Loss of RNA-Binding Protein RBMS1 Promotes a Metastatic Transcriptional Program in Colorectal Cancer

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Summary: Yu and colleagues combined computational and experimental techniques to identify a new post-transcriptional regulator of metastatic potential in colon cancer. This study reveals that the RNA-binding protein RBMS1 is a positive regulator of mRNA stability for multiple genes, including the tumor suppressor AKAP12 and a WNT pathway interacting protein, SDCBP, and its loss is a common event associated with poor prognosis.

See related article by Yu et al., p. 1410 (7).

Metastasis is the primary cause of cancer-related death; however, the cellular programs that mediate metastasis remain poorly understood. Studies of tumor genomes have had little success identifying specific genes or mutations exclusive to metastatic tumors. Rather, metastatic potential appears to depend on widespread changes in transcriptional activity (1). Focus has, therefore, turned to nongenetic regulation of gene expression programs to uncover the molecular mechanisms enabling metastasis. Accordingly, mediators of post-transcriptional regulation such as miRNAs (miR), long noncoding RNAs, small noncoding RNAs, and RNA-binding proteins (RBP) have received increasing scrutiny as possible mediators of oncogenic progression.

RBPs are of particular interest as post-transcriptional regulators, as they can broadly affect the activity of multiple target RNAs (2). A small number of RBPs could thus account for large changes in gene expression such as those observed in malignant tumors. Multiple studies have implicated RBPs in tumor progression, through regulation of expression of oncogenes, growth factors, and cell-cycle proteins (3), and several RBPs are recurrently downregulated or mutated across tumors (4), suggesting putative tumor-suppressive activities.

Mechanistically, RBPs regulate all aspects of the mRNA life cycle, including processing, localization, stability, modification, and translation (2), and have been found localized to chromatin at active promoters, implicating them as direct regulators of transcription (5). Advances in technologies for detecting protein–RNA interactions have greatly expanded the number of known RBPs, now estimated at more than 1,300, and enabled their systematic characterization (2). Large-scale screens have generated the first generation of RBP–target interaction maps and expanded our understanding of the physical interfaces by which RBPs recognize and interact with their targets. These developments set the stage for systematic interrogation of the post-transcriptional logic involved in transcript regulation, an early example being at scale investigation of RBP regulation of alternative splicing (6), and present new opportunities for methods and applications to study the role of RBP–target networks in cancer.

In this issue of Cancer Discovery, Yu and colleagues investigate RBP–target networks to identify RBPs that regulate metastatic gene expression programs, and identify a new regulator of metastasis in colorectal cancer (7). They present a novel regression-based approach, PRADA, which identifies RBPs whose expression change best explains the expression changes of their target genes. To gain insight into post-transcriptional mechanisms of metastasis, they applied PRADA to differential gene expression data obtained by comparing RNA levels between poorly and highly metastatic colorectal cancer cell lines. PRADA implicated the RBP RBMS1 as most strongly predictive of its regulon in this setting. Further analysis in patient-derived xenograft models and two paired pre/post-metastatic clinical samples confirmed decreased expression of RBMS1 and its regulon in the metastatic setting in vivo.

The authors next worked to uncover the mechanism by which RBMS1 regulates expression of its target mRNAs. As reduction of RBMS1 decreased expression of its regulon, the authors speculated it may function to stabilize its targets. Both in silico analysis of exonic versus intronic sequencing reads and assessment of mRNA half-life of RBMS1 target RNAs upon transcription inhibition supported this possibility. irCLIP profiling of RBMS1 targets confirmed the predicted target regulon used by PRADA and identified a bias for RBMS1 binding near 3′ untranslated regions (UTR). To verify that 3′ UTR proximal RBMS1 binding affects transcript stability, Yu and colleagues used GFP variants with 3′ UTR RBMS1 binding sites and confirmed an RBMS1-dependent effect on transcript levels. They further determined from mass spectrometry–based analysis that RBMS1 stabilization of mRNA frequently involved a second RBP, ELAVL1, which was necessary for expression of many RBMS1 targets.

Notably, ELAVL1 has also been implicated in colorectal cancer progression, where its localization to the cytoplasm and increased expression are associated with stabilization of prosurvival mRNAs including COX2 (8). In previous reports,
cytoplasmic ELAVL1 has been found to compete with miRs to stabilize oncogenic transcripts (9). The suggested coordination between ELAVL1 and RBMS1 could contribute additional specificity to mRNA stabilization, such that loss of RBMS1 could facilitate degradation of a subset of ELAVL1-stabilized targets (Fig. 1) while allowing others such as COX2 to be preserved.

Consistent with its ability to predict the expression of metastasis-associated genes, Yu and colleagues showed that RBMS1 loss in vitro and in vivo led to more effective metastatic colonization by colorectal cancer cells. Two direct downstream targets of RBMS1, AKAP12 and SDCBP, were identified as candidate mediators of the prometastatic effects of RBMS1 loss based on their consistent downregulation in the metastatic setting. Of these, knockdown of AKAP12 accounted for the majority of the effect of RBMS1 loss on colonization, implicating it as a major downstream target responsible for increased metastatic potential. AKAP12 was implicated as a negative regulator of metastasis in colorectal tumors, and its loss has been attributed to altered methylation of its promoter and inhibition by several miRNAs including miR-183 and miR-186 (10), which could potentially compete with RBMS1-mediated stabilization. Importantly, Yu and colleagues showed that RBMS1 and AKAP12 status, as well as a biomarker “metagene,” comprising 80 genes with irCHiP-validated 3′ UTR RBMS1-binding sites, were all predictive of relapse-free and overall survival in multiple patient cohorts. In some cases, RBMS1 silencing was found to be mediated by HDAC1, suggesting the therapeutic potential for HDAC inhibitors.

Thus, Yu and colleagues reveal RBMS1 as a novel suppressor of metastatic potential in colorectal cancer with clear prognostic and possible therapeutic implications. RBMS1 joins a short list of RBPs of relevance to this disease that already includes ELAVL1 (8). This study provides further evidence for a major role for post-transcriptional regulation in tumor progression and paves the way for future studies to identify RBPs that drive oncogenic expression programs.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**REFERENCES**

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