Where do NADH and FADH$_2$ come from??

Glycolysis and Citric Acid Cycle

**Lecture 8**

* Glycolysis

Citric acid cycle = Tricarboxylic acid (TCA) cycle = Krebs cycle

Anaerobic pathways

Catabolism of other carbon sources

Regulation of catabolic pathways

**Metabolic web**

Catabolic pathways yielding energy and building blocks

- Stage 1
  - Polymers to monomers

- Stage 2
  - Monomers to acetyl CoA
  - Yields limited ATP and NADH

- Stage 3
  - Oxidation of acetyl CoA to CO$_2$
  - Yields lots of NADH for respiration

Glycolysis (in cytosol)

Citric Acid Cycle (in mitochondrial matrix)
Energy must be released in small steps to be useful to the cell.

### Glycolysis overview

**Glucose (6 Carbons) → 2 Pyruvate (2 X 3 carbons) + energy**

**Three phases:**

1. **Input of energy (3 steps)**
2. **Cleavage of the 6-carbon molecule to 2 3-carbon molecules (2 steps)**
3. **Energy producing steps (5 steps)**

**ECB 13-1**

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**Glycolysis - phase 1 - input of energy**

6 carbon  → glucose

Hexokinase (Phosphorylation)

ATP → ADP

6 carbon  → glucose-6-phosphate

Phosphoglucone isomerase (6 member ring to 5 member ring)

6 carbon  → fructose-6-phosphate

Phosphofructokinase (Phosphorylation)

fructose, 6-phosphate → ATP → ADP

6 carbon  → 1,6-bisphosphate

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2
**Glycolysis - phase 2** - cleavage of the 6-carbon compound into two 3-carbon compounds

6 carbon

Fructose 1,6-bisphosphate

Aldolase

Dihydroxyacetone phosphate

3 carbon

Triose isomerase

Glyceraldehyde 3-phosphate

3 carbon

Glycolysis - phase 3 - Energy-producing steps

3 carbon

Glyceraldehyde 3-phosphate

NAD+ NADH

1,3-bisphosphoglycerate

NAD+ NADH

Glyceraldehyde 3-phosphate dehydrogenase

Phosphoglycerate kinase

Phosphoglyceromutase

Enolase

Pyruvate kinase

Pyruvate

Structures in Panel 13-1

Energy conversions in steps 6 & 7

Don't need to know structures or enzymes, but know energy conversions
Glycolysis - energy yield

Three phases:

1. Input of energy (3 steps)
   - 1.6-Carbon (glucose) to 1.6-carbon (fructose 1,6-bisphosphate)
     - 2 ATP used

2. Cleavage of the 6-carbon cmpd to 2 3-carbon cmpds (2 steps)
   - 1.6-carbon (fructose 1,6-bisphosphate) to 2 3-carbon (glyceraldehyde 3-phosphate)
     - No energy use/production

3. Energy producing steps (5 steps)
   - 2 3-carbon (glyceraldehyde 3-phosphate) to 2 3-carbon (pyruvate)
     - 1 NADH and 2 ATP per 3C compound
     - 2 NADH and 4 ATP total

Net yield: 2 NADH + 2 ATP

Lecture 8

Glycolysis

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Summary of Citric Acid Cycle (mitochondrial matrix)

Pyruvate imported into mitochondria under aerobic conditions

Converted to acetyl CoA

Acetyl CoA enters the TCA cycle

Energy captured as NADH (FADH, GTP)

EC 13.7

EB 13.7
In mitochondrial matrix

**Pyruvate to acetyl CoA**

Pyruvate dehydrogenase complex

NAD+ → NADH

2-carbon pyruvate → 3-carbon pyruvate → Acetyl CoA

$\text{CH}_3\text{COOH}$ → $\text{CH}_3\text{CO}^+\text{CoA}$

See ECB 13-8

**Acetyl CoA structure**

Acetyl CoA

ATP

Adenine

Ribose

ECB 3-37

**Overview of Citric Acid Cycle**

Input: 2-carbon acetyl CoA

Circular pathway ("cycle") composed of 8 steps

2 acetyl groups completely oxidized to 2 CO$_2$

Yields 3 NADH, 1 FADH$_2$, and 1 GTP per acetyl CoA
Summarize Citric Acid Cycle

8 steps that generate a circular path ("cycle")

"our city is kept safe and sound from menaces"
Glycolysis and TCA cycle completely oxidize glucose to CO₂ and H₂O.

Energy is stored as reducing power (NADH, FADH₂), high energy phosphate bonds (ATP, GTP) and covalent bond energy (CO₂, H₂O).

