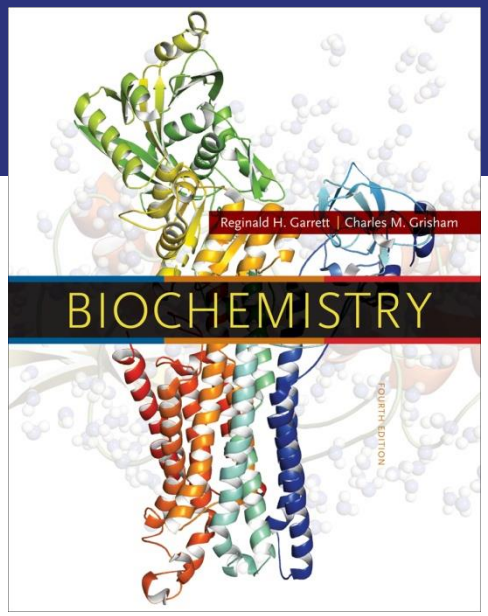


Reginald H. Garrett
Charles M. Grisham

Chapter 27
Metabolic Integration and Organ Specialization

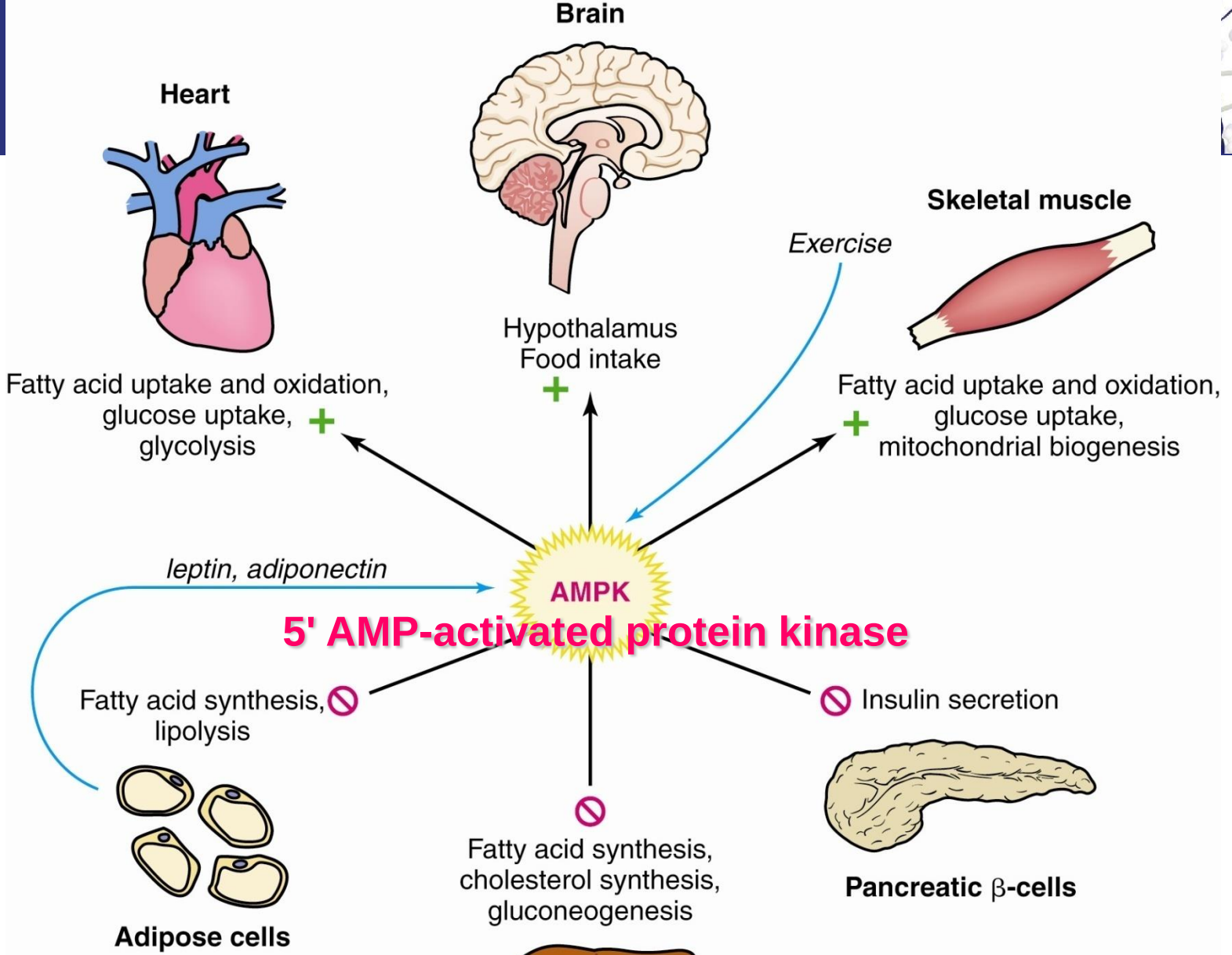
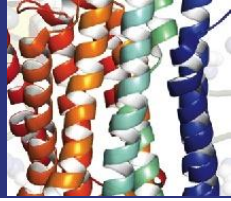


Figure 27.6 AMPK regulation of energy production and consumption in mammals.

27.5 How Is Metabolism Integrated in a Multicellular Organism?



- Organ systems in complex multicellular organisms have arisen to carry out specific functions
- Such specialization depends on coordination of metabolic responsibilities among organs so that the organism as a whole can thrive
- Organs differ in the metabolic fuels they prefer as substrates for energy production (see Figure 27.7)
- The major fuel depots in animals are **glycogen** in live and muscle; **triacylglycerols** in adipose tissue; and **protein**, mostly in skeletal muscle
- The usual order of preference for use of these is glycogen > triacylglycerol > protein

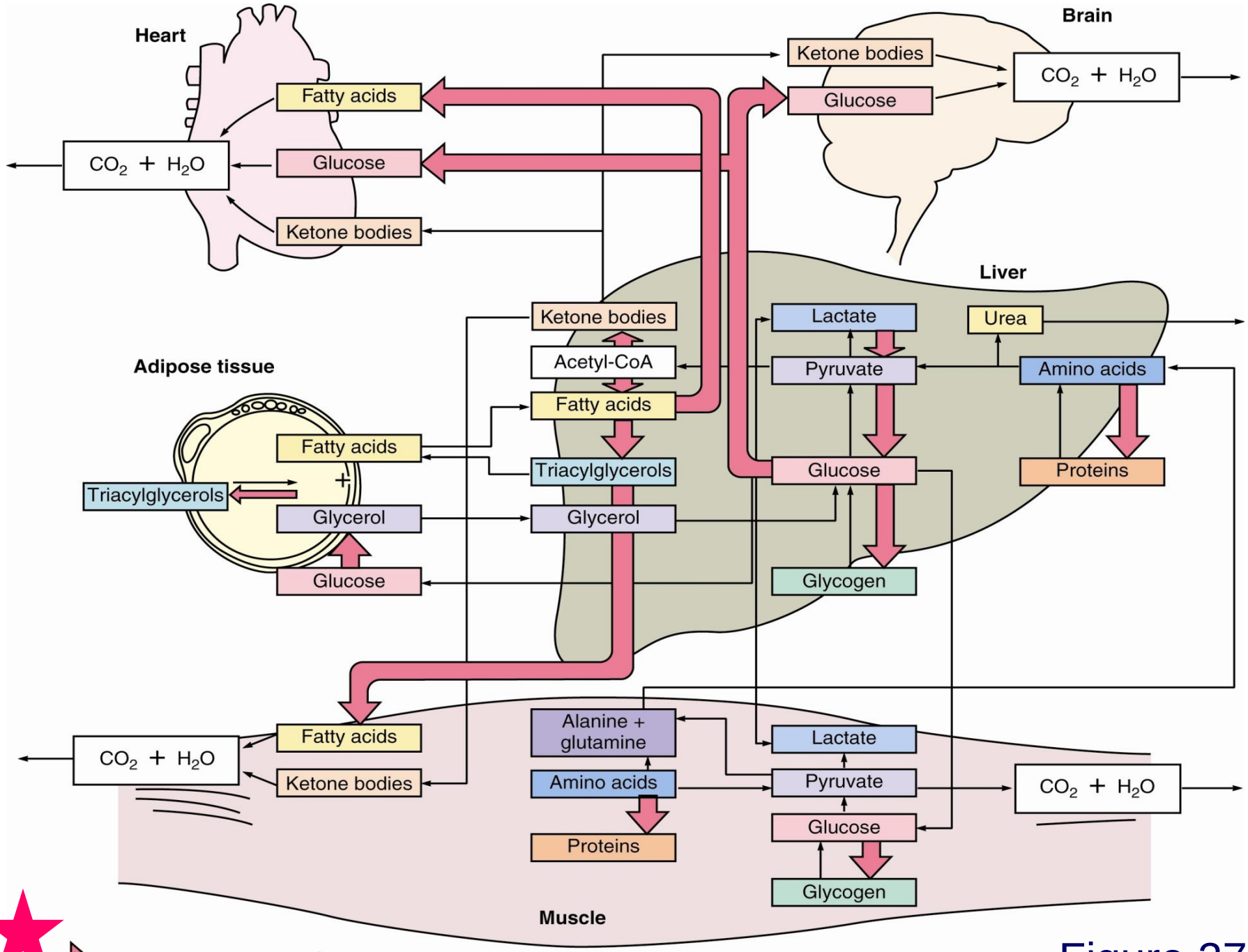

Heart
Fatty acids
Glucose
Ketone bodies
CO_2 + H_2O
Brain
Ketone bodies
Glucose
CO_2 + H_2O
Liver
Ketone bodies
Acetyl-CoA
Fatty acids
Triacylglycerols
Glycerol
Lactate
Pyruvate
Glucose
Glycogen
Urea
Amino acids
Proteins
Adipose tissue
Fatty acids
Triacylglycerols
Glycerol
Glucose
Fatty acids
Ketone bodies
CO_2 + H_2O
Alanine + glutamine
Amino acids
Proteins
Lactate
Pyruvate
Glucose
Glycogen
CO_2 + H_2O
Muscle
Red arrows indicate preferred routes in the well-fed state

Figure 27.7

27.5 How Is Metabolism Integrated in a Multicellular Organism?

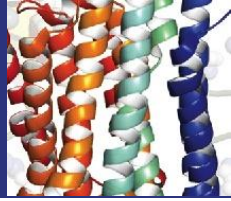
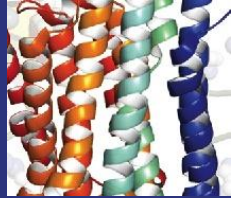


