CDK8-MEDIATOR COMPLEX PLAYS POSITIVE TRANSCRIPTIONAL ROLE IN MYC-AMPLIFIED MEDULLOBLASTOMA

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Purpose: Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Group 3 MB, characterized by MYC amplification, carries a 50-60% 5-year survival expectancy. Current molecular therapies fail to outperform the standard therapy of surgical resection, CSI, and chemotherapy. Treatment can result in long-term therapy induced morbidity so there is a critical need to identify novel therapeutic targets. We investigate cyclin dependent kinase 8 (CDK8), a mediator complex-associated transcriptional regulator identified in a CRISPR druggable target screen in MYC-amplified MB.

Methods: Group 3 MB cells grown in supplemented DMEM. Protein expression analysis done with western blots (4-20% SDS-PAGE). Spheroid live cell imaging used to observe cell growth with titrated CDK8 chemical inhibitors Senexin B (10-2000nM) and BI-1347 (0.25-50nM).

Results: We demonstrated the role of CDK8 in survival and proliferation of MB. We found in MB subtypes, cells express CDK8 at levels 20 to 30-fold higher than normal cerebellum. CDK8 chemical inhibition revealed reduction in cell growth with IC50 in the nanomolar range (Sen B IC50 = 218.6 nM; BI-1347 IC50 = 2.591 nM). We are investigating the role of CDK8 in giving growth advantage to MYC expressing tumor cells and the impact of CDK8 depletion on mediator-complex stability.

Conclusions: Our results suggest that CDK8 plays a positive transcriptional role in MYC-amplified MB. We hypothesize this occurs through loss of kinase phosphorylation at the CTD of RNA polymerase II, an interaction well characterized in yeast. While CDK8 has been implicated in other cancers, its role in MB is not yet known. The mechanistic elucidation of CDK8 in MYC-amplified MB could provide insight into its potential role as a clinical therapeutic target.