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# The Mechanobiology of Articular Cartilage: Bearing the Burden of Osteoarthritis

**Johannah Sanchez-Adams**[1], **Holly A. Leddy**[1], **Amy L. McNulty**[1], **Christopher J. O'Conor**[1,2], and **Farshid Guilak**[1,2]

[1]Department of Orthopaedic Surgery, Duke University Medical Center, Durham, NC 27710

[2]University of North Carolina/North Carolina State University Joint Department of Biomedical Engineering, UNC School of Medicine, Chapel Hill, NC 27599

## Abstract

Articular cartilage injuries and degenerative joint diseases are responsible for progressive pain and disability in millions of people worldwide, yet there is currently no treatment available to restore full joint functionality. As the tissue functions under mechanical load, an understanding of the physiologic or pathologic effects of biomechanical factors on cartilage physiology is of particular interest. Here we highlight studies that have measured cartilage deformation at scales ranging from the macroscale to the microscale, as well as the responses of the resident cartilage cells, chondrocytes, to mechanical loading using *in vitro* and *in vivo* approaches. From these studies, it is clear that there exists a complex interplay between mechanical, inflammatory, and biochemical factors that can either support or inhibit cartilage matrix homeostasis under normal or pathologic conditions. Understanding these interactions is an important step toward developing tissue engineering approaches and therapeutic interventions for cartilage pathologies.

### Keywords

Chondrocyte; Osteoarthritis; Mechanotransduction; Loading; Strain; Deformation; Magnetic Resonance Imaging; Atomic Force Microscopy; Pericellular Matrix; Extracellular Matrix; Inflammation; Interleukin-1; Proinflammatory Cytokines; Animal Models; Growth Factors

## 1: Introduction

Articular cartilage serves a critical mechanical role in diarthrodial joints by providing a smooth, lubricated surface that allows joint articulation while minimizing wear. It also acts to support and distribute forces across the joint during activities of daily living. Under normal physiologic conditions, the cells in cartilage, chondrocytes, synthesize and maintain crucial extracellular matrix (ECM) components that confer the functional properties of cartilage [1]. However, under pathologic conditions, such as osteoarthritis (OA), chondrocytes exhibit an imbalance of anabolic and catabolic activities that are characterized

Corresponding author: Farshid Guilak, 375 Medical Sciences Research Bldg., Box 3093, Duke University Medical Center, Durham, NC 27710, Phone: 919-684-2521, Fax: 919-681-8490, guilak@duke.edu.

by degenerative changes in the cartilage matrix and other joint tissues, including the subchondral bone and synovium [2, 3].

Far more than a disease of simple “wear and tear”, OA represents a family of diseases that involve active processes by which cartilage and the surrounding tissues respond pathologically to environmental factors, particularly mechanical loading. Physical activity in healthy, asymptomatic adults reduces the risk of cartilage thinning, cartilage defects, and bone marrow lesions [4], demonstrating the protective role that joint loading can play in a physiologic biochemical and biomechanical environment. On the other hand, biomechanical risk factors for OA, such as obesity, trauma, and joint destabilization [5], illustrate the central role that mechanical factors in an altered biochemical and/or biomechanical setting can have in OA development and progression [6]. In this regard, understanding the interplay between cartilage loading and other biological factors within the joint can provide insight into the factors that influence OA disease progression, and may help identify targets for therapeutic intervention. The goal of this review is to examine the interactions of these biomechanical and biological factors in cartilage and their effects on chondrocytes to help inform our understanding of cartilage diseases, such as OA.

## 2: Cartilage Loading and Deformation in Health and Disease

### 2.1 Cartilage Tissue Level Deformation

In healthy cartilage, the unique composition and complex structure of the ECM confers specific mechanical properties that allow the tissue to withstand a lifetime of cyclic loading deformation [1]. Cartilage ECM is primarily composed of water, negatively-charged proteoglycans, and fibrillar and non-fibrillar collagens. During cartilage loading, water in this highly hydrated tissue is gradually squeezed out of the tissue, causing direct tissue, cellular, and nuclear strains [7]. Concomitantly, mechanical loading of cartilage generates secondary biophysical signals such as hydrostatic and osmotic pressures, and their importance in cartilage mechanobiology will be discussed in later sections.

