ST. ANNE'S UNIVERSITY HOSPITAL BRNO / INTERNATIONAL CLINICAL RESEARCH CENTER

Mechanobiology of Disease Group

The effect of biomechanical stress on RBM20-induced dilated cardiomyopathy

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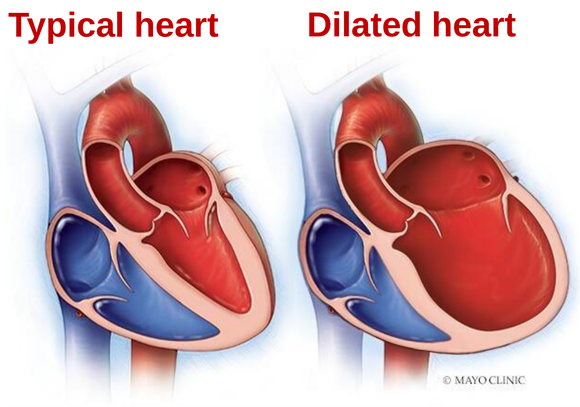
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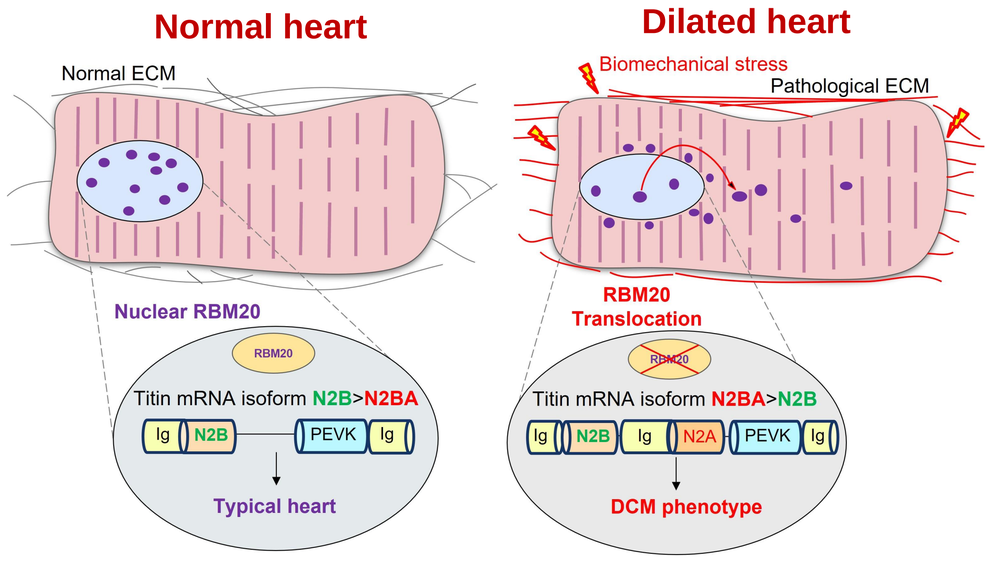
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Background

Dilated cardiomyopathy (DCM) is the most prevalent non-ischemic cause of heart failure, affecting roughly 1 in 250 individuals[1]. Specifically, the mutations in splicing regulator RNA-binding motif 20 (RBM20) are known to cause an aggressive form of DCM. RBM20 mutants directly impact the splicing of the giant sarcomeric protein titin, leading to the expression of the more fetal isoform (N2BA) of titin, which is one of the main contributors of the disease progression[2]. One of the key hallmarks of DCM is the pathological remodeling of extracellular matrix (ECM) components, leading to myocardial fibrosis[3]. We use an human induced pluripotent stem cell line-derived cardiomyocyte (iPSC-CM) model to explain the effect of ECM-associated stress on RBM20 localization and its impact on titin splicing. We believe the outcome will enable mechanotherapy to mitigate DCM.

