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REVIEW

The role of FcεRI expressed in dendritic cells and monocytes

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Abstract Early studies regarding the function of FcεRI in dendritic cells (DCs) and monocytes have focused on its role in mediating inflammatory signaling and enhancing T cell immunity. It has been the case in part because FcεRI is the major receptor that mediates allergic inflammatory signaling in mast cells and basophils and because DCs and monocytes are antigen presenting cells capable of activating naïve and/or effector T cells. These studies have led to the general belief that FcεRI-mediated DC signaling and antigen presentation promote development and activation of Th2 cells and contribute to allergic inflammatory diseases. However, this belief has long suffered from a lack of evidence. Recently, studies have emerged that provide evidence supporting an opposing role: that FcεRI on DCs instead promotes immune homeostasis and regulation. In this review, we will update the current status of our understanding of FcεRI biology and function, with a specific focus on DCs and monocytes.

Keywords High affinity IgE receptor · FcεRI · Dendritic cell · Monocyte · Endocytosis · Signaling · Antigen presentation

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Introduction

FcεRI is constitutively expressed by mast cells and basophils, and captures IgE in its monomeric form owing to its remarkably high affinity to IgE ($K_d = 10^{-10}$ M). When IgE/FcεRI complexes on these cells are engaged and crosslinked by allergens, a signaling cascade is initiated that results in extracellular release of various inflammatory mediators [1, 2]. One example of such mediators is histamine, which dilates blood vessels and makes their walls abnormally permeable, creating hives. FcεRI is also expressed in dendritic cells (DCs), both conventional and plasmacytoid DCs, and monocytes in humans. DCs and monocytes are both antigen-presenting cells that endocytose antigens, and process and present them to antigen-specific T cells via antigen presenting molecules including the major histocompatibility complex (MHC) [3, 4]. The antigen presenting activity of DCs plays an important role in the development of antigen-specific immunity by activating naïve T cells and assisting in T helper cell skewing [5, 6]. DC antigen presenting activity also plays an essential role in establishing and maintaining tolerance either by deleting self-reactive T cells or by generating the immune suppressive regulatory T cells [7]. DCs and monocytes also act as innate immune cells. They produce various cytokines and chemokines in response to danger signals such as microbes and tissue damage-associated molecules [8]. In particular, plasmacytoid DCs produce copious amounts of type 1 IFN in response to viral infection signal. Sensing of these signals is mediated by a variety of receptors expressed on the surface and endosomal compartment of the cells [9, 10].

Although the expression of FcεRI in DCs and monocytes has been known for more than two decades, its functional role is not clearly understood—in part, because

studies have suffered from a lack of essential reagents. Rodents are the vertebrate species most commonly used in research laboratories because of their availability, size, low cost, ease of handling and fast reproduction rate. Rodents constitutively express high levels of FcεRI in mast cells and basophils in a fashion similar to humans, and thus have served as excellent animal models and cellular sources for studying the role of FcεRI on these cell types. However, rodents do not express FcεRI in DCs and monocytes under homeostatic condition while humans do. Therefore, studies in this field have been limited to in vitro experiments using DCs and monocytes obtained from human donors. Although monocytes are available more readily than any other primary human cells, only a small fraction of the cells express FcεRI, and the level of expression is considerably reduced upon culture. DCs are not only scarce in most tissues, but are comprised of many subsets whose markers and functions are not completely understood. All these drawbacks have markedly slowed down the progress in the field.

In recent years, however, substantial advancement has been made in the characterization of human DC subsets. Subset-specific markers have been identified, which have allowed for examination of DCs in situ by microscopy in a variety of human tissues. Identification of markers has also helped with isolation and further characterization of DCs by flow cytometry and various biochemical assays. Beyond improvements in DC identification, advancements have been also made in culturing human DCs. DCs can be derived from blood monocytes or $CD34^+$ blood precursors, and some of these cultured DCs express FcεRI in a stable manner. Finally, the advent of genetic engineering technology has led to the creation of mouse strains that express human FcεRI in DCs and/or monocytes in a pattern that resembles human. These mouse strains made it possible to examine the role of human FcεRI in vivo, and furthermore to examine the role of DCs and monocytes in FcεRI function. In this review, we will describe these advancements in detail and summarize the current understanding of FcεRI biology in DCs and monocytes. Occasionally, it will be compared with FcεRI biology in mast cells and basophils, and highlighted for its distinctiveness.

FcεRI expression specificity and heterogeneity in DCs and monocytes

FcεRI expression in DCs was first observed in the skin epidermis, where a distinct subset of DCs named Langerhans cells was found [11, 12]. Immunohistochemical and flow cytometry studies showed that epidermal skin cells labeled by the anti-CD1a antibody, a specific marker of Langerhans cells, were also labeled by an anti-FcεRIα antibody as well as IgE [11, 12]. Immunogold labeling electron microscopy study also showed that epidermal skin cells that contained Birbeck granules in the cytosol, the specific characteristics of Langerhans cells, were decorated by anti-FcεRI antibody-conjugated gold particles on their surface [12]. Subsequently, $CD1a^+FcεRIα^+$ cells were detected in many other peripheral tissues including the airway [13], oral mucosa [14], nasal mucosa [15], and gastrointestinal tract [16].

