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Review

Mechanisms of lamellar collagen formation in connective tissues

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ABSTRACT

The objective of tissue engineering is to regenerate functional tissues. Engineering functional tissues requires an understanding of the mechanisms that guide the formation and evolution of structure in the extracellular matrix (ECM). In particular, the three-dimensional (3D) collagen fiber arrangement is important as it is the key structural determinant that provides mechanical integrity and biological function. In this review, we survey the current knowledge on collagen organization mechanisms that can be applied to create well-structured functional lamellar tissues and in particular intervertebral disc and cornea. Thus far, the mechanisms behind the formation of cross-aligned collagen fibers in the lamellar structures is not fully understood. We start with cell-induced collagen alignment and strain-stabilization behavior mechanisms which can explain a single anisotropically aligned collagen fiber layer. These mechanisms may explain why there is anisotropy in a single layer in the first place. However, they cannot explain why a consecutive collagen layer is laid down with an alternating alignment. Therefore, we explored another mechanism, called liquid crystal phasing. While dense concentrations of collagen show such behavior, there is little evidence that the conditions for liquid crystal phasing are actually met *in vivo*. Instead, lysyl aldehyde-derived collagen cross-links have been found essential for correct lamellar matrix deposition. Furthermore, we suggest that supra-cellular (tissue-level) shear stress may be instrumental in the alignment of collagen fibers. Understanding the potential mechanisms behind the lamellar collagen structure in connective tissues will lead to further improvement of the regeneration strategies of functional complex lamellar tissues.

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1. Introduction

The functionality of a lamellar tissue -such as the annulus fibrosus of the intervertebral disc (Fig. 1A) and the cornea (Fig. 1B) whose collagen fibers are organized in layers with alternating orientation-is connected with its structure [1]. Although enormous progress has been made in tissue engineering, no engineered tissue has entered routine clinical practice yet mainly because they do not have the appropriate structure and function of their native counterparts [4,5]. During embryonic development, collagen fibers in many tissues, such as the cornea, assemble in consecutive layers with alternating orientation [6,7]. Reconstruction of such a complex native-like structure requires control over the fibrous arrangement of collagen and other matrix components. Disordered structures such as tumors or fibrotic tissue are disfunctional because tissue function strongly depends on ECM fiber arrangement [8]. Creating such structures thus is an essential aspect of functional tissue engineering.

Collagen is the main fibrous and structural protein of the ECM and a major determinant of mechanical properties of connective tissues [1,9,10]. Collagen structural arrangement results in long term *in vivo* biomechanical stability of engineered tissues [1,11], but the mechanisms that create collagen anisotropy are not well

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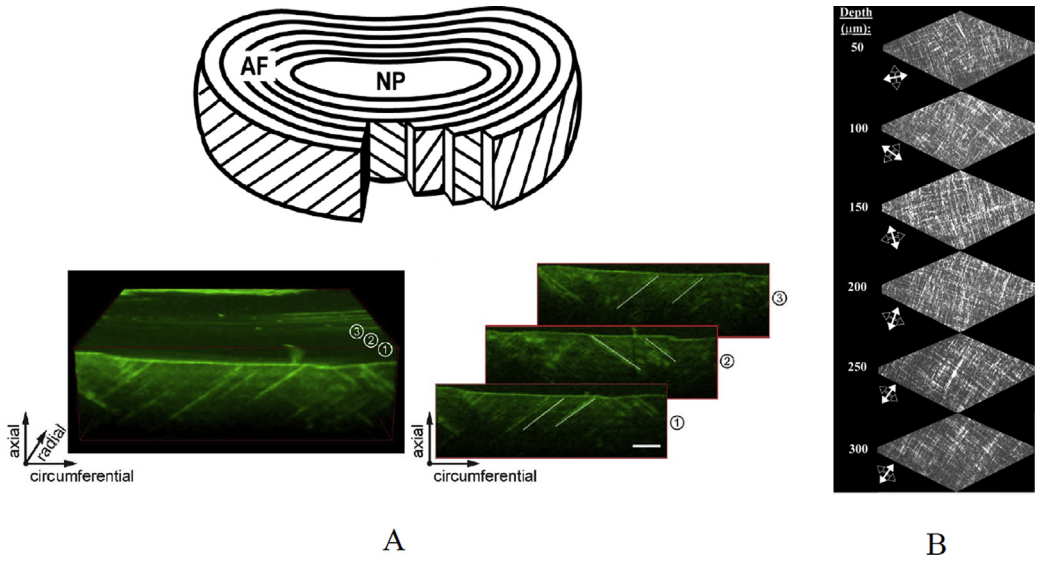

