BCMB 8020
April 13,2006

Glycogen

Most common storage form of glucose in animals, bacteria (yeast)

Branched polymer of α1,4- & α1,6-linked glucose

Similar to amylopectin; but with smaller and more frequent branching: branching every 8-12 residues

In animals glycogen is stored largely in the liver and muscle

In mammals glycogen can make up ~10% liver mass & 2% of muscle mass

Glycogen use in animals

Insulin | **glucagon** or **adrenaline**
(fasting) **(flight or fight)**

Excess Glucose →→ GLYCOGEN →→replenished glucose
(i.e. after feeding)

glycogen synthesis | **glycogenolysis**

In vertebrates ~ 2/3 of dietary glucose is converted to glycogen

transported in blood

Food → Glucose → intestine → cells → converted to Glc-6-P

absorbed ***hexokinase***

liver (GLUT1)

muscle (*GLUT4, GLUT 1)

***=**insulin stimulated

The stimulation of glycogen synthesis is one of the major physiological responses modulated by insulin

The exact mechanism by which insulin stimulates glycogen synthesis is not known

Insulin:

*** Controls uptake and transport of glucose (GLUT4)**

*** Regulates phosphorylation and activation state of glycogen biosynthetic and catabolic enzymes (glycogen synthase; glycogen phosphorylase)**

Steps in Glycogen Synthesis

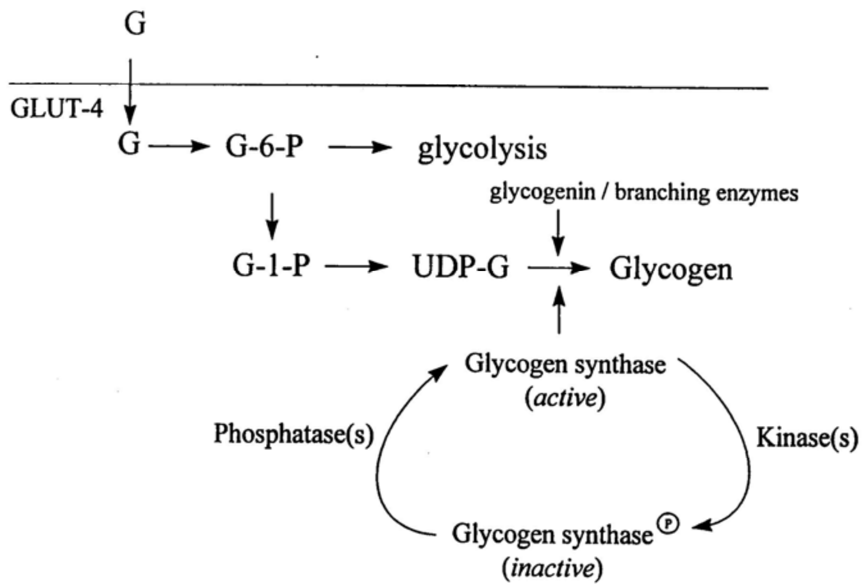
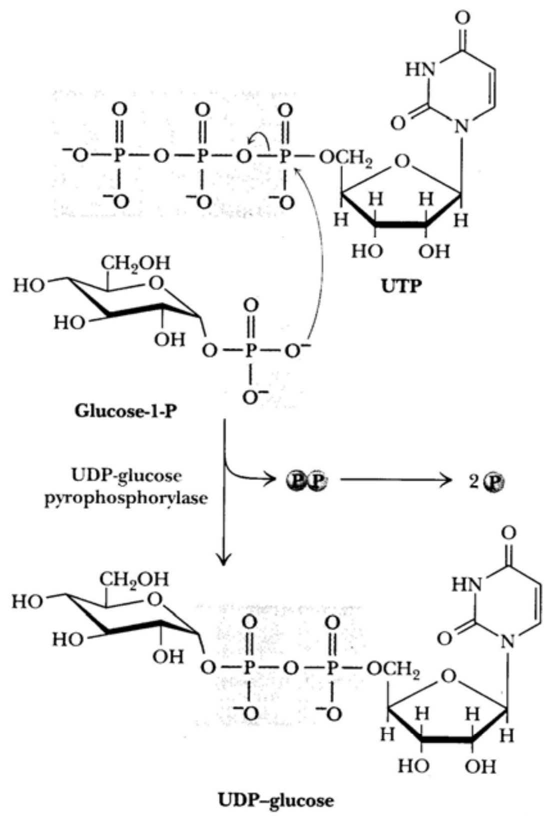


