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Differential Roles of IL-18 in Allergic Airway Disease: Induction of Eotaxin by Resident Cell Populations Exacerbates Eosinophil Accumulation

Emma Campbell,* Steven L. Kunkel,* Robert M. Strieter,† and Nicholas W. Lukacs*‡

Cytokine regulation during an allergic response can dictate the severity of the inflammation and resulting injury. In the present study, we have examined the systemic and local effects of IL-18, a Th1-associated cytokine, on a cockroach allergen-induced airway response. In initial studies, temporal increases in IL-18 levels were observed within the lungs. When IL-18 was neutralized systemically the allergen-associated eosinophil accumulation was significantly accelerated 5-fold by 8 h postchallenge, suggesting a regulatory role for IL-18. Recombinant IL-18 (200 ng) was instilled into the airway at the time of allergen challenge to examine whether a direct impact on local eosinophil accumulation could be induced. When IL-18 was instilled, a significant increase in peribronchial eosinophil accumulation was observed in allergic mice as well as in nonallergic mice. A possible mechanism was observed in a significant increase in eotaxin, but not other eosinophil chemotactic factors, in bronchoalveolar lavage fluid after IL-18 instillation. The role of eotaxin was confirmed using eotaxin −/− mice, which demonstrated significantly less eosinophil accumulation compared with littermate controls. IL-18 was subsequently shown to induce eosinophil production from bronchial epithelial cells and isolated macrophages in vitro assays. The clinical relevance of these findings was determined in treated mice and demonstrated that neutralization of IL-18 exacerbated, whereas exogenous IL-18 had no effect on airway hyperreactivity.

Altogether, these data demonstrate that IL-18 may have multiple functions during an immune response that differ depending upon the local or systemic effects. The Journal of Immunology, 2000, 164: 1096–1102.

T he induction and maintenance of allergic airway inflammation appears to depend on the complex interactions between a number of cytokines and chemokines. Depending on whether the system is driven toward a predominantly Th1 versus Th2 phenotype is critical in determining the direction of an inflammatory response (1–7). The onset of allergic airway inflammation is driven by a characteristic Th2 pattern of cytokines, namely, IL-4, IL-5, and IL-13. IL-4 is pivotal as the driving cytokine toward this phenotype and is important in inducing B cell growth and IgE class switching (8, 9). IL-5 plays an essential role in maintaining the survival and initiating the systemic release of eosinophils from the bone marrow leading to their accumulation around the airways, a defining hallmark of allergic asthmatic disease (10, 11). In contrast, Th1-associated cytokines are antagonistic for the induction of Th2-type responses. Accordingly, recombinant IFN-γ as well as IL-12 (a potent inducer of IFN-γ) have been demonstrated to inhibit airway eosinophilia and associated bronchial hyperreactivity in murine models of allergic airway disease (12, 13).

A recently identified cytokine, IL-18, has been described as a mediator inducing IFN-γ release from Th1 cells, CD8+ T cells, and NK cells, synergizing with IL-12 (14–20). The IL-18 receptor complex is proposed to include a low-affinity chain, IL-18R α, identified as the IL-1 receptor family member, IL-1R protein (IL-1Rrp) and a second chain, IL-18R β, that does not bind IL-18 directly, but is recruited once α-chain binding occurs (21–25). This has led to suggestions that IL-18 is related to the IL-1 family (14, 26, 27). In addition, recent evidence suggests that IL-18 augments IFN-γ production in a similar manner as IL-1. IL-1, as well as TNF, has been identified as a cytokine released early in the inflammatory response initiating cytokine cascades. These results are consistent with its ability to recruit IL-1 receptor-activating kinase, leading to the translocation of NF-κB (17, 18). The results from the present studies indicate a more complicated pleiotrophic role for IL-18 than simply induction of IFN-γ production, and may indicate a role in a broad spectrum of inflammatory events. Systemically, neutralization of IL-18 demonstrated a predicted function of altered immune regulation with exacerbated airway eosinophil accumulation and airway hyperreactivity. In contrast, local IL-18 production appears to also exacerbate eosinophil accumulation through the activation of eotaxin from local cell populations, thus demonstrating the complexity of IL-18 biology.

