Markers of asthma: An overview.

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Abstract

Introduction
Asthma is caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis, with each gene having its own tendency to be influenced by the environment.

Methods
By the end of 2010, 100 genes had been associated with asthma in six or more separate populations, including IL-1 (α,β), IL-8, IL-3,4,5,9,10,12,13, TNF-α, PIM1, PAF-2, TGFβ1, SOD-1,2, CD24, CBR1, SYBL-1, iNOS, TCRC, EGFR, VDR, CCR2, and ADAM33, among others.

Result
In conventional thinking the involvement of IgE in mast cell activation requires the cross-linking of FcεRI-bound IgE by antigen or anti-IgE antibodies. In a transcriptome analysis of 8793 genes, sensitization of mast cells with monoclonal IgE alone, was found to upregulate 58 genes more than 2-fold compared with their levels in unsensitized mast cells. These genes included those for cytokines; chemokines; and chemokine receptors. Asthma is one of the most serious and intriguing allergic diseases. Asthma aggregates within families and is a complex multifactorial disease with the involvement of environment and genetic components. The mechanism of action of Anti-IgE monoclonal antibody in the treatment of allergic disorders is believed to be multifactorial, and includes effects mediated through altered production of redox metabolites such as total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide.

Conclusion
More studies are needed to determine the exact function of these genes, gene-environment interactions which are undoubtedly complex. The mechanism of action of Anti-IgE monoclonal antibody in the treatment of allergic disorders is believed to be multifactorial.

Introduction
Allergic asthma is a chronic respiratory disease that affects 300 million people throughout the world and its prevalence has increased in the world over the last 25 years. Asthma is common chronic inflammatory disease of the airways characterised by variable and attacks of cough and breathlessness, usually precipitated by an environmental trigger (air pollution, cold, dry air, smoke, etc.). The sequence of immunopathogenesis is unclear but there is clearly a genetic predisposition. Asthma is caused by multiple interacting genes, some having a protective effect and others contributing to the disease pathogenesis, with each gene having its own tendency to be influenced by the environment.

Methods
By the end of 2010, 100 genes had been associated with asthma in six or more separate populations, including GSTM1, IL-1 (α,β), IL-1RN, IL-1R1, IL-8, IL-3,4,5,9,10,12,13, NAT2CTLA4, SPINK5, LTC4S, SLP-76, EGR-1, PTGER3, CLCA1, V-CAM 1, TNF-α, PIM1, PAF-2, ARG1, GSTM1, A3AR, CHA, LELP1, TGFβ1, SOD-1, CD24, CBR1, SYBL-1, iNOS, TCRC, EGFR, GPR1, PAF, CCR2, FceRIβ, PHF11, ACE, STAT-6, VDR, CC-16, IL4, IRAK-3, CD69, IL-18, MUC-2, eNOS;NOS3, CMA1, and ADAM33, among others. Some of these genes may also be involved with other phenotypes such as helminthic infections (FceRIβ and IL-4), COPD, cardiovascular diseases, congenital thrombotic thrombocytopenia, Crohn’s disease (ADAM33) renal cell carcinoma, blood malignancies (PHF11), tuberculosis (TB), hyperparathyroidism, prostate cancer, insulin dependent diabetes mellitus, leprosy and chronic hepatitis B infection (vitamin D receptor: VDR). 2

Results
Current treatment consists in administering corticoids that treat the symptoms and temporarily relieve the disorder, but without curing it. An alternative, long-lasting treatment for allergic asthma is based on a specific immunotherapeutic protocol commonly known as desensitization. Repeated, increased doses of the allergen are administered in order to decrease the hypersensitivity and reduce the symptoms in the event of subsequent exposure. However, the efficiency of this protocol is limited and varies greatly from one patient to another. The researchers first tried proving the efficiency of this DNA-based vaccination against the specific allergen Derf1, using a relevant animal model developed by the Bronchial and Allergic Pathologies team led by Antoine Magnan. In Europe and Mediterranean region of Turkey, Dermatophagoides farinae 1 (Derf1) is a very common allergen carried by the dust mite Dermatophagoides farinae. More than half of patients presenting allergies to dust mites produce specific IgE type antibodies (Derf1) against this substance that are characteristic of asthma. In practice, the researchers associated useful genetic sequences of the allergen Derf1 with a nanovector consisting of a synthetic polymer. This DNA sequence, transported by a sort of "molecular taxi" into the muscle cells that ensure protein synthesis of the allergen, modulated the allergic response in asthmatic animals 4,5.

