Allergic asthma: influence of genetic and environmental factors

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Allergic asthma is a chronic, airway inflammatory disease in which exposure to allergens cause intermittent attacks of breathlessness, airway hyper-reactivity, wheezing and cough. Allergic asthma has been called a “syndrome” resulting from a complex interplay between genetic and environmental factors. Worldwide more than 300 million individuals are affected by this disease, and in the US alone it is estimated that more than 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 to the animal models in which T-helper 2 (TH2) cell response is the dominant feature, in human asthma as an initial exposure to allergen results in TH2-dependent stimulation of immune response that mediates the production of immunoglobulin E (IgE) and cytokines. Re-exposure to allergen then activates mast cells, which release mediators such as histamines and leukotrienes that recruit other cells including TH2 cells, which mediate the inflammatory response in the lungs. In this review, 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.

Asthma is a highly prevalent (330 million people worldwide) chronic inflammatory disease of the conducting airways of the respiratory system (reviewed in 1, 2). It is a complex syndrome in which allergen exposure often induces intermittent attacks of breathlessness, airway hyper-reactivity, wheezing and coughs (3). During the past six decades, the worldwide incidence as well as severity of asthma has 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 the developing world (1-6). It is estimated that more than 35 million people in the US alone develop asthma during their life-time, and more than three fourths of these individuals suffer from allergies (1, 5). During the past three 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 (Th2) response is the dominant feature, the pathogenesis of human allergic asthma involves an initial exposure of an allergen mediating Th2-dependent stimulation of an immune response resulting in 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 Th2 cells that mediate the inflammatory response in the airways (reviewed in 8). Thus, while Th2 axis plays a critical role in initiating the IgE response and airway inflammation, the presence of an allergen-specific IgE does not necessarily culminate in asthma. In this minireview we shall discuss what makes allergic asthma a complex disease in which genetic and environmental factors merge to cause pathogenesis.

**Current understanding of allergic asthma pathogenesis.** While several types of asthma have been recognized clinically, allergic asthma is the most common form of the disease (reviewed in 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- (FceRI) and low-affinity (FceRII; CD23) IgE receptors, occur in a wide variety of cell types including the dendritic cells (DCs) and B cells (Fig. 1a). 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 FceRI on mast cells as well as basophils, and IgE-bound FceRI crosslinking by specific antigen mediate the release of inflammatory mediators (eg. histamine and leukotrienes) by mast cells (Fig.1b) leading to the inflammatory response. The regulation of IgE production and its relationship to the development of Th2 cells that drive IgE responses have been reviewed (8). 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). While both in animal models as well as in 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. Further, it is likely that IgE participates in triggering mast cell-mediated acute- and late-phase airflow obstruction (10). Allergen exposure also triggers activation of the 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 the monocyte-derived dendritic cells (DCs), initiates the pathway to inflammation. Recently, it has been 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 Th2 cells are readily detectable (13). Recently, several excellent reviews have been published on Th2 cell differentiation (14-17), which the readers may consider for
detail knowledge on this subject. The TH2 cells secrete cytokines, which promote the synthesis of allergen-specific immunoglobulin E (IgE). These cytokines also promote presentation of antigens (allergens) to CD4⁺ T cells, which facilitates both DCs as well as the T-cells to elicit TH2 cell responses (18, 19). In addition, activated TH2 cells also secrete the cytokines, interleukin-5 (IL-5), IL-9 and IL-13, which facilitate the recruitment of eosinophils and promote growth of mast cells, respectively and ultimately, stimulating AHR, characteristically found in asthma (9, 20). However, recent experiments indicate that TH2 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 the DCs in the lungs can induce the TH2 response (22) suggesting that lung DCs are the major antigen presenting cells (APCs) and are essential for TH2 response during allergen-mediated airway inflammation.

In addition to the recruitment of TH2 cells, allergen-challenge also facilitates the recruitment of other inflammatory cells such as the mast cells, basophils and eosinophils. However, the recent reports indicate that these cells in addition to being inflammatory, also participate as APCs and initiate or enhance TH2 responses (9). Among 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 crosslinking of allergen-specific IgE (23) or via Toll-like receptor ligands or by cytokines such as IL-33 (24). Further, mast cells in addition to releasing histamines and cysteinyl leukotrienes elaborate various cytokines such as IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-10, IL-13, IL-16, transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNFα) and chemokines such as TCA-3, RANTES, MCP-1 and MIP1-α (reviewed in 25). In Fig. 2, the pathways that lead to allergic asthma are summarized.

