

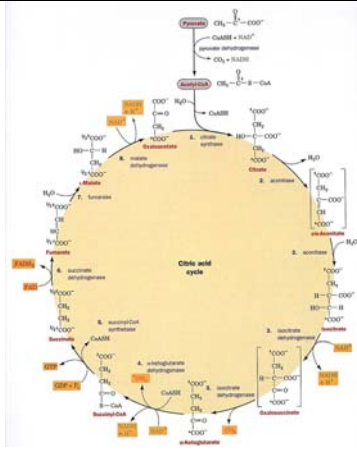
## The Citric Acid Cycle II

11/17/2009

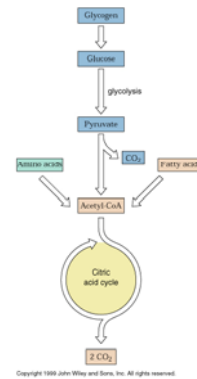
## The Citric acid cycle

It is called the Krebs cycle or the tricarboxylic and is the "hub" of the metabolic system. It accounts for the majority of carbohydrate, fatty acid and amino acid oxidation. It also accounts for a majority of the generation of these compounds and others as well.

**Amphibolic - acts both catabolically and anabolically**

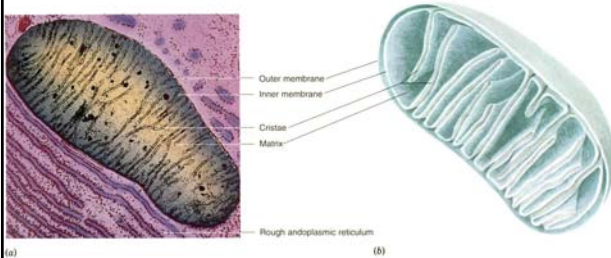


## Overview



## The citric acid cycle enzymes are found in the matrix of the mitochondria

Substrates have to flow across the outer and inner parts of the mitochondria

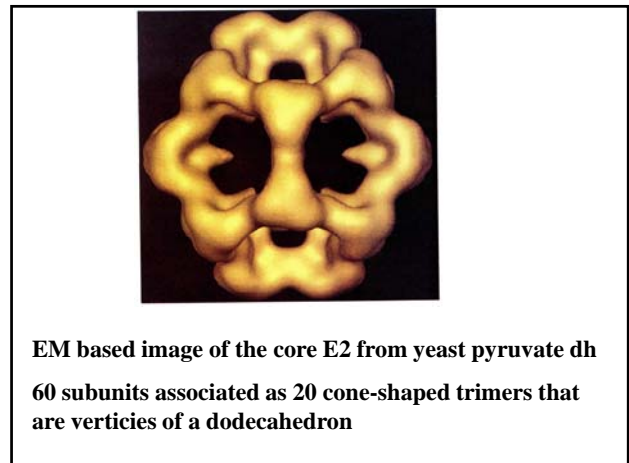
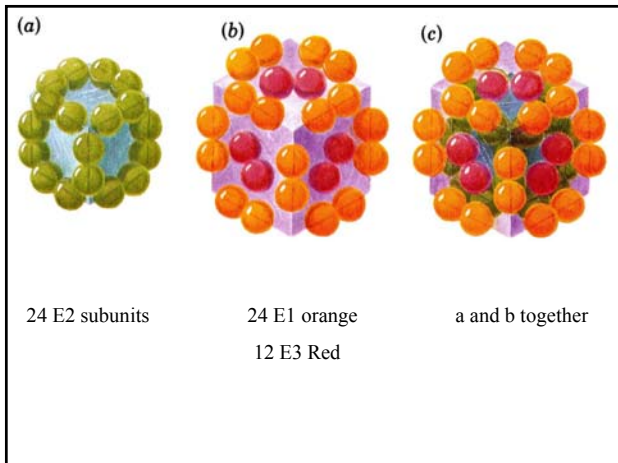


## Pyruvate dehydrogenase

A multienzyme complexes are groups of non covalently associated enzymes that catalyze two or more sequential steps in a metabolic pathway.

**Molecular weight of 4,600,000 Da**

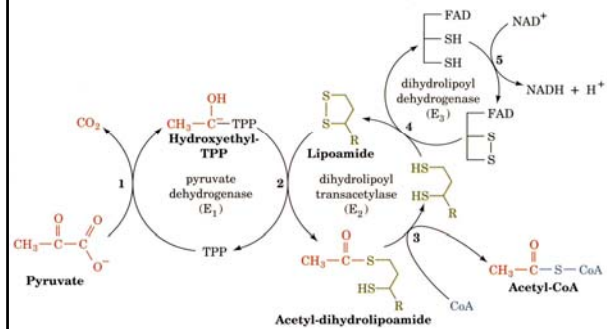
	E. coli	yeast
Pyruvate dehydrogenase -- E1	24	60
dihydrolipoyl transacetylase --E2	24	60
dihydrolipoyl dehydrogenase--E3	12	12



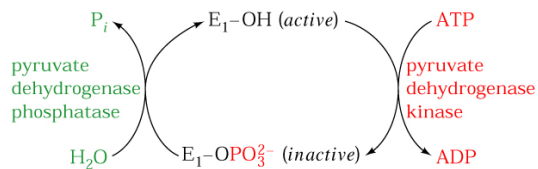
### Why such a complex set of enzymes?

