The ageing niche: Does the Hippo control it all?

THE UNIVERSITY of EDINBURGH | Institute for Regeneration and Repair

Centre for Inflammation Research

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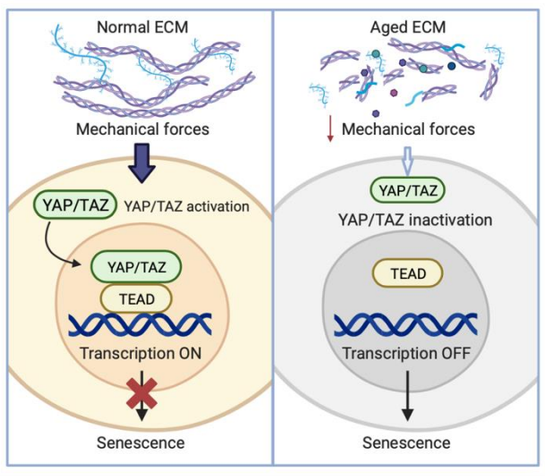
Introduction

- Extracellular matrix (**ECM**) function in cellular communication and as structural support
- Biomechanical properties of ECM are altered with ageing, including ECM stiffening, abnormal protein expression, and elevated hydrostatic pressure which hinder tissue regeneration

What is regulating mechano-signals in ageing?

- The **Hippo pathway** is mechanotransductive and regulates organ size and cell proliferation
- Yes-Associated Protein (**YAP**) and Transcriptional Co-Activator with PDZ-binding Domain (**TAZ**) are the downstream effectors of the Hippo pathway
- YAP/TAZ activity declines in aged stromal cells
- Sustaining YAP/TAZ activity suppresses ageing features



