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Signal transduction and chemotaxis in mast cells

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ABSTRACT

Mast cells play crucial roles in both innate and adaptive arms of the immune system. Along with basophils, mast cells are essential effector cells for allergic inflammation that causes asthma, allergic rhinitis, food allergy and atopic dermatitis. Mast cells are usually increased in inflammatory sites of allergy and, upon activation, release various chemical, lipid, peptide and protein mediators of allergic reactions. Since antigen/immunoglobulin E (IgE)-mediated activation of these cells is a central event to trigger allergic reactions, innumerable studies have been conducted on how these cells are activated through cross-linking of the high-affinity IgE receptor (FcεRI). Development of mature mast cells from their progenitor cells is under the influence of several growth factors, of which the stem cell factor (SCF) seems to be the most important. Therefore, how SCF induces mast cell development and activation via its receptor, KIT, has been studied extensively, including a cross-talk between KIT and FcεRI signaling pathways. Although our understanding of the signaling mechanisms of the FcεRI and KIT pathways is far from complete, pharmaceutical applications of the knowledge about these pathways are underway. This review will focus on recent progresses in FcεRI and KIT signaling and chemotaxis.

1. Introduction

Mast cells are terminally differentiated cells of the hematopoietic origin that are involved in both innate and adaptive immunity (Bischoff, 2007; Kalesnikoff and Galli, 2008; Abraham and John, 2010). Mast cells originate from myeloid precursors that are released from bone marrow into blood circulation. Once they acquire proper signals through their chemoattractant receptors, they migrate to the target tissues that are strategically located at the host–environment interface (Okayama and Kawakami, 2006; Halova et al., 2012). Numbers of tissue mast cells are tightly regulated not only by migration, but also by proliferation and survival, as mast cells are long-lived cells capable of surviving for months. Under pathological conditions, tissue mast cell homeostasis could be disturbed and the number and distribution of mast cells quickly changed (Okayama and Kawakami, 2006). Mast cell chemoattractants include antigens recognized by immunoglobulins E (IgE), stem cell factor (SCF), different chemokines, cytokines, and leukotrienes. Many of them are also produced by mast cells to attract various cell types of the immune system as well as other mast cells and their precursors to modulate their amount by autocrine and/or paracrine mechanisms (Halova et al., 2012).

Mature mast cells express on their plasma membrane numerous receptors which, after binding of the corresponding ligands, can induce cell activation leading to the release of various inflammatory mediators. The most prominent is the high-affinity receptor for IgE (FcεRI), which has been implicated in an array of acute as well as chronic reactions including allergic rhinitis, asthma, anaphylaxis and atopic dermatitis. Antigen/IgE-mediated activation of mast cells is a multistep process, eventually leading to degranulation of preformed granules containing histamine, heparin, various proteases, tumor necrosis factor (TNF)-α, and other inflammatory mediators and *de novo* synthesis of cytokines, chemokines, eicosanoids, and other immune mediators. FcεRI-mediated activation events are modulated by engagement of other surface receptors such as KIT, adenosine receptors, prostaglandin (PG) receptors and many others. These receptors play multiple roles in differentiation, proliferation, chemotaxis and in setting a threshold for mast cell triggering (Gilfillan and Tkaczyk, 2006).

In industrial countries, mast cell-associated diseases are a serious problem, solution of which requires new strategies for development of new therapeutics. Detailed understanding of mast cell signaling events at the molecular levels could contribute to such developments. In this review we summarize recent findings

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on the early stages of antigen- and SCF-induced mast cell activation as well as mast cell chemotaxis.

2. Signal transduction

Mast cells express on their plasma membrane numerous receptors that are involved in cell migration and activation. The most extensively studied are FcεRI and KIT.

