

## **ABSTRACT**

Cervical cancer cells produce increased amounts of IL-6. However, these cells poorly respond to autocrine IL-6 due to the loss of IL-6 receptors. Recently it has been shown that IL-6 may not only function as a pro-inflammatory cytokine but also has immunosuppressive properties. Thus IL-6 affects the differentiation of dendritic cells. We hypothesised that IL-6 could alter the function of antigen presenting cells residing within a tumour. As it is still unclear, which factors lead to dendritic cell maturation within a tumour, a toll like receptor signal (LPS) and a T cell like signal (CD40L) were used in an in vitro model system to study the impact of IL-6 on dendritic cell biology.

Dendritic cells were differentiated from peripheral blood monocytes. IL-6 strongly inhibited the expression of the chemokine receptor CCR7 when matured with LPS resulting in impaired migration towards its ligand SLC and ELC. In vivo the expression of this receptor induced during maturation plays a pivotal role in the migration of dendritic cells from peripheral tissue into lymphoid tissue. CD40L could overcome this suppressive effect on CCR7 in dendritic cells. Despite low CCR7 expression in the case of LPS, these cells were matured as judged by increased expression of the maturation-associated molecules DC-LAMP, MHC class II and CD86, unchanged CD80 and CD40 and intermediate to high CD83 expression levels. Intracellularly, IL-6 impaired binding activity of the transcription factor NF $\kappa$ B which is known to control CCR7 expression. In contrast, LPS-mediated activation of the p38 mitogen activated protein kinase was not suppressed but rather enhanced by IL-6, most likely contributing to the higher expression levels of other maturation-associated molecules. Neutralisation experiments revealed a role of autocrine IL-10 in IL-6 mediated CCR7 suppression. IL-6 showed a strong suppression of Th1 cytokine IL-12 production even when added to the already differentiated DC. Both the Th1 cytokine IFN- $\gamma$  as well as cytokine IL-4 failed to reverse the effect of IL-6. Whereas activity of known IL-12 inhibiting molecules IL-10, MCP-1, TNF-receptor associated factors and intracellular kinases were investigated. IL-6 induced changes could only be correlated to changes in NF $\kappa$ B binding activity. In summary our results show two possible mechanisms, how IL-6 may contribute to failure of tumour immune control via functionally impaired dendritic cells.