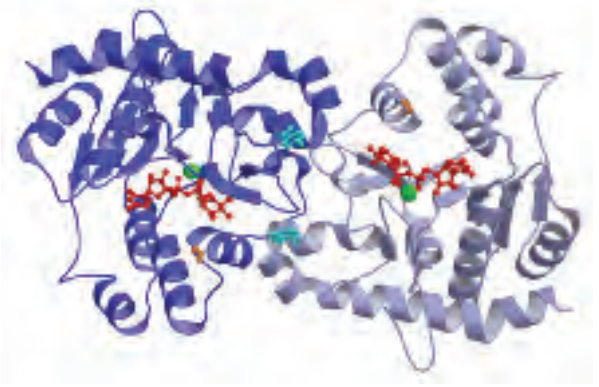


chapter 15

PRINCIPLES OF METABOLIC REGULATION: GLUCOSE AND GLYCOGEN

Formation of liver glycogen from lactic acid is thus seen to establish an important connection between the metabolism of the muscle and that of the liver. Muscle glycogen becomes available as blood sugar through the intervention of the liver, and blood sugar in turn is converted into muscle glycogen. There exists therefore a complete cycle of the glucose molecule in the body . . . Epinephrine was found to accelerate this cycle in the direction of muscle glycogen to liver glycogen . . . Insulin, on the other hand, was found to accelerate the cycle in the direction of blood glucose to muscle glycogen.

—*C. F. Cori and G. T. Cori, article in* Journal of Biological Chemistry, *1929*

Metabolic regulation, a central theme in biochemistry, is one of the most remarkable features of a living cell. Of the thousands of enzyme-catalyzed reactions that can take place in a cell, there is probably not one that escapes some form of regulation. Although it is convenient (and perhaps essential) in writing a textbook to divide metabolic processes into "pathways" that play discrete roles in the cell's economy, no such separation exists inside the cell. Rather, each of the pathways we discuss in this book is inextricably intertwined with all the other cellular pathways in a multidimensional network of reactions (Fig. 15–1). For example, in Chapter 14 we discussed three possible fates for glucose 6-phosphate in a hepatocyte: passage into glycolysis for the production of ATP, passage into the pentose phosphate pathway for the production of NADPH and pentose phosphates, or hydrolysis to glucose and phosphate to replenish blood glucose. In fact, glucose 6-phosphate has a number of other possible fates; it may, for example, be used to synthesize other sugars, such as glucosamine, galactose, galactosamine, fucose, and neuraminic acid, for use in protein glycosylation, or it may be partially degraded to provide acetyl-CoA for fatty acid and sterol synthesis. In the extreme case, the bacterium *Escherichia coli* can use glucose to produce the carbon skeleton of every one of its molecules. When a cell "decides" to use glucose 6-phosphate for one purpose, that decision affects all the other pathways for which glucose 6-phosphate is a precursor or intermediate; any change in the allocation of glucose 6-phosphate to one pathway affects, directly or indirectly, the metabolite flow through all the others.

Such changes in allocation are common in the life of a cell. Louis Pasteur was the first to describe the large (greater than tenfold) increase in glucose consumption by a yeast culture when it was shifted from aerobic to anaerobic conditions. This phenomenon, called the

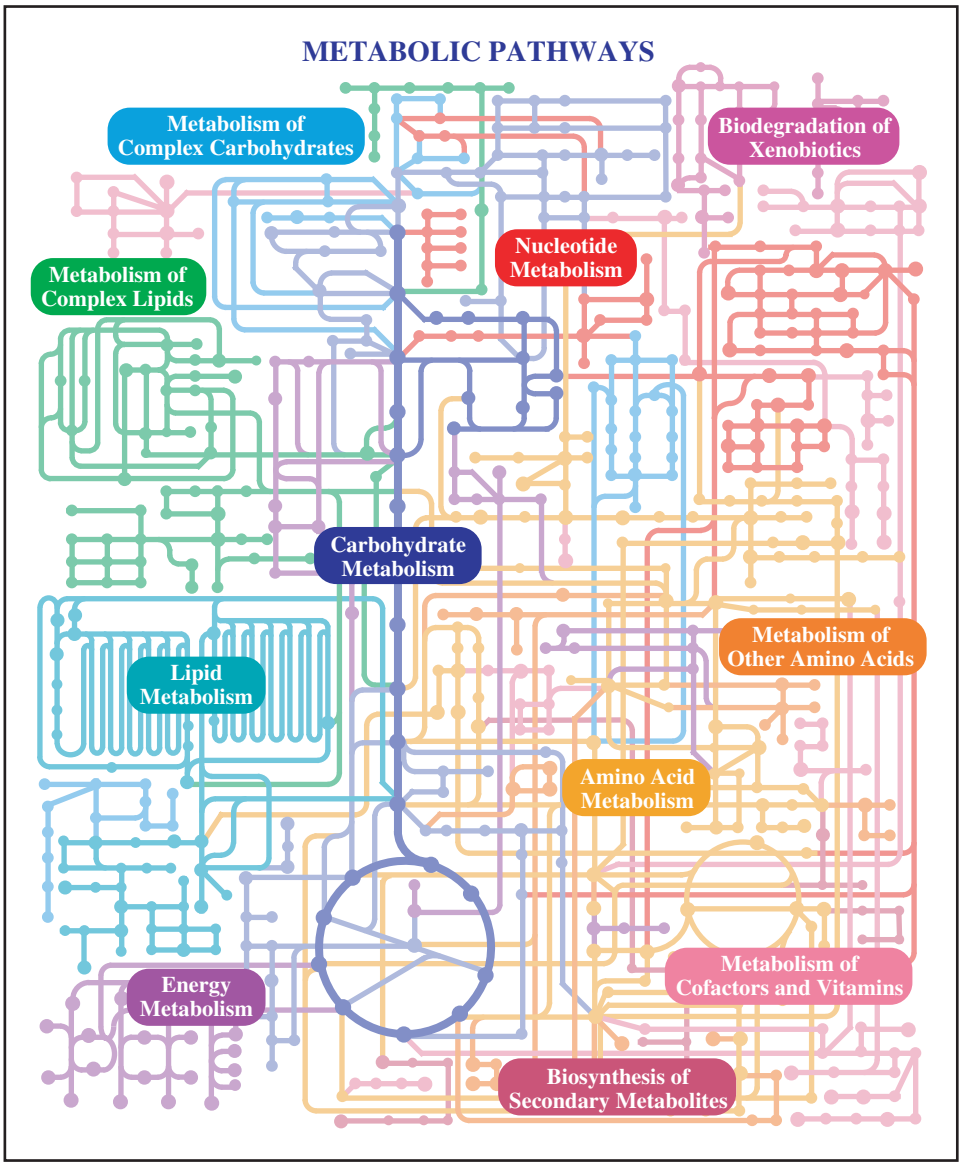


FIGURE 15–1 Metabolism as a three-dimensional meshwork. A typical eukaryotic cell has the capacity to make about 30,000 different proteins, which catalyze thousands of different reactions involving many hundreds of metabolites, most shared by more than one "pathway." This overview image of metabolic pathways is from the online KEGG (Kyoto Encyclopedia of Genes and Genomes) PATHWAY database (www.genome.ad.jp/kegg/pathway/map/map01100.html). Each area can be further expanded for increasingly detailed information, to the level of specific enzymes and intermediates.

