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Glycogen metabolism in humans☆·☆☆

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ABSTRACT

In the human body, glycogen is a branched polymer of glucose stored mainly in the liver and the skeletal muscle that supplies glucose to the blood stream during fasting periods and to the muscle cells during muscle contraction. Glycogen has been identified in other tissues such as brain, heart, kidney, adipose tissue, and erythrocytes, but glycogen function in these tissues is mostly unknown. Glycogen synthesis requires a series of reactions that include glucose entrance into the cell through transporters, phosphorylation of glucose to glucose 6-phosphate, isomerization to glucose 1-phosphate, and formation of uridine 5′-diphosphate-glucose, which is the direct glucose donor for glycogen synthesis. Glycogenin catalyzes the formation of a short glucose polymer that is extended by the action of glycogen synthase. Glycogen branching enzyme introduces branch points in the glycogen particle at even intervals. Laforin and malin are proteins involved in glycogen assembly but their specific function remains elusive in humans. Glycogen is accumulated in the liver primarily during the postprandial period and in the skeletal muscle predominantly after exercise. In the cytosol, glycogen breakdown or glycogenolysis is carried out by two enzymes, glycogen phosphorylase which releases glucose 1-phosphate from the linear chains of glycogen, and glycogen debranching enzyme which untangles the branch points. In the lysosomes, glycogen degradation is catalyzed by α-glucosidase. The glucose 6-phosphatase system catalyzes the dephosphorylation of glucose 6-phosphate to glucose, a necessary step for free glucose to leave the cell. Mutations in the genes encoding the enzymes involved in glycogen metabolism cause glycogen storage diseases.

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1. Introduction

Glycogen is a branched polymer of glucose that contains a minor amount of phosphate and glucosamine. In the linear chains, the glucose residues are connected by α-1,4-glycosidic linkages while α-1,6-glycosidic bonds create the branch points. Branches within normal glycogen are distributed at even intervals resulting in a structure with spherical shape. The source and function of phosphate and glucosamine in human glycogen are unclear. The glycogen particle consists of up to 55.000 glucose residues. In skeletal muscle, glycogen particles have a size of 10–44 nm in diameter while in the liver measure approximately 110–290 nm. Glycogen can be identified by electron microscopy inside the cells [1].

The synthesis of glycogen requires the coordinated action of a number of enzymes (Fig. 1). Glucose enters the cells via glucose transporters, being phosphorylated to glucose 6-phosphate by hexokinase isoenzymes. The next step is the isomerization of glucose 6-phosphate into glucose 1-phosphate by phosphoglucomutase-1. Then, uridine 5′-diphosphate (UDP)-glucose pyrophosphorylase catalyzes the formation of UDP-glucose from glucose 1-phosphate. UDP-glucose is the immediate glucose donor for glycogen construction. Glycogenin initiates the synthesis of glycogen by autoglycosylation transporting glucose from UDP-glucose to itself and forming a short linear chain of about 10–20 glucose moieties. The elongation of this initial glycogen sequence is catalyzed by glycogen synthase that transfers a glycosyl moiety from UDP-glucose to the growing glycogen strand, providing the α-1,4-glycosidic linkages between glucose residues. The branching enzyme introduces branch points in the glycogen particle, by creating α-1,6 glycosidic bonds at regular intervals. Laforin and malin are proteins of undefined function in humans that influence glycogen assembly.

The source of the glucose residues that form the glycogen particle is either the ingested food (direct pathway of glycogen synthesis) or the gluconeogenesis route (indirect pathway), in which gluconeogenic precursors such as lactate and alanine produce glucose 6-phosphate that may be used to synthesize glycogen.

Glycogen degradation takes place both in the cytoplasm and inside the lysosomes. In the cytosol, glycogen breakdown is accomplished by the coordinated action of two enzymes, glycogen phosphorylase, which releases glucose 1-phosphate by untangling the α-1,4-glycosidic linkages, and glycogen debranching enzyme that unfastens the branch points releasing free glucose (Fig. 2). Glucose 1-phosphate derived from glycogen in the cytosol may be isomerized into glucose 6-phosphate which is dephosphorylated to free glucose by glucose 6-phosphatase (Fig. 3) in order for glucose to leave the cell via glucose transporters. In the lysosomes, the breakdown of glycogen is accomplished by the lysosomal enzyme acid α-glucosidase or acid maltase (Fig. 4).

Molecular changes in the genes that encode enzymes involved in glycogen metabolism may cause glycogen storage diseases (GSDs) by interfering either with glycogen synthesis or with glycogen degradation (Table 1). In addition, some mutations in genes that code enzymes implicated in the glycolytic pathway have been labeled as glycogen storage diseases (Fig. 5).

2. Glycogen synthesis

2.1. Glucose uptake: glucose transporters

In most human tissues glucose crosses the plasma membrane and enters into the cells through glucose transporters via facilitated transport.

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