COLLAGEN - STRUCTURE, PROPERTIES AND APPLICATION

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Abstract

Collagen is the dominant component of the extracellular matrix of mammals. It occurs almost in all animal tissues. Collagen is a highly heterogeneous protein. The collagen protein family is characterized by great diversity in terms of structure, occurrence, and function. Up till now, 29 types of collagens proteins have been classified. The representation of individual types of collagen has certain common features. The most important property is the above-average mechanical strength that results directly from the spatial structure. Collagen is a building material for most tissues and organs. It also plays an important role in the process of cell growth and differentiation, which results from the specific structure of collagen fibers as well as their ability to adhere. The development of research techniques allowed to study in detail the molecular structure and properties of collagen. Therefore, collagen has become a subject of interest in many branches of science. Synthetic recombinant collagen fibers were developed as the basis of collagen biomaterials for medical applications, including implantology or gynecology. The specific structure of collagen also makes it applicable as a protein carrier in drug delivery systems (DDS), particularly in the treatment of cancer and genetic diseases. The use of tissue regenerative abilities and an interdisciplinary look at the properties of collagen and collagen-based biomaterials may constitute the future of medical development.

Keywords: *collagen, collagen structure, physicochemical properties, biological properties, DDS, physicochemical techniques, atelocollagen*

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Introduction

Collagen constitutes about 25% of all human proteins. Its name refers to the family of collagen proteins which differ in characteristic, location, molecular and spatial structure. Collagen is highly heterogeneous. Fibers chains are coded by different genes and biosynthesized in various tissues. Specific features of individual collagen types are the result of differences in post-translational modifications. Collagen is the dominant element of connective tissue extracellular matrix (ECM). Due to its physicochemical properties, collagen is responsible for the integrity, strength and elasticity of tissues. This natural biopolymer is constantly synthesized in the body by various cells in different amounts, depending on the current demand. Collagen plays an important role in the healing process, tissue growth, regeneration, and also participates in the processes of cells adhesion, growth and differentiation. These collagen functions take place mainly due to the specific structure of its fibers. This spatial structure, called a superhelix, provides the beneficial properties of collagen, especially very high mechanical strength [1-4].

The characteristic features of collagen fibers, their common occurrence, and relatively easy accessibility are still of interest to scientists from different research fields. In certain areas of medicine and industry collagen has been widely used as a biopolymer compatible with the human body. Yet the use of collagen as a biomaterial is still being explored [5].

Collagen structure

A basic structural unit of collagen is tropocollagen - α-helix left-handed molecule, composed of three polypeptide, spirally wound chains. Collagen fibers are formed through the aggregation of tropocollagen molecules by the electrostatic and hydrophobic side bonds. Further aggregation creates cross-links, such as covalent or non-covalent bonds between the fibrils Lysine – Lysine (Lys-Lys) and Hydroxyproline – Hydroxyproline (Hyl-Hyl) amino acids pairs [1,6,7].

The structure of the collagen molecule mainly results from the interaction between the components building polypeptides. The amino acids composition and their amount in polypeptide chains differ between different types of collagen. However, they show some common structural features. Six different types of subunits have been described and they consist of three identical (homotrimer) or three different (heterotrimer) chains or the mixture of the same two and one different chains. The collagen molecule does not only consist of helical fragments – the non-helical domains are also characteristic for some types of collagen [1,3,6].

Glycine (Gly) is the main collagen amino acid. It is about every third amino acid residue in a single polypeptide chain (approx. 35%). Proline (Pro) is the second abundant amino acid, present in an amount of 12% of all amino acids. Rarely occurring but important are lysine (Lys) and alanine (Ala), as well as aspartic (Asp), glutamic (Glu) and arginine (Arg) amino acids. A characteristic feature of the collagen molecular structure is the occurrence of nearly equimolar amounts of basic and acidic amino acids. In addition, a significant concentration of hydroxyproline (Hyp) and hydroxylysine (Hyl) can be distinguished in the composition of the polypeptide chain. These two amino acids are already formed in the post-translational and enzymatic protein processing and are responsible for the formation of higher-order structures [1,3,6,8].

