

## **Dissecting Micro-environmental Contributions to the Pathogenesis of Myelodysplastic Syndromes**

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Abstract: Myelodysplastic syndromes (MDS) represent clonal disorders of aberrant hematopoietic stem cells in which one third of patients transform into acute myelogenous leukemia (AML) with allogeneic stem cell transplantation as the only curative treatment. The role of the hematopoietic microenvironment (HMEV) in the maintenance and initiation of MDS has remained unclear though model systems have provided strong evidence for its potential as a driver of disease. Our approach is to leverage the mouse models that defined specific subsets of marrow mesenchymal cells in myelodysplasia, identify their human counterparts, develop methods of isolating those cells, examine freshly isolated cells from patients, and then test candidate molecular alterations. Using this approach, we have developed the necessary methods, and assembled early indications of a distinct molecular profile of MDS-associated human HMEV cells. This includes the identification of several extracellular matrix proteins, cytokines, and adhesion molecules as aberrantly expressed in MDS-associated HMEV cells. We now seek to extend our primary patient data set to enhance candidate selection confidence and determine the functional impact of test candidate molecules using two systems. First, we will introduce molecular alterations in co-culture and ossicle implant systems of human cells and second, we will introduce molecular alterations in HMEV of mice and evaluate the kinetics of disease of TET2-, ASXL1-, or SRSF2-mutant hematopoietic cells. In this way, we will define molecular interactions within the HMEV that participate in MDS pathophysiology. Successful accomplishment of this project will define therapeutic targets in a disease that is urgently in need of new approaches.