

Abstract

Phosphoglucomutase 1 (PGM1) interconverts Glucose(Glc)-6-P and Glc-1-P. Disruption impairs both glycogen metabolism, and glycosylation, the latter manifesting as a congenital disorder of glycosylation (PGM1-CDG). Based on decreased galactosylation in truncated glycan chains, D-galactose (D-Gal) was administered to PGM1-CDG patients and was shown to markedly reverse many of the disease symptoms. The treatment mechanism(s) however have not been understood. Here, principally using tracer-based metabolomics, we report that Gal treatment of PGM1-CDG fibroblasts metabolically re-wires their sugar metabolism and replenishes depleted levels of the activated sugars UDP-Glc and UDP-Gal, so required for ER and Golgi linked glycosylation respectively. To this end, we further show that UDP-Gal is incorporated into mature *de novo* glycans. We also probed other potential mechanisms of galactose's action, such as through altered PGM1 activity, central carbon metabolism or mitochondrial function, but did not observe any effect of the treatment.