The Role of Matrix Stiffness in Protein Folding Machineries

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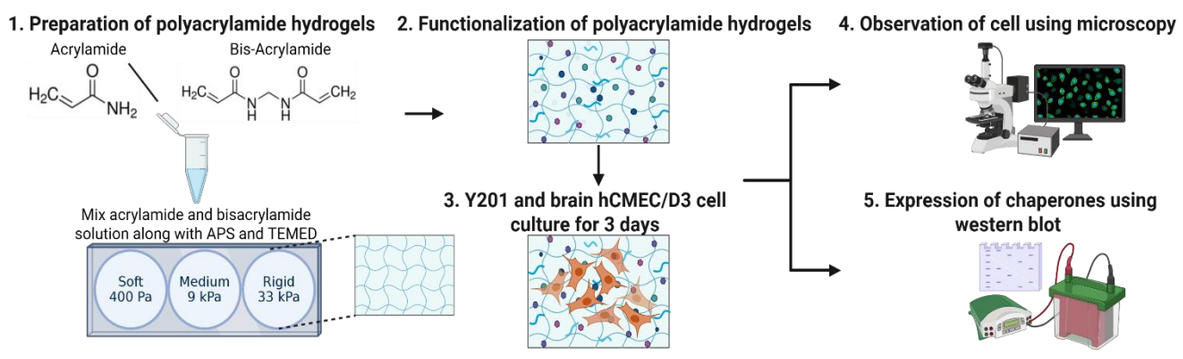
1. Introduction

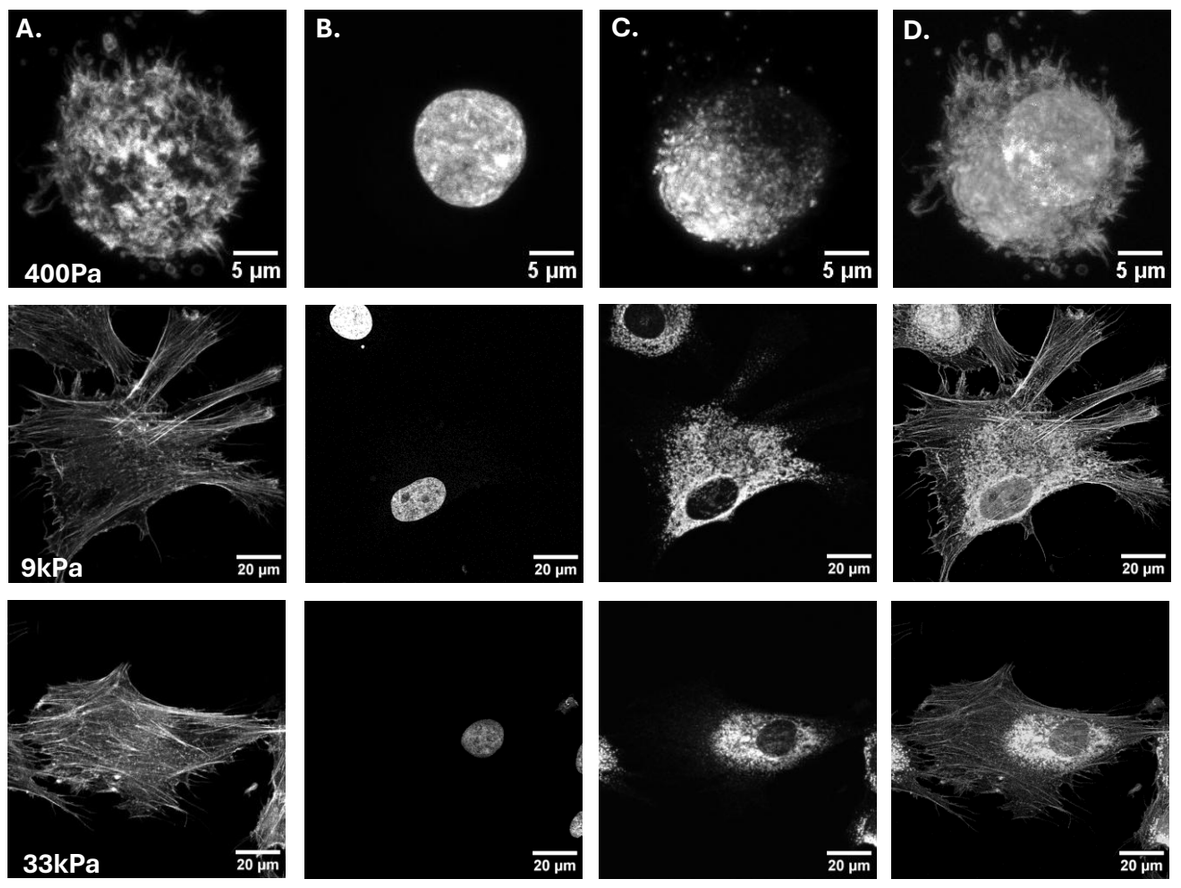
Background. Tissue stiffening in diseases alters extracellular matrix (ECM) mechanics and is linked to impaired proteostasis of the endoplasmic reticulum (ER). Yet whether the ER itself is mechanosensitive and how mechanical cues regulate its protein-folding capacity remains elusive.

