Biochemistry

Editorial

Cite This: Biochemistry 2019, 58, 4655−4656

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Introducing the Mechanical Forces in Biochemistry Special Issue

Biological systems are commonly exposed to mechanical perturbation, which may modulate many biochemical processes, including those that drive cell growth, cell migration, cellular physiology, and development.[1,2] The sensing and transduction of mechanical force can occur in the nucleus, in the cytoplasm, and at cell membranes, both internal and external. Force is invariably sensed by a mechanochemical switch at the start of a biochemical pathway, for example, by a stretch-activated ion channel in the cell membrane. Such a biochemical pathway then of course reports on the mechanical stress, but it may itself feed back into modulating the initial response to mechanical force, resulting in a strong interplay between the biochemistry and the mechanical force.[3,4] It is now also well-known that biochemical processes in the cell may themselves generate mechanical forces.[5,6] Mechanical forces therefore play an important role in information transfer inside and between cells. Not surprisingly then, mechanotransduction affects the progression of many diseases, including cancer and cardiomyopathies.

The extracellular matrix (ECM) plays an important role in providing mechanical support not only to cells and tissues but also to places where many biochemical signals are initiated and transduced in the cell. The ECM is therefore where an intimate give and take between mechanical forces and biochemistry occurs. Biochemical processes at the cell surface, as elsewhere, are invariably driven by interactions between molecules, and the Perspective by Goult and colleagues examines how mechanical force modulates binding constants with an emphasis on mechanotransduction at the cell surface.[7] Proteins have malleable structures sensitive to force. Mechanical force can cause a conformational change that exposes a cryptic binding site. The ubiquitously expressed Filamin A, an actin cross-linking protein that interacts with integrin at the cell surface, is an example of a protein that mediates mechanotransduction in this manner. In two articles, Nakamura and colleagues have characterized the interaction of two proteins, smoothelin and fimbacin, with mechanically activated Filamin A in which a cryptic binding site is exposed.[8,9] The Perspective by Haldar examines in detail how the signaling hub of integrin-talin at the cell surface is involved in the regulation of cell signaling pathways that mediate how the cell responds to mechanical forces.[10] The Perspective by Smith and colleagues highlights how mechanical forces affect ECM remodeling, ligand binding, and homeostasis and how the interplay between mechanical force and biochemistry plays a role in wound healing as well as in disease progression.[11]

Another setting where biochemical processes affect force generation is in the ribosome. A nascent protein chain exiting through the ribosome exit tunnel may undergo partial folding or may be inserted or translocated across membranes, or may bind to chaperone machinery. These biochemical processes generate forces that are transmitted back to the catalytic center, and these mechanical forces affect translation rates. The Perspective by O'Brien and colleagues examines this coupling of mechanical forces and biochemical processes during translation.[12]

Protein machines function by converting chemical energy stored in their structure or supplied by chemical bond hydrolysis, binding energy, or energy in the form of electrochemical gradients into mechanical force. They play important roles in cellular biochemistry, including in gene expression and replication, protein folding and unfolding, protein degradation, translocation across membranes, muscle physiology, cell adhesion, and membrane fusion. The transport of material within a cell is carried out by motor proteins such as the kinesins and myosins, which move even large cargoes such as mitochondria and chromosomes. The article by Sivaramakrishnan and colleagues describes how the stiffness of the linkage between cargo and mysosin affects anchoring to actin and the length of individual steps taken by the motor protein.[13] It has been known for more than a century that mechanical forces can modulate cellular form and shape. Integral membrane proteins, as well as peripheral membrane proteins that oligomerize at the cell membrane, can exert mechanical force that results in membrane curvature, and membrane curvature and packing in turn exert a force that can modulate the functioning of integral membrane proteins. The article by Beales and colleagues examines how silver nanoparticles, increasingly being used in disease diagnosis and therapy, affect the mechanical properties and fluidity of membranes, especially when they aggregate at the cell surface.[14]

The complexity of the folding reactions of biomolecules is rarely revealed in bulk measurements especially when ensemble-averaging measurements are taken. It is only when methods such as time-resolved FRET or hydrogen exchange-mass spectrometry are used, in a manner that can distinguish between subpopulations of molecules present together, that the roughness of the folding free energy landscape is revealed. The ability to directly apply mechanical forces to individual biomolecules, using either atomic force microscopy or optical traps, has also provided great insight into the study of protein folding. Intermediates on and off folding pathways, misfolded states, multiple folding and unfolding pathways, and folding by many continuous steps have all been detected in single-molecule studies. The article by Li and colleagues examines the unfolding of a topologically complex, slip-knotted protein, PADC.[15] Two-state unfolding is observed for a majority of molecules. Very interestingly, a small fraction unfold through intermediate states that lack well-defined specific structure. The article by Rief and colleagues describes how single-molecule mechanical experiments have provided valuable insight into the interaction between subdomains of the nucleotide binding domain of the DnaK chaperone and, thereby, how signals are transferred inside a protein

Special Issue: Mechanical Forces in Biochemistry

Received: November 10, 2019
Published: November 26, 2019

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DOI: 10.1021/acs.biochem.9b00999
Biochemistry 2019, 58, 4655−4656

molecule.[16] The Perspective by Liu and colleagues describes how single-molecule mechanical manipulation is starting to reveal how the biochemistry of DNA is affected by proteins that bind to it, and bend, twist, and stretch it.[17]

The study of the interplay of mechanical force and biochemistry is an exciting interdisciplinary endeavor of many physicists, chemists, and biologists. Progress in this endeavor continues to benefit from the development of cutting-edge techniques, whether for sensing or applying mechanical force, or for detecting biochemical change with exquisite sensitivity, or for detecting physicochemical change with super-resolution microscopy, or for manipulating single biomolecules. Much is being learned about the inner workings of biomolecules and of biochemical pathways, from using mechanical force to perturb them. May the Force be with Biochemistry.

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Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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