Pasteur effect, occurs without a significant change in the concentration of ATP or any of the hundreds of metabolic intermediates and products derived from glucose. A similar change takes place in cells of skeletal muscle when a sprinter leaves the starting blocks. The ability of a cell to carry out all these interlocking metabolic processes simultaneously—obtaining every product in the amount needed and at the right time, in the face of major perturbations from outside, and without generating leftovers—is an *astounding* accomplishment.

In this chapter we look at mechanisms of metabolic regulation, using the pathways in which glucose is an intermediate to illustrate some general principles. First we consider the pathways by which glycogen is synthesized and broken down, a very well-studied case of metabolic regulation. Then we look at the general roles of regulation in achieving metabolic homeostasis. Focusing on the pathways that connect pyruvate with glycogen in both directions, we next consider the specific regulatory properties of the participating enzymes and the ways in which the cell accomplishes coordinated regulation of catabolic and anabolic pathways. Finally, we discuss metabolic control analysis, a system for treating complex metabolic interactions quantitatively, and consider some surprising results of its application.

In selecting carbohydrate metabolism to illustrate the principles of metabolic regulation, we have artificially separated the metabolism of fats and carbohydrates. In fact, these two activities are very tightly integrated, as we shall see in Chapter 23.

15.1 The Metabolism of Glycogen in Animals

In a wide range of organisms, excess glucose is converted to polymeric forms for storage—glycogen in vertebrates and many microorganisms, starch in plants. In vertebrates, glycogen is found primarily in the liver and skeletal muscle; it may represent up to 10% of the weight of liver and 1% to 2% of the weight of muscle. If this much glucose were dissolved in the cytosol of a hepatocyte, its concentration would be about 0.4 M, enough to dominate the osmotic properties of the cell. When stored as a long polymer (glycogen), however, the same mass of glucose has a concentration of only 0.01 μM. Glycogen is stored in large cytosolic granules. The elementary particle of glycogen, the β-particle, about 21 nm in diameter, consists of up to 55,000 glucose residues with about 2,000 nonreducing ends. Twenty to 40 of these particles cluster together to form α-rosettes, easily seen with the microscope in tissue samples from well-fed animals (Fig. 15–2) but essentially absent after a 24-hour fast.

The glycogen in muscle is there to provide a quick source of energy for either aerobic or anaerobic metabolism. Muscle glycogen can be exhausted in less than an hour during vigorous activity. Liver glycogen serves as a reservoir of glucose for other tissues when dietary glucose is not available (between meals or during a fast); this is especially important for the neurons of the brain, which cannot use fatty acids as fuel. Liver glycogen can be depleted in 12 to 24 hours. In humans, the total amount of energy stored as glycogen is far less than the amount stored as fat (triacylglycerol) (see Table 23–5), but fats cannot be converted to glucose in mammals and cannot be catabolized anaerobically.

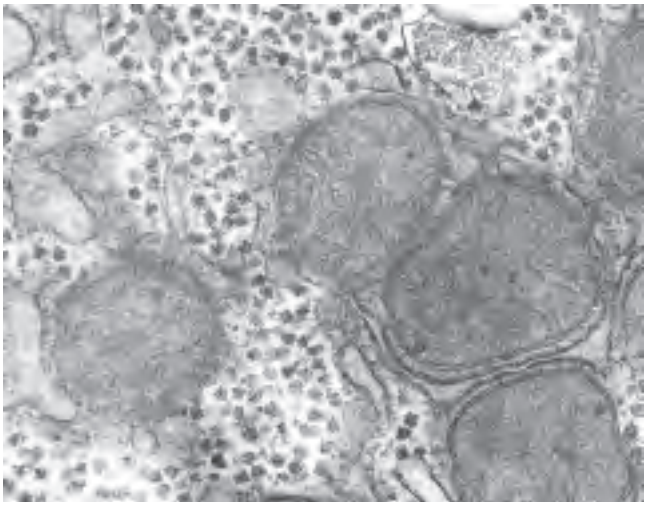


FIGURE 15–2 Glycogen granules in a hepatocyte. Glycogen is a storage form of carbohydrate in cells, especially hepatocytes, as illustrated here. Glycogen appears as electron-dense particles, often in aggregates or rosettes. In hepatocytes the glycogen is closely associated with tubules of the smooth endoplasmic reticulum. Many mitochondria are also present.

Glycogen granules are complex aggregates of glycogen and the enzymes that synthesize it and degrade it, as well as the machinery for regulating these enzymes. The general mechanisms for storing and mobilizing glycogen are the same in muscle and liver, but the enzymes differ in subtle yet important ways that reflect the different roles of glycogen in the two tissues. Glycogen is also obtained in the diet and broken down in the gut, and this involves a separate set of hydrolytic enzymes that convert glycogen (and starch) to free glucose.

The transformations of glucose discussed in this chapter and in Chapter 14 are central to the metabolism of most organisms, microbial, animal, or plant. We begin with a discussion of the *catabolic* pathways from glycogen to glucose 6-phosphate **(glycogenolysis)** and from glucose 6-phosphate to pyruvate **(glycolysis),** then turn to the *anabolic* pathways from pyruvate to glucose **(gluconeogenesis)** and from glucose to glycogen **(glycogenesis).**

Glycogen Breakdown Is Catalyzed by Glycogen Phosphorylase

In skeletal muscle and liver, the glucose units of the outer branches of glycogen enter the glycolytic pathway through the action of three enzymes: glycogen phosphorylase, glycogen debranching enzyme, and phosphoglucomutase. Glycogen phosphorylase catalyzes the reaction in which an (α1→4) glycosidic linkage between two glucose residues at a nonreducing end of glycogen undergoes attack by inorganic phosphate (P_i), removing the terminal glucose residue as α-D-glucose 1-phosphate (Fig. 15–3). This *phosphorolysis* reaction is different from the *hydrolysis* of glycosidic bonds by amylase during intestinal degradation of dietary glycogen and starch. In phosphorolysis, some of the energy of the glycosidic bond is preserved in the formation of the phosphate ester, glucose 1-phosphate.

