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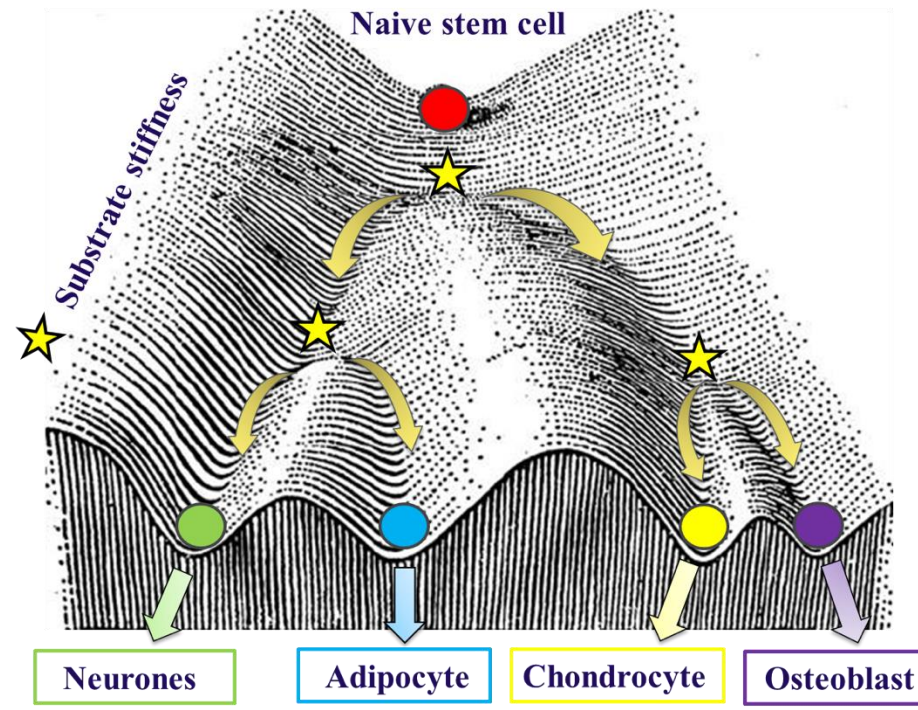
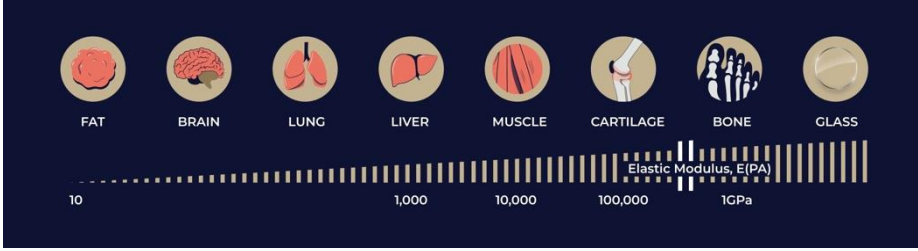
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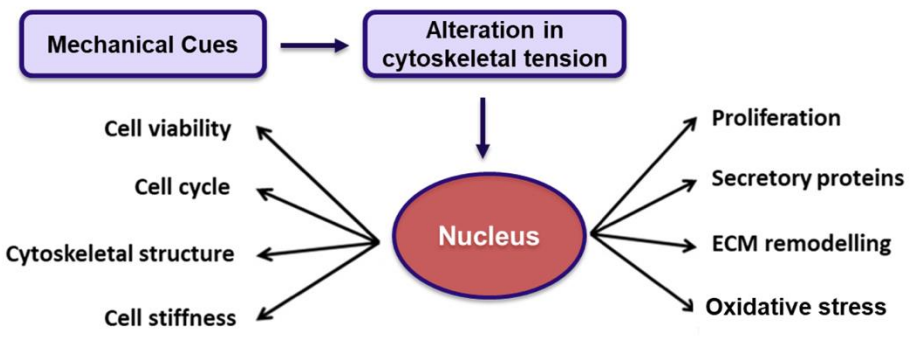
Abstract

Substrate stiffness regulates the fate and function of human mesenchymal stem cells (hMSCs), influencing cell spreading, traction, and lineage commitment. Soft substrates promote chromatin condensation and adipogenic differentiation, whereas stiff substrates induce chromatin decondensation and osteogenic commitment. We asked, whether altering chromatin structure alone can override stiffness-dependent phenotypes. hMSCs cultured on soft hydrogels were treated with Valproic acid (VA), a histone deacetylase inhibitor that induces chromatin decondensation, while cells on stiff hydrogels were treated with Anacardic acid (ANA), a histone acetyltransferase inhibitor that promotes chromatin condensation. Changing the chromatin compaction overrode the effect of substrate rigidity mediated effects and reveal chromatin's central role in influencing the rigidity specific effects.

