

Applicant's Name: Eli E. Bar, Ph.D.

Applicant's Division: Neuropathology

“Hedgehog Signaling Promotes Medulloblastoma Survival via Bcl2”

Eli E. Bar, Aneeka Chaudhry, Charles G. Eberhart

Background: Deregulation of the Hedgehog pathway has been implicated in the development of medulloblastoma, the most frequent malignant brain tumor in children. Transcriptional induction of antiapoptotic factors such as Bcl2 is a major mechanism for apoptosis avoidance in cancer cells.

Design: We investigated whether Hedgehog might regulate survival in medulloblastoma via upregulation of Bcl2.

Results: We found that the Hedgehog pathway effectors Gli1 and Gli2 colocalize with Bcl2 in regions of decreased apoptosis in a subset of nodular medulloblastoma. Transient overexpression of Gli1 and Gli2 induced a Bcl2 transcriptional reporter and increased Bcl2 protein levels, while stable overexpression of Gli1 was associated with increased Bcl2 mRNA. The Hedgehog antagonist cyclopamine blocked expression of the Hh pathway targets PTCH1 and Gli1 and increased apoptosis in DAOY medulloblastoma cells. Apoptotic induction caused by cyclopamine could be rescued in part by enforced expression of Gli1 or Bcl2. Hh pathway blockade also sensitized medulloblastoma to the effects of the pro-apoptotic agent lovastatin.

Conclusion: These data demonstrate that Bcl2 is an important mediator of Hh activity in medulloblastoma, and suggest new strategies for combined chemotherapeutic regimens.