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Induced Pluripotent Stem Cells in Cardiovascular Precision Medicine

Induced pluripotent stem cells (iPSCs) are derived from somatic cells obtained from human subjects. iPSCs can be used for disease modelling, drug screening, and regenerative therapy. iPSCs have the potential to revolutionise patient care as part of precision medicine tailored to the individual.



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Derived from terminally differentiated cells, iPSCs avoid the ethical problems of embryonic stem cells (ESCs). With patient consent, somatic cells can be obtained from a blood sample drawn from a vein to isolate peripheral blood mononuclear cells (PBMCs) or a skin sample that is used to isolate fibroblasts. Using a genetically engineered virus that overexpresses the transcription factors octamer-binding protein 3/4 (OCT 3/4; also known as POU5F1), SRY (sex determining region Y)-box 2 (SOX2), Myc proto-oncogene protein (c MYC), and Krüppel-like factor 4 (KLF4), the somatic cells are reprogrammed to become iPSCs (Takahashi et al. 2007). The iPSCs can then be differentiated into any tissue cell type using recombinant protein factors (Zhang et al. 2009). With this approach, iPSCs can be used to generate cardiovascular tissue to study complex disease states (Burridge et al. 2014; Orlova et al. 2014). iPSC disease modelling will vastly improve our ability to diagnose, prognosticate and treat cardiovascular disease.

Disease Modelling

iPSCs have advanced our understanding of the molecular mechanisms of diseases such as dilated cardiomyopathy, hypertrophic cardiomyopathy, long QT syndrome, and arrhythmogenic right ventricular cardiomyopathy (Kim et al. 2013; Lan et al. 2013; Moretti et al. 2010; Sun et al. 2012; Wu et al. 2015). The traditional method of studying human diseases uses animal models or patient-derived tissue samples. Animal models, however, are problematic due to inherent differences in physiology, reproducibility, ethical concerns and poor correlation with human clinical trial data. Patient-derived tissue samples are an excellent model for studying disease, but are limited in abundance and availability. In contrast, iPSCs can be differentiated into any tissue types, including cardiac muscle cells and endothelial cells lining the inside of all blood vessels. In contrast, iPSCs be used to identify genes responsible for a disease. Subsequently, powerful new gene editing tools can be used to study molecular mechanisms of disease (Hsu et al. 2014).

Uncovering disease mechanisms can lead to the identification of new disease-specific biomarkers as well

as targets for new drug therapies (Mercola et al. 2013). Disease-specific biomarkers can expedite the diagnosis of diseases and effectively predict their responses to therapies, allowing for personalised treatment of each patient. Furthermore, when mechanistic studies identify novel drug targets, patient-derived iPSCs can be used to screen for beneficial versus toxic drug effects specific to the genetic makeup of each patient. By contrast, it is not possible to predict these effects accurately with prior approaches that use traditional animal models.

**“IPSC DISEASE MODELLING
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CARDIOVASCULAR DISEASE”**

Drug Screening

iPSC-derived tissues are unique to each individual. Not only can they be used to study individual susceptibilities to diseases, but they can also lead to tailored therapy, or personalised medicine. Patient-specific iPSC-derived tissue can be tested with conventional drug therapies to reveal the optimal treatment for each patient, avoiding a costly and inefficient trial-and-error approach that is prone to adverse reactions (Liang et al. 2013; Mathur et al. 2015). For example, the medical management of atrial fibrillation is complex. A doctor and patient discuss issues such as the risks and benefits of anticoagulation and, depending on symptoms, either a rate control or rhythm control strategy. Finding the optimal therapeutic regiment for a patient with atrial fibrillation, however, is challenging, time-consuming and can result in frequent emergency room visits, not to mention adverse side effects which are potentially life-threatening. By contrast, in the future, iPSCs from a patient with atrial fibrillation may be used to generate cardiomyocytes that could be safely tested with different rate and rhythm control agents. Using various in vitro assays, the optimal drug and dose could be determined empirically in a dish, thus avoiding drug titration and undesirable side effects.



Figure 1. iPSC Precision Medicine in Cardiovascular Research

A blood sample from a patient is used to make induced pluripotent stem cells (iPSCs). The iPSCs can be differentiated into any cell type using growth factors. The iPSC-derived tissue can subsequently be used for disease modelling, drug screening or regenerative medicine.

The iPSC-derived tissues may also enhance clinical trials. For example, a medication may not have an overall effect on a large population of patients despite selection for patients with optimal demographics and risk factors. Although a subpopulation may respond to a treatment, the effect is masked by non-response in the larger heterogeneous population. To address this problem, population-based studies using patient-derived iPSCs could preselect patients with an optimal risk-to-benefit ratio prior to starting the clinical trial. A rhythm control medication for atrial fibrillation, for instance, could be tested in iPSC-cardiomyocytes from atrial fibrillation patients to predict who would respond to a drug and also to test for adverse side effects such as drug-induced arrhythmias. Patients identified to have safe and efficacious responses in the iPSC screening would be subsequently enrolled into the trial. This enriched sample population would have a larger chance of beneficial effect, which would improve power and possibly reduce cohort size. If the drug were approved for clinical use, an iPSC-cardiomyocyte screen could be used to predict which patients in a general population would enjoy the greatest benefit for the new drug in comparison to other antiarrhythmic agents.

Regenerative Medicine

Regenerative medicine is the holy grail of stem cell research. iPSCs represent a limitless source of tissue that could repair or replace organs (Lu et al. 2013). Because they are autologous, the use of iPSCs could avoid immunosuppression that complicates standard organ transplants. Moreover, if the genetic cause of a patient's disease is known, the mutation could be corrected with genome editing and a replacement organ could be synthesised in vitro and implanted. For example, patients with Marfan syndrome have a mutation in the fibrillin gene that causes valvulopathy and a dilated aorta. Over time, the valve and the aorta may need to be replaced with a prosthetic valve and aortic graft. With regenerative therapy using iPSCs, the genetic mutation could be corrected with gene editing and a new aortic valve and aorta synthesised from iPSCs. However, there are several obstacles to translating regenerative therapies from the bench to clinical practice. From primary tissue collection to generating terminally differentiated iPSC-derived tissue, regenerative medicine requires an enormous amount of time

and financial cost. Even under ideal conditions, the iPSC-derived tissues are notorious for batch to batch variability and immaturity. If regenerative therapy could overcome these hurdles, U.S. Food and Drug Administration approval would require that the iPSC-derived tissue be delivered in a targeted manner with no immunogenicity, tumorigenicity or toxicity (Neofytou et al. 2015). In addition, the transition to complex tissue and organ structure is challenging, since the three-dimensional structural organisation of tissues is lost in a petri dish. Nevertheless, advances in biomechanical engineering and emerging 3D printing technologies could make it possible to emulate the environmental configuration that facilitates the transformation of a complex cellular structure into an organ.

Conclusion

In summary, iPSCs are a powerful new modality in clinical medicine. They will not only enhance our understanding of diseases and lead to the discovery of new drug therapies, but will also advance personalised medicine and expedite clinical trials by enriching patient populations. The regenerative powers of iPSCs have yet to be fully realised, but may one day lead to definitive treatments of end-organ dysfunction. ■

KEY POINTS

- ✓ Induced pluripotent stem cells (iPSCs) are derived from somatic cells obtained from human subjects
- ✓ iPSCs can be used for disease modelling, drug screening, and regenerative therapy
- ✓ iPSCs have the potential to revolutionise patient care as part of precision medicine tailored to the individual



REFERENCES

For full references, please email edito@healthmanagement.org or visit the website

