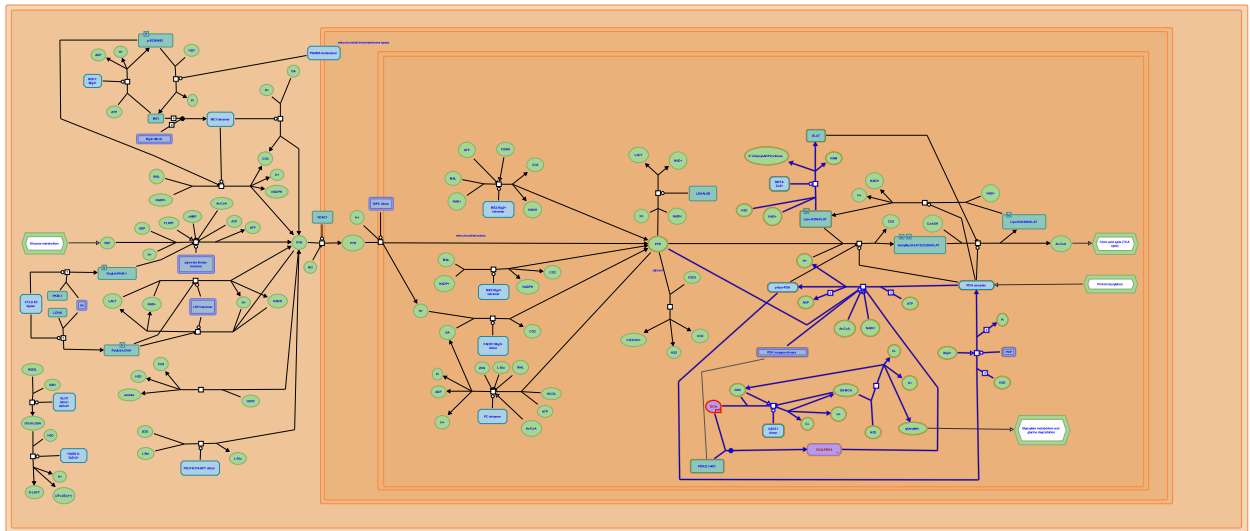


# Regulation of pyruvate dehydrogenase (PDH) complex



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

01/04/2024

## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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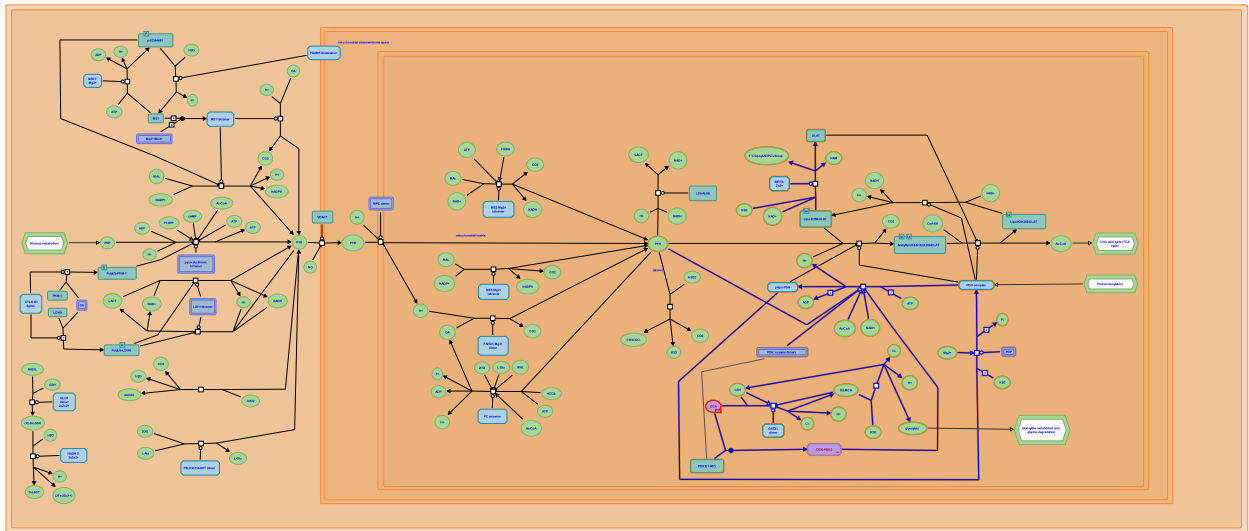
Reactome database release: 88

