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RESEARCH ARTICLE | CARDIOLOGY

Mechanical load inhibits cancer growth in mouse and human hearts

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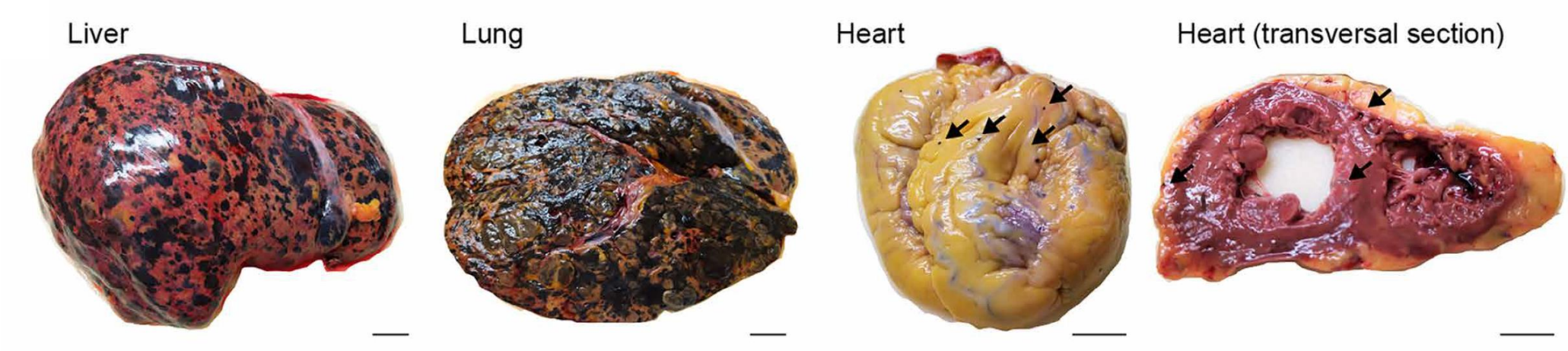
Career History

Since January 2015, Group Leader, Cardiovascular Biology Laboratory, International Centre for Genetic Engineering and Biotechnology, ICGEB, Trieste, Italy
2007-2014, Staff Scientist, Molecular Medicine Laboratory, ICGEB Trieste, Italy.
2006-2007, Postdoctoral Fellow (Marie Curie EIF), Center for Transgene Technology & Gene Therapy, Flanders Interuniversity Institute for Biotechnology (VIB)/KU Leuven, Belgium.
2001-2005, PhD Student at the ISAS/ICGEB Trieste, Italy.
1994-2000, Pre-doctoral student and fellow at ICGEB, Trieste, Italy.

- Cellular and molecular interactions controlling vessel formation and tissue growth in development and disease
- The overall goal of the research activity is to develop novel therapeutic approaches for tissue revascularization and cancer.

Why is the heart rarely affected by cancer?

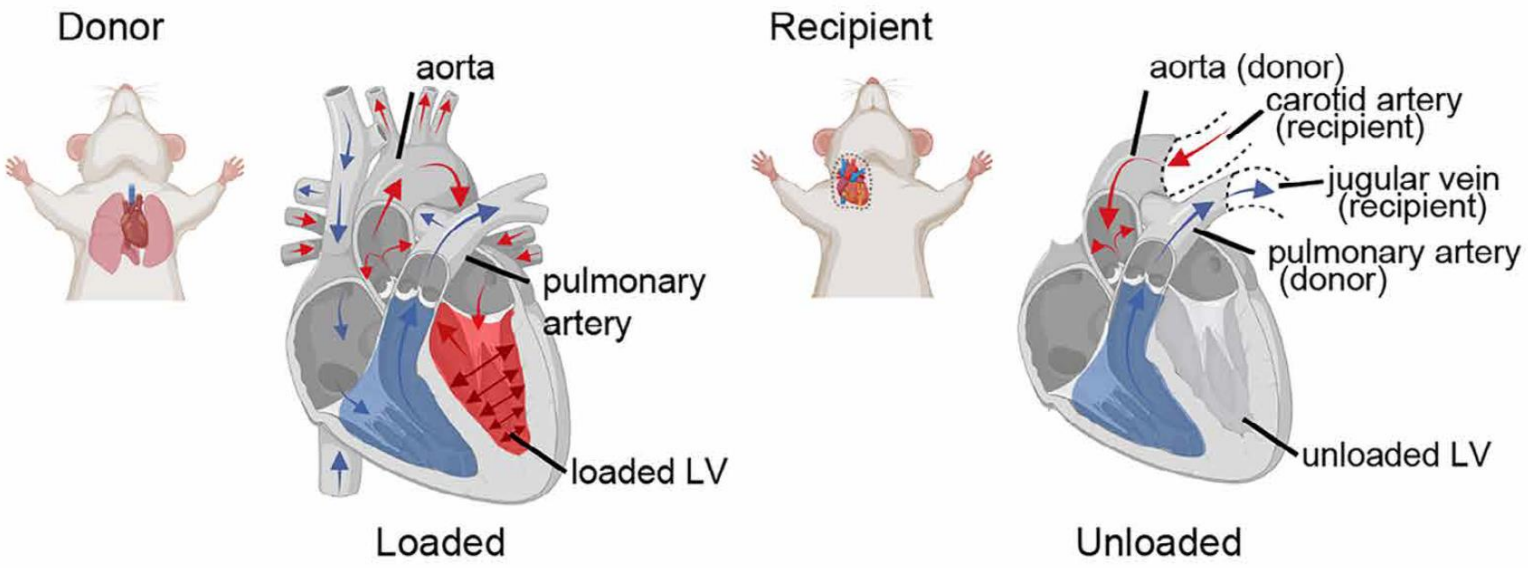
- *The heart contains abundant oxygen whereas cancer cells prefer an environment with low oxygen levels*
- *The blood flow washed away the cancer cells*
- *The expression of genes in the heart has certain characteristics*
- *The heart is beating*



Gross appearance of en bloc resection of liver, lung, and heart from a patient affected by a metastatic uveal melanoma (黑色素瘤)

Known hypothesis: *Mechanical load has been proposed as a major mechanism halting cardiomyocyte proliferation early after birth, thus limiting the regenerative potential of the adult mammalian heart*

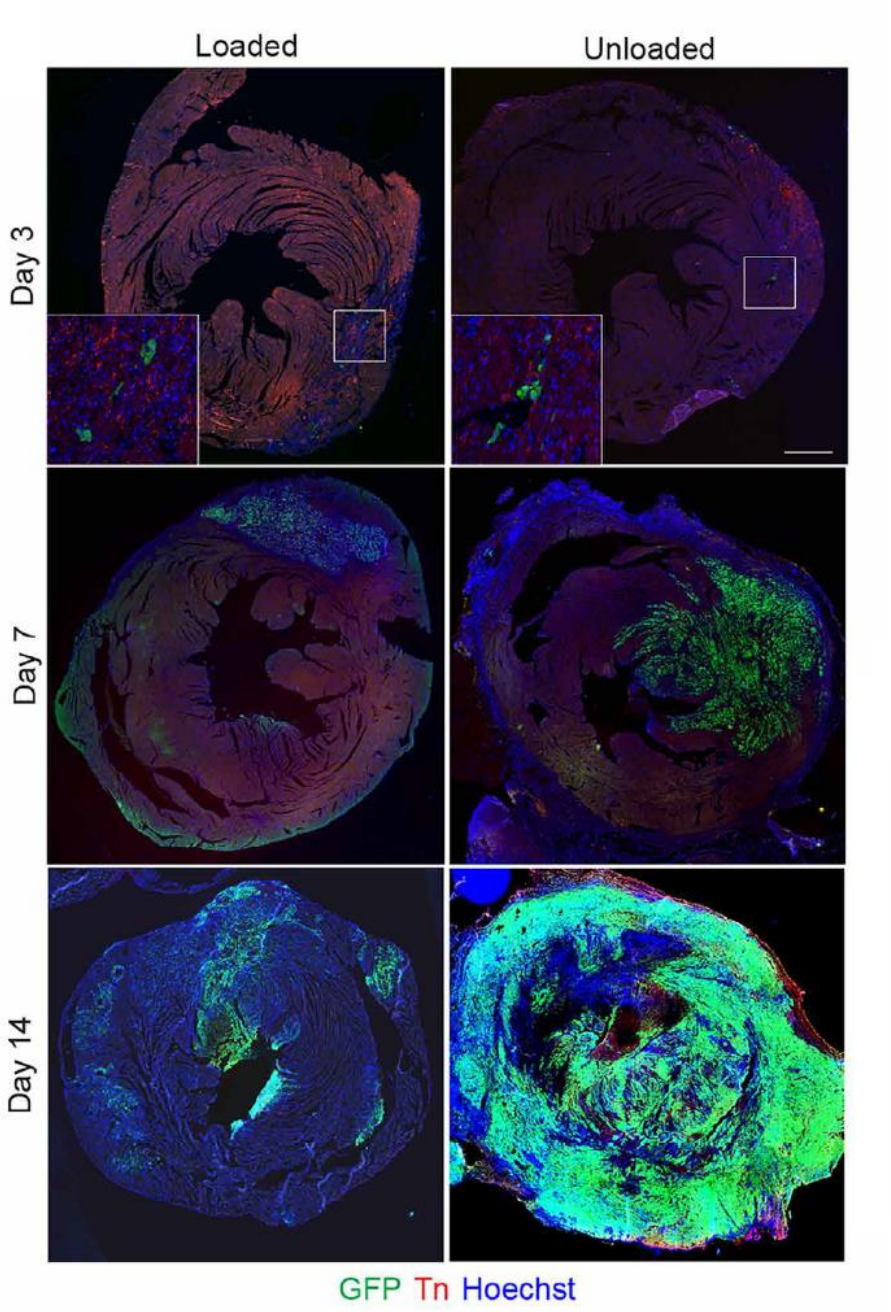
Author hypothesis: *Mechanical load could similarly hamper the proliferation of cancer cells in the heart*



