Original article

IL-13 is essential to the late-phase response in allergic rhinitis

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Background: The pathophysiology of the early- and late-phase nasal response to allergen challenge is not completely defined. Recent technical advances enable direct monitoring of these responses in mice.
Objective: IL-13 is detected in the nasal membranes of both human beings and mice with allergic rhinitis, but its role in disease pathogenesis is unclear. We measured early and late nasal allergic responses after treatment with soluble IL-13Rα2–IgG fusion protein (sIL-13Rα2–Fc), and in IL-13–deficient mice (IL-13$^{-/-}$).
Methods: IL-13$^{-/-}$ mice (BALB/c background) and wild-type mice were sensitized to ovalbumin by intraperitoneal injection and then challenged intranasally with ovalbumin without sedation. The sIL-13Rα2–Fc or control human IgG was administered by intraperitoneal (i.p.) injection 24 hours and 1 hour before each ovalbumin challenge. Early nasal responses after the 4th ovalbumin challenge and late nasal responses 24 hours after the 6th ovalbumin challenge were assessed.
Results: Sensitized/challenged wild-type mice treated with sIL-13Rα2–Fc or IL-13$^{-/-}$ mice demonstrated significantly reduced late nasal responses in face of persistent nasal tissue eosinophilia; the early nasal response was little affected by targeting IL-13. Goblet cell hyperplasia was not detected in nasal membranes.
Conclusion: The data indicate that IL-13 is a major contributor to the development of a late nasal response with little influence on the early response, and without affecting nasal eosinophilic inflammation. Inhibition of IL-13 may have an important therapeutic application in preventing the persistent nasal blockage in allergic rhinitis.
Clinical implications: Current therapies for allergic rhinitis may not take into account the important differences in the pathophysiology of the early and late responses and the important role of IL-13 in sustaining chronic nasal congestion and obstruction. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: *Allergic rhinitis, early phase, late phase, nasal resistance, IL-13*

Abbreviations used

AR:	Allergic rhinitis
MBP:	Major basic protein
OVA:	Ovalbumin
PAS:	Period acid-Schiff
RF:	Respiratory frequency
Rna:	Nasal resistance
sIL:	Soluble IL
WT:	Wild-type

IL-13 is an important cytokine that regulates inflammatory and T_H2 immune responses.[1,2] IL-13 shares many activities with IL-4, in large part because both use a common receptor subunit (IL-4Rα-chain) as part of their receptor.[3,4] As a result, IL-13 like IL-4, acts on B cells and stimulates both proliferation and IgE synthesis in these cells.[5,6] However, IL-13 but not IL-4 appears to be an effector cytokine that directly contributes to bronchial hyperreactivity and mucus overproduction in mouse models of asthma.[7-9] IL-13 has been shown to be produced by T cells, B cells, mast cells, basophils, eosinophils, and natural killer cells.[1,10-14]

In allergic rhinitis, the IL-13 gene is expressed in the nasal mucosa of patients with perennial allergic rhinitis (AR) or after allergen provocation.[15,16] We also reported that wild-type (WT) mice that were sensitized and challenged (intranasally) exhibited increased levels of IL-13 in nasal tissue homogenates compared with challenged-only mice.[17] However, the role of IL-13 in the development of the early and/or late phase of AR is not defined.

In a previous study, we reported a novel approach to evaluate both the early phase nasal response that appears 15 minutes after challenge as well as the late phase nasal response or continuing nasal obstruction, 24 hours after the last intranasal challenge.[17] In the approach used, the changes were restricted to the upper airways because these mice showed no lower airway hyperresponsiveness. In the current study, the role of IL-13 in the early and late phase nasal responses was determined by using 2 complementary approaches: administration of an inhibitor of IL-13 (soluble IL-13Rα2–IgG fusion protein, sIL-13Rα2–Fc) and IL-13–deficient (IL-13$^{-/-}$) mice.

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METHODS

Animals

BALB/cByJ mice were obtained from Jackson Laboratories (Bar Harbor, Me). IL-13$^{-/-}$ mice (BALB/c background; provided by Dr D. Umetsu Harvard University, Boston, Mass) were maintained and bred in the animal facility at National Jewish. These mice were housed under specific pathogen-free conditions and maintained on an ovalbumin (OVA)-free diet. Both female and male mice, 12 to 16 weeks old, were used in these experiments. All experimental animals used in this study were under a protocol approved by the Institutional Animal Care and Use Committee of the National Jewish Medical and Research Center.