Collagen-forming polypeptide chains are characterized by the presence of repeatable amino acid sequences, where the most common sequence is proline and the next one - Gly-Pro-Hyp (FIG. 1).

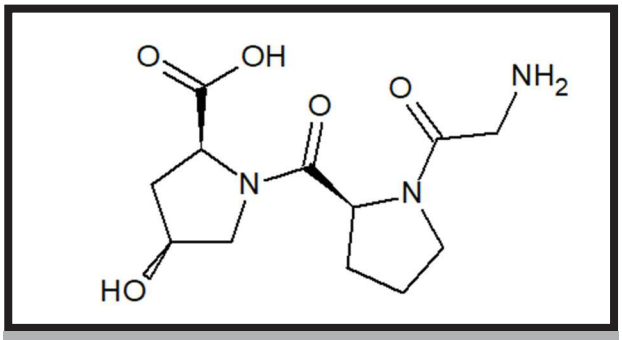

FIG. 1. The structural formula of Gly-Pro-Hyp amino acid sequence.

A slightly less common amino acid sequence is Gly-Pro-Ala. This repeatability is important for the collagen spatial structure. The systematic presence of Gly allows the formation of hydrogen bonds between its molecules. Consistency and regularity are the most important factors that significantly increase the strength of the entire helical structure. The aqueous environment plays an important role in this process as it stabilizes the hydrogen bonds. However, it has been proved that if the structure regularity is interfered the collagen molecule shows considerable flexibility. It means that the lower regularity in amino acid sequence, the greater number of kinks in the polypeptide chain. This relationship determines the elasticity of collagen molecule [3,4,6-10].

There are 29 types of collagen. The classification has been presented in FIG. 2.

