Mast cell signal transduction from the high-affinity IgE receptor

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Antigen-mediated aggregation of IgE bound to its high-affinity receptor on mast cells or basophils initiates a complex series of biochemical events, resulting in the release of mediators that cause allergic inflammation and anaphylactic reactions. Recent progress has defined the molecular pathways that are involved in stimulating these cells and has shown the importance of protein tyrosine kinases in the subsequent reactions. The activation pathways are regulated both positively and negatively by the interactions of numerous signaling molecules.

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Abbreviations

$[Ca^{2+}]_i$	concentration of intracellular free Ca^{2+}
BMMC	bone-marrow-derived mast cell
ERK	extracellular-signal-regulated kinase
Gab	Grb2-associated binder-like protein
IL	interleukin
IP_3	inositol-1,4,5-trisphosphate
ITAM	immunoreceptor tyrosine-based activation motif
ITIM	immunoreceptor tyrosine-based inhibition motif
JNK	Jun amino-terminal kinase
LAT	linker for activation of T cells
MAFA	mast cell function-associated antigen
MAP	mitogen-activated protein
NTAL	non-T cell activation linker
PH	pleckstrin homology
PI3K	phosphatidylinositol 3-kinase
PIP_2	phosphatidylinositol-4,5-bisphosphate
PIP_3	phosphatidylinositol-3,4,5-trisphosphate
PKC	protein kinase C
PLC	phospholipase C
PLD	phospholipase D
RBL	rat basophilic leukemia
SH	Src homology
SHIP	SH2-containing inositol phosphatase
SLP-76	SH2-containing leukocyte-specific protein of 76 kDa

Introduction

Mast cells or basophils are activated through the interaction of receptors on their cell surface with secretagogues. This interaction initiates a series of biochemical events resulting in the release of biologically active mediators that cause allergic reactions. The major mechanism for the stimulation of these cells is the interaction of antigen with IgE bound to its high-affinity receptor, FcεRI, on the cell surface. This interaction results in the release of preformed mediators from granules and the generation of newly synthesized mediators, such as the products of arachidonic acid metabolism and cytokines.

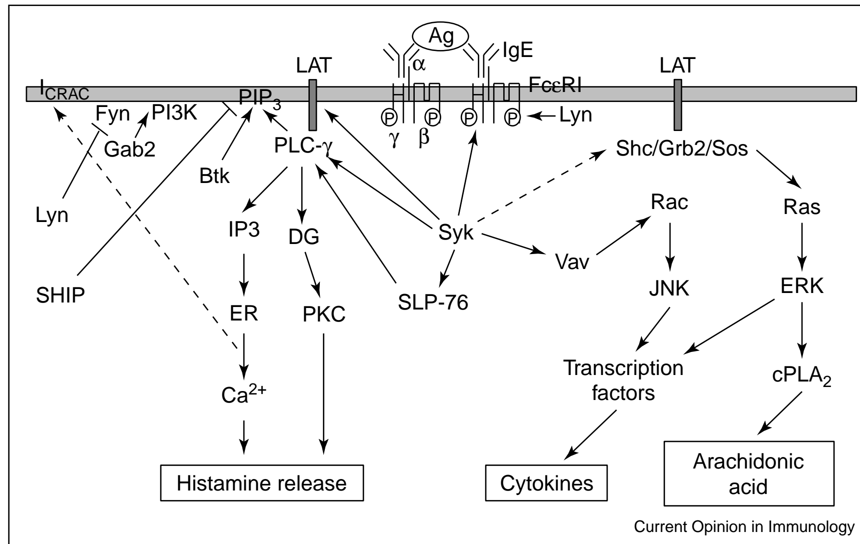
In this review, I summarize current knowledge on the intracellular events that occur when FcεRI is aggregated by binding its specific antigen; however, binding of IgE to FcεRI without the presence of antigen can also generate signals that stimulate mast cell proliferation without resulting in overt degranulation [1]. Interestingly, crystallography studies of the structure of the anti-DNP (2,4-dinitrophenyl) IgE that has strong activity for this function shows that this molecule has multiple conformations [2••]. The Fab of this IgE may bind with low affinity to other cell-surface proteins and may activate cellular enzymes, resulting in an increase in intracellular concentration of free Ca^{2+} ($[Ca^{2+}]_i$) and the expression of histidine decarboxylase [3].

