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Induced Pluripotent Stem Cells-Emphasis on Transcriptomics and Recent Advances in Therapeutic Potential

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Abstract

In our previous review we reviewed the history of embryonic stem cells, advantages and disadvantages of ESC, parthenogenetic ESC and their therapeutic applications, cloning along with merits of SCNT, in this shot commentary we have just concentrated on induced pluripotent stem cells, mainly their transcriptomics, along with special emphasis on global transcriptomics in candidate oocyte factors and various advances in therapeutic applications.

Keywords: Cell mass; Transcription; Leukemia inhibitory factor; Oct4; Telomerase; Neural stem cells; Crisper/Cas9

Introduction

ESC is a set of pluripotent cells unique in character which are obtained from the 'inner cell mass of the pre implantation embryo. They can then undergo asymmetric divisions whereby they either duplicate themselves or differentiate themselves into another cell type. It is important to identify genes involved in the regulation of stem cell function to examine the effects of altered gene expression in ES and other stem cells e.g. core networks of transcription factors (TF's) such as Oct4, Nanog and sox2 govern key gene regulatory pathways networks for the maintenance of self-renewal and pluripotency of mouse and human cells. These TF's are modulated by specific external factors through signal transduction pathways e.g. leukemia inhibitory factor (LIF/Stat3, mitogen activated protein kinase1/3 (Mapk1/3) TGFβ superfamily and Wnt glycogen synthase kinase 3β (Gsk3b) [1]. Inhibitor of Mapk1/3and Gsk3b signalling enhances the derivation of ES cells and helps to maintain ESC in a full pluripotency ('ground' or 'naive' state) [2]. Recent data also indicates 20-25 nucleotide RNA's also known as microRNA's play an important role in regulating cell cycle progression in ES cells and miR128 prevents the differentiation of haematopoietic progenitor cells [3].

iPS by NT

Naturally development progresses occur from totipotent fertilized eggs to pluripotent epiblast cells to multipotent cells and finally to differentiated cells. The reverse of the terminal differentiated cells to totipotent or pluripotent cells known as nuclear programming can thus be seen as an uphill gradient that never occurs in normal conditions. However nuclear programming has been achieved using nuclear transplantation, or nuclear transfer (NT), procedures which are often known as cloning, where the nucleus of a differentiated cell is transferred into an enucleated oocyte. Although this is an error prone process with very low success rate, live animals have been produced using adult somatic donor cells in sheep, mice and other mammals. In mice, it has been demonstrated that ES cells derived from blastocysts made by somatic cell and are indistinguishable from normal ES cell. NT can be used potentially to produce patient specific ES cells carrying a genome identical to that of the patient. However the successful implementation of this procedure in humans has not been reported. Settling aside the technical and ethical issues, limited availability of human oocytes will be a major problem of clinical applications for NT. Alternatively; successful nuclear reprogramming of somatic cells by fusing them with ES cells has been demonstrated in mice and humans. However it is not yet clear how ES Cell derived DNA can be removed from hybrid cells [4].

iPS by TF's

Direct conversion of the terminally differentiated cells into ES cells is also known as induced pluripotent (iPS) cell by transiently overexpressing a combination of key TF's. The original method was to infect mouse embryonic fibroblasts cells with retro virus vectors carrying four TF's (Pou5f1 (Oct4), Sox2, Klf4, cMYC) and to identify rare ES like cells in culture by Takatashu and yamanaska in 2006.This was soon adapted to human cells, followed by a more refined procedure (e.g. the use of fewer TF's, different cell types, along with different gene delivery methods). Use of protein cocktails and a variety of small molecules has also been acutely pursued, as the goal to produce patient specific iPS cells without altering their genetic makeup [4,5].

Characteristics of iPS

Fully reprogrammed cells express a network of pluripotency genes with levels comparable to that in ES cells like OCT4, SOX2 and NANOG2, and they reactivate telomerase gene expression while down regulating THY1 and up regulating SSEA1 [6]. iPS cells which are generated by virus mediated reprogramming silence proviral genes. Then the endogenous pluripotency genes are activated and this event is paired with the expression of the embryonic antigen SSEA-3, tissue relatedantigen-1-60(TRA-1-60), TRA-1-81, DNA methyl transferase 3β (DNMT3β) and REX 1 [7]. Epigenetic reprogramming genomic

wide is essential for fully reprogrammed cells, with the degree of success being measured in part by methylation status of the promoters of the genes responsible for maintaining pluripotency, as well as genes required for maintaining differentiation [8]. Reactivation of the silent X chromosome, which occurs late during reprogramming is another important step for epigenetic reprogramming and represents a hallmark of ground state pluripotency [8-10].

