Nasal epithelial cells: effector cells in allergy
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Outline of the thesis
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Allergic diseases affect a large part of the western population, with a prevalence of more than 20% in the U.S.A.\(^1\). Though it seems a relatively harmless disease, its impact on society is enormous\(^2\). Patients have symptoms like runny nose, blocked nose, itching of the nose and/or eyes, sneezing, impaired smelling, and impaired hearing. These symptoms significantly affect their quality of life and performance on the job\(^3\). It has been estimated that absenteeism and low productivity due to allergies has cost U.S. companies more than $250 million in 1998\(^4\). Although these indirect costs are high, they are just a fraction compared to the estimated direct healthcare costs of allergic rhinitis, which in 1996 were more than $6 billion\(^5\).

Effective treatment will improve quality of life and will also reduce the indirect and direct costs associated with the disease. Although, the two predominant treatments for nasal allergies, corticosteroids and antihistamines, are effective in a large group of patients, not all patients are satisfied with their current treatment\(^2\). Corticosteroids, due to their broad action, may cause unwanted side-effects, whereas antihistamines only work at the end of the immunological cascade, which may be responsible for their limited efficacy in asthma\(^6\). By developing new medication that specifically targets the beginning of the allergic response instead of effector cells, the efficacy and specificity of treatment might increase.

An interesting target for the development of new drugs is the airway epithelium, being the first cells an allergen encounters\(^7\), and the easiest to target with topical drugs. With this as a starting point we started our research to investigate how epithelial cells respond to allergen exposure. In particular we wanted to know if this response can teach us anything about the possible role of the epithelium in allergic inflammation.

In chapter 1 we describe the different receptors epithelial cells have on their surface and which they can use to detect changes in their environment. The three main groups are Toll-Like Receptors, NOD-Like Receptors and Protease Activated Receptors.
In chapter 2 we investigate the response of airway epithelial cells to house dust mite allergen. By starting off with this cell line we hope to find genes that are regulated by exposure to house dust mite (HDM), and identify the processes these genes are involved in. This is the first step on the track that will lead to better understanding the role of the epithelium in the mucosal response to allergens.

The next step we take in chapter 3 where we look into healthy and allergic epithelium to see if we can find differences between them, and if these differences are default or that they only appear after exposure to house dust mite extract. In a four group study we compared the changes induced by exposure to HDM, but we were also able to look at initial differences in expression of these genes.

After these two steps we wanted to focus on the similarities that can be found between the airway epithelial cell line described in chapter 2 and the primary nasal epithelial cells described in chapter 3. In chapter 4 we compare expression levels and response to allergen exposure in H292 cells and primary nasal epithelial cells from healthy and allergic individuals. This will allow us to further define the response of epithelial cells to HDM exposure.

All the experiments so far have been using HDM extract, a crude mix of many different proteins, some known to be able to activate a receptor on epithelial cells. In chapter 5 we expand our repertoire of stimulants by looking into the response of the airway epithelial cells to proteolytic stimulation, leading to damage of the epithelial layer.

The response of epithelial cells consists often of production of cytokines and chemokines, which are known to have an effect on cells of the adaptive immune system, which in turn will also produce such mediators. In chapter 6 we investigate the response of nasal epithelial cells to the proinflammatory cytokines TNF-α and IL-17, hoping to unravel some of the more complex cross talk mechanisms that can be found in allergic inflammation.
Finally in chapter 7 we address the implications of the data in this thesis, and explore the opportunities for further research.

In this thesis we hope to answer many of the above questions and by answering these questions we want to get insight into the role of nasal epithelial cells in allergy. This insight might lead to new strategies for treatment of allergic inflammation in the nose, thereby decreasing symptoms and improving the quality of life in patients suffering from allergic rhinitis.

Reference List