Introduction to Metabolism

• Metabolic Pathways
  • Catabolism vs Anabolism
• Pathways for energy production
  • Glycolysis
  • Citric acid (TCA, Krebs) cycle
  • Electron transport
• Enzyme nomenclature
• ATP as energy currency
• Redox reactions
  • balancing
  • NAD and FAD
  • ½ reactions
Metabolic Pathways

- Conserved in different organisms
- Each step consists of small changes
- Overall irreversible (but most of the individual steps are not)
- Regulated (usually at initial step(s))
- Usually committed after the initial steps
- Compartmentalized in eukaryotes
What you need to know:

- **Input and output** metabolites
- Steps that control flux
- How flux through pathway is controlled
- Cellular location of metabolic steps
- Selected enzyme mechanisms
- Selected substrates/products
- **DO NOT Memorize** Pathway!!!!!!
• Catabolism (degradative)
  – Conversion of a diverse set of compounds to a small number of simple compounds for energy production

• Anabolism (synthetic)
  – Conversion of a small number of simple compounds to complex organic molecules
Catabolic and anabolic pathways with common compounds....

- Often these share enzymes
  
  1  2  3  2  1  4
  
  \[A \rightarrow B \rightarrow C \rightarrow D\]
  \[C \rightarrow B \rightarrow A\]
  \[D \rightarrow C\]

- Key steps utilize different enzymes
  - These steps are regulated so the cell is not making and degrading the same molecules at the same time
  - Unique reactions include at least one in which the reverse reaction is energetically unfavorable

- Ways to regulate catabolism vs. anabolism
  - Substrate concentration, allosteric regulation, compartmentalization
  - Common themes we will see over the next few weeks.
Central Pathways of Energy Production:

- **Intracellular locations**
  - Glycolysis - Cytosol
  - Fatty Acid Oxidation: Inner matrix of mitochondria
  - Citric Acid Cycle (TCA): Inner matrix of mitochondria
  - Oxidative Phosphorylation: Inner membrane of mitochondria
Energy Transactions: Organic compounds (e.g. glucose) → Electron Carriers (NADH, FADH$_2$) → Proton Gradient → ATP

Energy Utilization:
Chemical synthesis reactions (e.g. protein synthesis, DNA synthesis)
Mechanical work (e.g. transport, muscle function)
Electrical work (e.g. nerve conduction)
General Enzyme Nomenclature:

Name - usually consists of three parts:
i) the substrate is used to name the enzyme, Keep in mind that many enzymatic reactions run in both directions in metabolism, consequently the “product” may be used to name the enzyme.
ii) the nature of the chemical reaction.
iii) Most names end in “ase”

Examples: amylase and cellulase
A. **Phosphatase**: Removes a phosphate group from a substrate, via hydrolysis – no ATP/ADP involved. e.g. glucose-6 phosphatase.

B. **Kinase**: transfers a phosphate group from ATP to another compound e.g. hexokinase.

C. **Dehydrogenase**: Removes/adds hydrogens by oxidation/reduction. Usually require NAD⁺/NADH or FAD/FADH₂ as co-factors/co-substrates. e.g. succinate dehydrogenase.
ATP and phosphate hydrolysis

Reduces electrostatic repulsion

\[
\Delta G^\circ = -30 \text{Kj/mol}
\]

\[
\Delta G^\circ = -15 \text{Kj/mol}
\]
Redox chemistry

- $\text{Fe}^{3+} + \text{Cu}^+ \leftrightarrow \text{Fe}^{2+} + \text{Cu}^{2+}$

This can be broken down into two half reactions:

1. $\text{Cu}^+ \leftrightarrow \text{Cu}^{2+} + e^-$ oxidation
2. $\text{Fe}^{3+} + e^- \leftrightarrow \text{Fe}^{2+}$ reduction

Loss of electrons or hydrogen atom ($H^+ + e^-$) = oxidation

Gain of electrons or hydrogen atom ($H^+ + e^-$) = reduction
Loss of electrons or hydrogen atom \((H^+ + e^-) = \text{oxidation}\)

Gain of electrons or hydrogen atom \((H^+ + e^-) = \text{reduction}\)

- LEO GER- lose electrons oxidation, gain electrons reduction
- OIL RIG- oxidation involves loss, reduction involves gain
• In general, an oxidized molecule loses energy, and the energy is captured by the reduced molecule that gains energy
Two steps for balancing an organic redox reaction

i) If oxygen is needed to balance the reaction, use $\text{H}_2\text{O}$.

ii) Use $\text{H}^+$, or $\text{H}^+ + \text{e}^-$, or $\text{e}^-$ to balance hydrogen atoms and/or charge.

