



Research Progress of Induced Pluripotent Stem Cells and Their Clinical Application Prospects

Junming Zhang^{1,2,3}, Dawei Zhang² and Jiang Peng^{3*}

¹Postgraduate Training Base of Jinzhou Medical University, China

²The Fourth Medical Center of the PLA General Hospital, China

³The 960th Hospital of the Joint Logistic Support Force, China

***Corresponding author:** Jiang Peng, Institute of Orthopedics, the Fourth Medical Center, Chinese PLA General Hospital, Beijing 100853, China, Email: pengjiang301@126.com

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Abstract

Induced pluripotent stem cells (iPSCs) have attracted widespread attention in the field of regenerative medicine in recent years as a revolutionary cell regeneration technology. The generation mechanism and unique characteristics of iPSCs demonstrate great potential in various applications, including regenerative medicine, drug screening, and disease model construction. Despite numerous studies revealing the application prospects of iPSCs, there are still many challenges in their clinical transformation process, such as cell safety, functional stability, and ethical issues. This article aims to review the research progress of iPSCs, analyze their potential and obstacles in clinical applications, and look forward to future development directions, in order to provide references for related research.

Keywords: Induced Pluripotent Stem Cells; Stem Cell Technology; Regenerative Medicine; Clinical Applications; Disease Models

Introduction

Induced pluripotent stem cells (iPSCs) are multipotent stem cells reprogrammed from somatic cells by transfecting specific transcription factors. Since their discovery in 2006, iPSCs have attracted widespread attention due to their ability to proliferate indefinitely and differentiate into various cell types. Compared to embryonic stem cells, iPSCs have fewer ethical controversies and can be generated from the patient's own cells, thereby reducing the risk of immune rejection. The discovery of iPSCs has not only provided new models for basic research but also brought hope for clinical therapies, especially in the fields of regenerative medicine, disease models, and drug screening.

In recent years, significant progress has been made in iPSCs research. Researchers have explored the potential applications of iPSCs in various diseases, including diabetes, cardiovascular diseases, and neurodegenerative diseases. For example, by converting human pancreatic β cells into iPSCs, researchers can better understand the development of the pancreas and the function of β cells, providing new insights for diabetes treatment [1]. Additionally, iPSCs have been used in cancer immunotherapy research, where scientists are working to differentiate iPSCs into immune cells to enhance the immune response against tumors [2].

In summary, iPSCs, as an emerging cell type, are pushing the frontiers of biomedical research. This article will review

the research progress of iPSCs, discuss their importance in basic research and clinical applications, and analyze future development directions. We will conduct an in-depth discussion on the generation, phenotypic characteristics, application fields, and challenges faced by iPSCs, aiming to provide references and insights for further research.

Main Body

Mechanism of iPSCs Generation

Selection and Application of Transcription Factors: The generation of induced pluripotent stem cells (iPSCs) relies on specific transcription factors. The Yamanaka factors, namely Oct4, Sox2, Klf4, and c-Myc, are the most commonly used transcription factors, which reprogram somatic cells to revert to a pluripotent state. These transcription factors promote dedifferentiation and maintenance of pluripotency by regulating gene expression networks. Research shows that the combination of transcription factors and their expression levels significantly affect the efficiency of iPSCs generation. For example, the deletion of certain cell cycle inhibitors (such as p27 or p18) can significantly enhance the efficiency of iPSC generation, indicating that the regulation of the cell cycle plays a key role in the reprogramming process [3]. Furthermore, the selection of transcription factors can also be optimized based on different starting cell types to improve reprogramming efficiency [4]. At the application level, transcription factors can be delivered through various methods such as virus vectors and chemical inducers to achieve effective reprogramming of somatic cells. In summary, the selection and application of transcription factors are one of the core factors influencing the generation of iPSCs.

The process of cell reprogramming: Cell reprogramming is a complex multi-stage process that involves a comprehensive remodeling of gene expression and changes in epigenetic states. The initial stage of reprogramming is typically initiated by the introduction of transcription factors, leading to the activation of pluripotency genes and the suppression of differentiation-related gene expression. Studies have shown that cells undergo multiple intermediate states during the reprogramming process, which may affect the final reprogramming efficiency. For example, some cells exhibit heterogeneity in the early stages of reprogramming, resulting in differences in reprogramming efficiency among different cell populations [5]. Additionally, factors such as the metabolic state of the cells, the cell cycle, and the extracellular environment also have a significant impact on the reprogramming process. By optimizing the composition of the culture medium and cell culture conditions, the reprogramming efficiency and the quality of the generated iPSCs can be further improved [6]. Therefore, understanding the specific mechanisms and processes of reprogramming is

of great significance for enhancing the generation efficiency of iPSCs.

