TRPV1 Mechanosensing drives cytoskeletal and nuclear remodeling in Osteosarcoma cells

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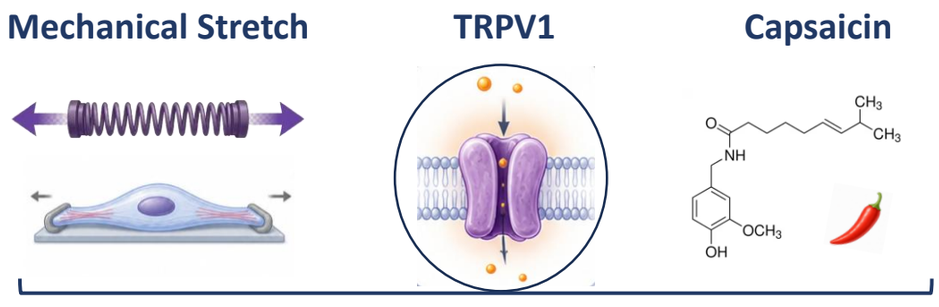
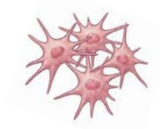
BACKGROUND

Osteosarcoma (OS) is an aggressive, highly metastatic bone cancer in which mechanobiology influences tumor progression. We previously showed that **1Hz uniaxial cyclic stretch** differentially regulates aggressive traits in **U-2 OS** and **SAOS-2** cells through the **mechanosensitive ion channel TRPV1**. Notably, TRPV1 chemical activation by **Capsaicin** faithfully mimics this mechanical strain.



METHODOLOGY

OS Cell lines



U-2 OS

SAOS-2

Treatments

Capsaicin
TRPV1 Agonist

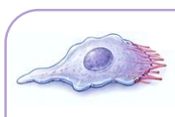
AMG 9010
TRPV1 Inhibitor

Cytochalasin D
Actin Polymerization Inhibitor

Y27632
RhoA/ROCK Inhibitor

DN KASH Domains
LINC Complex Dirsuption

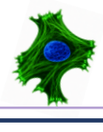
Readouts



Focal Adhesions

Nuclear Size

Cell Adhesion



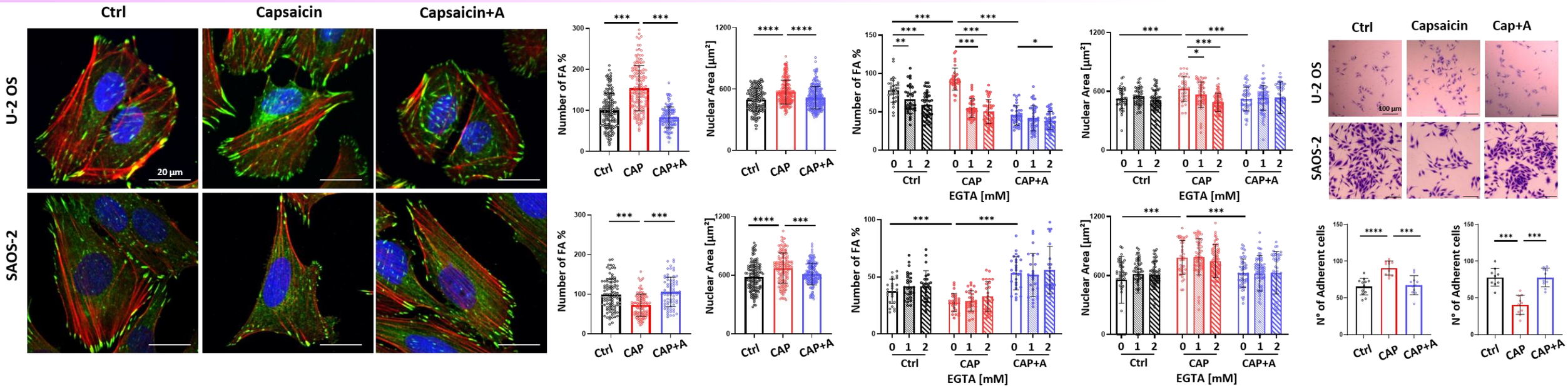
Perinuclear Actin and Nesprin-2G Organization

OBJECTIVE

This study investigates the **molecular pathways** downstream of TRPV1 activation that drive **cytoskeletal** and **nuclear remodeling**. Elucidating this novel mechanotransduction axis is crucial for identifying innovative **therapeutic targets** to halt osteosarcoma progression and metastasis.

