Enzymes involved in L-lactate metabolism in humans

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Abstract: L-lactate formation occurs via the reduction of pyruvate catalyzed by lactate dehydrogenase. L-lactate removal takes place via its oxidation into pyruvate, which may be oxidized or converted into glucose. Pyruvate oxidation involves the cooperative effort of pyruvate dehydrogenase, the tricarboxylic acid cycle, and the mitochondrial respiratory chain. Enzymes of the gluconeogenesis pathway sequentially convert pyruvate into glucose. In addition, pyruvate may undergo reversible transamination to alanine by alanine aminotransferase. Enzymes involved in L-lactate metabolism are crucial to diabetes pathophysiology and therapy. Elevated plasma alanine aminotransferase concentration has been associated with insulin resistance. Polymorphisms in the G6PC2 gene have been associated with fasting glucose concentration and insulin secretion. In diabetes patients, pyruvate dehydrogenase is down-regulated and the activity of pyruvate carboxylase is diminished in the pancreatic islets. Inhibitors of fructose 1,6-bisphosphatase are being investigated as potential therapy for type 2 diabetes. In addition, enzymes implicated in L-lactate metabolism have revealed to be important in cancer cell homeostasis. Many human tumors have higher LDH5 levels than normal tissues. The LDHC gene is expressed in a broad range of tumors. The activation of PDH is a potential mediator in the body response that protects against cancer and PDH activation has been observed to reduce glioblastoma growth. The expression of PDK1 may serve as a biomarker of poor prognosis in gastric cancer. Mitochondrial DNA mutations have been detected in a number of human cancers. Genes encoding succinate dehydrogenase have tumor suppressor functions and consequently mutations in these genes may cause a variety of tumors.

Keywords: Lactate dehydrogenase; alanine aminotransferase; pyruvate dehydrogenase; tricarboxylic acid cycle; mitochondrial respiratory chain; gluconeogenesis

Abbreviations: ALT: alanine aminotransferase. ATP: adenine triphosphate. CoA: coenzyme A. FAD: flavin adenine dinucleotide. GPT: glutamate pyruvate transaminase. GSD: glycogen storage disease. LDH: lactate dehydrogenase. NAD^+: oxidized nicotinamide adenine dinucleotide. NADH: reduced nicotinamide adenine dinucleotide. PDH: pyruvate dehydrogenase. PDK: pyruvate dehydrogenase kinase. PDP: pyruvate dehydrogenase phosphatase. PEPCK: phosphoenolpyruvate carboxykinase. TCA: tricarboxylic acid.