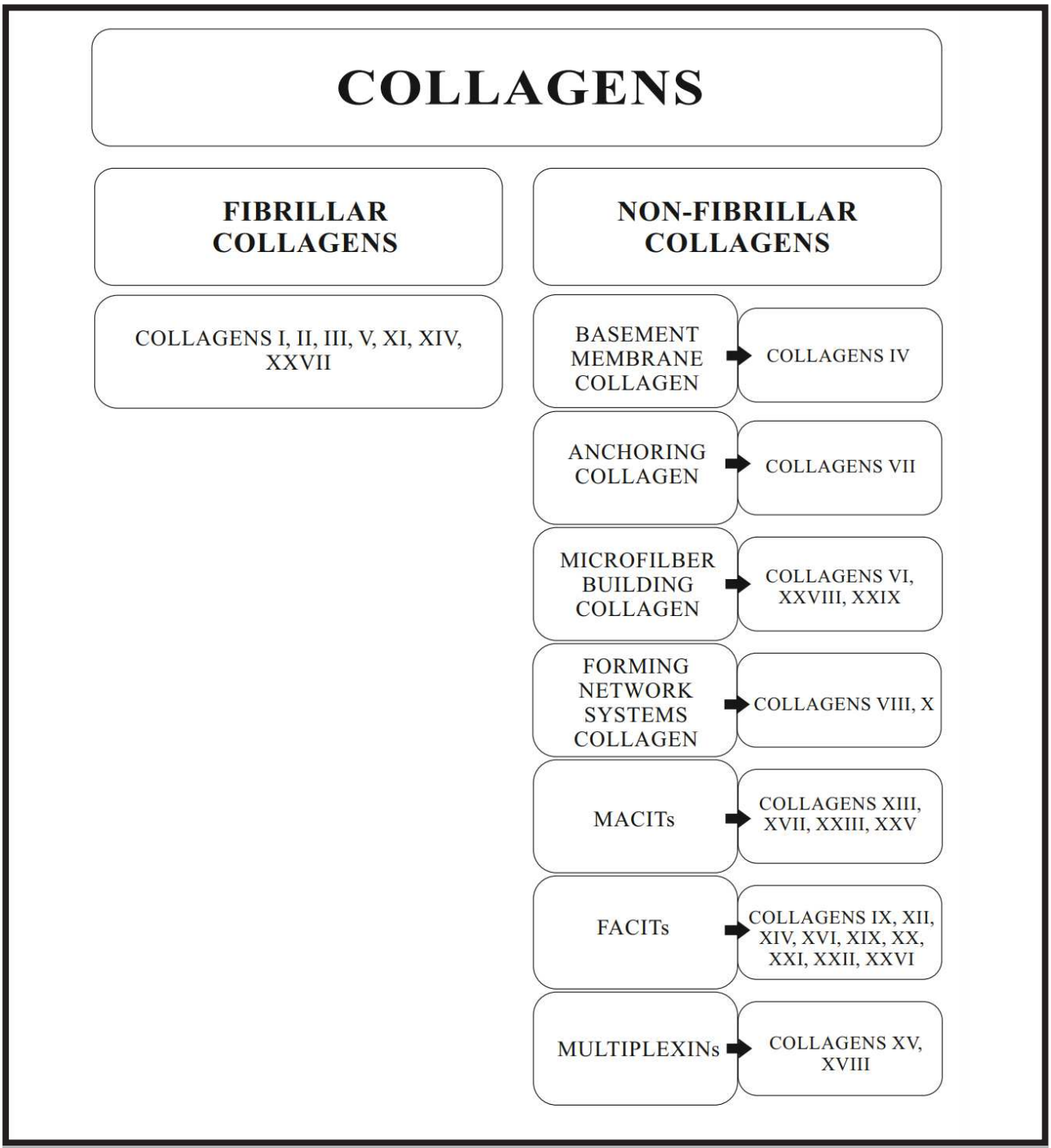

FIG. 2. The collagen proteins family.

The collagen proteins family classification is based on the differences in structure, location and properties of individual types. The two main collagen groups are: fibrillar collagen and non-fibrillar one [11,12]. Fibrillar collagen forms fibrils, constituting about 90% of all collagen presented in the human body. It is encoded by 11 genes and formed from three helically rolled up polypeptide chains, separated by short non-helical fragments called teleopeptides. The spatial structure of fibrillar collagen is cross-striated with transverse bands repeating every 64–67 nm. Non-fibrillar collagen is much more differential in terms of structure, location and properties. Although it amounts only to 10% of all the collagen in the human body, it is a vital part of many organs [8,13-15].

TABLE 1 presents the types of fibrillar and non-fibrillar collagen with examples of their location in tissues.

TABLE 1. Location of a) fibrillar and b) non-fibrillar collagen in tissues. Adapted from [12] with additional data from: [8,11,13-15].

a)	Fibrillar Collagen
Collagen Type	Location
I	skin, bones, tendons, cornea
II	gristle, vitreous body
III	skin, vessels, intestine, uterus
V	skin, bones, cornea, placenta
XI	gristle, intervertebral disc
XXIV	bones, cornea
XXVII	gristle
b)	**Non-fibrillar Collagen**
Collagen Type	Location
IV	basal membrane, capillaries
VI	bones, vessels, skin, cornea, gristle
VII	mucous membranes, skin, bladder, umbilical cord, amniotic fluid
VIII	skin, brain, heart, kidneys, vessels, bones, gristle
IX	cornea, vitreous body, gristle
X	gristle
XII	gristle, tendons, skin
XIII	skeletal muscles, heart, eye, skin, endothelial cells
XIV	vessels, eye, nerves, tendons, bones, skin, gristle
XV	capillary vessels, ovaries, heart, testicles, skin, placenta, kidneys
XVI	heart, skin, kidneys, smooth muscle
XVII	skin
XVIII	kidneys, lungs, liver
XIX	skin, kidneys, liver, placenta, spleen, prostate gland
XX	corneal epithelium
XXI	stomach, kidneys, vessels, heart, placenta, skeletal muscles
XXII	tissue connections
XXIII	metastatic carcinogenic cells
XXV	eye, brain, heart, testicles
XXVI	testicles, ovaries
XXVIII	nervous system cells
XXIX	skin

