4: Fibrous Proteins

Overview

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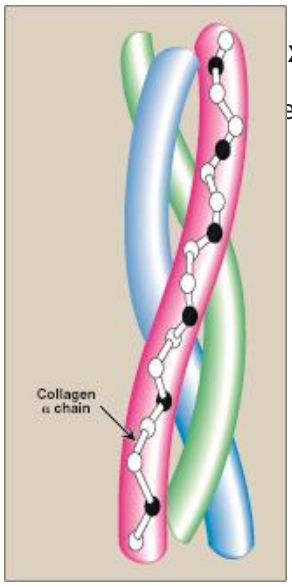
Fibrous proteins are usually folded into either extended filaments or sheet-like structures, with repeated amino acid sequences. They are relatively insoluble and provide structural or protective function in our tissues, such as in connective tissues, tendons, bone, and muscle fibers. Collagen and elastin are examples of commonly occurring, well-characterized fibrous proteins of the extracellular matrix (ECM). Collagen and elastin serve structural functions in the body, and are components of the skin, connective tissue, blood vessel walls, and the sclera and cornea of the eye. Each fibrous protein exhibits special mechanical properties, resulting from its unique structure, which is obtained by combining specific amino acids into repeated, secondary structural elements. This is in contrast to globular proteins (discussed in Chapter 3), whose shapes are the result of complex interactions between secondary, tertiary, and, sometimes, quaternary structural elements.

Collagen

Listen

Collagen is the most abundant protein in the human body. A typical collagen molecule is a long, rigid structure in which three polypeptides (referred to as α chains) are wound around one another in a rope-like triple helix (Fig. 4.1). Although this triple helix is found in all collagen molecules throughout the body, the many subtypes of collagen are further organized and dictated by the structural role collagen plays in a particular organ. In some tissues, collagen may be dispersed as a gel that gives support to the structure, such as in the ECM or the vitreous humor of the eye. In other tissues, collagen may be bundled in tight, parallel fibers that provide great strength, as in tendons. In the cornea of the eye, collagen is stacked so as to transmit light with a minimum of scattering. Collagen of bone occurs as fibers arranged at an angle to each other so as to resist mechanical shear from any direction.

FIGURE 4.1



x of collagen formed from three α chains.

emselves are helical in structure.)

Types

The collagen superfamily of proteins includes >25 collagen types as well as additional proteins that have collagen-like domains. The three polypeptide α chains are held together by interchain hydrogen bonds. Variations in the amino acid sequence of the α chains result in structural components that are about the same size (~1,000 amino acids long) but with slightly different properties. These α chains are combined to form the various types of collagen found in the tissues. For example, the most common collagen, type I, contains two chains called α1 and one chain called α2 ($\alpha 1_2 \alpha 2$), whereas type II collagen contains three α1 chains ($\alpha 1_3$). The collagens can be organized into three groups, based on their location and functions in the body (Fig. 4.2).

Fibril-forming collagens

Types I, II, and III are the fibrillar collagens, with a rope-like structure described above for a typical collagen molecule. In the electron microscope, these linear polymers of fibrils have characteristic banding patterns, reflecting the regular staggered packing of the individual collagen molecules in the fibril (Fig. 4.3). Type I collagen fibers (composed of collagen fibrils) are found in supporting elements of high tensile strength (e.g., tendons and corneas), whereas fibers formed from type II collagen molecules are restricted to cartilaginous structures. The fibers derived from type III collagen are prevalent in more distensible tissues such as blood vessels.

Network-forming collagens

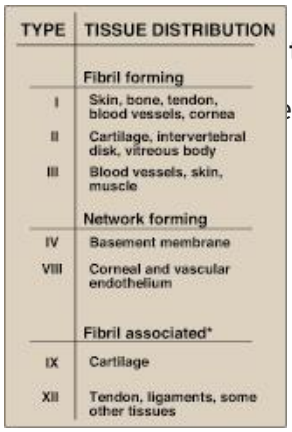
Types IV and VIII form a three-dimensional mesh, rather than distinct fibrils (Fig. 4.4). For example, type IV molecules assemble into a sheet or meshwork that constitutes a major part of basement membranes.

Basement membranes are thin, sheet-like structures that provide mechanical support for adjacent cells and function as a semipermeable filtration barrier to macromolecules in organs such as the kidney and the lung.

Fibril-associated collagens

Types IX and XII bind to the surface of collagen fibrils, linking these fibrils to one another and to other components in the ECM (Fig. 4.2).

