

1  *Metabolism*

Chapter 6

2  *Metabolism*

- Totality of an organism's chemical processes
- Emergent property from specific molecular interactions within the cell
- Management of cellular resources: material and energy

3  *2 metabolic pathways*

- Catabolic pathways: metabolic pathways which release energy by breaking down complex molecules to simpler cmpds (cell respiration)
- (CATABOLIC: CATACLISMIC)
- Anabolic pathways: these pathways CONSUME energy to build complicated molecules from simpler ones (photosynthesis)

4  *Metabolic reactions are coupled*

- Most metabolic reactions are coupled so that the energy released from a catabolic reaction can be used to drive an anabolic one

5  *Distinguish between kinetic and potential energy*

- Energy: capacity to do work
- Kinetic energy: energy in the process of doing work (energy of motion) heat, light
- Potential energy: energy that matter posses because of its location or arrangement (energy of position)
- In the Earth's gravitational field, an object on a hill or water behind a dam
- Chemical energy is potential energy stored in molecules because of the arrangement of nuclei and electrons in its atoms

6  *Transformation of energy*

- Kinetic energy of sunlight can be transformed into potential energy of chemical bonds during photosynthesis
- Potential energy in the chemical bonds of gasoline can be transformed into kinetic mechanical energy which pushes the pistons of the engine

7  *Distinguish between open and closed systems*

- Closed system: collection of matter under study which is isolated from its surroundings
- Open system: system in which energy can be transferred between the system and its surroundings

8  *1<sup>st</sup> and 2<sup>nd</sup> Laws of Thermodynamics*

- Thermodynamics: study of energy transformations
- 1<sup>st</sup>: energy can be transferred and transformed, but it cannot be created or destroyed (energy of the universe is constant)
- 2<sup>nd</sup>: every energy transfer of transformation makes the universe more disordered (every process increases the entropy of the universe)
- Entropy: quantitative measure of disorder that is proportional to randomness (designated

by the letter S)

- 9  *Why don't living organisms violate the 2<sup>nd</sup> Law of thermodynamics?*
- The entropy of a system may decrease, but the entropy of the system plus its surroundings must always increase. If the system is open, highly ordered organisms don't violate the 2<sup>nd</sup> law.
  - They maintain highly ordered structure at the expense of increased entropy of their surroundings
  - Take in complex high energy molecules such as food and extract chemical energy to create and maintain order
  - Return to the surroundings simpler low energy molecules (CO<sub>2</sub> and H<sub>2</sub>) and heat
- 10  *Energy Transformation in organisms*
- An increase in complexity, whether of an organism as it develops or through the evolution of more complex organisms, is also consistent with the second law as long as the total entropy of the universe, the system and its surroundings, increases.
    - Organisms are islands of low entropy in an increasingly random universe.
- 11  *heat*
- Energy can be transformed, but part of it is dissipated as heat which is largely unavailable to do work.
  - Heat energy can perform work if there is a heat gradient resulting in heat flow from warmer to cooler. (consequently order is maintained and the 2<sup>nd</sup> law is not violated)
  - Quantity of energy in the universe is constant, but its QUALITY is not.
- 12  *Heat is energy in a random state*
- In most energy transformations, ordered forms of energy are converted at least partly to heat.
    - Automobiles convert only 25% of the energy in gasoline into motion; the rest is lost as heat.
    - Living cells unavoidably convert organized forms of energy to heat.
    - The metabolic breakdown of food ultimately is released as heat even if some of it is diverted temporarily to perform work for the organism.
  - Heat is energy in its most random state.
- 13  *Distinguish between entropy and enthalpy.*
- The amount of energy that is available to do work is free energy (G)
  - $G = H - TS$
  - G – Gibbs free energy (available to do work)
  - H – enthalpy or total energy
  - T – temperature in K
  - S - entropy
- 14  *Free energy vs total energy*
- Free energy is the portion of a system's energy available to do work
  - Total energy (enthalpy) is all energy-not just the high quality energy
  - Entropy is a quantitative measure of disorder that is proportional to randomness (S)
- 15  *Gibbs Equation*

$\Delta G = \Delta H - T\Delta S$

- Delta is always change
- Delta G is change in free energy
- Delta H is change in total energy
- Delta S is change in entropy
- T is absolute temperature in K

16  *What influence the maximum amount of useable energy that can be harvested from a reaction?*

- During a chemical rx, reactant molecule must absorb energy for their bonds to break, and that energy is released when bonds form btwn rearranged atoms of the products.
- Net energy consumed or released when reactants are converted to products is the net difference btwn the energy consumed to break chemical bonds or reactants and the energy released from the formation of the products.

