

## Capture of leptomeningeal cancer cell and macrophage iron metabolism

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Abstract: Spread of cancer cells into the spinal-fluid-filled leptomeninges, or Leptomeningeal metastasis (LM), results in rapid neurologic deterioration and death. In LM, the leptomeningeal space contains very low concentrations of extracellular iron and abundant inflammatory cells. Cancer cells must overcome both low iron and inflammatory signaling to grow in the leptomeninges. We hypothesize that cancer cells exploit their epigenetic freedom such that CSF inflammatory signals enable metabolic reprogramming of iron-dependent pathways. In contrast, the macrophage's constrained epigenetic identity results in a consistent inability to adapt to iron scarcity within the CSF, despite inflammatory signals, resulting in impaired macrophage function. To address this hypothesis, we will carry out metabolomic and epigenetic characterization of clinical samples at the bulk and single-cell level. We will then employ mouse models of LM to discover major metabolic shifts within the cancer cells that result from metabolic demands within this unique microenvironment. In parallel, we will apply these same strategies to profile the leptomeningeal macrophage population. Together, this work will generate a comprehensive metabolic and epigenetic of the spinal fluid, the cancer, and the macrophages within the leptomeninges. Our laboratories possess shared interest in spinal fluid biology and complementary sets of techniques and know-how. Together, we are poised to uncover novel, clinically-relevant biology in the minimally-explored leptomeningeal space.