

Role of IL-9 in the pathophysiology of allergic diseases

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Considerable evidence from both human and animal studies indicates that CD4⁺ cells are the predominant cell type involved in the regulation of airway inflammation through the expression of T_H2-type cytokines. The effects of T_H2-type cytokines, particularly IL-4 and IL-5, on inflammatory and structural cells in airways have been studied in great detail. They were shown to be important for inflammatory cell maturation, activation and proliferation, IgE production, chemokine expression, mucus secretion, and bronchial hyperresponsiveness. Recent work has shown the potential importance of another T_H2-type cytokine, IL-9. The development of transgenic mice overexpressing IL-9 has suggested a key role for this cytokine in the development of the asthmatic phenotype, including eosinophilic inflammation, bronchial hyperresponsiveness, elevated IgE levels, and increased mucus secretion. IL-9 has been shown to act on many cell types involved in asthma, including T cells, B cells, mast cells, eosinophils, neutrophils, and epithelial cells, and thus might be important in the pathophysiology of allergic asthma. (J Allergy Clin Immunol 2001;107:575-82.)

Key words: IL-9, inflammatory cells, cytokines, asthma, bronchial hyperresponsiveness

IL-9 is a T_H2-type cytokine first described in the mouse as a potent T cell and mast cell growth factor.¹⁻³ This pluripotent regulatory cytokine inhibits lymphokine production by IFN- γ -producing CD4⁺ T cells and promotes proliferation of CD8⁺ T cells.⁴ Moreover, IL-9 promotes the production of IgE by B cells,⁵ induces chemokine and mucus secretion by bronchial epithelial cells,^{6,7} and leads to mast cell proliferation.⁸ Recently, a number of key observations have suggested that this cytokine may play a prominent role in asthma pathology. Linkage analysis studies have demonstrated an associa-

Abbreviations used

AP:	Activator of protein
BHR:	Bronchial hyperresponsiveness
IL-9R:	IL-9 receptor
NP:	Nasal polyposis
PMN:	Polymorphonuclear neutrophil
STAT:	Signal transducer and activator of transcription

tion between the *IL9* gene locus and atopy, including both elevated serum IgE levels and airway hyperresponsiveness.⁹⁻¹¹ This review includes a brief description of the IL-9/IL-9 receptor (IL-9R) system, as well as the IL-9-producing cells. The focus, however, will be on the effects of this cytokine on inflammatory cell types associated with allergic diseases.

THE STRUCTURE AND GENOMIC ARCHITECTURE OF IL-9/IL-9R

IL-9

IL-9 is a member of the 4-helix bundle cytokine family, which includes cytokines, such as IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, and IL-15. Both human IL-9 and murine IL-9 consist of a 14-kd glycoprotein, the mature form of which is composed of 144 amino acids along with a signal sequence of 18 amino acids.^{2,12,13} The IL-9 protein contains a high proportion of cationic amino acid residues and 10 cysteines and has 4 N-linked glycosylation sites. The homology between human and murine IL-9 is 55% at the protein level and 69% at the nucleotide level.² Murine IL-9 has been shown to be active on human cells, but the human form is not active on murine cells.²

The human *IL9* gene has been shown to reside within the T_H2 cytokine cluster in the region q31-35 on chromosome 5.^{14,15} This region, found on the long arm of the chromosome, has also been shown to contain the closely linked genes encoding for IL-3, IL-4, IL-5, and GM-CSF.^{9,16} The mouse *IL-9* gene, however, has been localized on chromosome 13.¹⁷ Both human and murine genes encoding IL-9 exhibit similar genomic organization and are composed of 5 exons and 4 introns over approximately 4 kb.² The 5' flanking regions of both mouse and human genes have shown specific binding sequences for the activator of protein 1 (AP-1) and AP-2 transcription