While the anti-CD1a antibody had been most frequently used to identify DCs in human peripheral tissues, a breakthrough was made in identification of human DC subsets in circulation through finding of the novel markers named blood dendritic cell antigen (BDCA) 1, 2, 3, and 4 [17]. BDCA1 is expressed in the major subset of conventional DCs that occupy approximately 80 % of circulating DCs and are homologous to mouse $CD11b^+$ DCs [18]. BDCA3 is expressed in $XCR1^+$ minor subset of conventional DCs that are uniquely efficient at presenting exogenous antigens to $CD8^+$ T cells, similarly to mouse $CD8^+$ DCs [19–22]. BDCA2 and BDCA4 are both expressed in plasmacytoid DCs, a separate group from conventional DCs. Each unique $BDCA^+$ DC subset found in blood was also found in peripheral tissues such as lungs [23, 24]. Notably, Langerhans cells and other mucosal DCs that express CD1a also expressed BDCA1, but not all $BDCA1^+$ DCs expressed CD1a [23, 25], implying that BDCA1 is a more encompassing marker for classical DCs than CD1a. FcεRI expression analysis using these BDCA markers demonstrated that $BDCA1^+$ DCs expressed FcεRI at fairly high levels, in a homogeneous manner, and through many different tissue sites. Plasmacytoid DCs also express FcεRI homogeneously, but at substantially lower levels than $BDCA1^+$ DCs. Distinctly, $BDCA3^+$ DCs do not express FcεRI [17, 26–28].

FcεRI expression in monocytes was first characterized in atopic blood donors and later in healthy individuals [29, 30]. FcεRI expression appears to be limited only to a small subset of monocytes characterized by the expression of CD2 [31]. $CD2^+$ monocytes are $CD16^-$ and occupy less than 5 % of the total monocytes in peripheral blood. Studies have shown that $CD2^+$ monocytes rapidly obtain DC-like features in culture, including the expression of CD83 and the ability to activate allo-reactive T cells [32, 33]. Therefore, it is conceivable that $CD2^+$ monocytes differentiate to DCs in the peripheral tissues, thus contributing to the pool of peripheral DCs that express FcεRI. Considering that monocytes also differentiate into macrophages, but macrophages do not express FcεRI [34], it is further tempting to consider that $FcεRI^+$ monocytes may represent those fated to become DCs.

Unlike monocytes, DCs can be differentiated from precursor cells in vitro. For example, culturing whole blood

monocytes with IL-4 and GM-CSF leads to the expression of DC markers such as CD1a [35]. However, this culturing leads to the down-regulation and almost complete loss of FcεRI expression by differentiated DCs although the degree of down-regulation is modest when the monocytes are originated from atopic donors [36]. Interestingly, this down-regulation is inhibited by adding reducing agents or IgE to cultures [36, 37]. As an alternative to monocyte differentiation, DCs can be also differentiated from $CD34^+$ blood progenitor cells by culturing with GM-CSF, TNF-α, SCF, Flt3L, and TGF-β [38, 39]. Differentiated DCs express CD1a and FcεRI, and interestingly, the level of FcεRI expression is regulated by the concentration of TGF-β in culture [40].

FcεRI structure in DCs and monocytes

FcεRI in DCs and monocytes is comprised of an α-subunit and two γ-subunits [27, 29, 41]. The α-subunit is a transmembrane protein that is necessary and sufficient for IgE binding [42]. The two domains of its extracellular portion adopts the shape of an inverted 'v', the second of which binds one dimeric IgE-Fc molecule asymmetrically through interactions at two sites—thus forming a 1:1 protein complex of IgE:FcεRI [43]. Upon binding to FcεRIα, IgE adopts a unique bent conformation and this conformational change contributes to the remarkably slow dissociation rate from FcεRI [44]. The α-subunit is also a glycoprotein. The glycosylation does not seem to be required for IgE binding, as unglycosylated recombinant FcεRIα made in *E. coli* is capable of binding IgE without a significant loss in affinity [45]. However, proper glycosylation is required for the receptor to effectively fold in the endoplasmic reticulum (ER) and traffic to the plasma membrane [46, 47]. Interestingly, a recent SDS-PAGE analysis has shown that glycosylated FcεRIα in DCs migrates a little faster than that in basophils [48], implicating FcεRIα may be modified by distinct glycan moieties depending on cell type of its expression, similarly to FcγRIIIα [49].

The γ-subunit of FcεRI is a transmembrane protein that acts as a common adaptor molecule for various Fc receptors such as FcγRI (CD64), and FcγRIIIA (CD16A) [50, 51]. It associates as a homodimer formed via a disulfide bond linked between N-terminal cysteine amino acids. The N-terminus also bears an immunoreceptor tyrosine-based activation motif (ITAM), which is phosphorylated upon FcεRI engagement and plays an essential role in transmitting activation signals in mast cells and basophils [52]. A similar role is believed to be played in DCs and monocytes.