FIGURE 4.2

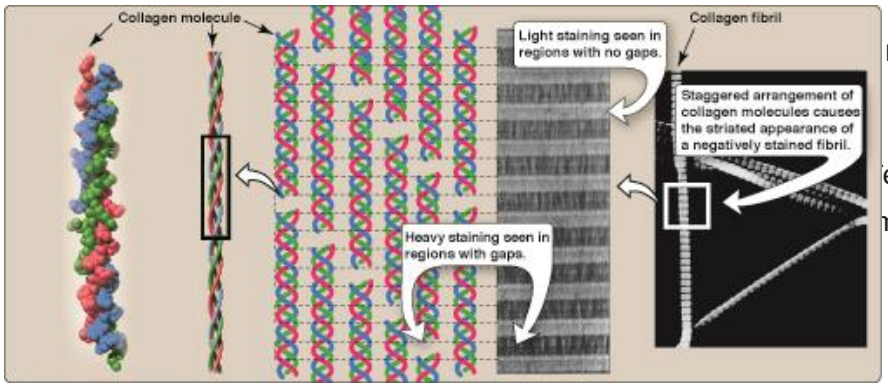


TYPE	TISSUE DISTRIBUTION
	Fibril forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, skin, muscle
	Network forming
IV	Basement membrane
VIII	Corneal and vascular endothelium
	Fibril associated*
IX	Cartilage
XII	Tendon, ligaments, some other tissues

types of collagen.

ed collagens with interrupted triple helices are known as FACIT.)

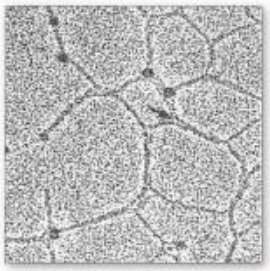
FIGURE 4.3



reflecting the regularly staggered

exas A&M University Kingsville. Collagen mistry. 3rd ed. Boston, MA: Addison

FIGURE 4.4



of a polygonal network formed by association of collagen type IV monomers.

co PD, Birk DE, Mecham RP, eds. Extracellular Matrix Assembly and Structure. San Diego, 94.

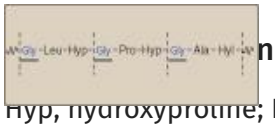
Structure

Unlike most globular proteins that are folded into compact structures, collagen, a fibrous protein, has an elongated, triple-helix structure that is stabilized by interchain hydrogen bonds.

Amino acid sequence

Collagen is rich in proline and glycine, both of which are important in the formation of the triple-stranded helix. Proline facilitates the formation of the helical conformation of each α chain because its ring structure causes "kinks" in the peptide chain. (Note: The presence of proline dictates that the helical conformation of the α chain cannot be an α helix [see p. 16].) Glycine, the smallest amino acid, is found in every third position of each polypeptide chain. Glycine fits into the restricted spaces where the three chains of the helix come together. The glycine residues are part of a repeating sequence, –Gly–X–Y–, where X is frequently proline, and Y is often hydroxyproline (but can be hydroxylysine, Fig. 4.5). Thus, most of the α chain can be regarded as a polytripeptide whose sequence can be represented as $(–Gly–Pro–Hyp–)_{333}$.

FIGURE 4.5



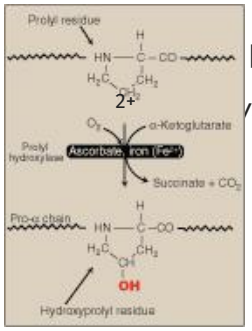
nce of a portion of the α1 chain of collagen.

Hyp, hydroxyproline; Hyl, hydroxylysine.

Hydroxyproline and hydroxylysine

Collagen contains hydroxyproline and hydroxylysine, which are nonstandard amino acids (see p. 1) not present in most other proteins. These unique amino acids result from the hydroxylation of some of the proline and lysine residues after their incorporation into polypeptide chains (Fig. 4.6). Therefore, hydroxylation is a posttranslational modification (see p. 509). (Note: The presence of hydroxyproline maximizes formation of interchain hydrogen bonds that stabilize the triple-helical structure.)

