Fine-tuning of mast cell activation by FcεRIβ chain

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INTRODUCTION

Mast cells play a key role in allergic reaction and disorders through the high affinity receptor for IgE (FcεRI) which is primarily activated by IgE and antigen complex. In humans, mast cells express two types of FcεRI on the cell surface, tetrameric αβγ2 and trimeric αγ2, whereas in mice, the tetrameric αβγ2 type is exclusively expressed. In human allergic inflammation lesions, mast cells increase in number and preferentially express the αβγ2 type FcεRI. By contrast, in the lesion of non-allergic inflammation, mast cells mainly express the αγ2 type. Since the β chain amplifies the expression and signaling of FcεRI, mast cell effector functions and allergic reaction in vivo are enhanced in the presence of the β chain. In contrast, a truncated β chain isoform (βT) inhibits FcεRI surface expression. The human FcεRIβ gene contains seven exons and a repressor element located in the forth intron, through which FcεRIβ transcription is repressed in the presence of GM-CSF. Regarding the additional signal regulatory function of the β chain, the β chain ITAM has dual (positive and negative) functions in the regulation of the mast cell activation. Namely, the FcεRIβ chain ITAM enhances the mast cell activation signal triggered by a low-intensity (weak) stimulation whereas it suppresses the signal triggered by high-intensity (strong) stimulation. In an oxazolone-induced mouse CHS model, IgE-mediated mast cell activation is required and the β chain ITAM is critically involved. Adenosine receptor, one of the GPCRs, triggers a synergistic degranulation response with FcεRI in mast cells, for which the β chain ITAM crucially plays positive role, possibly reflecting the in vivo allergic response. These regulatory functions of the FcεRIβ ITAM finely tune FcεRI-induced mast cell activation depending on the stimulation strength, enabling the FcεRIβ chain to become a potential molecular target for the development of new strategies for therapeutic interventions for allergies.

Keywords: mast cell, FcεRI, FcεRIβ chain, ITAM, signal transduction, allergy
hypersensitivity (CHS) mouse model (Kobayashi et al., 2010). The role of the β ITAM has also been examined using this mouse model.

In this review we have mainly focused on recent findings regarding the roles of the FcεRIβ chain, especially the dual (positive and negative) regulatory roles of the FcεRIβ chain ITAM, both in vitro and in vivo. Detailed reviews on FcεRI signaling, including this topic, are available (Kraft et al., 2004; Rivera and Gilfillan, 2006; Kraft and Kinet, 2007; Rivera et al., 2008). Findings regarding the novel roles of the FcεRIβ chain in the fine-tuning of mast cell activation will contribute to investigation in new areas for the development of therapeutic interventions for allergic diseases.

**STRUCTURE OF THE FcεRIβ-CHAIN**

The cDNA for the FcεRIβ chain was identified from a cDNA library derived from a rat mucosal mast cell tumor in 1988 (Kinet et al., 1988). Subsequent studies identified mouse and human FcεRIβ chain counterparts (Blank et al., 1989; Ra et al., 1989; Küster et al., 1992). The human and mouse FcεRIβ chain genes contain seven exons. The start and stop codons are located in exon 1 and exon 7, respectively (Figure 1A). The homology among the amino acid sequences of the rat, mouse, and human β chain proteins is approximately 69% (Küster et al., 1992).

Recent studies have demonstrated that the human FcεRIβ chain gene encodes two additional spliced products (Donnadieu et al., 2003; Fiebiger et al., 2005; Cruse et al., 2010). These splicing variants produce two truncated proteins, which are designated βT and MS4A2truc (Figures 1B,C). βT retains the fifth intron, which contains a stop codon. Unlike βT, MS4A2truc, a novel β isoform, does not retain this intron sequence and lacks exon 3. Whether the murine FcεRIβ chain gene also encodes βT and/or MS4A2truc is currently unclear.

