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Title: Examining the role of chromatin modifying enzymes in medulloblastoma by utilizing a chemical library

Background: Medulloblastoma (MB) is the most common paediatric brain tumor that arises during infancy and childhood and is a major cause of cancer related-morbidity and mortality in children. Recently, medulloblastomas are described as four distinct molecular subgroups (Wnt, sonic hedgehog, Group 3 and Group 4), which have distinct transcriptional, cytogenetic, and mutational spectra. Next-generation studies have revealed that adult medulloblastomas involve remarkably more somatic SNVs and indels than paediatric counterparts, suggesting that epigenetic deregulation might have a foremost role in the initiation and progression of paediatric medulloblastomas.

Materials and Methods: Chemical library containing 46 inhibitors against different chromatin modifying enzymes (CMEs) was used in order to investigate their role in medulloblastoma. ATP-based cell viability assay was used to examine the cell death in a dose-dependent manner in cancer cells and non-malignant cells. The downstream molecular changes upon inhibitor treatment was examined by qRT-PCR. Induction of apoptosis was revealed by increased levels of cleaved PARP by western blotting.

Results: The function of chromatin modifying enzymes (CMEs) in medulloblastoma was investigated by utilizing a chemical library, which was composed of 46 inhibitors against different CMEs. The screen revealed 7 potential inhibitors that induced cell death in a dose-dependent manner in DAOY and D283 MB cell lines and a primary cell line significantly. Among those, inhibitors targeting histone deacetylases (HDACs) and different histone demethylases (HDMs) were present and these compounds were relatively non-toxic to normal cells. As their roles have been ill-defined in medulloblastomas, we focused on HDMs and investigated the downstream molecular changes upon inhibitor treatment by qRT-PCR and western blotting. We observed that pro-apoptotic genes were upregulated in favour of enhanced apoptosis and cells underwent apoptosis as revealed by PARP cleavage.

Conclusion: In conclusion, our results suggest that targeting specific HDMs by specific inhibitors can be a promising therapeutic approach for medulloblastoma patients.