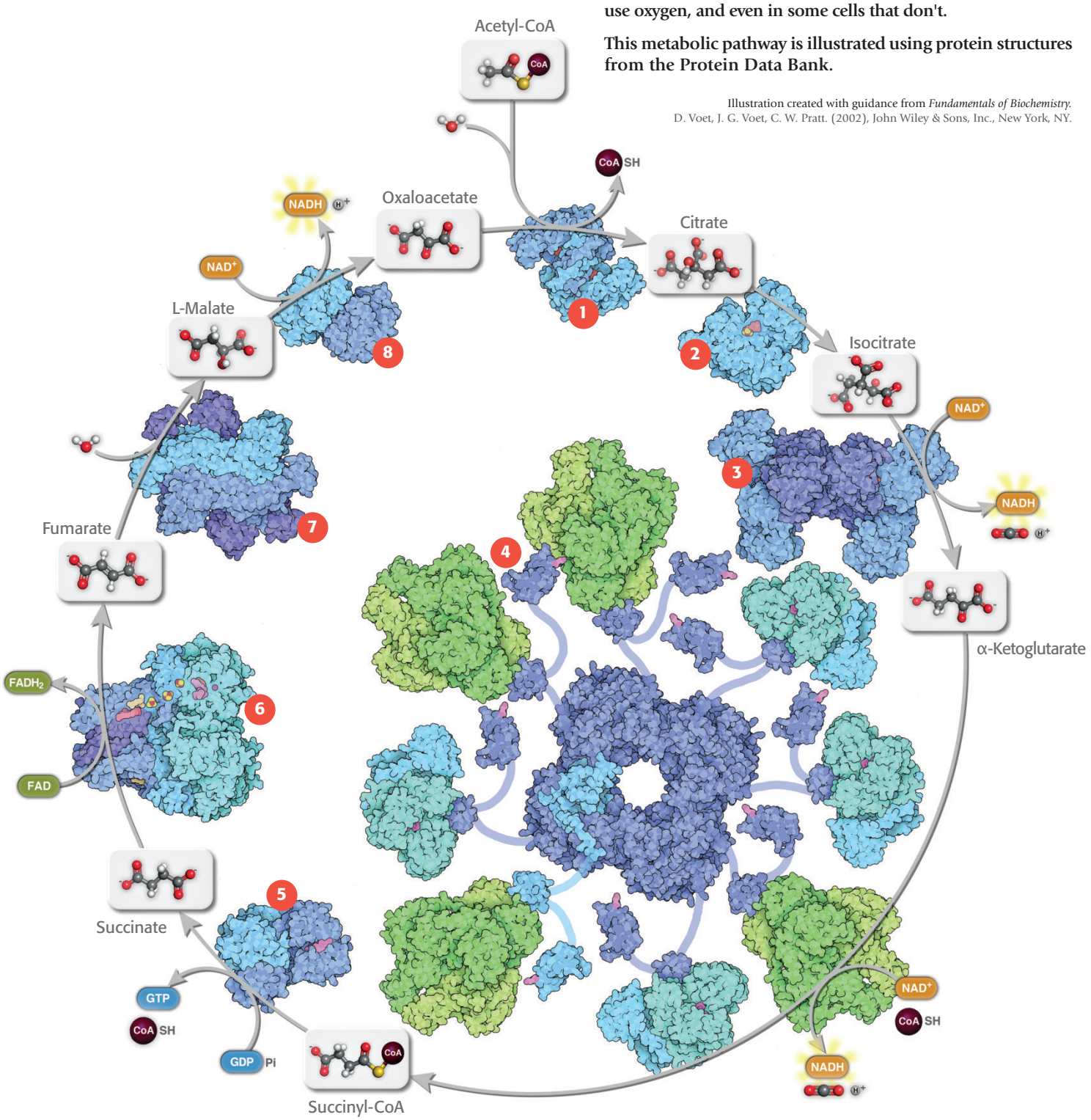
The Structures of the Citric Acid Cycle

Also known as the Krebs cycle or the tricarboxylic acid cycle, the *citric acid cycle* is at the center of cellular metabolism. It plays a starring role in both the process of energy production and biosynthesis. The cycle finishes the sugar-breaking job started in glycolysis and fuels the production of ATP in the process. It is also a central hub in biosynthetic reactions, providing intermediates that are used to build amino acids and other molecules. Citric acid cycle enzymes are found in all cells that use oxygen, and even in some cells that don't.

This metabolic pathway is illustrated using protein structures from the Protein Data Bank.

Illustration created with guidance from *Fundamentals of Biochemistry.* D. Voet, J. G. Voet, C. W. Pratt. (2002), John Wiley & Sons, Inc., New York, NY.



Eight Reactions

The eight reactions of the citric acid cycle use the small molecule *oxaloacetate* as a catalyst. The cycle starts by addition of an acetyl group to oxaloacetate, then, over the course of eight steps, the acetyl group is completely broken apart, finally restoring the oxaloacetate molecule for another round.

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Powerhouse of Energy

The citric acid cycle provides electrons that fuel the process of oxidative phosphorylation–our major source of ATP and energy. As the acetyl group is broken down, electrons are stored in the carrier NADH and delivered to the large protein complexes that generate the proton gradient that powers ATP synthase.

The Enzymes of the Krebs Cycle

1 Citrate Synthase

The cycle gets started with the enzyme citrate synthase. The pyruvate dehydrogenase complex has previously connected an acetyl group to the carrier coenzyme A, which holds it in an activated form. Citrate synthase pops off the acetyl group and adds it to oxaloacetate, forming citric acid.