This document contains 1 pathway and 6 reactions ([see Table of Contents](#))

## Regulation of pyruvate dehydrogenase (PDH) complex ↗

**Stable identifier:** R-HSA-204174

**Compartments:** mitochondrial matrix



 reactome

The mitochondrial pyruvate dehydrogenase (PDH) complex catalyzes the oxidative decarboxylation of pyruvate, linking glycolysis to the tricarboxylic acid cycle and fatty acid synthesis. PDH inactivation is crucial for glucose conservation when glucose is scarce, while adequate PDH activity is required to allow both ATP and fatty acid production from glucose. The mechanisms that control human PDH activity include its phosphorylation (inactivation) by pyruvate dehydrogenase kinases (PDK 1-4) and its dephosphorylation (activation, reactivation) by pyruvate dehydrogenase phosphate phosphatases (PDP 1 and 2). Isoform-specific differences in kinetic parameters, regulation, and phosphorylation site specificity of the PDKs introduce variations in the regulation of PDC activity in differing endocrine and metabolic states (Sugden and Holness 2003). Further, PDH is inhibited by SIRT4 and the drug dichloroacetic acid (DCA).

### Literature references

Holness, MJ., Sugden, MC. (2003). Recent advances in mechanisms regulating glucose oxidation at the level of the pyruvate dehydrogenase complex by PDKs. *Am J Physiol Endocrinol Metab*, 284, E855-62. ↗

### Editions

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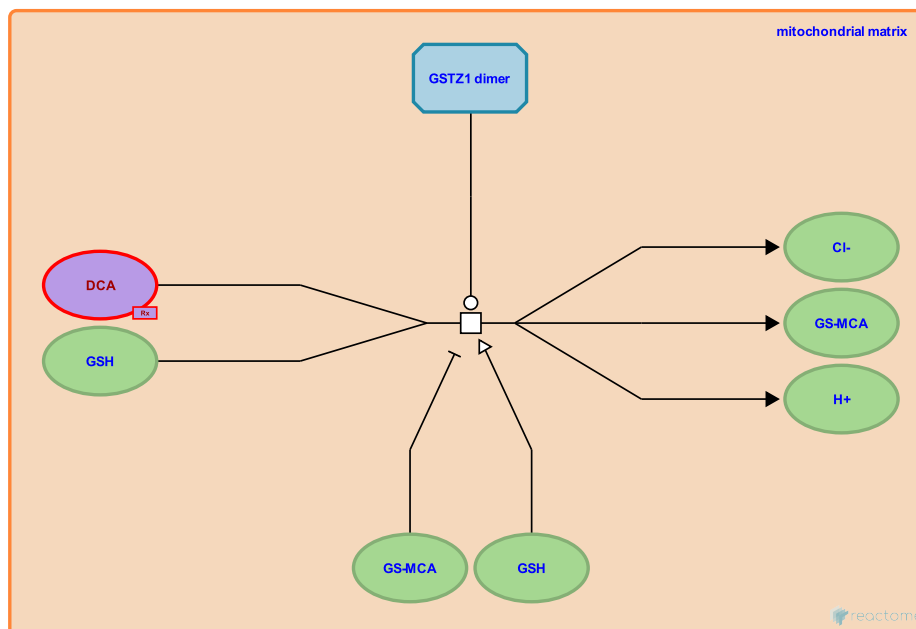
## GSTZ1 dimer dehalogenates DCA ↗

