S-Nitrosoglutathione and Hypoxia-Inducible Factor-1 Confer Chemoresistance

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Abstract

BCNU (1,3-bis[2-chloroethyl]-1-nitrosourea) is the mainstay in glioblastoma multiform chemotherapy with only minimal effects. BCNU may kill tumor cells via carbamoylating cytotoxicity, which irreversibly inhibits glutathione reductase with resultant accumulation of oxidized form of glutathione causing oxidative stress. S-nitrosoglutathione (GSNO) is a product of glutathione and nitric oxide interaction. We report that GSNO formation may underlie carbamoylating chemoresistance mediated by activation of inducible nitric oxide synthase. Transactivation of hypoxia-inducible factor-1 (HIF-1)-responsive genes reduces oxidative stress caused by glutathione depletion. We also noted that preconditioning of C6 glioma cells to induce HIF-1 and its downstream genes confers chemoresistance against carbamoylating cytotoxicity of BCNU.