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Content

INVESTIGATION OF THE ROLE OF THE GLUCOSE-6-PHOSPHATE TRANSLOCASE IN THE ACTIVATION OF AUTOPHAGY AND GLYCOGEN-SELECTIVE AUTOPHAGY IN GLYCOGEN STORAGE DISEASE TYPE IB PATIENTS

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Introduction: Glycogen storage disease type Ib (GSD-Ib) is characterized by a deficiency of glucose-6-phosphate translocase (G6PT) encoded by the *SLC37A4* gene, affecting glucose homeostasis and disrupting autophagy. Recent findings suggest that G6PT may also play a role in autophagy and glycogen-selective autophagy (glycophagy) activation independent of its transport function. To investigate this hypothesis, two groups of GSD-Ib patients carrying variants with different effects on G6PT transport activity and stability (p.Asn27Lys and p.Leu348Valfs*53), were compared to the control group of subjects.

Methods: The relative expression levels of *SLC37A4* gene, autophagy (*mTOR*, *ULK1*, *PRKAG1*), and glycophagy markers (*GABARAPL1*, *GAA*, *STBD1*) were assessed in mononuclear cells of GSD Ib patients (four carrying p.Asn27Lys and four carrying p.Leu348Valfs*53 variant) compared to control group using RT-qPCR. Statistical analysis was performed using one-way ANOVA followed by a post-hoc t-test.

Results: The p.Asn27Lys group exhibited 1.5-2.5 times higher expression of *SLC37A4* and autophagy markers, while the p.Leu348Valfs*53 group showed downregulation by approximately 50% compared to the control group. Glycophagy markers were increased twofold in both patient groups, except for *GAA*, which had similar expression levels as the control group.

Conclusion: Individuals carrying the p.Asn27Lys variant display the presence of *SLC37A4* transcript in their cells, which correlates with autophagy activation. Conversely, in patients with the p.Leu348Valfs*53 variant *SLC37A4* is downregulated, indicating compromised autophagy activation. These findings support the role of G6PT in autophagy activation, independent of its transport activity. Furthermore, the elevated expression of glycophagy markers observed in both patient groups can be attributed to the accumulated glycogen.

Key words: glycogen storage disease type Ib; glucose-6-phosphate translocase; autophagy; glycogen-selective autophagy

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