

Investigating CDK12 and CDK13 as Therapeutic Targets in Group 3 Medulloblastoma

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Background
Group 3 medulloblastoma (G3 MB) is the most aggressive MB subtype, driven by profound deregulation of transcriptional and post-transcriptional programs. Transcriptional cyclin-dependent kinases (CDKs), which regulate both processes, have emerged as promising therapeutic targets, and their inhibitors show efficacy in several cancers, including MB. Among them, CDK12 and CDK13 promote transcriptional elongation by phosphorylating RNA polymerase II, coupling transcription with pre-mRNA processing. We found G3 MB cells to be highly sensitive to pharmacological inhibition of these kinases, prompting investigation of their individual contributions to the oncogenic phenotype of G3 MB.

Methods
CDK12 and/or CDK13 were depleted in G3 MB cells, and proliferation, colony formation, spheroid growth, and cell-cycle distribution were assessed in vitro. Tumorigenic capacity in vivo was evaluated through orthotopic xenograft models. RNA-seq was used to characterize gene expression alterations following kinase loss.

Results
Loss of either kinase impaired proliferation, colony formation, and spheroid growth, with stronger effects upon co-depletion, indicating redundancy in sustaining viability. Both knockdowns increased the sub-G1 fraction; however, only CDK13 depletion triggered apoptosis, revealing distinct mechanisms by which CDK12 and CDK13 regulate survival. In vivo, CDK12 loss modestly reduced tumor growth, whereas CDK13 depletion markedly suppressed tumor formation, and dual loss abolished it—an effect likely driven by apoptosis uniquely induced by CDK13 loss. Transcriptomic profiling further highlighted their divergence: CDK12 depletion broadly reprogrammed gene expression, downregulating DNA repair and mitotic spindle pathways. By contrast, CDK13 loss altered fewer transcripts without strong pathway enrichment, pointing to an essential but less specific role in tumor maintenance.

Conclusion
These findings reveal both overlapping and distinct functions of CDK12 and CDK13 in G3 MB, highlighting dependence on CDK13 for tumorigenesis. While our data identify CDK13 as a promising vulnerability, further studies are required to clarify mechanisms underlying this dependency and evaluate its therapeutic potential in G3 MB.