

Biomedical
Science

Molecular
Genetics



BMS 23110B | Fall 2026-2027

Protein Activity & Regulation
Introduction to Metabolism



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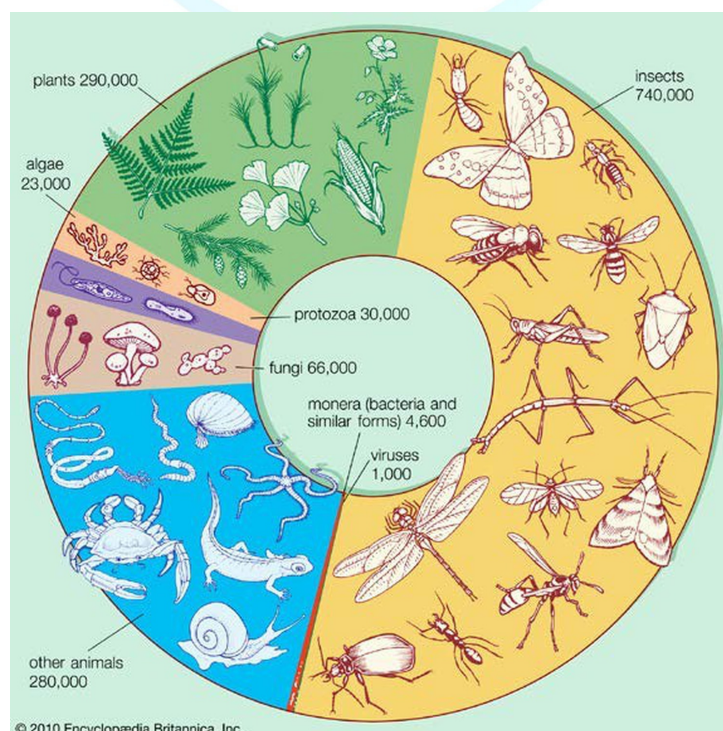
The Universal Pathways of Life

More than **10 million species** may be living on Earth, and several hundred million species may have come and gone throughout the course of evolution.

Multicellular organisms have a striking **specialization of cell types or tissues**.

Despite this extraordinary diversity, the biochemistry of living cells is **surprisingly similar** — not only in the chemical composition and structure of cellular components, but also in the metabolic routes by which the components are modified.

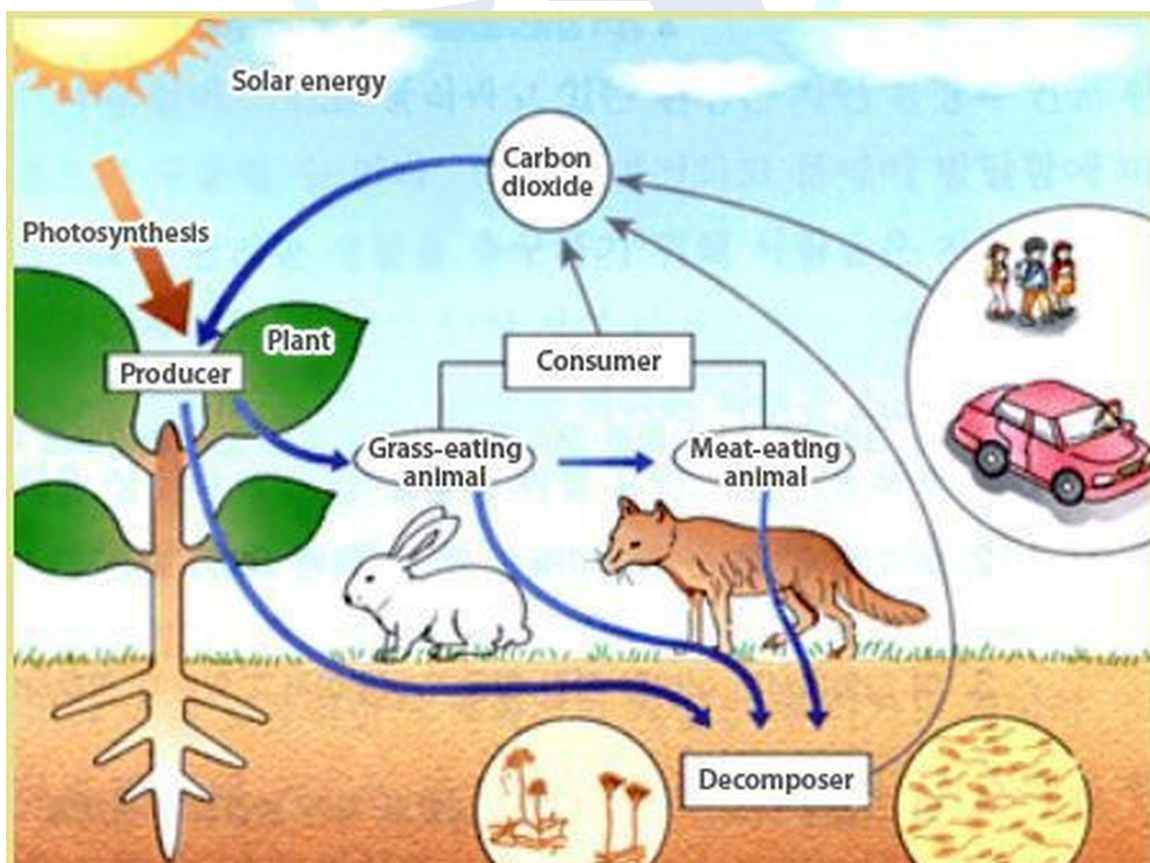
These **universal pathways** are the key to understanding metabolism. Once you have learned the fundamental conserved pathways, you can appreciate the additional pathways that have evolved in some species.