TABLE 27.1 Energy Metabolism in Major Vertebrate Organs

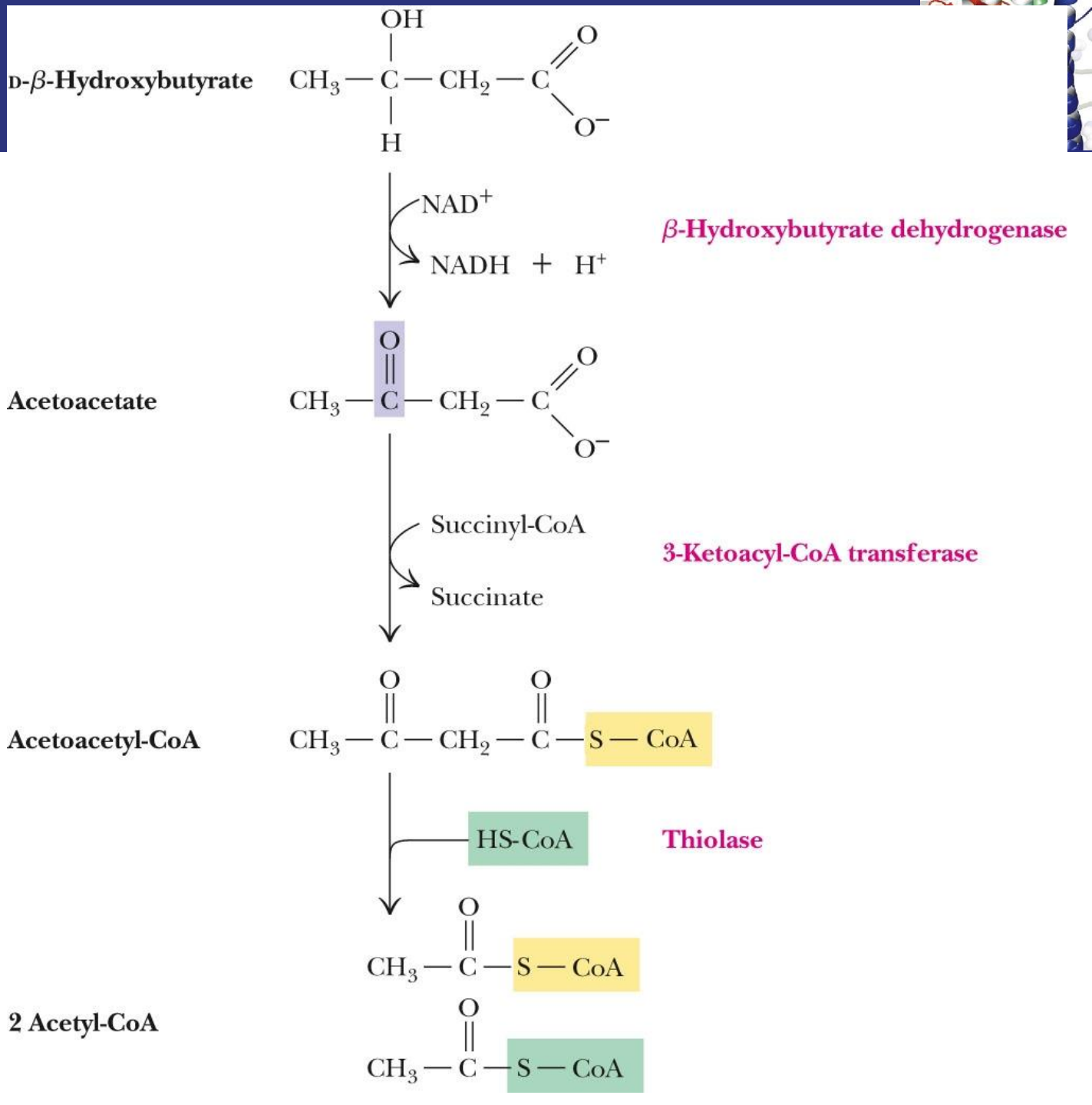
Organ	Energy Reservoir	Preferred Substrate	Energy Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen	Fatty acids	None
Skeletal muscle (strenuous exercise)	None	Glucose from glycogen	Lactate
Heart muscle	Glycogen	Fatty acids	None
Adipose tissue	Triacylglycerol	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerol	Amino acids, glucose, fatty acids	Fatty acids, glucose, ketone bodies

The Brain Has a High Metabolism and Normally Uses Only Glucose as a Fuel

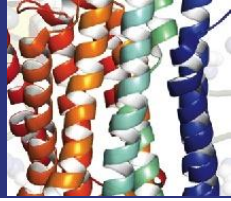


- The brain has very high metabolism but has no fuel reserves
- This means the brain needs a constant supply of glucose
- In fasting conditions, the brain can use **β-hydroxybutyrate** (from fatty acids), converting it to **acetyl-CoA** in the TCA cycle
- This allows the brain to use fat as fuel

Figure 27.8 Ketone bodies such as β-hydroxybutyrate provide the brain with a source of acetyl-CoA when glucose is unavailable.

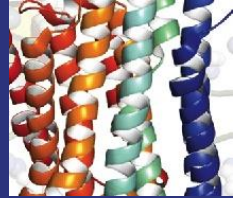


Creatine Kinase and Phosphocreatine Provide an Energy Reserve in Muscle



- Muscles must be prepared for rapid provision of energy
- **Creatine kinase** and **phosphocreatine** act as a buffer system, providing additional ATP for contraction
- Glycogen provides additional energy, releasing glucose for glycolysis
- Glycolysis is capable of explosive bursts of activity
- The flux of glucose-6-P through glycolysis can increase 2000-fold almost instantaneously
- Glycolysis rapidly lowers pH, causing muscle fatigue

Creatine Kinase and Phosphocreatine Provide an Energy Reserve in Muscle



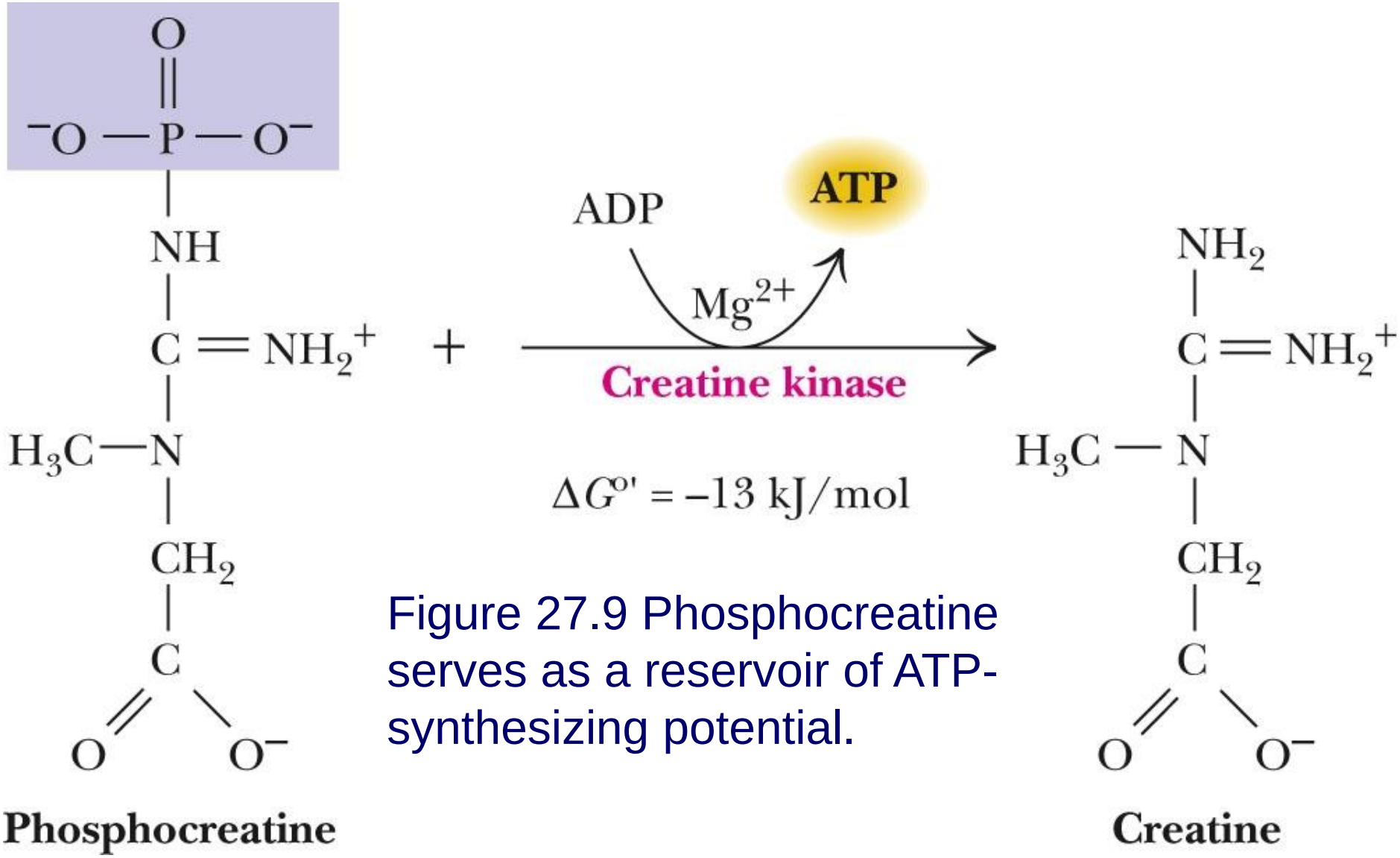
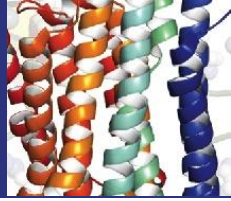


Figure 27.9 Phosphocreatine serves as a reservoir of ATP-synthesizing potential.