Fig. 1. (A) Upper, schematic illustration of the intervertebral disc composed of a gel-like center called nucleus pulposus (NP) and lamellar layers of collagen fibers with alternating directions called annulus fibrosus (AF). Lower, 3D representation of the ovine AF using optical coherence tomography. Individual images on the right side with circled numbers (taken from approximately the location of corresponding numbers in the left image) show how collagen orientation is changed in depth. Scale bar represents 500 μm. Reprinted from Han et al. [2], with permission from John Wiley and Sons, copyright 2015. (B) Collagen orientation changes with depth in chicken cornea. The arrows indicate the two principal directions. Reprinted from Boote et al. [3], with permission from Investigative ophthalmology & visual science, copyright 2011.

understood. Therefore, we will review the underlying mechanisms behind collagen fiber alignment to create functional lamellar tissues *in vitro*.

Many researchers have suggested that cells are the driving force behind matrix anisotropy [12–18]. Cells generate traction forces during tissue development, and the exerted force on the ECM is generally largest along the main axis of the cells [12–14]. The resulting mechanical stress applied to the tissue is considered to be responsible for the (re-)organization of collagen fibers [15–18]. Also, cell-generated forces can collectively create supra-cellular or tissue-level stresses, which affect alignment of the cells and collagen fibers as they are often aligned with the maximum shear stress [19,20]. Other researchers have suggested that preferred alignment occurs due to the strain-stabilization behavior in which fibers under mechanical strain are supported against remodeling through enzymatic degradation. Thus, collagen fibrils can assemble into specific patterns even in an a-cellular context [21,22]. These two mechanisms can describe simple one layer anisotropic alignment of collagen fibers. However, it is not clear how multiple-layers of collagen fibers stack together in lamellae-like tissues.

Another mechanism called liquid crystalline behavior has been presented as a potential underlying mechanism behind multi-layered cross-aligned tissues [23–27]. Liquid crystal is a state of material in between the liquid and the crystal in which the material can flow like a fluid and has orientational order like a solid. It is as yet unclear under which specific conditions this state happens *in vivo* and how to replicate that in a physiological condition *in vitro*.

It is also not fully understood yet which mechanism or maybe combination of mechanisms are creating the multi-layered structural arrangement of collagen in native tissues. The aim of this review paper is to provide the current thinking on the potential of these mechanisms to establish a self-assembled arrangement of collagen fiber network *in vitro*. We first provide an overview on collagen fibrillogenesis and the important components controlling individual collagen fibril formation. Then, we review the mechanisms involved in suprafibrillar and tissue-specific collagen arrangement which are less understood.

2. Collagen fibrillogenesis

In vitro, collagen fibril self-assembly from collagen molecules is a spontaneous and entropy-driven procedure caused by the loss of solvent from the collagen solution [28]. Purified collagen molecules in acidic solutions can bind to each other and assemble to fibrils at a certain concentration, temperature and pH with no other molecules involved [29]. The structure of the fibrils formed *in vitro* depends on environmental factors like buffer composition and temperature [1]. It was shown, for instance, that phosphate is an essential element in the formation of well periodically banded collagen fibrils, and fibrils formed at lower temperatures (~20 °C) had a larger diameter than those formed at higher temperatures [30]. Although *in vitro* relevant parameters can be controlled, replicating structures with a unique morphology and defined size remains a challenge. Self assembly of proteins such as collagen can also be guided by external forces such as electric field to create structures with a unique morphology *in vitro* [31].

Fibril formation *in vivo* or by cultured cells is much more complex since about 50 molecules are known to interact with the fibrillary collagen molecules [29,32]. Collagen fibril formation needs regulators, such as fibronectin and collagen binding integrins, as well as nucleators, like collagen V and XI [29]. Collagen fibril assembly was completely inhibited in human smooth muscle cell cultures by inhibition of fibronectin assembly and the presence of an anti-α5β1 integrin antibody [33]. An anti-α2β1 integrin antibody inhibited the assembly of collagen fibrils in the same study [33]. Ledger et al. showed localization of fibronectin and procollagen in the secretory pathways of cultured fibroblasts meaning that these proteins interact within the cells before secretion in the ECM [34]. Thus, *in vivo*, other factors are in place to control what is otherwise a protein self-assembly process.

Collagen V, as a collagen fibril nucleator, is an important regulator of collagen fibril diameter [35–37]. Collagen V is co-distributed with collagen I in the same fibrils [35]. Analysis on collagen fibril structure in the cornea of mice with targeted deletion of Col5a1 gene showed that fibril diameter was increased and the density of the fibrils was decreased as compared to those seen in

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