Pyridoxal phosphate is an essential cofactor in the glycogen phosphorylase reaction; its phosphate group acts as a general acid catalyst, promoting attack by P_i on the glycosidic bond. (This is an unusual role for this cofactor; its more typical role is as a cofactor in amino acid metabolism; see Fig. 18–6.)

Glycogen phosphorylase acts repetitively on the nonreducing ends of glycogen branches until it reaches a point four glucose residues away from an (α1→6) branch point (see Fig. 7–15), where its action stops. Further degradation by glycogen phosphorylase can occur only after the **debranching enzyme,** formally known as **oligo (α1→6) to (α1→4) glucantransferase,** catalyzes two successive reactions that transfer

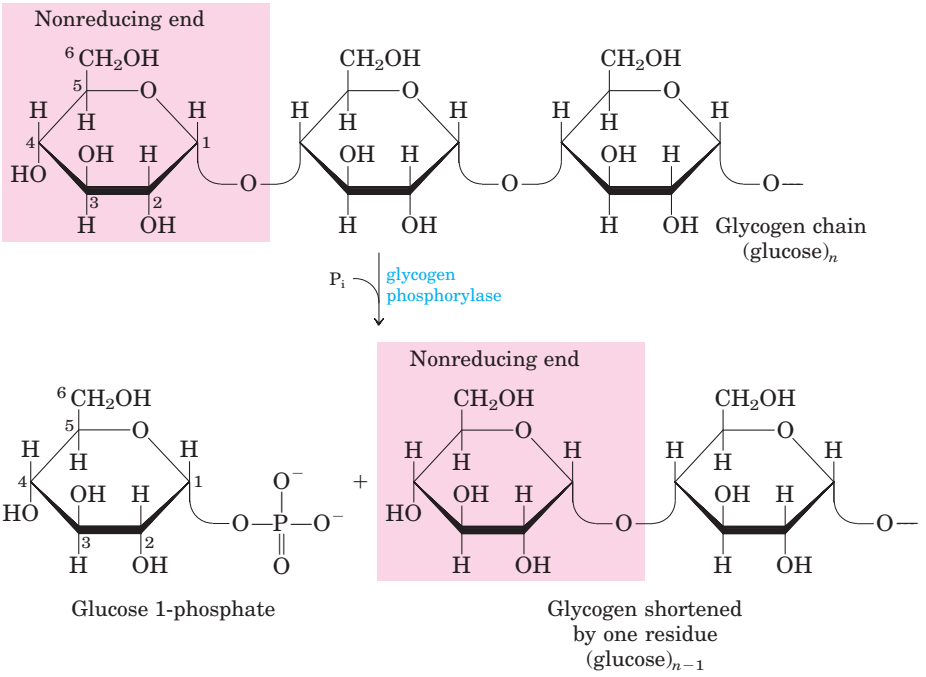
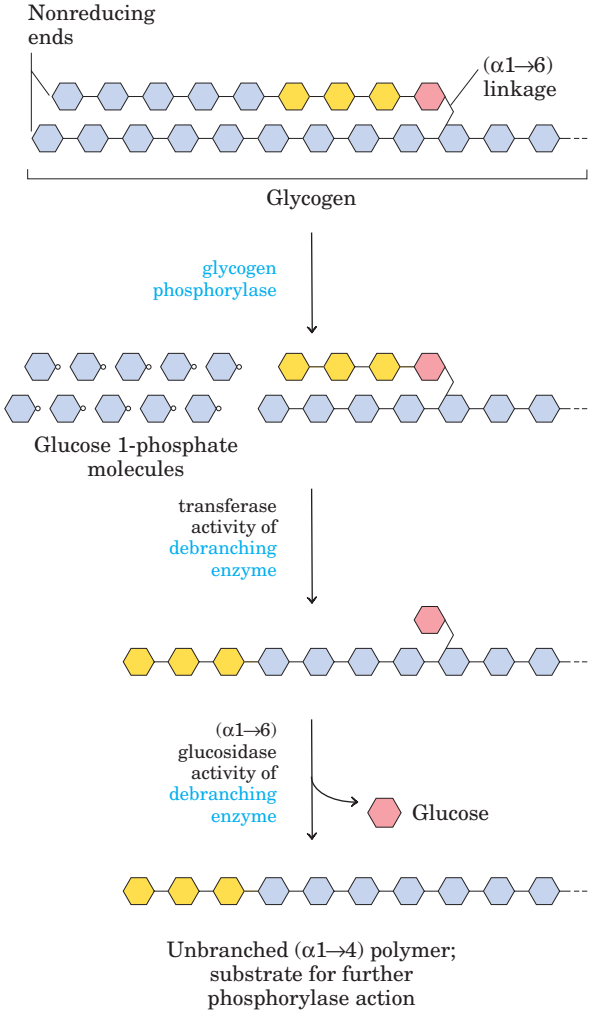


FIGURE 15–3 Removal of a terminal glucose residue from the nonreducing end of a glycogen chain by glycogen phosphorylase. This process is repetitive; the enzyme removes successive glucose residues until it reaches the fourth glucose unit from a branch point (see Fig. 15–4).



branches (Fig. 15–4). Once these branches are transferred and the glucosyl residue at C-6 is hydrolyzed, glycogen phosphorylase activity can continue.

Glucose 1-Phosphate Can Enter Glycolysis or, in Liver, Replenish Blood Glucose

Glucose 1-phosphate, the end product of the glycogen phosphorylase reaction, is converted to glucose 6-phosphate by **phosphoglucomutase,** which catalyzes the reversible reaction

$$\text{Glucose 1-phosphate} \rightleftharpoons \text{glucose 6-phosphate}$$

Initially phosphorylated at a Ser residue, the enzyme donates a phosphoryl group to C-6 of the substrate, then accepts a phosphoryl group from C-1 (Fig. 15–5).

The glucose 6-phosphate formed from glycogen in skeletal muscle can enter glycolysis and serve as an energy source to support muscle contraction. In liver,

FIGURE 15–4 Glycogen breakdown near an (α1→6) branch point. Following sequential removal of terminal glucose residues by glycogen phosphorylase (see Fig. 15–3), glucose residues near a branch are removed in a two-step process that requires a bifunctional "debranching enzyme." First, the transferase activity of the enzyme shifts a block of three glucose residues from the branch to a nearby nonreducing end, to which they are reattached in (α1→4) linkage. The single glucose residue remaining at the branch point, in (α1→6) linkage, is then released as free glucose by the enzyme's (α1→6) glucosidase activity. The glucose residues are shown in shorthand form, which omits the —H, —OH, and —CH_2OH groups from the pyranose rings.

