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Collagen interactions: Drug design and delivery☆

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ABSTRACT

Collagen is a major component in a wide range of drug delivery systems and biomaterial applications. Its basic physical and structural properties, together with its low immunogenicity and natural turnover, are keys to its biocompatibility and effectiveness. In addition to its material properties, the collagen triple-helix interacts with a large number of molecules that trigger biological events. Collagen interactions with cell surface receptors regulate many cellular processes, while interactions with other ECM components are critical for matrix structure and remodeling. Collagen also interacts with enzymes involved in its biosynthesis and degradation, including matrix metalloproteinases. Over the past decade, much information has been gained about the nature and specificity of collagen interactions with its partners. These studies have defined collagen sequences responsible for binding and the high-resolution structures of triple-helical peptides bound to its natural binding partners. Strategies to target collagen interactions are already being developed, including the use of monoclonal antibodies to interfere with collagen fibril formation and the use of triple-helical peptides to direct liposomes to melanoma cells. The molecular information about collagen interactions will further serve as a foundation for computational studies to design small molecules that can interfere with specific interactions or target tumor cells. Intelligent control of collagen biological interactions within a material context will expand the effectiveness of collagen-based drug delivery.

Contents

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1. Background

Collagen, the most abundant protein in the human body, has a long history as a natural material for diverse biomedical applications, including drug delivery [1,2]. Animal tissues rich in type I collagen are important sources of leather, cosmetic and gelatin products, in addition to biomedical devices and implants. From a physical perspective, collagen forms a rod-like triple-helix which self-associates to form a staggered array in D-periodic fibrils. The fibrils are cross-linked to provide mechanical strength and integrity to the extracellular matrix, and the distribution of fibril diameters, as well as the degree of cross-linking, strongly influence the tensile strength and elasticity of tissues. Extracted collagen molecules or fibers can form hydrogels, films or sponges that can be used as hemostatic pads, wound dressings, grafts and scaffolds for surgery and tissue engineering [3–6]. A better understanding of the interactions between collagen and its environment would enhance its widespread utility in health-related products.

In addition to its material properties, there has been increasing appreciation of the biological importance of collagen in cell signaling and regulation of extracellular matrix (ECM) function. The collagen triple-helix interacts with a large number of molecules that trigger biological events. Collagen interactions with cell surface receptors regulate many cellular process including adhesion, proliferation and migration [7], while interactions with other ECM components are critical for matrix structure and remodeling. In addition, the tight winding of its triple-helix structure makes collagen largely non-immunogenic, resulting in excellent biocompatibility of collagen-derived materials. Details about the immune response to native and denatured collagen are discussed in several reviews [1,8]. Another important property of collagen-based materials is their natural degradation in the body. Collagens typically have a long lifetime, but a regulated breakdown is necessary during tissue turnover, remodeling and wound healing. The triple-helix structure is resistant to common proteases, but members of the matrix metalloproteinase (MMP) family can cleave native and denatured collagen at specific sites, leading to eventual breakdown of collagenous biomaterials in the body. Over the past decade, much information has been gained about the interactions of collagen with cell surface receptors, other ECM components and enzymes such as MMPs. Knowledge of these interactions allows for the possibility of new approaches in drug discovery, targeting and delivery.

The combination of its natural hierarchical physical structures and biological interactions makes collagen an attractive candidate for a wide range of biomedical applications, which have proved effective in many cases. There are a number of excellent review papers that have focused on advances in the use of collagen materials as drug delivery vehicles [9–12]. The biological signals present within every animal collagen molecule for cell receptor binding, degradation, and matrix organization means that collagen within every biomaterial and drug delivery vehicle will naturally interact with its environment. This can lead to unintended consequences or to unregulated processes. The important progress in understanding the nature and specificity of collagen interactions which has taken place in recent years sets the stage for more intentional, regulated biological activities within collagen-based materials. This review will focus on collagen interactions with cell receptors, other ECM proteins and enzymes, and consider the implications of these interactions for directed drug delivery and designer biomaterials.

2. The collagen molecule: an interaction perspective

Proteins which contain a triple-helix domain and which play a structural role in the ECM are classified as collagens. The human family of collagens currently includes 28 distinct genetic types, and may be broadly divided into fibrillar types and non-fibrillar collagens (see [13] for a recent review). The fibrillar types I, II and III form typical collagen fibrils with an axial periodicity of 67 nm and are the most abundant collagens. Different genetic types exhibit a tissue-specific distribution: type I in bone, skin, tendon, cornea; type II in cartilage and the vitreous; and type III, together with type I, in skin, blood vessels and more flexible tissues. Type I collagen is a heterotrimer consisting of two $\alpha1$(I) chains and one $\alpha2$(I) chain, and this most abundant collagen forms the basis of most biomaterial applications. Type II and III collagens show homology to the $\alpha1$ chain of type I collagen, but are homotrimers. The non-fibrillar collagens include type IV collagen, which forms network-like structures in basement membranes, as well as FACIT collagens and membrane-associated collagens.

Fibrillar collagens extracted in bulk from tissues such as cow hide, pig intestines or fish skin represent the dominant collagen protein used for biomedical applications. To complement extracted animal collagens, the production of recombinant human collagen has been extensively explored [11] and significant advances have been made. Expression of recombinant human collagen in mammalian cell lines has led to the generation of constructs with variations in individual residues or in the organization of the D-periodic elements [14–16], but the small yields limit the use of such material in practical applications. Efforts are ongoing to produce human collagen in recombinant systems such as yeast, insect cells and plants [17,18]. The task of large-scale expression of stable and functional recombinant animal collagens is far from simple, in large part due to the requirement for post-translational proline hydroxylation for animal collagen stability. Recent findings of collagen-like proteins in bacteria suggest that these triple helix-forming proteins may represent alternative biosynthetic collagen materials that could enhance current collagen sources [19,20].

In this section, the nature of the triple-helix is considered as well as the features of the structure that direct interactions with other proteins.

2.1. Collagen structure

In the 1950s, fiber X-ray diffraction studies, together with amino acid composition/sequence data and model building, led to the proposal of a triple-helix as the molecular structure for collagen [21,22]. In this structure, three polyproline II-like polypeptide chains are supercoiled about a common axis. The close packing of the three chains near the central axis requires Gly as every third residue, generating the characteristic collagen (Gly-Xaa-Yaa)$_n$ repeating sequence. The Gly residues

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