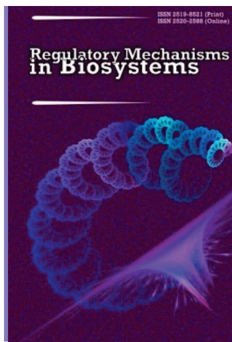

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Induced pluripotent stem cells for cardiovascular therapeutics: Progress and perspectives

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The discovery of methods for reprogramming adult somatic cells into induced pluripotent stem cells (iPSCs) opens up prospects of developing personalized cell-based therapy options for a variety of human diseases as well as disease modeling and new drug discovery. Like embryonic stem cells, iPSCs can give rise to various cell types of the human body and are amenable to genetic correction. This allows usage of iPSCs in the development of modern therapies for many virtually incurable human diseases. The review summarizes progress in iPSC research in the context of application in the cardiovascular field including modeling cardiovascular disease, drug study, tissue engineering, and perspectives for personalized cardiovascular medicine.

Keywords: cardiovascular; cell-based therapy; induced pluripotent stem cells; iPSCs; regenerative medicine; stem cell reprogramming.

Introduction

The field of stem cell biology and regenerative medicine has been dramatically impacted by the discovery of reprogramming somatic cells into induced pluripotent stem cells (iPSCs) (Takahashi & Yamanaka, 2006; Okita et al., 2007). This has opened new horizons for human therapy. iPSC-technology holds an unprecedent potential for generation of patient-specific pluripotent stem cells able to bypass immune rejection and to be a source for tissue replacement therapy and an invaluable tool for modeling various diseases. Stem cells can be renewed through their division and differentiate into different cell lines. Based on their origin, all stem cells can be divided into embryonic stem cells (ESCs), iPSCs, and adult stem cells, such as mesenchymal stem cells (MSCs). According to the ability to differentiate into other cell types, stem cells can also be classified in totipotent with the most differentiation potential, pluripotent, multipotent, oligopotent, and unipotent cells. ESCs represent pluripotent cells originated from the blastocyst and capable of giving rise to three germ layers (Gepstein, 2002). These cells are regarded as a renewable cell source for the regeneration of all tissues of the body (Gepstein, 2002). MSCs are able to differentiate into discrete cell types only (multipotent) and represent adult heterogeneous cells expressing a high level of pluripotent markers (Zomer et al., 2015). Unlike ESCs and MSCs, iPSCs represent somatic cells reprogrammed to give rise to cells with pluripotent capabilities. However, iPSCs share many similar properties with ECSs and MSCs, such as differentiation potential and the capability to form embryoid body, teratomas and chimeras.

Since iPSCs can be expanded indefinitely and are able to differentiate into all three germ layers, this allows the generation of patient-specific pluripotent stem cells, which can be genetically corrected and then differentiated into any autologous adult cell lineage and autografted to a patient (Takahashi & Yamanaka, 2006). An important feature of iPSCs is also their unlimited proliferation in vitro while maintaining their pluripotency (Okita et al., 2007). Autologous patient-specific iPSCs have the potential to provide an unlimited source of cells for gene and cell therapies for specific human diseases having unlimited proliferative and self-renewal capacities and extensive differentiation capability into a wide range of adult somatic cell types. Recently, significant advances have been achieved in safety and efficiency of iPSCs generation opening the possibility to expand iPSC-based technology into clinical application. On the other hand, although iPSCs have a tremendous potential for cell-based drug screening, cell transplantation therapy, and disease modeling, extensive analyses are still required to prove the safety and reliability of the technology for clinical application.

Generation of iPSCs

Encouraged by the findings that unfertilized eggs and ESCs contain a set of factors that can confer pluripotency to somatic cells, Takahashi & Yamanaka (2006) have identified embryonic transcription factors that are responsible for the restoration of pluripotency in adult somatic cells. Of such factors known to be involved in the process of self-renewal, commonly associated with cell transformation and implicated in the maintenance of ESCs pluripotency, four factors have been determined to be required to recover iPSCs: OCT4 (octamer-binding transcription factor 4, POU5F1), SOX2 (sex determining region Y related high mobility group box 2), c-MYC (a proto-oncogene from myelocytomatosis oncogenes family of transcription factors), and KLF4 (Krüppel-like factor 4) (Takahashi & Yamanaka, 2006; Okita et al., 2007).

A marker of cell stemness OCT4 is a key transcriptional factor responsible for the maintenance of pluripotency in ESCs (Okumura-Nakanishi et al., 2005). In addition, OCT4 contributes to the rapid stem cell cycle by transcriptional inhibition of cyclin-dependent kinase inhibitor 1 (p21Cip1, CDKN1A) (Lee et al., 2010). The transcription factor SOX2 is also essential for maintaining cell pluripotency (Boyer et al., 2005; Loh et al., 2006) comprising a regulatory complex with OCT4 and reduced expression protein 1 (Rex1, ZFP42) and activating transcription of the other pluripotency factors (Okumura-Nakanishi et al., 2005; Shi et al., 2006) under the control of a transcriptional regulator nucleophosmin 1 (NPM1) (Johansson & Simonsson, 2010). The c-MYC, the proto-oncogene with multiple downstream targets, enhances cell proliferation and transformation, resulting in self-renewal of stem cells (Adhikary & Eilers, 2005). Many c-MYC binding sites are associated with histone acetyltransferase complexes, and the c-MYC protein can induce global histone acetylation allowing OCT4 and SOX2 to bind to other inaccessible sites (Fernandez

et al., 2003). c-MYC act early to repress somatic cell genes and binding to OCT4, SOX2, and KLF4 may be a later step in the mechanisms of somatic cell reprogramming (Sridharan et al., 2009). KLF4, a member of the zinc finger transcription factors family, is an oncogene contributing to the long-term maintenance of the ESC-like phenotype (Lin et al., 2005). The role for KLF4 in cell reprogramming is to control the transcription by downregulating expression of the tumour protein p53 and the transcriptional factor Nanog (NANOG) (Lin et al., 2005). Also, KLF4 can activate transcription by interacting with histone acetyltransferase p300 (EP300) and p21Cip1. This suppresses cell proliferation and reciprocally acts with c-MYC (Zhang et al., 2000a; Evans et al., 2007). It has been demonstrated that an increment of the OCT4 transgene in the reprogramming cocktail enhances induction of iPSCs, whereas the increments in SOX2, KLF4, and c-MYC reduce the reprogramming efficiency (Papapetrou et al., 2009).

These four so called "Yamanaka factors", OCT4, SOX2, KLF4, and c-MYC (also commonly abbreviated as OSKM), have been widely used to successfully reprogram human and animal somatic cell types into a pluripotent state (Aasen et al., 2008; Hanna et al., 2008; Yoshida et al., 2009; Woltjen et al., 2009; Papapetrou et al., 2009; Kaji et al., 2009; Esteban et al., 2010; Ban et al., 2011; Subramanyam et al., 2011; Anokye-Danso et al., 2011; Deng et al., 2012; Bar-Nur et al., 2014; Umegaki-Arao et al., 2014; Schlaeger et al., 2015; Bueno et al., 2016; Deng et al., 2016; Burnett et al., 2016; Sayed et al., 2020; Merkle et al., 2021; Martello et al., 2022). c-MYC can be replaced in OSKM with another member of the family, l-MYC (Tang et al., 2018). Reprogramming of different cells to iPSCs by transduction of three factors only, OCT4, SOX2, and KLF4, has also been demonstrated, however, with relatively low efficiency (Aasen et al., 2008; Esteban et al., 2010; Hörnblad & Remeseiro, 2022). Some researchers have limited the number of the Yamanaka reprogramming factors sufficient to generate iPSCs to only two of them, OCT4/KLF4 (Kim et al., 2008), OCT4/SOX2 (Huangfu et al., 2008), or even single OCT4 (Kim et al., 2009; Tsai et al., 2011). Other authors have suggested that OCT4 can be completely omitted and SOX2, KLF4, and c-MYC only are essential for iPSCs generation with an enhanced developmental potential (Velychko et al., 2019). The homeobox protein Nkx-3.1 (NKX3-1) has been identified as an early and transiently expressed transcription factor that activates OCT4 and can replace the latter in iPSC induction (Mai et al., 2018). OCT4 can also be replaced by OCT4 targeting proteins such as the nuclear receptor 5A2 (NR5A2), or some transcription factors such as Tet methylcytosine dioxygenase 1 (TET1), bromodeoxyuridine, and Sal-like protein 4 (SALL4) (Eguchi et al., 2016). One recent study has demonstrated that OSKM directly targets a regulatory gene network required for the induction and establishment of pluripotency, consisting of nine transcriptional regulators: CBFA2T3, GLI2, IRF6, NANOG, OVOL1, RCAN1, TAF1C, TEAD4, and TFAP4 (Papathanasiou et al., 2021). However, specification of cell fate is highly plastic during somatic cell reprogramming and can lead to distinct gene expression along the iPSC pathway accompanied by transient expression of genes of unrelated lineages (Deng et al., 2021). Such genome plasticity can alter cell fate through replication-mediated passive DNA demethylation, active DNA demethylation mediated by the family of DNA demethylases Tet, and chromatin-mediated mechanisms (Meir & Li, 2021).