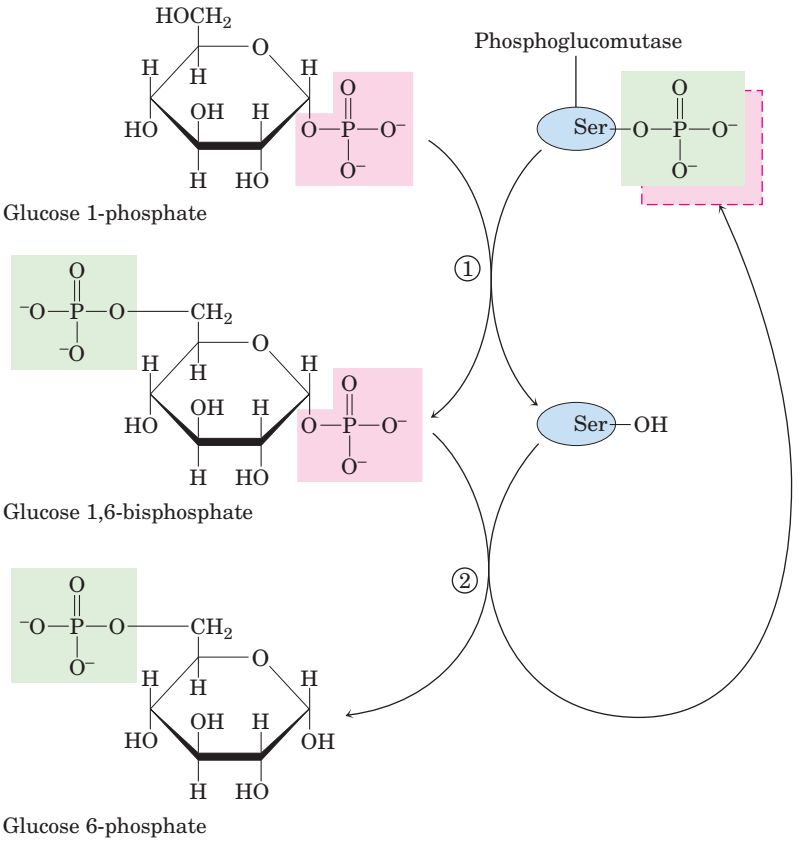


FIGURE 15–5 Reaction catalyzed by phosphoglucomutase. The reaction begins with the enzyme phosphorylated on a Ser residue. In step ①, the enzyme donates its phosphoryl group (green) to glucose 1-phosphate, producing glucose 1,6-bisphosphate. In step ②, the phosphoryl group at C-1 of glucose 1,6-bisphosphate (red) is transferred back to the enzyme, re-forming the phosphoenzyme and producing glucose 6-phosphate.

glycogen breakdown serves a different purpose: to release glucose into the blood when the blood glucose level drops, as it does between meals. This requires an enzyme, glucose 6-phosphatase, that is present in liver and kidney but not in other tissues. The enzyme is an integral membrane protein of the endoplasmic reticulum, predicted to contain nine transmembrane helices, with its active site on the lumenal side of the ER. Glucose 6-phosphate formed in the cytosol is transported into the ER lumen by a specific transporter (T1) (Fig. 15–6) and hydrolyzed at the lumenal surface by the glucose 6-phosphatase. The resulting P_i and glucose are thought to be carried back into the cytosol by two different transporters (T2 and T3), and the glucose leaves

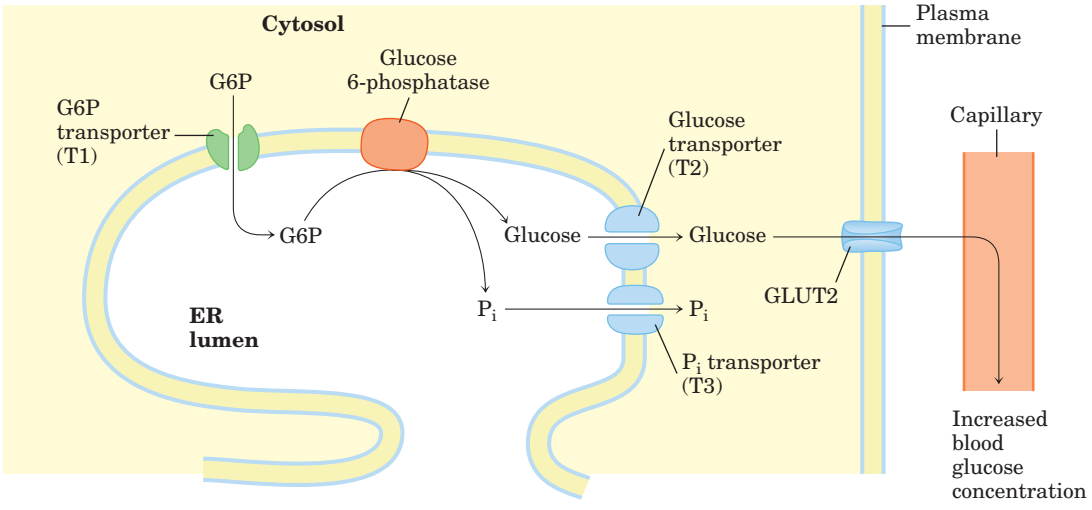


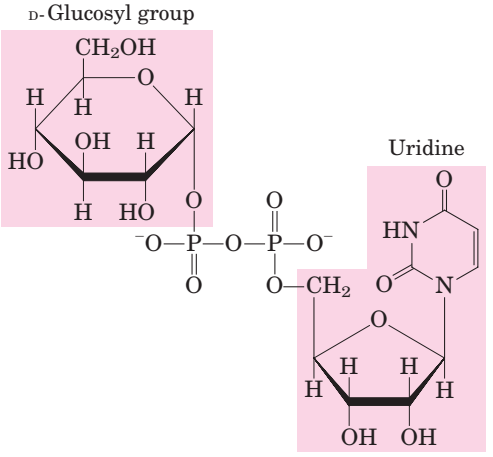
FIGURE 15–6 Hydrolysis of glucose 6-phosphate by glucose 6-phosphatase of the ER. The catalytic site of glucose 6-phosphatase faces the lumen of the ER. A glucose 6-phosphate (G6P) transporter (T1) carries the substrate from the cytosol to the lumen, and the products glucose and P_i pass to the cytosol on specific transporters (T2 and T3). Glucose leaves the cell via the GLUT2 transporter in the plasma membrane.

the hepatocyte via yet another transporter in the plasma membrane (GLUT2). Notice that by having the active site of glucose 6-phosphatase inside the ER lumen, the cell separates this reaction from the process of glycolysis, which takes place in the cytosol and would be aborted by the action of glucose 6-phosphatase. Genetic defects in either glucose 6-phosphatase or T1 lead to serious derangement of glycogen metabolism, resulting in type Ia glycogen storage disease (Box 15–1).

Because muscle and adipose tissue lack glucose 6-phosphatase, they cannot convert the glucose 6-phosphate formed by glycogen breakdown to glucose, and these tissues therefore do not contribute glucose to the blood.

