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Review:

Induced pluripotent stem cells: origins, applications, and future perspectives*

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Abstract: Embryonic stem (ES) cells are widely used for different purposes, including gene targeting, cell therapy, tissue repair, organ regeneration, and so on. However, studies and applications of ES cells are hindered by ethical issues regarding cell sources. To circumvent ethical disputes, great efforts have been taken to generate ES cell-like cells, which are not derived from the inner cell mass of blastocyst-stage embryos. In 2006, Yamanaka *et al*. first reprogrammed mouse embryonic fibroblasts into ES cell-like cells called induced pluripotent stem (iPS) cells. About one year later, Yamanaka *et al.* and Thomson *et al.* independently reprogrammed human somatic cells into iPS cells. Since the first generation of iPS cells, they have now been derived from quite a few different kinds of cell types. In particular, the use of peripheral blood facilitates research on iPS cells because of safety, easy availability, and plenty of cell sources. Now iPS cells have been used for cell therapy, disease modeling, and drug discovery. In this review, we describe the generations, applications, potential issues, and future perspectives of iPS cells.

Key words: Induced pluripotent stem cells, Origin, Peripheral blood cells, Application, Potential issues
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1 Introduction

Embryonic stem (ES) cells are pluripotent cells which were derived from the inner cell mass of blastocyst-stage embryos. Pluripotency is the potential that one type of cells can differentiate into various kinds of cells, such as muscle cells, neural cells, and even germ cells. Based on this property, ES cells can generate any type of cell to meet the requirements of different applications. ES cells are also capable of self-renewal; they can be semi-permanently cultured on feeder cells, which supply necessary growth factors for ES cells.

Mouse ES cells were established by Evans and Kaufman (1981). At present, most of gene-targeted and transgenic mice are generated via mouse ES cells. Basic research on gene functions can be carried out on these animal models. However, research and clinical applications on human ES cells, which were established by Thomson *et al*. (1998), have been restricted by ethical issues regarding cell sources and immunological rejection in cell therapy. Most debates on ethics are concentrated on the morality of destroying human embryos for the benefit of other people. Obtaining stem cells from oocytes and embryos is full of disputes regarding the onset of personhood and reproduction. Furthermore, immunizing antigens from different ES cells are obviously different. After transplanted into a recipient, somatic cells, which were derived from human ES cells, may be rejected by the recipient's immune system. Therefore, it is necessary to make patient-specific pluripotent stem cells.

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Scientists have attempted to reprogram somatic cells to develop a new kind of stem cell with self-renewal properties and pluripotency through many methods, such as nuclear transfer (Wilmut *et al*., 1997; Chesné *et al*., 2002) and cell fusion (Ying *et al*., 2002). However, all methods cannot do without the pluripotency of the cell nucleus in animals. As early as 1962, in fact, Gurdon (1962) found that the differentiation of animal cells is reversible. In the classic experiment, he replaced the nuclei in unfertilized frogs' eggs with the nuclei from intestinal cells. The modified eggs finally still developed into normal tadpoles. This means that the DNA of adult cells in frogs still contains all the genetic information as would be found in the nucleus of the zygote. In 1996, the birth of Dolly indicated that a mammal could be successfully cloned from adult cells (Wilmut *et al*., 1997). In 2006, a Japanese group made a remarkable breakthrough. Takahashi and Yamanaka (2006) generated induced pluripotent stem (iPS) cells by over-expressing a few types of transcription factors. iPS cells without ethical arguments have self-renewal properties and pluripotency just like ES cells. In 2012, Gurdon and Yamanaka received the Nobel Prize in physiology or medicine for their researches.

Here we review the initial development of iPS cells and their applications in pharmacology and medicine, especially the usage of peripheral blood as an easily accessible source for deriving iPS cells. In addition, we also provide discussions on potential issues and future perspectives for iPS cells.

