Project title:

Therapeutically addressing TAMEP mediated blood tumor barrier formation

Summary of achievements: Most patients diagnosed with glioblastomas (GBMs) die from tumor relapse after multi-modal therapy comprising neurosurgical resection, irradiation- and chemo-therapy. One reason for treatment failure is that GBMs are regionally shielded from blood-borne therapeutics through a vascular barrier (the blood-tumor-barrier; BTB). With funding provided by the Anni Hofmann Stiftung for the years 2024 and 2025 we have uncovered a cell biological process promoting BTB formation by a fraction of parenchymal progenitor cells named TAMEP-progenitors, which were discovered by us previously. Generally, the intratumoral accumulation of non-transformed, progenitor cells in brain tumors can have profound impact on tumor evolution and heterogeneity. However, direct effects of distinct parenchymal progenitor cell components, including TAMEP-progenitors, on the tumor microenvironment remained to be explored. Using transgenic mouse models for the manipulation of vascular cells in GBM we uncovered a strategy for efficient and persistent manipulation of pathological vascularization. Lineage tracing in transgenic, tumor bearing models combined with single cell transcriptomics highlighted TAMEP-progenitors as GBM-specific avascular cells with a high capacity to promote extracellular matrix maturation during pathological vascularization. Transgenically controlled ablation or pharmacological modulation of TAMEP-progenitors in GBM corroborated an essential role for TAMEP-progenitors in morphological and functional maturation of GBM vessels via matrisome crosslinking. In particular, TAMEP-progenitors regulated tumor vascularization via collagen-crosslinking and promoted blood-tumor barrier (BTB) formation via Lysyl oxidases (LOX). This indicates an essential role for TAMEP-progenitors in BTB constitution and vessel supply in brain tumors, which provides new perspectives for GBM therapy.