



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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