Melanoma

Major finding: *SAMMSON* is expressed in the majority of human melanomas and promotes cell growth and survival.

Mechanism: SAMMSON binds to p32, promoting p32-mediated mitochondrial functions and melanoma cell survival.

Impact: SAMMSON inhibition may effectively target melanoma cells and sensitize them to MAPK inhibition.

SAMMSON LONG NONCODING RNA IS ESSENTIAL FOR MELANOMA CELL VIABILITY

Focal amplifications of chromosome 3p13-3p14 in a subset of melanomas are associated with a poor prognosis. The melanoma specific oncogene *MITF* is located within this amplicon; however, the possible contribution of other loci to the development of melanoma has not been determined. Using data from The Cancer Genome Atlas, Leucci and colleagues discovered that chromosome 3p amplifications in melanoma encompass the *SAMMSON* long noncoding RNA (lncRNA) and although *MITF* and *SAMMSON* were coamplified in about 10% of melanomas, SAMMSON and MITF levels were not generally correlated. Further, SAMMSON was expressed in the majority of malignant melanomas but was barely detectable in normal melanocytes and benign lesions, suggesting that it is induced as cells become fully transformed, and is a candidate biomarker of malignant melanoma. Putative SOX binding sites were present upstream of *SAMMSON*, and SOX10 knockdown reduced *SAMMSON* expression, indicating that *SAMMSON* is a SOX10 target gene. SAMMSON silencing reduced melanoma cell growth and survival independent of the transcriptional state of *BRAF*, *NRAS*, or *TP53*, and cells that are intrinsically resistant to BRAF inhibition were sensitive to SAMMSON silencing. Further, SAMMSON silencing enhanced the effects of BRAF and MEK inhibitors, and cells with acquired resistance to BRAF inhibition remained sensitive to SAMMSON targeting. SAMMSON was shown to bind directly to the mitochondrial metabolism protein p32, and promoted its mitochondrial localization and function. SAMMSON silencing phenocopied the effects of p32 silencing, causing functional and structural defects including fewer and fragmented cristae, and reduced density of the mitochondrial matrix, suggesting that SAMMSON silencing kills melanoma cells in part through disruption of p32-mediated mitochondrial functions. Inhibition of SAMMSON in patient-derived melanoma xenografts was well tolerated, reduced tumor proliferation, enhanced apoptosis, and potentiated the effects of BRAF inhibition. Together these results indicate that SAMMSON may be an informative biomarker of melanoma malignancy, and SAMMSON inhibition may reduce melanoma cell growth and survival. ■

Leucci E, Vendramin R, Spinazzi M, Laurette P, Fiers M, Wouters J, et al. Melanoma addiction to the long non-coding RNA SAMMSON. *Nature 2016;531:518–22.*

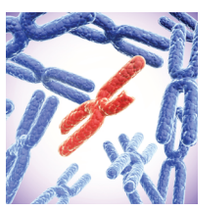
Tumor Suppressors

Major finding: Deletions at the *Trp53* locus drive cancer in part through co-deletion of other tumor suppressors.

Clinical relevance: 17p deletions may promote more aggressive and chemoresistant tumors than *TP53* deletion alone.

Impact: Segmental chromosomal deletions may give a selective advantage through reduced dosage of multiple genes.

TP53 IS NOT THE ONLY DRIVER OF CHROMOSOME 17p LOSS



The *TP53* tumor suppressor gene is frequently inactivated in tumors through a two-hit mechanism wherein one allele harbors a missense mutation and the other allele is deleted in a larger segmental deletion of human chromosome 17p. Because this region contains over 300 other genes, Liu, Chen, and colleagues hypothesized that the loss of other genes in this region in addition to *TP53* might drive selection for chromosome 17p loss. To test this hypothesis, 17p deletion was modeled by generating mice in which Cre recombinase could induce heterozygous deletion of a 4-Mb region of mouse chromosome 11 (11B3), which is syntenic to human 17p13.1 and includes *Trp53*. Deletion of 11B3 in the Eμ-Myc non-Hodgkin lymphoma mouse model resulted in rapid lymphoma development, and compared with lymphomas with focal *Trp53* deletion, 11B3-deleted tumors displayed a more mature B-cell type phenotype and enhanced chemotherapeutic resistance to certain agents. Similarly, in an acute myeloid leukemia model, 11B3 deletion also promoted aggressive tumors and reduced survival compared to *Trp53* deletion alone, and reduced sensitivity to the BET inhibitor JQ1. In most lymphoma-associated 17p deletions, the *E1F5A* tumor suppressor is deleted along with *TP53*, suggesting that *E1F5A* loss may contribute to the tumorigenic effects of 17p deletion. Indeed, knockdown of both *Trp53* and *Eif5a* produced more rapidly growing lymphomas than either alone. An shRNA library screen targeting the approximately 100 protein coding genes co-deleted with *Trp53* identified 17 additional genes, including *Alox15b*, whose loss promoted tumorigenesis. Similar to *Eif5a*, knockdown of *Alox15b* and *Trp53* accelerated tumorigenesis compared with *Trp53* knockdown alone. These findings suggest that the effects of 17p deletion may not be solely attributable to p53 loss and illustrate that segmental deletion events can affect tumor progression and resistance to treatment through disruption of multiple genes. ■

Liu Y, Chen C, Xu Z, Scuoppo C, Rillahan CD, Gao J, et al. Deletions linked to TP53 loss drive cancer through p53-independent mechanisms. Nature 2016;531:471–5.