

Medulloblastoma is the most common type of malignant brain cancer in the pediatric population, with different subtypes conferring different prognoses. MYC-driven medulloblastoma (MB) has a poor 5-year survival rate, due to lack of therapeutic targets and frequent metastasis to the CSF. MYC overexpression causes malignant cell sensitization to apoptosis via transcriptional dysregulation and increased proliferation. A CRISPR-Cas9 essentiality screen was done to identify MYC-MB therapeutic targets on 1,140 genes. CDK12 was identified as a top essential gene for MYC-MB viability. Using shRNA genetic depletion as well as small molecule inhibitors of CDK12 in *in vitro* studies, we observe a decrease in tumor growth and increase in apoptosis. CDK12 inhibition causes a decrease in expression of DNA damage response genes, as well as disruption of transcriptional elongation via RNA polymerase II inhibition. This inhibition desensitizes tumor cells to apoptosis, while enhancing sensitivity to DNA damaging agents. These studies identify CDK12 inhibition as a possible therapeutic target for MYC-amplified medulloblastoma.