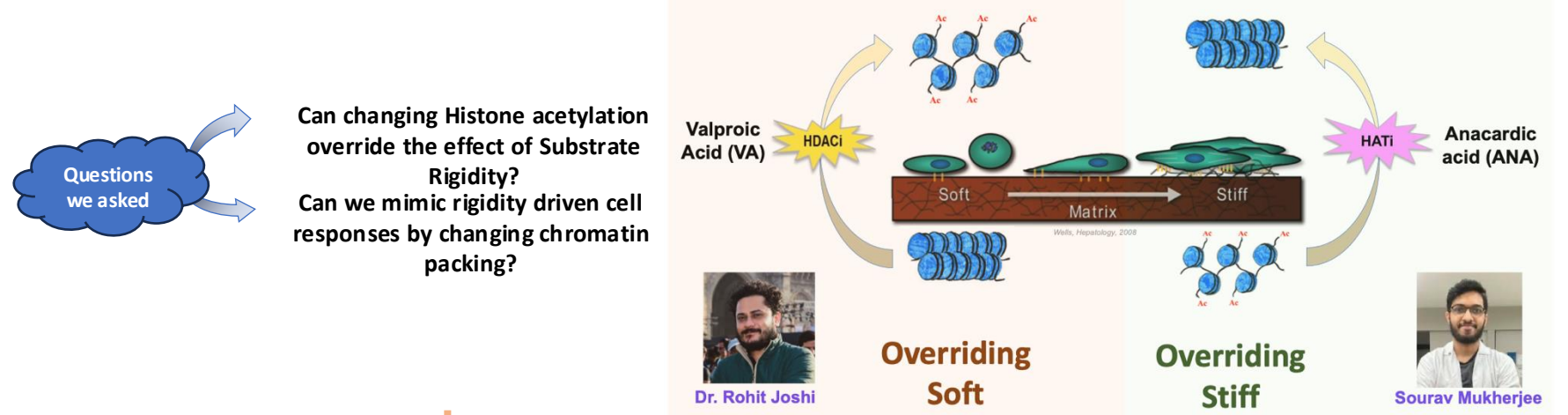
Why Stiffness is Important?



