Macrophages in the healthy and the tumor-bearing brain: linking single-cell transcriptomics to function

Macrophage phenotypes differ between different tissues and even within one tissue. By dissecting border regions of the steady-state brain (choroid plexus, dura mater, subdural meninges) and combining single-cell RNA sequencing with high-dimensional cytometry, bulk RNA-sequencing, fate-mapping and microscopy, we reveal the remarkable diversity of non-parenchymal brain macrophages. Border-associated macrophages (BAMs) residing in these brain regions consisted of distinct subsets that exhibited tissue-specific transcriptional signatures and underwent strong compositional changes during postnatal development. BAM ontogeny correlated with niche accessibility, but subsets displayed distinct self-renewal capacities upon depletion and repopulation.

We then relied on single-cell RNA sequencing to unravel the complexity of the Glioblastoma multiforme (GBM) immune landscape, both in mouse and human. GBM is an invariably fatal primary malignant brain tumor. Within the myeloid compartment, the single-cell data suggest the presence of ontogenically distinct macrophage populations in these tumors, which is corroborated by lineage tracing and adoptive transfer experiments. Multi-parametric flow cytometry allowed for cell sorting of the various macrophage and DC subsets from GBM tumors, which was followed by an extensive functional profiling. This showed clear differences in the macrophage/DC activation state, T-cell stimulatory and suppressive capacities, phagocytic activity and pro-angiogenic potential.

Questions:

1. What would be the fundamentally different functions of tissue-resident versus bone marrow-derived macrophages, if any?
2. Nature or nurture: can ontogenically distinct macrophages become indistinguishable in the same microenvironment?
3. Macrophage depletion or macrophage reprogramming as cancer therapy?

Reading:

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