Nasal epithelial cells: effector cells in allergy

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Allergic diseases are very prevalent in the western population, even more than 20% of the general population in the U.S.A. Patients suffering from allergic rhinitis have symptoms like runny nose, blocked nose, itching of the nose and/or eyes, sneezing, impaired smelling, and impaired hearing. Although these symptoms are not lethal they do affect the patients' quality of life and performance on the job. The costs that are involved in this disease are enormous; it has been estimated that absenteeism and low productivity due to allergies has cost U.S. companies more than $250 million in 1998 which is only a part of the costs since the estimated direct healthcare costs of allergic rhinitis, were more than $6 billion in 1996.

While most other research on allergy has focused on the cells of the acquired immune system our focus in this thesis is on the epithelial cells. The epithelial cells are a part of the nasal mucosa, and being at the surface they play an important role as a barrier, shielding the underlying tissues from the hazardous influences from outside. However they are more than a physical barrier, since they are themselves capable of responding to for instance allergens and pathogens. When they respond they produce cytokines and chemokines, which are important signals for cells in general, but also for cells of the acquired immune system. In our research we set out to see if epithelial cells are involved in allergic reactions, and if they are what their role in this reaction is. By investigating differences between epithelial cells of healthy and allergic individuals we hope to learn more about this. If the function of epithelial cells influences the immune system this would open up new options for the development of treatment.

In chapter 1 we describe three families of receptors that are present on epithelial cells and that play a role in the response against pathogens and allergens. These three main groups are Toll-Like Receptors, NOD-Like Receptors, and Protease Activated Receptors. We also describe the signaling
pathways that are activated when these receptors are triggered.

In chapter 2 we investigated the response of airway epithelial cells to house dust mite allergen. In an epithelial cell line we find a large number of genes that are up-regulated upon allergen exposure. Most of these genes play a role in cell communication, among which are chemokines and cytokines. We also find genes involved in other processes, such as immunity and defense, receptor activity, and enzyme inhibitor activity. In network analysis we can see what the described interactions are between all genes that are up-regulated after allergen exposure and found a central role for TNF-α.

In chapter 2 we have shown how an airway epithelial cell line responds to allergen exposure, in chapter 3 we have looked into primary nasal epithelial cells, both of healthy and allergic volunteers. Here again we saw up-regulation of genes, but mainly in the healthy control group. When we looked at the gene expression levels of these genes in allergic individuals we saw that these genes were already expressed at a high level and therefore could not increase their expression levels any further. We defined this as the activated state. The genes involved were again involved in cell communication, signal transduction, and transcription factor activity. In a network analysis similar to the epithelial cell line data we saw that the differences in the activated state were also reflected in transcription factors, the regulators of gene expression.

Now that we have established that epithelial cells respond to allergens in a cell line and in primary nasal epithelial cells, we looked into 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 have investigated if an epithelial cell line can be used as a model to study epithelial response to allergen. We concluded that the cell line more closely resembles nasal epithelial cell from healthy controls than of allergic individuals, but also that important aspects of the regulated genes are very different. For instance, the number of genes that is affected in the cell line far
exceeds that in primary cells.

The allergen we have used in the experiments described in chapter 2, 3, and 4 contains proteolytic enzymes that cleave the receptor which leads to activation. In chapter 5 we have looked into the response of the airway epithelial cells to a purified proteolytic enzyme, leading to damage of the epithelial layer. We have found that if damage is induced in the presence of such an enzyme the response is much stronger than when similar damage is induced in a non-enzymatic way.

In all our experiments we have found epithelial cells produce cytokines and chemokines in response to proteolytic allergens or enzymes. What is known is that not only these cytokines have an influence on cells of the immune system, but that they can also have an effect on epithelial cells themselves. In chapter 6 we have investigated the response of nasal epithelial cells to the pro-inflammatory cytokines TNF-α and IL-17. Here we found that these two cytokines can have a synergistic effect on the production of some cytokines. Strikingly enough for INF-γ we found that the synergistic effect only occurs in epithelial cells of healthy individuals and not in allergic individuals.

Finally in chapter 7 we discuss how this research has given us more insight into the processes that take place in allergy, and in particular the role the epithelial cells play in this. We have described the differences between epithelial cells of allergic and healthy individuals. These differences point towards different mechanisms of regulation that can influence the allergic response. The insights gained in our research can help to develop new treatments that have an effect on epithelial cells and that influence the immune response via the mucosa. In addition new tools can be developed for the diagnosis of allergy in young children.