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REVIEW ARTICLE

Promising Therapeutic Approach by Induced Pluripotent Stem Cells (iPSCs)

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ABSTRACT

Background: Since few decade stem cell research is being more crucial as it has the ability to renew their own population and to differentiate into specialized population of cells. To overcome the immune rejection, ethical issue of embryonic stem cells, and for more practical point of view, patients own body cells be reprogrammed to assume a stem cell like state called induced pluripotent cells (iPSCs) which maintain all the essential properties of embryonic stem cells.

Aim: The use of iPS cells for differentiating into various cell type of body and derived differentiate cells to provide personalized cells for cell based therapy is the great aim and it opened the new avenue for regenerative medicine.

Objectives: The capability of induced pluripotent stem cells (iPSC) is tremendous as it infinitely divided and differentiated into many different cell types. Hence objective is to use iPSCs to model several diseases to unravel the mechanism of alterations in these diseases.

Material: Various approaches were used to induce iPSCs such as delivering reprogramming factors (Oct4, Sox2, Klf4 & c-Myc) into somatic cells or by using a cocktail of small-molecule compounds that modulate various signaling pathways.

Result: The tissue of patients are used to generate immune-matched supply of pluripotent stem cells to test or screen the drug and study the specific cause for that disease in patient specific way. The stem cell research including iPS cells has received a significant amount of public attention for neurodegenerative diseases, diabetics and other tissue specific diseases.

Conclusion: Great benefits are expected in this field as researchers take advantage of the tremendous potential regenerative properties of induced pluripotent stem cells for promising therapeutic applications, which is described in this article.

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KEY MESSAGE

The advances in the generation of iPSCs and especially from patients own tissue is an important asset for drug screening and disease therapy.

KEYWORD

• Induced pluripotent Stem cells (iPSCs) • Reprogramming • Differentiation • Personalized Medicine • Immune rejection

INTRODUCTION

Successful introduction of antibiotics and vaccines have dramatically improved the health status of people all over the world. However divesting illness such as heart diseases, diabetes, cancer and nervous system diseases are continuing challenges of people everywhere. Since few decade stem cell research is being more crucial as it has the ability to renew their own population and to differentiate into specialized population of cells. Embryonic stem cells have the ability for self-renewal for unlimited period and can differentiate into three germ layers to give rise to any type of cells/tissue. However the immune-rejection and ethical issue remain be a hurdle in the embryonic stem cell research for successful use of regenerative medicine. To overcome these obstacles and for more practical point of view, patients own body cells can be reprogrammed artificially to assume a stem cell like state called induced pluripotent stem cells (iPSCs) which maintain all the essential properties of embryonic stem cells[1]. The use of iPS cells opened the new avenue for stem cell-based alternative testing methods in neurodegenerative disease, liver diseases, heart diseases and other diseases[2]. The development of iPS cells and derived differentiate cells hold the expected potential to provide personalized cells for cell based therapy[3]. More specifically the idea is to use the tissue of patient to generate immune-matched supply of pluripotent stem cells[4]. The human iPS cell research being pushed into a spotlight because of its important to create new oversight mechanisms to conduct of biomedical research in consistent with broad social values and legal requirements. The emphasis is given to use the patient specific peripheral blood cells for derivation of iPS cells and then these iPSCs differentiate into disease specific cells such as insulin producing cells and neurodegenerative diseases and all. The implantation of self-derived insulin-producing cells into diabetic patient can be a promising step for type 1 diabetes[5]. Each compartment of human brain serves particular purpose, designed for the specific information flow where specific neurons play a prominent role through their interneural connections and indispensable for signaling pathways communicating the synaptic plasticity to learning and memory. In neurodegenerative diseases such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Multiple Sclerosis (MS) and Amyotrophic Lateral sclerosis ALS, human induced pluripotent cells derived from peripheral blood cells served as a unique solution in a patient specific way[6]. Human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (CMs) provide a powerful tool and used as a potential substitute for animal models, for safety testing, drug screening and modeling cardiovascular diseases[7,8].

Recent advances in epithelial stem cell biology have significantly improved our understanding of wound regeneration mechanisms and have provided a basis for developing hiPSCs cell-based wound healing therapies. Skin maintains homeostasis through very organized fashion, yet complex mechanisms and any injury or damage to skin results in cutaneous wounds. Use of iPSCs for differentiation into skin cells (keratinocytes, fibroblasts, melanocytes and immune-cells) for wound healing is a complex multifactorial process involving the interaction of inflammation, granulation tissue formation, re-epithelialization, and angiogenesis[9].