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factors, which may explain the induction of IL-9 by phorbol esters.² Moreover, a consensus sequence for IFN-regulating factor 1 was also identified in the 5' promoter region, the functional significance of which has yet to be elucidated. Indeed, the 5' regulatory region of the *IL9* gene was found to contain sequences also seen in similar regions of the *IL1*, *IL2*, *IL3*, *IL4*, *IL5*, *IL6*, and *GM-CSF* genes, suggesting common regulatory mechanisms.¹⁸

IL-9R

The IL-9R belongs to the hematopoietin receptor superfamily, which includes many other cytokine receptors, such as IL-2, IL-3, IL-4, IL-5, IL-7, and IL-10 receptor. The IL-9R consists of a ligand-specific α subunit (IL-9R α) and a common γ_c chain also present in IL-2, IL-4, IL-7, and IL-15 receptor complexes.¹⁹ IL-9R α can be produced in both soluble and membrane-bound forms.

The human *IL9RA* gene is located in the long arm pseudoautosomal region of the X_q and Y_q chromosomes close to the telomere.²⁰⁻²² The gene is composed of 11 exons and 10 introns over an approximate range of 17 kb.²¹ The murine *IL9RA* gene has been located on chromosome 11.²² Analysis of the 5' flanking region of the human *IL9RA* gene has revealed no TATA box and has demonstrated possible binding sequences for AP-1, AP-2, AP-3, and nuclear factor κ B transcription factors,²¹ illustrating a potential transcriptional control of the *IL9RA* gene.

The human IL-9R α gene product is a protein composed of 522 amino acid residues showing 53% homology with its 468 amino acid murine counterpart.²³ Subsequently, several structural variants of the *IL9RA* have been identified.²¹ More recently, a common splice variant of the *IL9RA* gene that is incapable of binding IL-9 and mediating signal transduction was found and may be involved in downregulating IL-9R function.²⁴

The signal transduction in IL-9-mediated responses has been shown to be dependent on the Janus kinase-signal transducer and activator of transcription (STAT) pathway. Demoulin et al²⁵ observed the constitutive association of Janus kinase 1 with the IL-9R and noted the presence of IL-9-induced activated complexes containing STAT-1, STAT-3, and STAT-5. This was confirmed by the observed presence of STAT-1 and STAT-3 homodimers and STAT-1/STAT-3 heterodimers after heteromerization of IL-9R α and common γ subunits.²⁶ The reported activation of STAT factors has been shown to be required in IL-9-induced proliferation and inhibition of glucocorticoid-induced apoptosis in T cells.^{26,27} Mutations resulting in the upregulation of STAT-5 activation led to enhanced lymphoid tumorigenesis, illustrating the key role that the STAT proteins play in IL-9 transduction and T-cell development.²⁸

CELLULAR SOURCES OF IL-9

T cells

Clinical studies, as well as murine models, have shown that T cells play a central role in asthma. In respect to the profile of cytokines, local T_H2-type profile of cytokines, including IL-9, has been shown to be pro-

duced within the airways of asthmatic subjects.^{29,30} The major cellular source of IL-9 is the T lymphocyte, notably that of the CD4⁺ T_H2 subset,^{2,31} which is consistent with in vivo data from asthmatic subjects.²⁹ Strong expression of IL-9 was observed after the stimulation of human PBMCs with anti-CD3 antibodies, and this expression was significantly enhanced by the presence of various T-cell mitogens, including phorbol myristate acetate.² Subsequently, evidence from in vitro studies has shown the involvement of many cytokines in *IL9* gene expression. IL-2 has been shown to induce IL-9 expression in both normal and leukemic phorbol myristate acetate-stimulated human T cells, which was suppressed by anti-IL-2 antibody³² but reversed by the addition of IL-4 and IL-10.³³ Further analysis of the kinetics of cytokine expression suggest that a cascade of cytokines are involved in IL-9 expression. IL-2 is required for IL-4 production, a combination of IL-2 and IL-4 is required for IL-10 production, and a combination of IL-4 and IL-10 is required for IL-9 induction.³³

