Glycogenolysis

Glycogenolysis is the breakdown of glycogen (n) to glucose-6-phosphate and glycogen (n-1). Glycogen branches are catabolized by the sequential removal of glucose monomers via phosphorolysis, by the enzyme glycogen phosphorylase.

Glycogenolysis is known to play an essential role in cell proliferation and potassium homeostasis and involves the glycogen phosphorylase isoenzyme BB (GPBB). Plasma GPBB was correlated with TMZ-resistance. Elevated plasma GPBB concentrations were found to be more frequent in a temozolomide resistance cohort of patients with poor survival rates. TMZ inhibits cell proliferation and induces TMZ resistance by upregulating the expression of O(6)-methylguanine-DNA methyltransferase (MGMT). This process requires glycogenolysis, which was confirmed herein by treatment with 1,4-dideoxy-1,4-imino-D-arabinitol hydrochloride, a glycogenolysis inhibitor and a special GPBB inhibitor. Acute TMZ treatment leads to upregulation of [Ca2+]i, extracellular-regulated kinase (ERK)1/2 phosphorylation, and chronic TMZ treatment leads to upregulation of the expression of Na,K-ATPase, ERK1/2, and MGMT protein. Upregulation was abolished for each of these by inhibitors of transient receptor potential channel 1 and the inositol trisphosphate receptor. L-channel [Ca2+]i inhibitors and RyR antagonists had no such effect. These results demonstrate that [Ca2+]i-dependent glycogenolysis participates in acquired glioma TMZ-resistance by upregulating MGMT via a Na,K-ATPase/ERK1/2 signaling pathway. GPBB and glycogenolysis may therefore represent novel therapeutic targets for overcoming TMZ-resistant gliomas [1)]

1)
Xu J, Zhang Y, Guo X, Sun T. Glycogenolysis in Acquired Glioma Resistance to Temozolomide: A Role for the [Ca2+]i-dependent Activation of Na,K-ATPase/ERK1/2 Signaling. Front Pharmacol. 2018 Aug 7;9:873. doi: 10.3389/fphar.2018.00873. PMID: 30131700; PMCID: PMC6090282.