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METABOLISM OF THE COVALENT PHOSPHATE IN GLYCOGEN

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Abstract:

Glycogen is a highly branched polymer of glucose that functions to store glucose residues for future metabolic use. Skeletal muscle and liver comprise the largest glycogen reserves and play critical roles in maintaining whole body glucose homeostasis. In addition to glucose, glycogen contains small amounts of covalent phosphate of unknown function, origin and structure. Evidence to support the involvement of glycogen associated phosphate in glycogen metabolism comes from patients with Lafora Disease. Lafora disease is an autosomal recessive, fatal form of progressive myoclonus epilepsy. Approximately 90% of cases of Lafora disease are caused by mutations in either the EPM2A or EPM2B genes that encode, respectively, a dual specificity phosphatase called laforin and an E3 ubiquitin ligase called malin. Lafora patients accumulate intracellular inclusion bodies, known as Lafora bodies that are primarily composed of poorly branched, insoluble glycogen-like polymers. We have shown that laforin is a glycogen phosphatase capable of releasing phosphate from glycogen in

vitro and that this activity is dependent on a functional carbohydrate binding domain. In studies of laforin knockout mice, we observed a progressive change in the properties and structure of glycogen that paralleled the formation of Lafora bodies. Glycogen isolated from these mice showed increased glycogen phosphate, up to 6-fold ($p < 0.001$) compared to WT, providing strong evidence that laforin acts as a glycogen phosphatase in vivo. Furthermore we have demonstrated that glycogen synthase introduces phosphate into glycogen during synthesis by transferring the beta-phosphate of UDP-glucose into the polymer and that laforin is capable of releasing the phosphate incorporated by glycogen synthase. Analysis of mammalian glycogen revealed the presence of covalently linked phosphate at the 2 hydroxyl and the 3 hydroxyl of glucose residues in the polysaccharide, providing the first direct evidence of the chemical nature of the phosphate linkage. We envision a glycogen damage/repair process, analogous to errors during DNA synthesis that are subsequently repaired. We propose that laforin action parallels that of DNA repair enzymes and Lafora disease results from the inability of the phosphatase to repair damaged glycogen, adding another biological polymer to the list of those prone to errors by their respective polymerizing enzymes.

Description:

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