In the murine system IL-9 production involves both IL-4-dependent⁴ and IL-4-independent pathways.³⁴ IL-10 has shown a modulatory influence on IL-9 induction in the mouse,³⁴ and the presence of IL-2 is required for murine production of IL-9.³⁵ Interestingly, cultured naive CD45 RA⁺ T cells have been shown to produce IL-9 after addition of IL-4 and IL-10, suggesting that cytokine production by naive T cells can in fact be modulated by factors produced by activated CD45 RO⁺ T cells during a polyclonal immune response.³³

Mast cells

Mast cells within the airways of asthmatic subjects are known to be a source of cytokines. The range of cytokines produced by mast cells includes T_H1-type (IFN- γ and IL-12) and T_H2-type (IL-4, IL-5, and IL-13) cytokines.³⁶⁻³⁸ Recently, mast cells have also proven to be potent producers of IL-9. In cultured murine bone marrow-derived mast cells, IL-1, in combination with either ionomycin or IgE-antigen complexes, induced an increase in expression of IL-9 protein and mRNA.³ A related study by the same group found a marked increase in IL-9 mRNA and protein production in activated murine bone marrow-derived mast cells after stimulation with kit ligand or IL-10.³⁹ Detailed analysis revealed that IL-10, as well as kit ligand, increased the promoter activity. In this system anti-IL-4R and anti-IL-10 neutralizing antibodies significantly reduced the production of IL-9 by murine bone marrow-derived mast cells.^{3,39} These studies indicate that the regulatory mechanisms for IL-9 generation by mast cells involve cytokines that also participate in the regulation of T_H2 cells and of naive CD4⁺ T cells.

On the basis of this finding, it is tempting to speculate that the production of IL-9 by mast cells could play a prominent role in the development of late asthmatic reactions. Furthermore, IL-9 production can be augmented by IL-1, which can be detected in airway walls during late asthmatic reactions,⁴⁰ and this effect can be further enhanced by IL-10 and kit ligand, which are both produced

by bronchial epithelial cells.^{41,42} Recently, it has been reported that intratracheal injections of kit ligand increase airway hyperreactivity in allergic and normal mice.⁴³

Eosinophils

We have recently demonstrated the expression of IL-9 mRNA in human peripheral blood eosinophils, as well as in an eosinophil-differentiated HL-60 cell line.⁴⁴ The expression of IL-9 was shown to be heterogeneous among individual donors, yet there was a significant difference between the percentage of IL-9⁺ eosinophils in asthmatic subjects compared with normal control subjects, as determined by means of immunocytochemistry and in situ hybridization.⁴⁴ The study also showed detectable levels of IL-9 released into the medium by eosinophils from asthmatic subjects. Culturing these cells with TNF- α or IL-1 β led to increased levels of IL-9 in the supernatant. In contrast, eosinophils from normal control subjects show no spontaneous release of IL-9, suggesting that in vivo eosinophils from asthmatic subjects are somehow primed or activated. Traditionally, eosinophils have been viewed as effector cells in the development of the inflammatory response. However, it is now clear that these cells may also play an active role in the modulation and potentiation of the immune response through their ability to produce pluripotent cytokines, including IL-9.

REGULATORY ROLE OF IL-9 IN INFLAMMATORY CELLS ASSOCIATED WITH ALLERGIC DISEASES

The regulatory role of IL-9 in inflammatory cells associated with allergic diseases is illustrated in Fig 1.

T lymphocytes

IL-9, originally called P40 or T cell–derived growth factor III, showed a distinct ability to support the growth of cultured helper T cells in the absence of antigen, and this was shown to be independent of IL-2 and IL-4.¹ Recently, IL-9 demonstrated an ability to rescue T_H2-type T-cell clones from apoptosis induced by deprivation of IL-2, and the expression of IL-9R α was necessary for the antiapoptotic signals mediated by IL-9.⁴⁵ IL-9 has been shown to inhibit dexamethasone-induced apoptosis in a thymic lymphoma cell line and murine factor–dependent T-cell line.^{46,47} In vivo studies have shown that airway selective overexpression of IL-9 in the lung of transgenic mice resulted in T-cell infiltration.⁴⁸ Interestingly, it has been found that signaling through the α chain of the IL-9R led to an increase in the number of developed T cells in a fetal thymus organ-culture system.⁴⁹ Along with the data from IL-9–transgenic mice, this suggests that IL-9 plays a critical role in the early stages of T-cell development.

