SUMMARY

Dndritic cells (DCs) respond to changes in their lipid environment by altering gene expression and immunophenotype. Some of these alterations are mediated via the nuclear receptor superfamily. In previous works nuclear receptors such as PPARs, RAR and VDR, that are found to be expressed at high levels in differentiating DCs and are activated upon exposure to various lipids such as fatty acids, retinoids or by active Vitamin D3, were found to support a tolerogenic DC phenotype. Their effect on DC functions involved interaction with stimulatory effects such as TLR ligands (2, 3, 4, and 7) and cytokine productions resulting in a reduced capacity to stimulate T-cell proliferation. Despite the well-characterized role of LXR in macrophage biology little is known about its the contribution to DC biology. In our work we investiagted the role of LXR in dendritic cell differentiation and functions. We carried out a systematic analysis of LXR, activated by synthetic ligands or naturally occurring oxysterols in developing human monocyte derived dendritic cells. We found that LXRs are present and can be activated throughout dendritic cell differentiation in monocyte as well as blood derived DCs. Administration of LXR specific natural or synthetic activators induced target gene expression accompanied by increased expression of DC maturation markers such as CD80 and CD86. In mature DCs LXR activation augmented the production of inflammatory cytokines IL-12, TNFα, IL-6 and IL-8 and resulted in an increased capacity to activate CD4+ T cell proliferation upon ligation with TLR4 or TLR3 ligands. These effects appear to be underpinned by prolonged NFκB signaling. Supporting such an inflammatory role we found that LXR positive DCs are present in reactive lymph nodes from patients with tuberculosis and sarcoidosis and was present also in DCs of tumor associated lymph nodes. In our extended studies on the cross-talk of inflammatory pathways and lipid activated nuclear receptors we found that PPARγ was induced in monoctyes upon *Mycobacterium bovis BCG* infection and showed that PPARγ coordinates lipid metabolism and inflammation in BCG-infected macrophages, potentially affecting mycobacterial pathogenesis. We propose that activation of LXR and PPARγ represents a novel lipid-signaling paradigm that alters the inflammatory response of human DCs and plays a pivotal role in the host vs. pathogen interactions.

Keywords: nuclear receptors, inflammation, LXR, PPARg, macrophages, dendritic cells