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Molecular and cellular mechanisms of allergic disease

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The molecular and cellular mechanisms mediating the allergic inflammatory cascade involve multiple mediators, cell types, and pathways. Of particular interest are the pathways regulated by the T_H2 lymphocyte, which result in release of IL-4 (important to IgE synthesis) and IL-5 (important to eosinophil proliferation). IL-4 regulates differentiation of naïve T_H0 cells to develop a T_H2 phenotype and stimulates B cells to produce IgE. Cross-linking by allergen of IgE affixed to high-affinity receptors on mast cells and basophils triggers degranulation and the release of preformed inflammatory mediators (important to the early phase response), and subsequently initiates synthesis and the release of lipid mediators and cytokines (which may contribute to the late phase response). Eosinophils may also play a prominent role in the development of bronchial hyperreactivity. IL-5, which is a lineage-specific eosinophil growth factor, increases the formation of eosinophils from progenitor cells and, in concert with CCR3 active chemokines, increases their trafficking to sites of allergic inflammation. An improved understanding of the basic mechanisms of allergic inflammation has led to the discovery of molecular targets involved in the initial events of the inflammatory cascade. Potential targets for the development of novel therapies for allergic disease include IgE, the T_H2 lymphocyte, and T_H2–derived cytokines, IL-4 and IL-5. (J Allergy Clin Immunol 2001;108:S65-71.)

Key words: *Allergic inflammation, mast cell, eosinophil, IgE, IL-4, IL-5, T_H2 cell*

The allergic cascade is a well-characterized inflammatory process that has been previously described in detail.[1-4]

Abbreviations used
CD23: Low-affinity IgE receptor
CD40L: CD40 ligand
CpG: Cytosine and guanine
FcεRI: High-affinity IgE receptor
FcεRII: Low-affinity IgE receptor
GM-CSF: Granulocyte-macrophage colony-stimulating factor
MBP: Major basic protein
PAF: Platelet-activating factor
TNF: Tumor necrosis factor

This review focuses on 2 specific arms of the allergic cascade: synthesis of IL-4 by the T_H2 cell, which stimulates B cells to produce IgE, and synthesis of the lineage-specific eosinophil growth factor IL-5 by the T_H2 cell.[5] IgE and eosinophils are both important components of allergic inflammation that distinguish it from other forms of inflammatory disease. IgE binds to mast cells, triggering their degranulation, and participates in antigen presentation, while eosinophils produce a variety of proinflammatory mediators that can induce bronchial hyperreactivity.

Both IgE and eosinophils continue to be the subjects of intensive research aimed at clarifying their role in allergic inflammation and identifying potential new treatments for allergy and asthma. Given the increasingly high prevalence and morbidity of allergic diseases worldwide,[6,7] a welcome development is the emergence of new treatments designed to inhibit the basic mechanisms of allergic inflammation and subsequently asthma, rather than simply masking the symptoms. To provide a basis for understanding current therapeutic targets in allergy and asthma that are now under active investigation, this article discusses the molecular mechanisms of IgE synthesis and signaling, as well as the pathways related to eosinophil formation and tissue recruitment.

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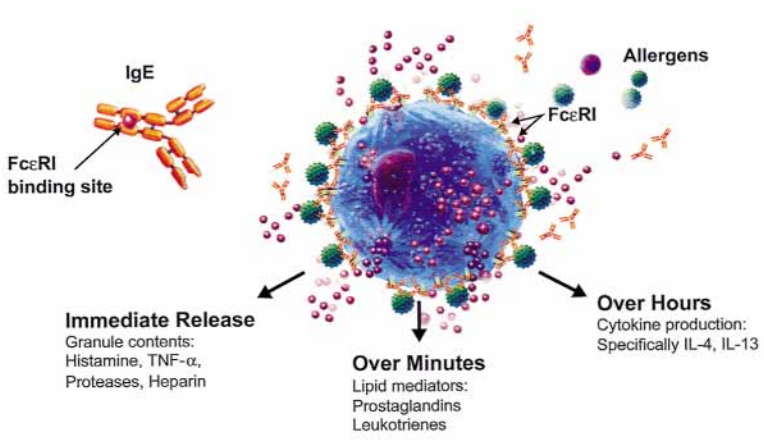

FIG 1. IgE-Dependent release of inflammatory mediators. IgE binds to high- and low-affinity receptors (FcεRI or FcεRII) on effector cells. The inflammatory cascade is initiated when a critical mass of IgE antibodies bound to effector cells is cross-linked by allergen. This results in the degranulation of effector cells and the release of a comprehensive array of mediators that are causally linked to the pathophysiology of allergic asthma.