Mast cells

Mast cells play a central role in inflammatory and immediate allergic reactions. Cross-linking of allergen-

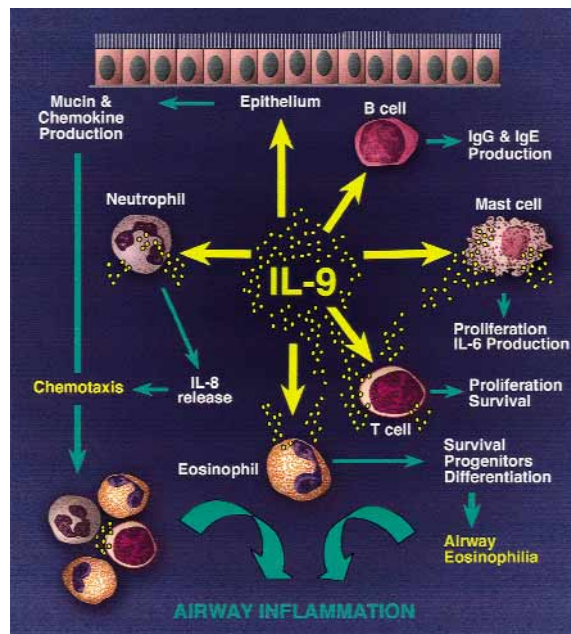


FIG 1. Potential role of IL-9 during allergic inflammation in the airways. IL-9, a T_H2 cytokine, has a pleiotropic activity on inflammatory and structural cells associated with asthma, such as mast cells, T cells, eosinophils, and epithelial cells. Within the lung, IL-9 is mainly produced by T cells and, to a lesser extent, granulocytes. The effect of IL-9 (yellow arrows) leads to various immunologic processes (green arrows), including eosinophil survival, chemokines, and mucus production. These pathways may provide a potential mechanism to explain airway inflammation.

specific IgE bound to high-affinity receptors for IgE on mast cells leads to cell activation and release of potent inflammatory mediators. These mediators act on the vasculature, smooth muscle, connective tissue, mucous glands, and inflammatory cells, leading to bronchoconstriction and enhancement of airway inflammation.^{50,51} Studies in vitro have shown that recombinant IL-9 supported the growth of bone marrow–derived mast cell lines,^{1,2} induced IL-6 secretion by these cells, and led to increased survival and proliferation of primary mast cell cultures.⁸ Moreover, recombinant IL-9 in the presence of kit ligand led to enhanced long-term survival of murine bone marrow–derived mast cells.⁵² These studies provide a mechanistic explanation for the increased number of mast cells observed in the airway epithelium of IL-9–transgenic mice.⁴⁸ This also suggests that the accumulation of mast cells within the airways of asthmatic subjects may be particularly attributed to the recruitment, enhanced survival and proliferation, or local differentiation of mast cells as a consequence of IL-9 produced by T_H2 lymphocytes.

B lymphocytes

Studies in transgenic mice overexpressing IL-9 showed increased serum levels of all Ig isotypes, including IgE,^{53,54} accompanied by an expansion of lymphocytes from the B1 subset (Mac⁺ IgM⁺).⁵⁴ Furthermore, accumulation of B cells has been detected in the lungs of IL-

