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Episomal Induced Pluripotent Stem Cells: Functional and Potential Therapeutic Applications

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Abstract

The term episomal induced pluripotent stem cells (EiPSCs) refers to somatic cells that are reprogrammed into induced pluripotent stem cells (iPSCs) using non-integrative episomal vector methods. This reprogramming process has a better safety profile compared with integrative methods using viruses. There is a current trend toward using episomal plasmid reprogramming to generate iPSCs because of the improved safety profile. Clinical reports of potential human cell sources that have been successfully reprogrammed into EiPSCs are increasing, but no review or summary has been published. The functional applications of EiPSCs and their potential uses in various conditions have been described, and these may be applicable to clinical scenarios. This review summarizes the current direction of EiPSC research and the properties of these cells with the aim of explaining their potential role in clinical applications and functional restoration.

Keywords

Episomal induced pluripotent stem cells, EiPSCs, iPS, therapeutic application

Introduction

Application of the reprogramming techniques first developed by Yamanaka et al.[1] has made possible the conversion of somatic cells to pluripotent stem cells that resemble embryonic stem cells (ESCs). ESCs have been touted as the "Holy Grail" for unrestricted regeneration because of their potential to differentiate into any cell lineage in the body and to replace damaged tissue. Opponents of this technique commonly cite the potential for unethical use or donation of ESCs, which are potential sources of life and embryo formation. With the development of a method to create induced pluripotent stem cells (iPSCs), it is possible to harness the regenerative properties of iPSCs, which resemble ESCs, yet without the ethical controversies associated with the sources of ESCs.

For research purposes, iPSCs can be readily cultured in the laboratory from various somatic cells. Somatic cells of various lineages have been shown to be capable of changing both their morphology and pluripotent potential through the overexpression of four main pluripotent factors: Oct3/4, Sox2, Klf4, and c-Myc (OSKM). The replacement of c-Myc and Klf4 by Nanog and Lin28 has also been shown to be possible when used in conjunction with Oct3/4 and Sox2 during the reprogramming of cells into iPSCs[2]. Overexpression of Oct4, Sox2, and Nanog can also reprogram human fetal gut mesentery-derived cells into iPSCs[3]. Although Nanog is a dispensable reprogramming factor[4], it has been reported to be essential for the ability for self-renewal[5] and generation of stable iPSCs[6]. In some cases, such as adult mouse neural stem cells, expression of only one factor (Oct4) is sufficient for the generation of iPSCs[7], even using episomal reprogramming[8]. A possible reason is the endogenous expression of Sox2, c-Myc, and Klf4 in neural stem cells. In addition, downregulation of p53 using knockdown[9] and knockout[10] methods can markedly improve the efficiency of iPSC generation[11], and only Oct4 and Sox2 are sufficient for iPSC generation under conditions of p53

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loss[12]. One possible mechanism to explain the suppression of iPSC generation by p53 is through the inhibition of the expression of Nanog and Oct4[13]. Certain somatic and adult stem cells, such as keratinocytes[14] and dental pulp stem cells[15], have a greater propensity to be reprogrammed into iPSCs compared with fibroblasts.

The introduction of these pluripotent reprogramming techniques can be divided into integrative and non-integrative methods. When first discovered, viral transduction was used for the insertion of the OSKM genes into the somatic cell genome. However, this may cause disruption to the host's genome and, with the use of the proto-oncogene c-Myc, gene reactivation could increase the risk of transgene-derived tumor formation[16,17]. Other methods have been used to reprogram somatic cells into iPSCs. In particular, non-integrative methods such as episomal plasmid delivery of pluripotent OSK genes without c-Myc have been touted as a safer alternative for iPSC generation[18,19]. Episomal plasmid vectors are also combined with p53 knockdown to generate iPSCs[10,20,21]. This review focuses on studies of the use of iPSCs generated using episomal plasmids, which are termed "episomal iPSCs" (EiPSCs) to reflect their origin.

Integrative Methods of iPSC Production

Potential issues with integrative methods of iPSC production include the inadvertent introduction of potentially harmful viral components that express certain oncogenes that may lead to tumor formation. Insertion of genes also carries the risk of disrupting the expression of host cell tumor suppressor genes, especially if the insertions occur in an open reading frame or alter the expression of oncogenes in close proximity[17]. Several viral systems have been introduced to circumvent this issue such as Cre-deletable[22] or inducible lentiviruses, which reduce the risk of integration, although concerns have been raised about the use of viral vectors for therapeutic applications. Cre-deletable lentiviruses refer to a Cre recombinase-mediated deletion of a viral genome once integration is complete. This allows for the time-controlled integration, which is self-limiting and hence minimizes the chance of permanent viral genomic integration. Inducible lentivirus commonly refers to a tetracycline- or doxycycline-inducible expression system in lentiviruses, which allows the activation or deactivation of viral genomic DNA in the presence of tetracycline. This also provides some control over the duration of the viral genomic presence and, therefore, the risk of integration with the host genome.

Non-Integrative Methods of iPSC Production

The use of plasmids for the introduction of OSK pluripotent transcription factors has been described, and this method has been successful for reprogramming somatic and adult stem cells. The use of integration-defective viral delivery systems (adenoviruses[23], Sendai viruses[24]), piggyBac systems[25], minicircle vectors[26], episomal delivery[19], mRNA delivery[27], protein delivery[28], and chemical induction[29] in the production of iPSCs has been described. The piggyBac transposition system allows the direct cutting and pasting of sections of DNA to allow insertion and removal of certain sections. Specific deletion and insertion of reprogramming genes can be performed. Minicircle vectors are small circular plasmid derivatives that are freed from all prokaryotic vector parts or bacterial plasmid DNA. However, these are not in widespread use because of the intensive production process. The delivery of mRNA and protein can be much more costly for experimental purposes, and the mRNA or protein is not always inducible downstream. Chemical induction uses specific sets of chemicals and mutagens to allow the reprogramming of cells. By subjecting cells to a specific set of chemicals, researchers have shown that cells can be reprogrammed to their pluripotent state. However, this method is extremely laborious and has unknown safety parameters at present. Episomal plasmid delivery is cost effective, and the plasmid does not integrate when used with common transfection methods. This method provides an effective method for the delivery of plasmids into cells for reprogramming[30]. The plasmids are readily available on multiple gene platforms and are removed from the host cell through cell division and serial dilution. The use of non-integrative methods of iPSC production has the advantage of producing iPSCs that are free of transgene integration. This has been confirmed by polymerase chain reaction (PCR) analysis, which shows no residual transgenes of viral origin[31]. For example, the Yamanaka group reported that no residual episomal plasmid DNA could be detected in clones after 11–20 passages[20].