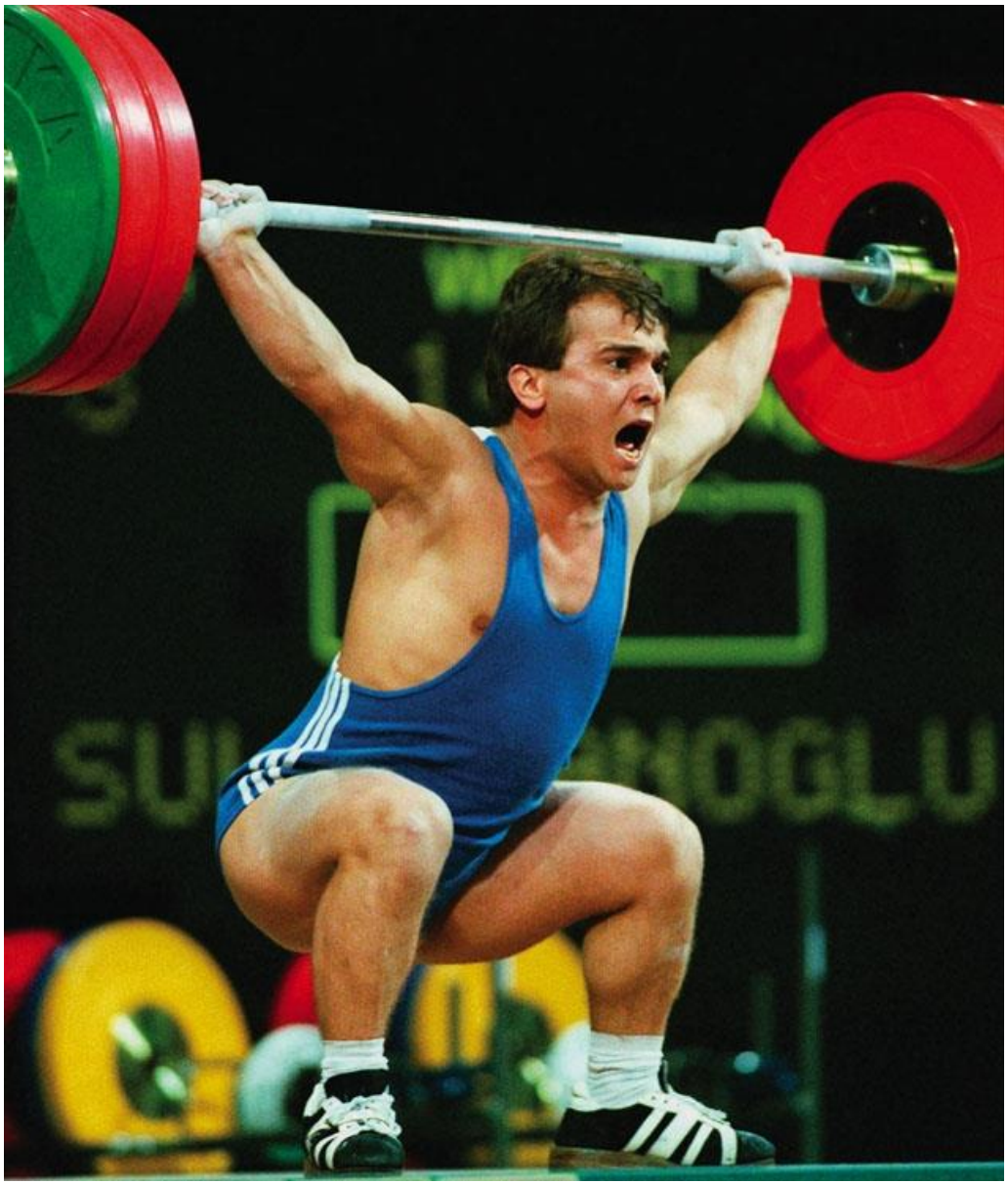
Athletic Performance Enhancement with Creatine Supplements?



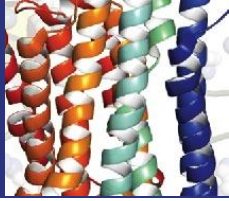
- The creatine pool in a 70 kg (154 lb) human body is about 120 grams
- Of this creatine, 95% is stored in the skeletal and smooth muscles, about 70% of which is in the form of phosphocreatine
- Supplementing the diet with 20 to 30 grams of creatine per day for 4 to 21 days can increase the muscle creatine pool by as much as 50%
- Studies show that such supplementation can improve athletic performance in high-intensity, short-duration events, but no benefit in endurance events
- The FDA advises consumers to consult a physician before using creatine as a supplement

Athletic Performance Enhancement with Creatine Supplements?

Creatine supplements may enhance performance for high-intensity, short-duration events such as weight-lifting.

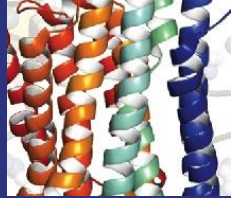


Athletic Performance Enhancement with Creatine Supplements?



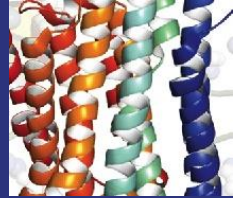
Creatine supplements provide no benefit in endurance events such as distance running. Phosphocreatine restores and maintains ATP levels for a few seconds, but no more.

Muscle Protein Degradation Provides the Fuel of Last Resort for the Organism



- During fasting or extended high levels of activity, amino acids in skeletal muscle are degraded to pyruvate, which can be transaminated to alanine
- Alanine circulates to liver, where it is converted back to pyruvate - food for gluconeogenesis
- This is a fuel of last resort for the fasting or exhausted organism

Muscle Protein Degradation Provides the Fuel of Last Resort for the Organism



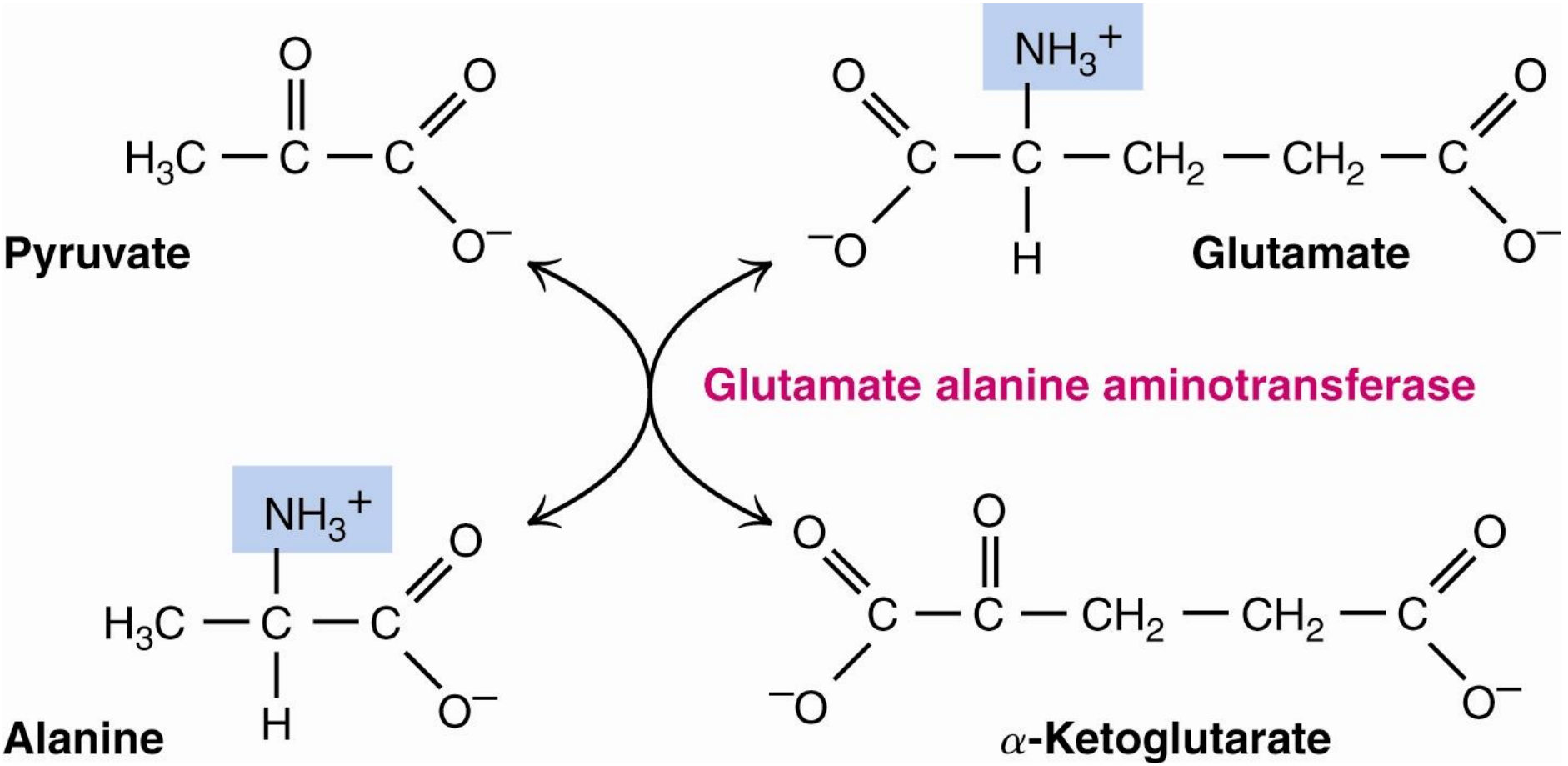
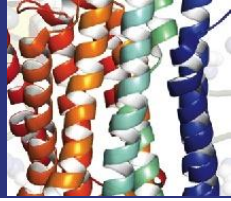


Figure 27.10 The transamination of pyruvate to alanine by glutamate:alanine aminotransferase.

The Liver is the Major Metabolic Processing Center in Vertebrates



- Most of the incoming nutrients that pass through the intestines are routed via **the portal vein** to the liver for processing and distribution
- Liver activity centers around **glucose-6-phosphate**
- Glucose-6-phosphate can be:
  - converted to glycogen
  - released as blood glucose,
  - used to generate NADPH and pentoses via the pentose phosphate pathway,
  - or catabolized to acetyl-CoA for fatty acid synthesis or for energy production in oxidative phosphorylation

