TGF-β signaling in cancer

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i hörsal Ragnar Sandberg, Medicinaregatan 5, Göteborg, måndagen den 6 december 2010, kl. 09.00

av

Erik Johansson

Fakultetsopponent:
Docent Serhiy Souchelnytskyi
Institutionen för Onkologi-Patologi, Karolinska Universitetssjukhuset, Solna

Avhandlingen baseras på följande delarbeten:


IV. Johansson E, Zeng Z, Yoshida T, Funa K. Nuclear receptor TLX inhibits TGF-β signaling in neuroblastoma. Manuscript

UNIVERSITY OF GOTHENBURG
TGF-β signaling in cancer

Erik Johansson

Department of Medical Chemistry and Cell Biology, Institute of Biomedicine, the Sahlgrenska Academy at the University of Gothenburg, Sweden 2010

Abstract

Transforming Growth Factor Beta (TGF-β) is a cytokine regulating a wide range of cellular processes such as proliferation, differentiation, and migration. At the early stages of cancer development TGF-β functions as a tumor suppressor, mainly due to its inhibitory effect on cellular growth, but during cancer progression, mutations in TGF-β signal components switches TGF-β into a promoter of cancer cell proliferation, survival and metastasis. The aim of this thesis was to study the role of TGF-β signaling in the progression of two different cancer types - diffuse-type gastric carcinoma and neuroblastoma. Furthermore, we wanted to investigate the function in neuroblastoma of the nuclear receptor TLX, a protein involved in neuronal stem cell maintenance, and if TLX interacts with TGF-β signaling.

We found that disruption of TGF-β signaling in diffuse-type gastric carcinoma cells led to accelerated tumor growth in vivo through the induction of angiogenesis, possibly due to the repression of anti-angiogenic proteins including TIMP2. In addition, TGF-β repressed expression of the cancer stem cell marker ABCG2 and diminished a subpopulation of cancer-initiating cells within the main cancer cell population, leading to reduced tumor formation. TLX expression in neuroblastoma cells inhibited VHL-dependent degradation of HIF2α, which then could bind and activate the VEGF promoter. Silencing of TLX induced VHL protein levels, reduced hypoxia-dependent induction of HIF2α and inhibited cell proliferation. Furthermore, we found that TLX knockdown induced TGF-β response in neuroblastoma cells as seen by increased TGF-β dependent expression of its target genes p21 and Smad7. TLX physically interacts with Smad3 and knockdown of TLX led to increased TGF-β dependent nuclear translocation of Smad2/3.

In conclusion, the results from this thesis suggest that TGF-β signaling has an important tumor suppressive role in diffuse-type gastric carcinoma, due to both inhibition of tumor angiogenesis and repression of a cancer-initiating subpopulation of cancer cells. Furthermore, TLX was shown to be important for neuroblastoma cell proliferation, with a possible role in hypoxia-induced angiogenesis as well as in the regulation of TGF-β signaling in neuroblastoma.