BI/CH 422/622

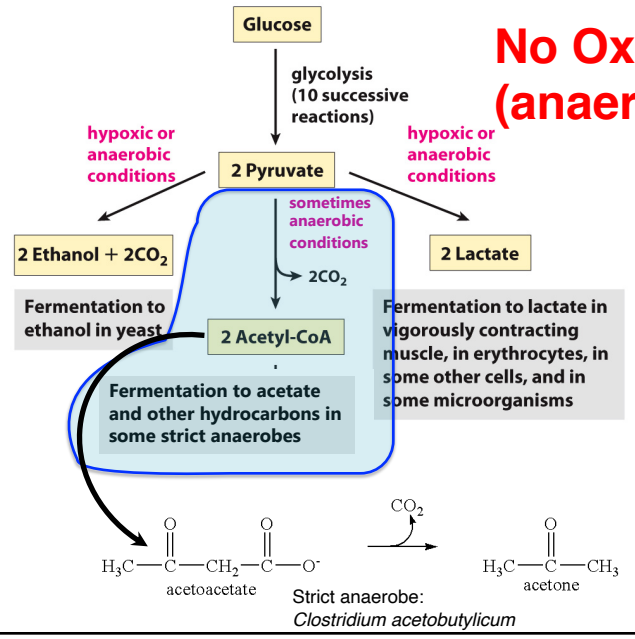
OUTLINE:

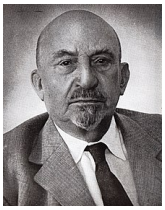
Introduction and review
Transport
Glycogenolysis
Glycolysis
- Introduction & overview; 2 phases
- Phase I
- Phase II
- Summary: logic, energetics, labeling studies

Other sugars
Pasteur: Anaerobic vs Aerobic
Fermentations
- Lactate-lactate dehydrogenase
- Acetoacetate decarboxylase
- Ethanol-pyruvate decarboxylase & alcohol dehydrogenase

