Splicing

Major finding: RBM4 inhibits cancer cell growth and migration by regulating cancer-associated gene splicing.

Mechanism: RBM4 shifts BCL-X splicing to promote apoptosis and antagonizes the oncogenic splicing factor SRSF1.

Impact: Restoring expression of the RBM4 tumor suppressor may inhibit the progression of various cancers.

RBM4-REGULATED ALTERNATIVE SPLICING SUPPRESSES TUMORIGENESIS

Dysregulation of alternative splicing has been implicated in tumor progression, but the mechanisms by which changes in the expression and activity of splicing factors promote tumorigenesis are not completely understood. The oncogenic splicing factor serine/arginine–rich splicing factor 1 (SRSF1) has been shown to modulate the splicing of many cancer-associated genes, including those that activate the mTOR pathway. Wang and colleagues investigated the role of another splicing factor, RNA-binding motif protein 4 (RBM4), in the regulation of alternative splicing and tumor progression. RBM4 suppressed various alternative splicing events in a sequence-specific manner via direct binding to pre-mRNA and negatively regulated the splicing of many cancer-associated genes, such as those involved in proliferation, cell migration, and apoptosis. RBM4 expression inhibited cancer cell proliferation and migration and impaired xenograft tumor growth *in vivo*, suggesting that RBM4 functions as a tumor suppressor. Consistent with this idea, RBM4 stimulated cancer cell apoptosis by inducing a shift in the alternative splicing of BCL2-like 1 (BCL2L1, also known as BCL-X), resulting in increased expression of the proapoptotic BCL-XS isoform and decreased expression of the antiapoptotic BCL-XL isoform. The tumor-suppressive effects of RBM4 were mediated in part by BCL-X splicing, as concomitant expression of BCL-XL partially restored lung cancer cell proliferation and migration and enhanced xenograft tumor growth. In addition, RBM4 specifically reduced the expression of SRSF1 and antagonized its oncogenic activity via competitive binding to similar *cis*-elements in pre-mRNAs; coexpression of RBM4 prevented the oncogenic splicing of several SRSF1-regulated genes, including BCL-XL, and inhibited SRSF1-driven mTOR activation. RBM4 expression was decreased in human non–small cell lung cancer samples with increased BCL-XL, and elevated RBM4 expression correlated with prolonged survival in several cancer types. These findings identify RBM4 as a tumor-suppressive splicing factor and suggest that restoration of RBM4 expression may limit tumor growth and progression. ■

Wang Y, Chen D, Qian H, Tsai YS, Shao S, Liu Q, et al. The splicing factor RBM4 controls apoptosis, proliferation, and migration to suppress tumor progression. Cancer Cell 2014;26:374–89.

Oncogenes

Major finding: *FAL1* is an oncogenic lncRNA that promotes cancer cell growth in part via repression of p21.

Mechanism: *FAL1* regulates the transcription of genes including *CDKN1A* via stabilization of BMI1.

Impact: *FAL1* may be a marker of poor prognosis and a potential therapeutic target in ovarian cancer.

THE FOCALLY AMPLIFIED lncRNA *FAL1* EXHIBITS ONCOGENIC ACTIVITY

A large percentage of somatic copy-number alterations (SCNA) in cancer cells occur in regions lacking protein-coding genes, adding to the challenge of identifying driver SCNAs that directly promote tumorigenesis. Long noncoding RNAs (lncRNA) are aberrantly expressed in many cancers and have been implicated as both oncogenes and tumor suppressors; however, whether recurrent genomic alterations in lncRNAs contribute to tumor growth remains unclear. Hu and colleagues characterized the genome-wide SCNA profile of lncRNAs across 12 cancer types and found that lncRNA genes exhibited high-frequency and cancer type–specific copy-number gains and losses. Functional screening of lncRNAs that demonstrated focal copy-number gain and RNA expression in cancer cell lines identified focally amplified lncRNA on chromosome 1 (*FAL1*) as a candidate oncogenic lncRNA. Depletion of *FAL1* decreased the clonogenicity of cancer cell lines and impaired xenograft tumor growth, whereas *FAL1* overexpression enhanced transformation. The oncogenic activity of *FAL1* was mediated in part by its interaction with BMI1, a component of the chromatin-modifying Polycomb repressive complex 1, which resulted in increased stabilization of BMI1 protein and transcriptional repression of genes involved in processes such as cell proliferation and apoptosis. In particular, repression of cyclin-dependent kinase inhibitor 1A (*CDKN1A*, which encodes p21) was required for the protumorigenic functions of *FAL1*; knockdown of *FAL1* stimulated cell-cycle arrest and senescence, which were both rescued by concomitant p21 depletion. Intriguingly, amplification and RNA expression of *FAL1* were increased in late-stage ovarian tumors as compared with early-stage tumors and were associated with reduced survival in patients with late-stage ovarian cancer. Furthermore, siRNA-mediated inhibition of *FAL1* diminished tumor growth in an orthotopic mouse model of late-stage ovarian cancer. These results demonstrate the utility of this integrated approach to identify oncogenic lncRNAs and suggest that *FAL1* may represent a prognostic biomarker and therapeutic target in ovarian cancer. ■

Hu X, Feng Y, Zhang D, Zhao SD, Hu Z, Greshock J, et al. A functional genomic approach identifies FAL1 *as an oncogenic long noncoding RNA that associates with BMI1 and represses p21 expression in cancer. Cancer Cell 2014;26:344–57.*