It is worth of mentioning that in mast cells and basophils, some, if not all, FcεRI molecules associate with an additional protein subunit, FcεRIβ. The FcεRIβ subunit is a membrane protein composed of four transmembrane and two cytoplasmic domains, one of which contains an ITAM. This additional ITAM is not required for, but markedly amplifies, signal transduction triggered by FcεRI engagement [53]. Expression of FcεRIβ also enhances FcεRIα transport to the plasma membranes [54]. FcεRIβ expression has been reported in Langerhans cells; they demonstrated the presence of FcεRIβ mRNA by RT-PCR after enrichment of Langerhans cells from epidermal cell suspension [12]. However, a later study that used highly purified Langerhans cells (>98 %) showed the lack of FcεRIβ in these cells [55]. Thus, it is possible that early samples may have contained contaminating mast cells from the Langerhans cell purification process. Additional DC subsets including $BDCA1^+$ DCs, plasmacytoid DCs, and monocytes have been examined for the expression of FcεRIβ, but none of these cells were found to express it. Thus, DCs and monocytes, distinct from mast cells and basophils, appear to express FcεRI only in its trimeric form.

FcεRI intracellular trafficking in DCs and monocytes

Secretory trafficking

Upon synthesis, the FcεRI α-subunit is inserted to the ER membranes and glycosylated at its luminal sites. This process is dependent on cotranslational assembly with the γ-subunits [56]. The γ-subunit also facilitates the ER exit of FcεRIα by masking an ER retention/retrieval signal present in the α-subunit cytoplasmic tail [57]. Consequently, the level of γ-subunit expressed in cells makes a substantial impact on the level of FcεRI found on the plasma membrane. For example, Langerhans cells hardly express FcεRIγ while expressing substantial levels of FcεRIα [58]. Because of their FcεRIγ deficiency, FcεRIα in these cells fails to move to the plasma membranes and instead accumulates in the ER. Similarly, DCs derived from monocytes in vitro also lack FcεRIγ, and thus express little or no FcεRI at the plasma membrane [36]. However, DCs derived from monocytes of patients with atopic dermatitis express detectable levels of FcεRI on their surface. An attractive explanation for these differences lies in the finding that DCs derived from atopic donors expressed FcεRIγ, which would have promoted FcεRIα exit from ER and led to the transport of trimeric receptor to the plasma membranes [36].

$BDCA1^+$ DCs isolated from blood express both FcεRIα and FcεRIγ, and the level of their surface FcεRI expression is fairly high. In these cells, FcεRIα is not detected in the ER or in the Golgi, nor is the immature species of FcεRIα

detected, defined as FcεRIα that still contains its high mannose carbohydrates attached in ER [48]. This high mannose glycans are later modified to a more complex form of glycans in the Golgi—a process referred to as FcεRIα maturation [56]. Thus, the absence of immature FcεRIα species together with the absence of FcεRI in ER and Golgi strongly suggest that FcεRI efficiently matures and traffics to the plasma membranes in BDCA1$^+$ DCs. Considering that immature FcεRIα is readily detected in human basophils, both by microscopy and western blot analysis [48, 59], it is conceivable that the efficiency of secretory trafficking of FcεRI might be higher in DCs than basophils. Unlike basophils, however, mast cell FcεRI is not detected in the ER, but instead found in the Golgi [60]. It will be interesting to directly determine and compare the efficiency of FcεRI secretory trafficking between these cell types, as it may be relevant to the unique functional roles played by FcεRI in these cells.

Endocytic trafficking

Treating blood DCs with anti-FcεRI antibodies or anti-NP IgE/NP-BSA complexes, which would synchronously crosslink FcεRI molecules on the surface of the cells, results in approximately 90 % of FcεRI disappearing from plasma membrane within 10 min [61]. Microscopy studies revealed that crosslinked surface FcεRI enters the cells and reaches the lysosomes where FcεRI-bound IgE is degraded over time [61]. This finding indicates that FcεRI in DCs is rapidly endocytosed and transported to the lysosomes upon crosslinking. In fact, similar crosslinking-dependent endocytosis of FcεRI has been also described in mast cells, in which crosslinking initiates ubiquitination of FcεRI β- and γ-subunits, which leads FcεRI to clathrin coated pits where the physical process of endocytosis occurs [62].

Interestingly, a recent study has shown that FcεRI in DCs and monocytes is endocytosed and transported to the lysosomes in a constitutive manner. Microscopic study of human blood DCs and monocytes revealed that a large fraction of FcεRI in these cells resides in the lysosomes under homeostatic condition and that these cells contain appreciable amounts of IgE inside the cells [48]. While there could presumably be a physiologic FcεRI-crosslinker in the blood, monomeric IgE added to DCs in culture was also spontaneously internalized [48]. Thus, it is likely that DCs constantly internalize FcεRI in a crosslinking-independent manner, and IgE bound to the FcεRI is also internalized during this process. Importantly, no such constitutive internalization of IgE was observed in mast cells or basophils [48]. This finding strongly suggests that DCs and monocytes operate a unique mechanism by which FcεRI is constitutively endocytosed and sorted to the lysosomes.

