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**Contractile deficits in engineered cardiac microtissues as a result of MYBPC3 deficiency and mechanical overload.**

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**Public Summary:**

The integration of in vitro cardiac tissue models, human induced pluripotent stem cells (hiPSCs) and genome-editing tools allows for the enhanced interrogation of physiological phenotypes and recapitulation of disease pathologies. Here, using a cardiac tissue model consisting of filamentous three-dimensional matrices populated with cardiomyocytes derived from healthy wild-type (WT) hiPSCs (WT hiPSC-CMs) or isogenic hiPSCs deficient in the sarcomere protein cardiac myosin-binding protein C (MYBPC3(-/-) hiPSC-CMs), we show that the WT microtissues adapted to the mechanical environment with increased contraction force commensurate to matrix stiffness, whereas the MYBPC3(-/-) microtissues exhibited impaired force development kinetics regardless of matrix stiffness and deficient contraction force only when grown on matrices with high fibre stiffness. Under mechanical overload, the MYBPC3(-/-) microtissues had a higher degree of calcium transient abnormalities, and exhibited an accelerated decay of calcium dynamics as well as calcium desensitization, which accelerated when contracting against stiffer fibres. Our findings suggest that MYBPC3 deficiency and the presence of environmental stresses synergistically lead to contractile deficits in cardiac tissues.

**Scientific Abstract:**

The integration of in vitro cardiac tissue models, human induced pluripotent stem cells (hiPSCs) and genome-editing tools allows for the enhanced interrogation of physiological phenotypes and recapitulation of disease pathologies. Here, using a cardiac tissue model consisting of filamentous three-dimensional matrices populated with cardiomyocytes derived from healthy wild-type (WT) hiPSCs (WT hiPSC-CMs) or isogenic hiPSCs deficient in the sarcomere protein cardiac myosin-binding protein C (MYBPC3(-/-) hiPSC-CMs), we show that the WT microtissues adapted to the mechanical environment with increased contraction force commensurate to matrix stiffness, whereas the MYBPC3(-/-) microtissues exhibited impaired force development kinetics regardless of matrix stiffness and deficient contraction force only when grown on matrices with high fibre stiffness. Under mechanical overload, the MYBPC3(-/-) microtissues had a higher degree of calcium transient abnormalities, and exhibited an accelerated decay of calcium dynamics as well as calcium desensitization, which accelerated when contracting against stiffer fibres. Our findings suggest that MYBPC3 deficiency and the presence of environmental stresses synergistically lead to contractile deficits in cardiac tissues.

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