Dermal Exposure to Toll-like Receptor Ligands and Cutaneous Allergen Sensitisation Blocks Development of Asthma via IFN-gamma-dependent Mechanisms

The increase in atopy and asthma is related to improved hygiene status and reduced Th1-type immune responses according to the hygiene hypothesis. The authors of this article found that allergen sensitisation through skin with toll-like receptor 4 (TLR4) ligand lipopolysaccharide (LPS) and TLR2 ligand Pam3Cys but not with TLR3 ligand Poly(I:C), decreases Th2-type allergic responses and airway reactivity. LPS shifted the balance toward Th1-type immunity by inducing interferon-γ production.

Bacterial components are suggested to have a role in the development of protective immunity. Toll-like receptors (TLRs) recognise pathogen-associated microbial patterns activating the innate immune system. In atopic dermatitis, the skin barrier is disrupted and microbial components and allergens can penetrate easily through the skin. The research group investigated the role of various TLR ligands in the development of asthma by mimicking the natural route of sensitisation from the skin to asthmatic symptoms.

The research group sensitised mice intradermally with PBS, OVA (ovalbumin), and OVA in combination with low or high doses of TLR ligands Pam3Cys (TLR2), poly(I:C) (TLR3), and LPS (TLR4). After 3 intranasal OVA challenges the samples were analysed. High doses of LPS and Pam3Cys significantly attenuated airway responsiveness to metacholine and the total number of cells and inflammatory cells in bronchoalveolar lavage fluid were significantly reduced. Also the expression of Th2-type cytokines IL-4, IL-5, and IL-13 in lung tissue was decreased. LPS also elicited a significant increase in IFN-γ mRNA levels in the lung tissue. Dermal exposure to LPS and Pam3Cys reduced the number of OVA+CD11c+ dendritic cells in draining lymph nodes and LPS enhanced the expression of activation markers CD80 and CD86. OVA and LPS enhanced the number of CD8+ T cells and their IFN-γ production. Depletion the mice of CD8+ T cells with anti-mouse CD8 mAb injections before OVA challenge resulted in significantly reduced IFN-γ mRNA levels in the lung tissue, increased Th2-type cytokines IL-5 and IL-13 and increased numbers of eosinophils in BAL fluid in mice treated with LPS. These results show the major role of IFN-γ in mediating the suppressive effect LPS on airway inflammation.

The authors show that identical exposure regimes of different TLR ligands exhibit various effects on the Th2 inflammatory response: TLR2 and TLR4 ligands induced protective effects, whereas TLR3 ligand even augmented the Th2-type response. The authors propose that different dose, time, and administration routes elicit qualitatively distinct signals trough TLRs, influencing T-cell polarisation. The authors conclude that the results emphasise the importance of restoring the skin barrier function and also highlight the role of cross-talk between the dermal microbiome and the host in the development of allergies.

The first author of the study, Rita Haapakoski, works as a postdoctoral research fellow at the Oxford University Department of Psychiatry. The study group, headed by Professor Harri Alenius, has elucidated the role of the immune mechanisms of allergies and immunotherapeutic mechanisms of asthma at the Finnish Institute of Occupational Health, Helsinki, Finland.