



Review

Collagen for bone tissue regeneration

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ABSTRACT

In the last decades, increased knowledge about the organization, structure and properties of collagen (particularly concerning interactions between cells and collagen-based materials) has inspired scientists and engineers to design innovative collagen-based biomaterials and to develop novel tissue-engineering products. The design of resorbable collagen-based medical implants requires understanding the tissue/organ anatomy and biological function as well as the role of collagen's physicochemical properties and structure in tissue/organ regeneration. Bone is a complex tissue that plays a critical role in diverse metabolic processes mediated by calcium delivery as well as in hematopoiesis whilst maintaining skeleton strength. A wide variety of collagen-based scaffolds have been proposed for different tissue engineering applications. These scaffolds are designed to promote a biological response, such as cell interaction, and to work as artificial biomimetic extracellular matrices that guide tissue regeneration. This paper critically reviews the current understanding of the complex hierarchical structure and properties of native collagen molecules, and describes the scientific challenge of manufacturing collagen-based materials with suitable properties and shapes for specific biomedical applications, with special emphasis on bone tissue engineering. The analysis of the state of the art in the field reveals the presence of innovative techniques for scaffold and material manufacturing that are currently opening the way to the preparation of biomimetic substrates that modulate cell interaction for improved substitution, restoration, retention or enhancement of bone tissue function.

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1. Introduction

In mammals, collagen is the most abundant protein, constituting more than one-third by weight of body protein tissue [1]. Around 28 types of collagen [2] have so far been identified and, among these, type I collagen is the most prevalent type found in the extracellular matrix (ECM), especially in tissues such as tendon and bone [2,3]. The ECM plays an important role in the morphogenesis and cellular metabolism of new tissues, conferring mechanical and biochemical properties [2]. Collagen has potential as a biomaterial for bone tissue engineering due to its abundance, biocompatibility, high porosity, facility for combination with other materials, easy processing, hydrophilicity, low antigenicity, absorbability in the body, etc. [4,5].

1.1. Collagen structure

Collagen protein has a complex hierarchical conformation divided in four structures: primary structure (amino acid triplet),

secondary structure (the α -helix), tertiary structure (triple helix) and quaternary structure (fibrils) [2].

1.1.1. Primary structure: amino acid triplet

Collagen protein is recognized by the characteristic domain of proline-rich Gly-X-Y polypeptide (Fig. 1) with two unique features: (i) Gly is found every third residue with the strict repeating –(Gly-X-Y)_n– tripeptide sequence along the entire length of the ~1000 amino acid chain. However, a single substitution of a Gly with an Ala residue has been found in the crystal structure of a triple-helical molecule after 10 repeating Pro-Hyp-Gly units [6]. (ii) A high proportion of residues (~20%) in the tripeptide sequences is frequently comprised of proline (X) and hydroxyproline (Y). Hydroxyproline is not commonly found in other proteins, while in collagen it constitutes more than 50% of the total amino acid content [7,8].

1.1.2. Secondary structure: α -helix

The α -chains are formed by repetitions of the tripeptide –(Gly-X-Y)_n– and are linked to each other, building the characteristic triple helix of type I, II and III collagen [9]. The non-helical domains are at the end of the α -chains, where the C-terminus is involved in the initiation of triple-helix formation and the N-terminus is

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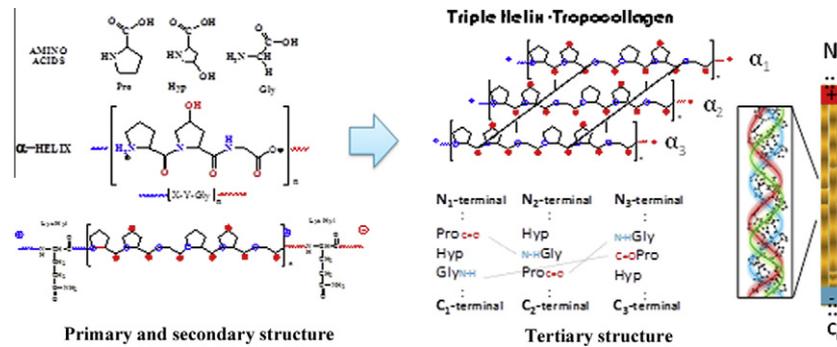


Fig.1. Schematic drawing of the hierarchical structure of collagen: primary, secondary and tertiary structure.

involved in the regulation of primary fibril diameters. The short non-helical telopeptides of collagen are linked by covalent cross-links which form between the collagen molecules and/or between collagen and other molecules present in the ECM [2,10].

