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Targeting Resistance in Medulloblastoma

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Abstract

Medulloblastoma is the most common malignant brain tumor of childhood. Although the current treatment protocols for this cancer have improved overall survival, they lead to devastating and lifelong sequelae and mortality remains high in recurrent and metastatic disease. Novel targeted therapies are crucial to improve survival in these children without treatment-related toxicity.

Medulloblastoma development is largely driven by deregulation of normal cerebellar proliferation wherein aberrant sonic hedgehog (Shh) pathway signaling plays a critical role. Activating mutations of Shh genes are frequent in medulloblastoma and promote their rapid growth. Poor outcomes in Shh-driven tumors have prompted the evaluation of targeted agents against the Shh pathway but these have had limited success - likely due to the upregulation of additional oncogenic pathways including the Ras/MAPK pathway and HIF-1α. These pathways stimulate glycolysis in part by activating the 6-phosphofructo-2-kinase/fructose-2,6 bisphosphatase family of enzymes (PFKFB1-4). The PFKFBs produce fructose-2,6-bisphosphate (F26BP), a potent activator of 6-phosphofructo-1-kinase, a rate-limiting step in glycolysis. We found that the PFKFB4 enzyme is highly expressed in a series of patient-derived medulloblastomas and correlated significantly with expression of the Shh pathway effector Smoothened (SMO). Through HIF-1α upregulation, we observed that hypoxia strongly induced PFKFB4 expression in Shh-active medulloblastoma cells and that silencing PFKFB4 in these cells markedly suppressed F26BP and glycolytic flux to lactate and significantly decreased cell survival and proliferation, more prominently in hypoxia, indicating that PFKFB4 may be preferentially required for survival and growth under hypoxia. We found that co-silencing PFKFB4 and Shh proteins significantly reduced cell survival and that co-targeting PFKFB4 (with a novel small molecule inhibitor) and Shh effectors synergistically decreased cell viability. To mimic Shh antagonist resistance, we subjected Shh medulloblastoma cells to prolonged Shh inhibitor exposure and have found

> that these cells show increased proliferation and glycolysis and increased expression of PFKFB4 and are more sensitive to PFKFB4 inhibition. Taken together, our data indicate that targeting PFKFB4 may be a valid therapeutic option in aggressive, treatment-resistant medulloblastoma and strongly support the examination of PFKFB4 inhibitors in these tumors.

This is the full abstract presented at the Experimental Biology meeting and is only available in HTML format. There are no additional versions or additional content available for this abstract.