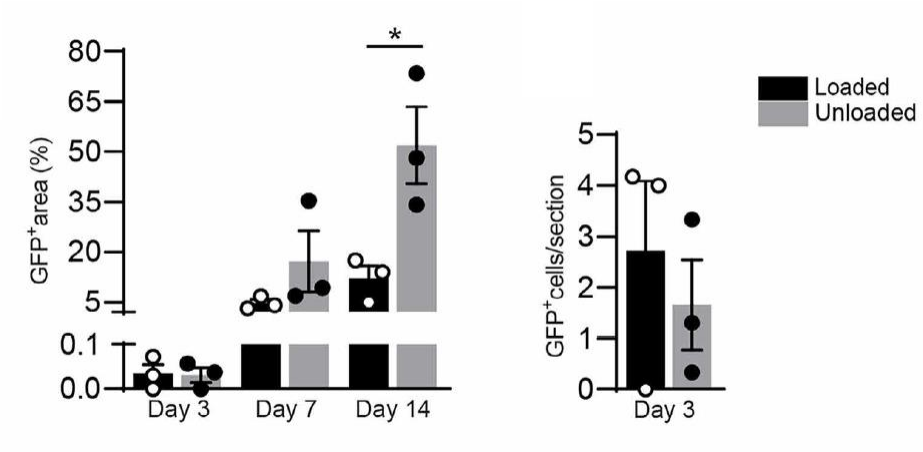
the aorta (主动脉) → carotid artery (颈动脉)
the pulmonary artery (肺动脉)→ external jugular vein (颈外静脉)

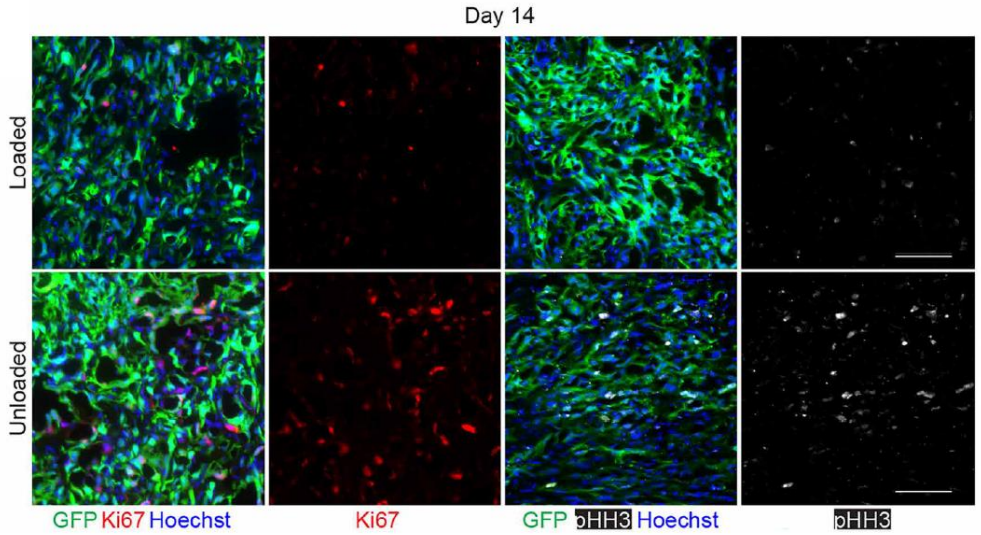
thereby restoring perfusion in the absence of mechanical load within the left ventricle (LV, 左心室)

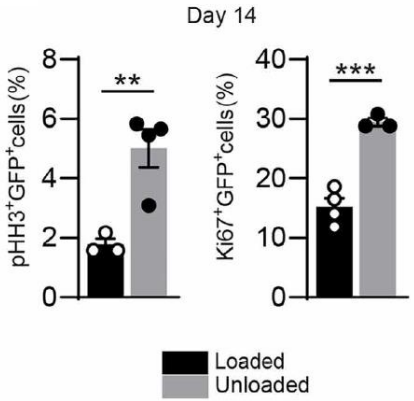
The authors injected 1×10^5 lung adenocarcinoma LG1233 cancer cells stably expressing green fluorescent protein (GFP) intramyocardially into the LV of both loaded and unloaded hearts.



lung cancer cells form larger tumors in unloaded hearts than in control (loaded) hearts and that this is due to increased cell proliferation in unloaded conditions.

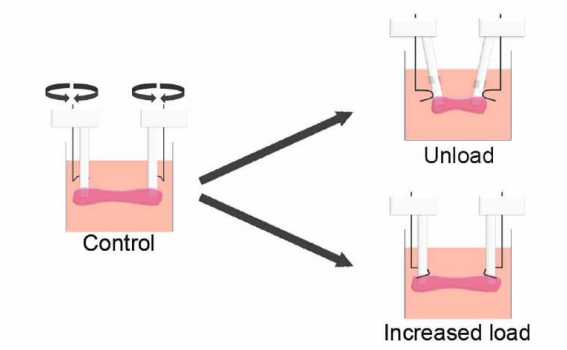


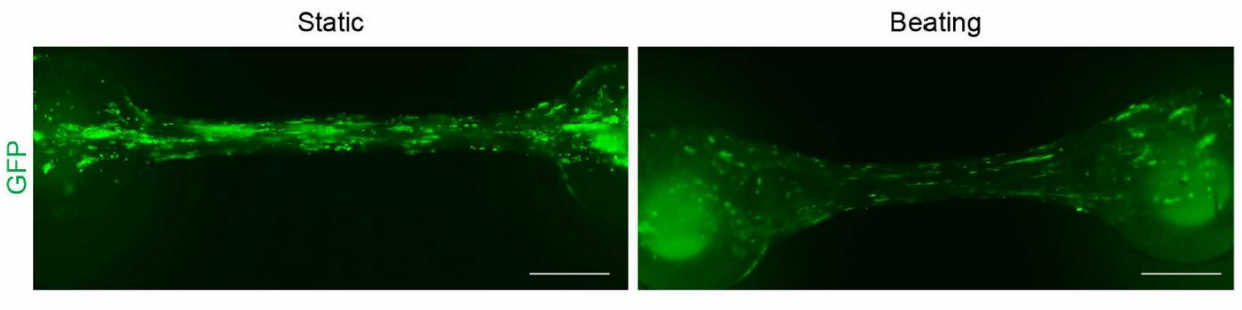


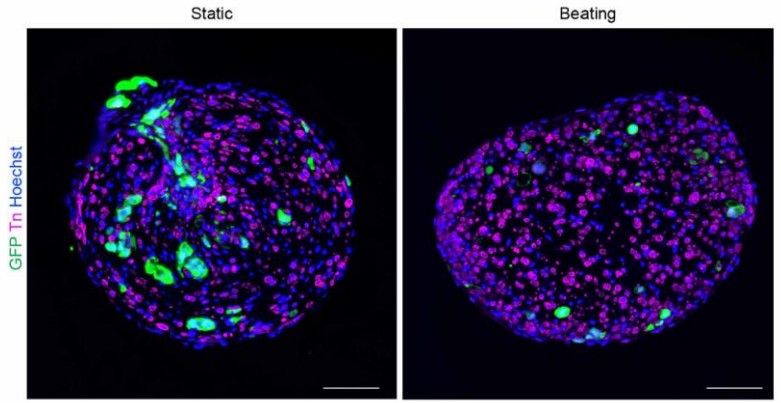


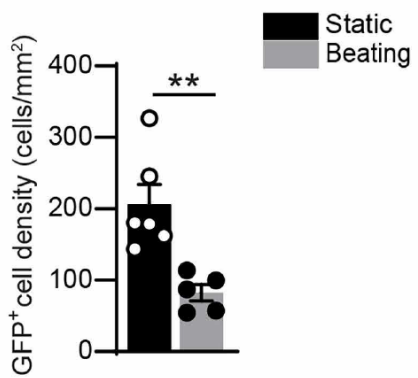
Ki67+, pHH3+: cell proliferative markers