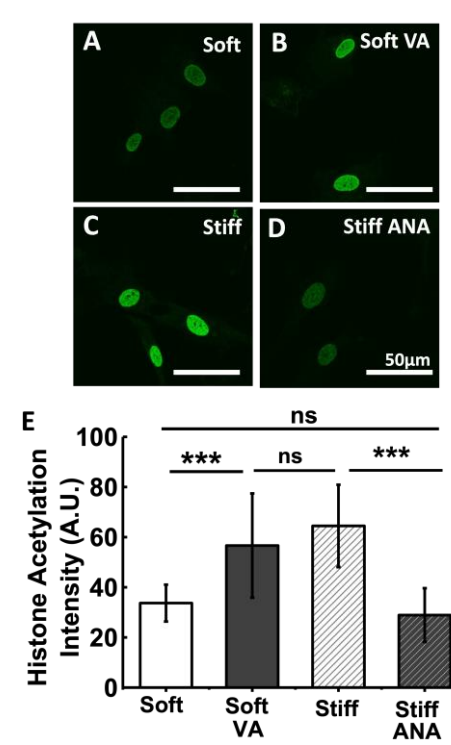
Modified from Waddington landscape



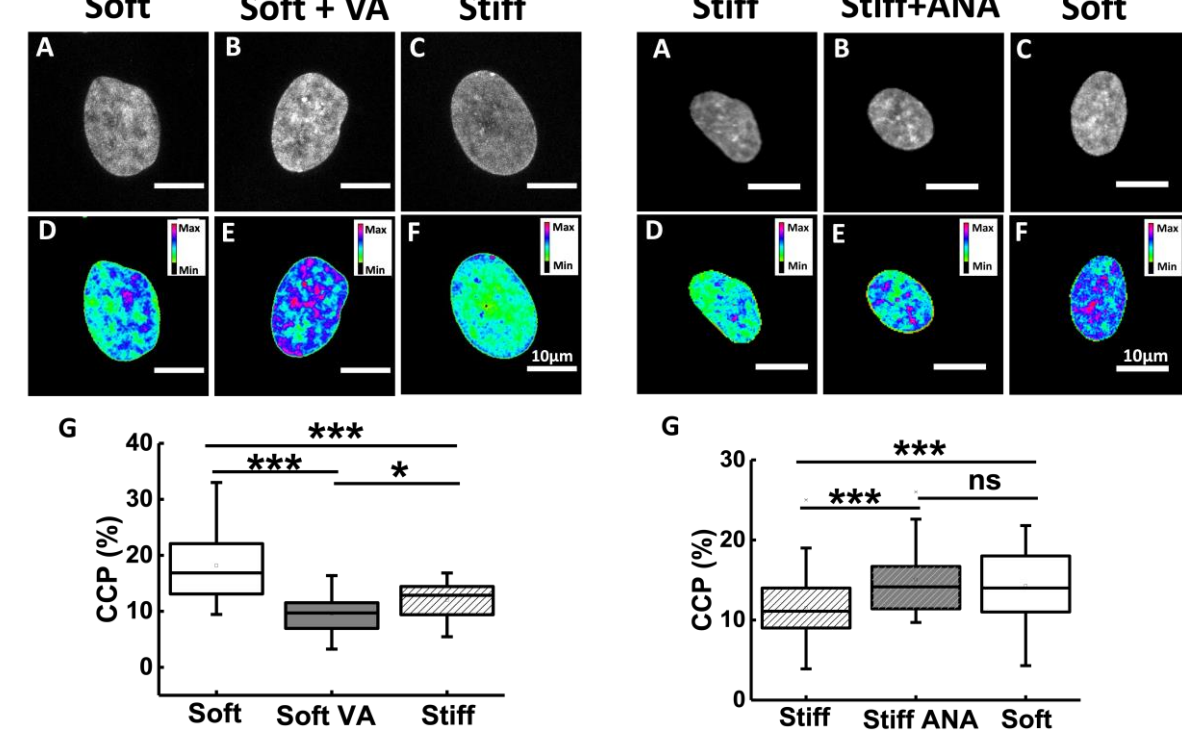
Reversing the Mechanoresponse Pathway: Outside-In Signalling



