Clinical characterization of allergic sensitization patterns and the role of mucosal dendritic cells
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Chapter 1

Introduction and outline
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Allergic rhinitis

Allergy is a systemic disorder that can manifest in different target organs, such as the nose, lungs and skin. Allergic rhinitis (AR) is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation of the nasal mucosa after allergen exposure \(^{(1)}\). Symptoms include nasal obstruction, rhinorrhea, post nasal drainage, nasal itching and sneezing. AR is classified based on duration and severity into intermittent and persistent disease, which can clinically present as mild or moderate-severe disease. AR is an important health problem due to its prevalence and possible impact on sleep, work or school performance, and social life. For the best outcome in symptom reduction patients should be treated according to evidence based clinical guidelines, such as the Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations \(^{(2)}\). Other conditions commonly associated with AR are conjunctivitis, asthma, sinusitis, nasal polyposis, and otitis media. The costs incurred by these conditions are substantial. Rhinitis and asthma are common co-morbidities shown in epidemiological studies, as well as based on similar physiological and pathological characteristics. This has led to the concept of “one airway, one disease”, and the concept of a common therapeutic approach \(^{(2,3)}\).

Allergic sensitization and inflammation

In susceptible individuals, exposure to aero-allergens leads to allergic sensitization, which is characterized by the production of specific IgE directed against these proteins. Antigen-presenting cells, such as dendritic cells, in the nasal mucosa start this process by binding of the allergen, processing the captured allergen, and presenting it to T cells. Allergic inflammation in the airway mucosa of AR and asthma subjects is regulated by allergen-specific T helper 2 (Th2) cells, which produce key cytokines like IL-4, IL-5 and IL-13 that regulate the isotype switching and synthesis of allergen-specific IgE from B cells which is a critical step in the allergic cascade \(^{(4)}\). Allergen-specific IgE binds to the high-affinity IgE receptors present on the surface of mast cells and other effector cells in the nasal mucosa. Once mast cells are sensitized, re-exposure to this specific allergen causes cross-linking of IgE molecules, leading to mast cell degranulation and initiation of various pro-inflammatory events, such as synthesis of interleukins and infiltration of inflammatory cells. Subsequent upregulation of adhesion molecule expression on the vascular endothelium permits migration of eosinophils to the site of allergic inflammation (Figure 1). The allergic response is separated into two distinct processes termed the early- and late-phase response. The early phase starts within minutes of allergen exposure and is primarily due to mast cell release of pre-formed mediators, such as histamine, tryptase, chymase, kinins, and heparin, and other rapidly synthesized substances such as cysteinyi leukotrienes, interleukins, prostaglandins, and platelet-activating factor. Clinically, this process results in
mucous gland stimulation leading to rhinorrhoea, and sensory nerve stimulation leading
to sneezing and itching. The late phase response is characterized by the recruitment and
migration of inflammatory cells to the nasal mucosa, including eosinophils, basophils,
neutrophils, newly synthesized mast cells, and macrophages. Inflammation is sustained
by release of additional mediators with continued inflammatory cell recruitment. The late-
phase response of allergic rhinitis is mainly characterized by vasodilation which results in
mucosal swelling and nasal obstruction.

The pathophysiological mechanism underlying AR and asthma is likely to be a similar
inflammatory process, and specific allergen provocation of the nasal mucosa induces
allergic inflammation of the bronchial mucosa (6). Vise versa, segmental bronchial
provocation also leads to allergic inflammation in the nasal mucosa (5;6).

Dendritic cells

Dendritic cells (DCs) are key cells in innate and adaptive immune responses that play a role
in the pathophysiology of many diseases. An appropriate balanced immune response is
critical for healthy state, while an unbalanced and/or excessively vigorous response may
lead to immunopathogenesis, such as autoimmune diseases and allergic diseases. For many
vital functions, such as respiration (upper and lower airways), absorption (gastrointestinal
tract), and excretion (urinary tract, large intestine) the mucosal surfaces are inevitably
exposed to innumerous environmental proteins from inhaled antigens, food particles,
commensal flora and pathogens. Dendritic cells process external information and direct
innate and adaptive immune responses to achieve host defense and homeostasis. Failure of this system leads to induction and maintenance of chronic inflammation (7).