2 Generations of iPS cells

When mouse somatic cells are hybridized with mouse ES cells, their nuclei can be reprogrammed. The hybridized somatic cells have the ability of differentiating into endoderm, mesoderm, and ectoderm cells. These findings demonstrated that reprogramming factors expressed in ES cells could induce pluripotency in somatic cells. The most difficult part in reprogramming somatic cells is how to find these reprogramming factors which can convert somatic cells to pluripotent stem cells. Now this problem has been solved by the Fbx15-Neo reporter system. *Fbx15* is a gene which was expressed specifically in ES cells. Normal fibroblasts cannot survive in the presence of Geneticin (G418), an analog of Neomycin (Neo) used for screening ES cells. Therefore, candidate reprogramming factors can be screened via fibroblasts with a Neo resistance gene in their *Fbx15* locus. Fibroblast reprogrammed by the candidate reprogramming factors can activate the *Fbx15* locus, which leads to the expression of the Neo resistance gene. Thereby, the fibroblasts can survive in the presence of G418.

Takahashi and Yamanaka (2006) selected 24 genes, which were important transcripts of ES cells and oncogenes as candidate reprogramming factors. Different combinations of these candidates were introduced into mouse embryonic fibroblasts in order to screen proper reprogramming factors via the Fbx15-Neo reporter system. If these candidate genes could reprogram the fibroblasts, G418-resistant stem cell-like colonies would appear about two weeks later. Finally, the 24 candidates were narrowed down to four transcription factor genes. After introduction of the retroviral mediated factors *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*, mouse embryonic fibroblasts were reprogrammed into ES cell-like cells called iPS cells. This was a revolutionary breakthrough that immediately sparked immense interest so that many scientists subsequently focused on this research. However, some key pluripotent genes were not fully activated by the four transcription factor genes. Therefore, the fibroblasts were only partially reprogrammed. When the iPS cells were injected into mouse blastocysts, they could not generate postnatal chimeras or contribute to the germline. In fact, pluripotent iPS cell lines were not established until 2007. Live chimeras and germline transmitted mice were derived from these iPS cells through blastocyst injection (Maherali *et al*., 2007; Okita *et al*., 2007; Wernig *et al*., 2007). Zhao *et al*. (2009) and Kang *et al*. (2009) used iPS cells to generate germline transmitted mice through tetraploid complementation. As mentioned above, research in different laboratories indicates that iPS cells, which are similar to ES cells, have the potential to differentiate into any cell type.

Takahashi *et al*. (2007) and Yu *et al*. (2007) independently reprogrammed human somatic cells to iPS cells. The former used *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc* on human dermal fibroblasts when the latter used *Oct3/4*, *Sox2*, *Nanog*, and *Lin28* on human somatic cells. Both researches demonstrated that

human iPS cells resemble human ES cells in many aspects, such as morphology, proliferation, pluripotency markers, gene expression profiles, epigenetic status, and differentiation potential. These findings revealed that human iPS cells have the capability of replacing human ES cells. Human iPS cells provide the correct direction of addressing the ethical disputes over stem cell sources and immunological rejection in cell therapy.

Since the first iPS cell line was established by Yamanaka in 2006, scientists have made efforts to improve the safety and efficiency of the reprogramming process, including single (Si-Tayeb *et al*., 2010) and multiple transient transfections (Okita *et al*., 2008), non-integrating vectors (Stadtfeld *et al*., 2008a; Yu *et al*., 2009; Okita *et al*., 2011), excisable vectors (Kaji *et al*., 2009; Lacoste *et al*., 2009; Woltjen *et al*., 2009), direct protein transduction (Kim D. *et al*., 2009; Zhou *et al*., 2009; Cho *et al*., 2010), RNA-based Sendai viruses (SeVs) (Fusaki *et al*., 2009; Nishimura *et al*., 2010; Seki *et al*., 2010), mRNA-based transcription factor delivery (Warren *et al*., 2010; Yakubov *et al*., 2010), microRNA transfections (Maehr *et al*., 2009), and the use of chemical compounds (Desponts and Ding, 2010; Li and Ding, 2010).

Recently, small-molecule compounds have been used to generate mouse iPS cells from somatic cells (Hou *et al*., 2013). Small-molecule compounds have advantages over other inducers because they can be cell-permeable, nonimmunogenic, easily synthesized, and cost-effective. Moreover, their effects on inhibiting and activating the function of specific proteins are often reversible and can be reversed by varying the concentrations. It is a milestone in the field of iPS cells. In the future, this chemical reprogramming strategy will be hotspots for reprogramming different somatic cells.