Deformation caused by mechanical loading is typically reported as strain, defined in one dimension as the change in thickness divided by the original thickness. The measurement of cartilage strains under *in vivo* loading conditions has been challenging; however, recent advances in imaging, such as magnetic resonance imaging (MRI), alone or in combination with high-speed dual-fluoroscopy, have allowed measurements of cartilage deformation during or after various activities (Figure 1A) [8–6]. These studies show that cartilage strains are dependent on both the anatomic location within the joint, as well as the specific activity undertaken. For example, a relatively short bout of running (20 minutes) leads to transient cartilage strains of approximately 20% in the weight bearing regions of the femur, while in the tibia, strains of up to 30% are observed following activity [11]. With walking, peak strains in the tibiofemoral contact area range from 7 to 23%, and tend to result in higher strains on the medial side of the joint [15]. Due to the biphasic (solid/fluid) nature of cartilage, the tissue exhibits significant viscoelastic behavior and takes time to recover its original height after loading. Thus, the repeated loading of the tissue over the course of a day, without time to recover to its original height, results in decreased cartilage thickness from morning to evening. This strain accumulates through the course of the day and

recovers overnight. Diurnal cartilage strains vary significantly with location in the knee, ranging from 11% (medial tibia) to no significant diurnal strain in certain locations, such as the femoral groove [9].

Cartilage strains also vary significantly with injury and disease, and these altered loading patterns may impact subsequent OA progression. In individuals with a high body mass index (BMI), a known risk factor for OA, the diurnal cartilage strain in the medial tibia increases significantly from 3% to 5% [10]. In another example, full weight bearing in the ankles of patients suffering from chronic lateral ankle instability increases cartilage strain by 8% when compared to the uninjured ankle [8]. Furthermore, the location of the peak strain also moves anteriorly and laterally, which corresponds to the location where patients with lateral ankle instability tend to develop OA. Similarly, loss of the anterior cruciate ligament (ACL), another risk factor for OA development, also coincides with increased knee strains upon weight bearing [16]. On the other hand, deep knee bends cause less strain in knee cartilage of older individuals (ages 50–78) than in young individuals (ages 20–30), indicating that age can have an effect on cartilage deformation [12]. These examples illustrate the importance of cartilage loading patterns on maintaining cartilage health, and underscore cartilage loading as a critical factor toward understanding cartilage pathology.

### 2.2 The Micromechanical Environment of Chondrocytes

As the tissue is compressed, the hierarchical structure of articular cartilage results in a complex and non-uniform deformation field at the tissue and cell levels, which in turn may influence the responses of chondrocytes to joint loading [17–19]. In particular the chondron, which encompasses both the chondrocyte and its pericellular matrix (PCM), shows variable deformation in different zones of the tissue when cartilage is subjected to macroscale compression [20]. In the superficial zone, where the ECM modulus is the lowest, cells within the chondron are shielded from ECM strains as compared to those in the deeper zones, where the PCM serves to amplify strain magnitudes relative to those in the ECM. This finding indicates that the PCM plays a role in regulating cellular strains throughout the tissue depth to provide a more uniform environment for the chondrocytes, perhaps protecting the cells from injurious strain [20–22]. In this context, the PCM has emerged as a potential transducer of mechanical signals in cartilage, showing an ability to either amplify or attenuate local mechanical strains, as well as to convert tissue deformation to physicochemical [23] or biochemical changes [24] in the chondrocyte microenvironment.

The ability of the PCM to perform these functions is tied to its unique structure and biochemical composition, which impart specific biomechanical and physicochemical properties. The mechanical properties of the PCM have been measured using a variety of techniques, including micropipette aspiration [25], atomic force microscopy (AFM) [26, 27], and computational models [28]. Together, these techniques confirm that the chondrocyte PCM has an intermediate modulus between the modulus of the cell and the surrounding ECM. More recent advances in AFM techniques have allowed for spatial mapping *in situ* of PCM and local ECM properties, and have revealed that the cartilage PCM is isotropic, and its modulus is constant throughout the depth of the tissue [29]. Interestingly, these findings

are in stark contrast with local ECM properties, which show distinct anisotropy and zonal variations in elastic modulus [29].

