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

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Purpose of Study: Medulloblastoma (MB) is the most common malignant pediatric brain tumor and a heterogenous cancer with four distinct molecular subtypes. Group 3 MB, characterized by MYC amplification, carries a poor prognosis with a 50-60% 5-year survival expectancy. Current molecular therapies fail to outperform the standard therapy of surgical resection, CSI, and adjuvant chemotherapy. This treatment outcome is unsatisfactory due to significant long-term therapy induced morbidity. Therefore, there is a critical need to identify effective novel therapeutic targets. In this study, we investigate the role of cyclin dependent kinase 8 (CDK8), a mediator complex-associated transcriptional regulator as it was identified in a CRISPR druggable target screen in MYC-amplified MB.

Methods Used: Group 3 MB cells grown in DMEM supplemented with FBS, sodium pyruvate, penicillin-streptomycin, and non-essential amino acids or L-glutamine. Protein expression analysis completed with western blotting on 4-20% SDS-PAGE. Spheroid live cell imaging used to observe growth inhibition with titrated CDK8 chemical inhibitors Senexin B (10-2000nM) and BI-1347 (0.25-50nM).

Summary of Results: Here we demonstrated the role of CDK8 in survival and proliferation of MB. We found amongst multiple MB subtypes, cells express CDK8 at levels 20 to 30-fold higher than normal cerebellum. Spheroid live cell imaging revealed marked reduction in cell growth with chemical inhibition of CDK8 with IC50 in the nanomolar range (Senexin B IC₅₀ = 218.6 nM; BI-1347 IC₅₀ = 2.591 nM). We are investigating the biology 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 previously been implicated in colorectal cancer and BCR-ABL leukemia, its role in MB has not been established. The mechanistic elucidation of CDK8 in MYC-amplified MB could provide further information into its potential role as a clinical therapeutic candidate.