Metabolism: An Overview

Objectives:
I. Define the terms metabolism, catabolism, anabolism, and regulatory reactions.
II. Define the terms exergonic and endogonic.
III. Discuss the four common themes of cellular metabolism.
IV. Define a “Metabolic Pathway”.
V. Describe the six (6) characteristics of Metabolic Pathways.
   A. How does the cell force an endogonic reaction to completion?
   B. Understand the concept of coupled chemical reactions.
VI. Describe the stages of catabolism of dietary carbohydrates, proteins, and lipids.
   A. Preparative pathways versus the two final common pathways of catabolism
   B. Hydrolysis of macromolecules into monomeric subunits.
   C. Conversion of monomeric subunits into a form that can be completely oxidized to CO2 and H2O.
   D. Complete oxidation and production of ATP.
VII. Removing intermediates (intermediate products) from catabolic pathways as precursors for the anabolic pathways.

Basic concepts and principles governing all of metabolism need to be discussed, before we venture forth into the study of specific metabolic pathways.

First some definitions:

METABOLISM is the sum total of all of the chemical reactions that occur within a living cell. Depending upon the cell type, there can be from less than one hundred to over a thousand different reactions occurring simultaneously within the cell.

CATABOLISM or CATABOLIC REACTIONS degrades large biomolecules liberating smaller molecular building blocks. These smaller building blocks can be utilized during anabolic processes or they can be completely oxidized to CO2 and H2O liberating energy. Some of the energy liberated by catabolic reactions is trapped by the cell in high energy acid anhydride bonds within molecules, e.g., ATP, GTP etc.; or as high energy electrons on electron carriers, e.g., NADH, FADH2, etc. The energy that the cell does not trap is used to maintain body temperature or given off as heat.

ANABOLISM or ANABOLIC REACTIONS takes smaller molecular building blocks (precursors) as well as energy and combines them into the large biopolymers necessary for cell growth and maintenance. The energy for these reactions comes from the hydrolysis of high energy acid anhydride bonds and/or from high energy electrons donated by electron carriers.

REGULATORY REACTIONS control or take part in the control of cellular metabolism. Regulatory reactions include the reactions stimulated or inhibited by hormones. For example the reactions catalyzed by Adenylate Cyclase, Protein Kinase A, Phospholipase C, Protein Kinase C, etc. are all considered regulatory
reactions. The reactions catalyzed by allosteric enzymes that are part of anabolism or catabolism are also considered regulatory reactions because positive allosteric effectors increase the rates of these reactions and negative allosteric modulators decrease the reaction rates.

There are four common themes of cellular function:

1. Cells extract energy from external sources in order to drive energy consuming reactions. The external sources can be light and/or organic molecules.
2. Cells maintain specific internal concentrations of ions (e.g., \( \text{HCO}_3^- \), \( \text{PO}_4^{3-} \), \( \text{Cl}^- \), \( \text{Na}^+ \), \( \text{K}^+ \), \( \text{Ca}^{2+} \), \( \text{Mg}^{2+} \), \( \text{Mn}^{2+} \), etc.), metabolic intermediates (glucose, amino acids, ATP, NAD\(^+\), Coenzyme A, etc.), and enzymes. Cell membranes provide the physical barrier that segregate cell components from one another and from the external environment. A large proportion of the energy generated by the cell is expended to maintain these concentration gradients.
3. Cells grow and reproduce according to a blueprint encoded in the genetic material.
4. Cells respond to environmental influences. These influences are communicated to the cell by signal molecules.

Metabolism is arbitrarily divided into the reactions of carbohydrates, lipids, amino acids, and nucleotides. Within these four branches of metabolism a number of different and distinct pathways will be examined. A pathway is a sequence of discrete interrelated enzyme catalyzed reactions that perform a single specific function for the cell or has a single specific end product required by the cell. The steps within a pathway are simple organic reactions catalyzed by specific enzymes. This series of discrete enzyme catalyzed steps allows the cell to efficiently trap the energy released during the pathway, minimizes the energy the cell needs to expend to perform a specific task, and/or allows the cell to control the flux and flow of metabolites through a specific pathway. When a pathway is defined the beginning and end of the pathway are arbitrarily set. This arbitrary definition of beginning and end was made in order to make the study of metabolic pathways easy and coherent. You, as students of biochemistry, must remember that the individual pathways do not exist in a vacuum. The various pathways function in concert. Changes in the metabolic flux through one pathway very often affects the flux of metabolites through the other pathways.

**Metabolic Pathways:**

- can be linear, where some precursor molecule enters the pathway and a needed product comes out the end.

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A → B → C → D → W → X → Y → Z
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can be circular. In a circular pathway the precursor combines with an intermediate of the pathway and is carried around the pathway by common intermediates. The “last” reaction of the cyclic pathway regenerates the substrate of the “first” reaction.

- can be spiral. The enzymes of a spiral pathway are used repeatedly to either build a polymer from small precursor monomers or break a polymer down into monomers.

**METABOLIC PATHWAYS:**

1. are FLEXIBLE. They respond to a wide variety of internal and external environmental changes.

