Small talk in the tumor microenvironment – the contribution of fibroblasts and endothelial cells to the malignant phenotype

AKADEMISK AVHANDLING
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av

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ABSTRACT

Cancer is the result of aberrant cells developing into tumor cells that act in concert with the micro- and macroenvironment like any other organ in our bodies. The cells and molecules of the tumor microenvironment are important contributors to the tumorigenic process. However, we are still far from understanding the full complexity and intricate molecular interactions that affect the process.

We show that platelet derived growth factor (PDGF)-CC, expressed by tumor cells, recruit cancer-associated fibroblasts (CAFs) to the tumor microenvironment resulting in an accelerated tumor growth rate. Among the CAFs, we identify three different subclasses by their variable expression of fibroblast specific protein (FSP)-1 and PDGF receptor (PDGFR)-α. Two of these subclasses express osteopontin (OPN), which is responsible for the increased tumor growth rate. In subsequent studies, we reveal that PDGF-CC expression is high in breast cancer and that PDGF-CC presence in epithelial cells is an independent prognostic marker for patient survival in a large cohort of patients. We also developed a monoclonal antibody for PDGF-CC, which as a monotherapy reduces tumor growth rate proving the in vivo efficacy of targeting PDGF-CC.

Transforming growth factor (TGF)-β family members have been attributed complex and contradictory effects on angiogenesis. We have studied the effect of ablation of endoglin or activin receptor like kinase1 (ALK1) in tumor models. Targeting endoglin results in resistance and no effect on tumor growth or vessel density. We do however detect increased metastatic seeding as a consequence of endothelial to mesenchymal transition (EndMT). Endoglin deficiency prolongs the tumor sensitivity to anti-angiogenic therapy that otherwise induce resistance. However, pharmacological and genetic targeting of ALK1 results in reduction of tumor formation and burden due to decrease in the vessel density. Molecular characterization reveals that the combination of TGF-β and bone morphogenic protein (BMP)-9 is responsible for inducing activation of endothelial cells and angiogenesis.