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Chapter 2

Thesis aim and outline
The interaction between epithelial tumor cells and their microenvironment is of crucial importance in cancer progression. Both direct cell-cell contact and paracrine signaling, as well as more long distant effects of cytokines and chemokines are involved in tumor progression and metastatic spread. Therefore, the tumor microenvironment (TME) has been recognized an important player in cancer progression and its potential as a therapeutic target is extensively explored. This thesis describes studies on the transforming growth factor-β (TGF-β) and bone morphogenetic protein (BMP)-mediated interactions between tumor cells and specific TME components and evaluates their potential as a therapeutic target in either breast- or colorectal cancer (CRC). In patients, we have observed changed TGF-β/BMP signaling in both tumor cells and the TME in various solid tumors. To study TGF-β/BMP-mediated interactions between tumor cells and stromal cells, we have developed \textit{in vitro} and \textit{in vivo} models systems. The aim of this thesis is to unravel the pro-tumorigenic role of TGF-β/BMP-mediated interactions in the TME, with a specific interest in the co-receptor endoglin, and assess their potential as a therapeutic target.

In \textbf{chapter 3}, the potential of using endoglin as a target for tumor imaging and anti-angiogenic therapies is extensively discussed. Endoglin expression on endothelial cells will be the main focus of this review, although other cell types are also discussed. \textbf{Chapter 4} describes studies on the anti-angiogenic properties of ALK1-Fc, an ALK1 ligand trap. The results show, improved tumor vessel quality and therefore better delivery of chemotherapeutic agents in several different solid tumors. Combined targeting of the pro-angiogenic vascular endothelial growth factor (VEGF) and TGF-β/endoglin signaling pathways in breast cancer is discussed in \textbf{chapter 5}. This study illustrated, using both \textit{in vitro} and \textit{in vivo} models, that dual targeting of pro-angiogenic pathways decreased angiogenesis to a higher extent than targeting both pathways separately. More importantly targeting of endoglin, using either the neutralizing antibody TRC105 or and endoglin ligand trap, decreased metastatic spread in a mouse model for breast cancer. TGF-β-mediated interactions between cancer-associated fibroblasts (CAFs) and epithelial tumor cells will be described in \textbf{chapter 6}. This study showed a cancer-promoting feedback loop which is the result of hyperactivated TGF-β signaling in CAFs, leading to increased TGF-β production and protease secretion, which ultimately leads to increased invasive behavior. The role of endoglin on CAFs is more extensively researched in CRC, described in \textbf{chapter 7}. Endoglin expression on CAFs at the invasive border of colorectal tumors proved to be a predictive factor for metastatic disease in early stage CRC. \textit{In vitro} and \textit{in vivo} studies described in this chapter show a role for endoglin in CAF invasion and endoglin appears to be involved in CRC metastasis. Finally, \textbf{chapter 8} reports on the fibroblast-specific role of endoglin in CRC which was assessed in a mouse model for chemically-induced CRC. Fibroblast-specific knock out of endoglin resulted in enhanced tumorigenesis in this model, accompanied by expansion of the stromal tumor component and increased infiltration of specific immune cells subsets. In \textbf{chapter 9}, the data of the different studies are summarized and discussed.