Fibrous Proteins

4

I. OVERVIEW

Collagen and elastin are examples of common, well-characterized fibrous proteins that serve structural functions in the body. For example, collagen and elastin are found as components of skin, connective tissue, blood vessel walls, and sclera and cornea of the eye. Each fibrous protein exhibits special mechanical properties, resulting from its unique structure, which are obtained by combining specific amino acids into reg ular, secondary structural elements. This is in contrast to globular proteins, whose shapes are the result of complex interactions between secondary, tertiary, and, sometimes, quaternary structural elements.

I. COLLAGEN

Collagen is the most abundant protein in the human body. A typical col lagen 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 (Figure 4.1). Although these molecules are found throughout the body, their types and organization are dictated by the structural role collagen plays in a particular organ. In some tissues, collagen may be dispersed as a gel that give support to the structure, as in the extracel lular matrix 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.

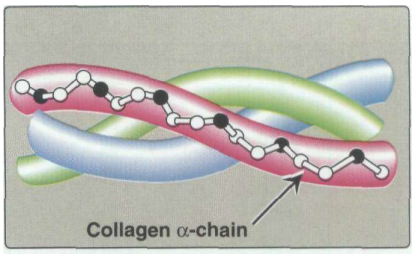

Figure 4.1
Triple-stranded helix of collagen.

A. Types of collagen

The collagen superfamily of proteins includes more than twenty colla gen types, as well as additional proteins that have collagen-like domains. The three polypeptide α-chains are held together by hydro gen bonds between the chains. Variations in the amino acid sequence of the α-chains result in structural components that are about the same size (approximately 1000 amino acids long), but with slightly dif ferent 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 a1 and one chain called

TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, fetal skin
	Network-forming
IV	Basement membrane
VII	Beneath stratified squamous epithelia
	Fibril-associated
IX	Cartilage
XII	Tendon, ligaments, some other tissues

Figure 4.2
The most abundant types of collagen.

$\alpha 2$ ($\alpha 1_2 \alpha 2$), whereas type II collagen contains three $\alpha 1$ chains ($\alpha 1_3$). The collagens can be organized into three groups, based on their location and functions in the body (Figure 4.2).

1. **Fibril-forming collagens:** Types I, II, and III are the fibrillar collagens, and have the 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 (Figure 4.3). Type I collagen fibers are found in supporting elements of high tensile strength (for example, tendon and cornea), whereas fibers formed from type II collagen molecules are restricted to cartilaginous structures. The fibrils derived from type III collagen are prevalent in more distensible tissues, such as blood vessels.

2. **Network-forming collagens:** Types IV and VII form a three-dimensional mesh, rather than distinct fibrils (Figure 4.4). For example, type IV molecules assemble into a sheet or meshwork that constitutes a major part of basement membranes. [Note: **Basement membranes** are thin, sheet-like structures that provide mechanical support for adjacent cells, and function as a semipermeable filtration barrier for macromolecules in organs such as the kidney and the lung.]

3. **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 extracellular matrix (see Figure 4.2).

