Targeting the PI3K/AKT/mTOR signaling pathway in medulloblastoma.

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Abstract

Medulloblastoma is the most common malignant childhood brain tumor and is associated with a poor outcome. There is an urgent need to develop novel targeted therapeutic approaches for medulloblastoma, which will arise from an enhanced understanding of the disease at the molecular level. Medulloblastoma has been recognized to be a heterogeneous disease, and no recurrent cancer gene mutations have been found, although many of the mutations described so far affect key intracellular signaling pathways, such as sonic hedgehog (SHH) and Wnt/β-catenin. The PI3K/AKT/mTOR (PAM) signaling pathway controls key cellular responses, such as cell growth and proliferation, survival, migration and metabolism. Over the last decades, it has been recognized that this intracellular signaling pathway is frequently activated by genetic and epigenetic alterations in malignant brain tumors, including medulloblastoma. Clinical trials have started to evaluate the safety and efficacy of agents targeting this pathway in malignant brain tumors. Due to the complexity of the PAM signaling pathway, there remain significant difficulties in the development of novel therapeutic approaches. The future challenges in developing effective treatments for cancer patients include the development of predictive biomarkers and combinatorial approaches to effectively target multiple signal transduction pathways. In this review article, we will summarize the current knowledge about the role of PAM signaling in medulloblastoma and discuss the strategies that are currently being evaluated with targeted agents against this pathway.

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