The Energetics of Life

- The activities of living organisms do **not depend solely** on the biomolecules and on the multitude of smaller molecules and ions found in cells.
- Life also requires the **input of energy**.
- Living organisms are constantly transforming energy into **useful work** to sustain themselves, to grow, and to reproduce.
- The breakdown of organic compounds in both photosynthetic and nonphotosynthetic organisms **releases energy** that can be used to drive the synthesis of new molecules and macromolecules.





Metabolism, Bioenergetics & Thermodynamics

Metabolism

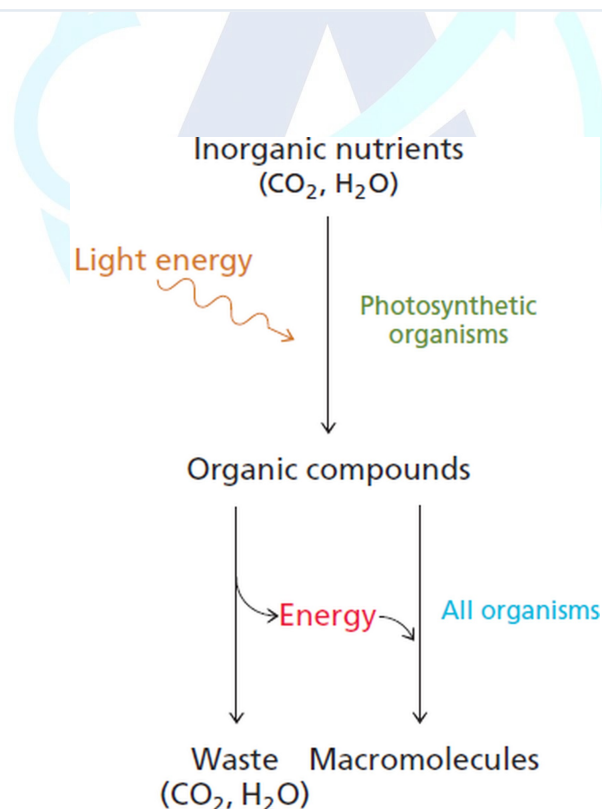
Describes the myriad reactions in which organic compounds are **synthesized and degraded**, and useful energy is **extracted, stored, and used**.

Bioenergetics

The study of the **changes in energy** during metabolic reactions.

Thermodynamics

A branch of physical science that deals with **energy changes**. Bioenergetics is part of this field.



▲ **Energy flow.** Photosynthetic organisms capture the energy of sunlight and use it to synthesize organic compounds. The breakdown of these compounds in both photosynthetic and nonphotosynthetic organisms generates energy needed for the synthesis of macromolecules and for other cellular requirements.



Reaction Rates

The **rate, or speed**, of a chemical reaction depends on the **concentration of the reactants**.



We indicate the concentration of a reacting molecule by enclosing its symbol in square brackets. **[A]** means "the concentration of A" — usually expressed in moles per liter (M).

The rate is **directly proportional** to the product of the concentrations of A and B, described by a proportionality constant **k**, more commonly called a **rate constant**.

$$\text{rate} = k[A][B]$$

Almost all biochemical reactions are **reversible** — C and D can collide and react to produce A and B. The reverse rate depends on the concentrations of C and D and a different rate constant. By convention the forward rate constant is **k₁** and the reverse rate constant is **k₋₁**.

Mixing high concentrations of A and B with no C or D drives the reaction **left to right only**. As A and B decrease and C and D accumulate, the **reverse reaction becomes significant**.



