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Review

Collagen-based cell migration models in vitro and in vivo

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ABSTRACT

Fibrillar collagen is the most abundant extracellular matrix (ECM) constituent which maintains the structure of most interstitial tissues and organs, including skin, gut, and breast. Density and spatial alignments of the three-dimensional (3D) collagen architecture define mechanical tissue properties, i.e. stiffness and porosity, which guide or oppose cell migration and positioning in different contexts, such as morphogenesis, regeneration, immune response, and cancer progression. To reproduce interstitial cell movement in vitro with high in vivo fidelity, 3D collagen lattices are being reconstituted from extracted collagen monomers, resulting in the re-assembly of a fibrillar meshwork of defined porosity and stiffness. With a focus on tumor invasion studies, we here evaluate different in vitro collagen-based cell invasion models, employing either pepsinized or non-pepsinized collagen extracts, and compare their structure to connective tissue in vivo, including mouse dermis and mammary gland, chick chorioallantoic membrane (CAM), and human dermis. Using confocal reflection and two-photon-excited second harmonic generation (SHG) microscopy, we here show that, depending on the collagen source, in vitro models yield homogeneous fibrillar texture with a quite narrow range of pore size variation, whereas all in vivo scaffolds comprise a range from low- to high-density fibrillar networks and heterogeneous pore sizes within the same tissue. Future in-depth comparison of structure and physical properties between 3D ECM-based models in vitro and in vivo are mandatory to better understand the mechanisms and limits of interstitial cell movements in distinct tissue environments.

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Abbreviations: ECM, extracellular matrix; 3D, three-dimensional; SHG, second harmonic generation; CAM, chorioallantoic membrane; DSFC, dorsal skin fold chamber; DED, de-epidermized dermis.

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1. Introduction

In vertebrates, the ECM comprises at least two distinct types of scaffolds. Whereas basement membranes form a dense, flat protein meshwork underlying and anchoring epithelial and endothelial cells, interstitial connective tissues consist of 3D meshworks of heterogeneous texture and composition. The main ECM component of interstitial tissues is fibrillar type I collagen that forms up to 90% protein content of connective tissues. The physical stability of connective tissues is mostly mediated by collagen fibrils, which are mechanically stable and provide a scaffold to which other ECM proteins such as fibronectin and gylcosaminoglycans connect.

After fibroblast-mediated synthesis of procollagen molecules, fibrillogenesis is initiated by the cleavage of N- and C-terminal propeptides from monomeric collagen, followed by the spontaneous collagen self-assembly into fibrils (Fig. 1A). Fibrils then receive slow secondary modification by stromal cell-derived lysyl oxidase (LOX) which generates aldehyde groups at telopeptide-located lysyl or hydroxylysyl-residues that then spontaneously form aldimide (Schiff-base) cross-links with amino groups from a neighbouring collagen monomer [1,2]. This chemical modification leads to the formation of collagen fibrils and bundled fibres of enhanced mechanical stability [3].

Depending on further tissue-specific modifications and functions, such as protective or tensile stress-bearing tasks, collagen fibres are cross-linked to different extent and organized into quite heterogeneous structures. Interstitial connective tissue below epithelia contain porous but heterogeneously textured collagen networks, including thick bundles alternating with loosely organized thin fibres hosting blood and lymph vessels, and additional ECM components such as elastic fibres and fibronectin. Often these upper loose zones are connected to dense connective tissue and fat tissue. This basic organization is preserved in dermis, interstitial tissue of the gut and most parenchymatous organs. Collagen-rich ECM undergoes life-long remodeling and re-shaping by tissue cells such as fibroblasts that create adhesion receptor-mediated tension on ECM and physiologic slow proteolytic matrix turnover, a process that may become enhanced during wound healing or disease [4–7]. Interstitial ECM, on the other hand, influences cellular functions, besides acting as a major reservoir of releasable growth factors and peptide mediators, by physical characteristics, such as by fibre thickness, orientation, density, stiffness, or pore size between fibres [8–11]. These tissue structure-imposed changes on cell function are mediated by at least two distinct but interdependent mechanisms: (i) by mechanosensor-mediated and additional signaling cascades [12,13] and (ii) by guidance and confinement, respectively, of the cell body resulting in a shape adaptation in order to move [14,15]. Dimensionality as an additional aspect of tissue geometry influences cell–matrix interaction and consecutive movement which may take place along a single fibre (1D migration), across a sheet-like surface (2D movement), or through a spatially complex meshwork of fibrils (3D migration) [9,11,16–18]. Whereas 1D and 2D models provide important insights into the organization of molecular machineries underlying cell adhesion and migration, 3D migration models are instrumental in modeling cell dynamics with high fidelity to in vivo behaviour [19]. We here assess different 3D collagen-based models in vitro and in vivo, with a focus on the comparison of physical structure and spacing characteristics of collagen for the study of tumor cell movement.

2. Methods to visualize the 3D architecture of fibrillar collagens

The detection of fibrillar collagen from in vitro lattices or in tissues can be achieved by several approaches that are based on distinct physicochemical parameters, using either dried processed or hydrated samples. Fixed and chemically processed fibrillar collagens are traditionally assessed either in histological sections, transmission or scanning electron microscopy (SEM), revealing collagen organization and, particularly when using SEM, additional contrast-producing solid structures [20]. Whereas the fibre geometry is preserved to high degree, these approaches do not allow the three-dimensional reconstruction of collagen architecture with sufficient fidelity, due to structural changes introduced by sample slicing, shrinkage artifacts and collapse. In contrast, the 3D fibrillar collagen organization in hydrated state can be directly visualized from native or fixed samples by confocal reflection (*syn.* backscatter) microscopy [21] or two-photon-excited SHG microscopy [22,23]. Therefore, the latter two approaches provide more exact spacing information quantifiable by manual and automated image analysis approaches and computation [21,24].

2.1. Confocal reflection microscopy

For confocal reflection, light is introduced into the sample and the signal reflected by solid-state structures is detected in backward direction, thus any laser wavelength and sufficiently sensitive detection system will support this approach. Reflection of light occurs at interfaces between materials with different refractive indices, such as glass–water, collagen fibre–water, or cell membrane–water transitions, thus it is intrinsically non-specific and even cannot be distinguished from autofluorescence. However, it represents a powerful approach for high-contrast imaging of fibrillar scaffolds and (often fluorescently labelled) cells therein [18,21,25].

2.2. SHG

For the detection of fibrillar collagen structures within connective tissue in vivo, SHG is the method of choice. It is often visualized in conjunction with SHG from other structures, such as striated muscle, and tissue autofluorescence, including elastic fibres and endogenous, intracellular fluorophores [23,26]. The basic physical principle of SHG consists in the frequency-doubling of light by crystal-like repetitive non-centrosymmetric structures, particularly polymers of helical proteins.

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