Pyruvate
- pyruvate dehydrogenase complex

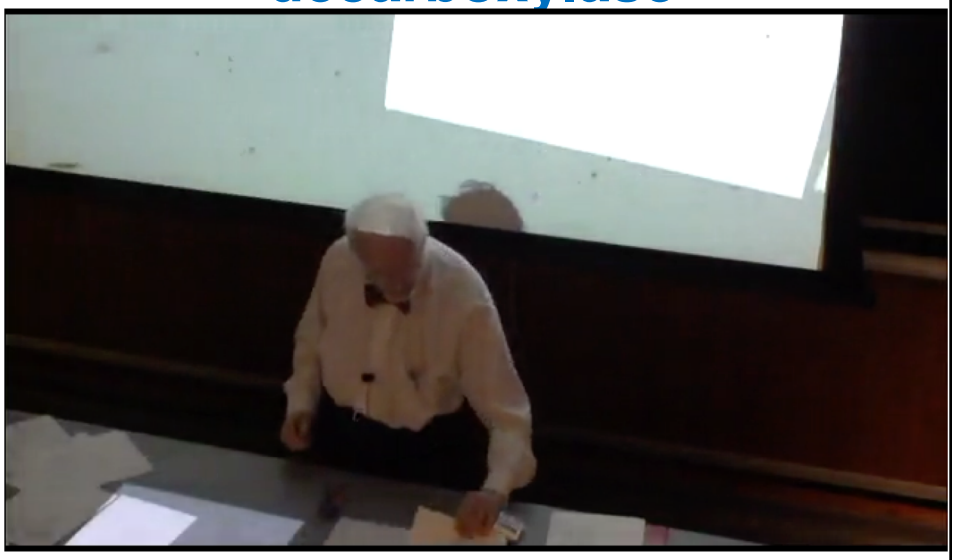
Fates of Pyruvate



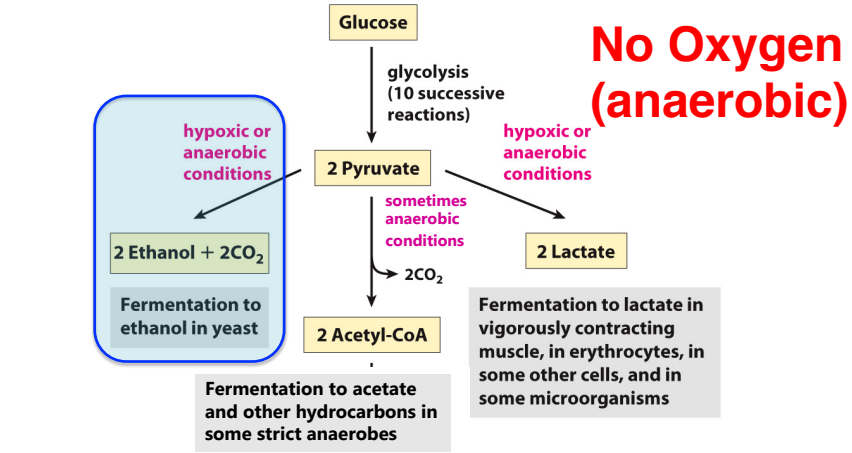


Chaim Weizmann

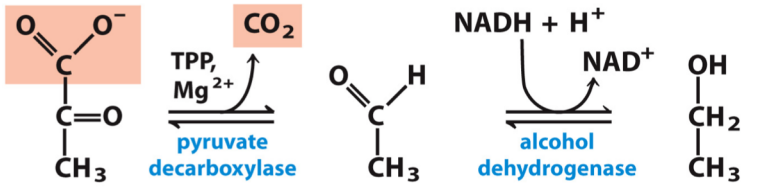
Fermentation: Acetoacetate decarboxylase



Fates of Pyruvate

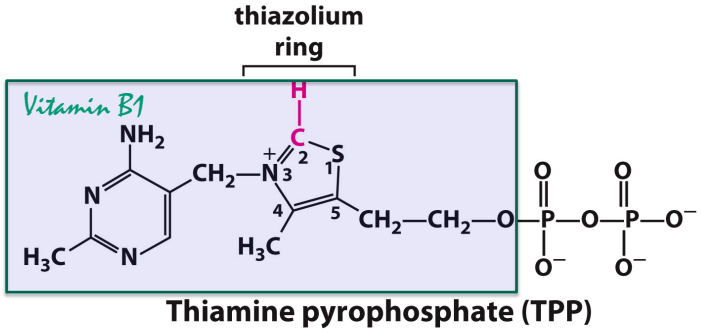


Fermentation: Ethanol



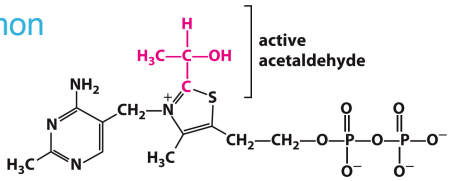
- Two-step reduction of pyruvate to ethanol
- Humans do not have pyruvate decarboxylase.
- Humans express alcohol dehydrogenase for ethanol metabolism, but is largely used in the reverse reaction, then *aldehyde dehydrogenase* takes it to acetate (recall the different forms with different K_m values for why some people get flush).
- Both steps require cofactors.
  - pyruvate decarboxylase: Mg^{++} and thiamine pyrophosphate (TPP)
  - alcohol dehydrogenase: Zn^{++} and NAD^+
- CO_2 produced in the first step is responsible for:
  - carbonation in beer
  - dough rising when baking bread

Fermentation: Pyruvate decarboxylase



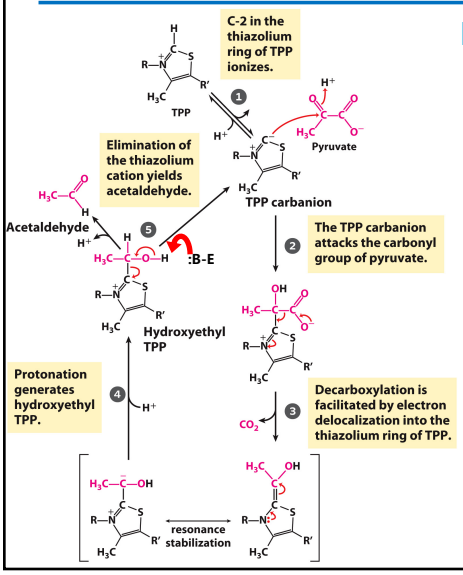
Thiamine pyrophosphate (TPP)

TPP is a Common Acetaldehyde Carrier



Hydroxyethyl thiamine pyrophosphate

Fermentation: Pyruvate decarboxylase

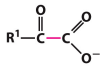
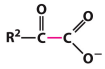
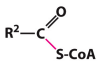
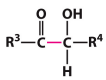
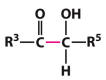


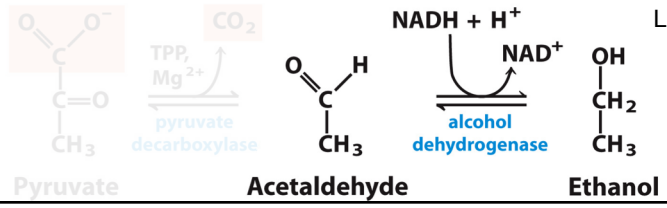
Is a Common Acetaldehyde Carrier

- TPP forms a covalent bond with carbonyl carbon, forming an alcohol, and resulting in release of CO_2.
- TPP then allows rearrangement of and protonation of carbonyl carbon to release from complex.

