

A Matter of gravity–mechanotransduction: how mechanical forces influence biological materials

Abstract

Transduction of mechanical energy into chemical energy represents the means by which biological tissues have adapted to life in a gravitational field. One pathway associated with collagen based mechanotransduction involves integrins, a family of cell surface embedded proteins that provide a link between the extracellular environment and intracellular elements.

While increased stress as a result of the presence of pressure from an implant or suturing can have a negative effect on tissue stability, up-regulation of mechanotransduction appears to occur when tensional loads are applied to tissues. Tension appears to have positive effects on wound healing in a number of studies resulting in macromolecular synthesis and cell division.

The purpose of this mini-review is to summarize recent studies that examine factors that influence integrin mediated mechanotransduction and how these influences affect implants, wound healing and other important biological processes.

Keywords: mechanotransduction, collagen, vacuum assisted wound healing, physical therapy, bone, skin

Abbreviations: ECM, extracellular matrix; IACs, integrin associated complexes; FAs, focal adhesions

Introduction

Gravity has a major influence on the synthesis and catabolism of biological macromolecules; tissues are added or removed in response to the addition or loss of mechanical stimulation, respectively.¹ Transduction of mechanical energy into chemical energy represents the means by which biological tissues have adapted to life in a gravitational field.^{1,2} The human body is a composite of macromolecular structures that support the musculoskeleton, provide a mechanism for locomotion and movement, and allow for homeostasis by regulating physiological functions.³ They are primarily composed of extracellular matrix (ECM) containing collagen, the most abundant protein found in the human body.^{3,4} Collagen fibers are found either in a mineralized form, in bone, or in a fibrous form in most other tissues and organs.³ Fibrous collagen is a protein in the form of a coiled-coil that stores, transmits and dissipates mechanical energy in tissues as well as prevents premature mechanical failure.^{4,5}

As recently as the 1980s, it was believed that collagen fibers were passive mechanical elements that give shape to tissues while preventing premature mechanical failure.^{6,7} However, it was later suggested that collagen fibers play a major role in converting external forces applied to tissues into changes in cell division and macromolecular synthesis within tissues.⁸ The purpose of this mini-review is to provide a brief overview of transduction of mechanical forces into changes in cellular behavior and cellular synthesis of macromolecules as a result of changes in mechanical loading (mechanotransduction).^{1,8}

There are many examples of mechanotransduction in everyday life. The classic example of mechanotransduction occurs as a result of weight lifting. Not only does the weight lifter gain in muscle mass by applying external loads to his or her skeletal muscle, but

through stretching of the skin that covers the muscles, the athlete gains additional skin to cover the expanded muscular tissue. Another example of mechanotransduction occurs during mechanical labor. A carpenter experiences an increase in skin thickness by repeatedly using a hammer that applies a compressive force to the outer layer of skin. The repeated compressive force applied to the skin leads to thickening of the epidermis, the top layer of skin. Finally, it is well known that astronauts that reside in a gravity free state for long periods of time experience resorption of collagen and mineral from their long bones.⁹

Integrin mediated mechanotransduction

One pathway associated with collagen based mechanotransduction involves integrins, a family of cell surface embedded proteins that provide a link between the extracellular environment and intracellular elements.^{8,10} Cells are believed to sense intrinsic mechanical properties of ECM by applying traction forces to the collagen fibers.⁸ Collagen fibers of the ECM bind to transmembrane integrins which in turn span the cell membrane and connect to actin filaments within the cell. The combination of integrins and actin filaments form integrin associated complexes (IACs) that assemble into focal adhesions (FAs).⁸ FAs display a complex three dimensional organization containing three layers.¹¹ The vertical layer consists of a FA outer layer containing integrin receptors. The intermediate layer couples the layer containing the integrin receptors and the inner layer that is involved in force generation and mechanosensing.^{11,12}

Changes in traction forces between cells and the ECM are the mechanism by which cells respond to external mechanical signals.⁸ However, since the moduli of the collagen molecule has been estimated to be between 4 (1) and 9 GPa^{1,13} while that of single cell is only in the kPa range, it is likely that cells respond to changes in strain rather than changes in the modulus or force.¹ In this manner the shear strain applied to cells that reside on the surface of the collagen fibers

probably upregulate mechanochemical transduction. Tensional forces applied directly to cells bound to collagen fibers would probably result in cellular disruption and ultimately tissue failure.