More recent investigations in specific PCM molecular constituents via combined immunofluorescence staining and AFM probing of PCM properties indicate that the biomechanical properties of the PCM is heavily influenced by its biochemical makeup [27, 30]. Of particular interest is the finding that the PCM shows high resistance to enzymatic degradation [31], which may help protect the cell from tissue breakdown in an inflammatory environment, such as that observed in OA. It is known, however, that the chondrocyte PCM is enlarged and less stiff in OA cartilage, as compared to healthy cartilage [32]. Thus, despite some innate resistance to degradation, the micromechanical environment of the chondrocyte can be affected in OA. The precise cause of these changes remains under investigation, but the increased synthesis of matrix macromolecules as well as degradative enzymes (i.e., matrix metalloproteases (MMPs), aggrecanases, elastase, etc.) in the OA joint play a role in this phenomenon. A potential early event may be the disruption of the PCM by the serine protease, high temperature requirement A1 (HTRA1), which can be induced by TGF-β1 upon biomechanical stress [33].

## 3: Mechanical Loading at the Chondrocyte Level

### 3.1 Effects of Loading on Chondrocytes

Chondrocytes respond to mechanical load, as a means of regulating growth, cellular differentiation, and metabolism in the cartilage ECM, throughout development and maturation. However, while mechanical loading of chondrocytes is an important stimulator of matrix synthesis, certain types of loading can provoke pathologic responses. This contrast between the protective versus pathologic response of chondrocytes to mechanical loading is well documented in studies of physiologic loading and cartilage injury (Figure 1B) [34–41]. Cartilage responds to physiologic magnitudes of dynamic compression (~10–20%) with enhanced synthesis of ECM molecules, including proteoglycans, collagens, and cartilage oligomeric matrix protein (COMP) [42–45]. Importantly, the responses of chondrocytes to mechanical loading are highly dependent on parameters such as frequency, strain-rate, loading history, and loading amplitude. For example, super-physiologic magnitudes of loading (>20%) fail to enhance matrix production [42], while static or very low frequency loading [46] inhibits matrix synthesis. The damaging effects of high magnitude, high strain-rate impact loading are likely a combination of direct cellular damage, such as chondrocyte apoptosis and necrosis [47, 48], as well as a shift of chondrocyte-mediated matrix metabolism towards catabolism [41, 49, 50]. Interestingly, the surviving cell population after impact loading lacks a biosynthetic response to dynamic, physiologic levels of loading that uninjured explants normally exhibit [50], suggesting that sustained alteration of chondrocyte mechanotransduction occurs following injury, even when the tissue is returned to an apparently normal biomechanical setting.

In the cartilage ECM, highly negatively charged sulfated proteoglycans attract counterions to maintain electroneutrality, which in turn creates an osmotic differential with the synovial fluid. This osmotic gradient confers a swelling pressure to the proteoglycans to expand, but their expansion is restrained by the collagen network. As the tissue is compressed, water is

gradually exuded from the tissue. However, during the initial stages of cartilage loading, the low permeability of the tissue leads to fluid pressurization, exposing the chondrocytes to increases in hydrostatic pressure. With prolonged and/or higher magnitude loads, exudation of interstitial water and ions leads to not only direct deformation, but also to the generation of numerous indirect biophysical signals, such as streaming potentials, fluid flow, and changes in local pH and osmolarity [51]. These phenomena are largely due to the compaction of the entangled proteoglycans increasing the fixed charge density, thus increasing the concentration of dissolved ions within the tissue. With removal of loading, water is reabsorbed, and the biophysical environment returns to its initial state, leading to dynamic changes in these parameters with dynamic loading regimes.

