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*Am J Physiol Lung Cell Mol Physiol* 291:312-321, 2006. First published Mar 31, 2006;  
doi:10.1152/ajplung.00005.2006

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# The high-affinity IgE receptor (FcεRI): a critical regulator of airway smooth muscle cells?

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**Gounni, Abdelilah Soussi.** The high-affinity IgE receptor (FcεRI): a critical regulator of airway smooth muscle cells? *Am J Physiol Lung Cell Mol Physiol* 291: L312–L321, 2006. First published March 31, 2006; doi:10.1152/ajplung.00005.2006.—The airway smooth muscle (ASM) has been typically described as a contractile tissue, responding to neurotransmitters and inflammatory mediators. However, it has recently been recognized that ASM cells can also secrete cytokines and chemokines and express cell adhesion molecules that are important for the perpetuation and modulation of airway inflammation. Recent progress has revealed the importance of IgE Fc receptors in stimulating and modulating the function of these cells. In particular, the high-affinity receptor for IgE (FcεRI) has been identified in primary human ASM cells in vitro and in vivo within bronchial biopsies of atopic asthmatic individuals. Moreover, activation of this receptor has been found to induce marked increases in the intracellular calcium concentrations and T helper 2 cytokines and chemokines release. This and other evidence discussed in this review provide an emerging view of FcεRI/IgE network as a critical modulator of ASM cell function in allergic asthma.

immunoglobulin E; asthma

ASTHMA IS A CHRONIC INFLAMMATORY DISEASE of the bronchial airway clinically characterized by airway obstruction, enhanced bronchial responsiveness, and airway inflammation (13, 51). The inflammatory component of this disease includes an increased number of activated T lymphocytes, mast cells, eosinophils, and neutrophils within the airway lumen and bronchial submucosa (13, 82). Considerable evidence from human and animal studies indicates that CD4<sup>+</sup> T cells are the predominant cell type involved in the regulation of airway inflammation through the expression of T helper 2 (Th2) cytokines (49).

Besides inflammatory cells, airway smooth muscle (ASM) cells are key determinants of asthma owing to their ability to contract in response to inflammatory cell products (95). Because of intrinsic phenotype plasticity, airway myocytes also exhibit a capacity for multifunctional behavior and are actively involved in local inflammation and fibrosis (47). Emerging evidence suggests that ASM cells can contribute directly to the pathogenesis of asthma by expressing cell adhesion and costimulatory molecules and by secreting multiple proinflammatory cytokines and chemokines that may perpetuate airway inflammation and the development of airway remodeling in vivo (47, 83). Recent studies have added to our knowledge of the biology of this intriguing cell type and defined a new role of ASM in allergic asthma. In particular, it has been proposed that ASM cells may contribute to airway inflammation and remodeling by mechanisms depending on Fc receptor activation (43). In this review, we will briefly introduce Fcε receptors and discuss the role of high- and low-affinity receptor for IgE

(FcεRI; and FcεRII/CD23) activation and the consequences on ASM cell function.

## FcεR NETWORK AND ALLERGIC ASTHMA

It is well recognized that most asthma is associated with atopy, characterized by an increased synthesis of IgE against the most common allergens (13). After sensitization of susceptible individuals and the synthesis of allergen-specific IgE, atopic individuals respond to environmental allergens with a type I hypersensitivity reaction (13). Allergens interact with basophil or mast cell-bound-specific IgE and trigger cross-linking of the FcεRI (29, 33, 61). This cross-linking provokes a cascade of events, including cell degranulation and the release of inflammatory mediators such as histamine, leukotrienes, and a number of cytokines and chemokines (61). Collectively, these mediators orchestrate the early inflammatory response with mucosal edema and smooth muscle contraction, resulting in allergic diseases such as asthma. So far, two types of Fcε receptors have been identified: the low-affinity receptors for IgE or FcεRII/CD23 (11, 20) and the high-affinity receptor for IgE, FcεRI (61).

## FcεRI

FcεRI is a member of the multichain immune recognition receptor family and was first described as a tetrameric complex (αβγ<sub>2</sub>) (61). The α-chain, a member of the immunoglobulin superfamily, contains the binding site for IgE (22, 63, 65, 90). The β-subunit, with its four transmembrane domains separating NH<sub>2</sub>- and COOH-terminal cytoplasmic tails, functions to amplify signaling responses (23, 24, 62). The two disulfide-linked γ-subunits are members of the γ/ζ/η family of antigen receptor subunits, consist essentially of a transmembrane region and cytoplasmic tail, and are critical for receptor signaling

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(61). Both  $\beta$ - and  $\gamma$ -subunits are responsible for the downstream propagation of the signal through the phosphorylation of their immunoreceptor tyrosine-based activation motif (ITAM) (61).