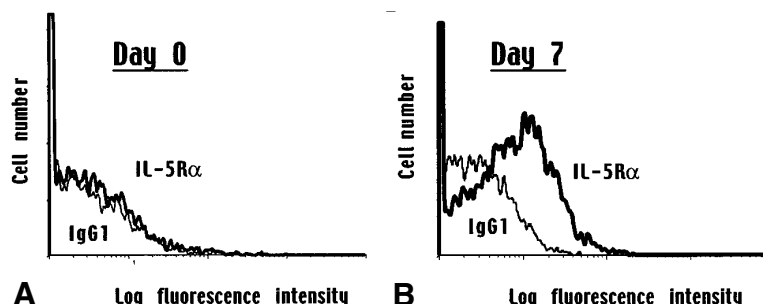


FIG 2. Effect of IL-9 on IL-5R α expression by human CD34 $^{+}$ progenitor cells. Human umbilical cord blood CD34 $^{+}$ progenitor cells were cultured with IL-9 alone (1 ng/mL) or IL-3 and IL-5 (1 ng/mL each). Initial plating density was 1×10^5 cells/mL. **A**, Flow cytometric analysis of IL-5R α expression by CD34 $^{+}$ cells at day 0 and after culture in IL-9 at 1 ng/mL for 7 days. One representative experiment of 5 is shown. (From Soussi-Gounni et al. *Blood* 2000;96:2163-71. Copyright the American Society of Hematology.)

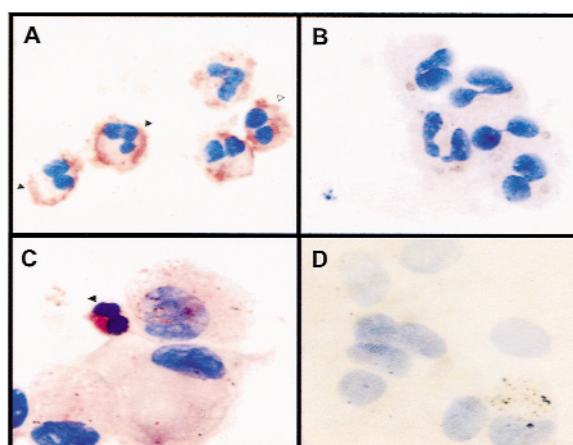


FIG 3. Detection of IL-9R immunoreactivity on peripheral blood and BAL eosinophils. **A**, Specific staining was detected on the cell membrane (filled arrow), as well as the cytoplasm (open arrow), of purified peripheral blood human eosinophils. **C**, Positive staining in a BAL eosinophil (filled arrow) from an asthmatic individual. Normal rabbit serum was used as the negative control for the peripheral blood eosinophils (**B**) and BAL cells (**D**). (From Soussi-Gounni et al. *Blood*. 2000;96:2163-71. Copyright the American Society of Hematology.)

9-transgenic mice.⁴⁸ Although there is no evidence to prove this in human subjects *in vivo*, IL-9 potentiated IL-4-induced IgE and IgG production in cultured human peripheral blood B cells.⁵⁵ A similar potentiation of IL-4-induced production of IgG1 and IgE was seen in murine B lymphocytes, with no effect on B-cell survival.⁵ More recently, the production of IgE and IgG4 induced by IL-7 in human PBMCs was potentiated by the presence of T cells and factors, such as IL-9 and soluble CD23. Neutralizing anti-IL-9 and anti-CD23 antibodies led to decreased IL-7-induced IgE synthesis.⁵⁶ Thus it is thought that IL-9 plays a key role in the regulation of Ig synthesis through a direct action on B lymphocytes, probably of the B1 subset. Combined with observed IL-9-mediated induction of the high-affinity IgE receptor and inflammatory mediators,^{3,52,57} this might offer an explanation for the mechanism by which IL-9 may enhance IgE-based inflammation and hyperresponsiveness in asthma.

