

Biochemical and Genetic Investigation of Oncogenic TOR-dependent Regulation of RNA Metabolism and Tumorigenesis Using Cross-Species Approaches

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Abstract: A lack of coordination between cell growth, metabolism, and nutrient availability is a hallmark of malignancy. Oncogenic signals drive metabolic reprogramming of anabolic and catabolic pathways, leading to continual growth even under nutrient scarcity. Understanding how nutrient deprivation limits cell growth and how cancer cells evade this regulation is key to the identification of effective therapeutic strategies for cancer. Aberrant RNA processing (splicing, UTR processing, and chemical modifications) is implicated in tumorigenesis. However, studies addressing how oncogenic signaling pathways rewire these processes are scarce. The target of rapamycin (TOR) is a protein kinase and nutrient signaling integrator that has been linked to many human cancers. We have recently observed that TOR signaling controls key RNA metabolic processes in *Drosophila* and mammals. In addition, our TOR phospho-proteomic screens have led to the identification of TOR-dependent phosphorylation events in several enzymes linked to RNA metabolism. To characterize which RNA processing machinery functionally contributes to metabolic reprogramming and cancer phenotypes, we propose a cross-species analysis involving: 1) Identification and characterization of new RNA processing units linked to cancer in *Drosophila* (genetic assays) and mammalian cell systems (molecular biology and biochemical assays); 2) Investigation into the mechanism of how the RNA processing machinery is regulated by nutrient and oncogenic signals; and 3) Examination of the functional relevance of these events in tumor growth and metabolism, using *Drosophila* genetic models, human cancer cell lines and mouse xenograft studies. Altogether, our discovery of TOR-dependent regulation of conserved RNA metabolic processes will provide rationale for characterization of new cancer biomarkers and therapeutics targeting RNA processing downstream of oncogenic signaling pathways.