**Location:** [Regulation of pyruvate dehydrogenase \(PDH\) complex](#)

**Stable identifier:** R-HSA-9011595

**Type:** transition

**Compartments:** mitochondrial matrix



In the liver, dimeric glutathione S-transferase zeta 1 (GSTZ1 dimer, aka maleylacetoacetate isomerase, MAAI) mediates the dechlorination of the drug dichloroacetate (DCA) to glyoxylate (Ammini & Stacpoole 2003, Stacpoole et al. 1998, 2008). GSTZ1 is primarily found both in the cytosol and mitochondria (Li et al. 2011). Glyoxylate, the primary metabolite of DCA metabolism, is ultimately converted to oxalate and glycine. The reaction requires (but does not consume) glutathione (GSH). GSTZ1 also catalyses the penultimate step in tyrosine catabolism, thus avoiding the accumulation of toxic tyrosine intermediates. DCA inhibits its own metabolism apparently by a post-translationally mediated inhibition of hepatic GSTZ1 (Stacpoole et al. 1998). GSTZ1 inhibition can cause the build-up of tyrosine intermediates which are able to form protein adducts. Chronic administration of DCA in adult rodents, dogs and some humans causes reversible peripheral neuropathy and hepatotoxicity, possibly because of these reactive tyrosine intermediates (Stacpoole et al. 1998, James et al. 2017). The rate of GSTZ1 inactivation by DCA is influenced by age, GSTZ1 haplotype and cellular chloride concentration (Shroads et al. 2008, 2012, 2015, Jahn et al. 2016, James et al. 2017).

**Followed by:** [GS-MCA spontaneously hydrolyzes](#)

## Literature references

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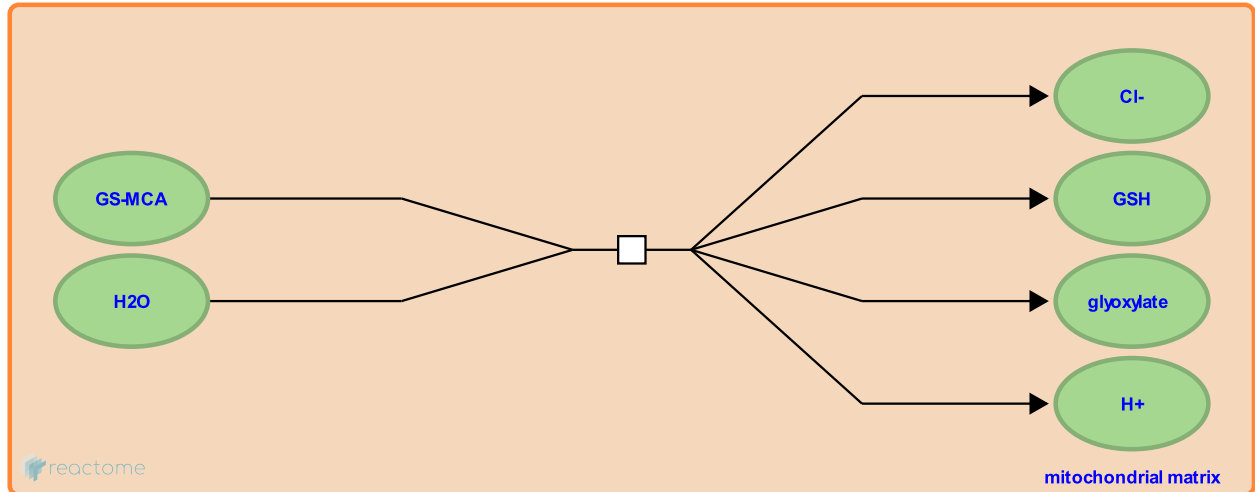
## GS-MCA spontaneously hydrolyzes ↗

**Location:** [Regulation of pyruvate dehydrogenase \(PDH\) complex](#)

**Stable identifier:** R-HSA-9863531

**Type:** transition

**Compartments:** mitochondrial matrix



GS-MCA spontaneously hydrolyzes into GSH, glyoxylate, chloride, and a proton (Tong et al., 1998).