Two components of the oriP and Epstein–Barr nuclear antigen-1 (EBNA-1) are also used widely in episomal plasmids[32–38]. Yu et al. reported that human iPSCs that are completely free of plasmids and transgene sequences could be derived from fibroblasts by a single transfection with oriP/EBNA-1-based episomal plasmids[39–42]. The footprint-free iPSCs make them safer for clinical application because of the loss of plasmids and transgenes. OriP/EBNA-1 plasmids have a wide host cell range for episomal reprogramming, and a single transfection of episomal plasmids is sufficient for iPSC generation. Compared with the original episomal plasmids without EBNA-1, oriP/EBNA-1 can improve the efficiency of iPSC generation[43] through the oriP/EBNA-1-mediated nuclear import and retention of vector DNA[44]. It can replicate only once per cell cycle. Episomal DNA is lost from cells at a rate of 5% per cell generation because of defects in plasmid synthesis and partitioning[45]. Subsequently, episome-free iPSCs can be easily harvested. Although plasmids appear in the first few cell passages immediately after transfection, many studies have used PCR analysis to show complete loss of plasmids and transgenes during extended cell culture[20,39–42,46–58]. The time point of successful loss of episomes varies between different somatic cell types. The oriP/EBNA-1-based episomal plasmids have

been proven to generate iPSCs very efficiently without the risk of transgenic sequences inserted into the somatic cell genome. Certain comments exist saying iPSCs generated using episomal plasmids with EBNA-1 expressed have residual episomal DNA. This does not appear to be true after reviewing the data presented by Yu et al.[39], where the group demonstrated that in fact that there were no residual plasmids and transgenes in iPSCs generated by EBNA-based plasmids using PCR and Southern blot analysis.

In an interesting experiment, the efficiency of reprogramming was compared between various methods for generating iPSCs. Reprogramming success rates were similarly high, at around 80%, with Sendai-viral, episomal, and lentivirus methods. mRNA methods alone were reported to have a lower success rate because of massive cell death and detachment. Episomal methods seem to be a good method for producing iPSCs, and the materials can be manufactured using current good manufacturing practice compatible processes (cGMP). As such, episomal methods remain very useful in the clinical setting[59].

Human EiPSC Sources

Multiple cell lineages from humans have been reprogrammed into iPSCs using episomal plasmids. Episomal plasmid reprogramming differs markedly from other forms of reprogramming techniques, such as retroviral transduction, and varied success rates have been reported. Recent trends include the increasing use of episomal plasmid methods for reprogramming various types of human cells for research use and potential clinical applications. The human cells reported to have been successfully reprogrammed into EiPSCs include fibroblasts, epithelial cells, keratinocytes, mononuclear cells from adult peripheral blood, cord blood cells, amniotic fluid stem cells, mesenchymal stromal cells, lymphoblasts, lamina propria progenitor cells from oral mucosa, and urothelial cells obtained from urine. A summary of these reported human EiPSC sources is shown in Table 1[8,20,21,32–43,47–52,55,56,58,60–207]. The variety of cell lineages that can be reprogrammed by episomal techniques demonstrates the versatility of this technique, which has been used in many laboratories around the world.

The ease of obtaining several of the human cell types, such as those in peripheral blood or urine, for reprogramming make this method less invasive for donors, and there is an equivalent success rate for producing EiPSCs of similar nature. Obtaining EiPSCs from donors with known specific genetic manipulations also allows for the establishment of cell lines for further research, especially with regards to future developments of gene therapy for these specific conditions. Episomal plasmids have been used to generate EiPSCs from various somatic cells of differing origins. Human mesenchymal stromal cells have been developed into EiPSCs through the episomal plasmid-based expression of Oct4, Sox2, Nanog, Lin28, SV40LT, Klf4, and c-Myc[60]. Other sources reported include human fetal foreskin fibroblasts, and $CD34^+$ cells from cord and peripheral human blood, which shows that peripheral blood mononuclear cells may be a good source of cells for iPSC reprogramming especially because of the low invasiveness when obtaining samples.

Gene Delivery Methods

Delivery of plasmids into cells for reprogramming has been described. These methods include electroporation techniques (using Nucleofector kits), liposomal magnetofection, and Lipofectamine transfection reagents. Liposomal transfection using magnetofection[208] or Lipofectamine refers to the delivery of plasmid DNA via liposomes and allows the merging of cationic liposomes carrying the DNA into the cells. Electroporation is the use of an electric current across cell membranes, which forcibly opens their channels to allow entry of reagents. This method has been described widely and has a higher rate of delivery efficiency but is known to cause cell damage[209]. The use of non-liposomal transfection reagents for episomal plasmid delivery, such as FuGENE HD, has also been reported to have good transfection efficiencies[210]. The company produces a proprietary formula that is touted as non-liposomal but can still deliver DNA and plasmids into cells and therefore works as a transfection kit. Recent work has also shown promise in producing EiPSCs using small molecules instead of feeder cells. A cocktail of molecules has been described for the reprogramming of human somatic cells to iPSCs. These include the MEK inhibitor PD0325901, GSK3β inhibitor CHIR99021, TGF-β/activin/nodal receptor inhibitor A-83-01, ROCK inhibitor HA-100, and human leukemia inhibitory factor[40].

In Vivo Animal Model Applications

Cardiogenic Regeneration

Much attention has focused on the use of iPSCs in cardiac regeneration especially after cardiac infarction, which causes loss of cardiomyocytes that cannot regenerate and are replaced with scar tissue. Both EiPSCs and iPSCs have been differentiated into cardiomyocytes, which shows their potential use in both autologous and allogeneic therapies. A recent study demonstrated that allogeneic EiPSCs cultured from cynomolgus monkeys, when differentiated into cardiomyocytes and injected intramuscularly infarcted cardiac muscle, induced remuscularization of infarcted muscle tissue. Fibroblasts obtained from the monkeys were reprogrammed using episomal plasmids into EiPSCs, and the EiPSCs-derived cardiomyocytes were then injected into the infarcted cardiac muscle. After a clinical regimen of immunosuppression using methylprednisolone and tacrolimus, the hearts showed improvement in cardiac contractile function without any signs of rejection on postoperative week 12[211]. The results are promising in showing that direct application of EiPSCs-derived cardiomyocytes is possible. The local environment and conditions under which the EiPSCs were directly

Table 1. Summary of Reported Human EiPSC sources available in the Literature.

