**Chapter 17**

*Metabolism – An Overview*

**Biochemistry**

*by*

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**Outline of Chapter 17**

1. Is metabolism similar in different organisms?
2. What can be learned from metabolic maps?
3. How do anabolic and catabolic processes form the core of metabolic pathways?
4. What experiments can be used to elucidate metabolic pathways?
5. What can the metabolome tell us about a biological system?
6. What food substances form the basis of human nutrition?

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**17.1 – Is Metabolism Similar in Different Organisms?**

• Organisms show a marked similarity in their major metabolic pathways
• All life descended from a common ancestral form
  – For example, Glycolysis, the metabolic pathway by which energy is released from glucose and captured in the form of ATP under anaerobic condition, is common to almost every cell

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**Metabolism**

• Metabolism represents the sum of the chemical changes that convert nutrients into energy and the chemically complex products of cells
• Metabolism consists of literally hundreds of enzymatic reactions organized into discrete pathways
• These pathways proceed in a stepwise fashion, transforming substrates into end products through many specific chemical intermediates
• Metabolism is sometimes referred to as intermediary metabolism
Living things exhibit metabolic diversity

- Although most cells have the same basic set of central metabolic pathways, different cells are characterized by the alternative pathways
  - There is also significant diversity
- Classification:
  - Based on carbon requirement: Autotrophs use CO₂; Heterotrophs use organic carbon
  - Based on energy source: Phototrophs use light; Chemotrophs use Glc, inorganic compounds NH₄⁺ & S

### Table

<table>
<thead>
<tr>
<th>Classification</th>
<th>Carbon Source</th>
<th>Energy Source</th>
<th>Electron Donor</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phototrophs</td>
<td>CO₂</td>
<td>Light</td>
<td>H₂O, H₂, S, other inorganic compounds</td>
<td>Green plants, algae, cyanobacteria, photosynthetic bacteria</td>
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<tr>
<td>Chemotrophs</td>
<td>Organic compounds</td>
<td>Light</td>
<td>Organic compounds</td>
<td>Nonphototrophic bacteria</td>
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<tr>
<td>Chemoautotrophs</td>
<td>Organic compounds</td>
<td>Oxidation-reduction reactions</td>
<td>NH₄⁺, NO₃⁻, SO₄²⁻, H₂S</td>
<td>Nitifying bacteria, iron- and sulfur-oxidizing bacteria</td>
</tr>
<tr>
<td>Chemoorganotrophs</td>
<td>Organic compounds</td>
<td>Oxidation-reduction reactions</td>
<td>Organic compounds (e.g., Glc)</td>
<td>Respiration in roots, photosynthetic cells in the dark</td>
</tr>
</tbody>
</table>

The Sun is Primary Energy for Life

- The flow of energy in the biosphere and the carbon and oxygen cycles are intimately related
- Phototrophs use light to drive synthesis of organic molecules
- Heterotrophs use these organic molecules as building blocks
- CO₂, O₂, and H₂O are recycled
17.2 What Can Be Learned From Metabolic Maps?

- Metabolism consists of catabolism and anabolism
- Catabolism: degradative pathways
  - Usually energy-yielding
- Anabolism: biosynthetic pathways
  - Usually energy-requiring
- Metabolic maps portray the principal reactions of intermediary metabolism
- When the major metabolic routes are known and functions are understood, the maps become easy to follow, in spite of their complexity

Metabolism

- The metabolism map can be viewed as a set of dots and lines
  - Intermediate as a black dot
  - Enzyme as a line
  - More than 1000 different enzymes and 500 intermediates
  - About 80% of the intermediates connect to only one or two lines

<table>
<thead>
<tr>
<th>Lines</th>
<th>Dots</th>
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<tbody>
<tr>
<td>1 or 2</td>
<td>410</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>6 or more</td>
<td>8</td>
</tr>
</tbody>
</table>
Figure 17.3
The metabolic map as a set of dots and lines. The heavy dots and lines trace the central energy-releasing pathways known as glycolysis and the citric acid cycle.

