CELL MECHANICS AND MECHANOBIOLOGY

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Contents

Summary

Mechanical signals are important regulators of cell behavior. Key to understanding their role is the fact that cells are able to sense and respond to mechanical signals. In order to unravel the interplay between mechanics and biology one needs to embrace experimental and computational methods, stemming from engineering as well as biological disciplines, and integrate them into an interdisciplinary research field called mechanobiology. In this chapter we will first describe the structural and mechanical properties of a cell and its components, as these properties will have important consequences for the way mechanical signals are converted into a biochemical response. Experimental techniques to measure and computational models to capture these properties will be highlighted. Once we have addressed some key aspects of cell mechanics, we will continue by describing some key mechanisms of how mechanical signals can modulate cell behavior. Again, insights from experimental as well as computational studies will be reviewed. Given the broadness of the field, we will either focus on generic mechanisms, or limit ourselves to a few examples and case studies.

1. Introduction

Mechanical signals are important regulators of organ and tissue development, growth, remodeling, regeneration and disease. Key to understanding their role is the fact that cells are able to sense and respond to mechanical signals. While the sensory aspect is

generally termed mechanosensing, the entire process of sensing mechanical signals and converting them into a biochemical response is called mechanotransduction (see e.g. Ingber (2008) or its definition in the Medical Subject Headings (MeSH®) of the US National Library of Medicine, see http://www.ncbi.nlm.nih.gov/pubmed/). The term mechanobiology first appeared in the scientific literature in 1998, and was defined by Dennis Carter as the study of how mechanical or physical conditions regulate biological processes (Carter et al., 1998). At that time, Carter and co-workers were studying the importance of mechanical influences for bone fracture healing. They developed mechanoregulation diagrams that relate local mechanical stimuli to skeletal tissue regeneration, in this way expressing that the local mechanical environment may favor cell differentiation towards specific tissue types. The term mechanobiology was first introduced in a study that did not look at mechanotransduction at the cellular level, but instead made use of well-established engineering methods to calculate mechanical stimuli at the tissue level (such as the finite element method). Similar concepts were also reviewed by van der Meulen and Huiskes in a survey article on (tissue) mechanobiology of skeletal tissues (van der Meulen and Huiskes, 2002). Nowadays, mechanobiology stands for a very interdisciplinary research field that embraces methods – experimental as well as computational - from engineering as well as biological disciplines, among others to unravel mechanotransduction principles. As such, it is not surprising that this book chapter will merge knowledge from both disciplines.

Mechanical loads are present in virtually all organs of the human body in the form of gravitational forces. Organ- or tissue-specific loading conditions can e.g. be found in the musculo-skeletal systems, where muscle loading is responsible for propulsion of the human body, and together with gravitational forces, joint forces and moments determine locomotion. It will lead to the mechanical loading, and therefore the development of local mechanical stresses and deformations of different tissues, such as bone, cartilage, tendon and ligament. Other examples can be found in the cardiovascular system, where the pumping action of the heart is responsible for the development of blood flow and pressure. Cardiac and vascular tissues will be exposed to pulsating hydrostatic pressures and flow induced shear stresses. Other examples are lung tissue, which is cyclically stretched during breathing, and dermal tissues, which are exposed to tensile, compressive and shearing forces. Interestingly, our senses of hearing and touching are also initiated through a mechanical stimulus.

In general, the local mechanical environment at the tissue level will be the consequence of the simultaneous action of ‘external’ (i.e. originating from the environment) as well as ‘internal’ (i.e. originating from the tissue itself) forces, leading to tissue deformations that are governed by the ‘passive’ and ‘active’ (contractile) constitutive properties of the cells and tissues respectively (see section 2 for more explanation). As mechanotransduction takes place at the cellular and subcellular level, the study of mechanobiological processes clearly involves a multiscale approach, where mechanical loading needs to be transduced from organ to tissue levels and further down to the cellular and subcellular levels. Similar to the tissue level, we will see that for the mechanical properties of a cell we can make a distinction between a passive and an active component, which will be important for understanding mechanotransduction.

