This paper is available online at www.jbc.org
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 286, NO. 38, pp. 32883–32889, September 23, 2011
Printed in the U.S.A.

Allergic Asthma: Influence of Genetic and Environmental Factors*

Published, JBC Papers in Press, July 28, 2011, DOI 10.1074/jbc.R110.197046

Anil B. Mukherjee[1] **and Zhongjian Zhang**
From the Section on Developmental Genetics, Program on Developmental Endocrinology and Genetics, Eunice Kennedy Shriver NICHD, National Institutes of Health, Bethesda, Maryland 20892-1830

Allergic asthma is a chronic airway inflammatory disease in which exposure to allergens causes intermittent attacks of breathlessness, airway hyper-reactivity, wheezing, and coughing. Allergic asthma has been called a "syndrome" resulting from a complex interplay between genetic and environmental factors. Worldwide, >300 million individuals are affected by this disease, and in the United States alone, it is estimated that >35 million people, mostly children, suffer from asthma. Although animal models, linkage analyses, and genome-wide association studies have identified numerous candidate genes, a solid definition of allergic asthma has not yet emerged; however, such studies have contributed to our understanding of the multiple pathways to this syndrome. In contrast with animal models, in which T-helper 2 (T_H2) cell response is the dominant feature, in human asthma, an initial exposure to allergen results in T_H2 cell-dependent stimulation of the immune response that mediates the production of IgE and cytokines. Re-exposure to allergen then activates mast cells, which release mediators such as histamines and leukotrienes that recruit other cells, including T_H2 cells, which mediate the inflammatory response in the lungs. In this minireview, we discuss the current understanding of how associated genetic and environmental factors increase the complexity of allergic asthma and the challenges allergic asthma poses for the development of novel approaches to effective treatment and prevention.

Allergic Asthma: A Complex Syndrome

Asthma is a highly prevalent (330 million people affected worldwide) chronic inflammatory disease of the conducting airways of the respiratory system (American Academy of Allergy, Asthma and Immunology and reviewed in Ref. 2). It is a complex syndrome in which allergen exposure often induces intermittent attacks of breathlessness, airway hyper-reactivity, wheezing, and coughing (3). During the past 6 decades, the worldwide incidence and severity of asthma have steadily increased. Allergic asthma is one aspect of atopic disease, which is also increasing. This disease has become an expanding burden on public health services in both industrialized and developing countries (1–6). It is estimated that >35 million people in the United States alone develop asthma during their lifetime, and more than three-fourths of these individuals suffer from allergies (1, 5). During the past 3 decades, much has been learned about the pathogenesis of allergen-induced airway inflammation, which is recognized as one of the predominant underlying causes of allergic asthma. Currently, it is recognized that allergic asthma is a complex disease that results from interactions between multiple genetic and environmental factors (7). Moreover, the advances in molecular genetics and the use of animal models have advanced our understanding of the pathogenic mechanism(s) of various aspects of this complex disease, and it is expected that further advance in this area will facilitate the development of novel and more effective therapeutic approaches. It should be noted, however, that the mouse models of allergic asthma do not exactly replicate the human disease. In contrast to the mouse models, in which T-helper 2 (T_H2)[2] cell response is the dominant feature, the pathogenesis of human allergic asthma involves an initial exposure to an allergen that results in T_H2 cell-dependent stimulation of the immune response that mediates the production of IgE and cytokines. Repeated exposure to allergen then activates mast cells, which release mediators that facilitate recruitment of other cell types, including T_H2 cells, which mediate the inflammatory response in the airways (reviewed in Ref. 8). Thus, although the T_H2 axis plays a critical role in initiating the IgE response and airway inflammation, the presence of allergen-specific IgE does not necessarily culminate in asthma. In this minireview, we discuss what makes allergic asthma a complex disease in which genetic and environmental factors merge to cause pathogenesis.

Current Understanding of Allergic Asthma Pathogenesis

Although several types of asthma have been recognized clinically, allergic asthma is the most common form of the disease (reviewed in Ref. 9). In susceptible individuals, the initiation of allergen sensitivity occurs at the mucosal surfaces, where environmental allergens meet the mucosal epithelia. The interaction of inhaled allergen(s) with sensitized immune cells in the airway results in allergic asthma. Allergic rhinitis, atopic dermatitis, and asthma, which constitute atopic conditions, occur in individuals with markedly increased levels of IgE antibodies (10). The expression of high-affinity (FcεRI) and low-affinity (FcεRII; CD23) IgE receptors occurs in a wide variety of cell types, including dendritic cells (DCs) and B cells (Fig. 1). IgE bound to these receptors on B cells and DCs facilitates the uptake of allergen by these cells, promoting allergen presentation to T cells, which mediate secondary immune responses. The majority of IgE is bound by FcεRI on mast cells as well as basophils, and IgE-bound FcεRI cross-linking by a specific anti-

* This work was supported by the National Institutes of Health Intramural Research Program of Eunice Kennedy Shriver NICHD. This is the second article in the Thematic Minireview Series on Molecular Bases of Disease: Asthma. This minireview will be reprinted in the 2011 Minireview Compendium, which will be available in January, 2012.

[1] To whom correspondence should be addressed. E-mail: mukherja@exchange.nih.gov.

[2] The abbreviations used are: T_H2, T-helper 2; FcεR, Fcε receptor; DC, dendritic cell; AHR, airway hyper-reactivity; APC, antigen-presenting cell; OVA, ovalbumin; T_{reg}, regulatory T; UG, uteroglobin.

