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Review

Tissue mechanics and fibrosis ☆

Rebecca G. Wells *

The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

Mechanical forces are essential to the development and progression of fibrosis, and are likely to be as important as soluble factors. These forces regulate the phenotype and proliferation of myofibroblasts and other cells in damaged tissues, the activation of growth factors, the structure and mechanics of the matrix, and, potentially, tissue patterning. Better understanding of the variety and magnitude of forces, the characteristics of those forces in biological tissues, and their impact on fibrosis in multiple tissues is needed and may lead to identification of important new therapeutic targets. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

1. Introduction

Mechanical forces are essential to the development, progression, and (potentially) regression of tissue fibrosis. Although often ignored in studies and models of fibrosis, particularly in the era of genomics and proteomics, mechanical signals are similar to chemical signals in their range of effects and are likely to be equally important. The mechanical forces that act in fibrosis are highly varied, and may mediate individual cell phenotypes as well as global architectural changes. Understanding the role of mechanics in fibrosis is key to understanding the basic pathophysiological mechanisms of fibrotic diseases as well as developing new therapies.

2. Forces

There are multiple forces at work in tissues. These include tension and compressive forces (forces which pull or push perpendicular to the surface of an object) and shear forces (which are parallel to the surface) (Fig. 1A). These forces exert *stress* on objects, defined as force (in Newtons (N)) normalized to the area over which it acts and expressed in units of pascals (1 Pa = 1 pN/μm^2). Forces in tissues result from cell-generated tension, fluid flow, stretch, and hydrostatic/osmotic pressure, which are resisted to variable extents by tissue stiffness. These forces collectively regulate the phenotype and proliferation of myofibroblasts and other cells in damaged tissues, the activation of growth factors, and the structure and mechanics of the matrix — all of which are central to fibrosis.

There are important differences between signaling from mechanical (force-generated) stimuli and signaling from soluble (chemical) stimuli [1]. Soluble signals, such as growth factors, diffuse radially and provide limited directional information, while mechanical signals can be highly directional and thereby convey complex information in three dimensions. This is particularly important for cells of the same type, which can communicate over long ranges *via* mechanical signals; for autocrine soluble signals, cells cannot build up concentration gradients relative to their neighbors. Mechanical signals, which decay as a function of 1/r (where r is the radius) when they are transmitted through an elastic continuum and decay even more gradually when transmitted directly through filamentous elements of the matrix, are also communicated over longer length scales than soluble signals, which decay as 1/r^2. For example, some *strains* (deformations caused by forces) can be transmitted over distances of hundreds of microns [2]. Additionally, mechanical signals can be regulated rapidly. While chemical signals require translation into second messenger cascades, mechanical signals are often transmitted directly, without the need for diffusible intermediates. Thus, force-mediated signals can be started and stopped rapidly compared to soluble signals, allowing increased control in time.

It is important to note that changes in the mechanical properties of tissues, like changes in the level or distribution of soluble factors, can both cause and result from fibrosis. In the same way that a profibrogenic growth factor like transforming growth factor-β (TGF-β) stimulates myofibroblast activation and is then produced by those same myofibroblasts, thereby perpetuating fibrosis, myofibroblasts can be activated in response to mechanical forces and then perpetuate fibrosis by altering the mechanical environment.

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* The University of Pennsylvania, 905 BRB II/III, 415 Curie Blvd., Philadelphia, PA 19104, USA. Tel.: +1 215 573 1860; fax: +1 215 573 2024.
E-mail address: rgwells@mail.med.upenn.edu.

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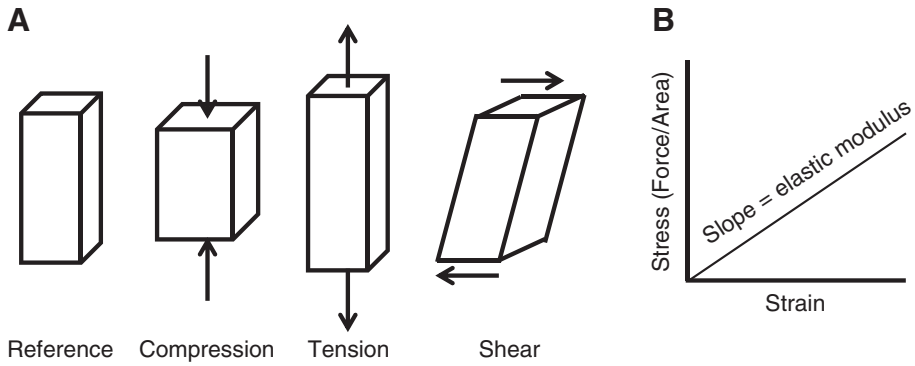

Fig. 1. Forces affecting tissues. A) Forces acting on tissues. B) The elastic modulus of a material is the slope of the *stress* (force per unit area) plotted against the *strain* (deformation). The diagram demonstrates *linear elasticity*, where the stress/strain relationship is constant. In reality, most biological materials demonstrate *non-linear elasticity*, such that the elastic modulus changes as strain increases.

