Bidirectional Cellular Reprogramming: An Approach to Identify Candidate Drug Targets and Biomarkers

Monika Ehnman*, Carina Strell, Beat W Schäfer, Janet Shipley, Hong Qian and Arne Östman

Background and project overview
- PDGF receptors (PDGFR) are expressed in sarcoma cells and stromal cells in a context-dependent manner.
- A PDGFR-targeting agent was recently approved for advanced sarcoma, but the target cell is unclear.
- We have shown that stromal PDGFR expression in rhabdomyosarcoma associates with subtype and metastasis.
- Here, we explore bidirectional cellular reprogramming of tumor cells and stromal cells in rhabdomyosarcoma—especially considering pathways with potential PDGFR crosstalk.

Rhabdomyosarcoma
RMS is the most common soft tissue sarcoma of childhood. Current multimodality regimens involve surgery, chemotherapy and radiation, but are not always effective. Advances in overall treatment efficacy and reduced toxicity are likely to be derived from targeted therapies.

Summary
Normal PDGFR positive stromal cells have inhibitory effects on RMS growth, but are reprogrammed by tumor cells during tumor progression. We have studied this process and developed an approach for identifying candidate drug targets and biomarkers involved in tumor progression.

Conclusions
1) Benefits of PDGFR targeting might be restricted to cases where PDGFRs support tumor-stimulatory stromal cell subsets
2) Blocking of sarcoma-induced reprogramming of tumor-inhibitory stromal cells might be a therapeutic strategy for metastatic growth

Results
RD sarcoma cells subvert the growth-inhibitory phenotypes of tumor-naïve stromal cells.

Figure 1. Schematic overview: In vivo model systems for studies on crosstalk between tumor cells and stromal cells in sarcoma

Model system 1: With primary SkMS cells

Model system 2: With primary BJ cells

Figure 2. Gene expression analysis of BJ stromal cell response during education by tumor cells (Model system 2).

Future directions
We are currently exploring therapeutic targeting of identified candidate proteins involved in bidirectional cellular reprogramming during tumor progression. Both tumor cell and stromal cell responses are characterized.