- 1 Enzymatic reactions rates are limited by diffusion, with shorter distance between subunits a enzyme can almost direct the substrate from one subunit (catalytic site) to another.
2. Channeling metabolic intermediates between successive enzymes minimizes side reactions
3. The reactions of a multienzyme complex can be coordinately controlled

### The five reactions of the pyruvate dehydrogenase multi enzyme complex

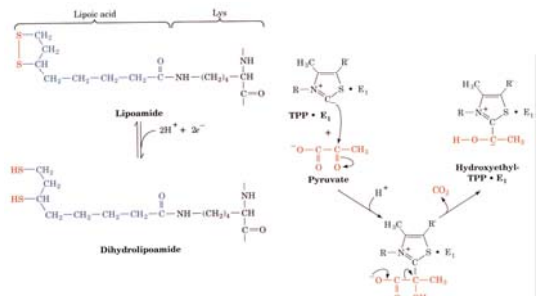
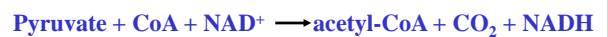


### Covalent modification of eukaryotic pyruvate dehydrogenase



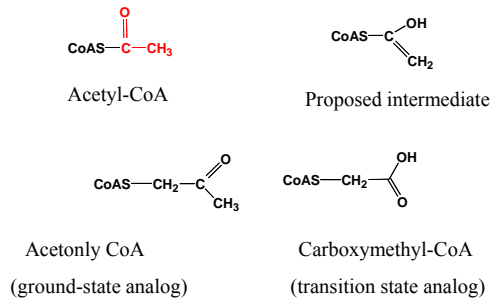
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### The enzyme requires five coenzymes and five reactions

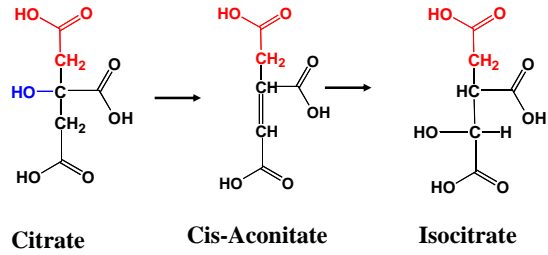




**Induced fit needs binding of oxaloacetate before Acetyl CoA can bind.**

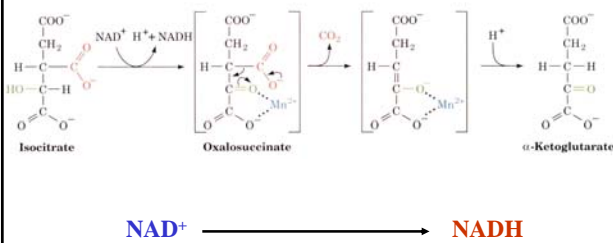


### Aconitase

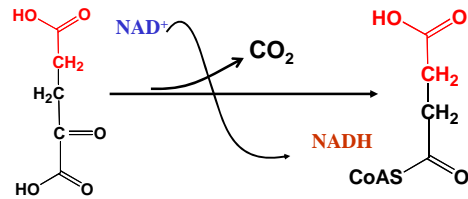


**The double bond is placed on the Pro-R arm**

### NAD<sup>+</sup>- Dependent Isocitrate dehydrogenase

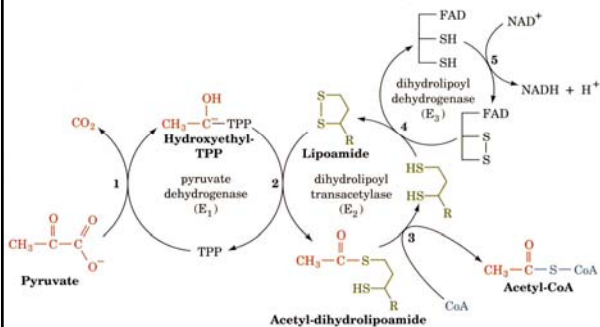


### $\alpha$ -Ketoglutarate dehydrogenase

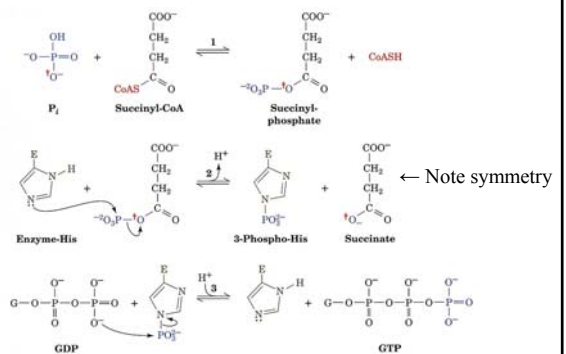


This enzyme is just like pyruvate dehydrogenase, a multi enzyme complex that is specific for longer CoA derivatives