Type of cell	Source	Patient conditions	Method of transfection	Further differentiation	Author
Fibroblasts	Fetal foreskin	Healthy	Electroporation	N/A	Yu et al.[39,40], Matz and Adjave[62], Tandon et al.[63], Tidball et al.[64], Kamath et al.[65], Kim et al.[66], Schmitt et al.[67], Mah et al.[68]
Fibroblasts	Fetal foreskin	Healthy	Electroporation	$CD235a^{+}CD45^{-}$ leukocyte-free red blood cells	Dias et al.[69]
Fibroblasts	Fetal foreskin	Healthy	Electroporation	Cardiomyocytes	Mehta et al.[70]
Fibroblasts	Fetal foreskin	Healthy	Electroporation	Hepatocyte-like cells	Wruck and Adjave[71]
Fibroblasts; Fibroblasts	Fetal lung	Healthy	Poly(beta-amino ester) nanoparticles; Electroporation	Neuronal cells	Bhise et al.[72]
Fibroblasts	Fetal foreskin	Healthy	Lipofectamine 3000 reagent	N/A	Skrzypczyk et al.[73]
Fibroblasts	Fetal right musculus quadriceps femoris	Healthy	Lipofectamine 3000 reagent	N/A	Csobonyeiova et al.[74]
Fibroblasts	Fetal foreskin	Homozygous α-thalassemia (−SEA/−SEA)	Electroporation	N/A	Tangprasittipap et al.[75]
Fibroblasts	Fetal epidermal tissue from rim of open neural placode and spinal cord	Spina bifda aperta (SBA)	Electroporation	Neurospheres	Bamba et al.[76]
Fibroblasts	Adult skin	Healthy	Electroporation	N/A	Bharathan et al.[36], Weltner et al.[37], Yu et al.[40], Wong et al.[77], Bang et al.[78], Hey et al.[79], Jaffer et al.[80], Trevisan et al.[81], Fidan et al.[82], Wang et al.[83], Chen et al.[84], Polanco et al.[85], Willmann et al.[86], Høffding et al.[87]
Fibroblasts	Adult skin	Healthy	Electroporation; Lipofectamine 3000 reagent; Nucleofector system	N/A	Manzini et al.[88]
Fibroblasts	Adult skin	Healthy	Electroporation	Neural stem cells	Capetian et al.[89]
Fibroblasts	Adult skin	Healthy	Electroporation	Motor neurons	Hu et al.[51]
Fibroblasts	Adult skin	Healthy	Electroporation	Neural cells	Wang et al.[90]
Fibroblasts	Adult skin	Healthy	Electroporation	Neural stem cells, motor neurons, cardiomyocytes, and fibroblasts	Requena et al.[91]
Fibroblasts	Adult skin	Healthy	Electroporation	Dopaminergic neurons and retinal pigment epithelial cells	Okita et al.[20]
Fibroblasts	Adult skin	Healthy	Electroporation	Smooth muscle progenitor cells	Zhou et al.[92]
Fibroblasts	Adult skin	Healthy	Electroporation	Retinal pigment epithelial cells	Li et al.[93]
Fibroblasts	Adult skin	Healthy	Electroporation	Cardiomyocytes	Sequiera et al.[94]
Fibroblasts	Adult skin	Healthy	FuGENE HD reagent	Hepatocyte-like and cardiac myocyte-like cells	Si-Tayeb et al.[95]
Fibroblasts	Adult gingival tissues	Healthy	Electroporation	Periodontal cells	Yin et al.[96]
Fibroblasts	Adult skin	Huntington's disease	Electroporation	N/A	Tidball et al.[21]
Fibroblasts	Adult skin	Fibrodysplasia ossificans progressiva caused by a missense mutation in ACVR1 gene	Electroporation	N/A	Hayashi et al.[35]
Fibroblasts	Adult skin	Spinocerebellar ataxia type 3	Electroporation	N/A	Hansen et al.[97,98]
Fibroblasts	Adult skin	Frontotemporal dementia caused by mutations in microtubule-associated protein tau (MAPT) gene	Electroporation	N/A	Rasmussen et al.[99–101]
Fibroblasts	Adult skin	Maturity-onset diabetes of the young 4 and type [2] diabetes mellitus caused by mutations in PDX1 gene	Electroporation	N/A	Wang et al.[52,102]
Fibroblasts	Adult skin	Autosomal recessive Stargardt disease caused by compound heterozygous mutations in ABCA4 gene	Electroporation	N/A	Claassen et al.[103]
Fibroblasts	Adult skin	X-Chromosomal disease	Electroporation	N/A	Hinz et al.[121]
Fibroblasts	Adult skin	Becker muscular dystrophy (BMD) caused by mutations in dystrophin gene on chromosome Xp21	Electroporation	N/A	Gowran et al.[105]

(continued)

Table 1. (continued)

