Autophagy: Chapter 16. Enhancement of Cell Death in High-Grade Glioma Cells: Role of N-(4-Hydroxyphenyl) Retinamide-Induced Autophagy

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Despite clinical advancements, high-grade glioma continues to remain incurable in the majority of patients, largely due to recurrence of the tumor caused by resistance towards the conventional therapies. The therapeutic goal of cancer treatment has been to trigger cancer cell death through apoptosis; however, the cancer cells develop resistance to apoptosis induction. This underscores the need to identify newer chemotherapeutic strategies that can maximize apoptosis or induce alternate mode of cell death in apoptosis-resistant cells. For these reasons, autophagy, which can play a role in cell survival or cell death, is receiving scientific attention as a target to modulate the cell death response of cancer cells. Of interest, autophagy has been shown to be induced by a number of current and experimental glioma therapies. Further, a better understanding of the link between apoptosis and autophagy might allow development of more effective therapies for high-grade gliomas. N-(4-hydroxyphenyl) retinamide (4-HPR) is a potent synthetic retinoid with anticancer activity in a variety of tumors, which is largely dependent on its ability to engage apoptotic pathways in transformed cells, and its relative lack of adverse side effects in vivo. We have identified a novel role for 4-HPR in high-grade glioma cell lines: the ability to induce autophagy at a lower concentration and apoptosis at a higher concentration, leading to elimination of cancer cells. Notably, inhibition of autophagy at a lower concentration sensitizes high-grade glioma cells to 4-HPR-induced apoptosis, suggesting a survival-promoting role for 4-HPR-induced autophagy. These findings propose further evaluation of autophagy inhibition in combination with 4-HPR in high-grade gliomas to achieve higher efficacy and prevent recurrence of these malignancies.

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