

Activation of PDGF pathway links LMNA mutation to dilated cardiomyopathy.

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Public Summary:

Scientific Abstract:

Lamin A/C (LMNA) is one of the most frequently mutated genes associated with dilated cardiomyopathy (DCM). DCM related to mutations in LMNA is a common inherited cardiomyopathy that is associated with systolic dysfunction and cardiac arrhythmias. Here we modelled the LMNA-related DCM in vitro using patient-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). Electrophysiological studies showed that the mutant iPSC-CMs displayed aberrant calcium homeostasis that led to arrhythmias at the single-cell level. Mechanistically, we show that the platelet-derived growth factor (PDGF) signalling pathway is activated in mutant iPSC-CMs compared to isogenic control iPSC-CMs. Conversely, pharmacological and molecular inhibition of the PDGF signalling pathway ameliorated the arrhythmic phenotypes of mutant iPSC-CMs in vitro. Taken together, our findings suggest that the activation of the PDGF pathway contributes to the pathogenesis of LMNA-related DCM and point to PDGF receptor-beta (PDGFRB) as a potential therapeutic target.

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