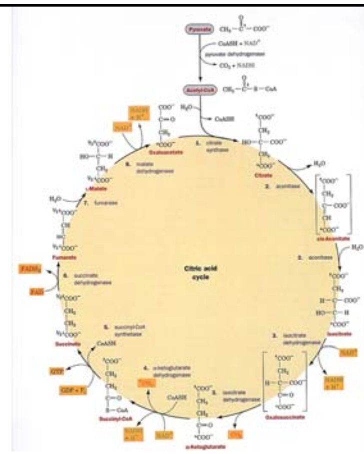
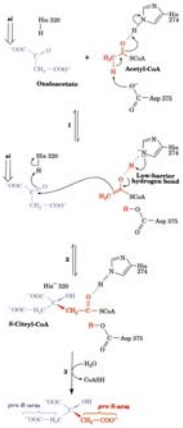
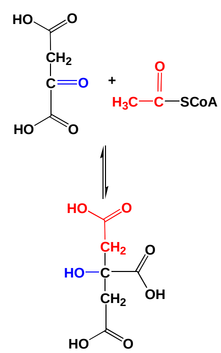
TCA & Pentose Phosphate Pathway
12/01/2009

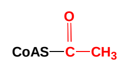


Citrate Synthase

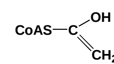




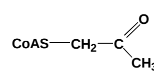
Induced fit needs binding of oxaloacetate before Acetyl CoA can bind.



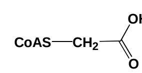
Acetyl-CoA



Proposed intermediate

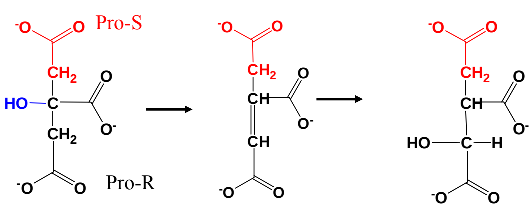


Acetonly CoA
(ground-state analog)



Carboxymethyl-CoA
(transition state analog)

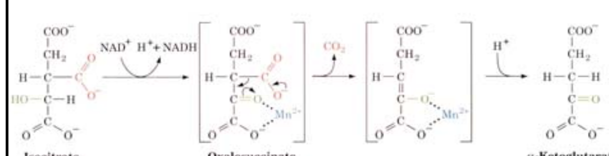
Aconitase



Citrate   Cis-Aconitate   Isocitrate

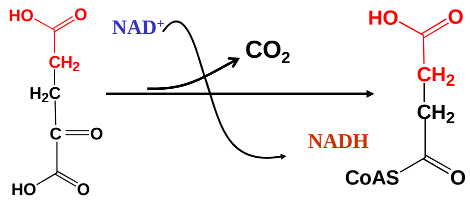
The double bond is placed on the Pro-R arm

NAD$^+$- Dependent Isocitrate dehydrogenase



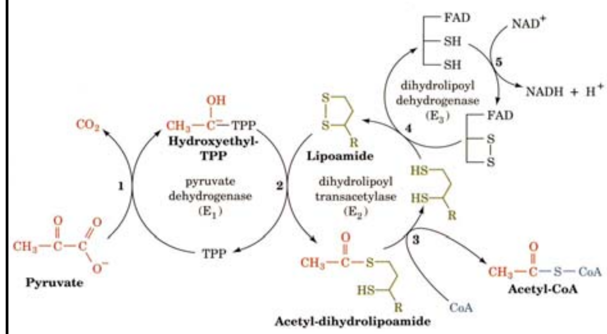
NAD$^+$ ⟶ NADH

α-Ketoglutarate dehydrogenase

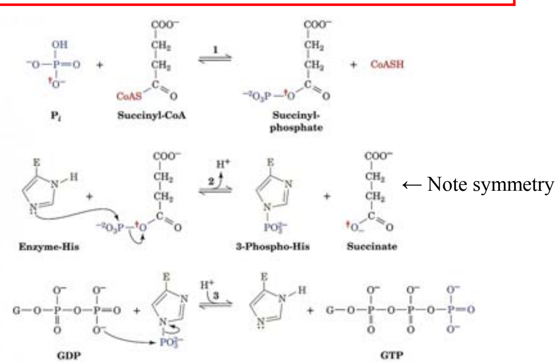


This enzyme is just like pyruvate dehydrogenase, a multi enzyme complex that is specific for longer CoA derivatives

