Glycogen Phosphorylase L

- Glycogenolysis in Acquired Glioma Resistance to Temozolomide: A Role for the [Ca²⁺]_i-dependent Activation of Na,K-ATPase/ERK_{1/2} Signaling
- Pancreatic response to mild non-insulin-induced hypoglycemia does not involve extrinsic neural input
- Growth hormone acutely increases glucose output by hepatocytes isolated from hypophysectomized rats
- Representative enzymes of energy supplying metabolism in the normal and denervated human brachial biceps, deltoid and anterior tibial muscles (author's transl)

Glycogen Phosphorylase L (PYGL): Overview

Glycogen phosphorylase L (PYGL) is an isoform of glycogen phosphorylase predominantly expressed in the liver. This enzyme plays a crucial role in glycogen metabolism, catalyzing the breakdown of glycogen into glucose-1-phosphate (G1P). This process is vital for maintaining blood glucose levels, particularly during fasting or periods of increased energy demand.

Structure and Function - **Gene**: The PYGL gene encodes the liver isoform of glycogen phosphorylase. - **Function**: The enzyme facilitates the phosphorolysis of glycogen, cleaving α-1,4 glycosidic bonds. It is regulated by hormonal signals and allosteric interactions. - **Activity Regulation**:

1. **Hormonal**: Activated by glucagon and epinephrine via cAMP-dependent phosphorylation, promoting glycogen breakdown in response to low blood glucose levels.
2. **Allosteric**: Inhibited by glucose and ATP, indicating sufficient energy supply. Activated by AMP during low energy states.

Clinical Relevance - **Glycogen Storage Disease Type VI (Hers Disease)**:

1. **Cause**: Mutations in the PYGL gene lead to reduced or absent glycogen phosphorylase activity in the liver.
2. **Symptoms**: Hepatomegaly, mild fasting hypoglycemia, growth retardation, and ketosis.
3. **Diagnosis**: Based on genetic testing and liver biopsy showing abnormal glycogen storage.
4. **Management**: Dietary interventions to prevent hypoglycemia, including frequent meals and cornstarch supplementation.

Biological Significance - PYGL is crucial for glucose homeostasis. The liver's ability to mobilize glycogen stores depends on this enzyme, especially during fasting or stress. - Dysfunction in PYGL has downstream effects on metabolism, highlighting its significance in energy regulation and potential therapeutic targeting for metabolic disorders.

Research and Therapeutic Insights - **Potential Target in Metabolic Disorders**: Modulating PYGL activity could be explored in diseases like diabetes, where glycogen breakdown plays a role in hyperglycemia. - **Drug Development**: Inhibitors or activators of PYGL could provide therapeutic strategies for conditions involving glycogen storage and glucose metabolism.

Glycogenolysis is known to play an essential role in cell proliferation and potassium homeostasis and

involves the glycogen phosphorylase isoenzyme BB (GPBB). In this investigation, plasma GPBB was correlated with TMZ-resistance. Elevated plasma GPBB concentrations were found to be more frequent in a TMZ-resistant 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.