DCs play a central immunoregulatory role that mainly relies on the ligation of specific receptors that initiate and modulate DC maturation resulting in the development of functionally different effector DC subsets that selectively promote Th1-, Th2-, Th17-, or regulatory T cell responses (8). DC subtypes differ in their functional potential, and the expression of function is flexible and regulated by environmental factors (9).

Table 1. Cellular expression of tissue DCs

<table>
<thead>
<tr>
<th>DC markers</th>
<th>Synonym</th>
<th>Cellular expression</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD1a</td>
<td>Thymocytes, DCs (Langerhans cells)</td>
<td>(19)</td>
<td></td>
</tr>
<tr>
<td>CD1c</td>
<td>BDCA-1</td>
<td>Thymocytes, subsets of B cells, myeloid DCs</td>
<td>(19)</td>
</tr>
<tr>
<td>CD11c</td>
<td>Myeloid DCs</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td>CD123</td>
<td>Plasmacytoid DCs</td>
<td>(18)</td>
<td></td>
</tr>
<tr>
<td>CD141</td>
<td>BDCA-3, thrombomodulin</td>
<td>Myeloid DCs, endothelial cells</td>
<td>(20)</td>
</tr>
<tr>
<td>CD207</td>
<td>Langerin</td>
<td>Langerhans cells</td>
<td>(21,22)</td>
</tr>
<tr>
<td>CD208</td>
<td>DC-LAMP</td>
<td>Mature DCs</td>
<td>(12)</td>
</tr>
<tr>
<td>CD209</td>
<td>DC-SIGN</td>
<td>DCs, macrophages</td>
<td>(10,16)</td>
</tr>
<tr>
<td>CD303</td>
<td>BDCA-2</td>
<td>Plasmacytoid DCs</td>
<td>(14)</td>
</tr>
<tr>
<td>CD304</td>
<td>BDCA-4, neuropilin-1</td>
<td>Plasmacytoid DCs, endothelial cells</td>
<td>(15)</td>
</tr>
<tr>
<td>S-100</td>
<td>Schwann cells, melanocytes, glial cells, chondrocytes, macrophages, Langerhans cells, dendritic cells, and keratinocytes</td>
<td>(11,17)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Markers used for the characterization of DC populations in blood and tissue

<table>
<thead>
<tr>
<th>Location</th>
<th>Lineage</th>
<th>DC subsets</th>
<th>Markers</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood DCs</td>
<td>Myeloid</td>
<td>CD11c+</td>
<td>CD1c</td>
<td>(24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CD16</td>
<td>(14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>BDCA3</td>
<td>(26)</td>
</tr>
<tr>
<td></td>
<td>Plasmacytoid</td>
<td>CD11c-</td>
<td>CD123, BDCA2, BDCA4</td>
<td>(14,23,26)</td>
</tr>
<tr>
<td>Tissue DCs</td>
<td>Myeloid</td>
<td>Langerhans DCs</td>
<td>CD1a</td>
<td>(19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>langerin</td>
<td>(21,22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>S-100</td>
<td>(11,17)</td>
</tr>
<tr>
<td>Interstitial DCs</td>
<td>immature</td>
<td>CD209</td>
<td>(10,16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mature</td>
<td>CD83</td>
<td>(29,30)</td>
<td></td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td>Plasmacytoid DCs</td>
<td>CD123, BDCA2, BDCA4</td>
<td>(14,23,26)</td>
<td></td>
</tr>
</tbody>
</table>
DCs form a network of specialized antigen presenting cells sampling the environment for danger signals. The expression of cell surface molecules is variable depending on their origin, maturation status, function, and localization. In peripheral blood and tissues distinct subsets of DCs have been identified (Table 1) (10-22), including Langerhans cells, myeloid and plasmacytoid DCs. For characterization of human DC subsets, a series of markers have been proposed (Table 2) (11;14;16;17;19;21-30).

Langerhans type dendritic cells are named after Paul Langerhans, who observed a population of dendritic cells in the epidermis of human skin by using a gold chloride stain in 1868 as a medical student in Berlin (Figure 2) (31). For a long time these cells were considered specific skin cells, and only much later similar cells were described in the nasal mucosa. Fokkens et al. found dendritic CD-1(T6), HLA-DR expressing cells, resembling Langerhans cells in the epithelium and lamina propria of nasal mucosa in patients with grass-pollen allergy, with significantly more cells in epithelium of nasal biopsy samples of patients with grass-pollen allergy during the grass-pollen season than in epithelium of non-allergic control subjects. Double-staining also identified expression of IgE on CD-1-positive cells, and these cells increased after nasal allergen provocation (22-24).