Here, I first discuss our present understanding of the pathways and molecules involved in the FcεRI-induced stimulation of basophil and mast cell signaling, and I then review recent publications. A valuable resource is the proceedings of a symposium on signal transduction during the activation and development of mast cells and basophils [4••].

Current model of FcεRI-mediated mast cell activation

Whereas the extracellular domain of the α chain of FcεRI binds IgE, the β and γ subunits of FcεRI and their associated enzymes, such as the protein tyrosine kinase Lyn, are essential in the subsequent signal transduction (Figure 1). Aggregation of the receptors results in phosphorylation, usually by Lyn, of the tyrosine residues in the immunoreceptor tyrosine-based activation motif (ITAM) of both the β and the γ subunits of the FcεRI. The tyrosine-phosphorylated ITAMs then act as scaffolds for the binding of additional cytoplasmic signaling molecules with Src homology domain 2 (SH2) domains, such as the cytoplasmic protein tyrosine kinase Syk, which binds mainly to the γ subunit of the receptor through its two SH2 domains. This interaction results in a conformational change of Syk, followed by its activation and autophosphorylation. Activated Syk then either directly or indirectly tyrosine phosphorylates several proteins, including

Figure 1



FcεRI-mediated signaling pathways in mast cells. The events shown are initiated by the interaction of antigen (Ag) with IgE bound to the extracellular domain of the α chain of FcεRI. This initial interaction results in phosphorylation (P) of the tyrosine residues in the ITAM of both the β and the γ subunits of the FcεRI by Lyn, which is associated with the receptor. The tyrosine-phosphorylated ITAM then recruits the cytoplasmic protein tyrosine kinase Syk, which binds by its two SH2 domains to the ITAM of the γ subunit of FcεRI. This binding induces both a conformational change of Syk and its activation, which leads to the tyrosine phosphorylation of other proteins, including LAT, PLC-γ1, SLP-76, Vav, and PLC-γ2. Receptor aggregation also results in the Fyn-dependent tyrosine phosphorylation of Gab2, which binds the p85 subunit of PI3K and recruits it to the membrane. PI3K catalyzes the formation of PIP_3 in the membrane, which attracts many proteins containing PH domains, such as Btk and PLC-γ. Tyrosine-phosphorylated PLC-γ in the membrane hydrolyzes PIP_2, forming IP_3 and 1,2-diacylglycerol — second messengers that release Ca^{2+} from internal stores and activate PKC, respectively. The binding of IP_3 to specific receptors in the endoplasmic reticulum results in a depletion of Ca^{2+} stores, which activates store-operated Ca^{2+} entry (I_{CRAC}) from the extracellular medium. Btk, SLP-76, LAT and PLC-γ are all essential for generating signals for the sustained Ca^{2+} influx. Tyrosine phosphorylation and activation of other enzymes and adaptors, including Vav, Shc, Grb2 and Sos, stimulate small GTPases such as Rac, Ras and Rho. These pathways lead to activation of the ERK, JNK and p38 MAP kinases, histamine release, the phosphorylation of transcription factors that induce synthesis of new cytokines, and the activation of cytoplasmic phospholipase A_2 ($cPLA_2$) to release arachidonic acid. Although these arrows imply a linear cascade, the actual interactions are much more complex as many of the molecules initiate both positive and negative effects. Arrows indicate a positive effect, whereas bars indicate a negative interaction. CRAC, Ca^{2+}-release-activated Ca^{2+} channel; ER, endoplasmic reticulum.

linker for activation of T cells (LAT), SH2-containing leukocyte-specific protein of 76 kDa (SLP-76), Vav, phospholipase C-γ1 (PLC-γ1) and PLC-γ2.

