Mast cells and basophils express a high-affinity receptor, called FcεRI, which is specific for the Fc portion of IgE and therefore avidly binds IgE antibodies. IgE-coated mast cells are said to be *sensitized*, because they are sensitive to subsequent encounter with the specific antigen. **When a mast cell, armed with IgE antibodies previously produced in response to an antigen, is exposed to the same antigen, the cell is activated, leading eventually to the release of an arsenal of powerful mediators responsible for the clinical features of immediate hypersensitivity reactions.** In the first step in the sequence of mast cell activation, the antigen binds to the IgE antibodies previously attached to the mast cells. Multivalent antigens bind to and cross-link adjacent IgE antibodies. The underlying Fcε receptors are brought together, and this activates signal transduction pathways from the cytoplasmic portion of the receptors. These signals lead to the production of mediators that are responsible for the initial, sometimes explosive, symptoms of immediate hypersensitivity, and they also set into motion the events that lead to the late-phase reaction.

Mediators of Immediate Hypersensitivity

Mast cell activation leads to degranulation, with the discharge of preformed (primary) mediators that are stored in the granules, and de novo synthesis and release of secondary mediators, including lipid products and cytokines (Fig. 6-15).

Preformed Mediators. Mediators contained within mast cell granules are the first to be released and can be divided into three categories:

- *Vasoactive amines*. The most important mast cell-derived amine is *histamine* (Chapter 3). Histamine causes intense smooth muscle contraction, increased vascular permeability, and increased mucus secretion by nasal, bronchial, and gastric glands.
- *Enzymes.* These are contained in the granule matrix and include neutral proteases (chymase, tryptase) and several acid hydrolases. The enzymes cause tissue damage and lead to the generation of kinins and activated components of complement (e.g., C3a) by acting on their precursor proteins.
- *Proteoglycans.* These include heparin, a well-known anticoagulant, and chondroitin sulfate. The proteoglycans serve to package and store the amines in the granules.

Lipid Mediators. The major *lipid mediators* are arachidonic acid–derived products (Chapter 3). Reactions in the mast cell membranes lead to activation of phospholipase A_2, an enzyme that converts membrane phospholipids to *arachidonic acid.* This is the parent compound from which leukotrienes and prostaglandins are produced by the 5-lipoxygenase and cyclooxygenase pathways, respectively.

- *Leukotrienes.* Leukotrienes C_4 and D_4 are the most potent vasoactive and spasmogenic agents known. On a molar basis, they are several thousand times more active than histamine in increasing vascular permeability and causing bronchial smooth muscle contraction. Leukotriene B_4 is highly chemotactic for neutrophils, eosinophils, and monocytes.

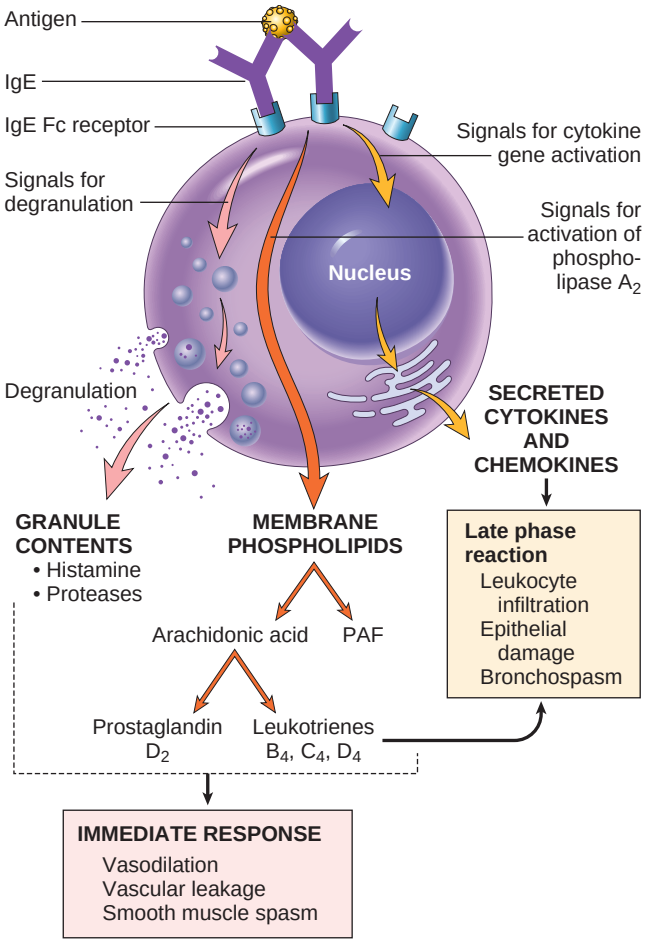

Figure 6-15 Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. PAF, Platelet-activating factor.

- *Prostaglandin D_2.* This is the most abundant mediator produced in mast cells by the cyclooxygenase pathway. It causes intense bronchospasm as well as increased mucus secretion.
- *Platelet-activating factor (PAF).* PAF (Chapter 3) is a lipid mediator produced by some mast cell populations but it is not derived from arachidonic acid. It causes platelet aggregation, release of histamine, bronchospasm, increased vascular permeability, and vasodilation. Its role in immediate hypersensitivity reactions is not well established.

Cytokines. Mast cells are sources of many cytokines, which may play an important role at several stages of immediate hypersensitivity reactions. The cytokines include: TNF, IL-1, and chemokines, which promote leukocyte recruitment (typical of the late-phase reaction); IL-4, which amplifies the T_H2 response; and numerous others. The inflammatory cells that are recruited by mast cell-derived TNF and chemokines are additional sources of cytokines and of histamine-releasing factors that cause further mast cell degranulation.

These mediators are responsible for the manifestations of immediate hypersensitivity reactions. Some, such as histamine and leukotrienes, are released rapidly from sensitized mast cells and are responsible for the intense

www.PTools.ir