The structure of Fc $\epsilon$ RI varies according to species. In mice, Fc $\epsilon$ RI  $\beta$ -chain is required for cell surface expression of Fc $\epsilon$ RI so that Fc $\epsilon$ RI is expressed as  $\alpha\beta\gamma_2$  tetramers, whereas in humans Fc $\epsilon$ RI can be expressed as an  $\alpha\beta\gamma_2$  or  $\alpha\gamma_2$  complex depending on cell type (61) (Fig. 1). For instance, in human antigen-presenting cells, Fc $\epsilon$ RI is expressed as a trimeric ( $\alpha\gamma_2$ ) complex (8, 74–76, 81, 107) and as a tetramer ( $\alpha\beta\gamma_2$ ) in mast cells (29). However, in the case of human eosinophils (36, 98), platelets (53), and neutrophils (35), although both mRNA and protein for the  $\beta$ -chain have been detected, the existence of a functional  $\alpha\gamma_2$  complex could not be ruled out.

Recently, extensive advances have been made in the study of Fc $\epsilon$ RI signaling pathways (99). Cross-linking Fc $\epsilon$ RI via IgE-bound multivalent antigen initiates a series of biochemical events starting with the Src family protein tyrosine kinase Lyn that phosphorylates the ITAM motifs of both Fc $\epsilon$ RI  $\beta$ - and  $\gamma$ -chains (14, 55, 105, 110). This event leads to the propagation of signals through subsequent activation of additional cytoplasmic signaling molecules with Src homology domain 2 (SH2) domains such as the protein kinase Syk (48, 96). Activated Syk (97, 117) mediates phosphorylation of several proteins including linker for activation of T cells, SH2-containing leukocyte-specific protein of 76 kDa, Vav, PLC- $\gamma$ 1, and PLC- $\gamma$ 2 (99). More recently, Parravicini et al. (84) have demonstrated that Fc $\epsilon$ RI aggregation activates Fyn leading to the adapter protein Grb2-associated binderlike protein 2 (Gab2) tyrosine phosphorylation. Gab2 binds to the p85 subunit of phosphatidylinositol 3-kinase leading to phosphatidylinositol-3,4,5 triphosphate production and recruitment of pleckstrin homology domains to the membrane, i.e., Btk, PLC- $\gamma$ 1, and PLC- $\gamma$ 2 and phosphoinositide-dependent protein kinase 1, subsequently resulting in release of calcium from internal stores. Other reports have also demonstrated that Fc $\epsilon$ RI early events lead to activation of ERK-associated MAPKs (Vav, Raf1, MEK) and small

GTPases (Rac, Ras, Rho) (52, 101). These events lead to activation of MAPK pathways (ERK, JNK, and p38 MAP) (38, 52), exocytosis of granules, and generation of leukotrienes and cytokines (Fig. 2).

#### Fc $\epsilon$ RII/CD23

Fc $\epsilon$ RII/CD23 is a 45-kDa single-chain glycoprotein that belongs to the family of type II integral membrane proteins displaying a lectin-binding motif (60). CD23 undergoes natural proteolytic cleavage to yield fragments of 37, 33, and 25 kDa, components of soluble CD23 (19). CD23 is widely expressed in hematopoietic cells including B cells, eosinophils, platelets, and monocytes (11). Two variants of CD23 have been described, CD23a and CD23b, resulting from alternative splicing and translational initiation at different sites (1, 114, 115). CD23a is constitutively expressed on B cells and subpopulations of eosinophils, whereas CD23b is inducible by IL-4 on various immune cell types, including B cells, monocytes, macrophages, neutrophils, and others (11).

Previous evidence has demonstrated the involvement of CD23 and its soluble (s) forms in B cell differentiation (11). Furthermore, at least in humans, sCD23 can exert cytokine-like properties. In conjunction with IL-1, sCD23 can enhance growth of myeloid and T cell precursors, is costimulatory for mast cell activation, and inhibits germinal center B cell apoptosis (21). The latter activities may be due to the ability of CD23 to interact with the complement receptor 2 (CR2/CD21) (5, 10). Moreover, CD23 can also regulate IgE production in vivo. Indeed, CD23 knockout mice showed an antigen-specific IgE-mediated response defect, and transgenic mice exhibited reduced serum IgE levels (85, 86).

Recent reports suggest that CD23 plays a central role in food allergic reaction. CD23 protein has been identified on human and rodent intestinal epithelial cells (7, 116). Furthermore, studies in allergic rats showed that enhanced intestinal trans-epithelial antigen transport is mediated by IgE and CD23 (112). More recent studies have demonstrated a clear role of