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

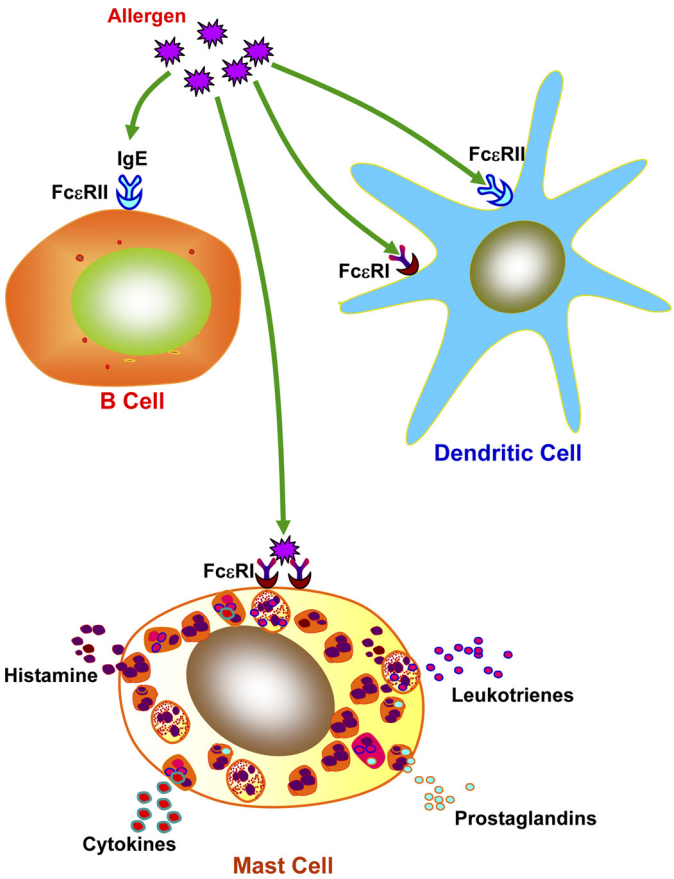

FIGURE 1. **IgE-mediated allergic response.** A wide variety of immune cells such as DCs and B cells express the low-affinity IgE receptor, FcεRII (CD23). Uptake of allergen is mediated via IgE-bound FcεRI and FcεRII on APCs, augmenting secondary immune responses. The mast cells and basophils express the high-affinity IgE receptor, FcεRI, which binds IgE, and the cross-linking of IgE-bound FcεRI on these cells mediates release of proinflammatory mediators such as histamine, prostaglandins, leukotrienes, cytokines, and enzymes that lead to biological manifestation of allergy (8).

gen mediates the release of inflammatory mediators (*e.g.* histamine and leukotrienes) by mast cells (Fig. 1), leading to the inflammatory response. The regulation of IgE production and its relationship to the development of T_H2 cells that drive IgE responses have been reviewed (8). An enhanced tendency toward airway hyper-reactivity (AHR) culminating in bronchial smooth muscle contraction, characteristically found in patients with asthma, is often linked to high IgE levels (11). Moreover, it has been reported that, in cohorts of children with asthma and physiologic evidence of AHR, high serum levels of IgE are detectable (12). Although, in both animal models and humans, some component of asthmatic pathophysiology, especially acute reactions to allergen, may be IgE-mediated, the other features of this disease may arise independently of IgE. Thus, in atopic families, inhalation of allergens and subsequent production of IgE are associated with predisposition to allergic asthma. Furthermore, it is likely that IgE participates in triggering mast cell-mediated acute- and late-phase airflow obstruction (10). Allergen exposure also triggers activation of bone marrow-derived and non-bone marrow-derived cells of the innate immune system, which eventually leads to the secretion of various cytokines (3). The recruitment of antigen-processing cells, most likely monocyte-derived DCs, initiates the pathway to inflammation. Recently, it was reported that basophils may also be involved in certain situations. Moreover, it has been reported that, in the airways of patients with asthma and especially in those patients suffering from allergic asthma, allergen-specific T_H2 cells are readily detectable (13). Recently, several excellent reviews were published on T_H2 cell differentiation (14–17), which may be referred to for detail knowledge on this subject. The T_H2 cells secrete cytokines, which promote the synthesis of allergen-specific IgE. These cytokines also promote presentation of antigens (allergens) to $CD4^+$ T cells, which facilitate both DCs and T cells in eliciting T_H2 cell responses (18, 19). In addition, activated T_H2 cells also secrete the cytokines IL-5, IL-9 and IL-13, which facilitate the recruitment of eosinophils and promote the growth of mast cells, respectively, ultimately stimulating AHR, characteristically found in asthma (9, 20). However, recent experiments indicate that T_H2 cells fail to produce IL-4, IL-5, or IL-13 without $CD11c^+$ DCs (9, 21). Interestingly, adoptively transferred, bone marrow-derived, antigen-loaded DCs or DCs in lungs can induce the T_H2 cell response (22), suggesting that lung DCs are the major antigen-presenting cells (APCs) and are essential for T_H2 cell response during allergen-mediated airway inflammation.

In addition to the recruitment of T_H2 cells, allergen challenge also facilitates the recruitment of other inflammatory cells such as mast cells, basophils, and eosinophils. However, a recent report indicates that, in addition to being inflammatory, these cells also participate as APCs and initiate or enhance T_H2 cell responses (9). Among the three cell types, mast cells can initiate immediate hypersensitivity responses by releasing histamines in response to both IgE-mediated adaptive and innate immune responses. Moreover, mast cells can be activated via cross-linking of allergen-specific IgE (23) or via Toll-like receptor ligands or cytokines such as IL-33 (24). Furthermore, in addition to releasing histamines and cysteinyl leukotrienes, mast cells secrete various cytokines such as IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, TGF-β, and TNF-α and chemokines such as TCA-3, RANTES, MCP-1, and MIP-1α (reviewed in Ref. 25). In Fig. 2, the pathways that lead to allergic asthma are summarized.

Genetic Susceptibility to Allergy and Asthma

As stated above, asthma and asthma-related syndromes are complex diseases in which an interplay of strong genetic and environmental components leads to pathogenesis (reviewed in Refs. 7 and 26–32). It is well known that many individuals are predisposed to developing allergic reactions to substances that do not generally elicit immune response. These atopic individuals are thought to be genetically predisposed to develop hypersensitivity to substances such as pollens, antibiotics, and perfumes. Numerous studies have shown that atopy is familial in nature. Elevated levels of IgE have been detected in patients with allergic diseases (7), and IgE production is tightly controlled. Recently, it was reported that NF-IL3, a transcriptional regulator, may control IgE production (33). Early studies reported the prevalence of allergic disease in first degree relatives of affected individuals (34, 35). Subsequently, studies in monozygotic and dizygotic twins have shown a positive correlation with regard to allergic disease traits such as total serum