FIGURE 4.6



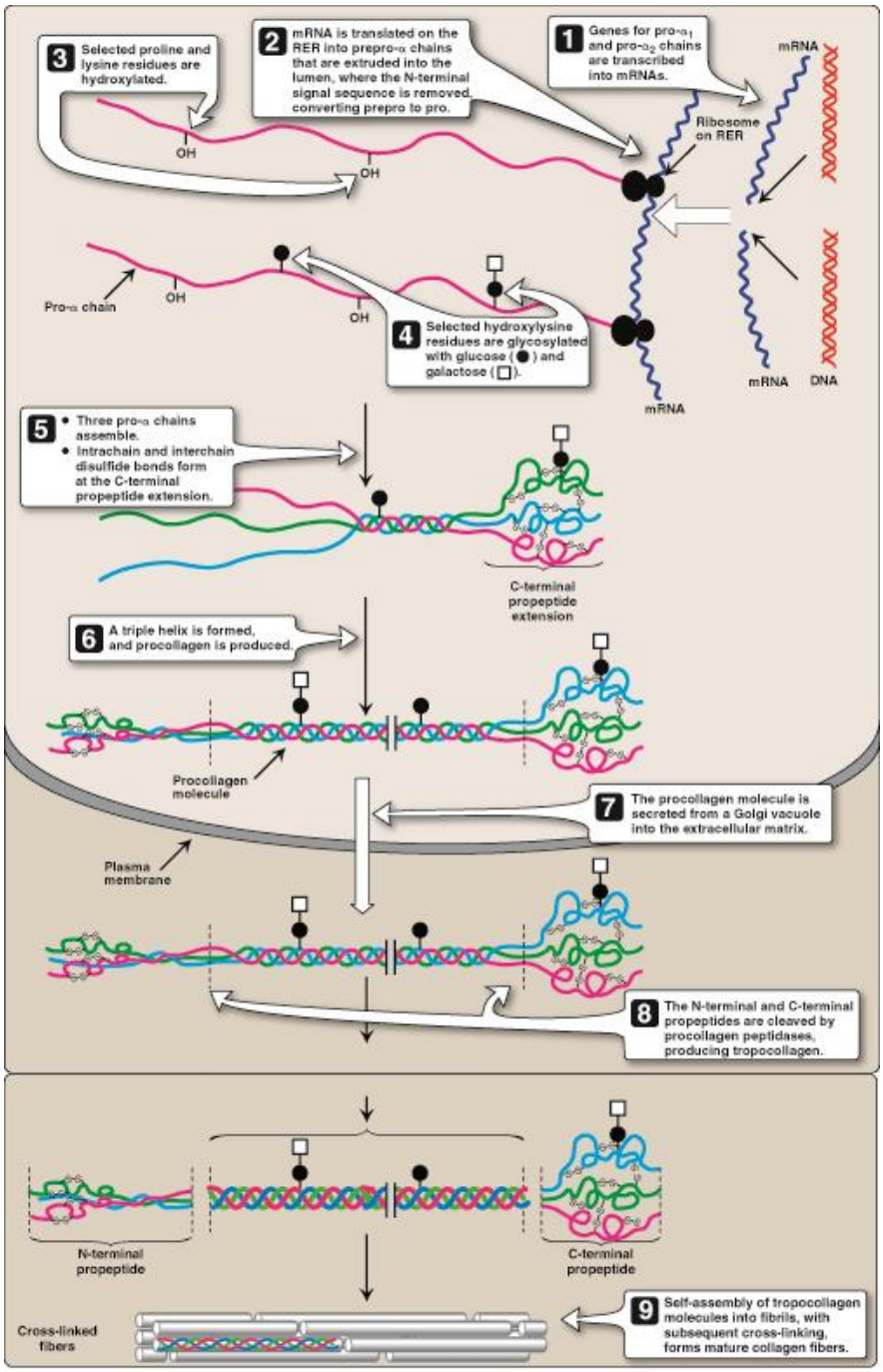
proline residues in pro-α chains of collagen by *prolyl hydroxylase*.

ylase cofactor) is protected from oxidation to Fe^{3+} by ascorbate [vitamin C].)

Glycosylation

The hydroxyl group of the hydroxylysine residues of collagen may be enzymatically glycosylated. Most commonly, glucose and galactose are sequentially attached to the polypeptide chain prior to triple-helix formation (Fig. 4.7).

FIGURE 4.7



Biosynthesis

The polypeptide precursors of the collagen molecule are synthesized in fibroblasts (or in the related osteoblasts of bone and chondroblasts of cartilage). They are enzymically modified and form the triple helix, which gets secreted into the ECM. After additional enzymic modification, the mature extracellular collagen fibrils aggregate and become cross-linked to form collagen fibers.

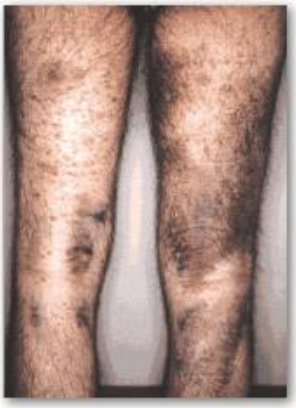
Pro-α chain formation

Collagen is one of many proteins that normally function outside of cells. Like most proteins produced for export, the newly synthesized polypeptide precursors of α chains (prepro-α chains) contain a special amino acid sequence at their amino (N)-terminal ends. This sequence acts as a signal that, in the absence of additional signals, targets the polypeptide being synthesized for secretion from the cell. The signal sequence facilitates the binding of ribosomes to the rough endoplasmic reticulum (RER) and directs the passage of the prepro-α chain into the lumen of the RER. The signal sequence is rapidly cleaved in the lumen to yield a precursor of collagen called a pro-α chain (Fig. 4.7).