Aim. We use tuneable polyacrylamide hydrogels to test how ECM stiffness regulates ER function and ER resident chaperone expression, suggesting a potential mechano-proteostasis link that could reshape our understanding of disease and regeneration.



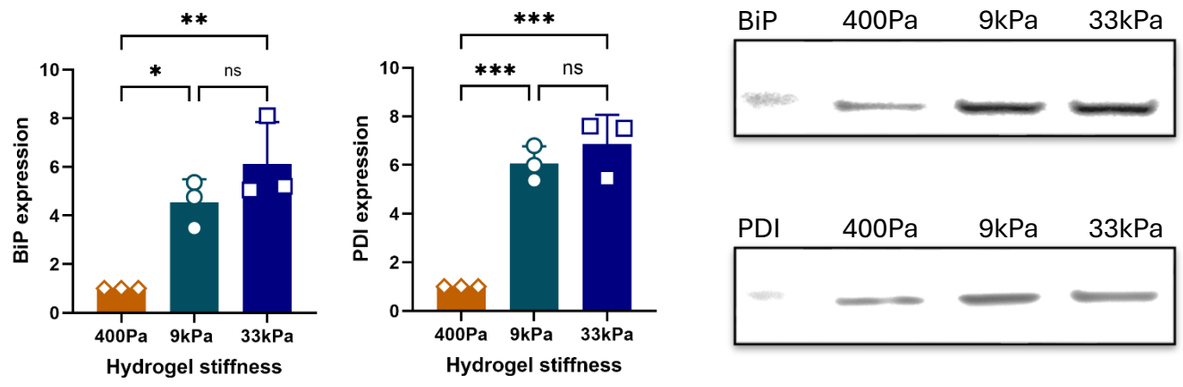
Workflow for polyacrylamide hydrogel preparation, cell culture, microscopy analysis, and western blot for chaperone expression assessment.