Glycolysis: glucose to 2 pyruvate:
Glucose (6C) to 2 pyruvate (2 X 3C)
2 NADH + 2 ATP per glucose

Pyruvate dehydrogenase step:
Pyruvate (3C) to Acetyl CoA (2C)
1 NADH per pyruvate
2 NADH per glucose

Citric Acid Cycle:
Acetyl CoA (2C) to 2 CO₂
3 NADH + 1 FADH + 1 GTP per Acetyl CoA
6 NADH + 2 FADH + 2 GTP per glucose

Combined: 10 NADH + 2 FADH + 4 ATP

Each NADH and FADH₂ donates 2 e⁻ to mitochondrial e⁻ transport chain.

Recall 10 H⁺ moved per NADH, 6 H⁺ per FADH₂.
Bookkeeping of ATP yield
Per glucose: 10 NADH + 2 FADH + 4 ATP per glucose

ATP Synthase:
  4 H+ per ATP

NADH:
  10 H+ per NADH
  So: 2.5 ATP per NADH
  10 NADH x 2.5 ATP/NADH = 25 ATP

FADH₂:
  6 H+ per FADH₂
  So 1.5 ATP per FADH₂
  2 FADH₂ x 1.5 ATP/FADH₂ = 3 ATP

1 glucose = 25 ATP (NADH) + 3 ATP (FADH₂) + 4 ATP = 32 ATP

Efficiency of glycolysis and respiration

\[ \Delta G_{\text{gly + resp}} = -686 \text{ Kcal/mol} \]

Make 32 ATP
  Hydrolysis of 1 ATP yields 7.4 to 11 kcal/mol
  32 x 7.4 = 237 kcal/mol are captured in ATP
  \( \frac{32 x 7.4}{686} \approx 0.35 \text{ or 35\% of total energy released is captured} \)
  \( \Delta E = W + q \) (much energy is lost as heat)

Energy conversions from glycolysis to oxidative phosphorylation

Glycolysis - covalent bond energy of glucose is converted to bond energy of pyruvate and ATP, plus reducing power in NADH

Citric Acid Cycle - bond energy of acetyl CoA is converted to bond energy of CO₂ and GTP, plus reducing power of NADH and FADH₂

Respiration - Electron transport - reducing power of NADH and FADH₂ is converted to electrochemical gradient of H⁺

Oxidative phosphorylation - electrochemical gradient of H⁺ is converted to bond energy of ATP
Lecture 8

Glycolysis

Citric Acid Cycle

*Anaerobic pathways

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Regulation of catabolic pathways

Mitochondrial e- transport stops in the absence of O$_2$

Oxygen is the terminal electron acceptor

What happens?

Anaerobic metabolism-fermentation

Purpose of anaerobic metabolism is to regenerate NAD$^+$

Muscle

Yeast
Lecture 8

Glycolysis
Citric Acid Cycle
Anaerobic pathways
*Catabolism of other carbon sources
Regulation of catabolic pathways

Proteins as C source

Energy stored as polysaccharide and lipids

Glycogen (similar to starch)

Triacylglycerol (fat or oil)
Fatty Acid catabolized by β-oxidation (cyclic pathway)

- FA shorter by 2 carbons; repeat pathway
- Energy from oxidation of alcohol to ketone

Glycolysis and Citric Acid Cycle Provide the Building Blocks for Biosynthesis (Anabolic pathways)

- ECB 13-23

Chloroplasts and mitochondria act together to provide metabolites and energy

- ECB 13-22

Chloroplast exports sugars, not ATP or NADPH
Mitochondrion exports ATP
Global carbon cycle

CO₂ levels are rising

Greenhouse effect

Rise in CO₂ does not cause rise in photosynthesis due to other limitations (e.g., nutrients)

C=O absorbs IR radiated by Earth after solar heating; predicts atmosphere is warming
Global temperatures

Last 1000 years

Reservoirs of CO₂

Carbon Dioxide is Exchanged Between Three Major Reservoirs

THE ATMOSPHERE

THE OCEANS

THE LANDS

Most of the CO₂ fluxes are from biological sources

Burning of fossil fuels takes net balance from negative to positive (emission)

Can discriminate CO₂ from fossil fuels from other sources (resp.) by its isotopic composition (C13, C14)

Global Carbon Cycle Fluxes

IPCC (2001)
Seasonal variation in atmospheric CO₂ levels

Seasonal variation in photosynthesis and respiration in temperate zone
- Low CO₂ at height of summer in northern hemisphere
- Time of maximum photosynthesis

Seasonal variation in CO₂ is limited to northern hemisphere

Land mass of Earth is mainly in northern hemisphere, hence variation in photosynthesis and respiration are magnified.