Endocytosis of FcεRI bound by IgE draws a particular attention because previous literatures have extensively described the role of IgE in inhibiting FcεRI endocytosis. Repetitive injection of IgE into mice results in a substantial increase in the surface expression of FcεRI in mast cells and basophils [63, 64]. Conversely, mast cells and basophils from IgE-deficient mice have significantly reduced FcεRI compared to those from wild type mice [63, 64]. In vitro, addition of IgE to cultures of FcεRI-expressing cells also increases FcεRI surface levels [63–66]. Mechanism studies have shown that this increase in plasma membrane expression of FcεRI upon IgE binding is not by the increase in FcεRI synthesis but by the decrease in FcεRI endocytosis [65, 67], leading the conclusion that IgE binding stabilizes FcεRI at the plasma membrane by inhibiting its internalization and degradation. However, these previous studies were performed using human basophils [66, 67], bone marrow-derived mouse mast cells [64] and hFcεRI-transfected cell lines of either hematopoietic or non-hematopoietic origin expressing either trimeric or tetrameric FcεRI [65], but not DCs or monocytes isolated from human tissues. In fact, a similar study performed using human Langerhans cells has shown that FcεRI surface levels decrease during ex vivo culture, and this decrease is not prevented by addition of IgE [58]. A recent study using blood DCs in children has shown no correlation between FcεRI in conventional DCs and serum IgE unless serum IgE levels reached certain threshold [68]. More recently, FcεRI expression in blood DCs and basophils in adults were examined in reference to a broad range of serum IgE. While FcεRI in basophils sharply increased in correlation with serum IgE levels, FcεRI in DCs remained fairly flat [48], suggesting that DCs control FcεRI surface levels distinctly from basophils in a manner independent of extracellular IgE.

FcεRI function in DCs and monocytes

Signaling: immune stimulatory or suppressive

FcεRI-mediated signaling has been extensively studied in mast cells. Cross-linking of IgE bound to FcεRI with multivalent antigen triggers a series of biochemical events that culminate in multiple mast cell effector functions [69–71]. Signaling is initiated through the phosphorylation of ITAMs in the cytoplasmic tails of the FcεRIβ and FcεRIγ subunits by the Src protein tyrosine kinases such as Lyn, which are recruited upon clustering of FcεRI. The phosphorylated ITAMs then recruit the kinase Syk, which mediates activation of the adaptor molecules LAT and SLP76, resulting in calcium mobilization. Ultimately, FcεRI aggregation results in initiation of the allergic

inflammatory process by eliciting mast cell degranulation with a rapid release of preformed vasoactive amines like histamine and the de novo synthesis of proinflammatory cytokines like TNF-α and IL-6.

Comparatively little is known of the signaling events following FcεRI engagement in DCs and monocytes. Particularly, early signaling events have been poorly characterized; no studies have directly shown that the ITAMs of the FcεRIγ subunit are phosphorylated following FcεRI crosslinking in DCs or monocytes. In mast cells and basophils, FcεRI proximal signaling is largely dependent on the FcεRIβ subunit, which markedly reduces the extent of FcεRI crosslinking required for initiation of signaling [53]. Since monocytes and DCs lack FcεRIβ, FcεRI signaling in these cells may require heavy crosslinking of FcεRI, which may be hard to achieve due to its constitutively endocytosis. Nevertheless, FcεRI crosslinking has been shown to induce protein tyrosine phosphorylation and calcium mobilization in Langerhans cells [55]. It also induces activation of NF-κB in Langerhans cells, monocytes, and monocyte-derived DCs [72]. The NF-κB activation is preceded by serine phosphorylation of IκB-α. The activated NF-κB complexes contain p50 and p65 subunits, and leads to the synthesis and release of TNF-α and MCP-1 (CCL-2) from monocytes and monocyte-derived DCs [72].

Consistent with the role of NF-κB in increasing transcription of proinflammatory mediators, FcεRI crosslinking in monocytes and DCs, results in the production of TNF-α and IL-6 [73–76]. Blood conventional DCs also produce CCL-28, a chemokine that recruits T and B cells and eosinophils [77]. Inflammatory DCs cultured from monocytes were shown to produce IL-12 and IL-18, which are both potent proinflammatory and IFN-γ producing cytokines [78]. These studies suggest that FcεRI signaling in DCs and monocytes may promote inflammation by upregulating the production of cytokines and chemokines that activate and recruit a variety of types of inflammatory cells.

However, studies also suggest an anti-inflammatory and immune suppressive role of FcεRI signaling. FcεRI crosslinking in monocytes and DCs has been shown to induce high amounts of the anti-inflammatory cytokine IL-10, which subsequently acts in an autocrine fashion and negatively regulates production of TNF-α in these cells [74–76, 79]. Additionally, a high-throughput analysis has been performed to identify genes regulated by FcεRI signaling in a non-biased manner. This study has revealed that at relatively later time points following FcεRI-crosslinking, monocytes upregulate the expression of indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme in the catabolism of tryptophan [80]. IDO production from macrophages and DCs, and consequent depletion of tryptophan, have been shown to inhibit T cell proliferation in part by activating a cellular stress response or by inducing activation and regulatory function of functionally quiescent regulatory T cells [81, 82]. Indeed, FcεRI-crosslinked monocytes markedly suppressed proliferation of T cells in vitro and this suppression was reverted when the culture was supplemented with tryptophan or an IDO inhibitor [80].