The effects and significance of these dynamic biophysical signals have constituted the subject of a number of recent investigations. For example, chondrocytes are known to increase ECM production in response to dynamic hydrostatic pressure [52, 53] and dynamic osmotic changes [54], similar to their response to mechanical loading. Though it is unclear whether chondrocytes in loaded tissue *in vivo* are responding to deformation of the tissue and cells or to these secondary biophysical effects, *in vitro* experiments that deliver individual mechanical or biophysical signals suggest that each of these parameters contributes to mechanical regulation of cartilage homeostasis. Furthermore, defining the mechanisms of mechanotransduction should be highly useful in addressing this question.

### 3.2 Chondrocyte Mechanotransduction

A number of key transduction mechanisms have been identified that facilitate the mechanically-driven enhancement of cartilage ECM biosynthesis and functional properties, including mechanosensitive ion channels [55, 56] and signaling through integrins [57] and primary cilia [58]. Transient receptor potential vanilloid 4 (TRPV4) is an osmo-mechanosensitive ion channel highly expressed in articular chondrocytes [55]. TRPV4-mediated $Ca^{2+}$ signaling in response to mechanical loading plays a primary role in the enhanced matrix biosynthesis and decreased expression of catabolic and proinflammatory genes in chondrocytes after moderate, dynamic loading [54]. Specifically inhibiting TRPV4 prevents loading-mediated increases in matrix synthesis, and activating TRPV4 in the absence of loading increases matrix synthesis in a manner analogous to loading [54]. As a ubiquitous second-messenger, mechanically-induced $Ca^{2+}$ signaling is an especially attractive regulator of mechanotransduction, as it is known to regulate multiple signaling pathways, including nuclear factor of activated T lymphocytes (NFAT), protein kinase C, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), c-Jun N-terminal kinase 1 (JNK1), and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) [59]. In superficial zone chondrocytes, the mechanically-driven enhancement of Prg4 (lubricin) expression, appears to involve a number of signaling pathways that also involve intracellular $Ca^{2+}$ signaling, including ATP/P2X7 and PKA/CREB [60]. Additional studies have further proposed TGF-β/Smad, Erk1/2, p38, and ciliary signaling [55, 61], as well as integrin/FAK signaling [62–64] in mediating the responses of chondrocytes to loading.

Though less is known about the transduction of mechanical load in pathologic settings, these processes appear to involve the enhancement of catabolic effectors, such as MMPs and aggrecanases [65, 66], and recent studies suggest the involvement of ciliary signaling [67] and histone modification [68]. Further mechanistic studies in the setting of injurious loading, or joint impact followed by physiologic loading, will reveal clinically relevant information for the treatment of patients following destabilizing and traumatic joint injuries.

### 3.3 Animal Models of Cartilage Loading

Animal models of joint loading provide additional data supporting the role of mechanical factors in cartilage physiology, as well as pathology. The two most common animal models of altered joint loading are ACL transection (ACLT), which causes increased joint laxity [69], and meniscal injury or meniscectomy, which alters cartilage contact pressure distributions [70]. Both of these models lead to degenerative joint changes similar to human joint injury [71, 72], and have been effective in identifying a number of disease-modifying enzymes, including ADAMTS5 [73], MMP-13 [74], and PAR-2 [75]. Furthermore, knockout mouse models have shed light on the interaction between mechanical loading and arthritis by examining OA development in mice lacking critical elements in mechanotransduction pathways. For example, mice lacking TRPV4 develop OA earlier than wild type mice [76], and mice lacking type VI collagen, a key structural element of the PCM, have softer PCMs and develop OA in the hip earlier than wild type mice [25]. Mice lacking primary cilia also show signs of OA development [77]. Altered joint loading by ACLT or meniscal injury combined with knockout mouse models will likely play an integral role in unraveling the complicated interaction of pathologic loading and cartilage homeostasis.