Type of cell	Source	Patient conditions	Method of transfection	Further differentiation	Author
Fibroblasts	Adult skin	Spinocerebellar ataxia type 3 (SCA3, also known as Machado-Joseph disease) caused by a CAG trinucleotide repeat expansion in ATXN3 gene	Electroporation	N/A	Hayer et al.[106]
Fibroblasts	Adult skin	Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) caused by a heterozygous mutation in CSF1R gene	Electroporation	N/A	Hayer et al.[107]
Fibroblasts	Adult skin	Healthy and kidney disease caused by an autosomal dominant mutation in HNF4A gene	Electroporation	N/A	Howden et al.[108]
Fibroblasts	Adult skin	Prostate adenocarcinoma (PCa)	Electroporation	N/A	Kahounová et al.[109]
Fibroblasts	Adult skin	Spinocerebellar ataxia type 3 (SCA3)	Electroporation	N/A	Ritthaphai et al.[110]
Fibroblasts	Adult skin	Dravet syndrome caused by a heterozygous R1525X mutation in SCN1A gene	Electroporation	N/A	Tanaka et al.[111]
Fibroblasts	Adult skin	Mucoplysaccharydosis IIIA (MPSIIIA)	Electroporation	N/A	Vallejo et al.[112]
Fibroblasts	Adult skin	Mucopolysaccharydosis IIIB (MPSIIIB)	Electroporation	N/A	Vallejo-Diez et al.[113]
Fibroblasts	Adult skin	Late-onset non-syndromic retinitis pigmentosa caused by compound heterozygous mutations in CLN3 gene	Electroporation	N/A	Zhang et al.[114]
Fibroblasts	Adult skin	Autosomal recessive Alport syndrome (ARAS) caused by a homozygous COL4A3 mutation	Electroporation	N/A	Kuebler et al.[115]
Fibroblasts	Adult skin	X-linked Alport syndrome (XLAS) caused by hemizygous COL4A5 mutations in exon 41 or exon 46	Electroporation	N/A	Kuebler et al.[116]
Fibroblasts	Adult skin	Duchenne muscular dystrophy (DMD) lacking DMD exons 49 and 50	Electroporation	N/A	Spaltro et al.[117]
Fibroblasts	Adult skin	Leber's hereditary optic neuropathy (LHON)	Electroporation	N/A	Hung et al.[118]
Fibroblasts	Adult skin	Low-grade steatosis	Electroporation	N/A	Kawala et al.[119]
Fibroblasts	Adult skin	Fibrodysplasia ossificans progressiva syndrome caused by a mutation in ACVR1 gene	Electroporation	N/A	Kim et al.[120]
Fibroblasts	Adult skin	Alzheimer's disease caused by mutations in PSEN1 gene	Electroporation	N/A	Li et al.[121,122], Poon et al.[123], Tubsuwan et al.[124]
Fibroblasts	Adult skin	Familial Mediterranean Fever (FMF)	Electroporation	N/A	Fidan et al.[125]
Fibroblasts	Adult skin	Turner syndrome (TS) caused by monosomy X	Electroporation	N/A	Luo et al.[126]
Fibroblasts	Adult skin; Fetal skin	Retinitis pigmentosa; Severe combined immunodeficiency	Electroporation	N/A	Howden et al.[127]
Fibroblasts	Adult skin	Ankylosing spondylitis; Sjögren's syndrome; Systemic lupus erythematosus	Electroporation	Hematopoietic and mesenchymal lineages	Son et al.[47]
Fibroblasts	Adult skin	Retinitis pigmentosa-11 caused by a dominant nonsense mutation in PRPF31 gene	Electroporation	Retinal organoids	McLenachan et al.[128]
Fibroblasts	Adult skin	Rare neurodevelopmental disorders (NDDs)	Electroporation	Forebrain neurons	Bell et al.[129]
Fibroblasts	Adult skin	Down syndrome	Electroporation	Neuronal cells	Briggs et al.[130]
Fibroblasts	Adult skin	Alzheimer's disease caused by mutations in PSEN1 gene	Electroporation	Mature neurons with amyloidogenic properties	Mahairaki et al.[131]
Fibroblasts	Adult skin	Low-density lipoprotein receptor (LDLR) deficiency familial hypercholesterolemia (FH)	Electroporation	Hepatocyte-like cells	Ramakrishnan et al.[132]
Keratinocytes	Adult skin	Healthy	FuGENE HD reagent	N/A	Piao et al.[133]
Mononuclear cells	Fetal peripheral blood	Healthy	Electroporation	N/A	Dowey et al.[134]
Mononuclear cells	Neonatal peripheral blood and cord blood	Lung disease	Electroporation	N/A	Kamath et al.[135]
Mononuclear cells	Adult peripheral blood	Healthy	Electroporation	N/A	Okita et al.[43], Wen et al.[136,137], Wang et al.[138,139], Su et al.[140], Tangprasittipap et al.[141], Mack et al.[142], Chou et al.[143]
Mononuclear cells	Adult peripheral blood	Healthy	Electroporation	Cardiovascular progenitor cells	Hu et al.[61]
Mononuclear cells	Adult peripheral blood	Healthy	Electroporation	Ventricular cardiomyocyte	Weng et al.[144]

(continued)

Table 1. (continued)

Type of cell	Source	Patient conditions	Method of transfection	Further differentiation	Author
Mononuclear cells	Adult peripheral blood	Healthy	Electroporation	Hepatocytes	Liu et al.[145]
Mononuclear cells	Adult bone marrow	Healthy	Electroporation	Mesenchymal stem cells	TheinHan et al.[146]
Mononuclear cells	Adult peripheral blood	Alzheimer's disease	Electroporation	N/A	Wang et al.[147–150]
Mononuclear cells	Adult peripheral blood	Bipolar disorder (BD)	Electroporation	N/A	Wang et al.[151]
Mononuclear cells	Adult peripheral blood	Obsessive compulsive disorder (OCD)	Electroporation	N/A	Wang et al.[152]
Mononuclear cells	Adult peripheral blood	Parkinson disease	Electroporation	N/A	Zhao et al.[153]
Mononuclear cells	Adult peripheral blood	Complete dopa-responsive dystonia (DYT5) caused by a GCH1 mutation	Electroporation	N/A	Murakami et al.[154]
Mononuclear cells	Adult peripheral blood	Hypertrophic cardiomyopathy caused by mutations in beta-myosin heavy chain (MYH7) gene	Electroporation	N/A	Ross et al.[155]
Mononuclear cells	Adult peripheral blood	Sickle cell anemia (SCA)	Electroporation	$CD34^{+}CD45^{+}$ hematopoietic stem and progenitor cells	Junqueira Reis et al.[156]
Mononuclear cells	Adult peripheral blood	Myocardial infarction	Electroporation	Cardiomyocytes	Malecki et al.[157]
Mononuclear cells	Adult bone marrow	Healthy	Electroporation	Mesenchymal stem cells, adipocytes, chondrocytes, and osteoblasts	Tang et al.[158]
Mononuclear cells	Adult peripheral blood and bone marrow	Myelodysplastic syndromes (MDS)	Electroporation	$CD34^{+}CD45^{+}$ hematopoietic stem and progenitor cells (HPC), and $CD71^{+}CD235a+$ erythroid cells	Hsu et al.[159]
Mononuclear cells	Fetal cord blood and neoplastic bone marrow; Adult patient	Healthy; Chronicmyeloid leukemia	Electroporation	$CD34^{+}CD43^{+}$ hematopoietic progenitors, $CD34^{+}CD31^{+}CD43^{-}$ endothelial cells, and $CD34^{+}CD31^{-}CD43^{-}$ mesenchymal cells; N/A	Hu et al.[41,160]
Erythroblast	Adult peripheral blood	Healthy	Electroporation	N/A	Varga et al.[161]
Erythroblast	Adult peripheral blood	Ataxia-Telangiectasia (A-T) caused by compound heterozygous null mutations in ATM kinase gene at chromosome 11q22	Electroporation	Neural Stem Cells	Bhatt et al.[162,163]
Cord blood $CD34^{+}$ cells	Fetal cord blood	Healthy	Electroporation	N/A	Chou et al.[48], Meng et al.[56], Su et al.[164], Fernandes et al.[165–167]
Amniotic fluid cells	Fetal amniotic fluid	Healthy	Electroporation	N/A	Slamecka et al.[168], He et al.[169]
Amniotic fluid cells	Fetal amniotic fluid	Healthy	Fugene HD reagent	Neural cells	Wilson et al.[170]
Amniotic fluid cells	Fetal amniotic fluid	Trisomy 18 (18T)	Electroporation	N/A	Xing et al.[171]
Mesenchymal stromal cells	Fetal amnion	Healthy	Electroporation	N/A	Slamecka et al.[172]
Mesenchymal stromal cells	Fetal femur	Healthy	Electroporation	N/A	Megges et al.[60]
Mesenchymal stromal cells	Adult femur	Healthy	Electroporation	N/A	Göbel et al.[173], Foja et al.[174]
Mesenchymal stromal cells	Adult subcutaneous fat	Healthy	Electroporation	N/A	Qu et al.[175]
Mesenchymal stromal cells	Adult dental pulp	Healthy	Electroporation	Neural progenitor cells	Thekkeparambil Chandrabose et al.[176], Saitoh et al.[177]
Mesenchymal stromal cells	Adult parotid gland	Squamous cell carcinoma of oral cavity	Electroporation	N/A	Yan et al.[178]
Neural stem cells	Neonate	Healthy	Electroporation	N/A	Marchetto et al.[58]
Neural stem cells	Fetal cortical tissue	Healthy	Electroporation	Neural cells	Zhou et al.[8]
Lymphoblast	Adult peripheral blood	Healthy	Electroporation	N/A	Schroter et al.[179]
Lymphoblast	Adult peripheral blood	Healthy	Electroporation	Neurons, spinal motor neurons, and intestinal organoids	Barrett et al.[180]
Lymphoblast	Adult peripheral blood	Parkinson's disease	Electroporation	N/A	Kumar et al.[49]
Lymphoblast	Adult peripheral blood	Alzheimer's disease caused by a TREM2 missense mutation	Electroporation	N/A	Schroter et al.[181]
Lymphoblast	Adult peripheral blood	Alzheimer's disease caused by a homozygous APOE4 allele mutation	Electroporation	N/A	Zulfiqar et al.[182,183]
Lymphoblast	Adult peripheral blood	Alzheimer's disease with different genotypes of a functional copy number variation in the AD risk gene CR1; AD with TREM2 p.R47H variant	Electroporation	N/A	Schröter et al.[184,185]
Lymphoblast	Adult peripheral blood	APOE ε3/ε3 genotype and expressing CR1 isoform F/F (low risk of Alzheimer's disease)	Electroporation	N/A	Martins et al.[186]