Additional data further support the role of FcεRI signaling in immune-suppression. Toll-like Receptor (TLR) 7 and TLR 9 mediate activation of PDCs during viral infection resulting in the production of type 1 IFNs such as IFN-α and -β. Several studies have shown that FcεRI aggregation significantly reduced the production of IFN-α and IFN-β by plasmacytoid DCs stimulated with CpG-A (a ligand of TLR9), influenza virus, or gardiquimod (a TLR 7 agonist) [76, 83, 84]. This down-regulation in IFN responses was accompanied by a concomitant reduction in the transcription of TLR 7 or TLR 9 [76, 84]. More recently, it was shown that FcεRI crosslinking in monocyte-derived DCs reduces production of CCL-2 following stimulation with lipopolysaccharide, a ligand of TLR 4 [85], suggesting that FcεRI signaling interferes with TLR signaling not only in plasmacytoid DCs but also monocyte-derived DCs and possibly conventional DCs.

Antigen presentation: immunogenic or tolerogenic

Dendritic cells and monocytes are professional antigen presenting cells in humans. Therefore, the identification of FcεRI expression in these cells naturally prompted the question of whether this receptor might facilitate presentation of IgE-bound antigens. Studies using multivalent antigens that bind and crosslink IgE/FcεRI complexes have shown that these antigens were rapidly internalized by DCs and monocytes, processed by lysosomal proteases, loaded onto MHC II, and presented to antigen-specific $CD4^+$ T cells, resulting in their proliferation [41, 61]. IgE loading was crucial to efficient antigen presentation because antigens added to cells in the absence of IgE were presented at a 100 to 1000-fold lower efficiency [41]. These findings suggest that FcεRI facilitates presentation of IgE-bound antigens, such as allergens, to T cells—implicating its contribution to T cell-mediated inflammation in allergic diseases. More recently, plasmacytoid DCs loaded with Bet v1 allergen-IgE immune complexes were shown to induce activation of autologous naïve CD4 T cells producing higher amounts of IL-4 and lower levels of IFN-γ than T cells cocultured with untreated plasmacytoid DCs [27]. A similar response has been also observed with naïve T cells cocultured with blood $BDCA1^+$ DCs loaded with Der p1 allergen-IgE immune complexes [86]. These studies suggest that FcεRI in DCs not only enhances activation of effector CD4 T cells but also mediates priming of Th2 cells.

Recently, the role of FcεRI in antigen presentation by DCs was further examined in vivo using transgenic mice [85, 87]. This strain expresses the human FcεRIα under the control of the DC-restricted, constitutively active CD11c promoter. The human FcεRIα expressed in DCs forms a complex with mouse FcεRIγ, transports to the plasma membranes, and binds circulating murine IgE albeit at a reduced affinity compared to human IgE. Two independent groups used these mice and examined whether DCs of this mouse present IgE-bound antigens better than DCs of wild type mouse, and if so, whether the antigen presentation results in Th2 cell priming [85]. While both studies concluded that FcεRI greatly enhances DC presentation of IgE-bound antigens in vivo, they reached contradictory conclusions regarding Th2 cell priming; one study found improved Th2 cell generation [87], but the other found no evidence of any improvement [85]. The reason behind this contradiction is not completely clear, but additional studies remain to be seen to clearly answer this long-standing question.

Another recent study examined the role of FcεRI in DC antigen presentation using a unique hFcεRIα-Tg mouse strain in a distinct experimental setting [88]. This study used mice that express hFcεRIα under the control of human FcεRIα promoter [89]. Accordingly, this mouse expresses hFcεRIα in cell types where it is also expressed in humans, including mast cells, basophils, monocytes, and DCs, both conventional and plasmacytoid DCs. In this study, the mice were injected with a recombinant protein consisting of the human IgE Fc domain covalently linked to a specific peptide antigen, and examined for the presentation of the antigen to antigen-specific $CD4^+$ T cells that had been adoptively transferred into the mice. Thus, this study examined the role of FcεRI in mediating presentation of IgE-bound monovalent antigen. The antigen was effectively presented by DCs to naïve T cells, resulting in T cell proliferation. However, the proliferation was transient and was followed by systemic deletion of the antigen-specific T cells from the mice. Furthermore, the mice became resistant to developing T cell immune responses against the antigen at later challenges. These findings suggest that FcεRI facilitates DC presentation of IgE-bound antigens and that this presentation results in antigen-specific T cell tolerance as long as the IgE-bound antigens do not crosslink FcεRI. Although such occasion remains to be identified in physiologic conditions, it may pertain to the production of natural IgE following tissue damage and its potential role in immune regulation. For example, helminth infection causes massive damage in the intestines and lungs, and is followed by production of high amounts of IgE antibodies, which are not specific for parasites but are polyclonal in nature [90, 91]. In addition, surgery and burns, both involving potentially severe tissue damage, are also accompanied by the production of considerable amounts of polyclonal IgE [92, 93]. Although the specificity of these IgE molecules remains to be determined, they are believed to be natural IgE, which is of low affinity and poly-specific against various self-antigens including phosphatidylcholine [94]. This natural IgE may promote DC recognition of self antigens released during tissue damage via FcεRI—but this recognition is not likely to cause FcεRI crosslinking because the likelihood of that an antigen-specific IgE molecule to be adjacent to the same antigen-specific IgE molecule is extremely low. In addition, IgE bound to FcεRI will be rapidly internalized by DCs via constitutive FcεRI endocytic trafficking, which will further minimize the likelihood of FcεRI crosslinking. Consequently, the IgE-bound self-antigens would be internalized in the absence of FcεRI crosslinking, subsequently presented to self-reactive T cells, which in turn would be deleted. Thus, IgE generated following tissue damage may play an important role in preventing autoimmunity from developing against self-antigens released during the damage by focusing the antigens to FcεRI-expressing DCs, which induces deletional T cell tolerance against those antigens. In this context, FcεRI in DCs would contribute to immune tolerance to self-antigens.