Receptor aggregation also results in the Fyn-dependent tyrosine phosphorylation of Grb2-associated binder-like protein 2 (Gab2), which then binds the p85 subunit of phosphatidylinositol 3-kinase (PI3K). The membrane recruitment of PI3K arising from the Gab2–p85 interaction catalyzes the conversion of phosphatidylinositol-4, 5-bisphosphate (PIP_2) to phosphatidylinositol-3,4,5-trisphosphate (PIP_3). The PIP_3 in the membrane attracts many proteins containing pleckstrin homology (PH) domains to the membrane, such as Btk, PLC-γ1, PLC-γ2 and phosphoinositide-dependent protein kinase 1.

Tyrosine-phosphorylated PLC-γ1 and PLC-γ2 catalyze the hydrolysis of PIP_2, resulting in the generation of inositol-1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol — second messengers that release Ca^{2+} from internal stores and activate protein kinase C (PKC), respectively. The initial rise in $[Ca^{2+}]_i$ is caused by the binding of IP_3 to specific intracellular receptors and results in a depletion of Ca^{2+} stores, which then activates store-operated Ca^{2+} entry from the extracellular medium. The tyrosine phosphorylation and activation of Btk, SLP-76, LAT and PLC-γ are essential to generate signals for a sustained Ca^{2+} influx. By electron microscopy, two domains have been observed on the inside of the plasma membrane: a primary one around FcεRI, including PLC-γ2, Gab2 and the p85 subunit of PI3K; and a secondary domain organized around LAT, incorporating PLC-γ1 and also p85 [5].

Many of these reactions occur in membrane rafts — structures that are important for molecular interactions [6]. These early events then result in the activation of other enzymes and adaptors, including Vav, Shc, Grb2 and SOS, which then stimulate small GTPases such as Rac, Ras and Rho. These pathways lead to activation of the extracellular-signal-regulated kinase (ERK), Jun amino-terminal kinase (JNK) and p38 mitogen-activated

protein (MAP) kinase pathways, histamine release, phosphorylation of transcription factors that induce the synthesis of new cytokines, and activation of cytoplasmic phospholipase A2 ($cPLA_2$) to release arachidonic acid.

Below, I discuss in more detail recent publications that have influenced our understanding of the events that occur during mast cell signaling.

The protein tyrosine kinases

Src family

The tyrosine kinases Csk and Ctk phosphorylate the carboxy-terminal regulatory tyrosine of Src family kinases, thereby suppressing their activity; conversely, dephosphorylation of this tyrosine by a phosphatase, or the interaction of the SH3 domain of Src kinases with proline-rich regions of other molecules, results in their activation. Csk-binding protein (also known as phosphoprotein associated with glycosphingolipid domains [PAG]) is a recently identified palmitylated transmembrane protein that localizes to membrane rafts, where it binds and regulates the function of the Csk kinases. FcεRI stimulation results in increased tyrosine phosphorylation of Csk-binding protein (Cbp), which recruits Csk to the membrane rafts, thereby inhibiting the function of Lyn. Overexpression of Cbp in the rat basophilic leukemia (RBL) 2H3 cell line inhibits Ca^{2+} influx and degranulation, suggesting that this protein functions as a negative regulator of FcεRI signaling [7].

Aggregation of FcεRI results in the activation of a pathway dependent on Fyn kinase that cooperates with signals generated by Syk. In this pathway, Fyn kinase mediates the tyrosine phosphorylation of Gab2. Phosphorylated Gab2 then binds PI3K, and this complex translocates to the membrane where it generates PIP_3 to recruit proteins containing PH domains to the membrane. These PH-domain-containing molecules are essential for the downstream propagation of signals, such that in the absence of Fyn there is about a 70% decrease in degranulation of bone-marrow-derived mast cells (BMMCs; [8••]).