Fig. 1. Schematic model showing sequential steps of glycogen synthesis. Glucose (G) enters the cells of insulin-sensitive tissues by a facilitative transport process mediated by insulin-sensitive glucose transporter protein, GLUT 4. GLUT 4 is translocated from cytosol to the plasma membrane in response to insulin. G is then converted to glucose-6-phosphate (G-6-P) by hexokinase. which then either enters into glycolysis and/or is converted to glucose-1-phosphate (G-1-P) by phosphoglucomutase. G-1-P, in the presence of UTP and UDP-glucose pyrophosphorylase is converted to UDP-G, an active glucose donating molecule, which donates glucosyl residue to glycogen molecule. Glycogen synthase catalyzes the transfer of glucosyl units from UDP-glucose to the nonreducing ends of glycogen molecule. Glycogenin/branching enzyme help add glucose to growing chain of glycogen molecule. Glycogen synthase itself cycles between an active and inactive state. Phosphorylation by protein kinase(s) leads to decrease in glycogen synthase activity (i.e. inactive form) whereas dephosphorylation catalyzed by protein phosphatase(s) causes activation of the enzyme (i.e. active state).

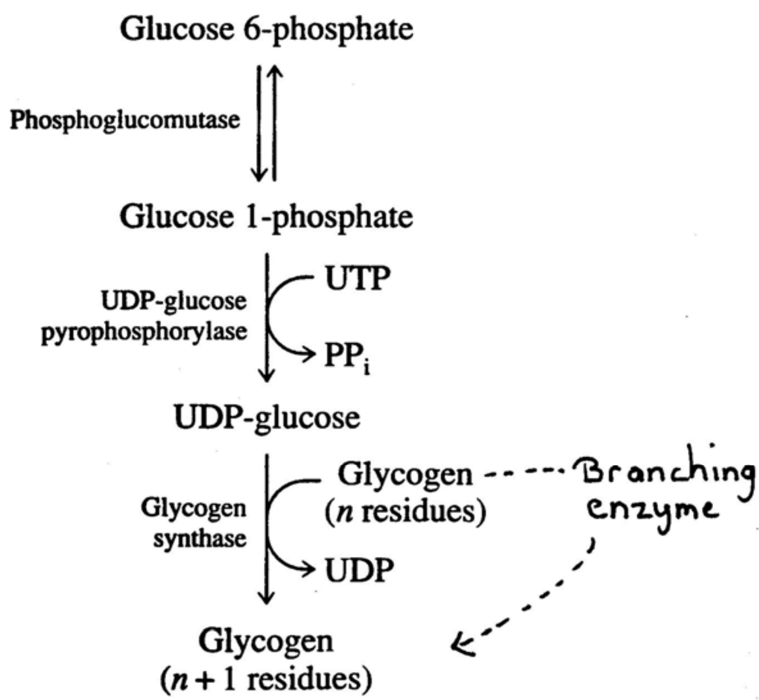
Synthesis of the chemically activated substrate for glycogen synthesis, UDP-Glc, by UDP-Glc pyrophosphorylase

(Luis Leloir, discovered NDP-sugars)

The synthesis of UDP-Glc is driven by the subsequent hydrolysis of pyrophosphate


UTP
Glucose-1-P
UDP-glucose
pyrophosphorylase
2 P
UDP–glucose

Simplified reactions for the bulk of glycogen synthesis



The question of how glycogen synthesis was initiated remained open for many years. It is now known that glycogen synthesis begins by the Mn++-dependent self glucosylation of glycogenin on Tyr194 to form a glycogenin with an average glucan chain of DP 8 (maltooctaose).