Equilibria

The ratio of product concentrations to reactant concentrations defines the **equilibrium constant, K_{eq}** .

$$K_{eq} = [C][D] / [A][B] = k_1 / k_{-1}$$

The equilibrium constant is also equal to the ratio of the forward and reverse rate constants; since k_1 and k_{-1} are constants, **so is K_{eq}** once the reaction reaches equilibrium.

$$K_{eq} = 1$$

The forward and reverse rate constants have the **same values**.

$$10^{-3} \text{ to } 10^3$$

The usual range — meaning the rate of one of the reactions is **much faster** than the other.

If $K_{eq} = 10^3$, the reaction proceeds mostly to the right, and the final concentrations of C and D will be **much higher** than those of A and B.



Metabolism Is the Sum of Cellular Reactions

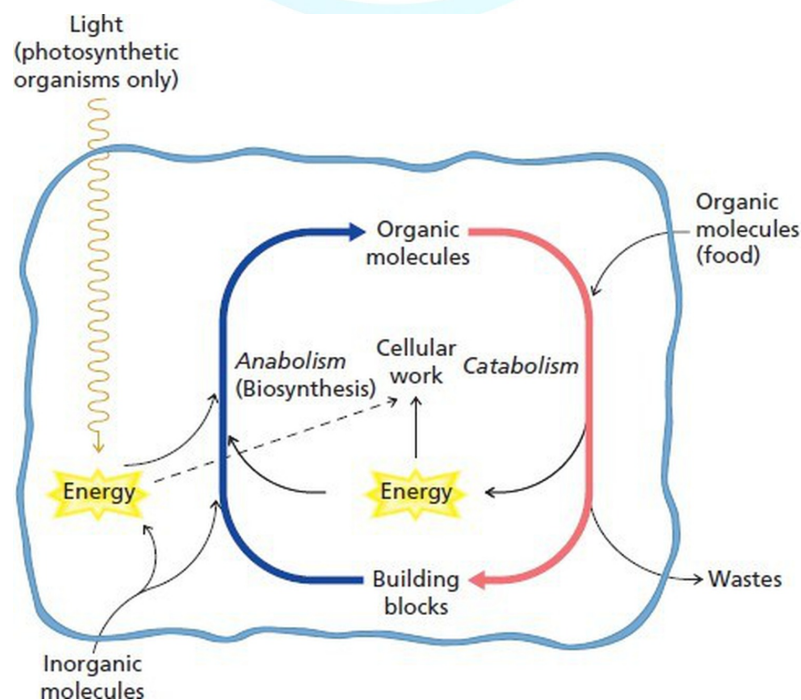
Metabolism — the entire network of **chemical reactions** carried out by living cells.

Metabolites — small molecule **intermediates** in the degradation and synthesis of polymers.

Catabolic reactions — **degrade** molecules to create smaller molecules and energy.

Anabolic reactions — **synthesize** molecules for cell maintenance, growth and reproduction.

Amphibolic reactions — a third class, involved in **both anabolic and catabolic** pathways.





Five Common Themes in Metabolism

1

Organisms or cells maintain **specific internal concentrations** of inorganic ions, metabolites and enzymes.

2

Organisms **extract energy from external sources** to drive energy-consuming reactions.

3

Organisms grow and reproduce according to instructions encoded in the **genetic material**.

4

Organisms **respond to environmental influences**.

5

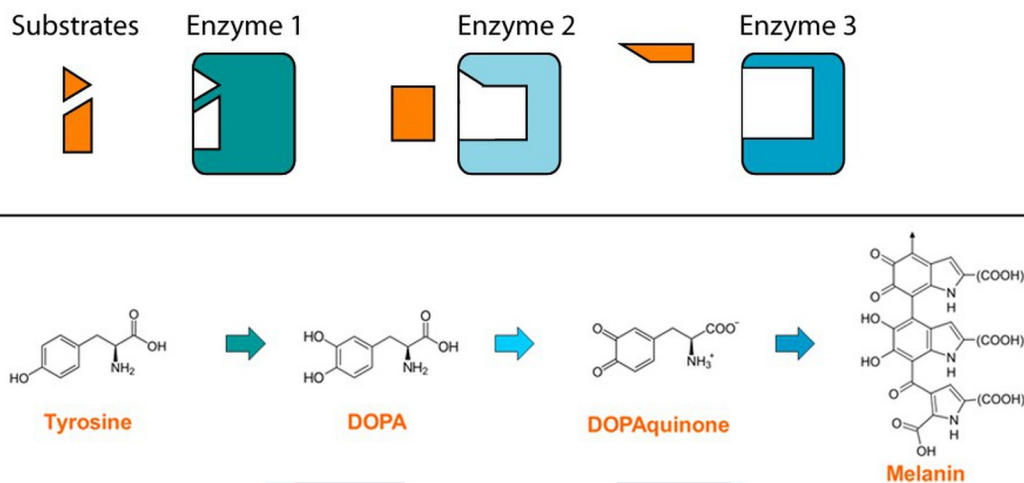
Cells are **not static** — cell components are continually synthesized and degraded, i.e. undergo **turnover**.



