SciTechnol
International Publisher of Science, Technology and Medicine

Advanced Biomedical Research and Innovation

Investigating the pathogenicity of LMNA variants in human pluripotent stem cell-cardiomyocytes using CRISPR/Cas9 technology

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Abstract

Dilated cardiomyopathy (DCM), which is characterized by dilation of left or both ventricles and systolic dysfunction, comprises many hospitalized cardiomyopathy cases and has major impact on public health. About 48% of DCM cases are familiar with over 60 causative genes identified to date. Among them, mutations in LMNA gene (encoding nuclear protein Lamin A/C) account for 6% of families with DCM. Modern sequencing technologies, e.g. whole-exome-sequencing (WES), has identified numerous genetic variants in LMNA gene, however the pathogenicity of these variants and the molecular mechanisms leading to DCM remain unknown. This project aims to utilize induced pluripotent stem cells (iPSC) as a model system to phenotypically characterize LMNA mutations causing DCM and to design novel genome editing strategies to recapitulate the disease phenotype by applying the state of the art CRISPR/Cas9 technology. This allows the interrogation of genetic mutations to decipher the genotype-phenotype relationship in a more precise and measurable manner. CRISPR/Cas9 genome editing of healthy wild-type IPSCs were performed to create mutant isogenic IPSC lines by introducing an LMNA variant identified in DCM patients in order to recapitulate the disease phenotype in comparison with patient-derived IPSCs. CRISPR edited and patient specific IPSCs, together with the relevant control IPSCs were subsequently differentiated to cardiomyocytes and assessed for phenotypic and functional characteristics. The powerful combination of IPSC-based disease modelling and CRISPR-Cas9 genome editing will provide us insight into the contribution of these LMNA genetic variants to the pathogenesis of DCM and to study VUS functional phenotypes in a patient specific manner. These findings can then be used for early disease detection, diagnosis and clinical management of patients, leading to an improvement in patient healthcare. This platform represents a promising tool for assessing DCM-associated VUS specifically and can significantly contribute to precision medicine for the study of genetic diseases in the near future.

Biography

Wong Ly completed her Bachelor's degree in Biomedical Engineering at the University of Melbourne, Australia and PhD at the University of Queensland, Australia focused on targeted gene therapy for cardiac regeneration. She was a postdoctoral fellow at CSIRO manufacturing at Victoria, Australia working on pluripotent stem cell reporter cell lines using genome editing. She is currently appointed as a postdoctoral researcher at the Department of Genetics and Cell Biology, Maastricht University, Netherlands, studying the pathogenicity of genetic variants of DCM in IPSC-cardiomyocytes using CRISPR/Cas9 technology.

3rd Global Conference on Tissue Engineering and Regenerative Medicine, Stem Cell Research, June 29-30, 2020

Citation: Wong Ly, *Investigating the pathogenicity of LMNA variants in human pluripotent stem cell-cardiomyocytes using CRISPR/Cas9 technology*, Regenerative Medicine 2020, 3rd Global Conference on Tissue Engineering and Regenerative Medicine, Stem Cell Research, June 29-30, 2020, Pages 07