Collagen biosynthesis

The collagen protein family is coded by 44 genes located on the 17th pair of chromosomes. Collagen biosynthesis consists of many steps and occurs in different regions inside and outside the cell [8]. The beginning of this process does not differ much from the synthesis of every other protein in the human body. The biosynthesis begins with the transcription of genetic information in the cell nucleus, then the mRNA transcript leaves out the nucleus and goes to the endoplasmic reticulum (ER) where the genetic information is translated. As a result of this process, a new molecule, called pre – procollagen, is formed. Pre – procollagen in its structure contains a signal peptide fragment that is responsible for identifying and delivering the polypeptide molecule to the appropriate place in the ER. The other characteristic fragments of this chain are the terminal fragments located at both ends. Thanks to them proper polypeptide chains are selected to form procollagen αhelix. They also prevent the premature formation of collagen fibrils [2,4].

The post-translational modification consists of three steps and takes place in the ER. First, the signal peptide is cut off, using a signal peptidase. Next, the Lys and Pro hydroxylation takes place with the participation of lysine hydroxylase, prolyl-4-hydroxylase and prolyl-3-hydroxylase. This is one of the primary stages of collagen biosynthesis that requires an appropriate environment reaction, which is provided by the presence of ascorbic acid, molecular oxygen, iron ions (II) and α-ketoglutarate. Due to the post-translational modification, it is possible to create hydrogen bonds stabilizing the spatial structure of this protein [2,4,11,16].

The final step of post-translational modification is glycosylation. The reaction occurs in the presence of glucosyltransferase and galactosyltransferase while glucose or galactose is attached to the Hyp residues. The formed polypeptide chains have an ability to self–aggregate and the new aggregated structure is called procollagen. Procollagen is stabilized by hydrogen and disulfide bonds and the oligosaccharide fragments get attached to its molecule in the Golgi apparatus. It is the last modification before the procollagen transport to the ECM [2,4]. In ECM, using N – proteinase and C – proteinase, the terminal propeptides are removed and tropocollagen is formed. Tropocollagen is able to aggregate with tropocollagen molecules spontaneously, thus forming collagen fibrils. Collagen fibrils are the final stage of collagen protein biosynthesis [2,4]. Collagen biodegradation in the body is a complicated process that can be divided into two types: extracellular and intracellular [2]. The intracellular biodegradation occurs in the process of collagen endocytosis by cells capable of phagocytosis [2,5], while extracellular biodegradation occurs due to extracellular matrix metalloproteinases (MMPs). After their activation, the triple helix spatial structure is destroyed through the degradation of peptide bonds between the pairs of amino acids: glycine-isoleucine and glycine-leucine. The collagen molecule disintegrates into two molecules in a ratio 3:1. The collagen disintegration products denature and become water-soluble in the environment [1,2,17,18].

The collagen synthesis in the human body depends on the constitutional specifics, yet it is conditioned by environmental factors. For instance, the collagen precursors synthesis (pro-collagen) can be stimulated by mechanical stress. It has been shown that collagen synthesis and degradation increase under the influence of short-term and long-term exercise [19]. Chang J. et. al. proved that the collagen synthesis may alter during 24 h cycles. Such a conclusion was based on the transmission electron microscopy observations of Achilles tendons extracted from mice [20].

Collagen in medicine – physicochemical and biological properties

The physicochemical properties of collagen are the result of its molecular structure. The most important features of collagen proteins include very high tensile and tear strength which protects the tissue against mechanical damage. The collagen fibers resistance to mechanical forces increases in direct proportion to the fiber age and cross-linking. This cross-linking is also associated with the fact that collagen binds the remaining elements of the ECM, ensuring the integrity of the tissues it occurs in. [1-3].