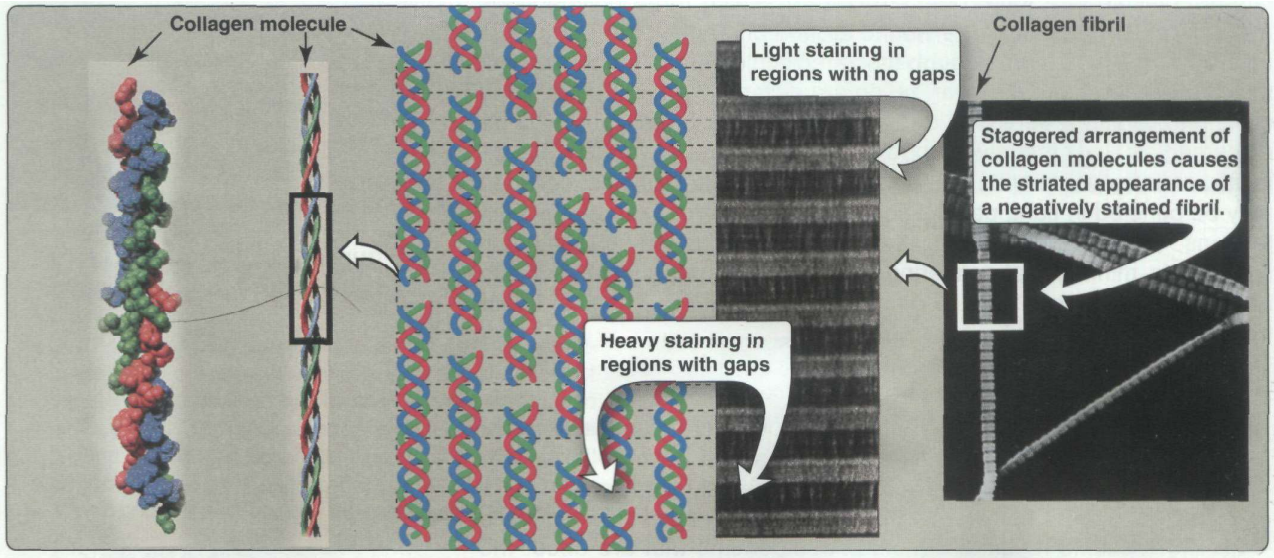

Figure 4.3
Collagen fibrils at right have a characteristic banding pattern, reflecting the regularly staggered packing of the individual collagen molecules in the fibril.

B. Structure of collagen

1. **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. **Glycine,** the smallest amino acid, is found in every third position of the polypeptide chain. It 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** or **hydroxylysine** (Figure 4.5). Thus, most of the α-chain can be regarded as a polytripeptide whose sequence can be represented as **$(–Gly–X–Y–)_{333}$**

2. **Triple-helical structure:** Unlike most globular proteins that are folded into compact structures, collagen, a fibrous protein, has an elongated, triple-helical structure that places many of its amino acid side chains on the surface of the triple-helical molecule. [Note: This allows bond formation between the exposed R-groups of neighboring collagen monomers, resulting in their aggregation into long fibers.]

3. **Hydroxyproline and hydroxylysine:** Collagen contains hydroxy proline (hyp) and hydroxylysine (hyl), which are not present in most other proteins. These residues result from the hydroxylation of some of the proline and lysine residues after their incorporation into polypeptide chains (Figure 4.6). The hydroxylation is, thus, an example of **posttranslational modification** (see p. 440). Hydroxy proline is important in stabilizing the triple-helical structure of colla gen because it maximizes interchain hydrogen bond formation.

4. **Glycosylation:** The hydroxyl group of the **hydroxylysine** residues of collagen may be enzymatically glycosylated. Most commonly, glucose and galactose are sequentially attached to the poly peptide chain prior to triple-helix formation (Figure 4.7).

C. Biosynthesis of collagen

The polypeptide precursors of the collagen molecule are formed in **fibroblasts** (or in the related **osteoblasts** of bone and **chondro blasts** of cartilage), and are secreted into the **extracellular matrix.** After enzymic modification, the mature collagen monomers aggre gate and become cross-linked to form collagen fibrils.

1. **Formation of pro-a-chains:** 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 contain a special amino acid sequence at their N-terminal ends. This acts as a signal that the polypeptide being synthesized is des tined to leave the cell. The **signal sequence** facilitates the binding of ribosomes to the rough endoplasmic reticulum (RER), and directs the passage of the polypeptide chain into the cisternae of the RER. The signal sequence is rapidly cleaved in the endoplas mic reticulum to yield a precursor of collagen called a **pro-α-chain** (see Figure 4.7).

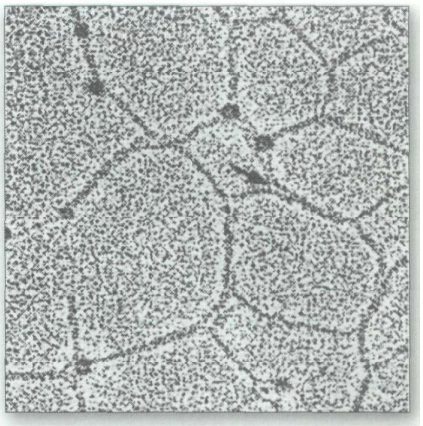

Figure 4.4
Electron micrograph of a polygonal network formed by association of collagen type IV monomers.

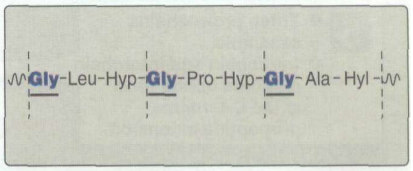

Figure 4.5
Amino acid sequence of a portion of the α1-chain of collagen. [Note: Hyp is hydroxyproline and Hyl is hydroxylysine.]