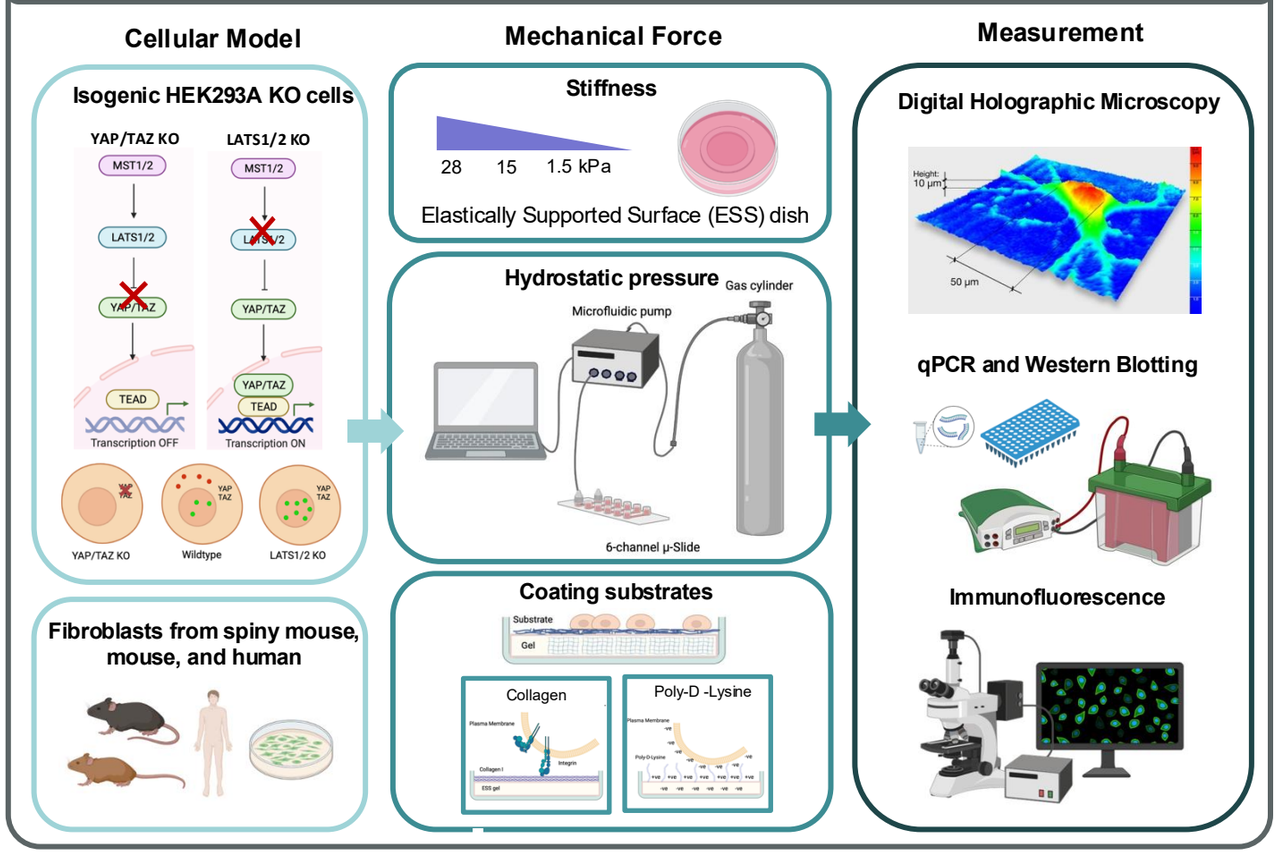
Hypothesis

YAP/TAZ regulates cellular responses to mechanical changes in the aged ECM

Aims

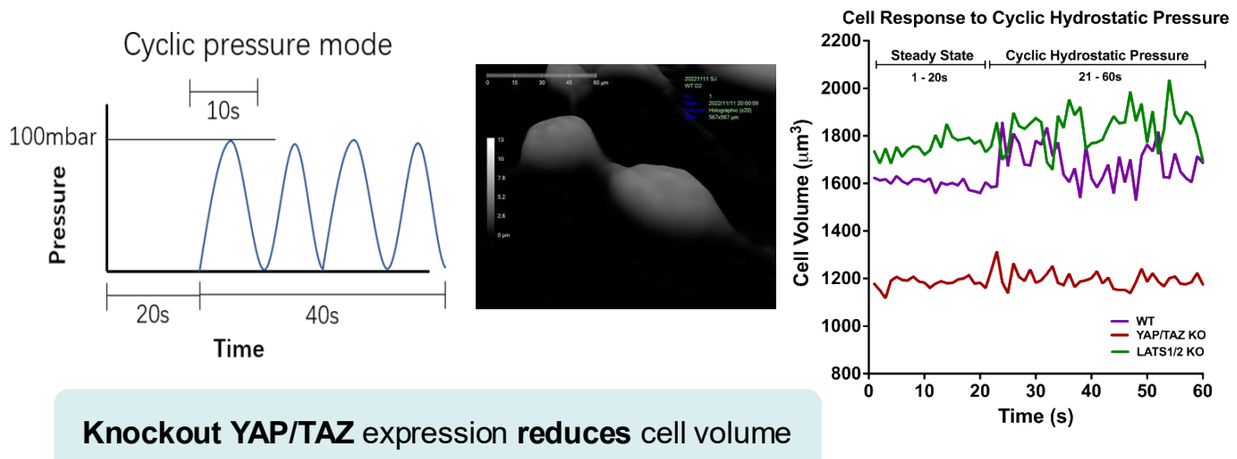
1) Characterize the cellular responses to age induced mechanical ECM changes
2) Determine YAP/TAZ and the corresponding signalling pathway's role in sensing physical stimuli and regulating cellular responses in the ageing niche

