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.


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<sup>H</sup>) with reduced expression of cyclin A2 in addition to its CDK-dependent functions.

In MEFs, treatment with small-molecule inhibitors of USP7 reduced tumor growth, 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.

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