Novelty of iPSCs:

In current years, human induced pluripotent stem cells (hiPSCs) provide several advantages and the traditional two-dimensional (2D) cell culture is gradually being replaced by three-dimensional (3D) organoid-based research. Induced pluripotent stem cells derived organoids represents the complex organ or tissue architecture in vivo. The 3D organoid culture is making most notable impact and

mimics the native organs both by structural components as well as by functionality[10-12]. Without altering the stability of physiological and genetic information, these 3D organoids can be maintained in for a long-term period in *in vitro* settings using appropriate media conditions[11]. Most importantly, induced pluripotent stem cells (iPSCs) retain similar features to embryonic stem cells (ESCs), and ethical hurdle is not there. Among various methods to isolate iPS cells the more efficient one is mRNA method which is less time taking, most advanced and with high efficiency[13,14]. It is of no doubt that induced pluripotent stem cells have been used in a multidisciplinary way from studying disease mechanism to screening of drugs. Immuno matched cells give better preference for study disease mechanism[12]. It is possible; theoretically, any type of disease can be modelled and replicated using patient-specific iPSC-derived cells. However, to recapitulate the phenotype of the disease is difficult due to complexity of disease causality[15], but for this continuous effort in under trial. Animal model has not been physiologically relevant and do not reciprocate all the features of a specific disorders in human. Recent reports suggest that disease specific iPSC can be differentiated and faithfully recapitulate disease phenotype[16].

In a convenient, cost effective and scalable way, patient specific peripheral blood reprogrammed efficiently and successfully differentiated into functional cells of body. In many neurodegenerative diseases mature nerve cells are lost and brain tissue samples are rarely available for testing. Moreover in neurodegeneration specific population of neuron or brain reason are uniquely susceptible for disease. To overcome these problems iPS cells showed a new solution in which patients own somatic cells that are reprogrammed to establish pluripotent stem cells. Induced pluripotent stem cell model provides the potential strength for detail modeling of sporadic as well as for familial disease with the cause and consequences of diseases. The pathogenic APP-E693Δ mutation and a sporadic Alzheimer Disease patient produce intracellular Aβ oligomers and the patient's iPSCs derived neuronal cells provided an experimental system for addressing whether such oligomers would cause cellular stress and the killing of neurons and how such intracellular[17]. Alzheimers Disease -iPSCs (AD-iPSCs) model was established that recapitulated the vital phenotypes of Alzheimer's from two familial AD patients carrying the APP D678H mutation and aberrant accumulation of Aβ and tau phosphorylation were confirmed as important features of diminished neurite outgrowth[18]. Study showed that iPSCs derived neural cells from a patient carrying E693Δ mutation, and the use of these neural cells Aβ oligomers might contribute to the disease pathogenesis, despite only one patient carrying the E693Δ mutation being available[17]. In another study the hyperphosphorylation of TAU protein has been compared in familial AD (fAD) and sporadic AD (sAD) iPSC-derived neurons and the study indicated that iPSC technology is appropriate to model both fAD and sAD and may offer a platform for developing new treatment strategy[19]. Further it has been shown that the more sensitive oxidative stress response and higher susceptibility to exogenously added synthetic Aβ1–42 peptide solution of AD-iPSCs lines[19].

Hence the patient derived iPS cell is of great value to explore the mechanism of misfolded or abnormally formed proteins and how these proteins bring disturbances in normal function of neuron, memory loss, synapse dysfunction and neural network to affect the whole brain function. For the clinical use of iPS cells for neurodegenerative diseases or any diseases the correct understanding of normal processes of age matched family member's healthy tissues/ cells verses abnormal tissue/cells will be the ultimate control. In figure 1 overview of the patient specific iPSCs and differentiated cells are shown below.

Once pluripotency is established, different colony expanded for differentiation of various types of cell population such as neuronal populations or glial populations to monitor the mechanism of disease progression and used to study the detailed mechanism from initiation and progression of disease. To repair the damaged tissue or regenerate the diseased tissue, induced pluripotent cells hold the best possible potential. In order to investigate the pathophysiology and drug development, the landmark discovery of human induced pluripotent stem cells has opened a new window. Before iPS cell technology becomes relevant for human therapeutics, several significant barriers and obstacles that must be overcome. In a convenient, cost effective and stable way, cryopreserved peripheral blood can be reprogrammed efficiently[20].

