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High-Affinity IgE Receptors on Dendritic Cells Exacerbate Th2-Dependent Inflammation

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The IgE-mediated and Th2-dependent late-phase reaction remains a mechanistically enigmatic and daunting element of human allergic inflammation. In this study, we uncover the FcεRI on dendritic cells (DCs) as a key in vivo component of this form of allergy. Because rodent, unlike human, DCs lack FcεRI, this mechanism could be revealed only by using a new transgenic mouse model with human-like FcεRI expression on DCs. In the presence of IgE and allergen, FcεRI+ DCs instructed naïve T cells to differentiate into Th2 cells in vitro and boosted allergen-specific Th2 responses and Th2-dependent eosinophilia at the site of allergen exposure in vivo. Thus, FcεRI on DCs drives the cascade of pathogenic reactions linking the initial allergen capture by IgE with subsequent Th2-dominated T cell responses and the development of late-phase allergic tissue inflammation. The Journal of Immunology, 2011, 187: 164–171.

During an allergic response, the short-lived immediate reaction is followed by a delayed inflammatory tissue response, the late-phase allergic reaction (LAR) (1). LARs, in contrast to early-phase reactions, can persist for up to several days and are characterized by inflammatory tissue infiltrates containing Th2 cells, APCs, and eosinophils (2–4). Eosinophils are the main effector cells of LARs, because they release mediators that induce tissue damage and cause severe organ dysfunction (5–9). In human allergic asthma, LARs can lead to ventilatory insufficiency that, if untreated, can be fatal. Frequent occurrence of pulmonary LARs promotes eosinophil-dominated chronic atopic inflammation, including tissue remodeling and irreversible functional changes in affected organs (9). These attributes make LARs the leading cause of morbidity and mortality in human type 1 allergies (10, 11).

Allergen-mediated cross-linking of Ag-specific IgE bound to high-affinity IgE receptors (FcεRI) on mast cells initiates the early-phase reaction in type 1 allergy (12). The LAR, in contrast, follows the sequelae of T cell-mediated delayed-type (type IV) hypersensitivity. Unlike the classical delayed-type hypersensitivity, the induction of LAR is mediated by allergen-specific Th2 and not Th1 cells (13). Mechanistically, in humans the early-phase reaction and the LAR are independent of each other; this is clearly shown by the fact that drugs that efficiently inhibit either mast cell secretion or the effects of mast cell mediators cannot prevent LAR-associated lung inflammation (14). Murine models recapitulate the dichotomous nature of early- and late-phase responses in allergy. For example, mast cell-deficient mice do not develop early-phase reactions, but are capable of developing LAR-associated tissue eosinophilia (15).

Despite this mechanistic dissociation of the early- and delayed-type reactions, in humans both of these responses are evidently driven by IgE. This was shown by studies in patients with allergies an asthma, in whom treatment with the humanized anti-IgE mAb omalizumab reduced the mast cell-dependent early-phase reaction and the subsequent LAR in the lungs (16). These data also emphasize that the occurrence of LARs in humans depends on the IgE-mediated activation of effector cells, other than mast cells.

Mice constitutively express FcεRI only on mast cells and basophils, but lack its expression on any of the APCs (17). APCs in humans, most notably dendritic cells (DCs), constitutively express FcεRI (18–21). In vitro experiments have shown that IgE bound to FcεRI on human DCs increases Ag uptake, processing,
and presentation to memory CD4+ T cells (18). Therefore we hypothesized that FceRI on DCs may be important for the regulation of delayed-type allergic inflammation in vivo. In this study, we describe a new transgenic (TG) mouse strain with human FceRIex expression targeted to DCs. This animal model allowed us to study in vivo consequences of human-like constitutive FceRI expression on DCs for the induction of T cell immunity.

Materials and Methods

Mice and treatment

The hufFeRla gene was amplified by PCR and inserted into the plasmid vector pRRES2-EGFP (Clontech). The resulting hufFeRla-IRE5-EGFP cassette was cloned downstream of the murine CD11c promoter in a vector pIRES2-EGFP (Clontech). The resulting hufFeRla cassette was cloned downstream of the murine CD11c promoter in a vector pIRES2-EGFP (Clontech). The resulting huFc cassette was cloned downstream of the murine CD11c promoter in a vector pIRES2-EGFP (Clontech). The resulting huFc cassette was cloned downstream of the murine CD11c promoter in a vector pIRES2-EGFP (Clontech).