Eosinophils

Airway eosinophilia has been recognized as a predominant feature of allergic asthma, and elevated numbers within the inflammatory infiltrate are often associated with disease severity.^{58,59} Eosinophil-derived proinflammatory and profibrotic mediators lead to tissue damage and chronic changes in airway structure and function.^{60,61} Clinical and experimental evidence suggests that T lymphocytes elicit an indirect albeit critical role in allergic inflammation and the associated symptomology by increasing the level of circulating eosinophils, upregulating their adhesive and migratory properties, and prolonging their survival in tissue sites. This enhanced survival is mediated through the production of T_H2-type cytokines, including IL-4 and IL-5. IL-5, along with IL-3 and GM-CSF, induces the differentiation of eosinophils from progenitors in the bone marrow, increases the pool of available eosinophils in the circulation, and promotes local eosinophil survival. Marked eosinophilia was observed in transgenic mice that overexpress IL-9^{6,48} and in naive mice administered with recombinant IL-9 intratracheally.⁶² Previous studies have demonstrated the important role of IL-5 in the enhancement of terminal differentiation of committed eosinophil precursors.⁶³ Increased responsiveness of eosinophil progenitor cells to IL-5 may be a key factor in the development of blood and tissue eosinophilia. We have investigated the link between IL-9 and IL-5 in relation to eosinophil differentiation and survival. The addition of IL-9 to CD34 $^{+}$ cells cultured in IL-3 and IL-5 was shown to enhance eosinophil development. Moreover, IL-9 alone was demonstrated to upregulate the expression of IL-5R α on human CD34 $^{+}$ cord blood progenitor cells (Fig 2).⁶⁴ The same study also observed IL-9-induced upregulation of IL-5R α during terminal eosinophil differentiation of the HL-60 cell line. These data suggest that by increasing responsiveness of precursor cells to other cytokines, such as IL-5, IL-9 can in fact promote tissue eosinophilia. The expression of IL-9R α by mature human peripheral blood eosinophils was also demonstrated at the mRNA and protein level (Fig 3).⁶⁴ Functional analyses demonstrated that recombinant human IL-9 inhibited *in vitro* human peripheral blood eosinophil apoptosis (Fig 4).⁶⁴ These result in mature eosinophils com-

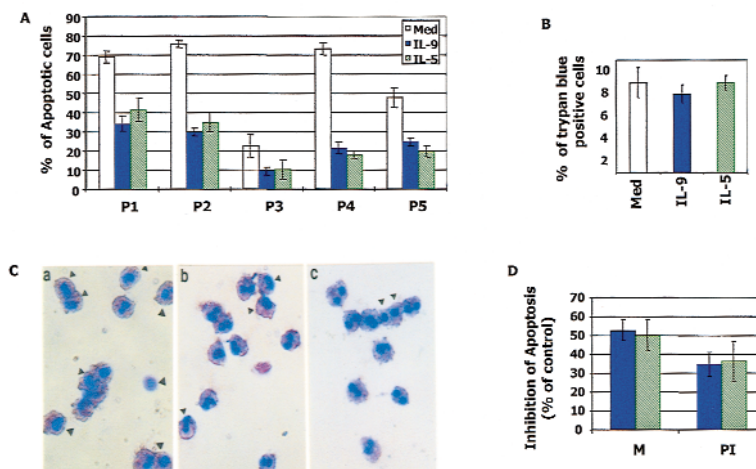


FIG 4. Effect of IL-9 on peripheral blood human eosinophil survival. **A**, Percentage of apoptotic eosinophils from different patients treated for 18 hours with IL-9 (filled bar), IL-5 (dashed bar), or medium alone (open bar). **B**, No significant difference in cell viability was observed among the 3 culture conditions at 18 hours, as assessed by trypan blue exclusion. **C**, Morphologic alteration of nuclei was evaluated by using Diff-Quick staining. Freshly purified peripheral blood eosinophils stimulated with IL-9 (10 ng/mL, panel b) or IL-5 (10 ng/mL, panel c) showed less apoptotic cells (indicated by arrows) compared with medium alone (panel a). **D**, Similar results were obtained with either morphology assessment (M) or DNA fragmentation assay with propidium iodide (PI) and flow cytometric analysis. DNA fragmentation was assessed by means of analysis of the staining characteristics of fixed permeabilized cells exposed to the DNA binding dye propidium iodide. Analysis was performed by using flow cytometry on a FACScan machine. Data are given as means $\pm$ SD of 3 independent experiments. (From Soussi-Gounni et al. *Blood* 2000;96:2163-71. Copyright the American Society of Hematology.)

combined with noted effects on CD34⁺ hematopoietic progenitors suggest a mechanism by which IL-9 may potentiate in vivo eosinophil function and tissue eosinophilia through inhibition of apoptosis and promotion of IL-5-mediated eosinophil differentiation and maturation.