3 Cell sources for deriving iPS cells

Moreover, many other cell sources are also used in research on iPS cells. Up to now, iPS cells have been derived from many different species, such as mice, humans, rats, marmosets, rhesus monkeys, pigs, and rabbits (Table 1). However, most iPS cell lines cannot generate live chimeras. Because of the successful reprogramming of the fibroblasts, many different cell types have been analyzed for their capacity to be reprogrammed. The cell types successfully reprogrammed contain hepatocytes, gastric epithelial cells, keratinocytes, stomach cells, mesenchymal cells, neural stem cells, pancreatic cells, B and T lymphocytes, blood progenitor cells, cord blood cells, peripheral blood cells, and so on (Table 1).

4 Advantages of peripheral blood over other cell sources for iPS cells

The generation of patient-specific iPS cells is a critical step in cell therapy and other clinical applications. As shown in Table 1, human iPS cells are normally derived from dermal fibroblasts because of their accessibility and relatively high reprogramming efficiency. However, skin biopsy and a prolonged period of expansion in cell culture are required prior to using dermal fibroblasts. During skin biopsy, the exposure of the dermis to ultraviolet light might increase the risk for chromosomal aberrations. In addition, it cannot be ignored that patients would experience the pain and the risk of infection when obtaining dermal fibroblasts. These issues limit the wide application of iPS cells.

Blood cells are the most easily accessible source of patients' tissues for reprogramming because it is not need to maintain cell cultures extensively prior to reprogramming experiments. Furthermore, the venipuncture is safer than skin biopsy. And numerous peripheral blood samples have already been frozen and stored in blood banks, so we can directly generate human iPS cells via these samples.

The reprogramming of peripheral blood cells started with research on mice in 2008. Hanna *et al*. (2008) utilized retroviral-mediated factors (*Oct3/4*, *Klf4*, *Sox2*, and *c-Myc*) to reprogram mouse B lymphocytes. In the experiment, they improved the reprogramming efficiency by either ectopic expression of the myeloid transcription factor CCAAT/enhancer-binding-protein-α or knockdown of the B cell transcription factor Pax5. Hong *et al*. (2009) generated iPS cells from mouse T lymphocytes by the introduction of *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc* in a p53-null background.

