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# Biological Characterization of iPSCs and Its Applications

Feiyuan Zheng *

Nanning No.3 Middle School, Nanning, Guangxi, 530201, China

* Corresponding Author Email: xiaoy@ldy.edu.rs

**Abstract.** Induced pluripotent stem cells (iPSCs) are pluripotent stem cells obtained by reprogramming somatic cells with transcription factors (e.g., OCT4, SOX2, KLF4, c-Myc), and have self-renewal and differentiation potentials similar to embryonic stem cells (ESCs). Their pluripotency allows differentiation into various cell types, maintained by core transcription factors and regulated by signaling pathways. Different species' iPSCs need specific culture conditions. iPSCs can self - renew through certain pathways, useful in high-throughput screening. They have low immunogenicity due to mechanisms like low MHC expression. Their epigenetic plasticity shows in reprogramming and differentiation. Also, iPSCs are gene-editing compatible, enabling correction of genetic diseases. In this paper, we will present the current research results of iPSCs and the future challenges of iPSCs by describing their biological properties and their corresponding applications.

**Keywords:** IPSCs, disease modeling, drug screening, immunotherapy.

## 1. Introduction

The discovery of induced pluripotent stem cells (iPSCs) and their analysis and treatment in oncology analysis and clinical treatment of tumors have provided new possibilities. 2006, Japanese experts Shinya Yamanaka and his team programmed mouse fibroblasts into pluripotent stem cells by using four types of transcription factors (OCT4, SOX2, KLF4, and G-MYC). This breakthrough study not only found iPSCs but also made iPSCs an important tool for regenerative drugs [1]. In 2007, scientists reprogrammed human somatic cells (e.g., skin cells) into iPSCs, which further promoted their application in disease models and personalized drugs [2]. Since then, the reprogramming technology of iPSCs has been improved by experts' analysis. At the chemical reprogramming level, Deng Hongkui's team at Peking University developed a small-molecule induction method that can generate human iPSCs within 10 days, with a success rate of up to 100% and is suitable for resistant cells that are difficult to treat by traditional techniques [3]. At the biotechnology level, scientists have explored non-viral reprogramming methods—non-integrating vectors (e.g., Sendai virus, plasmids) combine chemical small molecules—which have improved the safety of iPSCs for clinical applications.

Applications: iPSCs are mainly used in regenerative medicine, treat neurological diseases (Parkinson's disease, Alzheimer's disease, cardiovascular disease, corneal repair .....), tumor analysis (tumor-like organ model establishment, genetic tumor syndrome research, tumor immunotherapy), as well as cardiac adjustment, corneal adjustment, etc. [4]. In the future, iPSCs-derived tumor-related organs can be used for high-throughput medicine screening to speed up anticancer drug development; with CRISPR technology, iPSCs can be edited by immune cells to improve tumor targeting. However, because of the residual undifferentiated iPSCs and accumulating gene mutations, iPSCs still have tumorigenic risk.

In this paper, we will introduce iPSCS for tumor treatment from several aspects, including the basic biological properties of iPSCs, applying iPSCs in tumor research, and the application of iPSCs in tumor clinical treatment. An overview of the biological properties of iPSCs and related applications.

## 2. Pluripotency

Unlike the totipotent of embryonic stem cells, the pluripotent of iPSCs refers to their potential to differentiate into all cell types of the three embryonic layers (endoderm, mesoderm, and ectoderm),

which is the core difference between them and ordinary somatic and adult stem cells. iPSCs' pluripotency is maintained by a network of core transcription factors, of which OCT4, SOX2, KLF4, and c-MYC are the 2 minimal transcription factor combinations that induce the reprogramming of somatic cells into iPSCs. Signaling pathways also play important roles in regulating the pluripotent of iPSCs.

Various species of iPSCs may require other cultural conditions to maintain their pluripotent state. Mouse iPSCs require LIF (Leukemia Inhibitory Factor) and serum to maintain their “naive” pluripotent state, whereas human iPSCs are closer to the “primed” pluripotent state and require the support of factors such as activin A and bFGF. This difference reflects the biological differences in embryonic development between species. In turn, pluripotent can be verified by teratoma formation assays (demonstrating the ability to differentiate into three embryonic tissues), chimera-forming ability (demonstrating the ability to participate in embryonic development), and, most rigorously, by tetraploid complementation assays (demonstrating the ability to support complete embryonic development). The study demonstrated that high-quality mouse iPSCs could generate “all-iPSC” mice by the tetraploid complementation test, which dispelled early concerns about the differences in developmental potential and pluripotent between iPSCs and ESCs [5].