2. Cell Response to Substrate Stiffness

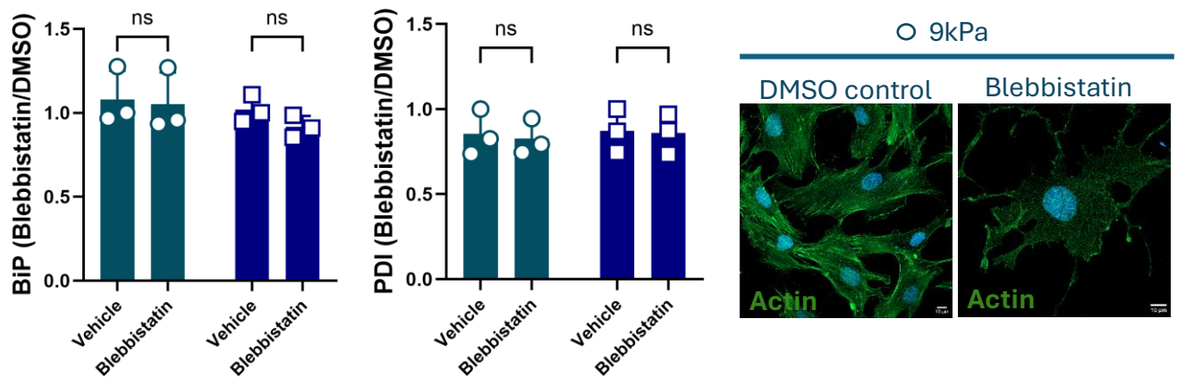


Cell and ER area increase on stiff substrates, where cells spread and form stress fibres, but decrease on soft substrates compared to stiff; (A) Actin, (B) DAPI, (C) ER, (D) Merged.

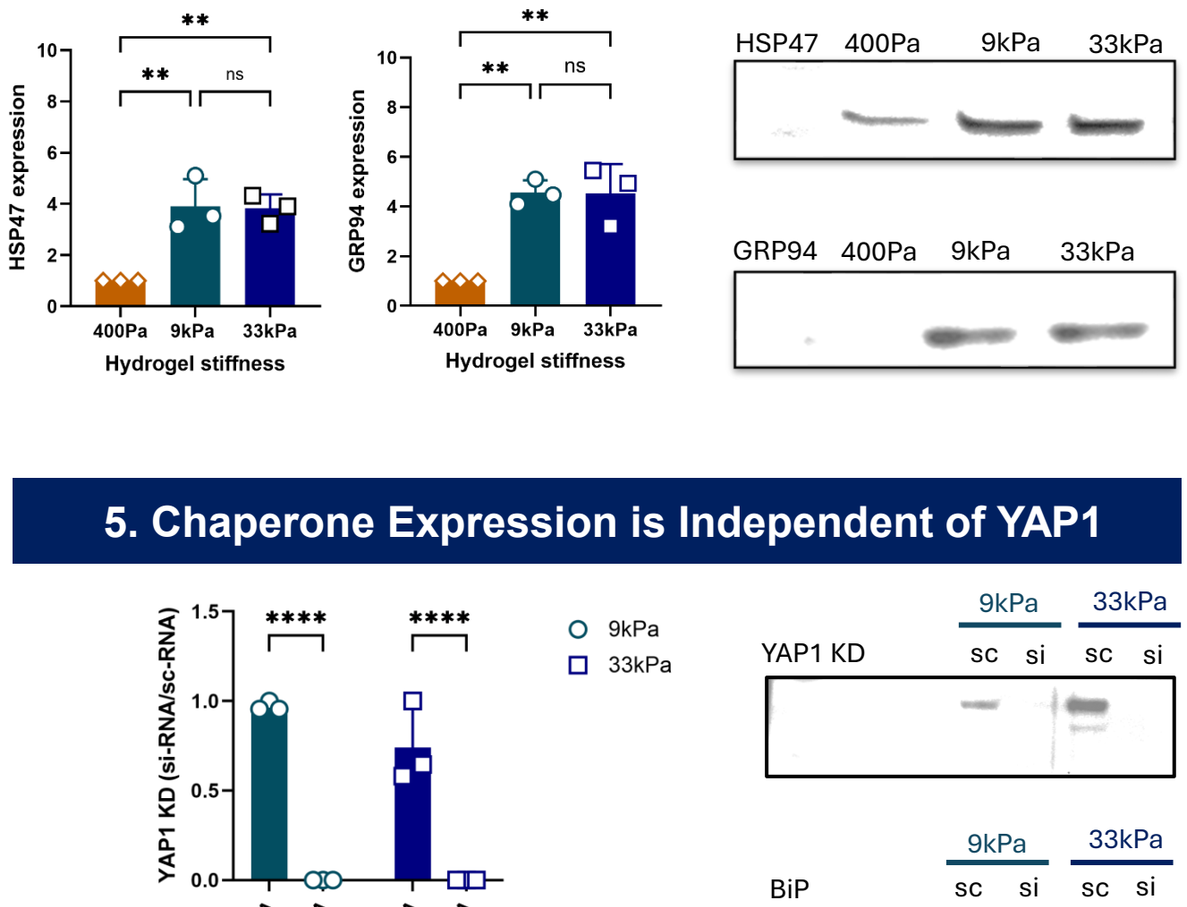
3. Stiffness Regulates Chaperone Expression