Fer family

There is FcεRI-mediated activation of Fer and of the related Fps/Fes tyrosine kinases; however, Fer kinase is not required for degranulation and the release of leukotrienes and cytokines [9]. These Fer-null cells have decreased p38 MAP kinase activation and decreased motility after FcεRI stimulation, suggesting that Fer kinase regulates only some late steps of signaling in mast cells.

Syk

A loss of degranulation is observed in Syk-null cells and, in an *in vivo* rat model of asthma, aerosolized Syk antisense oligodeoxynucleotides inhibit antigen-induced responses [10]. The stable expression in RBL 2H3 cells of single-chain antibodies directed against Syk inhibits degranulation by blocking the activation of Btk and PLC-γ2 [11]. Basophils from some human donors do not degranulate after FcεRI aggregation, probably due to a decrease in the expression of Syk protein, although there are no changes in the level of Syk mRNA. Inhibitors of proteasome-mediated degradation increase the level of Syk proteins, suggesting that the ubiquitin pathway regulates Syk protein in non-stimulated and stimulated cells [12,13•]. This ubiquitination involves c-Cbl and requires the kinase activity of Syk.

The linker region of Syk, located between the second SH2 and the kinase domain, is important in regulating its function. The linker region has three conserved tyrosines, one of these (Tyr317) has been shown to function as a negative regulator. The second, Tyr342, is phosphorylated after receptor aggregation and is crucial for signaling the tyrosine phosphorylation of LAT, SLP-76 and PLC-γ2, but not Vav. By contrast, the third tyrosine, Tyr346, is minimally phosphorylated and has less effect than the others on FcεR1-dependent mast cell degranulation [14•].

BTK

Downregulation of Btk in RBL 2H3 cells by transfection with short interfering RNA (siRNA) oligonucleotides has been shown to decrease expression of the protein and to result in a decrease in histamine release [15].

Other enzymes

Protein tyrosine phosphatases

The protein tyrosine phosphatase MEG2 is present in the secretory granules of mast cells. Overexpression of this protein in RBL-2H3 cells causes a marked enlargement of the granules, although they still contain granular markers such as carboxypeptidase E. This phosphatase may regulate granule formation [16].

PI3K

Among the different isoforms of PI3K, the class 1A variant is activated after FcεRI aggregation. *In vivo*, mice that lack the p85 regulatory subunit of this class of PI3K have fewer numbers of mast cells in the peritoneum and the gastrointestinal tract, but normal numbers in the skin [17]. *In vitro*, these BMMCs degranulate normally after FcεRI aggregation, but not after stimulation by the c-Kit receptor.

Redundant mechanisms recruit PI3K to the membrane, including those dependent on the adaptors LAT and Gab2, which are important regulators of mast cell degranulation (see below). PIP_3 generated by PI3K is degraded by SH2-containing inositol phosphatase (SHIP), an important negative regulator of mast cell activation. Degranulation and cytokine production is higher in SHIP-negative BMMCs than in wild-type BMMCs; this

correlates with an enhanced activation of p38, JNK and PKC and is probably dependent on pathways mediated by the nuclear factor NF-κB [18].

The class 1B PI3K isoforms (including PI3K-γ) are activated by G-protein-coupled receptors and may be involved in FcεRI-induced cell signaling [19••]. FcεRI-induced Ca^{2+} influx and degranulation are decreased in PI3K-γ-null BMMCs. Experiments suggest that there may be an autocrine feedback loop, whereby adenosine released from the mast cells binds the G-protein-coupled A3 adenosine receptors to increase PIP_3 transiently in cells and to enhance the IgE-induced influx of Ca^{2+} and degranulation.

