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Advances in Human Pluripotent Stem Cells for Regenerative Medicine and Drug Discovery

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Introduction

TThe emerging Human Pluripotent Stem Cell (hPSC) technology brings many excitements for regenerative medicine and drug discovery [1]. Rapid advancements in hPSCs have been made in the past several years, including defined culture systems, procedures of directed differentiation, the demonstration of hPSC applications in drug screening, the establishment of various disease models, and the evaluation of therapeutic potential in treating incurable diseases through transplantation. This article highlights recent advancements in these areas and the current challenges for clinical applications based on hPSC technology.

hPSCs for Drug Discovery and Disease Modeling

hPSCs can provide a large amount of physiologically relevant human cells for drug screening [2]. The traditional models using cell lines and animals cannot fully recapitulate the human cell function. During drug discovery, about 90% of drug candidates cannot reach the stage of clinical trials due to the side effects and efficacy issues [3]. The derivation of hPSCs, especially Induced Pluripotent Stem Cells (iPSCs) from specific patients, opens a new era for disease modeling and drug discovery. Since the derivation of motor neurons from iPSCs of an 82-year old patient with a familial form of *Amyotrophic Lateral Sclerosis* (*ALS*), numerous types of neurological diseases and heart diseases have been modeled through the iPSCs [4]. For examples, iPSC-derived dopaminergic neurons have been used to evaluate 44 compounds that have demonstrated therapeutic effects in rodent models while only 16 showed significant neuroprotection effects using disease-relevant human cells [5]. A library of iPSC-derived cardiomyocytes from patients with various cardiac disorders (e.g. long QT syndrome, familial hypotrophic cardiomyopathy, and familial dilated cardiomyopathy) has been established [6]. The disease-specific cardiomyocytes demonstrated the increased susceptibility to cardiotoxic drugs that were not observed from the cells derived from healthy donors. These studies demonstrated the importance of using disease-relevant human cells for drug discovery, which offers a huge economic benefit to identify the drug candidates.

hPSCs for Regenerative Medicine

While the use of hPSC-derived cells for regenerative medicine has more hurdles compared to drug discovery due to the tumorigenecity and immunogenecity, the attractive unlimited cells of human source motivate the exploration of hPSCs for regenerative medicine [7]. The use of oligodendrocyte progenitors in spinal cord injury models and the retinal pigment epithelial cells for treating macular degenerations have been attempted in clinical trials [8]. The therapeutic potentials of hPSC derivatives, however, still require tremendous work and numerous preclinical studies. Transplantation of midbrain dopamine neurons derived from hPSCs showed long-term engraftment and behavior improvement in Parkinson's disease models using mice, rats, and monkeys as testing species [9]. The integration of hPSC-derived cortical neurons with *in vivo* mouse brain circuits showed the developmental connectivity for brain repair [10]. HPSC-derived cells also provide novel sources for tissue engineering studies. iPSC-derived cardiac progenitor cells have been used to repopulate the decellularized heart scaffolds and showed the response to β-adrenergic agonist isoproterenol and displayed normal electrophysiology of heart tissue [11]. The formation of 3-Dimentional (3-D) liver bud by co-culturing iPSC-derived hepatic endoderm cells with human mesenchymal stem cells and human umbilical vein endothelial cells regenerated vascularized and metabolically active human liver *in vivo* [12]. All these studies demonstrated the therapeutic potential of hPSCs in regenerative medicine.

hPSC Expansion Systems

To fulfill the potential of hPSCs, efficient expansion and differentiation systems are required. The culture systems of hPSCs have evolved from feeder culture to feeder-free defined culture systems through the development of defined media, defined substrates, and controlled environmental cues for self-renewal [13-16]. In the absence of serum albumin and β-mercaptoethanol, eight essential components of hPSC growth media (i.e. E8 medium) were identified [17]. The defined substrates include the specific laminin isoforms, vitronectin peptides, and synthetic polymers such as Poly [2-(Methacryloyloxy) Ethyl Dimethyl-(3-Sulfopropyl) Ammonium Hydroxide] (PMEDSAH) [18,19]. Environmentally, the biomechanical properties of extracellular substrates and biochemical molecules (e.g. O_2, small molecules to alter the metabolism) also were found as potent regulators for hPSC expansion [20-22]. To understand the factors leading to the heterogeneity of hPSCs and the cellular responses to the culture condition change, a high-throughput fingerprinting platform has been established recently to control cell fate [23].