Metabolic Pathways

The vast majority of metabolic reactions are **catalyzed by enzymes**, so a complete description of metabolism includes not only the reactants, intermediates and products of cellular reactions, but also the **characteristics of the relevant enzymes**.

S DeMain



Pathways Are Sequences of Reactions

- Metabolism includes **all enzyme reactions**.
- Metabolism can be subdivided into **branches**.

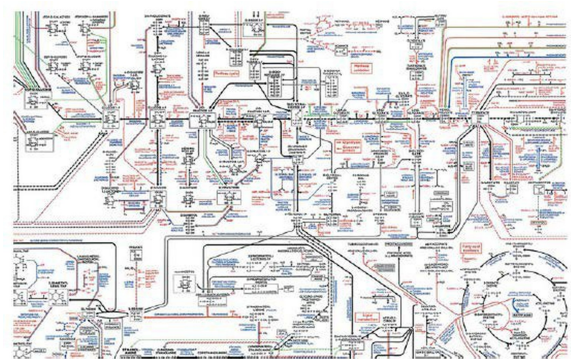
THE FOUR MAJOR GROUPS OF BIOMOLECULES

Carbohydrates

Lipids

Amino Acids

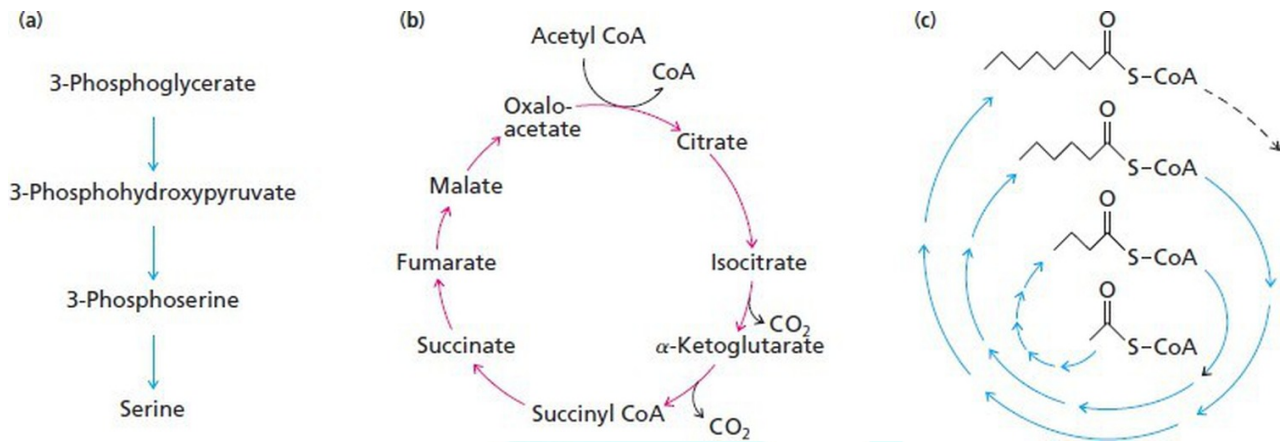
Nucleotides



Part of a large metabolic chart published by Roche Applied Science.



Forms of Metabolic Pathways



a. Linear

The biosynthesis of **serine** is an example of a linear metabolic pathway. The product of each step is the **substrate for the next step**.

b. Cyclic

The sequence of reactions forms a **closed loop**. In the **citric acid cycle**, an acetyl group is metabolized via reactions that regenerate the intermediates of the cycle.

c. Spiral

In **fatty acid biosynthesis**, the same set of enzymes catalyzes a **progressive lengthening** of the acyl chain.

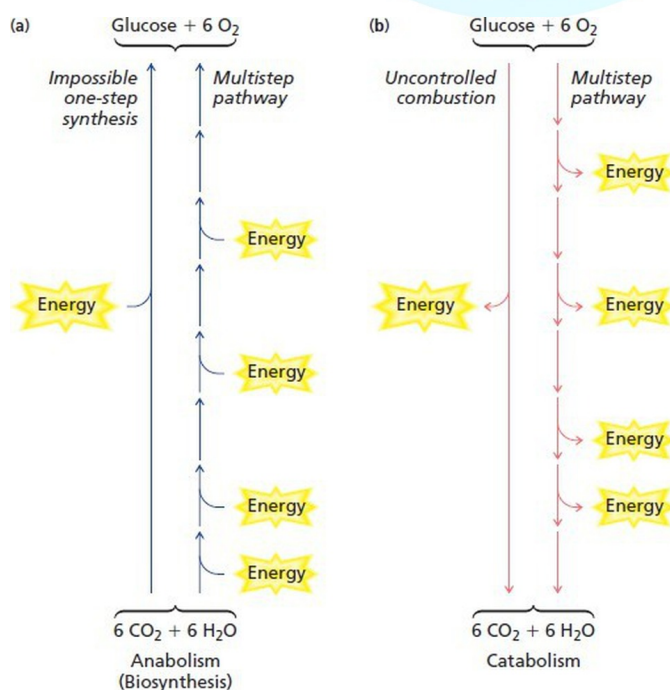


Metabolism Proceeds by Discrete Steps

Each enzyme in a multi-step pathway usually catalyzes only **one single step** in the pathway. Control points occur in multistep pathways.

