New Insights of LXR Signalling Inhibition of Cancer Proliferation and Inflammation

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Liver X receptors (LXRs) are ligand-activated transcription factors belonging to the nuclear receptor (NR) superfamily. Up-to-date, more than 1900 publications have established the role of LXRs in cholesterol homeostasis, lipogenesis, glucose metabolism, atherosclerosis, proliferation, and inflammation. In this thesis we have focused mainly on the role of LXR in proliferation and inflammation.

In Paper I we studied the role of LXR on the inhibition of proliferation in breast cancer cell lines through PI3K/AKT signalling pathway. Phosphorylation of several protein kinases in this pathway was reduced upon LXR activation, such as AKT and PI3K. Expression of both phosphatases PTEN and PHLPP, which directly regulate PI3K product (PIP3) and AKT respectively, was induced by LXR on transcriptional and protein levels. Furthermore, we showed that LXRβ was main executer of the anti-proliferative effect in human MCF7 breast cancer cell line.

In Paper II we continued the findings of paper I to explore more the role of LXR in inhibition of proliferation in human breast cancer cell line in relation to signalling pathway. In this study we investigated whether LXR regulates mTOR complex pathway in human breast carcinoma cell line. Thus, we identified that activated LXR inhibited proliferation of MCF7 cell via mTORC1 by affecting the phosphorylation of Raptor at Ser792 and mTOR at Ser2448, and its downstream target p70S6K and 4EBP1. Our data showed that there was no direct effect of LXR on the phosphorylation status of mTORC2. We further identified that LXR stimulation induced proliferation of MCF7 cells when Raptor was depleted, suggesting the crucial role of Raptor in LXR inhibition of cell proliferation.

In Paper III we investigated the impact of LXR agonists on triple negative human breast cancer using a patient-derived xenograft model. Primary tumors from patients were grafted into immune-compromised mice, where the tumour was allowed to expand. The primary tumour was then collected and used for subsequent xenografts, for generating a large mouse colony, all bearing tumors were shown that maintained the characteristics of the original tumour. We found that activation of LXR reduced progression of triple negative breast tumors in vivo. Moreover, we showed that LXR reduced phosphorylation of AKT at Ser473 residue, decreased expression of the proliferation marker Ki67, as well as reduction of both α-SMA (smooth muscle actin) and capillary density. The last two are angiogenic markers, thus suggesting a role of LXR in regulation of angiogenesis.

In Paper IV we demonstrated a protective role of LXR in inflammatory bowel disease (IBD). We used dextran sodium sulfate (DSS) and 2,4,6-trinitrobenzene sulfonic acid (TNBS) to induce colitis in mice. We observed that LXR deficient mice showed severe and fast disease progression with slower recovery as well as decreased survival rates. In addition, activation of LXR reduced the infiltration of immune cells and the expression of inflammatory cytokines, chemokines in the colon epithelium of mice. In patients with IBD, expression of both LXRα and LXRβ were significantly suppressed in inflamed colon compared with healthy controls.