Although subtle differences exist between iPS and ESC, initial differences were found in the functional differences in teratoma formation as well as *in vitro* differentiation assays. In a study it was found that the parent of origin may influence the differentiation capacity of the resultant iPS cell. In one study mouse bone marrow derived and B-cell derived iPS cells showed more efficient differentiation along, haematopoietic lineages than did fibroblast derived iPS cells or neural progenitor derived iPS cells lines. Treatment of these neural progenitors derived iPS with trichostatin A, which is a potent histone diacetylase inhibitor, plus 5-azacytidine, a methylation resistant cytosine analogue increased the blood forming capacity of these cells, which suggests that their limitations were due to epigenetic modifications. Although the bone marrow and neural-progenitor derived iPS cells contributed well to all tissues in the chimaera assay including the germ line, the fibroblast derived iPS cells contributed only poorly [10].

Further iPS cells derived from retinal pigment epithelial cells show an increase propensity to differentiate back into these cells as compared to ES cells or iPS derived from other tissues [11]. Bar Nur et al. showed that iPS cells generated from human pancreatic islet β cells retain open chromatin at key β cell genes loci, which correlates with a greater propensity to differentiate into insulin producing cells both *in vivo* as well as *in vitro* as compared to ESC or isogenic non β-cell derived iPS cells [12]. Also such functional differences are seen in disease modelling. E.g. Fragile X syndrome is caused by aberrant silencing in FMR1 gene during human development. iPS cells reprogrammed from adult fibroblasts from individual with Fragile X Syndrome failed to reactivate the FMR1 gene, whereas ES cells derived from embryos with the syndrome as diagnosed by pre implantation genetic testing, expressed FMR1 [13]. Thus the potential for epigenetic memory in fragile X syndrome derived iPS cells and ESC cells must be considered when studying this and many other potential conditions.

Further the reprogramming cells to pluripotent state require global epigenetic remodelling and introduce epigenetic changes, some essential, others inadvertently introduced. Although overall iPS cell DNA methylome closely resembles human ES-Cell DNA-methylome iPS cells have significant variability in their somatic memory and aberrant iPS cell specific differential methylation. Though some studies suggested that this occurs in a passage-dependent manner-other studies have shown that differentially methylated regions (DMR) in iPS cells are transmitted to different progeny at a considerable frequency which cannot be erased by passaging [14]. There are remarkable global similarities between the DNA methylomes of generic iPS and ES cells; however, a core set of DMRs which seem to represent hotspots of failed epigenetic reprogramming have been identified [14]. These DMRs are mainly present at the telomere and centromere region being, enriched in genes which are important for the development processes [14,15]. Kim et al. showed that more DMRs are present in mouse iPS cells as compared to ntES or embryo derived ES cells [10]. Since these DMRs did not pertain to specific loci, they don't represent consistent differences between iPS cells and ES cells. Also the residual iPS-cell specific methylation in many iPS cells isolates links to the tissue of origin and thus ultimately affects the differentiation capability [10,14]. Further Kim et al. showed that there can be distinct residual signatures to enable myeloid and lymphoid origins of blood derived iPS cells, while in non-haematopoietic cells like fibroblasts, neural progenitors residual repressive methylation at loci which are required for haematopoietic fate reduces blood forming potential *in vitro*. In these exogenous supplementation neural progenitor derived iPS cells with the cytokine WNT3A can increase the blood forming potential of these cells as does treatment of cultures with demethylating agents or knockout of DNMT1 expression to immediately convert reprogrammed cells into fully pluripotent cells and emphasizing that how manipulating culture conditions can modify these epigenetic marks and incomplete reprogramming can be overcome [10].

Role of Oocyte Candidate Transcriptomic Factors

Global epigenetic analysis has shown that mammalian metaphase II oocytes have a greater capacity to epigenetically reprogrammed somatic cell nuclei towards ESC like state [10,13,16]. Recently Zhou et al. demonstrated a T-cell dependent immune response upon transplantation into a perfectly matched syngeneic mouse, a phenomenon which is not seen in syngeneic transplantation of ESC [17]. Hence it was considered maybe oocytes possess specific factors which are lacking in current factor based reprogramming approaches. With the suggestion by various authors on global genetic analysis that mammalian metaphase II oocytes may possess a higher capacity to epigenetically reprogram somatic cell nuclei toward an embryonic stem cell (ESC) line like state, Awe et al. proposed, based on the suggestions of Gurdon and Wilmut that the oocyte maybe involved in loosening somatic chromatin [18] and thereby providing the transcription regulatory apparatus access to repressed genes by which they would significantly increase epigenetic reprogramming [19].

