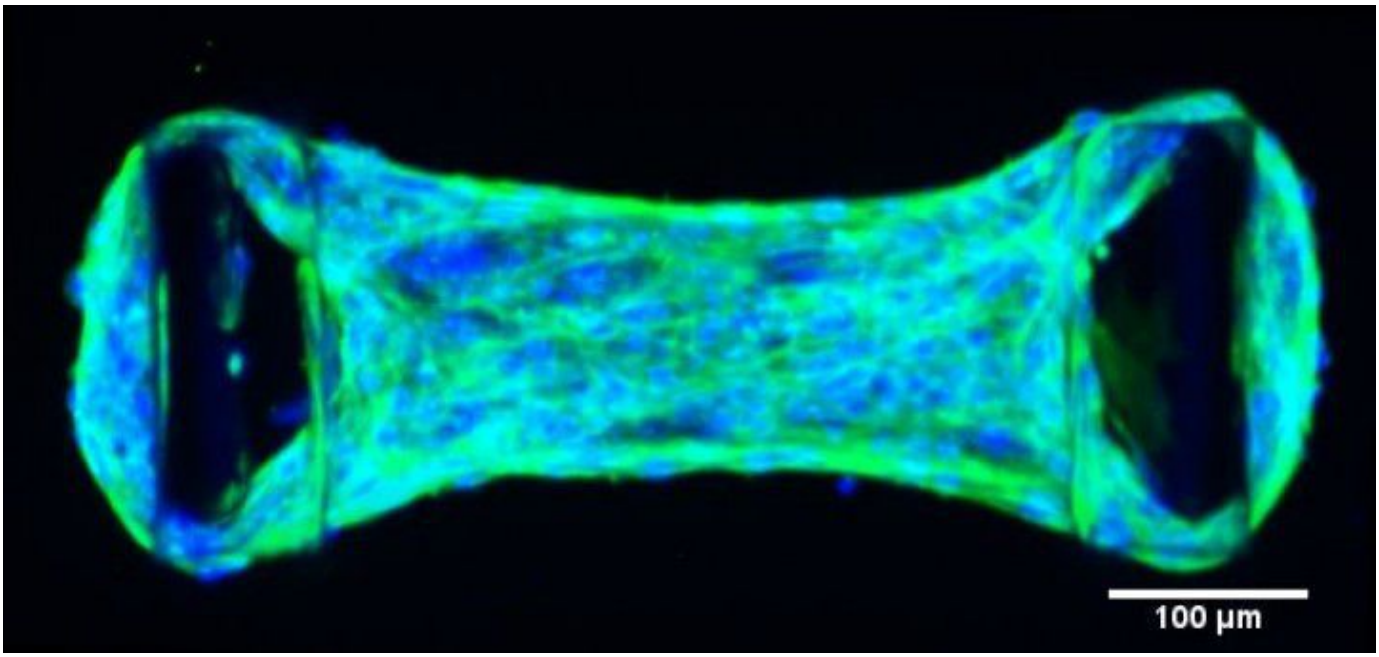
Biofísica Magazine

COMMENTARIES / NEWS

Engineered heart-tissue via cellular reprograming: A new tool for research and diagnosis

15/10/2015



Engineered cardiac tissue. Image kindly provided by John T. Hinson (Brigham and Women's Hospital, Boston, USA)

Jorge Alegre-Cebollada, *CNIC (Madrid, Spain)*.

Commentary to *Titin mutations in iPS cells define sarcomere insufficiency as a cause of dilated cardiomyopathy* (Hinson, et al. *Science*, **2015**, 349: 982-986).

The heart is a mechanical machine in charge of pumping blood against gravity and friction. Severe diseases develop when the mechanical properties of the heart muscle fail. Among them, there are several forms of familial cardiomyopathies that are caused by mutations in sarcomeric proteins with a mechanical role, such as titin. However, geneticists and cardiologists still have a hard time figuring out whether a particular mutation found in a patient causes disease or not, which prevents genetic diagnosis of relatives. Basic research in cardiomyopathies is also hampered because of the lack of appropriate disease models for every and each one of the individual mutations found in patients.

A recent report describes cellular reprograming techniques to obtain patient-derived induced pluripotent

stem cells (iPS) that can be differentiated into engineered heart-tissue-like structures, whose mechanical properties can be studied in the lab [1]. These engineered tissues recapitulate several important features of the myocardium such as sarcomerogenesis and contractility. These novel patient-derived cardiac microtissues are an exciting new tool that can be used to learn more about how cardiomyopathies develop. For example, from the Biophysics point of view, these tissues can be used to understand how a point mutation in a sarcomeric protein can lead to deficits in contractility and remodeling of the heart. There are also reasons for being optimistic regarding potential translational applications.

The paper by Hinson et al. reports that dilated cardiomyopathy (DCM)-derived engineered tissue where titin is truncated in heterozygosis shows deficits in contractility. The authors suggest that mutations of uncertain clinical significance could be evaluated using the same mechanical approach to define pathogenicity. No doubt this is an enticing proposal. However, although results are encouraging, there are a number of observations that merit future experimental work to fully validate the system:

- The authors do not find any mechanical defect at the single-cell level.
- Engineered tissues express fetal forms of titin with longer I-band segments and less exon skipping. Since the existence of exon skipping diminishes or even abolishes pathogenicity of truncations at the I-band [2], the observation that exon skipping happens less often in engineered tissues questions their predictive power, particularly for mutations of titin occurring in the I-band.
- The expression of some key cardiac genes is different in engineered tissues with respect to myocardium.

All of these concerns come down to the fact that engineered microtissues do not fully recapitulate native cardiac tissue. Future research has to determine to what extent such differences may prevent diagnostic applications. In the meantime, we can expect to learn many new things about the pathophysiology of familial DCM using the iPS system. Maybe more importantly, this new platform could be used to evaluate tailored therapeutic approaches.

References

1. Hinson JT, *et al.* "Titin mutations in iPS cells define sarcomere insufficiency as a cause of dilated cardiomyopathy". *Science*, **2015**, 349: 982. DOI:10.1126/science.aaa5458.
2. Roberts AM, *et al.* "Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease". *Sci Transl Med* **2015**, 7: 270ra276. DOI: 10.1126/scitranslmed.3010134.