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Revealing potential cardiac manifestation of ADPKD using iPS cell-derived cardiomyocytes

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iPS technology has opened new avenues for disease modelling and regenerative medicine [1]. iPS cells can be generated from any individual with their genetic background and disease mutations, promising further evolution towards personalised medicine. Recent advances in differentiation approaches of iPS cells has enabled generation of kidney and other organoids, providing new opportunities to study genetic diseases in human tissue platforms [2,3]. Further, CRISPR/Cas9 genome editing provides a complementary approach to model genetic diseases without the need to collect patient cells [4].

Polycystic kidney disease (PKD) is the most prevalent genetic kidney disease, which causes cyst formation and organ dysfunction in the kidney and liver. PKD can also exhibit heart valve disease and brain aneurysms. Using CRISPR-mutants of PKD1 or PKD2, causative genes of autosomal dominant PKD (ADPKD), an *in vitro* model of cystogenesis has been demonstrated using kidney organoids [5]. In this issue of *EBioMedicine*, Lee et al. reported a potential causal association of PKD gene mutations with arrhythmias using ADPKD patient-derived iPS cells [6].

Studies indicate a higher risk of cardiac complications such as atrial fibrillation and left ventricular hypertrophy in ADPKD patients. However, it can be difficult to investigate a direct causal association of PKD mutations with cardiac complications in clinical studies, since PKD patients often exhibit chronic kidney disease and hypertension which increases the risk of cardiac disease. Lee et al. used iPS technology to generate cardiomyocytes from ADPKD patients with PKD1 or PKD2 mutations, so that the potential effects of PKD mutations on arrhythmias could be studied *in vitro* [6]. ADPKD patient-derived cardiomyocytes showed lower levels of sarcoplasmic reticulum calcium content, and PKD2-mutant cardiomyocytes demonstrated a slower beating rate. PKD1-mutant cardiomyocytes exhibited a significant increase in beating frequency when treated with an L-type calcium channel blocker. β-adrenergic agonist provoked more delayed afterdepolarizations, one of proarrhythmogenic characteristics, in both PKD1- and PKD2-mutants than in controls. These observations indicate that PKD mutations may directly affect calcium cycling in cardiomyocytes and cause arrhythmias in ADPKD patients. Of note, recent studies indicate that PKD1 and PKD2 modulate calcium cycling and functional properties of cardiomyocytes [7], further supporting the novel insight from Lee's study.

Although more confirmatory studies need to be conducted, Lee's study may suggest the need for a more careful assessment of arrhythmias in ADPKD patients, especially when L-type calcium channel blockers or β-adrenergic agonists are prescribed. A careful evaluation of arrhythmias may prevent ADPKD patients from serious cardiac events. On the other hand, further research using patient iPS-derived cardiomyocytes *in vitro* may highlight abnormal responses to antihypertensive and/or anti-arrhythmic drugs which are often prescribed to ADPKD patients. Ultimately, using patient-specific iPS lines, we may be able to predict responses to those drugs as personalised medicine in the future.

Recent iPS studies including Lee's are encouraging to develop disease models, drug screening systems, and personalised medicine approaches, yet there are still many challenges to be conquered. Lee et al. used a human embryonic stem cell line, H9, as a normal control while iPS cells generated from ADPKD patients were used to investigate cardiac manifestation. ADPKD patient-derived iPS cells possessed mutations in PKD1 or PKD2, yet there could be also differences in genetic background and epigenetic modifications. Single nucleotide polymorphisms (SNPs) other than mutations in PKD1 or PKD2 may have caused abnormalities that were observed in iPS cell-derived cardiomyocytes in Lee's study. Differences in epigenetic modifications may also cause abnormal responses to cardiac medications. Indeed, Nishizawa et al. reported that epigenetic variation between human iPS cell lines is the indicator of differentiation capacity [8], indicating careful attention to epigenetic modifications during iPS reprogramming may be necessary when we evaluate phenotypic outcomes in disease modelling with iPS cells. Thus, the CRISPR genome editing approach would be an important addition to patient-derived iPS disease modelling, since an isogenic control line can be used as a control line.

Another major challenge is the reproducibility of differentiation protocols. Volpato et al. reported poor inter-laboratory reproducibility of the differential gene expression signature in iPS cell-derived neurons generated using a well-defined differentiation protocol [9]. Further, a recent study demonstrated inter-experimental and interclonal variation

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of kidney organoid differentiation in the same laboratory, which were strongly associated with nephron patterning [10]. Although it is not easy to set a gold standard of iPS differentiation to certain lineage cells or tissues due to the fundamental difference between *in vivo* and *in vitro*, the appropriate quality control of differentiated cells and organoids should be considered for reproducible differentiation and disease modelling results.

Nevertheless, iPS technology is rapidly evolving and enabling development of better models of human disease which I believe will provide novel insights into disease mechanisms and develop new therapeutic approaches for patients.

Author declaration

The author declares no conflicts of interest.

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