**Preceded by:** [GSTZ1 dimer dehalogenates DCA](#)

### Literature references

Board, PG., Tong, Z., Anders, MW. (1998). Glutathione transferase zeta-catalyzed biotransformation of dichloroacetic acid and other alpha-haloacids. *Chem Res Toxicol*, 11, 1332-8. ↗

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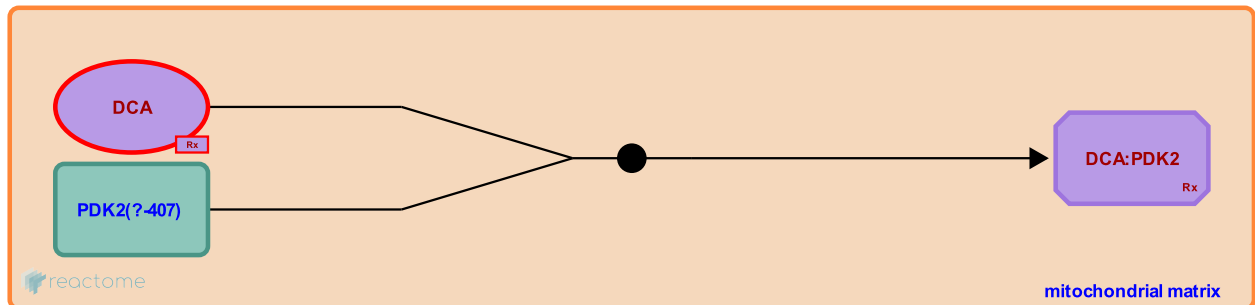
## DCA binds PDK2 ↗

**Location:** Regulation of pyruvate dehydrogenase (PDH) complex

**Stable identifier:** R-HSA-9011543

**Type:** binding

**Compartments:** mitochondrial matrix



The expression of pyruvate dehydrogenase kinases (PDKs) is induced in starvation, diabetes and cancer. Of the four human PDKs, PDK2 is the most ubiquitously expressed kinase and is most susceptible to inhibition by the drug dichloroacetate (DCA), an acid salt analogue of acetic acid. DCA binds to a hydrophobic pocket in the N-terminal domain of PDK2 and, in the presence of ADP, disrupts the binding of the kinase to the lipoyl (E2) domain of the pyruvate dehydrogenase complex and thus inhibits aberrant PDK activity (Klyuyeva et al. 2007, Li et al. 2009, Roche et al. 2001, James et al. 2017).

### Literature references

Tuganova, A., Klyuyeva, A., Popov, KM. (2007). Amino acid residues responsible for the recognition of dichloroacetate by pyruvate dehydrogenase kinase 2. *FEBS Lett.*, 581, 2988-92. ↗

Li, J., Chuang, DT., Kato, M. (2009). Pivotal role of the C-terminal DW-motif in mediating inhibition of pyruvate dehydrogenase kinase 2 by dichloroacetate. *J. Biol. Chem.*, 284, 34458-67. ↗