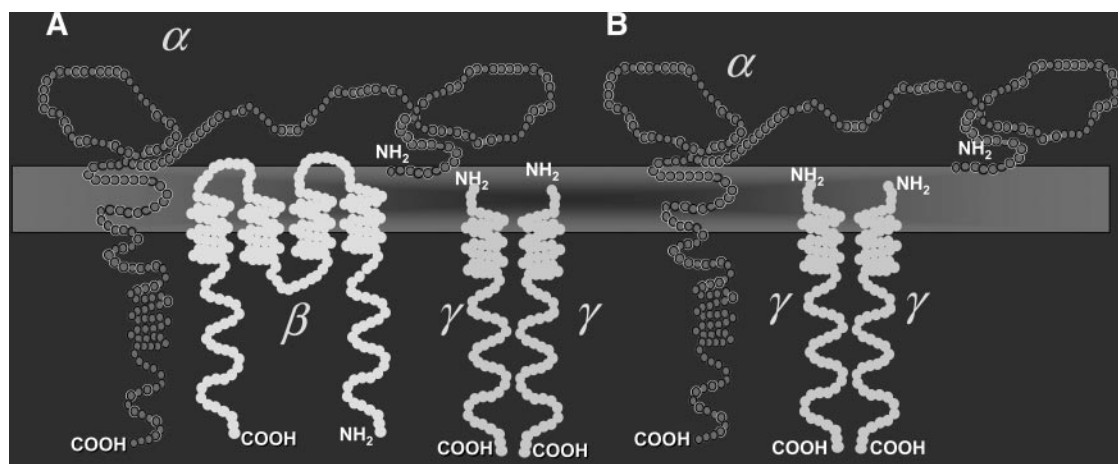
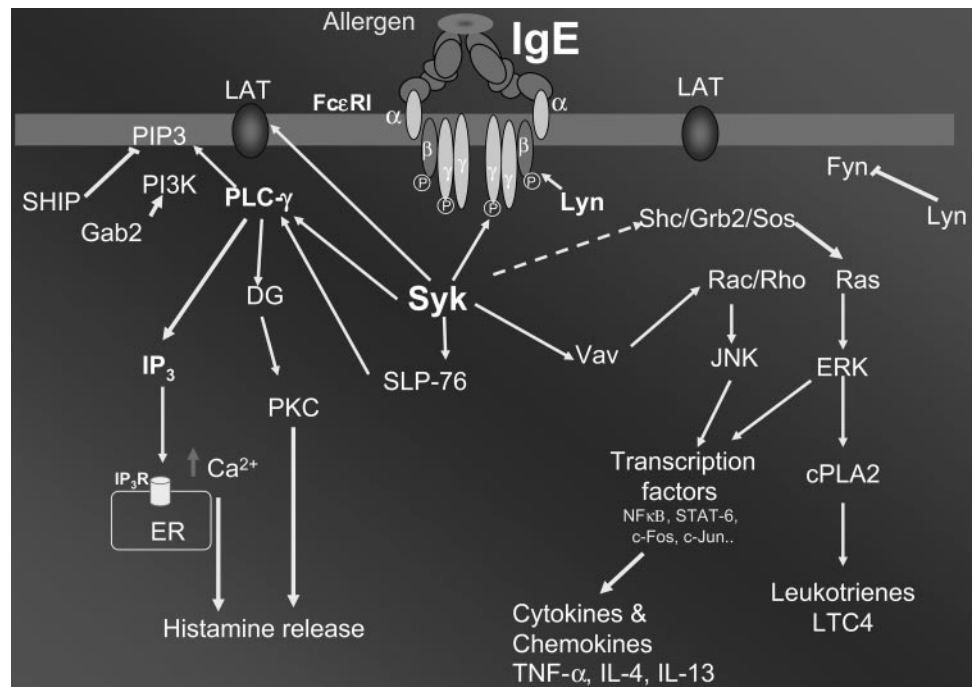


Fig. 1. Structure of the high-affinity IgE receptor (Fc $\epsilon$ RI). A: Fc $\epsilon$ RI was first described as a tetrameric complex ( $\alpha\beta\gamma_2$ ). The  $\alpha$ -chain, a member of the immunoglobulin superfamily, is composed of 2 extracellular immunoglobulin-related domains, 1 transmembrane domain, and a short cytoplasmic tail. The extracellular domain contains the binding site for IgE. The  $\beta$ -subunit has 4 transmembrane domains separating NH<sub>2</sub>- and COOH-terminal cytoplasmic tails. The  $\gamma$ -subunit is a member of the  $\gamma/\zeta/\eta$  family of antigen receptor subunits and consists essentially of a transmembrane region and a cytoplasmic tail. In rodent, Fc $\epsilon$ RI  $\beta$ -chain is required for cell surface expression of Fc $\epsilon$ RI so that Fc $\epsilon$ RI is only expressed as  $\alpha\beta\gamma_2$  tetramers on mast cells and basophils. B: in human monocytic lineage, e.g., dendritic cells, monocytes, and Langerhans cells, Fc $\epsilon$ RI is expressed exclusively as an  $\alpha\gamma_2$  complex.

Fig. 2. Schematic diagram of FcεRI-mediated signaling events in mast cells. After FcεRI cross-linking, various tyrosine kinases are activated starting with Lyn that revert from an inactive to an active state. Once activated, Lyn phosphorylates the β- and γ-chain immunoreceptor tyrosine-based activation motifs. Syk is then recruited and gets activated by Lyn. These events represent a key initiating step in the signal transduction cascade. The signal is propagated through multiple signaling pathways including the small GTPase pathway, the PLC/calcium pathway, the phosphatidylinositol 3-kinase (PI3K) pathway, and the MAPKs pathway. Ultimately, these signals lead to an increase of intracellular calcium release, cell degranulation, transcription factor activation, and expression of target genes such as cytokines and leukotrienes. P, phosphorylation of tyrosine residue; cPLA-2, cytoplasmic phospholipase A2; DG, 1,2-diacylglycerol; Gab, Grb2-associated binder-like protein; IP3, inositol-1,4,5-triphosphate; LAT, linker for activation of T cells; SHIP, SH2 containing inositol phosphatase; SLP76, SH2 containing leukocyte specific protein of 76kDa.