To test this hypothesis they tested a list of candidate oocyte reprogramming factors (CORF) which are significantly expressed in metaphase II oocyte. Having focused on 2 different species in earlier studies unbiased global analysis of oocytes from 3 species (human, rhesus monkey, mouse) demonstrated 8 CORF's (ARID2, ASFTA, ASFTB, DPPA3, ING3, MSL3, HIFOO and KDM6B) having significant ($p<0.05$, $FC>3$) expression in oocytes of all 3 species, having well established roles in loosening up chromatin structure. Besides that they identified additional CORF's which fit with their proposed chromatin opening fate transformation (COFT) model. 1) ARID2, which plays a key role in activating gene expression through the PBAF chromatin remodelling complex [20]. 2) ASF1A and ASF1S which are histone-remodelling chaperones that cooperate with chromatin assembly factor 1 (CAF1), which plays a key role in remodelling chromatin in pluripotent embryonic cells [21,22]. 3) BRDT which plays a role in the reorganization of acetylated chromatin in germ cells [23]. 4) DPPA3 and DPPA5 which are pluripotency associated factors with DPPA3 in particular playing a known role in altering chromatin structure in oocytes [24,25]. 5) Rps6ka5 which contributes to gene activation by histone phosphorylation [22]. 6) TADA2L, a component of the ATAC complex which has histone acetyl transferase (HAT) activity on histones H4 and H2A [22]. 7) ING3, a component of the NuA4 HAT x that is involved in transcriptional activation of select genes principally by acetylation of nucleosomal histones H4 and H2A [22]. 8A) MLL3, which activates transcription through methylation of Lys-4 of Histone H3 and is essential in maintaining the haematopoietic stem cell state [26]. 8B). MSL3, a component of the MSL complex that

is responsible for majority of histone H4 acetylation at Lys-16 which is implicate in the formation of more open chromatin structure, specially by inhibiting the formation of the compact 30-nanometer-like fibres and impending the ability of chromatin to form cross -fibre interactions [27]. 9) NCOA3, a nuclear receptor co-activator that displays HAT Activity [22]. 10) HIFOO, the oocyte specific linker histones that has greater mobility than somatic histones and plays, a key role in generating the increased instability of the embryonic chromatin structure following fertilization and somatic cell nuclear transfer [28] and KDM6B, a histone demethylase that specifically demethylases Lys-27 of Histone H3 here by prevents the formation of repressive chromatin through polycromb group (PcG) protein complex PRC1 building [29]. These CORF's may be able to augment both Takayashus and Shinya Yamannaki's previous identified reprogramming factors (Oct4 or POU5F1), Sox2, Kruppel Like Factor4 (KLF4), cMYC and potentially facilitate the removal of epigenetic memory in induced Pluripotent stem cells and reduce the expression of immunogenicity of genes in iPSc derivatives, having applications in personalized PSC based therapeutic.

Therapeutic Applications of iPS Cells

Generating disease specific and patient specific iPS cells through reprogramming has become routine. Mechanistic insights into a variety of diseases to carryout *in-vitro* drug screening to evaluate potential therapeutic and to explore gene repair.

(i) Lee et al. used iPS cells to demonstrate disease modelling and drug screening for familial dyautonomia, caused by a single point mutation in the gene encoding the inhibitor of NFκB (IκB)-kinase complex associated protein (IKBKAP) which manifest as an extensive defect of ANS and dysfunction in small fibre sensory neurons. With the development iPS cells from patients with familial dysautonomia, investigators produced peripheral and central nervous system precursors and found three disease related phenotypes. After screening with multiple compounds, they showed that the kinetin could partially normalize the abnormal phenotype, which is a plant hormone [30].

(ii) Several research groups have generated models of long QT syndrome, congenital disease with 12 types, each of which is associated with abnormal ion channel function, a prolonged QT interval on an ECG and a high risk of sudden cardiac death due to ventricular fibrillation. In animal models lot of work has been done to study the underlying mechanisms of this syndrome, but cardiomyocytes having distinct electrophysiological properties which differ between species, lack of *in vitro* sources of human cardiomyocytes along with difficulty in modelling patient specific variations impeded studying this.

