Inhibition of polyamine synthesis and uptake reduces tumor progression and prolongs survival in mouse models of neuroblastoma

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Abstract

Amplification of the *MYCN* oncogene is associated with an aggressive phenotype and poor outcome in childhood neuroblastoma. Polyamines are highly regulated essential cations that are frequently elevated in cancer cells, and the rate-limiting enzyme in polyamine synthesis, ornithine decarboxylase 1 (ODC1), is a direct transcriptional target of MYCN. Treatment of neuroblastoma cells with the ODC1 inhibitor difluoromethylornithine (DFMO), although a promising therapeutic strategy, is only partially effective at impeding neuroblastoma cell growth due to activation of compensatory mechanisms resulting in increased polyamine uptake from the surrounding microenvironment. In this study, we identified solute carrier family 3 member 2 (SLC3A2) as the key transporter involved in polyamine uptake in neuroblastoma. Knockdown of SLC3A2 in neuroblastoma cells reduced the uptake of the radiolabeled polyamine spermidine, and DFMO treatment increased SLC3A2 protein. In addition, MYCN directly increased polyamine synthesis and promoted neuroblastoma cell proliferation by regulating SLC3A2 and other regulatory components of the polyamine pathway. Inhibiting polyamine uptake with the small-molecule drug AMXT 1501, in combination with DFMO, prevented or delayed tumor development in neuroblastoma-prone mice and extended survival in rodent models of established tumors. Our findings suggest that combining AMXT 1501

and DFMO with standard chemotherapy might be an effective strategy for treating neuroblastoma.

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