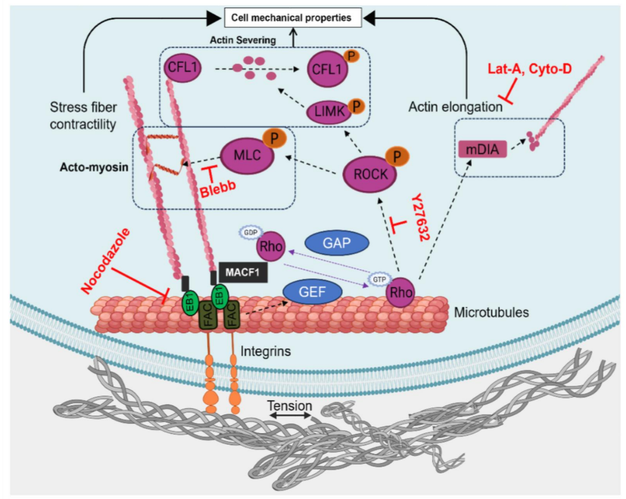


Hypothesis

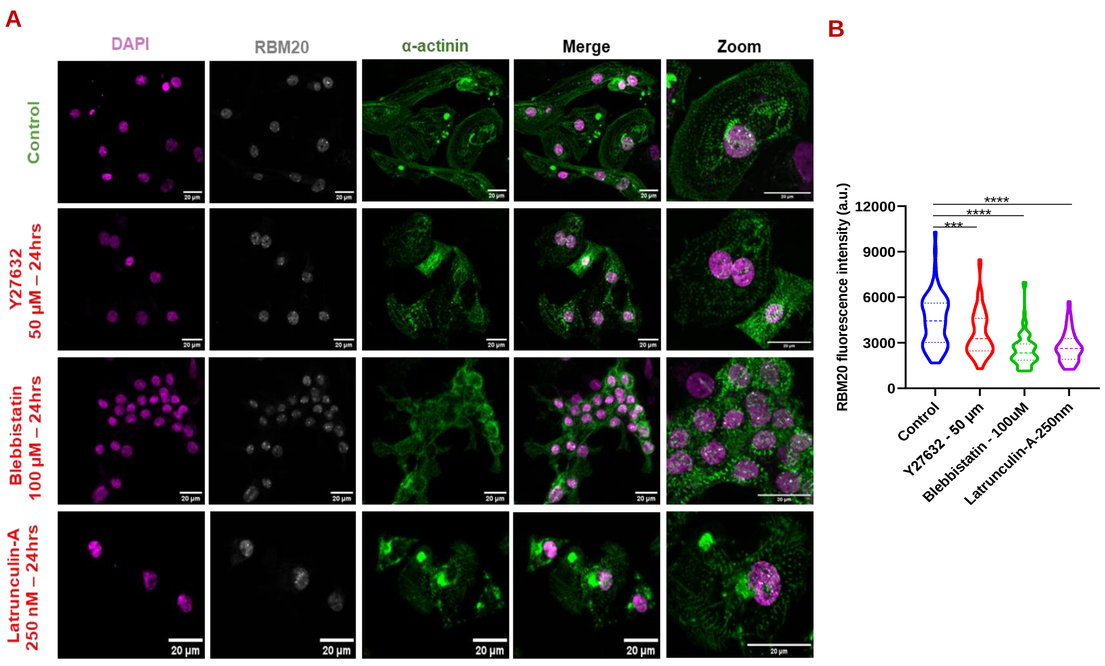


Objectives

- Mechanical perturbation/stimulation of iPSC-CMs to induce RBM20 localization change: i) tension inhibitors exposure, ii) surface micropatterning, iii) stretching (Mechanoculture Fx)
- Evaluate functional changes of RBM20 upon mechanical perturbation in CMs (the abovementioned experimental settings): the titin splicing patterns using RT –qPCR.
- Identification of alternative splicing events induced by mechanical stress using Nanopore sequencing.

