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 chemoradiation 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 microenvironment (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.