17  *Spontaneous processes*

- Reaction that will occur without additional energy
- $\Delta G$  or free energy of a system DECREASES ( $\Delta G < 0$ )

18  *2 major factors capable of driving spontaneous processes*

- A decrease in enthalpy ( $-\Delta H$ ) and an increase in entropy ( $+\Delta S$ ) reduce the free energy of a system and contribute to the spontaneity of a process
- Higher temperature enhances the effect of an entropy change: greater kinetic energy of molecules tends to disrupt order as the chances for random collisions increase
- When enthalpy & entropy changes in a system have an opposite effect on free energy, temp may determine whether or not the rx will be spontaneous
- (protein denaturation vs greater kinetic energy of molecules)

19  *Equilibrium*

- A system at equilibrium is at maximum stability.
  - In a chemical reaction at equilibrium, the rate of forward and backward reactions are equal and there is no change in the concentration of products or reactants.
  - At equilibrium  $\Delta G = 0$  and the system can do no work.
- Movements away from equilibrium are nonspontaneous and require the addition of energy from an outside energy source (the surroundings).

20  *Distinguish between exergonic and endergonic reactions*

- Exergonic reaction proceeds with a net loss of free energy
- Endergonic reaction is an energy requiring reaction that proceeds with a net gain of free energy; it absorbs free energy from its surroundings

21  *Exergonic Reactions*

22  *Cellular Respiration*

- The magnitude of delta G for an exergonic reaction is the maximum amount of work the reaction can perform.
  - For the overall reaction of cellular respiration:

- $C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$
- $\Delta G = -686 \text{ kcal/mol}$
- Through this reaction 686 kcal have been made available to do work in the cell.
- The products have 686 kcal less energy than the reactants.

23  *Endergonic reactions*

24  *Photosynthesis*

- If cellular respiration releases 686 kcal, then photosynthesis, the reverse reaction, must require an equivalent investment of energy.
  - $\Delta G = + 686 \text{ kcal / mol}$ .
- Photosynthesis is steeply endergonic, powered by the absorption of light energy.

25  *Exergonic reactions endergonic*

- Chemical products have less free energy than the reactant molecules
  - Reaction is energetically downhill
  - Spontaneous reaction
  - $\Delta G$  is negative
  - $-\Delta G$  is the maximum amount of work the rx can perform
- Products store energy than reactants
  - Reaction is energetically uphill
  - Nonspontaneous rx
  - $\Delta G$  is positive
  - $+\Delta G$  is the minimum amount of work required to drive the rx

26  *There is a relationship between chemical equilibrium and free energy change of a rx*

- As a rx approaches equilibrium, the free energy of the system decreases (spontaneous and exergonic reactions)
- When a rx is pushed away from equilibrium, the free energy of system increases (nonspontaneous and endergonic rx)
- When a reaction reaches equilibrium,  $\Delta G=0$ , because there is no net change in the system

27  *Metabolic disequilibrium*

- Reactions in closed systems eventually reach equilibrium and can do no work.
- A cell that has reached metabolic equilibrium has a  $\Delta G = 0$  and is dead!
- Metabolic disequilibrium is one of the defining features of life.

28  *Equilibrium:  $\Delta G=0$*

29  *Maintaining disequilibrium*

- Cells maintain disequilibrium because they are open with a constant flow of material in and out of the cell.
- A cell continues to do work throughout its life.

- 30  *Continuous flows of materials or energy into a system and out of the system*
- 31  *Harvesting Free Energy*
- A catabolic process in a cell releases free energy in a series of reactions, not in a single step.
  - Some reversible reactions of respiration are constantly “pulled” in one direction as the product of one reaction does not accumulate, but becomes the reactant in the next step.
- 32  *Releasing energy in steps*
- 33  *Energy transfers*
- Sunlight provides a daily source of free energy for the photosynthetic organisms in the environment.
  - Nonphotosynthetic organisms depend on a transfer of free energy from photosynthetic organisms in the form of organic molecules.
- 34  *ATP powers cellular work by coupling exergonic reactions to endergonic reactions*
- A cell does three main kinds of work:
    - *Mechanical work*, beating of cilia, contraction of muscle cells, and movement of chromosomes
    - *Transport work*, pumping substances across membranes against the direction of spontaneous movement
    - *Chemical work*, driving endergonic reactions such as the synthesis of polymers from monomers.
  - In most cases, the immediate source of energy that powers cellular work is ATP.
- 35  *ATP*
- **ATP (adenosine triphosphate)** is a type of nucleotide consisting of the nitrogenous base adenine, the sugar ribose, and a chain of three phosphate groups.
- 36  *Structure of ATP*
- 37  *Harvesting ATP energy*
- The bonds between phosphate groups can be broken by hydrolysis.
    - Hydrolysis of the end phosphate group forms adenosine diphosphate [ATP → ADP + P<sub>i</sub>] and releases 7.3 kcal of energy per mole of ATP under standard conditions.
    - In the cell  $\Delta G$  is about -13 kcal/mol.
- 38  *Hydrolysis of ATP*