Hydroxylation

The pro-α chains are processed by a number of enzymes within the lumen of the RER while the polypeptides are still being synthesized (Fig. 4.7). Proline and lysine residues found in the Y-position of the –Gly–X–Y– sequence can be hydroxylated to form hydroxyproline and hydroxylysine residues. These hydroxylation reactions require molecular oxygen, ferrous iron (Fe^{2+}), and the reducing agent vitamin C (ascorbic acid, see p. 427), without which the hydroxylating enzymes, prolyl hydroxylase, and lysyl hydroxylase, are unable to function (see Fig. 4.6). In the case of ascorbic acid deficiency (and, therefore, a lack of proline and lysine hydroxylation), the formation of interchain H-bonds and the formation of a stable triple helix are impaired. Additionally, collagen fibrils cannot be cross-linked (see 7. below), greatly decreasing the tensile strength of the assembled fiber. The resulting deficiency disease is known as scurvy. Patients with scurvy often show ecchymoses (bruise-like discolorations) and petechiae on the limbs as a result of subcutaneous extravasation (leakage) of blood due to capillary fragility (Fig. 4.8). Other symptoms also include gum disease, loosening of the teeth, and poor wound healing.

FIGURE 4.8



old man with scurvy.

al medicine. *N Engl J Med*. 1995;332(24):1611.

Glycosylation

Some hydroxylysine residues are modified by glycosylation with glucose or glucosyl-galactose (Fig. 4.7).

Assembly and secretion

After hydroxylation and glycosylation, three pro-α chains form procollagen, a precursor of collagen that has a central region of triple helix flanked by the nonhelical N- and carboxyl (C)-terminal extensions called propeptides (Fig. 4.7). The formation of procollagen begins with formation of interchain disulfide bonds between the C-terminal extensions of the pro-α chains. This brings the three α chains into an alignment favorable for triple helix formation. The procollagen molecules move through the Golgi apparatus, where they are packaged in secretory vesicles. The vesicles fuse with the cell membrane, causing the release of procollagen molecules into the extracellular space.

Extracellular cleavage of procollagen molecules

After their release, the triple-helical procollagen molecules are cleaved by *N*- and *C-procollagen peptidases*, which remove the terminal propeptides, producing tropocollagen molecules.

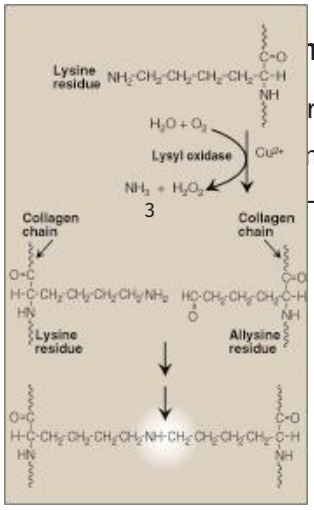
Collagen fibril formation

Tropocollagen molecules spontaneously associate to form collagen fibrils. The fibrils form an ordered, parallel array, with adjacent collagen molecules arranged in a staggered pattern formed by approximately three-quarters of each molecule overlapping the neighboring molecule (Fig. 4.7).

Cross-link formation

The array of collagen fibril molecules serves as a substrate for lysyl oxidase. This copper-containing extracellular enzyme oxidatively deaminates some of the lysine and hydroxylysine residues in collagen. The reactive aldehydes (allysine and hydroxyallysine) that result from the deamination reactions can spontaneously condense with lysine or hydroxylysine residues in neighboring collagen molecules to form covalent cross-links and, thus, mature collagen fibers (Fig. 4.9). (Note: Cross-links can also form between two allysine residues.)

FIGURE 4.9



nks in collagen.

reversibly inhibited by a toxin present in seeds from *Lathyrus odoratus* [sweet pea], nown as lathyrism that is characterized by skeletal and vascular problems.) Cu^{2+}, H_2O_2, hydrogen peroxide.

Lysyl oxidase is one of several copper-containing enzymes. Others include ceruloplasmin (see p. 451), cytochrome c oxidase (see p. 84), dopamine hydroxylase (see p. 318), superoxide dismutase (see p. 163), and tyrosinase (see p. 303). Disruption in copper homeostasis causes copper deficiency (X-linked Menkes syndrome) or overload (Wilson disease) (see p. 449).

Degradation

Normal collagens fibers are highly stable molecules, having half-lives as long as several years. However, connective tissue is dynamic and is constantly being remodeled, often in response to growth or injury of the tissue. Breakdown of collagen fibers is dependent on the proteolytic action of collagenases, which are part of a large family of matrix metalloproteinases. For type I collagen, the cleavage site is specific, generating three-quarter and one-quarter length fragments. These fragments are further degraded by other matrix proteinases.

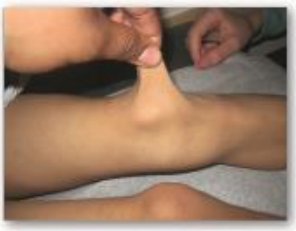
Collagenopathies

Defects in any one of the many steps in collagen fiber synthesis can result in a genetic disease involving an inability of collagen to form fibers properly and, therefore, an inability to provide tissues with the needed tensile strength normally provided by collagen. More than 1,000 mutations have been identified in 23 genes coding for 13 of the collagen types. The following are examples of diseases (collagenopathies) that are the result of defective collagen synthesis.