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

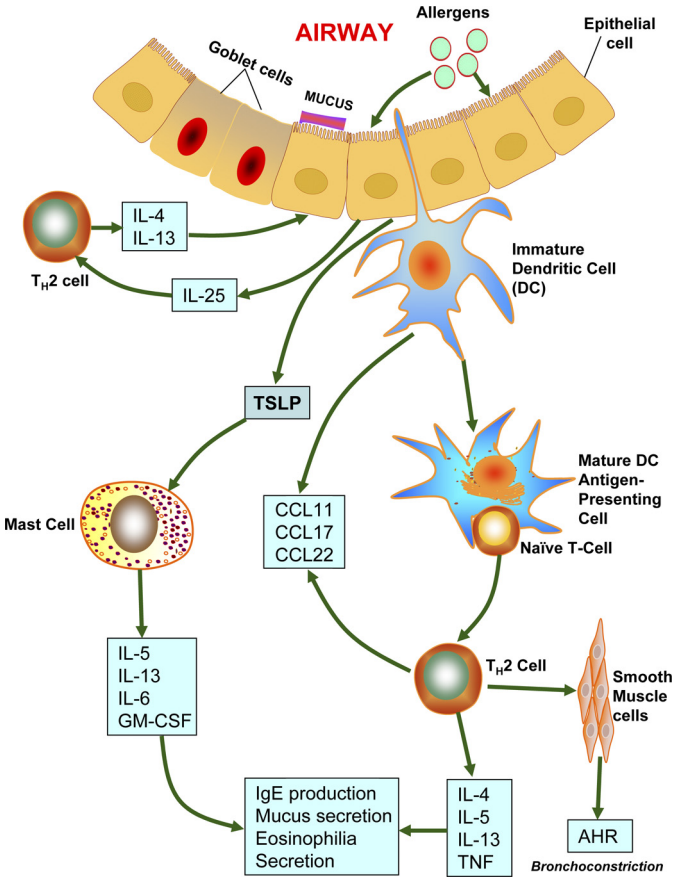

FIGURE 2. **Possible pathways to allergic asthma.** Allergens reaching the airways via inhaled air are taken up and processed by DCs that are primed by thymic stromal lymphopoietin (*TSLP*) secreted by airway epithelial cells. These allergens also cause the mast cells to release CCL17 and CCL22. CCL17 and CCL22 act on CCR4 (CC chemokine receptor 4), which mediates chemotactic migration of T_H2 cells. T_H2 cells play critical roles in orchestrating the allergen-induced inflammatory response by releasing IL-4 and IL-13. These interleukins also stimulate IgE production by B cells. These activated B cells also produce IL-5 (required for eosinophilic inflammation) and IL-9 (stimulator of mast cell proliferation). Airway epithelial cells release CCL11, stimulating recruitment of eosinophils via CCR3. Individuals suffering from allergic asthma may have defective T_{reg} cells, which favor further T_H2 cell proliferation and differentiation. Allergens also stimulate activation of sensitized mast cells by cross-linking surface-bound IgE molecules. In turn, activated mast cells secrete mediators of bronchoconstriction such as histamines, prostaglandin D_2, and cysteinyl leukotrienes (2).

IgE levels, methacholine sensitivity in the lungs, and skin test results being 2-fold higher among monozygotic twins than dizygotic twins. Moreover, children of asthmatic parents are more likely to develop asthma than those of parents without any history of atopy. Studies on atopic disease in human and animal populations have facilitated the identification of susceptibility genes encoding class II MHC, FcϵRIβ, RANTES, IL-4 receptor α, β-adrenergic receptor, T cell receptor α, and mast cell chymase. Furthermore, evidence suggests that genetic loci on human chromosomes 5, 6, and 11 are likely to harbor atopy genes. A thorough review of the molecular genetics of allergic diseases provides insight into the complexity of the atopic disease and why the identification of specific atopy genes remains challenging (reviewed in Ref. 36).

During the past decade, knowledge on asthma genetics has progressed significantly, and several genes or gene loci associated with asthma- and/or atopy-related syndromes have been identified. However, most of these genes have only modest effects, and the majority of these genes have not been systematically tested to determine whether the results are replicable in different populations. Several excellent reviews on the genetics of allergy and asthma have been published (2, 7, 26–32). In this minireview, we discuss only those genes that have shown functional and immunological links for susceptibility to asthma and allergy. In general, asthma susceptibility genes are classified into four main groups (reviewed in Refs. 7, 26, and 32): (i) innate immunity and immunoregulatory genes; (ii) genes associated with T_H2 cell differentiation and effector functions; (iii) genes associated with mucosal immunity and epithelial biology; and (iv) genes linked to lung function, airway remodeling, and severity of the disease (7, 26, 32). The interactions among the genes in the first three groups and those identified by positional cloning have been reviewed in detail (32) and are summarized in Fig. 3. The genes included in the first group have been discovered through association studies and are thought to be involved in triggering the immune response and stimulating differentiation of $CD4^+$ T helper cells. These genes encode pattern recognition receptors CD14 (monocyte differentiation antigen 14), NOD1 (nucleotide-binding, oligomerization domain-containing 1), NOD2, TLR2 (Toll-like receptor 2), TLR4, TLR6, and TLR10; cytokines regulating immune responses such as TGF-β1 and IL-10; the transcription factor STAT3 (signal transducer and activator of transcription 3); molecules that facilitate antigen presentation such as the *HLA-DR*, *HLA-DP*, and *HLA-DQ* alleles; and the prostaglandin receptor. Asthma susceptibility genes that belong to the second group regulate T_H2 cell differentiation and T_H2 cell effector functions (26): *FCER1B*, *GATA3* (GATA-binding protein 3), *IL4*, *IL4RA* (interleukin-4 receptor α-chain), *IL5*, *IL5RA*, *IL12B*, *IL13*, *STAT6*, and *TBX21* (T-box 21; also known as T-bet). Several genes are expressed in epithelial cells and are included in the third group. These genes encode chemokines CCL5 (CC chemokine ligand 5), CCL11, CCL24, and CCL26; factors involved in maintaining the integrity of the epithelial cell barrier (FLG (filaggrin) and SPINK5 (serine protease inhibitor Kazal-type 5)); antimicrobial peptide DEFB1 (defensin β1); and anti-inflammatory protein CC10/CC16 (Clara cell-specific 16 kDa protein; also known as SCGB1A1 and uteroglobin). The fourth group of asthma susceptibility genes has been identified by positional cloning. It includes *ADAM33* (a disintegrin and metalloproteinase domain 33), *COL29A1* (collagen type XXIX α-1; also called *COL6A5* (collagen type VI α-5)), *DPP10* (dipeptidyl peptidase 10), *GPRA* (G-protein-coupled receptor for asthma susceptibility; also known as *NPSR1* and *GPRA154*), *HLA-G*, *IRAKM* (interleukin-1 receptor-associated kinase M), and *PHF11* (plant homeodomain finger protein 11), which are expressed in the epithelium and/or smooth muscle cells.

Several genes (including *ADAM33*, *DPP10*, *PHF11*, *TIM-1*, *GPRA*, *OPN3*, *ORMDL3*, and *PDE4D*) that are associated with atopy and asthma have been identified via association studies and positional cloning (37). The genes encoding the T cell immunoglobulin domain, the mucin-like domain (*TIM*) family (38, 39), and ADAM33 on human chromosome 20p13 are associated with asthma and AHR (40). In addition to association studies and positional cloning, genome-wide association stud-

