SHH medulloblastoma treatment

For patients whose tumors are driven by mutations in the sonic hedgehog (SHH) pathway, SHH antagonists offer some hope. However, many SHH-associated medulloblastomas do not respond to these drugs, and those that do may develop resistance. Therefore, more effective treatment strategies are needed for both SHH and non-SHH-associated medulloblastoma [1)].

One such strategy involves targeting the cells that are critical for maintaining tumor growth, known as tumor-propagating cells (TPC).

Data provide strong evidence that Quisinostat or other class I HDAC inhibitors might be therapeutically useful for patients with SHH MB including those resistant to SMO inhibition [2)].

Markant et al., previously identified a population of TPCs in tumors from patched mutant mice, a model for SHH-dependent medulloblastoma. These cells express the surface antigen CD15/SSEA-1 and have elevated levels of genes associated with the G2-M phases of the cell cycle. They show that CD15(+) cells progress more rapidly through the cell cycle than CD15(-) cells and contain an increased proportion of cells in G2-M, suggesting that they might be vulnerable to inhibitors of this phase. Indeed, exposure of tumor cells to inhibitors of Aurora kinase (Aurk) and Polo-like kinases (Plk), key regulators of G2-M, induces cell-cycle arrest, apoptosis, and enhanced sensitivity to conventional chemotherapy. Moreover, treatment of tumor-bearing mice with these agents significantly inhibits tumor progression. Importantly, cells from human patient-derived medulloblastoma xenografts are also sensitive to Aurk and Plk inhibitors. The findings suggest that targeting G2-M regulators may represent a novel approach for treatment of human medulloblastoma [3)].

1)
Kieran MW. Targeted treatment for sonic hedgehog-dependent medulloblastoma. Neuro Oncol. 2014 Aug;16(8):1037-47. doi: 10.1093/neuonc/nou109. Review. PubMed PMID: 24951114; PubMed Central PMCID: PMC4096181.
2)
Pak E, MacKenzie EL, Zhao X, Pazyra-Murphy MF, Park PMC, Wu L, Shaw DL, Addleson EC, Cayer SS, Lopez BG, Agar NYR, Rubin LL, Qi J, Merk DJ, Segal RA. A large-scale drug screen identifies selective inhibitors of class I HDACs as a potential therapeutic option for SHH medulloblastoma. Neuro Oncol. 2019 May 16. pii: noz089. doi: 10.1093/neuonc/noz089. [Epub ahead of print] PubMed PMID: 31111916.
3)
Markant SL, Esparza LA, Sun J, Barton KL, McCoig LM, Grant GA, Crawford JR, Levy ML, Northcott PA, Shih D, Remke M, Taylor MD, Wechsler-Reya RJ. Targeting sonic hedgehog-associated medulloblastoma through inhibition of Aurora and Polo-like kinases. Cancer Res. 2013 Oct 15;73(20):6310-22. doi: 10.1158/0008-5472.CAN-12-4258. PubMed PMID: 24067506; PubMed Central PMCID: PMC3800039.