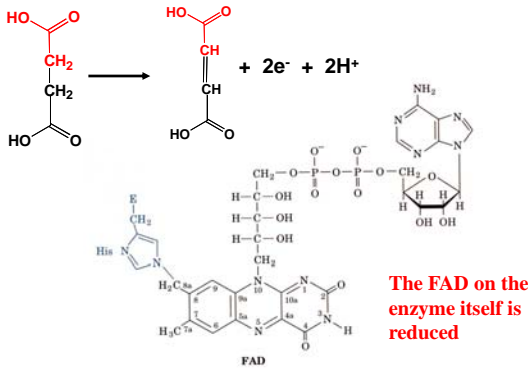
**Refresh: The five reactions of the pyruvate dehydrogenase multi enzyme complex**



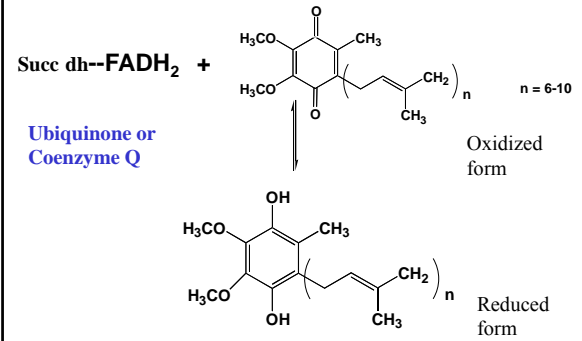
### Succinyl-CoA Synthetase or succinate thiokinase



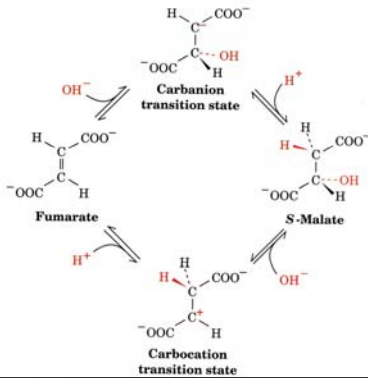
## Succinate dehydrogenase



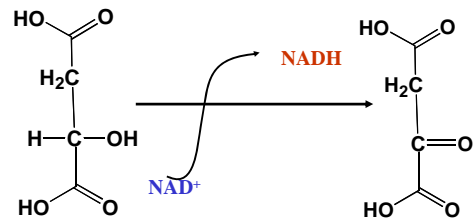
## Succinate dehydrogenase is the only membrane bound enzyme in the citrate cycle



## Fumarase



## Malate dehydrogenase

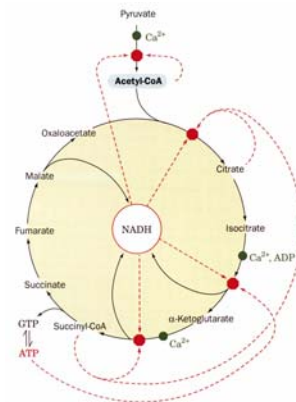


## Regulation of the citric acid cycle

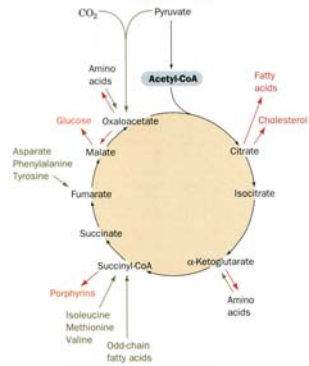
Standard free energy changes in the citric acid cycle

Reaction	Enzyme	$\Delta G^{\circ'}$	$\Delta G'$
1	Citrate synthase	-31.5	Negative
2	Aconitase	~5	~0
3	Isocitrate dh	-21	Negative
4	$\alpha$ -KG dh	-33	Negative
5	Succinyl-CoA synthase	-20.1	~0
6	Succinate dh	+6	~0
7	Fumarase	-3.4	~0
8	Malate dh	+29.7	~0

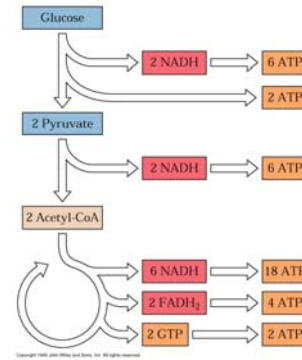
## The points of regulation of the cycle



**Citric acid cycle intermediates are always in flux**



**A single molecule of glucose can potentially yield ~38 molecules of ATP**



**Next Lecture  
Thursday 11/19/09  
Exam II Review**