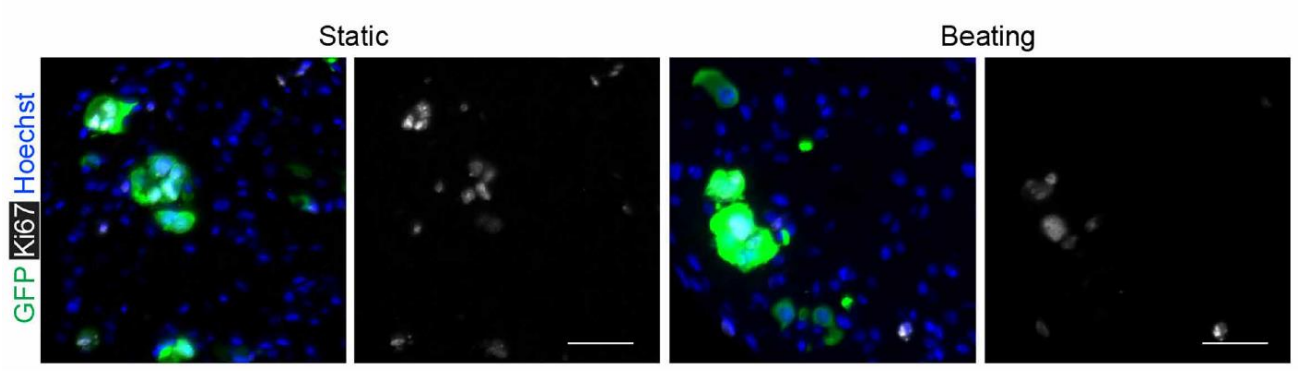
Load modulation in EHTs reproduces the effect of cardiac unloading in vivo and that modulation of mechanical load has comparable effects on the proliferation of cardiac and cancer cells both in vivo and in EHTs

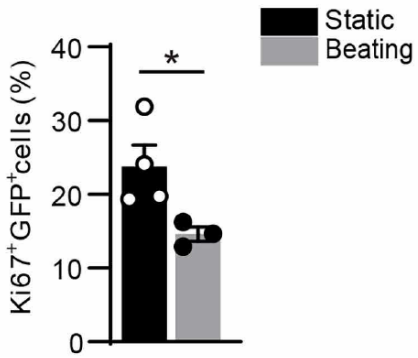




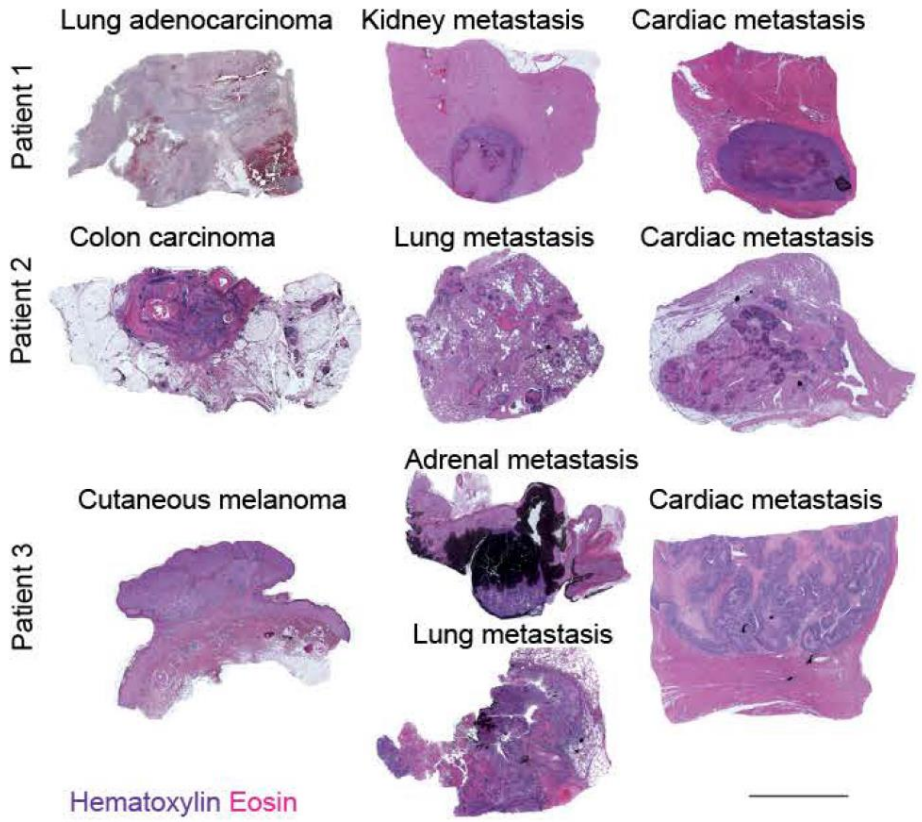




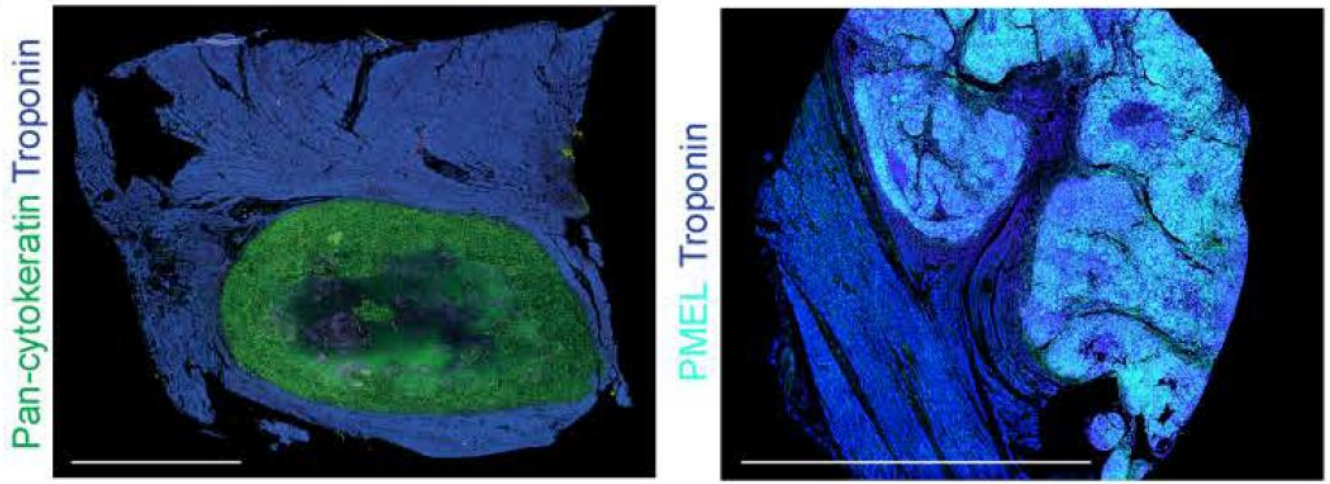




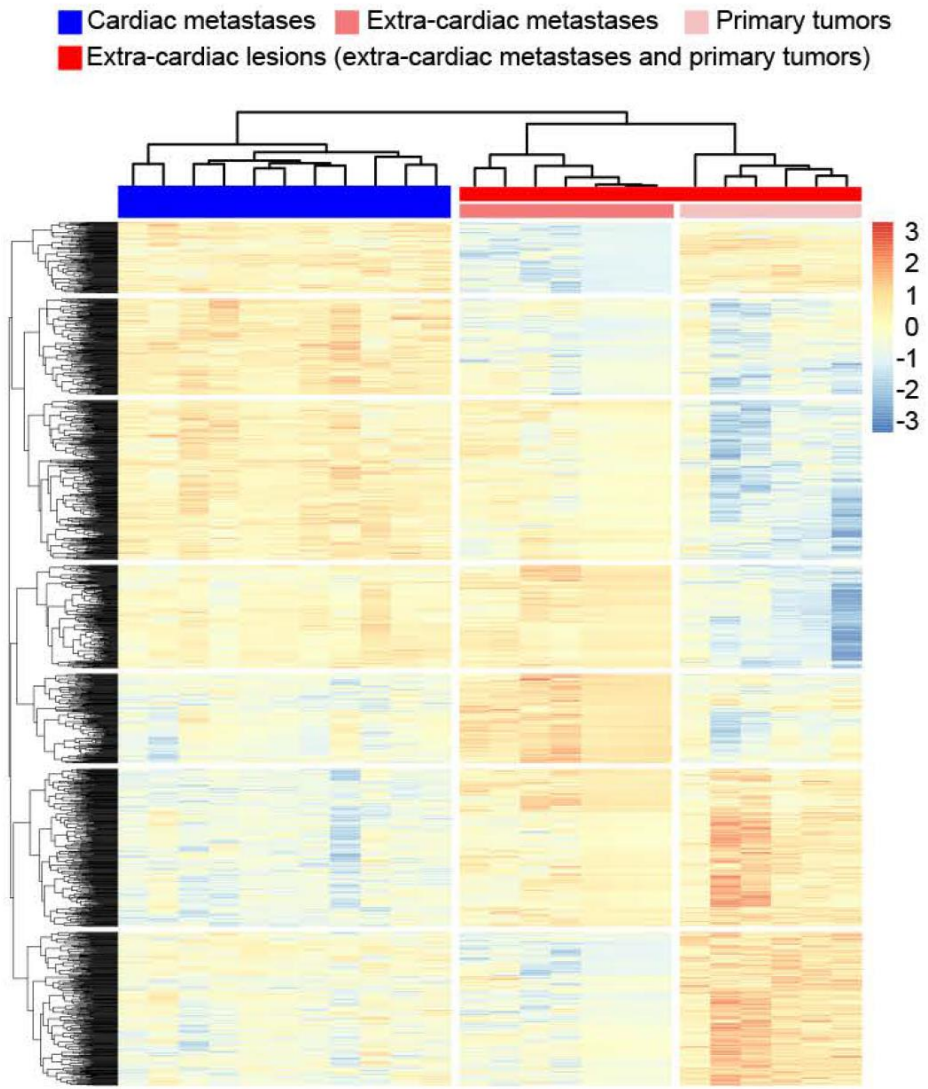
What's the molecular mechanisms of cancer cells sense mechanical stimuli in the beating heart and translate them into inhibition of cell proliferation?