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

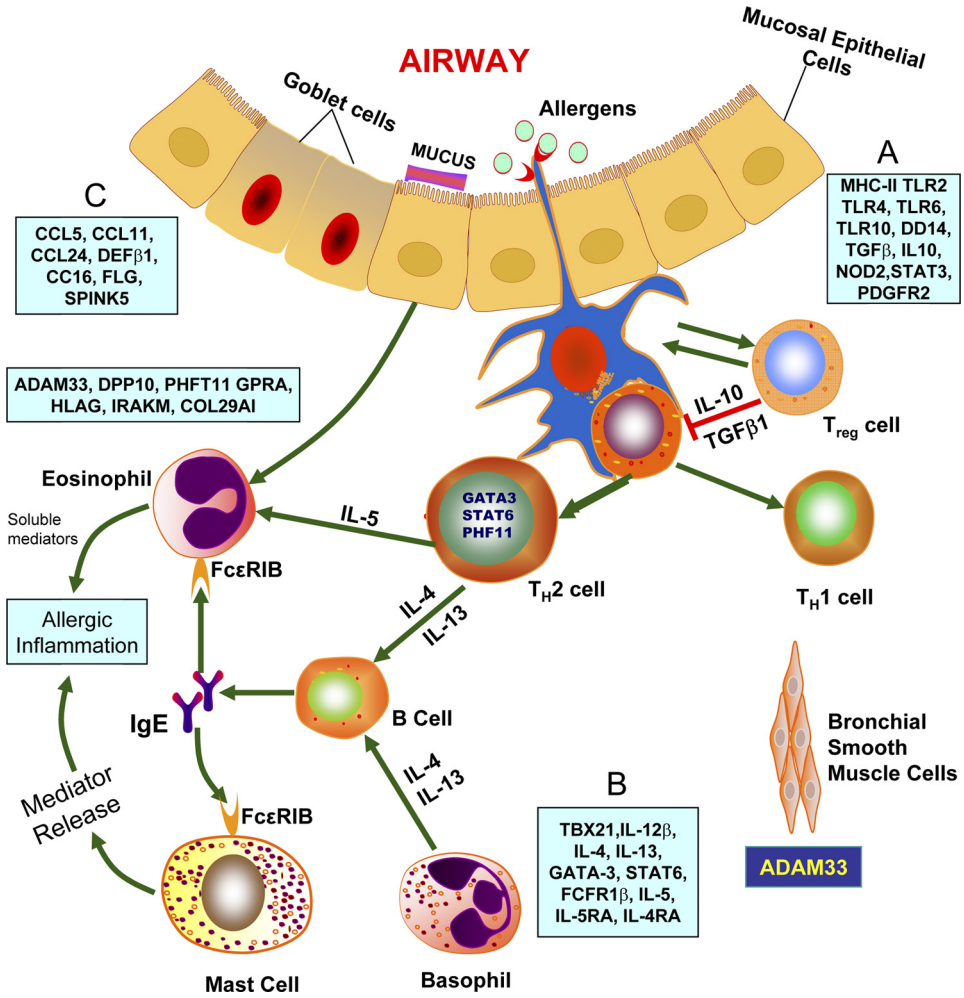

FIGURE 3. **Genes identified by association studies or positional cloning.** The genes that are associated with asthma/atopy are divided into four groups (26). *A*, the first group of genes is associated with triggering the allergic response via differentiation of $CD4^+$ T helper cells. This group includes genes encoding CD14, TLR2, TLR4, TLR6, TLR10, NOD1, and NOD2, which are known as pattern recognition receptors. This group also includes genes that encode immunoregulatory cytokines such as IL-10 and TGF-β1; the transcription factor STAT3; antigen-presenting facilitator genes such as the *HLA-DR*, *HLA-DQ*, and *HLA-DP* alleles; and prostaglandin E receptor 2. *B*, the second group of genes includes *GATA3*, *TBX21*, *IL4*, *IL13*, *IL4RA*, *FCER1B*, *IL5*, *IL5RA*, *STAT6*, and *IL12B*, which regulate T_H2 cell differentiation and effector functions. *C*, the third group includes genes encoding chemokines CCL5, CCL11, CCL24, and CCL26; antimicrobial peptide DEFB1; anti-inflammatory protein CC16 (also called UG); and factors responsible for maintaining the epithelial cell barrier such as SPINK5 and FLG. The positional cloning method has been used to identify the following genes expressed in the epithelia and smooth muscles: *ADAM33*, *COL29A1*, *DPP10*, *GPRA*, *HLA-G*, *IRAKM*, and *PHF11* (26).

ies have also been carried out to identify asthma susceptibility genes (27–32). This method utilizes SNPs for screening across the whole genome to identify novel disease susceptibility genes without the bias of prior knowledge. However, because of the lack of biological correlates, in some instances, the genes identified by this method have raised questions about the true relevance of these genes to the disease (32). Three independent reports were published recently (41–43) in which asthma susceptibility genes were identified utilizing knowledge from asthma genetics as well as asthma biology. As stated above, most of the identified genes have not been rigorously tested as to whether the results are replicable in different populations.

Gene Expression in Allergic Airway Inflammation and Allergic Asthma

Our knowledge of the allergen-mediated inflammatory response in airways has been greatly advanced by the availability of mouse models of allergic asthma. The hallmark of allergic asthma immunopathology is the infiltration of the airways by eosinophils and T_H2 cells (44). Recruitment of T_H2 cells to the lungs mediates the development of eosinophilic inflammation and AHR (9). Mice can be sensitized to foreign antigens (allergens), including ovalbumin (OVA), by introducing this antigen combined with an adjuvant such as alum (45). Immunization with OVA in alum causes IgE and IgG_1 production. When subjected to repeated exposure to the allergen, OVA-sensitized mice develop airway eosinophilia, hyperplasia of mucus-secreting goblet cells, and AHR, which are some of the characteristic features of allergic asthma. When these changes occur chronically, they lead to airway remodeling (46), which is also characteristically found in allergic asthma. It should be noted that, although allergen-specific T_H2 cells can be induced in mice (26) and in non-human primates (47), there are substantial differences between human and animal models of allergic airway disease (reviewed in Ref. 48).

To characterize gene expression in allergic airway inflammation, gene microarrays have been used (49, 50). The profiling of

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

gene expression by microarray has been used to characterize asthma-related genes in both humans and mice (see Table 1 in Ref. 51). The Gene Expression Omnibus (GEO) Database (www.ncbi.nlm.nih.gov/geo/) contains data sets on gene expression in allergic asthma models, intratracheal treatment with IL-13 (called allergen-induced goblet cells), T cells from atopic and asthma patients, allergen provocation in IL-13 knock-out mice, asthma exacerbation factors, and other studies related to allergy.

