Mast Cell Activation and Mediator Release

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Introduction

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Since 1950, an important role of mast cells in anaphylaxis was anticipated from the observations that damage to mast cells always occurs when antigen was injected into intact sensitized animals or when a piece
of sensitized tissue is incubated with the specific antigen. In 1960, Mota and da Silva [1] isolated rat peritoneal mast cells from sensitized animals, exposed the cells to antigen, and observed the degranulation. In human reaginic hypersensitivity, Middleton observed that exposure of peripheral blood leukocytes from atopic patients to an allergen resulted in the release of histamine, and the methodology for antigen-induced histamine release from leukocytes was established by Lichtenstein and Osier [2]. At this stage, however, neither the mechanisms of histamine release nor target cells for antigen were known, because leukocytes employed in the experiments were consisted of a variety of cells. After IgE was characterized, the protein was detected on the surface of basophil granulocytes, but not on the other types of leukocytes, and the binding of IgE to basophils was also demonstrated by using radiolabeled IgE [3]. Application of the same technique to tissue cells proved that IgE binds to mast cells with high affinity, and the reaction of cell-bound IgE with either antigen or anti-IgE resulted in the release of chemical mediators such as histamine and slow-reacting substance of anaphylaxis (SRS-A, leukotrienes) [4]. A series of work by Austen [5] established that a variety of chemical mediators are released directly from mast cells through allergen-IgE antibody reactions on the cells surface.

Development of techniques for purification of mast cells and information on the relationship between IgE and mast cells enabled immunochemical, biochemical, and pharmacological analyses of mediator release from mast cells and basophils. In the past several years, different approaches have been made by several investigators. This volume of ‘Progress in Ishizaka X

Allergy’ was mainly focused to early stage of mast cell activation. Although mediator release from mast cells can be obtained through mechanisms other than IgE, this volume was focused to IgE-mediated reactions. In the first chapter, Galli and coworkers made a comprehensive review on the morphology of basophils and mast cells. Main issues in this chapter are detailed description of ultrastructural patterns of degranulation. The chapter also covers new developments on cultured mast cells/basophils. Recent studies demonstrated two types of mast cells; serosal and mucosal mast cells. They are different in T cell requirements for differentiation, nature of mediators released upon activation, and proteoglycans in the cells (c.f. Chapter V). Cultured mast cells and, particularly, mast cell clones from certain origins will be quite useful for characterization of different types of mast cells and biochemical analysis of mediator release. Presence of high-affinity receptors for IgE on mast cells and basophils
was suspected from the binding of IgE to these cells. Equilibrium constant for the binding of human IgE to the receptors on basophils has been estimated from the concentration of IgE in the serum and the proportion of receptors occupied at equilibrium [6]. After rat IgE became available, Kulczycki and Metzger [7] measured the association constant and the dissociation constant of the binding reaction, and the receptors on rat mast cells were chemically identified by Conrad and Froese [8]. In this volume, Froese has summarized current knowledges on mast cell IgE receptors. IgE receptors (or FceR) on rat mast cells and basophilic leukemia cells are probably the best-known receptors in the field of immunology. Froese has discussed some details about heterogeneity of the receptors. Among several membrane components having affinity for IgE, a chain (or R component by Froese) is the receptor which binds IgE with high affinity, and mast cells are triggered for mediator release through the receptors. Recent evidence suggested that alpha chain is associated with 30 K membrane component (beta chain) which is not exposed to the cell surface. Possible role of this component in triggering mediator release would be a problem to be investigated in the future. As indicated in Chapter III, direct bridging of IgE receptors by divalent anti-receptor antibody triggers mast cells for histamine release. In this chapter, Ishizaka and Ishizaka described early biochemical events resulting from the bridging of the receptors and leading to histamine release. She has shown that membrane-associated proteolytic enzyme(s), methyltransferases and adenylate cyclase, are activated by bridging of IgE receptors. Evidence was presented that methyltransferases are involved in the activation of adenylate cyclase, and essential for calcium-influx, which leads to the activation of other enzymes, such as phospholipase, for mediator release. It is not known, however, what the substrate of proteolytic enzyme is, and how activation of this enzyme leads to the activation of methyltransferases. Another important question remaining to solved is how phospholipid methylation induces calcium influx.

In chapter IV, Winslow and Austen focused their discussion to the possible role of cyclic AMP and cyclic AMP (cAMP) dependent protein kinase in the process of mediator release. It has been shown that elevation of intracellular cAMP level prior to receptor bridging prevents the mediator release from mast cells. Using derivatives of adenosine, they have shown that inhibition of an initial rise in cAMP resulted in the inhibition of mediator release, while an enhancement of the initial rise in cAMP resulted in an enhancement of mediator release. They also observed the
activation of cAMP-dependent protein kinase in mast cells upon challenge with anti-IgE. From these findings, they proposed intimate connection between IgE receptors and adenylate cyclase through coupling factor (G/F protein) and suggested that the initial rise in cAMP and consequent activation of cAMP-dependent protein kinase are involved in the biochemical process of mediator release. Their view is supported by observations by Ishizaka and Ishizaka (chapter III) that coupling factor (G/F protein) is involved in the activation of adenylate cyclase induced by receptor bridging. Combining experimental results described in Chapter III, with the concept of Winslow and Austen, cAMP-dependent protein kinase may be involved in the induction of calcium influx. A question to be answered in the future is why cAMP rise prior to antigen challenge prevents the mediator release.

Most of the experiments on the early biochemical events of mediator release have been carried out using rat mast cells. However, recent experiments clearly showed that the same (or similar) enzymes, such as serine protease, methyltransferases, and adenylate cyclase, are activated, when purified human mast cells were challenged by anti-IgE [9]. Therefore, biochemical process for the IgE-mediated activation of mast cells would be common in both rat and human mast cells.

This volume is concluded by structure and function of the chemical mediators of mast cells by Schwartz and Austen, who covered chemistry and biology of preformed mediators such as histamine, proteoglycans, and a variety of enzymes, and newly formed mediators such as prostaglandins and leukotrienes. Biosynthesis of these mediators from arachidonic acid and enzymes involved in the synthesis are reviewed. It is known that arachidonic acid is derived from membrane phospholipids by the action of phospholipase A2 or by sequential action of phospholipase C and diacylglycerol lipase. It is reasonable to speculate that either mobilization or influx of calcium induces the activation of phospholipase for the release of arachidonic acid, which then proceeds either the cyclooxygenase pathway to prostaglandins and thromboxanes or the lipoxygenase pathways to leukotrienes. One may figure out general principles of biochemical pathway from the bridging of IgE receptors to the formation of potent chemical mediators such as leukotrienes and prostaglandins. However, our knowledges on biochemical processes of mediator release is not sufficient to explain the ultrastructural pattern of degranulation (described in Chapter I). Considering that chemical mediators from mast cells will explain acute inflammation in IgE-mediated allergic diseases, further
biochemical analysis of mast cell activation may provide new directions in the treatment of allergic diseases.

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