Fermentation: Pyruvate decarboxylase

TABLE 14-1 Some TPP-Dependent Reactions

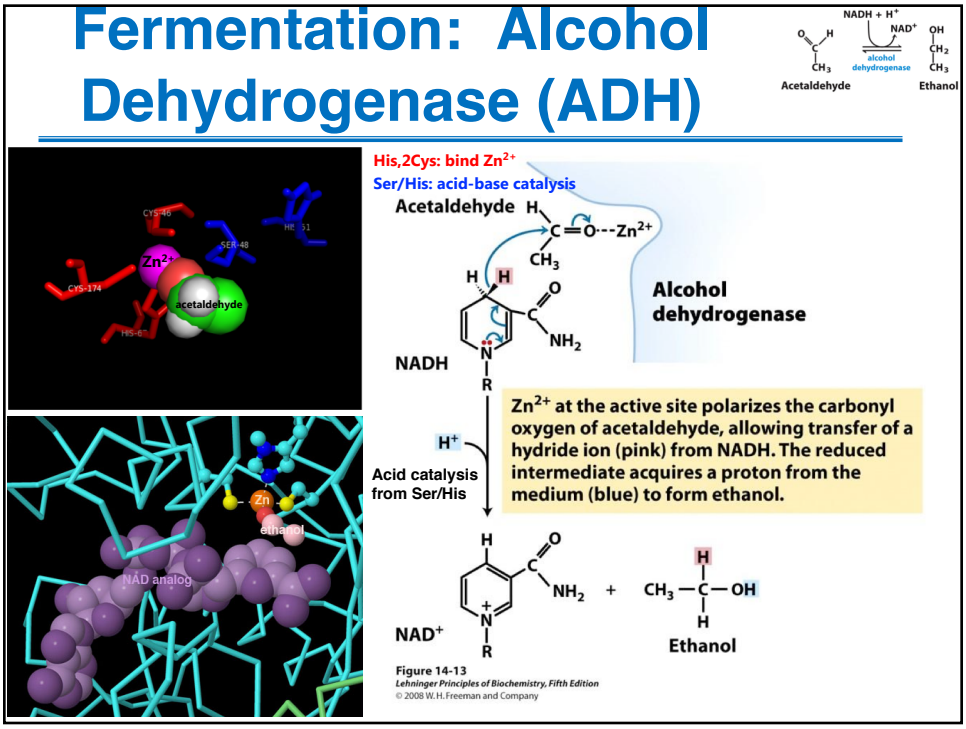
Enzyme	Pathway(s)	Bond cleaved	Bond formed
Pyruvate decarboxylase	Ethanol fermentation		
Pyruvate dehydrogenase α-Ketoglutarate dehydrogenase	Synthesis of acetyl-CoA Citric acid cycle		
Transketolase	Carbon-assimilation reactions Pentose phosphate pathway		



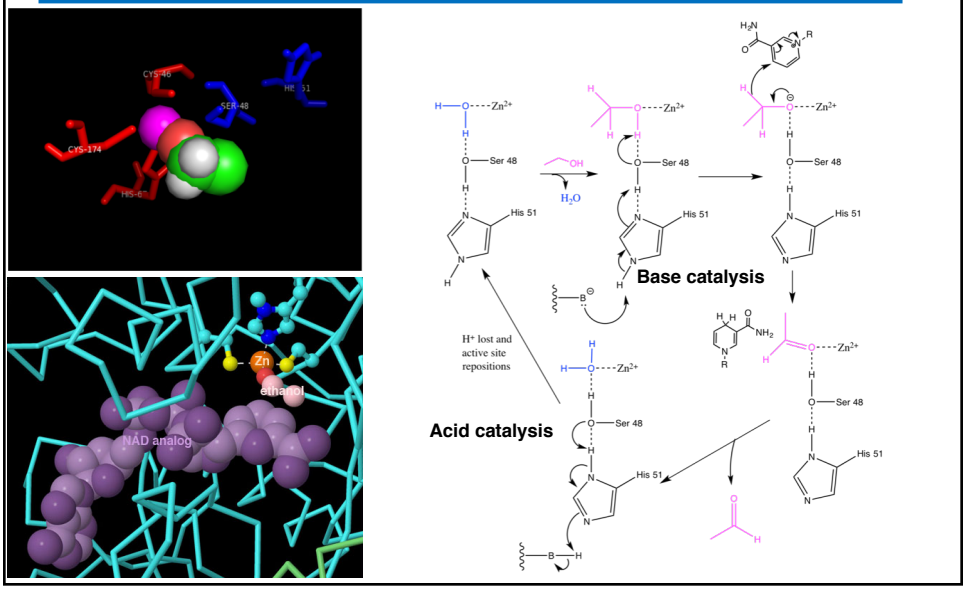
Like LDH, highly thermodynamically favorable ($\Delta G^{\circ\prime}$ = –6 kcal/mol)