Due to the spatial structure of superhelix and its ability to retain water, collagen is insoluble in water. This feature makes its resistant to proteolytic enzymes, such as trypsin, chymotrypsin or pepsin. Water solubility plays a significant role in the proper biochemical process. However, this process can be limited by adding sulphate anions (IV) and (VI), metal cations Na^+ and K^+, as well as a solution of NaCl [1,2].

Depending on the temperature, collagen denatures in two steps. This process is slower and slightly different from other proteins. In the first stage, the superhelix structure is broken by the hydrophobic and hydrogen bonds degradation and this process is reversible. In the next stage, the helical structures are destroyed and transformed into globular ones. The temperature range necessary for the collagen degradation is between 5°C and 50°C, depending on the molecule structure and the reaction conditions (pH, the concentration of salts and electrolytes and amount of hydroxyproline residues in collagen). Collagen changes its consistency, plasticity and viscosity under the thermal treatment or due to various solutions of acids and bases, both inorganic and organic. The knowledge of these properties was crucial to determine the preparation methods and obtain collagen proteins for research [13,21-23].

In addition to supporting and building functions, collagen has the ability to bind ligands of various origins, thus taking an indirect part in the biochemical processes in the surrounding tissue. Collagen binds to integrins and other mediator proteins, thereby they mediate the cells signal transmission, regulate the cells proliferation and proper migration inside the tissue. They also interact with proteoglycans, providing specific tissues with appropriate mechanical properties. Biosynthesis and biodegradation are also dependent on the collagen binding to other substances, such as collagenases or protein chaperones [24,25].

Collagen is also involved in the process of neoplastic cell formation, angiogenesis and metastasis. The tumor microenvironment influences the ECM, resulting in the deposition of fibronectin, proteoglycans and collagen types I, III, IV. It promotes tumor progression through the increased mutual cells adhesion, cells polarity disorders, and the increasing growth factor signaling [26].

Moreover, collagen has a positive effect on the proper immune system functioning, mainly through the impact on the complement system functioning. Collagen also binds the C1r or C1s components that are responsible for activating the system and enhancing the immune response. Due to the characteristic spatial structure, collagen also has the ability to nonspecific binding of polyanionic compounds, such as oxidized low–density lipoprotein (LDL). The list of ligands that can be bound by collagen is very long and is constantly expanding. Some of them bind only to a specific type of collagen, while others bind nonspecifically and more spontaneously. Unfortunately, not all ligand binding regions in the collagen molecule have been accurately characterized and described [27-34].

Thanks to the detailed knowledge of the molecular structure and physicochemical properties, collagen has become an object of interest in many scientific areas, e.g. nanotechnology or biomedical engineering. Numerous studies have allowed to create synthetic, recombinant collagen fibers to produce collagen biomaterials with different structure and function [12,35,36].

Among others, collagen-based biomaterials engage atecollagen. It is the type I collagen derivative deprived of telopeptide fragments that are responsible for the lack of immunogenicity. Due to low toxicity, antigenicity, common occurrence and ease of obtaining, collagen is a safe building unit for materials synthesis. Collagen-based materials are biocompatible and biodegradable. They are often used in reconstructive medicine, implantology and pharmacology [12,35,37].

Insoluble and porous collagen sponges are one of the many collagen-based biomaterials. They are formed during the lyophilization of acid or alkaline animal collagen aqueous solutions. The sponges pore size can be controlled during production and depends on the amount of dry collagen mass and the speed of solution freezing. Collagen sponges are able to absorb liquids. During the production process, they are enriched by elastin, glycosaminoglycans or fibronectin, making them more flexible. Additional cross-linking of these materials, using glutaraldehyde and conjugated with poli(hydroxyethylmethacrylate), increases their mechanical strength.

