Nanomechanical properties of the cytoskeleton influence neuronal function in C. elegans

Michael Krieg[1],

[1]ICFO, Av CF Gauss 3, Castelldefels, Spain
michael.krieg@icfo.eu

Abstract

The millimeter scale mechanics of biological tissues is an emergent character originating from the material properties of the constituent cells and their mutual adhesive interactions. Likewise, the cell is an inhomogenous, non-isotropic and non-linear material composed of thousands of different components that interact transiently and/or permanently. Despite this complexity, previous research has shown that a few dominating elements of the cytoskeleton are largely responsible for the cellular strain response to mechanical stress. Thus, it is plausible that these mechanoresponsive molecules also endow some functionality to the cell - a property that has been largely investigated decoupled from the cellular physiology[1].

During my talk, I will highlight recent progress to understand the interplay between cellular and molecular nanomechanics and their role in regulating cellular physiology[2]. I focus on work on the nervous system of the roundworm *Caenorhabditis elegans*, which is a popular experimental system to combine engineering, biophysics and cell biology, due to its stereotyped body plan, known structural connectome and amenable genetics. *C elegans* uses a set of different sensory neurons to navigate its habitat which endow the animals to process chemical and mechanical stimuli in a changing environment. Some of these neurons respond to minute mechanical forces delivered to the skin of the animal, while others respond to stresses generated within the animals that originate from muscle contraction during locomotion. How these stresses are borne by molecular mechanics, transmitted within biological tissues and activate biochemical pathways is one of the last challenges in mechanosensory biology[2]. This lack of understanding is largely due in part to the absence of appropriate techniques to investigate the effect of mechanical properties of cells and neurons within living organisms at the level of a single molecule. With a combination of genetically encoded reporters for mechanical stress and calcium, together with piconewton force measurements, we investigate the mechanotransmission pathways leading to physiological response to mechanical stress. To our surprise, a single point defect in cytoskeletal proteins can have a large consequence on the stability of neurons against mechanical stresses, leading to a functional deficit[3].
We also introduce novel microfluidic devices (Ref [4] and in prep.) that enables the delivery of precise stresses to immobilized animals while reading out mechanical deformations and physiological functions. Using these technologies, we showed that a ubiquitously expressed protein of the cortical actin cytoskeleton, called β-spectrin, has neuron-specific role on mechanosensation and is subjected to mechanical stress during physiological processes. Mutations in this protein lead to a failure to properly sense forces and consequently severe uncoordination. Strikingly, similar mutations in the linker regions of b-spectrin have been shown to destabilize adjacent domains with consequences on overall cytoskeletal flexibility that lead to hemolytic diseases in humans[5]. Since the molecules are ubiquitously expressed in mammalian central nervous system and highly conserved among different species including humans, the results from our experimental paradigm bridge the gap between tissue culture and the clinics and are thus critical for our understanding of complex mechanical systems such as the brain.

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