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Neuroblastoma

Major finding: USP7 deubiquitinates MYCN to enhance its stability and transcriptional activity in neuroblastoma.

Clinical relevance: Elevated USP7 expression is associated with a poor prognosis in patients with neuroblastoma.

Impact: USP7 may be a therapeutic target in *MYCN*-amplified tumors.

USP7 TARGETING MAY SUPPRESS *MYCN*-AMPLIFIED TUMOR GROWTH

The activity of MYCN, which is amplified in several tumor types such as neuroblastoma, is tightly regulated by ubiquitin-dependent degradation, suggesting the potential for strategies to control MYCN activity by modulating its ubiquitination. Tavana and colleagues discovered that depletion of the ubiquitin specific peptidase 7 (USP7; also known as HAUSP), which is known to deubiquitinate p53, resulted in reduced levels of MYCN *in vitro* and *in vivo*. MYCN regulation by USP7 was p53-independent and *MYCN* mRNA expression was not reduced, indicating a transcription-independent effect on protein levels. USP7 bound directly to MYCN in a region with low sequence homology to MYC, suggesting USP7 specificity for MYCN over MYC. The USP7–MYCN interaction required USP7 catalytic activity to stabilize MYCN and increase its half-life, and USP7 overexpression reduced the levels of ubiquitinated MYCN, suggesting that USP7 directly deubiquitinates MYCN to prevent its degradation. Consistent with these findings, depletion of USP7 in *MYCN*-amplified neuroblastoma cell lines reduced MYCN protein expression and suppressed proliferation and colony formation. In a panel of neuroblastoma cell lines, treatment with small-molecule inhibitors of USP7 caused a reduction in MYCN protein levels, which was reversed by the addition of a proteasome inhibitor. Further, USP7 inhibition suppressed cell growth and colony formation specifically in the *MYCN*-amplified cells. Analysis of gene expression data from patients with neuroblastoma revealed that high levels of USP7 were associated with high-risk neuroblastoma, reduced overall survival, and increased MYCN activity, based on expression of MYCN-signature genes. Moreover, small-molecule inhibition of USP7 reduced tumor growth in *MYCN*-amplified xenografts, but not nonamplified xenografts, and was well tolerated in mice. In addition to demonstrating that USP7 deubiquitinates MYCN to promote its stability, these findings suggest that USP7 inhibitors may reduce MYCN levels and tumor growth in *MYCN*-amplified tumors and that further investigation of such compounds for the treatment of neuroblastoma is warranted. ■

Tavana O, Li D, Dai C, Lopez G, Banerjee D, Kon N, et al. HAUSP deubiquitinates and stabilizes N-Myc in neuroblastoma. Nat Med 2016;22:1180–6.

Tumorigenesis

Major finding: Cyclin A2 binds to *Mre11* mRNA to promote *Mre11* translation and repair of replication errors.

Concept: Cyclin A2 loss promotes chromosomal instability and spontaneous and carcinogen-induced tumor development.

Impact: Cyclins may play broader cellular roles than previously appreciated.

CYCLIN A2 HAS A CDK-INDEPENDENT ROLE AS AN RNA BINDING PROTEIN

Cyclin A2 (encoded by *CCNA2*) is responsible for activating the cyclin-dependent kinases CDK1 and CDK2 to induce S-phase chromosome duplication and initiate mitosis. As both underexpression and overexpression of cyclin A2 have been linked to poor outcome in tumors, the role of cyclin A2 in tumor progression is unclear. Because complete loss of cyclin A2 is embryonically lethal, Kanakkanthara and colleagues developed a hypomorphic *Ccna2* allele (*Ccna2*^{H}) with reduced expression of cyclin A2 to better understand its role in tumorigenesis. *Ccna2*$^{-/H}$ mice had a marked reduction in cyclin A2 protein in tissues with a high mitotic index but relatively normal levels in tissues with less actively dividing cells. *Ccna2*$^{-/H}$ mice were more susceptible to spontaneous and carcinogen-induced tumors than *Ccna2*$^{+/+}$ mice, indicating that cyclin A2 insufficiency promotes malignant transformation. Mouse embryonic fibroblasts (MEF) from *Ccna2*$^{-/H}$ mice exhibited increased aneuploidy due to chromosome segregation errors such as lagging chromosomes and chromatin bridges. Additionally, in *Ccna2*$^{-/H}$ MEFs, DNA replication forks progressed more slowly and stalled more frequently than in *Ccna2*$^{+/+}$MEFs, leading to an increased rate of DNA double-strand breaks. Consistent with these findings, expression of MRE11, a component of the MRN complex that is critical for DSB repair and replication fork restart, was reduced in *Ccna2*$^{-/H}$ MEFs. Mechanistically, cyclin A2 bound directly to the 3'UTR of *Mre11* mRNA in a CDK-independent manner to promote its translation, and thus depletion of cyclin A2 resulted in a reduction in MRE11. Ectopic expression of MRE11 in *Ccna2*$^{-/H}$ cells rescued double-strand breaks and chromosome defects, suggesting that MRE11 insufficiency is responsible for these effects. In addition to suggesting that cyclin A2 insufficiency promotes tumorigenesis, these findings reveal a previously undescribed function for a cyclin as an RNA-binding protein in addition to its CDK-dependent functions. ■

Kanakkanthara A, Jeganathan KB, Limzerwala JF, Baker DJ, Hamada M, Nam HJ, et al. Cyclin A2 is an RNA binding protein that controls Mre11 *mRNA translation. Science 2016;353:1549–52.*

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