Neutrophils

Recently, it has been demonstrated that polymorphonuclear neutrophils (PMNs) can not only produce a number of functionally diverse substances, including cytokines, but also express receptors that have been implicated in different inflammatory reactions, including allergy.^{61,65-67} The expression of IL-9R α has been observed in freshly isolated human peripheral blood PMNs, as well as in BAL-derived PMNs from asthmatic patients (Fig 5).⁶⁸ The expression of the IL-9R α protein on human PMNs was widely heterogeneous, but a significant difference was found between the percentage of IL-9R α ⁺ PMNs in asthmatic subjects compared with normal control subjects, suggesting that the expression of IL-9R α is under regulatory control. Previous reports have indicated that T_H2 cytokines, particularly GM-CSF and IL-4, exert several actions on PMNs, including stimulation or alteration of surface receptor expression.⁶⁹⁻⁷¹ We have shown that both IL-4 and GM-CSF upregulate the expression of IL-9R α in PMNs.⁷² IL-9 has also been shown to induce the production and release of IL-8 by human PMNs from asthmatic subjects in a dose-dependent manner, an effect that was blocked by anti-IL-9 neutralizing antibody (Fig 6).⁶⁸ Moreover, the use of anti-IL-9 neutralizing antibody had no effect on GM-CSF-induced IL-8 release. These

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FIG 5. Detection of IL-9R immunoreactivity on human peripheral blood and BAL PMNs. A representative example of IL-9R α immunopositive cells in peripheral blood PMNs and BAL from an asthmatic donor (**A** and **B**). Specific staining was detected by using anti-IL-9R α mAb both at the cell surface and in the cytoplasm (arrow in **A**). No staining could be detected when mouse IgG1 isotype-matched control was used as the first antibody (**C**). Double immunolocalization of the IL-9R α chain and neutrophil elastase on BAL cells from an asthmatic patient. The IL-9R α -immunopositive cell (fluorescence staining) also showed staining with elastase antibody (red staining). (From Soussi-Gounni et al. *J Immunol* 2001;166:2768-74. Copyright © 2001 by The American Association of Immunologists.)

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FIG 6. Effect of IL-9 on the release of IL-8 by PMNs. **A**, Stimulation of PMNs with recombinant IL-9 induce a significant release of IL-8, an effect that is significantly inhibited by goat polyclonal anti-IL-9 antibody but not by isotype-matched control. **B**, Recombinant GM-CSF-induced IL-8 from PMNs is not affected by pretreatment with neutralizing anti-IL-9 antibody. PMNs were pretreated with goat polyclonal anti-IL-9 antibody for 1 hour at 37°C and then stimulated or not with recombinant IL-9 or GM-CSF for 18 hours. Immunoreactive IL-8 within the supernatants was quantitated by using an ELISA kit obtained from R&D Systems (Minneapolis, Minn), according to the manufacturer's protocol. The sensitivity limit of these kits is 10 pg/mL. Data are expressed as means $\pm$ SD of 3 individual experiments performed in duplicate. (From J Immunol 2001;166:2768-74. Copyright © 2001 by The American Association of Immunologists.)

findings on PMNs, along with the effect of IL-9 on C-C chemokine release by epithelial cells,⁶ provide a possible mechanism by which IL-9 may contribute to chemokine production, inflammatory cell infiltration, and amplification of the inflammatory response.