**Genetic susceptibility to allergy and asthma.** As stated earlier in this review, asthma and asthma-related syndromes are complex diseases in which interplay of strong genetic and environmental components leads to pathogenesis (reviewed in 7, 26-32). It has been 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 commonly used 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 has been reported that NF-IL3, a transcriptional regulator, may control IgE production (33). The early studies have 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 total serum IgE levels, methacholine sensitivity in the lungs and skin test results being two fold higher among monozygotic twins than dizygotic twins. Moreover, children of asthmatic parents are found to be more likely to develop asthma than those from 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, FcεRI-β, RANTES, IL-4 receptor alpha, β-adrenergic receptor, T-cell receptor alpha and mast cell chymase. Further, evidence has been amassed to
suggest that genetic loci on human chromosome 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 36).

During the past decade knowledge in 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 are not 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) and the readers interested in obtaining in-depth knowledge in this area may consider perusing these articles. In this review, we shall 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 4 main groups (reviewed in 7, 26, 32): (i) the innate immunity and immunoregulatory genes, (ii) genes associated with T_{H}2 cell differentiation and effector functions, (iii) genes associated with mucosal immunity and epithelial biology and (iv) genes that are 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 are discovered through association studies and are thought to be involved with triggering the immune response and stimulating differentiation of CD4^{+} T helper (T_{H})-cells. The genes included in this group are those encoding the pattern recognition receptors (CD14, NOD1, NOD2, TLR2, TLR4, TLR6 and TLR10), cytokines regulating immune response (TGFB1 and IL10), the transcription factor STAT3, molecules that facilitate antigen presentation (HLA-DR, HLA-DP and HLA-DQ alleles) and the prostaglandin receptor, (PGE_{2}R). Asthma susceptibility genes belonging to the second group are those that regulate T_{H}2-cell differentiation and T_{H}2-cell effector functions (26): FCER1B, GATA3, IL4, IL4RA, IL5, IL5RA, IL12B, IL13, STAT6 and TBX21). Several genes are expressed in epithelial cells, which are included in the third group. These genes encode chemokines (CCL5, CCL11, CCL24 and CCL26), factors involved in maintaining the integrity of the epithelial-cell barrier (FLG and SPINK5), antimicrobial peptides (DEFB1) and anti-inflammatory protein CC10/CC16, also known as uteroglobin. The group of asthma susceptibility genes is identified by positional cloning. It includes ADAM33, COL29A1, DPP10, GPRA, HLA-G, IRAKM and PHF11, which are expressed in the epithelium and/or smooth muscle cells. Several genes including ADAM33, DPP10, PHF11, TIM-1, GPRA, ORMDL3 and PDE4D that are associated with atopy and asthma have been identified via association studies and positional cloning (37). The genes encoding T cell immunoglobulin domain, mucin-like domain (TIM) family (38, 39) as well as the disintegrin and metalloproteinase domain 33 (ADAM33) on human chromosome 20p13 are associated with asthma and AHR (40). In addition to association studies and positional cloning, genome-wide association studies have also been carried out to identify asthma-susceptibility genes (27-32). This method utilizes single nucleotide polymorphisms (SNPs) for screening across the whole genome to identify novel disease susceptibility genes without the bias of prior knowledge. However, due to 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). Recently, three independent reports have been published (41-43) in which asthma susceptibility genes have been identified utilizing knowledge from asthma genetics as well as asthma biology. As stated earlier in this discussion, 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 allergen-mediated inflammatory response in the 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 Th2 cells (44). Recruitment of Th2 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 adjuvant such as alum (45). Immunization with OVA in alum causes IgE and IgG1 production. When subjected to repeated exposure to the allergen, the OVA-sensitized mice develop airway eosinophilia, hyperplasia of mucous 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 while allergen specific Th2 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 48).

To characterize gene expression in allergic airway inflammation, gene micro-arrays have been used (49, 50). The profiling of gene expression by microarray has been used to characterize asthma related genes in both humans and mice (Table 1 in ref. 51) can be evaluated. The readers are referred to the Gene Expression Omnibus (GEO) database (http://www.ncbi.nlm.nih.gov/geo/) which contains dataset 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 knockout 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 Th2 cells, which are regulated by regulatory T (Treg) cells and thus, both Th2 and Treg cells are studied by gene expression profiling. Microarray analyses of Th1 and Th2 cells differentiated from cord blood T lymphocytes have allowed Rogge et al. (52) to demonstrate that out of 6000 genes studies 215 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 Treg cells facilitated the discovery that IL-10 and inducible costimulator (ICOS) promote regulation of effector cells (55). Other investigations related to allergic-inflammation provide 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 while 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 studies 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 while 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 that suppresses the allergen-mediated inflammatory response. An example of such a gene is uteroglobin (UG; 59) also known as Clara cell 10 or CC10kDa protein (60). UG is a secretory protein, which manifests immunomodulatory, anti-chemotactic and anti-inflammatory properties (reviewed in 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-knockout (UG-KO) mice (62) develop increased susceptibility to allergen-induced airway inflammation. Recently, it has been reported that UG suppresses allergen (OVA)-induced airway inflammatory response by blocking prostaglandin D$_2$ (PGD$_2$) receptor-mediated function (63). This protein has also been reported to inhibit T$_{H}$2-cell differentiation by acting on DCs (64, 65). Interestingly, human orthologs of murine squamous cell carcinoma antigen-2 (SCCA-2/serpinb3a), a serine protease inhibitor associated with allergic inflammation, are overexpressed in the airways of asthma patients (reviewed in 66). Most interestingly, SCCA2 is expressed at high levels in the airways of UG-KO mice and is further augmented by allergen challenge; treatment of these mice with recombinant UG abrogated the allergen-induced elevation of SCCA gene expression (67). Further, UG also inhibits allergen-induced T$_{H}$2 differentiation by down-regulating the expression of serum amyloid A (SAA) and suppressor of cytokine signaling-3 (SOCS-3) gene (68), which play critical regulatory roles in the initiation and maintenance of T$_{H}$2 mediated allergic airway inflammatory response (69).