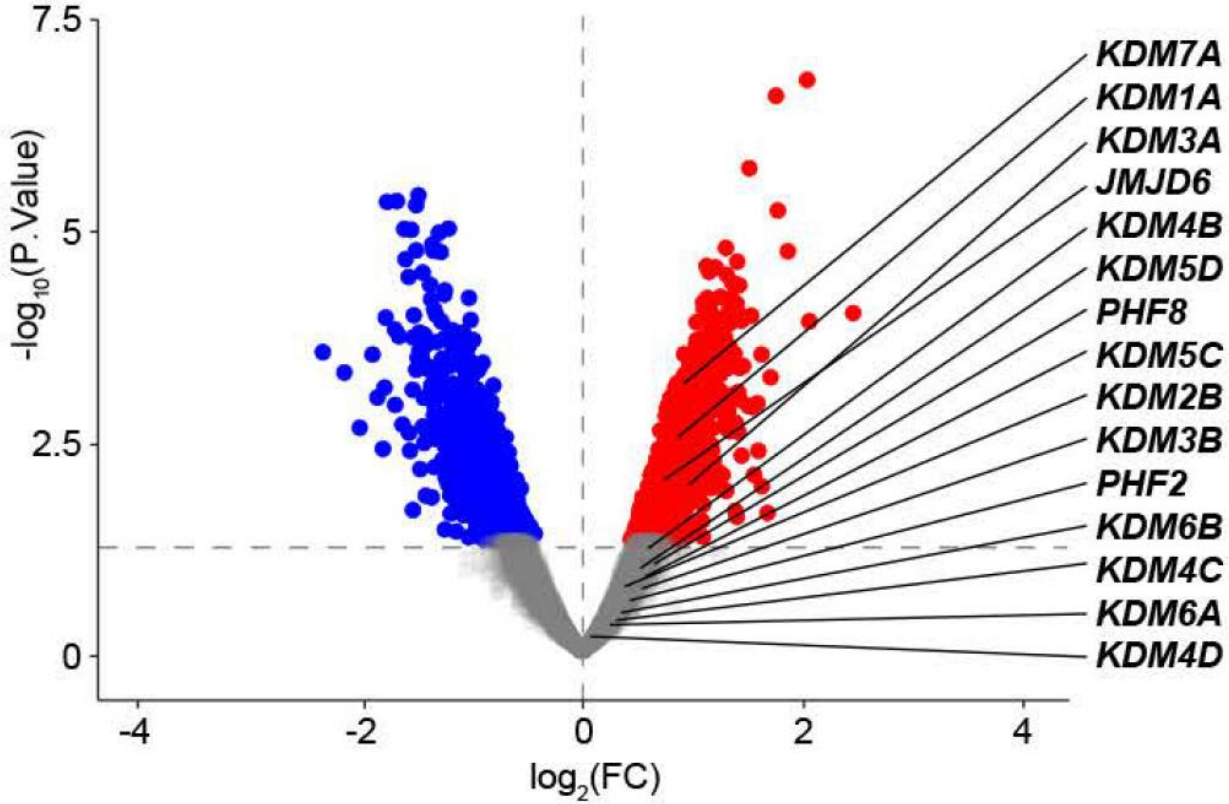
Spatial transcriptomics using the GeoMX technology, which allows profiling the transcriptome of specific cell types by capturing cells identified by specific markers



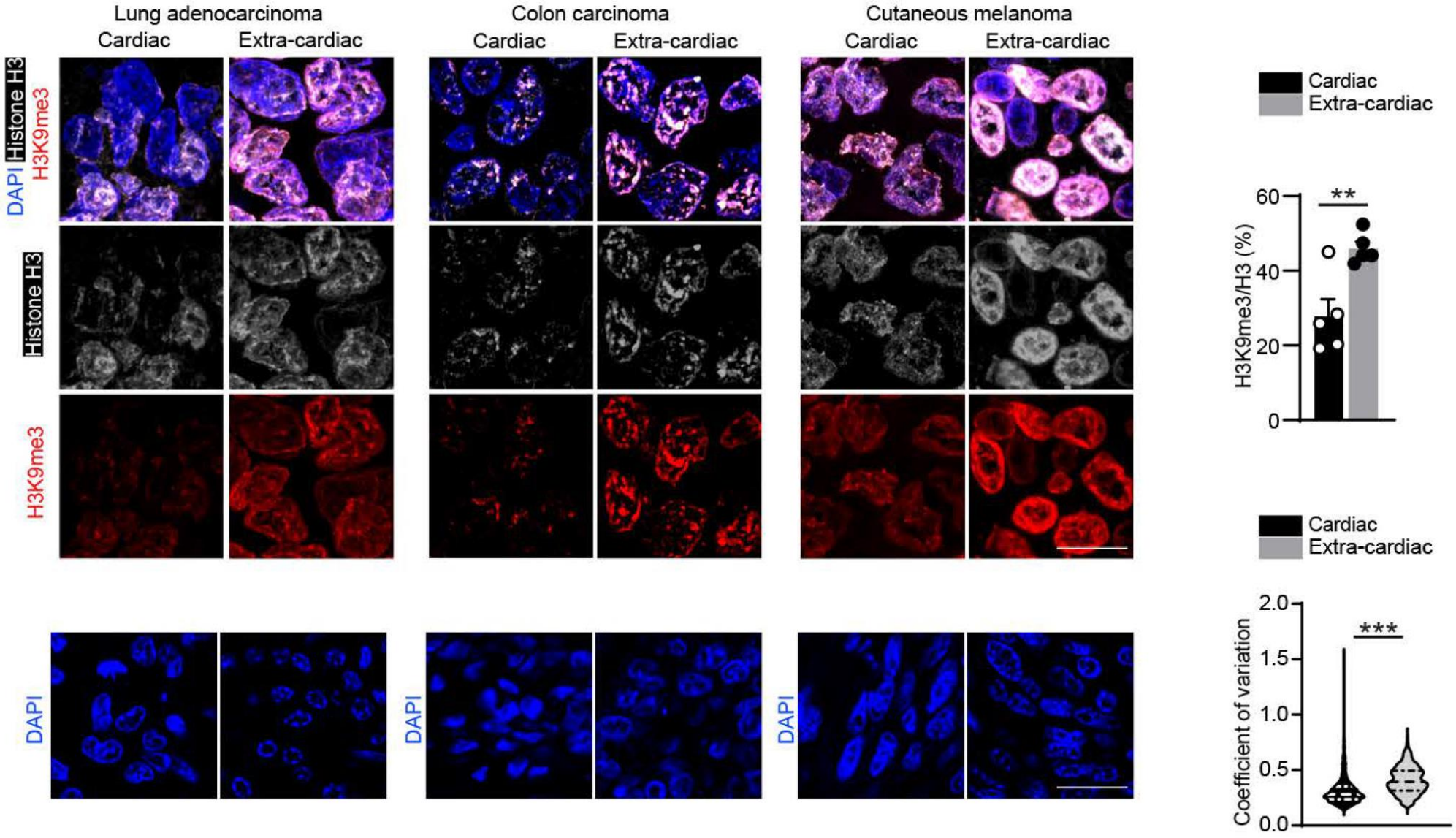
Cardiac metastases shared a common transcriptional profile independent from the origin of the tumor