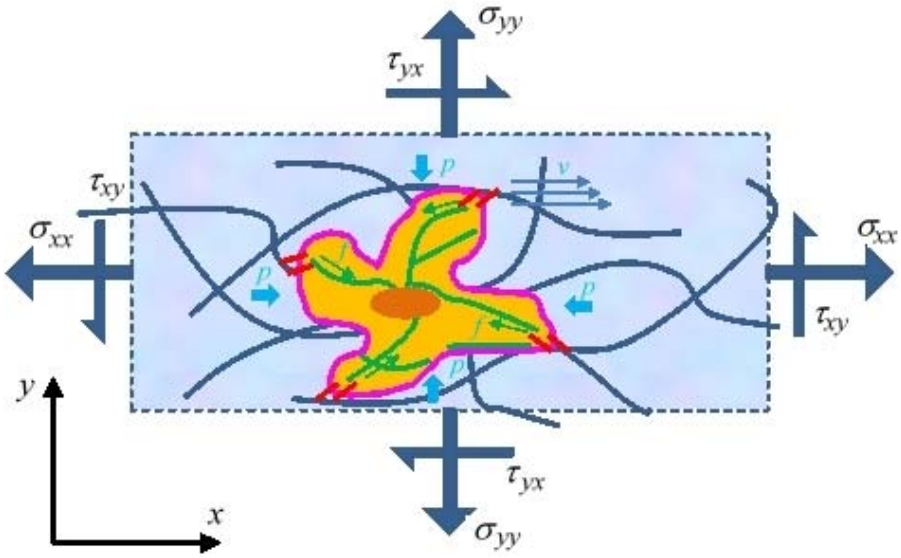

Figure 1. Schematic overview of mechanical signals for a cell (cytoplasm = orange, cell membrane= pink, nucleus = brown, cytoskeletal filaments = green) in a hydrated (bluish background), fibrillar extracellular matrix (ECM fibrils = dark blue). Adhesional complexes (red) enable the cell to bind to ECM fibrils. Cytoskeletal filaments are connecting adhesional complexes to the nucleus. External loads lead to matrix stresses (σ = normal stress, τ = shear stress; thick, dark blue arrows) and strains, as well as interstitial fluid pressures (p; light blue arrows) and fluid velocity fields (v; thin, dark blue arrows). Tissue deformation can be sensed by the cell through adhesional complexes, which can be further transduced to cytoskeletal filaments (filamentous forces f; green arrows) down to the nucleus. Fluid velocity fields can lead to drag forces on ECM fibrils as well as cellular components (cell membrane, adhesional complexes), which again may be further transduced via adhesional complexes. Extracellular fluid pressure may be transduced through the cell membrane to the cell's cytosol and organelles. Apart from mechanical signals, induced by external load, the cell's cytoskeletal filaments (through acto-myosin interaction) can exert active, contractile forces (f; green arrows) on the ECM, which are transduced via adhesional complexes.

A biological system aims at maintaining certain microenvironmental variables at a constant level, a property which is termed homeostasis. In order to do so, the system must possess negative feedback mechanisms that enable to respond to a deviation from the normal (i.e., homeostatic) values of microenvironmental variables, in a way to restore these to the homeostatic values. Well known examples are the regulation of body temperature, blood pH and glucose levels. Interestingly, load-bearing tissues seem to be characterized by homeostasis of mechanical quantities such as stress or strain, meaning that a deviation from a certain 'homeostatic' stress/strain level will induce tissue remodeling or adaptation in order to restore the mechanical integrity (i.e., the respective level of stress/strain). Such a behavior can be mathematically translated into a simple first order system:

