Universität Basel

Research Project

Combined Microglia Modulation and Tumor Targeting Against Glioblastoma

Third-party funded project

Project title Combined Microglia Modulation and Tumor Targeting Against Glioblastoma
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Background. Glioblastoma multiforme (GBM) is a fatal brain tumor that is resistant to all treatments. Besides other non-neoplastic stromal cells, the tumor microenvironment (TME) of GBM consists of a large, dynamic compartment of immune system related cells. Main players of the immune TME (iTME) are tumor infiltrating brain-resident microglia, macrophages (Mf), and T-lymphocytes. GBMs are capable of subverting the iTME to facilitate their own growth by re-educating it for their own purposes. Therefore, instead of targeting the tumor cells directly, modulation of the iTME is likely to be a promising approach to combat the disease. Multiple strategies that target either adaptive or innate compartments of the iTME are currently being evaluated.

Preliminary data. Previously, we designed a novel orthotopic patient-derived xenograft mouse model with genetically color-coded Mf and microglia, and modulated tumor-associated Mf and microglia (termed tumor-associated macrophages, TAMs) of the GBM-iTME by pharmacological means. The blockade of the “don’t eat me” signal CD47 on tumor cells with anti-CD47 antibodies *in vivo* prompted both Mf- and microglia-induced phagocytosis. Moreover, it led to morphological changes in microglia, detectable with cranial *in vivo* imaging. The efficacy of anti-CD47 treatment was preserved in mice lacking *Ccr2*, limiting Mf recruitment to the brain. Anti-CD47-induced GBM phagocytosis by microglia was sufficient to lessen the tumor burden significantly. Under anti-CD47 treatment, Mf changed their transcriptional profile towards a pro-inflammatory, M1-polarized signature, whereas microglia displayed a loss of M2 genes. Thus, microglia are a potential target of innate iTME modulation in GBM.

Hypothesis and research aims. The interplay between the adaptive immune system and microglia in the setting of innate immune modulation has not been studied thus far. Based on the results of our previous research, we hypothesize that microglia modulation can enhance an adaptive immune response. To test this, we propose to determine the response of the adaptive immune system in GBM after *genetic or local pharmacological* microglia modulation in *vivo*. Further, we hypothesize that immunotherapeutic interventions in GBM are insufficient if delivered as systemic monotherapies, because of tumor-cell heterogeneity, the immunosuppressive iTME, and the obstacle of the blood brain barrier. To optimize this, we propose to combine local microglia modulation with systemic T-cell checkpoint inhibitors to achieve therapeutic synergy. Strategies to specifically target GBM neoplastic cells, e.g. with signaling pathway inhibitors, have failed for similar reasons. Therefore, we hypothesize that local reprogramming of microglia within the GBM-iTME facilitates the action of tumor-specific strategies. Among others, EGFRvIII is a promising tumor antigen currently used as a target in clinical trials. Thus, we propose to combine local

anti-CD47 mediated microglia modulation with intratumoral EGFRvIII-specific chimeric antigen receptor (CAR) T-cell application to induce better tumor control.

GBM tumor cells display a vast regional heterogeneity. However, the phenotypical differences of tumor-associated microglia in human GBM are unknown. We hypothesize that intratumoral microglia exhibit a region-specific functional heterogeneity, influenced by paracrine crosstalk with the tumor cells. This is especially important at the invasion zone of the tumor, where tumor recurrence prevails. To assess this microglial heterogeneity, we aim to characterize the region-specific phenotype of tumor-associated microglia in defined locations of resected GBM tissue obtained from a mouse model, and from human patients.

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