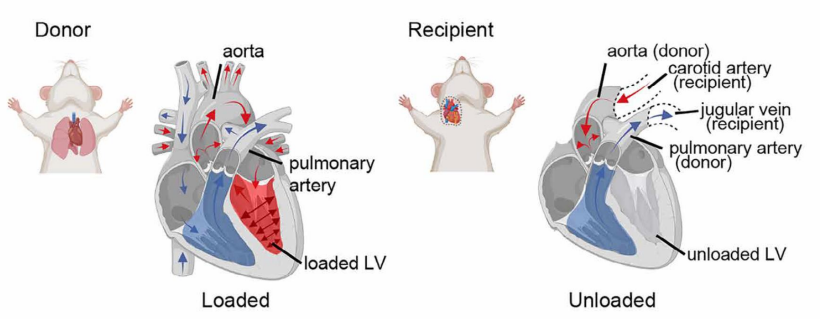
The most enriched pathway in cardiac metastases was "histone demethylation", and most histone demethylases were particularly up-regulated



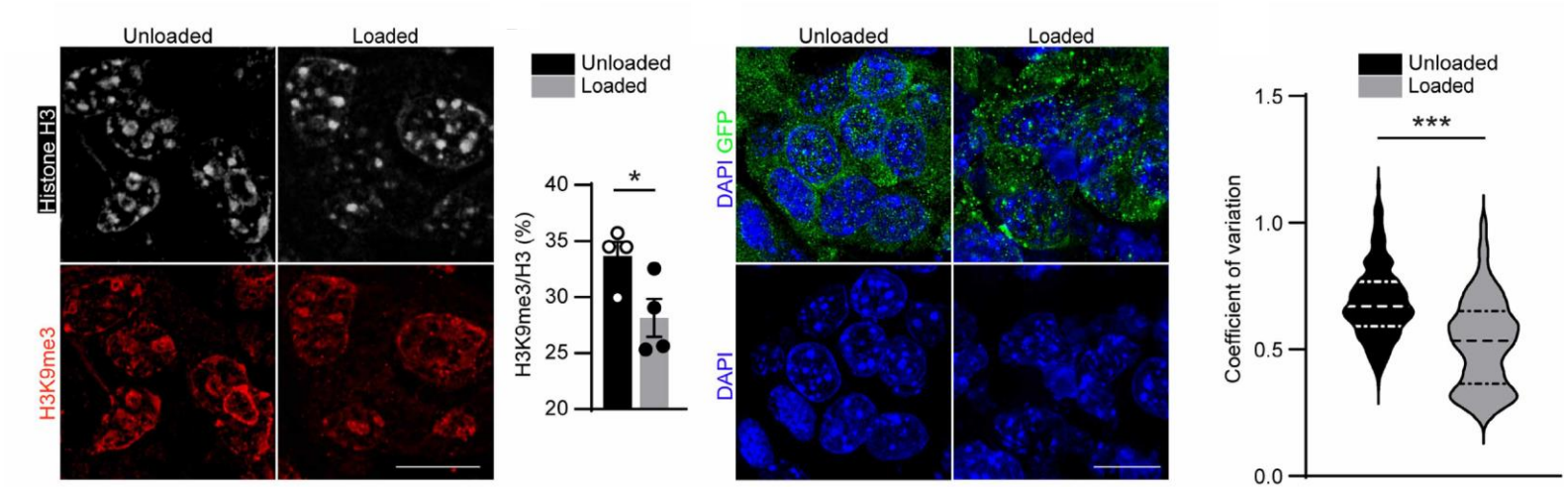
The levels of histone 3 lysine 9 trimethylation (H3K9me3) were lower in the nuclei of cardiac metastases compared with those detected in primary tumors and extracardiac metastases

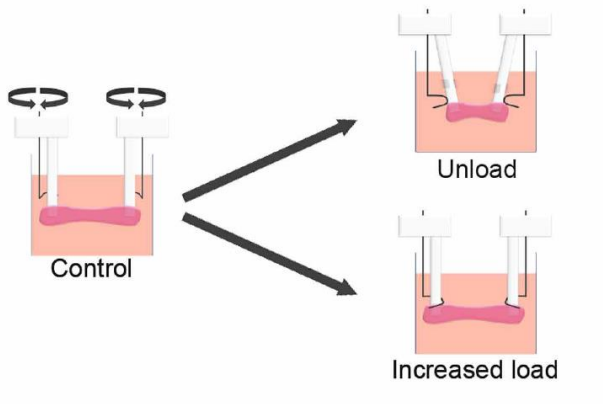


Mechanical load reduces chromatin compaction and H3K9me, with relevant modification in chromatin accessibility in genomic regions that control cancer cell proliferation both in vivo and in vitro (EHTs)