TABLE I. Examples of mast-cell–derived mediators

Preformed mediators	Newly generated mediators	Cytokines
Histamine	Prostaglandin D_2	TNF-α
Heparin	Leukotriene C_4	IL-4
Tryptase	Thromboxane A2	IL-5
Chymase	PAF	IL-6

IMPORTANCE OF IgE IN ALLERGIC INFLAMMATION AND ASTHMA

The critical role of IgE in both the early and the late phases of allergic inflammation is well established.[2,8] Genetic analyses of families with asthma have shown a link between bronchial hyperresponsiveness and IgE levels.[9] IgE influences the allergic inflammatory response by interacting with the high-affinity IgE receptor (FcεRI) on mast cells and basophils, and by binding to the low-affinity IgE receptor (CD23 or FcεRII) to augment cellular and humoral immune responses.

Activation of mast cells

Mast cells are key participants in allergic inflammation, containing a potent array of inflammatory mediators (Table I). Initially, IgE binds to the high-affinity IgE receptor on tissue mast cells. The cross-linking of bound IgE to FcεRI by allergen then triggers mast-cell degranulation.[10] This results not only in the release of preformed mast-cell inflammatory mediators, such as histamine and tryptase, but also in the synthesis and release of newly generated lipid mediators, such as leukotriene C_4 and prostaglandin D_2, and in the transcription of numerous cytokines, such as TNF (Fig 1).[11] After their release by mast cells, these mediators of immediate hypersensitivity reactions rapidly induce bronchial mucosa edema, mucus secretion, and smooth-muscle contraction, and subsequently participate in eliciting an inflammatory-cell infiltrate within the bronchial mucosa. Similarly, the binding of IgE to FcεRI on basophils, followed by cross-linking by allergen, results in basophil degranulation with release of preformed inflammatory mediators, and in the synthesis of lipid mediators and cytokines.[12]

Enhancement of B-cell immune responses

In addition to its ability to activate mast cells, IgE can bind to the low-affinity IgE receptor CD23 (or FcεRII) on B cells, thus influencing the function of these cells.[13,14] IgE interactions with the CD23 receptor provide an important mechanism by which allergen-specific IgE can augment cellular and humoral immune responses in allergic inflammation and asthma. For example, passive sensitization of B cells with IgE substantially enhances B-cell immune responses, such as the presentation of antigen. In addition, the presence of antigen-specific IgE has been shown to amplify the in vitro production of IgE in a CD23-dependent manner.

The augmentation of IgE-mediated immune responses through interactions between IgE and the CD23 receptor observed in vitro has also been found in studies performed in vivo.[15-17] Titers of serum IgE have been shown to increase after an immunogen and a dose of antigen-specific IgE are injected intravenously. This effect can be completely abolished by in vivo pretreatment with anti-CD23 antibodies. These observations suggest that the presence of preformed allergen-specific IgE in the bronchial mucosa might enhance active immune responses to subsequent allergen inhalation.

Regulation of IgE receptor levels

An interesting relationship exists between IgE and its receptors, in that IgE is capable of modulating the level of expression of its own high- and low-affinity IgE receptors.[15,18-20] For example, higher IgE levels are associated with increased numbers of IgE receptors expressed on mast cells and on basophils. Thus, IgE affects positive feedback mechanisms that enhance FcεRI receptor den-