## 4: Interaction of Cartilage Loading and Biochemical Factors

### 4.1 Biomechanics and Inflammation

Injury and arthritic degradation affect both the biomechanical as well as the biochemical environments of cartilage. Following joint injury and in OA joints, inflammatory cytokines are upregulated [78], with median synovial fluid concentrations of IL-1α and IL-1β rising to 43 pg/mL and 109 pg/mL, respectively, in mild OA joints, and 288 pg/mL and 122 pg/mL in moderate OA joints [79]. While OA is known to inhibit secretion of the active form of IL-1β in articular cartilage [80], inflammatory cytokines are known to be produced by other tissues in the joint, such as the synovium [81] and infrapatellar fat pad [82]. Treatment of articular cartilage explants with physiological concentrations of IL-1 (which are far lower than most *in vitro* studies) increases $Ca^{2+}$ signaling, MMP activity, sulfated glycosaminoglycan (S-GAG) degradation, release of the proinflammatory mediator nitric oxide (NO), and leads to decreases in the mechanical properties of healthy cartilage [79]. The pleiotropic and concurrent effects of catabolic mediators on the biochemical and biomechanical properties of the cartilage environment highlight the interrelationship that exists between biomechanical factors and inflammatory factors in the joint [83, 84].

Generally, physiologic magnitudes of mechanical loading suppress the proinflammatory and catabolic effects of IL-1, while injurious magnitudes of loading activate proinflammatory

and catabolic pathways leading to cartilage degradation. Dynamic compression of articular cartilage explants at physiologic magnitudes blocks IL-1 induced increases in the mRNA levels of the degradative enzymes ADAMTS-4, ADAMTS-5, MMP-1, and MMP-3 [85] and aggrecan breakdown [86], and increases TIMP-3 expression, suggesting a net decrease in MMP activity under these conditions [85]. Dynamic 15% compression of agarose-embedded primary chondrocytes also decreases IL-1 mediated production of the proinflammatory mediators NO and prostaglandin E2 ($PGE_2$) and increases matrix biosynthesis rates [87]. Additional studies using the agarose-embedded chondrocyte model system in the presence of IL-1 and inhibitors of the MAPK signaling pathways have shown that dynamic compression increases chondrocyte proliferation and proteoglycan synthesis, suggesting the potential therapeutic benefit of biophysical and/or pharmacologic interventions to block IL-1 induced cartilage degradation [88]. Chondrocytes in two-dimensional bioreactor systems also respond to cyclic tensile strain with a reduction in IL-1-induced catabolic activity (nitric oxide synthase 2 (NOS2), cyclooxygenase 2 (COX2), and MMP-1 mRNA and protein levels) and a loading-mediated enhancement of chondrosupportive gene expression (TIMP-2, type II collagen, and aggrecan mRNA levels) and proteoglycan synthesis [89].

Individually, dynamic strain and IL-1 induce similar signaling cascades, such as ERK1/2 phosphorylation [90]. The differential effects of these two stimuli, however, may lie upstream of ERK1/2 phosphorylation. For example, IL-1 activates B-Raf kinase activity, while dynamic strain causes the activation of c-Raf kinase activity, and furthermore, causes inhibition of IL-1 induced B-Raf activation. Perhaps these unique signaling phenomena may explain the differential processing of mechanical signals in the presence of inflammation. ERK1/2 activation also occurs three-times faster in response to mechanical signals than IL-1. Therefore, perhaps by upstream activation of kinases in response to dynamic strain, initiates a feedback loop to suppress the signaling cascades activated by IL-1 [90].

Experimental and theoretical modeling studies reveal that inflammation is differentially regulated at low (10%) and high (30%) magnitudes of dynamic compressive strain [91]. In the presence of IL-1 at low magnitudes, NOS2 transcription is suppressed and this correlates with attenuation of the NF-κB signaling pathway, which activates transcription of proinflammatory genes. At high magnitudes of dynamic compressive strain, NOS2 expression is activated, promoting a proinflammatory environment with pathologic loading. Furthermore, static compression of cartilage explants at 50% strain in the presence of IL-1 receptor antagonist (IL 1ra) increases proteoglycan synthesis and upregulates IL-1 and NOS2 transcription [92]. These findings further suggest that injurious magnitudes of loading activate proinflammatory mediators and ultimately catabolic pathways that lead to cartilage degradation. Furthermore, a recent study has shown that immobilization can prevent degenerative changes in a mouse model of joint injury by decreasing mechanically-induced protease expression, further demonstrating the important role of mechanical loading [93]. While the complex signaling and regulatory cascades between biomechanical factors and inflammatory mediators in cartilage are slowly being elucidated, the effects of a variety of other biochemical factors, such as anabolic growth factors, and mechanical loading on chondrocytes must also be considered in order to identify potential targets for OA therapy.