Overriding the Acetylation

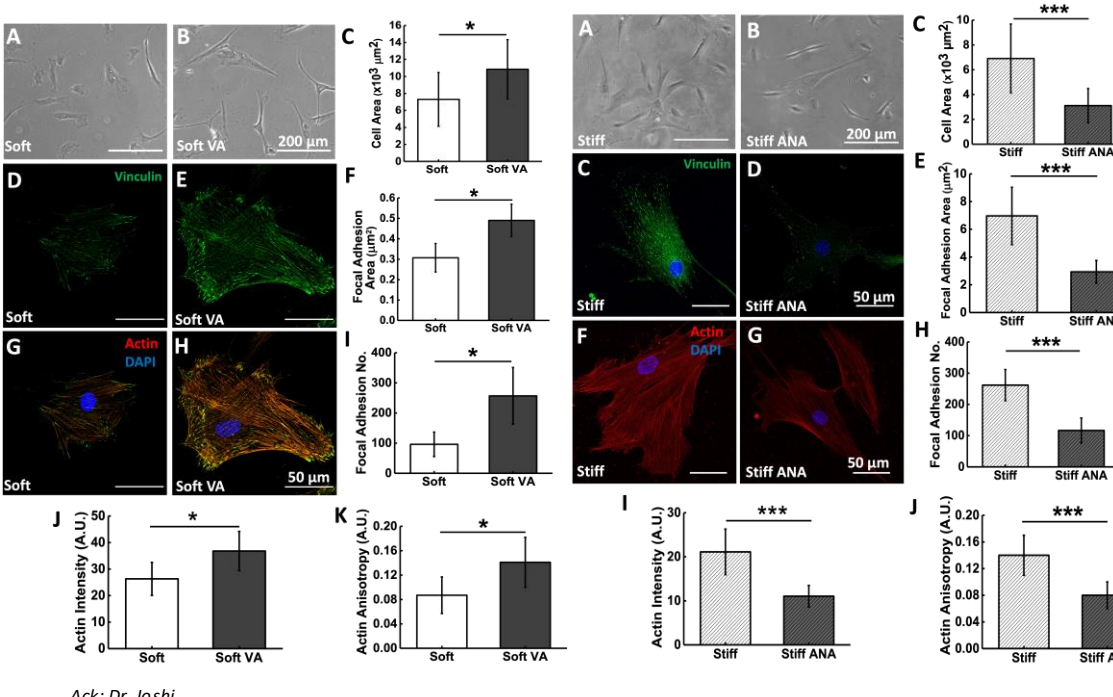


Remodelling the Chromatin Packaging



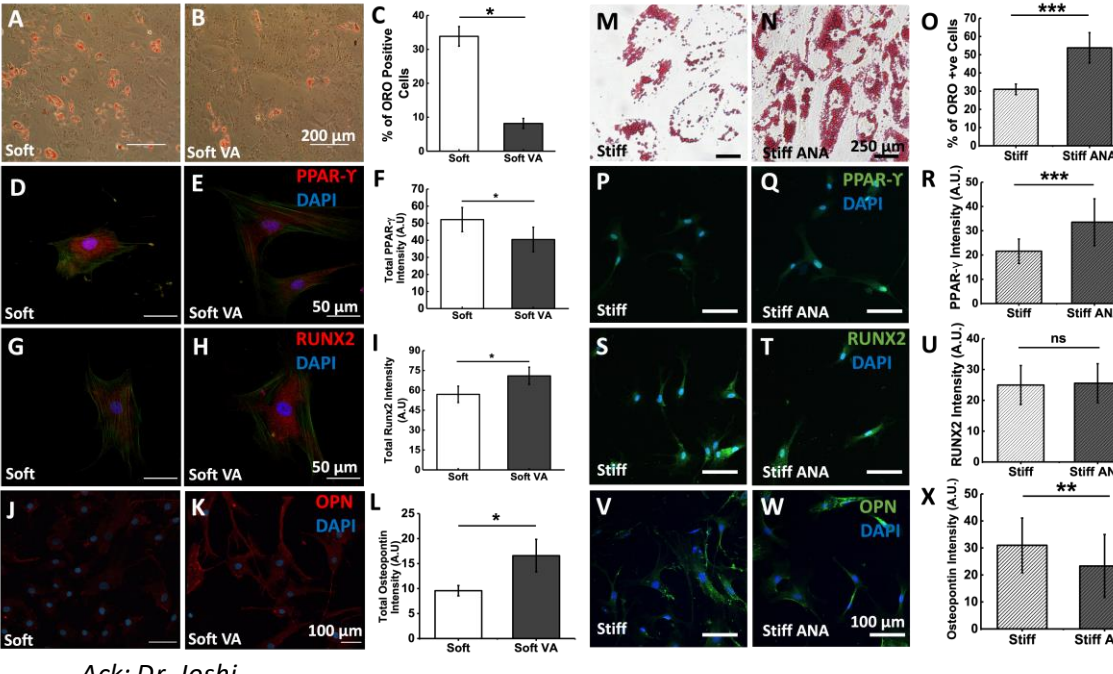
Overriding the hMSC Morphology