Steps in glycogen synthesis

Self-glucosylation of glycogenin (~37 kD) on Tyr-194 in a glycosidic linkage

UDP-Glc + Proglycogen Synthase + Branching Enzyme → Proglycogen (~ 400,000 daltons; ~DP 2470)

Proglycogen + UDP-Glc + Macroglycogen Synthase + Branching Enzyme → Macroglycogen (~ 10^7 daltons; ~DP 61,728)

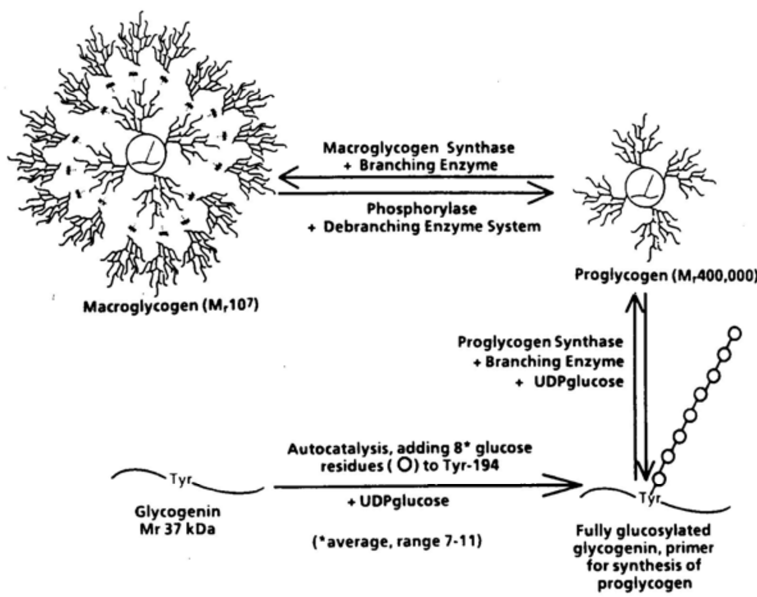


Figure 3. From glycogenin to proglycogen to macroglycogen, as described by Lomako et al. (38) and modified to incorporate later information (21, 23). Glycogenin autocatalytically adds glucose from UDPglucose to its Tyr–194 and then an average of a further seven residues to form the protein–bound maltosaccharides that serve as the primer for the synthesis of proglycogen by a form of glycogen synthase (proglycogen synthase), distinct in its properties from the "classical" synthase (macroglycogen synthase) that takes proglycogen to macroglycogen, the limiting M_r for which, in muscle, is 10^7 (3). Proglycogen also functions as an intermediate in glycogen breakdown (34). Whether there are distinct forms of phosphorylase, branching and debranching enzymes for the separate stages, is not known. The relative and absolute amounts of some of these components in different tissues are shown in Table 1. The priming chain shown here as 8 glucose residues corresponds to the average length of elongation but in actuality ranges from 7 to 11 glucose residues (23).For the origin of the glycogen branching pattern shown here, see ref 3.

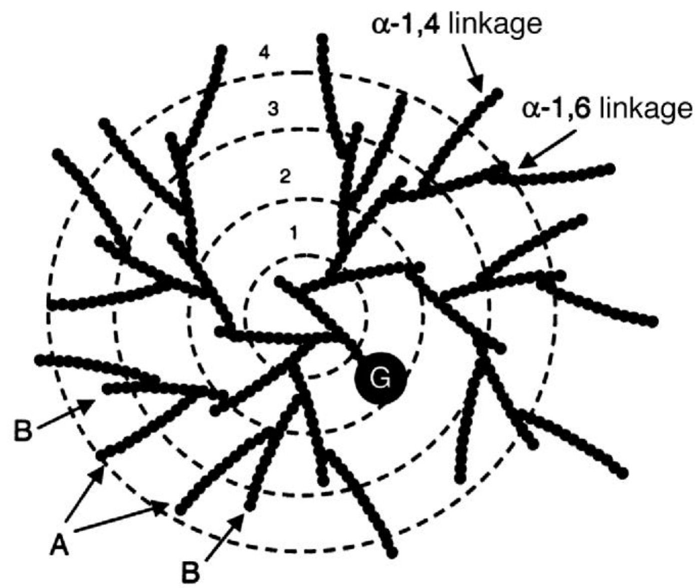


Figure 1. Diagram illustrating the first four tiers of the glycogen granule. Each B chain is linked by α-1–6 glycosidic bonds, whereas each A chain is unbranched and is linked by α-1–4 glycosidic bonds. G, glycogenin, the self-glycosylating protein primer of glycogen.

