Preface: *Mechanobiology*, why not?

HISTORY OF MECHANOBIOLOGY

Mechanobiology is, in some ways, a new field. The first reference to the term *mechanobiology* in the US government's PubMed database was by Marjolein van der Meulen in 1993.[1] Indeed, the term mechanobiology was coined specifically for this paper at a meeting of the Stanford-Palo Alto Bone Remodeling club. The group had realized that biomechanical neither was the correct description for the phenomenon they were describing nor was it sufficient to use the adjective "mechanical" to modify biological terms.[2] They noted

The term mechanobiological is used to emphasize that the mechanical effects we are modeling are also dependent upon a biological response.[1]

Within a few years, a number of papers from laboratories at Stanford and the Palo Alto VA adopted the term. It came into more widespread use throughout the 1990s. One of the seminal definitions of the term appeared in the article *"Why Mechanobiology?"* published in the *Journal of Biomechanics* in 2001.[3] In this article the authors laid out the central precept of mechanobiology for the skeleton:

The premise of mechanobiology is that these biological processes are regulated by signals to cells generated by mechanical loading, a concept dating back to Roux.[4] *The relevant questions include how external and muscle loads are transferred to the tissues, how the cells sense these loads, and how the signals are translated into the cascade of biochemical reactions to produce cell expression or differentiation. Ultimately, we want to predict growth and differentiation in quantitative terms, based on a given force exerted on a given tissue matrix populated by cells.*[3]

This definition has been readily adapted to other tissues by changing "muscle loading" to a variety of force generators and "tissue matrix populated by cells" with any number of tissues or even cells themselves. At the same time that a new field was being defined, the authors noted that it was in some ways a very old field. The underlying principles of mechanobiology were outlined a century earlier in the work by Julius Wolff and Wilhelm Roux. Wolff published his monograph "Das Gesetz der Transformation der Knochen" ("The Law of Bone Remodeling")[5,6] in 1892, and Roux published "Der Kampf Der Theile im Organismus" ("The Challenges to the Parts in the Organism") in which he proposed the idea of functional adaptation to external stimuli in 1881.[4] In 1885, Roux published a second treatise on developmental mechanics ("Die Entwicklungsmechanik; ein neuer Zweig der biologischen Wissenschaft" or "Developmental mechanics: a new branch of biological science").[7,8]

Before the emergence of the term mechanobiology, a significant amount of research was described by the ubiquitously applied misnomer "Wolff's law for ...", which was used to describe the concept of tissue adaptation or healing under the influence of mechanical loads in tendons, ligaments,[9–11] and skin,[12] among other tissues.[13]

"Wolff's law" has certainly seen its share of criticism for its simplicity, conflation of differing processes, overreliance on mechanics relative to hormonal and nutritional factors, and incorrect understanding of mechanics.[14,15] Similarly, Roux's writings intermixed concepts of heredity and adaptation, using examples of ducks and cows. However, one must remember that the existence of cells had only been known for a few decades at the time, Charles Darwin was a contemporary, and the discovery of DNA was far in the future. In this context, these researchers established concepts and asked questions that remain at the heart of mechanobiology today, even if their initial hypotheses have been superseded and augmented with newly discovered biological structures and phenomena over time.

Much of the early work in mechanobiology focused on the musculoskeletal system, formalizing the ideas and incorporating growing knowledge of cellular processes. Advanced mechanical analysis, made possible by the finite element method, provided a means to calculate the spatial distribution of the mechanical signal, which was correlated to locations of bone formation or resorption or to changes in the local density of the bone.[16–18] Similarly, cartilage[19] and tendon[20–22]

adaptation and remodeling were simulated using algorithms that incorporated mechanical cues. Cardiovascular mechanobiology research also grew, leveraging similar computational methods but applying differing theories of cellular response and remodeling.[23] As computational power has grown, cell and molecular level knowledge has been incorporated into simulations to include the local cell density, the density of local signaling molecules, and nutrient diffusion.[24,25]

MECHANOBIOLOGY ACROSS LENGTH SCALES

At the largest length scales, mechanobiology has been used to explain how activities of daily living and environment affect the composition, geometry, or healing of the tissue. For example, multiple mechanobiological models have attempted to predict the shape and scaling of bones with respect to mechanical loading[26,27] or to investigate rehabilitation regimens that can best reestablish normal function.[28]

At the tissue scale the focus is often on the changes in extracellular matrix (ECM) properties. In these models the cell populations can often aggregate as concentrations. The interactions of cells with the matrix are quantified by the local strain or fluid flow. The choice of constitutive model has proven to be important in many instances, with fiber-reinforced or poroelastic descriptions improving the fidelity of calculations of the mechanical behavior. The mechanobiological processes are hypothesized to alter the mechanical properties by defining rate laws for any or all of the constitutive parameters that depend on the number and the state of the various cells. Nutrients or signaling molecules can also be described by concentrations. Their diffusion and convection are typically governed by classical laws, but additional production and consumption laws must also be postulated based on the cell populations present.