IgE clearance

IgE has the shortest serum half-life (approximately 2 days) among five immunoglobulin isotypes [95, 96]. In an interesting mathematical study of immunoglobulin metabolism, it was found that IgE differs from other immunoglobulins in that it undergoes substantial catabolism at extravascular sites [96]. The study proposed that the extravascular catabolism is part of a unique mechanism specific for IgE, which is related to unique interactions of IgE with cells expressing FcεRI in the peripheral tissues. This interaction was considered to exert two potential effects on overall IgE survival; on one hand, it may result in sequestration and persistence of IgE molecules in local tissue sites. On the other hand, it may be followed by subsequent catabolism of IgE by the cells. Interestingly, they concluded that IgE catabolism after interaction with cells is a quantitatively more significant phenomenon than IgE sequestration.

Nevertheless, the role of FcεRI-expressing cells in IgE catabolism has been difficult to prove experimentally. IgE bound to FcεRI on mast cells persists as long as the cells are alive, which suggests that IgE bound to mast cells is stabilized rather than catabolized. Furthermore, mast cell-deficient mice were found to clear IgE at a similar rate to wild type mice [97]. FcεRI-deficient mice also cleared IgE similarly to wild type mice [98]. These findings have

provided strong evidences supporting the hypothesis that FcεRI-expressing cells do not contribute to IgE catabolism. However, humans differ from mice; in this case, in that human also express FcεRI in monocytes and DCs. The role of these cells in IgE catabolism has not been examined until recently.

The recent finding that FcεRI is constitutively endocytosed and transported to the lysosomes in human monocytes and DCs invited the question of whether IgE bound to FcεRI in these cells would be also endocytosed and transported to the lysosomes, and possibly degraded by lysosomal proteases. Indeed, IgE bound to DCs but not basophils were rapidly endocytosed, transported to the lysosomes, and degraded [48]. To take it a step further, this study was extended to determine the role of monocytes and DCs in IgE catabolism in vivo [48]. The aforementioned hFcεRIα-Tg mice that express human FcεRIα under the human promoter were used in this study because these mice recapitulated not only the cell-type specific expression of FcεRI but also the unique cell type-specific intracellular trafficking of the receptor; human FcεRI was localized in endolysosomes in transgenic murine DCs and monocytes while it was localized in the plasma membranes in mast cells and basophils [48]. Human IgE injected to these mice was internalized by DCs and monocytes but not by mast cells and basophils. Furthermore, the transgenic mice cleared IgE at a much faster rate than non-transgenic control mice, and the rate of clearance correlated with the prevalence of monocytes and DCs. This study reveals that FcεRI-mediated constitutive internalization of IgE by DCs and monocytes promotes serum IgE clearance, implicating its role in IgE homeostasis.

Association with diseases of FcεRI-expressing DCs and monocytes

Atopic dermatitis

Atopic dermatitis, or eczema, is an inflammatory skin disease characterized by red and itchy dry rashes on the skin. The lesions are infiltrated by inflammatory cells and accompanied by keratinocyte metaplasia, and are often associated with high levels of total IgE and allergen-specific IgE. Blood monocytes from atopic dermatitis patients express significantly higher levels of FcεRI than those from healthy individuals, implicating them in this disease. Crosslinking of FcεRI in monocytes promotes differentiation of the monocytes to histamine receptor 1 (H1R)-expressing macrophages with high proinflammatory properties and increased histamine biosynthesis in vitro [99]. In agreement with these in vitro findings, H1R-expressing $CD68^{+}$ macrophages were also found in high amounts in the dermal compartment of AD skin lesions. Considering that histamine is one of the most important mediators of allergic inflammatory reactions, FcεRI signaling in monocytes may contribute to the generation of macrophages that initiate the inflammatory activities of histamines, aggravating skin inflammation in atopic dermatitis.

In addition to macrophages, the skin lesions of atopic dermatitis are infiltrated by a large numbers of DCs; namely, IDECs (inflammatory dendritic epidermal cells), which express distinctively high levels of FcεRI on their surface [100]. Culturing monocytes with IL-4 and GM-CSF under reducing conditions generates DCs with similar phenotypes to IDEC, including high levels of FcεRI [37]. These IDEC-like DCs produce inflammatory cytokines and chemokines including IL-12, and IL-18 upon FcεRI crosslinking, which are enriched in lesion of atopic skin [78]. This finding suggests that FcεRI signaling in IDEC may be a significant contributor to the skin inflammation in this disease.

