Metabolism

What is it?

A set of chemical reactions that:
1. Allows organisms to extract energy from the environment
2. Allows organisms to synthesize the molecules necessary for life

Why study it?

1. The most central aspect of biochemistry
2. Constitutes much of the minimal set of chemical reactions required for life:
   
   Hemophilus influenza
   1700 proteins
   1/2 of proteins are metabolic enzymes
3. Longest studied and best understood aspect of biochemistry
4. Illustrates general principles of biochemistry
5. Many metabolic diseases

What do you need to know?

See Dr. Soukup’s diagram of metabolic pathways
You will know main reactions in these pathways
More importantly, you will know why it works, how it works, how it’s regulated
Understand the principles
Metabolism

Six principles

1. Metabolism is controlled kinetically by enzymes
2. Metabolic reactions occur in many small steps - “pathways”
3. A few important molecules carry the “currencies” of metabolism
4. Coupled reactions drive energy-requiring processes
5. Biosynthetic and degradative pathways are distinct
6. Metabolic pathways are regulated and integrated
Metabolism

1. Metabolism is controlled kinetically by enzymes

*How organic chemistry works:*
- One rxn per vessel
- Rxns go toward thermodynamic equilibrium
- Efficiencies of rxns <100%
- Few stereospecific rxns
- Extreme conditions used

*How metabolism works:*
- Hundreds of rxns simultaneously
- System maintained far from equilibrium
- Rxns extremely efficient, no accumulating intermediates
- Stereospecific rxns are the rule
- Everything occurs under constant conditions

*How do our bodies do this?*
- Under biological conditions most rxns slow - cells use enzymes to catalyze rxns
- 500-1000 different metabolic enzymes
- Cells control which rxns occur and how fast
Metabolism

2. Metabolic reactions occur in many small steps - “pathways”

Example: oxidation of glc to get energy

In organic chemistry:
\[ \text{C}_6\text{H}_{12}\text{O}_6 + 6\text{O}_2 \rightarrow 6\text{CO}_2 + 6\text{H}_2\text{O} + \text{flames} \quad \Delta G^\circ = -2840 \text{ kJ/mol} \]

In biochemistry:
~24 serial steps

Pathways = strings of rxns coupled together for a common purpose
Each pathway has a name

24 steps are divided into 3 pathways

\[ \text{Glucose} \quad \xrightarrow{\text{Glycolysis}} \quad \xrightarrow{\text{Citric acid cycle}} \quad \xrightarrow{\text{Oxidative phosphorylation}} \quad \text{CO}_2 + \text{H}_2\text{O} + \text{energy} \]

Glucose 10 steps 9 steps \sim 5 steps
2. Metabolic reactions occur in many small steps - “pathways”

Why so many steps?
Many enzymes in series result in complex transformation
Energy released at a small step can be captured efficiently
Cells mainly use one type of energy packet (ATP) to fuel any small step
Different metabolic processes can be integrated

Degradative pathways converge on common products
Biosynthetic pathways diverge from common building blocks
Metabolism

3. A few important molecules carry the “currencies” of metabolism

(A) Small molecular components:
Coenzyme A carries two carbon acetyl units

(B) Reducing packet:
NAD+

(C) Energy packet:
ATP
3. A few important molecules carry the “currencies” of metabolism

(A) Small molecular components: Coenzyme A

Thioester linkage has a large energy of hydrolysis
\[ \text{AcetylCoA} + H_2O \rightleftharpoons \text{Acetate} + \text{CoA} \quad \Delta G^\circ = -31.4 \text{ kJ/mol} \]

Acetyl CoA can transfer acetyl groups to other molecules:
\[ \text{AcetylCoA} + R \rightleftharpoons \text{Acetyl-R} + \text{CoA} \quad \Delta G^\circ = -18.8 \text{ kJ/mol} \]

Other carriers of chemical groups exist as well
Metabolism

3. A few important molecules carry the “currencies” of metabolism

(B) Reducing packet: NAD+

A lot of oxidation/reduction rxns occur in metabolism
Example:
\[ C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \]

Transfer of electrons from glucose (being oxidized) to oxygen (being reduced)

Accepts a hydride, H\(^{-}\), 2 electrons + 1 proton

Other electron carriers, NADP\(^{+}\), FAD, FMN
Metabolism

3. A few important molecules carry the “currencies” of metabolism

(C) Energy packet: ATP
Energy stored in phosphoanhydride bonds

\[
\text{Adenosine 5'}-\text{triphosphate (ATP)} \\
\text{H}_2\text{O} \quad \Delta G^o = -30.5 \text{ kJ/mol} \quad \text{H}_2\text{O} \\
\text{Adenosine 5'}-\text{diphosphate (ADP)} \quad \text{Adenosine 5'}-\text{monophosphate (AMP)} \\
+ \quad \text{Inorganic phosphate (P}_i\text{)} \quad \text{Inorganic pyrophosphate (P}_i\text{)}
\]

ATP is only for immediate energy exchange

Typical half-life for ATP <1 minute
Long-term energy storage: fats, carbs
Metabolism

4. Coupled reactions drive energy-requiring processes

Thermodynamic consequences:

A ⇔ B  \[\Delta G^\circ = +16.7 \text{ kJ/mol}\]
\[K_{eq} = 1.15 \times 10^{-3}\]
so at equil, \([B]/[A] \sim 1/1000\)

A + ATP + H\(_2\)O ⇔ B + ADP + P\(_i\) + H+
\[\Delta G^\circ = -13.8 \text{ kJ/mol}\]
\[K_{eq} = 2.67 \times 10^2\]
\[[\text{ATP}]/[\text{ADP}] [P_i] \sim 500\]
so at equil, \([B]/[A] \sim 100,000\)

Equilibrium shifted by \(10^8\)
Metabolism

5. Biosynthetic and degradative pathways are distinct

Certain pathways carry out opposite transformations:
Glycolysis/Gluconeogenesis
β-oxidation/fatty acid biosynthesis

Degradative pathways - catabolic
Biosynthetic pathways - anabolic
5. **Biosynthetic and degradative pathways are distinct**

How does the cell prevent a futile cycle?

Corresponding catabolic and anabolic pathways have one or more distinct enzymes that can be separately controlled.

*Could result in a futile cycle!*
6. Metabolic pathways are regulated and integrated

When glucose is available, result depends on conditions:
ATP low, \text{glc} oxidized
ATP high, glycogen synthesis
ATP high and lipids needed, glycolysis, then fatty acid biosynthesis
Metabolism

6. Metabolic pathways are regulated and integrated

Metabolic pathways are regulated
  Example: rate of glycolysis increases 100-fold in working muscle vs. resting muscle
Various pathways must be integrated to work together

How does the body do this?
1. Accessibility of substrates can be varied (usually regulated by changes in hormones: insulin, glucagon)
2. Amounts of enzymes varied (also regulated)
3. Catalytic efficiency of enzymes varied
   modify enzyme - phosphorylation
   allosteric effectors bind to enzymes and de/activate them
Interesting sidepoint:

CoA, NAD\(^+\), and ATP are all ribonucleotides or derivatives of ribonucelotides, components of RNA.

RNA plays central role in many aspects of biochemistry
RNA may have been the original macromolecule in evolution of life on earth
Modern metabolic carriers may be relics of the “RNA world”