The allergen-induced responses in allergic asthma are driven predominantly by effector T cells, mostly by T_H2 cells, which are regulated by regulatory T (T_{reg}) cells, and thus, both T_H2 and T_{reg} cells have been studied by gene expression profiling. Microarray analyses of T_H1 and T_H2 cells differentiated from cord blood T lymphocytes have enabled Rogge *et al.* (52) to demonstrate that 215 of 6000 genes studied were differentially expressed among the two T cell subsets. Studies with $CD4^+$ T cells from patients with atopy or allergic asthma activated *in vitro* have shown differential gene expression in the two types of allergic disorders (53). Similar studies have facilitated discovery of a family of genes called ephrins, which are associated with allergic asthma pathology (54). Gene expression profiling using T_{reg} cells facilitated the discovery that IL-10 and ICOS (inducible costimulator) promote regulation of effector cells (55). Other investigations related to allergic inflammation have provided gene expression profiles using eosinophils (56) and basophils (57). Similar studies were conducted on a transcriptome level to determine the differentiation of DCs by contact allergens that can also trigger airway inflammation and AHR (58). It should be noted, however, that, although a vast amount of data from investigations on gene expression profiles have been amassed, only a small portion of this information has been used to advance our knowledge on the molecular mechanism(s) of allergic asthma. This may be due to the fact that the roles of numerous transcription factors, signaling molecules, and enzymes in allergic asthma have not yet been fully elucidated. Thus, many recent studies have focused on gene expression that could be associated with specific functions such as chemotaxis, inflammation, and cytokine regulation.

One of the puzzling phenomena in allergic diseases, especially allergic asthma, is that, although our airways are exposed to myriads of allergens on a daily basis, only a small percentage of the world's population suffers from allergic asthma. Thus, although the incidence of allergic asthma continues to rise, the majority of the world's population manages to avert allergic inflammatory diseases, including allergic asthma. Therefore, it is likely that some genes constitutively expressed in the airways maintain homeostasis in the mammalian respiratory system, which suppresses the allergen-mediated inflammatory response. An example of such a gene is uteroglobin (UG) (59), also known as CC10 (60). UG is a secretory protein that manifests immunomodulatory, anti-chemotactic, and anti-inflammatory properties (reviewed in Ref. 61). This protein is produced and secreted by the mucosal epithelia of all organs that communicate with the external environment. Moreover, it is constitutively expressed at a high level in the airway epithelial cells, and UG knock-out mice (62) develop increased susceptibility to allergen-induced airway inflammation. Recently, it was reported that UG suppresses the allergen (OVA)-induced airway inflammatory response by blocking prostaglandin D_2 receptor-mediated function (63). This protein has also been reported to inhibit T_H2 cell differentiation by acting on DCs (64, 65). Interestingly, human orthologs of murine *scca2*/*serpinb3a* (squamous cell carcinoma antigen 2), a serine protease inhibitor associated with allergic inflammation, are overexpressed in the airways of asthma patients (reviewed in Ref. 66). Most interestingly, *scca2* is expressed at high levels in the airways of UG knock-out mice and is further augmented by allergen challenge; treatment of these mice with recombinant UG abrogates the allergen-induced elevation of *scca* gene expression (67). Furthermore, UG also inhibits allergen-induced T_H2 cell differentiation by down-regulating the expression of serum amyloid A and the *SOCS-3* (suppressor of cytokine signaling 3) gene (68), which play critical regulatory roles in the initiation and maintenance of the T_H2 cell-mediated allergic airway inflammatory response (69).

Studies in humans and mouse models of allergic asthma have shown that the *TIM* family of genes is associated with allergen-mediated diseases (38). It has also been reported that monoclonal antibodies directed against mouse TIM-1 suppress allergen-mediated inflammation in various organs, including the lungs (70–73). More recently, using a humanized mouse model generated by injecting peripheral blood monocytes from asthma patients into immunocompromised severe combined immunodeficient mice, Sonar *et al.* (74) reported that monoclonal antibody against TIM-1 suppressed the production of proinflammatory T_H2 cytokines and prevented AHR. These results clearly demonstrated that the TIM-1 pathway plays a critical role in allergic asthma, and more importantly, antagonizing TIM-1 may provide therapeutic benefit to patients with allergic asthma and other immune-mediated inflammatory disorders.

Most intriguingly, the discovery of a mutant mouse strain called "flaky tail" in the Jackson Laboratory in 1958 and the strain reported in 1972 (75) may provide new insight into the pathogenesis of atopic dermatitis (eczema) and allergic asthma. Recently, Fallon *et al.* (76) reported that flaky tail mice carry a homozygous frameshift mutation in the gene encoding filaggrin, a large structural protein that facilitates terminal differentiation of the epidermis and forms the skin barrier. Interestingly, this mutation closely resembles human FLG variants that cause ichthyosis vulgaris (77), a skin disorder that is a genetic risk for atopic dermatitis and associated allergic asthma (78, 79). Although the association between FLG mutation and atopic dermatitis is strong, it has been reported that nearly 40% of individuals carrying a null mutation of this gene do not develop the skin disease (80). This suggests that both genetic and environmental modifiers may be involved in the pathogenesis of atopic dermatitis and associated allergic asthma (81).

Environmental Factors Interacting with Genetic Factors in Allergic Asthma

As discussed above, although allergic diseases such as allergic asthma have predisposing genetic factors, the interaction of environmental factors in the pathogenesis of allergic diseases is compelling. Environmental factors (both ingested and inhaled) have been suggested to contribute to allergic asthma pathogenesis (reviewed in Ref. 27). Examples of the environmental fac-

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

tors include air pollutants, respiratory viruses, tobacco smoke, endotoxin, allergens in the air, and diet. Occupational environment can also trigger asthma in genetically susceptible individuals (82). Thus, studies on gene-environment interactions may advance our understanding of the complex mechanism(s) of allergic asthma (83–86). Genes encoding pattern recognition receptors such as TLR4 and CD14 are reported to recognize and clear bacterial endotoxin and LPS, and SNPs in these genes may initiate asthma pathology in early development (27). SNPs in *CD14*, *TLR4*, and other *TLR* genes have been found to have a modest risk of asthma susceptibility in atopic individuals (87). Similarly, SNPs in *TGFB1* (88), *IL10* (89), *DCNP1* (dendritic cell-associated nuclear protein 1) (90), and inflammatory cytokines and enzymes (91) have been reported to alter gene-environment interaction in allergic asthma. Polymorphisms in the TNF-α gene (92) and the risk of childhood asthma in relation to environmental tobacco smoke and SNPs in the q21 region of human chromosome 17 (93) also point to gene-environment interaction. The subject of gene-environment interactions in the pathogenesis of respiratory diseases has been recently reviewed (1, 7, 94).

Concluding Remarks and Perspectives

During the past decade, major advances have been made in our understanding of the immune mechanisms of allergic diseases, including allergic asthma. However, these advances have not yet resulted in the development of effective new therapeutic approaches. It is possible that our knowledge of interacting genetic and environmental factors affecting the pathogenesis of this disease remains incomplete. Thus, further advance in the genetics of allergic asthma and the interaction of candidate asthma genes with environmental factors may facilitate the development of novel therapies. One of the puzzling aspects of allergic asthma pathogenesis is the fact that, despite our exposure to myriads of antigens (allergens), only a relatively small portion of the total human population suffers from allergic diseases. Recent efforts to treat allergic diseases have been focused on the application of biological agents such as monoclonal antibodies to target specific cytokines and cell surface proteins associated with the allergic inflammatory response. For example, it has been demonstrated that blocking TIM-1 using specific monoclonal antibodies may prevent allergic inflammatory responses. These are welcome developments, although we should be cautious that these therapeutic approaches do not compromise the many facets of immune responses (some of which are poorly understood) that are essential for maintaining homeostasis in the human body.