Recent advances in the understanding of integrin mediated mechanotransduction are important to understand the relationship between external mechanical loading and the events that occur within the surrounding tissue.^{10,13} This suggests that any interruption of integrin mediated binding to the surrounding ECM at the cell–tissue interface has consequences in terms of modifying mechanotransduction and the cellular response to surrounding tissues.

Focal adhesion maturation requires further integrin clustering, intracellular F actin binding and reinforcement of linkages between actin and actomyosin. Activated integrins are coupled to F actin through actin binding proteins including talin and vinculin. These molecules are involved in the “molecular clutch” that is responsible for cell movement as a result of actin flow inside the cell as F actin is polymerized leading to force generation and propulsion of the cell body.¹⁴

Phosphorelay pathways that support mechanotransduction can be activated not only by integrin binding to ECMs, but by direct stretching of the following: cell membranes, ion channels, intracellular junctions, and growth factor and hormone receptors. Activation of these moieties leads to changes in protein synthesis, altered gene expression and cell mitosis.⁸ All these events occur at the cell–tissue interface and dictate rate, composition and extent of tissue that is deposited.^{15,16} Providing the correct boundary forces and stresses to equilibrate the cell–tissue interface is important to prevent cellular hyperplasia and excessive collagen deposition. If implantation of a medical device such as a breast implant creates pressure, or if there is too much pressure as a result of suturing skin after breast reduction surgery¹⁵ interruption of the normal lines of tension within the breast lead to changes in mechanotransduction that result in the deposition of a collagenous capsule or scar tissue.¹ Pressure generating wound dressings are known to cause changes in collagen metabolism in hypertrophic scar tissue¹⁶ suggesting that pressure either from a dressing or from an implant pressing on host tissue can cause tissue catabolism.

While increased stress as a result of the presence of pressure from breast implants can have a negative effect on tissue stability, up regulation of mechanotransduction appears to occur when tensional loads are applied to tissues. Tension appears to have positive effects on wound healing in a number of studies. Recent reviews suggest that negative pressure wound healing (that occur by applying a vacuum to wounds), physical therapy protocols, and extracorporeal shock¹⁶ wave therapy are treatments that promote healing through mechanotransduction.^{17,18} The link between movement biomechanics, physical therapy, and subsequent cellular and tissue mechanoadaptation is not well established; however, altered joint physiology has been shown to occur as a result of physical therapeutic intervention in osteoarthritis, anterior cruciate ligament reconstruction and total knee arthroplasty.¹⁸ In addition, pulsed electromagnetic fields for promotion of tendon healing and extracorporeal shock wave therapy for bone regeneration and chronic wound healing have gained acceptance.¹⁸ Extracorporeal shock wave therapy has been used to reduce scar pain in burn patients after wound recovery.¹⁶ Vacuum massage and negative pressure induced wound healing have also been studied for their effects on healing.

Conclusion

Mechanotransduction appears to be a powerful tool by which

vertebrates have adapted to life in a gravitational field. While compressive forces or a lack of tissue loading appear to lead to tissue destruction and atrophy, tensile forces appear to up-regulate mechanotransduction. At least one mechanism involves direct stretching of cell membrane components termed integrins that bind specifically to collagen fibers of the ECM. Once integrins are bound to collagen fibers they start a process by which cell membrane components form complexes that cluster and transmit information into the cell nucleus that regulate the synthesis of proteins and the turning on and off genes that control cell division. While mechanotransduction is a complex process, it does provide details of how macromolecules in tissues can be converted from passive components into elements that actively change as a result of the mechanical environments in which they find themselves.

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Conflict of interest

The author declares no conflict of interest.

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