Studies in humans and in mouse model of allergic asthma have shown that TIM family of genes is associated with allergen-mediated diseases (38). It has also been reported that monoclonal antibodies directed against mouse TIM-1 suppresses 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 immunodeficient severe combined immunodeficient mice, Sonar et al. have reported that monoclonal antibody against TIM-1 suppressed the production of pro-inflammatory T$_{H}$2 cytokines and prevented AHR (74). These results have clearly demonstrated that 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 “flacky tail” in the Jackson Laboratory in 1958 and that reported in 1972 (75) may provide new insight into the pathogenesis of atopic dermatitis (eczema) and allergic asthma. Recently, Fallon and coworkers (76) have reported that flacky tail mice carry homozygous frameshift mutation in the gene encoding filaggrin, a large structural protein that facilitates terminal differentiation of the epidermis and forms skin barrier. Interestingly, this mutation closely resembles FLG variants in humans that cause ichthyosis vulgaris (77), a skin disorder, which is a genetic risk for atopic dermatitis and associated allergic asthma (78, 79). While this association between FLG mutation and atopic dermatitis is strong, it has been reported that nearly 40% of individuals carrying null mutation in this gene do not develop the skin disease (80). This may suggest 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 earlier, while allergic diseases such as allergic asthma have predisposing genetic factors, the interaction of environmental factors in the pathogenesis of allergic diseases are compelling. Environmental factors (both ingested and inhaled) have been suggested to contribute to allergic-asthma pathogenesis (reviewed in 27). Examples of the environmental factors 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 Toll-like receptor-4 (TLR4) and CD14 are reported to recognize and clear bacterial endotoxin, LPS, and single nucleotide polymorphisms (SNPs) of these genes may initiate asthma pathology in early development (27). Atopic individuals who carry SNPs in the CD14, TLR4 and other TLR genes have been found to modify the risk of asthma susceptibility (87). Similarly, SNPs in the TGF-β1 (88), IL-10 (89), DC-associated nuclear protein-1 (DCNP1) (90), 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 recently been reviewed (7, 94, 95).

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 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 allergic inflammatory response. For example, it has been demonstrated that blocking TM-1 by 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.

1The abbreviations used are: TH2, T-helper 2; IgE, immunoglobulin E; DCs., Dendritic cells; ADAM33, a disintegrin and metalloproteinase domain 33; AHR, airway hyper-responsiveness; APC, antigen presenting cell; CC16, Clara cell-specific 16 kDa protein (also known as SCGB1A1); CCL, CC-chemokine ligand; CD14, monocyte differentiation antigen 14; COL29A1, Collagen type XXIX alpha-1 (also called COL6A5, Collagen alpha-5 (VI) chain); DCNP1, dendritic cell associated nuclear protein-1; DEFB1, defensin B1; DPP10, dipeptidyl peptidase 10; FCERIB, high-affinity Fc receptor for IgE B-chain; FLG, filaggrin; GATA3, GATA-binding protein 3; GPR A, G-protein-coupled receptor for asthma susceptibility (also known as NPSR1 and GPR154); IL, interleukin; IL4RA, interleukin-4 receptor (α-chain); IL5RA, interleukin 5 receptor (α-chain); IRAKM, interleukin-1 receptor-associated kinase 1; NOD, nucleotide-binding, oligomerization-domain-containing; PGD2R, prostaglandin D2 receptor; PGE2R, prostaglandin E2 receptor; PHF11, plant homeodomain finger protein 11; SCCA, squamous cell carcinoma antigen; SOCS-3, suppressor of cytokine signaling-3; SPINK5, serine protease inhibitor, Kazal-type, 5; STAT, signal transducer and activator of transcription; TBX21, T-box 21 (also known as T-bet); TCR, T-cell receptor; TGFb1, transforming growth factor-β1; TLR, Toll-like receptor; TReg, regulatory T cell; UG, uteroglobin.

