Modeling Treatment Response for Lamin A/C Related Dilated Cardiomyopathy in Human Induced Pluripotent Stem Cells.

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Abstract

BACKGROUND: Precision medicine is an emerging approach to disease treatment and prevention that takes into account individual variability in the environment, lifestyle, and genetic makeup of patients. Patient-specific human induced pluripotent stem cells hold promise to transform precision medicine into real-life clinical practice. Lamin A/C (LMNA)-related cardiomyopathy is the most common inherited cardiomyopathy in which a substantial proportion of mutations in the LMNA gene are of nonsense mutation. PTC124 induces translational read-through over the premature stop codon and restores production of the full-length proteins from the affected genes. In this study we generated human induced pluripotent stem cells-derived cardiomyocytes from patients who harbored different LMNA mutations (nonsense and frameshift) to evaluate the potential therapeutic effects of PTC124 in LMNA-related cardiomyopathy.

METHODS AND RESULTS: We generated human induced pluripotent stem cells lines from 3 patients who carried distinctive mutations (R225X, Q354X, and T518fs) in the LMNA gene. The cardiomyocytes derived from these human induced pluripotent stem cells lines reproduced the pathophysiological hallmarks of LMNA-related cardiomyopathy. Interestingly, PTC124 treatment increased the production of full-length LMNA proteins in only the R225X mutant, not in other mutations. Functional evaluation experiments on the R225X mutant further demonstrated that PTC124 treatment not only reduced nuclear blebbing and electrical stress-induced apoptosis but also improved the excitation-contraction coupling of the affected cardiomyocytes.

CONCLUSIONS: Using cardiomyocytes derived from human induced pluripotent stem cells carrying different LMNA mutations, we demonstrated that the effect of PTC124 is codon selective. A premature stop codon UGA appeared to be most responsive to PTC124 treatment.

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