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PROCEEDINGS

Experimental and Computational Elucidation of Mechanical Forces on Cell Nucleus

Miao Huang[1], Maedeh Lotfi[1], Heyang Wang[4], Hayley Sussman[5], Kevin Connell[1], Quang Vo[1], Malisa Sarntinoranont[1], Hitomi Yamaguchi[1], Juan Guan[2] and Xin Tang[1,3,*]

[1]Department of Mechanical and Aerospace Engineering, University of Florida (UF), Gainesville, FL, 32611, USA
[2]Department of Chemical Biology & Medicinal Chemistry, University of Texas at Austin, TX, 78712, USA
[3]UF Health Cancer Center (UFHCC), Gainesville, FL, 32611, USA
[4]Department of Mechanical Engineering, Northwestern University, Evanston, IL, 60208, USA
[5]Department of Biomedical Engineering, University of Virginia, Charlottesville, VA, 22901, USA
[*]Corresponding Author: Xin Tang. Email: xin.tang@ufl.edu

ABSTRACT

Mechanotransduction, i.e., living cells sense and transduce mechanical forces into intracellular biochemical signaling and gene expression, is ubiquitous across diverse organisms. Increasing evidence suggests that mechanotransduction significantly influences cell functions and its mis-regulation is at the heart of various pathologies. A quantitative characterization of the relationship between mechanical forces and resulted mechanotransduction is pivotal in understanding the rules of life and innovating new therapeutic strategies [1-3]. However, while such relationship on the cell surface membrane and cytoskeleton have been well studied, little is known about whether/how mechanical forces applied on the cell interior nucleus ("headquarter of the cell") quantitatively trigger mechanotransduction [4-5]. This is because conventional techniques cannot simultaneously access, manipulate, and record the mechano-chemo-genetic dynamics inside the cell nucleus. In this presentation, we will present our new results on (1) the experimental characterization of the translocation of YAP (Yes-associated protein) induced by quantitative force applied directly on the nucleus; and (2) computation-guided quantification of applied mechanical forces [6-7]. Our results suggest that magnetic microbeads can regulate the dynamic YAP translocation and downstream gene transcription while avoiding the interruption of cytoskeleton and corresponding important cell functions. Our experimental and computational results advance the understanding of the mechanisms of nuclear mechanotransduction and potentially contribute to the development of new therapies for tumor suppression targeting YAP.

KEYWORDS

Biomechanics; soft matter; mechanical microenvironment; YAP; functional imaging

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References

1. Xin, Y., Li, K. M., Huang, M., et al. (2023). Biophysics in Tumor Growth and Progression: from Single Mechano-sensitive Molecules to Mechanomedicine. *Oncogene, 42,* 3457-3490.
2. Liang, C. Y., Huang, M., Li, T. Q., et al. (2022). Towards an Integrative Understanding of Cancer Mechanobiology: Calcium, YAP, and MicroRNA Under Biophysical Forces. *Soft Matter, 18,* 1112-1148.
3. Huang, M., Wang, H. Y., Mackey, C., et al. (2023). YAP at the Crossroads of Biomechanics and Drug Resistance in Human Cancer. *International Journal of Molecular Science, 24(15),* 12491.
4. Liang, C. Y., Zhang, Q., Chen, X., et al. (2022). Human cancer cells generate spontaneous calcium transients and intercellular waves that modulate tumor growth. *Biomaterials, 290,* 121823.
5. Liang, C. Y., Huang, M., Tanaka, M., et al. (2023). Functional Interrogation of Ca^{2+} Signals in Human Cancer Cells *In Vitro* and *Ex Vivo* by Fluorescent Microscopy and Molecular Tools. *Methods in Molecular Biology, 2679,* 95-125.
6. Huang, M., Wang, H. Y., Delgado, A. A, et al. (2022). Combining 3D Magnetic Force Actuator and Multi-Functional Fluorescence Imaging to Study Nucleus Mechanobiology. *Journal of Visualized Experiments, 185,* e64098.
7. Luo, Q., Zhang, J., Lin, G., Huang, M., Tanaka, M., et al (2022). Automatic multi-functional integration program (AMFIP) towards all-optical mechanobiology interrogation. *PLOS One*, *17(7),* e0266098.