Interaction and regulation of asthma susceptibility genes

av

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ABSTRACT

Asthma is a disorder characterized by symptoms such as wheezing, shortness of breath, chest tightness or coughing. It is a chronic inflammation in the airways and the inflammation is usually accompanied by limitations in airflow as a result of hyper-secretion of mucus and broncho-constriction. Asthma commonly coincides with other allergic diseases such as allergic sensitization and rhinoconjunctivitis. The prevalence of asthma and allergy in children is highest in affluent countries with up to 20% in English speaking countries. Asthma and allergic disease are complex disorders and have long been known to be influenced by both heritable components and environmental factors.

The overall aim with this thesis was to investigate asthma susceptibility genes and their genetic role, biological dependency, as well as how they interact in a context-dependent manner, either with other genes (I) or with environmental factors (II). We studied the functional difference between splice variants of a previously identified asthma susceptibility gene showing unique expression patterns in asthmatic patients (III). We also aimed to define global gene expression patterns in asthmatic children that could reveal novel insight about characteristics of severe therapy-resistant asthma in children (IV).

In study I, we examined the biologically linked asthma susceptibility gene Tenascin C (TNC) and its genetic role in asthma and allergy. We also investigated the biological and genetic interactions between TNC and the previously genetically identified asthma susceptibility gene Neuropeptide S receptor 1 (NPSR1). In study II, we investigated the interactive effects of NPSR1 and environmental exposures related to farming lifestyle, as well as the effect of lipopolysaccharide (LPS), a proxy for farm animal exposure, on NPSR1 expression. We provide data showing that TNC has an independent genetic role in certain allergic diseases. We show biological interplay by a dose-dependent upregulation of TNC expression upon NPS-NPSR1 activation, and we conclude that interaction occurs between TNC and NPSR1 altering the outcome of asthma and allergy. Genetic variations in NPSR1 are not only dependent on other genes, but can also modify the effect of the environment, on the development of allergic diseases. Farm animal contact and farm milk consumption, introduced early in a child’s life, has been proven to show protective effects against development of allergic diseases. In study II, we demonstrate that the protective effect of farm animal contact can be further modified depending on genetic variations in NPSR1, especially if the contact is initiated later in life. We also identified increased NPSR1 expression upon LPS stimulation of human monocytes. From these two studies we can confirm that interactive effects, both biological and genetic, are important in the development of asthma and allergy. We could also see that the genetic dependency is most likely to occur when the main effect of the individual genes, or environmental factors, investigated are not that dominant.

In study III, we investigated the function of NPSR1 in more detail. The NPSR1 gene encodes two functional receptor variants (A and B) with distinct intracellular C-termini. Previous studies have illustrated different expression pattern, especially in asthmatic airways, between the two receptor variants. We could in study III demonstrate that, upon activation, both receptor variants A and B signals through the same pathways and induces expression of in principal identical set of genes. However, with few exceptions, variant A constantly induced stronger signaling effects than variant B. The effect was seen on both second messenger level and on downstream gene expression. These findings suggest an isoform specific link to NPSR1's role in allergic airways.

Among children with asthma around 5% suffer from chronic symptoms and/or severe exacerbation despite extensive treatment. The causes of this severe, therapy resistant asthma in childhood are poorly understood. In study IV we aimed to investigate global differences in gene expression in white blood cells from patients with severe, therapy-resistant asthma (SA, n=20), patients with controlled but persistent asthma (CA, n=20) and a group of healthy controls (Ctrl, n=19). We identified 1378 genes to be significantly differentially expressed between any of the contrasts (CA-Ctrl, SA-CA, SA-Ctrl) demonstrating that there are differences in gene expression between groups of asthma. Functional annotation and enrichment analysis identified three significantly differentially expressed pathways; bitter taste transduction, (upregulated mostly in SA), natural killer cell mediated cytotoxicity (upregulated in CA) and N-glycan biosynthesis (downregulated in SA). The bitter taste receptor family (TAS2Rs) has recently been shown to play a protective role in asthmatic airways e.g. by dilation of airways upon stimulation with bitter substances. Our finding is the first to propose a role for TAS2Rs in asthma outside the airway system. In conclusion our data indicates a separation in gene expression patterns between children with severe, therapy resistant asthma and controlled asthma, and suggests pathways revealing novel insight about the characteristics of severe therapy-resistant asthma.

From the finding in this thesis we can conclude and confirm that there is always a complex interplay between several genes and environmental factors altering the outcome of allergic disease. It is important to investigate these genes in more detail to unravel the functional mode of action. We can also see that by investigating clear defined subgroups of asthma it might be possible to identify new therapeutic targets for asthma.