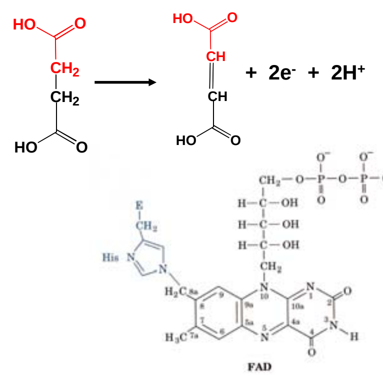
Refresh:The five reactions of the pyruvate dehydrogenase multi enzyme complex



Succinyl-CoA Synthetase or succinate thiokinase



Succinate dehydrogenase

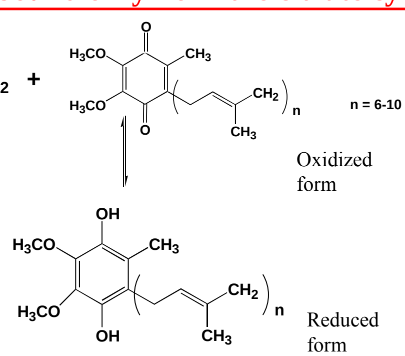


The FAD on the enzyme itself is reduced

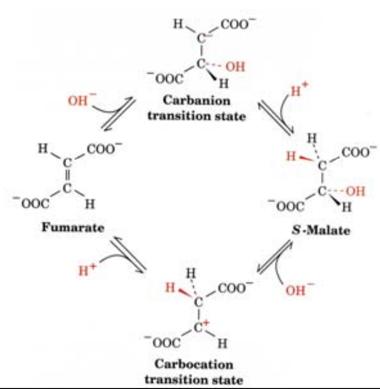
Succinate dehydrogenase is the only membrane bound enzyme in the citrate cycle

Succ dh--$FADH_2$ +

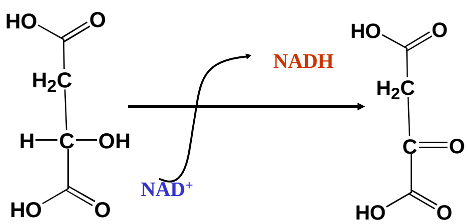
Ubiquinone or Coenzyme Q



Fumarase



Malate dehydrogenase

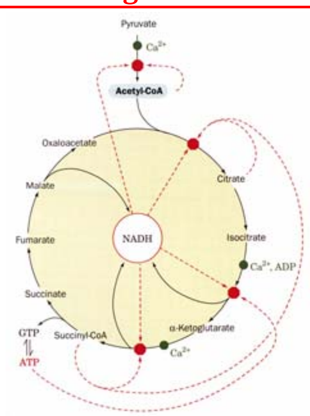


Regulation of the citric acid cycle

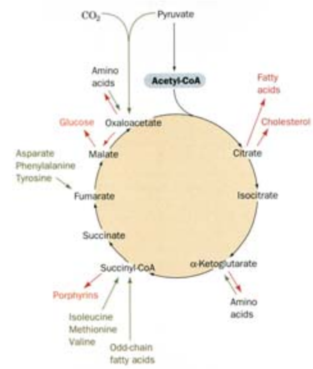
Standard free energy changes in the citric acid cycle

Reaction	Enzyme	ΔG°'	ΔG'
1	Citrate synthase	-31.5	Negative
2	Aconitase	~5	~0
3	Isocitrate dh	-21	Negative
4	α-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