CD23 and a novel CD23b-derived alternative splice form CD23bΔ5 in rapid transepithelial transport of IgE/allergen complexes and subsequent delivery of intact antigen to mast cells in the subepithelial compartment (77, 78).

#### FcεR IN ASM CELLS

Besides the effect of IgE on immune cells, cumulative data have clearly demonstrated that serum IgE plays an important role in the pathogenesis of smooth muscle hyperreactivity (66, 69, 87). In particular, bronchial hyperresponsiveness was shown to be associated with serum IgE levels (87), and incubation of ASM cells with serum from atopic individuals, which contained high levels of IgE, was shown to induce hyperreactivity in isolated airway preparations (9, 72, 108). In addition, IgE caused abnormal smooth muscle contractile function through binding to smooth muscle cell membrane and caused subsequent hyperpolarization (102).

#### FcεRII/CD23-MEDIATED PROASTHMATIC CHANGES IN ASM CELLS

ASM cells express various membrane-bound receptors that directly or indirectly modulate their response to agonist-mediated contraction or relaxation (16, 43, 59). In an early study, Hakonarson et al. (45) have examined the relative contribution of β-adrenoceptor-coupled transmembrane signaling mechanisms in passively sensitized rabbit tracheal smooth muscle (TSM) with serum from atopic asthmatic or non-atopic healthy subjects. The authors demonstrated that during half-maximal isometric contraction of the tissues with acetylcholine, the sensitized tissues exhibited significant attenuation of both their maximal relaxation and sensitivity to cumulative administration of isoproterenol or PGE<sub>2</sub>. Interestingly, the relaxation responses to forskolin, a diterpene that directly activates adenylate cyclase, were similar in both tissue groups. Furthermore, the attenuated relaxation to isoproterenol and PGE<sub>2</sub> in sensi-

tized TSM was ablated by pretreatment with the muscarinic M<sub>2</sub> receptor antagonists or with pertussis toxin. This was also associated with decreased accumulation of cAMP in response to isoproterenol administration. Together, the authors concluded that impaired β-adrenoceptor-mediated relaxation in atopic-sensitized airways is associated with increased muscarinic M<sub>2</sub> receptor/G<sub>i</sub> protein-coupled expression and function.

Recently, the same group trying to investigate the mechanism underlying the induction of changes in ASM responsiveness in the atopic-sensitized state showed that both human and rabbit ASM tissues were able to constitutively express FcεRII/CD23 and Fc receptors for IgG, FcγRI (CD64), FcγRII (CD32), and FcγRIII (CD16) (42, 44). Furthermore, FcεRII/CD23 expression was upregulated on treatment with atopic asthmatic serum, containing high levels of IgE or exogenously administered IgE immune complexes (42, 44). Activation of FcεRII/CD23 by IgE immune complexes or atopic asthmatic serum provoked "proasthmatic-like" changes in ASM responsiveness, i.e., increased contractility or attenuated relaxation, which could be inhibited by a monoclonal anti-CD23 neutralizing antibody (42, 44). More recently, FcεRII/CD23 expression in human ASM cells was shown to be induced by IL-4, granulocyte/macrophage colony-stimulating factor (GM-CSF), or in combination (6). Expression of CD23 in response to IL-4, GM-CSF, or IL-4/GM-CSF was accompanied by changes in cell morphology including depolymerization of isoactin fibers, cell spreading, and membrane ruffling, suggesting ASM cell hypertrophy. Furthermore, in another study, sensitization of ASM cells with IgE elicited sequential autocrine release of IL-13 and IL-5, which may contribute to changes in ASM cell responsiveness that characterize the atopic asthmatic phenotype, including heightened agonist-mediated constrictor responsiveness and impaired β-adrenoceptor-mediated ASM cell relaxation (41, 46).

Another report found that rhinovirus inoculation provoked the induction of both mRNA and membrane-bound CD23 protein in nonsensitized ASM cells, an effect that was further potentiated in ASM cells sensitized with atopic asthmatic serum (40). These findings imply a cooperative action of rhinovirus and IgE sensitization in the induction of proasthmatic changes in ASM cells (40). Together, these data suggest that FcεRI/CD23 can be expressed by human ASM cells and can participate in proasthmatic-like changes of these cells by at least modulating cell migration or a change in the synthetic function of the cells.

#### EXPRESSION OF FcεRI IN ASM CELLS

We have recently demonstrated that human ASM cells express FcεRI (37). The expression of FcεRI α, β, and γ mRNA in cultured bronchial/TSM (B/TSM) cells was detected using RT-PCR analysis. Expression of FcεRI/CD23 mRNA by ASM cells was also detected as previously reported (42). Furthermore, a similar expression pattern was detected in ASM cells obtained from bronchial biopsies of two asthmatic patients (37) and in ASM cells isolated from the central airway of five pathologically uninvolved segments of resected lung specimens (unpublished results). The possibility that a nonspecific expression of FcεRI transcripts by a small number of mast cells, present in our preparations, could have contributed to the FcεRI RNA expression was ruled out since tryptase RNA expression was not detected in our smooth muscle RNA preparations. Therefore, the expression of FcεRI α-chain was specific to ASM cells and was not just an incidence of mast cell contamination.