Materials and Methods

Animals

Female CBA/J mice were purchased from The Jackson Laboratory (Bar Harbor, ME) and were maintained under standard pathogen-free conditions. Eotaxin knockout mice and their littermate controls (F2 generation) were a gift from Dr. Rodrigo Bravo of Bristol-Myers Squibb (New York, NY) as described previously (28).

Sensitization and induction of the airway response

To induce a Th2-type response, normal mice were sensitized and challenged with cockroach allergen as described previously (29). Briefly, mice were immunized with 10 μg of cockroach allergen (Bayer, Elkhart, IN) in incomplete Freund’s adjuvant on day 0. To localize the response to the lung, the mice were given an intranasal administration of 10 μg of cockroach allergen in 10 μl of diluent on day 14. This initial intranasal challenge with Ag induced little cellular infiltrate. Mice were then challenged 6 days later by intratracheal administration of 10 μg of cockroach allergen...
in 50 µl of sterile. In depletion studies, mice were pretreated with polyclonal rabbit anti-murine IL-18 Abs (0.5 ml, titers of 10^11/mg) given i.p. at 1 h before intratracheal Ag challenge. Control animals received 0.5 ml of normal rabbit serum.

**Effect of recombinant murine IL-18 protein on airway inflammation in normal and sensitized mice**

Normal CBA/J mice were anesthetized with ketamine (Bayer), and the trachea was exposed and preholed using a 24-gauge needle before direct instillation of 200 ng of endotoxin-free recombinant murine IL-18 in 50 µl. To assess inflammatory responses in sensitized animals, mice were immunized with cockroach allergen as described above, but coadministered IL-18 (or saline/BSA vehicle as a control) with cockroach allergen during the challenge phase (60-µl volume instilled). Airway inflammation was analyzed at varying time points after instillation.

**Morphometric analysis of airway and peribronchial eosinophil accumulation**

To assess migration of eosinophils into the airway, we subjected the mice to a 1-ml bronchoalveolar lavage (BAL) with PBS containing 25 mM EDTA at various time points after challenge. The cells were then dispersed using a cytospin (Shandon, Runcorn, U.K.) and differentially stained with Wright-Giemsa stain. The cell types (mononuclear phagocytes, lymphocytes, neutrophils, and eosinophils) were expressed as a percentage based on 200 total cells counted/sample. Lung tissue was preserved with 4% paraformaldehyde at various time points after challenge. The fixed lungs were embedded in paraffin and multiple 50-µm sections were differentially stained with Wright-Giemsa for the identification of eosinophils and viewed at x1000. The individual eosinophils were counted from 100 high-powered fields per lung at each time point using multiple step sections of lung. The eosinophils counted were only in the peribronchial region; this assumed the enumeration of only those eosinophils within or immediately adjacent to an airway. The inflammation observed in this model was completely associated with the airway with little or no alveolitis.

**Isolation of leukocytes to characterize the activity/expression of IL-18**

Eosinophils were obtained from the peritoneum of Schistosoma mansoni-infected mice as described previously (30). Eosinophils were further purified using a two-step procedure including plastic plate adherence for 60 min, followed by magnetic cell separation system magnetic bead-negative selection with Abs specific for CD4, CD8, and class II-positive cell populations. The purity of the cells was >95% after the final step. Macrophages were isolated from peritoneum of normal mice using 1-ml washes of PBS containing 5 mM EDTA.

**Production of anti-IL-18 Abs**

Rabbit anti-murine IL-18 Abs were prepared by multiple-site immunization of New Zealand White rabbits with recombinant murine IL-18 (R&D Systems, Rochester, MN) in CFA. Polyclonal Abs were titred by direct ELISA and specifically verified by the failure to cross-react to mIL-1, hIL-18, TNF, mIL-2, mIL-1α, mTNF, murine macrophage-inflammatory protein-1 (mMIP-1α), IL-6, murine monocyte chemoattractant protein-1 (mMCP-1), and mIL-1β, human monocyte chemoattractant protein-1, hIL-8, hRANTES, hMIP-1α, hTNF, and hMIP-1β. The IgG portion of the serum was purified over a protein A column and used in a sandwich ELISA and for in vivo neutralization. The quality of the Ab was assessed using a Con A-stimulated lymphocyte assay and measuring IFN production. A 1:200 dilution of Ab was sufficient to inhibit the effects of 30 ng/ml of rIL-18 in vitro assays.