Table 1 iPS cells derived from different species and somatic cell types

Species	Cell type	Factor or chemical	Vector	Reference
Mouse	Fibroblast	OKSM or OKS	Retrovirus	Takahashi and Yamanaka, 2006; Nakagawa *et al*., 2008; Wernig *et al*., 2008
	Fibroblast	OSE or KSNr	Retrovirus	Feng *et al*., 2009; Heng *et al*., 2010
	Fibroblast	mir302/367 cluster	Lentivirus	Anokye-Danso *et al*., 2011
	Fibroblast	OKSM	PB transposon and 2A peptides	Kaji *et al*., 2009
	Fibroblast	Proteins (OKSM)	Poly-arginine	Zhou *et al*., 2009
	Fibroblast	OKSM	Plasmid or adenovirus	Okita *et al*., 2008; Stadtfeld *et al*., 2008a
	Dermal papilla	OKM or OK	Retrovirus	Tsai *et al*., 2010
	Melanocyte	OKM	Drug-inducible lentivirus	Utikal *et al*., 2009
	Mature B and T cell	OKSM	Retrovirus	Eminli *et al*., 2009
	Myeloid progenitor	OKSM	Retrovirus	Eminli *et al*., 2009
	Hematopoietic stem cell	OKSM	Retrovirus	Eminli *et al*., 2009
	Pancreatic β cell	OKSM	Drug-inducible lentivirus	Stadtfeld *et al*., 2008b
	Intestinal epithelial cell	OKSM	Drug-inducible lentivirus	Wernig *et al*., 2008
	Hepatocyte	OKS	Retrovirus	Aoi *et al*., 2008
	Gastric epithelial cell	OKSM	Retrovirus	Aoi *et al*., 2008
	Adipose stem cell	OKSM	Retrovirus	Sugii *et al*., 2010
	Neural stem cell	OK or O	Retrovirus	Kim *et al*., 2008; 2009b
Human	Fibroblast	OKSM or OKS	Retrovirus	Takahashi *et al*., 2007; Nakagawa *et al*., 2008
	Fibroblast	OSLN	Lentivirus	Yu *et al*., 2007
	Fibroblast	OKSM or OKS	Floxed lentivirus	Soldner *et al*., 2009
	Fibroblast	OS and valproic acid	Retrovirus	Huangfu *et al*., 2008
	Fibroblast	Proteins (OKSM)	Poly-arginine	Kim D. *et al*., 2009
	Fibroblast	OKSM	Adenovirus	Zhou and Freed, 2009
	HUVEC	OKSM	Retrovirus	Lagarkova *et al*., 2010
	Peripheral blood cell	OKSM	Drug-inducible lentivirus	Loh *et al*., 2010; Staerk *et al*., 2010
	Cord blood endothelial cell	OSLN	Lentivirus	Haase *et al*., 2009
	Cord blood stem cell	OKSM or OS	Retrovirus	Eminli *et al*., 2009; Giorgetti *et al*., 2009
	Adipose stem cell	OKSM	Lentivirus	Sun *et al*., 2009
	Adipose stem cell	OKS	Retrovirus	Aoki *et al*., 2010
	Amniotic cell	OKSM	Retrovirus	Li C. *et al*., 2009
	Amniotic cell	OSN	Lentivirus	Zhao *et al*., 2010
	Neural stem cell	O	Retrovirus	Kim J.B. *et al*., 2009a
	Marrow mesenchymal cell	OKSM or OK	Retrovirus	Park *et al*., 2008
	Adipose stem cell	OSLN	Nonviral minicircle DNA	Park *et al*., 2008
	Hepatocyte	OKSM	Retrovirus	Liu *et al*., 2010
	Astrocyte	OKSM	Retrovirus	Ruiz *et al*., 2010
	Keratinocyte	OKSM or OKS	Retrovirus	Aasen *et al*., 2008
Pig	Fibroblast	OKSM	Drug-inducible lentivirus	Wu *et al*., 2009
Rabbit	Hepatocyte and stomach cell	OKSM	Lentivirus	Honda *et al*., 2010
Rat	Fibroblast	OKS	Retrovirus	Chang *et al*., 2010
	Fibroblast	OKSM	Lentivirus	Liao *et al*., 2009
	Neural progenitor cell	OKS	Retrovirus	Chang *et al*., 2010
	Liver progenitor cell	OKS	Retrovirus	Li W. *et al*., 2009
Marmoset	Fibroblast	OKSM	Retrovirus	Wu *et al*., 2010
Rhesus monkey	Fibroblast	OKSM	Retrovirus	Liu *et al*., 2008

HUVEC: human umbilical vein endothelial cell; O: *Oct3/4*; S: *Sox2*; K: *Klf4*; M: *c-Myc*; E: *Esrrb*; L: *Lin28*; N: *Nanog*; Nr: *Nr52a*

After mouse peripheral blood cells were reprogrammed, Haase *et al*. (2009) generated human iPS cells from cord blood (CB). It is an advantage that CB can be obtained from public and commercial CB banks without any risk to donors. Ye Z. *et al*. (2009) derived human iPS cells from previously frozen CB and $CD34^+$ cells of healthy adult donors. However, the use of CB is still limited because it can only be obtained from neonates.