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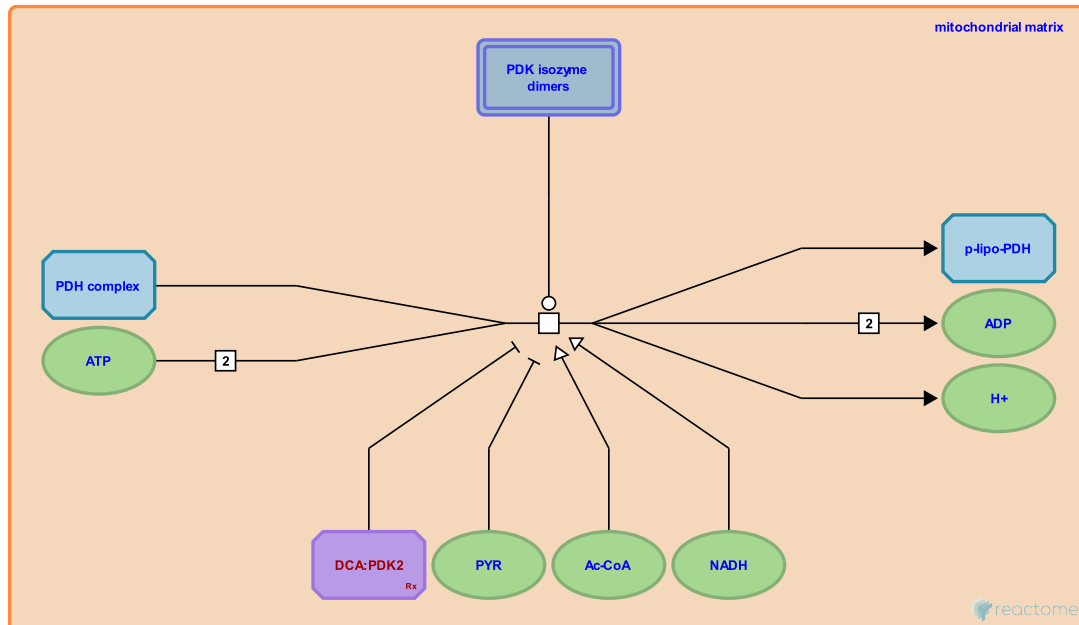
## PDK isozymes phosphorylate PDHC subunit E1 ↗

**Location:** Regulation of pyruvate dehydrogenase (PDH) complex

**Stable identifier:** R-HSA-203946

**Type:** transition

**Compartments:** mitochondrial matrix



In the nucleus, cellular retinoic acid-binding protein 1 or 2 (CRABP1 or 2), bound to all-trans-retinoic acid (atRA), directly binds to the heterodimeric complex of retinoic acid receptor alpha RXRA) and peroxisome proliferator-activated receptor delta (PPAR $\delta$ ). When bound to PPAR $\delta$ , atRA can significantly increase the expression of proteins involved in energy metabolism such as PDK via induction of PPAR $\delta$  (Wolf 2010).

The mitochondrial pyruvate dehydrogenase (PDH) complex (lipo-PDH) irreversibly decarboxylates pyruvate to acetyl CoA, thereby serving to oxidatively remove lactate, which is in equilibrium with pyruvate and link glycolysis in the cytosol to the tricarboxylic acid cycle in the mitochondria matrix. In the mitochondrial matrix, Pyruvate Dehydrogenase Kinase (PDK) catalyzes the phosphorylation of serine residues of the E1 alpha subunit of the PDH complex, inactivating it. Pyruvate negatively regulates this reaction, and NADH and acetyl CoA positively regulate it (Bao et al. 2004). Four PDK isozymes have been identified and shown to catalyze the phosphorylation of E1 alpha in vitro (Gudi et al. 1995, Kolobova et al. 2001, Rowles et al. 1996). They differ in their expression patterns and quantitative responses to regulatory small molecules. All four isoforms catalyze the phosphorylation of serine residues 293 ("site 1") and 300 ("site 2"); PDK1 can also catalyze the phosphorylation of serine 232 ("site 3"). Phosphorylation of a single site in a single E1 alpha subunit is sufficient for enzyme inactivation (Bowker-Kinley et al., 1998; Gudi et al., 1995; Kolobova et al., 2001; Korotchikina and Patel, 2001). The PDH-PDK axis is emerging as an important therapeutic point in genetic mitochondrial diseases, pulmonary arterial hypertension, and cancer, where cellular metabolism is perturbed (James et al. 2017). Dichloroacetate (DCA) is an acid salt analog of acetic acid used to inhibit PDK (Li et al. 2009). The effect is to keep the PDH complex active, thus stimulating mitochondrial oxidative metabolism. Chronic DCA administration may cause reversible peripheral neuropathy in adults (Kaufmann et al. 2006) but is well tolerated in children and adolescents suffering from the primary mitochondrial disease lactic acidosis (Abdelmalak et al. 2013, Stacpoole et al. 2008). The Warburg effect is the observation that cancer cells prefer aerobic glycolysis to oxidative phosphorylation (Warburg 1956). Whether this effect is the consequence of genetic dysregulation in cancer or the cause of cancer remains unknown. It stands true for most types of cancer cells and has become one of the hallmarks of cancer. Aerobic glycolysis produces ATP at a much faster rate than oxidative phosphorylation, conferring growth advantages to tumor cells. DCA, binding to and inhibiting PDK isoforms, promotes a shift from glycolysis to oxidative phosphorylation and reverses the Warburg effect. Its potential role, alone or in combination, in several cancers is being investigated (Kankotia & Stacpoole, 2014, Tran et al., 2016; reviewed in Wang et al., 2021; Park et al., 2023).

