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ORIGINAL ARTICLE

PROMISES OF INDUCED PLURIPOTENT STEM CELLS IN A THERAPEUTIC CONTEXT

HIMANSU KUMAR AND C.V.S.SIVA PRASAD

Division of Applied Science and IRCB, Indian Institute of Information Technology Allahabad, Allahabad , India,

Abstract:

Transformation of somatic cells into induced pluripotent stem cells (IPSC) has opened a new page in the clinical world. In 2006, Yamanaka and Takahashi have shown that the four reprogramming factors namely OCT4, NANOG, SOX2, and LIN28 are sufficient for the reprogramming of somatic cells into IPSC. Fortunately these IPSC are containing all essential features of embryonic stem cells and finally it leads to specific tissue regeneration. Although there are certain limitations of IPSC like low efficiency of IPSC generation, reprogramming process is highly time consuming and viral vector based delivery of transcription factors into target may induce mutations in the genome. In this review we would like to focus on comprehensive knowledge about IPSC, derivation mechanism of IPSC, clinical application of IPSC and technical challenges for the implementation of the IPSC into biomedical and therapeutic applications.

KEYWORDS:

IPSC, Reprogramming factors, transcription factors, and Somatic cells.

INTRODUCTION:

Stem cells are present in all multicellular organisms with two characteristic features like (1) Self-renewal, ability for numerous mitotic cell divisions to maintain their undifferentiated state and (2) Potency can differentiate into specific cell types [1]. There are two types of stem cells namely Embryonic stem cells and Adult stem cells. Controversy in clinical use of embryonic stem cells led to the emergence of IPSC technology. IPSC are artificially obtained pluripotent stem cells which are derived from adult somatic cells with the help of different reprogramming factors like OCT4,

NANOG,SOX2, and LIN28 [2]. IPSC are having similar property as natural stem cells like differentiability and potency, chimera formation, embryoid formation, methylation pattern of chromatin and expression of genes and proteins. In 2007 two group of scientist from Japan and America announced that the adult somatic cell can be transformed into stem cells with the help of some specific transcription factors.

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S.No.	Year wise advancement in IPSC research	
1	August 2006	First IPSC produced from mouse cells by Yamanaka *et al.*[2]
2	November 2007	IPSC produced from human cells by Yamanaka *et al.*[2]
3	2008	Techniques that removes oncogenes after induction of pluripotency. By: Kaplen *et al.*[3]
4	October 2008	Plasmid vector based reprogramming by Yamnaka lab.
5	November 2008	IPSC developed from testis germline of human.
6	2009	Produced patient specific IPSC, By Kim *et al.*[4]
7	2010	First trial of embryonic stem cell in humans.[5]

Table 1: Major breakthrough of Induced Pluripotent Stem Cells

GENERATION MECHANISM OF IPSC

Embryo is the natural source of the human stem cells, so the culturing and growth of the stem cell requires destruction of the embryo and finally which leads to the controversy. To overcome this controversy generation of the IPSC emerges out. Traditionally there are number of methods to generate IPSC like:

1.Transfer of Somatic cell nuclear into Oocytes: Basic procedure for this technique is to transfer the nuclear component of somatic donor cell to enucleated oocytes. After the fusion of both components they are subjected to stimulate the generation of IPSC in in-vitro condition [6][7].
2.Cell fusion: In this method the somatic cell and embryonic stem cell are subjected to hybridize and fused cell induced the reprogramming of somatic cells into IPSC [9].
3.Reprogramming through cell extract: In this technique the extract of embryonic stem cells or pluripotent cells are being extracted and inserted into somatic cells and this extracts leads to the reprogramming of the somatic cells into IPSC [10].
4.Direct reprogramming: In this technique reprogramming factors like NANOG, SOX2, OCT4 etc., are incorporated into somatic cells and subjected to grow in a medium [42]. It has been reported that these reprogramming factors are responsible for the induction of regeneration property.

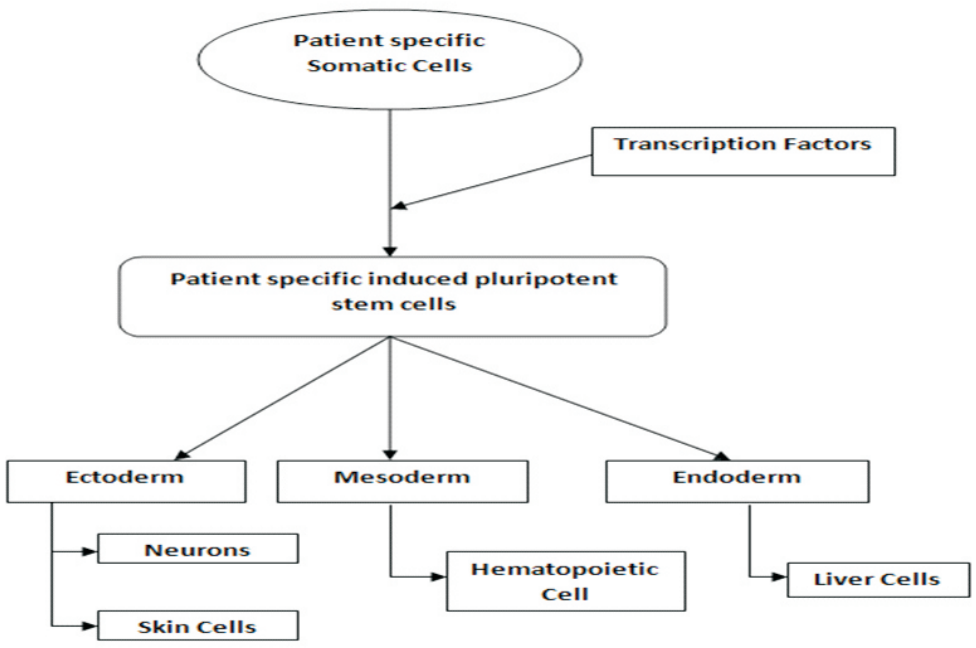

Fig 1: Flow diagram for Generation of Patient-specific Induced Pluripotent Stem Cells.
[8]Features of IPSC

