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Pattern-recognition receptors in airway inflammation

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av
Anna-Karin Ekman
Medicine Magister

Huvudhandledare:
Professor Lars Olaf Cardell
Karolinska Institutet
Institutionen för Klinisk Vetenskap, Intervention och Teknik (CLINTEC)
Enheten för Öron-, Näs-, Halssjukdomar

Bihandledare:
Docent Mikael Adner
Karolinska Institutet
Institutionen för Miljömedicin
Enheten för Experimentell Astma- och Allergiforskning

Fakultetsopponent:
Professor Anders Lindén
Sahlgrenska akademin
Institutionen för Medicin
Avdelningen för Invärtesmedicin/Lungmedicin och Allergologi

Betygsnämnd:
Docent Caroline Olgart Höglund
Karolinska Institutet
Institutionen för Medicin, Solna (MedS)
Enheten för Lungmedicin

Docent Ola Winqvist
Karolinska Institutet
Institutionen för Medicin, Solna (MedS)
Enheten för Klinisk Allergiforskning

Docent Monika Stenkvist
Akademiska sjukhuset
Institutionen för Kirurgiska Vetenskaper
Öron-, näs- och halssjukdomar

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ABSTRACT

Allergic rhinitis and asthma are inflammatory diseases known to be impaired by bacterial and viral infections. The mechanisms involved are to some extent unknown. The recent identification of pattern-recognition receptors (PRRs) with the ability to recognize microbial structures might provide a clue. This thesis, comprising 6 papers, was aimed to characterize the presence and function of two PRRs families, the Toll- and Nod-like receptors (TLRs/NLRs) and their role in airway inflammation

In the first three papers various aspects of nasal challenge with TLR4 stimulating ligand lipopolysaccharide (LPS) were investigated. LPS is found in the cell wall of gram-negative bacteria. The first study demonstrated that the upper airways could be used as a model for inflammatory events in the lung, by evaluating inhibition of LPS-induced neutrophil inflammation in the nose. The nasal model was found to mimic the responses seen in a lower airway study of similar design, but without signs of systemic activation or adverse effects. This suggests the nasal LPS model to be a safe and convenient alternative to lower airway provocations. The nasal model was then used in the second paper to analyze the role of macrophage inflammatory protein (MIP)-1α. The LPS challenge resulted in a neutrophil-mediated secretion of MIP-1α, dependent on nuclear factor (NF)-κB, protein kinase (PK)C and p38 mitogen activated protein kinase (MAPK) pathways. LPS also delayed neutrophil apoptosis *in vitro*, suggesting that the secretion of MIP-1α may be boosted by a prolonged neutrophil survival.

In paper three patients with symptomatic allergic rhinitis displayed a systemic up-regulation of TLR4 expression in leukocytes in nasal lavage, blood and bone marrow during pollen season. Challenge with LPS in patients exposed to allergens resulted in a release of a variety of cytokines. No such cytokine release was seen with either allergen or LPS alone. The systemic up-regulation of TLR4 seen during on-going allergic rhinitis, might contribute to the observed increase in response when LPS was applied together with allergen. These results further strengthen the suggestion that a local infection may exacerbate or aggravate allergic symptoms.

The fourth study visualized the effects of allergen on two major populations of dendritic cells, the myeloid dendritic cells (mDCs) and the plasmacytoid dendritic cells (pDCs), in the nose of patients with allergic rhinitis. Allergen challenge increased the number of pDCs in the nasal sub-epithelium. *In vitro* studies of pDCs revealed that they could be activated by tumor necrosis factor (TNF)-α, interleukin (IL)-4 and CpG stimulation, and that TNF-α caused a higher activation among atopic than non-atopic subjects. This supports the notion of mDCs and pDCs as distinct populations with different roles in the allergic process. Further, it suggests that the pDCs play an active role in the course of allergic rhinitis.

In the fifth study isolated guinea pig tracheas segments were stimulated for three days with the TLR7 agonists R837 and R848. The stimulation was found to reduce the airway smooth muscle contraction via p38, MAPK and NF-κB related mechanisms, independent of the epithelium. This indicates that TLR7 has a protective role against virus infection and that TLR7 deficiency might be a cause for airway disease.

The final paper characterized the expression and function of NLRs in neutrophils, with focus on the three NLRs NOD1, NOD2 and NLRP3. Protein and mRNA for NOD2 and NLRP3 were found in isolated neutrophils. Activation of the former receptor resulted in IL-8 secretion and a change in neutrophil phenotype, while activation of the latter receptor caused secretion of IL-1β. Both NOD2 and NLRP3 increased neutrophil migration. Together this signals the existence of a previously unknown pathway for activation of these cells.

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