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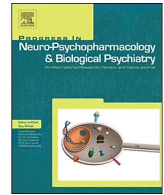

Stem cell contributions to neurological disease modeling and personalized medicine

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A B S T R A C T

Human induced pluripotent stem cells (iPSCs) represent a revolutionary tool for disease modeling and drug discovery. The generation of tissue-relevant cell types exhibiting a patient's genetic and molecular background offers the ability to develop individual and effective therapies. In this review, we present some major achievements in the neuroscience field using iPSCs and discuss promising perspectives in personalized medicine. In addition to disease modeling, the understanding of the cellular and molecular basis of neurological disorders is explored, including the discovery of new targets and potential drugs. Ultimately, we highlight how iPSC technology, together with genome editing approaches, may bring a deep impact on pre-clinical trials by reducing costs and increasing the success of treatments in a personalized fashion.

1. Background

Human induced pluripotent stem cells (hiPSCs) were first introduced in 2007 through the reprogramming of human somatic cells with four transcription factors: Oct3/4, Sox2, Klf4 and c-Myc (Takahashi et al., 2007). These induced pluripotent stem cells (iPSCs) closely resemble embryonic stem cells (ESCs) due to their potential to terminally differentiate into cell types from the three germ layers after exposure to a specific cocktail of growth factors and culture conditions (Thomson et al., 1998; Takahashi et al., 2007). The development of the iPSC field is promising in both basic biological and translational research, allowing the manipulation of human cells for therapeutic purposes. This is especially true for disease modeling and personalized medicine.

Prior to human stem cell technology, animal models were a major source of basic knowledge in multiple scientific areas, such as neuroscience, biochemistry, and physiology. Animal models have provided substantial insight into the roles of specific genes and molecular and cellular signaling pathways (Johnston and Fields, 2005). The utilization of animal models has enabled advances in the biological sciences without compromising the life of an actual human being. However, care must be taken when extrapolating information between organisms due to inherent limitations imposed by interspecies differences (Table 1).

Animal models are valuable for studying monogenic disorders; however, modeling diseases that arise from genetic mutations at multiple loci are extremely challenging (Quadrato et al., 2016). Although post-mortem brain tissue is an alternative for studying neurological illnesses, it only provides an end-stage snapshot of alterations in brain structure at both cellular and molecular levels. Furthermore, post-mortem brain tissue does not provide any temporal or mechanistic insights into disease pathogenesis. Hence, it is necessary to develop a more suitable preclinical model able to recapitulate the pathophysiology of human disease processes and to serve as a platform for target identification and therapeutic approaches. In this review, we briefly discuss the different aspects of cellular reprogramming, the use of iPSC-derived neurons for patient-specific disease modeling, and the discovery of novel therapies and biotechnology applications in the field of personalized medicine.

2. The potential of disease-specific stem cells

One of the most remarkable achievements in disease modeling

Abbreviations: ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; BD, bipolar disorder; CAS, CRISPR-associated proteins; CRISPR, clustered regularly interspaced short palindromic repeats; ESC, embryonic stem cell; FXS, fragile X syndrome; FMR1, fragile X mental retardation 1; hiPSC, human induced pluripotent stem cells; HTS, high-throughput screening (HTS); IKAP, I-κ-B-kinase-associated protein; iPSC, induced pluripotent stem cell; PD, Parkinson's disease; TRPC6, transient receptor potential cation channel 6; RTT, Rett syndrome; SMA, spinal muscular atrophy; SMN1, survival motor neuron 1 protein (SMN1); TALEN, transcription activator-like effector nucleases; ZFN, zinc-finger nuclease

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Table 1
Comparison of conventional disease models *versus* iPSC disease models.

Conventional disease models	iPSC disease models
Animals limited by interspecies differences that cannot reproduce clinical symptoms or pathology of human diseases, such as manifestations in behavior or differences in physiology and genetics.	iPSC disease models circumvent interspecies limitations imposed in animal models – they generate cell types in relevant species.
Animals capture complete environment and cellular interactions of multiple cell types within specific tissue environment in an *in vivo* setting.	*In vitro* cellular environment may not encapsulate all cell types and interactions and is artificially mimicking *in vivo* environment. Furthermore, cells carry genetic and epigenetic changes from reprogramming.
Animals can model monogenic disorders. Disorders of multiple genetic origin will be difficult to recapitulate due to the genetic engineering required. Difficult to model sporadic disorders in animals.	The model can be patient- or disease-specific depending on, if a disorder is monogenic, polygenic or sporadic.
Post-mortem brain tissue for elucidating disease information only provides a fixed end-stage perspective of disease.	Ability to study neurodevelopment and pathogenesis of disease *in vitro*, capturing temporal and mechanistic dysfunctions.
Animals provide *in vivo* models for drug screening. Coupled with human iPSC models, these will strengthen preclinical screening.	Species-specific preclinical model for drug screening in relevant cell types. Overcome limitations placed by interspecies differences and can test in multiple cell types.
Animals are an established model for drug testing. However, low percentages of drugs approved using animal models will pass clinical trials (< 15%).	Costly compared to animal models.

