Melanoma

Major finding: *PPP2R3B* dosage is associated with sex chromosome status and outcome in melanoma.

Mechanism: PPP2R3B stabilizes the CD6–CDT1 interaction to delay DNA replication and suppress melanoma growth.

Impact: As a sex-linked tumor suppressor, PPP2R3B may explain the gender differences in melanoma prognoses.

PPP2R3B IS A SEX-LINKED MELANOMA TUMOR SUPPRESSOR GENE

In patients with melanoma, males tend to have a poorer prognosis than females, but the biological mechanisms underlying this sex difference have not been elucidated. Van Kempen and colleagues hypothesized that differences in gene dosage from the sex chromosomes might contribute to the sex differences in melanoma. Analysis of primary melanomas revealed that loss of the inactive X chromosome (Xi) is associated with a poorer distant metastasis-free survival. Moreover, men with Y chromosome loss also had a poorer prognosis, prompting the investigation of the pseudoautosomal region (PAR), which is present on both the X and Y chromosomes and commonly escapes inactivation on Xi. Decreased expression of one PAR gene, protein phosphatase 2 regulatory subunit B, beta (*PPP2R3B*), encoding PR70, was associated with shorter survival in patients with melanoma. Despite its location within the PAR, *PPP2R3B* expression was lower in males than in females, and in females, loss of Xi also resulted in reduced expression. In melanoma cell lines, high *PPP2R3B* expression

was associated with reduced cell growth, and overexpression of PR70 prevented 3-D colony formation. Further, overexpression of PR70 reduced melanoma xenograft growth *in vivo*, suggesting a role as a tumor suppressor. However, in contrast to classic tumor suppressor genes, *PPP2R3B* is not frequently mutated in melanoma. Mechanistically, PR70 overexpression disrupted the interaction between CDC6 and CDT1, which is crucial in initiating the firing of DNA replication origins. Thus, PR70 overexpression delayed the progression from G1 to S phase by limiting replication origin firing. Altogether, these findings identify *PPP2R3B* as a sex-linked tumor suppressor gene and suggest that its differential expression may explain the poorer prognosis in male patients with melanoma. ■

van Kempen LC, Redpath M, Elchebly M, Klein KO, Papadakis AI, Wilmott JS, et al. The protein phosphatase 2A regulatory subunit PR70 is a gonosomal melanoma tumor suppressor gene. Sci Transl Med 2016;8:369ra177.

Colorectal Cancer

Major finding: NLRC3 negatively regulates PI3K–mTOR signaling to inhibit colon tumorigenesis.

Mechanism: NLRC3 binds to the PI3K p85 subunit to prevent p85–p110α heterodimerization and repress p85 activity.

Impact: Restoration of NLRC3 function may be a therapeutic strategy for treating patients with colorectal cancer.

THE CYTOPLASMIC SENSOR NLRC3 INHIBITS mTOR SIGNALING IN TUMORS

The nucleotide-binding oligomerization domain-like receptor (NLR) CARD domain containing 3 (*NLRC3*) is a cytoplasmic sensor that negatively regulates host immune responses mediated by signaling pathways activated by Toll-like receptors and the cytosolic DNA sensor stimulator of interferon genes. While other NLR family members have been shown to drive or suppress tumorigenesis, it is unknown whether NLRC3 is involved in tumorigenesis. To ascertain the role of NLRC3 in carcinogenesis, Karki, Man, and colleagues evaluated murine models of carcinogen-induced and spontaneous colorectal tumors in wild-type (WT) and *Nlrc3*$^{-/-}$ mice. Both carcinogen-treated *Nlrc3*$^{-/-}$ mice and *Apc*$^{Min/+}$*Nlrc3*$^{-/-}$ mice exhibited significant increases in tumor growth, colorectal dysplasia, and colonic inflammation compared to carcinogen-treated WT mice, suggesting that NLRC3 suppresses colorectal tumorigenesis. Similarly, *Nlrc3*$^{-/-}$ mice exhibited increases in intestinal crypt proliferation and the ability to form intestinal organoids compared with WT mice. Assessment of cytokine production and bone marrow chimera studies revealed that NLRC3 mediated inflammation in an inflammasome-independent manner and that the tumor-inhibitory effect of NLRC3 was predominant in intestinal epithelial cells, respectively. Interrogation of the intracellular PI3K–AKT–mTOR signaling pathway, which is commonly upregulated in human cancers, revealed that *Nlrc3*$^{-/-}$ mice exhibited increased phosphorylation of AKT at the mTOR phosphorylation site and the pyruvate dehydrogenase kinase 1 phosphorylation site, which activates mTOR signaling. Further, loss of NLRC3 resulted in the colocalization of mTOR with lysosomal-associated membrane protein 1, which mediates lysosomal mTOR signaling, and NLRC3 coimmunoprecipitated with the PI3K p85 regulatory subunit, decreased p85 phosphorylation, and inhibited the association of p85 with the PI3K p110α catalytic subunit. Additionally, the administration of a dual PI3K–mTOR inhibitor to *Apc*$^{Min/+}$*Nlrc3*$^{-/-}$ mice and *Apc*$^{Min/+}$ mice reduced the tumor burden of *Apc*$^{Min/+}$*Nlrc3*$^{-/-}$ mice to a level observed in *Apc*$^{Min/+}$ mice. Collectively, these results identify NLRC3 as a negative regulator of PI3K–mTOR signaling and characterize the potential inhibitory role of NLRC3 in colorectal tumorigenesis. ■

Karki R, Man SM, Malireddi RK, Kesavardhana S, Zhu Q, Burton AR, et al. NLRC3 is an inhibitory sensor of PI3K-mTOR pathways in cancer. Nature 2016;540:583–7.