Title: SRSF3 shapes the structure and processing of miR-17-92 cluster in colorectal cancer

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Keywords:
SRSF3, pri-miRNA processing, RNA structure, molecular biology, cancer

Abstract
MicroRNAs (miRNAs) regulate one third of genes post-transcriptionally, thus affecting most biological processes including key roles in cancer pathogenesis. Almost a half of mammalian miRNAs are generated from miRNA clusters, but the regulation of cluster-derived miRNAs is enigmatic. We recently demonstrated that SRSF3 controls the selective processing of miR-17-92 cluster (aka OncomiR-1) in colorectal cancer cells. SRSF3 binding to multiple CNNC sites downstream of Drosha cleavage sites within miR-17-92 was required for the efficient processing of the cluster, SRSF3 depletion particularly compromising the processing of two paralog miRNAs, miR-17 and miR-20a. In addition to SRSF3 binding to the CNNC sites, SRSF3 RS-domain was essential for miR-17-92 processing. SHAPE-MaP probing demonstrated that SRSF3 binding disrupted both local and distant base pairing, resulting in global changes in miR-17-92 structure. These data suggest a model where SRSF3 binding, and potentially its RS-domain interactions, facilitate an RNA structure that modulates miR-17-92 processing. SRSF3-mediated increase in miR-17/20a levels inhibited the cell cycle inhibitor p21, promoting self-renewal in normal and colorectal cancer cells. To fully understand the mechanisms of SRSF3-mediated structural changes and regulation of the miR-17-92 processing, we are currently investigating the protein composition of miR-17-92 ribonucleoprotein (RNP) complex. Our aim is to uncover how miR-17-92 RNP structure impacts its function and how it could be modulated to develop novel RNP-targeting cancer therapies.