Acknowledgments—We thank I. Owens, J. Y. Chou, and S. W. Levin for critical review of the manuscript and helpful suggestions.

REFERENCES

1. Garantziotis, S., and Schwartz, D. A. (2010) *Annu. Rev. Public Health* **31,** 37–51
2. Barnes, P. J. (2008) *Nat. Rev. Immunol.* **8,** 183–192
3. Locksley, R. M. (2010) *Cell* **140,** 777–783
4. Mannino, D. M., and Buist, A. S. (2007) *Lancet* **370,** 765–773
5. Pearce, N., Aït-Khaled, N., Beasley, R., Mallol, J., Keil, U., Mitchell, E., Robertson C., and the ISAAC Phase Three Study Group (2007) *Thorax* **62,** 758–766
6. Akinbami, L. J. (2006) *Advance Data from Vital and Health Statistics*, pp. 1–24, National Center for Health Statistics, Hyattsville, MD
7. Holloway, J. W., Yang, I. A., and Holgate, S. T. (2010) *J. Allergy Clin. Immunol.* **125,** S81–S94
8. Geha, R. S., Jabara, H. H., and Brodeur, S. R. (2003) *Nat. Rev. Immunol.* **3,** 721–732
9. Kim, H. Y., DeKruyff, R. H., and Umetsu, D. T. (2010) *Nat. Immunol.* **11,** 577–584
10. Oettgen, H. C., and Geha, R. S. (2001) *J. Allergy Clin. Immunol.* **107,** 429–440
11. Postma, D. S., Bleecker, E. R., Amelung, P. J., Holroyd, K. J., Xu, J., Panhuysen, C. I., Meyers, D. A., and Levitt, R. C. (1995) *N. Engl. J. Med.* **333,** 894–900
12. Sears, M.R., Burrows, B., Flannery, E. M., Herbison, G. P., Hewitt, C. J., Holdaway, and M. D. (1991) *N. Engl. J. Med.* **325,** 1067–1071
13. Robinson, D. S., Hamid, Q., Ying, S., Tsicopoulos, A., Barkans, J., Bentley, A. M., Corrigan, C., Durham, S. R., and Kay, A. B. (1992) *N. Engl. J. Med.* **326,** 298–304
14. Zhu, J., Yamane, H., and Paul, W. E. (2010) *Annu. Rev. Immunol.* **28,** 445–489
15. Paul, W. E., and Zhu, J. (2010) *Nat. Rev. Immunol.* **10,** 225–235
16. Amsen, D., Spilianakis, C. G., and Flavell, R. A. (2009) *Curr. Opin. Immunol.* **21,** 153–160
17. Sokol, C. L., and Medzhitov, R. (2010) *Curr. Opin. Immunol.* **22,** 73–77
18. Saenz, S. A., Taylor, B. C., and Artis, D. (2008) *Immunol. Rev.* **226,** 172–190
19. Finkelman, F. (2001) in *Samter's Immunologic Diseases* (Austen, K. F., Frank, M. M., Atkinson, J. P., and Cantor, H., eds) 6th Ed., pp. 111–126, Lippincott Williams & Wilkins, Philadelphia
20. Holgate, S. T., and Polosa, R. (2008) *Nat. Rev. Immunol.* **8,** 218–230
21. van Rijt, L. S., Jung, S., Kleinjan, A., Vos, N., Willart, M., Duez, C., Hoogsteden, H. C., and Lambrecht, B. N. (2005) *J. Exp. Med.* **201,** 981–991
22. Lambrecht, B. N., De Veerman, M., Coyle, A. J., Gutierrez-Ramos, J. C., Thielemans, K., and Pauwels, R. A. (2000) *J. Clin. Invest.* **106,** 551–559
23. Prussin, C., and Metcalfe, D. D. (2006) *J. Allergy Clin. Immunol.* **117,** S450–S456
24. Silver, M. R., Margulis, A., Wood, N., Goldman, S. J., Kasaian, M., and Chaudhary, D. (2010) *Inflamm. Res.* **59,** 207–218
25. Barrett, N. A., and Austen, K. F. (2009) *Immunity* **31,** 425–437
26. Vercelli, D. (2008) *Nat. Rev. Immunol.* **8,** 169–182
27. Ober, C., and Hoffjan, S. (2006) *Genes Immun.* **7,** 95–100
28. Wills-Karp, M., and Ewart, S. L. (2004) *Nat. Rev. Genet.* **5,** 376–387
29. Cookson, W. (2004) *Nat. Rev. Immunol.* **4,** 978–988
30. Guerra, S., and Martinez, F. D. (2008) *Annu. Rev. Med.* **59,** 327–341
31. Bossé, Y., and Hudson, T. J. (2007) *Annu. Rev. Med.* **58,** 171–184
32. Vercelli, D. (2010) *J. Allergy Clin. Immunol.* **125,** 347–348
33. Rothman, P. B. (2010) *Trans. Am. Clin. Climatol. Assoc.* **121,** 156–171
34. Sibbald, B., Horn, M. E., Brain, E. A., and Gregg, I. (1980) *Thorax* **35,** 671–674
35. Taylor, B, and Broom, B. C. (1981) *Ann. Allergy* **47,** 197–199
36. Ono, S. J. (2000) *Annu. Rev. Immunol.* **18,** 347–366
37. Agrawal, D. K., and Shao, Z. (2010) *Curr. Allergy Asthma Rep.* **10,** 39–48
38. McIntire, J. J., Umetsu, S. E., Akbari, O., Potter, M., Kuchroo, V. K., Barsh, G. S., Freeman, G. J., Umetsu, D. T., and DeKruyff, R. H. (2001) *Nat. Immunol.* **2,** 1109–1116
39. McIntire, J. J., Umetsu, D. T., and DeKruyff, R. H. (2004) *Springer Semin. Immunopathol.* **25,** 335–348
40. Van Eerdewegh, P., Little, R. D., Dupuis, J., Del Mastro, R. G., Falls, K., Simon, J., Torrey, D., Pandit, S., McKenny, J., Braunschweiger, K., Walsh, A., Liu, Z., Hayward, B., Folz, C., Manning, S. P., Bawa, A., Saracino, L., Thackston, M., Benchekroun, Y., Capparell, N., Wang, M., Adair, R., Feng, Y., Dubois, J., FitzGerald, M. G., Huang, H., Gibson, R., Allen, K. M., Pedan, A., Danzig, M. R., Umland, S. P., Egan, R. W., Cuss, F. M., Rorke, S., Clough, J. B., Holloway, J. W., Holgate, S. T., and Keith, T. P. (2002) *Nature* **418,** 426–430
41. Wu, H., Romieu, I., Shi, M., Hancock, D. B., Li, H., Sienra-Monge, J. J., Chiu, G. Y., Xu, H., del Rio-Navarro, B. E., and London, S. J. (2010) *J.*

