

# Decoding vascular aging: Substrate stiffness and shear stress orchestrate endothelial inflammation and remodeling via mechanosensitive pathways

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## Background

Vascular aging is a progressive condition leading to cardiovascular disease

Blood vessels lose elasticity and stiffen

Consequences:

- Atherosclerosis
- Stroke
- Heart attack
- Cognitive decline
- Kidney disease

No effective treatments for reversing vessel stiffening

## Aims

Define the endothelial signaling pathways and genes involved in vessel stiffening via transcriptomics analysis

Elucidate how altered hemodynamics and vessel stiffening influence endothelial physiology

## Methods

Used a bioengineered microfluidic model of vascular aging

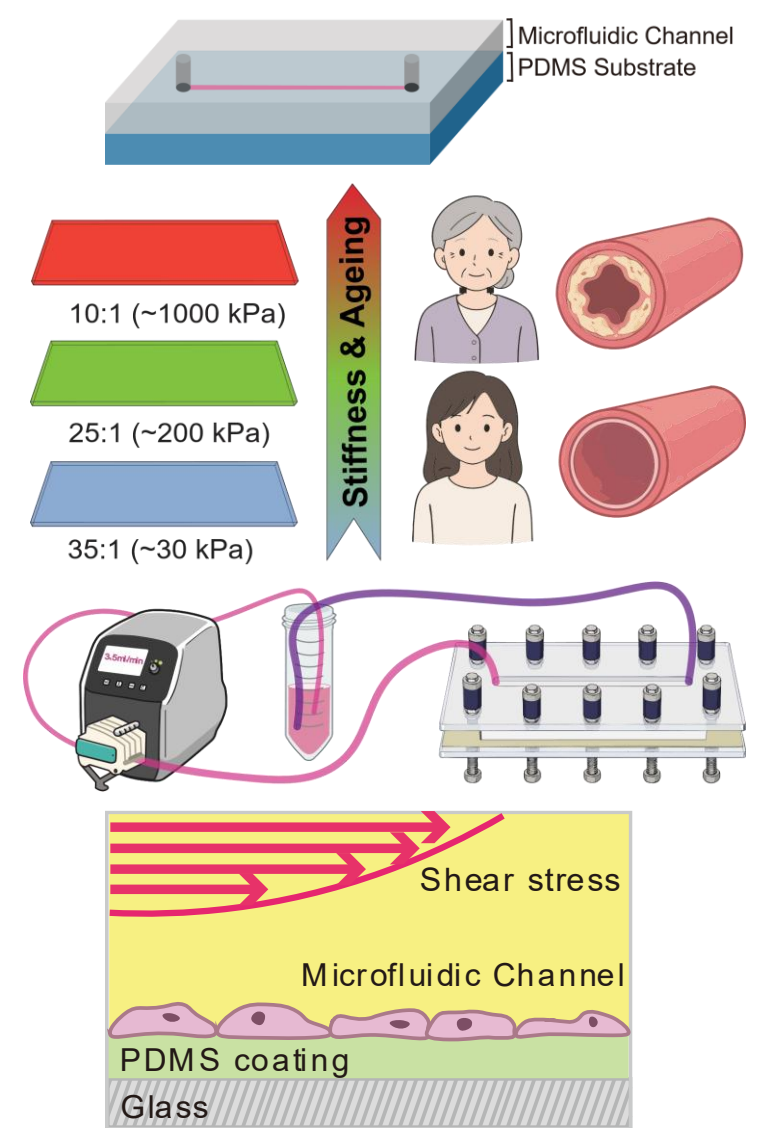
Application of shear stress to human aortic endothelial cells (HAECs)

- Physiological (10 dyne/cm<sup>2</sup>)
- Pathological (2 dyne/cm<sup>2</sup>)