Intraperitoneal sensitization and nasal challenge

Mice were assigned to either control or treatment groups on the basis of the following: mice were sensitized by intraperitoneal injection of 20 μg OVA (Grade V; Sigma Chemical, St Louis, Mo) emulsified in 2.25 mg alum (AlumImuject; Pierce, Rockford, Ill) in a total volume of 100 μL on days 0 and 14. This was followed by daily challenge with nasal instillation of OVA diluted in PBS (20 μL of 25 mg/mL) without anesthesia from days 28 to 33. Two groups were monitored: the OVA/OVA group, which received OVA sensitization followed by OVA instillation in the nostril every 24 hours, and the PBS/OVA group, which received OVA intranasally daily without intraperitoneal sensitization. The solutions were shown to contain less than 1 EU LPS/mg protein.

Administration of sIL-13Rα2-Fc

Murine sIL-13Rα2-Fc was prepared as previously described[18] and was administered by i.p. injection (300 μg/mouse) 24 hours and 1 hour before each of the daily OVA challenges. As a control, human IgG (control IgG) was administered in the same fashion.

Determination of the early nasal response

Previously, we demonstrated that sensitized mice showed a significant decrease in respiratory frequency (RF) after intranasal allergen challenge and these decreases in RF were highly correlated with increased nasal resistance (Rna), measured directly.[17] The immediate response elicited after the 4th OVA nasal challenge was shown to be a reliable indicator of the early nasal response. Mice received OVA (20 μL of a 25 mg/mL solution) via the nostril, and were then placed back into the box. RF was measured at 4, 10, 15, 20, 25, 30, and 60 minutes. Persistent nasal blockage that influences baseline values did not develop in sensitized mice challenged in this way. RF was monitored in unrestrained conscious animals using single-chamber, whole body plethysmography (Buxco, Troy, NY). Before measurements, mice were left in the chambers for 20 minutes with constant airflow. The air valves were then closed for 3 minutes, followed by ventilation for 2 minutes. This procedure was repeated twice to allow accommodation to the apparatus, and then the measurements of respiratory parameters were performed 3 times for a total of 9 minutes. For each 15 respirations, RF was recorded automatically and averaged. In each 3-minute period, the mean of the 10 lowest averages was taken as the RF value for that period; this minimized any distortion of values because of movement. We compared this mean RF to baseline RF.

Determination of the late nasal response manifested as persistent nasal blockage

Sensitized mice showed a persistent and significant decrease in RF 24 hours after 6 daily challenges. This decrease in RF was shown to be the result of persistent nasal blockage.[17] The data confirmed that Rna and RF measured 24 hours after the 6th challenge was an appropriate measure of the late nasal response. Twenty-four hours before the 1st challenge and 24 hours after the 6th antigen challenge, RF was monitored in unrestrained conscious animals using whole body plethysmography as described.[17] For Rna measurements, each mouse was anesthetized with pentobarbital sodium (50 mg/kg ip) and fixed in a supine position. Tracheostomized mice were mechanically ventilated (160 breaths/min, tidal volume to 0.15 μL). A blunt 19-gauge needle was carefully inserted into the nasopharynx from the larynx via the pharynx after laryngotomy, and was connected to a custom-designed ventilator (FlexiVent; Scireq, Montreal, Quebec, Canada). The resistive properties of the respiratory system were determined at constant volume using forced oscillations in the ventilator. Rna was analyzed with the FlexiVent software.

Measurement of total and OVA-specific antibodies

Serum levels of total IgE, OVA-specific IgE and IgG_1 were measured by ELISA as previously described.[19]

Histologic studies

The skulls of mice were skinned, and the nasal portion was excised from the head along the line of both eye sockets. The tip of the nose area containing incisor teeth was also removed. The tissues were fixed in 10% formalin and decalcified with decalcifying solution (Richard-Allan Scientific, Kalamazoo, Mich). Cells containing eosinophilic major basic protein (MBP) were identified by immunohistochemical staining as previously described using rabbit antimouse MBP (kindly provided by Dr J. J. Lee, Mayo Clinic, Scottsdale, Ariz).[19] The content of the nasal septum at the level of midlateral meatus was evaluated under ×10 power fields in the lower, middle, and higher septum with a Leica microscope (Leica DMRXMA, Leica Microsystems, Wetzlar, Germany) equipped with a fluorescein filter system. Numbers of eosinophils in nasal septal tissues, except cartilage, were evaluated by using the IPLab2 software (Signal Analytics, Vienna, Va) for Macintosh.