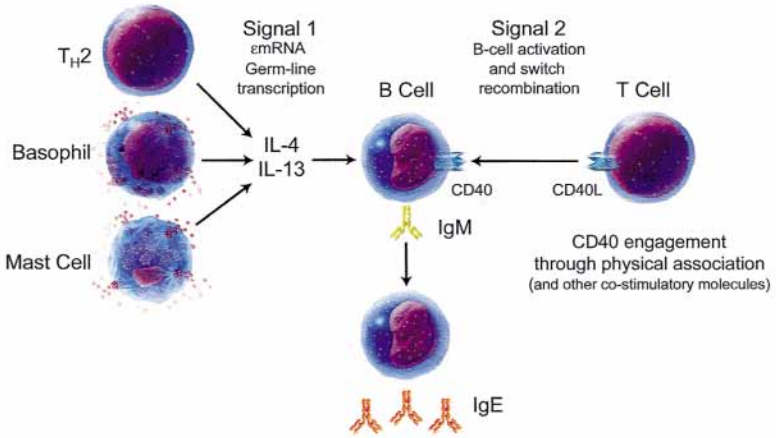

FIG 2. Initiation of IgE synthesis. Two signals are required to stimulate IgM-bearing B cells to undergo heavy-chain switching and secrete IgE. The first signal is delivered from IL-4 or IL-13, which induce B cells to initiate transcription of germ-line mRNA for IgE antibodies. The second signal is provided by the interaction of CD40 with its ligand, CD40L, which activates the genetic rearrangement (deletional switch recombination).[28]

sity and the excitability of mast cells. IgE-mediated up-regulation of FcεRI substantially enhances the ability of mast cells or basophils sensitized with IgE to degranulate in response to allergen challenge, and increased release of mast-cell or basophil cytokines such as IL-4 leads to increased IgE levels and IgE receptor density.

Accordingly, the down-regulation of IgE levels and IgE receptor levels on mast cells tends to decrease the potential of the mast cells to release inflammatory mediators. In a study by Yamaguchi et al,[18] IgE-deficient mice were found to have 4-fold to 5-fold fewer FcεRI receptors on mast cells, as compared with wild-type mice. These observations were extended to studies of human basophils by MacGlashan et al,[21,22] who infused anti-IgE (omalizumab) into human subjects and found that the levels of basophil IgE receptors were decreased both in vitro and in vivo. Although the same effect has not yet been shown to be directly associated with mast cells in human disease, these studies provide strong evidence that by reducing IgE levels, it is potentially possible to reduce IgE receptor levels on mast cells, thus decreasing the excitability of mast cells in the presence of an allergen.

In addition to its effects on the FcεRI receptor, IgE is capable of up-regulating CD23. Up-regulation of the CD23 receptor is thought to increase allergic responses in the bronchial mucosa through the enhancement of antigen uptake and presentation.[15] IgE-deficient mice have nearly 3 times fewer CD23 receptors on B cells, as compared with wild-type mice.[20] Moreover, studies show that CD23-deficient mice cannot augment immune responses mediated by IgE.[23,24]

From a therapeutic standpoint, why is it desirable to inhibit IgE? The inhibition of IgE leads to the down-regulation of both high- and low-affinity IgE receptors, resulting in decreased mediator release from basophils and mast cells. The administration of anti-IgE (omalizumab) to human subjects has been found to inhibit mast-cell activation and IgE-mediated antigen presentation, thus suppressing the allergic inflammatory response.[25,26] Omalizumab has also been found to be efficacious in the management of asthma in human beings.[27] (The articles by T. B. Casale, MD, and H. A. Boushey, Jr, MD, published elsewhere in this supplement, present current results from studies on the effects of omalizumab in patients with allergic rhinitis and asthma.)

Molecular signals for IgE production

Two signals are needed for B cells to make the isotype switch for synthesizing IgE (Fig 2).[28] The first signal is provided by the cytokines IL-4 or IL-13. These cytokines stimulate transcription at the Cε locus, which contains the exons encoding the constant region domains of the IgE ε-heavy chain.[15] The second signal is delivered by the interaction of the CD40 ligand (CD40L) on the surface of T cells with the CD40 receptor on the B-cell membrane. This interaction activates the needed genetic rearrangement, or more specifically, the deletional switch recombination, and brings into proximity all of the elements of the functional ε-heavy chain.[15]

The importance of IL-4 and IL-13 to IgE responses is suggested from studies of IL-4– and IL-13–deficient mice, which have impaired T_H2 responses along with decreased IgE production and CD23 expression.[15] Mice with targeted deletion of IL-13 have shown an attenuation of allergic response.[29,30] Also, IL-4– or IL-13–double-deficient mice have had more severe T_H2 impairment than have IL-4–deficient mice.[31] The significance of the second signal for IgE isotype switch recombination is suggested from studies of mice with targeted disruption of the CD40L or CD40 genes. These mice lack serum IgE, and their B cells fail to undergo isotype switching in vivo and in vitro after immunization with T-cell–dependent antigens.[15]

