6.4: Gluconeogenesis

The anabolic counterpart to glycolysis is gluconeogenesis, which occurs mostly in the cells of the liver and kidney. In seven of the eleven reactions of gluconeogenesis (starting from pyruvate), the same enzymes are used as in glycolysis, but the reaction directions are reversed. Notably, the $\Delta G$ values of these reactions in the cell are typically near zero, meaning their direction can be readily controlled by changing substrate and product concentrations.

Figure 6.4.1: Metabolic Redox
The three regulated enzymes of glycolysis all catalyze reactions whose ΔG values are not close to zero, making manipulation of reaction direction non-trivial. Consequently, cells employ "work-around" reactions catalyzed by four different enzymes to favor gluconeogenesis, when appropriate.

Two of the enzymes (pyruvate carboxylase and PEP carboxykinase -PEPCK) catalyze reactions that bypass pyruvate kinase. F1,6BPase bypasses PFK and G6Pase bypasses hexokinase. Notably, pyruvate carboxylase and G6Pase are found in the mitochondria and endoplasmic reticulum, respectively, whereas the other two are found in the cytoplasm along with all of the enzymes of glycolysis. As a result, all of glycolysis and most of gluconeogenesis occurs in the cytoplasm. Controlling these pathways then becomes of critical importance because cells generally need to minimize the extent to which paired anabolic and catabolic pathways are occurring simultaneously, lest they waste energy and make no tangible product except heat. The mechanisms of controlling these pathways work, in some ways, in opposite fashions, called reciprocal regulation (see above).

![Figure 6.4.2: Gluconeogenesis and Glycolysis](https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Free_and_Easy_(Ahern_and_Rajagopal)/06%3A...)

Besides reciprocal regulation, other mechanisms help control gluconeogenesis. First, PEPCK is controlled largely at the level of synthesis. Overexpression of PEPCK (stimulated by glucagon, glucocorticoids, and cAMP and inhibited by insulin) causes symptoms of diabetes. Pyruvate carboxylase is sequestered in the mitochondrion and is sensitive to acetyl-CoA, which is an allosteric activator. Acetyl-CoA concentrations increase as the citric acid cycle activity decreases. Glucose-6-phosphatase is present in low concentrations in many tissues, but is found most abundantly and importantly in the major gluconeogenic organs -- the liver and kidney cortex.
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