Is it redox? A redox reaction has occurred if electrons are consumed or released
Examples of redox reactions

- Alkane $\rightleftharpoons$ Alkene

- Alcohol $\rightleftharpoons$ Ketone

Chemical reactions:

- $\text{alkane} + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{alkene}$
- $\text{alcohol} + 2\text{H}^+ + 2\text{e}^- \rightarrow \text{ketone}$
Is the conversion of an aldehyde to carboxylic acid a redox reaction?

\[
\text{aldehyde} \quad \overset{\text{H}_2\text{O}}{\rightleftharpoons} \quad \text{carboxylic acid}
\]

\[
\text{aldehyde} + \text{H}_2\text{O} \quad \rightleftharpoons \quad \text{carboxylic acid}
\]
• Example: Is the conversion of ethene to ethanol a redox reaction?

\[ \text{H}_2\text{C} = \text{CH}_2 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{CH}_2\text{OH} \]

No electrons are consumed or gained, not a redox reaction...
Organic electron carriers (Redox couples)

- Two compounds are widely used in biological reductions and oxidations. These are *nicotinamide adenine dinucleotide* (**NAD**) and *flavin adenine dinucleotide* (**FAD**).
NAD+ is loosely bound to enzyme and is a co-substrate
FAD is tightly bound to enzymes and is thus considered a **cofactor**, i.e. an essential non-amino acid component of an enzyme.
Lecture 27: Introduction to Metabolism

Key Points
- Metabolic pathways
- Anabolism vs. catabolism
- Energy production and location
- Enzyme nomenclature
- ATP energy content
- Redox reactions
- Half-reactions

Metabolic pathways are:
1. Conserved in different organisms.
2. Consist of a number of small changes
3. Overall irreversible (but most of the individual steps are not)
4. Usually committed after the initial steps
5. Regulated (usually at initial step(s))
6. Compartamentalized in eukaryotes

What you need to know:
1. Input and output metabolites
2. Steps that control flux
3. How flux through pathway is controlled
4. Cellular location of metabolic steps
5. Selected enzyme mechanisms
6. Selected substrates/products

What you should not do: Memorize pathways.

Catabolism [degradative] – conversion of a diverse set of compounds to a small number of simple compounds for energy production.

Anabolism [synthetic] – conversion of a small number of simple compounds to complex organic molecules.
- Shared enzymes in pathways
- Unique enzymes prevent waste of resources
- Control by substrate concentration, allosteric regulation and compartmentalization

Central Pathways of Energy Production:
Intracellular locations:
- Glycolysis - cytosol
- Fatty Acid Oxidation: Inner matrix of mitochondria
- Citric Acid Cycle (TCA): Inner matrix of mitochondria
- Oxidative Phosphorylation: Inner membrane of mitochondria

Energy Transactions: Organic compounds (e.g. glucose) → Electron Carriers→Proton Gradient → ATP

Energy Utilization:
- Chemical synthesis reactions (e.g. protein synthesis, DNA synthesis
- Mechanical work (e.g. transport, muscle function)
- Electrical work (e.g. nerve conduction)
General Enzyme Nomenclature:
Name - usually consists of three parts:
i) the substrate is used to name the enzyme,
   Keep in mind that many enzymatic reactions run in both directions in metabolism,
   consequently the “product” may be used to name the enzyme.
ii) the nature of the chemical reaction.
iii) most names end in “-ase”

A. Phosphatase: Removes a phosphate group from a substrate, via hydrolysis – no ATP/ADP involved. e.g. glucose-6 phosphatase.

B. Kinase: transfers a phosphate group from ATP to another compound e.g. hexokinase.

C. Dehydrogenase: Removes/adds hydrogens by oxidation/reduction. Usually require NAD+/NADH or FAD/FADH$_2$ as co-factors/co-substrates. e.g. succinate dehydrogenase.

Biochemical Energetics:
1. Phosphate Hydrolysis:

2. Electrons (Redox Chemistry)
An example of a redox reaction involving inorganic metals: $\text{Fe}^{3+} + \text{Cu}^+ \leftrightarrow \text{Fe}^{2+} + \text{Cu}^{2+}$
This reaction can be broken down into two balanced half reactions:

$\text{Fe}^{3+} + e^- \leftrightarrow \text{Fe}^{2+}$
$\text{Cu}^+ \leftrightarrow \text{Cu}^{2+} + e^-$

In this case the iron is reduced from the 3$^+$ state to the 2$^+$ state while the copper is oxidized from the 1$^+$ state to the 2$^+$ state.

In biological oxidations and reductions the electrons are often carried by protons (i.e. hydrogen atom). Thus a general rule for oxidation-reduction are:

* Loss of electrons or hydrogen atom ($H^+ + e^-$) = oxidation
  Gain of electrons or hydrogen atom = reduction

There are several common acronyms to help you remember the above, here are two:

LEO GER - lose electrons oxidation, gain electron reduction.
OIL RIG - oxidation involves loss, reduction involves gain.
In the case of biological systems the redox state of an organic molecule may be difficult to discern. The following shows the oxidation (loss of hydrogen atoms) of three functional groups. Note that all of these reactions involve a two electron transfer.

Balancing organic redox reactions. It can be difficult to determine whether a change in an organic compound is an oxidation or not. The two steps for balancing an organic redox reaction are:

i) If oxygen is needed to balance the reaction, use \( \text{H}_2\text{O} \).

ii) Use \( \text{H}^+, \text{H}^+ + e^- \), or \( e^- \) to balance hydrogen atoms and/or charge.

A redox reaction has occurred if electrons are consumed or released.

Example: Is the conversion of ethene to ethanol a redox reaction?

**Organic Electron Carriers (Redox Couples):** Two compounds are widely used in biological reductions and oxidations. These are *nicotinamide adenine dinucleotide (NAD)* and *flavin adenine dinucleotide (FAD)*. If these compounds are involved it’s a good bet that a 2 electron oxidation/reduction has occurred.

- **NAD**\(^+\) is loosely bound to enzymes and can thus be considered a true substrate. Usually, two electrons are transferred and one proton.

- **FAD** is tightly bound to enzymes and is thus considered a **cofactor**, i.e. an essential non-amino acid component of an enzyme.