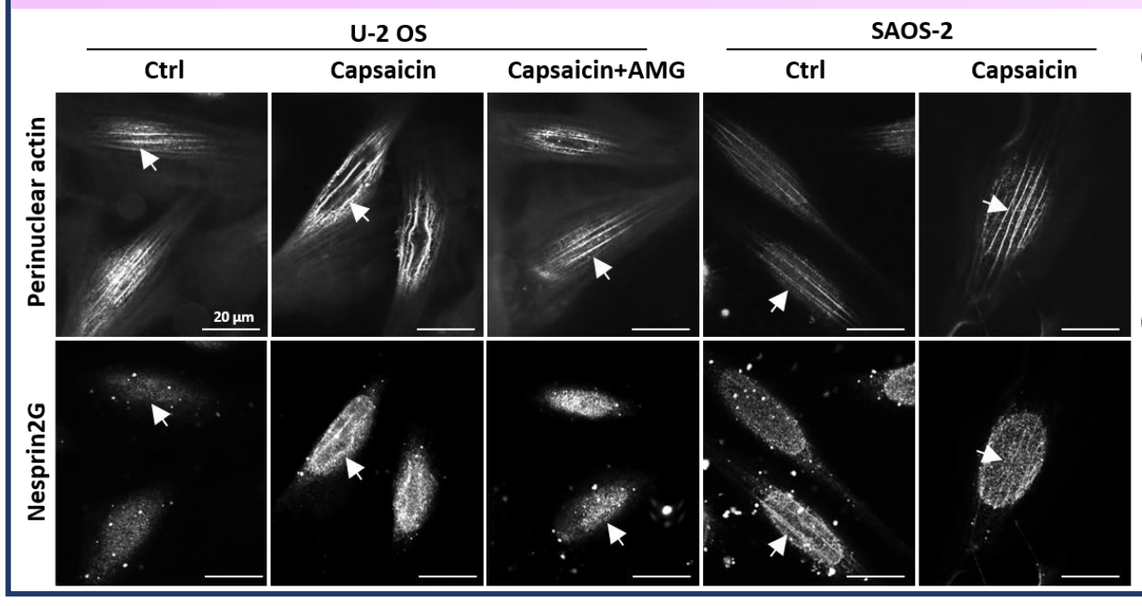
RESULTS

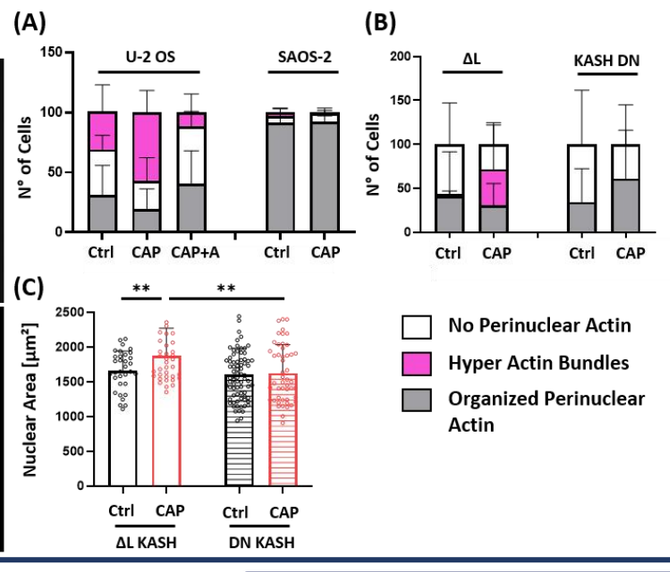
TRPV1 Activation Alters Focal Adhesions and Nuclear Area via Ca2+ influx



Left: Capsaicin-induced TRPV1 activation modulates **Focal Adhesion (FA)** number and **nuclear area**. These effects are abolished by **AMG9810 (A)** and prevented by **EGTA** in U-2 OS, but not in SAOS-2 cells. **Right:** Adhesion assays reveal that these structural changes impair **cell adhesion capability**.