Asthma

Asthma is a chronic inflammatory lung disease characterized by airway hyper-reactivity and excessive mucus production. Similar to atopic dermatitis, a major fraction of asthma is associated with high levels of total IgE and allergen-specific IgE in serum. It is also associated with both an increased expression of FcεRI in DCs and monocytes and an infiltration of airways with FcεRI-expressing DCs [13]. This infiltration by FcεRI-expressing DCs is associated with a specific subset of asthma characterized by a Th2 immune profile, namely Th2 high asthma [28, 101]. This subset of asthma is also accompanied by a more severe form of eosinophilia and subepithelial fibrosis compared to Th2 low asthma [101]. Thus, FcεRI signaling in DCs may be a contributing factor to Th2 inflammation and associated asthma pathologies.

The role of FcεRI-expressing DCs in Th2 asthma pathologies has been also implicated in studies that used wild type mice as the animal models. While wild type mice do not express FcεRI in DCs at steady state, mouse lung DCs do express FcεRI following infection by the mouse paramyxovirus Sendai virus [102]. This virus induces acute Th1 antiviral immune responses but also triggers a later switch to persistent Th2 inflammation, mucous cell metaplasia, and airway hyper-reactivity, reminiscent of asthma associated with respiratory viral infection. As no previous studies have shown FcεRI expression in mouse DCs, this study thoroughly tested FcεRI expression on the DCs using multiple methods including flow cytometry, western blot analysis, and RT-PCR. These methods consistently pointed to the induction of FcεRI expression in lung DCs following

the viral infection. This study further showed that crosslinking FcεRIα on lung DCs of the mice resulted in the production of the T cell chemoattractant CCL-28. Furthermore, FcεRIα-deficient mice had decreased CCL-28 and decreased recruitment of IL-13 producing CD4 T cells to the lung after viral infection. However, these decreases were reverted by transfer of DCs from wild type but not from FcεRI-deficient mice. Thus, this study suggests that FcεRI expressed in DCs contributes to allergic inflammation in the lung by recruiting Th2 cells that promote mucous cell metaplasia by mediating production of CCL-28.

In addition to mice infected with Sendai virus, mice intranasally challenged with house dust mite have been shown to express FcεRI in a distinct subset of DCs namely inflammatory DCs [103]. However, this finding was solely dependent on detection of FcεRI by flow cytometry using an anti-FcεRI monoclonal antibody, MAR-1. Although the MAR-1 antibody binds mouse FcεRI and has been frequently used to identify basophils and mast cells in mice, the degree of its specificity has not been extensively characterized. In fact, others and we have found that MAR-1 binds a subset of monocytes in FcεRIα-deficient mice under inflammatory conditions. Additionally, no functional role has been reported in association with FcεRI expressed by these inflammatory mouse DCs. Thus, further studies are required to verify FcεRI expression by these mouse inflammatory DCs as well as its functional significance.

The role of FcεRI expressed in DCs in asthma has been also examined using the CD11c-hFcεRIα-Tg mice that express hFcεRIα under control of the DC-specific CD11c promoter. One study showed that these mice produced a greater amount of IL-4 in the airways and developed a more severe form of lung eosinophilia compared to wild type mice, and that both phenotypes were completely dependent on IgE [87]. This finding suggests that FcεRI on DCs promotes asthma. However, another study showed that these mice develop a comparable level of airway inflammation to wild type mice indicated by similar amounts of TNF-α, IL-6, IL-13, IL-5 produced in the airways and a similar degree of eosinophil recruitment [85]. In addition, the mice failed to develop airway hyper-reactivity while wild type mice did [85]. These findings suggest that FcεRI on DCs may instead play a regulatory role in asthma. The apparent contradiction between these studies is not clearly explainable. It may be attributed to different microbiota in animals due to different housing facilities. Alternatively, it may be attributed to different asthma models used. The former employed an acute asthma model largely independent of mast cells while the latter adopted a chronic asthma model that significantly depends on mast cells. In fact, the latter study has shown that a smaller number of mast cells are recruited to the airways in the CD11c-hFcεRIα-Tg mice than wild type mice. Similar observation was made in a mast cell-dependent food allergy model [85]. Based on these results, perhaps FcεRI on DCs may specifically regulate mast cell-associated allergic inflammation.

Concluding remark

In this review, we have summarized the current knowledge of FcεRI biology on human DCs and monocytes. FcεRI is homogeneously and constitutively expressed by the major human DC subset, the BDCA1$^+$ conventional DCs, and also by BDCA2$^+$ plasmacytoid DCs throughout various tissue sites. FcεRI is also constitutively expressed in Langerhans cells, the distinct skin DC subset. Exceptions are the BDCA3$^+$ conventional DCs that lack FcεRI. Unlike DCs, monocytes express FcεRI in a heterogeneous and more regulated manner. In both monocytes and DCs, FcεRI is effectively transported to the plasma membranes but also effectively endocytosed. This endocytosis is not inhibited by IgE binding, thereby resulting in FcεRI-bound IgE entering the cells, reaching the lysosomes, and becoming subject to degradation (Fig. 1a). This distinct FcεRI trafficking may render monocytes and DCs an IgE cleaner as opposed to an IgE effector. When antigens come into the picture, FcεRI endocytosis reinforces the ability of DCs to internalize, process, and present antigens by focusing these activities toward antigens bound to IgE. The consequences of this antigen presentation may differ depending on whether or not FcεRI was crosslinked during engagement with antigens; in the absence of crosslinking, the antigen presentation results in deletional T cell tolerance whereas in the presence of crosslinking, it may result in development of effector T cells (Fig. 1b, c). Besides antigen presentation, FcεRI mediates intracellular signaling upon crosslinking (Fig. 1c). This signaling could either promote or inhibit immune stimulation depending on environmental factors including tissue sites, neighboring cells, and cytokines. Based on its ability to promote antigen presentation as well as to transmit signaling, FcεRI in DCs and monocytes has been suggested to contribute to allergic diseases by enhancing T cell immunity and inflammation. However, recent studies using murine models raise the possibility that it may instead function as the regulator of allergic inflammation.

