Translation Regulation in Acute Myeloid Leukemia

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Abstract: Oncogenes dramatically alter cellular physiology by inducing alterations in the transcriptome that ultimately lead to changes in the proteome; however, changes in protein expression may be due to alterations in protein stability as well as alterations in translation rates and efficiency. Unfortunately, measuring cellular transcripts by standard transcriptomic methods is insufficient to capture ongoing translation or protein expression since translation of specific transcripts can be regulated by numerous signaling pathways, translation initiation factors, components of the ribosome, and RNA binding proteins. Decoding how translational deregulation contributes to leukemia initiation and progression remains one of the major challenges in acute myeloid leukemia (AML) biology. While investigators have attempted to identify regulators of leukemia stem cells (LSCs) in AML by characterizing the transcriptome from total cellular RNA, such approaches are inadequate to characterize specific alterations in translation that take place at the level of the ribosome. We have identified a novel LSC marker in AML that allows prospective separation of LSCs from AML patient blasts. We have also shown that MSI2, an RNA binding protein and translational regulator, is required for LSC function. Thus, we have the necessary tools to elucidate the contribution of translational regulation to LSC function and identify genes that regulate LSC activity. We will also use these reagents to investigate how altered translation contributes to LSC maintenance by utilizing genetic and small molecule approaches to perturb translation in LSCs from patients and mice. We expect these studies to identify novel and critical regulators of LSC biology.