or lattice-like appearance.

Mast cells are distributed at cutaneous and mucosal surfaces and in submucosal tissues about venules and could influence the entry of foreign substances by their rapid response capability (Fig. 376-2). Upon stimulus-specific activation and secretory granule exocytosis, histamine and acid hydrolases are solubilized, whereas the neutral proteases, which are cationic, remain largely bound to the anionic proteoglycans, heparin and chondroitin sulfate E, with which they function as a complex. Histamine and the various lipid mediators (PGD_2, LTC_4/D_4/E_4, PAF) alter venular permeability, thereby allowing influx of plasma proteins such as complement and immunoglobulins, whereas LTB_4 mediates leukocyte–endothelial cell adhesion and subsequent directed migration (chemotaxis). The accumulation of leukocytes and plasma opsonins facilitates defense of the microenvironment. The inflammatory response can also be detrimental, as in asthma, where the smooth-muscle constrictor activity of the cysteinyl leukotrienes is evident and much more potent than that of histamine.

The cellular component of the mast cell–mediated inflammatory response is augmented and sustained by cytokines and chemokines. IgE-dependent activation of human skin mast cells in situ elicits TNF-α production and release, which in turn induces endothelial cell responses favoring leukocyte adhesion. Similarly, activation of purified human lung mast cells or cord blood–derived cultured mast cells in vitro results in substantial production of proinflammatory (TNF-α) and immunomodulatory cytokines (IL-4, IL-5, IL-13) and chemokines. Bronchial biopsy specimens from patients with asthma reveal that mast cells are immunohistochemically positive for IL-4 and IL-5, but that the predominant localization of IL-4, IL-5, and GM-CSF is to T cells, defined as T_H2 by this profile. IL-4 modulates the T cell phenotype to the T_H2 subtype, determines the isotype switch to IgE (as does IL-13), and upregulates FcεRI-mediated expression of cytokines by mast cells based on in vitro studies.

An immediate and late cellular phase of allergic inflammation can be induced in the skin, nose, or lung of some allergic humans with local allergen challenge. The immediate phase in the nose involves pruritus and watery discharge; in the lung, it involves bronchospasm and mucus secretion; and in the skin, it involves a wheal-and-flare response with pruritus. The reduced nasal patency, reduced pulmonary function, or erythema with swelling at the skin site in a late-phase response at 6–8 h is associated with biopsy findings of infiltrating and activated T_H2 cells, eosinophils, basophils, and some neutrophils. The progression from early mast cell activation to late cellular infiltration has been used as an experimental surrogate of rhinitis or asthma. However, in asthma, there is an intrinsic hyperreactivity of the airways independent of the associated inflammation. Moreover, early- and late-phase responses (at least in the lung) are far more sensitive to blockade of IgE-dependent mast cell activation (or actions of histamine and cysteinyl leukotrienes) than are spontaneous or virally induced asthma exacerbations.

Consideration of the mechanism of immediate-type hypersensitivity diseases in the human has focused largely on the IgE-dependent recognition of otherwise innocuous substances. A region of chromosome 5 (5q23-31) contains genes implicated in the control of IgE levels including IL-4 and IL-13, as well as IL-3 and IL-9, which are involved in mucosal mast cell hyperplasia, and IL-5 and GM-CSF, which are central to eosinophil development and their enhanced tissue viability. Genes with linkage to the specific IgE response to particular allergens include those encoding the major histocompatibility complex (MHC) and certain chains of the T cell receptor (TCR-αδ). The complexity of atopy and the associated diseases includes susceptibility, severity, and therapeutic responses, each of which is among the separate variables modulated by both innate and adaptive immune stimuli.

The induction of allergic disease requires sensitization of a predisposed individual to a specific allergen. The greatest propensity for the development of atopic allergy occurs in childhood and early adolescence. The allergen is processed by antigen-presenting cells of the monocytic lineage (particularly dendritic cells) located throughout the body at surfaces that contact the outside environment, such as the nose, lungs, eyes, skin, and intestine. These antigen-presenting cells present the epitope-bearing peptides via their MHC to T helper cells and their subsets. The T cell response depends both on cognate recognition and on the cytokine microenvironment provided by the antigen-presenting dendritic cells, with IL-4 directing a T_H2 subset, interferon (IFN) γ a T_H1 profile, and IL-6 with transforming growth factor β (TGF-β) a T_H17 subset. Allergens not only present antigenic epitopes via dendritic cells but also contain pattern recognition ligands that facilitate the immune response by direct initiation of cytokine generation from innate cell types such as basophils, mast cells, eosinophils, and others. The T_H2 response is associated with activation of specific B cells that can also present allergens or that transform into plasma cells for antibody production. Synthesis and release into the plasma of allergen-specific IgE results in sensitization of FcεR1-bearing cells such as mast cells and basophils, which become activated on exposure to the specific allergen. In certain diseases, including those associated with atopy, the monocyte and eosinophil populations can express a trimeric FcεR1, which lacks the β chain, and yet respond to its aggregation. An additional recently recognized class of c-*kit*-expressing innate cells

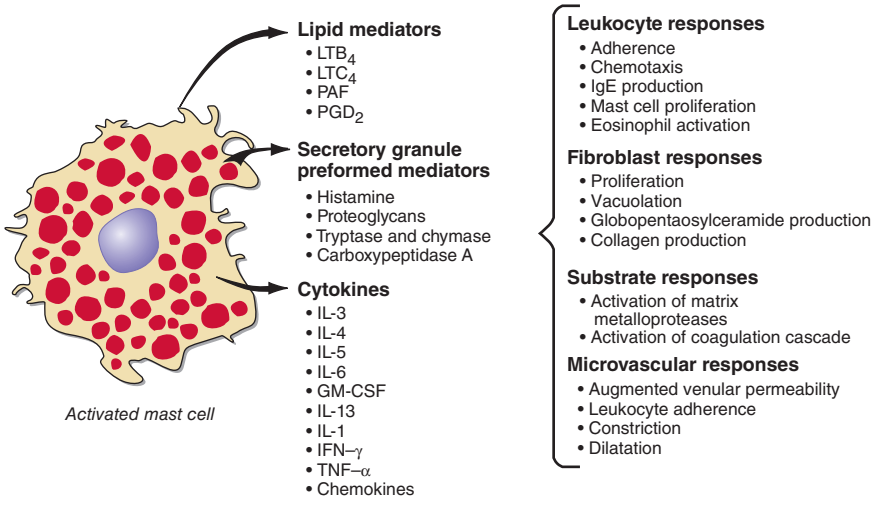

FIGURE 376-2 Bioactive mediators of three categories generated by IgE-dependent activation of murine mast cells can elicit common but sequential target cell effects leading to acute and sustained inflammatory responses. GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; LT, leukotriene; PAF, platelet-activating factor; PGD_2, prostaglandin D_2; TNF, tumor necrosis factor.