Factors Affecting Reprogramming Efficiency: Reprogramming efficiency is influenced by various factors, including cell type, expression levels of transcription factors, cell cycle status, and external environment. Firstly, the choice of starting cell type has a significant impact on reprogramming efficiency; for example, fibroblasts are generally considered the best starting cells for reprogramming, while other cell types may exhibit lower reprogramming efficiency [4]. Secondly, the expression levels and combinations of transcription factors also directly affect the success rate of reprogramming. Both excessively high and low expression of transcription factors may lead to decreased reprogramming efficiency. In addition, the metabolic status of the cells and the phases of the cell cycle can also influence reprogramming efficiency; studies have found that cells respond differently to reprogramming factors at different stages of the cell cycle [7]. Finally, the extracellular environment, such as the composition and mechanical properties of the culture medium, can also affect the reprogramming process of cells. Optimizing these conditions can effectively improve the generation efficiency of iPSCs [8]. By comprehensively considering these factors, new ideas and methods can be provided to enhance the generation efficiency of iPSCs.

Characteristics of iPSCs

Pluripotency and Self-renewal Ability: Induced pluripotent stem cells (iPSCs) are reprogrammed from somatic cells through the mediation of transcription factors. These cells possess pluripotency, allowing them to differentiate into various cell types of the three germ layers. The pluripotency of iPSCs arises not only from the expression of pluripotency marker genes (such as Oct4, Sox2, Klf4, and c-Myc) in their genome but is also closely related to their self-renewal ability. Studies have shown that iPSCs can proliferate indefinitely in vitro without losing their pluripotency, making them an ideal cell source for regenerative medicine and disease modeling. In-depth research on the metabolism and epigenetic characteristics of iPSCs has revealed that their self-renewal ability is closely related to the metabolic state of the cells and the supply of nutrients in the microenvironment. Compared to other stem cells, iPSCs have unique mechanisms for maintaining pluripotency and self-renewal ability, which presents broad prospects for them in basic research and clinical applications [8,9].

Identification of Marker Expression: The surface markers of iPSCs are key to identifying their pluripotency and characteristics. Commonly used pluripotency markers include SSEA-1, TRA-1-60, and Oct4, which play important indicative roles during the culture and differentiation of

iPSCs. Through techniques such as flow cytometry and immunofluorescence staining, researchers can effectively detect and analyze the expression of surface markers in iPSCs. Studies have found that the expression levels of these markers may change under different culture conditions and differentiation states, providing important information for understanding the biological characteristics of iPSCs. Furthermore, the surface markers of iPSCs are closely related to their functional characteristics, reflecting the cells' differentiation potential and self-renewal ability. Therefore, the identification of markers is particularly important in the research and application of iPSCs [10,11].

Genomic Stability and Epigenetic Features: Genomic stability is an important characteristic that must be considered in the clinical application of iPSCs. Although iPSCs can maintain pluripotency and self-renewal ability, their genomes may become unstable due to various factors, including the expression of transcription factors, culture conditions, and epigenetic modifications. Studies have shown that iPSCs retain some epigenetic memory from somatic cells during the reprogramming process, which may lead to inconsistent phenotypic expression during differentiation. Furthermore, the epigenetic features of iPSCs, such as DNA methylation and histone modifications, directly affect their gene expression profiles and cell fate determination. In-depth research on the genomic stability and epigenetic features of iPSCs can help optimize their culture and differentiation conditions, thereby enhancing their application potential in regenerative medicine [9,12,13].

Applications of iPSCs in Regenerative Medicine

Tissue Engineering and Regenerative Therapy: Induced pluripotent stem cells (iPSCs) exhibit tremendous potential in tissue engineering and regenerative therapy. iPSCs can be reprogrammed from adult somatic cells and possess the ability to differentiate into various cell types, making them a key tool in regenerative medicine. Research has shown that iPSCs can be used to repair and regenerate various tissues, including bone tissue and dental tissue, by generating specific cell types through in vitro culture and induced differentiation to meet clinical needs. In recent years, the application of iPSCs in dental and non-dental tissue regeneration has attracted widespread attention, with many studies exploring the regenerative potential and therapeutic effects of iPSC-derived cells both in vivo and in vitro [14,15]. Additionally, the ethical advantages of iPSCs and their applications in personalized medicine have led to deeper research in the field of regenerative medicine, greatly promoting the development of tissue engineering.