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FIG 3. Processes involved in eosinophilia. Eosinophils develop in the bone marrow in response to the stimulation of progenitor cells by IL-5. Mature eosinophils in the peripheral blood adhere to endothelial cells through the interaction of selectins and integrins (CD18 and very late antigen 4) with endothelial receptors for these molecules. On exposure to chemoattractant mediators, eosinophils undergo diapedesis between endothelial cells and migrate into the tissues. The accumulation of eosinophils is regulated by the generation of survival and activation factors (IL-3, IL-5, and GM-CSF) by T cells and probably mast cells. In response to extracellular-matrix components, eosinophils themselves can also generate the cytokines that prolong their survival. (Adapted with permission from Rothenberg ME. Eosinophilia. N Engl J Med 1998;338:1592-1600. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

TABLE II. Examples of eosinophil secretory products

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EOSINOPHILS

The recruitment of eosinophils into the airway is a prominent pathologic feature of patients with asthma. The eosinophil contains a variety of preformed cytoplasmic granule mediators, such as major basic protein (MBP). Eosinophils also synthesize such lipid mediators as leukotriene C_4 and platelet-activating factor (PAF), and cytokines such as GM-CSF, TNF, transforming growth factor (TGFβ), and IL-5 (Table II).[32] These mediators could enable eosinophils to have proinflammatory effects in the airway. Immunostaining of postmortem bronchial tissues has revealed the deposit of MBP, an eosinophil granule mediator, in the airways of subjects with status asthmaticus.[33]

Eosinophils and bronchial hyperreactivity in asthma

The recruitment of eosinophils into the airway can be reproduced experimentally in both mouse and human models of allergen-induced asthma.[34,35] A study of mice deficient in IL-5, a lineage-specific eosinophil growth factor, has demonstrated that the mice are unable to develop eosinophilia after allergen sensitization and challenge with ovalbumin and that they do not develop airway hyperresponsiveness to methacholine.[35] In another study, airway eosinophilia and hyperreactivity were shown to develop in human patients with asthma who inhaled IL-5, which suggests an important role for IL-5 and eosinophils in human asthmatic patients.[36] One mechanism by which

FIG 4. Eosinophil count in the peripheral blood of naïve mice. The absolute eosinophil count in the peripheral blood is shown for wild-type (+/+) and eotaxin null (–/–) mice. Results are expressed as mean ± standard error of the mean for +/+ (n = 12) and –/– (n = 14); $P = .007$. (Adapted from Rothenberg ME, MacLean JA, Pearlman E, et al. Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. J Exp Med 1997;185:785-90, by copyright permission of The Rockefeller University Press.)

eosinophils can induce bronchial hyperreactivity is suggested by studies of the eosinophil cytoplasmic granule MBP. Instillation of MBP into the airway in animal models in vivo induces bronchial hyperreactivity, possibly by effects on respiratory epithelium.[37]

Eosinophil trafficking to the lung

Not only does IL-5 stimulate CD34+ progenitor cells in the bone marrow to differentiate into eosinophils,[38] it also plays a central role in the mobilization of eosinophils from the bone marrow.[39] The release of mature eosinophils from the bone marrow is a multistep process, including the release of mature eosinophils from attachment to bone marrow stromal cells and extracellular matrix, the migration of eosinophils across the bone marrow sinus endothelium, and the release of eosinophils from the luminal surface of the endothelium. Once released from the bone marrow, eosinophils traffic through the bloodstream and migrate into tissue sites (Fig 3), where they recognize adhesion counterreceptors expressed by inflamed endothelium at sites of allergic inflammation.[40]

Eosinophil–endothelial cell interaction

The circulating eosinophil exits the microvasculature at sites of allergic inflammation by binding to inducible adhesion molecules expressed by endothelial cells. After the inhalation of allergen, cytokines, including IL-1, TNF, and IL-4, are released. These cytokines up-regulate adhesion molecule expression by endothelial cells. Studies using intravital videomicroscopy have visualized eosinophils in blood vessels in vivo and have demonstrated that eosinophil interactions with endothelium are characterized by sequential steps of rolling along the endothelium, firm adhesion to the endothelium, and transmigration across blood vessels into tissues.[41,42]