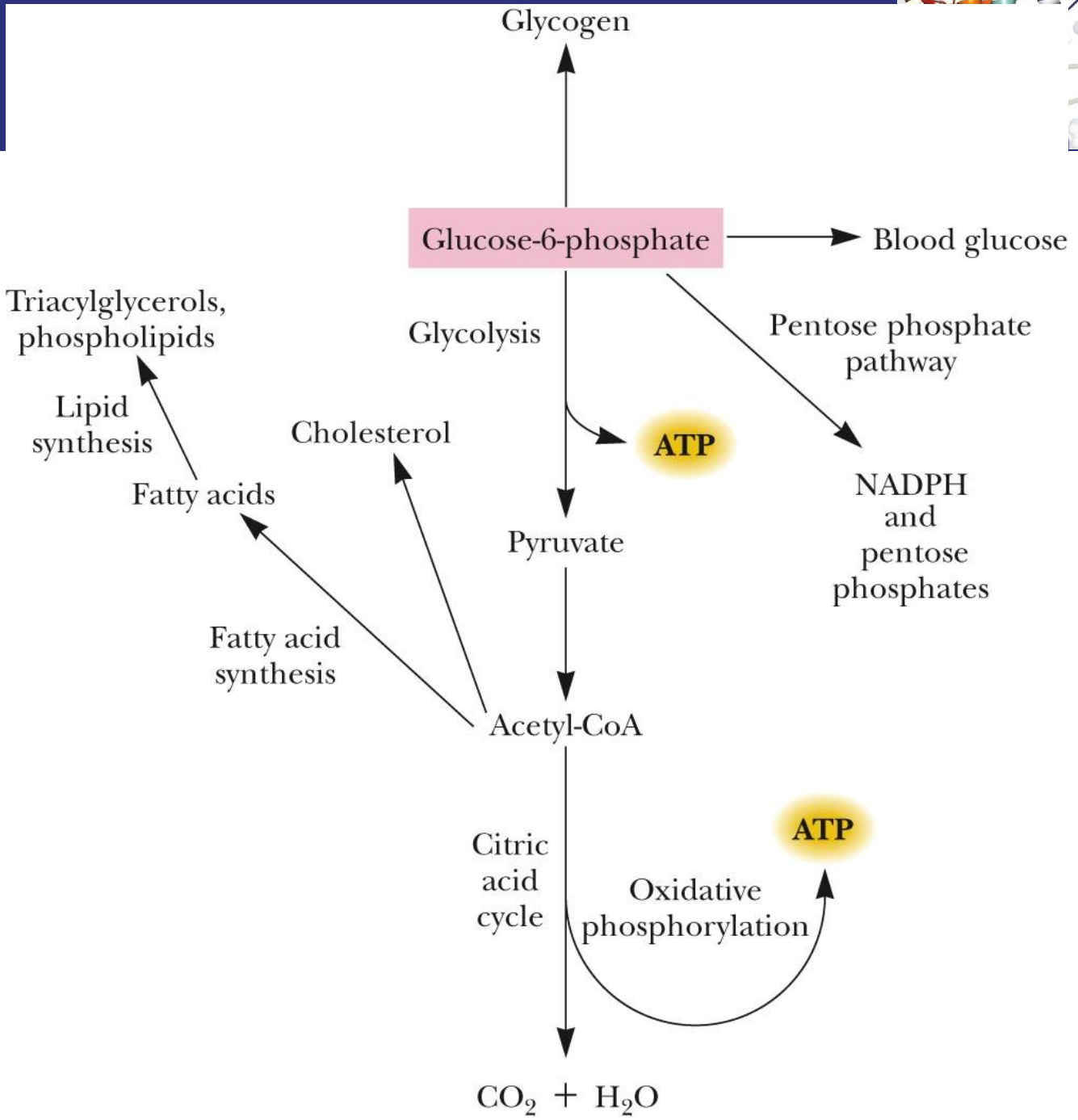
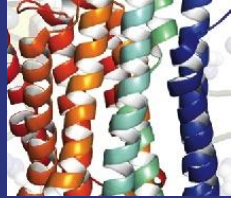


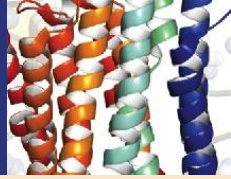
Figure 27.11 Metabolic conversions of glucose-6-phosphate in the liver.

27.6 What Regulates Our Eating Behavior?



- Approximately two-thirds of American are overweight
- One-third of Americans are clinically obese
- Obesity is the most important cause of type 2 diabetes
- Research into the regulatory controls on feeding behavior has become a medical urgency
- The hormones that control eating behavior come from many different tissues
- Hormones that regulate eating include:
  - Short-term regulators determine individual meals
  - Long-term regulators stabilize levels of body fat deposits

27.6 What Regulates Our Eating Behavior?



Agouti-Related Protein

Neuropeptide Y

Hypothalamus

Peptide Tyrosine Tyrosine in L cells in the mucosa of gastrointestinal tract, in ileum and colon

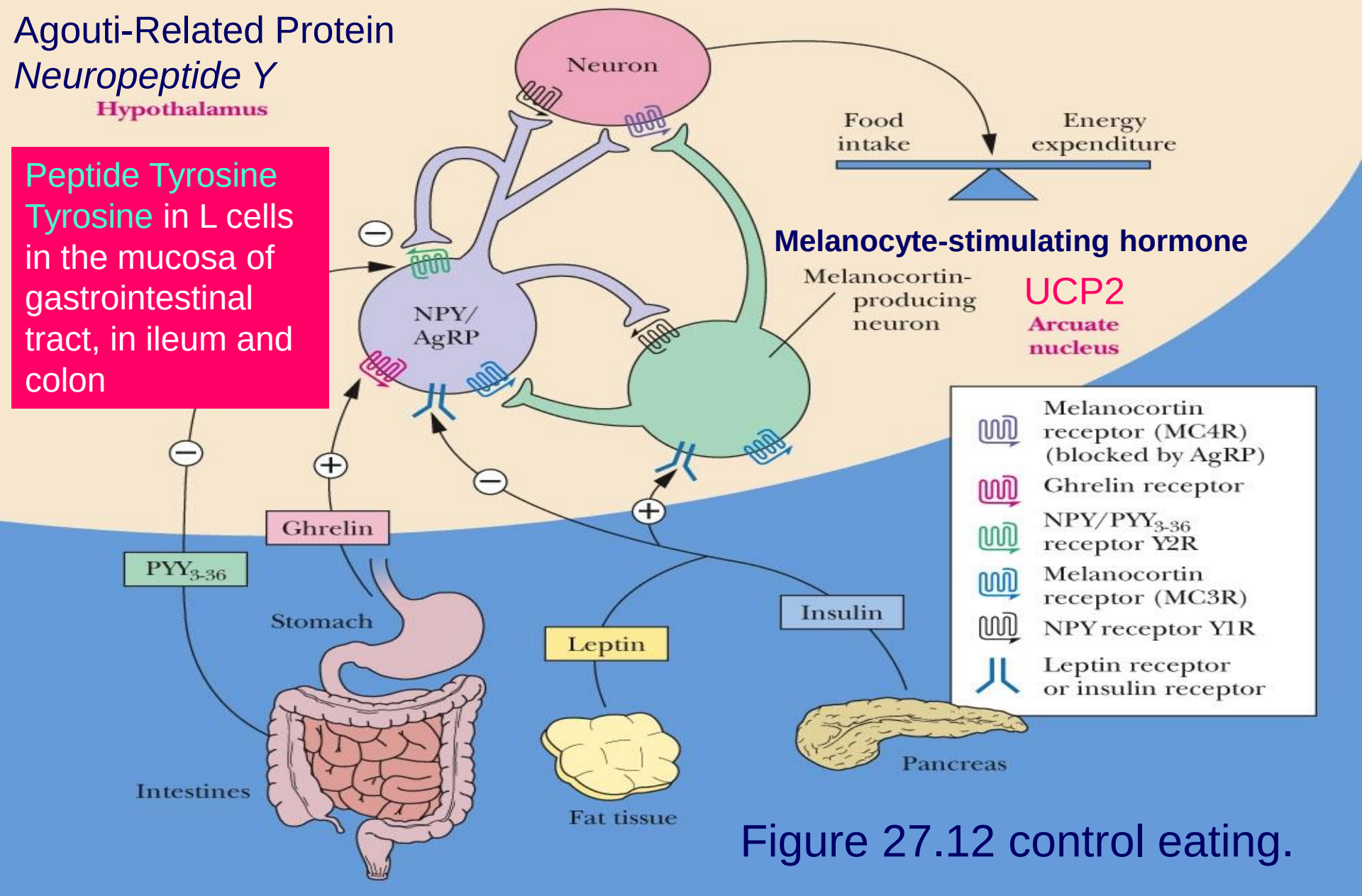
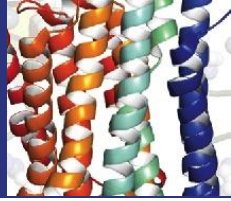


Figure 27.12 control eating.

27.7 Can You Really Live Longer by Eating Less?



- Caloric restriction leads to longevity-autophagy
- For most organisms, caloric restriction results in lower blood glucose levels, declines in glycogen and fat stores, enhanced responsiveness to insulin, lower body temperature, and diminished reproductive capacity
- Caloric restriction also diminishes the likelihood for development of many age-related diseases, including cancer, diabetes, and atherosclerosis

SIRT1 is a Key Regulator in Caloric Restriction

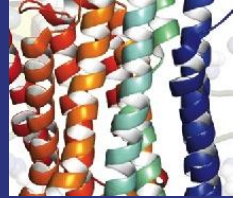
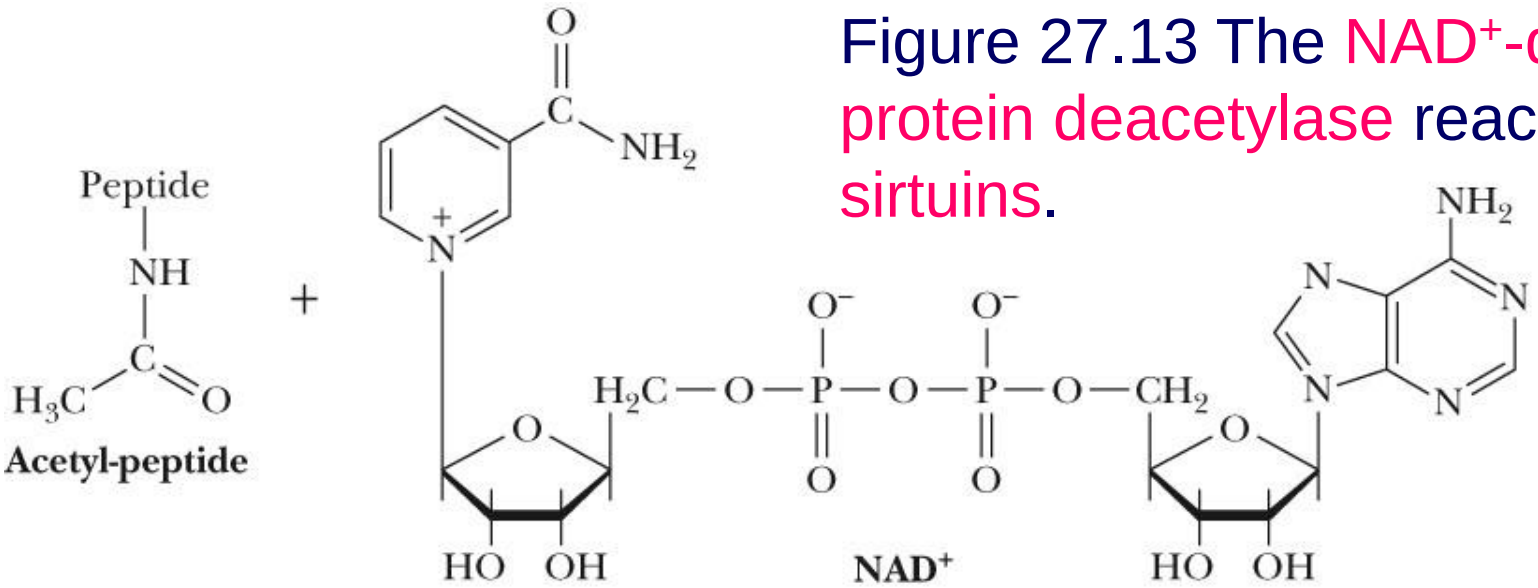
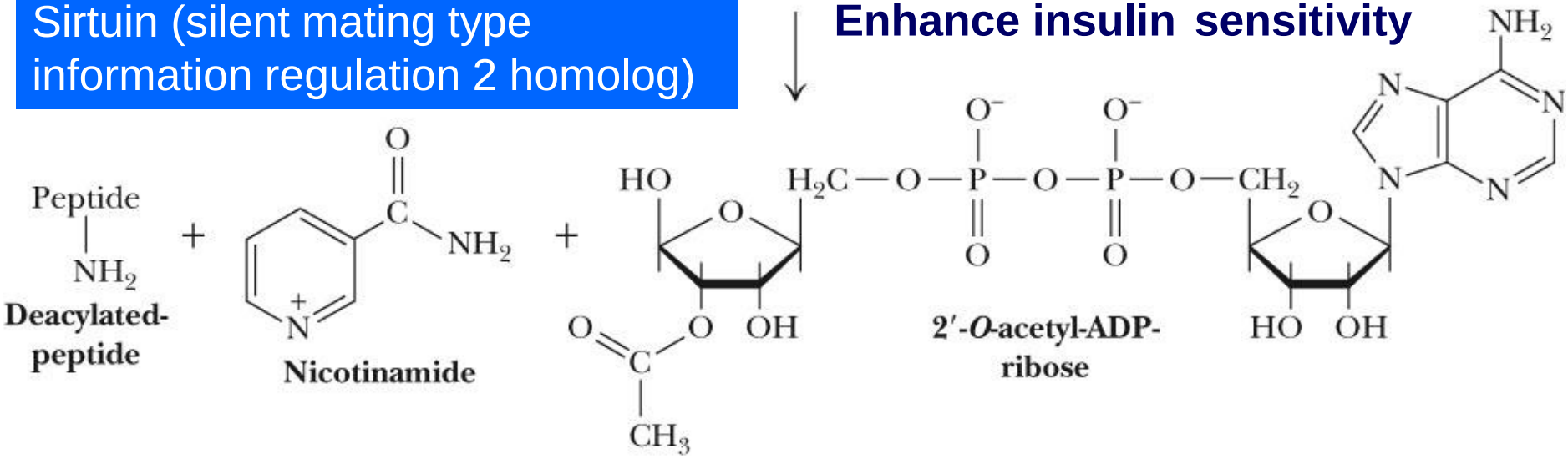