Immunization and lung challenge

Mice were immunized with 100 μg OVA (Sigma-Aldrich) or 1 μg Bet v 1 i.p. or epicutaneously weekly for 4 wk. Allergic lung inflammation was induced by challenge with aerosolized OVA (4% w/v) or birch pollen (Bet v 1). Mice and treatment

Microscopy

Fluorescence microscopy

Total RNA was isolated from single lung cell suspensions using RNeasy Minikit (Qiagen) and reverse-transcribed to cDNA using random hexamers (RNA PCR Kit, GeneAmp). Primer sequences for target genes and housekeeping gene 5-aminolevulinate synthase 1 (ALAS1): eotaxin 1 fwd 5'-TCC ACA GCG GTT CTA TTT-3'; rantes 5'-TGG CTA TGG CGT TCA GGC TTT-3'; rantes rev 5'-ACT AGA GCA AGT AAC AGC GAA GAA-3'; IL4 fwd 5'-CGA AGA ACA CCA CAG AGA GTG AGC TCC-3'; IL4 rev 5'-GAC TCA TGC ATG GTG CAT CTT ACG GAG CTG TGC GAC-3'; alasi 5'-TGG CCA TGT CTA CCA GGC-3'; alasi rev 5'-CCA GTG GAA GAG CAG TGG GAC-3'; target gene expression was determined by real time RT-PCR using LightCycler FastStart kits with SYBR Green (Roche). Data were presented as the relative ratio of target gene expression to housekeeping gene expression.

Lung histopathology

Lungs were removed, fixed in buffered formaldehde, and embedded in paraffin. The morphologic signs of LAR severity were ascertained by a certified pathologist under the microscope in 5-μm H&E-stained sections.

Fluorescence microscopy

Lung cryosections (7 μm) were fixed in 5% PFA for 4.5 h, washed with PBS, frozen in OCT medium (Sakura), and mounted on slides with Vectashield Mounting Medium (Vector Laboratories). Sections were examined using an LSM 510 confocal microscope (Zeiss).
**Results**

**TG mice express FcεRI on DCs**

We generated TG mice expressing the IgE-binding human FcεRIα-chain and eGFP under control of the DC-restricted, constitutively active CD11c promoter (α-DC TG mice) (Fig. 1A, Supplemental Fig. 1A). In these mice, discrete populations of eGFP+ cells were detected in spleen and lymph nodes as well as nonlymphoid organs (e.g., lung, intestine, liver) (Fig. 1B). eGFP+ cells were DCs, as shown by their high MHC class II expression, display of costimulatory molecules, and superior T cell stimulatory capacity (Fig. 1C). In contrast to wild type (WT) mice, DCs from α-DC TG bound human as well as murine IgE (Supplemental Fig. 1B, 1C). Basophils, T cells, B cells, mast cells, and NK cells from α-DC TG mice did not express the TG FcεRIα at the cell surface (Fig. 1D, Supplemental Fig. 1E, 1F; data not shown). TG DCs expressed FcεRI as a chimeric holoreceptor composed of the human FcεRIα-chain and the endogeneous murine FcεRIγ dimer (Fig. 1E). FcεRIγ was not detectable at the RNA or protein level in DCs (data not shown). Thus, murine and human DC-expressed FcεRI has the same subunit composition (18). Comparable to humans, α-DC TG mice expressed higher levels of FcεRI on myeloid DCs than on lymphoid or plasmacytoid DCs (Supplemental Fig. 1C, 1D) (22). DCs from α-DC TG mice, but not WT mice, took up and presented protein Ags in an IgE-dependent fashion (Fig. 1F), indicating human-like function of FcεRI on DCs. Whereas only DCs from α-DC TG animals were able to use the IgE-receptor-mediated Ag presentation pathway, the fluid phase Ag uptake in DCs from α-DC TG and WT mice was identical. Basal IgE serum levels were identical in naïve α-DC TG and WT mice (data not shown).

**DCs use FcεRI and IgE to augment Ag-specific T cell responses in vivo**

The in vivo binding of IgE to DCs was studied in naïve mice and mice immunized for OVA-specific IgE production. No IgE was detected on freshly isolated DCs of WT mice regardless of whether the mice were immunized with OVA (Fig. 2A). In contrast, DCs from α-DC TG mice displayed surface-bound IgE, which strongly increased upon elevation of serum IgE by immunization (Fig. 2A).