For detection of mucus-containing cells in formalin-fixed airway tissue, sections were stained with periodic acid-Schiff (PAS) and counterstained with hematoxylin. Numbers of goblet cells in nasal epithelial tissues were evaluated by using the IPLab2 software (Signal Analytics) for Macintosh.[20]

Statistical analysis

All results were expressed as the means ± SEMs. ANOVA was used to determine the levels of difference between all groups. Pairs of groups of samples distributed parametrically were compared by unpaired 2-tailed Student t test, and those samples with distributed nonparametrically were compared by Mann-Whitney U test. The *P* value for significance was set to .05.

RESULTS

IL-13–deficient and sIL-13Rα2–Fc—treated mice develop early phase nasal responses

To elucidate the role of IL-13 in the development of the early phase nasal response, we monitored RF after the 4th OVA challenge in both IL-13$^{-/-}$ and IL-13$^{+/+}$ mice as well as after treatment with sIL-13Rα2–Fc. Sensitized sIL-13Rα2–Fc—treated WT mice showed an early nasal response that was similar to control IgG-treated mice (Fig 1, *A*). Mice challenged alone (nonsensitized; *PBS/OVA*) did not develop an early phase response. IL-13$^{-/-}$ mice also developed an early phase nasal response, but it

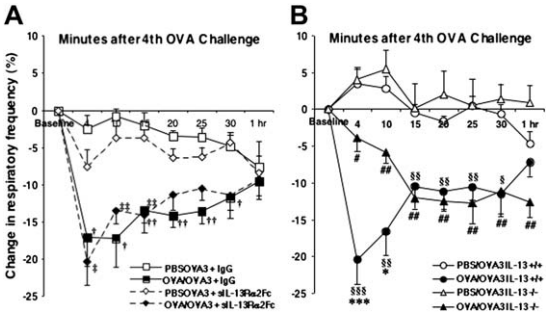

FIG 1. Respiratory frequency was monitored over a period of 60 minutes after a 4th allergen challenge in mice treated with an IL-13 inhibitor **(A)** or in IL-13–deficient mice **(B)**, n = 6 to 8 in each group. Expressed are the means ± SEMs for RF as a percentage of the value at baseline values before challenge. †$P < .05$ and ††$P < .01$ compared with the PBS/OVA3 treated with human IgG group; ‡$P < .05$ and ‡‡$P < .01$ compared with the PBS/OVA3 treated with sIL-13Rα2–Fc group; §$P < .05$, §§$P < .01$, and § §§$P < .001$ compared with the PBS/OVA3 WT group; *$P < .05$, **$P < .01$, and ***$P < .001$ compared with the OVA/OVA3 IL-13$^{-/-}$ group; #$P < .05$ and ##$P < .01$ compared with the PBS/OVA3 IL-13$^{-/-}$ group.

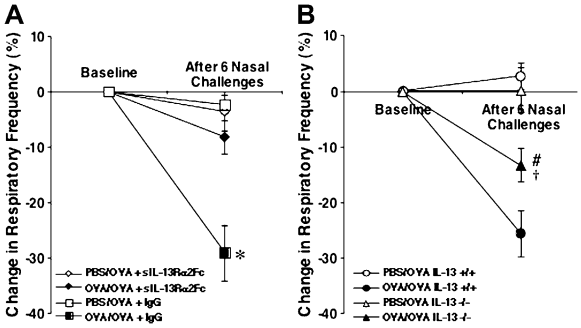

FIG 2. Changes in respiratory frequency after 6 OVA challenges. Respiratory frequency was assessed 24 hours before the 1st nasal challenge (baseline) and after 6 nasal challenges as described in Methods. Respiratory frequency were assessed in nonsensitized but challenged mice (PBS/OVA), and OVA sensitized and challenged mice (OVA/OVA) treated with sIL-13Rα2–Fc or with human IgG **(A)**, and in OVA sensitized and challenged IL-13$^{-/-}$ or IL-13$^{+/+}$ mice, or challenged-only IL-13$^{-/-}$ or IL-13$^{+/+}$ mice **(B)**, n = 6 to 8 in each group. Expressed are the means ± SEMs. *$P < .01$ compared with PBS/OVA WT mice treated with human IgG; #$P < .05$ compared with PBS/OVA WT (IL-13$^{+/+}$) mice; †$P < .05$ compared with OVA/OVA WT (IL-13$^{+/+}$) mice.