f*rom* Shearer: Exerc Sport Sci Rev, Volume 32(3).July 2004.120-126

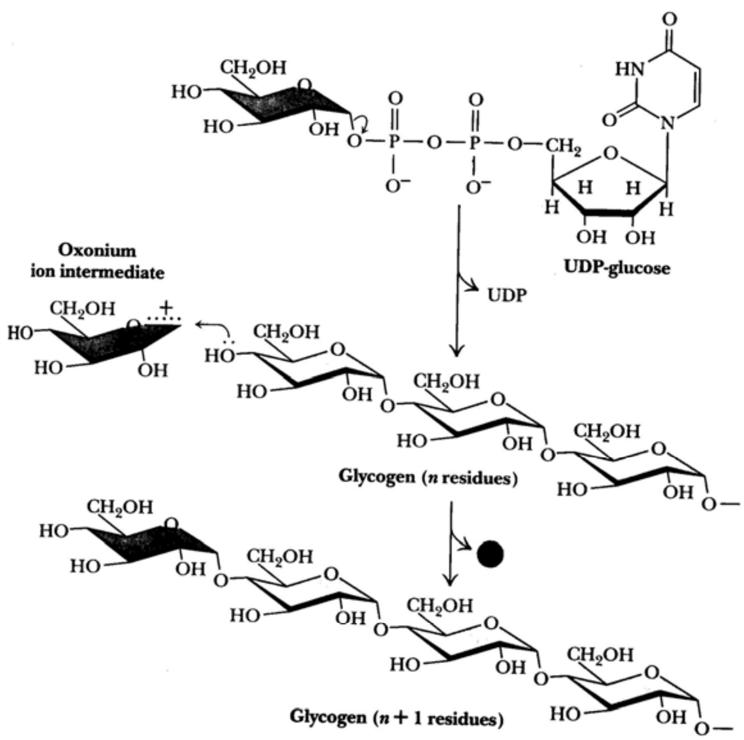


***Figure* 21.23** The glycogen synthase reaction. Cleavage of the C—O bond of UDP-glucose yields an oxonium intermediate (similar to that