research was the development of iPSC technology. The advent of iPSCs has already provided novel information and acceleration in the study of neurodevelopment, therapy discovery and regenerative medicine (Marchetto et al., 2010; Kang et al., 2014; Mariani et al., 2012). Nowhere is the potential of human iPSCs more apparent than in neuroscience. A major challenge in studying neurological disorders is the absence of a predictive preclinical model to elucidate their pathophysiology (Falk et al., 2016). Notable investments have been made to clarify disease mechanisms and unveil prospective therapies, but the outcomes have been modest (Dragunow, 2008). Nonetheless, the inability of animal models to provide translational value to the clinic has been revamped by stem cell technology. The unique ability of iPSCs to differentiate into disease-relevant cell types allows for the investigation of neural networks from patients with specific genetic or neurological phenotypes – a feat that was previously unavailable (Takahashi et al., 2007; Marchetto et al., 2010). Additionally, the recent development of 3D cerebral organoid cultures, or "mini-brains", has increased our ability to understand many neuropathies (Lancaster and Knoblich, 2014a,b). Besides representing an important tool for unlocking disease mechanisms, novel therapeutic targets and potential treatments, organoids provide great value in the elucidation of brain development and organization.

3. Generating stem cells in the dish

The generation of iPSCs is possible through cellular reprogramming, where virtually any somatic cell is able to "go back" to its embryonic state. Once reprogrammed, iPSCs have the potential to differentiate into any somatic cell type (Takahashi and Yamanaka, 2006; Takahashi et al., 2007). This dynamic feature of reprogramming a cell to pluripotency is invaluable and can be influenced by many factors. While some cell types might be more efficiently or kinetically favored for reprogramming than others, variables such as targeted pathways, transcription factors and delivery methods may also affect the process (Brouwer et al., 2016; Aasen et al., 2008; Nakagawa et al., 2007; Liu et al., 2013; Maherali et al., 2008; Warren et al., 2010; Kim et al., 2009b). Considering each of these factors during the reprogramming process will be crucial for further research.

The large spectrum of cell sources that have been reprogrammed serves as a proof-of-concept that somatic cells from any origin are indeed susceptible to this process. However, most iPSCs have been derived from mesodermal cells, including skin fibroblasts (Howden et al., 2015; Takahashi et al., 2007; Marchetto et al., 2010), hematopoietic lineages (Giorgetti et al., 2009; Loh et al., 2009; Kunisato et al., 2011), dental pulp (Chen et al., 2013; Takeda-Kawaguchi et al., 2014), urine (Zhou et al., 2012; Lee et al., 2014), adipose (Qu et al., 2012), amniotic fluid (Drews et al., 2015; Slamecka et al., 2016) and other mesenchymal cell sources (Yu et al., 2007; Wang et al., 2013; Vasko et al., 2016). Not as many cells of ectodermal origin have been reprogrammed; to note, keratinocytes (Aasen et al., 2008; Li et al., 2009), neural progenitors (Kim et al., 2009a) and melanocytes (Utikal et al., 2009). From endodermal origin, hepatocytes (Liu et al., 2010; Ohi et al., 2011) and pancreatic islet beta cells (Bar-Nur et al., 2011) have been used. Overall, although cells of mesodermal origin may be more susceptible to reprogramming, significant advances in the field have made reprogramming cells from any of the three germ layers feasible.

Various studies have shown that some cells are more easily reprogrammed from both, the velocity and efficiency standpoints. When reprogramming keratinocytes and fibroblasts, Aasen and coworkers showed that keratinocytes were 100-fold more efficient and two-fold faster in their reprogramming compared to fibroblasts, while still achieving cells that appeared indistinguishable from ESCs in colony morphology, growth properties, gene expression profiles and differentiation potential (Aasen et al., 2008). There are multiple explanations for the observed difference: unlike fibroblasts, keratinocytes do not need to undergo a mesenchymal-to-epithelial transition to give rise to iPSCs. Another reason could be the similarities in gene expression levels of stem cell markers between keratinocytes and iPSCs, compared to fibroblasts (Aasen et al., 2008). Thus, gene expression patterns or intrinsic elements are important contributors to the differences in the reprogramming outcome and indicate that some cell sources are more prone to pluripotency.

The storability and accessibility also need to be addressed: whether these cell sources can be stored for extended periods and if the process of collecting samples is highly invasive or inaccessible. Certain cells are more easily collected, such as epithelial cells present in the urine and cord blood samples, whereas fibroblasts require a more invasive procedure to be obtained; however, all three have been fully reprogrammed (Zhou et al., 2012; Giorgetti et al., 2009; Takahashi et al., 2007; Howden et al., 2015; Chen et al., 2013). In addition to its accessibility, the use of cord blood is further advantageous due to the reduced number of somatic mutations and flexibility in the handling of these cells (Giorgetti et al., 2009; Zhou et al., 2015). Altogether, tackling this concern will be crucial for the easy collection and storage of samples for future use.

In vitro studies have shown that reprogramming of immature or less terminally differentiated cell types displayed an increased efficiency when compared to fully differentiated cells (Eminli et al., 2009). Thus, choosing a more immature lineage may facilitate the reprogramming process. Furthermore, iPSCs have been shown to retain, at least partially, the epigenetic memory that predisposes their differentiation potential towards the original cell type. In this context, iPSCs derived from blood cells seem to prefer differentiating into hematopoietic cells, while fibroblast-derived iPSCs prefer to differentiate into the osteogenic

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