Regulatory roles of mechanical fluctuations in biology

Awardee: Béla Suki
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Awardee Institution: Boston University
Co-authors: Harikrishnan Parameswaran, Jasmin Imsirovic, and Erzsébet Bartolák-Suki
Co-authors' institutions: Boston University

Biological processes must obey the laws of mechanics. Consequently, most cell types are sensitive to their physical environment and physiological forces acting on cells play a dominating role in many regulatory cell functions. In the laboratory, such mechanotransduction is invariably studied using monotonous mechanical stimuli; however, cells in the body experience only irregular stimuli. Two salient examples are breathing and circulation in which cycle-by-cycle variations in tidal breath and beat-to-beat variations in blood pressure should influence cell function in all resident cells of the lung and the vasculature, respectively. Evolutionary forces should favor processes and structures that can adapt to and take advantage of such fluctuations. Accordingly, our central hypothesis is that physiological levels of variability in mechanical stimuli that are normally present in the body have fundamental regulatory roles in basic cell functions. If this hypothesis is true then the most basic cellular process, ATP generation by mitochondria, is regulated not by the mean stimulus to which cells can adapt, but the irregularity of the stimulus that maintains the cell under non-equilibrium conditions. We test this hypothesis in energetic vascular smooth muscle cells by exposing them in culture to variability in mechanical stretch. We find that ATP production is downregulated in vascular smooth muscle cells stretched with a monotonous pattern compared to cells stretched with physiological level of cycle-by-cycle stochastic variability in strain. Furthermore, there is an optimum level of variability that maximizes ATP generation and ROS production implying that changes in variability due to disease should also alter cell signaling. We also find that variable stretch enhances ATP production by increasing the expression of ATP-synthase's catalytic domain, cytochrome c oxidase and its tyrosine phosphorylation. These phenomena are mediated by the ability of variable stretch to increase the microtubule network's fractal dimension by altering fission-fusion dynamics and enhance the association between mitochondria and microtubules, which are destroyed during monotonous stretch that typifies current laboratory experimentation. Variable stretch also influences mitochondrial structure and function in other cell types such as fibroblasts and stem cells. Furthermore, stochastic regulation of mechanotransduction appears to be a general theme of biology: secretion of extracellular matrix molecules and cellular contraction are also influenced by the body's natural rhythms. Since such stochastic regulation represents normal physiology in vivo built into cell functions by a billion years of evolution, our results have implications for all ATP-dependent and mechanosensitive intracellular processes both in health and disease.