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Opinion

Induced Pluripotent Stem Cells—Derived Stem Cells: A Promising Tool for Disease Modeling

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Stem cells possess potential to undergo self-renewability giving rise to any cell type in the body known as pluripotency. This process, also known as differentiation, through which stem cells undergo several morphologic and genetic changes resulting in daughter cell lineages. The end point lineage depends on the growth and differentiation induction factors or proteins added to *in vitro* stem cell culture. These stem cells can be of embryonic source (embryonic stem cells (ESCs)) derived from the inner cell mass of embryo or induced-pluripotent stem cells (iPSCs) which are produced from reprogrammed somatic cells in the body.[1] In this commentary, we will focus on iPSCs and their contribution to disease modeling in the context of reproductive disorders.

Reprogramming of adult somatic cells into iPSCs is a valuable tool holding a promise for regenerative and personalized medicine in the future.[2] Introduction of pluripotency transcription factors or genes *Oct4*, *Sox2*, *Klf4* and *c-Myc* into somatic cells in order to reprogram or induce pluripotency ability in the resulting iPSCs. This pioneer work was first discovered and reported by Yamanaka and colleagues[3] which revolutionized the medical and scientific world. This novel idea devised a way to not only reprogram somatic cells into iPSC with a remarkable pluripotency potential same as ESCs, but also paved a path to generate iPSCs from subjects with diseases carrying gene mutations in order to model a disease.

iPSCs are innovative tools to study molecular mechanisms underlying a disease. Thus, iPSCs provide a robust cellular system to study disease-specific phenotypes. Specifically, iPSCs provide an immensely useful system to investigate pathogenetic mechanisms of diseases for which there is no absolute animal model such as neuronal diseases,[4] mitochondrial diseases, and metabolic diseases,[5] and lens-disorders.[6] iPSC-derived normal and disease-specific tissues or cells, owing to their pluripotency, enable us to establish a high-throughput screening system to strategize and identify therapies for diseases.

In the context of reproductive disease modeling, iPSCs may play a vital role in regenerating reproductive cells and tissues. Specially, female reproductive cells such as oocytes, endometrium, granulosa cells, etc., can be regenerated by reprogrammed female fibroblasts or oocyte-specific cells (e.g., granulosa cells). In a study, functional and steroidogenic ovarian granulosa cells were produced by human amniocyte-derived induced pluripotent stem cells (hAdiPSCs) which secreted estradiol *in vitro*. This provides an opportunity and platform to produce autologous ovarian tissue *ex vivo*[7,8] and thus can be pivotal in improving pregnancy success rate in *in vitro* fertilization (IVF). Furthermore, iPSC technology may provide *in vitro* differentiated ovarian cellular system to study mechanisms of ovarian diseases and high throughput system to screen novel therapeutics.[9] iPSC-derived diseased cell/tissue types can also be cultured in microfluidic chips[10] and manipulated using genome editing techniques (CRISPR) to silence or overexpress putative or candidate genes to check the effects of perturbation which may provide additional strategies to develop novel therapies.[11]

CONCLUSION

Due to lack of direct translatable animal models, it is needed that an *in vitro* cellular model derived from patient-derived iPSCs be created which provides a platform and cellular system to investigate pathogenetic mechanisms of diseases. Currently, various diseases due to nature of their rare occurrence and/or fatal outcomes, result in lack of patient tissue samples and specimen and subjects to characterize diseases. For example, in neurological rare metabolic disease, X-ALD, there is no genotype phenotype correction and due to inaccessibility of tissue samples, research presents caveats in discovery of biomarkers. The development of patient-derived stem cell model enables us to discover novel biomarkers of diseases and design and screen therapies.

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