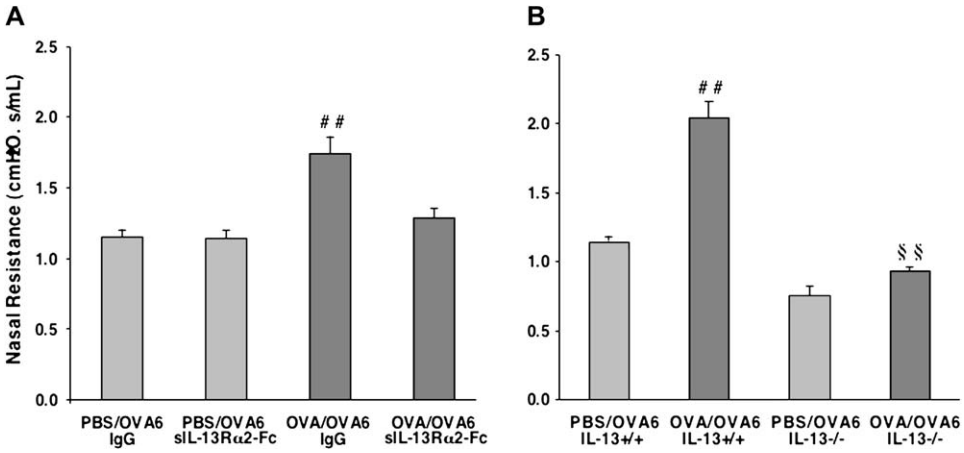

FIG 3. Nasal resistance. Nasal resistance was measured 24 hours after 6 allergen challenges in **(A)** nonsensitized but challenged WT mice (PBS/OVA6) and OVA sensitized and challenged mice (OVA/OVA6) treated with sIL-13Rα2–Fc or with human IgG **(and in B)** nonsensitized but challenged IL-13$^{+/+}$ or IL-13$^{-/-}$ mice (PBS/OVA6 IL-13$^{+/+}$ or IL-13$^{-/-}$) or OVA sensitized and challenged IL-13$^{+/+}$ or IL-13$^{-/-}$ mice (OVA/OVA6IL-13$^{+/+}$ or IL-13$^{-/-}$ mice). Each group n = 6 to 8. Expressed are the means ± SEMs. ##$P < .01$ compared with the PBS/OVA group; §§$P < .01$ compared with the OVA/OVA6 IL-13$^{+/+}$ group.

appeared to develop slower and was somewhat attenuated in comparison with IL-13$^{+/+}$ mice, but was significant when compared with nonsensitized, challenged-only controls (Fig 1, *B*).

IL-13$^{-/-}$ mice and sIL-13Rα2–Fc—treated WT mice fail to develop late phase nasal responses

To assess whether IL-13 plays a role in development of the late phase nasal response, we monitored RF and Rna 24 hours after the 6th nasal challenge. Mice challenged alone showed no change in RF (Fig 2). Sensitized and challenged WT mice treated with control IgG showed a significant decrease in RF (Fig 2, *A*) and in parallel, a significant increase in Rna (Fig 3, *A*). This was contrasted by the findings in sIL-13Rα2–Fc—treated mice, where the decrease in RF and increase in Rna were virtually eliminated, almost to levels seen in nonsensitized but challenged mice.

In IL-13$^{-/-}$ mice, RF values were significantly decreased compared with challenge only controls, although the decreases were significantly less than observed in IL-13$^{+/+}$ mice (Fig 2, *B*). These data suggested that IL-13 was contributing to the development of the late nasal response. This was even more evident when Rna levels were monitored (Fig 3, *B*). After sensitization and 6 nasal challenges, Rna values in the IL-13$^{-/-}$ mice were significantly lower than observed in their IL-13$^{+/+}$ littermates.

TABLE I. Antibody responses after 6 nasal challenges*

Group	OVA-specific (EU/mL)		Total Ig (ng/mL)
	IgE	IgG_1	IgE
PBS/OVA6 WT	<10	<10	<10
OVA/OVA6 WT	881 ± 130**†	5269 ± 271**	8065 ± 675**
OVA/OVA6 human-IgG	762 ± 19**†	4984 ± 227**	7330 ± 511**
OVA/OVA6 sIL-13Ra2–Fc	774 ± 90**†	4768 ± 209**	5963 ± 912**
PBS/OVA6 IL-$13^{-/-}$	69 ± 43	<10	<10
OVA/OVA6 IL-$13^{-/-}$	431 ± 98##	4662 ± 238##	7426 ± 608##

