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Institutionen för biovetenskaper och näringslära

The Antiproliferative Role of the Liver X Receptors in Breast and Colorectal Cancer

AKADEMISK AVHANDLING

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ABSTRACT

The liver X receptors (LXR α and LXR β) are members of the nuclear receptor superfamily of ligand activated transcription factors and have functions as regulators of lipid and glucose metabolism, as well as inflammatory response. In recent years, several reports have demonstrated an important role of LXRs in the control of cell proliferation.

In **Paper I** we demonstrate that LXR activation with synthetic agonist GW3965 leads to a strong antiproliferative effect in four different human breast cancer cell lines. We show that LXR activation induces an arrest at the G₁/S check point of the cell cycle with a hypophosphorylation of retinoblastoma protein and a downregulation of cell cycle modulators such as Skp2, cyclin A2 and cyclin D1. We further show that the antiproliferative function of LXRs is independent of lipid biosynthesis.

In **Paper II** we follow up the results in Paper I to elucidate more mechanisms of LXR activation in human breast cancer cell lines. Using microarray analysis, we find both cell line specific and common LXR target genes. The common responsive genes that were upregulated upon LXR activation are annotated to known metabolic functions of LXR, while the common downregulated genes mostly include those with function in cell cycle regulation and proliferation. Comparing the common downregulated gene set, with breast cancer tumour samples and patient data we find that patients with tumours expressing lower levels of these LXR target genes had better survival compared to patients with a higher expression of these genes. In addition, we identify the E2F family of transcription factors as mediators of the antiproliferative effect of LXR activation.

In **Paper III** we demonstrate that activation of LXRs with GW3965 decreases proliferation in human colorectal cell lines with a cell cycle arrest in the G₁ to S phase transition. We demonstrate a decreased expression of cell cycle promoters such as Skp2, CDK1, CDK2, CDK4, cyclin E, cyclin B1 and c-myc, as well as hypophosphorylation of retinoblastoma protein. Moreover, we show that LXR deficient mice have an increased proliferation in the colonic crypt compared to wild type mice. Also, activation of LXRs with GW3965 reduces proliferation in the colonic crypt of wild type mice.

In **Paper IV** we demonstrate that activation of LXRs dampens the inflammatory response by downregulating pro-inflammatory mediators in two different mouse models of colitis. In addition, LXR deficient mice have a faster and more severe disease progression. We further demonstrate that expression of LXR regulated genes is suppressed in colon samples from patients with either Crohn's disease or ulcerative colitis compared to healthy controls. Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is associated to increased risk of developing colorectal cancer. The data in Paper IV suggests the potential for LXR mediated inhibition of inflammation during IBD, thus reducing the risk for developing colorectal cancer.