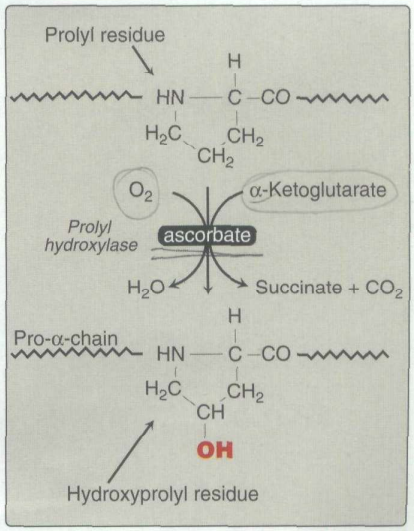

Figure 4.6
Hydroxylation of prolyl residues of pro-α-chains of collagen by *prolyl hydroxylase.*

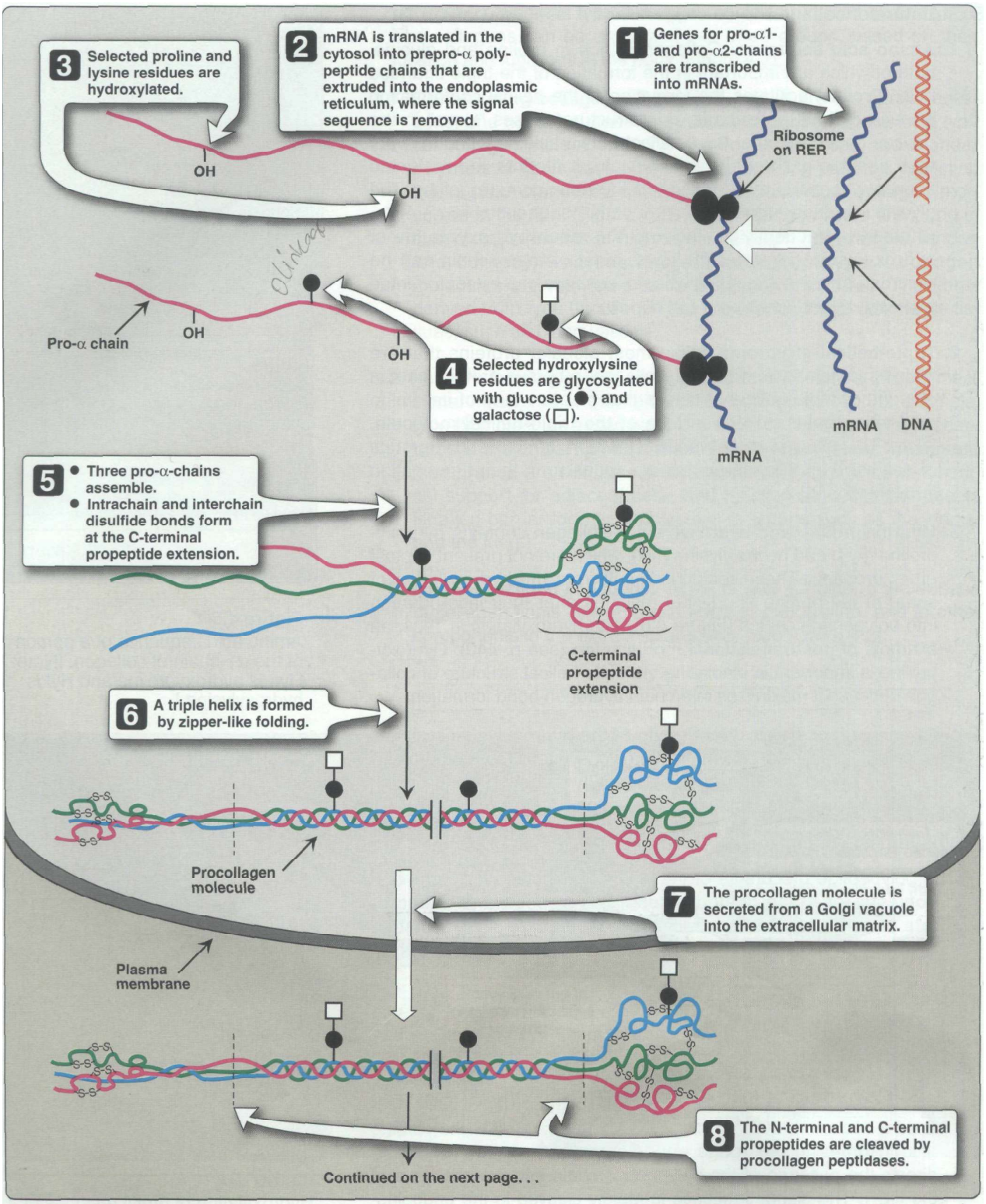

Figure 4.7
Formation of a collagen fibril. (*Continued on the next page*)

