Single cell multi-omics in defining how specific oncogenic alterations shape the immune microenvironment and responses to immunotherapy in experimental gliomas

Cancer cells should be recognized by the immune system that elicits anti-tumor responses resulting in tumor destruction. Unfortunately, anti-tumor immunity is often hampered by tumor-derived factors and the immunosuppressive tumor microenvironment. Microglia are the resident macrophages of the central nervous system (CNS) that perform numerous functions required for CNS development, as well as homeostasis, neuronal plasticity, surveillance, and repair. Depending on a stimulus from microenvironment microglia may turn on or out specific functions by activating different gene expression programs. Clinical and experimental studies demonstrated that malignant gliomas (common brain tumors with poor prognosis) induce accumulation of microglia and their re-education into tumor supportive cells. In fact, both CNS resident microglia and infiltrating peripheral myeloid cells orchestrate the local immune responses that essentially shape the outcome of gliomas. However, little is known about how these myeloid cell types orchestrate their context-specific responses in brain tumors with specific genetic alterations that impact the tumor microenvironment and systemic immunity. We propose to apply innovative techniques profiling transcriptomes of single cells in combination with unique mouse models of gliomas to identify unique transcriptional profiles of microglia and peripheral macrophage subsets as well as associated T lymphocytes to understand their functions. Glioblastomas are tumors poorly responding to immunotherapy with immune check point inhibitors. We plan to define if characteristics of immune composition of gliomas with predefined sets of genetic alterations resembling those observed in humans will determine tumor responses to immunotherapy. We propose to modulate the immune microenvironment of gliomas with specific compounds to improve immunotherapy outcomes. Defining precise functions of myeloid cell subpopulations in gliomas will open promising new avenues for subset-specific therapeutic interventions first in mouse, but also in humans. This proposal emphasizes on the requirement of interdisciplinary approaches in solving complex problems. In this interdisciplinary research project, we address urgent and valid scientific questions and plan employ newest available technologies to gain a new knowledge at the unprecedented level of a single immune cell from tumors. We may discover new immune subpopulations and information about molecular mechanisms underlying tumor immune evasion that could be specifically targeted. We will test in murine glioma models new combinatorial approaches targeting different cells in the microenvironment of gliomas aiming at awakening anti-tumor responses. This knowledge may allow exploring novel diagnostics and therapeutic options that can potentially be tailored to patients.