The Sugar Nucleotide UDP-Glucose Donates Glucose for Glycogen Synthesis

Many of the reactions in which hexoses are transformed or polymerized involve **sugar nucleotides,** compounds in which the anomeric carbon of a sugar is activated by attachment to a nucleotide through a phosphate ester linkage. Sugar nucleotides are the substrates for polymerization of monosaccharides into disaccharides, glycogen, starch, cellulose, and more complex extracellular polysaccharides. They are also key intermediates in the production of the aminohexoses and deoxyhexoses found in some of these polysaccharides, and in the synthesis of vitamin C (L-ascorbic acid). The role of sugar nucleotides in the biosynthesis of glycogen and many other carbohydrate derivatives was first discovered by the Argentine biochemist Luis Leloir.

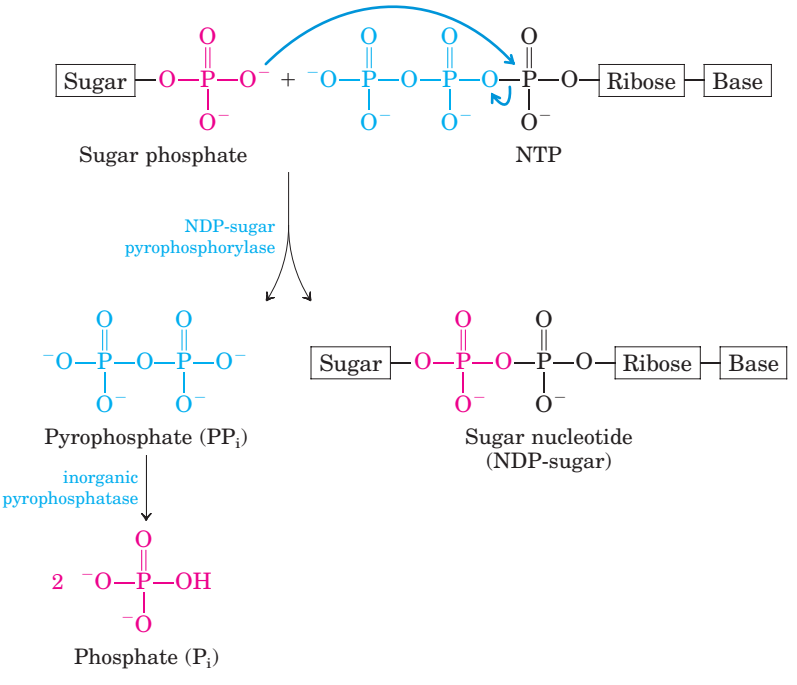


UDP-glucose
(a sugar nucleotide)

The suitability of sugar nucleotides for biosynthetic reactions stems from several properties:

1. Their formation is metabolically irreversible, contributing to the irreversibility of the synthetic pathways in which they are intermediates. The condensation of a nucleoside triphosphate with a hexose 1-phosphate to form a sugar nucleotide has a small positive free-energy change, but the reaction releases PP_i, which is rapidly hydrolyzed by inorganic pyrophosphatase in a reaction that is strongly exergonic ($\Delta G'^\circ = -19.2$ kJ/mol; Fig. 15–7). This keeps the cellular concentration of PP_i low, ensuring that the actual free-energy change in

Luis Leloir, 1906–1987



Net reaction: Sugar phosphate + NTP ⟶ NDP-sugar + $2P_i$

FIGURE 15–7 Formation of a sugar nucleotide. A condensation reaction occurs between a nucleoside triphosphate (NTP) and a sugar phosphate. The negatively charged oxygen on the sugar phosphate serves as a nucleophile, attacking the α phosphate of the nucleoside triphosphate and displacing pyrophosphate. The reaction is pulled in the forward direction by the hydrolysis of PP_i by inorganic pyrophosphatase.

BOX 15–1 WORKING IN BIOCHEMISTRY

Carl and Gerty Cori: Pioneers in Glycogen Metabolism and Disease

Much of what is written in present-day biochemistry textbooks about the metabolism of glycogen was discovered between about 1925 and 1950 by the remarkable husband and wife team of Carl F. Cori and Gerty T. Cori. Both trained in medicine in Europe at the end of World War I (she completed premedical studies and medical school in one year!). They left Europe together in 1922 to establish research laboratories in the United States, first for nine years in Buffalo, New York, at what is now the Roswell Park Memorial Institute, then from 1931 until the end of their lives at Washington University in St. Louis.

The Coris in Gerty Cori's laboratory, around 1947.

In their early physiological studies of the origin and fate of glycogen in animal muscle, the Coris demonstrated the conversion of glycogen to lactate in tissues, movement of lactate in the blood to the liver, and, in the liver, reconversion of lactate to glycogen—a pathway that came to be known as the Cori cycle (see Fig. 23–18). Pursuing these observations at the biochemical level, they showed that glycogen was mobilized in a phosphorolysis reaction catalyzed by the enzyme they discovered, glycogen phosphorylase. They identified the product of this reaction (the "Cori ester") as glucose 1-phosphate and showed that it could be reincorporated into glycogen in the reverse reaction. Although this did not prove to be the reaction by which glycogen is synthesized in cells, it was the first in vitro demonstration of the synthesis of a macromolecule from simple monomeric subunits, and it inspired others to search for polymerizing enzymes. Arthur Kornberg, discoverer of the first DNA polymerase, has said of his experience in the Coris' lab, "Glycogen phosphorylase, not base pairing, was what led me to DNA polymerase."

Gerty Cori became interested in human genetic diseases in which too much glycogen is stored in the liver. She was able to identify the biochemical defect in several of these diseases and to show that these diseases could be diagnosed by assays of the enzymes of glycogen metabolism in small samples of tissue obtained by biopsy. Table 1 summarizes what we now know about 13 genetic diseases of this sort. ■

Carl and Gerty Cori shared the Nobel Prize in Physiology or Medicine in 1947 with Bernardo Houssay of Argentina, who was cited for his studies of hormonal regulation of carbohydrate metabolism. The Cori laboratories in St. Louis became an international center of biochemical research in the 1940s and 1950s, and at least six scientists who trained with the Coris became Nobel laureates: Arthur Kornberg (for DNA synthesis, 1959), Severo Ochoa (for RNA synthesis, 1959), Luis Leloir (for the role of sugar nucleotides in

the cell is favorable. In effect, rapid removal of the product, driven by the large, negative free-energy change of PP_i hydrolysis, pulls the synthetic reaction forward, a common strategy in biological polymerization reactions.

2. Although the chemical transformations of sugar nucleotides do not involve the atoms of the nucleotide itself, the nucleotide moiety has many groups that can undergo noncovalent interactions with enzymes; the additional free energy of binding can contribute significantly to catalytic activity (Chapter 6; see also p. 301).