Methods

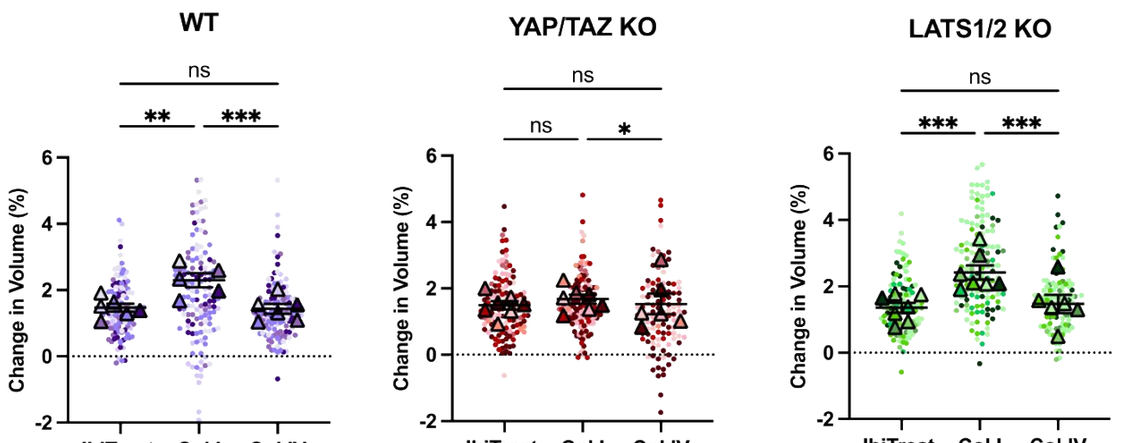


Results

Cellular responses to hydrostatic pressure and substrate change



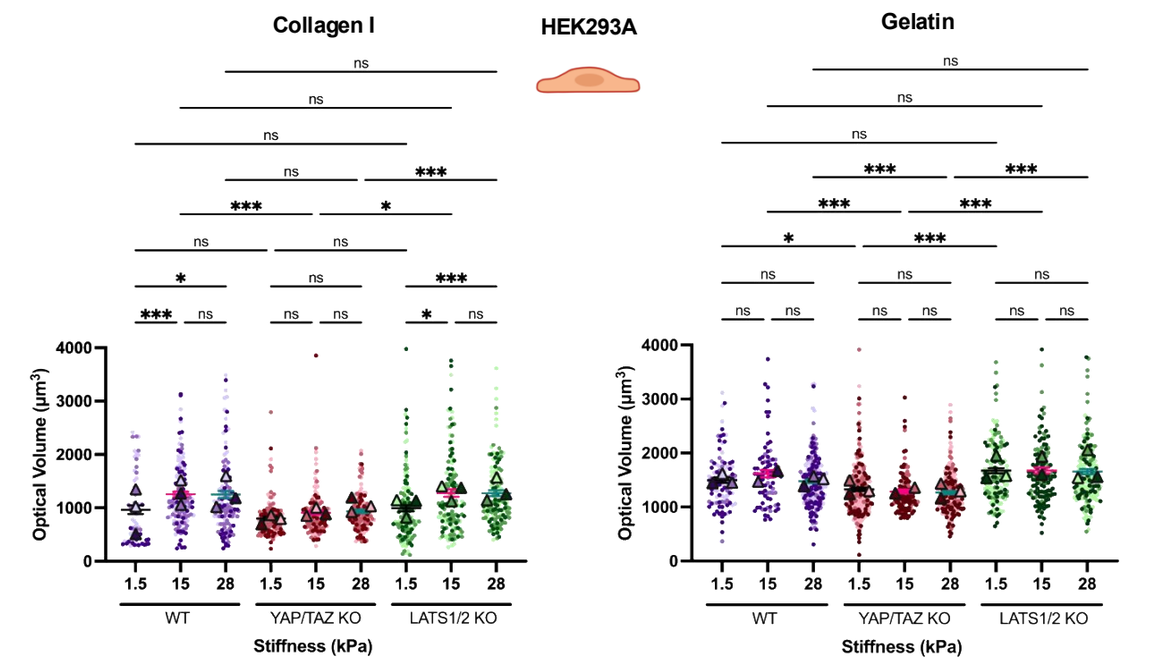
Knockout YAP/TAZ expression **reduces** cell volume



Collagen I increases cell volume change in response to oscillating hydrostatic pressure which appears **YAP/TAZ dependent**

Results

Cellular responses to stiffness and substrate change

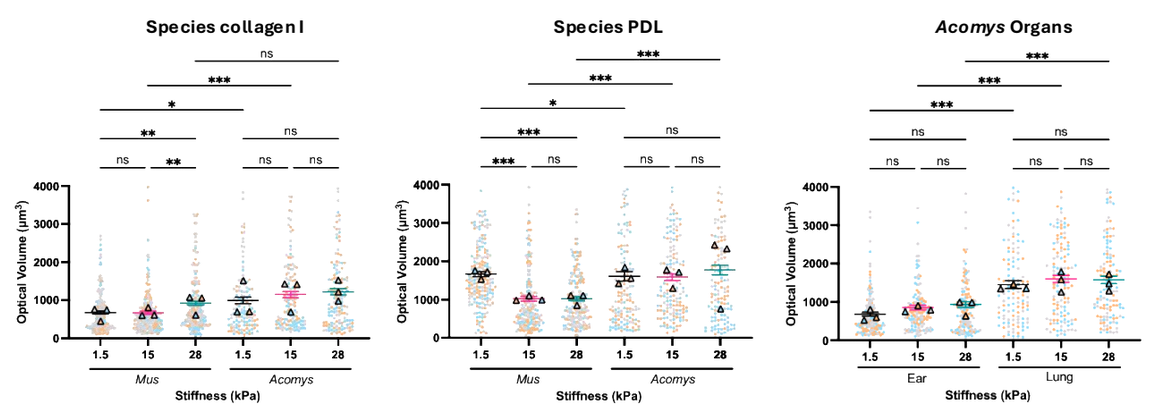


Hydrostatic pressure and collagen I **promote YAP nuclear translocation**

Stiffness induced change in	Genotype	ECM substrates				
		Collagen I	Fibronectin	Gelatin	PDL	GelMA
Volume	WT	Yes				Yes
	YAP/TAZ KO					
	LATS1/2 KO	Yes				Yes
Shape	WT	Yes	Yes	Yes		Yes
	YAP/TAZ KO		Yes			
	LATS1/2 KO	Yes	Yes			Yes

- Cellular responses to stiffness change are **substrate-dependent**
- Cells lacking YAP/TAZ showed **less responses to stiffness** changes across **most ECM coatings**

Fibroblasts



Acomys primary fibroblasts were **insensitive to stiffness** change comparing to *Mus*

RNAseq Responses to stiffness

Mus stiff	*Acomys* stiff
Inflammation	Inflammation
Adhesion	Adhesion
Migration	Migration
Apoptosis	Apoptosis
ECM remodelling	ECM remodelling
Fibroblasts activation	Fibroblasts activation
Wound healing	Wound healing

Upregulated
Downregulated
Mix

Distinctive transcriptional profiles between *Mus* and *Acomys* on different stiffness

Conclusions

Cell morphological changes in response to stiffness and hydrostatic pressure are ECM substrates and YAP/TAZ dependent

Future Directions

1) Identify molecular mechanism of HEK293A cellular response to H.P. and ECM substrates

2) Integrate multiple mechanical forces in 3D and analyze cellular responses

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