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011

Allergy Clin. Immunol. **125,** 321–327
42. Mathias, R. A., Grant, A. V., Rafaels, N., Hand, T., Gao, L., and Vergara, C., Tsai, Y. J., Yang, M., Campbell, M., Foster, C., Gao, P., Togias, A., Hansel, N. N., Diette, G., Adkinson, N. F., Liu, M. C., Faruque, M., Dunston, G. M., Watson, H. R., Bracken, M. B., Hoh, J., Maul, P., Maul, T., Jedlicka, A. E., Murray, T., Hetmanski, J. B., Ashworth, R., Ongaco, C. M., Hetrick, K. N., Doheny, K. F., Pugh, E. W., Rotimi, C. N., Ford, J., Eng, C., Burchard, E. G., Sleiman, P. M., Hakonarson, H., Forno, E., Raby, B. A., Weiss, S. T., Scott, A. F., Kabesch, M., Liang, L., Abecasis, G., Moffatt, M. F., Cookson, W. O., Ruczinski, I., Beaty, T. H., and Barnes, K. C. (2010) *J. Allergy Clin. Immunol.* **125,** 336–346
43. Li, X., Howard, T. D., Zheng, S. L., Haselkorn, T., Peters, S. P., Meyers, D. A., and Bleecker, E. R. (2010) *J. Allergy Clin. Immunol.* **125,** 328–335
44. Kay, A. B. (2001) *N. Engl. J. Med.* **344,** 30–37
45. Finkelman, F. D., and Wills-Karp, M. (2008) *J. Allergy Clin. Immunol.* **121,** 603–606
46. Holgate, S. T., Roberts, G., Arshad, H. S., Howarth, P. H., and Davies, D. E. (2009) *Proc. Am. Thorac. Soc.* **6,** 655–659
47. Zou, J., Young, S., Zhu, F., Gheyas, F., Skeans, S., Wan, Y., Wang, L., Ding, W., Billah, M., McClanahan, T., Coffman, R. L., Egan, R., and Umland, S. (2002) *Genome Biol.* **2002,** 3
48. Finkelman, F. D., Boyce, J. A., Vercelli, D., and Rothenberg, M. E. (2010) *J. Allergy Clin. Immunol.* **125,** 312–318
49. Sandler, N. G., Mentink-Kane, M. M., Cheever, A. W., and Wynn, T. A. (2003) *J. Immunol.* **171**, 3655–3667
50. Chtanova, T., Kemp, R. A., Sutherland, A. P., Ronchese, F., and Mackay, C. R. (2001) *J. Immunol.* **167,** 3057–3063
51. Schmidt-Weber, C. B. (2006) *Chem. Immunol. Allergy* **91,** 188–194
52. Rogge, L., Bianchi, E., Biffi, M., Bono, E., Chang, S. Y., Alexander, H., Santini, C., Ferrari, G., Sinigaglia, L., Seiler, M., Neeb, M., Mous, J., Sinigaglia, F., and Certa, U. (2000) *Nat. Genet.* **25,** 96–101
53. Wohlfahrt, J. G., Kunzmann, S., Menz, G., Kneist, W., Akdis, C. A., Blaser, K., and Schmidt-Weber, C. B. (2003) *Int. Arch. Allergy Immunol.* **131,** 272–282
54. Wohlfahrt, J. G., Karagiannidis, C., Kunzmann, S., Epstein, M. M., Kempf, W., Blaser, K., and Schmidt-Weber, C. B. (2004) *J. Immunol.* **172,** 843–850
55. Herman, A. E., Freeman, G. J., Mathis, D., and Benoist, C. (2004) *J. Exp. Med.* **199,** 1479–1489
56. Brenner, V., Lindauer, K., Parkar, A., Fordham, J., Hayes, I., Stow, M., Gama, R., Pollock, K., and Jupp, R. (2001) *J. Immunol. Methods* **250,** 15–28
57. Saito, H., Nakajima, T., and Matsumoto, K. (2001) *Int. Arch. Allergy Immunol.* **125,** 1–8
58. Ryan, C. A., Gildea, L. A., Hulette, B. C., Dearman, R. J., Kimber, I., and Gerberick, G. F. (2004) *Toxicol. Lett.* **150,** 301–316
59. Beier, H. M. (1968) *Biochim. Biophys. Acta* **160,** 289–291
60. Singh, G., and Katyal, S. L (2000) *Ann. N.Y. Acad. Sci.* **923,** 43–58
61. Mukherjee, A. B., Zhang, Z., and Chilton, B. S. (2007) *Endocr. Rev.* **28,** 707–725
62. Zhang, Z., Kundu, G. C., Yuan, C. J., Ward, J. M., Lee, E. J., DeMayo, F., Westphal, H., and Mukherjee, A. B. (1997) *Science* **276,** 1408–1412
63. Mandal, A. K., Zhang, Z., Ray, R., Choi, M. S., Chowdhury, B., Pattabiraman, N., and Mukherjee, A. B. (2004) *J. Exp. Med.* **199,** 1317–1330
64. Hung, C. H., Chen, L. C., Zhang, Z., Chowdhury, B., Lee, W. L., Plunkett, B., Chen, C. H., Myers, A. C., and Huang, S. K. (2004) *J. Allergy Clin. Immunol.* **114,** 664–670
65. Johansson, S., Wennergren, G., Aberg, N., and Rudin, A. (2007) (2007) *J. Allergy Clin. Immunol.* **120,** 308–314
66. Silverman, G. A., Bird, P. I., Carrell, R. W., Church, F. C., Coughlin, P. B., Gettins, P. G., Irving, J. A., Lomas, D. A., Luke, C. J., Moyer, R. W., Pemberton, P. A., Remold-O'Donnell, E., Salvesen, G. S., Travis, J., and Whisstock, J. C (2001) *J. Biol. Chem.* **276,** 33293–33296
67. Ray, R., Choi, M., Zhang, Z., Silverman, G. A., Askew, D., and Mukherjee, A. B. (2005) *J. Biol. Chem.* **280,** 9761–9764
68. Ray, R., Zhang, Z., Lee, Y. C., Gao, J. L., and Mukherjee, A. B. (2006) *FEBS Lett.* **580,** 6022–6026
69. Seki, Y., Inoue, H., Nagata, N., Hayashi, K., Fukuyama, S., Matsumoto, K., Komine, O., Hamano, S., Himeno, K., Inagaki-Ohara, K., Cacalano, N., O'Garra, A., Oshida, T., Saito, H., Johnston, J. A., Yoshimura, A., and Kubo, M. (2003) *Nat. Med.* **9,** 1047–1054