Ehlers–Danlos syndrome

Ehlers–Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders that result from heritable defects in the metabolism of fibrillar collagen molecules. EDS can be caused by a deficiency of collagen-processing enzymes (e.g., lysyl hydroxylase or N-procollagen peptidase) or from mutations in the amino acid sequences of collagen types I, III, and V. The classic form of EDS, caused by defects in type V collagen, is characterized by skin extensibility and fragility and joint hypermobility (Fig. 4.10). The vascular form, due to defects in type III collagen, is the most serious form of EDS because it is associated with potentially lethal arterial rupture. (Note: The classic and vascular forms show autosomal-dominant inheritance.) Collagen that contains mutant chains may have altered structure, secretion, or distribution, and it frequently is degraded. (Note: Incorporation of just one mutant chain may result in degradation of the triple helix. This is known as a dominant-negative effect.)

FIGURE 4.10



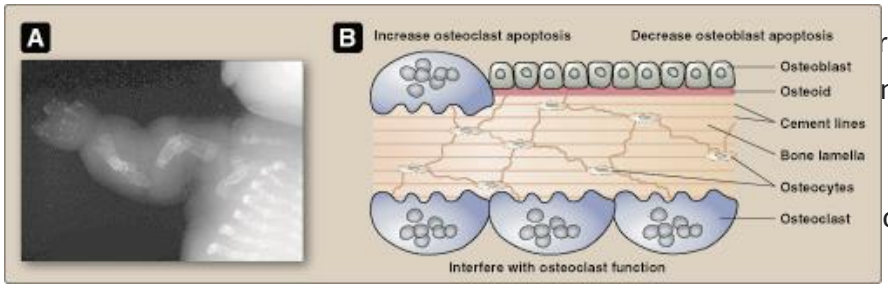
c Ehlers–Danlos syndrome and mechanism of bisphosphonates.

opathology and Dermatology. Wolters Kluwer; 2019, Figure 9-1A.

Osteogenesis imperfecta

This syndrome, known as “brittle bone disease,” is a genetic disorder of bone fragility characterized by bones that fracture easily, with minor or no trauma (Fig. 4.11). Over 80% of cases of osteogenesis imperfecta (OI) are caused by dominant mutations to the genes that encode the α1 or α2 chains in type I collagen. The most common mutations cause the replacement of glycine (in –Gly–X–Y–) by amino acids with bulky side chains. The resultant structurally abnormal α chains prevent the formation of the required triple-helical conformation. Phenotypic severity ranges from mild to lethal. Type I OI, the most common form, is characterized by mild bone fragility, hearing loss, and blue sclerae. Type II, the most severe form, is typically lethal in the perinatal period as a result of pulmonary complications. *In utero* fractures are seen (Fig. 4.11, left). Type III is also a severe form and is characterized by multiple fractures at birth, short stature, spinal curvature leading to a humped-back (kyphotic) appearance, and blue sclerae. Dentinogenesis imperfecta, a disorder of tooth development, may be seen in OI. OI is treated with bisphosphonates (Fig. 4.11, right), which function by inactivating osteoclasts, the cells that break down bone tissue. Bisphosphonates also increase apoptosis (cell death) of osteoclasts, and therefore inhibit the resorption of bone material. Bisphosphonates also decrease apoptosis of osteoblasts, the cells that lay down new bone matrix.

FIGURE 4.11



res appear *in utero*, as revealed by this
nates to treat OI patients. OI,

cs. 2nd ed. St. Louis, MO: Mosby; 1999.

Alport syndrome

This is a group of heterogeneous inherited disorders of basement membranes of the kidney, and frequently the cochlea and the eye, characterized by glomerulonephritis, hematuria, proteinuria, hypertension, and progression to end-stage renal disease (ESRD) and hearing loss during the second to fourth decades of life. This disorder is the result of mutations in type IV collagen genes, with a genetic frequency of approximately 1 case in 5,000. The most common form inherits as X-linked autosomal dominant. The pattern of inheritance and symptoms differ depending on which type IV collagen gene is involved.

Elastin

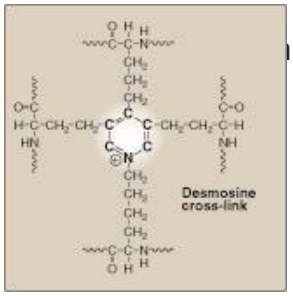
Listen

In contrast to collagen, which forms fibers that are tough and have high tensile strength, elastin is a fibrous protein with rubber-like properties found in connective tissue. Elastic fibers composed of elastin and glycoprotein microfibrils are found in the lungs, the walls of large arteries, and elastic ligaments. They can be stretched to several times their normal length but recoil to their original shape when the stretching force is relaxed.