*OVA-specific antibody and total Ig levels in the serum after 6 nasal challenges. Mice were sensitized and challenged as described in Methods. Serum Ig and antibody levels were assessed 24 hours after the 6th nasal challenge in nonsensitized but challenged WT (IL-$13^{+/+}$) mice (PBS/OVA6 WT), OVA sensitized and challenged mice (OVA/OVA6 WT), OVA sensitized and challenged mice treated with human IgG (OVA/OVA6 human IgG) or with sIL-13Ra2-Fc (OVA/OVA6 sIL-13Ra2–Fc), and nonsensitized but challenged IL-$13^{-/-}$ mice (PBS/OVA6 IL-$13^{-/-}$), and OVA sensitized and challenged IL-$13^{-/-}$ mice (OVA/OVA6 IL-$13^{-/-}$). N = 8 in each group. Means ± SEMs are shown. **P < .01 compared with the challenged-only WT group (PBS/OVA6 WT); ##P < .01 compared with the challenged-only IL-$13^{-/-}$ group (PBS/OVA6 IL-$13^{-/-}$); †P < .05 compared with the sensitized and challenged IL-$13^{-/-}$ group (OVA/OVA6 IL-$13^{-/-}$).

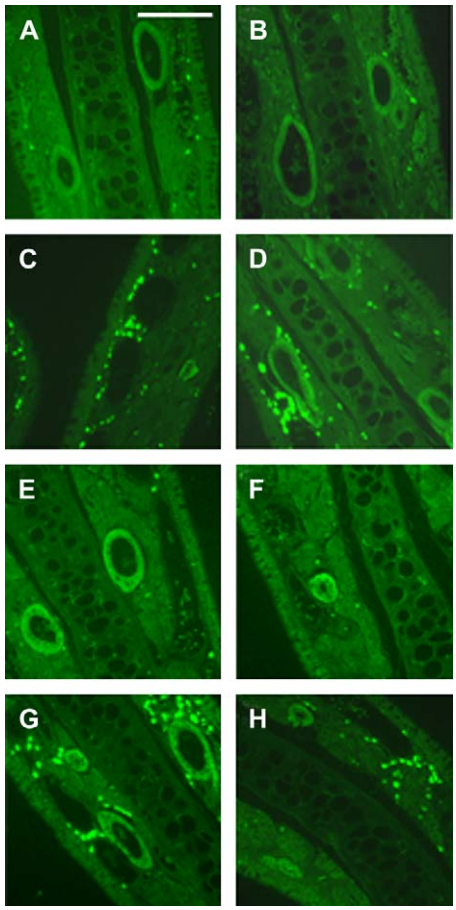

FIG 4. Eosinophil infiltration in nasal membranes. Histological assessment was carried out 24 hours after 6 allergen challenges in nonsensitized but challenged mice treated with human IgG **(A)** or sIL-13Rα2–Fc **(B)**, sensitized and challenged mice treated with human IgG **(C)** or sIL-13Rα2–Fc **(D)**, nonsensitized but challenged WT mice **(E)** or IL-$13^{-/-}$ mice **(F)**, and sensitized and challenged WT mice **(G)** or IL-$13^{-/-}$ mice **(H)**. Sections of nasal membrane tissue were stained with rabbit antimouse MBP. *Bar* = 100 μm.

Sensitization and nasal challenge with OVA increases total IgE and OVA-specific IgE and IgG_1

To assess the effect of allergen-specific antibody responses, serum levels of total IgE and OVA-specific IgE and IgG_1 were measured. OVA-sensitized WT mice, challenged 6 times, showed increased serum levels of total IgE and OVA-specific IgE and IgG_1 compared with nonsensitized and challenged mice (Table I). Total IgE and OVA-specific IgE and IgG_1 levels were similarly increased in sensitized and challenged WT mice treated with either sIL-13Rα2–Fc or control IgG (P < .01). Sensitized and (6 times) challenged IL-$13^{-/-}$ mice showed only a 50% increase in OVA-specific IgE compared with IL-$13^{+/+}$ controls, whereas total IgE and OVA-specific IgG_1 levels increased to the same levels (Table I).

Nasal eosinophil accumulation and goblet cells

After 6 days of OVA challenges, sensitized WT mice untreated or treated with control IgG demonstrated significant increases in nasal tissue eosinophil numbers compared with the nonsensitized but challenged mice (Figs 4 and 5). Mice treated with sIL-13Rα2–Fc showed similar increases in nasal eosinophil numbers comparable to the mice treated with control IgG. Sensitized and challenged IL-$13^{-/-}$ mice also showed a significant increase in eosinophilic infiltration, but it was lower than that detected in IL-$13^{+/+}$ mice (Figs 4 and 5).