In humans and mice, the FcεRIβ chain is a component of the tetrameric FcεRI complex, which is expressed in mast cells and basophils. The tetrameric form (αβγ₂) of FcεRI is composed of an α chain, a β chain, and a homodimer of γ chains. The full-length FcεRIβ chain protein spans the plasma membrane four times in a manner such that both its N- and C-terminal regions protrude toward the cytoplasm. The
C-terminal cytoplasmic region of the FcεRIβ chain possesses an ITAM, which is immediately phosphorylated upon FcεRI crosslinking.

REGULATION OF THE HUMAN FcεRIβ GENE EXPRESSION

A sequence located in the fourth intron has been shown to serve as a repressor element by screening for cis-acting elements over the entire region of the human FcεRIβ gene (Takahashi et al., 2003). This element binds the transcription factor MZF-1. The MZF-1 antisense inhibits the suppressive effect of the element on the FcεRIβ promoter and increases the quantity of FcεRIβ mRNA, indicating that MZF-1 represses human FcεRIβ gene expression via the element in the fourth intron. This transcriptional repression by MZF-1 requires FHL3 as a cofactor (Takahashi et al., 2005). Furthermore, MZF-1 and FHL3 form a complex with a high molecular mass by binding additional proteins in the nucleus. We identified NFY, which reportedly binds HDACs, as a constituent of the repressor complex in the fourth intron (Takahashi et al., 2006).

GM-CSF, which reportedly decreases FcεRI expression, induces the accumulation of FHL3 in the nucleus, in accordance with the repressive role of FHL3 in FcεRIβ expression. In the presence of GM-CSF, the C-subunit of NFY forms a ternary complex with MZF-1/FHL3 and recruits HDAC1 and HDAC2 on the fourth intron of FcεRIβ gene in human mast cells. As a result, HDACs repress FcεRIβ transcription by deacetylating histones (Figure 2). These mechanisms are involved not only in the cell type-specific repression of FcεRIβ expression in differentiating hematopoietic cells but also in the repression of FcεRIβ expression in peripheral cells, such as mast cells, under specific circumstances.

Although the existence of both FcεRIαβγ2 and αγ2 receptor subtypes was theoretically anticipated, the distribution of the FcεRIαβγ2 and αγ2 isoforms in human mast cells in vivo has not been determined. The precise pathophysiological roles of FcεRIβ in human atopic diseases remain unknown.

Atopic keratoconjunctivitis (AKC; Foster and Calonge, 1990; Tuft et al., 1991) and vernal keratoconjunctivitis (VKC) (Bonini et al., 2000) are the most severe form of chronic allergic conjunctivitis, showing the massive infiltration of mast cells and significantly high serum and tear IgE levels compared with those in normal controls (Tuft et al., 1991). VKC and AKC tend to form giant papillae at the upper tarsal conjunctiva (Abu el-Asrar et al., 1989; Tuft et al., 1991; Bonini et al., 2000). Histopathological analyses using an anti-FcεRIβ specific antibody (Matsuda et al., 2008) and performed by our group revealed that the densities of FcεRIβ+ cells, FcεRIα+ cells, tryptase+ cells, and the ratio of FcεRIβ+/tryptase+ cells were significantly increased in giant papillae compared with conjunctiva from non-allergic conjunctivitis patients with conjunctivochalasis and superior limbic keratoconjunctivitis (Matsuda et al., 2009; Figure 3). The ratio of the FcεRIβ+ mast cell number/FcεRIα+ mast cell number in the giant papillae was also significantly higher than that in the non-allergic conjunctivitis patients. FcεRIβ+ cells were preferentially localized within and around the epithelial tissue, suggesting that the FcεRIβ+ mast cells around the epithelium in the mucosa of allergic patients are easily able to access allergens.