In parallel with these macroscopic phenomenological models, novel methods were being developed to determine whether cells actually sense and respond to mechanical cues. Flow chambers, stretched surfaces, patterned surfaces, and materials of varying mechanical properties were all used to determine whether cells altered gene or protein expression in response to mechanical cues. Lower and upper bounds of shearing stresses, stretches, and pressures have since been established for mechanobiological response of a range of cell phenotypes. In a seminal paper, Engler and colleagues[29] showed that culturing stem cells on materials with differing constitutive properties alters their differentiation fate.

Mechanobiology is now studied as an inherently multiscale phenomenon. Starting from the cell scale, the role of mechanotransduction in sensing the presence or localized motions of surrounding cells or ECM is the first stage in the mechanobiological cascade. At this level, it is essential to understand how forces are transmitted to the physiologic structures that connect the cells to the ECM or to other cells—the integrins and the adherens, respectively—as well as the cytoskeleton and cell membrane, and how they are transduced into biochemical actions within the cell. Forces on these structures can induce gene translation, post-translational modification of proteins, or upregulation of secondary messengers that drive protein translation and cell differentiation through both autocrine and paracrine signaling. This signaling may alter local cell phenotypes, cell signaling, further ECM production and degradation, or the organization of ECM molecules.

WHY NOT MECHANOBIOLOGY?

Most cells contain the machinery necessary to sense and respond to loads, even if other factors may dominate their function. While mechanical loading is obviously an essential part of the function of musculoskeletal and cardiovascular tissues, almost all tissues are subjected to some mechanical forces and deformation. Both epithelial and endothelial surfaces can be subjected to fluid flows and stretching. Even baseline respiration in mammals causes cyclic motion and pressure changes in the thoracic and abdominal cavities, which would induce mechanical stress in the organs. For example, mechanobiology plays a role in liver regeneration[30] and normal kidney function.[31,32] Interestingly, molecules involved in mechanosensing in the kidney—yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ)—also play a role in bone mechanobiology[33,34] and many other cell lineages.[35] Identification of this and other molecular targets may provide a link to mechanobiological functions in other tissues and organ systems.

Over the past 25 years, mechanobiology has grown into a distinct field with research centers, journals, and conferences dedicated to its study. It is a uniquely interdisciplinary field that rests at an interface between engineering, biology, materials science, and physics. It relies on many other new and growing fields such as bioinformatics, gene editing, and high-resolution imaging to achieve its aims. Mechanobiology is now firmly established in the biology and bioengineering lexicon, and in 2018, 308 articles indexed in the PubMed database specifically used one of the terms mechanobiology

or mechanobiological in the abstract or title. There is an excellent textbook on mechanobiology,[36] and courses are offered at many universities. A multisite National Science Foundation is highly active, and there are other institutes and centers at universities throughout the world.

New technologies, including animal models, organ-/tissue-on-a-chip, and engineered tissues, coupled with gene editing and cellular level probes, have opened endless possibilities for mechanobiology research. It is now much easier to probe the mechanical response of systems and to understand how they are coupled to both health and disease. As such, we have entered the era of "why not mechanobiology."

OVERVIEW

In the first five chapters of this book, mechanobiological effects in different tissues are reviewed and discussed. As mechanobiology has taken root in various fields, the theories and methods have evolved independently. It is often valuable to look across fields to understand new potential pathways and molecules that may play similar or differing roles in other systems. Across these chapters, we can see the recurring themes of understanding the mechanical environment of the tissue and how that is translated to the cells. Many themes are repeated across these tissues, especially the role of cell-matrix and cell-cell adhesions via integrins, cadherens, and connexins. We can also see that similar pathways and cellular structures are involved in all tissues, but with varying effects.

Some key aspects of mechanosensing are addressed in the next two chapters. Cellular structures that can detect deformations of the matrix or the cell membrane, which can in turn be translated to gene and protein expression, cell proliferation, motility, and other physical actions that alter tissues, consume energy, or create waste products. Knowledge of how cells can act as sensors of force or matrix deformation is essential to study mechanobiology and understand the biological pathways that can potentially be activated by mechanics.

The experimental chapters describe unique approaches to study mechanobiology. Animal models, especially gene knockout and knockin models, provide a unique means to study mechanobiology. However, in vitro experiments in the context of tissue engineering and cell culture are essential complements to the in vivo models because they allow the mechanics of the system to be tightly controlled. In the context of tissue engineering, bioreactors can simultaneously serve as both developmental platforms for regenerative medicine and powerful experimental platforms for mechanobiology, especially when coupled with genetically engineered cell sources[37] or small molecule activators or inhibitors of pathways of interest. Underlying biological mechanisms can be further probed by cell culture using reporter cells to quantify the mechanics of individual cells.

The final two chapters consider modeling of mechanobiology in development and tissue morphogenesis. Computational modeling can provide the best approach to develop and test hypotheses in mechanobiology. Multiphysics modeling software allows researchers to explore the interactions of mechanics, transport, and growth and to explore scenarios that lead to experimentally testable hypotheses. Development provides a unique model with which to study mechanobiology because the tissue and organ morphology can change rapidly, and the effects of interventions are easily observed. Researchers have studied the mechanobiology of development using animal[38,39] and even human models.[40,41]

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