Research that has focused on understanding whether there are selective pathways responsible for eosinophil recruitment has demonstrated that eosinophils have both shared and distinct adhesion pathways with respect to neutrophils. For example, eosinophils use the same cell surface receptors (L-selectin and P-selectin glycoprotein-1) as neutrophils to roll on endothelium, but in addition are able to utilize $\alpha4\beta1$-integrins and $\alpha4\beta7$-integrins, which are not present on neutrophils.[41-46] Studies using adhesion molecule–deficient mice or mice treated with neutralizing antibodies to adhesion molecules have demonstrated the importance of these adhesion molecules to eosinophil recruitment.[44] Neutralizing antibodies to $\alpha4$-integrins improve airway function in some animal models of asthma in which eosinophil migration is only partially inhibited.[47,48] In the absence of inhibiting eosinophil recruitment, the anti–$\alpha4$-integrin antibodies may be exerting their beneficial effect by inhibiting activation of eosinophils in tissues. Thus, the benefit of anti–$\alpha4$-integrin therapy in models of asthma may relate to inhibition of eosinophil recruitment, inhibition of eosinophil activation, or effects on cell types other than eosinophils expressing $\alpha4$-integrin receptors.

Role of cytokines in eosinophil recruitment and chemotaxis

Allergen challenge induces the release of cytokines such as IL-1, TNF, and IL-4, which bind to receptors on endothelial cells and induce the subsequent expression of endothelial adhesion molecules important to eosinophil recruitment. Ongoing studies in the laboratory have demonstrated that, when challenged with allergen, mice genetically deficient in IL-1 or TNF receptors have reduced bronchoalveolar lavage (BAL) eosinophil recruitment, compared with that noted in wild-type mice.[49,50] Intravital microscopy of fluorescently labeled mouse eosinophils in the microvasculature of the allergen-challenged mouse mesentery demonstrates that eosinophil rolling, adhesion to endothelium, and transmigration across endothelium, are substantially inhibited in allergen-challenged IL-1 receptor type I–deficient mice, and in TNF-receptor–deficient mice, as compared with wild-type mice.[49,50] Overall, these studies demonstrate that cytokines such as IL-1 and TNF,

which are released after allergen challenge, are important in the induction of endothelial-cell adhesiveness, which is a prerequisite for the recruitment of circulating eosinophils. In addition, studies with IL-4 knockout mice have shown that airway eosinophilia and bronchial responsiveness are reduced, as compared with wild-type mice.[51]

Several chemokines important to eosinophil recruitment are expressed at sites of allergic inflammation after allergen challenge. The chemokine eotaxin has generated considerable interest because of its lineage-specific effect on eosinophils, as opposed to other cell types. Studies of eotaxin-deficient mice demonstrate that eotaxin is important in the early recruitment of eosinophils after allergen challenge (Fig 4).[52] However, eosinophil recruitment at later time points after allergen challenge is eotaxin–independent, suggesting an important role for several additional chemokines. A recent study with neutralizing antibodies demonstrated that chemokines such as RANTES, monocyte chemotactic protein-5, and macrophage inflammatory protein-1α are also important in eosinophil tissue recruitment.[53]

In human beings, future studies involving the inhibition of individual cytokines, chemokines, or their receptors are needed to assess their likely importance to eosinophil recruitment.

POTENTIAL THERAPEUTIC TARGETS IN ALLERGIC INFLAMMATION AND ASTHMA

Immunoglobulin E

Because of its importance as a mediator of allergic inflammation and allergic asthma, IgE is an obvious therapeutic target for investigators seeking to develop new treatments for allergy and asthma. Anti-IgE (omalizumab) has been shown to attenuate both early and late-phase responses in mildly asthmatic patients after the inhalation of allergens[25,26] and to reduce asthma exacerbations in patients with moderate to severe allergic asthma who are taking corticosteroids.[27] The use of omalizumab to decrease serum IgE levels, and therefore reduce its influence on the development of allergic inflammation, shows promise as a possible therapeutic strategy. Ultimately, this strategy may be used in the future as adjunctive treatment to reduce the use of corticosteroids by patients with asthma.