Because the shRNA-mediated diminution of the FcεRIβ chain in human mast cells significantly downregulated cell surface FcεRI expression, and IgE-dependent mediator release/production

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**FIGURE 2 | GM-CSF-induced repression of FcεRIβ gene expression in human mast cells.** HDACs, which were recruited to the human FcεRIβ gene through the element in the fourth intron by MZF-1/FHL3/NFY, repressed FcεRIβ transcription through the deacetylation of histones in the presence of GM-CSF.
The requirement of the FceRIβ chain for FceRI cell surface expression differs between rodents and humans. While the FceRIβ chain is required for surface expression of the receptor in rodents, human FceRI can be expressed on the cell surface in the absence of the FceRIβ chain. Therefore, human trimeric FceRI (αγ2) can be expressed in β chain-deficient cell types, such as monocytes, Langerhans cells, and dendritic cells.

However, the FceRIβ chain can enhance FceRI cell surface expression in humans by promoting the maturation (glycosylation) of the FceRIα chain protein (Donnadieu et al., 2000b). Donnadieu et al. showed that immature FceRIα chain protein accumulates in the ER in the absence of the FceRIβ chain protein. Moreover, the FceRIβ chain increases the stability of surface FceRI complexes (Donnadieu et al., 2000b). Trimeric FceRI complexes are unstable when exposed to a strong detergent (Triton-X100), whereas tetrameric FceRI complexes remain stable when exposed to the same detergent.

The presence of a full-length FceRIβ chain is thus widely believed to result in a fourfold to sixfold enhancement of FceRI surface expression. The truncated form of βT lacks the C-terminal cytoplasmic region, including the ITAM. Interestingly, the βT protein is unable to support the maturation of the nascent FceRIα chain. Therefore, FceRI surface expression was found to be unaltered following introduction of βT cDNA into CHO cells expressing trimeric FceRI (αγ2) (Fiebiger et al., 2005). However, the participation of the FceRIβ chain ITAM domain in the maturation of the FceRIα chain remains unclear. Further investigation is required to elucidate the role of the FceRIβ chain ITAM in this maturation process.

### Biological Functions of the FceRIβ Chain Related to FceRI Expression and Stability

The rapid tyrosyl phosphorylation of the FceRIβ and γ chain ITAMs is initiated; this, in turn, leads to effector functions, such as degranulation, the de novo synthesis of lipid mediators, and cytokine production. The tyrosine phosphorylation of the FceRIβ chain ITAM occurs through trans-phosphorylation by the src family tyrosine kinase (PTK) Lyn.

Earlier studies found that the FceRIβ chain acts as an amplifier of FceRIγ-mediated signaling. The mutation of two canonical tyrosines in the FceRIβ chain ITAM has been shown to abolish the phosphorylation of both the FceRIβ and γ chain ITAMs. These tyrosines include the conserved K118 in the γ chain ITAM, the de novo synthetic lipid mediators, and cytokine production. The tyrosine phosphorylation of the FceRIβ chain ITAM occurs through trans-phosphorylation by the src family tyrosine kinase Lyn.

**Basal Functions of the FceRIβ Chain in FceRI Signaling**

Upon the engagement of FceRI with IgE and a multivalent antigen, the rapid tyrosyl phosphorylation of the FceRIβ and γ chain ITAMs is initiated; this, in turn, leads to effector functions, such as degranulation, the de novo synthesis of lipid mediators, and cytokine production. The tyrosine phosphorylation of the FceRIβ chain ITAM occurs through trans-phosphorylation by the src family tyrosine kinase (PTK) Lyn.

The presence of a full-length FceRIβ chain is thus widely believed to result in a fivefold to sevenfold increase in FceRI signaling through the FceRIγ chain ITAM. Researchers have long recognized the classical function of the FceRIβ chain ITAM as a signal amplifier.
However, studies by our group recently revealed novel functions of the FcεRIβ chain ITAM and Lyn in the negative regulation of cell activation and effector functions.

