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The role of BMX in cancer stem cell state and ibrutinib sensitivity in pediatric high-grade glioma

Background: Annually, around 50,000 brain tumors are diagnosed in the United States, with gliomas comprising the majority. High-grade gliomas, including glioblastomas, represent a particularly aggressive subset, accounting for approximately 25% of adult and 15% of pediatric brain tumors. The treatment of high-grade gliomas has seen minimal advancement in recent years due to their complex and heterogeneous nature. A significant component of this heterogeneity is attributed to glioma stem cells (GSCs), which are stem-like, self-renewing, and resistant to conventional therapies. The stem cell state of GSCs is regulated by the BMX-STAT3 signaling axis. Ibrutinib, a known inhibitor of this axis, may offer a potential therapeutic strategy.

Methods: This study utilized patient-derived glioma stem cells for all experimental assays. We employed lentiviral-mediated delivery of shRNAs and overexpression constructs to manipulate gene expression. Cells were treated with varying concentrations of Ibrutinib for 6 days, and cell viability was evaluated using a luminescence-based assay. The self-renewal capacity of the cells was assessed through a limiting dilution assay. BMX and other stem cell markers were quantified using Western blot and qPCR techniques.

Results: Sensitivity to Ibrutinib varied significantly across different patient-derived samples, with a roughly 100-fold difference observed. A strong correlation was found between BMX expression levels and Ibrutinib sensitivity. Pediatric high-grade glioma samples exhibited particularly high sensitivity to Ibrutinib and low BMX expression. Knockdown of BMX in high-expressing cells increased sensitivity to Ibrutinib and reduced self-renewal potential. Additionally, some constructs led to decreased levels of stem cell markers such as SOX2 and OLIG2. We are currently in the process of overexpressing BMX in BMX-low lines to further investigate the relationship between BMX levels and Ibrutinib sensitivity.

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