**Quantitation of inflammatory mediators by specific ELISA**

The levels of cytokine and chemokine proteins in whole-lung homogenate and from cell-free supernatants were measured by specific ELISA using a modification of a double-ligand method as described previously (31, 32). Briefly, lung tissue was homogenized on ice using a tissue-tearor (Biospec Products, Racine, WI) for 30 s in 1 ml of PBS containing 0.05% Triton X-100. The resulting supernatant was isolated following centrifugation (10,000 x g). Flat-bottom 96-well microtiter plates (Nunc Immunoplate 1 96-F; Nunc, Roskilde, Denmark) were coated with 50 µl/well of rabbit polyclonal Abs, specific for the cytokine/chemokine in question, for 16 h at 4°C and then washed with PBS and 0.05% Tween 20. Nonspecific binding sites were blocked with 2% BSA in PBS and incubated for 90 min at 37°C. Plates were rinsed four times with wash buffer and cell-free supernatants were added (undiluted and 1/10) followed by incubation for 1 h at 37°C. Plates were washed four times, streptavidin-peroxidase conjugate (Bio-Rad, Richmond, CA) was added, and the plates were incubated for 30 min at 37°C. Plates were washed again and chromogen substrate (Bio-Rad) was added and incubated at room temperature to the desired extinction. The reaction was terminated with 50 µl/well of 3 M H₂SO₄ solution, and the plates were read at 490 nm in an ELISA reader. Standards were 0.5 log-arithmetic dilutions of recombinant protein from 1 pg/ml to 100 ng/ml.

**Measurement of airway hyperreactivity**

Airway hyperreactivity was measured using a Buxco mouse plethysmograph which is specifically designed for the low tidal volumes (Buxco, Troy, NY) as described previously (29). Briefly, the mouse to be tested was anesthetized with sodium pentobarbital and intubated via cannulation of the trachea with an 18-gauge metal tube. The mouse was subsequently ventilated with a Harvard pump ventilator (tidal volume, 0.4 ml; frequency, 120 breaths/min; positive end-expiratory pressure, 2.5–3.0 cm H₂O; Harvard Apparatus, Holliston, MA), and the tail vein was cannulated with a 27-gauge needle for injection of the methacholine challenge. The plethysmograph was sealed and readings were monitored by computer. Since the body is a closed system, change in lung volume was monitored by a change in box pressure (Pbox) which was measured by a differential transducer. The system was calibrated with a syringe that delivered a known volume of 2 ml. A second transducer was used to measure the pressure swings at the opening of the trachea tube (Ptp), referenced to the body box (i.e., pleural pressure) and to provide a measure of transpulmonary pressure (Ptp - Pbox = Ptp). The trachea was cannulated at a constant pressure of 20 cm of H₂O. Resistance was calculated by Buxco (Groton, CT) software by dividing the change in pressure (Pbox) by the change in flow (F) (dPbox/dF; units = cm H₂O/ml/s) at two time points from the volume curve based on a percentage of the inspiratory volume. The mouse was attached to the box and ventilated for 5 min before acquiring readings. Once baseline levels were stabilized and initial readings were taken, a methacholine challenge was given via the cannulated tail vein. After determining a dose-response curve (10–500 µg/kg), an optimal dose was chosen, 50 µg/kg of methacholine. This dose was used throughout the rest of the experiments in this study and induced little change in resistance in normal nonallergic mice. After the methacholine challenge, the response was monitored and the peak airway resistance was recorded as a measure of airway hyperreactivity.

**Statistics**

Statistical significance was determined using ANOVA with p values <0.05.

**Results**

**Expression of IL-18 in the murine lung**

Because IL-18 has been identified as a Th1-associated cytokine with the ability to alter immune function, we were interested in examining the systemic and local effects on Th2-type allergic responses. To determine whether significant levels of IL-18 could be detected in lungs of normal and allergic animals, whole-lung homogenates were assayed for IL-18 by ELISA. IL-18 was detectable in whole-lung homogenates of nonsensitized, nonchallenged CBA/J mice (8.2 ± 2.3 ng/lung). Interestingly, baseline levels of IL-18 were significantly higher in allergic compared with nonallergic mice at time 0 and continued to be significantly increased over control mice throughout the response (Fig. 1). The IL-18 within the lung is likely composed of both the pro-IL-18 form and the mature IL-18 species. In comparison, very low levels of IL-12 (<0.2 ng/lung) were detected in whole-lung homogenates during the response, consistent with a strong Th2-type response. Thus, increased levels of IL-18 could be detected locally within the lung during this IL-4-dependent, Th2-type response.

