Review

Mechanical properties of basement membrane in health and disease

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Abstract

Physical properties are differentiated characteristics of tissues that are essential to their function. For example, the function of bone depends on its rigidity, and the function of skin depends on its elasticity. The aggregate physical properties of tissues are determined by a collaborative relationship between their cells and matrix and are the product of genetic programs, circulating chemical signals, physical signals, and age. The mechanical properties of matrix and basement membranes in biologic systems are difficult to understand in detail because of their complexity and technical limitations of measurements. Matrix may contain fibrillary collagens, network collagens, other fibrillar proteins such as elastin, fibronectin, and laminins, proteoglycans, and can be a reservoir for growth factors. In each tissue and in different regions of the same tissue, matrix composition can vary. The goal of measuring the mechanical properties of matrix is to understand the physical environment experienced by specific cell types to be able to control cell behavior in vivo and for tissue engineering. At this time, such precise analysis is not possible. The general elastic properties of tissues are now better characterized, and model systems using limited numbers of matrix constituents permit improved understanding of the physical behavior of matrix and its effects on cells. This review will describe model systems for understanding problems of matrix elasticity, focus on a relatively new aspect of matrix mechanics, strain-stiffening, and the interactions of cells with matrix to produce overall tissue mechanical properties.

Introduction

Cells and tissues depend on chemical and physical extracellular signals for control of basic functions such as growth and differentiation, as well as the ability to respond to long- and short-term changes in the environment. Biologists and biochemists have focused on chemical signals for a number of reasons including their importance, the orientation of investigators, poor recognition of the roles of physical factors, difficulty in crossing disciplines, and difficulty in designing meaningful experimental systems to examine physical factors in biology. Generally, the physical state of a tissue was thought to be part of its character or a consequence of injury, and not an active ingredient in its behavior[13]. Over the last few years, the importance of physical signals in cell differentiation, stability of phenotype, malignancy, injury and repair, and stem cell niches have become evident, although the molecular details and mechanisms of these process largely remain to be defined[13,14].

Basement membranes, or matrix, have been considered relatively inert structures that provide static mechanical support such as scaffolds and function as barriers. However, it is now clear that they provide both biochemical and dynamic physical signals, and both sets of signals are integral to cell behavior and tissue function. Additionally, properties of tissues that have been ascribed to alterations in matrix such as stiffening with fibrosis or scarring may depend on changes in cell behavior as well as changes in matrix. The presence and state of cells in matrix can dramatically alter the mechanical behavior of the matrix or the aggregate behavior of a tissue or model system [20,28]. In this review, we will

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discuss the polymer structure of matrix, how matrix with different structure and composition can have different physical characteristics, how the mechanics of matrix can affect its function as a reservoir for growth factors, and how in some cases cells interact with matrix to affect the aggregate mechanical properties of a tissue.

Matrix is dynamic and is constantly synthesized and degraded by cells. Under normal conditions, these processes are in balance, and the structure and composition of the matrix remain relatively constant. In disease, matrix synthesis and degradation may become out of balance, infiltrating or transformed cells may change the composition of the matrix, and matrix cross-linking may change. All of these factors are likely to change the mechanical properties, but that is an area for future work, in part because the basic properties of matrix are now beginning to be understood in simple systems. In this review, these important areas that include matrix remodeling and turnover, the functions of matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), and cross-linking (lysyl oxidase, transglutaminases, and cell-independent factors such as advanced glycation end-products) will not be addressed.

Physical factors in biology

Appreciation of the role of physical factors in biology has increased as a result of the inability of chemical signaling to explain all biologic phenomena, improved experimental systems that allow measurement of the physical characteristics of biologic material, and more faithful modeling of biologic materials with simpler physical approaches. Although the correspondence between defined physical systems and biologic materials remains approximate, these systems have increasing explanatory power. A number of recent studies show that matrices with elastic properties quantitatively similar to native tissues, brain (soft), muscle (medium), and bone (stiff) are sufficient to specify development of mesenchymal stem cells along neuronal, muscle, or osteoblastic lineages[5]. Similar studies showed that matrices with similar elasticity values as muscle and brain were required for cultured muscle progenitor cells to maintain their ability to differentiate into muscle cells, and to support growth of neurons from brain cortical homogenates [7,9].

Mathematical or physical models of materials describe them as elastic or viscous (see Glossary) [12,13]. Elasticity refers to the ability of a solid material to return to its original shape after deformation when the deforming force is removed. Some of the deforming energy is stored in the material allowing it to regain its original shape. Examples include springs and rubber balls. Measurement of elasticity (resistance to deformation) involves applying a known or measured force to a substance and determining the degree of deformation. The quantity is an elastic modulus (E_{Mod}), the simplest form being a Young's modulus calculated from a linear deformation such as compressing an object with a rod or stretching it from a single point. The elastic modulus is reported in Pascals (Pa, Newtons/m^2). Viscosity refers to the resistance of a liquid to flow. Liquids deform in response to forces and remain deformed when the force is removed. The extent of deformation is not limited, but the rate at which deformation takes place in response to a force is determined by the magnitude of the force and the interactions of the molecules in the liquid. Viscosity is reported as Pa/s. Examples include water which offers minimal resistance to deformation, and molasses, which resist deformation, especially at low temperatures.

Application of physical methods to biologic material

Application of methods to measure the viscous and elastic properties of polymeric liquids, gels, and solids to biologic material and model systems such as reconstituted solutions of collagen or actin mixed with cross-linking proteins resulted in a better understanding to the basic physical properties of matrix, tissues, and cells. The elastic modulus of tissues ranges from a few hundred Pa for brain to hundreds of thousands of Pa for cartilage and bone. Even excluding calcified tissues such as bone with an E_{Mod} of hundreds of thousands of Pa, the range of E_{Mod} values for normal tissues is considerable. Brain and bone marrow have values of a few hundred Pa, normal liver is 500 Pa, renal glomeruli are 2000 Pa, striated muscle is 10,000 Pa, and aorta is 20,000 Pa[13,17]. In disease as matrix accumulates, its structure changes and tissues become stiffer, often losing their normal functions. These pathologic changes in tissues, referred to as fibrosis, are associated with altered matrix composition and structure, but also probably represent alterations in cell structure and function.

Regardless of the tissue or cell type, matrix and basement membranes contain a complex mixture polymeric proteins that includes fibrillar proteins such as collagens, elastin, laminins, and fibronectin. Matrix also contains glycosaminoglycans and proteoglycans, molecules with protein cores covalently linked to repeating disaccharide subunits. A third component of matrix includes molecules such as heparan sulfate, perlecan, nidogen, and agrin, as well as hyaluronic acid. Collagens have a triple helical structure that forms fibers, and the fibers are commonly cross-liked to form