Figure 27.13 The NAD$^+$-dependent protein deacetylase reaction of sirtuins.

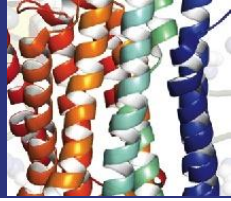


Sirtuin (silent mating type information regulation 2 homolog)

Enhance insulin sensitivity



Resveratrol in Red Wine is a Potent Activator of Sirtuin Activity



French people enjoy longevity despite a high-fat diet. Resveratrol may be the basis of this “French paradox”.

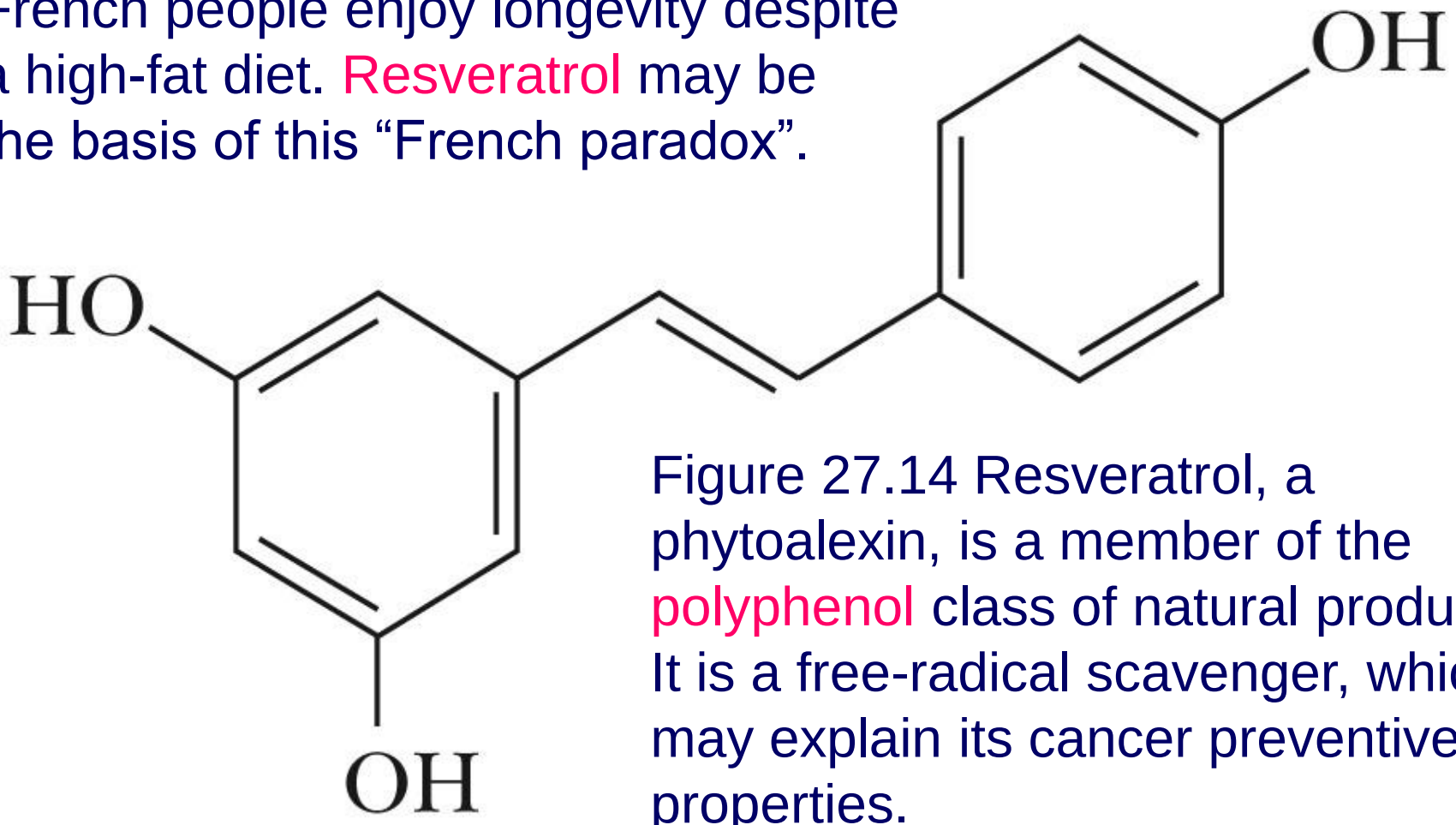
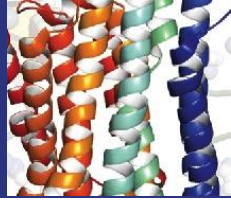


Figure 27.14 Resveratrol, a phytoalexin, is a member of the polyphenol class of natural products. It is a free-radical scavenger, which may explain its cancer preventive properties.

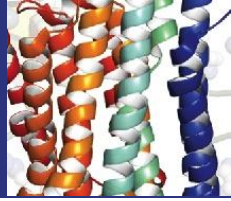
Activator of Sirtuin

Resveratrol (*trans*-3,4′,5-trihydroxystilbene)



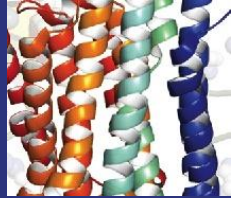
Chapter 31
Completing the Protein Life Cycle: Folding, Processing, and Degradation

Many Processes Introduce Variations into the Products of Protein-Encoding Genes



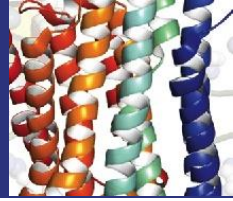
- The number of proteins in the human proteome may far exceed the number of protein-encoding genes
- Reasons for this include:
  - Gene rearrangments and alternative splicing
  - RNA editing and proteolytic processing
  - Isozymes and protein sharing
  - Protein-protein interactions
  - Covalent modifications of proteins
- This chapter explores the folding, processing, and degradation of proteins

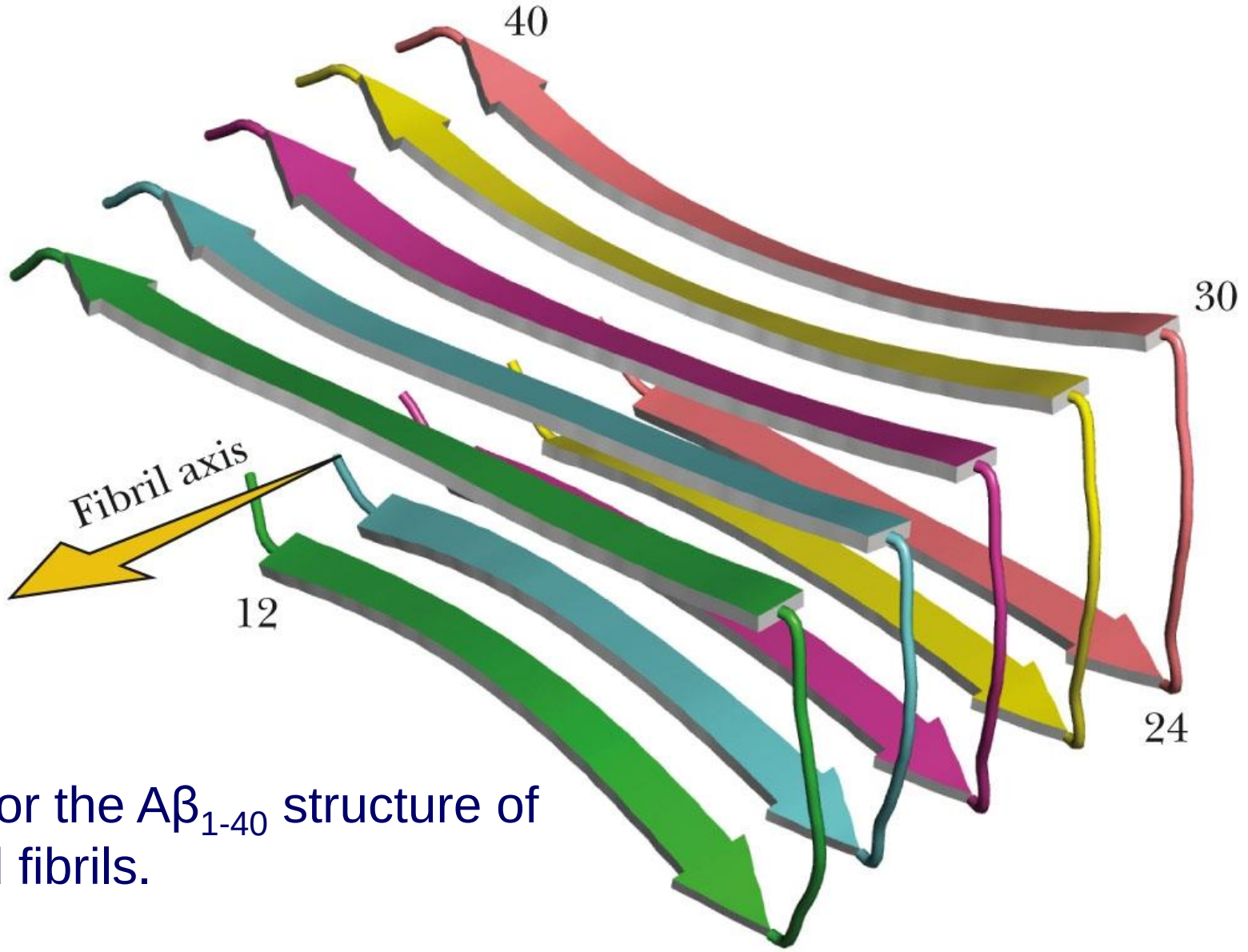
Several Diseases are Caused by Accumulation of Protein Deposits