Overriding the Cell Spreading Area and Cytoskeleton



Ack: Dr. Joshi

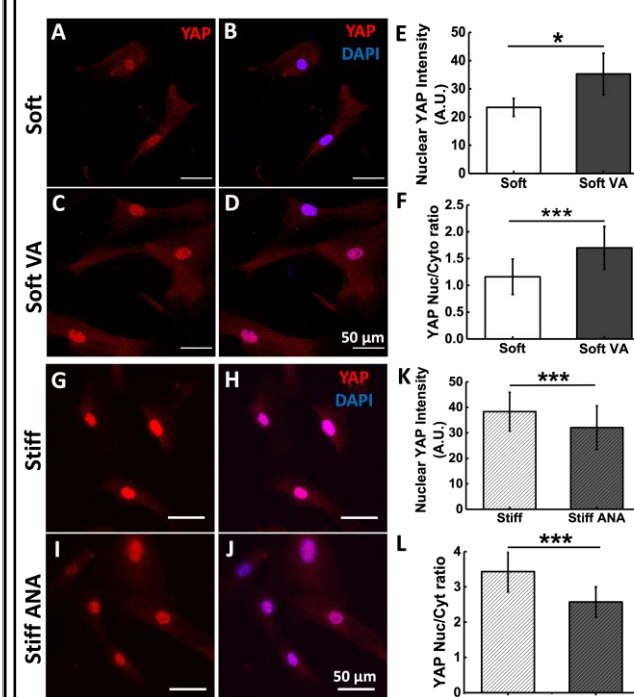
Overriding the Cell Fate



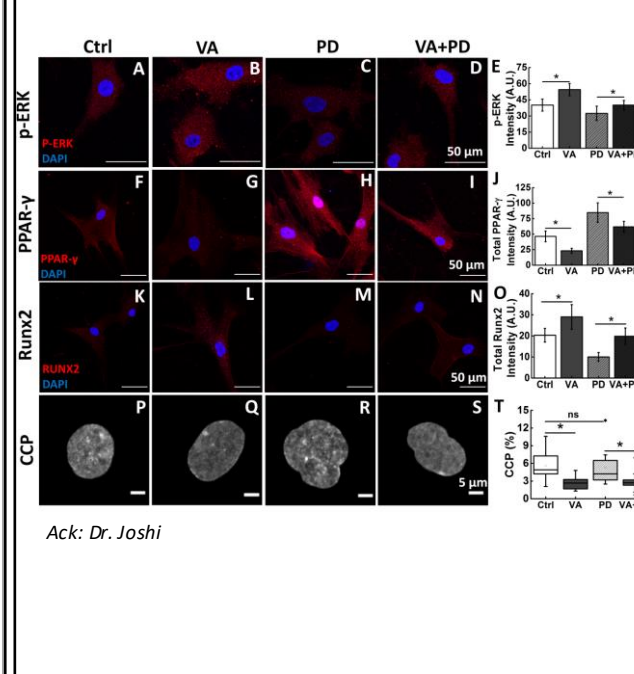
Ack: Dr. Joshi

What is the Mechanism?