Collagen sponges are used in medicine as a dressing for burn wounds and bedsores. They can be soaked with antibiotics, usually gentamicin, acting as drug carriers. Collagen sponges protect tissue against infection. The presence of opened and semi-closed pores in collagen sponges allows for the quick and prolonged local effect of the drug, which depends on the biodegradation rate. The advantage of this type of biomaterials is also a possibility to obtain the maximum drug concentration in the appropriate place and to reduce the side effects during the antibiotic therapy [12,18,35,36,38].

In the structure of collagen hydrogels, there are numerous dispersed water molecules. They can be formed in the process of spontaneous polymerization which already takes place in physiological conditions. The spatial structure of collagen gels is maintained thanks to strong electrostatic interactions and hydrophobic bonds. Due to the large fluid accumulation inside the gel, they have the ability to effectively exchange ions and metabolites with the surrounding tissue. The rich cross-linking of collagen gels is the reason for keeping fluids inside the biomaterial structure, which affects its characteristic mechanical properties and application. Collagen hydrogels can be compressed, in a more or less controlled manner, depending on the application.

Due to their properties and structure similar to soft tissues, collagen gels have found wide clinical application. Microgels based on collagen type I are mainly used. Depending on the type of cells, they can be used to regenerate and rebuild different types of tissues. Collagen type II is also used in hydrogels. Its structure and functionality resembles cartilage. It stimulates the differentiation of mesenchymal stem cells towards chondrocytes, therefore collagen type II gels have been used in the regeneration of this type of tissue. The examples of hydrogel applications are presented in TABLE 2 [12,35,36,38].

TABLE 2. Hydrogels in medicine. Adapted from: [12,18,35,36,38].

Types of collagen	Types of cells	Application
Collagen type I	Fibroblasts	Dermis regeneration
	Cardiomyocytes	Heart muscle reconstruction
	Growth factors and polypeptides	Promote polarity nerve cells, alignment and increase adhesion
Collagen type II		Cartilage regeneration

TABLE 3. Examples of the use of collagen as a biomaterial in medicine. Adopted from [12,18].

Medicine area	Biomaterial form	Application
Skin regeneration	Collagen type I hydrogels with fibroblasts	Reproduction of skin defects
	Compensated collagen hydrogels	Skin reconstruction *in vitro* and *in vivo*
	Hydrogel with liposomes	Drug delivery in skin during regeneration, accelerating the wound healing process
	Collagen sponges	Treatment of severe burns and bedsores
Dental surgery and implantology	Collagen membranes	Post-implant skin regeneration, closure of sinus fistulas, treatment of bone and cartilage tissue defects
Ophthalmology	Collagen films and membranes	Treatment of corneal defective, reconstruction of the corneal epithelium after surgical removal, drug delivery to the surface of the eyeball
Urology/Gynecology	Collagen materials containing bladder cells, muscle cells or fibroblasts	Bladder plastic surgery, treatment of urethral stricture
Orthopedics	Scaffold based on polyurethane with collagen type I hydrogel and TGFβ-1 [45], sponge structure collagen implants [46]	Treatment of vertebrae [45]. collagen meniscus (Menaflex - CMI, ReGen Biologics, Franklin Lakes, New Jersey) [46]
Laryngology	Collagen hydrogel, autologous grafts from skin [47]	Nestorian function of vocal cords and epiglottis [47]
Neurology (in the experimental stages)	Various collagen materials	Peripheral nerves regeneration
Aesthetic medicine	Masks, gels, creams, injection preparations	Wrinkle filling, scar regeneration, improve facial contours, lips, overall skin improvement

Collagen films are very thin and durable. The film thickness is between 0.1 to 0.5 mm. They are formed by evaporating the solution that may contain medical substances, such as gentamycin or tetracyclines. Collagen films and membranes are useful in ophthalmology, in the treatment of corneal infections and wound healing. They can also be used indirectly to cover other biomaterials to change their surface properties. Collagen films containing rapamycin are used in the production of coronary stents and drug–free collagen film are used to produce lenses. Their function is protecting lenses from mechanical damage [12,35,36,38]. The examples of using biomaterial are presented in TABLE 3.