- 1 Multiple-step pathways permit **control of energy input and output**.
- 2 Energy flow is mediated by **energy donors and acceptors** that carry discrete quanta of energy.
- 3 Catabolic multi-step pathways provide energy in **smaller stepwise amounts**.

A multistep enzyme pathway releases energy in **smaller amounts** that can be used by the cell — compare single-step with multi-step pathways below.



◀ **Figure 10.5**
Single-step versus multistep pathways. (a) The synthesis of glucose cannot be accomplished in a single step. Multistep synthesis is coupled to the input of small quanta of energy from ATP and NADH. (b) The uncontrolled combustion of glucose releases a large amount of energy all at once. A multistep enzyme-catalyzed pathway releases the same amount of energy but conserves much of it in a manageable form.



Metabolic Pathways Are Regulated

- Metabolism is **highly regulated** to permit organisms to respond to changing conditions.
- Most pathways are **reversible**.

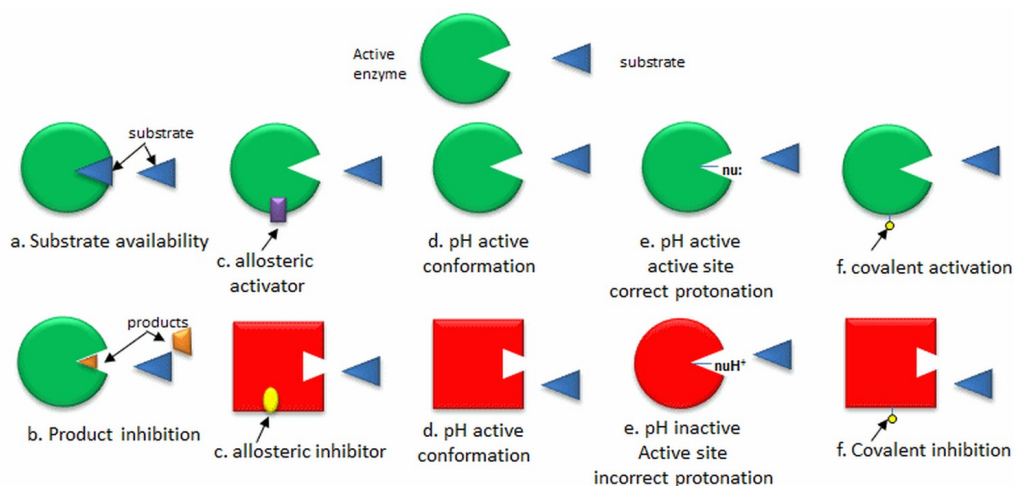
Flux — the **flow of material** through a metabolic pathway.

FLUX DEPENDS UPON

Supply of substrates

Removal of products

Pathway enzyme activities





Two Common Patterns of Regulation

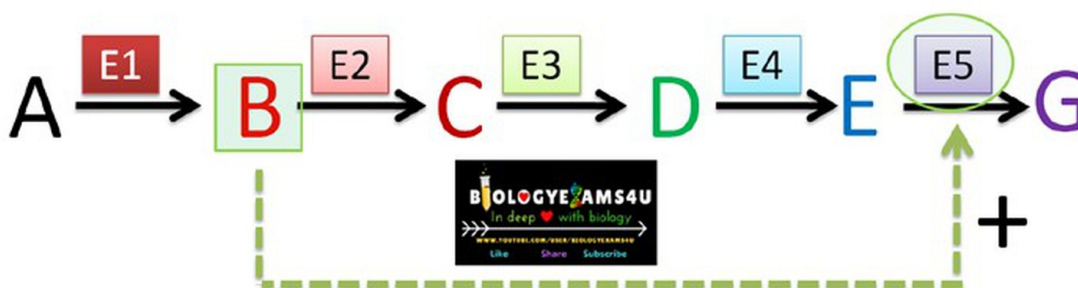
1. Feedback inhibition

Occurs when a product — usually the **end product** of a pathway — controls the rate of its own synthesis through **inhibition of an early step**, usually the first committed step.

2. Feed-forward activation

Occurs when a metabolite produced **early in a pathway** activates an enzyme that catalyzes a reaction **further down the pathway**.