(continued)

Table 1. (continued)

Type of cell	Source	Patient conditions	Method of transfection	Further differentiation	Author
T cells	Adult peripheral blood	Healthy	Electroporation	Neuronal cells	Tsai et al.[33]
T cells	Adult peripheral blood	Age-related macular degeneration	Electroporation	Retinal pigment epithelial cells	Chang et al.[34]
B cells	Adult peripheral blood	Healthy	Electroporation	N/A	Choi et al.[55]
B cells	Adult peripheral blood	Healthy	Electroporation	Hematopoietic, cardiac, neural, and hepatocyte-like lineages	Rajesh et al.[42]
B cells	Adult peripheral blood	Parkinson's disease	Electroporation	Neurospheres, and neural cells	Fujimori et al.[187]
Lamina propria progenitor cells	Adult oral mucosal	Healthy	Electroporation	N/A	Howard-Jones et al.[188]
Oral mucosa epithelial stem cells	Adult oral mucosal	Healthy	Electroporation	N/A	Alvisi et al.[189]
Oral mucosa epithelial stem cells	Adult oral mucosal	Ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome caused by a R279H mutation in TP63 gene	Electroporation	N/A	Trevisan et al.[190]
Urine cells	Adult urine	Healthy	Electroporation	N/A	Wang et al.[191]
Urine cells	Adult urine	Healthy	Electroporation	Hepatocyte-like cells	Si-Tayeb et al.[192]
Urine cells	Adult urine	Multiple endocrine neoplasia type 1 (MEN1) (also termed Wermer syndrome) caused by mutations in tumor suppressor gene MEN1	Electroporation	N/A	Guo et al.[193]
Urine cells	Adult urine	Type 2 long QT syndrome caused by a mutation in HERG A561P gene	Electroporation	Cardiomyocytes	Jouni et al.[194]
Urine progenitor cells	Adult urine	Healthy	Lipofectamine 3000 reagent	N/A	Steichen et al.[195]
Urine epithelial cells	Adult urine	Healthy	Electroporation	N/A	Ju et al.[196]
Urine epithelial cells	Adult urine	Healthy	Electroporation	Hepatocytes	Sauer et al.[50]
Urine epithelial cells	Adult urine	Phenylketonuria (PKU)	Electroporation	N/A	Qi et al.[197]
Urine epithelial cells	Adult urine	Spinal muscular atrophy (SMA) caused by mutations in survival motor neuron 1 (SMN1) gene	Electroporation	Motor neurons	Zhou et al.[198]
SIX2-positive renal cells	Adult urine	An African male expressing the CYP2D6 *4/*17 variant which confers intermediate drug metabolizing activity	Electroporation	N/A	Bohndorf et al.[199]
Epicardium-derived cells	Adult atrial biopsy	Healthy	Electroporation	N/A	Paulitschek et al.[200]
Neonatal fibroblasts; Adult skin fibroblasts; Urine epithelial cells; Amniotic fluid cells	Neonatal and adult skin; adult urine	Healthy	PEI reagent	N/A	Drozd et al.[32]
Fibroblasts; Urine epithelial cells	Adult skin; adult urine	Healthy	PEI reagent	Insulin producing cells	Walczak et al.[38]
Fibroblasts; Mononuclear cells	Adult skin; Adult peripheral blood	Healthy	Electroporation	Cardiomyocytes, endothelial cells, and neuronal cell	Diecke et al.[201]
Fibroblasts; Mononuclear cells	Adult skin; Adult peripheral blood	Kawasaki disease (KD)	Electroporation	Vascular endothelial cells	Ikeda et al.[202]
Mononuclear cells; Mesenchymal stromal cells	Adult peripheral blood and bone marrow	Healthy	Electroporation	N/A	Cheng et al.[203]
Fetal fibroblasts; Adult fibroblasts; Keratinocytes; Cord blood $CD34^+$ cells	Fetal skin; Adult skin; Adult skin; Fetal cord blood	Healthy	Electroporation	N/A	Park et al.[204]
Fibroblasts; Cord blood $CD34^+$ cells	Adult skin; Fetal cord blood	Healthy	Electroporation	Vascular progenitor cells	Park et al.[205]
Fibroblasts; Keratinocytes	Adult skin; Hair follicle	Timothy syndrome with cardiac arrhythmias	Lipofectamine 2000 reagent	Cardiomyocytes	Song et al.[206]
Cancer cells	Adult lung	Adenocarcinoma	X-tremeGENE transfection reagent	N/A	Zhao et al.[207]