This reaction pulls the entire fermentation pathway.

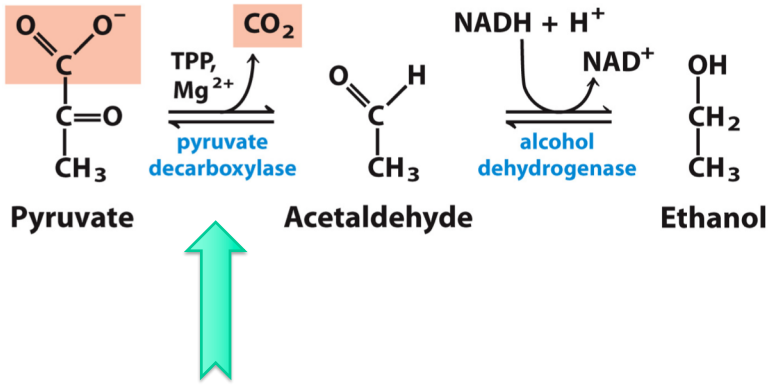
Fermentation: Alcohol Dehydrogenase (ADH)



Fermentation: Alcohol Dehydrogenase (ADH)

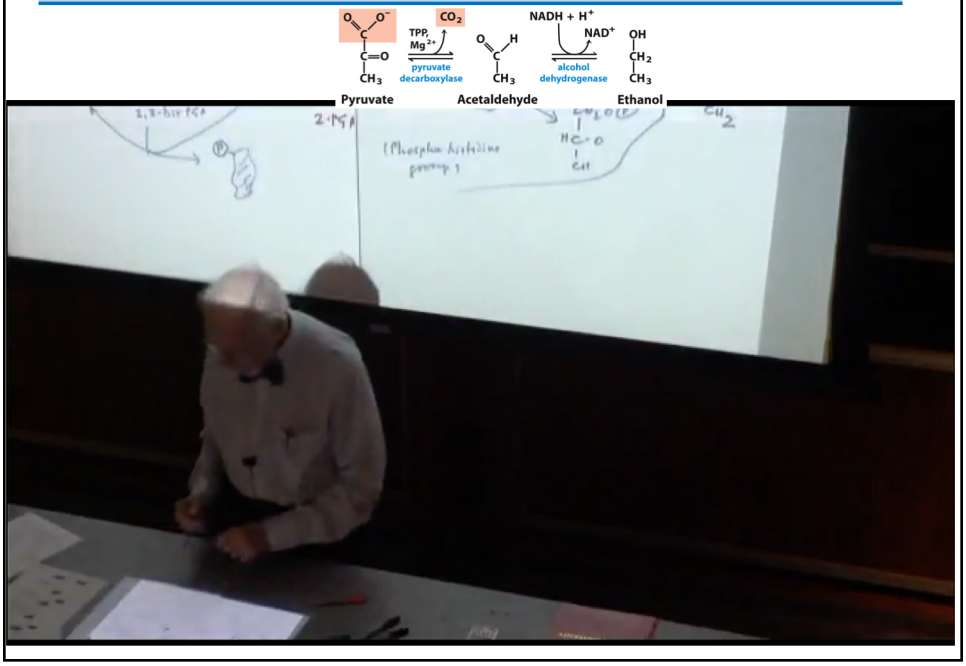


Fermentation: Ethanol

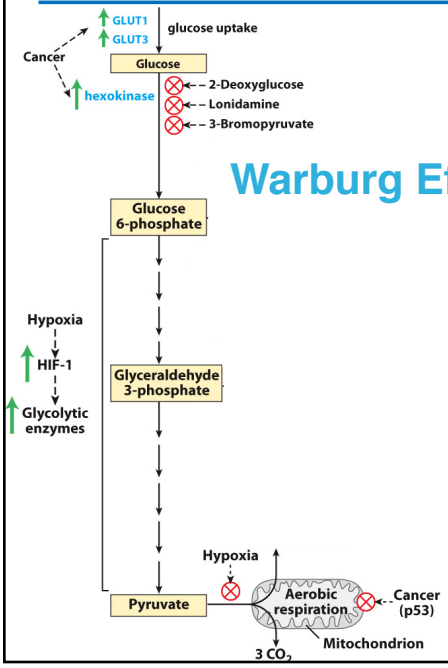


Humans are missing the gene for this enzyme.

Fermentation: Ethanol



Fermentation

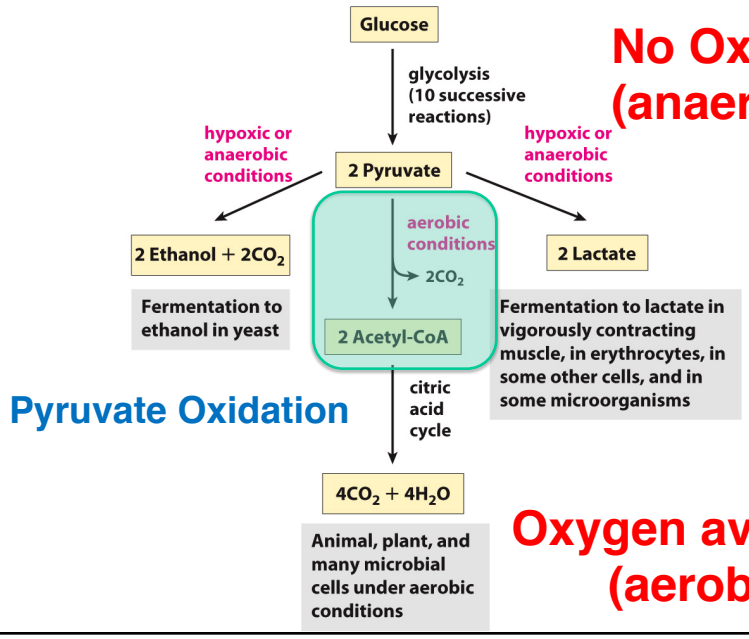


Glycolysis Occurs at Elevated Rates in Tumor Cells

Warburg Effect