Feed Forward Activation

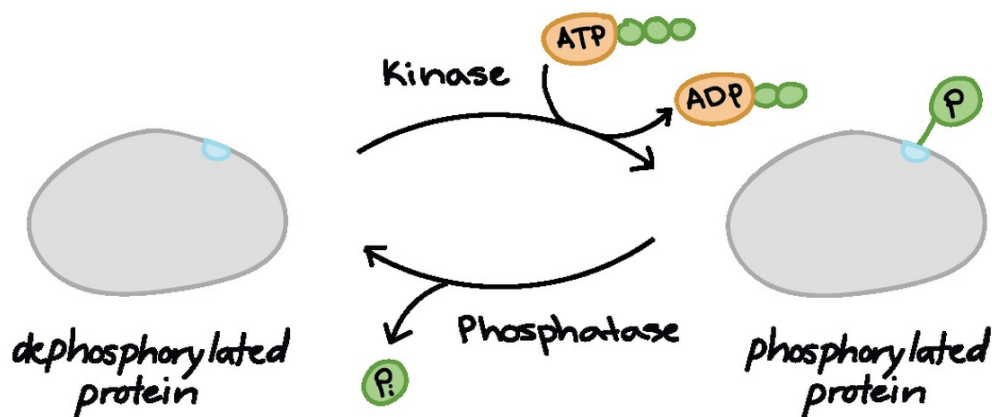


In Feed-forward activation, a metabolite produced **early in a pathway** activates an **enzyme** that catalyze a reaction **further down the pathway**



The Activity of Interconvertible Enzymes

- Interconvertible enzyme activity can be **rapidly and reversibly altered** by covalent modification.
- **Protein kinases** phosphorylate enzymes (+ ATP).
- **Protein phosphatases** remove phosphoryl groups.
- The initial signal may be **amplified** by the "cascade" nature of this signaling.



Individual enzymes differ in whether their response to phosphorylation is **activation** or **deactivation**.



Major Pathways in Cells — Metabolic Fuels

Three major nutrients are consumed by **mammals**.

1. Carbohydrates

Provide **energy**

2. Proteins

Provide **amino acids** for protein synthesis, and some energy

3. Fats

Triacylglycerols provide **energy**, and also lipids for **membrane synthesis**

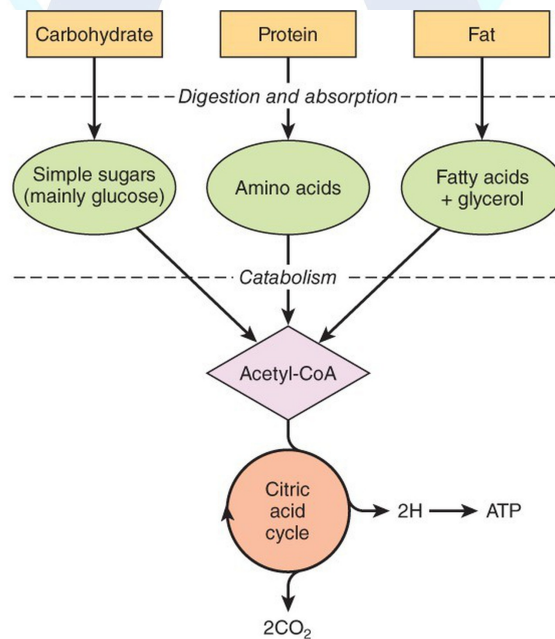


FIGURE 14-1 Outline of the pathways for the catabolism of carbohydrate, protein, and fat. All these pathways lead to the production of acetyl-CoA, which is oxidized in the citric acid cycle, ultimately yielding ATP by the process of oxidative phosphorylation.



