HYPOXIA INHIBITS PACLITAXEL-INDUCED APOPTOSIS THROUGH ADENOSINE-MEDIATED PHOSPHORYLATION OF BAD IN GLIOBLASTOMA CELLS

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Solid tumors contain hypoxic cells that are resistant to radiotherapy and chemotherapy. The resistance in glioblastoma has been linked to the expression of antiapoptotic Bcl-2 family members. In this study, we found that in human glioblastoma cells hypoxia induces the phosphorylation of the Bcl-2 family protein Bad, thus protecting hypoxic cells from paclitaxel-induced apoptosis. Akt activation is required for the hypoxia-induced protection. In contrast, the ERK1/2 activities have only a partial effect. We also demonstrated that the degradation of adenosine with adenosine deaminase, the knockdown of A_3 adenosine receptor expression by gene silencing as well as the blockade of this receptor through A_3 receptor antagonists blocked the hypoxia-induced phosphorylation of Bad and the prolonged cell survival following treatment with paclitaxel in hypoxia. Thus, the adenosinergic signaling may be an essential component in the hypoxia survival pathway. These results suggest that hypoxia-induced chemoresistance of human glioblastoma cells may occur in a novel mechanism involving activation of adenosine-A_3 receptor-Akt pathway which mediates Bad inactivation and favors cell survival.