The pluripotent of iPSCs enables them to generate various types of cells (e.g., immune cells, stromal cells) in the tumor environment, and to construct more accurate tumor models. Yinxiong Li's team at the Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, constructed a MEN1 disease model using reprogrammed urinary cells from multiple endocrine neoplasm type I patients as iPSCs, which recapitulated the hyper insulin secretion model and identified the GLP-1R pathway as a potential therapeutic target [6]. In addition, the differentiated cells can be used to replace normal tissues damaged in tumor treatment (e.g., reconstruction of hematopoietic system functioning after chemotherapy).

## 3. Self-renewal

The iPSCs can proliferate in vitro and remain undifferentiated, which is highly suitable for large - scale culture as reported in [7]. Their self - renewal is associated with specific signaling pathways. For mouse iPSCs, the LIF/STAT3 pathway is involved. Here, leukemia inhibitory factor (LIF) activates STAT3, which in turn promotes self - renewal. In the case of human iPSCs, the FGF/ERK pathway plays a role. Basic adult fibroblast growth factor (bFGF) supports value - added through ERK signaling, yet excessive activation of this pathway may lead to differentiation.

Consequently, iPSCs are applicable in several high - throughput screening scenarios. Firstly, in drug discovery and development, disease - specific iPSCs can be utilized to screen for small molecules that regulate disease - related pathways. Secondly, for toxicity testing, iPSCs - differentiated cardiomyocytes are valuable for detecting drug - induced arrhythmias, and iPSCs - derived stem cells are useful for assessing the toxicity of drug metabolites. Thirdly, in disease mechanism research, by using CRISPR to correct patient iPSCs, it becomes possible to screen for compounds that can reverse phenotypes, such as in the case of cystic fibrosis.

iPSCs possess several advantages in high - throughput screening applications. They are scalable, and compared to animal models, they are closer to human physiology, which enables the screening for individualized therapeutic regimens. However, it should be noted that iPSCs also have certain shortcomings, such as batch variations and high costs. Additionally, further research is needed to better standardize the production and use of iPSCs to minimize these issues and fully exploit their potential in various applications.

## 4. Low Immunogenicity

Autologous iPSCs (from the patient's cells) have a low risk of immune rejection after transplantation. There are several mechanisms.

Low expression of MHC molecules: Undifferentiated iPSCs have low expression of major histocompatibility complex (MHC I/II), which reduces the risk of recognition by host T cells.

Immunomodulatory factor secretion: iPSCs may secrete anti-inflammatory cytokines (e.g., TGF-β, IL-10) or express immune checkpoint molecules (e.g., PD-L1) to inhibit immune cell attack. (3) Gene editing optimization: Knockdown of MHC genes or overexpression of immunosuppressive molecules (e.g., HLA-G) by CRISPR and other techniques to further reduce immune rejection.

Studies have shown that undifferentiated iPSCs are immunogenic and can trigger antitumor immune responses, including lymphocyte infiltration and increased cytokine release. However, the insufficient antigenicity of iPSCs and the immunosuppressive tumor microenvironment limit their therapeutic efficacy. To improve efficacy, the researchers enhanced the immunogenicity of iPSCs by radiation treatment (e.g., 50 Gy irradiation) and combined it with neoantigenic design (NA-iPSCs) and radiotherapy, which boosted antitumor effects. In animal models, this combination therapy achieved a complete remission rate of 37.5% and reduced the risk of metastasis [8]. In addition, the low immunogenicity of iPSCs reduces the risk of immune rejection, and after repairing the genetic defects of the patient's cells through gene editing, they are then differentiated into target cells (e.g., pancreatic β-cells, cardiomyocytes) for transplantation. For example, patients with type 2 diabetes have achieved blood glucose control through iPSC-derived islet tissue transplantation.