### 4.2 Effects of Load and Growth Factors on Chondrocytes

Mechanical stimulation of cartilage also exhibits complex interactions with anabolic factors and processes. Many studies have shown that incubation with growth factors and mechanical stimulation of either cartilage explants or isolated chondrocytes can cause additive or synergistic effects on matrix synthesis and organization [24, 94–98]. For example, dynamic loading enhances the effects of insulin-like growth factor-I (IGF-I) on proteoglycan and collagen synthesis in articular cartilage explants in a synergistic manner [95]. This synergy is also observed when chondrocyte-seeded agarose is exposed to dynamic loading in combination with IGF-I or transforming growth factor beta-1 (TGF-β1) [96]. Static compression, on the other hand, significantly diminishes the anabolic effect of IGF-I [97].

Hydrostatic pressure also interacts strongly with anabolic growth factors. For example, the combination of TGF-β1 and hydrostatic pressure cause additive effects on aggregate and Young's modulus of self-assembled cartilage tissue and synergistic effects on collagen content [98]. Rather than simply integrating the external cues of soluble anabolic factors, chondrocytes appear to also modulate the endogenous production and signaling of these anabolic pathways when exposed to biomechanical cues [54, 99]. Furthermore, this two-way interaction between biomechanical cues and growth factor signaling provides a potential mechanism for how growth factor signaling is both altered by and influences OA progression [100].

A complete understanding of how mechanical stimulation interacts with growth factors has yet to be achieved, but each new investigation illuminates the potential mechanisms of these interactions. For example, the PCM surrounding each chondrocyte functions not only as a mechanical transducer, but also serves to sequester and retain growth factors in the microenvironment of the chondrocyte. In fact, the pericellular component perlecan is uniquely able to sequester basic fibroblast growth factor (bFGF) [94], which is essential for signal transduction during articular cartilage loading [24]. However, aberrant mechanical stimulation, such as that observed in OA joints, is also associated with increases in TGF-β1 which can trigger production of HTRA1, a protease that degrades PCM components [33]. Therefore, interactions between articular cartilage loading and the biochemical factors surrounding chondrocytes can have a significant effect on chondrocyte metabolism. Interactions, such as these, that show promise in producing cartilage matrix components may be used to inhibit OA progression and/or regenerate cartilage.

## 5: Conclusions

The lack of therapeutic interventions following cartilage injury or disease and the important mechanical function of the tissue has prompted numerous studies investigating the influence of loading on cartilage homeostasis and metabolism. These studies have revealed the complex biochemical and biomechanical hierarchy of articular cartilage and the important roles of loading, inflammation, and growth factors on chondrocyte signaling pathways. It is clear that inflammatory mediators, such as IL-1, play a significant role in modulating the response of chondrocytes to mechanical load, and that depending on the mode, magnitude, duration of application, and combination with growth factors, mechanical loading can have either beneficial or detrimental effects on the tissue.

Given the strong links between inflammation, mechanical load, and cartilage homeostasis, targeting receptors of inflammatory mediators and chondrocyte mechanotransduction machinery, such as the TRPV4 ion channel and primary cilia, may be direct ways of controlling the response of chondrocytes to pathologic loading or disease [101]. While more work needs to be done to understand chondrocyte signaling in pathologic conditions, the present data support biomechanics and mechanobiology of articular cartilage as crucial regulators of cartilage health and disease.