- Tumor cells often grow faster than angiogenesis allows growth of capillaries to aerate them, resulting in anaerobic metabolism.
- Tumor cells increased expression of LDH.
- Use to generate intermediates
- Compounds that inhibit key steps in glycolysis can kill cancer cells by limiting energy production.

Fates of Pyruvate

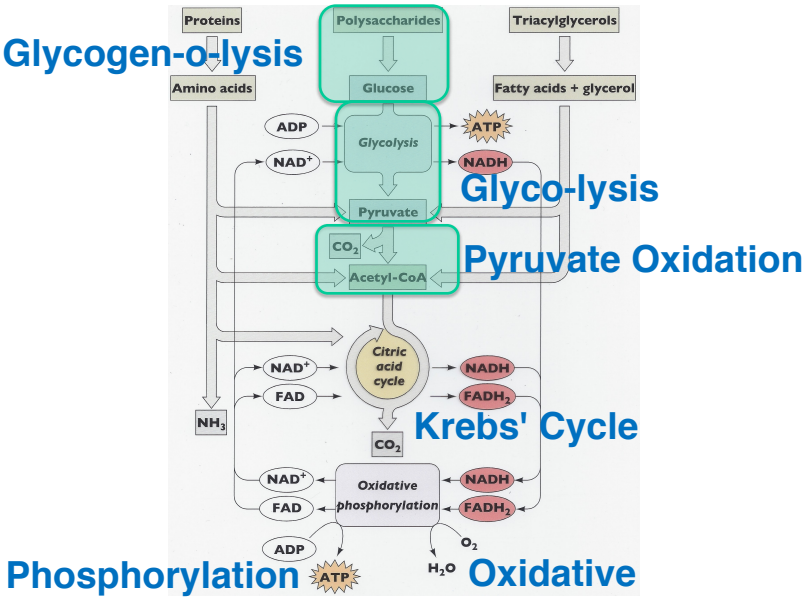


Pyruvate Oxidation

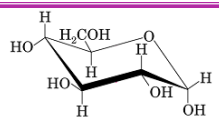
ONLY when O_2 is present

- This is why its called cellular *respiration.*
- The end result will be the COMPLETE oxidation of carbon to CO_2

