Institutionen för Biovetenskaper och Näringslära

Exploring the Genome-Wide Impact of Estrogen Receptor Alpha and Estrogen Receptor Beta in Breast and Colon Cancer Cells

AKADEMISK AVHANDLING
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av
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ABSTRACT

Estrogen signaling is involved in the development and progression of breast cancer and is implicated to be protective in colon cancer. Estrogenic actions are conveyed through transcriptional regulation by ligand stimulated estrogen receptors (ERα and ERβ). ERα is upregulated in most breast cancers and is responsible for the proliferative effect of estrogen. ERβ on the other hand is usually downregulated, and studies indicate an antiproliferative function. Therapies targeting ERα are available and commonly used in the treatment of breast cancer. In the normal colonic epithelia, however, ERβ is the most abundant estrogen receptor and the suggested mediator of the protective effects of estrogen in colon cancer. The role of ERβ in breast cancer and colon cancer is not well understood. Thus, exploring the genome-wide impact and contribution of both receptors in estrogen responsive cancers would substantially help to identify novel therapeutic and preventive strategies for these cancers.

In Paper I, we examined differences in transcriptional regulation between ERα and ERβ in the breast cancer cell line T47D. We could show that ERβ often exhibited an opposing effect on ERα-regulated genes within proliferation and regulation of cell cycle. We also demonstrated a set of genes only regulated by ERβ, indicating that, despite the high homology between the two receptors, there are differences in their transcriptional targets. The fact that ERβ opposed ERα indicates that ERβ activation may be of value in the treatment of breast cancer. To further explore the transcriptional role of ERα in breast cancer, we performed large-scale analyses of microRNA in 24 hours estrogen treated ERα-expressing T47D cells, Paper II. However, we found no evidence of direct and rapid regulation of mature miRNAs by ERα.

In Paper III, we studied ERβ gene regulation in colon cancer cells. We could show that ERβ-expressing xenografts grew significantly slower than those lacking ERβ. Further we demonstrated that ERβ induced a transcriptional response independently of ERα and induced inhibition of the proto-oncogene MYC and other G1-phase cell cycle genes. In Paper IV, we dissected the regulatory networks of ERβ-induced transcriptional changes in human colon cancer cells. The set of genes changed by ERβ varied in different colon cancer cell lines, however, corresponded to the same biological processes such as cell cycle regulation and kinase activity. In addition, we identified the ERβ-driven downregulation of the transcription factor PROX1 as a key mechanism behind a large proportion of the transcriptional changes. In Paper V, we studied the effect of long term expression of ERβ on the miRNA pool in SW480 colon cancer cells. While we could not show a direct and rapid effect of ERα on the miRNome, we showed that long term expression of ERβ did induce large changes in the miRNA pool in colon cancer cells. In particular, we found the oncogenic miR-17-92 cluster to be downregulated and proposed this to be a consequence of the ERβ-induced downregulation of MYC.

In conclusion, we have shown that ERβ is antiproliferative in breast and colon cancer cells, both when co-expressed with ERα and alone, as well as identified key signaling pathways. We suggest that activation of ERβ will have a beneficial effect for treatment or prevention of estrogen dependent cancers.