Compartmentation & Interorgan Metabolism

Compartmentation of metabolic processes **permits:**

Separate **pools of metabolites** within a cell

Simultaneous operation of **opposing metabolic paths**

High **local concentrations** of metabolites

Coordinated regulation of enzymes

EXAMPLE

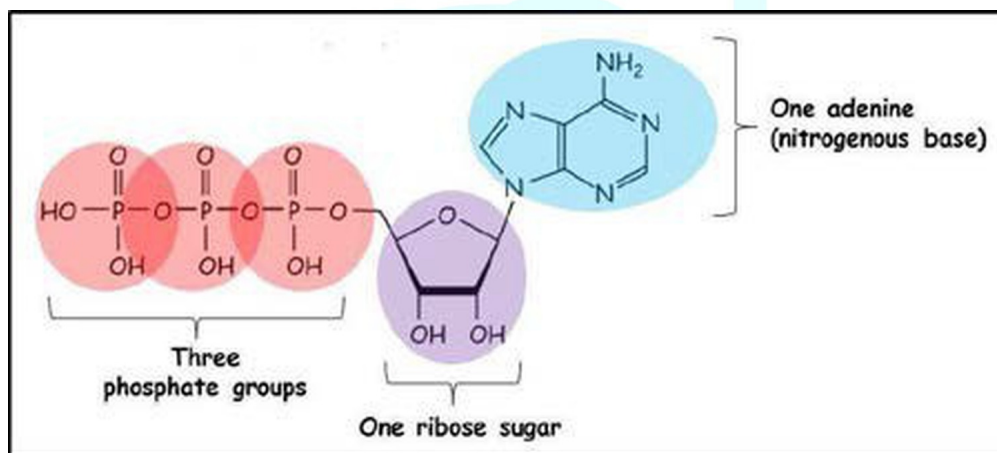
Fatty acid **synthesis** enzymes sit in the **cytosol**; fatty acid **breakdown** enzymes sit in the **mitochondria**.





The Free Energy of ATP Hydrolysis

ATP is a donor of several metabolic groups — usually a **phosphoryl group**, leaving ADP, or an **AMP group**. ATP and the other nucleoside triphosphates (UTP, GTP, CTP) are often referred to as **energy-rich compounds**.



WHY SO MUCH ENERGY IS RELEASED FROM THE PHOSPHOANHYDRIDE LINKAGES

- 1 **Electrostatic repulsion.** Repulsion among the negatively charged oxygen atoms of the phosphoanhydride groups of ATP is **less after hydrolysis**.
- 2 **Solvation effects.** The products — ADP and inorganic phosphate, or AMP and inorganic pyrophosphate — are **better solvated** than ATP itself.
- 3 **Resonance stabilization.** The products of hydrolysis are **more stable** than ATP.



The Metabolic Roles of ATP

The **activated compound** can be either a metabolite or the side chain of an amino acid residue in the **active site of an enzyme**. The intermediate then reacts with a **second substrate** to complete the reaction.

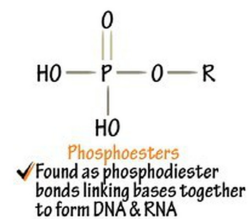


Phosphoryl Group Transfer

The ability of a phosphorylated compound to transfer its phosphoryl group(s) is termed its **phosphoryl group transfer potential**.

Some compounds, such as **phosphoesters**, are **poor phosphoryl group donors** — they have a group transfer potential less than that of ATP.

The group transfer potential is a measure of the **free energy required** for formation of the phosphorylated compound.

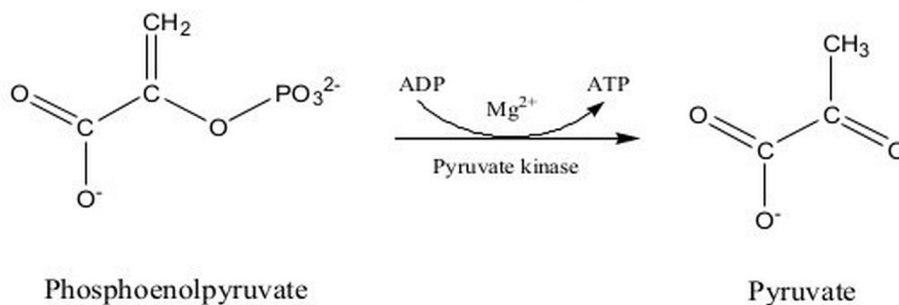




Production of ATP by Phosphoryl Group Transfer

- Often, one **kinase** catalyzes transfer of a phosphoryl group from an excellent donor to ADP to form ATP, which then acts as a **donor for a different kinase reaction**.
- Phosphoenolpyruvate** and **1,3-bisphosphoglycerate** are two common metabolites that have higher energy than ATP, even under conditions found inside the cell.
- Some of these compounds are intermediates in **catabolic pathways**; others are **energy storage compounds**.

Glycolysis: Step 10



- Pyruvate kinase catalyzes irreversible transfer of phosphate from PEP to ADP to form ATP (2nd substrate-level phosphorylation) and pyruvate.

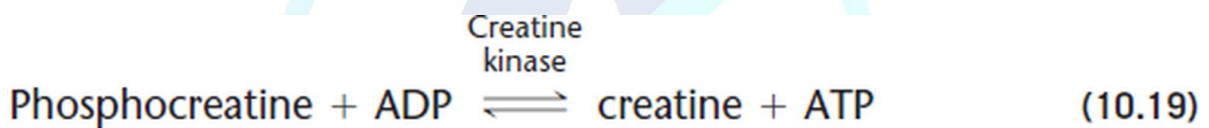
In cells, this **metabolically irreversible reaction** is an important source of ATP.



Phosphagens

Phosphagens — including **phosphocreatine** and **phosphoarginine** — are “high energy” phosphate storage molecules found in **animal muscle cells**, and have higher group transfer potentials than ATP.