Surface expression of FcεRI by human ASM cells was also studied using flow cytometry with a MAb directed against human FcεRI α-chain (MAb15-1). The expression pattern was variable according to individual donors (37), which is consis-

tent with previous reports in monocytes (75), dendritic cells (76), eosinophils (34), and neutrophils (35), indicating a level of regulation. Interestingly, FcεRI immunoreactivity was also detected in vivo within ASM cells in bronchial biopsy specimens from six mild atopic asthmatic subjects (37). Because previous reports have described FcεRI-positive cells, i.e., mast cells (12), in the vicinity of the ASM cell layer, we further used an immunofluorescence technique with anti-FcεRI α-chain MAb on isolated ASM cells and demonstrated FcεRI α-chain protein expression within the isolated ASM cells. Interestingly, the expression of FcεRI by both mast cell and ASM cell and the close vicinity of mast cells within the ASM cell suggest that this cross talk may play a predominant role in asthma and may be amplified by an IgE-dependent mechanism. It is plausible that ASM cells may recruit, retain, and activate mast cells through release of cytokines, chemokines, and growth factors after FcεRI cross-linking (Fig. 3). In vivo, human ASM cells have been shown to produce Th2 cytokines (IL-4, IL-5, GM-CSF) and CC and CXC chemokines (RANTES/CCL5, eotaxin-1/CCL11, macrophage inflammatory protein-1/CCL2, interferon inducible protein 10/CCL19) upon IL-1β or TNF stimulation (47). Furthermore, atopic asthmatic airways showed constitutive expression of eotaxin-1/CCL12 within ASM cell layers (31), and human ASM cells are capable of producing both soluble and membrane-bound stem cell factor (15, 57). Together, these observations provide a potential mechanism by which mast cells are recruited to ASM layer (Fig. 3). Interestingly, in vitro activation of human mast cells via FcεRI increased CC chemokine receptor (CCR)-3 surface presentation. Because FcεRI cross-linking mediated release of eotaxin-1/CCL11 in ASM cells, it may be possible that human mast cell/ASM cell cross talk occurs by rapidly mobilizing CCR-3 to their surface to respond to eotaxin-1/CCL11 generated by FcεRI-activated ASM cells. Conversely, TNF-α-derived mast

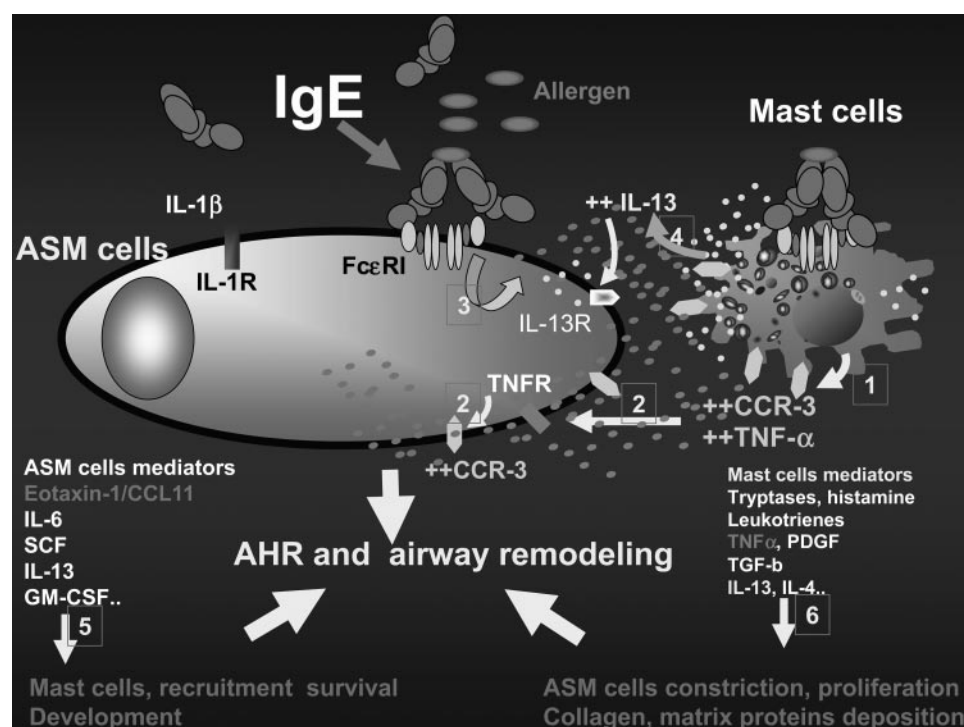


Fig. 3. Potential cross talk between airway smooth muscle (ASM) cells and mast cells via FcεRI-dependent activation. Upon FcεRI cross-linking, mast cells upregulate CC chemokine receptor-3 (CCR-3) (88) and release TNF-α (33) (event 1) that can induce CCR3 on ASM cells (54) (event 2), whereas ASM cells after FcεRI activation release eotaxin-1/CCL11 (37) (event 3) that, concurrently with FcεRI cross-linking, enhances IL-13 expression by mast cells (88). This in turn may alter ASM cell constriction response (event 4) (41). Other potential mechanisms are shown (events 5 and 6) and may involve, among others, SCF and IL-6 produced by ASM cells and TGF-β and tryptase by mast cells. All together, these effects could contribute to airway hyperresponsiveness (AHR) and remodeling in asthma. GM-CSF, granulocyte/macrophage colony-stimulating factor; TGF, transforming growth factor; CSCF, stem cell factor.

cells following FcεRI cross-linking (33) can induce CCR-3 in ASM cells, as recently demonstrated (54). Furthermore, increased IL-13 generation by eotaxin-1/CCL1-stimulated human mast cells (88) may alter ASM cell constrictor response (41) (Fig. 3).

