TGF-β signaling in cancer

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I. **Johansson E**, Komuro A, Iwata C, Hagiwara A, Fuse Y, Watanabe A, Morishita Y, Aburatani H, Funa K, Kano MR, Miyazono K. Exogenous introduction of tissue inhibitor of metalloproteinase 2 reduces accelerated growth of TGF-β-disrupted diffuse-type gastric carcinoma.
Journal of Cancer Science 2010 Nov; 101(11):2398-2403

II. Ehata S, **Johansson E**, Katayama R, Koike S, Watanabe A, Hoshino Y, Katsuno Y, Komuro A, Koinuma D, Kano MR, Yashiro M, Hirakawa K, Aburatani H, Fujita N, Miyazono K. Transforming growth factor-β decreases the cancer-initiating cell population within diffuse-type gastric carcinoma cells.
Accepted manuscript, Oncogene 2010

III. Zeng Z, Yoshida T, **Johansson E**, Lakshminarasimhan Chavali P, Hayashi A, Funa K. TLX controls angiogenesis through interaction with the Von Hippel-Lindau protein.
Manuscript

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

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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.

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