Structure

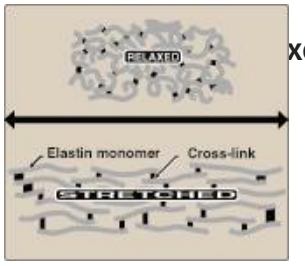
Elastin is an insoluble protein polymer generated from a precursor, tropoelastin, which is a soluble polypeptide composed of ~700 amino acids that are primarily small and nonpolar (e.g., glycine, alanine, and valine). Elastin is also rich in proline and lysine but contains few hydroxyproline and hydroxylysine. Tropoelastin is secreted by the cell into the ECM. There, it interacts with specific glycoprotein microfibrils, such as fibrillin, which function as a scaffold onto which tropoelastin is deposited. Some of the lysyl side chains of the tropoelastin polypeptides are oxidatively deaminated by lysyl oxidase, forming allysine residues. Three of the allysyl side chains plus one unaltered lysyl side chain from the same or neighboring polypeptides form a desmosine cross-link (Fig. 4.12). This produces elastin, an extensively interconnected, rubbery network that can stretch and bend in any direction when stressed, giving connective tissue elasticity (Fig. 4.13). Mutations in the fibrillin-1 protein are responsible for Marfan syndrome, a connective tissue disorder characterized by impaired structural integrity in the skeleton, the eye, and the cardiovascular system. With this disease, abnormal fibrillin protein is incorporated into microfibrils along with normal fibrillin, inhibiting the formation of functional microfibrils. Patients with Marfan syndrome are frequently tall, with long slender arms, legs, fingers, and toes. They will have flexible joints and may have scoliosis. The heart and aorta are often affected as well, and there is an increased risk for mitral valve prolapse or aortic aneurysm. (Note: Patients with Marfan syndrome, OI, or EDS may have blue sclerae due to tissue thinning that allows underlying pigment to show through.)

FIGURE 4.12



ık unique to elastin.

FIGURE 4.13



xed and stretched conformations.

α1-Antitrypsin in elastin degradation

Blood and other body fluids contain a protein, α_1-antitrypsin (AAT), which inhibits a number of proteolytic enzymes (called peptidases, proteases, or proteinases) that hydrolyze and destroy proteins. (Note: The inhibitor was originally named AAT because it inhibits the activity of trypsin, a proteolytic enzyme synthesized as trypsinogen by the pancreas [see p. 274].) AAT has the important physiologic role of inhibiting neutrophil elastase, a powerful protease that is released into the extracellular space and degrades elastin of alveolar walls as well as other structural proteins in a variety of tissues (Fig. 4.14). Most of the AAT found in plasma is synthesized and secreted by the liver. Extrahepatic synthesis also occurs.

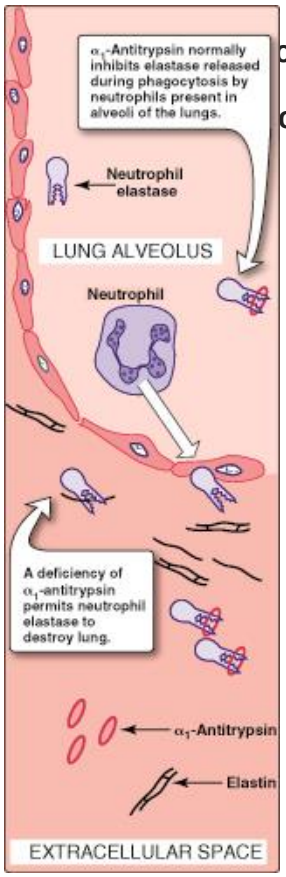
α1-Antitrypsin in the lungs

In the normal lung, the alveoli are chronically exposed to low levels of neutrophil elastase released from activated and degenerating neutrophils. The proteolytic activity of elastase can destroy the elastin in alveolar walls if unopposed by the action of AAT, the most important inhibitor of neutrophil elastase (Fig. 4.14). Because lung tissue cannot regenerate, the destruction of the connective tissue of alveolar walls caused by an imbalance between the protease and its inhibitor results in pulmonary disease.