Loh *et al*. (2010), Seki *et al*. (2010), and Staerk *et al*. (2010) independently derived iPS cells from human peripheral blood cells. Loh *et al*. (2010) separated mononuclear cells (PBMCs) and $CD34^+$ cells ($PBCD34^+$) from peripheral blood samples, which were then collected through venipuncture and Ficoll density centrifugation. After infection with lentiviruses expressing *Klf4*, *Sox2*, *Oct3/4*, and *c-Myc*, $PBCD34^+$ cells showed a reprogramming efficiency of 0.002%, whereas PBMCs showed relatively low values of 0.0008% to 0.001%. Staerk *et al*. (2010) utilized a doxycycline-inducible lentivirus construct to derive iPS cells from T lymphocytes and myeloid cells which were cultured in IL-7 or G-CSF, GM-CSF, IL-3, and IL-6; this lentivirus construct could encode four reprogramming factors (*Oct3/4*, *Sox2*, *Klf4*, and *c-Myc*) into a polycistronic expression cassette (pHAGE2-TetOminiCMV-hSTEMCCA). Their results showed that the reprogramming efficiency of T lymphocytes was higher than that of myeloid cells. Because T lymphocytes exhibited a higher proliferation rate and had a better long-term growth potential in vitro than myeloid cells, Seki *et al*. (2010) induced T lymphocytes into iPS cells by a temperature-sensitive mutant SeV vector encoding human *Oct3/4*, *Sox2*, *Klf4*, and *c-Myc* with an efficiency of 0.1%. This SeV vector is a non-integrating type, and it could not proliferate at standard culture temperatures. So these characteristics significantly increase the safety for the generation of iPS cells. Chou *et al*. (2011) generated iPS cells from newborn CB and adult peripheral blood mononuclear cells with an improved EBNA1/OriP plasmid. By this new reprogramming vector, iPS cells were derived from peripheral blood cells within 14 d, instead of 28 to 30 d as in a previous work on fibroblasts.

The research and findings provide the evidence that human iPS cells from peripheral blood cells are comparable to human ES cells in terms of morphology, surface antigens, pluripotency gene expression, DNA methylation, and differentiation potential. iPS cells from mononuclear cells of peripheral blood can be considered reliable and safe. Therefore, methods of generating iPS cells from human peripheral blood cells will accelerate research on and promote clinical applications of iPS cells in the future.

Interestingly, human iPS cells can also differentiate into peripheral blood cells because of their pluripotency. Lei *et al*. (2012) made human iPS cells differentiate into both conventional and antigen-specific T lymphocytes for T cell-based immunotherapy by utilizing either in vitro or in vivo induction systems. The recently established human iPS cells by Ebihara *et al*. (2012) represent potentially unlimited safe sources of donor-free red blood cells for blood transfusion, as they can proliferate indefinitely in vitro without the potential for infectious disease via blood transfusion.

5 Applications of iPS cells

Similar to ES cells, mouse iPS cells are able to differentiate into any type of cell, and even have the capability of germline transmission (Maherali *et al*., 2007; Okita *et al*., 2007; Wernig *et al*., 2007; Kang *et al*., 2009; Zhao *et al*., 2009). This means that we can obtain various differentiated cells in large quantities for research and therapy. For example, Zhu *et al*. (2012) and Easley *et al*. (2012) independently investigated the differentiation potential of human and mouse iPS cells into spermatogonial stem cells and late-stage male germ cells. The derivation of male germ cells from iPS cells represents potential applications in the treatment of male infertility and provides a model for uncovering the molecular mechanisms underlying male germ cell development.

Up to now, iPS cells have had main applications in three major areas: human disease modeling (Zhang *et al*., 2012), regenerative medicine, and drug discovery (Fig. 1).

5.1 Disease modeling

For many human genetic diseases, therapeutic research is hindered by problems regarding the source of experimental materials. iPS cells can overcome these issues by establishing disease-specific models.

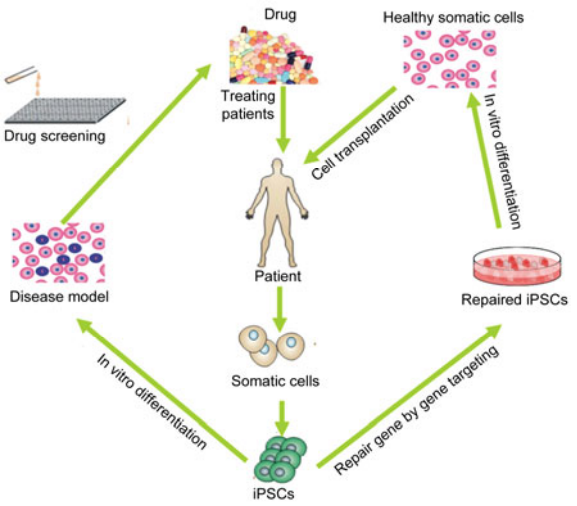

Fig. 1 A schematic illustration for the applications of iPS cells (iPSCs) in treating human disease
Modified from Stadtfeld and Hochedlinger (2010)

