Disrupting anti-apoptotic BCL-xL sensitizes SHH-driven medulloblastomas to SHH inhibition

Rishita Chamarthi

Medulloblastoma is the most common malignant pediatric brain tumor, and it develops in the cerebellum. Current treatments for this tumor result in an eighty percent five-year survival rate, however, treatment still fails 20% of patients and treatment-induced toxicities can lead to long-term neurocognitive deficits in patients. Therefore, there is a need to develop novel less-toxic therapeutic options for patients, to increase survival rates while minimizing treatment-induced side effects. The proliferation pathway that increases tumor growth rate is the SHH pathway. The pro-apoptotic pathway is governed by the BAX protein. Bcl-xL inhibits BAX from oligomerizing stopping immediate apoptosis. Therefore, it was hypothesized that targeting proliferation by inhibiting SHH signaling pharmacologically using POx-Vismodegib will sensitize medulloblastomas to Bcl-xL deletion. After the POx-Vismodegib drug regiment, it was found that MSmo/Bcl-xL KO mice had a significantly increased survival rate compared to MSmo mice without treatment. MSmo/Bcl-xL KO mice and MSmo/Bcl-xL WT mice did not have significantly different survival rates with a p-value of 0.14. It was noted that Bcl-xL deletion led to no residual tumors in MSmo/Bcl-xL KO mice which was not seen in MSmo mice with Bcl-xL intact tumors.