**Preceded by:** PDP1,2 dephosphorylate p-lipo-PDH

**Followed by:** PDP1,2 dephosphorylate p-lipo-PDH



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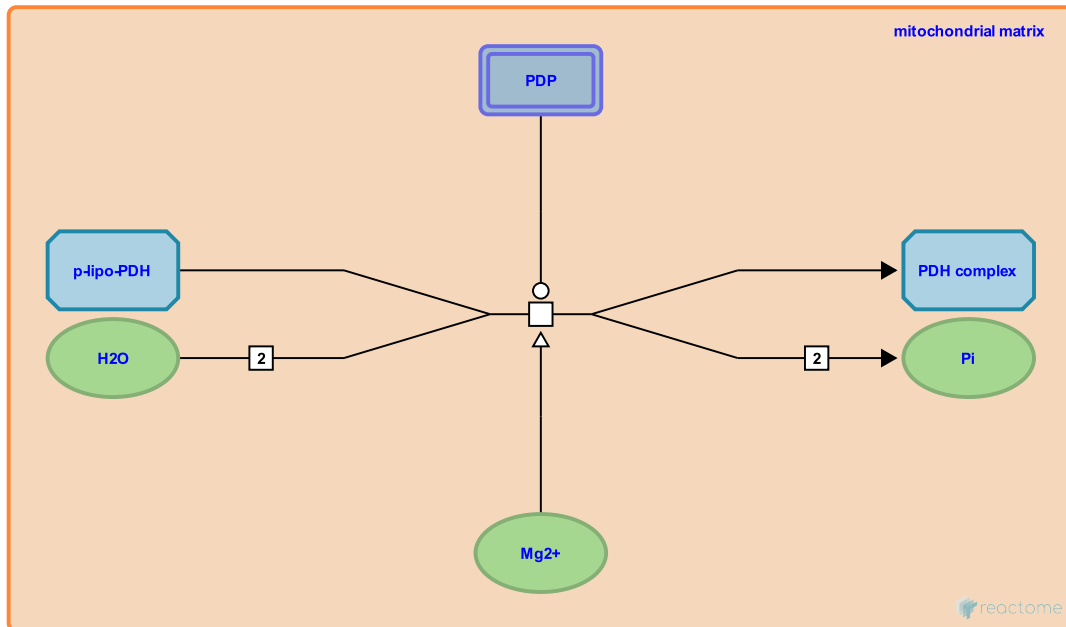
## PDP1,2 dephosphorylate p-lipo-PDH ↗

**Location:** [Regulation of pyruvate dehydrogenase \(PDH\) complex](#)

**Stable identifier:** R-HSA-204169

**Type:** transition

**Compartments:** mitochondrial matrix



Pyruvate dehydrogenase phosphatase (PDP) in the mitochondrial matrix catalyzes the hydrolytic removal of phosphate groups from phosphoserine residues in the E1 alpha subunit of the pyruvate dehydrogenase complex. The active form of PDP is a heterodimer of a catalytic subunit and a regulatory one. Two isoforms of the catalytic subunit have been identified and biochemically characterized (Huang et al. 1998) and mutations in PDP1 have been associated with PDP deficiency in vivo (Maj et al. 2005). The properties of the human regulatory subunit have been deduced from those of its bovine homologue (Lawson et al. 1997). The activity of PDP1 is greatly enhanced through Ca<sup>2+</sup>-dependent binding of the catalytic subunit (PDP1c) to the L2 (inner lipoyl) domain of dihydrolipoyl acetyltransferase (E2), which is also integrated in the pyruvate dehydrogenase complex. PDP activity requires Mg<sup>2+</sup> (Huang et al. 1998).