39  *Phosphate bonds of ATP*

- While the phosphate bonds of ATP are sometimes referred to as high-energy phosphate bonds, these are actually fairly weak covalent bonds.
- They are unstable however and their hydrolysis yields energy as the products are more stable.
- The phosphate bonds are weak because each of the three phosphate groups has a negative charge
- Their repulsion contributes to the instability of this region of the ATP molecule.

40  *Phosphorylation*

- In the cell the energy from the hydrolysis of ATP is coupled directly to endergonic processes by transferring the phosphate group to another molecule.
  - This molecule is now **phosphorylated**.
  - This molecule is now more reactive.

41  **Fig. 6.9 The energy released by the hydrolysis of ATP is harnessed to the endergonic reaction that synthesizes glutamine from glutamic acid through the transfer of a phosphate group from ATP.**

42  *ATP is renewable resource*

- ATP is a renewable resource that is continually regenerated by adding a phosphate group to ADP.
  - The energy to support renewal comes from catabolic reactions in the cell.
  - In a working muscle cell the entire pool of ATP is recycled once each minute, over 10 million ATP consumed and regenerated per second per cell.
- Regeneration, an endergonic process, requires an investment of energy:  $\Delta G = 7.3$  kcal/mol.

43  *Coupled reactions of ATP*

44  *Enzymes*

1. Enzymes speed up metabolic reactions by lowering energy barriers
2. Enzymes are substrate specific
3. The active site in an enzyme's catalytic center
4. A cell's physical and chemical environment affects enzyme activity

45  *Enzymes speed up metabolic reactions by lowering energy barriers*

- A **catalyst** is a chemical agent that changes the rate of a reaction without being consumed by the reaction.
  - An **enzyme** is a catalytic protein.

- Enzymes regulate the movement of molecules through metabolic pathways.

46  *Hydrolysis of sucrose*

47  *Energy in Exergonic Reactions*

- Even in an exergonic reaction, the reactants must absorb energy from their surroundings, the **free energy of activation** or **activation energy** ( $E_A$ ), to break the bonds.
  - This energy makes the reactants unstable, increases the speed of the reactant molecules, and creates more powerful collisions.
- In exergonic reactions, not only is the activation energy released back to the surroundings, but even more energy is released with the formation of new bonds.

48  *Activation Energy*

- Activation energy is the amount of energy necessary to push the reactants over an energy barrier.
  - At the summit the molecules are at an unstable point, the transition state.
  - The difference between free energy of the products and the free energy of the reactants is the delta G.

49  *Activation Energy crosses threshold*

50  *Most reactions are not spontaneous*

- For some processes, the barrier is not high and the thermal energy provided by room temperature is sufficient to reach the transition state.
- In most cases,  $E_A$  is higher and a significant input of energy is required.
  - A spark plug provides the energy to energize gasoline.
  - Without activation energy, the hydrocarbons of gasoline are too stable to react with oxygen.

51  *Bridging the Activation Energy gap*

- The laws of thermodynamics would seem to favor the breakdown of proteins, DNA, and other complex molecules.
  - However, in the temperatures typical of the cell there is not enough energy for a vast majority of molecules to make it over the hump of activation energy.
  - Yet, a cell must be metabolically active.
  - Heat would speed reactions, but it would also denature proteins and kill cells.

52  *How Enzymes bridge gap*

- Enzyme speed reactions by lowering  $E_A$ .
  - The transition state can then be reached even at moderate temperatures.
- Enzymes do not change delta G.
  - It hastens reactions that would occur eventually.
  - Because enzymes are so selective,

they determine which chemical processes will occur at any time

53  *Activation Energy*

54  *Catabolic and Anabolic Reactions involve breaking and making bonds*

- Chemical reactions between molecules involve both bond breaking and bond forming.
  - To hydrolyze sucrose, the bond between glucose and fructose must be broken and then new bonds formed with a hydrogen ion and hydroxyl group from water.

