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MDM2 targeting PROTAC stabilizes p53 and inhibits neuroblastoma growth

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Neuroblastoma (NB) is a solid tumor originating from the extracranial sympathetic nervous system in the pediatric population. Despite recent advances in dose-intensive chemotherapy, radiation, and surgical regimens, NB often recurs as a metastatic and drug-resistant tumor. In view of these challenges, it is important to identify novel molecular targets and develop effective therapeutic regimens for NB. MDM2 is a known negative regulator of tumor suppressor p53, and inhibition of MDM2 has been shown to be an effective therapeutic strategy for multiple cancers, including NB. There are multiple potent, non-peptide, small-molecule MDM2 inhibitors in clinical development. The recent development of PROteolysis TArgeting Chimera (PROTAC) based MDM2 inhibitors provides selective degradation of MDM2 and leads to effective p53 stabilization. In the present study, we used a specific MDM2 targeting PROTAC, MD224 in NB, to determine the pre-clinical effects of inhibiting NB growth using a PROTAC-based MDM2 inhibitor. First, we analyzed multiple NB patient datasets and found that MDM2 expression is inversely correlated with the overall survival of NB patients. Additionally, high MDM2 levels were found to be correlated with high MYCN cases and overall disease progression, highlighting the role of MDM2 in NB pathogenesis. This data also highlights the importance of MDM2 as a molecular target in NB. Our data for cytotoxicity and clonogenic studies show that MD224 significantly and, in a dose-dependent manner, inhibits NB proliferation and colony formation. We also observed a significantly higher MD224-mediated inhibition of proliferation and colony formation in MYCN-amplified cell lines compared to non-amplified cell lines. Additionally, MDM2 inhibition significantly induces apoptosis in different NB cell lines compared to control treatments. Furthermore, we used NB 3D spheroid models that mimic in vivo NB tumor growth and found that MD224 significantly and in a dose-dependent manner inhibits 3D spheroid growth and volume compared to control treatments. Moreover, we have observed stabilization and increase in p53 level in response to MD224 treatment in comparison to control. As expected, the MD224 significantly inhibits NB cell cycle progression by inhibiting the cell cycle S phase in different NB cell lines. Overall, our data show that using MD224 and MDM2 targeting PROTAC molecules is an effective therapeutic strategy for high-risk NB. Further research and development into MDM2 targeting PROTAC will pave the way for efficient clinical translation and hold significant promise for effective NB treatment.