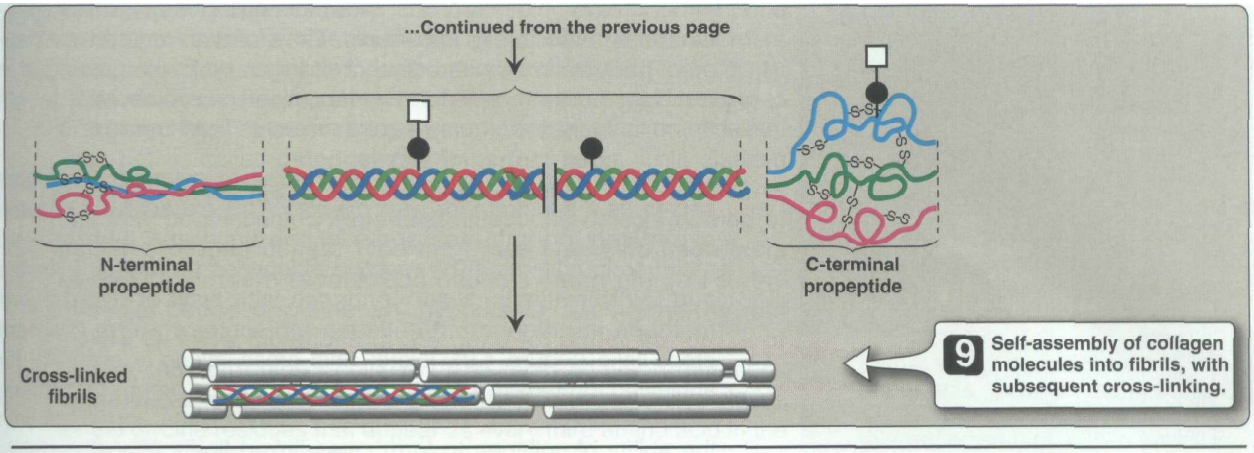

Figure 4.7
Formation of a collagen fibril. (*Continued from the previous page*)

2. **Hydroxylation:** The pro-α-chains are processed by a number of enzymic steps within the lumen of the RER while the polypeptides are still being synthesized (see Figure 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 and the reducing agent vitamin C (ascorbic acid, see p. 375), without which the hydroxylating enzymes, *prolyl hydroxylase* and *lysyl hydroxylase,* are unable to function (see Figure 4.6). In the case of **ascorbic acid deficiency** (and, therefore, a lack of prolyl and lysyl hydroxylation), collagen fibers cannot be cross-linked (see below), greatly decreasing the tensile strength of the assembled fiber. One resulting deficiency disease is known as **scurvy.** Patients with ascorbic acid deficiency also often show bruises on the limbs as a result of subcutaneous extravascation of blood (**capillary fragility;** Figure 4.8).

3. **Glycosylation:** Some hydroxylysine residues are modified by glycosylation with glucose or glucosyl-galactose (see Figure 4.7).

4. **Assembly and secretion:** After hydroxylation and glycosylation, pro-α-chains form **procollagen,** a precursor of collagen that has a central region of triple helix flanked by the non-helical amino- and carboxyl-terminal extensions called **propeptides** (see Figure 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 helix formation. The procollagen molecules are translocated to 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.

5. **Extracellular cleavage of procollagen molecules:** After their release, the procollagen molecules are cleaved by *N-* and *C-procollagen peptidases,* which remove the terminal propeptides, releasing triple-helical collagen molecules.

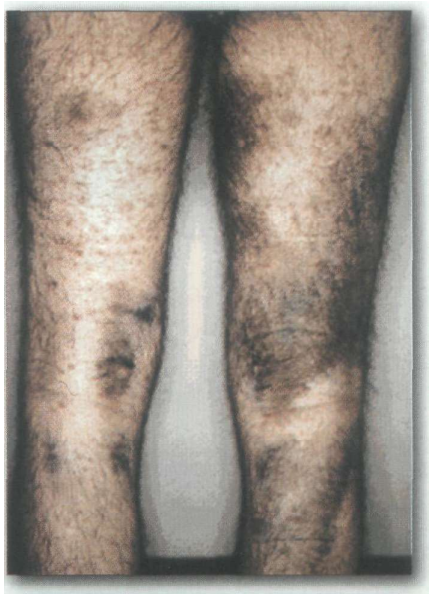

Figure 4.8
The legs of a 46-year-old man with scurvy.