Derived IPSC are posses similar property as compared to the natural embryonic stem cells, these properties are:

1.Cellular morphology: Most of the IPSC have same morphological property like high nucleo-cytoplasmic ratio, flat and tightly packed colonies etc. Various studies shows that the IPSC like dermal fibroblast and mesenchymal cells are derived from different patients of Down syndrome and Parkinson disease are showing similar morphology [15&16].
2.Genetic profiles: Genetic profiles of IPSC cells are showing similarity to normal embryonic stem cells. The IPSC of Human and Mouse are also showing genomic similarity, which is important for generation of high quality IPSC. Microarray analysis of IPSC shows that the expression of IPSC varies in different culture medium; hence genomic stability and efficient culture medium are prime concern for the generation of IPS cells [43].
3.Epigenetic status: Epigenetic status is important to access the completion of reprogramming of somatic cells into IPSC, because it is controlling the activity of the genes as regulatory genes. Major epigenetic modifications are DNA methylations, histone modifications etc [2 & 44].
4.Pluripotency: Immunocytochemistry study revealed that IPSC are able to differentiate into all three germ layers ectoderm, mesoderm and endoderm [2]. Histological study also shows that the potential of pluripotency is similar to the ESC [2 & 43].

IMPLEMENTATION OF INDUCED PLURIPOTENT CELLS IN THERAPEUTIC CONTEXT

Derivation of natural embryonic stem cell is controversial because of destruction of embryo, to overcome this problem IPSCs are become efficient clinical tool for the cure of various disorders. Applications of the IPSC are not only limited in to transplantation of the organ and tissue engineering but also it may be useful into clinical testing of the new drugs.

S.N.	Disease category	Disease	References
1	Neural	Amyotrophic lateral sclerosis	[14]
		Parkinson's disease	[11, 12, 15, 16]
		Huntington's disease	[11, 17]
		Lesch-Nyhan syndrome	[11]
		Rett syndrome Familial dysautonomia	[18] [19]
		Angelman syndrome	[20]
		Prader-Willi syndrome	[20, 21]
		Friedreich's ataxia	[22]
		Rett syndrome	[23]
		Schizophrenia	[24]
2	Immune system	ADA-SCID Scleroderma	[11] [25]
		Primaryimmunodeficiency	[26]
		Duchenne muscular dystrophy	[11]
3	Muscular	Duchenne muscular dystrophy	[11]
		Spinal muscular atrophy	[11] [13]
		Duchenne muscular dystrophy	[27]
4	Blood	Thalassemia Sickle cell anemia	[28, 29]
		Chronic myeloid leukemia	[25,30]
5	Heart	Long QTsyndrome	[31, 32]
		Juvenile diabetes mellitus Shwachman-Bodian-Diamond syndrome	[11]
6	Pancreas	Type Idiabetes	[33]
7	Skin	Leopardsyndrome Recessive dystrophic, Epidermolysis bullosa	[34],[35]
8	Bone marrow	Fanconi anemia Myeloproliferative diseases	[36,37]
9	Liver	Liver diseases: a1-antitrypsin deficiency	[37]
10	Lung	Lung diseases: cystic fibrosis, a-1 antitrypsin deficiency-related emphysema	[25]
11	Eye	Retinitis pigmentosa gyrate atrophy	[39][40][41]
12	Premature ageing	Dyskeratosis congenital	[39]
13	Others	Down syndrome	[11]
		Hurler syndrome Gaucher disease	[26] [11]
		Fragile Xsyndrome	[38]

Table 2: Induced Pluripotent Stem Cell lines and their application in various diseases:

Technical challenges in using IPSC as therapeutics [8]

i.Generation of reprogramming factors (OCT4, SOX2, and NANOG etc.) free IPSC cells to reduce genetic alteration in the obtained induced pluripotent stem cell lines.
ii.Generation of patient specific or disease specific phenotypes in in-vitro condition.
iii.Generation of patient specific or disease specific phenotypes in in-vivo condition.
iv.Effective strategies for the generation of markers for the identifications and genetic proof-reading.
Future prospect

The discovery of IPSC is a major advancement in the area of regenerative medicine, however expectations for the clinical use of IPSC are very high but still there are multiple concerns that have to be addressed properly. Generation of the effective human IPSC without integration of the DNA with patient's genome is still a challenge. Efficiency of the generated IPSC is also a serious concern especially human IPSC. There is an urgent need to understand molecular pathways of the reprogramming factors in order to get reprogramming without gene transfer. Integration of the interested genes via viral vector is also having its own limitations, although recent advancement in non-viral integration method may be the answer for the above said problems. Instead of technical issues ethical aspects of IPSC are also a major concern.

CONCLUDING REMARK

The breakthrough in stem cell research was due to discovery of reprogramming factors which are responsible for transformation of somatic cells into IPSC. These cells are having high similarity with original stem cells and later on can differentiate into three major germ layers. Although out of tremendous advantages of the use of induced pluripotent stem cells, in-vitro creation of these cells are still arduous task. Transformation of the somatic cells into induced pluripotent stem cells through viral vector is again a safety concern. The IPSC technology for disease specific clinical application and clinical trials for the treatment is still out of reach. Overall discussions and reviews on the use of IPSC in clinical prospect are still premature. Enormous amount of research and experiment has to be done for the direct use of IPSC in a therapeutic context. The IPSC technology gives promising results to provide new hope for stem cell based treatment.

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