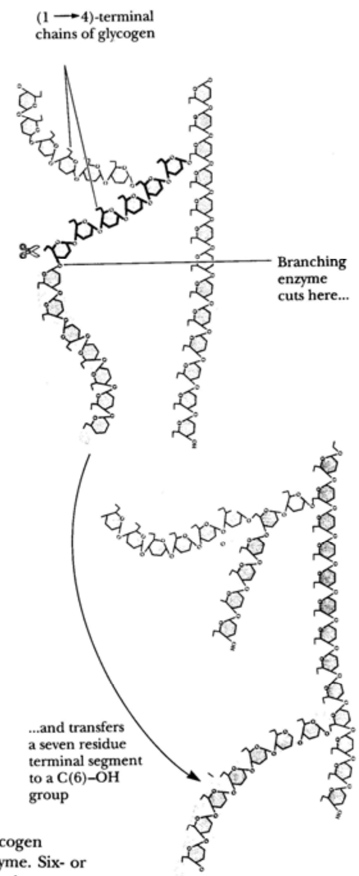
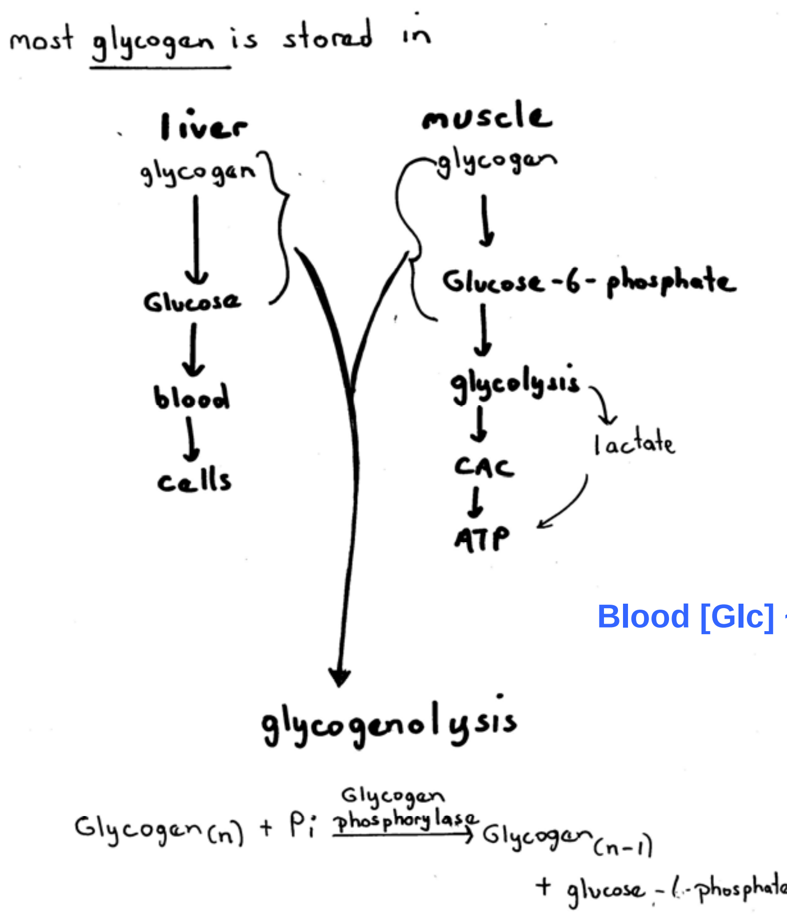
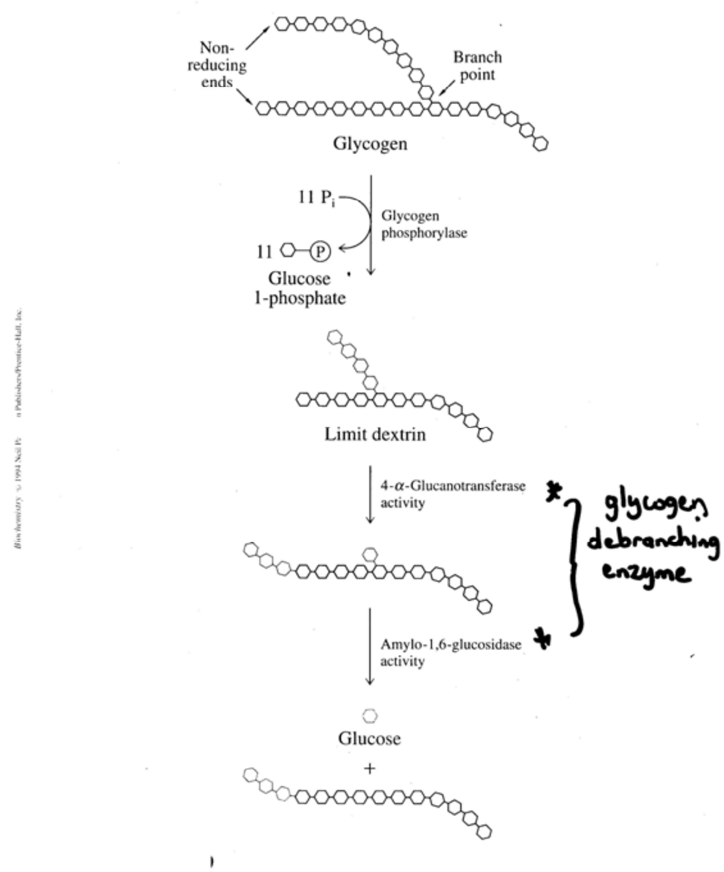


***Figure* 21.24** Formation of glycogen branches by the branching enzyme. Six- or seven-residue segments of a growing glycogen chain are transferred to the C-6 hydroxyl group of a glucose residue on the same or a nearby chain.



Blood [Glc] ~5 mM


Non-
reducing
ends
Branch
point
Glycogen
11 P_i
Glycogen
phosphorylase
11
Glucose
1-phosphate
Limit dextrin
4-α-Glucanotransferase
activity
glycogen
debranching
enzyme
Amylo-1,6-glucosidase
activity
Glucose
+

