

Basic and Therapeutic Application of Metastasis Suppressor microRNAs to Colorectal Cancer

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Abstract: Colorectal cancer kills more than 500,000 people annually worldwide as a result of metastatic progression. By combining *in vivo* selection with functional *in vivo* screening of 661 human microRNAs, we have identified miR-483-5p and miR-551a as robust endogenous suppressors of colorectal cancer metastasis in multiple human cancer lines. The silencing of these miRNAs significantly correlates with colon cancer progression across human cancer samples. These miRNAs suppress metastasis by targeting a common gene (creatine kinase B), which phosphorylates the metabolite creatine to yield phosphocreatine—a high-energy phosphate donor. We herein propose to further characterize this miRNA regulated metabolic network by identifying the enzymatic source of creatine within the body that drives metastasis. This could reveal an upstream 'druggable' target of this miRNA metabolic network. We will also apply our understanding of this regulatory network to develop a genetic model of colorectal metastasis where tumor progression is driven by conditional miR-483 and miR-551 inactivation in colonic epithelium. This model will allow us to test the role of T-cells, which have been clinically associated with colorectal cancer progression, in metastasis and will represent a unique resource for the scientific community. Finally, we will develop these microRNAs into a therapeutic modality by testing the effect of single-dose dual-miRNA adeno-associated viral delivery into mice bearing a collection of primary patient colorectal cancer grafts. These efforts will be propelled by the involvement of a highly collaborative team of basic and translational investigators with extensive expertise in colorectal cancer, microRNAs, metastasis biology, and immunology.