### FcεRI REGULATION

Early studies have shown a correlation between serum IgE levels and the number of IgE molecules bound by basophils (71). The basis of this correlation was not fully understood. However, it was hypothesized that a common factor was capable of regulating both IgE receptors and IgE levels or that the number of receptors was modulated by serum IgE concentrations. Subsequent studies have demonstrated that monomeric IgE upregulates FcεRI expression in a mast cell line (RBL-2H3) and human mast cells and basophils (28, 89). The proposed mechanism of IgE-mediated receptor upregulation was that IgE protected the bound receptors from degradation during receptor recycling. In support of this concept, mast cells from IgE-deficient mice express low levels of FcεRI, which can be upregulated by *in vitro* incubation of these cells with IgE or injection of IgE *in vivo* (111). Moreover, *in vitro* IgE can enhance FcεRI surface expression in mouse basophils (68), human mast cells, and basophils (70, 113). Because elevated specific IgE is consistently present in airway secretions from patients with bronchial asthma (17) and high levels of FcεRI expression are observed in monocytes, eosinophils, Langerhans cells, and neutrophils (35) from atopic asthmatic subjects, it is enticing to hypothesize that local IgE could enhance FcεRI expression on ASM cells, which in turn upon cross-linking with the specific Ag leads to inflammatory mediator release. Indeed, preliminary data from our laboratory revealed that incubation of ASM cells with various IgE concentrations resulted in FcεRI α-chain mRNA upregulation (unpublished data).

Regulation of FcεRI expression is not entirely dependent on IgE. Mast cells from IgE-deficient mice express low levels of FcεRI, which suggests that the basal levels are under the control of other mechanisms (111). Cytokines, particularly IL-4, have been shown to play a positive role in the transcription of FcεRI α-chain in human mast cells (106), human eosinophils from atopic dermatitis subjects (104), and human dendritic cells (30). In mice, however, IL-4 and also IL-10 decrease FcεRI expression specifically affecting FcR β-, but not FcR α- or FcR γ-, subunits (32, 93).

Although FcεRI expression in many human cell types does not rely on the FcR β-subunit, FcR β seems to upregulate surface expression and signal transduction capacity of basophil and mast cell FcεRI (23, 24). Interestingly, an FcR β-truncated (FcR βT) isoform was recently identified and seems to block FcεRI α-subunit maturation, impair its association with FcR γ-subunit, and increase its degradation through ubiquitin-proteasome-dependent mechanisms (25). A more recent study showed that FcR βT isoform competed with the wild-type FcR β-subunit during FcεRI assembly in the endoplasmic reticulum preventing proper folding of FcεRI α-chain, and it seemed that cotranslational endoplasmic reticulum assembly of FcεRI controlled the formation of a functional IgE-binding FcεRI (27). A subsequent report has also described two single nucleotide polymorphism mutations in potential transcription binding

sites of FcR β promoter region that enhanced its gene expression (80). Collectively, these data provide a potential connection between FcR β polymorphisms, FcεRI expression, and atopy.

### FcεRI-MEDIATED CALCIUM RELEASE IN ASM CELLS

Activation of FcεRI triggers many signaling pathways in inflammatory cells including phosphorylation of FcεRI β and γ by Lyn and the activation of Syk through its recruitment to FcεRI (99, 100). Activation of Syk is crucial for FcεRI downstream signals including phosphorylation of PLC-γ, calcium mobilization, and degranulation (99). Using the fluorescent dye fura-2, we found that FcεRI activation leads to marked transient increases in intracellular  $Ca^{2+}$  concentration in human ASM cells. Cross-linking of FcεRI by treating ASM cells with human IgE or anti-FcεRI α-chain MAb (15-1) followed by goat anti-mouse IgE or anti-mouse IgG1 induced marked mobilization of intracellular free  $Ca^{2+}$  within 5–10 s; a peak of cytosolic concentrations of  $Ca^{2+}$  (mean peak  $[Ca^{2+}]_i = 170$  nM) was attained between 10 and 30 s and returned to baseline values thereafter. There was no increase of  $Ca^{2+}$  when irrelevant MAb instead of anti-FcεRI MAb were used, but ASM cells responded well to acetylcholine (mean peak  $[Ca^{2+}]_i = 370$  nM) (37). Previous reports have demonstrated that contraction of smooth muscle is triggered by an increase in intracellular  $Ca^{2+}$  concentration in response to bronchospastic stimuli (3). Contractile agonists bind  $G_q$  protein-coupled receptors (GPCR), resulting in PLC activation. PLC in turn catalyzes the hydrolysis of  $PIP_2$  to  $IP_3$  and diacylglycerol.  $IP_3$  mediates the initial release of calcium from intracellular stores as the result of its binding to receptors on sarcoendoplasmic reticulum (3). In FcεRI-positive cells, particularly basophils, one the best-characterized signaling pathways involves Syk-mediated phosphorylation of PLC-γ, which leads to an increase of intracellular calcium concentrations and activation of the calcium/calmodulin-dependent serine-threonine phosphatase calcineurin (48, 61). In ASM, the elevation in intracellular calcium concentration activates the calcium/calmodulin-sensitive myosin light chain kinase, followed by phosphorylation of the regulatory myosin light chain and initiation of cross-bridge cycling between myosin and actin (2). Whether a cross talk exists between FcεRI and contractile agonist-mediated calcium signaling in ASM cells is not known at this time. Further studies are required to establish the signaling pathways involved in FcεRI activation of ASM cells and whether this pathway influences ASM cell contraction. Together, these data suggest that FcεRI activation in ASM cells can modulate calcium signaling and may promote a hyperresponsive phenotype of ASM cells (Fig. 4).