**Effect of Abs to IL-18 on airway inflammation associated with cockroach Ag sensitization and challenge**

The sensitization and challenge of animals with cockroach allergen is associated with an increase in peribronchial accumulation of
eosinophils (29). To determine whether IL-18 had a regulating role during the response, we treated animals with Abs specific for IL-18 and examined the inflammation that followed. Pretreating sensitized mice with Abs to IL-18 at 1 h before challenge greatly accelerated eosinophil accumulation at 8 h after challenge compared with normal rabbit serum controls (Fig. 2). By 72 h, there was little difference observed between control Ab and anti-IL-18 Ab-treated groups. Altogether, these data follow previous work with IL-18 indicating that it is a Th1-associated cytokine that is antagonistic to a Th2-type allergic airway response.

Effect of exogenous IL-18 on allergic airway responses

Since our studies with Abs against IL-18 suggested that this cytokine might confer a protective effect against inflammation during allergy, we were interested in whether recombinant IL-18 given locally within the airway would be beneficial. Sensitized mice were intratracheally cochallenged with Ag plus either IL-18 (200 ng/ml) or vehicle, and the inflammatory response was analyzed at various time points thereafter. The administration of rIL-18 had a surprising effect on the allergic airway inflammation (Fig. 3A). Examination of the peribronchial accumulation indicated no significant effect on the response at 8 h; however, a significant increase in eosinophils by 24 h after allergen challenge in the IL-18 to the control-treated group. Likewise, when eosinophils were examined in the BAL fluid a 4-fold increase in the number of eosinophils was detected in IL-18 compared with control-treated animals (Fig. 3B). Interestingly, the addition of exogenous IL-18 (200 ng) into the airway induced the production of IFN-γ (70 ± 8 pg/ml BAL), whereas allergen-only-treated animals had no detectable IFN-γ (<10 pg/ml). Lower doses of IL-18 (10 ng) had no effect on eosinophil accumulation or IFN-γ production (data not shown). Overall, the local role of IL-18 may be different from that of the systemic function elucidated by neutralization of IL-18 and by other investigators when IL-18 was given exogenously during sensitization in a systemic manner (33).

To investigate the role of IL-18 locally in the airway under nonallergic conditions, we assessed the effects of direct instillation of the rIL-18 in naive mice at various time points. At 8 h after instillation, neither rIL-18 nor vehicle induced any detectable accumulation of leukocytes around the airway, as observed with the allergen model above. However, at 24 h after instillation, a 2-fold increase in eosinophil accumulation around the airway was observed in IL-18-instilled compared with vehicle-instilled time-matched controls (Fig. 4A). Because there was delay in eosinophil accumulation in both allergic and naive mice, we hypothesized that intermediary eosinophil chemotactants might be induced by IL-18. Evaluation of BAL samples from naive animal studies demonstrated elevated eotaxin levels in IL-18 compared with vehicle-instilled animals at 24 h (Fig. 4B). No difference in eotaxin was
observed at 8 h after instillation. Other eosinophil chemoattracts were also examined, including MIP-1α, RANTES, monocyte chemoattractant protein-3, leukotriene B4, as well as histamine levels, and no significant differences were detected in IL-18 compared with vehicle-instilled animals. Importantly, to determine whether IL-18 had any direct effect on eosinophil migration, we examined this cytokine using a modified Boyden chamber with isolated eosinophils (95% purity). IL-18 did not directly induce eosinophil migration and had no significant effect on the migration induced by eotaxin or other chemotactic factors (data not shown). These unexpected observations of IL-18-induced eosinophilia demonstrated that although IL-18 may have the ability to participate in a Th1-type response, it also appears to be able to induce eotaxin production and increase eosinophilia in both allergic and naive mice.