Figure 2. Original identification of Langerhans cells in human epidermis by Paul Langerhans (1868) (31)
Dendritic cells in allergic disease

Dendritic cells are essential for Th2 differentiation of naïve CD4+ T cells. It has been well established that DCs play a pivotal role in several distinct phases of the allergic response in airway mucosa, not only in inducing the primary immune response to inhaled antigen leading to allergic sensitization, but also in the maintenance of eosinophilic airway inflammation (25;26).

Role of dendritic cells in allergic sensitization

In allergic subjects encountering inhaled antigen leads to maturation of respiratory mucosal DCs and migration to the draining lymph nodes where they control the activation and differentiation of antigen-specific T cells and formation of IgE secreting B cells. They provide antigen-MHC, co-stimulatory molecules and cytokines necessary for the expansion and differentiation of naïve T cells. Following an expansion phase, divided and differentiated T cells leave the lymph node as activated effector T cells that migrate back to the site of inflammation and will be (re)stimulated locally by activated DCs. In murine models of asthma, CD11b+ DCs induced sensitization to house dust mite allergen, and CD103+ DCs did not induce sensitization to house dust mite allergen (27). Depletion of DCs from the airways of naive mice prevented Th2 sensitization (32;33).

Role of dendritic cells in persistence of allergic inflammation

In murine respiratory mucosa, myeloid DCs (mDCs) play an essential role in sustaining a chronic eosinophilic airway inflammation (34), whereas plasmacytoid DCs (pDC) are important in maintaining tolerance to inhaled harmless antigen (31). CD11b+ DCs are necessary to induce a Th2 cell mediated immune response to low-dose HDM allergen (27). Lung DCs isolated from allergen-exposed mice and transferred to naive mice, induced allergen-specific Th2 cells (28). After conditional depletion of lung DCs of sensitized mice, development of Th2 cell mediated immunity in response to HDM allergen exposure did not occur (28;29;32). CD103+ DCs did not induce or maintain a Th2 type immune response to house dust mite allergen (27). Also in rats, DCs play a crucial role in maintaining the allergic response. When primed Th2 cells return to the effector site of the lung, phenotypically mature DCs are always seen in close proximity to effector T helper cells in sites of inflammation (33). In humans, elevated numbers of DCs in the nasal mucosa of allergic rhinitis subjects compared to healthy controls have been reported, as well as an increase in DCs after nasal allergen provocation (23;24;34-36).

Aim and outline of thesis

The main goal of this thesis is to investigate the role of dendritic cells in local regulation in the mucosal tissues in relation to observations of clinical response to allergen provocation.
in allergic disease. First we studied the difference in clinical response to nasal allergen provocation between subjects with different allergic sensitizations. A difference we had observed in an antihistamine-treatment study of patients with allergic rhinitis and asthma, to evaluate the “one airway, one disease” hypothesis on the level of therapy. This difference in clinical response to allergen challenge could not be explained by serum levels of allergen-specific IgE and IgG4, or in the biological activity of IgE (Chapters 4.1, and 4.2). Since dendritic cells are known to play a central role in the regulation of the immune response on various levels, we wanted to analyze whether presence, function, or regulation of dendritic cells could be responsible for this difference in clinical allergic response. Beside studying the role of dendritic cells in allergic disease, we explored different models of immunological dysfunction in mucosae of several organs, including nasal mucosa (in IgA nephropathy), pulmonary mucosa (in asthma and COPD), and colon mucosa (in Crohn’s disease). In these models the composition of dendritic cells and especially the difference in function between plasmacytoid and myeloid DCs seemed to play a major role in healthy and diseased state (Chapters 3.1, 3.2, 3.3, and 3.4). We analyzed the presence and distribution of DC subsets, and the influence of the ratio myeloid to plasmacytoid DCs, in the nasal and oral mucosa of allergic rhinitis and healthy subjects. In contrast to many other tissues, DCs of the oral mucosa are thought to promote tolerance in the absence of danger signals. To obtain a better understanding of the tolerogenic properties of DCs in maintaining homeostasis, we studied oral mucosal DC subsets in allergic and non-allergic subjects, and we compared these to nasal mucosa DCs in the same individuals (Chapters 2.1 and 2.2).

References