Figure 17.4
(a) The traditional view of a metabolic pathway is metabolite-centric.
(b) Julia Gerrard has proposed that a protein-centric view is more informative for some purposes.
(c) A simplified version of the protein-centric view where proteins in the pathway form multifunctional complexes. (see next slide)

Organization of Enzymes in Pathways
- Pathways consist of sequential enzymatic steps
- The enzymes may be
  1. Separate, soluble entities
  2. or may form a multienzyme complex
  3. or may be a membrane-bound system
- New research indicates that multienzyme complexes are more common than once thought
  - metabolons
17.3 – How Do Anabolic and Catabolic Processes Form the Core of Metabolism Pathways?

- Metabolism serves two fundamentally different purposes: the generation of energy to drive vital functions and synthesis of biological molecules.
- Metabolism consists of catabolism and anabolism.
- Catabolism: degradative pathways
  - Usually energy-yielding
  - Oxidative
- Anabolism: biosynthetic pathways
  - Energy-requiring
  - Reductive

Anabolism and Catabolism Are Not Mutually Exclusive

- Catabolism and anabolism occur simultaneously in the cell.
- The conflicting demands of concomitant catabolism and anabolism are managed by cells in two ways:
  1. The cell maintains tight and separate regulation of both catabolism and anabolism.
  2. Competing metabolic pathways are often localized within different cellular compartment.
The pathways of catabolism converge to a few end products

- Consists of three distinct stages
  - Stage 1: the nutrient macromolecules are broken down into their respective building blocks
  - Stage 2: building blocks are further degraded to yield an even more limit set of simpler metabolic intermediates
  - Stage 3: the oxidation of metabolic intermediates to generate the energy and to produce CO$_2$ and H$_2$O

Anabolic pathways diverge to synthesize many biomolecules

- The proteins, nucleic acids, lipids, and polysaccharides are constructed from appropriate building blocks via the pathways of anabolism
- The building blocks (amino acid, nucleotides, sugars, and fatty acids) can be generated from metabolites
- Some pathways serve both in catabolism and anabolism – citric acid cycle – Such pathways are amphibolic

Comparing Pathways

- Anabolic & catabolic pathways involving the same product are not the same enzymatic reactions
- Some steps may be common to both, others must be different - to ensure that each pathway is spontaneous
- This also allows regulation mechanisms to turn one pathway on and the other off
Parallel pathways of catabolism and anabolism must differ in at least one metabolic step in order that they can be regulated independently. Shown here are two possible arrangements of opposing catabolic and anabolic sequences between A and P. (a) The parallel sequences proceed via independent routes. (b) Only one reaction has two different enzymes, a catabolic one (E₃) and its anabolic counterpart (E₆). These provide sites for regulation.

**ATP Serves in a Cellular Energy Cycle**
- ATP is the energy currency of cells
- Phototrophs transform light energy into the chemical energy of ATP
- In heterotrophs, catabolism produces ATP, which drives activities of cells
- Energy released in the hydrolysis of ATP to ADP and Pi
- ATP cycle carries energy from photosynthesis or catabolism to the energy-requiring processes of cells

**NAD⁺ and NADH system in Metabolism**
- NAD⁺ collects electrons released from the substrates in oxidative reactions of catabolism
- Catabolism is oxidative - substrates lose reducing equivalents, usually H⁺ ions (hydride ion)
- The hydride ions are transferred in enzymatic dehydrogenase reactions from the substrates to NAD⁺ molecules, reducing them to NADH
- The ultimate oxidizing agent is O₂, becoming reduced to H₂O
- Oxidation reactions are exergonic, and the energy released is coupled with the formation of ATP
NADPH provides the reducing power for anabolic processes

- Anabolism is reductive
- The biosynthesis requires the reducing equivalents
- NADPH provides the reducing power (electrons) for anabolic processes
- In photosynthetic organism, the energy of light is used to pull electrons from water and transfer them to NAPD$^+$; O$_2$ is by-product of this process
Coenzymes and Vitamins Provide Unique Chemistry and Essential Nutrients to Pathways

- Vitamins are required in the diet, usually in trace amount, because they cannot be synthesized by the organism itself.
- Many vitamins are "coenzymes"—molecules that bring unusual chemistry to the enzyme active site.
- Vitamins and coenzymes are classified as "water-soluble" and "fat-soluble".
- The water-soluble coenzymes exhibit the most interesting chemistry.

