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Review

Mechanisms of Chemoresistance to Alkylating Agents in Malignant Glioma

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Intrinsic or acquired chemoresistance to alkylating agents is a major cause of treatment failure in patients with malignant brain tumors. Alkylating agents, the mainstay of treatment for brain tumors, damage the DNA and induce apoptosis, but the cytotoxic activity of these agents is dependent on DNA repair pathways. For example, O⁶-methylguanine DNA adducts can cause double-strand breaks, but this is dependent on a functional mismatch repair pathway. Thus, tumor cell lines deficient in mismatch repair are resistant to alkylating agents. Perhaps the most important mechanism of resistance to alkylating agents is the DNA repair enzyme O⁶-methylguanine methyltransferase, which can eliminate the cytotoxic O⁶-methylguanine DNA adduct before it causes

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harm. Another mechanism of resistance to alkylating agents is the base excision repair (BER) pathway. Consequently, efforts are ongoing to develop effective inhibitors of BER. Poly(ADP-ribose)polymerase plays a pivotal role in BER and is an important therapeutic target. Developing effective strategies to overcome chemoresistance requires the identification of reliable preclinical models that recapitulate human disease and which can be used to facilitate drug development. This article describes the diverse mechanisms of chemoresistance operating in malignant glioma and efforts to develop reliable preclinical models and novel pharmacologic approaches to overcome resistance to alkylating agents.

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