Targeting vascularized and hypoxic compartments in solid malignancies: from basic research to dogs with cancer

Project description: Angiogenesis, the formation of capillaries from pre-existing vessels, is key to meet the increased oxygen and nutrient demands of growing tumors. Due to this reliance of solid tumors on active vascularization, angiogenesis inhibitors (AIs) were expected to be highly effective in controlling, and perhaps curing, malignant diseases. However, AI-centered clinical trials on human cancer patients often revealed only short-lived benefits at poor response rates. Moreover, tumor-bearing mice treated with AIs showed enhanced recurrence and metastatic spread of the disease. This sobering outcome most likely originates from the selection of hypoxic tolerant cancer cell variants with an increased invasive behavior and a therapy- and radio-resistant phenotype. New cancer therapies, therefore, are needed to effectively and simultaneously target both aerobic and hypoxic compartments within solid tumors.

Hypoxic tumor cells primarily consume glucose delivered by blood, and in turn, fuel well-oxygenated tumor areas with lactate, the end product of anaerobic glycolysis. Cellular import of lactate can be inhibited by the MCT1-blocker alpha-cyano-4-hydroxycinnamate (CHC) to compel oxygenated tumor cells into using glucose instead of lactate as prime energy substrate. Treated with CHC, oxygenated cells have been found to compete with hypoxic cells for glucose, which may provide a highly efficient kill of hard-to-treat hypoxic cells.

We previously applied this concept to various human tumor cell lines explanted onto the chorioallantoic membrane (CAM) of live chicken embryos and found a significant increase, rather than diminishment, of tumor hypoxia and cell spread in response to AI monotherapy (manuscript in preparation). In contrast, combinatorial AI+CHC treatment clearly inhibited tumor growth and decreased tumor hypoxia and spread of cancer cells. Together with the Dept. for Small Animals we now aim to establish and compare CAM assays with mouse xenograft models for a better assessment of efficacy and safety of AI approaches relevant for veterinary and human oncology. By pursuing the impact of the inhibition of MCT1-driven lactate uptake on established AI interventions of canine tumors, both in monotherapeutic and combinatorial application, we aim to validate this novel approach at the model stage. Moreover, radiation response of treated tumor cells in CAM and xenograft models in combination with the clinical translation of our various therapies in animal patients (dogs) will be investigated.

Key words:
Tumor Hypoxia, Angiogenesis, Metastasis, HIF, Pimonidazole, Chorio-allantoic Membrane, Mouse xenograft, Sunitinib, Avastin, Razoxane, MCT1, Radioresistance.

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