Airway epithelial cells

The airway epithelium is thought to play an integral role in the inflammatory response because of its ability to produce a variety of cytokines and chemokines that promote the activation and proliferation of inflammatory cells. The effects of IL-9 on airway epithelial cell function have been investigated both in vitro and in vivo. Transgenic IL-9 mice exhibit increased levels of expression of eotaxin, macrophage inflammatory protein 1 α , and monocyte chemoattractant proteins 1, 3, and 5.⁶ Furthermore, an increased chemokine expression has also been demonstrated on cultured primary epithelial cells and epithelial cell lines stimulated with IL-9. The effect occurred even in the absence of IL-4, a well-known inducer of

chemokine expression in epithelial cells.⁶ Several studies have identified the constitutive expression of the α component of the IL-9R on human airway epithelial cells.^{7,73}

Increased mucin secretion is another characteristic feature of asthma, and it has been shown that IL-9-transgenic mice exhibit epithelial cell hypertrophy, accumulation of mucus within secretory cells, and subepithelial deposition of extracellular matrix proteins.⁴⁸ Expression of *MUC2* and *MUC5AC* genes was increased in an IL-9 transgenic mouse model.⁷ Furthermore, primary and cell line cultures of human epithelial cells also show increased expression of the mucin genes *MUC2* and *MUC5AC* after stimulation with IL-9.^{7,73}

IL-9 AND ASTHMA

The in vivo importance of IL-9 in the pathophysiology of asthma was first determined in animal models of airway inflammation. Nicolaides et al¹⁵ have described a close association between the *IL9* gene and bronchial hyperresponsiveness (BHR).¹⁵ Moreover, lung protein IL-9 levels are highly correlated with levels of airway responsiveness in mice.^{15,62} Furthermore, selective overexpression of the *IL9* gene within the lungs of transgenic mice resulted in massive airway inflammation, with infiltration of eosinophils and lymphocytes, mast cell hyperplasia, and increased subepithelial collagen deposition.⁴⁸ Another important finding was the accumulation of mucus-like material within nonciliated cells that accompanied goblet cell hyperplasia. These features were associated with a marked increase in airway responsiveness to inhaled methacholine.⁴⁸ More recently, our group has investigated the contribution of IL-9 to the pathogenesis of asthma by using bronchial biopsy specimens from patients with asthma and sarcoidosis and from atopic and nonatopic healthy control subjects. A highly significant difference in the expression of IL-9 mRNA and protein was detected in the airways of asthmatic subjects compared with those of all other groups.²⁹ In respect to cell type, CD3⁺ T cells and, to a lesser extent, eosinophils and neutrophils have been shown to be the main producers of IL-9 within the airways of asthmatic subjects. Indeed, both the degree of airflow obstruction (FEV₁) and airway responsiveness to methacholine were also significantly correlated with IL-9 mRNA expression levels.

Moreover, Lamblin et al⁷⁴ have recently reported that patients with nasal polyposis (NP) associated with asymptomatic BHR have an eosinophilic bronchial inflammation similar to that of asthmatic patients with NP.⁷⁴ To better evaluate the role of IL-9 in BHR, we have investigated the expression of IL-9 in bronchial biopsy specimens from patients with NP alone, NP associated with BHR, and NP associated with asthma. An increased number of IL-9 mRNA⁺ cells were detected in subjects with asthma and BHR compared with NP alone, respectively. However, there was no significant difference between subjects with asthma and BHR. These findings, along with the data from animal models,^{48,53} suggest that IL-9 may play a key role in regulating airway hyperresponsiveness.

CONCLUSION

These results demonstrate that IL-9 influences many aspects of the pathogenesis of asthma. Thus continued elucidation of the mechanisms of action of this cytokine, as well as its interactions with other pathways, will greatly enhance our understanding of inflammatory diseases, such as asthma. This may have important consequences in the field of asthma and allergy, and IL-9 should be considered as a novel therapeutic target for controlling the development of airway inflammation and hyperresponsiveness.

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