$$\frac{dm}{dt} = C(\psi - \psi_0) \quad (1)$$

where m is a tissue property (e.g. tissue mass, a geometrical or mechanical property), t is time, ψ is a variable accounting for the local mechanical environment, ψ_0 is its value at homeostasis and C is a rate parameter. The concept of stress homeostasis has proven to be very useful for a phenomenological description of tissue remodeling (adaptation) in various tissues, such as the intervertebral disc (Adams and Dolan, 2005), bone (Turner, 1998) or vascular tissues (Humphrey, 2008). As to arterial tissues it is well known from in vivo observations that an increase of blood flow (and therefore flow induced shear stress) leads to an arterial enlargement (without wall thickening), while a decreased blood flow (and shear stress) leads to a decrease of lumen diameter (by means of wall thickening at the inner layer, i.e. the intima) (Masuda et al., 1999). Taking wall shear stress as the driving mechanical stimulus and assuming that there exists a homeostatic shear stress value, it becomes clear that for both an increase as well as a decrease of blood flow, the tissue response aims at restoring stress homeostasis, and can therefore be captured by Equation 1. Clearly, this equation does not reveal anything on the cellular mechanisms that underlie this response. In vitro experiments are a powerful tool to study these mechanisms, in this case by culturing endothelial cells (the cells that line blood vessels) in vitro, and exposing them to controlled regimes of shear stress. Such experiments have clearly demonstrated that endothelial cells are responsive to wall shear stress (for a review see e.g. Ando and Yamamoto (2009)), among others by changing their synthesis of nitric oxide (NO), an important regulator of the activity of smooth muscle cells, which are the cells that are responsible for intimal thickening. The response of endothelial cells to wall shear stress has been found to be a key factor to the growth and destabilization of arterial plaques in atherosclerosis (Slager et al., 2005). This example shows the importance of mechanobiology for understanding tissue physiology (arterial remodeling) and pathophysiology (atherosclerosis), and the need for an integrative approach that combines in vivo, in vitro and *in silico* work. The latter enables to quantify the mechanical environment and to formulate a quantitative relation between this mechanical environment and a biological response (Humphrey, 2008). For an overview of other diseases where aetiology or clinical presentation is associated to abnormalities in mechanotransduction the reader is referred to the review by Ingber (2003).

Prior to describing how mechanical signals can be converted into a biochemical signal, it is a good starting point to first focus on the mechanical properties of a cell and its components, as these properties will have important consequences for mechanotransduction. We will therefore start with a description of the complex structural and mechanical behavior of the cell, and the way to measure and model different aspects of this behavior. Once we have established a cell mechanical basis, we will move to cell mechanobiology, present key players of mechanotransduction and examples of computational models of cell mechanobiology. Because of the broadness of the field, it is clearly not possible to give a comprehensive overview. We will therefore either focus on generic mechanisms, or limit ourselves to a few examples and case studies. Often, the reader will be referred to review papers that cover certain aspects into more detail.

2. Cell Mechanics

2.1. Overview

An integrated knowledge of cell mechanics is essential for understanding fundamental cellular processes, such as migration, shape stability, proliferation and differentiation. Taken together, these processes are responsible for the maintenance and regulation of physiological and pathophysiological behavior of biological tissues. To explain the dynamic and functional role of cells interacting with tissues, it is essential to determine the mechanical properties of cells.

Cell mechanical characteristics are very complex. The cell is a viscoelastic material similar to a viscous fluid (Desprat et al., 2005). Cell viscoelasticity is commonly evaluated through the complex shear modulus $G^* = G' + iG''$, which is defined as the complex ratio in the frequency domain between the applied stress and the resulting strain (Ferry, 1980). The real part (G') is called storage modulus and accounts for the elastic contribution, whereas the imaginary part (G'') is known as loss modulus and represents the dissipative contribution. Dynamic measurements of G^* have revealed that the viscoelastic behavior of living cells is timescale dependent (Fabry et al., 2001; Stamenovic 2006). Moreover, cell stiffness presents a high variability depending on the conditions and the measurement techniques, varying even several orders of magnitude being, in fact, in the order of tens to thousands of Pascals (Stamenovic and Wang, 2000). Another relevant characteristic of cells that is normally accepted in the literature is that they are a tensed/prestressed structure. In fact, there are filaments that bear a pre-existing tension even in the absence of external loading. Recent results have confirmed that inside the cell there is a filamentous network under tension: when these fibers are cut with a laser, they snap back (Kumar et al., 2006). This internal tension is due to molecular motors that generate forces transmitted by the cell to the extracellular matrix (ECM) (Wang et al., 2001). This internal prestress highly modifies the cell stiffness and its viscoelastic behavior. Therefore, the cell is characterized by a dual and interactive behavior: as passive material and active contractile system. The question that still remains unanswered is: which is the factor that regulates the value of this pre-stress within the cell? It seems that the concentration of certain solutes, specifically calcium ions, could control the value of this pre-stress in smooth muscle cells (Stålhand et al., 2008). As will be discussed below, this prestress is also highly important for explaining mechanotransduction phenomena. Another relevant property of cells is their ability to continually rearrange, disassemble and reform its local structures in function of the functionality of the cell in a specific process such as migration, contraction, proliferation and differentiation.