**INSIGHTS INTO THE NOVEL ROLES OF THE FcεRIβ CHAIN IN FcεRI SIGNALING AND MAST CELL ACTIVATION**

The generation of FcεRIβ chain KO mice (Hiraoka et al., 1999) and the development of retroviral gene transfer have contributed greatly to the establishment of FcεRI reconstitution systems in murine mast cells. This system allows us to investigate the biological functions of the FcεRIβ chain in mast cells. Polymorphisms (I181L, V183L, and E237G) in the coding region of the FcεRIβ chain have been found to be associated with allergic disorders. However, reconstitution studies did not find any effects of these variants on mast cell effector functions (Donnadieu et al., 2000a; Furumoto et al., 2004).

Interestingly, the ITAM sequence of the FcεRIβ chain is unique, differing from the consensus ITAM sequence. While the FcεRIγ chain ITAM (YTGLNTRSQETYETL) contains the consensus sequence (YxxL-xy-yxxL), the FcεRIβ chain ITAM (Y219EELHY225SPIY229SEL) contains a third non-canonical tyrosine (Y225) between two canonical tyrosine residues (Y219 and Y229; Figure 4). A mutational analysis of these tyrosine residues in the ITAM (tyrosine replaced with phenylalanine, Y→F) performed by our group revealed novel functions of the FcεRIβ chain (Furumoto et al., 2004).

The N-terminal canonical tyrosine (Y219) in the FcεRIβ chain ITAM is essential for the modulation of the effects of the FcεRIβ chain because of its ability to associate with Lyn upon FcεRI engagement, whereas the other canonical tyrosine (Y229) is dispensable for the interaction of the FcεRIβ chain with Lyn. Mast cells (αβγεβεβεγεβεεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγεβεβεγ
even when the FcεRI stimulation is of “lower intensity” than the threshold strength (Laflargue et al., 2002). Additionally, an early-phase allergic reaction in asthmatic subjects but not in non-asthmatic subjects is induced by the inhalation of a low-dose mite allergen (Bryant and Burns, 1976; Dohi et al., 1990; M’Raihi et al., 1990). These findings suggest that the augmentation of “low-intensity” FcεRI stimulus-mediated degranulation by an exacerbating factor, such as adenosine, may be responsible for the high susceptibility of asthmatic patients to low-dose allergens.

We recently reported a positive role for the FcεRIβ chain ITAM in the regulation of the synergistic degranulation response following “low-intensity” FcεRI stimulation and adenosine receptor stimulation, possibly reflecting in vivo allergic reactions (Nunomura et al., 2010). In this report, we demonstrated that adenosine fails to increase the degranulation response in αβγ2 mast cells. Conversely, the degranulation response of αβγ2, αβγ2, and αβγ2 mast cells was enhanced, suggesting that the two canonical tyrosine residues Y219 and Y229 in the FcεRIβ ITAM are sufficient for the amplification of the degranulation response by adenosine. This phenomenon was found to be associated with increased phosphorylation of Thr308 in Akt, reflecting PI3K activity.

However, the question of how the FcεRIβ chain ITAM regulates the amplification of the degranulation response and PI3K signaling remains. Of particular note, the tyrosine phosphorylation of the FcεRIβ chain was synergistically increased upon costimulation with FcεRI and adenosine receptors, representing one mechanism that mediates the synergy between the two signaling cascades. However, how adenosine receptor signaling enhances the FcεRI-mediated tyrosine phosphorylation of the FcεRIβ chain remains unclear. Further studies are needed to assess the potential role of adenosine receptors in this process.