55  *Activation Energy is Free Energy*

- Even in an exergonic reaction, the reactants must absorb energy from their surroundings, the **free energy of activation** or **activation energy** ( $E_A$ ), to break the bonds.
  - This energy makes the reactants unstable, increases the speed of the reactant molecules, and creates more powerful collisions.
- In exergonic reactions, not only is the activation energy released back to the surroundings, but even more energy is released with the formation of new bonds.

56  *Activation Energy*

- Activation energy is the amount of energy necessary to push the reactants over an energy barrier.
  - At the summit the molecules are at an unstable point, the transition state.
  - The difference between free energy of the products and the free energy of the reactants is the  $\Delta G$ .

57  *Threshold determines under what conditions reaction will take place*

- For some processes, the barrier is not high and the thermal energy provided by room temperature is sufficient to reach the transition state.
- In most cases,  $E_A$  is higher and a significant input of energy is required.
  - A spark plug provides the energy to energize gasoline.
  - Without activation energy, the hydrocarbons of gasoline are too stable to react with oxygen.

58  *Cells need enzymes to reduce threshold*

- The laws of thermodynamics would seem to favor the breakdown of proteins, DNA, and other complex molecules.
  - However, in the temperatures typical of the cell there is not enough energy for a vast majority of molecules to make it over the hump of activation energy.
  - Yet, a cell must be metabolically active.
  - Heat would speed reactions, but it would also denature proteins and kill cells

59  *Enzymes lower activation energy*

- Enzyme speed reactions by lowering  $E_A$ .
  - The transition state can then be reached even at moderate temperatures.
- Enzymes do not change  $\Delta G$ .
  - It hastens reactions that would occur eventually.
  - Because enzymes are so selective, they determine which chemical processes will occur at any time.

60  *Reducing the energy needed to get reaction started*

61  *Enzymes are substrate specific*

- A **substrate** is a reactant which binds to an enzyme.
- When a substrate or substrates binds to an enzyme, the enzyme catalyzes the conversion of the substrate to the product.
  - Sucrase is an enzyme that binds to sucrose and breaks the disaccharide into fructose and glucose.

62  *Active site*

63  *Active site is enzyme's catalytic center*

- In most cases substrates are held in the active site by weak interactions, such as hydrogen bonds and ionic bonds.
  - R groups of a few amino acids on the active site catalyze the conversion of substrate to product.

64  *Induced fit*

- The **active site** of an enzymes is typically a pocket or groove on the surface of the protein into which the substrate fits.
- The specificity of an enzyme is due to the fit between the active site and that of the substrate.
- As the substrate binds, the enzyme changes shape leading to a tighter **induced fit**, bringing chemical groups in position to catalyze the reaction.

65  *Induced fit of active site*

66  *Enzymes are efficient*

- A single enzyme molecule can catalyze thousands or more reactions a second.
- Enzymes are unaffected by the reaction and are reusable.
- Most metabolic enzymes can catalyze a reaction in both the forward and reverse direction.

- The actual direction depends on the relative concentrations of products and reactants.
- Enzymes catalyze reactions in the direction of equilibrium.

67  *Enzymes use a variety of mechanisms to lower activation energy and speed a reaction.*

- The active site orients substrates in the correct orientation for the reaction.
- As the active site binds the substrate, it may put stress on bonds that must be broken, making it easier to reach the transition state.
- R groups at the active site may create a conducive microenvironment for a specific reaction.
- Enzymes may even bind covalently to substrates in an intermediate step before returning to normal.

68  *Factors that affect rate of reaction*

- The rate that a specific number of enzymes converts substrates to products depends in part on substrate concentrations.
- At low substrate concentrations, an increase in substrate speeds binding to available active sites.
- However, there is a limit to how fast a reaction can occur.
- At some substrate concentrations, the active sites on all enzymes are engaged, called enzyme saturation.
- The only way to increase productivity at this point is to add more enzyme molecules.

69  *Homeostasis greatly affects enzymes' efficacy*

- The three-dimensional structures of enzymes (almost all proteins) depend on environmental conditions.
- Changes in shape influence the reaction rate.
- Some conditions lead to the most active conformation and lead to optimal rate of reaction

70  *Effect of Temperature on Enzymes*

- Temperature has a major impact on reaction rate.
  - As temperature increases, collisions between substrates and active sites occur more frequently as molecules move faster.
  - However, at some point thermal agitation begins to disrupt the weak bonds that stabilize the protein's active conformation and the protein denatures.
  - Each enzyme has an optimal temperature.

