Allosteric Regulation of Glucose-6-Phosphate Dehydrogenase by the Redox Sensor OpcA

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Glucose-6-phosphate dehydrogenase (G6PDH) is a key enzyme in the oxidative pentose phosphate (OPP) pathway, a fundamental route for the generation of reducing power and metabolic intermediates for biosynthetic processes. In photosynthetic organisms, G6PDH is redox-regulated to prevent futile cycles while carbon is being fixed. In cyanobacteria, regulation of G6PDH requires the redox sensor protein OpcA. Here, we used functional analysis to show that in *Synechocystis* sp. PCC 6803, OpcA binds G6PDH under all conditions, but complex formation enhances G6PDH activity when OpcA is oxidized and inhibits it when OpcA is reduced. To understand the molecular basis of this regulation, we determined the structures of cyanobacterial G6PDH and the G6PDH-OpcA complex by cryo-EM. OpcA binds the G6PDH tetramer and induces conformational changes in the active site of G6PDH. The redox sensitivity of OpcA is achieved through the formation of intramolecular disulfide bridges, which affect the allosteric regulation of G6PDH. Our findings unveil a novel and unique molecular mechanism governing the regulation of cyanobacterial OPP pathway.