To further examine the ability of IL-18 to induce eosinophilia through eotaxin generation, we instilled IL-18 into eotaxin −/− and littermate control mice. When we instilled rIL-18 into naive mice, a significant eosinophil accumulation was observed in wild type, but not eotaxin knockouts by 24 h after instillation (Fig. 5), confirming our previous results. No eosinophils were found in vehicle control-instilled mice. However, because there were some eosinophils that accumulated around the airways of eotaxin −/− mice when IL-18 was instilled, eosinops appears not to be the only factor involved. In additional experiments when we attempted to instill eotaxin directly into the airways of normal and allergic mice, few eosinophils could be found (data not shown). Thus, other events related to chemotaxis must also be controlled by IL-18. We also examined changes in eotaxin levels in systemically delivered anti-IL-18 experiments and found no significant difference in eotaxin levels in the local environment of the lung (data not shown), suggesting only an extrapulmonary effect during Ab administration.

**Effect of IL-18 on eotaxin release in vitro from individual cell populations**

We were next interested in the possible source of the IL-18-induced eotaxin production. Since epithelial cells and macrophages have been identified as a source of eotaxin in the lung, we examined the direct effect of IL-18 on cultures of isolated primary macrophages and on a murine bronchial epithelial cell line, LA4. IL-18 induced eotaxin release from both cell populations after 24 h of culture (Fig. 6). Although both the macrophages and epithelial cells produced constitutive levels of other chemokines, IL-18 only increased the production of eotaxin, consistent with the above in
FIGURE 7. Neutralization of IL-18 exacerbates airway hyperreactivity. Allergic mice were pretreated 1 h before allergen challenge with 0.5 ml of anti-IL-18 or control Ab i.p. In the same experiment, allergic mice were treated with rIL-18 (200 ng) intratracheally at the time of allergen challenge. Airway hyperreactivity was then evaluated after a methacholine challenge (50 μg/kg) via the tail vein at 24 h after challenge. Data represent means ± SE of the change in resistance after methacholine challenge of five mice per time point. *, p < 0.05.

vivo data. These data indicate that IL-18 can act as a potent activating factor with specific effects on a broad range of cell populations.

**Altered airway hyperreactivity in IL-18-depleted animals**

To determine whether the increased eosinophil accumulation had an effect on the physiological function of the response, treated mice were subjected to analysis of airway hyperreactivity. Using a mouse plethysmograph, mice treated with either anti-IL-18 or rIL-18 as above were ventilated, challenged with methacholine (50 μg/kg) i.v., and the airway hyperreactivity evaluated 24 h after allergen challenge (peak hyperreactive response). The data in Fig. 7 demonstrate that neutralization of IL-18 with specific Abs significantly exacerbated the airway hyperreactive response. In contrast, the introduction of exogenous IL-18 (100 ng/mouse) had no effect on the airway hyperreactivity, even though an increase in eosinophil accumulation was observed. Histological examination of the allergic mice treated with either anti-IL-18 or rIL-18 demonstrated differences in the intensity and the total number of eosinophils as well as mononuclear cell populations by 24 h after stimulation (Fig. 8). Altogether, these data demonstrate the importance of endogenous IL-18 for regulation of eosinophilia and airway hyperreactivity, whereas exogenous IL-18 treatment increased only the inflammatory component (especially eosinophils).

**Discussion**

The fine balance of cytokine cascades is critical in determining the evolution of an inflammatory response. The induction of a Th2 response is pivotal in the development and maintenance of allergic airway inflammation (2, 5, 34–36). It is not surprising therefore that considerable interest has focused on the Th1 cytokines that modulate allergic processes. IFN-γ has previously been demonstrated to attenuate eosinophilia associated with a murine model of allergic airway inflammation, as has IL-12, a potent inducer of IFN-γ (12, 13, 37, 38). Therefore, in our studies using a murine model of cockroach Ag-induced allergy, we were not surprised that neutralization of endogenous IL-18, a recently identified inducer of IFN-γ production (14, 15, 39), exacerbated eosinophilic airway inflammation and airway hyperreactivity. In these experiments, Abs were administered systemically before allergen challenge, and our results indicate that the presence of IL-18 during the induction of the allergic response might have a modulating effect on the subsequent airway inflammation. Interestingly, recent studies indicate that IL-18 receptor expression was selective for naive and Th1-type lymphocytes, but not Th2-type lymphocytes (22). In the present studies, it was surprising that exogenous recombinant murine IL-18 protein administered intratracheally to both normal and sensitized mice (at the time of allergen challenge) exacerbated the eosinophil response around the airways. Only a relatively high (pharmacologic), but not a lower (physiologic), dose of IL-18 induced the observed changes. A logical hypothesis is that IL-18 might generate an intermediary factor with eosinophil chemoattractant activity. A number of CC chemokines have been implicated in the pathogenesis of allergic airway inflammation by virtue of their ability to induce the selective migration of eosinophils as well as the fact that their production is up-regulated during human asthma (29, 40–47). We observed that the localized administration of IL-18 to the lung was associated with increased eotaxin levels in the airway. The proinflammatory and eosinophil accumulation effects of IL-18 in naive mice could be attenuated in eotaxin knockout mice compared with their littermate controls. Eotaxin was originally isolated from the BAL fluid of sensitized guinea pigs after allergen challenge and subsequently characterized as being a potent chemoattractant/activating factor for not only eosinophils, but also basophils and Th2 lymphocytes (48–51). Additional in vitro experiments revealed that IL-18 induced the release of eotaxin from isolated macrophages and cultures of a bronchial epithelial cell line. Thus, local IL-18 appears to increase eosinophil accumulation via eotaxin production from multiple cell populations.