Pyruvate Oxidation



Pyruvate Oxidation

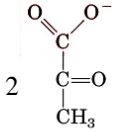


GLUCOSE

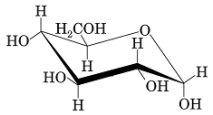
Glycolysis

$\Delta G'^{\circ} = -35$ kcal/mol

(–146 kJ/mol)



2 Pyruvate



Respiration (+ 6 O_2)

$\Delta G'^{\circ} = -678$ kcal/mol

(–2,840 kJ/mol)

6 CO_2 + 6 H_2O

- Process in which cells consume O_2 and produce CO_2
- Provides more energy (ATP) per glucose than glycolysis
- Process is slower than glycolysis
- Evolutionary origin: developed about 2,500 mya
- Used by animals, plants, and many microorganisms
- Other fuel sources (lipids and AA) converge on respiration.

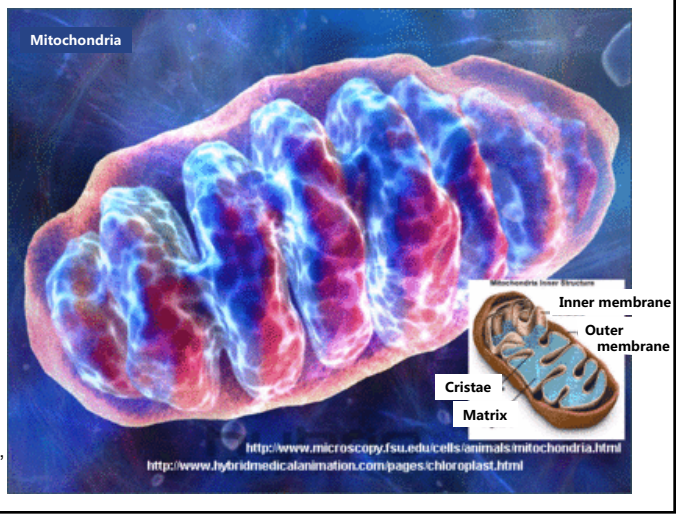
Occurs in three major stages:

1) Pyruvate oxidation (acetyl CoA production)
2) acetyl CoA oxidation (CO_2 production)
3) electron transfer and oxidative phosphorylation (H_2O production)

Pyruvate Oxidation

Localization: In Eukaryotes, Respiration is Localized to the Mitochondria (Compartmentation)

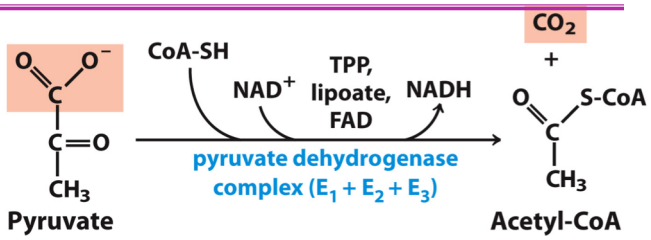
- Glycolysis occurs in the cytoplasm.
- Pyruvate Oxidation and Citric Acid Cycle occurs in the mitochondrial matrix.†
- Fantastic example of *Compartmentation*.
- Oxidative phosphorylation occurs in the inner membrane.



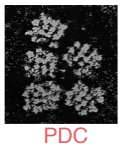
†Except succinate dehydrogenase, which is located in the inner membrane

Pyruvate Oxidation

Conversion of Pyruvate to Acetyl-CoA



- Net reaction:
  - oxidative decarboxylation of pyruvate
    - Means pyruvate will get oxidized as the carboxylate leaves (as CO_2)
  - first carbons of glucose to be fully oxidized (C3 & C4)
- Fairly simple reaction done by a complicated process.
- Highly thermodynamically favorable/irreversible ($\Delta G^{\circ\prime} = -8$ kcal/mol); mostly due to the loss of CO_2
- Catalyzed by the **Pyruvate Dehydrogenase Complex (PDC)**
  - Three main enzyme, each with multiple subunits: E1, E2, E3
  - Regulatory subunits: PD kinase & PD phosphatase
  - Overall structure of $E1_{96}$, $E2_{24}$, $E3_{24}$
  - requires 5 coenzymes
  - TPP, lipoic acid, and FAD are prosthetic groups.
  - NAD^+ and CoA-SH are co-substrates.



PDC