OSKM can be modified with the addition of some extra components to more successfully obtain iPSCs (Chou et al., 2011). Such components are human telomerase reverse transcriptase (hTERT) and SV40 large T antigen (SV40 LT). hTERT, a catalytic subunit of telomerases, can be activated by many transcription factors including c-MYC and other oncogenes, while cancer suppressing factors, such as p53, can suppress its activity (Ćukušić et al., 2008). hTERT has been found upregulated in both embryonic and adult stem cells elongating cell telomeres, and therefore, increasing cell lifespan and self-renewal properties of stem cells (Flores & Blasco, 2010). Somatic cells with hTERT upregulation showed a significantly increased rate of reprogramming into iPSCs (Utikal et al., 2009). SV40 LT, an oncoprotein derived from polyomavirus SV40, is capable of binding to the tumour suppressor protein p53 and other cellular factors, including transcriptional co-activators such as p300, and promoting DNA replication (Ahuja et al., 2005). Another inhibitor of p53, pifithrin A, also can be used to increase the efficiency of iPSC generation (Deng et al., 2012).

Alternative combination of reprogramming factors, so called "Thomson factors", has also been successfully used for reprogramming somatic cells into iPSCs and consists of OCT4, SOX2, Nanog and Lin-28 homolog A (LIN28) (Yu et al., 2007; Chou et al., 2011; Narsinh et al., 2011; Warren et al., 2012). Nanog is a transcription factor in ESCs maintaining the pluripotency by suppressing cell determination factors in cooperation with other transcription factors, such as OCT4, SOX2, and Rex1 (Boyer et al., 2005; Loh et al., 2006). Like SOX2, Nanog has been found to be a transcriptional activator for the ZFP42 promoter (Shi et al., 2006) and enhances the efficiency of the reprogramming (Hanna et al., 2009). LIN28, an RNA-binding protein, is thought to regulate stem cells self-renewal, highly expressed in ESCs, and is able to enhance the efficiency of iPSC reprogramming through the control of cell proliferation (Yu et al., 2007; Hanna et al., 2009; Chou et al., 2011; Warren et al., 2012). Some researchers have also used OSKM in combination with Nanog, LIN28, and SV40 LT (Hu et al., 2011; Tang et al., 2018; Ma et al., 2022), or OSKM supplemented with LIN28 alone to generate iPSCs (Warren et al., 2012; Liu et al., 2014; Burnett et al., 2016; Wang et al., 2022).

Highly efficient reprograming of somatic cells into iPSCs has also been achieved using a modified version of OCT4 fused with the myoblast determination protein 1 transactivation domain (MYOD1) in combination with SOX2, KLF4, c-MYC, LIN28, and Nanog (Warren et al., 2012). It has also been reported that some types of somatic cells can be reprogrammed into iPSCs with ectopic expression of the myeloid transcription factor CCAAT/enhancer-binding-protein α (CEBPA) or with specific knockdown of factor PAX5, a member of paired box proteins (PAX) transcription factor family (Hanna et al., 2008; Bueno et al., 2016). A reprogramming cocktail consisting of OCT4, SOX2, KLF4, and poly-(ADP-ribose) polymerase 1 (PARP1) replacing c-MYC can also be successfully used to effectively promote iPSC generation (Chien et al., 2018; Huang et al., 2018).

Various other factors can enhance the efficiency of somatic cell reprogramming into iPSCs. The estrogen-related receptor β (ESRRB), orphan nuclear receptor required for self-renewal of ESCs, can substitute for c-MYC and KLF4 during the induction of pluripotency (Feng et al., 2009). The reprogramming efficiency can also be enhanced by adding other extra factors such as undifferentiated embryonic cell transcription factor 1 (UTF1), SALL4, T-box transcription factor 3 (TBX3), and short hairpin RNAs (shRNAs) for p53 or p21 proteins (Yu et al., 2007). Apparently, different combinations of factors are more efficient and/or applicable for reprogramming certain types of somatic cell, especially in patient-specific disease lines.

Since the development of the first approaches for the generation of iPSCs, various modifications have been employed to increase efficiency and minimize or eliminate vector sequences integrated into the reprogrammed iPSC genome. The initial approaches were based on the integration of retro- and lentiviral vectors to deliver reprogramming factors into the cell (Takahashi & Yamanaka, 2006; Yu et al., 2007; Aasen et al., 2008; Kaji et al., 2009; Papapetrou et al., 2009; Deng et al., 2012; Umegaki-Arao et al., 2014; Merkle et al., 2021). However, retroviral vectors are not completely silenced during reprogramming and transgene integrations in the genome may result in failure of iPSCs differentiation (Okita et al., 2007; Umegaki-Arao et al., 2014). Also, retroviral transgene integration has a tumorigenic risk after transplantation. The lentivirus system allows delivery of the reprogramming factors separated by a self-cleaving peptide signal and iPSCs to be produced with a single insertion minimizing the genomic alteration (Merkle et al., 2021). A humanized version of such vectors (STEMCCA) has demonstrated a reprogramming efficiency of 0.1–1.5% (Somers et al., 2010). Genome integration-free approaches for iPSC generation are preferable and avoid the risk of permanent genetic modifications caused by insertional mutagenesis. Somatic cells have been successfully reprogrammed into iPSCs using non-integration strategy with expression of episomal plasmids encoding the reprogramming factors (Gonzalez et al., 2009; Tang et al., 2018; Kawai et al., 2019) and adenoviral vectors (Deng et al., 2016; Butterfield et al., 2020). However, the reprogramming efficiency of this method is low and may amount to 0.0002–0.0010% only (Stadtfeld et al., 2008). Another possibility for the genome integration-free cell reprogramming utilizes a nonintegrating RNA-containing murine respirovirus (Ban et al., 2011; Bueno et al., 2016;

Burnett et al., 2016; Gerami-Naini et al., 2016; Martello et al., 2022; Schmidt et al., 2022). Murine respirovirus (also known as Sendai virus, murine parainfluenza virus type 1, or hemagglutinating virus of Japan) is a negative-strand RNA virus belonging to the Paramyxoviridae family (Nakanishi & Otsu, 2012). It replicates in the cytoplasm of infected cells and does not go through a DNA phase that can integrate into the host genome, that can be successfully used for introducing foreign genes in a wide spectrum of host cells (Nakanishi & Otsu, 2012). Murine respirovirus vectors have been shown to induce reprogramming with efficiency 0.1–1.0% and its safety of reprogramming should be confirmed (Ban et al., 2011; Nakanishi & Otsu, 2012; Gerami-Naini et al., 2016). Alternatively, another non-integrating system, Epstein-Barr nuclear antigen 1-based episomal vectors (oriP/EBNA1) have been used to generate human iPSCs (Yu et al., 2007; Chou et al., 2011). However, transfection of oriP/EBNA1-based plasmids results in reprograming of only 0.0003–0.1000% of cells (Yu et al., 2007; Chou et al., 2011; Hu et al., 2011). This approach also is not clinically safe enough due to a potential risk of genomic integrations and mutagenesis. Several modified methods of the reprograming have been used employing minicircle vectors, small circular vectors containing only the eukaryotic promoter and complementary DNA to be expressed. Compared to traditional viral methods, this approach has higher transfection efficiencies and more stable transgene expression due to reduced silencing of exogenous genes (Narsinh et al., 2011). Minicircle expression vectors can generate iPSCs without the risk of insertional mutagenesis, but with a low efficiency of 0.005% reprogrammed cells (Narsinh et al., 2011). Another method, the liposomal magnetofection, is based on cationic lipids complexes assembly containing plasmids and superparamagnetic iron nanoparticles. These CombiMag-DNA complexes can be concentrated on the cell surface using magnetic field to transfect vectors into cells, allowing a short reprogramming time to be achieved (Park et al., 2012). Using the piggyBac transposon/transposase system encoding a reprogramming cassette to induce iPSCs may be a fairly safe approach since it can be completely excised from iPSCs after re-expression of the transposase (Kaji et al., 2009; Woltjen et al., 2009; Merkle et al., 2021). This technique has been shown to reprogram 0.02–0.05% of cells, however, it can also cause point mutations and chromosomal rearrangements (Kaji et al., 2009; Woltjen et al., 2009). Relatively recently, a novel non-transmissible and non-integrating measles virus vector, capable of transferring multiple genes simultaneously to a wide range of cells, has been developed to generate iPSCs (Hiramoto et al., 2019). The efficiency of iPSCs generation using this approach is low (from 0.002% to 0.024%) and the process is time consuming, however, the measles virus vector can establish iPSC without host genome integration and may be promising for future applications in gene therapy (Hiramoto et al., 2019).

Clinically applicable approaches require DNA-free delivery of reprogramming factors to avoid the potential integration of the exogenous DNA into the genome. One such potentially safe approach to generate iPSCs is the use of small molecules to replace the expression of reprogramming factors. These molecules can functionally substitute exogenous reprogramming factors and enhance the efficiency of reprogramming as well (Aasen et al., 2008; Feng et al., 2009; Lyssiotis et al., 2009; Zhang et al., 2012). Small molecules are also non-immunogenic and can be more easily administered and standardized. Some of them modulate chromatin modification and are represented by selective inhibitors of DNA methyltransferase, such as RG108 and 5-aza-2′-deoxycytidine (or decitabine); histone deacetylase inhibitors such as valproic acid, trichostatin A, suberoylanilide hydroxamic acid, and sodium butyrate; and the G9a histone methyltransferase inhibitors such as BIX-01294 (Yoshida et al., 2009; Warren et al., 2012). Another group of small reprograming molecules targets cell signaling pathways and is represented by mitogen-activated protein kinase kinase (MEK) inhibitor PD0325901, glycogen synthase kinase 3β (GSK3β) inhibitor CHIR99021, cyclin-dependent kinases (CDKs) inhibitor kenpaullone, inhibitors of the transforming growth factor β (TGFβ) signaling pathways A-83-01 and SB43152, (Lyssiotis et al., 2009), phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB, or Akt) activator PS48 (Zhu et al., 2010), and ascorbic acid (AA) (Esteban et al., 2010). Combined administration of AA and CHIR99021 has been demonstrated to facilitate OSKM-induced cell reprogramming into iPSCs to a greater extent than other combinations of small molecules (Bar-Nur et al., 2014).

