Assessing the function of chromatin modifying enzymes in medulloblastoma

Lokumcu T[1], Senbabaoglu F[1], Oppermann U[2], and Bagci-Onder T[1,*]
[1]Koç University School of Medicine, Brain Cancer Research and Therapy Laboratory, Istanbul, TURKEY
[2]Structural Genomics Consortium, University of Oxford, Headington, UK.

[*] Correspondence: tuonder@ku.edu.tr

Medulloblastoma is the most common pediatric 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 pediatric medulloblastomas. For this purpose, 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 significantly. Among those, inhibitors targeting histone deacetylases (HDACs) and different histone demethylases (HDMs) were present. 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. In conclusion, our results suggest that targeting specific HDMs by specific inhibitors can be a promising therapeutic approach for medulloblastoma patients.