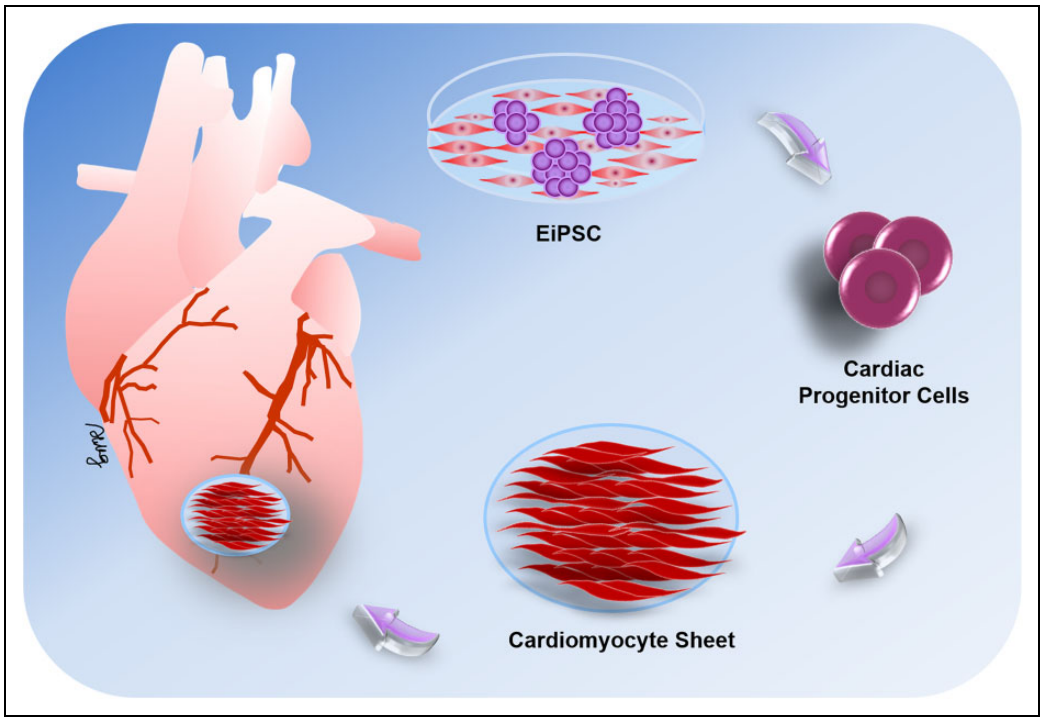

Figure 1. The potential application for cardiac cell sheet strategies using EiPSC-derived cardiomyocytes. EiPSCs can be differentiated into cardiac progenitor cells, which are then induced to form cardiomyocytes *in vitro*. These cardiomyocytes can then be organized into a cell sheet and applied to damaged areas of cardiac muscle *in vivo* via intracoronary or intracardiac injections or epicardially by tissue-engineered cardiac patches. The cell sheets exhibit regenerative capabilities and induce the restoration of cardiac function after muscle damage.

injected allowed for their direct use and differentiation according to clinical need. A diagram of the potential application for an EiPSCs-engineered cardiac cell sheet is shown in Fig. 1.

One problem with bioengineered tissue is that it cannot be used to create a large structure, which requires thorough oxygenation, because of the lack of vascularization in the bioengineered construct. EiPSCs were reported to regenerate vascular tissue if some were first converted to patient-specific cardiovascular progenitor cells, which then differentiated into vascular smooth muscle cells to make up the vascular scaffold present in blood vessels. This new development heralds the potential for integration and creation of larger bioengineered constructs that can become vascularized. This suggests the potential ability to design whole organs with vascularized networks made from the patient's cells, which are then attached using conventional surgical methods. This may allow the organ to be manufactured in the laboratory and vascularized[61].

Peripheral Nerve Regeneration

EiPSCs have shown promise in promoting the regeneration of peripheral nerves in a mouse sciatic transection model[212]. Transection or neurotmesis of peripheral nerves is notoriously difficult to recover and usually leads to wasting of motor end plates, muscle atrophy, and functional loss, which markedly impairs the patient's quality of life. In this mouse model, undifferentiated EiPSCs were applied to the transected ends of the sciatic nerves after coaptation of both ends by suturing. Compared with the negative control without cell administration, sciatic nerves treated with EiPSCs displayed significantly faster axonal regeneration and a ration of the degree of myelination to axonal diameter. These positive changes were similar to those observed in the ESC group, which acted as a positive control. The results of this study demonstrate the neuroregenerative potential of EiPSCs. One possible mechanism includes the increased expression of neutrotrophin-3, a neuronal growth factor, which can accelerate axonal regeneration and myelination. Direct application of EiPSCs to the site of injury and nerve transection presumably allowed the EiPSCs to act through a paracrine mechanism due to its direct effect and fast nature; they probably differentiate but rather, when applied to the environment, promoted sciatic nerve recovery through the upregulation of neutrotrophin-3 and subsequent secretion of neuronal growth factor by the EiPSCs themselves. The diagram in Fig. 2 shows a depiction of the actions of EiPSCs on mouse transected peripheral nerve regeneration.

Ischemic Stroke Therapy

Mouse embryonic fibroblasts reprogrammed into EiPSCs using episomal plasmid transfection were delivered and used