3. Like phosphate, the nucleotidyl group (UMP or AMP, for example) is an excellent leaving group, facilitating nucleophilic attack by activating the sugar carbon to which it is attached.

polysaccharide synthesis, 1970), Earl Sutherland (for the discovery of cAMP in the regulation of carbohydrate metabolism, 1971), Christian de Duve (for subcellular fractionation, 1974), and Edwin Krebs (for the discovery of phosphorylase kinase, 1991).

TABLE 1 Glycogen Storage Diseases of Humans

Type (name)	*Enzyme affected*	*Primary organ affected*	*Symptoms*
Type 0	Glycogen synthase	Liver	Low blood glucose, high ketone bodies, early death
Type Ia (von Gierke's)	Glucose 6-phosphatase	Liver	Enlarged liver, kidney failure
Type Ib	Microsomal glucose 6-phosphate translocase	Liver	As in Ia; also high susceptibility to bacterial infections
Type Ic	Microsomal P_i transporter	Liver	As in Ia
Type II (Pompe's)	Lysosomal glucosidase	Skeletal and cardiac muscle	Infantile form: death by age 2; juvenile form: muscle defects (myopathy); adult form: as in muscular dystrophy
Type IIIa (Cori's or Forbes's)	Debranching enzyme	Liver, skeletal and cardiac muscle	Enlarged liver in infants; myopathy
Type IIIb	Liver debranching enzyme (muscle enzyme normal)	Liver	Enlarged liver in infants
Type IV (Andersen's)	Branching enzyme	Liver, skeletal muscle	Enlarged liver and spleen, myoglobin in urine
Type V (McArdle's)	Muscle phosphorylase	Skeletal muscle	Exercise-induced cramps and pain; myoglobin in urine
Type VI (Hers's)	Liver phosphorylase	Liver	Enlarged liver
Type VII (Tarui's)	Muscle PFK-1	Muscle, erythrocytes	As in V; also hemolytic anemia
Type VIb, VIII, or IX	Phosphorylase kinase	Liver, leukocytes, muscle	Enlarged liver
Type XI (Fanconi-Bickel)	Glucose transporter (GLUT2)	Liver	Failure to thrive, enlarged liver, rickets, kidney dysfunction

4. By "tagging" some hexoses with nucleotidyl groups, cells can set them aside in a pool for one purpose (glycogen synthesis, for example), separate from hexose phosphates destined for another purpose (such as glycolysis).

Glycogen synthesis takes place in virtually all animal tissues but is especially prominent in the liver and skeletal muscles. The starting point for synthesis of glycogen is **glucose 6-phosphate.** As we saw in Chapter 14, this can be derived from free glucose in a reaction catalyzed by the isozymes **hexokinase I** and **hexokinase II** in muscle and **hexokinase IV** (glucokinase) in liver:

$$\text{D-Glucose} + \text{ATP} \longrightarrow \text{D-glucose 6-phosphate} + \text{ADP}$$

However, some ingested glucose takes a more roundabout path to glycogen. It is first taken up by erythrocytes and converted to lactate glycolytically; the lactate is then

taken up by the liver and converted to glucose 6-phosphate by gluconeogenesis.

To initiate glycogen synthesis, the glucose 6-phosphate is converted to **glucose 1-phosphate** in the phosphoglucomutase reaction:

$$\text{Glucose 6-phosphate} \rightleftharpoons \text{glucose 1-phosphate}$$

The product of this reaction is converted to UDP-glucose by the action of **UDP-glucose pyrophosphorylase,** in a key step of glycogen biosynthesis:

$$\text{Glucose 1-phosphate} + \text{UTP} \longrightarrow \text{UDP-glucose} + \text{PP}_i$$

Notice that this enzyme is named for the reverse reaction; in the cell, the reaction proceeds in the direction of UDP-glucose formation, because pyrophosphate is rapidly hydrolyzed by inorganic pyrophosphatase (Fig. 15–7).

UDP-glucose is the immediate donor of glucose residues in the reaction catalyzed by **glycogen synthase,** which promotes the transfer of the glucose residue from UDP-glucose to a nonreducing end of a branched glycogen molecule (Fig. 15–8). The overall equilibrium of the path from glucose 6-phosphate to lengthened glycogen greatly favors synthesis of glycogen.

Glycogen synthase cannot make the (α1→6) bonds found at the branch points of glycogen; these are formed by the glycogen-branching enzyme, also called **amylo (1→4) to (1→6) transglycosylase** or glycosyl-(4→6)-transferase. The glycogen-branching enzyme catalyzes transfer of a terminal fragment of 6 or 7 glucose residues from the nonreducing end of a glycogen branch having at least 11 residues to the C-6 hydroxyl group of a glucose residue at a more interior position of the same or another glycogen chain, thus creating a new branch (Fig. 15–9). Further glucose residues may be added to the new branch by glycogen synthase. The biological effect of branching is to make the glycogen molecule more soluble and to increase the number of nonreducing ends. This increases the number of sites accessible to glycogen phosphorylase and glycogen synthase, both of which act only at nonreducing ends.