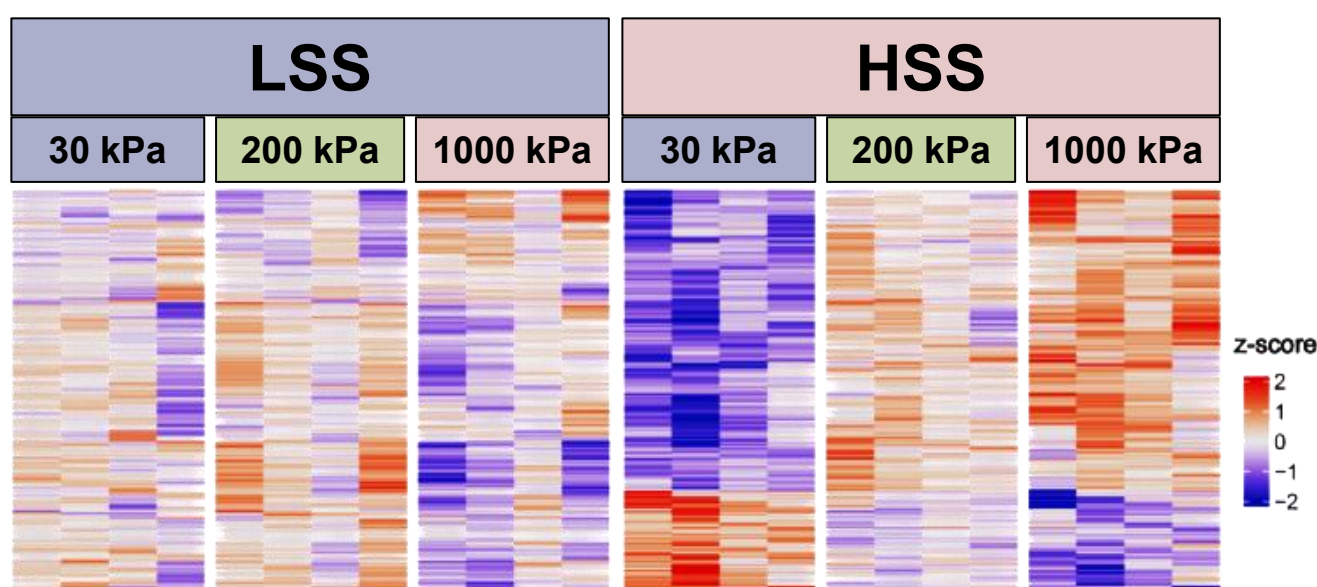
Analysis of enriched signaling pathways and differentially expressed genes via RNA sequencing

Aorta tissues collected from human cohorts stratified by stiffness

Assessed expression of markers involved in inflammation and ECM remodeling via in vitro and ex vivo immunostaining