**FCεRIβ CHAIN AMPLIFIES IgE-MEDIATED MAST CELL EFFECOR FUNCTIONS IN VIVO**

Mouse mutants for c-Kit that genetically lack mast cell populations can undergo engraftment with wild-type or genetically altered mast cells (Tsai et al., 2005; Metz et al., 2007). WBB6F1-W/Wv and KitW-sh/W-sh mice are two representative examples of mast cell-deficient mouse strains. Using the adoptive transfer of mast cells into these mast cell-deficient mice, several groups have investigated the role of mast cells in hapten-induced CHS. For instance, mast cells are required for the optimal elicitation of the cutaneous inflammation response associated with mouse models of oxazolone-induced CHS (Bryce et al., 2004; Nakae et al., 2005, 2006; Kakurai et al., 2006). Although the requirement of mast cells for the elicitation of CHS differs with the type and concentration of hapten, the CHS model employing oxazolone is suitable for investigating the in vivo effector functions of mast cells. A recent study by our group revealed that the abrogation of IgE-mediated mast cell activation in the effector phase prevents oxazolone-mediated CHS without affecting the immune response in the sensitization phase (Kobayashi et al., 2010).

Furthermore, using the adoptive transfer of αβγ2 and αβγ2 mast cells into WBB6F1-W/Wv mice, we investigated whether the FcεRIβ chain ITAM regulates the CHS response to oxazolone in mice. In the study, an amplifying role was demonstrated for the FcεRIβ chain ITAM in IgE-mediated in vivo mast cell effector functions, suggesting that the in vivo activation of mast cells may occur through “low-intensity FcεRI stimulation.”

**CONCLUDING REMARKS**

The major focus of this review was the novel roles of the FcεRIβ chain both in vitro and in vivo, especially the dual function of the β chain ITAM. In the β chain ITAM, an additional non-canonical tyrosine residue (Y225) is present between the two canonical residues (Y219, Y229). The β chain positively and negatively regulates FcεRI signaling in response to low-intensity and high-intensity (weak and strong) stimuli, respectively. Lyn kinase associates with the β chain ITAM (Y219) and has a dual-function in the regulation of FcεRI signaling (Furumoto et al., 2004). Hck and PLCβ3 suppress the negative roles of Lyn in mast cell activation.
(Hong et al., 2007; Xiao et al., 2011). Interactions among PLCβ3 and the β chain, Lyn, and SHIP-1 have been reported; in this context, PLCβ3 and SHIP-1 regulate mast cell cytokine production by suppressing Lyn and SHIP-1 activity. In this compartment, the β chain may provide a docking platform for the formation of a negative signalsom that includes Lyn, SHIP-1 and SHIP-1. Importantly the non-canonical tyrosine residue in the β chain ITAM (Y225) plays a crucial role in interaction between the β chain and SHIP-1 following FcεRI stimulation and in the negative regulation of FcεRI signaling (Furumoto et al., 2004). Regarding the molecular mechanisms for the bidirectional (positive and negative) regulation of the β chain in FcεRI-induced mast cell activation, unknown players and compartments requiring further investigation may exist. The elucidation of the underlying mechanisms responsible for bidercional response to the strength of the stimuli, such as the type and concentration of antigen, is particularly important. Deeper insights into the activation mechanisms for mast cells are needed for the development of mast cells biology and the pathophysiology of allergy.

In allergic inflammation lesions, such as giant papillae in AKC and atopic dermatitis, mast cells preferentially express the tetrameric αβγ2 type FcεRI (Matsuda et al., 2009), indicating that these mast cells are much more sensitive to antigen stimulation. In contrast, mast cells mainly express the trimeric αγ2 type FcεRI in specimens from non-allergic patients. A repressor element was found in the fourth intron of the FcεRIβ gene and a molecular mechanism to repress the FcεRIβ gene through this element has been elucidated (Takahashi et al., 2006). Further investigation of the regulation of FcεRIβ expression at both the translational and post translational levels, is required, especially for elucidating the mechanisms by which the β chain associates with cell surface-expressed FcεRI. When shRNA for the β chain or phosphorylated ITAM peptide of the β chain was introduced into human mast cells, Ag-IgE-induced histamine, PGD2, and cytokine release were almost completely abolished (unpublished data).

Recent findings regarding the roles of the FcεRIβ chain in fine-tuning of FcεRI signaling indicate that the β chain may be a novel molecular target for the development of new strategies for therapeutic interventions for allergies.

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May 2012 | Volume 3 | Article 112 | 7
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