Phospholipase Cγ

The PLC-γ1 and PLC-γ2 isoforms are both present in mast cells. Disruption of the gene encoding PLC-γ1 results in embryonic lethality; by contrast, mice deficient for PLC-γ2 survive but show defects in signaling through immune receptors. These PLC-γ2-deficient mice have normal numbers of mast cells but are resistant to IgE-mediated anaphylactic reactions. *In vitro*, the receptor-induced stimulation of BMMCs from these mice results in normal activation of MAP kinase and cytokine production, although the generation of IP_3, rise in $[Ca^{2+}]_i$, degranulation, and secretion of IL-6 are all decreased [20••].

Protein kinase C

Members of the PKC family are important transducers of signals for secretion in mast cells. PKC-δ is a member of a novel PKC subfamily that is dependent on 1,2-diacylglycerol but not on Ca^{2+}. In PKC-δ-null BMMCs, FcεRI-induced degranulation is enhanced in parallel with an increase in the $[Ca^{2+}]_i$ response at low antigen concentrations [21]. Tyrosine-phosphorylated PKC-δ binds Shc and SHIP in molecular interactions that may negatively regulate degranulation. Studies of Fyn- or Lyn-null BMMCs suggest, however, that PKC-δ may also have a positive role in enhancing degranulation [8••].

Phospholipase D

Whereas phospholipase D1 (PLD1) is localized to the secretory granules, PLD2 is present in the plasma membrane, but both are activated in FcεRI-stimulated cells and are probably involved in different steps of exocytosis [22–24]. Receptor aggregation recruits PLD1 to the plasma membrane and then it recycles back to granules. PLD activity is required for receptor-induced membrane ruffling and PLD2 is present in these membrane ruffles together with endogenous ADP ribosylation factor 6 [23]. The addition of antisense oligonucleotides of PLD1 to human BMMCs decreases expression of the protein and blocks activation of PLD and degranulation, suggesting that PLD1 is more important than is PLD2 in exocytosis [25].

SWAP-70

SWAP-70 is a recently recognized guanine nucleotide-exchange factor present in immature but not mature mast cells and BMMCs [26•,27•]. Although degranulation is decreased in SWAP-70-null BMMCs, the lack of SWAP-70 in mature mast cells suggests that SWAP-70 is not essential for degranulation.

Scramblase

Receptor aggregation results in the tyrosine phosphorylation of scramblase, an enzyme that is involved in moving phospholipids bidirectionally across the plasma membrane, for example, during the FcεRI-induced transient externalization of phosphatidylserine that is usually present on the inner leaflet of the membrane. In RBL-2H3 cells, overexpression of a mutant variant of scramblase, but not the wild-type enzyme, inhibits degranulation induced by the addition of a calcium ionophore and phorbol-12-myristate-13-acetate [28].

Adaptor molecules

Vav

This cytoplasmic protein regulates tyrosine phosphorylation of PLC-γ, generation of IP_3 and Ca^{2+} mobilization in BMMCs. After prolonged receptor activation (>30 min), Vav1 is detected in the nucleus as a component of the nuclear factor NFAT- and NF-κB-like complexes. Nuclear localization is regulated by the carboxy-terminal SH3 domain and a nuclear localization sequence in the PH domain of Vav [29••].

SLP-76

SLP-76 is essential for the FcεRI-induced influx of Ca^{2+} and for degranulation processes downstream of Syk. The amino-terminal and GADS (Grb2-like adaptor downstream of Shc)-binding domains of SLP-76, but not its SH2 domain, are essential for FcεRI-mediated degranulation and IL-6 secretion. But there are differences between the SLP-76 domains required for degranulation and those required for the release of IL-6, suggesting that these pathways diverge [30••].

The related molecule Clnk, also called MIST, may also function upstream of the rise in $[Ca^{2+}]_i$. Clnk binds signaling molecules including SKAP55 and SLAP-130, which recruit it to Fyn and Lyn [31].

LAT

LAT binds important signaling molecules such as Grb2, GADS, PLC-γ1, PI3K, SLP-76 and Cbl, and is therefore essential for the propagation of signals downstream of Syk.