Cell Replacement Therapy for Cardiovascular Diseases: Cardiovascular diseases are one of the leading causes

of death worldwide, and the loss of cardiomyocytes is a significant cause of heart failure. iPSCs, as an emerging strategy for cardiac regeneration therapy, can generate functional cardiomyocytes to replace damaged myocardial tissue. Studies have shown that iPSC-derived cardiomyocytes exhibit good cardiac repair capabilities in animal models, improving cardiac function through cell replacement or the secretion of growth factors [16,17]. Despite challenges such as immune rejection after cell transplantation, modifying the HLA gene of iPSCs through gene editing technology can significantly enhance their immunocompatibility, thereby improving the safety and efficacy of clinical applications [16,18]. These studies provide new ideas and directions for cell replacement therapy for cardiovascular diseases.

Treatment Potential of Neurodegenerative Diseases: Neurodegenerative diseases such as Alzheimer's Disease and Parkinson's disease have a severe impact on the quality of life of patients. Induced pluripotent stem cells (iPSCs) have shown significant application potential in the treatment of these diseases. By obtaining iPSCs from the somatic cells of patients, researchers can establish personalized disease models to explore the pathological mechanisms of the diseases and potential treatment methods [19,20]. iPSCs can not only differentiate into various types of neural cells but also replace damaged neural cells in vivo, providing new hope for the treatment of neurodegenerative diseases. However, the clinical application of iPSCs still faces the risk of tumor formation, making it crucial to conduct thorough safety assessments before cell transplantation [21,22]. Future research will further reveal the potential of iPSCs in the treatment of neurodegenerative diseases and provide a foundation for developing new treatment strategies.

Applications of iPSCs in Drug Screening and Toxicity Testing

Establishment of In Vitro Drug Screening Models: Induced pluripotent stem cells (iPSCs) provide a powerful in vitro model for drug screening. iPSCs can be reprogrammed from the somatic cells of patients, allowing researchers to obtain cells with specific genetic backgrounds, thereby better simulating the physiological and pathological states of human diseases. By differentiating iPSCs into specific types of cells (such as cardiomyocytes, hepatocytes, and neurons), researchers can assess the effects of drugs on these cells, screening for potential drug candidates. For example, using iPSC-derived cardiomyocytes (iPSC-CMs) for drug screening can effectively evaluate the cardiac toxicity of drugs, which is difficult to achieve in traditional animal models [23]. Additionally, combining Artificial Intelligence (AI) technology with image analysis methods can more accurately assess the pathological characteristics of cells and drug responses, providing new ideas and tools for drug screening [24].

Realization of Personalized Medicine: iPSCs have significant application potential in personalized medicine. By obtaining cells from patients and reprogramming them into iPSCs, doctors can create patient-specific cell models to test different drugs' responses in vitro. This approach not only enhances drug efficacy but also reduces the risk of adverse reactions. For example, studies have shown that using patient-derived iPSCs for drug screening can identify potential toxic reactions of specific drugs in certain patients, providing a basis for personalized treatment [25]. With the development of genomics and bioinformatics, a personalized medical model combining iPSCs is gradually taking shape, which will help formulate more precise treatment plans, especially in the treatment of complex diseases such as cancer and neurodegenerative diseases [26].

Study of Drug Response Mechanisms: Induced pluripotent stem cells (iPSCs) not only play a role in drug screening and personalized medicine but also provide a new platform for studying drug response mechanisms. By treating iPSC-derived cells with drugs, researchers can delve into the cellular and molecular mechanisms of drug action. For example, using iPSC-derived neuronal models, researchers can explore the mechanisms of action of drugs related to mental disorders, including how drugs affect neuronal development, synaptic function, and signal transmission [27]. Additionally, iPSCs can be used to study the effects of drugs on specific gene mutations, revealing the genetic basis of individual drug responses and providing important biological information for new drug development [28]. Through these studies, iPSCs offer significant experimental models for understanding the complexity of drug responses, advancing new drug development and clinical applications.

