2023 CMBEC45
Vancouver, B.C.
May 16-18, 2023
CMBES/SCGB

Smart hydrogel probes to measure complex tissue mechanics within engineered tumors

Benjamin E. Campbell, Christina Boghdady, Stephanie Mok, Luke McCaffrey, Christopher Moraes

***Abstract*—Measuring the rate of expansion of dispersible hydrogel microspheres embedded within engineered tumors is used to assess highly local viscoelastic tissue characteristics. We find that viscoelasticity is both heterogenous and closely correlated with invasive programs in breast cancer models.**

***Clinical Relevance*— establishes a potential diagnostic modality for metastatic risk via dynamism of tissue architecture.**

I. INTRODUCTION

Viscoelastic materials exhibit both elastic and time-dependent plasticity under load. These properties are now well-established to direct cell function[1], but measuring viscoelasticity within intact, living, 3D tissues is very challenging, particularly at the length scale relevant to individual cells[2],[3]. This is particularly important in cancer, in which cellular jamming is anticipated to drive metastasis. Here, we extend the use of our previously described thermoresponsive hydrogel microdroplet stiffness sensors [2] to measure viscoelasticity, by characterizing, measuring, and modelling expansion time dynamics in situ.

II. METHODS

Thermoresponsive hydrogel microdroplets that compact at temperatures above 32°C are fabricated in Poly-n-isopropylacrylamide (NiPAAm) [2] and embedded in engineered tumor models [4]. Rapid cooling causes the sensors to expand based on viscosity of the surrounding matrix. Calibration experiments in defined tissue phantoms and finite element (FEA) models allowed us to measure stress as a function of sensor size and actuation stroke length (Fig. 1A, B). Inverse FEA models were then used to characterize E and τ based on experimental expansion rates.

III. RESULTS

We confirmed that in linear elastic materials such as polyacrylamide gels, expansion completed within seconds of the applied temperature change. We then validated this method in live and fixed T47D tissues, and showed that as expected, viscoelastic characteristics of the tissues were dissipated on fixation. We then evaluated viscoelasticity within tumor models of differentially invasive cell lines, and found that non-invasive T47D and invasive MDAMB-231 spheroids exhibit similar local stiffnesses, but the time constants of sensor expansion are consistently lower in the invasive tissue, even in regions of similar stiffness, suggesting that internal local fluidity is a characteristic of quiescent tumors. We further demonstrate this principle in an inducible cell model system (Figure 1).

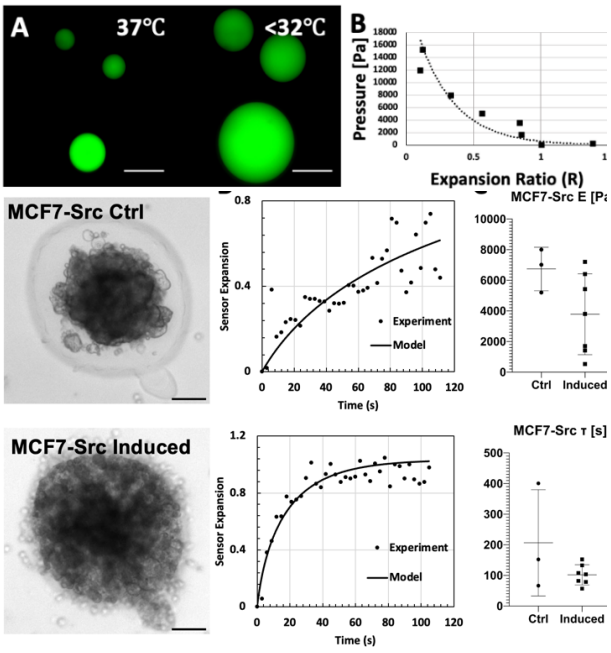

Fig. 1. (A) Engineered thermoresponsive hydrogel sensors. (B) Calibration curve of force-stroke length. Deconvolution of sensor expansion with the force-stroke curve allows (C, D) assessment of storage and loss modulus in quiescent (Ctrl) and invasive (Induced) modulus in a single-gene activatable inducible model of breast cancer

IV. DISCUSSION & CONCLUSION

We demonstrate that spheroids with different invasive potentials have distinct internal viscoelastic characteristics. Ultimately, changes in tissue viscoelasticity affects how those cells perceive their mechanical environment over time and thus, the ability of these sensors to quantify the viscoelastic properties as experienced by cells permits investigation of how mechanics and cell behavior interact.

REFERENCES

[1] Elosegui-Artola, A et al., *Nat. Mater.*, 22:117-127,2023.
[2] Mok, S et al., *Nat. Commun.*, 11:4457,2020.
[3] Serwane, F et al., *Nat. Methods.*, 14:181-186, 2017.
[4] Zhao, L et al., *Biofabrication.*, 11:045013, 2019.

*Research supported by funding from the Canadian Cancer Society (Grant Nos. 704422 and 706002) and the Canadian Institutes for Health Research (Grant No. 01871-000) to C.M. and L.M., the Natural Sciences and Research Council of Canada (NSERC) Discovery grants (RGPIN-2022-05165) and the Canada Research Chairs in Advanced Cellular Microenvironments to C.M..

C. Moraes is with the Dept. of Chemical Engineering, Biomedical Engineering, and the Goodman Cancer Institute, McGill University, QC Canada, ; e-mail: chris.moraes@mcgill.ca).