IL-13 is known to be essential to the induction of goblet cell metaplasia and mucus hyperproduction in the lower airways[7] and serves as an excellent biologic marker for IL-13 levels and activity. In a previous study, we demonstrated that IL-13 levels in the nasal membranes of sensitized and challenged mice were significantly higher than in challenged-only mice.[17] To assess the effects of IL-13 on nasal goblet cell numbers in sensitized and nasally challenged mice, nasal tissue was stained and goblet cells identified and quantified. As shown in Fig 5, PAS^+ cells

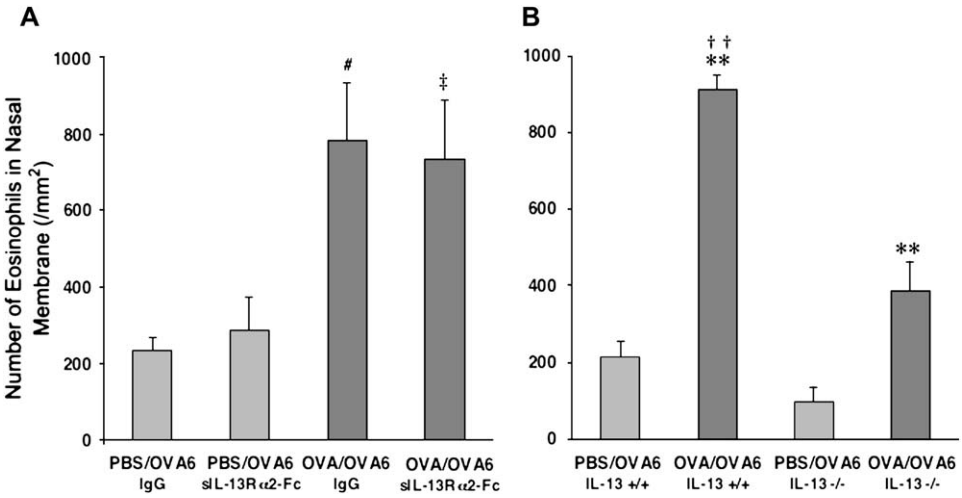

FIG 5. The number of eosinophils per mm^2 of nasal septum membrane excluding cartilage is shown. Each group n = 6 to 8. Expressed are the means ± SEMs. #$P < .05$ compared with the PBS/OVA6 treated with human IgG group; ‡$P < .05$ compared with the PBS/OVA6 treated with sIL-13Rα2–Fc group; **$P < .01$ compared with the PBS/OVA6 groups; ††$P < .01$ compared with the OVA/OVA6 IL-13$^{-/-}$ group.

were identified in all groups of mice including naive mice (Fig 6). The number of goblet cells was not altered by sensitization, challenge, or treatment (Fig 7). IL-13–deficient mice also showed nasal goblet cells, and the number was similar to those in WT mice (Figs 6 and 7).

DISCUSSION

IL-13 is an important cytokine that contributes to development of altered lower airway function and mucus hyperproduction in sensitized and challenged mice.[7-9] The IL-13 gene is expressed and IL-13 levels are increased in the nasal mucosa of both human beings[15,16] and mice[17] with AR, but its role in the development of AR has not been defined. In this study, we monitored development of early and late nasal responses[17] and demonstrated that IL-13 plays a critical role in the development of the late phase but not early nasal response. Two complementary approaches were used. In one, a specific decoy receptor for IL-13 was administered. The second used mice genetically manipulated not to express the IL-13 gene. Blockade of IL-13 was achieved after systemic administration of a soluble fusion protein sIL-13Rα2–Fc consisting of the extracellular domain of the murine IL-13 high-affinity receptor fused to the Fc portion of human IgG; this fusion protein specifically binds to and neutralizes IL-13.[20] The IL-13$^{-/-}$ mice have a disruption of the IL-13 gene[6] and cannot produce IL-13. Both approaches have been shown to be effective in normalizing airway function and airway inflammation after sensitization and challenge.[20] Both approaches demonstrated that in the upper (nasal) airways, mice administered sIL-13Rα2–Fc or IL-13$^{-/-}$ mice failed to develop the late nasal response, suggesting that IL-13 is involved in the full development of this response.