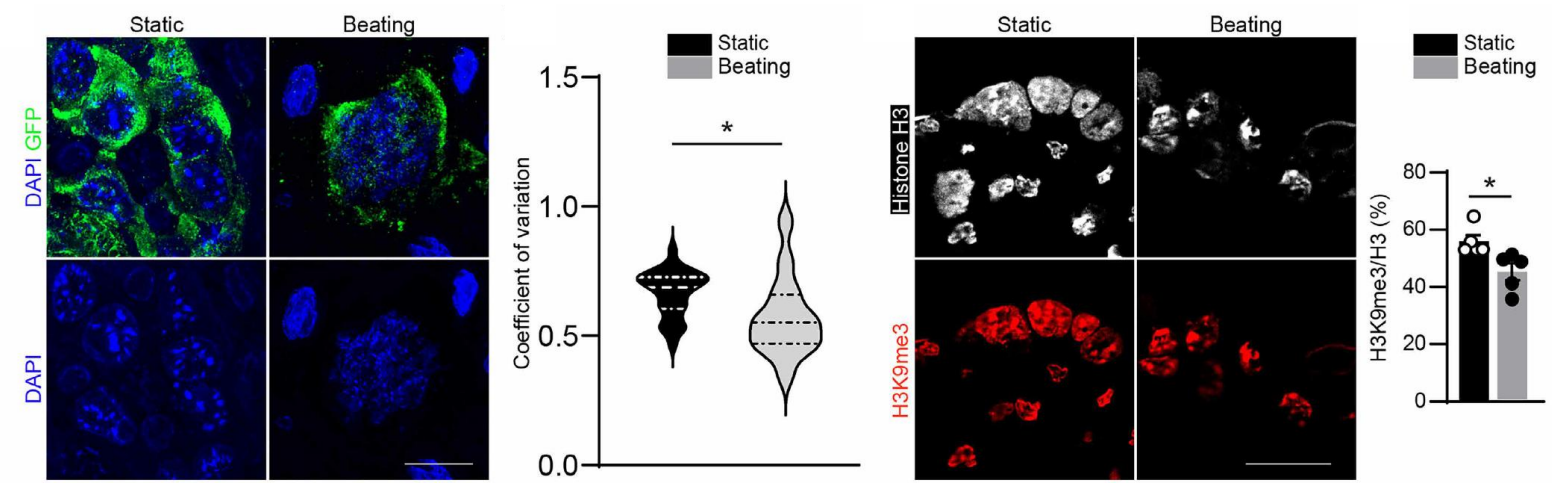


in vivo

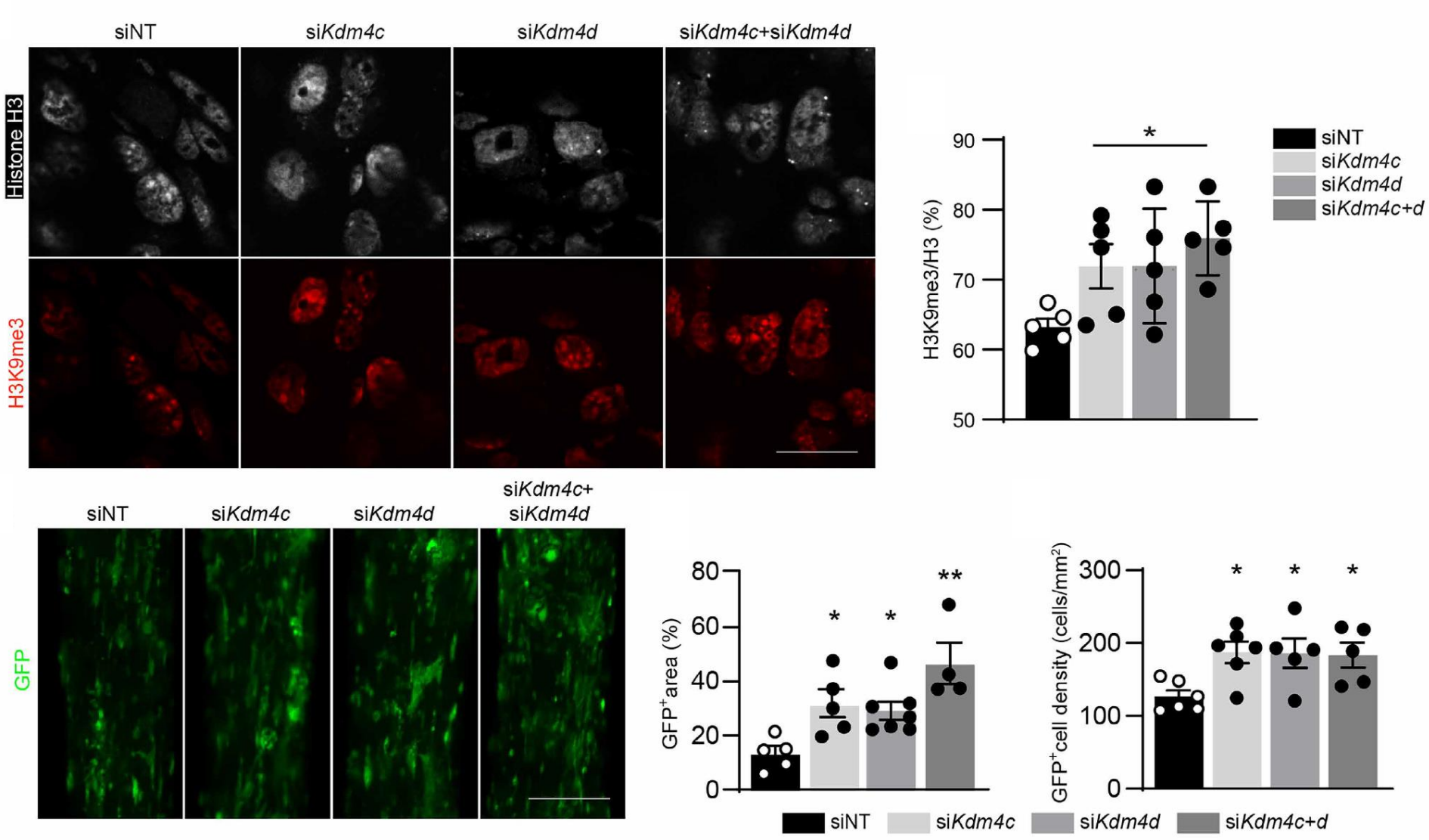




EHTs

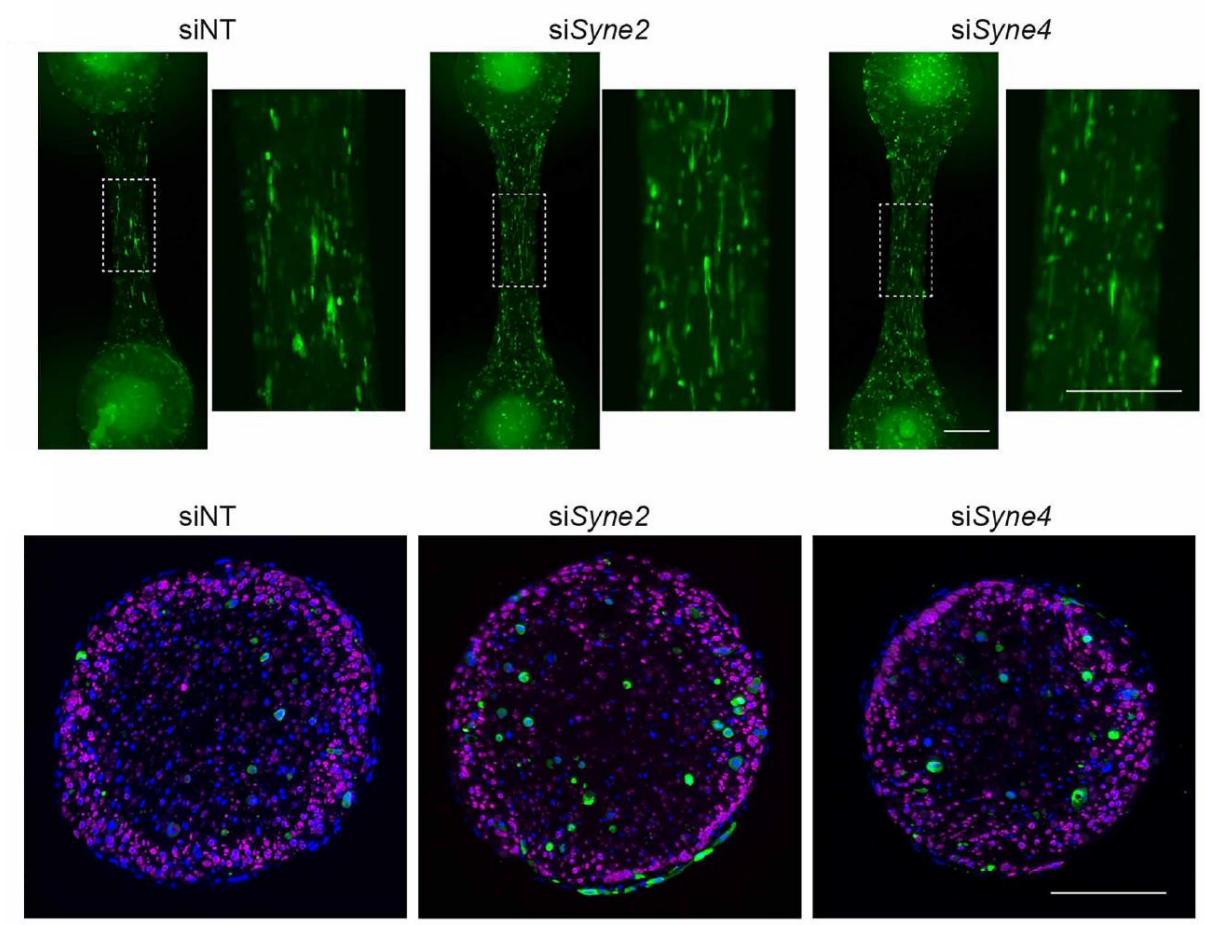


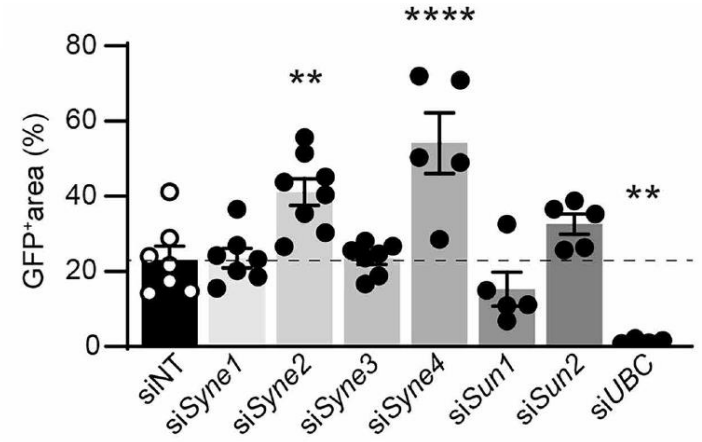
Silencing of both KDM4C and KDM4D as well as their combination in LG1233 cells in EHTs, resulted in increased H3K9me3. This increase was in turn associated with larger areas occupied by cancer cells as well as higher LG1233 cell density in beating EHTs

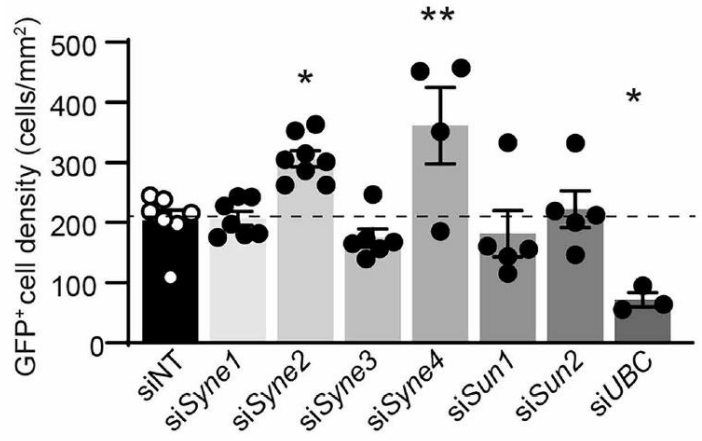


Mechanical load reduces chromatin compaction and H3K9me, but by which mechanical forces affect chromatin accessibility?

