Clinical characterization of allergic sensitization patterns and the role of mucosal dendritic cells

Reinartz, Susanne

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Summary

In this thesis we describe the differences in clinical response to allergen challenges in allergic rhinitis subjects with different allergic sensitizations. We investigated multiple steps in the allergic cascade with different immunological mechanisms to find an explanation for this difference in clinical response.

In Chapter 1 the definition and classification of allergic rhinitis are reviewed as well as the immunological mechanisms of allergic sensitization and inflammation. Furthermore, the role of dendritic cells in innate and adaptive immune responses is discussed, with emphasis on the appropriate balance between pro-inflammatory versus tolerogenic effects of different DC subsets. A disbalance may play a role in the pathophysiology of many diseases, such as autoimmune diseases and allergic diseases.

The role of dendritic cells in allergic rhinitis is studied in Chapter 2.

In Chapter 2.1 we report on the role of nasal mucosal dendritic cells in subjects with allergic rhinitis with different allergic sensitizations and compare this to healthy control subjects. Immunohistochemical staining was performed for myeloid, plasmacytoid and Langerhans-type DCs on nasal mucosa specimens taken from allergic rhinitis and control subjects before and after nasal allergen provocation. We found that numbers of mDCs, pDCs and Langerhans cells differ between subjects with different allergic sensitizations. At baseline BDCA-1+ cells were highest in the subjects mono-sensitized to grass pollen, which may play a role in persistent inflammation despite the absence of allergen outside the season. The dynamics after nasal allergen provocation were largest for several DC subsets in the nasal mucosa of HDM-monosensitized allergic subjects, while overall the dynamics were very limited for the polysensitized individuals. The mDC/pDC ratio is equal for allergic and healthy subjects, however after NP the ratio in healthy subjects decreases, while remaining the same in allergic subjects, suggesting a lack of immunosuppression in the allergic subjects.

Chapter 2.2 describes the composition of human dendritic cell subtypes in the oral mucosa of allergic and non-allergic individuals. We studied the tissue distribution of myeloid, plasmacytoid and Langerhans-type DCs in oral mucosa, and compared these to nasal mucosa DCs in the same individuals, which were studied in Chapter 2.1. We found significantly more CD141 positive mDCs in epithelium and CD1a positive Langerhans cells in the lamina propria of allergic subjects compared to healthy controls. CD303 positive pDCs were present in very low numbers both in healthy and allergic individuals.

Given the complexity and heterogeneity in function of dendritic cells, and the flexibility of DC subets in the expression of function, we tried to gain more insight in their role by studying distribution of DC subsets in several models of immunological dysfunction in Chapter 3.
In Chapter 3.1 we analyzed dendritic cells in nasal mucosa of IgA Nephropathy patients. Intranasal vaccination of patients with IgAN has shown mucosal and systemic IgA hyporesponsiveness. We investigated whether reduced numbers or altered subset distribution of DCs in nasal mucosa can explain this IgA hyporesponse in IgAN patients. We observed more CD1a positive cells in the epithelium, and more DC-SIGN positive cells in the lamina propria in IgAN patients compared to controls. No differences in BDCA-1 and BDCA-2 positive cells were found between patients and controls. In contrast to what we expected, results from this study suggest higher numbers of DCs in IgAN patients. The hyporesponsiveness in IgAN patients may be caused by functional differences in DCs.

The role of plasmacytoid DCs in the pathophysiology of chronic obstructive pulmonary disease (COPD) was studied in Chapter 3.2. pDCs were quantified in lungs of subjects with or without COPD by immunohistochemistry and flow cytometry. The influence of cigarette smoke extract on the function of pDCs in vitro was also investigated. In COPD, a GOLD stage dependent accumulation of pDC in lymphoid follicles is present, combined with an enhanced production of TNF-α and IL-8 by maturing pDCs. Exposing maturing pDC of healthy subjects to cigarette smoke extract in vitro revealed an attenuation of the expression of co-stimulatory molecules and impaired interferon-α production.

The characterization and quantification of myeloid and Langerhans-type DC subsets in small airways of current and ex-smokers with or without COPD is shown in Chapter 3.3. Two subsets of tissue resident pulmonary mDC were identified in single cell suspensions by flow cytometry: the langerin+ LDC and the DC-SIGN+ interstitial-type DC. Langerhans-type DCs partially expressed the markers CD1a and BDCA-1. In contrast, interstitial-type DC did not express langerin, CD1a or BDCA-1, but were more closely related to monocytes. Quantification of DC in the small airways revealed a higher number of Langerhans-type DCs in current smokers without COPD and in COPD patients compared to never smokers and ex-smokers without COPD. Importantly, there was no difference in the number of Langerhans-type DCs between current and ex-smoking COPD patients. Interestingly, the number of BDCA-1+ DC was significantly lower in COPD patients compared to never smokers and further decreased with the severity of the disease. Myeloid DC differentiation is altered in small airways of current smokers and COPD patients resulting in a selective accumulation of the Langerhans-type DC subset.

In Chapter 3.4 the role of DCs in the pathophysiology of Crohn’s disease is studied. In this study we have identified the phenotype and localization of DCs in the intestinal mucosa and mesenteric lymph nodes in patients with Crohn’s disease and non-IBD patients. We used immunohistochemistry to demonstrate that the DC markers S-100, CD83, DC-SIGN, CD1a, BDCA1, BDCA2, BDCA3, and BDCA4 each showed a different staining pattern, varying from localization in T-cell areas of lymph follicles, around blood vessels, or single cells in the lamina propria. Three different subpopulations of myeloid DCs populate the...
colon mucosa and MLN of non-CD and CD patients; (1) immature DC-SIGN positive DCs, (2) mature DCs that express S-100 or CD83, and (3) mature BDCA3 positive DCs. BDCA1 and CD1a expressing DCs were virtually absent in colon as well as mesenteric lymph nodes. Immature DCs are mainly localized at antigen-capturing sites, whereas mature DCs are present where antigen is presented, including the T-cell areas in colonic lymph follicles and mesenteric lymph nodes.

The clinical model section of Chapter 4 describes the difference in clinical response to different allergen challenges between subjects with different allergic sensitization patterns. In Chapter 4.1 we investigated the effect of eight day-treatment with desloratadine on systemic inflammation and on nasal and bronchial mucosal inflammation after nasal allergen provocation in subjects with grass pollen allergic rhinitis and asthma. The number of circulating eosinophils decreased during desloratadine treatment, suggesting that treatment with desloratadine reduces systemic eosinophilia and prevents the increase in circulating eosinophils after nasal allergen provocation. There was also a significant reduction in early bronchial clinical response.

However, airway mucosal inflammation is not altered by eight days of treatment with desloratadine. Subgroup analysis in this study demonstrated a less pronounced clinical response to nasal grass pollen allergen challenge in polysensitized subjects compared to grass pollen monosensitized subjects. Moreover, we observed an improvement in symptoms after desloratadine treatment in the polysensitized subjects, especially reflected in less blockage and nasal itching, lower total nasal symptom score and better peak nasal inspiratory flow, which we did not find in the grass pollen monosensitized subjects.

Our observation of a diminished response to grass pollen allergen challenge in subjects with concurrent house dust mite allergy was confirmed in Chapter 4.2. In this study we showed that the clinical difference could not be explained by serum levels of allergen-specific IgE and IgG4 or in biological activity of IgE. The continuous allergen exposure in poly-sensitized subjects may alter local immuno-regulatory processes, leading to a reduced clinical response to allergen challenge.

A general discussion and overall conclusions from the results obtained in this thesis are presented in Chapter 5.