Marsha R. Rosner.* Regulation of Tumor Metastasis by MAP Kinase and MicroRNAs. Ben May Department of Cancer Research, University of Chicago, Chicago, IL 60637, USA.

Tumor metastasis suppressors are inhibitors of metastatic progression and colonization and, as such, represent important markers for prognosis and potential effectors of therapeutic treatment. However, the mechanisms by which metastasis suppressors function are generally not understood. Raf Kinase Inhibitory Protein (RKIP), an inhibitor of key regulatory pathways in mammalian cells including MAP kinase, has recently been implicated as a suppressor of metastasis (reviewed in (1)). RKIP is missing or depleted in a number of tumors including prostate, breast, melanoma, hepatocellular carcinoma, and colorectal, suggesting that it may function as a general metastasis suppressor for solid tumors**.** We have shown that one mechanism by which RKIP ensures chromosomal integrity and genomic stability is by preventing MAP kinase inhibition of Aurora B kinase and the spindle checkpoint (2).

Our recent studies have demonstrated that RKIP suppresses invasion and metastasis by inhibiting the MAP kinase (MAPK) signaling pathway and inducing the microRNA *let-7* (3). *Let-7*/miR-98 is an evolutionarily conserved microRNA family that has also been shown to suppress breast cancer stem cell properties (self-replication and pluripotent differentiation to multiple cell types) (4). Thus, the microRNA *let-7* is an important link between regulation of metastasis and regulation of embryonic and cancer stem cells. Although we have implicated *let-7* as a suppressor of breast cancer metastasis, few of the downstream signaling targets are known. To address this problem, we developed a novel approach that identified a RKIP/*let-7*-regulated signaling cascade involving transcription factors that regulate key bone metastasis genes. We utilized this signaling cascade to identify breast cancer patients at highest metastatic risk. Our results further demonstrate that the signaling context in which oncogenic genes are expressed is a major factor in determining their diagnostic, prognostic and therapeutic potential.

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