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Institutionen för kliniska vetenskaper, intervention och teknologi, Enheten för ÖNH-sjukdomar

Novel Potential Targets for Treatment of Airway Inflammation

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ABSTRACT

Allergy is a complex biological response mediated by several different cell types including B lymphocytes, T lymphocytes and eosinophils. From clinical observations it is well-known that microbial infections, in particular viruses, can cause exacerbation of allergic rhinitis and asthma. The underlying mechanisms are still far from understood but recent data indicate that an activation of the immune system via pattern-recognition receptors (PRRs) including NOD-like receptors (NLRs), RIG-like receptors (RLRs) and Toll-like receptors (TLRs) might play a role. These receptors recognize invading microorganisms and enable them to interact directly with an ongoing inflammatory response. In addition, the receptors have been linked to atopic disorders such as allergic rhinitis. Today, allergen-specific immunotherapy is the only treatment that in addition to relieving symptoms also changes the progress of the underlying allergic airway disease. This therapy is traditionally administered through subcutaneous injections during three to four years but recently, intralymphatic allergen-specific immunotherapy (ILIT) emerged as an effective and less time-consuming alternative.

The aim of this thesis is to investigate novel targets of potential use for treatment of airway inflammation with special focus on PRRs and ILIT.

The first part of the thesis (PAPERS I-III) is focused on NLRs and RLRs in human leukocytes. A range of NLRs and RLRs were detected at mRNA and protein levels. Their expression in B lymphocytes was generally higher in cells derived from peripheral blood than in cells from tonsils. In T cells, a differentiated expression was seen among $CD4^+$ and $CD8^+$ tonsillar cells. Stimulation with cognate ligands in combination with triggering of the B cell receptor (via IgM or IgD) or the T cell receptor (CD3/CD28) promoted lymphocyte activation as shown by enhanced proliferation, up-regulated expression of cell-surface markers, prolonged survival and secretion of cytokines. Concomitant stimulation via the NLR and TLR systems synergistically enhanced the proliferative responses of B cells. Altogether this indicates that lymphocytes have the ability to recognize pathogens via the PRR system and it supports the idea of a role for innate receptors also in the adaptive branch of the immune system.

Eosinophils expressed both NLRs and RLRs and stimulation with the NOD1 and NOD2 ligands promoted activation as manifested by the release of cytokines, enhanced survival, regulated expression of cell-surface markers and induced chemotactic migration. These events appeared to be related to the NF-κB pathway. Stimulation with the Th2-like cytokines IL-5 and GM-CSF augmented NLR-mediated activation. These findings suggest the NLRs to be a new activation pathway for eosinophils and possibly a link between respiratory infections and allergic exacerbations.

In the second part of the thesis (PAPERS IV-V), the clinical and cellular effects of ILIT are evaluated. Actively treated patients exhibited a clear improvement of their seasonal allergic symptoms as well as their nasal symptoms upon allergen challenge. The treatment increased the levels of allergen-specific IgE and decreased nasal inflammatory responses. On a cellular level, activation of $CD4^+$ T cells and granulocytes was induced along with reduced Th2 and regulatory T lymphocyte activity. These findings appear to confirm ILIT as a safe and effective therapy for allergic rhinitis and reveal new insights on the cellular mechanisms underlying its beneficial effects.

In summary, this thesis demonstrates a role for PRRs in lymphocytes and eosinophils and that ILIT is a safe and effective route that can be used for treating patients with allergic airway disorders. In the future, we hope that these findings can be used in the development of new and more effective treatment strategies for airway inflammation.

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