References


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Figure Legends

Figure 1: Immunoglobulin E (IgE) mediated allergic response. A wide variety of immune cells express IgE receptors. While the dendritic cells express both high-(FcεRI) and low affinity (FcεRII) IgE receptors, the B-cells express only low affinity IgE receptor, FcεRII. Uptake of allergen is mediated via IgE bound FcεRI and FcεRII on antigen presenting cells (APCs) augmenting secondary immune responses. The mast cells and basophils express high affinity IgE receptor, FcεRI, which binds IgE. The crosslinking of IgE-bound FcεRI on these cells mediates release of pro-inflammatory mediators such as histamine, prostaglandins, leukotrienes, cytokines and enzymes that lead to biological manifestation of allergy (8).

Figure 2: Possible pathways to allergic asthma. Allergens reaching the airways via inhaled air are taken up and processed by dendritic cells (DCs) that are primed by thymic stromal lymphopoietin (TSLP) secreted by airway epithelial cells. These allergens also cause the mast cells to release CC-chemokine ligand 17 (CCL17) and CCL22. CCL17 and CCL22 act on CC-chemokine receptor 4 (CCR4), which mediates chemotactic migration of T helper 2 (T_{H2}) cells. T_{H2} cells play critical roles in orchestrating allergen-induced inflammatory response by releasing interleukin-4 (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 chemochine receptor 3 (CCR3). Individuals suffering from
allergic asthma may have defective regulatory T (T_{Reg}) cells, which favor further T_{H2}-cell proliferation and differentiation. Allergens also stimulate activation of sensitized mast cells by crosslinking surface-bound IgE molecules. Activated mast cells in turn secrete mediators of bronchoconstriction such as histamines, prostaglandin D_{2} and cysteinyl leukotrienes (2).

**Figure 3: Genes identified by association studies or positional cloning.** The genes that are associated with asthma/atopy are divided into 4 groups. The first group (A) of genes is associated with triggering the allergic response via differentiation of CD4^{+} T helper (T_{H})-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 those that encode immunoregulatory cytokines such as IL10 and TGFβ1, the transcription factor STAT3, antigen presentation facilitator genes such as HLA-DR, HLA-DQ and HLA-DP alleles and the prostaglandin receptor, PGER2. Genes in group (B) includes GATA3, TBX21, IL4, IL13, IL4RA, FCER1B, IL5, IL5RA, STAT6 and IL12B, which regulate T_{H2}-cell differentiation and effector functions. The third group (C) includes CCL5, CCL11, CCL24 and CCL26 (chemokines), DEFB1 (antimicrobial peptides), CC16 also called UG (anti-inflammatory protein) and SPINK5 and FLG (factors responsible for maintaining epithelial-cell barrier). 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).
Figure 1

- **Mast Cell**
- **Dendritic Cell**
- Fc\(_{\varepsilon}\)RII
- Allergen
- B Cell
- IgE
- Fc\(_{\varepsilon}\)RI
- Fc\(_{\varepsilon}\)RII
- Histamine
- Leukotrienes
- Prostaglandins
- Cytokines
Figure 3

AIRWAY

Mucosal Epithelial Cells

A

MHC-II TLR2
TLR4, TLR6,
TLR10, DD14,
TGFβ, IL10,
NOD2,STAT3,
PDGFR2

C

CCL5, CCL11,
CCL24, DEFβ1,
CC16, FLG,
SPINK5

ADAM33, DPP10, PHF11 GPRA,
HLAG, IRAKM, COL29AI

Eosinophil

Soluble mediators

IgE

Mediator Release

SOLUBLE MEDIATORS

B

TBX21,IL-12β,
IL-4, IL-13,
GATA-3, STAT6,
FCFR1β, IL-5,
IL-5RA, IL-4RA

ADAM33

Mast Cell

Goblet cells

Allergens

MUCUS

Treg cell

T_H1 cell

T_H2 cell

TH2 cell

B Cell

Basophil

TH1 cell

Basophil

Bronchial Smooth Muscle Cells

GATA3

STAT6

PHF11

ADAM33, DPP10, PHF11 GPRA,
HLAG, IRAKM, COL29AI

ADAM33

IL-10

TGFβ1

Eosinophil

IgE

Soluble mediators

Mediator Release

SOLUBLE MEDIATORS

TBX21,IL-12β,
IL-4, IL-13,
GATA-3, STAT6,
FCFR1β, IL-5,
IL-5RA, IL-4RA

ADAM33

IL-5

TGFβ1

SOLUBLE MEDIATORS

TBX21,IL-12β,
IL-4, IL-13,
GATA-3, STAT6,
FCFR1β, IL-5,
IL-5RA, IL-4RA

ADAM33