

Single-cell Resolution of Emergent Clones in the Myelodysplastic Syndromes (MDS) During Therapy and Disease Progression

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Abstract: The genetic evolution of resistant tumor clones represents a significant challenge to cancer therapy, but such variegated cellular responses are difficult to discern when evaluating bulk cell populations. Resolving this tumor heterogeneity requires purification of cells in which clonal selection occurs, as well as advanced methods for molecular profiling. We have recently established novel biochemical methods and algorithms for creating and analyzing full-length cDNAs from single cells that allow us to perform highly accurate, single cell RNA-sequencing. These new technologies will provide an unprecedented opportunity to examine the cell-to-cell variation of active mutations in individual tumor cells. We will use these approaches to determine the clonal heterogeneity of disease-initiating cells, or stem cells, in patients with myelodysplastic syndrome (MDS), as these cells drive drug resistance and disease progression. We will also evaluate clonal selection and MDS stem cell transcriptional responses during disease progression as well as in response to one of the mainstays of MDS therapeutics, the DNA methyltransferase inhibitor decitabine. Finally, we will characterize the responses of xenografted primary MDS stem cells treated with decitabine in order to determine if xenograft models of MDS can mimic patient responses to therapy and provide a tool to predict treatment response and test novel therapeutics. We hypothesize that applying single-cell RNA-sequencing techniques to divergent patient responses to therapy will advance our understanding of MDS biology and provide novel paradigms to help predict clinical outcomes in MDS patients. Moreover, these techniques would serve as a general framework for single-cell analysis of other cancers.