MATURATION INDUCED TITIN ISOFORM SWITCHING IN 3D CARDIAC STIFFENING MODEL

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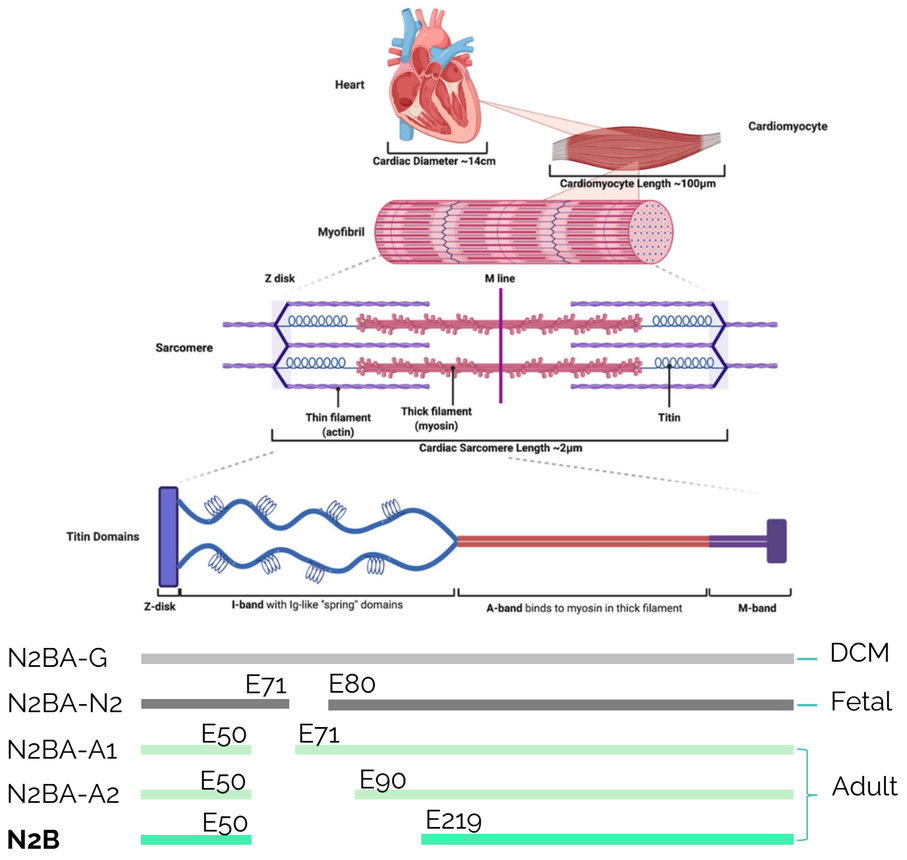
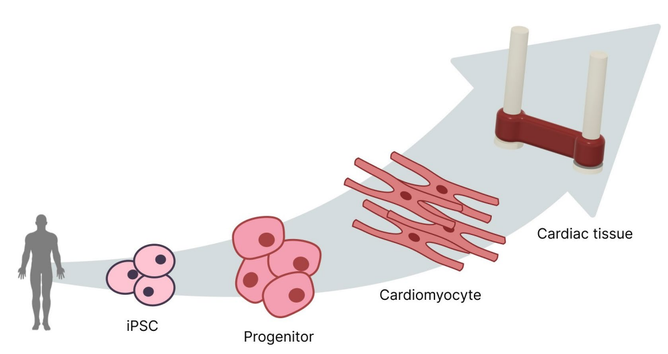
INTRODUCTION

- Heart Failure with preserved Ejection Fraction (HFpEF) is one of the main causes of death worldwide (1)
- There are no disease-modifying therapies for HFpEF as their discovery is being hampered by high clinicial trial failure rates (2)
- Cell maturity is lacking in current, human, in vitro cardiac models
- Cardiac stiffness impairs heart function in HFpEF
- Cardiomyocyte stiffness is regulated by adult titin (TTN) isoforms
- Titin isoforms switch during development and disease (3), with N2B being the most abundant in adult heart



METHODS

- Induced Pluripotent Stem Cell derived-Cardiomyocytes (iPSC-CMs) are cultured in 3D cardiac strips and stimulated with maturation agent (MA) for 10 days
- Contraction and relaxation parameters are recorded and analysed with a customised in-house software
- Resting tension is the force exerted by the tissue at rest, indicative of stiffness