The positively charged cationized polysaccharide from the mushroom *Pleurotus eryngii* has also been shown to enhance the process and efficiency of reprogramming and iPSCs generation (Deng et al., 2016). Activation of toll-like receptor 3 (TLR3, CD283) also leads to epigenetic modification and facilitates nuclear reprogramming by inducing factors (Lee et al., 2012). Application of 3-deazaneplanocin A, an inhibitor of S-adenosylhomocysteine hydrolase, in combination with GSK3β and mitogen-activated protein kinase (MAPK) signaling inhibition, demonstrated reprogramming results with efficiency 0.2% of cells (Hou et al., 2013).

iPSCs can also be generated without the use of nucleic acids by fusing reprogramming factors with cell penetrating proteins (Kim et al., 2009). The identification of a group of proteins with an enhanced ability to cross the plasma membrane in a receptor-independent manner has led to the discovery of a class of protein domains with cell-penetrating properties. The fusion of these domains with heterologous proteins, such as reprogramming factors, is sufficient to allow their rapid transduction into different cells. Examples of such cell penetrating peptides used for reprogramming somatic cells are the human immunodeficiency virus 1 transcriptional activator of twin-arginine translocation (Tat) protein and polyarginine (Kim et al., 2009). Although being a potentially safe approach, the low efficiency of iPSC generation with cell-penetrating proteins (0.001–0.006%) and technical difficulties associated with such proteins' purification do not allow transition of this methodology into the clinic.

Synthetic modified mRNAs encoding the reprogramming factors are more promising for the transgene-free generation of iPSCs. This approach enables the reprograming of a variety of somatic cells into iPSCs with a marked efficiency (1.4–4.4%) compared to other integration-free approaches and is able to produce high-quality clinically relevant iPSCs (Warren et al., 2012; Liu et al., 2014; Schlaeger et al., 2015; Boddy et al., 2020). On the other hand, a disadvantage of this approach is a daily delivery of modified mRNA molecules until the reprogramming is complete. Successful strategies of iPSCs generation with little or absent genome modifications have been reported mainly in murine cells, which are more amenable to reprogramming, and efficiency of these methods should be improved for human cells. It has also been shown that the modified mRNA method is inconsistent when applied to freshly isolated patient's cells (Schlaeger et al., 2015).

To date, micro RNAs (miRNAs) are the best recognized non-coding RNAs for maintenance and differentiation of pluripotent stem cells including iPSCs (Anokye-Danso et al., 2011; Farzaneh et al., 2019). The miRNAs, such as miR-200c, miR-291-3p, miR-294, miR-295, miR-302s, miR-302b, miR-367, miR-369s, and miR-372 that are specifically expressed in ESCs and regulate the progression of cells through the cell cycle, have been shown to enhance the efficiency of pluripotency induction by up to 15-fold (Yu et al., 2007; Anokye-Danso et al., 2011; Subramanyam et al., 2011; Burnett et al., 2016). However, the method for delivery of the reprogramming miRNAs also relies on the use of integrating lentiviral vectors. On the other hand, the combination of reprogramming modified mRNAs and miRNAs (miR-367 and miR-302s) has been shown to greatly enhance the reprogramming of human somatic cells into iPSCs with anefficiency of 90.7% (McGrath et al., 2020; Sokka et al., 2022). This methodology may allow the sequential generation of clinically relevant integration-free iPSCs with high efficiency from a patient's fibroblasts and may be applicable for the clinical translation of iPSCs (McGrath et al., 2020). In addition, this approach potentially reduces the cytotoxic and immunogenic effects, as well as the accumulation of mutations that arise in iPSCs due to extensive culturing of patient's cells or selective reprogramming of mutated founder cells. Repression of miR-132 and miR-212, exerting their functions through repression of the epigenetic modulators p300 and lysine-specific demethylase 5A (KDM5A) during iPSCs generation, also results in a significant increase in the reprogramming efficiency (Pfaff et al., 2017). Repression of miR-29a, which directly targets GSK3β, can also improve reprogramming of somatic cells transduced with OSK and OSKM lentiviral vectors (Fráguas et al., 2017).

Unlike ESCs, which can be derived from the developing embryo only, iPSCs have been generated from multiple cell types. To date, iPSCs have been successfully obtained by reprogramming various human and

animal somatic cells, such as fibroblasts (Takahashi & Yamanaka, 2006; Kaji et al., 2009; Gonzalez et al., 2009; Subramanyam et al., 2011; Ban et al., 2011; Deng et al., 2012; Hu et al., 2016; Wei et al., 2020; McGrath et al., 2020; Martello et al., 2022; Schmidt et al., 2022), melanocytes (Utikal Jet al., 2009; Abaci et al., 2016), keratinocytes (Aasen et al., 2008; Umegaki-Arao et al., 2014; Abaci et al., 2016), dermal papilla cells (Tsai et al., 2011; Abaci et al., 2016), renal epithelial cells (Cristo et al., 2017; Steinle et al., 2019), endothelial cells (ECs) (Hu et al., 2016), adipose stromal cells (Gu et al., 2012), skeletal myoblasts (Ahmed et al., 2011b; Pasha et al., 2011), cardiac progenitor cells (Hu et al., 2016), hematopoietic, cord and peripheral blood mononuclear cells (PBMC) (Hanna et al., 2008; Ban et al., 2011; Chou et al., 2011; Hu et al., 2011; Bueno et al., 2016; Ma et al., 2022; Shimoda et al., 2022; Wang et al., 2022), and other somatic cell types (Table 1).

Table 1
Application of iPSCs for disease modeling, therapeutics development, drug screening and safety testing for cardiovascular medicine

Condition	iPSC source	iPSC-derived cells	*In vitro*/*in vivo* model	Mutation affected gene	Reference
Coronary artery decease	Porcine adipose stromal cells	ECs	Immunodeficient mice	–	Gu et al., 2012
	Human dermal fibroblasts	ECs, VSMCs	Immunosuppressed Yorkshire pigs	–	Xiong et al., 2013
			Cell culture	*PHACTR1*	Gupta et al., 2017
Ischemic peripheral arterial disease	Mouse embryonic fibroblasts	ECs	Mice	–	Cochrane et al., 2017
	Human dermal fibroblasts	Pericytes	Immunodeficient mice	–	Dar et al., 2012
		Cord blood endothelial colony-forming cells	Immunodeficient mice	–	Prasain et al., 2014
		ECs	Immunodeficient mice	–	Rufaihah et al., 2011; Clayton et al., 2017; Foster et al., 2018
			Mice	–	Tan et al., 2018; Ye et al., 2019
Cigarette smoke endothelial dysfunction	Human dermal fibroblasts	ECs	Cell culture	–	Lee et al., *2019b;* Chu et al., *2020*
Vascular dysfunction in T1DM	Patient-derived dermal fibroblasts	ECs	Immunodeficient mice	–	Samuel et al., 2013
		ECs, pericytes	3D vascular networks in synthetic hydrogels	–	Chan et al., 2015
Vascular dysfunction in T2DM	Mouse tail tip fibroblasts	ECs	Mice	–	Gu et al., 2015
Vascular dysfunction in MODY	Patient-derived PBMC	ECs	Cell culture	*HNF1A*	Kachamakova-Trojanowska et al., 2019
Diabetic endotheliopathy	Human dermal fibroblasts	ECs	Cell culture	–	Ong et al., *2019*
White matter infarction	Human dermal fibroblasts	Brain microvascular ECs	Rats	–	Xu et al., *2020*
Ischemic retinopathy	Human dermal fibroblasts	ECs, VSMCs	Immunodeficient mice	–	Cho et al., *2020*
Chronic allogeneic vasculopathy	Mouse embryonic fibroblasts	-	Immunodeficient mice	–	Lu et al., *2020*
Heritable pulmonary arterial hypertension	Mouse embryonic fibroblasts	-	Rats	–	Huang et al., *2016*
	Patient-derived dermal fibroblasts	ECs	Cell culture	*BMPR2*	Sa et al., 2017
				BMPR2, corrected	Gu et al., 2017
		ECs, VSMCs	Cell culture	*BMPR2*	Kiskin et al., 2018
Arterial hypertension	Patient-derived PBMC	VSMCs	Cell culture	–	Biel et al. 2015
Alveolar capillary dysplasia	Patient-derived dermal fibroblasts	-	Cell culture	*FOXF1*	Slot et al., *2020*
Fibrodysplasia ossificans progressiva	Patient-derived urine epithelial cells	ECs, pericytes	Cell culture	*ALK2*	Cai et al., 2015
Aortic aneurysms in Marfan syndrome	Patient-derived dermal fibroblasts	VSMCs	Cell culture	*FBN1*	Granata et al., 2017
Idiopathic basal ganglia calcification	Patient-derived PBMC	ECs	Cell culture	*SLC20A2*	Sekine et al., *2019b*
Hutchinson-Gilford progeria syndrome	Patient-derived dermal fibroblasts	ECs, VSMCs, fibroblasts, neural progenitors, MSCs	Cell culture	*LMNA*	Zhang et al., *2011a*
		VSMCs	3D tissue engineered blood vessels	*LMNA*	Atchison et al., 2017
		ECs	3D tissue engineered blood vessels	*LMNA*	Matrone et al., *2019*
		ECs, VSMCs	3D tissue engineered blood vessels	*LMNA*	Atchison et al., *2020*
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL syndrome)	Patient-derived dermal fibroblasts	ECs, pericytes	3D tissue engineered blood vessels	*NOTCH3*	Kelleher et al., *2019*
			Cell culture	*NOTCH3*	Yamamoto et al., *2020*
		ECs, VSMCs	Cell culture	*NOTCH3*	Ling et al., *2019*
Fabry disease	Patient-derived dermal fibroblasts	ECs	Cell culture	*GLA*, corrected	Do et al., *2020*
Myocardial infarction	Mouse embryonic fibroblasts	–	Immunodeficient mice	–	Nelson et al., 2009
		Cardiac progenitor cells	Immunodeficient mice	–	Mauritz et al., 2011
	Mouse skeletal myoblasts	–	Immunodeficient mice	–	Ahmed et al., 2011a
					Ahmed et al., 2011b
	Mouse bone marrow MSCs	–	Immunodeficient mice	–	Buccini et al., 2012
	Mouse SMCs	CMs	Immunodeficient mice	–	Pasha et al., 2011
	Rat bone marrow cells	–	Rats	–	Zhang et al., 2011b
	Rat embryonic cardiac myoblasts	CMs	Immunocompetent rats	–	Singla et al., 2011