The T_H2 cell

The T_H2 cell is a potential therapeutic target in the development of new treatments because of its role in synthesizing IL-4, which stimulates the B cell to produce IgE, and because of its production of IL-5, which leads to increased eosinophil formation. Accordingly, approaches to inhibiting the T_H2 cell and its function in the immune response are currently under study. These approaches include the inhibition of transcription factors that control cellular T_H2 cytokine production. This strategy would affect both the production of IL-4, which drives IgE synthesis, and IL-5, which influences eosinophil formation.

One such transcription factor, GATA-3, controls the antigen-induced expression of IL-4, IL-5, and IL-13. Evidence supporting the role of GATA-3 in mouse models of asthma includes a study of GATA-3–deficient mice, in which researchers demonstrated reduced T_H2 cytokine response and decreased levels of IgE and eosinophil counts following allergen challenge.[54] Further study is required to determine whether small molecular inhibitors of GATA-3 could be used to suppress the function of the T_H2 cell and thereby reduce allergic inflammation.

Another potential approach for inhibiting T_H2-cell function that is currently under investigation is the use of cytosine and guanine (CpG) DNA sequences to bias the immune response toward a predominantly T_H1 response, instead of a pro-allergic T_H2 response. The CpG DNA sequences under study contain 6 base pairs of DNA, with a central CpG sequence, and are highly enriched in bacterial or mycobacterial DNA. These noncoding DNA sequences activate the innate immune system (macrophages, dendritic cells, natural killer cells) to actively secrete cytokines, such as IL-12 and IFN-γ, which drive the development of naïve T cells into T_H1 cells (as opposed to T_H2 cells). Studies of the effects of these DNA sequences in mice show inhibition of both eosinophilic inflammation and bronchial hyperreactivity.[55]

CONCLUSIONS

The allergic cascade is an extremely redundant process overall, with many cell types, mediators, and pathways resulting in the development of allergic inflammation. This redundancy provides investigators with numerous potential therapeutic targets for investigation in the suppression of allergic diseases. Not all of these potential targets, however, are likely to be equally promising, given the hierarchical nature of the allergic cascade and the effects of mediators at various points in the hierarchy. Furthest along in human studies are 2 important therapeutic targets, IgE and IL-4, that remain under active investigation by researchers seeking to develop highly effective novel treatments for allergic diseases.

REFERENCES

1. Pearlman DS. Pathophysiology of the inflammatory response. J Allergy Clin Immunol 1999;104:S132-37.
2. Leung DYM. Molecular basis of allergic diseases. Mol Genet Metab 1998;63:157-67.
3. Barnes PJ. Pathophysiology of allergic inflammation. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 5th ed. St. Louis: Mosby-Year Book; 1998. p. 356-65.
4. Kay AB. Concepts of allergy and hypersensitivity. In: Kay AB, ed. Allergy and allergic diseases. Oxford: Blackwell Science Ltd; 1997. p. 23-35.
5. Blumenthal MN. Principles of genetics. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 5th ed. St. Louis: Mosby-Year Book; 1998. p. 28-39.
6. Schafer T, Ring J. Epidemiology of allergic diseases. Allergy 1997;52:14-22.
7. Hartet TV, Peebles RS Jr . Epidemiology of asthma: the year in review. Curr Opin Pulm Med 2000;6:4-9.
8. Huang SK. Molecular modulation of allergic responses. J Allergy Clin Immunol 1998;102:887-92.