The mechanical properties of the cell are largely determined by four main components with a different contribution: the cytoskeleton (CSK), the membrane, the cytosol and the nucleus. The cytoskeleton (CSK) is a complex, heterogeneous and filamentous structure that extends from the nucleus to the cell membrane providing a continuous and dynamic connection between almost all cellular structures, defining the most significant mechanical characteristics of a cell. In fact, the CSK constitutes the dynamic skeleton of the cell from which the cell is able to change its shape, coordinate its movements, exert mechanical forces and sense the extracellular environment. It consists of a biopolymer

network consisting of three major components (see Table 1): filamentous actin (F-actin), intermediate filaments and microtubules. These cytoskeletal polymers are at length-scales (a few microns at most), all corresponding to semiflexible polymers. The thermal fluctuation of one-dimensional semiflexible polymers or filaments is governed by their bending energy and can be characterized using the concept of persistence length L_p. In the absence of thermal fluctuations at zero temperature filaments are straight because of their bending rigidity (K_b). Sufficiently large and thermally fluctuating filaments lose their straight conformation. Only subsystems with contour length $L \ll L_p$ appear rigid and maintain an average straight conformation. Larger filaments $L \gg L_p$, on the other hand, appear flexible. In the 'semiflexible' regime for which L is comparable to L_p, statistical mechanics is governed by the competition of the thermal energy T and the bending rigidity. In Table 1, we list the persistence lengths and bending rigidities associated to the polymers that constitute the cell CSK (Mofrad and Kamm, 2006).

	Diameter (nm)	**Persistence length (μm)**	**Bending stiffness (Nm^2)**	**Young's modulus (Pa)**
Actin filament	6-8	15	$7x10^{-26}$	$1.3\text{-}2.5x10^{9}$
Microtubule	25	6000	$2.6x10^{-23}$	$1.9x10^{9}$
Intermediate filament	10	1-3	$4\text{-}12x10^{-27}$	$2\text{-}5x10^{6}$

Table 1. geometrical and mechanical properties of cytoskeletal components

F-actin is the main component that regulates the mechanical behavior of the cell. In fact, its depolymerization implies a significant decrease in cell stiffness (Fabry et al., 2003; Trepat et al., 2005; Smith et al., 2005). In vitro experiments of reconstituted F-actin networks showed that tension sustained by the filaments plays a critical role in the network rheology (Gardel et al., 2006). Actin bundles can bind to myosin, a motor protein able to move the bundles relative to each other by hydrolyzing adenosine triphosphate (ATP), creating what is known as a stress fiber, which is a structure able to support forces in the cell. Therefore, actin filaments in conjunction with myosin are the main force-generating mechanisms of the actin CSK, playing a crucial role in the active behavior of the cell. Microtubules and intermediate filaments define the main passive behavior of the cell. Ingber (2003) proposed that cells are prestressed tensegrity structures with internal molecular struts and cables, with microtubules being effective at withstanding compression (the struts), and actin filaments being more adequate for working under tension. He hypothesized this theory based on the fact that microtubules often appear to be curved in living cells, whereas intermediate filaments are almost always linear. This is consistent with the engineering rule that tension straightens and compression buckles or bends the bar elements.

These elements that constitute the CSK create a crowded network of structural proteins that regulates cell shape and drives cell motions, being able to modify and orient this

filamentous structure in function of the mechanical and functional needs of the cell in a process known as CSK remodeling (Bursac et al., 2005).

The cell membrane is the layer that separates the cell interior from the extracellular environment. It is formed by a double layer of phospolipid molecules in which proteins are embedded. One of the main functions of the cell membrane is to regulate molecular transport between the cell interior and the extracellular environment. On the other hand, the cell membrane also has a mechanical function, by resisting bending and regulating cell shape.

The cytoplasm is formed by the cell content enclosed within the cell membrane and outside the nucleus. Apart from the CSK, the cytoplasm is formed by the cytosol, which is an aqueous solution formed by a myriad of proteins and molecules that fill the compartments of the cytoplasm.