Condition	iPSC source	iPSC-derived cells	*In vitro*/*in vivo* model	Mutation affected gene	Reference
	Rhesus macaque and human dermal fibroblasts	CMs	Rats	–	Zhao et al., *2018*
	Cynomolgus macaque lymphocytes	CMs	Cynomolgus macaques	–	Kashiyama et al., *2019*
	Human cord blood endothelial progenitor cells	–	Immunosuppressed Landrace pigs	–	Templin et al., 2012
	Human dermal fibroblasts	CMs, pericytes, ECs	3D bioengineered cardiac tissue, immunocompetent rats	–	Masumoto et al., 2016
		CMs, fibroblasts, ECs	3D bioengineered cardiac tissue, rats	–	Yeung et al., *2019*
		CMs	Immunodeficient mice	–	Lou et al., *2020*
		ECs	Rats	–	Kim et al., 2022a
Myocardial fibrosis and infarction	Chimpanzee and human dermal fibroblasts	CMs	Cell culture	–	Ward & Gilad, *2019*
Hypertrophic cardiomyopathy with diastolic dysfunction	Patients-derived PBMC	CMs	Cell culture	*MYH7*, *MYBPC*, *TNNT2*, corrected	Wu et al., *2019*
Familial hypertrophic cardiomyopathy	Patient-derived dermal fibroblasts	CMs	Cell culture	*MYH7*	Lan et al., 2013
				MYL2	Zhou et al., *2019*
LEOPARD syndrome	Patient-derived dermal fibroblasts	CMs	Cell culture	*PTPN11*	Carvajal-Vergara et al., 2010
Hypertrophic cardiomyopathy	Patient-derived dermal fibroblasts	CMs	Cell culture	*PRKAG*, corrected	Ben Jehuda et al., *2018*
Friedreich's ataxia	Patient-derived dermal fibroblasts	CMs	Cell culture	–	Bolotta et al., *2019*
				FXN, corrected	Li et al., *2019*
Fabry cardiomyopathy	Patient-derived dermal fibroblasts	CMs	Cell culture	*GLA*	Kuramoto et al., *2018*
Noonan syndrome	Patient-derived dermal fibroblasts	CMs	Cell culture	*RAF1*	Jaffré et al., *2019*
Ischemic cardiomyopathy	Human dermal fibroblasts	CMs	Immunosuppressed minipigs	–	Kawamura et al., 2012
Dilated cardiomyopathy	Patient-derived dermal fibroblasts	CMs	Cell culture	*TTN*	Schick et al., *2018*
	Patient-derived PBMC	CMs	Cell culture	*LMNA*	Shimoda et al., 2022
	Patient-derived PBMC and dermal fibroblasts	CMs, ECs	Cell culture	*LMNA* corrected	Sayed et al., 2020
Dilated cardiomyopathy with ataxia syndrome	Patient-derived PBMC	CMs	Cell culture	*DNAJC19*	Rohani et al., *2020*
Dilated cardiomyopathy and Emery-Dreifuss muscular dystrophy	Patient-derived PBMC	CMs	Cell culture	*LMNA*	Perepelina et al., *2020*
Diabetic cardiomyopathy	Patient-derived dermal fibroblasts	CMs	Cell culture	–	Drawnel et al., 2014; Bowman et al., *2019*
	Patient-derived urine epithelia cells	CMs	Cell culture	–	Tang et al., *2020*
Ventricular arrhythmias	Human dermal fibroblasts	CMs, ECs	3D bioengineered cardiac tissue, guinea pigs	–	Pecha et al., *2019*
Jervell and Lange-Nielsen syndrome	Patient-derived dermal fibroblasts	CMs	Cell culture	*KCNQ1*, corrected	Zhang et al., 2014
Jervell and Lange-Nielsen syndrome, long QT syndrome type 1	Patient-derived PBMC	–	Cell culture	*KCNQ1*, *KCNE1*	Kasai-Brunswick et al., 2018
Long QT syndrome type 1	Patient-derived dermal fibroblasts	CMs	Cell culture	*KCNQ1*	Moretti et al., 2010
Long QT syndrome type 2	Patient-derived PBMC	CMs	Cell culture	*KCNH2*	Mesquita et al., *2019*
Long QT syndrome type 5	Patient-derived PBMC	–	Cell culture	*KCNE1*	Zhang et al., *2020b*
Short QT syndrome	Patient-derived dermal fibroblasts	CMs	Cell culture	*KCNH2*, corrected	Guo et al., *2019*
Congenital heart disease	Patient-derived urine epithelia cells	–	Cell culture	*DAND5*	Cristo et al., *2017*
Atrial fibrillation	Patient-derived PBMC and dermal fibroblasts	CMs	Cell culture	*ZFHX3*, *PDE4DIP*, *CNN2*, *RYR3*, *NEFM*, *FLNC*, *MYLK*	Benzoni et al., *2020*
Brugada syndrome	Patient-derived dermal fibroblasts	CMs	Cell culture	*SCN5A*	Liang et al., *2016*
Myotonic dystrophy type 1	Patient-derived dermal fibroblasts	CMs	Cell culture	*DMPK*	Spitalieri et al., *2018*
Duchenne muscular dystrophy	Patient-derived dermal fibroblasts	CMs	Cell culture	*DMD*	Eisen et al., *2019*
Myotonic dystrophy associated with T1/2DM	Patient-derived urine epithelia cells	CMs	Cell culture	*DMD*	Kim et al., *2019*
Autosomal dominant polycystic kidney disease	Patient-derived PBMC	CMs	Cell culture	*PKD1*, *PKD2*	Lee et al., *2019a*
Left ventricular hypertrophy	Patient-derived dermal fibroblasts	CMs	Cell culture	*THBS1*	Zhi et al., 2012
Spinal muscular atrophy	Patient-derived dermal fibroblasts	CMs	Cell culture	*SMN1*	Khayrullina et al., *2020*
Huntington's disease	Patient-derived dermal fibroblasts	CMs	Cell culture	*HTT*	Joshi et al., *2019*
Pompe disease	Patient-derived dermal fibroblasts	CMs	Cell culture	*GAA*	Huang et al., *2011;* Raval et al., *2015*
Cardiotoxicity induced by anticancer drugs	Patient-derived dermal fibroblasts	CMs	Cell culture	–	Burridge et al., 2016
	Human dermal fibroblasts and PBMC	CMs, ECs, cardiac fibroblasts	Cell culture	–	Sharma et al., 2017
	Human dermal fibroblasts	CMs	Cell culture	–	Wang et al., *2019*
	Human pulmonary fibroblasts	CMs	Cell culture	–	Karhu et al., *2020*
Cardiotoxicity induced by psychoactive drugs	Human pulmonary fibroblasts	CMs	Cell culture	–	Zwartsen et al., *2019*

Condition	iPSC source	iPSC-derived cells	*In vitro*/*in vivo* model	Mutation affected gene	Reference
Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis	Patient-derived dermal fibroblasts	Cerebral microvascular ECs	Cell culture	*SOD1*, *SCNA1*, *PSEN1*, *HTT*	Katt et al., *2019*
Danon disease	Patient-derived dermal fibroblasts	Cerebral cortical neurons, CMs	Cell culture	*LAMP2*	Law et al., *2016*
Idiopathic basal ganglia calcification	Patient-derived PBMC	ECs	Cell culture	*PDGFB*	Sekine et al., *2019a*
Renal diseases	Human cord blood mononuclear cells	ECs	3D renal organoids	–	Leuning et al., *2018*
Autosomal dominant polycystic kidney disease	Patient-derived dermal fibroblasts	ECs, VSMCs	Cell culture	*PKD1*	Ameku et al., *2016*
Dermal wound healing	Human dermal fibroblasts	ECs, VSMCs	Mice	–	Kim et al., 2013
		ECs	Immunodeficient mice	–	Abaci et al., 2016; Clayton et al., 2018
		VSMCs	3D constructs	–	Duan et al., 2021; Islam et al., 2022
	Human Wharton's jelly MSCs	MSCs	Mice	–	Kim et al., 2018