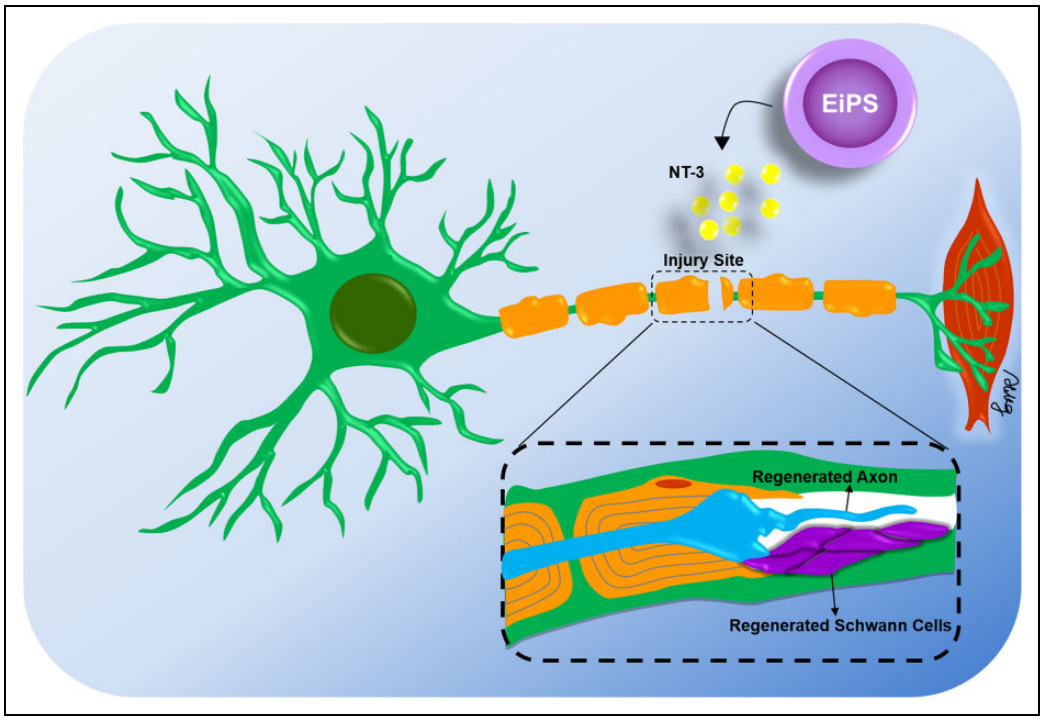

Figure 2. Topical application of EiPSCs to transected peripheral nerves. After surgical repair of transected peripheral nerves in a mouse sciatic nerve model, axonal regeneration was accelerated by topical application of EiPSCs to the site of injury. The increased production of neurotrophic factor-3 as a growth factor was one of the causes of acceleration of axonal growth and maintenance of muscle function and gait. Compared with negative controls without cell administrations, the regenerated axons exhibited a higher quality of myelination and more cells were obtained.

to treat mice in an ischemic stroke model[213]. To avoid oncogenic and virus integration, while generating EiPSCs, two expression plasmids, Oct4 and Sox2, were repeatedly transfected into fibroblasts under hypoxic condition. The EiPSCs were first differentiated into neural precursor cells before being injected into the brain of mice after the induced ischemic stroke. The authors observed evidence of the differentiation of precursor cells into neurons and astrocytes. They concluded that these observed changes resulted in better behavioral recovery including locomotor activity, beam walking, and rotarod movement compared with control mice.

Smooth Muscle Regeneration

The use of EiPSCs in the regeneration of smooth muscle cells for the treatment of stress-induced urinary incontinence has also been described[214]. Inadequate muscle sphincter function is a possible cause for urinary incontinence, and regeneration of smooth muscles at this sphincter may increase sphincter tone and hence urinary continence and control. The group here conducted experiments in rat urethral sphincters which were surgically weakened, resulting in urinary incontinence. Smooth muscle precursor cells were then differentiated from human EiPSCs and injected periurethrally to enhance muscle tone. Leak pressure and sphincter muscle electromyography were measured as markers of recovery. The group with the EiPSCs-derived smooth muscle injection showed recovery of the sphincter compared with the control without cell administration, which suggested that this method of treatment may be possible for restoration of urethral sphincter function.

EiPSCs currently have the potential for cardiac regeneration to replace damaged myocardium. The topical application of cells to regenerate a limited area appears promising, but reconstructing an entire cardiac structure requires further bioengineering advances to deliver blood supply to the entire organ. The use of EiPSCs in peripheral nerve regeneration can improve transected nerve recovery. Direct applications after surgical repair can enhance recovery through nerve growth factor secretion. In ischemic stroke therapy, EiPSCs may have potential for improving the recovery of damaged neural cells in the brain by differentiating into neurons and astrocytes, which should result in better motor recovery. EiPSCs can also play a role in regeneration of smooth muscle cells, leading to restoration of muscle sphincter function in urinary incontinence. A summary of the EiPSCs used in various functional studies is shown in Table 2[211–214].

Clinical Trials

Current clinical trials known at the time of writing this review all involve iPSCs derived from retroviral transduction. A trial of the replacement of retinal pigment epithelium

Table 2. Summary of EiPSCs used in Various Functional Studies.

Type of cell	Animal model	Method of transfection	Differentiated cell type	Functional application	Author
Mouse fibroblasts	Mouse	FuGENE HD reagent	Neural precursor cells	Ischemic stroke therapy	Liu et al.[213]
Mouse fibroblasts	Mouse	Lipofectamine 3000 reagent	N/A	Transected peripheral nerve recovery	Loh et al.[212]
Primate fibroblasts	Cynomolgus monkey	Electroporation	Cardiomyocytes	Myocardial infarction recovery	Shiba et al.[211]
Human fibroblasts	Rat	Electroporation	Smooth muscle cells	Urethral spincter recovery	Wang et al.[214]

cells (RPEs) in age-related macular degeneration (ARMD) was recently continued and is in progress. The human iPSCs used in this case were derived from retroviral reprogramming[215]. Human iPSC-derived RPE cell sheets were generated without any artificial scaffolds, express typical RPE cell markers, form tight junctions that exhibit polarized secretion of growth factors, and show phagocytotic ability and gene-expression patterns similar to those of native RPE cells. The monolayer cell sheets have potential use as a graft for tissue replacement therapy for ARMD.

The trial was temporarily halted because spontaneous genetic mutations were found in the generation of iPSCs[216]. The spontaneous mutations comprised six mutations, in which three genes had been deleted and another three nucleotides changed. One of the mutations was an "oncogene," which has a low-risk link to cancer. None of these mutations were present in the patient's original DNA makeup. The appearance of mutations was deemed to be either the result of the iPSC induction procedure or the presence at undetectable levels in the patient's somatic skin cells initially. As the risk of carcinogenesis was low, the trial was continued as planned[217].

Currently registered trials focus on platelet generation for treating various anemias. However, the research group faced the problem of the mass production of platelets required for effective clinical use. Other trials involve the differentiation of dopaminergic neurons piloted for use in Parkinson's disease. Retinal ganglion cells are also being used for treatment of glaucoma and optic neuropathies. Except for the current trial in Japan of the use of RPE cells for wet ARMD mentioned above, all of these trials are in the preclinical or animal model stages[218]. Guidelines for further clinical trials for stem cell research involving patients and iPSCs were issued by the International Society for Stem Cell Research in 2016. These guidelines suggest that the donor cell procurement should be checked for iPSCs intended for use in human, and that these cells should be excluded from specialized reviews because they are now acknowledged to have different implications in the treatment of disease compared with human ESCs[219].