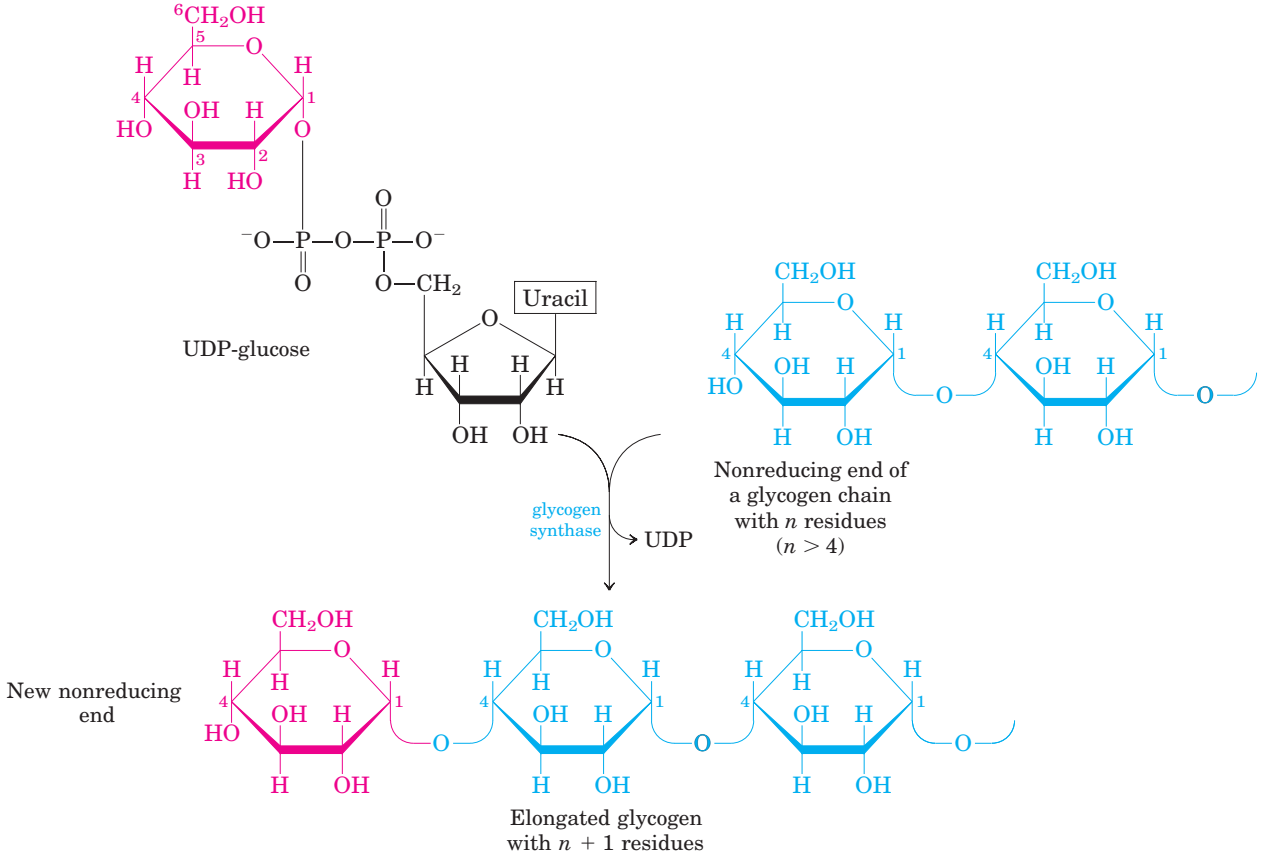


FIGURE 15–8 **Glycogen synthesis.** A glycogen chain is elongated by glycogen synthase. The enzyme transfers the glucose residue of UDP-glucose to the nonreducing end of a glycogen branch (see Fig. 7–15) to make a new (α1→4) linkage.

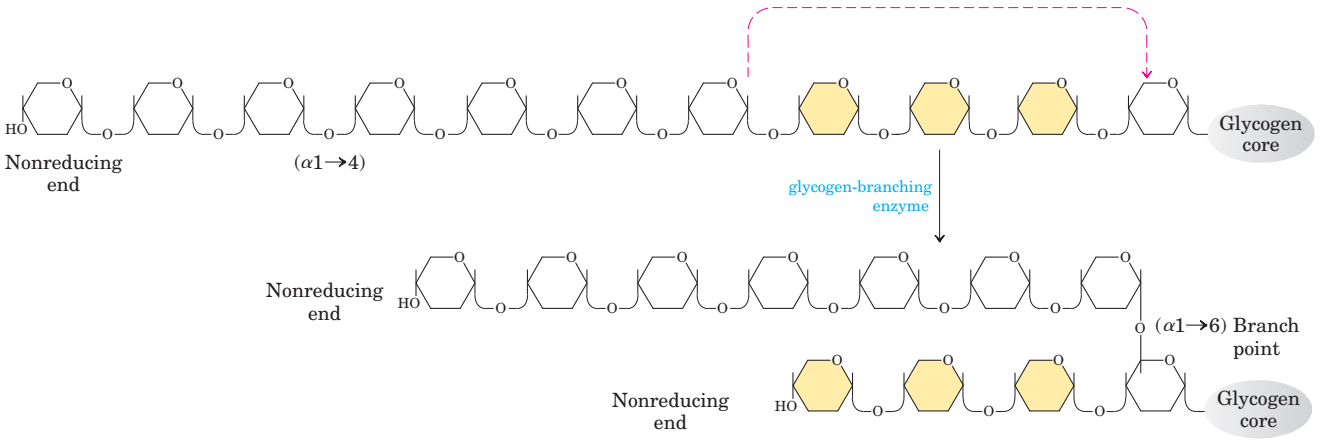


FIGURE 15–9 Branch synthesis in glycogen. The glycogen-branching enzyme (also called amylo (1→4) to (1→6) transglycosylase or glycosyl-(4→6)-transferase) forms a new branch point during glycogen synthesis.

Glycogenin Primes the Initial Sugar Residues in Glycogen

Glycogen synthase cannot initiate a new glycogen chain de novo. It requires a primer, usually a preformed (α1→4) polyglucose chain or branch having at least eight glucose residues. How is a *new* glycogen molecule initiated? The intriguing protein **glycogenin** (Fig. 15–10) is both the primer on which new chains are assembled and the enzyme that catalyzes their assembly. The first step in the synthesis of a new glycogen molecule is the transfer of a glucose residue from UDP-glucose to the hydroxyl group of Tyr^{194} of glycogenin, catalyzed by the protein's intrinsic glucosyltransferase activity (Fig. 15–11a). The nascent chain is extended by the sequential addition of seven more glucose residues, each derived from UDP-glucose; the reactions are catalyzed by the chain-extending activity of glycogenin. At this point, glycogen synthase takes over, further extending the glycogen chain. Glycogenin remains buried within the particle, covalently attached to the single reducing end of the glycogen molecule (Fig. 15–11b).