2. are REGULATED. The flow of a specific metabolite through a pathway is controlled in response to changes in the internal and/or external environment. This regulation is accomplished by three mechanisms:
   (1) Increasing or decreasing the amount of enzymes in the cell by increasing protein synthesis (induction) and/or increasing protein degradation.
   (2) Reversible Covalent Modification. The activity of key enzymes in a pathway can be modulated by the reversible transfer of PO₄⁻³ from ATP to specific serine, threonine, or tyrosine residues on enzyme. The addition of PO₄⁻³ by a protein kinase or the removal of PO₄⁻³ by a protein phosphatase stimulates or inhibits the activity of a key enzyme.
   (3) Allosteric regulation of key enzymes in the pathway. The allosteric enzymes of a pathway usually catalyze the rate controlling step(s) of the pathway. These rate controlling step(s) are usually at irreversible step(s) of the pathway, the chemical reaction is irreversible.

3. are SEGREGATED. Pathways are sequestered into different regions or organelles of the cell. For example, the pathway for fatty acid synthesis occurs in the cytoplasm whereas the pathway for fatty acid oxidation occurs in the mitochondria. This sequestration of pathways minimizes the diffusion of intermediates away from the pathway and prevents the formation of “FUTILE CYCLES”.

4. are CONTROLLED by THERMODYNAMIC PRINCIPLES. The cell cannot violate the laws of nature. Reactions that are spontaneous (-ΔG, Exergonic) in a test tube are spontaneous in the cell; reactions that are unfavorable (+ΔG, Endogonic) in a test tube are likewise unfavorable in the cell. The cell overcomes unfavorable, endogonic, reactions by coupling them to reactions in the pathway that are strongly exergonic. Often the unfavorable reaction is coupled to a reaction that involves the hydrolysis of ATP to ADP and PO₄⁻³ or ATP to AMP and pyrophosphate (P₂O₇⁻⁴). When a cell completely oxidizes a molecule to CO₂ and H₂O the amount of energy liberated is no different from the amount liberated when this molecule is completely oxidized in a bomb calorimeter. However, the cell is more efficient at trapping the liberated energy into useful work.

5. use DIFFERENT COSUBSTRATES and COENZYMES in different situations. For example the NAD⁺/NADH pair is most often used in catabolic pathways, NAD⁺ is the common oxidizing agent in catabolic pathways. The NADP⁺/NADPH pair is most often used in anabolic pathways, NADPH is the common reducing agent in anabolic reactions.

6. use ACTIVATED METABOLITES. In the initial steps of most metabolic pathways the metabolite to be
acted upon is “activated”. This activation process may involve the transfer of one or more phosphate
groups from ATP to the metabolite by kinase enzymes or it may involve the transfer of the
metabolite to a carrier molecule such as Coenzyme A. This activation process gets the metabolite
ready for entry into the pathway and “tags” it for a specific pathway. Different pathways use
different activation mechanisms.

The enzymes of a pathway can be
1. bound to cellular membranes, for example the mitochondrial membrane or the membranes of the
   endoplasmic reticulum.
2. organized into multi-enzyme complexes where they are tightly bound or covalently linked to each
   other.
3. separate soluble entities.

Organizing pathways along a membrane or into multi-enzyme complexes limits the possibility of
intermediates diffusing away from the pathway and makes the pathway more efficient. The most current
data suggests that one of the functions of the cytoskeleton, the continuous network of protein filaments and
tubules that crisscross the cytoplasm, is to serve as anchor points for the so-called “soluble enzymes”.
Anchoring the “soluble enzymes” along these protein filaments would organize them into functional
complexes in the cytoplasm of the cell. These functional complexes of “soluble” enzymes are call
METABOLONS.

The primary function of many of the catabolic pathways is to maintain the cellular concentration of ATP, the
energy currency of the cell. However, even under the most extreme conditions of energy depletion the
 cellular concentration of ATP changes very little. Upon going from an energy rich state to an energy poor
state the cellular concentration of ATP drops by a maximum of about 33%. This small decrease in cellular
ATP concentrations is accompanied by a large increase in cellular AMP concentrations. The concentration
of AMP can increase greater that 75 fold. The action of the enzyme Adenylate Kinase accounts for this
small decrease in ATP and large increase in AMP. As the ATP in consumed, the concentration of ADP
increases, and adenylate kinase catalyzes the following reaction:

\[
\text{ADP} + \text{ADP} \rightleftharpoons \text{ATP} + \text{AMP}
\]

Hence, as the cell goes from energy rich to energy poor, the concentration of ATP is maintained fairly
constant, but the concentration of AMP increases dramatically. Catabolic pathways are often controlled by
the ratio of ATP to AMP. This dramatic increase in AMP concentrations, via the action of adenylate kinase,
serves to stimulate catabolic pathways.

The catabolic pathways can be divided into two tiers. The first tier of catabolic pathways are called the
preparatory or conversion pathways. The second tier of pathways are the final common pathways.
Individual preparatory pathways for the monosaccharides, fatty acids and amino acids convert this large set
of substances into a small group of intermediates that can enter one of the two final common pathways. The
final common pathways are responsible for the final oxidation of these secondary intermediates to CO₂ and
H₂O and for the generation of the majority of ATP. The anabolic reactions draw intermediates, precursors,
and energy from the final common pathways and the catabolic conversion pathways for the synthesis of
complex biomolecules.
From the above discussions it should be apparent that metabolism needs to be studied at three levels.

1. The pathway itself needs to be studied. The pathway is the enzyme catalyzed steps that the cell follows to accomplish a specific task.
2. The control points of the pathway need to be examined. The controlling enzymes and how they are controlled (allosterically and/or reversible covalent modification) often give a clue as to how a pathway integrates with the other pathways.
3. The interrelationships between pathways must be explored. The individual pathways do not exist in a vacuum. They function in concert with one another. Changes in the metabolic flux through one pathway very often affects the flux of metabolites through the other pathways.