Glycogen phosphorylase isoenzyme BB

Overview

Glycogen phosphorylase isoenzyme BB (GPBB) is an isoform of glycogen phosphorylase primarily expressed in the **brain** and **heart**. This enzyme plays a critical role in glycogen metabolism by catalyzing the phosphorolytic cleavage of glycogen to glucose-1-phosphate (G1P), which can be further metabolized to meet cellular energy demands. —

Key Characteristics - **Gene**: Encoded by the **PYGB** gene. - **Tissue Distribution**:

1. High expression in the **brain** and **cardiac muscle**.
2. Functions to rapidly provide glucose-1-phosphate for energy, especially under conditions of stress or hypoxia.

- **Structure**:

1. Exists as a homodimer or homotetramer.
2. Includes regulatory sites for allosteric effectors and phosphorylation.

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Role in Metabolism 1. **Energy Provision**:

1. Converts glycogen to glucose-1-phosphate, which enters glycolysis for ATP production.
2. Particularly important in the brain and heart, where constant energy supply is critical.

2. **Stress Response**:

1. GPBB is activated during hypoxia, ischemia, or other stress conditions, ensuring energy availability when glucose uptake is limited.

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Clinical Relevance 1. **Ischemic Heart Disease**:

1. **GPBB as a Biomarker**:
    1. During myocardial ischemia, GPBB is released into the bloodstream due to glycogen mobilization.
    2. Elevated levels of GPBB in serum are used as a marker for **acute myocardial infarction (AMI)**.
2. **Diagnostic Value**:
    1. GPBB is an early biomarker, detectable within 2-4 hours of the onset of ischemia, offering a diagnostic advantage over traditional markers like troponins or CK-MB.

2. **Neurological Disorders**:

1. Alterations in GPBB expression or function may impact brain energy metabolism, potentially playing a role in conditions like hypoxic-ischemic encephalopathy or neurodegenerative diseases.

3. **Glycogen Storage Diseases**:

1. Although rare, mutations in the PYGB gene could theoretically disrupt glycogen metabolism in tissues expressing GPBB, leading to energy deficits.

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Regulation - **Covalent Modification**:

1. Activated by phosphorylation via **phosphorylase kinase**.
2. Dephosphorylated by protein phosphatase-1, leading to inactivation.

- **Allosteric Regulation**:

1. **Activators**: AMP (signals low energy), calcium (via muscle contraction or neural activity).
2. **Inhibitors**: ATP, glucose-6-phosphate (indicators of energy sufficiency).

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Research and Therapeutic Potential 1. **Cardiac Biomarker Development**:

1. GPBB inhibitors or modulators could have potential in managing ischemic heart disease by regulating glycogen mobilization.

2. **Neuroprotection**:

1. Targeting GPBB activity could mitigate energy deficits in ischemic or neurodegenerative conditions.

3. **Metabolic Engineering**:

1. Understanding GPBB's role in energy metabolism could inspire novel therapeutic approaches for metabolic diseases.

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Diagnostic Use in Acute Myocardial Infarction - **Advantages**:

1. Early detection: Detectable soon after ischemia onset.
2. Complementary to troponins for more comprehensive diagnostic coverage.

- **Limitations**:

1. Lack of specificity to cardiac tissue (also expressed in the brain).
2. Requires correlation with other clinical findings for accurate diagnosis.

Understanding the mechanistic basis for glioma temozolomide resistance is an important obstacle in developing an effective form of chemotherapy. 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 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)]

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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.