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Abstract:

Glycogen is a major energy reserve in most eukaryotes and its rate of synthesis is controlled by glycogen synthase. The activity of eukaryotic glycogen synthase is regulated by the allosteric activator glucose-6-phosphate, which can overcome the inhibitory effects of phosphorylation. The effects of phosphorylation and glucose-6-phosphate on glycogen synthase are mediated by a cluster of six arginines located within a stretch of 12 amino acids near the C-terminus of the enzyme’ s polypeptide chain. We studied isoform-2 of yeast glycogen synthase as a model to study the structural and molecular mechanisms that underlie the regulation of the eukaryotic enzymes and our primary tools of investigation were macromolecular X-ray crystallography, site-directed mutagenesis, intein-mediated peptide ligation and enzyme assays. We have solved the tetrameric structure of the yeast enzyme in two different activity states; the resting enzyme and the activated state when complexed with glucose-6-phosphate. Binding of glucose-6-phosphate to glycogen synthase induces large conformational changes that free the active site of the subunits to undergo conformational changes necessary to catalyze the reaction. Further, using site directed mutagenesis and intein-mediated peptide ligation to create specific phosphorylation states of the enzyme we were able to define specific roles for the arginine residues that mediate the

regulatory effects of phosphorylation and glucose-6-phosphate activation. Based on these studies, we propose a three state structural model for the regulation of the enzyme, which relate the observed conformational states to specific activity levels. In addition to these regulatory studies, we have also solved the structure of the enzyme complexed with UDP and with substrate analogs, which provide detailed insight into the catalytic mechanism of the enzyme and the ability of glycogen synthase to remain tightly bound to its substrate glycogen.

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