Journal of
Alzheimer's Disease & Parkinsonism

Hokayem et al., J Alzheimers Dis Parkinsonism 2016, 6:5
DOI: 10.4172/2161-0460.1000275

Short Communication Open Access

Blood Derived Induced Pluripotent Stem Cells (iPSCs): Benefits, Challenges and the Road Ahead

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Abstract

Since the creation of induced Pluripotent Stem Cells (iPSCs) ten years ago, hundreds of publications have demonstrated their considerable impact on disease modeling and therapy. In this commentary, we will summarize key milestones, benefits and challenges in the iPSC field. Furthermore, we will highlight blood as an effective and easily accessible source for patient-specific iPSCs derivation in the context of work done in our laboratory and others.

Introduction

In 2006, Takahashi and Yamanaka were the first to reprogram adult cells into embryonic-like pluripotent stem cells, or induced Pluripotent Stem Cells (iPSCs), in mice [1]. One year later, the same laboratory, as well as an independent research team, both reported successfully reprogramming human adult cells into iPSCs [2,3]. This *magnum opus* stirred a whirlwind of scientific research activity in the stem cell field over the past 10 years, yielding vast advances in basic research and disease modelling and hinting at potential applications in the clinical and therapeutic arenas (Figure 1) [4].

iPSC reprogramming is typically initiated in somatic cells via the overexpression of four key genes (Oct3/4, Klf4, c-myc and Sox2), termed the "Yamanaka factors" [1-3]. Once generated, iPSCs have the same properties as embryonic stem cells (ESCs) in that they can indefinitely self-renew and can differentiate into all body cell types, with the possible exception of extra-embryonic tissue cells like placental cells. Although iPSC has shown morphological, karyotype and gene expression characterization, that mimic ESCs, there appears to be differences in epigenetic marks (e.g. DNA methylation) [3,5]. That is, the process of reprogramming appears to rejuvenate the somatic cells so that they adopt a stem cell-like state [6-8]. However, the process of resetting the epigenetic marks takes longer than the time required of establishing pluripotency [9]. However, as the iPSC are passaged for longer periods of time, these epigenetic marks are lost and the iPSC will more and more resemble ESCs [10].

iPSCs have had a substantial impact on both the basic and clinical levels of biomedical research. To start, iPSCs offered a convenient alternative to ESCs which are ethically controversial due to the necessity of their creation from human embryos [11]. As such, it is impossible to know what medical ailments may occur over a lifetime if the embryo had developed into a person. In addition, there is so little source material when ESCs are collected that the genetic background cannot be determined prior to reprogramming. In contrast, iPSCs allow patient-specific lines to be generated for which a full clinical and genetic assessment can be made in advance of reprogramming. This allows research efforts to be focused on creating the most relevant models for studying disease. There is even the potential for patient-specific iPSCs, tissues and organs to be therapeutically used, free from the possibility of rejection by the host's body [12]. Interestingly, studies have shown that patient-specific iPSC lines represent a plentiful and critical resource for drug screening and could aid in the discovery of new disease treatments and therapies [13].

Nonetheless, the success of these recent scientific endeavors vastly relies on the capability of iPSCs to model human diseases. Indeed, iPSCs have proven to be critical in supplying patient-specific cell types and organoids that were otherwise inaccessible for studying normal human developmental processes, as well as, detecting and deciphering aberrant processes as a result of disease [11,13-15]. Hence, iPSCs present a prime source for research of the mechanistic pathobiology behind many pressing diseases affecting the human population like autism spectrum disorders, Alzheimer disease, Huntington disease, Parkinson disease, glaucoma, and gut and liver diseases, among others [13-18].

Peripheral Blood Mononuclear Cells (PBMCs) as Source for iPSCs Derivation

Since the first iPSCs were generated from skin fibroblasts, many other sources of adult somatic cells have been probed for their suitability for iPSC reprogramming [2,3].These cell types include peripheral blood mononuclear cells (PBMCs), neuronal progenitor cells, keratinocytes, hepatocytes, kidneys, muscles, adrenal glands, and fibroblasts of mouse tail tips [13,19]. Indeed, these sources exhibit various levels of ease, efficacy, and cost in iPSC production. Differences in efficiency of iPSC derivation from distinct sources have been attributed to the original epigenetic state of the adult somatic cell type and its requirement to go through multiple steps of de-differentiation (e.g. mesenchymal to epithelial transition) to reach a pluripotent state [19]. Our laboratory was the first to use PBMCs to generate patient-specific iPSCs from individuals with autism spectrum disorder (ASD) and has extensively studied the adequacy of this iPSC source and reprogramming methods for the purpose of modeling ASD [18]. Indeed, we have been able to efficaciously generate iPSCs from patient-specific PBMCs. These iPSCs were, in turn, successfully differentiated to GABAergic neurons [18].