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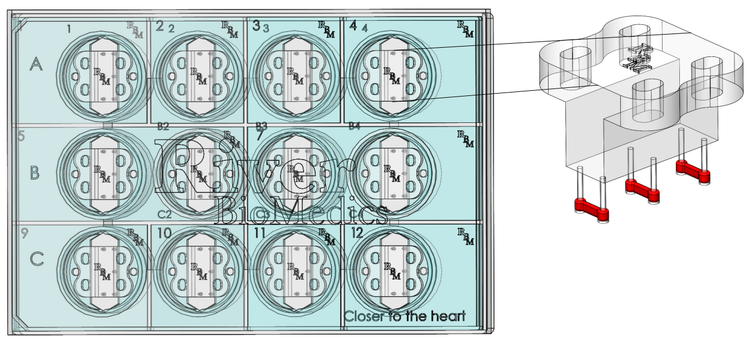
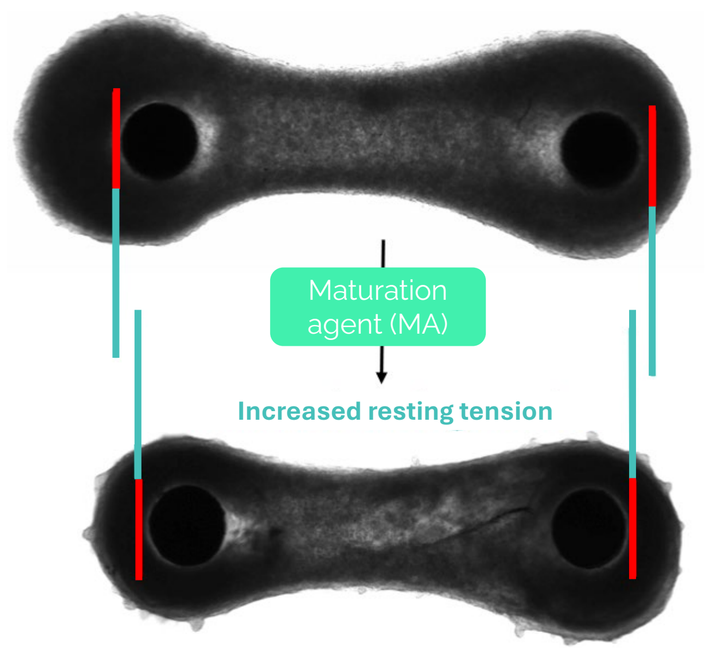
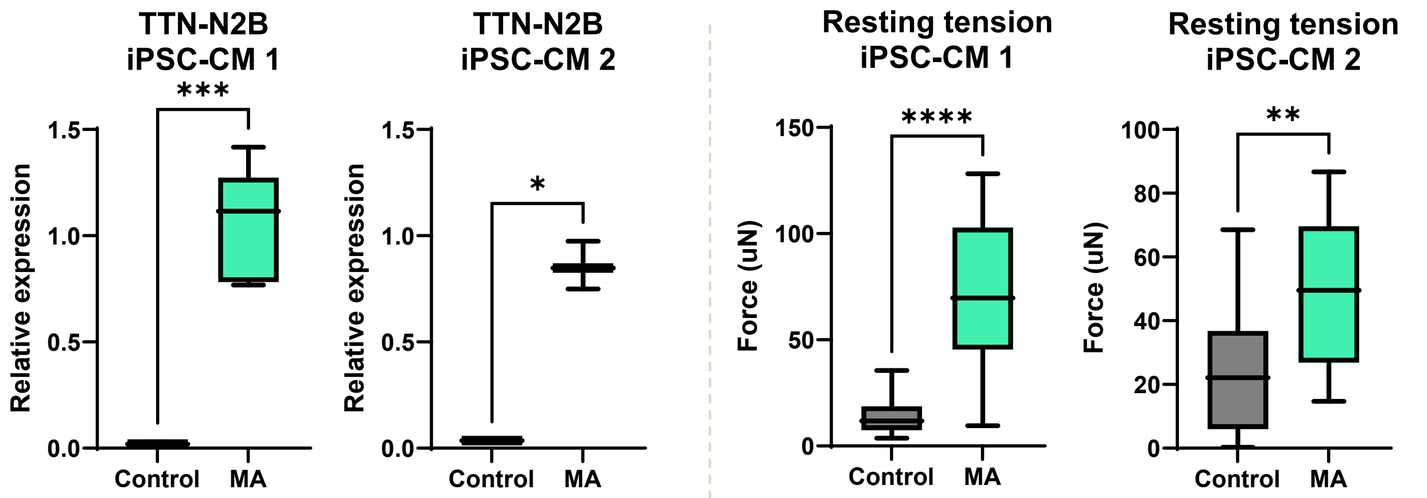




RESULTS

MA induces TTN isoform switch, which correlates with increased tissue stiffness



CONCLUSION

Increased TTN-N2B expression and increased resting tension indicate augmented cardiac stiffening through maturation

OUTLOOK

Potential for use of this model for target validation and drug discovery

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