2.1. FcεRI signaling

2.1.1. FcεRI

FcεRI belongs to the multichain immune receptor family that includes the T and B cell receptors and other Fc receptors. In mast cells and basophils the receptor is expressed as a tetrameric structure composed of one IgE-binding α subunit, one membrane-tetraspanning β subunit and a dimer of disulphide-linked γ subunits (Blank et al., 1989). In other cells such as monocytes, Langerhans cells and dendritic cells, FcεRI is also found in a trimeric form lacking the β subunit (Kinet, 1999). The α chain is responsible for binding the Fc part of IgE. The β chain stabilizes the receptor complex (Donnadieu et al., 2000) and amplifies spleen tyrosine kinase (SYK) phosphorylation resulting in higher magnitude of calcium mobilization while the γ chain dimer functions as an autonomous activation module (Lin et al., 1996). Each β and γ chain possesses one immunoreceptor tyrosine-based activation motif (ITAM) located in their cytoplasmic tails which are responsible for signal transduction and after phosphorylation serve as docking sites for molecules containing one or two Src homology (SH)2 domains (Cambier, 1995; Kinet, 1999). The β and γ chains are shared with other Fc receptors.

2.1.2. Protein kinases and phosphatases

Transduction of the signal from FcεRI is mediated and regulated via several kinases and phosphatases (Fig. 1). The Src family protein tyrosine kinases (SFKs) have a well-defined structure containing five functional domains: a variable N-terminal domain, an SH2 domain, an SH3 domain, a kinase domain and a C-terminal regulatory tail (Okada, 2012). LYN, FYN, HCK and FGR are the SFKs that have been shown to be involved in early stages of the FcεRI signaling. LYN is the most abundant SFK expressed in mast cells and its activity is essential for initial tyrosine phosphorylation of the ITAMs of the FcεRI β and γ chains. LYN plays both positive and negative regulatory roles in mast cell signaling but exact molecular mechanisms of its action still remain controversial. Discordant results were obtained from studies using LYN knockout mice (Table 1). All experiments concluded that in the absence of LYN Ca^{2+} mobilization is decreased (Nishizumi and Yamamoto, 1997; Kawakami et al., 2000; Parravicini et al., 2002; Hernandez-Hansen et al., 2004). However, some studies showed increased degranulation in bone marrow-derived cultured mast cells (BMMCs) from LYN knockout mice (Parravicini et al., 2002; Hernandez-Hansen et al., 2004; Odom et al., 2004), whereas in others absence of LYN had no effect on degranulation (Nishizumi and Yamamoto, 1997; Kawakami et al., 2000). An early study described opposite roles of LYN after activation of mast cells with high or low intensity; low-intensity stimulation suppressed LYN kinase activity and its association with FcεRI receptor, whereas high-intensity stimulation had an opposite effect (Xiao et al., 2005). Also studies on passive cutaneous anaphylaxis (PCA) and/or passive systemic anaphylaxis (PSA) gave different results. A first study showed an absence of PCA in LYN knockout mice (Hibbs et al., 1995). Later it was described that PSA in LYN knockout mice depends on age of the mice; in young mice (4 weeks old) it was increased, but in older mice (more than 7 weeks old) it was decreased (Odom et al., 2004). A follow-up study showed that the genetic background of mice affects the results. When BMMCs from Lyn knockout mice were compared to those from wild-type mice, antigen-induced degranulation was either decreased when derived from C57BL/6 mice, or increased when derived from 129/Sv mice (Yamashita et al., 2007). The authors suggested that different expression of FYN kinase in different mouse strains could be responsible for the observed differences.

It has been found that LYN-deficient mast cells exhibit enhanced FYN-dependent signals and degranulation, but reduced calcium responses (Parravicini et al., 2002). In contrast, FYN deficiency resulted in impaired degranulation, whereas calcium response was normal. Both FYN and LYN were found to be associated with