Applications of iPSCs in Disease Model Construction

Establishment of Genetic Disease Models: Since the discovery of induced pluripotent stem cells (iPSCs) technology in 2006, it has become an important tool for studying genetic disease models. iPSCs can be reprogrammed from patients' somatic cells, retaining the genomic information of the patients, which allows researchers to create cell models associated with specific genetic diseases. For example, studies have shown that using iPSCs from patients with hereditary retinal diseases can generate photoreceptor cells and retinal pigment epithelial cells, thereby exploring the pathogenesis and potential treatment strategies of these diseases in depth [29]. Furthermore, iPSCs have also demonstrated their potential in establishing cardiovascular disease models, where researchers can generate cardiomyocytes from iPSCs that can simulate the unique cardiac pathological features of patients, providing an important experimental platform for new drug development [30]. However, despite the broad

prospects for the application of iPSCs in genetic disease model construction, challenges remain, such as cellular heterogeneity, reprogramming efficiency, and long-term culture stability [31].

Applications in Tumor Research: The application of iPSCs in tumor research is also receiving increasing attention. By generating iPSCs from the somatic cells of tumor patients, researchers can create tumor-specific cell models that more accurately reflect the biological characteristics and drug responses of tumors. For example, using iPSC models, researchers can explore the molecular mechanisms of various tumors and subsequently screen for potential therapeutic drugs [31]. Additionally, iPSCs have been used to study the tumor microenvironment, helping to reveal the interactions between tumor cells and surrounding cells, which is crucial for understanding tumor aggressiveness and metastasis. Although iPSCs show great potential in tumor research, challenges such as tumor cell heterogeneity and model reproducibility need to be overcome to ensure the reliability of research results and the effectiveness of clinical translation [32,33].

Research on Infectious Diseases: In the study of infectious diseases, iPSCs also demonstrate significant application value. By generating iPSCs from the somatic cells of patients with infectious diseases, researchers can establish corresponding cell models to study the interactions between pathogens and host cells. For example, iPSCs can be used to investigate the infection mechanisms of pathogens such as HIV and influenza virus, and these models can help scientists understand how viruses evade host immune responses and lead to disease development [34]. Furthermore, iPSCs can also be used for drug screening, aiding in the development of new therapies for specific infectious diseases. By conducting high-throughput screening of iPSC-derived cells, researchers can quickly assess the efficacy and toxicity of drugs, providing data support for clinical treatment [35]. Nevertheless, the application of iPSCs in infectious disease research still faces numerous challenges, such as the complexity of constructing infection models and the biological relevance of results [36].

Conclusion

The development of induced pluripotent stem cells (iPSCs) shows great potential in the field of biomedical science and is gradually becoming an important tool in regenerative medicine, drug development, and disease model construction. Although the application prospects of iPSCs are exciting, there are still many technical and ethical challenges, such as cell safety, reprogramming efficiency, and standardization. These challenges not only affect the clinical application process of iPSCs but also require researchers to approach their potential with caution.

Firstly, regarding the safety of iPSCs, especially the risk of tumorigenesis, further research and validation are needed. Although studies have shown that iPSCs may introduce gene mutations or chromosomal instability during the reprogramming process, improving reprogramming techniques and screening methods is expected to reduce these risks. Additionally, standardized culture and differentiation protocols are key factors in improving the success rate of iPSCs in clinical applications.

Secondly, enhancing reprogramming efficiency is one of the urgent issues to be addressed in iPSCs research. Although existing reprogramming methods have made some progress, more efficient technologies need to be explored to improve the convenience and consistency of cell acquisition. Researchers are continuously exploring new strategies through gene editing technologies and small molecules to improve the reprogramming efficiency of iPSCs.

Finally, the application fields of iPSCs need to be further expanded. Future research should focus on exploring new applications of iPSCs in disease model construction and personalized medicine, especially in drug screening and treatment plan development for complex diseases. Through multidisciplinary collaboration, integrating research results from genomics, cell biology, and medicinal chemistry, it is expected to promote the clinical translation of iPSCs.

In summary, despite the many challenges faced in iPSCs research, their potential in fundamental research and clinical applications cannot be ignored. Through continuous technological innovation and in-depth ethical discussions, iPSCs are expected to play an increasingly important role in future medical practice, promoting the advancement of regenerative medicine.

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