Somatic cells exhibit different reprogramming capacity depending on their origin, proliferation rate, and gene expression profiles; and the selection of an appropriate donor line for reprogramming may be critical, not only for achieving the highest efficiency and quality of reprogramming, but also to attain maximum differentiation capacities of the resulting iPSCs. The reprogramming process has been extensively studied in fibroblasts and has been shown to follow an organized sequence of events that begins with suppression of somatic gene expression (Polo et al., 2012). The first step of reprogramming somatic cells into iPSCs requires a cell phenotype transition, initiated by the activation of the early pluripotency stage-specific embryonic antigen 1 (SSEA1) and alkaline phosphatase (ALP), and the inactivation of a differentiation related antigen Thy-1 (THY1, or CD90) followed by NANOG and POU5F1 pluripotency genes become involved and provide an independence from exogenous factor expression (Stadtfeld et al., 2008; Polo et al., 2012). OCT4, SOX2, and NANOG further induce the expression of stemness genes, such as STAT3 and ZIC3, and repress differentiation related genes, such as PAX6, ZFHX3, PRC2, CDKN1A, and ZFP42 (Boyer et al., 2005; Sridharan et al., 2009; Lee et al., 2010). OCT4 and SOX2 also regulate FGF4, UTF1, FBXO15, and POU5F1 genes (Okumura-Nakanishi et al., 2005). The expression level and balance of reprogramming factors are also important for iPSCs induction. Overexpression of NANOG, c-MYC and KLF4 has been shown to maintain pluripotency, whereas overexpression of OCT4 or SOX2 may result in cell differentiation (Papapetrou et al., 2009; Umegaki-Arao et al., 2014). iPSCs also expresses other pluripotency markers, such as PODXL, SSEA3, SSEA4, LIN28, DPPA2, DNMT3B, ZFP42, and cell surface antigen TRA-1-81, that characterized the fully reprogrammed state and capability to differentiate into cells of all three germ layers (Yu et al., 2007; Umegaki-Arao et al., 2014; Cai et al., 2015; Martello et al., 2022; Wang et al., 2022). The duration of the reprogramming also affects iPSCs induction. Continual cultivation of iPSCs yields a gene expression profile more similar to ESCs, suggesting that reprogramming continues even after establishment of iPSCs (Aasen et al., 2008). As the gene expression is regulated not only by transcription factors but also by epigenetic modifications, such as DNA methylation and methylation/acetylation of histones, the alteration of epigenetic modifications is also important for iPSCs induction. Also, epigenetic profiling of iPSCs revealed that the reprogrammed cells retain epigenetic marks of the cell type of origin (Kim et al., 2011), although these marks disappear upon continued cell passaging (Polo et al., 2012). This short-term genetic memory provides an advantage in achieving higher differentiation efficiency of early-passage iPSCs into the target adult cell lineage.

Application of iPSCs in vascular therapy

Human iPSC-derived vascular cells, as well as their progenitors, can serve as models to study vascular development, disease pathology, and drug screening, as well as provide a source of functional vascular cells for autologous cell-based therapies for human cardiovascular diseases. Successful generation of ECs, pericytes, and vascular smooth muscle cells (VSMCs) has been widely reported (Choi et al., 2009; Li et al., 2011; Rufaihah et al., 2011; Bajpai et al., 2012; Dar et al., 2012; Gu et al., 2012; Adams et al., 2013; Kim et al., 2013; Samuel et al., 2013; Wanjare et al., 2013; White et al., 2013; Di Bernardini et al., 2014; Lian et al., 2014; Lippmann et al., 2014; Orlova et al., 2014; Prasain et al., 2014; Zhang et al., 2014; Biel et al., 2015; Chan et al., 2015; Clayton et al., 2015; Nakayama et al., 2015; Patsch et al., 2015; Sivarapatna et al., 2015; Abaci et al., 2016; Hu et al., 2016; Liu et al., 2016; Wang et al., 2016; Clayton et al., 2017; Collado et al., 2017; Giacomelli et al., 2017; Paik et al., 2018; Tan et al., 2018; Halaidych et al., 2018; Kwong et al., 2019; Sayed et al., 2020; Kim et al., 2022a; Schmidt et al., 2022). Human iPSC-derived early ECs (or endothelial progenitor cells) can mature to functional ECs. Characteristic gene markers of endothelial progenitors derived from iPSCs are CDH5, PECAM1 (CD31), NT5E, CD34, ENG (CD105), PROM1 (CD133), VEGFR2 (CD309), VEGFR3, KIT (CD117), TEK (CD202b), LYVE1, NRP1, KLF2, ECSCR, GATA2, RUNX1, and ITGA4 (CD49d) (Choi et al., 2009; Li et al., 2011; Adams et al., 2013; Samuel et al., 2013; White et al., 2013; Lian et al., 2014; Orlova et al., 2014; Prasain et al., 2014; Chan et al., 2015; Liu et al., 2016; Wang et al., 2016; Giacomelli et al., 2017; Kurokawa et al., 2017; Lee et al., 2017; Vazão et al., 2017; Halaidych et al., 2018; Paik et al., 2018; Rosa et al., 2019; Sayed et al., 2020; Kim et al., 2022a). The resulting functional ECs originated from iPSC-derived early ECs expresses mature endothelial markers such as VWF, NOS3, PECAM1, ENG, CDH5, ICAM1 (CD54), VEGFR2, PTPRB, EGFL7, PLVAP), VEGFR1 (or FLT1), and CLDN5 (Lian et al., 2014; Chan et al., 2015; Morita et al., 2015; Patsch et al., 2015; Kurokawa et al., 2017; Lee et al., 2017; Smith et al., 2017; Paik et al., 2018; Wimmer et al., 2019; Sayed et al., 2020; Schmidt et al., 2022; Kim et al., 2022a). Differentiation of human iPSCs may require embryonic body formation or forced cell aggregation to form compact spheroids or spin embryonic bodies (Rufaihah et al., 2011; Samuel et al., 2013; White et al., 2013; Hu et al., 2016; Collado et al., 2017; Songstad et al., 2017). ECs derived from iPSCs could also be generated via mesoderm lineage of cardiovascular progenitors, expressing VEGFR2, MESP1, GATA2, and SNAI1, representing one of the earliest stages in mesoderm specification with subsequent differentiation of embryoid bodies and generation of endothelial progenitors (Samuel et al., 2013; White et al., 2013; Liu et al., 2016; Patsch et al., 2015; Giacomelli et al., 2017; Qian et al., 2017; Smith et al., 2017; Schmidt et al., 2022). The subpopulation of the progenitor cells then can be purified and directed with defined factors into a homogeneous pool of functional ECs (White et al., 2013) (Fig. 1). Mature human iPSC-derived ECs may represent transcriptional heterogeneity with four major subpopulations, characterized by elevated expression of CLDN5, APLNR, GJA5, and ESM1, respectively (Paik et al., 2018). ECs and pericytes, which have the potential to differentiate into contractile phenotype of VSMCs, can be efficiently derived from human iPSCs simultaneously and form an authentic vascular plexus during coculturing (Orlova et al., 2014). Cardiomyocytes (CMs) and ECs, integrating in complex three-dimensional (3D) structures *in vitro*, can also be differentiated simultaneously from human iPSCs following initial cardiac mesoderm induction (Giacomelli et al., 2017). However, the cellular origin of human iPSCs for reprograming into ECs may affect cell lineage differentiation

propensity due to the somatic memory of iPSCs, hence, somatic cells for reprograming should be carefully considered for usage in clinical translation (Hu et al., 2016).

Differentiation of human iPSCs into ECs can be promoted by activin A, basic fibroblast growth factor (bFGF), bone morphogenetic protein 4 (BMP4), vascular endothelial growth factor (VEGF), RA, miR-21, inhibitor of the activin A receptor-like kinase 5 (ALK5) and TGFβ receptors SB431542, erythropoietin (EPO), and transforming growth factor β1 (TGFβ1) (Rufaihah et al., 2011; White et al., 2013; Di Bernardini et al., 2014; Lian et al., 2014; Lippmann et al., 2014; Prasain et al., 2014; Zhang et al., 2014; Hu et al., 2016; Liu et al., 2016; Wang et al., 2016; Kurokawa et al., 2017) (Fig. 1). ECs and endothelial progenitors can be also produced from human iPSCs via GSK3β inhibition with CHIR99021 (Lian et al., 2014; Liu et al., 2016; Qian et al., 2017; Kim et al., 2022a) or overexpression of connective tissue growth factor (CTGF) in combination with fibroblast growth factor-inducible 14 receptor (Fn14), which can induce endogenous CTGF secretion (Songstad et al., 2017). Rapid and efficient differentiation of human and animal iPSCs into vascular ECs can be also achieved via mesodermal fate and subsequent exposure to VEGF in a combination with forskolin (Patsch et al., 2015), BMP4, activin A, VEGF, bFGF, and SB431542 (Wang et al., 2016; Sayed et al., 2020; Wei et al., 2020), or a combination of BMP4, activin A, CHIR99021, and VEGF (Giacomelli et al., 2017). Compliant substrates such as biocompatible elastomeric polydimethylsiloxane in combination with VEGF and SB431542 can modulate subsequent differentiation of human iPSC-derived ECs and effect their downstream commitment (Wang et al., 2016; Smith et al., 2017). Recently, an approach to efficiently generate human iPSC-derived endothelial progenitor cells based on the regulated induction of TAL1, LMO2, GATA2, and ETV2 has been proposed (Lange et al., 2020). Human iPSCs can be also differentiated into ECs using the combined VEGF, thymosin β4, and SB431542 as inductive agents for endothelial differentiation (Vazão et al., 2017).

