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Dissertations-Kurzfassung

Alternative activation of macrophages: gene expression profiling in vitro and analysis in atopic dermatitis ex vivo

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Introduction: Atopic dermatitis (AD) is an immune-mediated inflammation of the skin, often with a significant genetic component. Th2-type cytokines predominate in the acute phase of AD, but there is a shift to Th1 cell involvement and expression of IFN-γ in chronic lesions. Macrophages play an important role in the generation and regulation of immune responses in AD. The cells of the mononuclear phagocyte system are derived from pluripotent haematopoietic stem cells in bone marrow that further differentiate to finally become tissue macrophages. Type 2 activation refers to an alternative activation in the presence of IL-4 and IL-13 that signal through a common receptor chain, IL-4Ra. IL-4 is the main Th2-type cytokine.

Aims and general methodologies: This study aims at detecting common elements in the differential gene expression profiles of alternatively activated macrophages and peripheral blood monocytes of patients with atopic dermatitis. For this purpose: (1) the gene expression profiles of alternatively activated macrophages (stimulated by IL-4, TGF-β and IL-4-/TGF-β) were compared to those of control macrophages with the use of microarray analysis, (2) the differential gene expression patterns among these macrophage populations were confirmed via semiquantitative and real-time RT-PCR, and (3) the expression levels of candidate genes confirmed to be differentially expressed were analysed in monocytes from patients with atopic dermatitis as compared to healthy donors.

Results: The gene expression profile of IL-4-stimulated monocytes is marked by a prothrombotic tendency, promotion of inflammation-resolving lipoxins, inhibition of inflammatory leukotrienes, upregulation of CCL22 and CCL18, and downregulation of CXCL2 and of certain members of the TNF-α-receptor superfamily. IL-4-(co)stimulated monocytes exhibit a higher expression of Wnt5a ($p<0.1$ under IL-4 alone and $p<0.025$ under IL-4/TGF-β), Wnt5b ($p<0.025$), Norrin ($p<0.025$), and FOXQ1 ($p<0.05$), in comparison to non-stimulated monocytes, as confirmed by means of real-time RT-PCR. IL-4-(co)stimulated monocytes highly express Fzd8, Fzd7, Ryk, SFRP4, and lack Fzd4, the receptor of Norrin, as confirmed by means of semiquantitative PCR. Primary peripheral blood monocytes of patients with acute atopic dermatitis exhibit in real-time RT-PCR assays a significantly higher expression of FOXQ1 ($p<0.05$) in comparison to those of healthy non-atopic donors. No gene expression of Wnt5a, Wnt5b and NDP could be detected in blood monocytes of patients with atopic dermatitis.

Conclusions: IL-4-stimulated monocytes seem to exhibit a Wnt-gene expression profile which could be compatible with a preferential activation of non-canonical Wnt signalling pathways. Non-canonical Wnt signalling is crucial for cell polarity and oriented cell/tissue movement. FOXQ1, a transcription factor belonging to the forkhead protein family that has only been implicated in hair development, could act in monocytes as an intranuclear mediator of IL-4 effects. In this respect, it will be highly important to identify FOXQ1 target genes in M2 macrophages. FOXQ1 and its target genes could participate in regulating M2-mediated Th2 type inflammatory reactions such as atopic dermatitis and may allow development of novel therapeutic approaches.