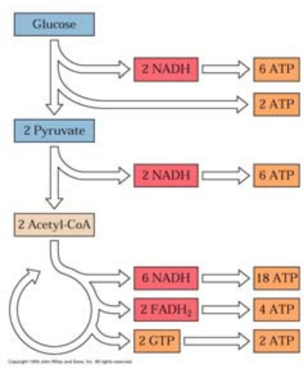
The points of regulation of the cycle



Citric acid cycle intermediates are always in flux



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



Phosphopentose pathway

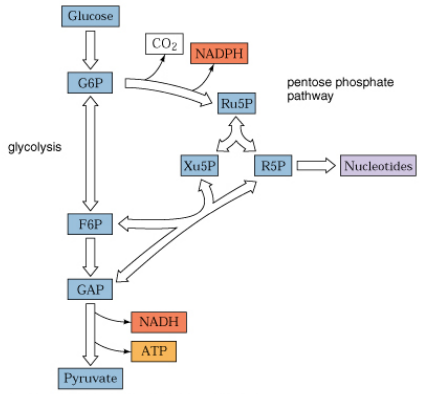
Produces NADPH and ribose-5-phosphate

NADH and NADPH although chemically similar they are not metabolically exchangeable.

Ratios of [NAD+]/[NADH] ~ 1000 favors metabolite oxidation, whereas ratios of [NADP+]/[NADPH] ~ 0.01 favors reductive biosynthesis.

Many anabolic pathways require the reducing power of NADPH for synthesis including Fatty acid synthesis and the synthesis of cholesterol.

$$3G\text{-}6\text{-}P + 6NADP^+ + 3H_2O \longrightarrow 6NADPH + 6H^+ + 3CO_2 + 2F6P + GAP$$



The pathway consists of three parts

1. Oxidative reactions:

3G-6-P + 6NADP$^+$ + 3H_2O 6NADPH + 3CO_2 + 3Ribulose-5-PO_4

2. Isomerization and epimerization reactions:

3Ribulose-5-PO_4 Ribose -5-PO_4 + 2Xylulose-5-PO_4

3. A series of C-C bond cleavage and formations:

Ribose-5-PO_4 + 2Xyluose-5-PO_4 2F-6-P + GAP

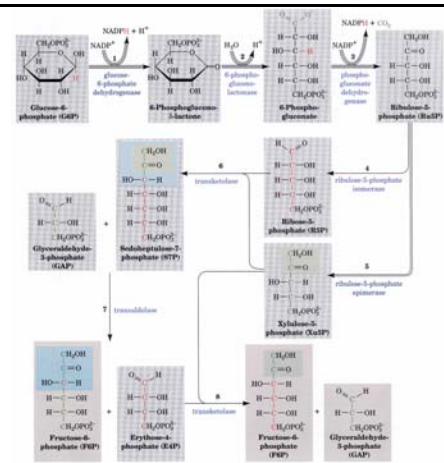
The transition of carbon skeletons in the Phosphopentose pathway

$$(6)\quad C_5 + C_5 \rightleftharpoons C_7 + C_3$$

$$(7)\quad C_7 + C_3 \rightleftharpoons C_6 + C_4$$

$$(8)\quad C_5 + C_4 \rightleftharpoons C_6 + C_3$$

$$(\text{Sum})\quad 3C_5 \rightleftharpoons 2C_6 + C_3$$



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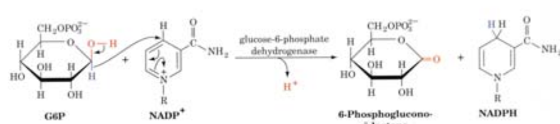
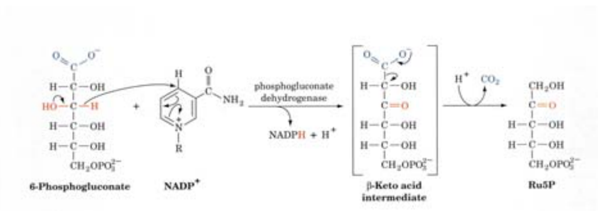
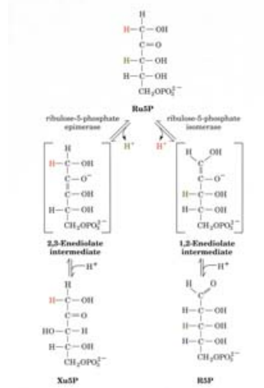
Glucose-6 phosphate dehydrogenase



Phosphogluconate dehydrogenase



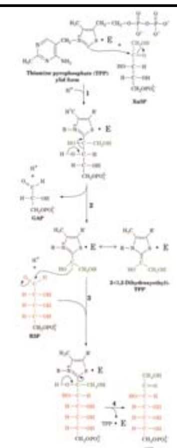
Ribulose-5-PO_4 isomerase



Two enzymes control the rearrangement of carbon skeletons which result in the production of Glyceraldehyde-3-phosphate and Fructose-6-phosphate.