α1-Antitrypsin deficiency and emphysema

In the United States, ~2% to 5% of patients with emphysema are predisposed to the disease by inherited defects in AAT. A number of different mutations in the gene for AAT are known to cause a deficiency of the protein, but one single purine base mutation (GAG to AAG, resulting in the substitution of lysine for glutamic acid at position 342 of the protein) is clinically the most widespread and severe. (Note: The mutated protein is termed the Z variant.) The mutation causes the normally monomeric AAT protein to misfold, polymerize, and aggregate within the RER of hepatocytes, resulting in decreased secretion of AAT by the liver. AAT deficiency is, therefore, a misfolded protein disease. (Note: The polymer that accumulates in hepatocytes may result in cirrhosis. Such hepatic damage is a leading cause for pediatric end-stage liver failure, which requires liver transplantation.) Because less AAT is secreted by the liver, blood levels of AAT are reduced, as is the amount of AAT that is available to lung tissues. In the United States, the AAT mutation is most common in Caucasians of Northern European ancestry. An individual must inherit two abnormal AAT alleles to be at risk for the development of emphysema. In a heterozygote, with one normal and one defective allele, the levels of AAT are sufficient to protect the alveoli from damage. (Note: Methionine 358 in AAT is required for the binding of the inhibitor to its target *proteases*. Smoking causes the oxidation and subsequent inactivation of the methionine, thereby rendering the inhibitor powerless to neutralize *elastase*. Smokers with AAT deficiency, therefore, have a considerably elevated rate of lung destruction and a poorer survival rate than nonsmokers with the deficiency.) The deficiency of *elastase* inhibitor can be treated by weekly augmentation therapy, that is, intravenous administration of AAT. The AAT diffuses from the blood into the lung, where it reaches therapeutic levels in the fluid surrounding the lung epithelial cells.

FIGURE 4.14



olar tissue by *elastase* released from neutrophils activated as part of the

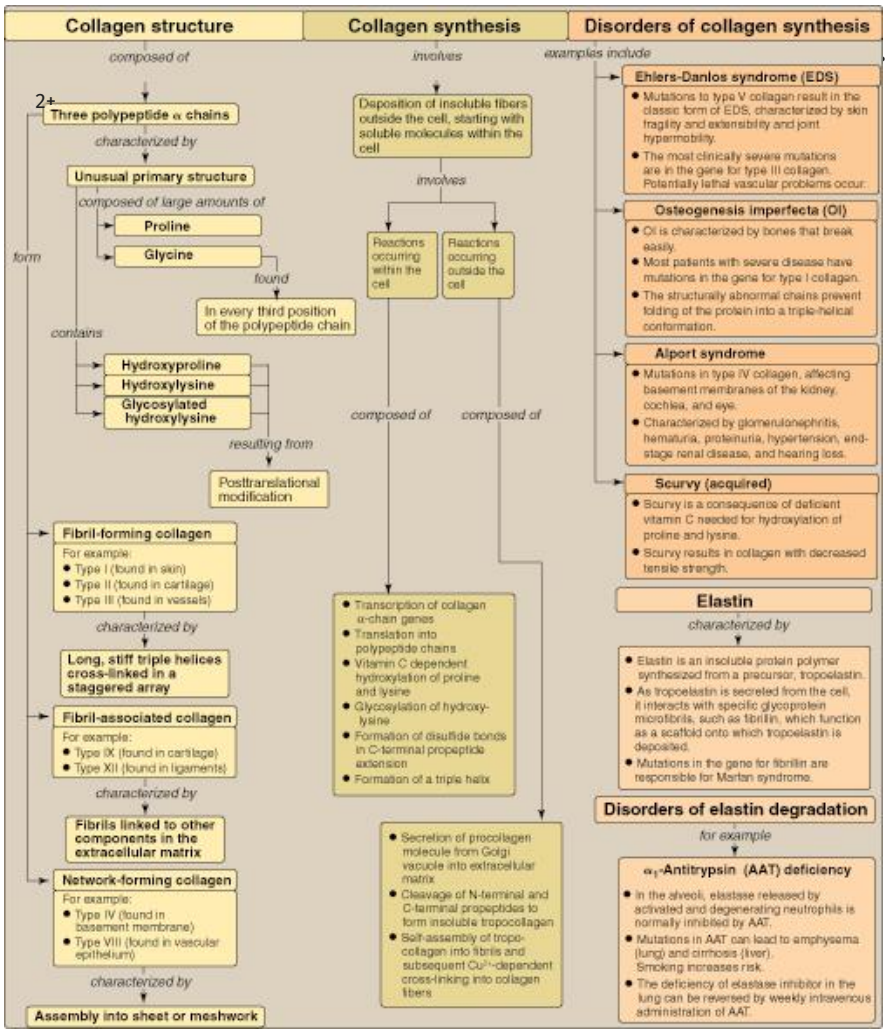
o air-borne pathogens.

Chapter Summary

Listen

- Collagen and elastin are structural fibrous proteins of the extracellular matrix (Fig. 4.15).

FIGURE 4.15



- **Collagen** contains an abundance of **proline**, **lysine**, and **glycine**, the latter occurring at every third position in the primary structure. It also contains **hydroxyproline**, **hydroxylysine**, and **glycosylated hydroxylysine**, each formed by posttranslational modification.
- Fibrillar collagen has a long, rigid structure, in which three collagen polypeptide α chains are wound around one another in a rope-like **triple helix** stabilized by **interchain hydrogen bonds**. Diseases of fibrillar collagen synthesis affect bones, joints, skin, and blood vessels.
- **Elastin** is a connective tissue protein with rubber-like properties in tissues such as the lung. **α_1-antitrypsin** (**AAT**), produced primarily by the liver, inhibits **elastase**-catalyzed degradation of elastin in the alveolar walls. A deficiency of AAT increases elastin degradation and can cause **emphysema** and, in some cases, **cirrhosis** of the liver.