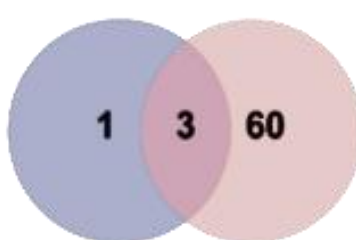


## Results



Up-regulated genes in 1000 kPa vs 30 kPa

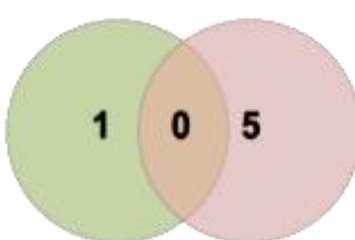
LSS HSS



# of DEGs up-regulated in HSS > LSS

Down-regulated genes in 30 kPa at HSS

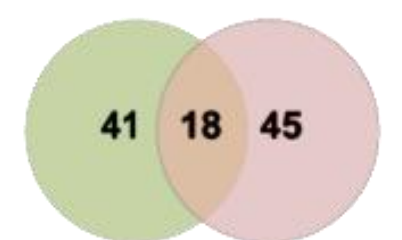
vs 200 kPa vs 1000 kPa



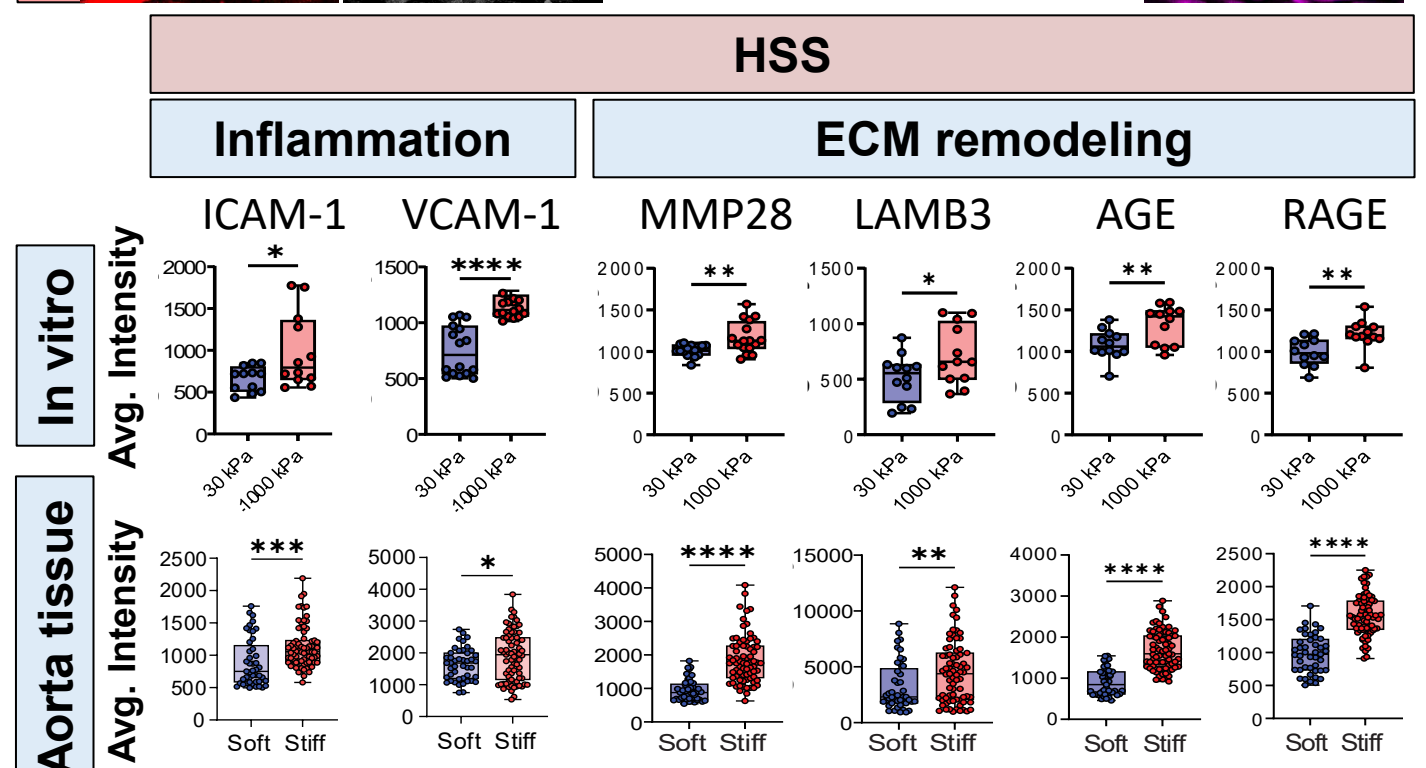
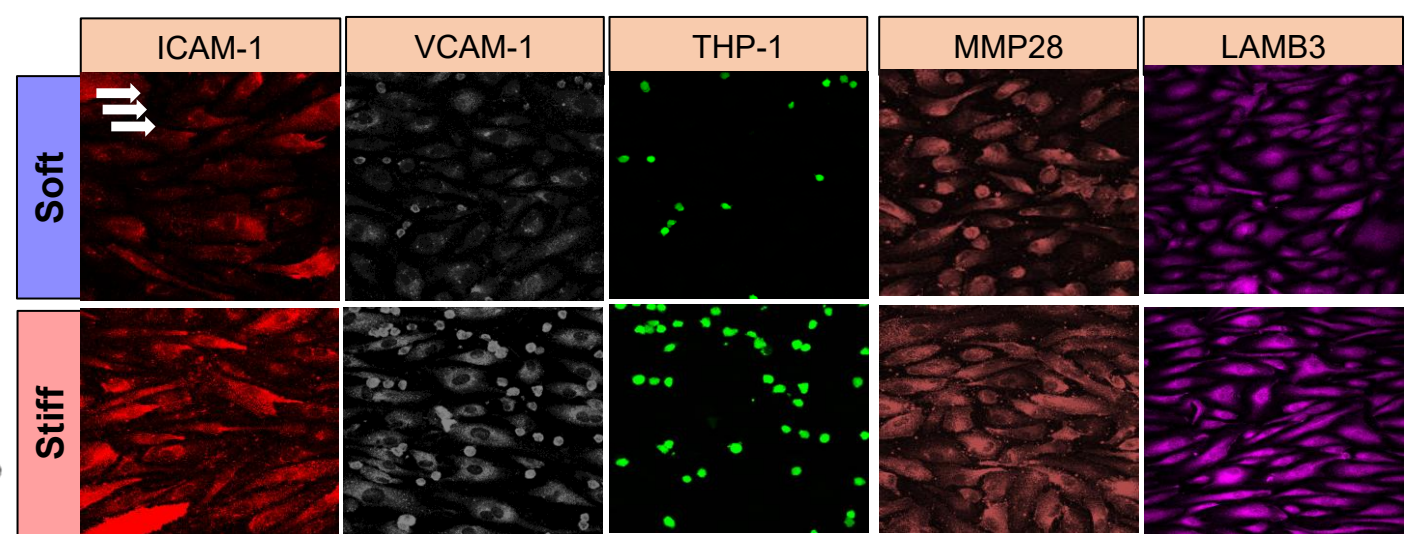
# of DEGs up-regulated in 1000 kPa > 200 & 30 kPa during HSS