The late nasal response in mice is manifested as persistent nasal blockage 24 hours after the last allergen

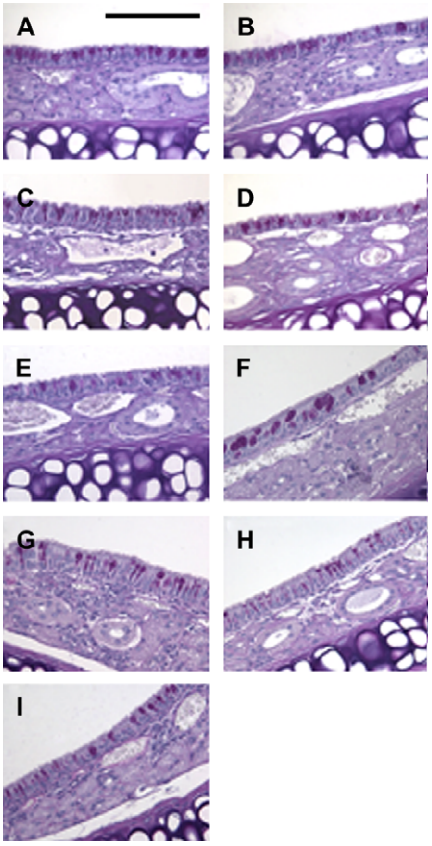

FIG 6. Tissue goblet cells. Goblet cells in nasal membranes of nonsensitized but challenged mice treated with human IgG **(A)** or sIL-13Rα2–Fc **(B)**, sensitized and challenged mice treated with human IgG **(C)** or sIL-13Rα2–Fc **(D)**, nonsensitized and nonchallenged WT mice **(E)**, nonsensitized but challenged WT mice **(F)** or IL-13$^{-/-}$ mice **(H)**, and sensitized and challenged WT mice **(G)** or IL-13$^{-/-}$ mice **(I)**. Nasal membranes were stained 24 hours after 6 allergen challenges. Sections of nasal membrane tissue were stained with PAS. *Bar* = 100 μm.

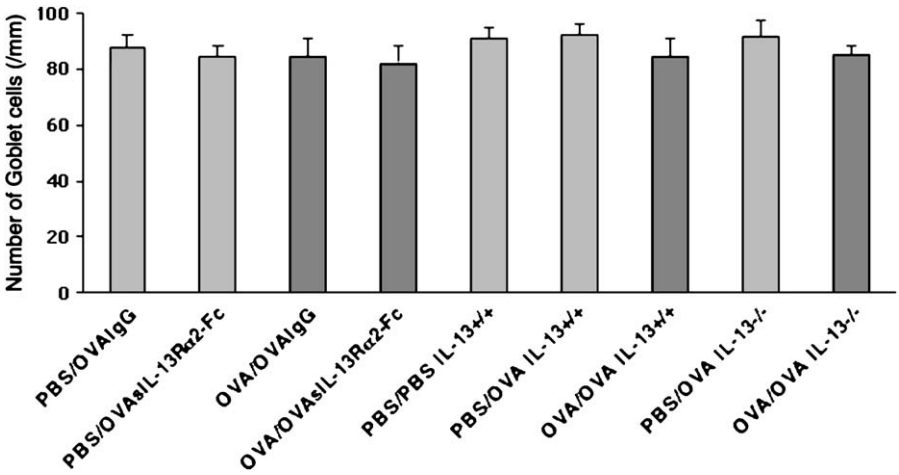

FIG 7. Goblet cells numbers in nasal membranes. The number of goblet cells is shown per mm^2 of nasal epithelial membrane. Each group n = 6 to 8. Expressed are the means ± SEMs.

challenge and is caused by nasal membrane swelling.[17] This response develops after 6 nasal challenges in sensitized mice.[17] In human beings with AR, after a single allergen challenge, approximately 30% to 40% of patients develop a late phase nasal reaction with an onset within 4 to 5 hours and peaking 6 to 12 hours after the challenge. This response is in the form of nasal obstruction, and to a lesser extent, rhinorrhea and sneezing.[21] Sustained nasal obstruction is one of the most common symptoms in chronic allergic rhinitis.[22] In situ hybridization studies have demonstrated increased mRNA expression for IL-4 and IL-5 during the late phase at 24 hours.[23,24] Elevations in IL-3 and GM-CSF expression have also been observed, but not increases in IL-2 or IFN-γ.[23] There appears to be a correlation between T_H2-type cytokine mRNA expression, particularly IL-5, and the number of activated ($EG2^+$) eosinophils in the nasal mucosa, suggesting that $CD4^+$ T-cell recruitment and activation and release of T_H2-type cytokines *in vivo* contribute to the development of the late phase response and nasal tissue eosinophilia.[23]