Non-T cell activation linker (NTAL), also known as linker for activation of B cells (LAB), is a newly identified molecule present in both B cells and mast cells that is structurally similar to LAT and, like LAT, localizes to lipid

rafts. It is tyrosine-phosphorylated after FcεRI aggregation and after phosphorylation associates with Grb2, Sos1, Gab1 and c-Cbl. Like LAT, NTAL may regulate Ca^{2+} influx [32•,33•].

Gab

The three members of the Gab family of proteins function as scaffolds that, after tyrosine phosphorylation, interact with several signaling molecules including PI3K, SHP-2, Grb2, PLC-γ, Lyn, Fyn and LAT. The number of mast cells is reduced in Gab2-deficient mice, and the BMMCs from these mice grow poorly in response to IL-3 or steel factor (or stem cell factor) [34]. Gab2-deficient BMMCs show decreased degranulation and cytokine gene expression after stimulation of FcεRI, owing to defective activation of PI3K [35].

As discussed above, the Fyn-induced tyrosine phosphorylation of Gab2 recruits PI3K to the membrane, which in turn generates PIP_3 [8••]. But Gab2 may also negatively regulate FcεRI-induced mast cell signaling: overexpression of Gab2 in RBL-2H3 cells inhibits FcεRI-induced tyrosine phosphorylation of the receptor subunits, activation of Syk and the $[Ca^{2+}]_i$ rise [36].

Gab3 is also expressed in mast cells; however, Gab3-null mice have a normal allergic response, indicating that Gab3 cannot functionally substitute for Gab2 [37].

DOK

Among the DOK family, DOK-1 and DOK-2, but not DOK-3, are tyrosine-phosphorylated after FcεRI aggregation, and DOK-1 is constitutively associated with the receptor [38,39]. Once phosphorylated, DOK-1 binds to other signaling molecules such as Nck, Cas, SHIP, Lyn and rasGAP, and functions to negatively regulate receptor-induced signaling to the Ras/Raf/ERK pathway and generation of TNF-α [38,39].

3BP2

After the aggregation of FcεRI, 3BP2 is rapidly tyrosine-phosphorylated and interacts with the chaperone protein 14-3-3 and Lyn [40]. Expression of a truncated variant of this protein in RBL-2H3 cells inhibits the receptor-induced phosphorylation of PLC-γ, the Ca^{2+} influx and degranulation, but not the activation of JNK or ERK [40].

Changes in intracellular calcium

Store-operated Ca^{2+} channels are activated when intracellular Ca^{2+} stores are emptied, and are essential for the rise in $[Ca^{2+}]_i$. The molecular identity of these channels is unknown but seems to be different from that of the known transient receptor potential (TRP) proteins [41–43]. It has been observed that mitochondria play an important role in regulating store-operated channels [44]. The lipo-oxygenase, but not the cyclo-oxygenase, pathway may be also involved in the activation of store-operated Ca^{2+} channels [45].

Sphingosine kinase, by generating the second messenger sphingosine-1-phosphate, may be involved in the rise in $[Ca^{2+}]_i$. The cytosolic sphingosine kinase rapidly translocates to the plasma membrane after receptor aggregation [25]. Experiments using antisense oligonucleotides suggested that the rapid transient increase in $[Ca^{2+}]_i$ was due to sphingosine kinase, whereas the slow secondary rise was due to PLC-γ1. Treating cells with antisense oligonucleotides to sphingosine kinase inhibits degranulation but not the generation of IP_3 [25].

Small GTP-binding proteins and granular fusion

Munc18 proteins regulate the SNAREs — proteins involved in granular fusion that results in exocytosis. In mast cells, Munc18-3 is localized in the plasma membrane, whereas Munc18-2 localizes to secretory granules where it may be involved in FcεRI-induced granule fusion and exocytosis [46]. Rab3D may also regulate SNAREs and granule size, although peritoneal mast cells from Rab3D-deficient mice are normal microscopically and granular fusion seems normal [47].