### FcεRI INDUCED CYTOKINE AND CHEMOKINE RELEASE IN ASM CELLS

Airway inflammation involves a complex and coordinated response of multiple inflammatory cells, mediators, and cytokines. We found that FcεRI activation on IgE/anti-IgE cross-linking on human ASM and B/TSM cells leads to release of eosinophil mobilizing and chemoattractant factors (IL-5 and eotaxin-1/CCL11) (37). Indeed, preincubation of B/TSM cells with IgE for 4 days followed by passive sensitization for 30 min with IgE to allow saturation of FcεRI, and then cross-

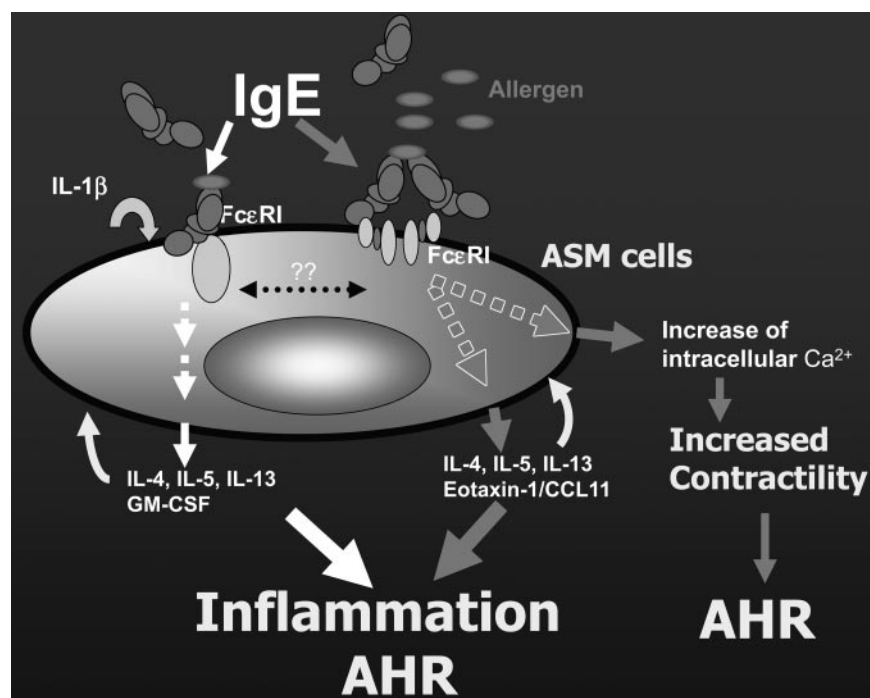


Fig. 4. FcεRI and FcεRII/CD23 activation in ASM cells. FcεR engagement in ASM cells induces marked increases in the intracellular calcium concentrations and T helper 2 cytokine and chemokine release (IL-4, IL-13, IL-5, GM-CSF, and eotaxin-1/CCL11) that may contribute directly or indirectly to airway inflammation and hyperresponsiveness. The cross talk between FcεRI and FcεRII is indicated by question marks.

linking with anti-human IgE, induced the synthesis and release of eotaxin-1/CCL11 and IL-5 (37).

It is currently accepted that the allergen-induced eosinophil accumulation within the lungs of atopic asthmatics is attributable to mature eosinophil migration from the circulation (92). Eotaxin-1/CCL11 has been demonstrated as a highly selective chemoattractant for eosinophils, basophils, and Th2 lymphocytes. It cooperates with IL-5 *in vivo* to induce eosinophil recruitment; IL-5 promotes mobilization of eosinophils from the bone marrow, whereas eotaxin-1/CCL11 recruits eosinophils in the tissue. Moreover, eotaxin-1/CCL11 has the ability to induce mast cell growth and eosinophil differentiation (67). Previously, data showed that human ASM cells expressed eotaxin-1/CCL11 after TNF- $\alpha$  and/or IL-1 $\beta$  stimulation (31). The eotaxin-1/CCL11 produced and secreted by ASM cells may amplify the chemokine signal generated by infiltrating inflammatory cells in the airway, thereby augmenting the recruitment of eosinophils, basophils, and Th2 lymphocytes to the airways. The accumulation of these inflammatory cells may subsequently contribute to the development of airway hyperresponsiveness, local inflammation, and tissue injury through the release of granular enzymes and other cytokines.