Next we investigated the in vivo consequences of this FcεRI-dependent IgE binding to DCs for subsequent T cell activation. As shown in Fig. 2B, Ag-specific T cell recall responses were enhanced in OVA-immunized α-DC TG mice when compared with WT controls. To explore whether IgE binding to DCs is linked to...
IgE-bound DCs prime naive T cells for Th2 differentiation and amplify Ag-specific Th2 responses in vivo

Next we asked whether IgE binding to FcεRI on DC, in addition to enhancing memory T cell responses, could also result in more efficient activation of naive T cells. To test this question, purified DCs were used to activate naive OVA-specific TCR–TG T cells in the presence of haptenized OVA and a hapten-specific IgE. As shown in Fig. 3A, naive CD4+ T cells proliferated much stronger at nonsaturating Ag concentrations when activated by IgE-loaded FcεRI+ DCs than in the absence of FcεRI. Mechanistically, the augmented T cell proliferation resulted from an increased rate of naive T cells pushed into cell cycle and an accelerated propagation through consecutive division rounds of already cycling cells (Supplemental Fig. 3A, 3B). Interestingly, IgE-FcεRI-dependent Ag presentation more efficiently amplified the proliferation of naive than of primed T cells (Supplemental Fig. 3C).

We also characterized the quality of the T cell responses elicited from naive OVA-specific T cells by DCs after either FcεRI-dependent or fluid phase Ag uptake. After Ag uptake in fluid phase, DCs activated naive OVA-specific T cells to produce IFN-γ, but little IL-4 (Fig. 3B). When OVA was targeted to FcεRI by IgE, in contrast, DCs induced Th2 differentiation characterized by increased IL-4/IFN-γ secretion ratios of splenocytes from naive and OVA-immunized TCR–TG T cells by DCs after either FcεRI-dependent or fluid phase Ag uptake. FcεRI+ DCs loaded with NP-specific IgE or unmodified DCs were used to activate naive OVA-specific TCR–TG T cells in the presence of NP-OVA and NP-specific IgE. [3H]Thymidine uptake was measured (mean cpm of triplicates). **p < 0.01. A, FcεRI+ DCs isolated from naive OVA-specific T cells by DCs after FcεRI-dependent Ag uptake. After Ag uptake in fluid phase, DCs activated naive OVA-specific T cells to produce IFN-γ, but little IL-4 (Fig. 3B). When OVA was targeted to FcεRI by IgE, in contrast, DCs induced Th2 differentiation characterized by increased IL-4/IFN-γ secretion ratios of splenocytes from naive and OVA-immunized TCR–TG T cells by DCs after either FcεRI-dependent or fluid phase Ag uptake. FcεRI+ DCs loaded with NP-specific IgE or unmodified DCs were used to activate naive OVA-specific TCR–TG T cells in the presence of NP-OVA and NP-specific IgE. [3H]Thymidine uptake was measured (mean cpm of triplicates). **p < 0.01. A, FcεRI+ DCs isolated from naive OVA-specific T cells by DCs after FcεRI-dependent Ag uptake. After Ag uptake in fluid phase, DCs activated naive OVA-specific T cells to produce IFN-γ, but little IL-4 (Fig. 3B). When OVA was targeted to FcεRI by IgE, in contrast, DCs induced Th2 differentiation characterized by increased IL-4/IFN-γ secretion ratios of splenocytes from naive and OVA-immunized TCR–TG T cells by DCs after either FcεRI-dependent or fluid phase Ag uptake. FcεRI+ DCs loaded with NP-specific IgE or unmodified DCs were used to activate naive OVA-specific TCR–TG T cells in the presence of NP-OVA and NP-specific IgE. [3H]Thymidine uptake was measured (mean cpm of triplicates). **p < 0.01. A, FcεRI+ DCs isolated from naive OVA-specific T cells by DCs after FcεRI-dependent Ag uptake. After Ag uptake in fluid phase, DCs activated naive OVA-specific T cells to produce IFN-γ, but little IL-4 (Fig. 3B). When OVA was targeted to FcεRI by IgE, in contrast, DCs induced Th2 differentiation characterized by increased IL-4/IFN-γ secretion ratios of splenocytes from naive and OVA-immunized TCR–TG T cells by DCs after either FcεRI-dependent or fluid phase Ag uptake. FcεRI+ DCs loaded with NP-specific IgE or unmodified DCs were used to activate naive OVA-specific TCR–TG T cells in the presence of NP-OVA and NP-specific IgE.
by enhanced IL-4 and reduced IFN-γ secretion (Fig. 3B). To determine whether FcεRI-dependent Th2 amplification occurred also in vivo, α-DC TG and WT mice were immunized with OVA i.p. or epicutaneously, and cytokine secretion from spleen cells was analyzed. Immunization via either route resulted in strongly amplified, Ag-dependent IL-4 and IL-5 secretion as well as increased Th2:Th1 cytokine ratios in α-DC TG compared with WT mice (Fig. 3C, 3D, Supplemental Fig. 3D–F).