There is no question that additional studies are required to clarify the functional role of FcεRI in DCs and monocytes. The recently emerged animal models are expected to continue serving useful reagents to the field. However, caution is urged, as they express the chimeric receptor composed of the human FcεRIα and the mouse FcεRIγ, which do not exist in either humans or mice. In addition,

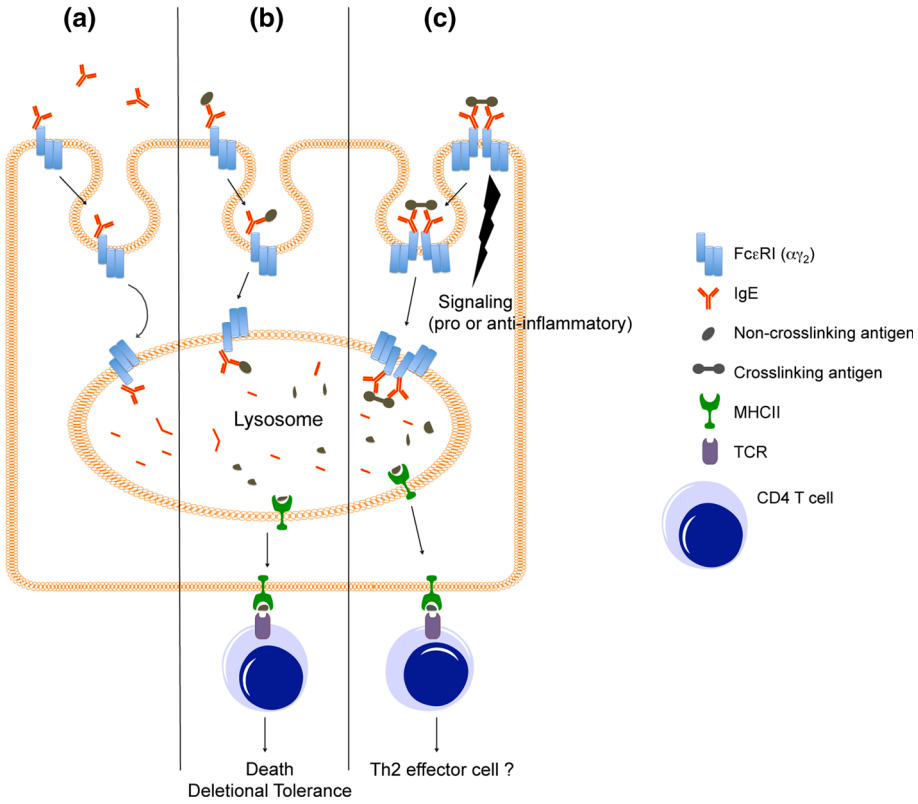

Fig. 1 Role of FcεRI in DCs and monocytes. **a** IgE clearance. FcεRI on DCs and monocytes captures extracellular IgE and takes it to the lysosome resulting in the intracellular degradation [48]. **b** T cell tolerance. FcεRI takes IgE-bound antigen to the lysosomes resulting in the generation of antigenic peptides. These peptides are loaded onto MHCII, transported to cell surface, and presented to antigen-specific $CD4^+$ T cells. This function is not dependent on FcεRI crosslinking; non-crosslinking antigens as well as crosslinking antigens are internalized and presented to $CD4^+$ T cells [61, 88]. When antigen presentation is made in the absence of FcεRI crosslinking, the antigen-recognizing T cells undergo apoptosis resulting in development of T cell tolerance [88]. **c** Pro- or anti-inflammation. FcεRI transmits intracellular signaling upon crosslinking that results in production of cytokines and chemokines of pro- or anti-inflammatory potential [72–78, 80, 102]. Crosslinked FcεRI takes IgE-bound antigens to the lysosomes, where the antigens are processed and loaded onto MHCII before being presented to $CD4^+$ T cells [61]. The functional outcome of this presentation is unclear as some studies suggest development of Th2 effector T cells [27, 86, 87] while others do not [85]

mouse DCs and monocytes may not behave the same as human counterparts. Therefore, studies using human cells will need to be accompanied with mouse models, and studies using mice will need to be thoroughly assessed for their validity and relevance to human physiology or disease. Alternatively, one may utilize a humanized mouse strain in which their immune cells were derived from human hematopoietic stem cells. In fact, a human PBMC-engrafted murine model of gut allergic inflammation has been recently developed [104]. This model depends on human FcεRI-expressing cells; thus, it could serve a tool to examine the role of FcεRI-expressing DCs or monocytes in gut allergic inflammation. It is clear that the field is moving fast forward, and a major progress is to be seen in the near future.

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