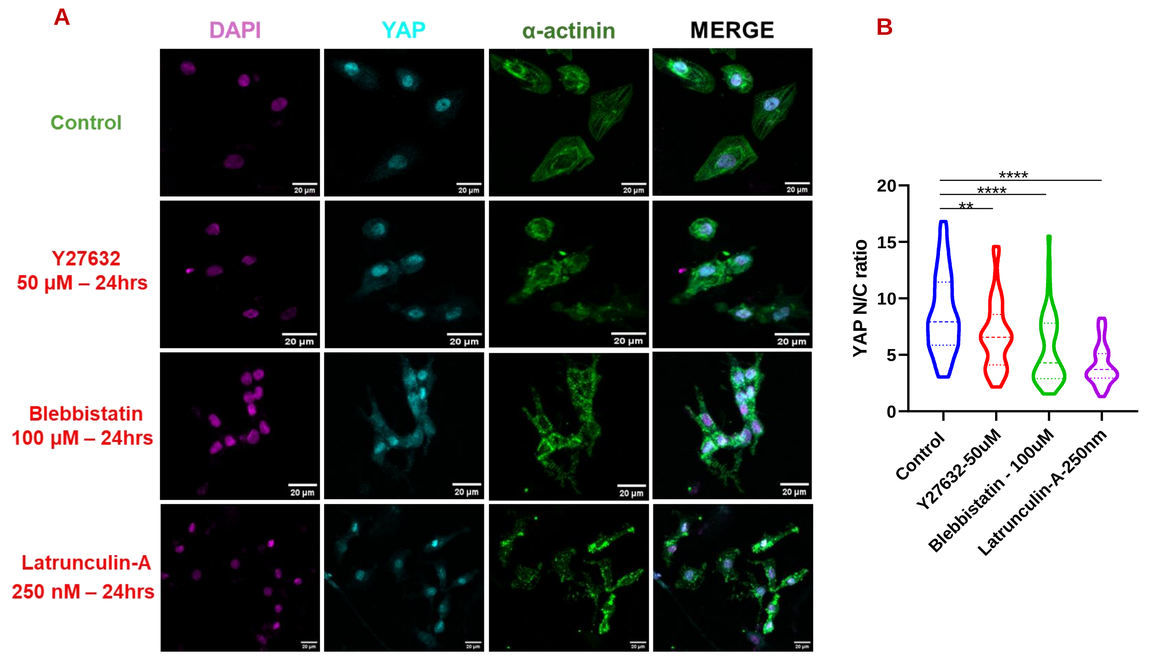


Tension inhibitors decrease RBM20 in iPSC-CMs



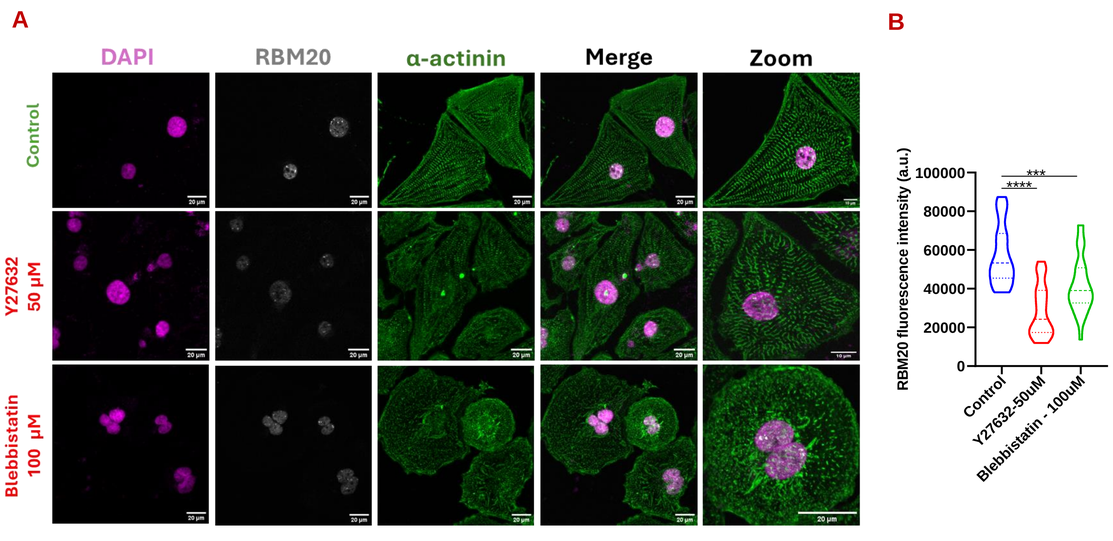
Tension inhibitors reduce RBM20 abundance in the nucleus of human iPSC-CMs – A) Representative confocal microscopy images depicting control and Y27632 (50 µM), Blebbistatin (100 µM) and Latrunculin-A (250nm). B) Corrected integrated density of RBM20 shown as a violin plot. Statistical significance was determined using an unpaired two-tailed Student's t-test.

Tension inhibitors promote YAP shuttling



Tension inhibitors induce nucleocytoplasmic shuttling of YAP – A) Representative confocal microscopy images depicting control and Y27632 (50 µM), Blebbistatin (100 µM) and Latrunculin-A (250nm). B) YAP (nuclear/cytoplasmic) mean intensity shown as a violin plot. Statistical significance was determined using an unpaired two-tailed Student's t-test.

Tension inhibitors decrease RBM20 in ESC-CMs



Tension inhibitors reduce RBM20 abundance in the nucleus of human ESC-CMs – A) Representative confocal microscopy images depicting control and Y27632 (50 µM), Blebbistatin (100 µM). B) Corrected integrated density of RBM20 shown as a violin plot. Statistical significance was determined using an unpaired two-tailed Student's t-test.

References

1. Gigli, M. et al. Nat Rev Cardiol 22, 183–198 (2025). doi:10.1038/s41569-024-01074-2.
2. Guo, W. et al. Nat Med 18, 766–73 (2012). doi:10.1038/nm.2693
3. Louzao-Martinez, L. et al. Int J Cardiol 220, 634–46 (2016). doi:10.1016/j.ijcard.2016.06.253

Acknowledgements

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