Exacerbation of allergic late-phase inflammation in α-DC TG mice

To explore whether FcεRI on DCs modifies tissue inflammation, we analyzed pulmonary infiltrates in OVA aerosol-challenged α-DC TG and WT mice. The challenge-dependent increase in CD45\(^+\) cell infiltration was 2.6-fold higher in lungs of α-DC TG mice, compared with WT mice (+78% versus +30%) (Fig. 4A). The CD45\(^+\) lung cell populations of α-DC TG mice and of WT mice, however, contained similar proportions of F4/80\(^+\) macrophages and T cells (Fig. 4B). Thus, T cells are increased to the same extent as the total CD45\(^+\) cell infiltrate in the lungs of α-DC TG mice. When we transferred OVA-specific T cells into subsequently OVA-challenged recipients, they underwent an average of 67% more cell divisions in the lungs of α-DC TG mice compared with WT controls (mean divisions in α-DC TG, 5.5; mean divisions in WT, 3.5) (Fig. 4C). Thus, the increased T cell numbers in the lungs of α-DC TG mice are, at least in part, due to an enhanced rate of allergen-dependent T cell proliferation in situ.

The most explicit feature of infiltrate composition in α-DC TG mice was the 2-fold increase in the percentage of pulmonary eosinophils compared with WT mice (Fig. 4B). This increase corrected by the increase in total CD45\(^+\) cell counts amounts to an overall 5.2-fold eosinophil predominance in the lungs of α-DC TG mice compared with WT mice. Eosinophils were present in interstitial and perivascular inflammatory cuffs and in the lung parenchyma, including the interalveolar space both in TG (Fig. 4D) and WT animals (not shown). Thus, the expression of FcεRI on DCs enhances lung T cell proliferation and tissue eosinophilia in allergic lung inflammation.

Airway-associated FcεRI\(^+\) DCs accumulate in allergic lung inflammation

CD11c\(^+\) lung cells, which include a subpopulation of lung macrophages and DCs, were slightly more abundant in α-DC TG mice than in WT mice (Fig. 4B). This observation led us to analyze the subset composition and detail of these cells in more detail. Interestingly, most CD11c\(^+\) cells were eGFP\(^+\) and FcεRI\(^+\) in noninflamed lungs of α-DC TG mice (Fig. 5A). When purified, those cells poorly presented Ag to T cells (Fig. 5B) and displayed high-level autofluorescence in WT and α-DC TG mice (Fig. 5C). Thus, eGFP CD11c\(^+\) cells qualify as lung macrophages (23). In striking contrast, the eGFP\(^+\)CD11c\(^+\) lung cells expressed FcεRI (Fig. 5A) and strongly presented Ag to T cells (Fig. 5B), but were not autofluorescent (Fig. 5C). Thus, eGFP expression marks the functionally relevant CD11c\(^+\) DC population in the lungs of α-DC TG mice. CD11c\(^+\) lung DCs were rare in naïve or mock-treated α-DC TG mice, but were increased an average of 9-fold after allergen challenge of sensitized mice (Fig. 5D). Histologically, in naïve or mock-treated α-DC TG mice, eGFP\(^+\) DCs localized close to bronchioles (Fig. 5E). In OVA-sensitized and challenged mice, large numbers of eGFP\(^+\) DCs infiltrated bronchioles and small bronchi as well as the alveolar lung parenchyma (Fig. 5E). Higher magnifications revealed that some of the eGFP\(^+\) DCs localized just beneath the bronchial epithelium and projected a discontinuous network of dendrites into the basal lamina (Fig. 5E).

