TAMEP shape neoplastic-angiogenesis in GBM

We described a progenitor cell-type of the brain tumor microenvironment, termed TAMEP-progenitor, which has a profound role in neoplastic angiogenesis in the brain. TAMEP-progenitors were specifically ablated by conditional *Sox2*-knockout, preventing the intratumoral accumulation of TAMEP. Our scRNAseq data indicated an aberrant, myeloid-like expression profile in TAMEP. This was subsequently validated in different models by transgenic-reporters and immunofluorescence-markers, for e.g. PU.1, CD11b, F4/80 or CX3CR1 (Back et al., 2005; Glass and Synowitz, 2014). However, despite this myeloid-appearance we could clearly show that TAMEP are not myeloid cells: We excluded that TAMEP (or their progenitors) derive from hematopoietic niches in the bone marrow (see previous report) and we ruled out that TAMEP derive from microglia using the Cx3cr1-creER2 model (Benz et al., 2008; Chen et al., 2017; Wieghofer et al., 2015).

We showed that a small and distinct population of cells with a myeloid expression-profile has specific impact on brain neoangiogenesis. A role for myeloid cells in GBM-angiogenesis was previously observed (Brandenburg et al., 2016; Mathivet et al., 2017). Reducing the numbers of monocyte-derived macrophages was exploited to improve chemotherapy, but had no direct tumor-suppressing effect (Mathivet et al., 2017). In contrast, CNS-specific ablation of CD11b-positive cells resulted in an overall reduction in intratumoral vessels and glioma size (Brandenburg et al., 2016). Hence, dissecting the set of CD11b-positive cells is interesting in order to establish strategies for direct anti-tumor effects. In this work we explored one GBM-associated subpopulation of CD11b-positve cells (TAMEP) with striking angiogenic capacity. Importantly, our study revealed that TAMEP-ablation impacted on intratumoral vascular basement-membranes and reduced Collagen-IV levels. This can explain the pronounced increase in vascular-permeability and –malformations observed in TAMEP-deficient GBM (Rannikmae et al., 2017; Tan and Markus, 2015). There is a range of substances allowing to pharmacologically alter Collagen-IV formation and we will explore this approach in order to recapitulate the vascular effects of TAMEP ablation (resulting in strongly diminished basement membrane formation and profoundly increased vascular leakyness). Combining an approach for improved delivery of substances into the brain with delivery of chemotherapeutics or other targeted therapeutic compounds is well suited to provide a new and improved strategy to treat GBM. In particular, this new therapeutic paradigm will serve to introduce highly efficient anti-tumorigenic agents into GBM that otherwise do not access primary brain tumors (due to the blood-tumor barrier). Altogether, the transient set of TAMEP is required for a dense and functional vascularization of GBM, thus offering Collagen-modulation as a new and promising therapeutic target in neurooncology. By uncovering this new treatment target we have fulfilled all milestones of the current funding period.