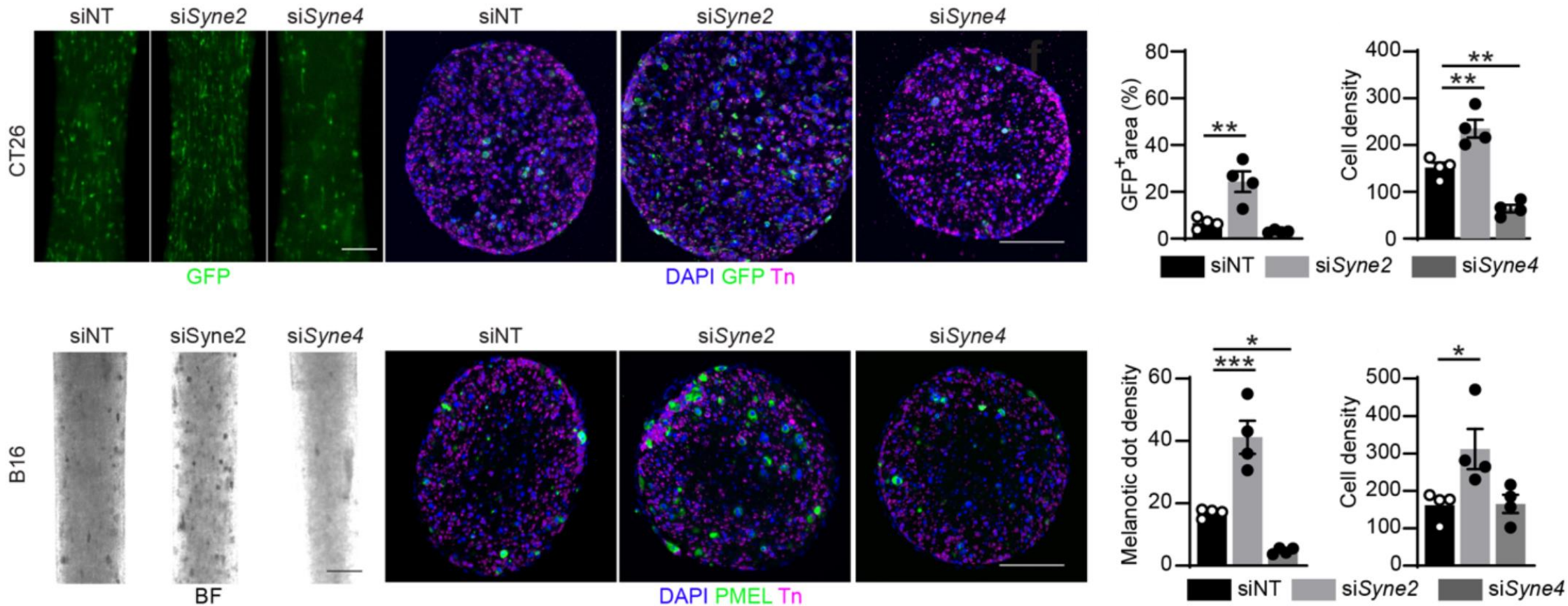
A key mechanotransducer, which translates extracellular stimuli into nuclear responses, is the linker of nucleoskeleton and cytoskeleton (LINC) complex, composed of nesprin (Syne1, Syne2, Syne3, and Syne4) and sun proteins (Sun1 and Sun2) in the outer and inner membrane, respectively







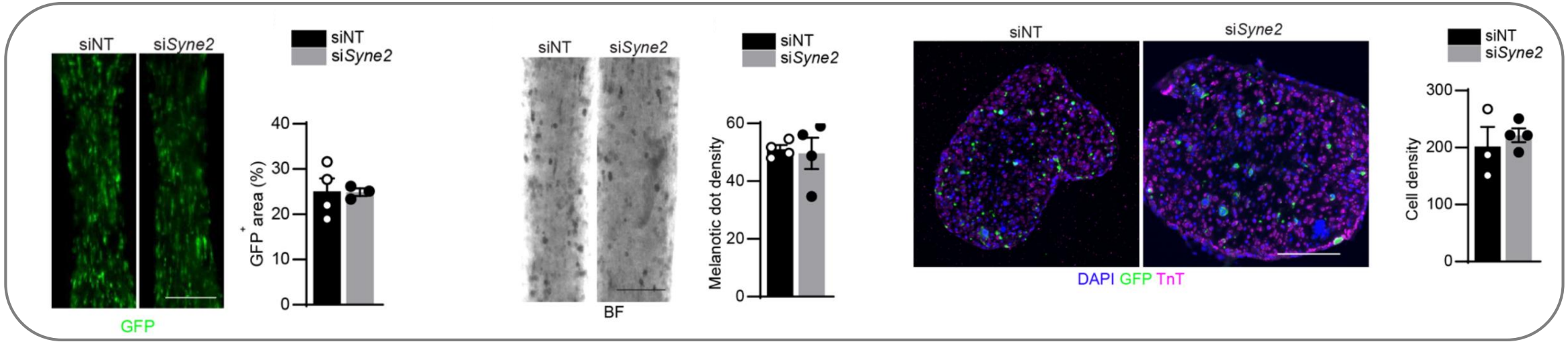
Silencing of Nesprin-2 resulted in increased area occupied by cancer cells and cell density within EHT cross-sections for both CT26 cells and B16-F10 cells, pointing to Nesprin-2(Syne2) as a key mechanotransducer in controlling the proliferation of multiple cancer cell types in beating cardiac tissues.