Chromatin Compaction Influence YAP

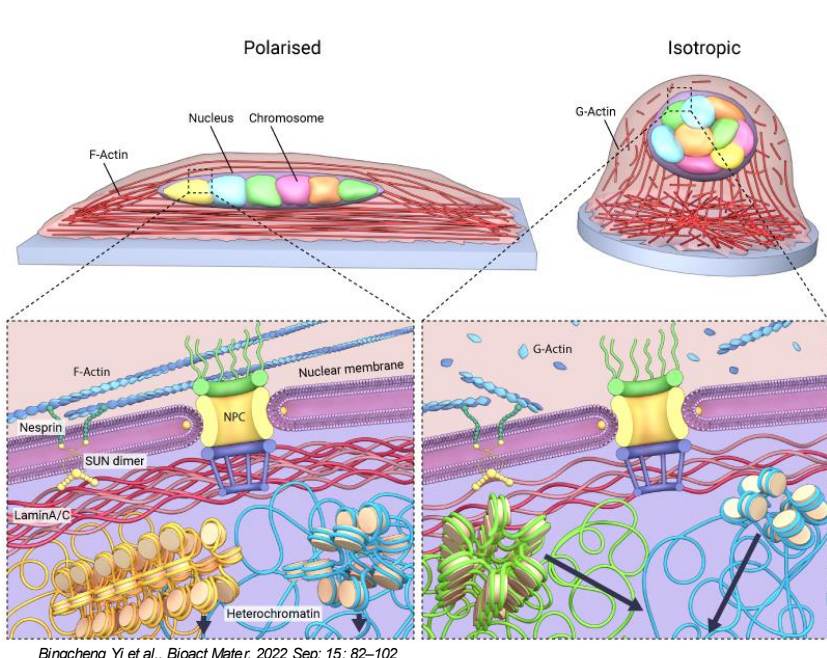


Overriding Effect is ERK Dependent

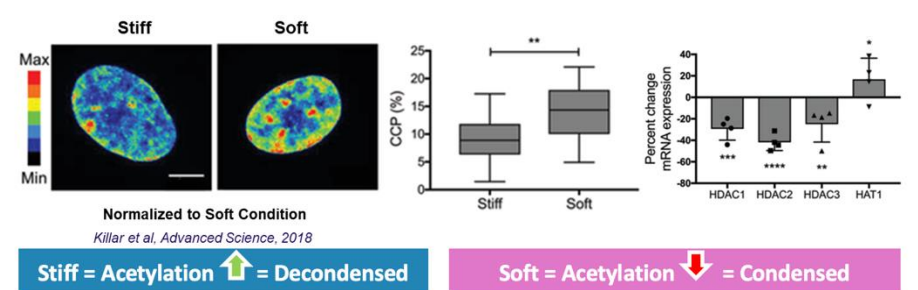


Ack: Dr. Joshi

Stiffness Controls Chromatin Packaging

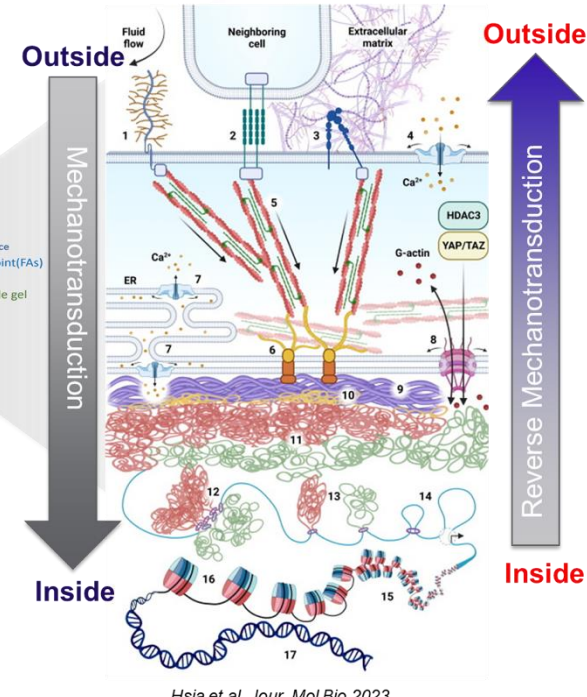
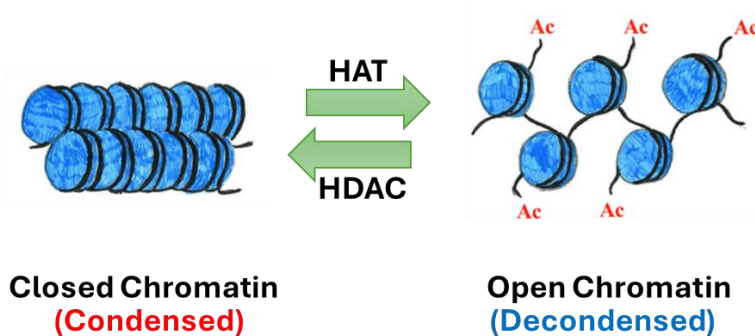


Bingcheng Yi et al., *Bioact Mater.* 2022 Sep; 15: 82-102

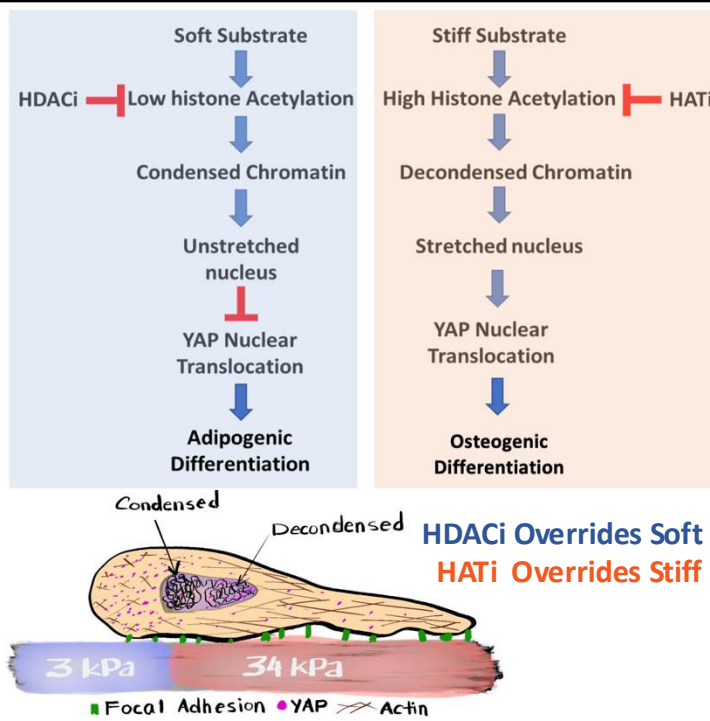


Normalized to Soft Condition
Kilar et al, *Advanced Science*, 2018

Stiff = Acetylation ↑ = Decondensed
Soft = Acetylation ↓ = Condensed



Hsieh et al, *Jour. Mol Bio* 2023



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- Chemical Engineering Dept., IIT Bombay
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MLab Website