Up-regulated genes at HSS

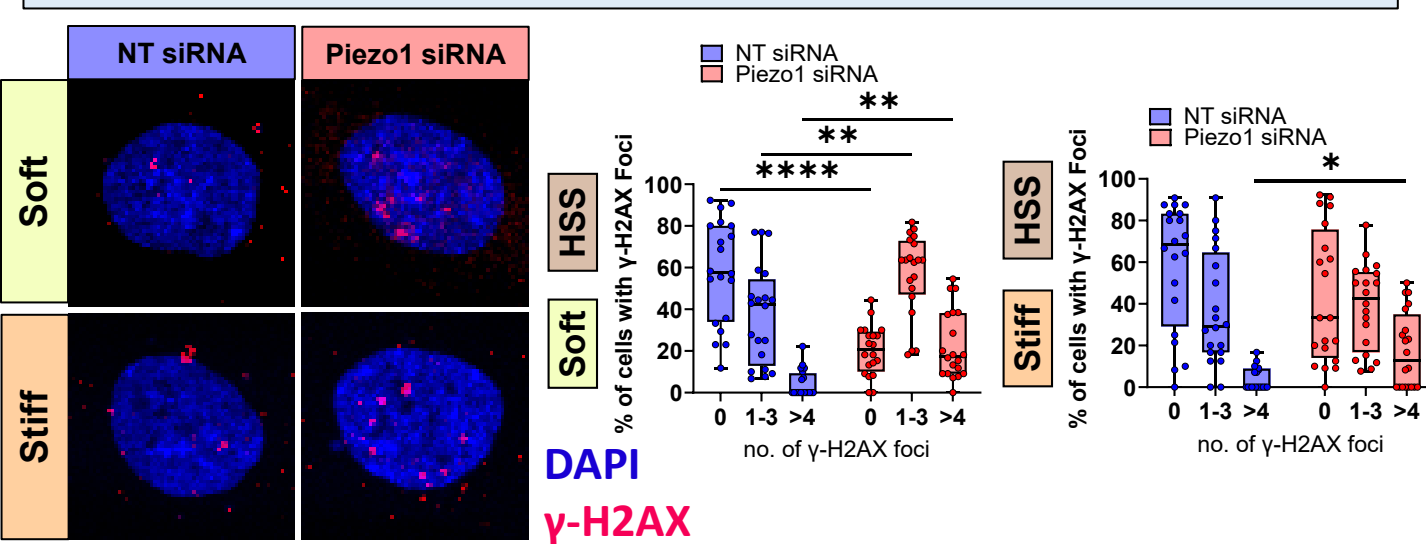
in 200 kPa in 1000 kPa vs 30 kPa vs 30 kPa



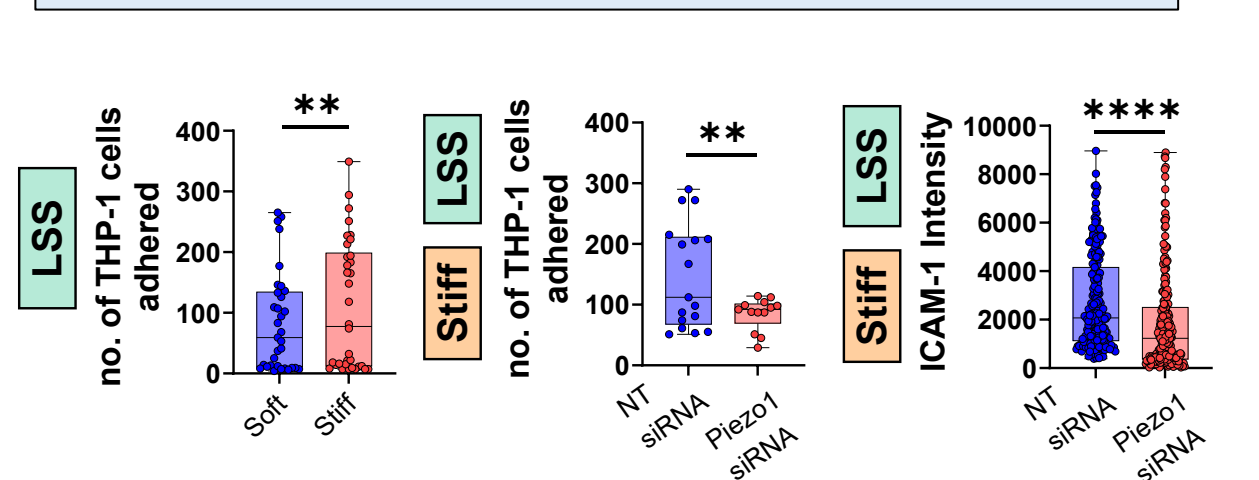
# of DEGs up-regulated in 1000 vs 30 kPa > 200 vs 30 kPa during HSS



### Piezo1 negatively regulates stiffness-induced senescence



### Piezo1 regulates of inflammation in stiff vessels



## Summary

**Inflammation:** up-regulation of ICAM-1, VCAM-1 leading to enhanced leukocyte adhesion

**ECM remodeling:** increased MMP28 and LAMB3 expression, elevated AGE-RAGE signaling

**Piezo1** regulates vessel stiffness-induced inflammation