Previously, we demonstrated that IL-13 levels in the nasal membrane increase 24 hours after the 6th nasal challenge in sensitized WT mice associated with nasal blockage.[17] In contrast, sensitized and challenged FcεRI-deficient mice, mice with a disruption of the α subunit of the high-affinity IgE receptor, showed lower levels of IL-13 and decreases in late nasal blockage. Strikingly, the number of infiltrating eosinophils in the $Fc\epsilon RI^{-/-}$ mice was similar to WT mice, dissociating late nasal obstruction and nasal tissue eosinophilia. In the current study, sensitized and challenged mice treated with sIL-13Rα2–Fc, the late nasal response was virtually abolished, but the mice nonetheless showed similar levels of eosinophilic infiltration in the nasal membrane compared with nontreated mice. These data implicate IL-13 in the development of the late phase response, but without an obvious requirement for eosinophils. Eosinophils may still be required, because it is possible that IL-13 plays a role in eosinophil activation. In the absence of a true marker for eosinophil activation, this cannot be excluded.

Development of the early phase nasal response appears to involve a different pathway and mediators. In previous work from this laboratory, using a similar approach, treatment with sIL-13Rα2–Fc did not abolish the allergen-induced early phase lower airway response but did attenuate the late phase lower airway response.[20] sIL-13Rα2–Fc treatment similarly did not affect the early nasal response, as demonstrated in the current study. Despite being somewhat complementary, there were nonetheless some discrepancies in the results obtained after sIL-13Rα2–Fc treatment and those in the $IL\text{-}13^{-/-}$ mice. Genetically manipulated $IL\text{-}13^{-/-}$ mice are deficient in IL-13 throughout the course of the experiment, including both the sensitization and challenge phases. Treatment with the IL-13 inhibitor represents more of a conditional reduction in IL-13, initiated after completion of the sensitization phase. As a result, several of the potential IL-13–regulated responses developing before the initiation of sIL-13Rα2–Fc treatment would have proceeded in an unimpeded manner. One example is ovalbumin-specific IgE, where production is initiated during the sensitization phase and boosted by challenge. The lower levels of ovalbumin-specific IgE in the IL-13–deficient mice versus the inhibitor-treated mice perhaps account for the lower and slower but nonetheless significant development of the early phase response in these mice. Endogenous IL-13 has also been shown to be necessary to induce and sustain the increase in MHC class II expression in dendritic cells or macrophages in lung, important antigen-presenting cells.[25]

There were also differences in the degree of eosinophilic infiltration in the nasal membranes after sIL-13Rα2–Fc treatment and in $IL\text{-}13^{-/-}$ mice. The role of IL-13 in tissue eosinophil accumulation is at best controversial, at least in the lower airways. On one hand, sIL-13Rα2–Fc treatment did not significantly affect allergen-induced pulmonary eosinophilia,[7] whereas in a secondary challenge model, sIL-13Rα2–Fc treatment

suppressed eosinophilic infiltration.[20] IL-13$^{-/-}$ mice also exhibited diminished accumulation of eosinophils in the lung after intraperitoneal sensitization with alum and 18 challenges.[26] In the current study, sIL-13Rα2–Fc treatment mice showed a similar degree of eosinophil infiltration in nasal membranes as controls, whereas IL-13$^{-/-}$ mice showed a lower accumulation of eosinophils compared with IL-13$^{+/+}$ mice. Conceivably, the extent of IL-13 inhibition by sIL-13Rα2–Fc treatment was not as complete as the absolute deficiency in IL-13 mice or that IL-13 is required to some extent during the sensitization phase to elicit maximum eosinophil accumulation during the challenge phase.

It was somewhat surprising to see PAS^{+} mucus-containing cells along the nasal epithelium with no obvious decrease in mice that were IL-13–deficient or treated with the sIL-13Rα2–Fc, or no obvious increase in sensitized and challenged WT mice, which showed significantly higher IL-13 levels in the nasal membrane.[17] IL-13 has emerged as a central mediator in goblet cell metaplasia. The responses in the nasal mucosa contrast with the lower airways, where nonsensitized but challenged mice fail to show any PAS^{+} cells, and in response to sensitization and challenge, large increases in numbers of PAS^{+} cells are seen, but are virtually eliminated in IL-13$^{-/-}$ mice or sIL-13Rα2–Fc—treated mice.[7,8,20] These findings distinguish the upper and lower airways in a major allergen-induced response and may imply that at least in the upper airways, other factors can contribute to goblet cell metaplasia.[27-29]

In summary, this report demonstrates that IL-13 is a major contributor to the development of the late phase nasal response with little apparent influence on the early phase response. Targeting IL-13 may have important therapeutic benefit in the prevention of nasal blockage in allergic rhinitis, a component which is not satisfactorily treated with currently available medications.

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