

# Glossary

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### **Amyloidosis**

A large, heterogeneous group of diseases characterized by themisfolding of extracellular protein. Misfolding occurs in parallel or as an alternative to physiological folding and generates insoluble protein aggregates (bundles of  $\beta$ -sheet fibrillar protein). Despite possessing heterogeneous structures and functions, fibrillar proteins are morphologically similar. Organ dysfunction results from the deposition and cytotoxic effects of insoluble amyloid proteins.

### **Beta-oxidation inhibitors**

Compounds or drugs that inhibit mitochondrial fatty acid beta-oxidation. They do so primarily by either directly inhibiting mitochondrial fatty acid betaoxidation enzymes (i.e., trimetazidine, an inhibitor of 3-ketoacyl CoA thiolase), or preventing the uptake of fatty acids into the mitochondria (i.e., perhexiline, an inhibitor of carnitine palmitoyl transferase).

### **Cardiomyopathy**

Cardiomyopathy simply means “heart muscle disease”, and refers to any type of deterioration of heart muscle function. If this dysfunction is due to ischemia, it is referred to as ischemic cardiomyopathy, or if it is due to underlying diabetes, it is referred to as diabetic cardiomyopathy.

### **Carnitine palmitoyl transferase 1 (CPT-1) inhibitors**

Compounds or drugs that inhibit the mitochondrial outer membrane enzyme CPT-1, which is the rate-limiting enzyme for mitochondrial fatty acid uptake and subsequent beta-oxidation. Therefore, CPT-1 inhibitors inhibit mitochondrial fatty acid beta-oxidation secondary to an inhibition of its uptake into the mitochondria.

### **Dichloroacetate (DCA)**

Dichloroacetate (DCA) is an inhibitor of pyruvate dehydrogenase kinase, which is the enzyme respon-

sible for phosphorylating and inactivating pyruvate dehydrogenase, the rate-limiting enzyme of glucose oxidation. DCA therefore activates pyruvate dehydrogenase and increases subsequent glucose oxidation rates.

### **Free fatty acids (FFAs)**

Acid moieties found in the circulation bound to albumin, or derived from triacylglycerol contained in chylomicrons or very-low density lipoprotein. Following cellular uptake, free fatty acids are activated via esterification to coenzyme A, and can be metabolized via mitochondrial fatty acid  $\beta$ -oxidation to generate reducing equivalents (e.g., nicotinamide adenine dinucleotide [NADH]) for the electron transport chain and oxidative phosphorylation.

### **Immunoabsorption (affinity chromatography)**

A chromatographic method for the purification of a specific molecule(s) from a complex mixture(s) based on the highly specific biological interaction between twomolecules (i.e., antibody and antigen). The interaction is usually reversible, and purification is achieved by immobilizing one of the molecules (affinity ligand) onto a solid matrix, thereby creating a stationary phase, while the target ligand is in a mobile phase as part of a complex mixture. Capture of the target molecule is typically followed by washing and elution, which results in the recovery of a purified molecular species.

### **Nicotinamide adenine dinucleotide (NAD<sup>+</sup>/NADH)**

A coenzyme critical to life in all living cells that consists of two nucleotides joined through a phosphate group. One of the nucleotides possesses an adenine base, whereas the other possesses nicotinamide. As a coenzyme, it is involved in numerous redox reactions that occur in metabolism. One of its major roles is to act as a reducing agent and electron donor during the electron transport chain, which is critical to adenosine-5'-triphosphate (ATP)

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production during the process of oxidative phosphorylation.

## Pyruvate dehydrogenase (PDH)

Pyruvate dehydrogenase (PDH) is a mitochondrial enzyme that catalyzes the committed step of pyruvate oxidation (i.e., oxidative decarboxylation), thereby generating acetyl coenzyme A (CoA) for the tricar-

boxylic acid cycle and nicotinamide adenine dinucleotide (NADH) for the electron transport chain. PDH is part of a multienzyme complex, consisting of PDH kinase and PDH phosphatase. Phosphorylation of PDH by PDH kinase inhibits its activity, while dephosphorylation by PDH phosphatase increases its activity. PDH activity is also sensitive to inhibition by substrate/product ratios as decreased ratios of  $\text{NAD}^+/\text{NADH}$  and  $\text{CoA}/\text{acetyl-CoA}$  decrease the rate of pyruvate oxidation.