Mechanism of Glycogen Phosphorylase

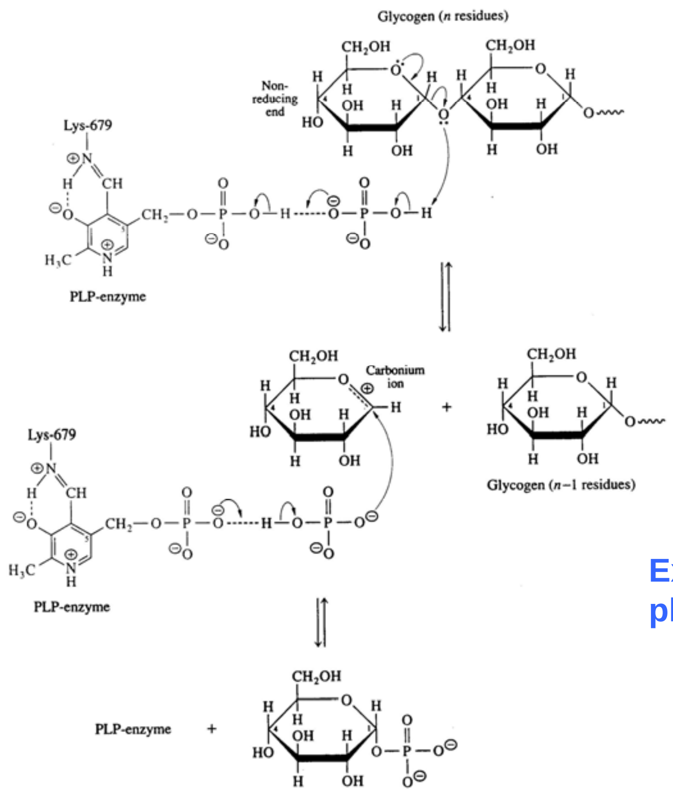
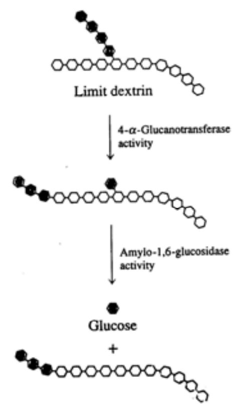


Figure 15·1

Example of phosphorolysis



specificity for branch

Enzymatic activities of the glycogen de-branching enzyme.

glycogen debranching enzyme has two separate activities

Glucose 1-phosphate ⇌ (phosphoglucomutase) Glucose 6-phosphate

Glucose 6-phosphate → glycolysis, glycogen synthesis, pentose phosphate pathway

in liver Glucose 6-phosphate + H_2O → Glucose + P_i (Glucose 6-phosphatase)

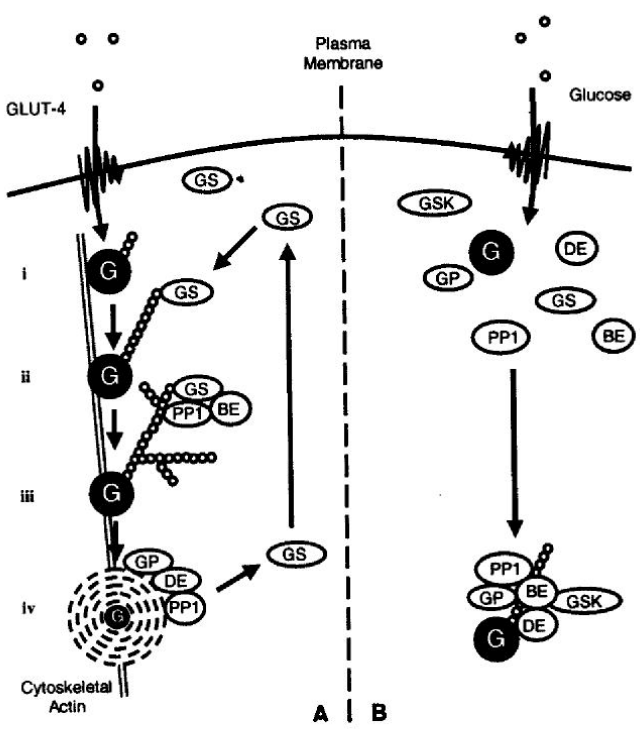


Figure 7. Proposed scheme of glycogen granule formation in skeletal muscle.
A. (*i*) Glycogenin initiates glycogen granule formation at the sarcolemmal membrane;

(*ii*) once initiation is complete, glycogen synthase attaches to the granule, resulting in its growth;

(*iii*) as soon as granules are of sufficient size, other glycogen-metabolizing enzymes attach to the granule;

(*iv*) glycogen synthase dissociates from the mature granule and returns to the sarcolemmal membrane, whereas the granule is translocated to its final location on actin filaments.

B. Incoming glucose is transported to the site of the granule. Here, initiation and the association of other proteins in the glycosome occur at the site of final granule location. G, glycogenin; GP, glycogen phosphorylase; GS, glycogen synthase; BE, branching enzyme; DE, debranching enzyme; PP1, protein phosphatase 1.

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