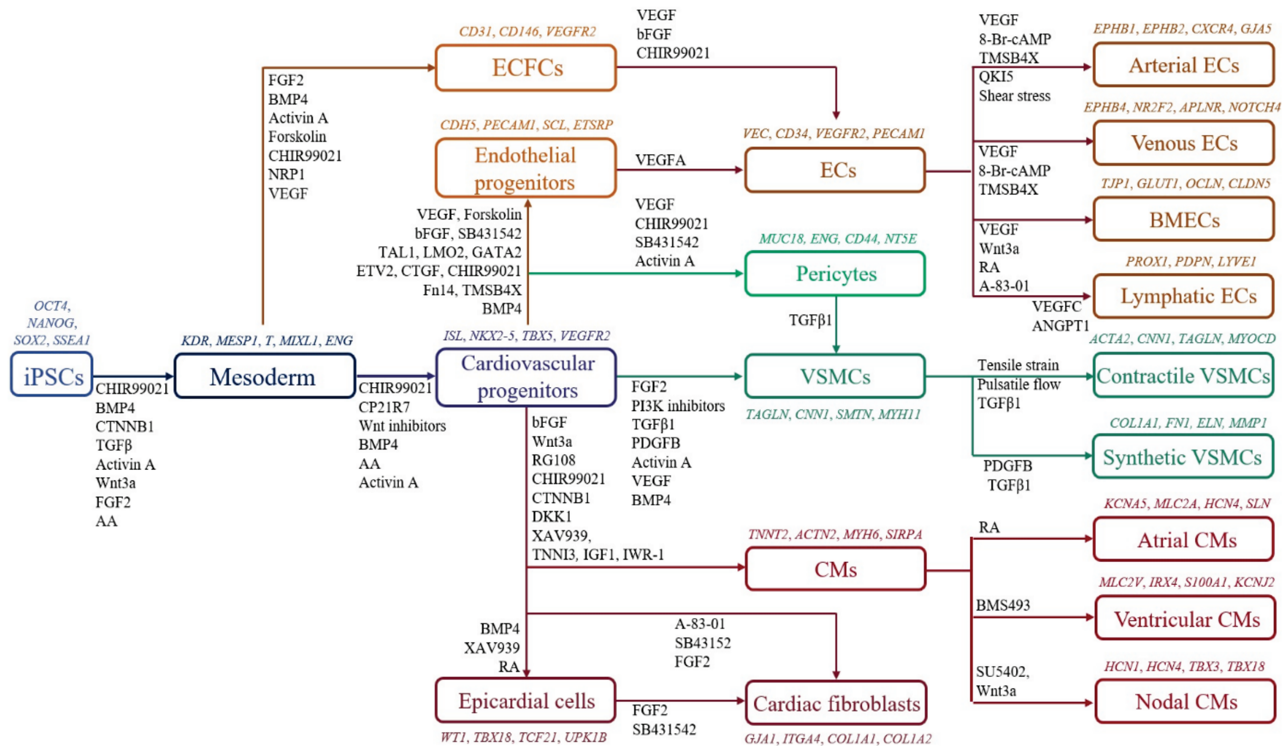

Fig. 1. Schematic view of the generation of cardiovascular cells from iPSCs showing pathways and promoters of cell type and subtype commitment, and lineage-specific markers of iPSC-derived cells: AA, ascorbic acid; ANGPT1, angiopoietin 1; bFGF, basic fibroblast growth factor; BMP4, bone morphogenetic protein 4; CTGF, connective tissue growth factor; CTNNB1, catenin β1; DKK1, dickkopf homolog 1; GATA2, GATA-binding factor 2; ETV2, Ets variant transcription factor 2; FGF2, fibroblast growth factor 2; Fn14, fibroblast growth factor-inducible 14 receptor; IGF1, insulin-like growth factor 1; LMO2, LIM domain only 2; NRP1, neuropilin-1; PI3K, phosphoinositide 3-kinase; PDGFB, platelet-derived growth factor B; QKI5, quaking RNA-binding protein 5; RA, Retinoic acid; TAL1, T-cell acute lymphocytic leukemia protein 1; TGFβ/β1, transforming growth factor β/β1; TMSB4X, thymosin β4; TNNI3, troponin I; VEGF, vascular endothelial growth factor; VEGFA/C, vascular endothelial growth factor A/C

The resulting ECs derived from human iPSCs can be comprised of arterial and venous subtypes that can be induced using different concentrations of VEGF and 8-bromoadenosine-3':5'-cyclic monophosphate (8-Br-cAMP) or a combination of vascular endothelial growth factor C (VEGFC) and angiopoietin 1 (ANGPT1), promoting the expression of a lymphatic endothelial cell phenotype (Rufaihah et al., 2011) (Fig. 1). Functional arterial- and venous-like ECs also can be generated from human iPSCs via endothelial precursor cells using BMP4 and bFGF, and then high and low concentrations of VEGF supplemented with thymosin β4 (TMSB4X) (Rosa et al., 2019). In arterial, venous, and lymphatic endothelial specification, venous ECs derived from iPSCs express EPHB4, NR2F2, APLNR, and NOTCH4, whereas specific markers of lymphatic ECs are PROX1, PDPN, and LYVE1 (Cochrane et al., 2017; Halaidych et al., 2018; Paik et al., 2018; Rosa et al., 2019; Sayed et al., 2020). iPSC-derived ECs with a mature arterial-like phenotype express EPHB1, EPHB2, CXCR4 (CD184), GJA5, NRP1, GJA4, DLL4, JAG1, HEY1, NOTCH1, STAT3, EFNB2, VEGFR2, and SOX17 (Sivarapatna et al., 2015; Cochrane et al., 2017; Halaidych et al., 2018; Paik et al., 2018; Rosa et al., 2019; Sayed et al., 2020). Characteristic cell markers of human iPSC-derived brain microvascular ECs are TJP1, GLUT1, OCLN, CLDN5, and ISL1 (Sances et al., 2018; Praça et al., 2019). These cells can be generated in a two-step differentiation of iPSCs into endothelial progenitor cells followed by specification in a brain capillary-like phenotype using VEGF, Wnt3a, and RA (Praça et al., 2019), or TGFβ inhibitor A-83-01 at a late stage of differentiation (Yamashita et al., 2020) (Fig. 1). Overexpression of the quaking RNA-binding protein 5 (QKI5) has also been reported to direct mouse and human iPSC-derived ECs differentiation towards the arterial linage (Cochrane et al., 2017). Shear stress has also been shown to effectively direct human iPSC-derived ECs toward a mature arterial-like phenotype (Sivarapatna et al., 2015; Huang et al., 2019). Human iPSCs can also be reprogrammed into cord-blood endothelial colony forming cell type (ECFCs, also known as outgrowth endothelial cells or late endothelial progenitors) that can be redirected into vasculature-forming cells and potentially used for restoration of endothelial function in patients with vascular diseases (Prasain et al., 2014). It has been demonstrated that the characteristic mechanism for the development

of ECFCs from iPSCs is a NRP1-mediated activation of VEGFR2 signaling (Prasain et al., 2014).

The transient expression of pluripotency factors in human and murine fibroblast followed by their directed differentiation (or trans-differentiation), which bypasses the pluripotent intermediate state, has also been proposed as an approach to derive ECs (Margariti et al., 2012; Clayton et al., 2015; Clayton et al., 2017). Human skin fibroblasts can be directly converted into ECs by overexpressing such transcription factor as OCT4 and KLF4 in the presence of bFGF, VEGF, BMP4, 8-Br-cAMP, and SB431542 (Li et al., 2013), or Ets variant transcription factor 2 (ETV2) in combination with doxycycline, valproic acid, and VEGF (Morita et al., 2015). In cooperation with endogenous forkhead box protein C2 (FOXC2), the ETV2 transduced in fibroblasts has been shown to induce the expression of important endothelial development factors such as FLI1, ERG, and TAL1 (Morita et al., 2015). A similar effect can be achieved using small-molecule polyinosinic:polycytidylic acid, an agonist of TLR3, combined with exogenous application of BMP4, VEGF, bFGF, and 8-Br-cAMP (Sayed et al., 2015).

Ischemia is the cause of tissue death in a number of diseases, such as coronary and peripheral artery disease, stroke, and diabetes mellitus (DM). Coronary artery disease (or ischemic heart disease) with associated myocardial infarction is the leading cause of morbidity and mortality worldwide, despite significant advances in the therapy. Existing therapy for atherosclerotic coronary and peripheral arterial disease is not always sufficient. Therapeutic neovascularization in the ischemic heart using autologous iPSC-derived cells is considered one of the potential strategies for cell-based cardiac repair. Studies employing animal models have shown that transplanted iPSCs and iPSC-derived vascular cells can promote angiogenesis and effective tissue revascularization via direct and paracrine mechanisms (Table 1).

Hyperglycemia in DM leads to aberrant angiogenesis in both micro- and macro-vessels and associated abnormalities in endothelial progenitor cells functionality. It may result in decreased neovascularization and affect wound healing processes in diabetic patients (Table 1). iPSC-derived ECs have been widely employed as a model to explore mechanisms and potential treatments for endothelial dysfunction associated with type 1 and 2 diabetes mellitus (T1/2DM) and maturity-onset diabetes of the young (MODY), and as an *in vitro* platform capable of recapitulating peripheral arterial disease (Table 1).

Human and animal ECs derived from iPSCs have also been used to study mechanisms and developing new therapeutic approaches for macular degeneration and ischemic retinopathies (Table 1) and can also be used as a source of human ECs to generate 3D microphysiological systems (often called "organ-on-a-chip") for studying human physiology, disease modeling, drug testing, and tissue engineering (Kurokawa et al., 2017; Schmidt et al., 2022) (Table 1).

