Defining the evolution and tumor microenvironment interactions of classic Hodgkin lymphoma through single-cell multi-omics and genetically engineered mouse models

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Abstract**:** Classic Hodgkin lymphoma (HL) is an aggressive malignancy with a peak incidence in adolescents and young adults. Current treatments with high-dose chemo-radiation often lead to long-term sequelae. Development of less toxic therapeutic options is hampered by the lack of disease models and challenges of studying the Hodgkin and Reed-Sternberg (HRS) cells. One difficulty is that HRS cells represent a small minority among a dense tumor micro-environment (TME). To address this challenge, our group has developed a novel FACS approach to isolate HRS cells, and executed the first exome, transcriptome, and genome sequencing in HL. The data revealed a clonally-complex tumor and extensive interactions of the HRS cells with the TME. Here, we propose to deconvolute the complexities of HL pathobiology via cutting edge single-cell multi-omics and novel murine modeling. We will dissect the lineage histories of primary HRS cells in relation to their cell identity via single-cell multi-omics that integrates somatic genotyping of driver mutations, copy number variations, B cell receptor clonotyping, and whole transcriptomic data within the same cells (Aim 1). We will also interrogate novel HRS-to-TME dependencies via single-cell transcriptomic profiling of the TME (together with HRS cells from the same tumor) and T-cells that are tightly adherent to the HRS cells (Aim 2). Finally, we propose a novel strategy for murine modeling of HL, as the first *in vivo* model, to accelerate translational impact (Aim 3). These studies have the potential to transform our understanding of HL biology for novel therapeutics and reveal fundamental principles of tumor evolution.