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a study conducted in a Mediterranean region of Turkey, the prevalence of asthma, allergic rhinitis, and allergic eye disease were detected as 8.2%, 10.8%, and 7.5%, respectively. In our previously study we showed that, while the wind speed and polination and temperature increased, the symptoms of the disease increased, too. Exacerbation of rhinitis and asthma symptoms was most commonly attributed to air pollution. Skin prick test (SPT) positivity for corylussavellana was significant in the age group of >40 years old. SPT positivity for plantagolanceolata, aspergillus fumigatus and D. pteronysinussus was significant in patients younger than 40 years old. The sensitivity for the grass, barley, weed, and tree allergen mixtures of SPT was significantly increased in May and June. During the month of May, air polination of gramineae was also increased 9. Mainstays of the treatment of difficult to control allergic severe persistent asthma include avoidance of allergens and other exacerbating factors, and control of common coexisting conditions such as postnasal drip, sleep apnea, rhinosinusitis and gastroesaphagial reflux. Other adjuvant therapies currently available include. Persistent allergic asthma that is refractory to usual treatment continues to be a challenge, but new biological therapies, such as omalizumab, benralizumab, mepolizumab offer hope to improve the quality of life and long-term prognosis of severe persistent allergic asthmatics. Since the discovery of IgE in 1967, the mechanisms of immediate-type hypersensitivity and allergy have been increasingly unraveled. IgE binds to the high-affinity IgE receptor (FceRI) on mast cells and basophils and mediates inflammatory cascades of the allergic response 8.

Discussion and conclusion

Allergic asthma is critically dependent on a series of cell adhesion molecule-mediated interactions between vascular endothelium and leukocytes, and elevation in total serum IgE. Omalizumab, a humanized mAb that binds to the CH3 domain, near the binding site for the high-affinity type-I IgE Fc receptors of human IgE, can neutralize free IgE and inhibit the IgE allergic pathway without sensitizing mast cell and basophils. Omalizumab is a humanized recombinant anti-IgE monoclonal antibody approved for therapeutic use both in adults and in children 9. The clinical benefit of omalizumab has been established in several large clinical trials 10,11,12,13,14. We demonstrated that significant changes in IL-1β, CXCL8, IL10, D-dimer, soluble OX-2, s TRAIL(sApo 2L), eosinophil cationic peptide, 25-hydroxyvitamin-D, homocysteine, ceruloplasmin oxidase activity, fractional exhaled nitric oxide, total IgE, pulmonary function tests and asthma control test, prior and after onset of treatment, giving evidence for a good therapeutic effect. Blood samples were taken on May or June during the highest air polination 15,16,17,18,19,20. Vitamin D has several effects on the innate and adaptive immune systems that might be relevant in the primary prevention of asthma, in the protection against or reduction of asthma morbidity, and in the modulation of the severity of asthma exacerbations 21. Cross-sectional data indicate that low 25-hydroxyvitamin-D levels in patients with mild to moderate asthma are correlated with poor asthma control, reduced lung function, reduced glucocorticoid response, more frequent exacerbations, and consequent increased steroid use. 25-hydroxyvitamin-D has effects on the innate and adaptive immune system. 25-hydroxyvitamin-D levels are associated with poor asthma control, reduced pulmonary function, increased medication intake and exacerbations. Little is known about 25-hydroxyvitamin-D in adult asthma patients or its association with asthma severity 21,22. More than that, 25-hydroxyvitamin-D triggers a homocysteine metabolizing enzyme and data from the Longitudinal Aging Study Amsterdam suggested a correlation between 25-hydroxyvitamin-D status and homocysteine levels 23. In our previously study we demonstrated that, the increase in homocysteine concentrations and decrease in also 25-hydroxyvitamin-D supports the possible allergic inflammation mechanism 15. Alternatively, the development of atopy may also be a direct effect of elevated homocysteine or some of its metabolites, which appears to exert a number of diverse effects on immune function. In addition, total homocysteine has been shown to increase in response to immune activation and cell proliferation during a non-allergic Th1-type immune response. Although much less is known about the health effects of sustained post load homocysteine concentrations, there is evidence that it has negative effects on platelet aggregation and endothelial function. A number of studies have indicated that homocysteine may contribute to the development and progression of atherosclerosis, a risk factor for cardiovascular diseases. However, the mechanisms by which homocysteine can induce vascular dysfunction are not fully understood 25,26.

In conventional thinking the involvement of IgE in mast cell activation requires the cross-linking of FcεRI-bound IgE by antigen or anti-IgE antibodies. In a transcriptome analysis of 8793 genes, sensitization of mast cells with monoclonal IgE alone, was found to upregulate 58 genes more than 2-fold compared with their levels in unsensitized mast cells. These genes included those for cytokines (IL-1β, IL-6, and colony-stimulating factor 1); chemokines (CXCL8,CCL7,CCL4);and chemokine receptors. 27,28. Asthma is one of the most serious and intriguing allergic diseases. Asthma aggregates within families and is a complex multifactorial disease with the involvement of environment and genetic components 29. The mechanism of action of Anti-IgE monoclonal antibody in the treatment of allergic disorders is believed to be multifactorial, and includes effects mediated through altered production of redox metabolites such as total antioxidant capacity, hydrogen peroxide, malondialdehyde and total nitric oxide 30. More studies are needed to determine the exact function of these genes, gene-environment interactions which are undoubtedly complex and remain elusive for the time being even with whole genome-wide association studies.
References

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