Collagen can be also used as a protein carrier in drug delivery systems (DDS). Their function is to deliver an old and new generation drug to the destination inside the body [39]. The connection between the carrier and the drug substance occurs thanks to the formation of a covalent bond. The carrier may be atelocollagen. This completely safe biomaterial has a positive charge to facilitate the transfer of pharmaceuticals. Collagen protein in drug delivery systems is primarily used to transport proteins and nucleic acids. It is applicable to treat cancer and genetic diseases. TABLE 4 presents the examples of drugs transported using DDS [34,39,40].

TABLE 4. Examples of drugs transported using DDS. Adapted from: [35,37-39].

Drug	Application
Interferon	Viral diseases treatment
Interleukin - 2	Immune deficiencies
Nerve Growth factor (NGF)	Central nervous system diseases treatment
Basic Fibroblast Growth Factor (bFGF)	Fracture treatment

Physicochemical techniques of collagen analysis

The complexed spatial structure and physicochemical properties of collagen can be analyzed using various techniques. The constantly expanding knowledge on this subject makes it possible to apply different collagen types as building materials in the medical industry [32,33,41].

To assess the structure of collagen fibers, two complementary techniques: transmission electron microscopy (TEM) and synchrotron X-ray scattering can be used. TEM provides information about local structural on the scale of 15 nm to several micrometers, while X-ray scattering gives general information about the packing collagen molecules. The morphology of fibrils and of whole collagen membranescan also be observed using a scanning electron microscope (SEM), however, this technique requires specific chemical preparation of the tested material [32,33,35]. TEM enables the analysis of collagen in biological systems, X-ray scattering can be used to investigate the structural features of fibrillar human collagen, while SEM – collagen morphology.

To determine the thermal stability of collagen and its derivatives, differential scanning calorimetry (DSC) is used. Miles et al. used DSC to determine the thermal stability of native and artificially cross-linked collagen, derived from rat tail tendon at different levels of hydration [42]. DSC can be used for thermal analysis during the collagen treatment and inflammatory pathological states (besides the classical histological methods).

The structural properties of collagen proteins can be described by circular dichroism (CD). CD describes the secondary structure and it determines the triple helix – the presence, profile and stability. This technique can also be used to assess the optical ability of collagen solutions and to monitor conformation changes in the structure of the polymer triple helix. CD in the wavelength range from 100 to 200 nm (vacuum ultraviolet - VUV) can also be used to determine the purity of collagen samples [43,44]. Spectroscopy CD could be helpful in the analysis of collagen based on biomaterials exposed to chemical and physical agents during their manufacturing for medical purposes.

In order to assess the collagen fibers elasticity, nuclear magnetic resonance spectroscopy (NMR) can be used [8]. NMR spectroscopy can also assess collagen in native ECM. The way collagen molecules move provides information about its mechanical and biological properties. Another interesting method to assess the collagen molecular structure without damage is the solid state NMR spectroscopy, performed both in vivo and in vitro. This technique can provide information about the aging process of collagen fibers and/or their molecular changes under the influence of an ongoing disease [47].

Summary

The collagen protein family is characterized by mechanical strength resulting from the spatial structure, wide structure diversity, occurrence and function. The super helical structure is unique in the world of animal proteins.

The regenerative potential of the human body is still the subject of numerous studies. Taking advantage of natural tissue regenerative abilities, along with the application of new technologies and biomaterials, is the future of medicine. The knowledge about collagen has gradually expanded with the progress of research techniques, enabling a thorough investigation of their structure. These proteins still remain a subject of research and our knowledge is not complete. Characteristic features, such as strength and common occurrence, have facilitated the use of collagen as a biomaterial for many clinical purposes. An interdisciplinary look at the possibilities of using collagen and biomaterials created on its basis can help to develop medicine and other scientific areas.

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