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Novel strategies to overcome chemoresistance in human glioblastoma

Qing Tang [1], Ting Ren [1], Peiying Bai [1], Xin Wang [2], Lijiao Zhao [1], Rugang Zhong [1], Guohui Sun [3]

Affiliations
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Abstract

Temozolomide (TMZ) is currently the first-line chemotherapeutic agent for the treatment of glioblastoma multiforme (GBM). However, the inherent heterogeneity of GBM often results in suboptimal outcomes, particularly due to varying degrees of resistance to TMZ. Over the past several decades, O^6-methylguanine-DNA methyltransferase (MGMT)-mediated DNA repair pathway has been extensively investigated as a target to overcome TMZ resistance. Nonetheless, the combination of small molecule covalent MGMT inhibitors with TMZ and other chemotherapeutic agents has frequently led to adverse clinical effects. Recently, additional mechanisms contributing to TMZ resistance have been identified, including epidermal growth factor receptor (EGFR) mutations, overactivation of intracellular signalling pathways, energy metabolism reprogramming or survival autophagy, and changes in tumor microenvironment (TME). These findings suggest that novel therapeutic strategies targeting these mechanisms hold promise for overcoming TMZ resistance in GBM patients. In this review, we summarize the latest advancements in understanding the mechanisms underlying intrinsic and acquired TMZ resistance. Additionally, we compile various small-molecule compounds with potential to mitigate chemoresistance in GBM. These mechanism-based compounds may enhance the sensitivity of GBM to TMZ and related chemotherapeutic agents, thereby improving overall survival rates in clinical practice.

Keywords: Chemotherapy; Drug resistance; Glioblastoma; MGMT; Temozolomide.