Cumulative data have suggested that IL-5 is the most important cytokine for the terminal differentiation of committed eosinophil precursors and is a potent inducer of eosinophil survival (92). In the presence of IL-5, which delays the apoptotic process (103), eosinophils may persist within bronchial mucosa and cause further damage to the airways. Furthermore, *in vitro* IL-5 has been shown to prime the bronchus for an exaggerated contraction to acetylcholine. The IL-5 effect on bronchial contractility was attenuated by antibodies to IL-5 (TRFK-5) and human IL-5R $\alpha$  (91). As such, FcεRI-dependent secretion of IL-5 by ASM cells may contribute to exaggerated airway inflammation and hyperresponsiveness through the re-

cruitment and enhanced survival of infiltrating eosinophils and by directly enhancing the contractile properties of ASM cells.

We also found that ASM cells stimulated via FcεRI released IL-4 and IL-13 but not IFN- $\gamma$ . Treatment with IgE for 4 days followed by passive sensitization and IgE cross-linking induced the synthesis and release of IL-4 and IL-13 in a dose-dependent manner (37). Interestingly, preincubation with IgE before passive sensitization and challenge was essential for IgE-mediated B/TSM cell release of Th2 cytokines (IL-4 and IL-13) because mediator release was mostly lacking when B/TSM cells were cultured without IgE. We also demonstrated protein expression of IL-4, IL-5, IL-13, and eotaxin-1/CCL11 in ASM cells obtained from an asthmatic patient (37), which supports the current concept of ASM as a potential source of multiple proinflammatory cytokines and chemokines.

IL-4 and IL-13 have a number of functions relevant to allergic diathesis, such as the regulation of isotype class switching in B cell to IgE synthesis (26), induction of adhesion molecule expression on endothelial cells (18), and promoting selective egress of eosinophils from the bloodstream (79, 94). Furthermore, recent studies have shown that both cytokines play a critical role in allergen-induced mucus production. In experimental models of allergic asthma (39, 109), selective neutralization of IL-13 ameliorated asthma symptoms, including airway hyperresponsiveness, eosinophil recruitment, and mucus overproduction (39). In accord with these studies, transgenic overexpression of IL-4 and IL-13 within the lung in mice is associated with key features of airway inflammation and remodeling in chronic severe asthma, including lymphocyte and eosinophil accumulation, mucus cell metaplasia, subepithelial fibrosis, and airway hyperresponsiveness (118). In light of the findings described above, the release of IL-4 and IL-13 after IgE-dependent activation of ASM cells via FcεRI, in combination with eotaxin-1/CCL11 and IL-5 release, may not

only accentuate airway inflammation but may also participate in airway hyperresponsiveness.

A selective eotaxin-1/CCL11 release from ASM cells has been demonstrated on IL-13 and IL-4 stimulation (50). The ultimate suggestion is that FcεRI cross-linking can induce IL-4 and IL-13 release, which in turn by an autocrine pathway leads to eotaxin-1/CCL11 and IL-5 release from ASM cells. A recent *in vivo* study using mice deficient in both eotaxin-1/CCL11 and IL-5 has implicated both factors not only in tissue accumulation of eosinophils but also in the ability of Ag-specific CD4<sup>+</sup> T cells to produce IL-13. In the same study, strong evidence suggests that IL-5 and eotaxin-1/CCL11 are a prerequisite for the development of airway hyperresponsiveness (73). Together, FcεRI activation of ASM cells may not only contribute to eosinophil migration but can also modulate Th2 cytokine production and subsequently airway hyperresponsiveness (Fig. 4).

Although substantial research in recent years has been performed on FcεRI and CD23/FcεRII in immune cells, the functional role of these receptors on structural cells such as ASM cells is not fully understood. In particular, it is not known whether IgE sensitization through FcεRI alone mediates ASM cell survival, as was demonstrated in mast cells (4, 56, 64) and monocytes (58), which may influence cell growth and or proliferation. The factors that influenced FcεRI and FcεRII expression and the contribution of each FcεR in ASM cell function within the airways, e.g., airway hyperresponsiveness and inflammation, have not been investigated. Finally, it is not clear whether FcεRI and FcεRII/CD23 signaling events in ASM cells are similar to those in immune cells, i.e., mast cells and B cells, respectively, and whether a regulatory cross talk exists between Fcγ (FcγRI, -RI, and RIII) (44) and FcεR, the latter and GPCR receptors in ASM cells.

Delineating the function and the molecular mechanisms of FcεRI/IgE-mediated ASM cell activation will greatly enhance our understanding of allergic asthma and will provide a rationale for better therapeutic intervention.

## GRANTS

A. Soussi Gounni is supported by the Canadian Institutes of Health Research New Investigator Award. The research is supported by grants from the Canadian Institutes of Health Research, Manitoba Health Research Council, Canada Foundation for Innovation, and the Toronto Hospital for Sick Children.

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