CT26: colon cancer cells
B16-F10: melanoma cells

No beating, no phenotype

Static conditions

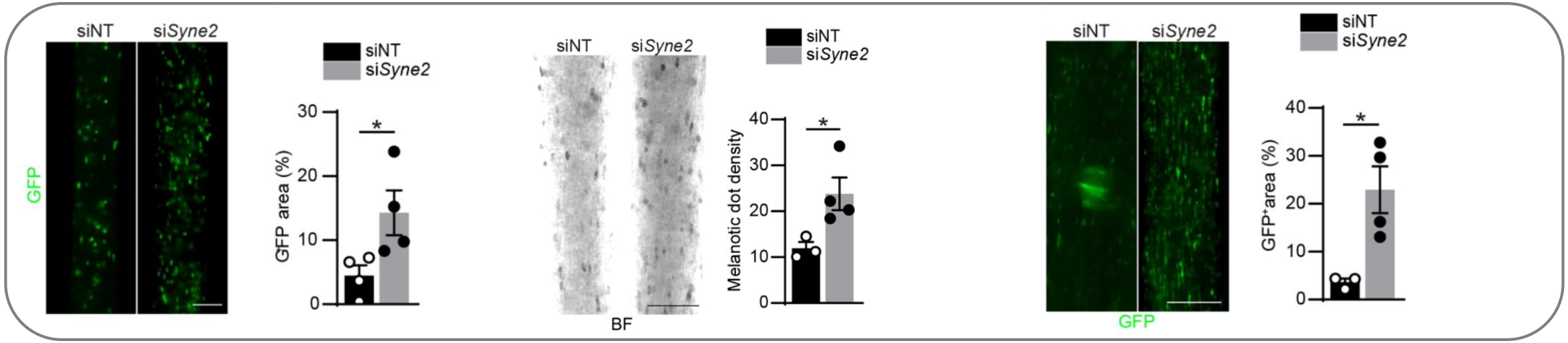


LG1233 GFP+ cancer cells

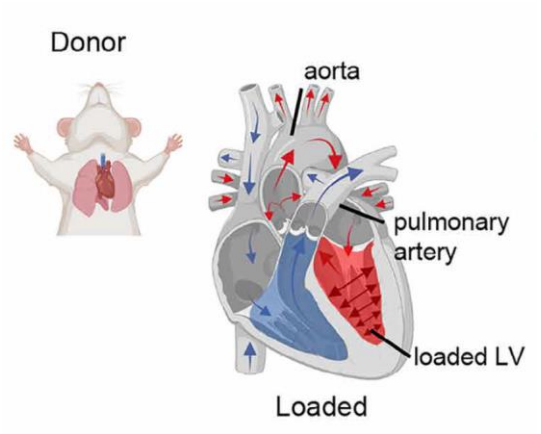
B16-F10 melanoma cells in

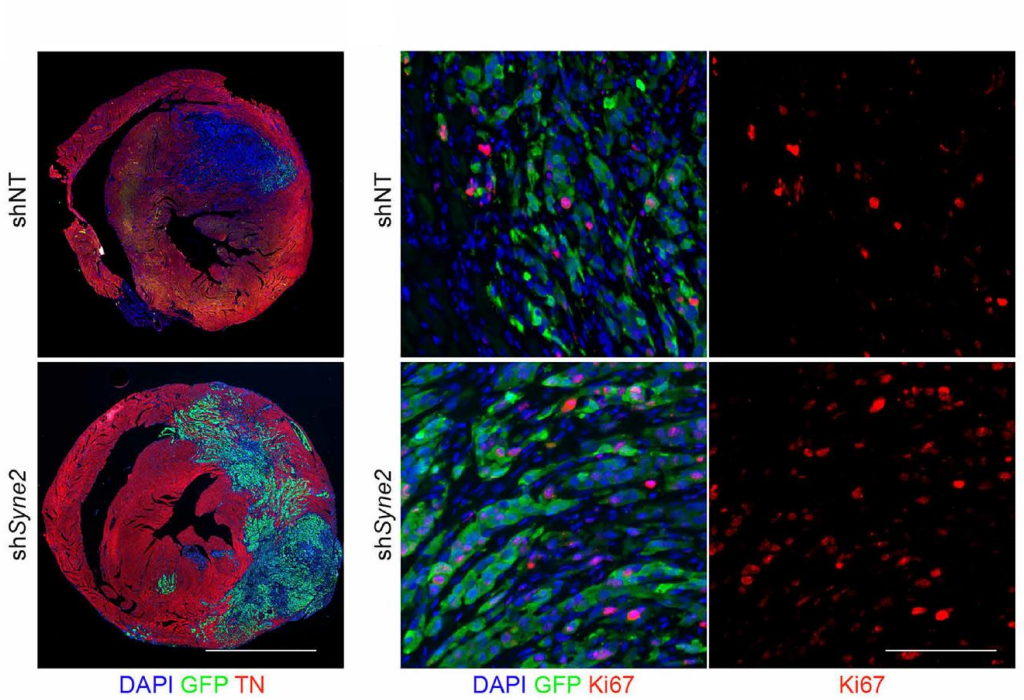
CT26: colon cancer cells

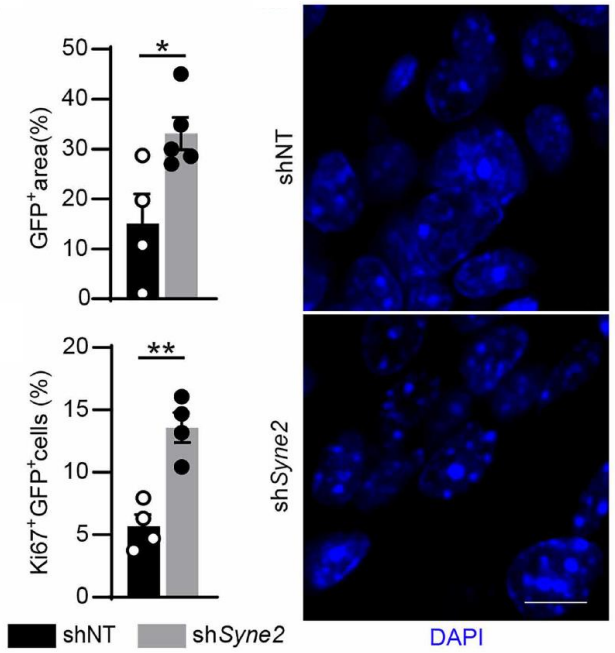
Beating conditions

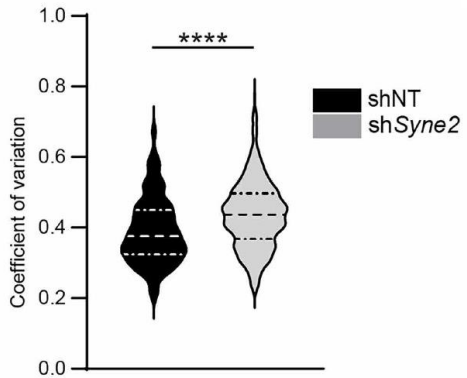


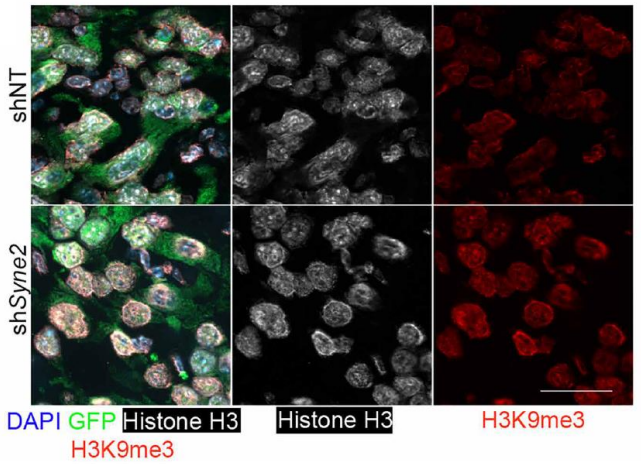
Nesprin-2 is a key mediator in this mechanotransduction process that inhibits cancer cell growth in the heart by in vivo validation

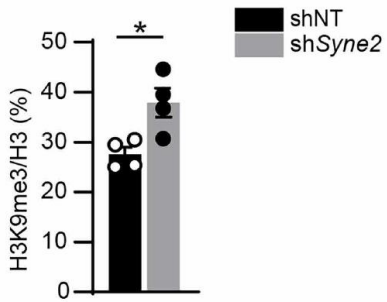




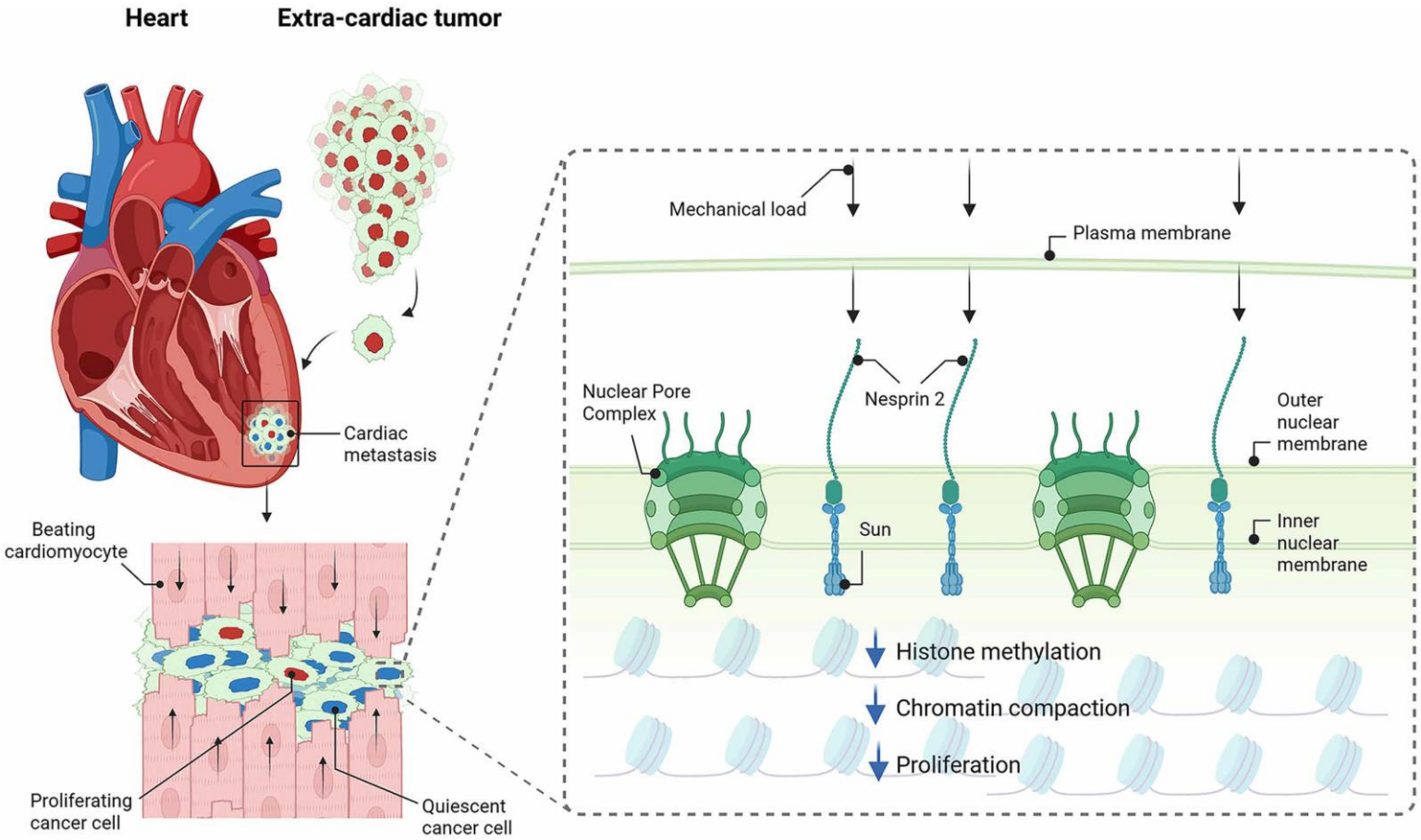








Take home message



- ***Loaded hearts can reduce cancers cells proliferation by in vivo and in vitro (EHTs model)***
- ***Mechanical load reduces chromatin compaction and H3K9me***
- ***Increased H3K9me3 in mechanical loaded condition showed larger areas of cancer cells***
- ***Nesprin-2 is a key mediator in this mechanotransduction process that inhibits cancer cell growth in the heart by in vivo and in vitro validation***

Limitation: The relationship between Nesprin-2 and H3K9me3 is weak