(iii) Moretti et al. differentiated iPS cells from individuals with type 1 long QT syndrome into cardiomyocytes and derived long prolonged action potentials in the ventricular and atrial cells as predicted [31]. With the use of this model they uncovered a dominant negative trafficking defect associated with particular mutation that causes this variant of long QT syndrome. Further these cardiomyocytes had increased susceptibility to catecholamine induced arrhythmias, and compounds which exacerbated the condition e.g. Isoprenaline were identified. Hence treatment of these cardiomyocytes with β-adrenergic receptor blockers attenuated the long QT phenotype.

(iv) Itzhaki et al. modelled type 2 long QT Syndrome in cardiomyocyes. They found that the long QT syndrome phenotype was aggravated by blockers of ERG-type potassium channels, whereas nifedipine, a calcium channel blocker and pinaclidil, an agonist of the ATP sensitive potassium channel, both ameliorated the long QT syndrome phenotype, as shown by decreased duration of action potentials in long QT syndrome cardiomyocytes, and eliminated early after depolarization's and the abolishment of all triggered arrhythmias. Limitation of this is excessive shortening of the action potential duration, leading to short QT syndrome [32].

(v) Aggarwal et al. explored a condition of telomere maintenance, known as dyskeratosis congenital, where they found, in its most severe form, dyskeratosis congenital is caused by a mutation in the dyskerin gene (DKC1), is X-linked, leads to shortened telomeres and premature senescence in cells and ultimately manifesting as degeneration of multiple tissues. The induction of iPS cells by reprogramming is accompanied by the induction of gene telomere reverse transcriptase (TERT), it did not limit the development and maintenance of iPS cells from individuals with dyskeratosis congenital. Despite the efficacy of iPS cells being poor, the authors could successfully reprogram patient fibroblast. Although the telomere length was immediately after reprogramming was shorter than that of the parental fibroblast population, continuous passage of some iPS cell lines has led to telomere elongation over time. This was accompanied by upregulation of expression of TERC, which encodes the RNA subunit of telomerase [33].

Further it was shown that TERT, TERC as well as DKC1, 2 were expressed higher at higher levels in dyskeratosis-congenital-derived iPS cells than in parental fibroblasts. The authors determined that the genes encoding the components of the telomerase pathway, including a cis element of the 3 regions of the TERC locus, which is essential for a transcriptionally active chromatin structure-were direct binding targets of the pluripotency associated transcription factors. On further analysis they found that the transcriptional silencing owing to a 3' deletion in the TERC locus leads to autosomal dominant form of dyskeratosis congenital by diminishing TERC transcription. Though telomere length is restored in dyskeratosis-congenital-derived iPS cells, differentiation into somatic cells is accompanied by a return to pathogenesis with low TERC expression and decay in telomere length. This shows that TERC RNA levels are dynamically regulated and that the pluripotent state of the cells is reversible, suggesting that drugs which elevate or stabilize TERC expression might rescue defective telomerase activity and provide therapeutic benefit [33].

(vi) In an independent study of reprogramming of cells from patients with dyskeratosis congenital Batista et al. [34], confirmed the general transcriptional upregulation of multiple telomerase components and the maintenance of telomere lengths in many clones [34]. However in this study no clones with elongated telomeres were identified. The different outcomes in 2 studies show the limitations of iPS cell based disease models which are imposed by clonal variation, due to technical infidelity of reprogramming [35]. Further before a given iPS cell model can be claimed truly representative of the disease, how many patients must be involved, and how many iPS cell lines must be derived from each patient. Hence all these issues need to be kept in mind while generating disease models and making claims on results from these models.

(vii) Besides using iPS cells for modelling diseases *in vitro*, the goal of developing patient specific stem cells has been motivated by the prospect of generating a ready supply of immune compatible cells and tissues for autologous transplantation. At present this clinical translation of iPS -cell based therapies seems more futuristic than the *in vitro* use of iPS cells for drug development but two studies have provided the proof in mouse models that the dream might one day be

realized by Jaerisch et al. who used homologous recombination to repair the genetic defect in iPS cells derived from a humanized model of sickle cell anaemia [36]. Directed differentiation of the repaired iPS cells into haematopoietic progenitors followed by transplantation of these cells into the affected mice led to the rescue of the disease phenotype. The gene-corrected -iPS cell derived haematopoietic progenitors showed stable engraftment and correction of disease phenotype.