Also, human iPSC-derived brain microvascular ECs and neural progenitor cells have been incorporated in the dual-channel spinal cord chip system and used as an *in vitro* model of human vascularized motor neural tissue (Sances et al., 2018). The blood-brain barrier chip system has also been created using human iPSC-derived brain microvascular ECs, neurons, astrocytes, and brain-like pericytes, representing an in vitro neurovascular unit that provides an important platform for modeling neurological disorders and drug screening (Lippmann et al., 2014; Qian et al., 2017; Canfield et al., 2019; Jamieson et al., 2019; Li et al., 2019; Martins Gomes et al., 2019; Neal et al., 2019; Nguyen et al., 2019; Vatine et al., 2019). Cells in such systems can be generated from the same iPSCs donor source, which gives an isogenic in vitro model (Canfield et al., 2019).

Gene correction in iPSCs promises a new approach for the treatment of vascular disorders associated with pathogenic gene mutations. In general, the iPSC-based therapeutic strategy for inherited disorders includes isolation of cells from a patient's biopsy; reprogramming these cells into iPSCs; safe correction of genetic defects in generated iPSCs; differentiation of corrected iPSCs into autologous cells for transplantation. Both uncorrected and corrected iPSCs can be utilized as a platform for disease modeling *in vitro* and *in vivo* and offer possibilities for gaining new insights into disease mechanisms and drug discovery (Table 1). There are several approaches to inducing homologous recombination that can be coupled with the generation of iPSCs to achieve genetic repair of inherited human diseases. Enhanced homologous recombination in iPSCs could be achieved using chimeric molecules composed of a nuclease domain and separate, customized DNA-recognition domains. These chimeric molecules can introduce double-strand breaks in a specific DNA sequence. The presence of exogenous donor DNA carrying the correct gene sequence and the homology to the sequence flanking the double-strand breaks triggers homologous recombination and replacement of the defective gene with the corrected one (Carlson et al., 2012). Zinc finger nucleases (ZFNs) (Zou et al., 2009; Carlson et al., 2012) and transcription activator-like effector nucleases (TALENs) systems (Christian et al., 2010; Hockemeyer et al., 2011; Carlson et al., 2012) are the main representatives of chimeric endonucleases capable of introducing specific double-strand breaks into genomic DNA and are widely used as tools for research and gene therapy. Another nuclease-based technique uses the clustered regularly interspaced short palindromic repeats/associated protein 9 (CRISPR/Cas9) systems, which when directed by short RNAs can induce precise cleavage at endogenous genomic loci with high efficiency (Cong et al., 2013; Butterfield et al., 2020; Sokka et al., 2022). These gene modification strategies have been successfully used on human and animal ESCs and iPSCs (Hockemeyer et al., 2009; Zou et al., 2009; Hockemeyer et al., 2011; Ben Jehuda et al., 2018; Butterfield et al., 2020; Sokka et al., 2022) (Table 1). To improve gene and cell therapy methodology for safe clinical use, CRISPR/Cas9 technology can be used to correct the pathogenic mutations in iPSCs from patients in combination with the piggyBac transposon system so that no residual gene fragments remain in the iPSC genome after correction of a mutation (Itoh et al., 2020). The generation of iPSCs, coupled with gene targeting, can solve many obstacles that are associated with gene correction in somatic cells. Unlike somatic cells, iPSCs can be expanded indefinitely, allowing the easier selection and expansion of corrected clones. Patient-specific iPSCs harbouring specific gene mutations and iPSC-derived vascular and cardiac cells (genetically corrected and uncorrected) have been generated from patients with various cardiovascular diseases (Table 1).

VSMCs derived from human iPSCs can also provide an unlimited cell source for autologous cell-based therapies and vascular disease models, as well as for studying pathophysiological mechanisms (Table 1). Differentiated iPSC-derived VSMCs express myogenic proteins such as ACTA2, TAGLN, MYH10, CALM1, CNN1, CALD1, myosin light chain genes, MYLK1, and late VSMCs differentiation marker MYH11, and demonstrate fibrillar organization and contractile responses to receptor- and non-receptor-mediated agonists characteristic of the development of VSMCs with the contractile phenotype (Bajpai et al., 2012; Biel et al., 2015; Patsch et al., 2015; Paik et al., 2018; Kwong et al., 2019; Duan et al., 2021; Islam et al., 2022). Cell surface markers such as PDGFRB (CD140b) and LRP1 (CD91) are present in both iPSC-derived progenitor and mature VSMCs (Biel et al., 2015). Human iPSCs can be differentiated into VSMCs using platelet-derived growth factor B (PDGFB) and TGFβ1 (Wanjare et al., 2013; Wanjare et al., 2015), or combination of BMP4 and VEGF (Biel et al., 2015) (Fig. 1). Depending on concentrations of the relevant factors, iPSCs can be directed into the synthetic VSMCs phenotype with increased expression of MMP1, MMP2, SMAD3, YAP1, and extracellular matrix proteins such as COL1A1 and FN1, and reduced expression of contractile proteins, or towards the contractile phenotype expressing F-actin, ACTA2, CNN1, TAGLN, and MYOCD (Wanjare et al., 2013; Wanjare et al., 2015). The contractile phenotype of mature VSMCs can be derived from human iPSCs using biomechanical tensile strain (Wanjare et al., 2015). Also, human iPSCs, differentiated into early VSMCs can be directed towards maturation into contractile smooth muscle tissue using a hybrid poly(ethylene glycol) dimethacrylate/poly (l-lactide) scaffold and exposure to pulsatile flow (Eoh et al., 2017). These cells demonstrate increased expression of extracellular matrix components such as ELN, FN1, and COL1A1, and can be effectively used for engineering elastic and functional human vascular smooth muscle tissue applicable in regenerative medicine (Eoh et al., 2017). Functional iPSC-derived VSMCs can be generated through an intermediate stage of multipotent MSCs or various mesoderm lineages expressing characteristic gene markers ENG, THY1, NT5E, PDGFRB, MIXL1, EOMES, and TBXT (Bajpai et al., 2012; Dar et al., 2012; Patsch et al., 2015; Schmidt et al., 2022) with the usage of BMP4 in combination

with GSK3β inhibitors CHIR99021 or CP21R7 (Patsch et al., 2015; Wanjare et al., 2015) (Fig. 1). MSCs derived from human iPSCs can then be directed to VSMCs by a combination of heparin and TGFβ1 or PDGFB with expression of myogenic markers and strong contractile function, suggesting that the cells have assumed terminal differentiation into the VSMCs phenotype (Bajpai et al., 2012; Patsch et al., 2015).

Bilayer vascular grafts that recapitulate cellular orientation and the anti-inflammatory properties of functional blood vessels have been successfully generated from ECs and VSMCs reprogrammed from human iPSCs (Nakayama et al., 2015) (Table 1). Human iPSC-derived ECs and VSMCs co-cultured under vascular region-specific blood flow hemodynamics have also proven useful for the modeling vascular diseases and testing new therapeutic approaches (Collado et al., 2017). In addition, ECs and VSMCs derived from human iPSCs cultured on a biodegradable polymer have been used to generate tissue-engineered vascular grafts that mimic the native multilayered architecture of blood vessels and can potentially be used for autologous vascular replacements (Generali et al., 2019).

Pericytes originated from human iPSCs have been shown to express common pericyte and MSC markers, such as MUC18 (CD146), ENG, CD44, NT5E, PDGFRB, NG2, and early contractile markers such as TAGLN, ACTA2 and CNN1, and can further differentiate into mature VSMCs in the presence of TGFβ (Dar et al., 2012; Orlova et al., 2014; Canfield et al., 2019; Wimmer et al., 2019) (Fig. 1). Pericytes represent a unique subtype of residing in microvessels perivascular cells with diverse angiogenic functions and multilineage developmental features of MSCs. Like VSMCs, this cell type can also be generated from human iPSC-derived propagated MSCs (Dar et al., 2012). Patient-specific iPSC-derived VSMCs and pericytes can successfully serve as a platform to elucidate the molecular mechanisms and to identify drug targets for various genetic vascular disorders (Table 1). Also, iPSC-derived ECs and VSMCs demonstrated acceleration of neovascularization in dermal wounds accelerating the healing (Table 1).