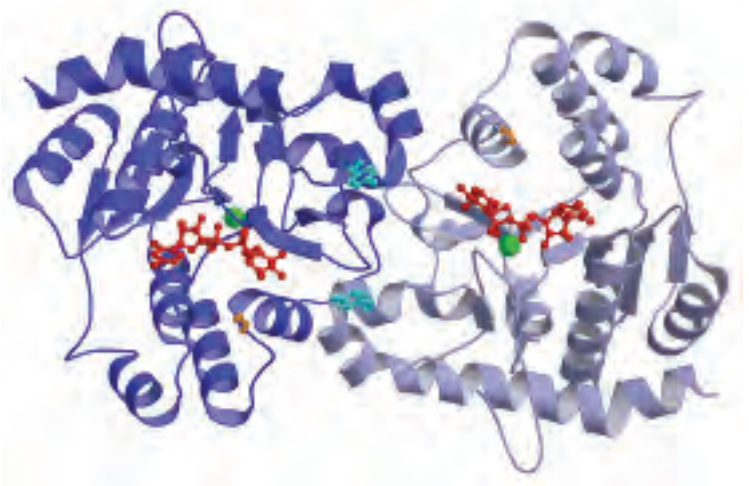
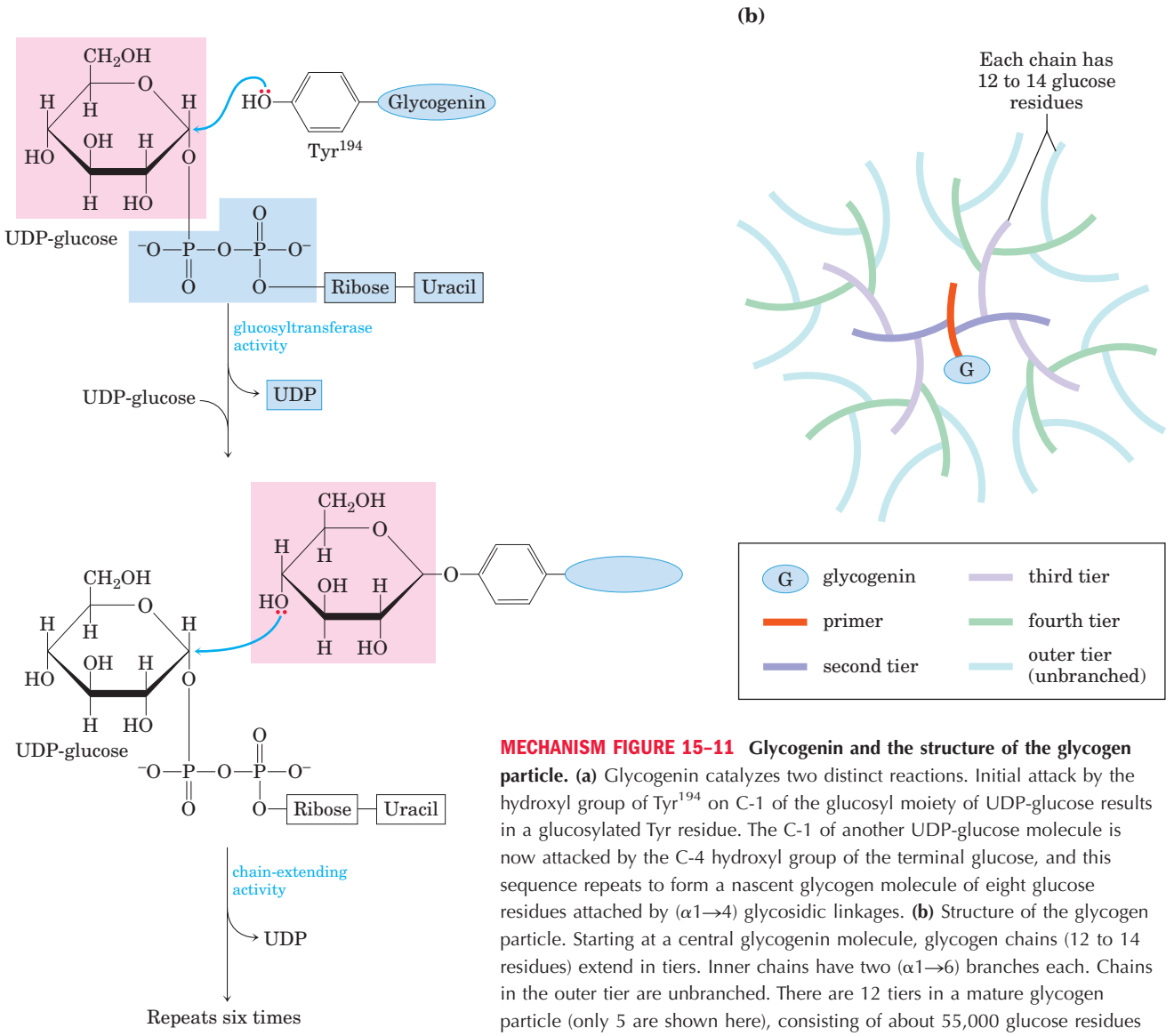


FIGURE 15–10 Glycogenin structure. (PDB 1D 1772) Muscle glycogenin (M_r 37,000) forms dimers in solution. Humans have a second isoform in liver, glycogenin-2. The substrate, UDP-glucose (shown as a red ball-and-stick structure), is bound to a Rossman fold near the amino terminus and is some distance from the Tyr^{194} residues (turquoise)—15 Å from that in the same monomer, 12 Å from that in the dimeric partner. Each UDP-glucose is bound through its phosphates to a Mn^{2+} ion (green) that is essential to catalysis. Mn^{2+} is believed to function as an electron-pair acceptor (Lewis acid) to stabilize the leaving group, UDP. The glycosidic bond in the product has the same configuration about the C-1 of glucose as the substrate UDP-glucose, suggesting that the transfer of glucose from UDP to Tyr^{194} occurs in two steps. The first step is probably a nucleophilic attack by Asp^{162} (orange), forming a temporary intermediate with inverted configuration. A second nucleophilic attack by Tyr^{194} then restores the starting configuration.



MECHANISM FIGURE 15–11 Glycogenin and the structure of the glycogen particle. (a) Glycogenin catalyzes two distinct reactions. Initial attack by the hydroxyl group of Tyr^{194} on C-1 of the glucosyl moiety of UDP-glucose results in a glucosylated Tyr residue. The C-1 of another UDP-glucose molecule is now attacked by the C-4 hydroxyl group of the terminal glucose, and this sequence repeats to form a nascent glycogen molecule of eight glucose residues attached by (α1→4) glycosidic linkages. **(b)** Structure of the glycogen particle. Starting at a central glycogenin molecule, glycogen chains (12 to 14 residues) extend in tiers. Inner chains have two (α1→6) branches each. Chains in the outer tier are unbranched. There are 12 tiers in a mature glycogen particle (only 5 are shown here), consisting of about 55,000 glucose residues in a molecule of about 21 nm diameter and M_r 10^7.

SUMMARY 15.1 The Metabolism of Glycogen in Animals

- Glycogen is stored in muscle and liver as large particles. Contained within the particles are the enzymes that metabolize glycogen, as well as regulatory enzymes.
- Glycogen phosphorylase catalyzes phosphorolytic cleavage at the nonreducing ends of glycogen chains, producing glucose 1-phosphate. The debranching enzyme transfers branches onto main chains and releases the residue at the (α1→6) branch as free glucose.
- Phosphoglucomutase interconverts glucose 1-phosphate and glucose 6-phosphate. Glucose 6-phosphate can enter glycolysis or, in liver, can be converted to free glucose by glucose 6-phosphatase in the endoplasmic reticulum, then released to replenish blood glucose.
- The sugar nucleotide UDP-glucose donates glucose residues to the nonreducing end of glycogen in the reaction catalyzed by glycogen synthase. A separate branching enzyme produces the (α1→6) linkages at branch points.
- New glycogen particles begin with the autocatalytic formation of a glycosidic bond between the glucose of UDP-glucose and a Tyr residue in the protein glycogenin, followed by addition of several glucose residues to form a primer that can be acted upon by glycogen synthase.