(viii) In another study from Jaenish group Werniig et al. derived dopaminergic neurons from iPS cells that, when implanted in the brain, became functionally integrated and improved rat model of Parkinson's disease [37]. Thus these studies provide proof of principle for using reprogramming with gene repair and self-replacement therapy for treating disease. This is not compounded by the use of immunosuppressive drugs to prevent tissue rejection, while harnessing targeted gene repair strategies e.g. Homologous recombination and zinc finger nucleases, to repair genetic defects. Unlimited population of stem cells can be differentiated into desired types by these strategies, for studying disease mechanisms, screening and developing drugs or for developing a suitable cell replacement therapy. It is still unclear if this would completely evade immune response with immune rejection of teratomas formed from iPS cells even in syngeneic mice [17].

Role of SSEA3AND MSC in Dermal Regeneration by Stem Cells

Crespo et al. studied stage specific embryonic antigen 3 (SSEA 3) expressing cells, exists in dermis of human skin, SSEA 3 being a glycophospholipid, which has been used to identify cells with stem cells like multipotent and pluripotent characteristics. These SSEA 3 expressing cells markedly increase in response to injury, which suggests they may have a possible role in regeneration. Thus SSEA 3 expressing regenerative associated (SERA) cells were derived through primary cell cultures, purified by fluorescent activated cell sorting (FACS) and characterized. The SERA cells demonstrated a global transcriptomic state that was similar to bone marrow, and fat derived mesenchymal stem cells (MSC's), with the highest expressing SSEA 3 expressing cells expressing CD105 (clone 35). Although, while a rare population of MSC's was seen in primary human skin cultures which could differentiate into adipocytes, osteoblasts, or chondrocytes, SERA cells did not possess this differentiation capacity which suggests that there are two different rare sub populations in adult human skin primary culture. Thus the identification, efficient purification and large scale expansion of these rare subpopulations (SERA cells and MSC's) from heterogeneous adult skin primary cell culture s may have applications for future patient specific cellular therapies [38].

Role of Neural Stem Cells in Alzheimers Disease

Byrne et al. reviewed how the advances in neural stem cells as well as human induced Pluripotent stem cells could provide hope for a cure in Alzheimers disease. Recent discovery by Blurton Jones that NSC can effectively deliver disease modifying therapeutic proteins throughout the murine brain of the best of model of brain AD along worth recent advances that neprilysin, a potent proteolyitic enzyme, a rate limiting enzyme in the degradation of amyloid beta (Aβ) which was originally tried by viral vector approach in human [39]. NSC's offers a potential solution to overcome the bottleneck of narrow viral delivery. The problem is that commonly used whole human foetal graft or NSC derived from foetal tissue would not be immunologically matched to the recipient [40]. Immunosuppressive drugs are expensive, inconvenient, toxic, and hence not ideal. The alternative approaches used is autologous NSC'S derived from human Ipsc's, which themselves have been derived from same patients. Suitable cells like skin cells (Figure 1). These cells could be genetically modified in a manner similar to the NSC modification process used by Blurton Jones.

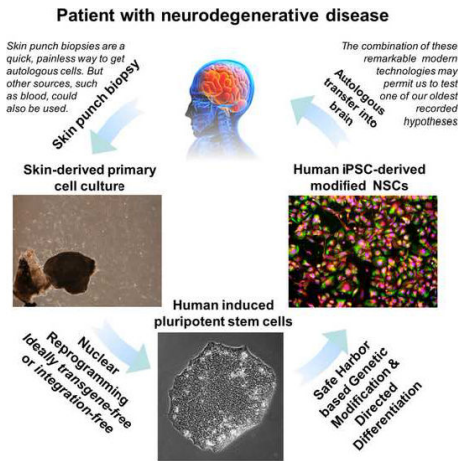

Figure 1: The concept of using human isolated pluripotent stem cells (iPSc's) and their neural stem cell (NSC) derivatives, alongside safe, harbours targeted genetic engineering to develop a personalized cellular therapy for Alzheimer's disease. Clinically relevant human iPSC's (passage 7) were derived from skin punch biopsies differentiated into NSC's and as shown on the right stained Pax 6 (green) and DAPI (blue). The figure is on the basis of unpublished data of Kaitlin Ingraham, Patriac Phelpsand James Byrne [41].

The problem of using viral vector is that they may induce insertional mutagenesis in a subset of cells [41]. One solution to that is the use of flexible and inexpensive genome editing technologies like the recently developed CRISPR/Cas9 system for targeting hIPSC. Also recent reports indicate that implanted iPSC derived NSC have demonstrated the ability to survive, migrate and differentiate and to restore lost neurological function [42,43]. Thus modified NSC may represent a critical solution we have been on lookout for the marked increased prevalence of AD in contemporary society [44].

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