9. Ober C. Do genetics play a role in the pathogenesis of asthma? J Allergy Clin Immunol 1998;101:S417-20.
10. Turner H, Kinet JP. Signaling through the high-affinity IgE receptor Fc epsilon RI. Nature 1999;25:B24-30.
11. Williams CM, Galli SJ. The diverse potential effector and immunoregulatory roles of mast cells in allergic disease. J Allergy Clin Immunol 2000;105:847-59.
12. Grant JA, Huamin L. Biology of basophils. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 5th ed. St. Louis: Mosby-Year Book; 1998. p. 277-84.
13. Delespesse G, Sarfati M, Wu CY, Fournier S, Letellier M. The low-affinity receptor for IgE. Immunol Rev 1992;125:77-97.
14. Waldschmidt TJ, Tygrett LT. The low-affinity IgE receptor (CD23) participates in B cell activation. Adv Exp Med Biol 1992;323:149-56.
15. Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. J Clin Invest 1999;104:829-35.
16. Heyman B, Tianmin L, Gustavsson S. In vivo enhancement of the specific antibody response via the low-affinity receptor for IgE. Eur J Immunol 1993;23:1739-42.
17. Gustavsson S, Hjulstrom S, Liu T, Heyman B. CD23/IgE-medicated regulation of the specific antibody response in vivo. J Immunol 1994;152:4793-800.
18. Yamaguchi M, Lantz CS, Oettgen HC, et al. IgE enhances mouse mast cell FcεRI expression in vitro and in vivo: evidence for a novel amplification mechanism in IgE-dependent reactions. J Exp Med 1997;185:663-72.
19. Saini SS, MacGlashan DWJ, Sterbinsky SA, et al. Down-regulation of human basophil IgE and FC epsilon RI alpha surface densities and mediator release by anti-IgE infusions is reversible in vitro and in vivo. J Immunol 1999;162:5624-30.
20. Kisselgof AB, Oettgen HC. The expression of murine B cell CD23, in vivo, is regulated by its ligand, IgE. Int Immunol 1998;10:1377-84.
21. MacGlashan DWJ, Bochner BS, Adelman DC, et al. Down-regulation of FcεRI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
22. MacGlashan DJ, McKenzie-White J, Chichester K, et al. In vitro regulation of FcepsilonRIalpha expression on human basophils by IgE antibody. Blood 1998;91:1633-43.
23. Fujiwara H, Kikutani H, Suematsu S, et al. The absence of IgE antibody–mediated augmentation of immune responses in CD23-deficient mice. Proc Natl Acad Sci USA 1994;91:6835-9.
24. Gustavsson S, Wernersson S, Heyman B. Restoration of the antibody response to IgE/antigen complexes in CD23-deficient mice by CD23+ spleen or bone marrow cells. J Immunol 2000;164:3990-5.
25. Boulet L-P, Chapman KR, Côte J, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. Am J Respir Crit Care Med 1997;155:1835-40.
26. Fahy JV, Fleming HE, Wong HH, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. Am J Respir Crit Care Med 1997;155:1828-34.
27. Milgrom H, Fick RB, Su JQ, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. N Engl J Med 1999;341:1966-73.
28. Bacharier LB, Geha RS. Molecular mechanism of IgE regulation. J Allergy Clin Immunol 2000;105:S547-58.
29. Wills-Karp M, Luyimbazi J, Xu X, et al. Interleukin-13: central mediator of allergic asthma. Science 1998;282:2258-61.
30. Grunig G, Warnock M, Wakil AE, et al. Requirement for IL-13 independently of IL-4 in experimental asthma. Science 1998;282:2261-3.
31. McKenzie GJ, Fallon PG, Emson CL, Grencis RK, McKenzie AN. Simultaneous disruption of interleukin (IL)-4 and IL-13 defines individual roles in T helper cell type 2–mediated responses. J Exp Med 1999; 189:1565-72.
32. Kita H, Adolphson CR, Gleich GJ. Biology of eosinophils. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 5th ed. St. Louis: Mosby-Year Book; 1998. p. 242-60.
33. Gleich GJ. Mechanisms of eosinophil–associated inflammation. J Allergy Clin Immunol 2000;105:651-63.
34. Broide DH, Paine MM, Firestein GS. Eosinophils express interluekin-5 and granulocyte macrophage–colony-stimulating factor mRNA at sites of allergic inflammation in asthmatics. J Clin Invest 1992;90:1414-24.