3. Tissue stiffness and stiffness sensing

The best-studied force in tissue fibrosis is tension generated in response to tissue stiffness. Tissue stiffness is measured as the elastic modulus, defined as the resistance to deformation, and is expressed as the magnitude of a *stress* (compression, elongation, or shear force, normalized to area) divided by the *strain* (deformation) induced by the stress (Fig. 1B). Young's elastic modulus (E) describes the resistance to a compressive or elongating force, while the shear elastic modulus (G) describes the resistance to a shear force. E and G are both expressed in units of Pa; for a perfectly elastic material that conserves volume (one that returns to its original shape when the stress is removed), E is three times G. Tissues, however, are not perfectly elastic but are viscoelastic, meaning that, like liquids, they have a viscosity, and that the strain in response to a stress changes with time [3,4]. Although the role of the elastic modulus in regulating cell behavior is the subject of increasing study, the role of the viscous component of tissues is poorly understood [5]. Tissues are also structurally heterogeneous and resist deformation to different extents depending on the direction in which a force is applied. Additionally, neither the elastic nor the viscous stress of most biological tissues varies linearly with strain; although this can be important in maintaining the mechanical characteristics and integrity of a given tissue, it is difficult to model and study [6].

Tissue stiffness is sensed when cells adhere to matrix proteins and apply tension, meeting resistance that reflects the stiffness of the tissue. The cellular actin–myosin cytoskeleton exerts tension on extracellular matrix proteins *via* integrin attachments located within focal adhesions; stiffer tissues result in increased resistance to the pulling force exerted by cells, contributing to strengthening that force [7,8]. Whether the mechanical force originating at the cell boundary is transmitted directly to the nucleus or to nuclear proteins (Yap/Taz, for example) [9], and whether signaling cascades are activated (potentially *via* focal adhesion kinase (FAK) or other focal adhesion proteins) as a result of tension at the site of the focal adhesion, are issues that have stimulated extensive investigation [10].

Normal tissues vary in their stiffness when measured over the same strains and time scales. The brain is very soft, with an elastic modulus around 100 Pa; the liver, while also soft, is slightly stiffer at 400–600 Pa, and the muscle and bone are stiffer still (10^4 and 10^6 Pa, respectively) [1]. It is clear from clinical practice that tissue stiffness changes in disease states. In the same way that we can easily tell by touch that a steel bar is stiffer than gelatin, palpation as part of the routine physical exam enables detection of differences in skin or liver stiffness and suggests that fibrotic tissues are stiffer than normal tissues. Multiple studies have shown that fibrotic lungs become stiffer in fibrosis, with elastic modulus values ranging from approximately 2 kPa for normal tissue to approximately 17 kPa for fibrotic tissue [11–13]. We have found normal livers *ex vivo* to have a shear modulus less than 1 kPa, while fibrotic livers range from 3 kPa to 22 kPa [14]. Transient elastography, which measures the elastic modulus, is widely used in clinical practice outside of the U.S. to assess the liver stiffness in patients with liver disease; although values vary from one study to the next, elastic moduli (measured at time scales that are shorter than those generally used for *ex vivo* studies) are typically less than 5 kPa for normal livers and greater than 12 kPa for cirrhotic livers [15].

Organs with established fibrosis are thought to be stiffer as a result of their increased quantity of extracellular matrix, in particular fibrillar collagens. It appears, however, that increased matrix alone is unlikely to account for increases in tissue stiffness in fibrosis and that stiffness and matrix quantity are not linearly related. Our studies suggest that increases in collagen and elastin cross-linking account for some of the increase in elastic modulus in liver fibrosis and that the mechanical properties of the injured liver change significantly early after injury, before significant matrix deposition has occurred [14,16]. This crosslinking appears to be initiated by lysyl oxidase family crosslinking enzymes; the changes in stiffness are consistent with the effects of lysyl oxidases in isolated collagen cushions, the vasculature, and different cancers (see below) [17–21]. The contribution of altered *cell* (as opposed to *matrix*) stiffness to tissue mechanics in fibrosis has not been established but may be considerable [12].

4. Other forces acting on tissues

Forces other than tension generated in response to tissue stiffness may also contribute to the development and progression of fibrosis. Tissues are subject to shear stress caused by fluid flow through the vasculature, ducts, and interstitium. Of these, vascular flow and the effects of shear stress on the vascular endothelium are best understood, in particular in the context of cardiovascular disease and remodeling (a form of injury and fibrosis, although not strictly speaking tissue fibrosis). Alterations in vessel geometry, flow rate, and fluid viscosity contribute to changes in shear stress, regulating the release by endothelial cells of growth factors, vasodilators like nitric oxide, and other soluble factors, and leading to long-term changes in gene and protein expression [22]. Mechanotransduction results from cell surface deformation (affecting ion channel function, cell surface receptors, the glycocalyx, the primary cilia, and the physical properties of the membrane) as well as the transmission of signals from the cell surface to distant regions of the cell, affecting cell-substratum and cell–cell interactions which in turn lead to changes in chemical signals [22,23]. Tissues such as the kidney, liver, and lung have significant amounts of flow through specialized vessels including the glomerulus in the kidney, sinusoids in the liver, and pulmonary vessels in the lung. Altered flow through these vessels may be both the cause and the result of tissue remodeling and fibrosis, and may also result in pathologic angiogenesis [24].