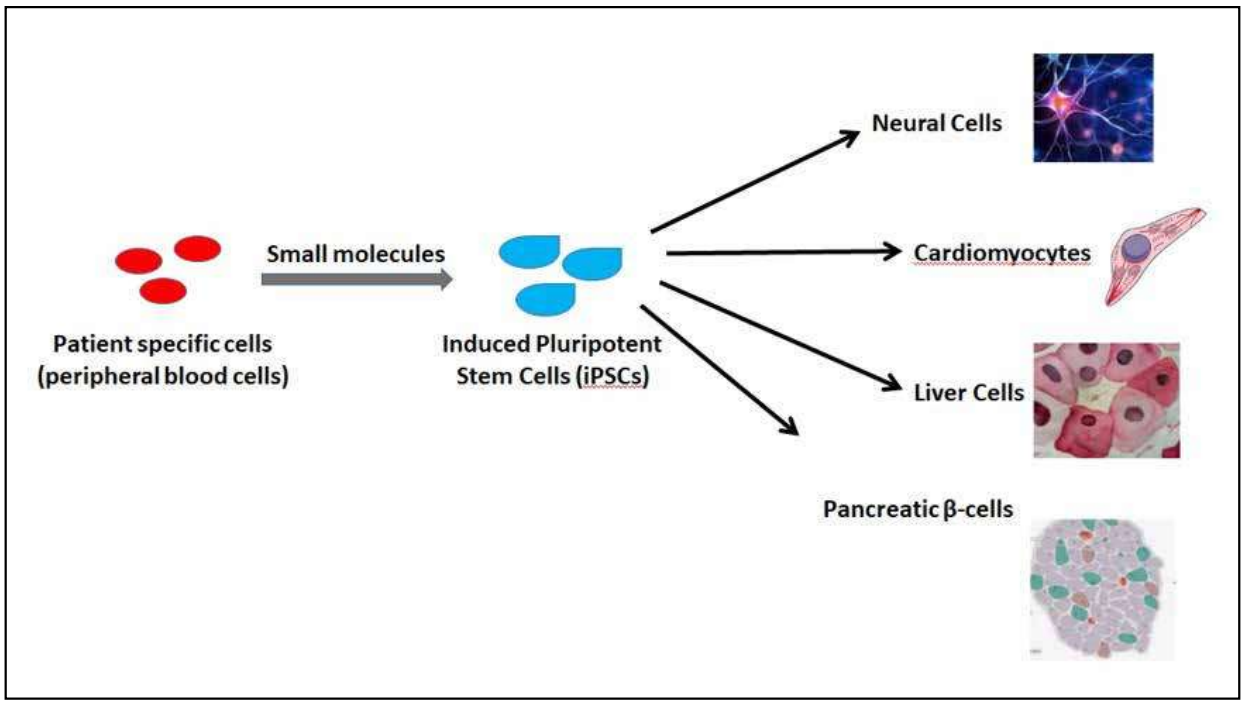

Figure 1: Overview of patient specific human iPSC cells and its differentiation to different specific cells of body

DISCUSSION

In spite of progress has been made on human iPSCs, number of obstacles are concerned and requisites need to be deeply attended. In order to control genetic and epigenetic stability of iPS cell lines for potential use in human therapies, several points taken into consideration like the reprogramming factors, culture conditions including small molecular supplements.[21] The successful testing methods for re-programming somatic cells into iPS cells need to be established to confirm the fact that the iPSCs technology is reliable. In this challenging endeavor of reprogramming somatic cells into iPS cells and their maintenance, risk steps be taken care for isolating induced pluripotent cells in large scale from the patient specific lymphocytes and/or hematopoetic stem cells. Screening of small molecules as initiators of cellular signaling is also a challenge for good manufacturing condition for reproducible manner. Scientific studies on hiPSCs were focused to obtain (i) patient specific peripheral blood for generation of the induced pluripotent stem cell (ii) intensive scrutiny of small molecules for differentiation of iPS cells into insulin producing cells and implantation of these cells into diabetic patient for promising cure (iii) patient specific iPSC differentiation into neurons of specific types such as cortical neuron, hippocampal neuron, dopaminergic neuron of basal ganglia and so on. More emphasis need to be given for obtaining functional cardiomyocytes, insulin producing cells from iPS cells is the promising therapeutic approach. Human iPSC cells have been used to reprogram for type 1 diabetics treatment[22]. The challenges in neurodegenerative diseases find the neuron's temporal position that may lies within a spectrum of disease conditions and can be influenced by both detrimental and beneficial factors[23]. As the safety concerns rise, it is essential to follow the clinical use of hiPSC cells and their differentiated cells/organoids for promising therapy.

CONCLUSION

Growing old is our destiny, but the discovery of the induced pluripotent stem cell (iPSC) technology using our body's somatic cells opened up with unprecedented opportunities in regenerative medicine, disease modeling and drug discovery that promote us for better health. Human iPSCs serve as the superior model than any other models. The safety and efficacy of Human iPSCs and the procedures need to be tested thoroughly. In near future, successful treatment by using iPSC technique will most likely be applicable for each and every patient. Adequate therapy for many diseases

does not exist so far and the real possibility for treatment and ultimate cure through human iPSCs will be a great boon.

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