- Protein misfolding is the cause of some diseases
- Amyloid plaques are protein deposits found in the brains of victims of neurodegenerative diseases – and in each case the protein is different
- Alzheimer's is caused both by extracellular amyloid deposits (of amyloid-β, or Aβ) and by intracellular tangles of microtubule-binding protein tau
- Parkinson's also involves tau
- Huntington's disease involves polyglutamate aggregates from mutant forms of **huntingtin**
- The tendency to form amyloid deposits may be a general property of proteins, and the evolution of chaperones may be a response to this problem

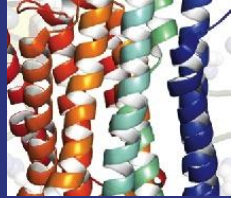
Several Diseases are Caused by Accumulation of Protein Deposits





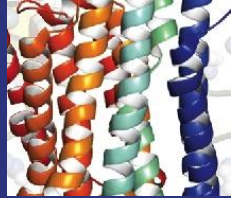
A model for the $A\beta_{1\text{-}40}$ structure of β-amyloid fibrils.

31.1 How Do Newly Synthesized Proteins Fold?



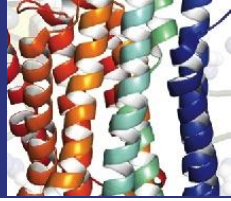
- Chaperones help some proteins fold
- Hsp70 chaperones bind to hydrophobic regions of extended polypeptides
- *E. coli* GroES-GroEL is an Hsp60 chaperonin
- Eukaryotic Hsp90 is a signal transduction protein chaperone

Chaperones Help Some Proteins Fold



- Chaperone proteins are found in all cells
- Many of these are designated **heat-shock proteins (HSPs)**
- The principal chaperones are Hsp70, Hsp60 (the **chaperonins**), and Hsp90
- Nascent proteins emerging from the ribosome are met by ribosome-associated chaperones, including:
  - **Trigger factor (TF)** in *E. coli*
  - **Nascent chain-associated complex (NAC)** in eukaryotes

Chaperones Help Some Proteins Fold



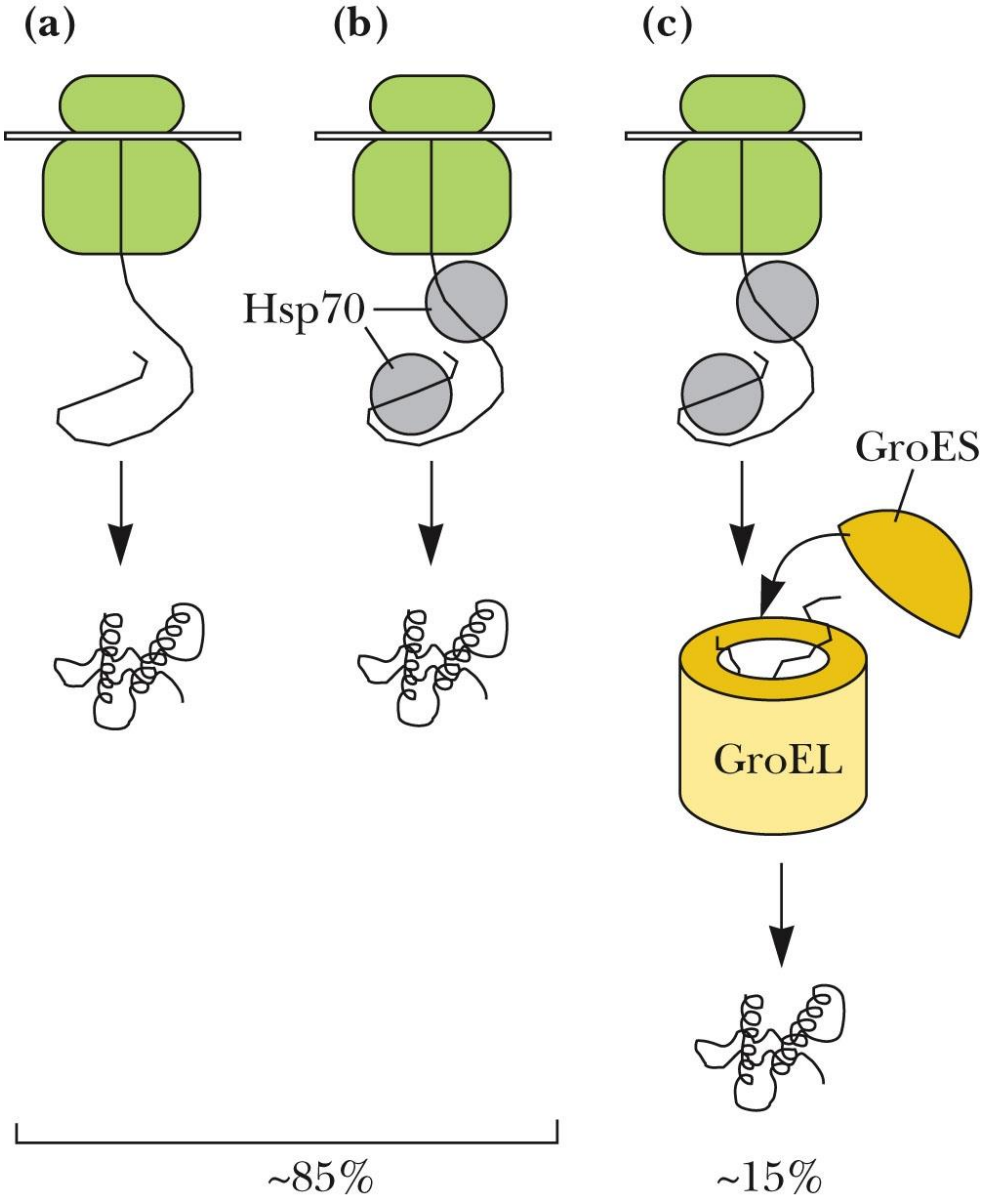
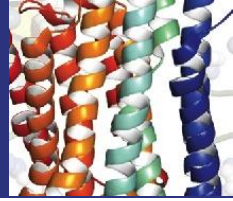


Figure 31.1 Protein folding pathways (a) Chaperone-independent folding. (b) Hsp70-assisted protein folding. (c) Folding assisted by Hsp70 and chaperonin complexes.

Hsp70 Chaperones Bind to Hydrophobic Regions of Extended Polypeptides



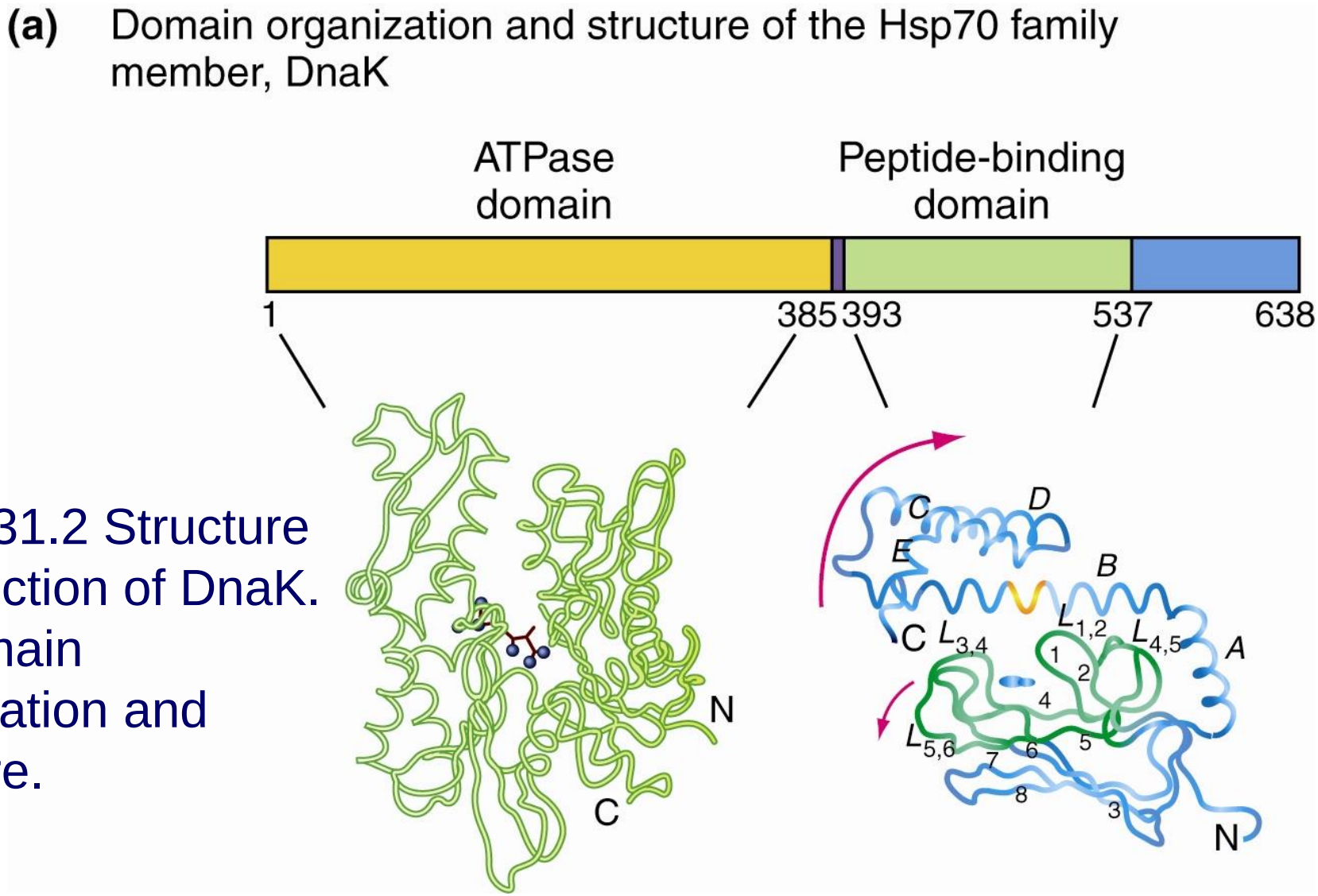
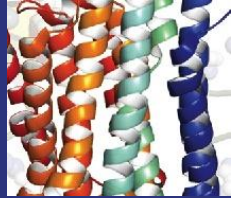


Figure 31.2 Structure and function of DnaK. (a) Domain organization and structure.

