Project 1.13. Using single-cell omics and spatial transcriptomics to unravel how specific genetic changes result in context-specific immune responses in experimental gliomas.

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Background:

Microglia are brain resident immune cells and have specific functions in healthy and diseased brain. Single-cell transcriptomics studies can reveal distinct cell subpopulations and dissect their functions. Our recent study revealed various functional subpopulations in a healthy mouse brain and microglia activation along with peripheral monocytes/macrophage infiltration in murine gliomas (*Ochocka et al. Nature Commun. 2021)*. Heterogeneity of myeloid subpopulations was confirmed at the protein level with CITE-seq and immunohistochemistry. Malignant gliomas have different genetic alterations that determine patients' survival outcomes and may result in differences in the anti-tumor response. We hypothesize that specific genetic background affects composition and functionality of myeloid and lymphoid cell types in TME. We sought to find how specific genetic changes result in context-specific immune responses in gliomas. We propose to explore the combination of unique mouse models of gliomas reflecting human pathology with high-dimensional technologies (single cell RNA and protein profiling, spatial transcriptomics and immunocytochemistry) in order to identify myeloid and lymphoid subsets with their unique transcriptional profiles and localization in the microenvironment of gliomas.

Aim:

We will use three genetically engineered glioma models and analyze microglia and peripheral monocytes/macrophage infiltration along with T cell infiltration in murine gliomas using single-cell omics (scRNAseq, CITE-seq, spatial transcriptomics). In particular, we will focus on genetic alterations known to affect survival of gliomas and employ recently generated glioma models: shp53/shPTEN, shp53/shPTEN/shATRX, shp53/shPTEN/shATRX/IDHmut, RCAS-PDGFB/RCAS-p53-gRNA and RCAS-PDGFB/RCAS-PTEN-gRNA gliomas that reflect subtypes of glioblastomas and have been obtained as glioma cell spheres from our collaborators). Immune cells (CD45+) will be immunosorted from the murine brains bearing gliomas with the defined genetic background. Computational analyses of NGS generated data will be performed to define functional subpopulations and the influence of the genotype. Visium Spatial Gene Expression, a next-generation molecular profiling solution for classifying tissue based on total mRNA, will be implemented. Maps the whole transcriptome with morphological context in fresh-frozen tissues from experimental gliomas will be detected to discover novel insights into disease pathology.

Requirements:

- Master degree in biology, biotechnology, bioinformatics, computer science, mathematics, physics etc.),
- Experience in biological data analysis, preferably in analyzing next generation sequencing data.
- Interest in tackling biological problems using computational methods.
- Good programming skills, preferably in R or Python,
- Fluency in written and spoken English.