FceRI on DCs exacerbates IgE-dependent pulmonary Th2 activation and eosinophil chemotraction into the lungs

The important question remained whether it is indeed the ligand-dependent function of DC-expressed FceRI that mediates the enhanced lung eosinophilia observed in α-DC TG mice. To explore this question, allergen-dependent eosinophil lung recruitment was also studied in IgE-deficient α-DC TG mice. As shown before, allergen-induced lung eosinophilia was significantly more pronounced in α-DC TG than in WT mice (Fig. 6A). Importantly, this enhancement of lung eosinophilia strictly depended on IgE, because it was entirely lost in IgE-deficient α-DC TG mice (Fig. 6A). Thus, the in vivo interaction of IgE with its high-affinity receptor expressed on DCs is essential for strong eosinophilic lung inflammation in response to allergen exposure.
We also screened by quantitative PCR for eosinophilia-regulating lung cytokines that are upregulated by DC-restricted FcεRI expression, but are downregulated by a superimposed lack of IgE. Eotaxin-1, in contrast to several other candidates, was overexpressed in the lungs of α-DC TG mice in WT mice and reverted to WT expression in the absence of IgE (Fig. 6B). In contrast, RANTES expression did not depend on DC-expressed FcεRI or IgE (Fig. 6B). Eotaxin expression in the lungs is considered dependent on Th2 cytokines released in situ. Among the Th2 cytokines tested, selective lung IL-4 expression strictly followed the FcεRI- and IgE-dependent regulation pattern of Eotaxin-1 (Fig. 6B). Thus, IL-4 and Eotaxin-1 lung expression is linked to FcεRI- and IgE-mediated lung eosinophilia, a condition that is not operative in WT mice but is assigned to mice by FcεRI expression on DCs.

**Discussion**

In type 1 allergic diseases, allergen-specific Th2 cells are critical both as regulators of allergen-specific IgE production and as effectors of delayed type atopic tissue inflammation (i.e., the LAR) (24). It has remained unclear whether IgE itself can regulate, via its high-affinity receptor on DCs, Th2 responses and Th2-dependent inflammation. Using α-DC TG mice, we show that allergen-specific IgE bound to FcεRI on DCs modifies the critical allergen threshold required for Th cell activation and, thus, strongly augments Th cell responses in vivo.

This IgE- and FcεRI-dependent Ag presentation by DCs increases primed Th cell responses both in vitro and in vivo. It also augments the activation of naive Ag-specific Th cells that may ensure that an enhanced repertoire of allergen-reactive Th cells can take part in the allergic response. IgE-FcεRI-dependent Ag presentation by DCs is not neutral in regard to the type of Ag-driven Th cell differentiation elicited. In this study, we demonstrate that FcεRI in the presence of IgE instructs DCs to push recently activated naive Th cells into the Th2 pathway of differentiation, while default Th1 development is comparatively suppressed. We conclude that IgE in the context of FcεRI+ DCs is an integral component of an amplifying, positive feedback loop designed to maximize Th2 responses.

The understanding of how DCs are turned into Th2-promoting APCs is of critical research interest in type 1 allergy, although only a few relevant mechanisms have been identified. Thymic stomal lymphopoietin and certain helminth products condition DCs for...
FIGURE 6. FceRI on DCs instigates IgE-dependent pulmonary Th2 activation and eosinophil chemotraction into the lung. A. IgE-dependent eosinophil lung infiltration in α-DC TG mice but not in WT mice. Lung eosinophils in naive or OVA-immunized WT (open bars), α-DC TG (black bars), and IgE^−/− α-DC TG mice (gray bars), after either PBS (−) or OVA inhalation, were counted by flow cytometry. Mean eosinophil counts (±SEM) relative to the counts in the group treated with PBS only as obtained with lungs from three mice per group are shown. **p < 0.01. n.d., not determined.

B. Th2 priming (25, 26), whereas OX40 ligand acts as a costimulatory, but not as a polarizing signal for Th2 expansion (27). Our new data demonstrate that a member of the family of Ig receptors, FceRI, can be added to the list of DC-modifying components of Th2 immunity. In contrast to the previously established factors, FceRI on DCs has its role both in Th2 priming and in the expansion of already primed Th2 cells.

Whereas the chain of molecular events leading to FceRI-dependent Th2 differentiation by DCs still needs to be fully uncovered, our data clearly show that the FceRI-amplified Th2 response is relevant for inflammation in vivo. This is demonstrated in our studies on Ag-dependent induction of inflammatory responses in murine lungs. FceRI on DCs increased the systemic and augmented the local allergen-specific Th2 activation in the lungs after airborne allergen exposure. The ensuing increased Th2 cytokine production in situ, including eosinophil chemoattractants, led to enhanced lung eosinophilia. Thus, the IgE-FceRI axis on DCs is causally connected to the regulation of the magnitude of tissue eosinophilia, the main cause for inflammatory organ dysfunction in human type 1 allergy.