Disease-specific iPS cells can form cell lineages reflecting the defects caused by a certain disease in patients. Some human diseases for which models have been established by patient-specific iPS cells include amyotrophic lateral sclerosis (Dimos *et al*., 2008), spinal muscular atrophy (Ebert *et al*., 2009), Parkinson's disease (Soldner *et al*., 2009), β-thalassemia (Ye L. *et al*., 2009), Rett syndrome (Hotta *et al*., 2009), adenosine deaminase deficiency-related severe combined immunodeficiency, Shwachman-Bodian-Diamond syndrome, Gaucher disease, Duchenne muscular dystrophy, Becker muscular dystrophy, Huntington's disease, type 1 diabetes mellitus, Down syndrome, and Lesch-Nyhan syndrome (carriers) (Park *et al*., 2008). Disease models based on iPS cells can result in both insights into the mechanisms of pathogenesis and the development of new drugs. Patient- and disease-specific therapies represent the most valuable outcome of the whole area of iPS cells. Considering the generation of a wide variety of cell types from iPS cells, these provide the potential to treat disorders of virtually all tissue systems in the body.

5.2 Regenerative medicine

Immunological rejection is a major issue in organ transplantation and cell therapy, because long-term treatment with immunosuppressive drugs would produce serious side effects. Patient-specific iPS cells have the immune markers of the patient, so they solve the problem of immunological rejection. In addition, disease-causing mutations can also be restored by gene targeting in patient-specific iPS cells. Repaired cells can differentiate into targeted cells. After transplanted into the diseased area, they can alleviate disease symptoms. To illustrate this, using a mouse model, Hanna *et al*. (2007) proved that iPS cells can be used to cure sickle cell anemia, a genetic blood disorder that renders red blood cells nonfunctional. The disease-causing mutation was repaired in iPS cells generated from the mouse model via gene targeting. The repaired iPS cells then differentiated into blood-forming progenitor cells. These healthy progenitors were transplanted into an anemic mouse where they can proliferate and generate normal red blood cells, thereby curing the disease. In fact, the application of patient-specific iPS cells for tissue replacement and cell therapy indicates what the ultimate goal of regenerative medicine is. At present, however, many limitations still affect the possibility to apply this personalized medicine. The main limitations are related to technical issues, including the development of safe and efficient methods for iPS generation as well as the choice of the most appropriate cell type for reprogramming.

5.3 Drug discovery

Before using novel drugs for treatment, we need to obtain reliable data on their potential toxic effects on humans. In drug discovery, the effects and side effects of novel drugs are usually tested in laboratory animals, such as mice, dogs, and pigs. However, these tests are costly and humans and animals have relatively significant differences. Moreover, animal tests are not effectively standardized. Now we can efficiently test novel drugs on disease models generated from patient-specific iPS cells. This approach will greatly facilitate research on pharmacology and toxicology. Some drugs have already been tested on iPS cells derived from patients suffering from various diseases, such as spinal muscular atrophy (Ebert *et al*., 2009), familial dysautonomia (Lee *et al*., 2009), and LEOPARD syndrome (Carvajal-Vergara *et al*., 2010). The fact that novel drugs alleviate "symptoms" in patient-specific iPS cells demonstrates their therapeutic potential. This method now has been applied to many other diseases and will benefit many patients.

6 Potential issues regarding iPS cells

Crucial experiments based on iPS cell technology have shed light on human diseases at the cellular and molecular levels. The application of iPS cells in drug discovery can reduce costs and increase the chances of success. Above all, iPS cells circumvent ethical disputes on ES cells and patient-specific iPS cells may resolve issues of immunological rejection in cell therapy.

