Mechanotransduction-The relationship between gravity, cells and tensile loading in extracellular matrix

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Abstract: Gravity plays a central role in vertebrate development and evolution. Mechanotransduction involves the tensile tethering of veins and arteries, connections between the epidermis and dermis in skin, tensile stress concentrations that occur at tissue interfaces, cell-cell interactions, cell-collagen fiber stress transfer in extracellular matrix and fluid shear flow. While attention in the past has been directed at understanding the myriad of biochemical players associated with mechanotransduction pathways, less attention has been focused on determining the tensile mechanical behavior of tissues in vivo. Fibroblasts sit on the surface of collagen fibers in living skin and exert a retractile force on the fibers. This retractile force pulls against the tension in collagen fibers in skin. After fibroblast-collagen fiber interactions are altered either by changes in fibroblast adhesion or after formation of cancer associated fibroblasts, and changes in cell junctions, alterations in the retractile force leads to changes in mechanotransduction. The purpose of this paper is to present a model of tensile forces that occur at the fibroblast-collagen fiber interface and how these forces are important in extracellular matrix physiology in health and disease.

Introduction

Gravity plays a central role in vertebrate development and evolution. Gravitational forces acting on mammalian tissues cause the net muscle forces required for locomotion to be higher on earth than on a body subjected to a microgravitational field (Silver, 2006). Thus mechanical forces required to do the work (mechanical energy) of locomotion must be sensed by cells and converted into chemical energy (synthesis of new tissue) when tissues experience moderate increases in loading over a period of time (Silver and Siperko, 2003). Mechanotransduction extends far beyond biochemical and biophysical musculoskeletal events that occur in vivo. Mechanotransduction involves the tensile tethering of veins and arteries in the cardiovascular system (Silver et al., 2021), connections between the epidermis and dermis in skin (Silver et al., 2002a), tensile stress concentrations that occur at interfaces between implants and natural tissues (Silver et al., 2018), cell-cell interactions at cell attachments (Dasgupta and McCollum, 2019), cell-collagen fiber stress transfer in extracellular matrix (ECM) (Silver and Siperko, 2003), and fluid shear flow in chondrocytes and bone cells (Pattappa et al., 2019; Jin et al., 2020). Mechanotransduction involves activation of a complex series of pathways including MAP kinase and other pathways that leads to a balance between tissue anabolism and catabolism that is influenced by genetic changes within the cell nucleus (Silver and Siperko, 2003; Silver et al., 2003; Dasgupta and McCollum, 2019).

While much attention has been directed to understand the myriad of biochemical players associated with mechanotransduction pathways and their behaviors in model systems, less attention has been focused on the tensile mechanical behavior of cells and tissues in vivo. Shear behavior of cardiovascular tissue, bone and other tissues where mechanotransduction has been shown to be influenced by fluid shear forces gives valuable information (Pattappa et al., 2019; Li et al., 2019; Jin et al., 2020); however, for most tissues the tensile forces that exist between cells and the collagen fibers provide a feed-back system that may be a factor that shifts the balance between tissue anabolism and catabolism.

Examples of the importance of tensile forces in tissues exist in skin, cardiovascular tissue and cartilage. Excision of these tissues results in changes in their geometry. Skin is under tension and contracts when it is excised (Silver et al., 2002). Arterial tissue also contracts and shrinks as much as 50% when removed from the cardiovascular system (Silver et al., 2021) while articular cartilage curls when it is released from a normal joint surface (Silver et al., 2002).

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The existence of Langer’s lines of tension in skin is well known to Plastic Surgeons and has been reviewed in the past and leads to a model of this interaction (Silver et al., 2002a) (see Figs. 1 and 2). It was concluded that the collagen fibers in skin have preferred lines of tension (Silver et al., 2002a) that lead to circular holes in cadaver skin elongating along the lines of tension when the surrounding skin is cut. However, Langer failed to address the observation that circular holes made in living skin remain circular after skin is excised (Silver and Siperko, 2003). The only explanation for this difference is that the cells in the living portion of skin also provide tension. Therefore, the fibroblasts that sit on the collagen fibers must exert contractile forces that oppose the tensile forces acting on the fibers to cause the skin around the circular defect to remain circular in living skin. Thus the relationship between cellular forces and the forces applied by collagen fibers of the extracellular matrix are important factors in tissue metabolism and changes seen in cardiovascular, cartilage and skin diseases to name a few examples.

Implantation of stiff cardiovascular implants and stents result in stress concentrations and overloading of vascular tissue (Snowhill et al., 2001). This contributes to intimal hyperplasia and stenosis especially in small diameter synthetic vascular grafts (Silver et al., 2018). In osteoarthritis, loss of chondrocyte differentiation and synthesis of proteoglycans and type II collagen results in a soft matrix that no longer stores elastic energy or can dissipate it efficiently (Silver et al., 2002). Increased cellular stiffness associated with basal cell and squamous cell carcinomas result in increased turnover of the dermal collagen and increased collagen deposition of fibrotic tissue (Silver et al., 2019). In this case changes in the cellular and tissue stiffness are associated with malignancy and perhaps eventual metastasis (Silver et al., 2019; Stanisavljevic et al., 2015). Chemical and thermal burns lead to increased stiffness of the granulation tissue and remodeled fibrous collagen deposited in the skin (Silver et al., 2020; Silver and Shah, 2020) as does the genetic changes associated with the disease Scleroderma (Odell et al., 2020). The observation that negative pressure applied to wounds (Huang et al, 2014) and suturing the edges of the wound together support the idea that stretching and tensile mechanical stress promotes healing. Providing tensile forces at the wound edges restores the balance of forces acting at the collagen fiber-fibroblast interface. This balance is somehow lost due to dysregulation in hypertrophic scarring (Dunn et al., 1985) and keloid formation.

All of the these examples underscore the need to further study the relationship between forces that exist between cells and collagen fibers in tissues in vivo in order to better understand the pathogenesis and diagnoses of a variety of diseases including cardiovascular diseases and cancer.

The relationship between tension in the parenchyma of many mammalian tissues and the cellular retractive forces holding the tissues together, suggest that the force equilibrium may play a widespread role in tissue metabolism under physiologic conditions. This equilibrium can be altered via changes in tissue external loading, cellular mutations, tissue injury and changes associated with aging. Of critical importance, considering the complexity of the possible biochemical actors involved in mechanotransduction in vitro, is to understand if the same pathways occur in vivo under normal tensile loading.

Further studies of the biochemical mechanotransduction pathways are needed under conditions that mimic the normal tensile loading patterns seen in vivo. This requires the development of new techniques to understand the level of tensile forces acting in vivo in each tissue. One new technique termed vibrational optical coherence tomography has been used to measure the tensile elastic modulus of several tissues in vivo (Silver et al., 2020, 2020a, 2021). These measurements are necessary to relate changes in the mechanical properties of tissues and alterations of...
mechanotransduction that occur in vivo that is associated with cardiovascular disease and metastatic cancer.

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