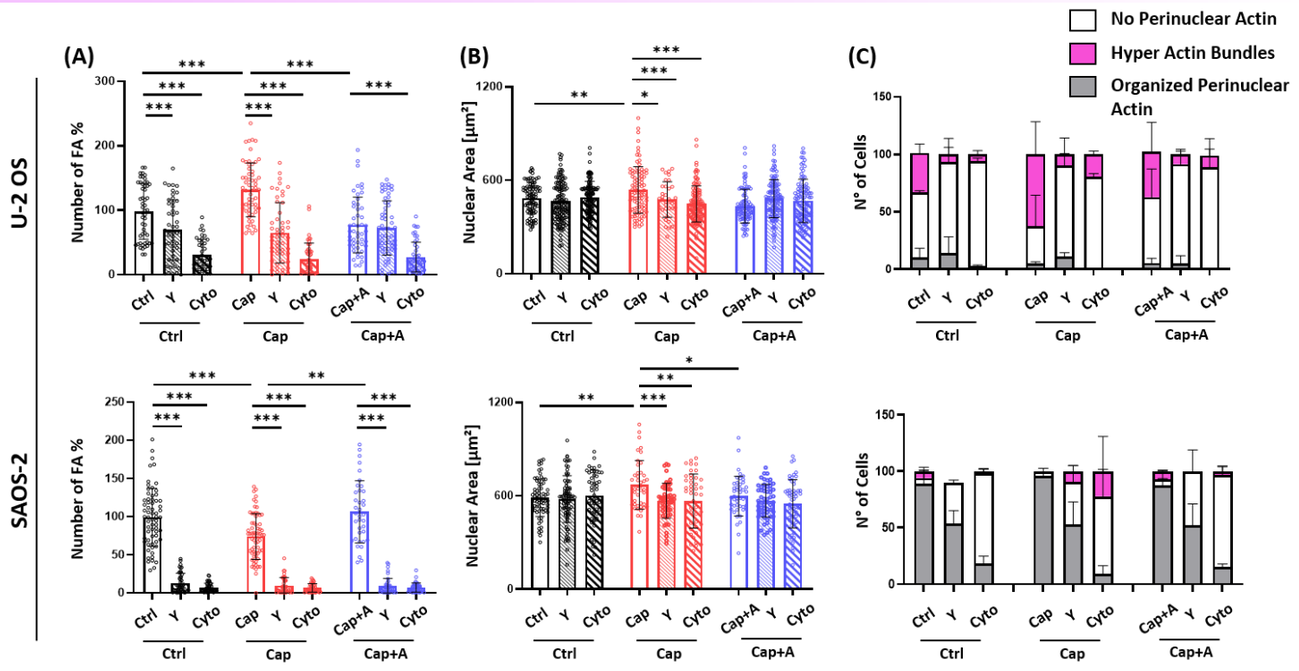
TRPV1-induced Hyper-actin bundles formation in aggressive U-2 OS cells through LINC-mediated nuclear–cytoskeletal coupling





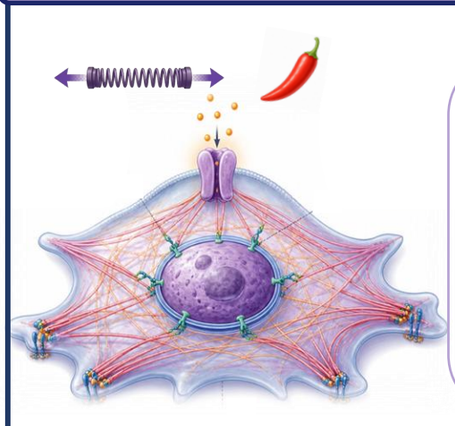
TRPV1 activation induces a reorganization of perinuclear actin structures exclusively in **U-2 OS** cells, promoting the formation of **hyper-actin bundles** and marked spatial remodeling of **Nesprin-2 Giant** (N2G) ***(A).*** Functional disruption of the LINC complex via **KASH dominant-negative domains (DN KASH)** prevents both these structural rearrangements (***B***) and abolishes the TRPV1-induced nuclear enlargement ***(C).***

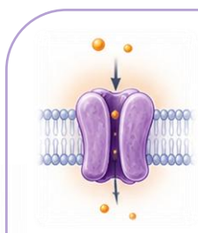
RhoA/ROCK Pathway is Required for TRPV1-Induced Remodeling



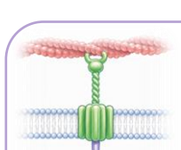
Pharmacological inhibition of the RhoA/ROCK pathway via **Y-27632 (Y)** or actin disruption via **Cytochalasin D (Cyto)** abolishes the effect induced by TRPV1 activation. Both treatments restore **focal adhesion number *(A),* nuclear enlargement *(B)*** and reverse **actin organization *(C)*** in both cell lines.

CONCLUSION





TRPV1 activation **triggers** a previously unrecognized **mechanotransduction pathway in osteosarcoma,** linking extracellular cues to cytoskeletal and nuclear remodeling.



The formation of **hyper-actin bundles** and nuclear enlargement requires **Ca^{2+}- dependent** signaling, **LINC-mediated** nuclear coupling and **RhoA/ROCK**-driven tension.

These responses are selectively observed in the **highly aggressive U-2 OS phenotype**, supporting TRPV1 and its downstream effectors as promising therapeutic targets in osteosarcoma.

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