Recent advances also emphasize the desire for large-scale expansion by using microcarrier-based (or scaffold-based) cultures and 3-D aggregate suspension cultures [20,24-27]. Both culture systems can be realized in bioreactors and have good scale-up potential. While microcarrier-based cultures have been shown to support hPSC expansion, their use for large-scale generation of differentiated cells has not been well studied [28]. Efforts are also directed to simplifying the coating of microcarriers and using defined media in the systems. For 3-D aggregate cultures, similarly, xeno-free culture components and aggregate size control have also been evaluated to better understand the characteristics and effects of the aggregate cultures [29].

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Thermoresponsive culture systems were also developed to ease the dissociation needs of hPSCs and enable the cell passaging in 3-D hydrogel-based systems [30,31]. Based on the phase transition behavior of the Poly(N-Isopropylacrylamide)-Co-Poly(Ethylene Glycol) (PNIPAAm-PEG) hydrogel from a liquid to a solid gel as the temperature is increased, hPSCs can be rapidly encapsulated and retrieved, which enabled the 20-fold expansion during 4-5 days and the maintenance of the lineage-specific differentiation potential [30,32].

hPSC Differentiation into Specific Lineages

The efficiency of the differentiation into specific lineages has improved significantly in recent years by modulating the developmental pathways rather than spontaneous differentiation. For example, the purity of cardiomyocytes derived from hPSCs has increased from less than 10% to 90% by temporally modulating Wnt, Activin/Nodal, and Bone Morphogenetic Protein (BMP) signaling during cardiac lineage commitments [33-35]. The differentiation of various types of neurons has also been significantly improved with the inhibition of dual SMAD signaling, the inhibition or activation of Wnt signaling, and the activation of sonic hedgehog pathway [9,36]. The protocols for generating specified forebrain interneurons, midbrain dopamine neurons, and the 3-D structures containing hindbrain regions have been developed recently to obtain not only the purified cells but also the complex 3-D organoids [9,36-38]. The differentiation into other lineages, such as pancreatic progenitor cells, hepatocytes, and hematopoietic cells, have also been demonstrated at high purities [8,39].

hPSC-Derived Cell Maturation

To date, hPSC-derived cells are still immature and more resemble fetal tissues. Numerous efforts are underway to enhance the maturation of the differentiated cells from hPSCs. While high-purity of neural progenitor cells have been derived from hPSCs, little has been done to derive functional neuronal subtypes which can form synapses and display the high-frequency trains of action potentials and other mature electrophysiology [40]. The maturation of hPSC-derived forebrain interneurons required 7 months which mimicked endogenous human neural development, while acceleration of the development will facilitate the hPSC applications [36]. Maturation study of hPSC-derived cardiomyocytes has been ongoing using various strategies rather than simple extending the culture time. Several approaches such as using 3-D scaffolds to create biomimetic cardiac wires, electrical stimulation, or stimulating adult cell energy metabolism have been investigated to improve cardiac cell maturation [41-45]. The initial success demonstrated the increased sensitivity to various drugs, including L-type Ca^{2+} channel blockers, Human *Ether-a-go-go*-Related Gene (hERG) K^+ channel blockers, and anti-arrhythmic drugs [42,44]. Additional novel strategies to promote differentiation and maturation of hPSC-derived cardiomyocytes are highly desirable and should be explored.

Conclusions and Perspectives

With the significant improvements in hPSC expansion and differentiation, more efforts are devoted to improving the function and maturation of hPSC-derived cells given the unique developmental potential of hPSCs. In this regard, the 3-D culture systems and the organogenesis studies become critical approaches to recreate the complex structures of a small region in the human bodies by deriving and differentiating iPSCs from the patients with various diseases. For clinical applications, more attentions and efforts need to be focused on large-scale generation of differentiated cell types. Compared to the relatively simple expansion and self-renewal of undifferentiated stem cells, it is much more challenging to generate functional differentiated cells as each type of cells and tissues uses a unique developmental path in their maturation process. Overall, in order to accelerate the applications of hPSCs it will require multiple advances in various fields including biology, chemistry, engineering, and material science.

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