An Acetylation Switch Modulates G6PD function

Fang Wu[1, 2] Eyal Arbely[1, 2, 3]

[1]Department of Chemistry, Ben Gurion University, Israel
[2]The National Institute for Biotechnology in the Negev, Ben Gurion University, Israel
[3]Department of Life Sciences, Ben Gurion University, Israel

Glucose-6-phosphate dehydrogenase (G6PD), the first and rate-limiting enzyme in the pentose phosphate pathway that catalyzes the formation of NADPH. G6PD deficiency is the most common blood disorder causing hemolytic anemia, with a prevalence of 1 in 20. To date, over 160 nonsynonymous mutations have been identified in G6PD, with pathogenic mutations clustering near the monomer-monomer interface and the allosteric $NADP^+$-binding site. Here, we found that acetylation can affect G6PD function using site-specifically acetylated variants, expressed in cultured mammalian cells and bacteria using genetic code expansion technology. Specifically, we confirm the inactivation of G6PD following acetylation of K403, a physiologically relevant acetylation site of wild-type G6PD. According to the crystal structure of K403-acetylated G6PD, acetylation at K403, within the structural $NADP^+$ binding site, induces local conformational that reshape the structure of the distant catalytic site. While these structural changes render the enzyme inactive, deacetylation by Sirt1 or Sirt2 can restore G6PD activity. Furthermore, K403 acetylation modulates the interaction of G6PD with p53 and affects with Fyn-mediated G6PD phosphorylation. p53, in turn, impairs Fyn-dependent phosphorylation of G6PD. Thus, modulating G6PD acetylation represents a plausible strategy to fine-tune G6PD function, which could provide new insights for developing G6PD-targeting therapy.