Application of iPSCs in cardiac repair

Functional CMs have also been successfully generated from animal and human iPSCs, providing a platform for novel approaches to cardiac repair (Gai et al., 2009; Zhang et al., 2011b; Pasha et al., 2011; Dubois et al., 2011; Ahmed et al., 2011b; Drawnel et al., 2014; Sayed et al., 2020) (also see Table 1). iPSC-derived cardiac progenitors can be differentiated into CMs expressing specific markers such as VEGFR2, PDGFRA, and early cardiac transcription factor NKX2-5 (Kattman et al., 2006; van Laake et al., 2010; Mauritz et al., 2011; White et al., 2013). Differentiation protocols aimed at generating CMs employ defined conditions containing specific growth factors important for cardiac development, such as activin A, BMP4, bFGF, Wnt3a, and in some cases, manipulations with the extracellular matrix (Mummery et al., 2012). iPSCs derived from different types of somatic cells, including skeletal myoblasts, have been shown to be successfully reprogrammed into CMs using small molecules, such as DNA methyltransferase inhibitor RG108 (Pasha et al., 2011), GSK3β inhibitors combined with inducible expression of catenin β1 (CTNNB1) shRNA or chemical inhibitors of Wnt signaling (Lian et al., 2012), VEGF, dickkopf homolog 1 (DKK1), and bFGF (White et al., 2013), or CHIR99021 and Wnt pathway inhibitor IWR-1 (Zhang et al., 2017) (Fig. 1). CMs derived from iPSCs exhibit spontaneous contractility and are morphologically, molecularly, and structurally similar to native CMs. These cells express early and late cardiac markers, such as SIRPA (CD172a), VCAM1 (CD106), miR-200a-c, ACTN1, TNNT2, TNNI3, transcription factor GATA4, MEF2C, NKX2-5, myosin VI (Ieda et al., 2010; Ahmed et al., 2011b; Dubois et al., 2011; Pasha et al., 2011; Buccini et al., 2012; Inagawa et al., 2012; Cochrane et al., 2017; Paik et al., 2018; Pianezzi et al., 2020), genes encoding ion channels and transporters that are responsible for contractile cardiac activity, such as CACNA1C, SCN5A, KCNQ1, KCNE1, KCNH2, KCNJ12, HCN4, SERCA2A, and NCX1 (Giacomelli et al., 2017; Treat et al., 2019; Pianezzi et al., 2020), and genes of ion channel regulators such as SLMAP, FGF12, and FHL1 (Biendarra-Tiegs et al., 2019). Human iPSCs can also be simultaneously differentiated into CMs and ECs via cardiac mesoderm, or early cardiovascular progenitors, expressing MESP1, TBX5, and ISL1, using a combination of BMP4, activin A and a small-molecule inhibitor of GSK3β CHIR99021, followed by inhibition of Wnt signaling with XAV939 for differentiation towards CM cell fate or using application of VEGF for cell differentiation towards endothelial lineage (Giacomelli et al., 2017).

Based on action potential characteristics, iPSC-derived CMs may represent nodal, atrial, and ventricular phenotypes and exhibit responsiveness to β-adrenergic stimulation (Zhang et al., 2011b; Paik et al., 2018). General markers of atrial CMs generated from iPSCs are KCNA5, MLC2A, GJA5, GJA1, KCNJ3, CACNA2D2, SCN1B, TWIK1, TASK1, SCN5A, KCND3, HCN4, SLN, and NR2F1 (Kane & Terracciano, 2017). The myosin light chain isoform MLC2V, S100A1, KCNJ2, RYR2, PLN, KCNA4, and IRX4 are ascribed as ventricular CMs markers, whereas HCN1, HCN4, TBX3, SHOX2, and GJA7 are highly expressed in iPSC-derived nodal myocytes (Kane & Terracciano, 2017). iPSC-derived CMs can be directed into homogeneous atrial or ventricular subtypes using BMS493 and retinoic acid (RA), respectively (Zhang et al., 2017) (Fig. 1). Nodal subtype of CMs can be derived from cardiovascular mesoderm progenitor cells by blocking fibroblast growth factor (FGF) signaling (Protze et al., 2017) or using canonical Wnt signaling ligand Wnt3a (Liang et al., 2020).

Cardiac fibroblasts represent the majority of cells in the mammalian heart and along with dermal fibroblasts can be directly reprogrammed into differentiated CMs with high efficiency using a combination of three developmental transcription factors GATA4, myocyte-specific enhancer factor 2C (MEF2C), and TBX5 (Ieda et al., 2010; Qian et al., 2012; Inagawa et al., 2012) (Fig. 1).

To accelerate maturation of human iPSC-derived CMs, human iPSCs have been engineered with a drug-inducible expression cassette driving the TNNI3 (Wheelwright et al., 2020). Thyroid hormone, dexamethasone, and insulin-like growth factor 1 (IGF1) also may stimulate maturation of human iPSC-derived CMs towards adult cardiac phenotype in generated 3D cardiac microtissues that recapitulate aspects of the native myocardium (Huang et al., 2020). It has been found that clinically approved L-type calcium channel blockers from multiple chemical classes enhance proliferation of iPSC-derived CMs as well (Woo et al., 2019). Somatic cell origin may also be one of the determinants of iPSC-derived CMs maturation. Human iPSCs generated from cardiac somatic cells displayed enhanced capacity toward cardiac re-differentiation compared to other sources for iPSCs as a result of the important role of epigenetic mechanisms (Pianezzi et al., 2020).

Myocardial infarction is one of the leading causes of morbidity and death throughout the world. A number of studies have been addressed to exploring potential of iPSC-derived CMs in repair of post-myocardial infarction (Table 1). The massive cell death following myocardial infarction dramatically decreases the reparative capacity of the heart and initiates their replacement with fibrous tissue resulting in significant heart failure. CMs derived from iPSCs may be a promising cell source for the repair of damaged myocardium in patients with extensive myocardial infarction. A growing number of studies have demonstrated the ability of iPSCs and iPSC-derived differentiated CMs to repair post-myocardial infarction heart (Table 1). Biomaterial-supported cardiac tissue has also been engineered using human iPSC-derived CMs, pericytes, and ECs (Table 1). Also, iPSC-derived CMs have been generated from patients with various cardiomyopathies to study cellular mechanisms and therapeutic targets (Table 1).

To study molecular mechanisms, disease modeling, and potential drug screening in diabetic cardiomyopathies, patient-specific CMs have also been generated from iPSCs of individuals with different types of DM (Drawnel et al., 2014; Bowman et al., 2019; Tang et al., 2020) (also see Table 1). Human iPSC-derived CMs, ECs and cardiac fibroblasts can be integrated into the beating cardiac microtissues and serve as a platform allowing modelling and testing relevant drugs for the treatment of cardiovascular diseases (Giacomelli et al., 2017, 2020). Murine and human iPSC-derived CMs have also been used to study the paracrine effect of cardiac microvascular ECs on cardiomyocyte gene expression and function, and have been applied in research for safety cardiac pharmacology (Jiang et al., 2019; Treat et al., 2019).

Patient-derived iPSCs have also been generated to study various types of arrhythmias, a cause of sudden cardiac death, connected to heritable

diseases, such as long and short QT syndromes, Brugada syndrome, familial form of atrial fibrillation, myotonic dystrophies, autosomal polycystic kidney disease and others cardiac disorders (Table 1). Hypertrophic cardiomyopathies are also prevalent hereditary cardiac disorders linked to a sudden cardiac death. To identify genetic predictors, elucidate the mechanisms underlying these diseases, investigate molecular signaling pathways that may promote their phenotypes, and identify novel therapies, iPSC-derived CMs have been generated from patients (Table 1).

A few clinical trials employing iPSC-derived CMs have recently been started. One of them was initiated in April 2022 in Japan (U.S. National Library of Medicine Clinical Trials Identifier: NCT04945018) by Heartseed Inc. to evaluate the safety and efficacy of iPSC-derived cardiomyocyte spheroids transplanted into severe heart failure patients with ischemic heart disease. Another Japanese company, Cuorips Inc., in collaboration with Osaka University in December 2019 launched a clinical trial aimed at confirming efficacy of human iPSC-derived cardiomyocyte sheet transplantation, and at evaluating its safety and tolerability in patients with severe ischemic cardiomyopathy (NCT04696328). Both trials are ongoing.

Conclusion

Considerable progress has been made in generating iPSCs from humans and animals, differentiating them into various tissues, including vascular and cardiac, and using them to study mechanisms of human diseases. However, the development of iPSC-based cell therapies is ongoing and only a few clinical studies employing iPSC-derived cells have been performed to date (Mandai et al., 2017; Schweitzer et al., 2020; Kim et al., 2022b). iPSC technology has a promising potential for the regenerative medicine and gene therapy; however, a lot of issues should be resolved to attain clinical applications of iPSCs and their derivatives. The safety of technologies for the generation, genetic correction, and differentiation of iPSCs still must be improved, and the expenses associated with gene correction in patient-derived iPSCs, and their subsequent autografting are still too high. The important challenges in the iPSC technology are reprogramming methods and variability among iPSCs lineages. Although genome integration-free approaches currently are widely used for the generation of iPSCs, the safety and reliability of these methods are still developing. Such challenges can be addressed by optimization of cell culture, reprogramming and differentiation protocols, and automated approaches. The establishment of selection criteria for iPSC-derived cells, such as cell-specific markers, rate of proliferation, and transcriptome study can help to minimize the variability among iPSC-derived lineages. Not unlike ESCs, iPSCs may also form teratomas when they are not completely differentiated into somatic cells. Although efficient differentiation protocols have been developed, currently available cell purification technologies may not completely separate the differentiated cells from undifferentiated iPSCs. This may pose a risk of transplanting undifferentiated or partially differentiated iPSCs into the patient. In addition, genomic abnormalities, such as the accumulation of mutations and aberrant DNA methylation of certain single bases, may occur in iPSCs following the reprogramming process or subsequent culture conditions (Ruiz et al., 2015; Von Joest et al., 2016). Therefore, more genomic and epigenetic studies should be performed for iPSC clinical applications.

Although autologous iPSCs can potentially be useful for treating patients without immune rejection, iPSCs may be immunogenic and more studies should be performed to rule out possibilities of an iPSC-mediated immune response in patients. Another aspect of immune rejection in iPSC-based therapy is related to gene correction in iPSCs. Reintroduction of a protein unfamiliar to the host cell may trigger an immune response and eventual rejection of corrected iPSC-derived cells. Prescreening for patients with heterozygous mutations or the expression of truncated, nonfunctional forms of the protein of interest may partially solve the issue of immune rejection on transplantation of corrected cells. On the other hand, an alternative approach has been recently provided employing human leukocyte antigen (HLA) haplotype homozygous donors to provide HLA matched iPSC derivatives to significant numbers of patients by establishing a haplobank of iPSCs (Lee et al., 2018). Despite some concerns related to clinical applications of iPSC-technology, it could be promising method to cure a wide variety of human cardiovascular diseases.

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