

The mRNA Methylation Program in Leukemia

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Abstract: Hematopoietic malignancies result from dysregulated self-renewal pathways and an altered differentiation program. Understanding this altered differentiation is essential for identifying novel therapeutic targets in acute myeloid leukemia (AML). Despite the many studies focusing on genetic and epigenetic regulators, it remains unclear if epitranscriptomic regulation is altered in AML and contributes to disease progression. Recent discoveries from our group and others have found that mRNAs are subjected to the base modification *N*⁶-methyladenosine (m⁶A) and this epitranscriptomic regulation is a potent regulator of mRNA stability and protein translation. m⁶A has emerged as a major regulator of cellular differentiation in studies of embryonic stem cell differentiation. Our preliminary studies suggest that elevated m⁶A is a hallmark of AML and is required for the blast state that characterizes this cancer. The m⁶A writer *Mettl3* is highly expressed in myeloid leukemia cells and is required for survival. Thus, we will characterize the role of m⁶A in leukemia by combining the strengths of the Kharas and Jaffrey laboratories. The Kharas laboratory has been studying RNA-binding proteins in normal and malignant hematopoietic self-renewal and the Jaffrey laboratory is one of the world's experts on RNA methylation. Utilizing technological innovations from the Jaffrey laboratory, we will create a functional nucleotide-level resolution map of m⁶A in leukemia and mechanistically determine how RNA methylation controls myeloid leukemia cell survival. Our studies will reveal a fundamentally new concept in AML involving aberrant gene regulation through an altered cancer epitranscriptome.