35. Foster P, Hogan SP, Ramsay AJ, Matthaei KI, Young IG. Interleukin-5 deficiency abolishes eosinophilia, airway hyperreactivity and lung damage in a mouse asthma model. J Exp Med 1996;183:195-201.
36. Shi HZ, Xiao CQ, Zhong D, et al. Effect of inhaled interleukin-5 on airway hyperreactivity and eosinophilia in asthmatics. Am J Respir Crit Care Med 1998;157:204-9.
37. Gleich GJ, Flavahan NA, Fujisawa T, Vanhoutte PM. The eosinophil as a mediator of damage to respiratory epithelium: a model for bronchial hyperreactivity. J Allergy Clin Immunol 1988;81:776-81.
38. Clutterbuck EJ, Hirst EM, Sanderson CJ. Human interluekin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GM-CSF. Blood 1989;73:1504-12.
39. Palframan RT, Collins PD, Severs NJ, Rothery S, Williams TJ, Rankin SM. Mechanisms of acute eosinophil mobilization from the bone marrow stimulated by interleukin 5: the role of specific adhesion molecules and phosphatidylinositol 3-kinase. J Exp Med 1998;9:1621-32.
40. Rothenberg ME. Eosinophilia. N Engl J Med 1998;338:1592-1600.
41. Sriramarao P, Von Andrian UH, Butcher EC. Alpha 4 beta 1, integrin and L-selectin mediate eosinophil rolling at physiological shear rates in vivo. J Immunol 1994;153:4238-46.
42. Sriramarao P, Norton CR, Borgstrom P, Di Scipio R, Wolitzky BA, Broide DH. E-selectin preferentially supports neutrophil but not eosinophil rolling under conditions of flow in vitro and in vivo. J Immunol 1996;157:4672-80.
43. Sung KLP, Yang L, Elices M, Jin G, Sriramarao P, Broide DH. Granulocyte-macrophage colony-stimulating factor regulates the functional adhesive state of very late antigen-4 expressed by eosinophils. J Immunol 1997;158:919-27.
44. Broide DH, Humber D, Sullivan S, Sriramarao P. Inhibition of eosinophil rolling and recruitment in P-selectin and intracellular adhesion molecule-1–deficient mice. Blood 1998;91:2847-56.
45. Symon FA, Walsh GM, Watson SR, Wardlaw AJ. Eosinophil adhesion to nasal polyp endothelium is P-selectin–dependent. J Exp Med 1994; 180:371-6.
46. Wein M, Sterbinsky SA, Bickel CA, Schleimer RP, Bochner BS. Comparison of human eosinophil and neutrophil ligands for P-selectin: ligands for P-selectin differ from those from E-selectin. Am J Respir Cell Mol Biol 1995;12:315-9.
47. Abraham WM, Sielczak MW, Ahmed A, et al. Alpha4-integrins mediate antigen-induced late bronchial responses and prolonged airway hyperresponsiveness in sheep. J Clin Invest 1994;93:776-87.
48. Henderson WR, Chi EY, Albert RK, et al. Blockade of CD49d (alpha-4 integrin) on intrapulmonary but not circulating leukocytes inhibits airway inflammation and hyperresponsiveness in a mouse model of asthma. J Clin Invest 1997;100:3083-92.
49. Broide DH, Campbell K, Gifford T. Inhibition of eosinophilic inflammation in allergen-challenged, IL-1 receptor type 1–deficient mice is associated with reduced eosinophil rolling and adhesion on vascular epithelium. Blood 2000;95:263-9.
50. Broide DH, Stachnick G, Casteneda D, Nayar J, Sriramarao P. Inhibition of eosinophilic inflammation in allergen challenged TNF receptor p55/p75- and TNF receptor p55-deficient mice. Am J Respir Cell Mol Biol 2001;24:304-11.
51. Brusselle G, Kips J, Joos G, Bluethmann H, Pauwels R. Allergen-induced airway inflammation and bronchial responsiveness in wild type and IL-4 deficient mice. Am J Respir Cell Mol Biol 1995;12:254-9.
52. Rothenberg ME, MacLean JA, Pearlman E, Luster AD, Leder P. Targeted disruption of the chemokine eotaxin partially reduces antigen-induced tissue eosinophilia. J Exp Med 1997;185:785-90.
53. Gonzalo JA, Lloyd CM, Wen D, et al. The coordinated action of CC chemokines in the lung orchestrates allergic inflammation and airway hyperresponsiveness. J Exp Med 1998;188:157-67.
54. Zhang DH, Yang L, Cohn L, et al. Inhibition of allergic inflammation in a murine model of asthma by expression of a dominant-negative mutant of GATA-3. Immunity 1999;11:473-82.
55. Broide D, Schwarze J, Tighe H, et al. Immunostimulatory DNA sequences inhibit IL-5, eosinophilic inflammation, and airway hyperresponsiveness in mice. J Immunol 1998;161:7054-62.