71  *Temperatures affect rates*

72  *pH and enzyme function*

- Because pH also influences shape and therefore reaction rate, each enzyme has an optimal pH too.
- This falls between pH 6 - 8 for most enzymes.

- However, digestive enzymes in the stomach are designed to work best at pH 2 while those in the intestine are optimal at pH 8, both matching their working environments.

73  *Difference in pH on function*

74  *Cofactors*

- Many enzymes require nonprotein helpers, **cofactors**, for catalytic activity.
  - They bind permanently to the enzyme or reversibly.
  - Some inorganic cofactors include zinc, iron, and copper.
- Organic cofactors, **coenzymes**, include vitamins or molecules derived from vitamins.
- The manners by which cofactors assist catalysis are diverse.

75  *Inhibitors*

- Binding by some molecules, inhibitors, prevent enzymes from catalyzing reactions.
  - If binding involves covalent bonds, then inhibition is often irreversible.
  - If binding is weak, inhibition may be reversible.
- If the inhibitor binds to the same site as the substrate, then it blocks substrate binding via **competitive inhibition**.

76  *Competitive Inhibitor*

77  *Binding to allosteric site*

- If the inhibitor binds somewhere other than the active site, it blocks substrate binding via **noncompetitive inhibition**.
- Binding by the inhibitor causes the enzyme to change shape, rendering the active site unreceptive at worst or less effective at catalyzing the reaction.
- Reversible inhibition of enzymes is a natural part of the regulation of metabolism.

78  *Noncompetitive Inhibitor*

79  *Metabolic control often depends on allosteric regulation*

- In many cases, the molecules that naturally regulate enzyme activity behave like reversible noncompetitive inhibitors.
- These molecules often bind weakly to a **allosteric site**, a specific receptor on the enzyme that is not the active site.
- Binding by these molecules can either inhibit or stimulate enzyme activity.

80  *Allosteric Regulation*

- Most allosterically regulated enzymes are constructed of two or more polypeptide chains.
- Each subunit has its own active site and allosteric sites are often located where subunits join.
- The whole protein oscillates between two conformational shapes, one active,

one inactive.

81  *Active and Inactive forms of enzymes*

82  *Stabilizing conformation*

- Some allosteric regulators, activators, stabilize the conformation that has a functional active site.
- Other regulators, inhibitors, stabilize the conformation that lacks an active site.

83  *Allosteric Regulation of Enzyme stability*

84  *Regulating Enzyme Activity*

- As the chemical conditions in the cell shift, the pattern of allosteric regulation will shift as well.
- In many cases both inhibitors and activators are similar enough in shape that they compete for the same allosteric sites.

85  *inhibitors and activators*

- These molecules may be products and substrates of a metabolic pathway.
- For example, some catabolic pathways have allosteric sites that are inhibited when ATP binds and activated when AMP binds.
- When ATP levels are low, AMP levels are high, and the pathway is turned on until ATP levels rise, AMP levels fall and inhibition by ATP dominates.

86  *Feedback Inhibition*

- One of the common methods of metabolic control is **feedback inhibition** in which a metabolic pathway is turned off by its end product.
- The end product acts as an inhibitor of an enzyme in the pathway.
- When the product is abundant the pathway is turned off, when rare the pathway is active.

87  *Cooperativity*

- In enzymes with multiple catalytic subunits, binding by a substrate to one active site stabilizes favorable conformational changes at all other subunits, a process called **cooperativity**.
- This mechanism amplifies the response of enzymes to substrates, priming the enzyme to accept additional substrates

88  *Stabilization of all subunits*

89  *The localization of enzymes within a cell helps order metabolism*

- Structures within the cell bring order to metabolic pathways.
- A team of enzymes for several steps of a metabolic pathway may be assembled

together as a multienzyme complex.

- The product from the first can then pass quickly to the next enzyme until the final product is released

90  *Enzyme location*

- Some enzymes and enzyme complexes have fixed locations within the cells as structural components of particular membranes.
- Others are confined within membrane-enclosed eukaryotic organelles.
- Both methods concentrate enzymes for efficiency.

91  *Enzymes embedded in membranes*

92  *Metabolism is emergent property*

- Metabolism is a concerted interplay of thousands of different kinds of molecules in the cell.