

#### PROCEEDINGS

## **Mechano-Regulated Intercellular Waves Among Cancer Cells**

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#### ABSTRACT

Cancer accounts for 12.6% of all human deaths worldwide and 90% of cancer-related deaths are due to metastasis: the dissemination of invasive tumor cells from the primary tumors to other vital organs [1-3]. However, how these invasive tumor cells coordinate with each other to achieve the dissemination remains unclear. Recently we discovered that human tumor cells can initiate and transmit previously unknown long-distance (~100s  $\mu$ m) intercellular biochemical waves in a microenvironment-mechanics-regulated manner. [4-5] In this presentation, we will present our new results on (1) the 2D/3D spatial-temporal characterization of the long-distance and the intra-/inter-cellular Ca<sup>2+</sup> signals; (2) the functional influences of mechanical microenvironment on the spatial-temporal properties of Ca<sup>2+</sup> dynamics (i.e., signaling symphony); and (3) the molecular mechanisms and biological consequences of the Ca<sup>2+</sup> dynamics during tumor progression and metastasis *in vivo*. To our knowledge, this study is the 1<sup>st</sup> report that shows the detailed characterization and mechanistic dissection of long-distance Ca<sup>2+</sup> waves in human cancer cells [4-5]. Our results advance the understanding of the mechano-regulated functions/mechanisms of Ca<sup>2+</sup> signals in human cancer and potentially contribute to the development of new therapies for tumor suppression.

### **KEYWORDS**

Biomechanics; cancer; mechanical microenvironment; Ca<sup>2+</sup> waves; functional imaging

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**Conflicts of Interest:** The authors declare that they have no conflicts of interest to report regarding the present study.

#### References

- 1. Xin, Y, Li, K. M., Huang, M., et al. (2023). Biophysics in Tumor Growth and Progression: from Single Mechanosensitive 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.
- Liang, C. Y., Huang, M., Tanaka, M., et al. (2023). Functional Interrogation of Ca<sup>2+</sup> Signals in Human Cancer Cells *In Vitro* and *Ex Vivo* by Fluorescent Microscopy and Molecular Tools. *Methods in Molecular Biology*, 2679, 95-125.