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Mechanism of action by which 5-NIdR acts as a therapeutic agent against brain cancer

College of Sciences and Health Professions

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Abstract

Approximately 10,000 people in the United States are diagnosed annually with a brain tumor. In addition, the prognosis for brain cancer patients is poor as these cancers have low survival rates of less than 10%. One important chemotherapeutic agent used to treat brain cancer is temozolomide, an alkylating agent that causes cell death by damaging DNA. In this project, we tested the ability of a specific non-natural nucleoside developed in our lab, designated 5-NIdR, to increase the efficacy of temozolomide against brain cancer. Animal studies using xenograft mice were performed to evaluate the in vivo efficacy of this drug combination against brain cancer. Results indicate that treatment with 5-NIdR does not affect the rate of tumor growth compared to treatment with vehicle control. While treatment with temozolomide slows the rate of tumor growth by 2-fold, more striking results are obtained when 5-NIdR is combined with temozolomide as this drug combination causes complete tumor regression within two weeks of treatment. To better define the cellular mechanism for this effect, a series of cell-based studies were performed to compare the cytotoxic effects of temozolomide alone and in combination with 5-NIdR. Flow cytometry experiments measuring Annexin V staining as a marker for apoptosis demonstrate that cells treated with 5-NIdR and temozolomide accumulate show significantly higher levels of apoptosis compared to cells treated with 5-NIdR or temozolomide alone. Experiments measuring cell-cycle progression demonstrate that treatment with 5-NIdR and temozolomide causes cancer cells to accumulate at S-phase before undergoing apoptosis. The block at S-phase likely results from the ability of 5-NIdR to inhibit the replication of damaged DNA created by temozolomide. Consistent with this mechanism, significantly higher levels of single- and double-strand DNA breaks are detected in cancer cells treated with 5-NIdR and temozolomide compared to cells treated individually with either agent. Collectively, these studies provide additional pharmacological evidence for combining 5-NIdR and temozolomide as a possible treatment strategy to effectively treat brain cancers.

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