1.1.3. Tertiary structure: triple helix

The triple helix, especially in collagen type I, is usually formed as a heterotrimer of two identical $\alpha_1(I)$ - and $\alpha_1(II)$ -chains and one $\alpha_2(I)$ -chain with about 1000 amino acids, and is approximately 300 nm in length (L) and 1.5 nm in diameter [9,11]. The three α -chains form a left-handed, rod-like helix, where the glycine residues are located around a central axis, while larger amino acids belonging to the X and Y residues (usually proline and hydroxyproline) occupy outer positions [9] (Fig. 1). The α -chains are linked to each other by hydrogen bonds through the single interstrand N-H(Gly)...O=C(X) as well as C α -H(Gly/Y)...O=C(X/Gly), which are the major stabilizing interactions of the α -triple helical and β -sheet protein structures [8,12,13]. Some studies of collagen molecule assembling have hypothesized that the C-terminal (COOH-terminal propeptide) globular domains of the $\alpha_2(I)$ -chain in the collagen type I play a crucial role in the initiation of the intermolecular assembly, chain association and stable collagen heterotrimer formation [14–16].

1.1.4. Quaternary structure: collagen fibrils

Collagen molecules are able to self-assemble into a supramolecular form via a quarter-stagger package pattern of five triple-helical collagen molecules highly oriented with D-periodic banding spaces, where D is ~ 67 nm (Fig. 2) [11,17]. The telopeptides, composed of non-helical regions about 20 amino acid residues in length, play an important role in the fibrillogenesis, contributing to the stabilization of the mature collagen molecules by cross-link formation [18]. In fact, collagen cross-links are divided into two types: enzymatic cross-links, mediated by lysine hydroxylase and lysyl oxidase; and non-enzymatic cross-links, commonly called glycation or oxidation induced Advanced glycation end products (AGE) cross-links [19]. Fig. 2 shows an example of enzymatic cross-linking mediated by lysyl oxidase. The two chemical forms of 3-hydroxypyridinium cross-linking, namely hydroxyl lysyl pyridinoline (HP) and lysyl pyridinoline (LP) cross-links, are formed between the amine side group present in the lysine and hydroxy lysine residues in collagen telopeptides, which are converted into aldehydes by the lysyl oxidase enzyme, and the specific active binding sites present in neighboring triple helices [10,11].

Various non-collagen proteins and bound water fill the space between cells and fibers of the connective tissue defining the features of the tissue. These macromolecules can be grouped into two main classes: glycosaminoglycans (GAGs) and glycoproteins [20]. Proteoglycans are complex molecules that resemble the shape of a brush used to clean test tubes and comprise around 80 GAG

chains bound covalently (with the exception of hyaluronic acid) to the central core of a protein. A large number of anionic charges, such as carboxyl and sulfate groups, are present in the GAGs and interact electrostatically with water molecules, regulating the hydration of the connective tissue, and with ECM proteins, such as collagen, forming an interlocked supramolecular matrix [20,21].

1.2. Applications of collagen

Historically, the industrial uses of collagen in the form of leather and gelatin are widespread, including photographic gelatin, cosmetics, food and pharmaceutical applications, enzyme production, etc. [22]. Collagen, as a fibrous protein, is the principal component of connective tissues in mammals. The fibrillar collagens are insoluble in their native structure but can be solubilized in aqueous solution if they are denatured to soluble procollagens [23]. The denaturation of collagen is an irreversible kinetic process [24] and it may be obtained by thermal treatment: once the helix-coil transition temperature (e.g. $\sim 37^\circ\text{C}$ for bovine collagen) is exceeded, collagen is converted into a randomly coiled gelatin [25]. Other methods to produce gelatin include acid or alkaline chemical treatments [22].

For the past decade, collagen has been among the most widely used biomaterials for biomedical applications, due to its excellent biological features and physicochemical properties [26]. Collagen may be easily modified by reaction of its functional groups, introducing cross-links or grafting biological molecules to create a wide variety of materials with tailored mechanical or biological properties [5,27,28]. The main drawbacks of collagen include the high costs of manufacturing (due to the time-consuming and complex procedures required for isolation and purification), careful selection of processing conditions to avoid denaturation, and high swelling in vivo, due to collagen hydrophilicity [21–22].

In recent years, demand for the development of innovative products aimed at the replacement, correction and improvement of poorly functioning tissues in humans or animals has increased. Collagen can be easily modified into different physical forms such as powder/particles, fibers/tubing, gel/solution, films/membranes, sponges, blends (with other polymers) and composites (with ceramics). Collagen has found a wide variety of applications in the field of medicine including: sutures, hemostatic agents, tissue replacement and regeneration (bone, cartilage, skin, blood vessels, trachea, esophagus, etc.), cosmetic surgery (lips, skin), dental composites, skin regeneration templates, membrane oxygenators, contraceptives (barrier method), biodegradable matrices, protective wrapping of nerves, implants, corneal bandage, contact lens, drug delivery, etc. [22,25,28].

In particular, among the various collagen types, type I collagen is the most abundant component of the ECM and may be used as scaffolding material, promoting cell migration, wound healing

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