The GroES-GroEL Complex of *E. coli* is an Hsp60 Chaperonin



- Hsp60 chaperones (known as chaperonins) assist some protein to complete folding after release from ribosomes
- Chaperonins sequester partially folded proteins in an enclosed space referred to as an “Anfinsen cage”
- Chaperonins are large, cylindrical protein complexes formed from two stacked rings of subunits
- The *E. coli* chaperonin is **GroES-GroEL** (Fig. 31.3c)
- Substrate peptides in this complex undergo forced unfolding followed by folding processes that bury hydrophobic residues to produce the native form
- This complex process is ATP-driven

The GroES-GroEL Complex of *E. coli* is an Hsp60 Chaperonin

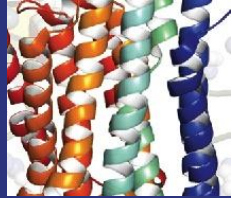
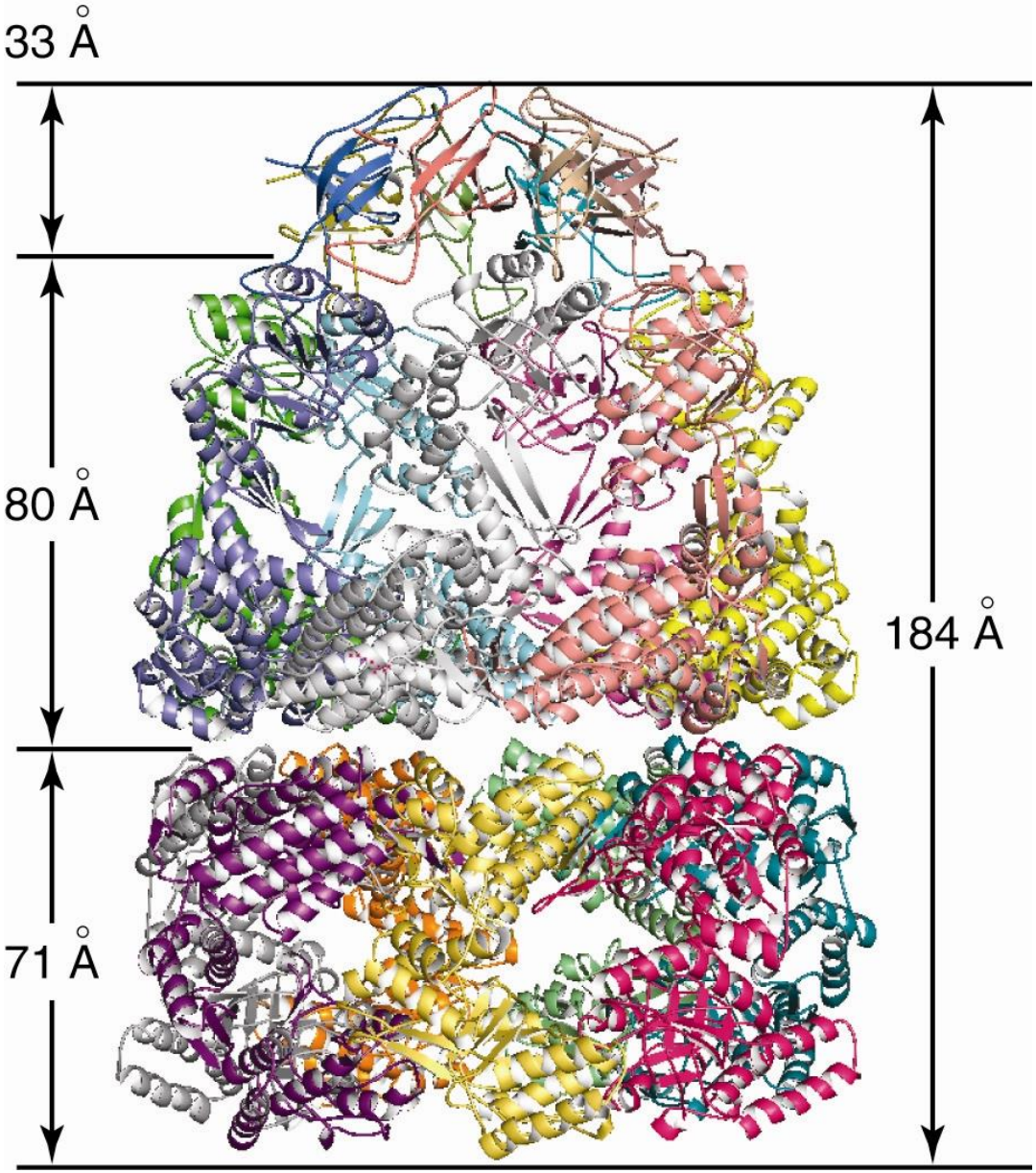
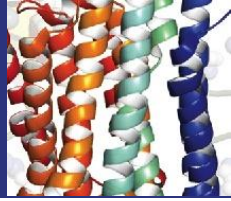


Figure 31.3 Structure and function of the GroES-GroEL complex. (a) Structure and overall dimensions of GroES-GroEL.



The GroES-GroEL Complex of *E. coli* is an Hsp60 Chaperonin



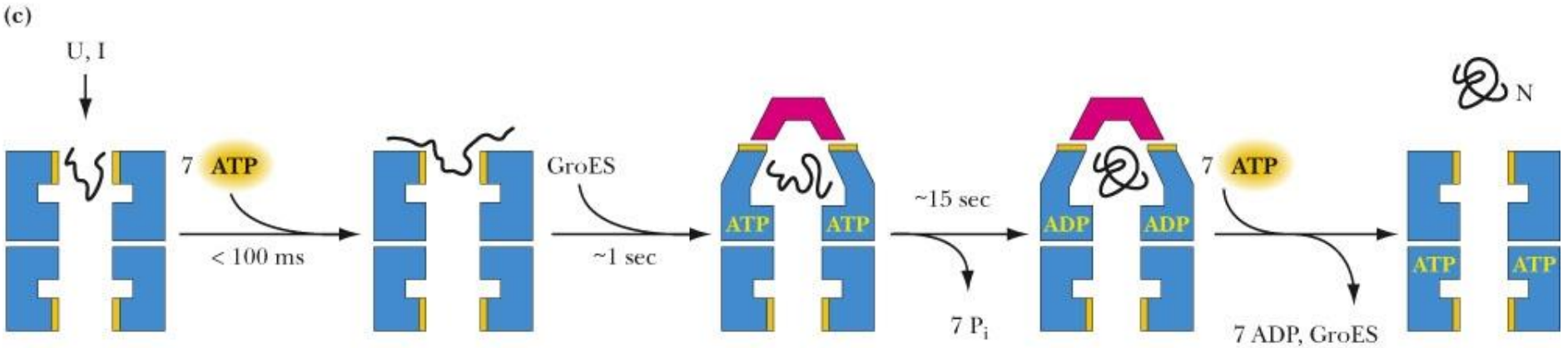
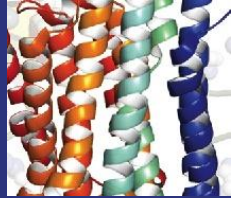


Figure 31.3 Structure and function of the GroES-GroEL complex. (c) Model of the GroEL cylinder (blue) in action. An unfolded (U) or partially folded (I) polypeptide binds to hydrophobic patches on the apical ring of α_7-subunits, followed by ATP binding, forced protein unfolding, and GroES (red) association.

31.4 How Does Protein Degradation Regulate Cellular Levels of Specific Proteins?



- Eukaryotic proteins are degraded by lysosomes or proteasomes
- Eukaryotic proteins are targeted for proteasome destruction by **ubiquitination**
- **Ubiquitin** is a highly conserved, 76-residue protein found widely in eukaryotes
- Proteins are condemned to degradation by ligation to ubiquitin
- Three other proteins – **E_1, E_2**, and **E_3** – are also involved in the ligation process
- E_1 is the **ubiquitin-activating enzyme**; E_2 is the **ubiquitin-carrier protein**; E_3 is the **ubiquitin-protein ligase**