Safety

The evidence for the safety of the use of EiPSCs in animal models is only now emerging, and there is a paucity of evidence in this area. Mice given EiPSCs at the site of the transected sciatic nerve displayed no formation of tumors locally at the site of application[212]. Distant sites and major organs were also examined histologically for the presence of tumors after 1 year of follow-up. Normal behavior and health of the mice were recorded, and no ill effects of EiPSCs were reported in this group. Another study found no aberrant growths from differentiated EiPSCs that were added to primate hearts regeneration after a myocardial infarction[211]. Neither macroscopic nor microscopic analysis revealed any evidence of tumor formation at 12 weeks after transplantation of the EiPSCs-derived cardiomyocytes. One possible reason is that the EiPSCs used were completely differentiated, with minimal residual EiPSCs present remaining after grafting, which resulted in no tumor formation. Because viral or integrative reprogramming techniques may alter gene expression, the use of episomal reprogramming techniques in the production of EiPSCs may reduce the risk of tumor transformation. Further evidence is required to understand more about the safety of the use of EiPSCs and to substantiate the hypothesized mechanisms of action. One possible future direction is to compare the formation of tumors in two groups—undifferentiated EiPSCs and iPSCs generated from other methods such as retroviruses grafted onto recipients. The possible lack of tumor formation seen in EiPSC-transplanted groups from such a study design would provide evidence of its safety.

Yamanaka Cell Bank: A Future in Autologous and Allo-iPSC Therapy

With the recent establishment of the Yamanaka stem cell bank at the RIKEN BioResource Center in Japan, several human iPSC cell lines have been produced in preparation for future research or clinical application. A switch to episomal methods of iPSC production is evident from the most recent human iPSC cell lines formed at the Yamanaka stem cell bank[220]. As mentioned previously, to enable use of the cells clinically, particular attention should be paid to the methods of iPSC production that favor episomal methods. The Yamanaka stem cell bank has successfully produced multiple human cell lines of EiPSCs using transformation of human cells from various types. EiPSCs have been produced from human skin fibroblasts (cell numbers HPS0076, HPS0077)[221,222], human cord blood (cell numbers HPS0328,

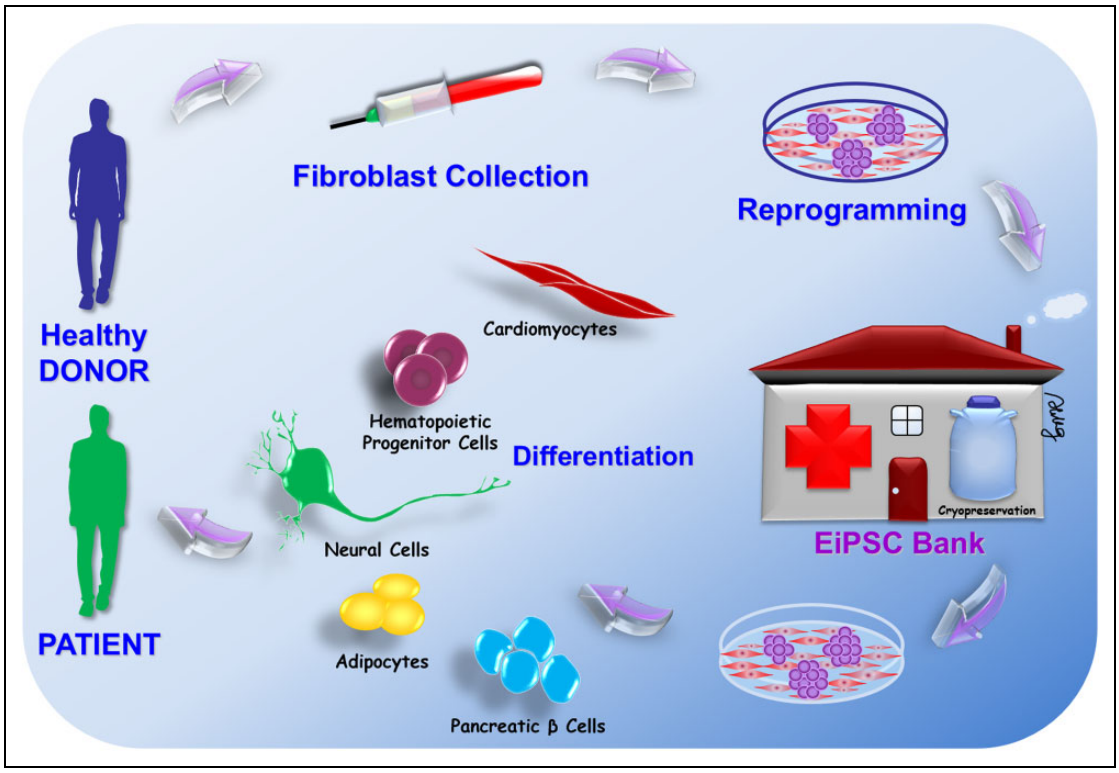

Figure 3. The potential for an EiPSC bank. The pluripotent potential of EiPSCs allows them to differentiate into various cell lineages for repair and regeneration. Fibroblasts from healthy donors can be harvested and reprogrammed into EiPSCs and stored in a cell bank. These EiPSCs can then be differentiated into various cell lineages for repair and regeneration according to the needs of individual patients. So far, these cells include cardiomyocytes, hematopoietic progenitor cells, neural cells, adipocytes, and pancreatic islet cells. Each of these cells can be used to replace damaged cells in patients and provide a novel therapeutic potential for each clinical scenario. For any allogeneic transfer of EiPSCs, MHC mismatch typing can first be performed to minimize any chance of MHC mismatch incompatibility before selecting the least antigenic EiPSC bank sample to be transferred to the patient.

HPS0331), and human peripheral blood (cell number HPS0360)[43]. Other than the two initial cell lines produced from human, which were obtained using retroviral transduction without c-Myc, the five more recently developed human EiPSC cell lines were produced purely via episomal vectors. A diagram showing the potential for an EiPSC bank is depicted in Fig. 3.

The immunogenicity of iPSCs generated remains an unknown area of research. A recent study showed a possible immune response toward smooth muscle cells derived from iPSCs but not the RPE from iPSCs[223]. Possible strategies for bypassing a possible immune response include the development of humanized iPSCs-derived RPE cells for transplantation. In a humanized mouse model, Zhao et al. found that the smooth muscle cells induced a strong antigenic response by the host's immune system which was not evident when RPE cells were used. The potential use of immunosuppression must be considered for the clinical use and clinical trials of iPSCs. If there is evidence of rejection of tissue as for a foreign host, immunosuppressants should be administered when the cells are delivered to the recipient. The use of iPSCs for treating Parkinson's disease has been reported in Japan. However, certain clinical considerations, such as the safety and therapeutic use of iPSCs in patients with Parkinson's disease, are needed. Clinical trials are underway for examining this aspect of iPSC use and treatment. Current rapid integration into its clinical use should continue to surface within the next few years[224].

Conclusion

The future of EiPSCs lies in the increasing trend for the use of cell therapy in the treatment of various diseases because of their regenerative properties. Differentiating these cells before use or their direct application requires further investigation. The immunogenicity of allogeneic EiPSCs will also need to be determined for the tissue both derived and differentiated from these cells.

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