Although the treatment of allergic mice with either anti-IL-18 or rIL-18 induced similar increases in eosinophil accumulation, the airway hyperreactivity responses demonstrated significant differences. The systemic neutralization of IL-18 drastically exacerbated airway hyperreactivity correlating with the increase in eosinophil accumulation, whereas local IL-18 administration had no significant effect on airway hyperreactivity. These studies suggest that the presence of eosinophils alone may not be enough to alter the response. Although we were not able to detect changes in IFN-γ, the neutralization of IL-18 may significantly alter the regulation of Th1- vs Th2-type responses. Previous studies have clearly indicated that IFN-γ has a regulatory effect on airway hyperreactivity responses. Furthermore, even though the eosinophil recruitment was augmented in the animals treated with IL-18, the physiological response was possibly kept in control by the presence of additional IFN-γ. Interestingly, examination of the histological section demonstrated an increase in eosinophil and mononuclear cell infiltration in both the anti-IL-18- and rIL-18-treated animals. The further dissection of these subpopulations may help to elucidate the differences in these two groups.

The ability for IL-18 to enhance inflammation locally during allergic airway responses differs from a previous study demonstrating that IL-18 can attenuate the eosinophil accumulation and airway responses (33). However, these previous studies administered the cytokine i.p. before allergen challenge during the sensitization phase and found an effect only in the presence of IL-12. In a systemic setting, IL-18 may impact the response primarily at the regional lymph nodes, altering the evolution of the response during the active immunization process. Our data would concur with these observations because the systemic neutralization of IL-18 up-regulated the eosinophil-associated responses. In contrast, when exogenous IL-18 was administered locally to the lung at the time of allergen challenge in the present studies, the effect was on increased eotaxin in the airway leading to enhancement of the chemoattractant gradients and eosinophil accumulation. In addition, IL-18 has recently been shown to increase ICAM-1 expression in epithelial cell populations (52), possibly further explaining how
rIL-18 could directly induce eosinophil accumulation around the airways of naive mice. These results are especially intriguing when considering recent studies that demonstrate that Th1-type cells have no apparent regulatory effect on an allergen-specific response and possibly intensify the inflammation and local damage in the lung (53, 54). Since levels of IL-18 in the lung increase during allergy, the local release of IL-18 may be physiologically relevant during the inflammatory response and enhance the increase of eosinophil accumulation. IL-18 has been reported to behave in a manner similar to IL-1, and it would, therefore, not be surprising to find that the two had similar pleiotropic functions. This may help explain why IL-18 cannot only induce eotaxin but also induce an “inflamed” environment in normal mice sufficient for eosinophil recruitment. Interestingly, preliminary experiments in our laboratory have demonstrated that a number of cell populations isolated from the lung can produce IL-18, including fibroblasts and smooth muscle cells (our unpublished data). Thus, locally generated IL-18 from multiple cell populations may alter the response in the airway without impacting on the overall Th cell phenotype generated in the draining lymph nodes. Overall, these studies suggest an ability of IL-18 to differentially effect an allergic response and further emphasize the importance of fully investigating and understanding the biology of immune mediators.

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