**Preceded by:** [PDK isozymes phosphorylate PDHC subunit E1](#)

**Followed by:** [PDK isozymes phosphorylate PDHC subunit E1](#)

### Literature references

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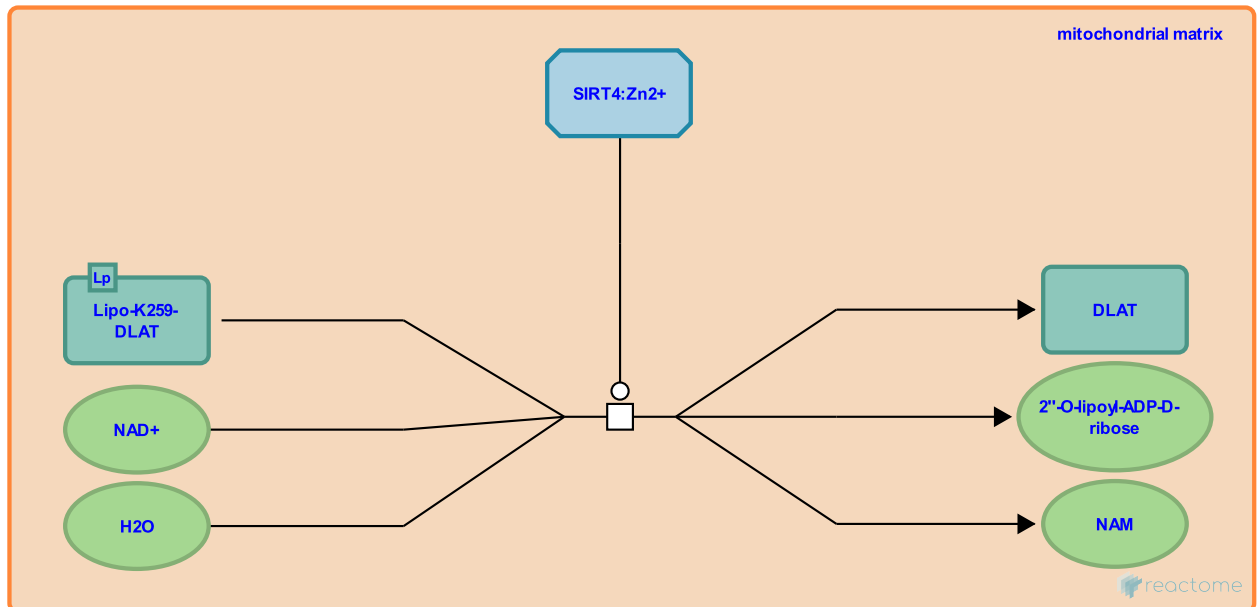
## SIRT4 cleaves lipoyl from DLAT ↗

**Location:** Regulation of pyruvate dehydrogenase (PDH) complex

**Stable identifier:** R-HSA-9861626

**Type:** transition

**Compartments:** mitochondrial matrix



Mitochondrial NAD-dependent protein lipoamidase sirtuin-4 (SIRT4) hydrolyzes the lipoamide cofactors from the E2 component dihydrolipoyllysine acetyltransferase (DLAT) of the PDH complex, diminishing PDH activity. The reaction also irreversibly degrades one NAD<sup>+</sup> molecule (Mathias et al., 2014). SIRT4 probably binds Zn<sup>2+</sup> as a cofactor (UniProt).

### Literature references

Greco, TM., Shenk, T., Rowland, EA., Cristea, IM., Oberstein, A., Mathias, RA. et al. (2014). Sirtuin 4 is a lipoamidase regulating pyruvate dehydrogenase complex activity. *Cell*, 159, 1615-25. ↗

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