The nucleus is constituted by two concentrated lipid membranes containing the DNA molecules that encode the genetic information. The CSK biopolymers surround the nucleus in a much higher density than in other cellular regions. In fact, actin and vimentin filaments have been reported to mediate force transfer to the nucleus (Maniotis et al., 1997) with important consequences in gene expression (see also below). The cell nucleus have been reported to be 10-fold stiffer than the surrounding cytoplasm (Maniotis et al., 1997; Gerace and Huber, 2012). Therefore, the nucleus could play an important role in the mechanical stabilization of the cell (Versaevel et al., 2012)

2.2. Experimental Techniques to Measure Cell Mechanical Properties

In order to study the complex mechanical behavior of cells dedicated methodologies have been developed, as described in several review papers (Bao & Suresh 2003; Kasza et al., 2007). One of the complicating aspects is to distinguish between the cell's active and passive behavior.

In order to evaluate how living cells behave in an active way exerting physical forces, micron-sized probe particles are embedded within the cell or in the surrounding substratum in specific positions to compute the fluctuations in their position as a consequence of cell activity. Particle tracking microscopy (PTM) consists on measuring the motion of probe particles, through video or laser tracking techniques, allowing to study the non-equilibrium phenomena associated to different processes such as thermal fluctuations, the activity of motor proteins, cytoskeletal remodeling, etc. (An et al., 2004; Bursac et al., 2005; Lenormand et al., 2007). Traction Force Microscopy (TFM) techniques (Butler et al., 2002; Sabass, et al., 2008; Legant et al., 2010) are based on the substrate deformation and are used to study the relationship between adherent cells and their underlying substrates.

The passive behavior of the cell as a material is strongly non-linear, which is typically found for a soft material, and structurally heterogeneous. This fact requires designing local mechanical experiments with a high accuracy in their measurements. The most common technique used to evaluate the local viscoelastic properties of a single cell is through micro-indentation by Atomic Force Microscopy (AFM) (Sunyer et al., 2009).

Since its invention in 1986 (Binning et al., 1986), it is one of the most valuable tools for imaging and testing matter at the nanometer scale. AFM consists of a microscale cantilever with a tip at its end that allows us to apply local stresses to the cell. The cantilever deflection is measured by laser reflection. Alternatively, a local stress can also be applied to a specific region of the cell by twisting or pulling a small magnetic bead that is attached to the cell (or one of its receptors). In Magnetic Tweezers (MT) or magnetic cytometry the resultant bead displacement is measured either with video microscopy or, to an even higher precision, with laser particle tracking. MT have been widely used to measure the viscoelasticity of cells (Bausch et al, 1998). The viscoelastic cell response can also be directly evaluated by deforming the whole cell (Peeters et al., 2005). Recent experiments demonstrate that the elasticity of a whole cell increases dramatically when it is stretched, in agreement with previous tests that related cell elasticity to internally generated prestress (Fabry et al., 2001; Wang et al., 2002; Trepat et al., 2005) and studies of the nonlinear cytoskeletal behavior (Kollmannsberger and Fabry, 2011). These facts imply that active prestress in the cytoskeleton may be a key parameter that determines cell elasticity. Therefore, it is difficult in the measurements of passive properties of cells to uncouple the effect of active cell properties, because they are continuously present.

To evaluate the mechanical properties of the CSK separately, there are in vitro studies of reconstituted cytoskeletal networks designed to mimic the properties of individual components of the cytoskeleton (Janmey et al., 2007). A major advantage of these networks is that their viscoelastic properties can be characterized by traditional engineering techniques, evaluating the time-dependent response to an imposed stress or strain.

2.3. Computational Modeling of Cell Mechanical Properties

The highly complex mechanical behavior of the cell makes its modeling very challenging, rendering it currently impossible to achieve a complete model able to take into account all the different known effects under different mechanical conditions. Therefore, as in traditional engineering materials, specific constitutive models have been defined to capture or reproduce specific phenomena of cells under certain mechanical conditions.

Different constitutive models have been presented that describe the mechanics of living cells as a simple elastic, viscoelastic or poro-viscoelastic continuum (Mofrad and Kamm, 2006, Lim et al., 2006), as a porous gel or soft glassy material (Fabry et al., 2001; Bursac et al., 2005; Deng et al., 2006; Mandapu et al., 2008), or as a tensegrity network incorporating discrete structural elements that bear compression (Ingber, 2003, 2008).

Continuum models present several limitations (Mofrad and Kamm, 2006): they normally lack a description of the cytoskeletal fibers and also exclude small Brownian motions caused by thermal fluctuations of the cytoskeleton, which have been shown to play a key role in cell motility (Mogilner and Oster, 1996).

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