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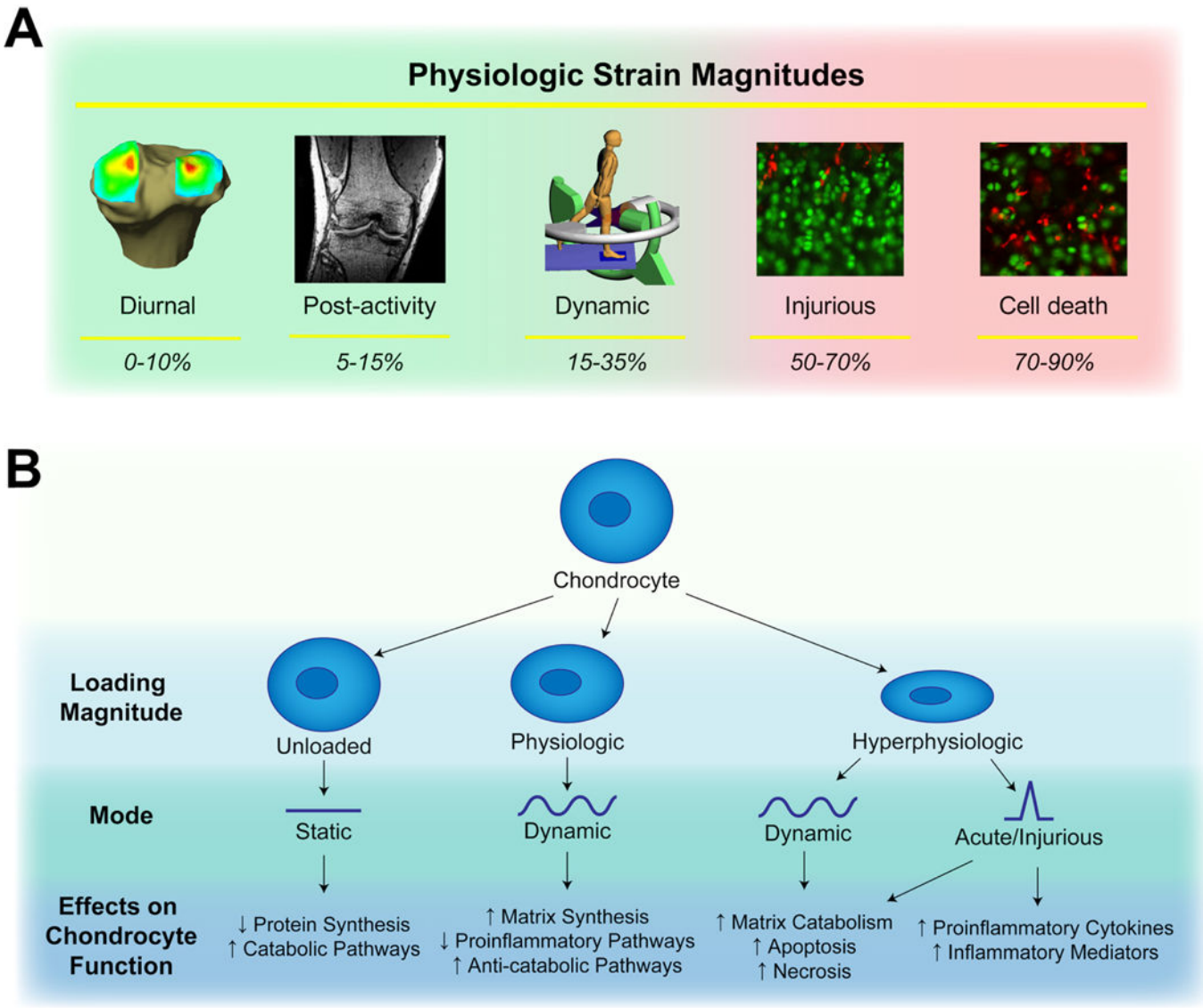


**Figure 1.**

A. Physiologic strain magnitudes measured in articular cartilage. During normal activities, diurnal strains range from 0–10% [9, 10], post activity strains range from 5–15% [12–14, 102], and dynamic strains during activity range from 15–35% [15, 16]. At higher nominal strain magnitudes (50–70%), mechanical compression can cause injury [35–39, 41], eventually inducing cell death via necrosis and apoptosis at strains of the highest levels (70–90%) [40, 47, 48]. B. Effects of different loading conditions on chondrocyte function. Static loading decreases cartilage metabolic activity [46], physiologic levels of dynamic loading can be anabolic or anti-inflammatory [42, 45, 85, 91, 95, 96], while hyperphysiologic levels of dynamic loading and injurious loading can induce catabolic or pro-inflammatory response [41, 49, 50, 91].