Study Questions

Listen

Choose the ONE best answer.

4.1. A 30-year-old female of Northern European ancestry presents with progressive dyspnea (shortness of breath). She denies the use of cigarettes. Family history reveals that her sister also has problems with her lungs. Which one of the following etiologies most likely explains this patient's pulmonary symptoms?

A. Deficiency in dietary vitamin C

B. Deficiency of α_1-antitrypsin

C. Deficiency of prolyl hydroxylase

D. Decreased elastase activity

E. Increased collagenase activity

Correct answer = B. α_1-Antitrypsin (AAT) deficiency is a genetic disorder that can cause pulmonary damage and emphysema even in the absence of cigarette use. A deficiency of AAT permits increased elastase activity to destroy elastin in the alveolar walls. AAT deficiency should be suspected when chronic obstructive pulmonary disease develops in a patient younger than age 45 years who does not have a history of chronic bronchitis or tobacco use or when multiple family members develop obstructive lung disease at an early age. Choices A, C, and E refer to collagen, not elastin.

4.2. A 7-month-old child “fell over” while crawling and now presents with a swollen leg. Imaging reveals a fracture of a bowed femur, secondary to minor trauma, and thin bones (see x-ray at right). Blue sclerae are also noted. At age 1 month, the infant had multiple fractures in various states of healing (right clavicle, right humerus, and right radius). A careful family history has ruled out nonaccidental trauma (child abuse) as a cause of the bone fractures. Which pairing of a defective (or deficient) molecule and the resulting pathology best fits this clinical description?

Berge LN, Marton V, Tranebjaerg L, et al. Prenatal diagnosis of osteogenesis imperfecta. *Acta Obstet Gynecol Scand*. 1995;74(4):321–323.

A. Elastin and emphysema

B. Fibrillin and Marfan disease

C. Type I collagen and osteogenesis imperfecta

D. Type V collagen and Ehlers–Danlos syndrome

E. Vitamin C and scurvy

Correct answer = C. The child most likely has osteogenesis imperfecta. Most cases arise from a defect in the genes encoding type I collagen. Bones in affected patients are thin, osteoporotic, often bowed, and extremely prone to fracture. Pulmonary problems are not seen in this child. Individuals with Marfan syndrome have impaired structural integrity of the skeleton, eyes, and cardiovascular system. Defects in type V collagen cause the classic form of Ehlers–Danlos syndrome characterized by skin extensibility and fragility and joint hypermobility. Scurvy caused by vitamin C deficiency is characterized by capillary fragility.

4.3. What is the differential basis of the liver and lung pathology seen in α_1-antitrypsin deficiency?

With α_1-antitrypsin (AAT) deficiency, the cirrhosis that can result is due to polymerization and retention of AAT in the liver, its site of synthesis. The alveolar damage is due to the retention-based deficiency of AAT (a serine protease inhibitor) in the lung such that elastase (a serine protease) is unopposed.

4.4. How and why is proline hydroxylated in collagen?

Proline is hydroxlyated by prolyl hydroxylase, an enzyme of the endoplasmic reticulum that requires oxygen, ferrous iron, and vitamin C. Hydroxylation increases interchain hydrogen bond formation, strengthening the triple helix of collagen. Vitamin C deficiency impairs hydroxylation.

4.5. A 60-year-old homeless male presents to the emergency room complaining of progressive fatigue, leg pain, and generalized weakness. He has bloody stools, shortness of breath, easy bruising, leg swelling, and a red rash on his arms and legs. He is taking no medications. On further questioning he reveals that his diet consists entirely of bread, canned meat, and beer. Closer examination of the rashes on his legs reveals corkscrew hairs and subepidermal red blood cell extravasation surrounding the hair follicles. What is the underlying problem in this patient?

A. Mutation of type V collagen

B. Mutation of type I collagen

C. Decreased prolyl hydroxylase and lysyl hydroxylase activity

D. Decreased circulating AAT levels

E. Mutation of fibrillin

Correct answer = C. The patient has scurvy, caused by a vitamin C deficiency. Vitamin C is required for prolyl hydroxylase and lysyl hydroxylase activity. Hydroxylation of proline and lysine residues in the –Gly-X-Y- sequence of collagen is essential for interchain H-bond formation and a stable collagen triple helix. A mutation in type V collagen is characteristic of EDS. A mutation in type I collagen is characteristic of OI. Decreased circulating AAT levels are the basis of AAT deficiency, which results in possible pulmonary damage and emphysema symptoms, or pediatric end-stage liver failure. A mutation in fibrillin is characteristic of Marfan syndrome.