Previous studies (28, 29) and our current observations in control animals have shown that IgE has no proinflammatory function in the regular asthma models in WT mice, in which FceRI is not expressed constitutively on DCs. This finding stands in contrast to human asthma, in which atopic lung inflammation was shown to depend on IgE (16, 30). The data presented in our study resolve this discrepancy by showing that the selective expression of FceRI on DCs suffices to confer to the murine model the characteristic IgE dependence of human late-phase atopic inflammation. In murine lungs, Th2 activation, Th2 cytokine production, and eosinophil chemoattraction depended in large parts on the in vivo interaction of IgE with FceRI on DCs. Thus, α-DC TG mice allowed us to identify an important mechanism of human type 1 allergy and thus provide a model to study in rodents allergic pathophysiology as relevant for human allergy.

Recent reports have demonstrated the critical role of Ag presentation by basophils for the induction of Th2 responses (31–33). DCs, which were FceRI^+ in these models, induced Th1 responses only. Our experiments recapitulate the selective Th1-promoting activity of WT DCs, but also show that the interaction of IgE with FceRI on DCs switches their function from being Th1-inducing to being Th2-inducing APCs. In the absence of IgE, FceRI expression does not induce the Th2 polarizing properties of the DCs. Thus, basophil but not FceRI-dependent DC functionality can be relevant for the initial Th2 priming much later on, manifesting in clinical allergy. However, for clinical allergy to develop, primary Th2 responses have to expand. In this expansion phase, as shown by our data, FceRI-dependent Ag presentation by DCs has its critical role by augmenting the Th2 pools from primed and perhaps naive reservoirs. A dominant role of basophils in this phase is unlikely based on their low abundance compared with FceRI^+ DCs in lymphoid and nonlymphoid organs. Thus, FceRI^+ DCs and basophils likely provide two independent pathways of Th2 immunity.

To our knowledge, α-DC TG mice also allowed for the first time the direct visualization of the relevant population of Th cell-activating DCs in the lung. This is experimentally important because the DC marker CD11c in the lung, in contrast to other organs, does not discriminate lung macrophages from DCs (23). Our data in α-DC TG mice show that in striking contrast to macrophages, immunostimulatory lung DCs selectively expressed eGFP and FceRI. These DCs resided within the epithelia of small airways or were juxtaposed to them and projected meshwork-forming dendrites into the bronchial basal lamina. Thus, IgE-armed FceRI^+ airway-associated DCs are in the position to be first to specifically interact with inhaled allergens. After Ag aerosol challenge, FceRI^+ DCs greatly increased in numbers and accumulated around small airways and in the lung parenchyma, which is also typically observed in human asthma (4, 34). This numeric increase of FceRI^+ DCs within the arising allergic inflammation is an important component of the allergic response, because it further increases the contribution of IgE-FceRI-dependent Th cell activation in the allergen-exposed tissue.

Recently, it has been demonstrated that a population of murine inflammatory lung DCs elicits Th2 immunity and is induced to express FceRI (35, 36). Provided the functionality of this induced rather than constitutive receptor expression, our data allow the conclusion that FceRI expression and not another yet unknown function of inflammatory DCs suffices for the promotion of Th2 responses. For the future, conclusive experiments on IgE-mediated regulation of this new subset of inflammatory DCs will have to await mice that allow conditional and selective ablation of FceRI on DCs.

In conclusion, FceRI on DCs is not decisive for the initial, limited allergen-specific Th2 response. However, once allergen-specific IgE is induced, DCs start to use FceRI as an allergen-focusing structure to specifically promote disease-eliciting Th2 responses. Thus, efficacious and persistent blockade of FceRI on DCs appears to be an interesting therapy for human type 1 allergy that finds support by the recent observation of Th2 rather than Th1 cytokine suppression by anti-IgE treatment of allergic humans (37). In an acute situation, this intervention should reduce the severity of allergic tissue inflammation whereas, if applied chronically, this therapy may correct substantially the Th2 bias of the underlying immune response. Our new model in α-DC TG
mice, which more faithfully reflects the human situation of type 1 allergy, will allow future experimental explorations of novel therapies targeting the trimeric human FcεRI on DCs.

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Disclosures
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