PDB ID: 1cts

2 Aconitase

The citrate formed in the first step is a bit too stable, so the second step moves an oxygen atom to create a more reactive isocitrate molecule. Aconitase performs this isomerization reaction, with the assistance of an iron-sulfur cluster.

PDB ID: 7acn

3 Isocitrate Dehydrogenase

The real work begins in the third step of the cycle. Isocitrate dehydrogenase, removes one of the carbon atoms, forming carbon dioxide, and transfers electrons to NADH.

PDB ID: 3blw

4 2-Oxoglutarate Dehydrogenase Complex

The fourth step is performed by a huge complex, composed of three types of enzymes connected by flexible linkers. A lot of things happen in this complex: another carbon atom is released as carbon dioxide, electrons are transferred to NADH, and the remaining part of the molecule is connected to coenzyme A.

PDB IDs: 1e2o, 1bbl, 1pmr, 2eq7, 2jgd

5 Succinyl-CoA Synthetase

This is the only step in the cycle where ATP is made directly. The bond between succinate and coenzyme A is particularly unstable, and provides the energy needed to build a molecule of ATP. In mitochondria, the enzyme actually creates GTP in the reaction, which is converted to ATP by the enzyme nucleoside diphosphate kinase.

PDB ID: 2fp4

6 Succinate Dehydrogenase

In the sixth step, succinate dehydrogenase, found in the membrane, links its citric acid cycle task directly to the electron transport chain. It extracts hydrogen atoms from succinate and transfers them first to the carrier FAD and finally to the mobile electron carrier ubiquinone.

PDB ID: 1nek

7 Fumarase

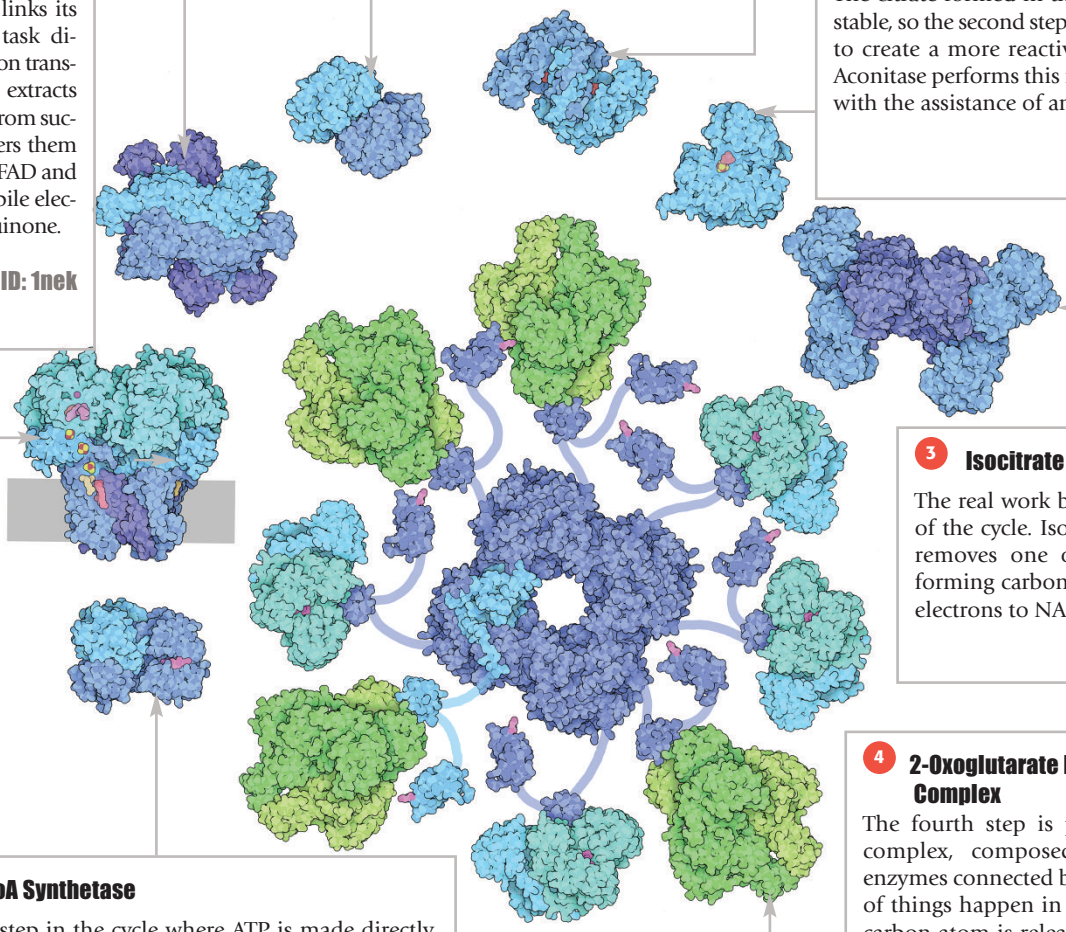
The seventh step is performed by fumarase, which adds a water molecule to get everything ready for the final step of the cycle.

PDB ID: 1fuo

8 Malate Dehydrogenase

The final step recreates oxaloacetate, transferring electrons to NADH in the process. Malate dehydrogenase is found in both the mitochondrion and the cytoplasm, forming part of a shuttle that transports electrons across the mitochondrial membrane.

PDB ID: 1mld



The structures shown here, taken from several different organisms, are described further in the October 2012 *Molecule of the Month* (**doi:10.2210/rcsb_pdb/mom_2012_10**). Visit **pdb101.rcsb.org** for more.

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