Transketolase transfers C2 units: TPP requiring enzyme like pyruvate dehydrogenase

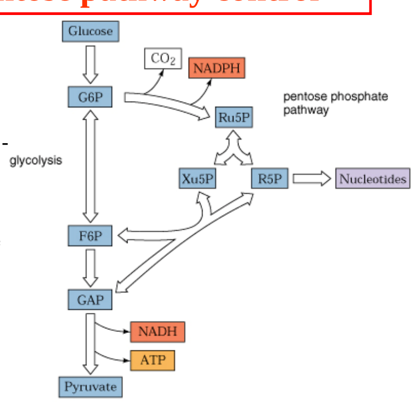
Transaldolase transfers C3 units: uses a shiffs base with an active lysine group



Transketolase requires TPP

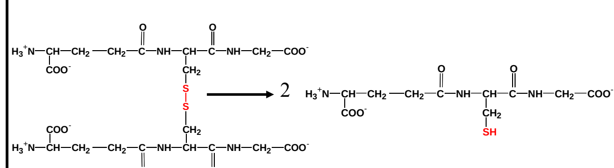
The pentose pathway control

The need for NADPH is controlled by glucose dehydrogenase, however, when ribose - 5-phosphate is needed (DNA and RNA synthesis) it can be made from the reverse of the transaldolase and transketolase reactions from Fructose-6-PO_4 and GAP



NADPH is needed for glutathione reductase

Reduced glutathione is needed for glutathione peroxidase, which destroy hydrogen peroxide and organic peroxides. This enzyme requires selenium as a cofactor.



Glutathione keeps proteins with reduced sulfhydryls

—SH from oxidizing to R—S—S—R'

P-SH + P'-SH + O_2 ⟶ P-S-S-P' + H_2O

P-S-S-P'

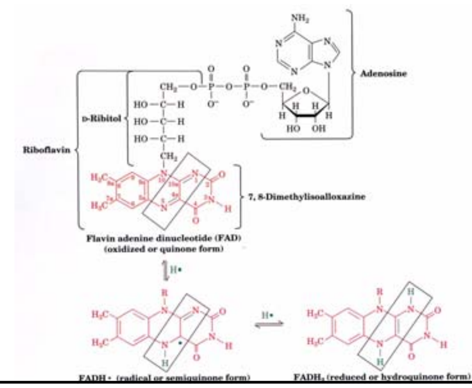
↓ **G-SH**

P-SH + G-S-S-P

↓ **G-SH**

G-S-S-G + HS-P

Glutathione reductase contains FAD



Reaction of glutathione with peroxides

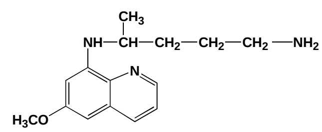
2GSH + RA-O-O-H ⟶ G-S-S-H + ROH + H_2O

A **steady supply of glutathione is required for erythrocyte integrity**

~ 400,000,000 individuals are deficient in glucose dehydrogenase!

Without a fully functioning glucose dehydrogenase, glutathione concentrations Hemolytic Anemia can occur if certain drugs are used.

Primaquine, an antimalarial drug is problematic with individuals with glucose dehydrogenase deficiencies



Primaquine

Similar effects are seen when people eat Fava beans. Fava beans stimulate peroxide formation and the demand for NADPH can not be met.

Mature red blood cells lack a nucleus and the ability to make new proteins and membranes. Damage cannot be repaired so cells lyse.

A defective G-6-P dh confers a selective advantage on individuals living where malaria is endemic. However, only heterozygotic females are resistant to malaria, not males. *Plasmodium falciparum* can adopt to a cell with decreased levels of phosphopentose products. This enzyme is in the X chromosome and females with two x chromosomes produce half good and half bad blood cells. Plasmodium cannot adapt to the G-6-P dh deficiency if it is sporadic or random.

Next (Last) Lecture Tuesday 12/03/09 Comprehensive Exam Review Session