Enzymatic Reactions in the Ligation of Ubiquitin to Proteins

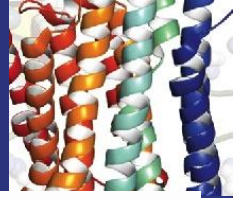
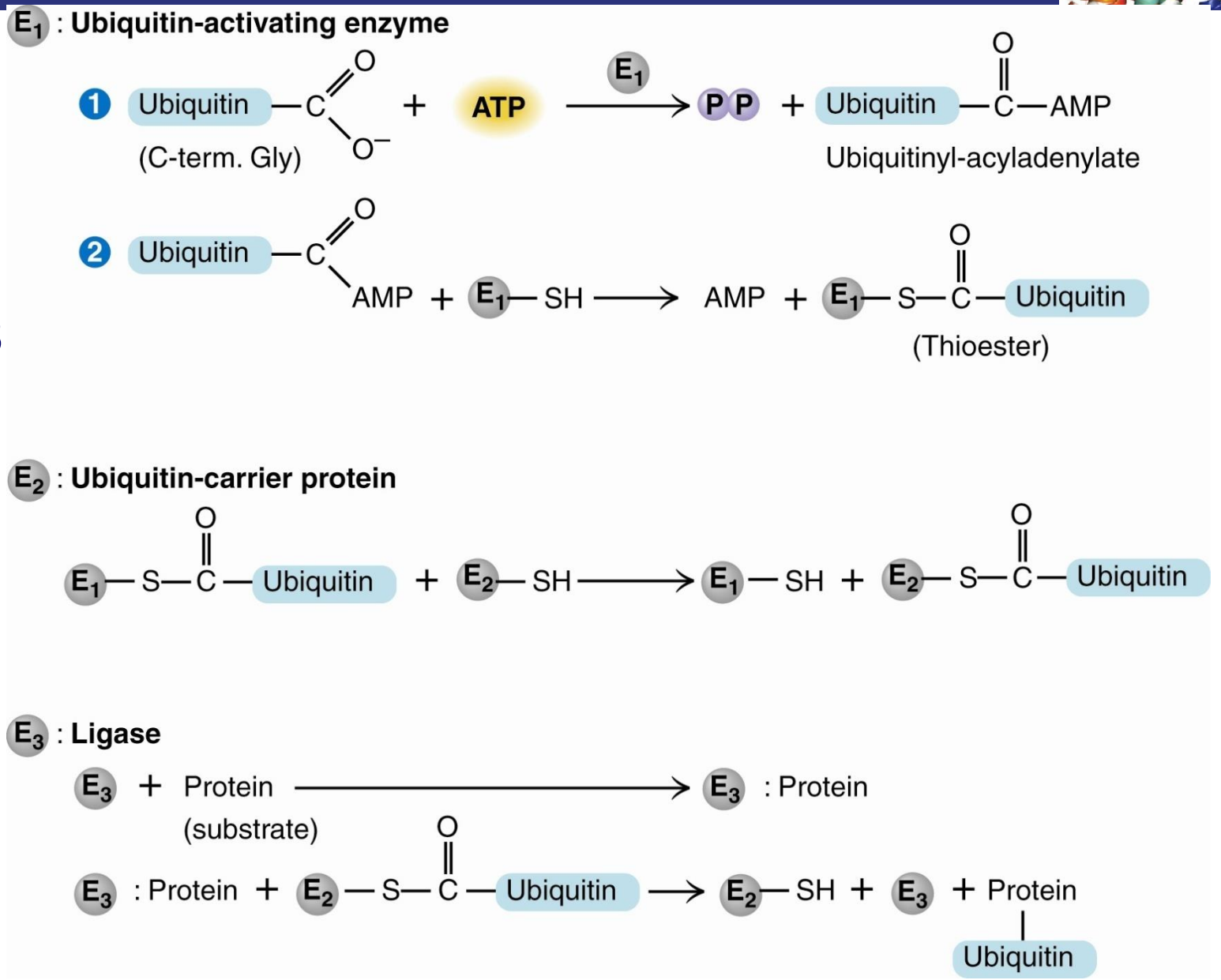
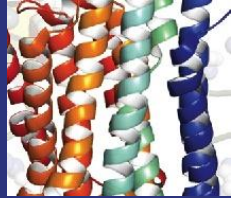


Figure 31.8



Eukaryotic Cells Contain Two Forms of Proteasomes



- Eukaryotic cells contain two forms of proteasomes: the **20S proteasomes** and **26S proteasomes**
- The 26S proteasome is a 45 nm-long structure composed of a 20S proteasome plus two additional structures known as **19S regulators** (Figure 31.10)
- The 19S cap structures on the ends of 26S proteasomes select ubiquitinated proteins for degradation in the core cavity
- ATPase modules mediate the unfolding of proteins in the proteasome
- The base of the 19S regulators consists of a hexameric ring of AAA-ATPases

The Ubiquitin-Proteasome Degradation Pathway

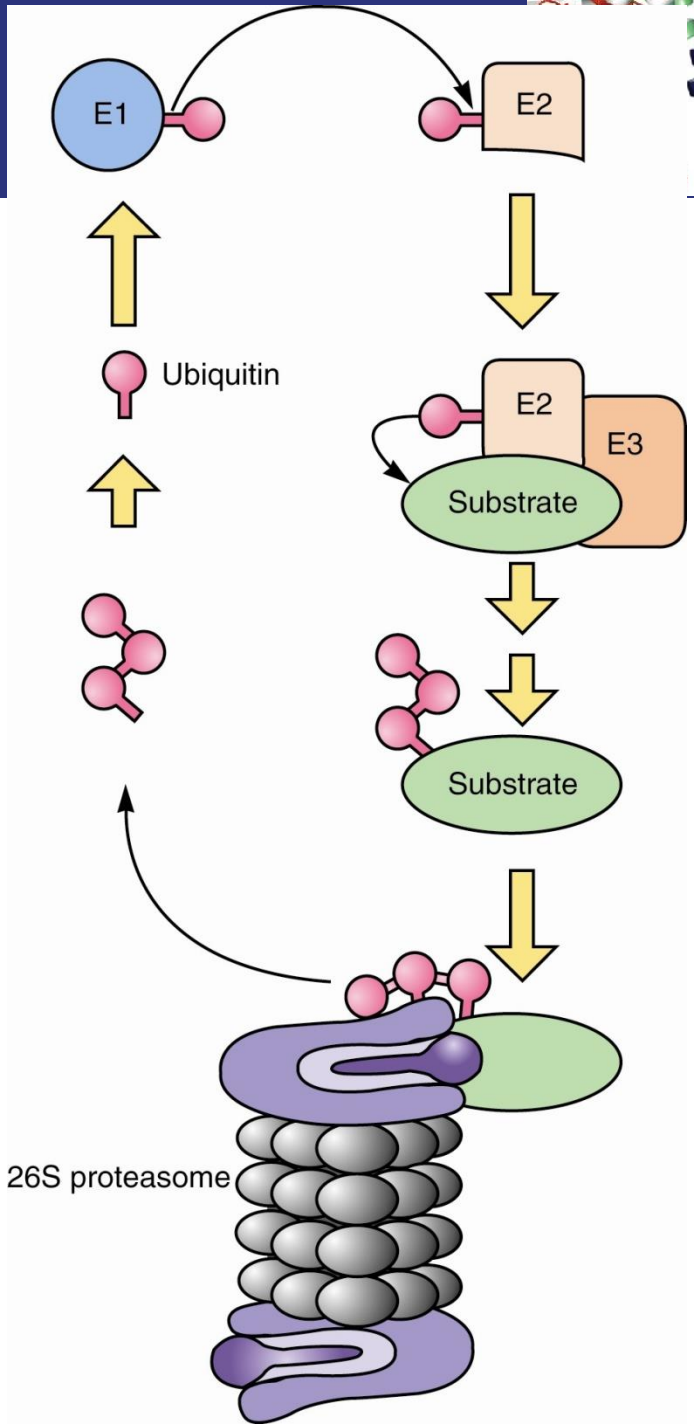
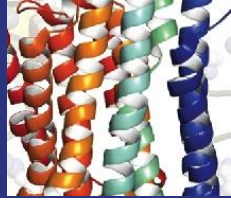


Figure 31.11 Diagram of the ubiquitin-proteasome degradation pathway. Pink “lollipop” structures symbolize ubiquitin molecules.

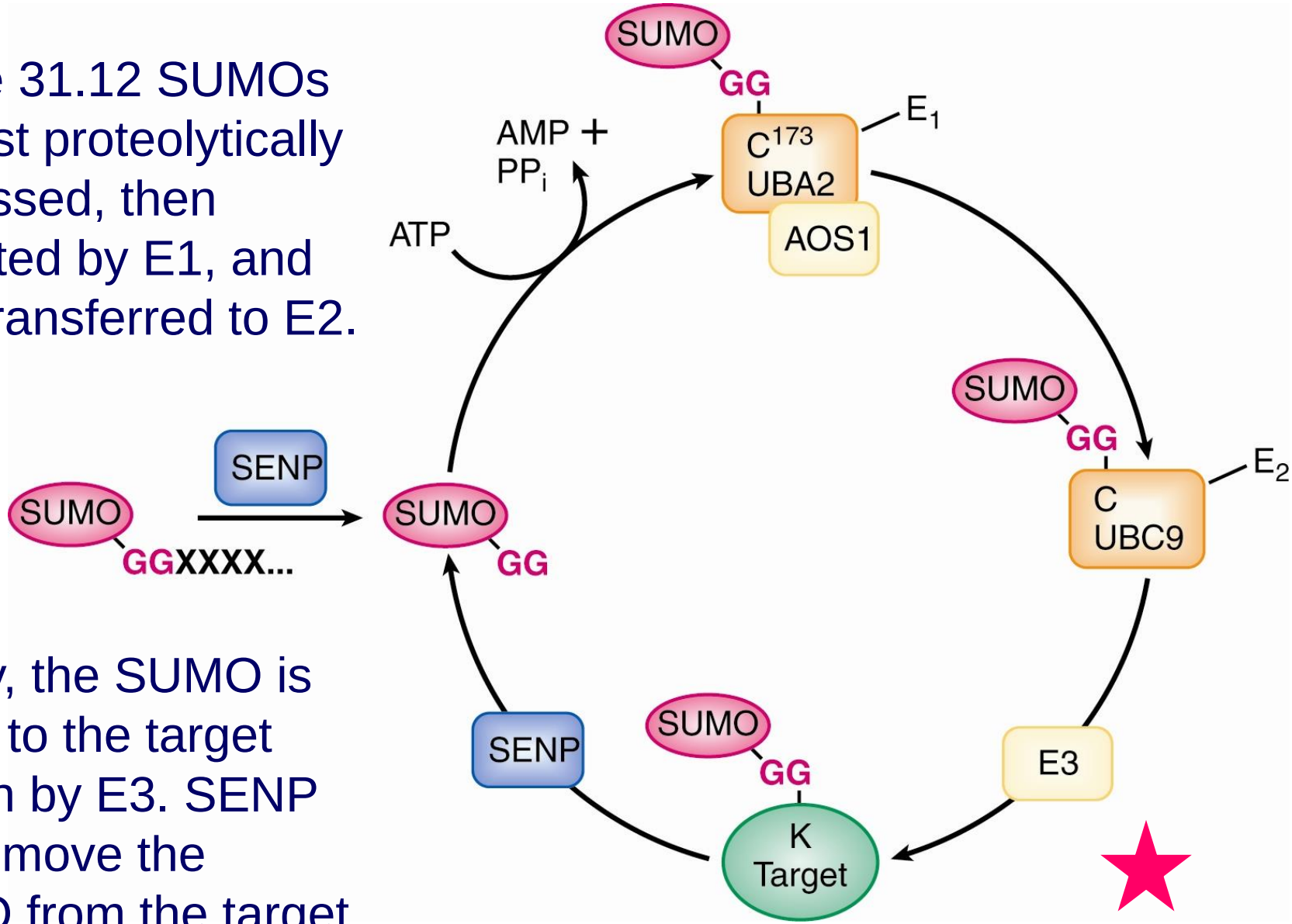
Small Ubiquitin-Like Protein Modifiers Are Post-Translational Regulators



- **Small ubiquitin-like protein modifiers (SUMOs)** are a highly conserved family of proteins found in all eukaryotic cells
- SUMOs are covalently ligated to lysine residues in target proteins by a three-enzyme conjugation system
- Sumoylated proteins are not targeted for destruction
- Instead, sumoylation alters the ability of the modified protein to interact with other proteins

The Mechanism of Reversible Sumoylation

Figure 31.12 SUMOs are first proteolytically processed, then activated by E1, and then transferred to E2.



Finally, the SUMO is linked to the target protein by E3. SENP can remove the SUMO from the target.

Protein Triage – A Model for Quality Control

Depending on the severity of damage, non-native proteins are directed to chaperones for refolding or targeted for destruction by a proteasome.