70. Encinas, J. A., Janssen, E. M., Weiner, D. B., Calarota, S. A., Nieto, D., Moll, T., Carlo, D. J., and Moss, R. B. (2005) *J. Allergy Clin. Immunol.* **116,** 1343–1349
71. Sizing, I. D., Bailly, V., McCoon, P., Chang, W., Rao, S., Pablo, L., Rennard, R., Walsh, M., Li, Z., Zafari, M., Dobles, M., Tarilonte, L., Miklasz, S., Majeau, G., Godbout, K., Scott, M. L., and Rennert, P. D. (2007) *J. Immunol.* **178,** 2249–2261
72. Fukushima, A., Sumi, T., Fukuda, K., Kumagai, N., Nishida, T., Akiba, H., Okumura, K., Yagita, H., and Ueno, H. (2007) *Biochem. Biophys. Res. Commun.* **353,** 211–216
73. Feng, B. S., Chen, X., He, S. H., Zheng, P. Y., Foster, J., Xing, Z., Bienenstock, J., and Yang, P. C. (2008) *J. Allergy Clin. Immunol.* **122,** 55–61
74. Sonar, S. S., Hsu, Y. M., Conrad, M. L., Majeau, G. R., Kilic, A., Garber, E., Gao, Y., Nwankwo, C., Willer, G., Dudda, J. C., Kim, H., Bailly, V., Pagenstecher, A., Rennert, P. D., and Renz, H. (2010) *J. Clin. Invest.* **120,** 2767–2781
75. Lane, P. W. (1972) *J. Hered.* **63,** 135–140
76. Fallon, P. G., Sasaki, T., Sandilands, A., Campbell, L. E., Saunders, S. P., Mangan, N. E., Callanan, J. J., Kawasaki, H., Shiohama, A., Kubo, A., Sundberg, J. P., Presland, R. B., Fleckman, P., Shimizu, N., Kudoh, J., Irvine, A. D., Amagai, M., and McLean, W. H. (2009) *Nat. Genet.* **41,** 602–608
77. Smith, F. J., Irvine, A. D., Terron-Kwiatkowski, A., Sandilands, A., Campbell, L. E., Zhao, Y., Liao, H., Evans, A. T., Goudie, D. R., Lewis-Jones, S., Arseculeratne, G., Munro, C. S., Sergeant, A., O'Regan, G., Bale, S. J., Compton, J. G., DiGiovanna, J. J., Presland, R. B., Fleckman, P., and McLean, W. H. (2006) *Nat. Genet.* **38,** 337–342
78. Palmer, C. N., Irvine, A. D., Terron-Kwiatkowski, A., Zhao, Y., Liao, H., Lee, S. P., Goudie, D. R., Sandilands, A., Campbell, L. E., Smith, F. J., O'Regan, G. M., Watson, R. M., Cecil, J. E., Bale, S. J., Compton, J. G., DiGiovanna, J. J., Fleckman, P., Lewis-Jones, S., Arseculeratne, G., Sergeant, A., Munro, C. S., El Houate, B., McElreavey, K., Halkjaer, L. B., Bisgaard, H., Mukhopadhyay, S., and McLean, W. H. (2006) *Nat. Genet.* **38,** 441–446
79. Baurecht, H., Irvine, A. D., Novak, N., Illig, T., Bühler, B., Ring, J., Wagenpfeil, S., and Weidinger, S. (2007) *J. Allergy Clin. Immunol.* **120,** 1406–1412
80. O'Regan, G. M., Sandilands, A., McLean, W. H., and Irvine, A. D. (2008) *J. Allergy Clin. Immunol.* **122,** 689–693
81. Vercelli, D. (2009) *Nat. Genet.* **41,** 512–513
82. Mapp, C. E. (2005) *Curr. Opin. Allergy Clin. Immunol.* **5,** 113–118
83. Cookson, W. (1999) *Nature* **402,** B5–B11
84. Marks, G. B. (2006) *Clin. Exp. Pharmacol. Physiol.* **33,** 285–289
85. Yang, I. A., and Holloway, J. W. (2007) *Clin. Exp. Allergy* **37,** 1264–1266
86. Miller, R. L., and Ho, S. M. (2008) *Am. J. Respir. Crit. Care Med.* **177,** 567–573
87. Smit, L. A., Siroux, V., Bouzigon, E., Oryszczyn, M. P., Lathrop, M., Demenais, F., and Kauffmann, F. (2009) *Am. J. Respir. Crit. Care Med.* **179,** 363–368
88. Sharma, S., Raby, B. A., Hunninghake, G. M., Soto-Quirós, M., Avila, L., Murphy, A. J., Lasky-Su, J., Klanderman, B. J., Sylvia, J. S., Weiss, S. T., and Celedón, J. C. (2009) *Am. J. Respir. Crit. Care Med.* **179,** 356–362
89. Hunninghake, G. M., Soto-Quirós, M. E., Lasky-Su, J., Avila, L., Ly, N. P., Liang, C., Klanderman, B. J., Raby, B. A., Gold, D. R., Weiss, S. T., and Celedón, J. C. (2008) *J. Allergy Clin. Immunol.* **122,** 93–98
90. Kim, Y., Park, C. S., Shin, H. D., Choi, J. W., Cheong, H. S., Park, B. L., Choi, Y. H., Jang, A. S., Park, S. W., Lee, Y. M., Lee, E. J., Park, S. G., Lee, J. Y., Lee, J. K., Han, B. G., Oh, B., and Kimm, K. (2007) *Genes Immun.* **8,** 369–378
91. Yang, I. A., Fong, K. M., Zimmerman, P. V., Holgate, S. T., and Holloway, J. W. (2008) *Thorax* **63,** 555–563
92. Wu, H., Romieu, I., Sienra-Monge, J. J., del Rio-Navarro, B. E., Anderson, D. M., Dunn, E. W., Steiner, L. L., Lara-Sanchez Idel, C., and London, S. J. (2007) *Environ. Health Perspect.* **115,** 616–622
93. Bouzigon, E., Corda, E., Aschard, H., Dizier, M. H., Boland, A., Bousquet, J., Chateigner, N., Gormand, F., Just, J., Le Moual, N., Scheinmann, P., Siroux, V., Vervloet, D., Zelenika, D., Pin, I., Kauffmann, F., Lathrop, M., and Demenais, F. (2008) *N. Engl. J. Med.* **359,** 1985–1994
94. Schwartz, D. A. (2010) *Proc. Am. Thorac. Soc.* **7,** 123–125

Downloaded from www.jbc.org at Congregazione Figli Immacolata Concezione, on December 13, 2011