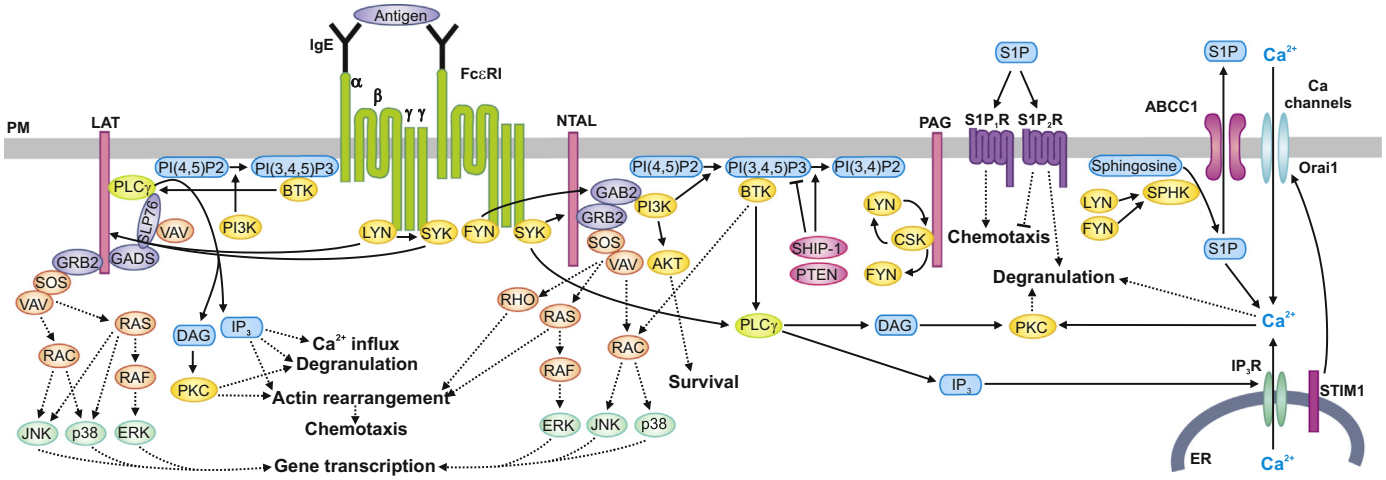

Fig. 1. FcεRI-mediated signaling events. The first biochemically defined step in antigen-mediated aggregation of the IgE-FcεRI complexes is tyrosine phosphorylation of the FcεRI β and γ subunits by LYN kinase. This is followed by binding of SYK to FcεRI γ subunit leading to phosphorylation and activation of SYK. These kinases then phosphorylate downstream signaling targets. SYK phosphorylates transmembrane adapter proteins NTAL and LAT and thus creates binding sites for various SH2-containing proteins like GRB2. In this way PI3K and GAB2 are brought to the plasma membrane (PM). PM-bound PI3K phosphorylates $PI(4,5)P_2$ and generates $PI(3,4,5)P_3$. Production of $PI(3,4,5)P_3$ can be negatively regulated by SHIP-1 and PTEN by conversion of $PI(3,4,5)P_3$ to $PI(3,4)P_2$ and $PI(4,5)P_2$, respectively. Several PH domain-containing proteins, including BTK and PLCγ, are recruited to the membrane-bound $PI(3,4,5)P_3$. PLCγ hydrolyzes $PI(4,5)P_2$ to generate the second messengers, diacylglycerol (DAG) and IP_3. IP_3 binds to the ER-bound IP_3 receptor (IP_3R) and triggers the release of Ca^{2+} from the ER. Depletion of Ca^{2+} from the ER leads to interaction of STIM1 with the Orai1 PM-associated protein, opening the PM-bound calcium channels and influx of extracellular Ca^{2+} into the cytoplasm. LYN and FYN kinases also activate SPHKs which induce conversion of sphingosine into S1P, which is secreted from the cell through ABCC1 (a member of the ATP-binding cassette transporter family). The extracellular S1P binds to $S1P_1R$ and $S1P_2R$, which are involved in cell migration and degranulation. Some other signaling proteins (SLP-76, VAV, GADS, SOS, RAC, RAS, RAF, JNK, p38, ERK, PKC, RHO, AKT, PAG, and CSK), which are involved in Ca^{2+} influx, degranulation, actin rearrangement, chemotaxis, and/or gene transcription, are also indicated.