Secretory carrier membrane protein 1 (SCAMP1) and SCAMP2 are present in mast cells and are important for vesicle recycling. These are present in the plasma membrane associated with SNARE proteins and play a role in exocytosis [48]. Secernin 1 is a 50 kDa cytosolic protein that may regulate degranulation of mast cells [49]. It increases both the extent of secretion and the sensitivity of cells to Ca^{2+} when added to cells permeabilized with streptolysin-O. A mast-cell-restricted Ras guanine-nucleotide-releasing protein (mRasGRP4) has been identified that, by activating Ras, may be important in the final stages of mast cell development and in the regulation of prostaglandin D_2 synthetase [50].

Inhibiting the release reaction

The extent of degranulation of cells results from a balance between activation and inhibitory signals. Many signaling molecules initiate both activating and inhibitory signals; for example, Lyn-induced phosphorylation of the ITAM is essential for activation pathways, whereas its phosphorylation of the immunoreceptor tyrosine-based inhibition motif (ITIM) recruits inhibitory signaling molecules. By contrast, other intracellular molecules such as SHIP and c-Cbl seem to act only as negative regulators. Inhibitory signals also result when several transmembrane proteins are crosslinked or when they are coaggregated with FcεRI. The cytoplasmic domain of these molecules has an ITIM sequence that, when phosphorylated, recruits negative signaling molecules such as SHIP, SHP-1 and SHP-2.

FcγRIIB

The coaggregation of FcγRIIB, the low-affinity receptor for IgG, with FcεRI leads to the rapid phosphorylation of the tyrosine in the ITIM of FcγRIIB, which subsequently recruits SHIP, SHP-2 and SHP-1. This results in the inhibition of FcεRI-mediated degranulation. SHIP associates with Shc, DOK-1 and RasGAP; however, DOK-1 may not be essential as coaggregation still inhibits signaling in DOK-1-negative BMMCs [39]. A chimeric fusion protein containing part of the Fc portion of IgG and IgE crosslinks FcεRI to FcγRIIB, and inhibits antigen-induced Syk phosphorylation and the degranulation of human basophils [51].

Mast cell function-associated antigen

Mast cell function-associated antigen (MAFA) is a transmembrane protein, aggregation of which inhibits FcεRI-induced cell activation. MAFA is in close proximity to, or directly associated with, FcεRI [52]. The clustering of MAFA results in an increase in the tyrosine phosphorylation of the adaptor protein DOK-1 and SHIP, which in turn inhibits the Ras signaling pathway and cell proliferation [53].

PECAM-1

Stimulation of FcεRI results in the tyrosine phosphorylation of PECAM-1 (also known as CD31), a transmembrane protein with an ITIM sequence, which then binds SHP-2. Both local and generalized anaphylactic reactions are enhanced in PECAM-1-deficient mice, and BMMCs from these mice show enhanced degranulation [54•]. This suggests that PECAM-1 is a negative regulator of FcεRI-mediated reactions.

Conclusions

Aggregation of the high-affinity IgE receptor FcεRI activates a complex series of reactions that eventually leads to the exocytosis of granules and the generation of leukotrienes and cytokines. These products result from a complex network of enzymes and adaptors, many of which interact to regulate the downstream propagation of signals. The representation, such as that shown in Figure 1, of these events with arrows pointing from one molecule to another is a gross simplification of the cellular interactions. Many of these molecules not only activate downstream events but also initiate feedback loops that regulate upstream events. The extent of the release of inflammatory mediators therefore depends on the balance between these positive and negative signals, which may have different effects on the products produced [55•].

During the past decade, there has been a tremendous increase in our understanding of the intracellular pathways that activate basophils and mast cells. The development of selective pharmaceutical agents that inhibit these pathways would be very useful for the treatment of allergic inflammation.

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