## 5. Epigenetic Plasticity

The epigenetic plasticity ofiPSCs refers to their ability to retain the epigenetic memory of the source tissues during reprogramming, as well as their ability to exhibit dynamic epigenetic regulation during differentiation. It is manifested in the following aspects. (1) Epigenetic resetting during reprogramming: iPSCs are acquired by reprogramming somatic cells (e.g., fibroblasts), a process that requires erasing the epigenetic memory of the original cells (e.g., tissue-specific methylation patterns) and reconstructing pluripotent-related epigenetic features (e.g., pluripotent gene promoter methylation, such as OCT4, NANOG).

However, incomplete reprogramming may lead to residual epigenetic memory and affect the differentiation potential of iPSCs. (2) Epigenetic dynamics during differentiation: iPSCs need to activate or repress the expression of specific genes when they differentiate into specific cell types, which depends on the precise regulation of epigenetic modifications (e.g., promoter demethylation of SOX1 gene in neural differentiation). (3) Response to external stimuli: Culture conditions (e.g., hypoxia, growth factors), small molecule compounds, or epigenetic drugs (e.g. the DNA methylation inhibitor 5-aza) can induce changes in the epigenetic state of iPSCs. Application level: epigenetic memory of iPSCs can be used to study early events in disease development. For example, pancreatic cancer studies have found that epigenetic plasticity plays a key role in tumor initiation, affecting intercellular communication and microenvironmental remodeling. In addition, in neurodegenerative diseases (e.g., Alzheimer's disease) and psychiatric disorders (e.g., depression), aberrant epigenetic regulation of iPSCs may mimic disease-associated gene expression changes [9].

## 6. Gene Editing Compatibility

The iPSCs are highly amenable to gene editing procedures like CRISPR - Cas9. This is of great significance as it enables the modification of genes that are associated with cancer development. For instance, genes that are directly or indirectly involved in oncogenesis can be altered. Moreover, it can also be used to enhance the antitumor functions within the cells. There are a variety of gene editing techniques available for modifying iPSCs.

Firstly, CRISPR - Cas9 is the most prevalently utilized gene editing tool when it comes to efficient knock - out (Knock - out) and targeted insertion (Knock - in) of iPSCs, as demonstrated in reference [10]. This system has been widely studied and applied in many research fields related to iPSCs.

Secondly, CRISPR - Cas12a (for example, AsCas12a Ultra) is another important gene editing option. Compared with Cas9, Cas12a exhibits a higher level of specificity. It also has different protospacer - adjacent motif (PAM) sequences, such as TTTV. This characteristic makes it suitable for certain genomic sites that are difficult to edit using Cas9, as indicated in reference [11].

Furthermore, it is remarkable that the edited iPSCs retain the ability to differentiate into target cell types. These target cell types include but are not limited to neurons, cardiomyocytes, and immune cells. And during the differentiation process, they can still preserve the edited genetic characteristics.

Consequently, iPSCs can be harnessed for the correction of genetic diseases. iPSCs can be generated through the reprogramming of patients' somatic cells. Subsequently, disease - causing mutations can be rectified by gene editing techniques, with CRISPR - Cas9 being a prime example. For example, by leveraging the CRISPR - Cas9 precision genome editing system, there have been revolutionary methodological advancements in the study of hematologic diseases. In the cases of hemophilia and thalassemia, researchers have been able to repair the chromosomal inversion of the F8 gene using CRISPR - Cas9, thereby restoring the function of coagulation factor VIII, as reported in reference [12].

## 7. Conclusion

The iPSCs possess multiple remarkable properties. Their pluripotency, self-renewal, low immunogenicity, epigenetic plasticity and gene-editing compatibility offer great potential in various fields. They can be used for disease modeling, drug discovery, toxicity testing, and genetic disease correction. However, challenges like batch variations and high costs need to be addressed for their broader application.

This paper analyzes, summarizes, and discusses the biological properties of iPSCs, such as pluripotency, self-renewal ability, low immunogenicity, epigenetic plasticity, and compatibility with gene editing, based on which iPSCs have demonstrated their advantages in the fields of disease modeling and mechanism research, regenerative medicine and tissue repair, drug screening and toxicity testing, and personalized medicine. However, iPSCs still face problems such as carcinogenicity risk, low reprogramming efficiency, standardization, and large-scale production. With the iteration of technology, iPSCs is expected to become a core tool for the next generation of cell therapy and promote the development of precision medicine.

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