17.4 – What Experiments Can Be Used to Elucidate Metabolic Pathways?

- Eduard Buchner (late 19th century) showed that fermentation of glucose in extract of broken yeast cells yielded ethanol and carbon dioxide.
- This led to a search for intermediates of glucose breakdown.
- Metabolic inhibitors were important tools for elucidating the pathway steps.
- Mutations also were used to create specific metabolic blocks.

Figure 17.13
The use of inhibitors to reveal the sequence of reactions in a metabolic pathway. (a) Control: Under normal conditions, the steady-state concentrations of a series of intermediates will be determined by the relative activities of the enzymes in the pathway. (b) Plus Inhibitor: In the presence of an inhibitor (in this case, an inhibitor of enzyme 4), intermediates upstream of the metabolic block (B, C, and D) accumulate, revealing themselves as intermediates in the pathway. The concentration of intermediates lying downstream (E and F) will fall.
Isotopic Tracers Can Be Used as Metabolic Probes

- Substrates labeled with an isotopic form of some element can be fed to cells and used to elucidate metabolic sequences
- Radioactive isotopes: $^{14}$C, $^3$H, $^{32}$P
- Stable ‘heavy’ isotopes: $^{18}$O, $^{15}$N

$$\text{CO}_2 + \text{H}_2\text{O} \rightarrow (\text{CH}_2\text{O}) + \text{O}_2$$

$$\text{C}^{16}\text{O}_2 + 2\text{H}_2^{18}\text{O} \rightarrow (\text{CH}_2^{16}\text{O}) + \text{H}_2^{16}\text{O} + ^{18}\text{O}_2$$

NMR Spectroscopy is a Noninvasive Metabolic Probe

- The nuclei of certain atomic isotopes have magnetic moments
- Such nuclei can absorb radio-frequency energy in the presence of a magnetic field at a unique resonant frequency
- The nuclear magnetic resonance (NMR) absorption is influence in predictable ways by the chemical nature of its neighboring atoms and by its dynamic behavior (motion)
- For these reasons, NMR signals can provide a wide range of structural and dynamic information about biomolecules
With NMR spectroscopy one can observe the metabolism of a living subject in real time. These NMR spectra show the changes in ATP, creatine-P (phosphocreatine), and Pi levels in the forearm muscle of a human subjected to 19 minutes of exercise. Note that the three P atoms of ATP (α, β, and γ) have different chemical shifts, reflecting their different chemical environments.

Metabolic Pathways Are Compartmentalized Within Cells

- Eukaryotic cells are extensively compartmentalized by an endomembrane system
- The flow of metabolic intermediates in the cell is spatially as well as chemically segregated
17.5 What Can the Metabolome Tell Us About a Biological System?

- The **metabolome** is the complete set of low-molecular weight molecules present in an organism or excreted by it under a given set of physiological conditions
- **Metabolomics** is the systematic identification and quantitation of all these metabolites in a given organism or sample
- The comprehensive information sets of systems biology from the genome, the transcriptome, the proteome, and metabolome will combine to provide incisive descriptions of biological systems and detailed understanding of many human diseases

- Even simple organisms present daunting challenges for metabolomic analyses
- **Mass spectrometry (MS)** and **nuclear magnetic resonance (NMR)** are both powerful techniques for metabolomic analysis
- **MS** offers unmatched sensitivity for detection of metabolites at low concentrations
- **NMR** provides remarkable resolution and discrimination of metabolites in complex mixtures
17.6 – What Food Substances Form the Basis of Human Nutrition?

- The use of foods by organisms is termed nutrition.
- Food includes the macronutrients—protein, carbohydrate, and lipid—and the micronutrients—including vitamins and minerals.
- **Protein** is a rich source of nitrogen and also provides essential amino acids.
- **Carbohydrates** provide metabolic energy and essential components for nucleotides and nucleic acids.
- **Lipids** provide essential fatty acids that are key components of membranes and also important signal molecules.
- **Fiber** may be soluble—pectins and gums or insoluble—cellulose and lignins.