Currently, in the field of iPS cells, scientists have developed more efficient methods of deriving iPS cells from various cell sources, including those from patients who suffer from different diseases. More progress and new innovations regarding iPS cells will be made in the near future. However, some problems remain to be solved in the clinical application of iPS cells. Many genomic changes, including chromosomal aneuploidy, translocations, point mutations, megabase-scale duplications and/or deletions, and so on, have been observed in human iPS cells; these problems may limit the therapeutic potential of iPS cells. As suggested recently by Gore *et al*. (2011), in the exome sequencing of 22 human iPS cell lines obtained from seven laboratories by five different methods, they found 124 point mutations in the iPS cell lines, but no mutations in the parental cells. This study identified many missense mutations related to the protein function modification and point mutations in genes implicated in cancers. Although the reprogramming process itself might cause genomic anomalies, not all anomalies result from it, because genomic alterations have been identified in human iPS cells produced through different techniques, including non-integrating methods such as those that use synthetic mRNAs (Warren *et al*., 2010). In spite of the fact that the low efficiency of reprogramming is one of the hurdles that prevents the area from moving forward, compared with improving reprogramming efficiency, solving problems in chromosomal anomalies in iPS cells is more important. Thus, in the future, obtaining iPS cells with the fewest genomic alterations should be the focus in the field of iPS cells. The causes of chromosomal abnormalities during reprogramming somatic cells need to be investigated as well.

In addition, some other questions remain: What is the mechanism for iPS cell induction? What are the optimal reprogramming factors? How do we reduce risks of insertion mutagenesis in the genome of iPS cells? How do we achieve directed differentiation? How do we evaluate the safeness of iPS cells in clinical applications? Obtaining the answers to these questions requires thorough analyses of the induction process and the epigenetics of iPS cells. Furthermore, a reliable evaluation system on clinical trials needs to be established. The clarification of these questions might improve the application of iPS technology as well as the length and quality of life for people in the future.

7 Future perspectives

The generation of iPS cells is regarded as a milestone for life science (Fig. 2). In spite of the problems mentioned in the last section, the advantages of iPS cells cannot be ignored. iPS cells can avoid ethical disputes as well as immunological rejection in cell therapy. Moreover, disease models generated from iPS cells can be used to study the mechanisms of human genetic disorders and test the effects of novel drugs (Fig. 1). iPS cell biology has admittedly become a new field within stem cell research that covers various important and attractive scientific areas.

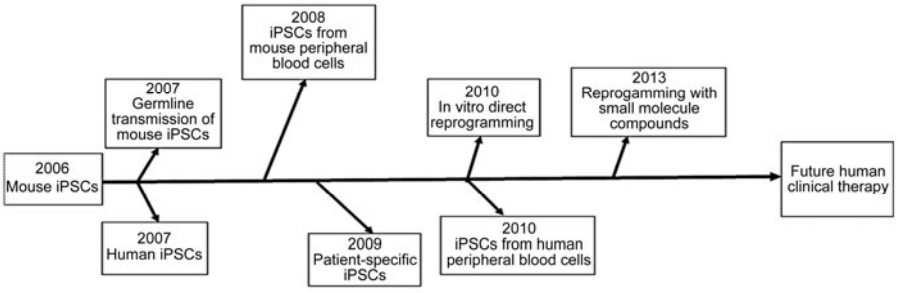

Fig. 2 History and milestones of iPS cell (iPSC) research
Modified from Yamanaka (2012)

The whole area of iPS cells is a hot topic in biomedical research and is rapidly approaching its clinical utilization. The future clinical application of iPS cells needs a more comprehensive knowledge of the reprogramming process. Recent advancements, especially the iPS cells derived from peripheral blood and chemical reprogramming strategy, have increased their therapeutic potential. Along with the improvement of iPS cell technology, clinical therapy based on iPS cells will be put on the agenda in the foreseeable future.

Compliance with ethics guidelines

Jing ZHAO, Wen-jie JIANG, Chen SUN, Cong-zhe HOU, Xiao-mei YANG, and Jian-gang GAO declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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