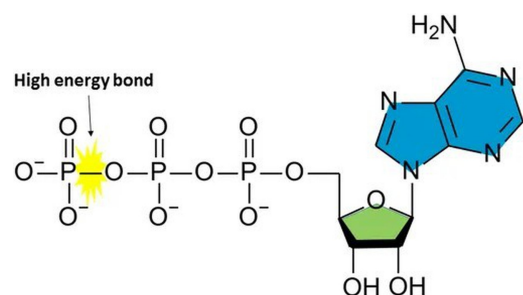
In resting muscle, the concentration of phosphocreatine is about **fivefold higher** than that of ATP. When ATP levels fall, **creatine kinase** catalyzes rapid replenishment of ATP through transfer of the activated phosphoryl group from phosphocreatine to ADP.



ATP as the Carrier

Because ATP has an **intermediate** phosphoryl group transfer potential, it is thermodynamically suited as a **carrier of phosphoryl groups**.

Not surprisingly, ATP mediates **most chemical energy transfers** in all organisms.

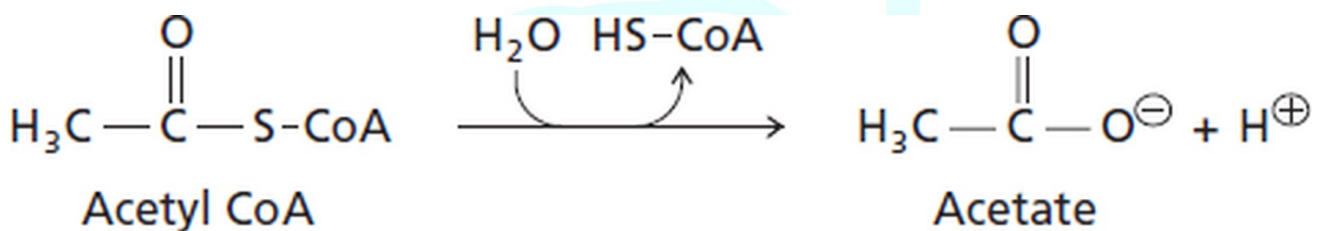


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Thioesters Have High Free Energies of Hydrolysis

Thioesters are another class of “high energy” compounds forming part of the **currency of metabolism**. **Acetyl CoA** is one example — it occupies a **central position** in metabolism.



The high energy of thioester reactions can be used in **generating ATP equivalents**.

KEY CONCEPT

The high energy of hydrolysis of a CoA thioester is used in the **fifth step of the citric acid cycle**, when the thioester succinyl CoA reacts with GDP (or sometimes ADP) and P_i to form GTP (or ATP).



Experimental Methods for Studying Metabolism

Reaction conditions used with isolated reactants in the test tube (**in vitro**) are often very different from the reaction conditions in the intact cell (**in vivo**).

1

A classical approach to unraveling metabolic pathways is to **add a substrate** to preparations of tissues, cells or subcellular fractions, then follow the emergence of intermediates and end products.

2

The fate of a substrate is easier to trace when the substrate has been **specifically labeled**.

3

Valuable information can be acquired by studying **mutations in single genes** associated with the production of inactive or defective individual enzyme forms.

4

The investigation of **mutant organisms** has helped identify enzymes and intermediates of numerous metabolic pathways.

In humans, enzyme defects are manifested in **metabolic diseases**. Hundreds of **single-gene diseases** are known.



To Summarise...

DEFINE

3

The core terms

- Metabolism — synthesis, degradation, energy
- Bioenergetics — energy change in reactions
- Thermodynamics — the wider physical science

REACTIONS

3

Classes of reaction

- Catabolic — degrade, release energy
- Anabolic — synthesize for growth
- Amphibolic — serve both directions

KINETICS

 K_{eq}

Rates and equilibria

- $\text{rate} = k[A][B]$; forward k_1 , reverse k_{-1}
- $K_{eq} = [C][D]/[A][B] = k_1/k_{-1}$
- Usual range 10^{-3} to 10^3

THEMES

5

Common to all metabolism

- Internal concentrations are maintained
- Energy is extracted from external sources
- Growth, response, and constant turnover

PATHWAYS

3

Forms a pathway can take

- Linear — serine biosynthesis
- Cyclic — the citric acid cycle
- Spiral — fatty acid biosynthesis

ATP

3

Why hydrolysis releases energy

- Electrostatic repulsion is less after hydrolysis
- Products are better solvated than ATP
- Products are more stable — resonance

THE THREAD THROUGH THE LECTURE

ATP has an **intermediate** phosphoryl group transfer potential, which is exactly what makes it a **carrier** rather than an endpoint — it mediates most chemical energy transfers in all organisms.