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Received October 13, 2016; **Accepted** October 18, 2016; **Published** October 25, 2016

Citation: Hokayem JEI, Cukier HN, Dykxhoorn DM (2016) Blood Derived Induced Pluripotent Stem Cells (iPSCs): Benefits, Challenges and the Road Ahead. J Alzheimers Dis Parkinsonism 6: 275. doi: 10.4172/2161-0460.1000275

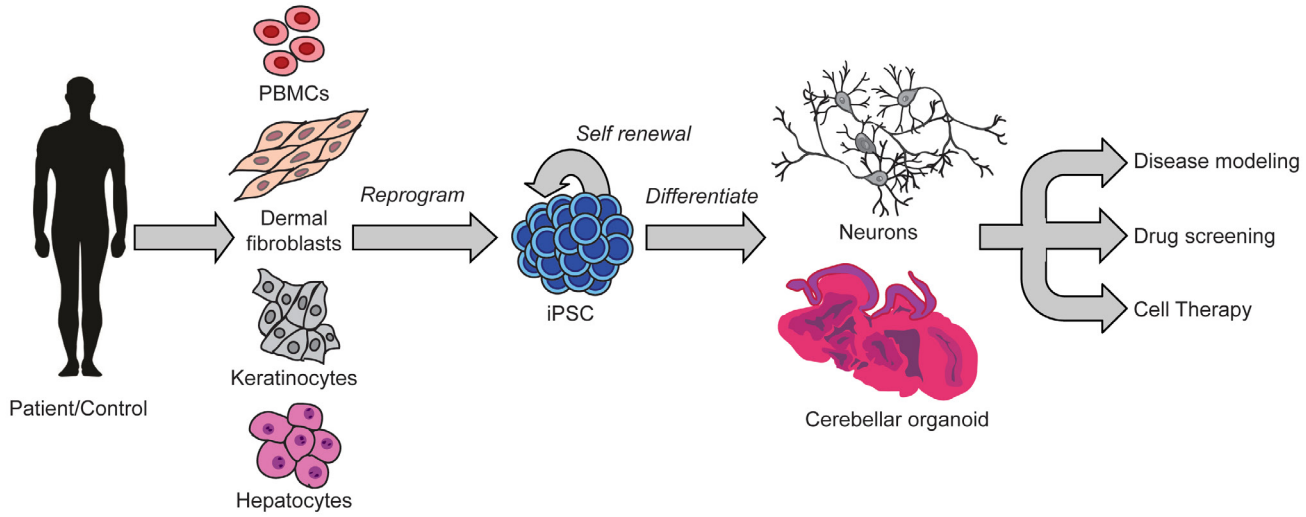

Figure 1: Schema depicting the use of iPSCs derived from different sources in disease modeling, drug screening and cell therapy.

Moreover, recent studies demonstrate the successful derivation of iPSCs from PBMCs collected from Alzheimer disease (AD) and Parkinson disease (PD) patients [20-25]. Undeniably, blood is becoming a routinely used source for iPSC generation.

Benefits of PBMCs as a Source for iPSC Derivation

PBMCs isolated from whole blood present many benefits for the derivation of iPSCs. First of all, blood can be collected relatively easily from patients as compared to collecting dermal fibroblasts through a whole skin biopsy procedure. Moreover, drawing blood is routinely performed in clinical settings or even out in the field; all that is required is a trained phlebotomist without the need of either highly specialized staff or the use of expensive anesthetics and surgical tools. Therefore, acquiring blood samples from patients is a routine, relatively cheap, and much less intrusive procedure as compared to skin biopsies, which can help patients overcome the psychological barrier of participating in research and clinical trials. In our experience, this latter point is crucial for successful ascertainment of patients because it allows access to a larger number of willing participants. Moreover, time is needed for the expansion of dermal fibroblasts *in vitro* before reaching adequate numbers needed for reprogramming while PBMCs collected from blood can be reprogrammed immediately after extraction [1,2,18]. Furthermore, in our experience, reprogramming success is not adversely affected when performed on PBMCs extracted from aged patients, in clear contrast with dermal fibroblasts extracted from elderly patients. In support of this convenient source of iPSCs we, as well as other laboratories, have successfully demonstrated the feasibility of using this accessible resource for cell reprogramming and modeling diseases like ASD, AD and PD [3,20-25].

Challenges of PBMCs as a Source for iPSC Derivation

Despite the benefits that PBMCs provide, they still pose a few challenges for iPSC derivation. Indeed, once blood is collected, temperature fluctuations and an extended timeframe to the isolation of the PBMCs can adversely affect the quality of the sample. Another challenge to using blood as a source material is that it can be difficult to study patients who have clotting disorders [26,27]. These later disorders could hinder successful extraction of needed PBMC numbers from blood, and subsequently negatively affects reprogramming success and iPSC derivation.

Another challenge is the carryover of epigenetic marks from PBMCs to the reprogrammed iPSCs. This could affect the pluripotency potential of the derived iPSCs because of "epigenetic memory", making it difficult to differentiate to certain types of cells. Evidence in the literature has shown that this issue can be circumvented by extending the number of passages the iPSC undergo to reach a basal state of epigenetic marks needed for full differentiation potential [9].

Finally, iPSCs derived from all sources pose a critical challenge regarding quality control. Since the different derived lines may have a varied differentiation potential, they must indeed be fully tested as such for quality control. In line with this train of thought, a battery of tests have been recently proposed to ensure cell line identity, genomic stability, pluripotency potential and check for residual reprogramming factors [28].

The Future of PBMC Derived iPSCs

Despite the challenges described above, PBMC-derived iPSC lines are a valuable resource for the advancement of research and therapies for many critical diseases. Indeed, the scientific community has rightfully invested huge resources to successfully tackle these challenges. Remaining to see is how government agencies are going to streamline funding and law-making in order to cope with fast approaching clinical applications of PBMC-derived iPSCs. To date, only one human trial using iPSCs has been reported; this key study used the cells to treat macular degeneration. This same trial has was halted because of the presence of two non-tumorigenic genetic changes found in the patient specific iPSCs and the differentiated Retinal Pigment Epithelium sheets generated [4]. Nonetheless, one can imagine the plethora of clinical trials that will emerge in the near future and their vast potential to impact how we ameliorate human disease.

Acknowledgement

This work was supported by the NIH grant 5P50NS071674 (DMD).

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