4. Chaperone Expression is Contractility Independent

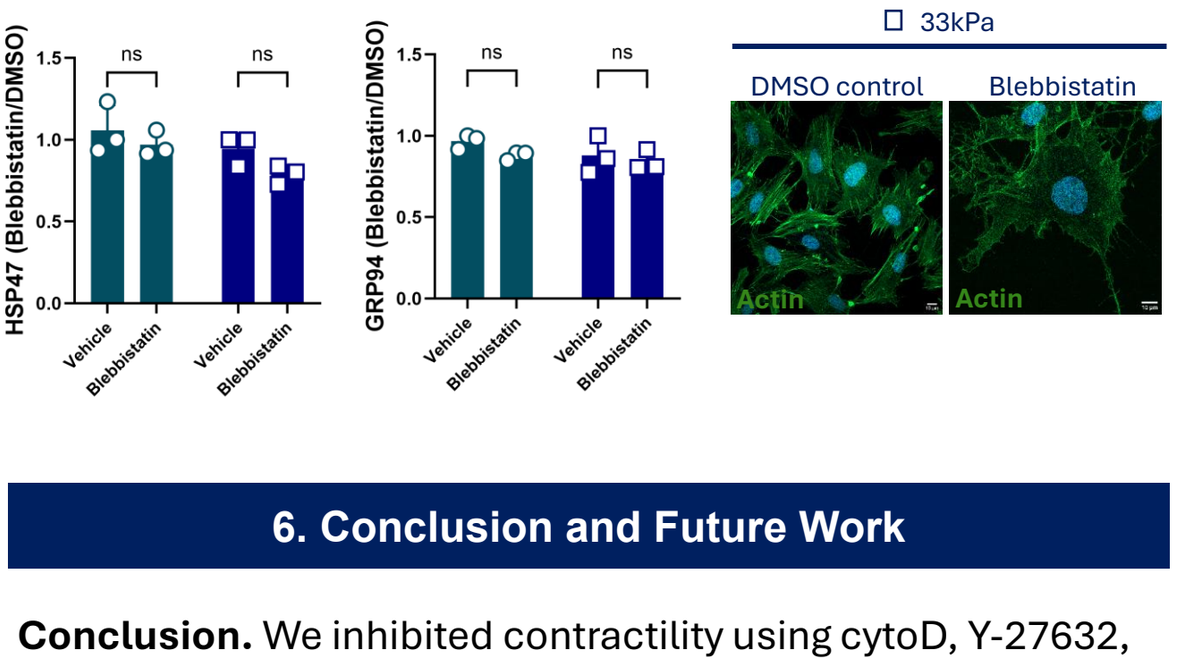


5. Chaperone Expression is Independent of YAP1



6. Conclusion and Future Work

Conclusion. We inhibited contractility using cytoD, Y-27632, and blebbistatin, and targeted mechanotransduction pathways by knocking down YAP1 and talin-1. Chaperone levels remain unchanged, pointing to a regulatory mechanism independent of contractile signaling.



Future work. Cells regulate chaperone expression through pathways beyond classical mechanotransduction, and identifying this mechanism is the next step.

REFERENCES:
(1)Phuyal, S. et al. *Trends Cell Biol.* 33(12), 1049-1061 (2023), https://doi.org/10.1016/j.tcb.2023.05.001
(2)Cheng, D. et al. *Biochem. Soc. Trans.* 51(5), 1897-1906 (2023), https://doi.org/10.1042/BST20230042

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