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Invited Review

INVITED REVIEW

Disease modelling using human iPSCs

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Introduction to iPSC Technology

Human embryonic stem cells (hESCs) paved the way for the development of induced pluripotent stem cells (iPSCs). First derived and described by James Thomson in 1998, hESCs demonstrated that human pluripotent stem cells could be cultivated and could differentiate into all three germ layers, albeit as part of a teratoma in a mouse (1). Importantly, the development of hESC lines established media recipes and cell culture techniques comprising the cornerstone for iPSC derivation (1). Furthermore, they enabled researchers to gain experience culturing these somewhat peculiar and difficult stem cells and establish differentiation protocols (1–5). The lack of patient-specific hESCs prompted focus to be shifted to establishing banks of hESCs that would be representative of entire populations (6). In parallel, the use of somatic cell nuclear transfer (SCNT) or cloning to generate human patient-specific stem cell lines was developed (7). Neither approach ameliorated the ethical issues surrounding the use of sensitive human tissues (in vitro derived embryos and human oocytes) and the possibility that the process would be used to create genetically-modified human beings.

In 2006, Shinya Yamanaka rocked the stem cell world by reporting the first iPSCs from murine fibroblasts (8). Built upon previous experiments that identified transcription factors differentially expressed between pluripotent stem cells and differentiated cells (9), Takahashi and Yamanaka tested the ability of 20 factors *en masse* to convert somatic cells into pluripotent stem cells. After narrowing the number of required factors down to four—known widely as the Yamanaka four: OCT4, SOX2, KLF4 and C-MYC—he and James Thomson independently reported the reprogramming of human fibroblasts into pluripotent stem cells (10,11). Although additional factors were added to the mix, the community has largely settled on the Yamanaka four plus or minus LIN28 as being the most efficient way to reprogram human somatic cells into iPSCs.

The development of human iPSCs from patient-specific samples has revolutionized the study of human genetic disorders over the past 10 years. The next 10 years are certain to see more rapid development of targeted therapeutics for some of these disorders, thanks to this technological advance.

State of the iPSC Art

Improvements to the process of epigenetic reprogramming into iPSCs followed rapidly due to the fervour behind the exciting technology. Different cell types permissive for reprogramming were tested to improve reprogramming efficiency, reduce the number of factors required for reprogramming, or to reduce the invasiveness of obtaining patient samples. Fibroblasts derived from dermal punch biopsies were first used to derive iPSCs (10,11). Owing to previously banked fibroblasts from individuals with genetic disorders, iPSCs could be derived from many disorders without seeking additional skin biopsies. Nonetheless, obtaining a skin punch biopsy from a new or rare patient to establish fibroblast lines and derive iPSCs is somewhat invasive. Neural stem cells and renal tubular cells were shown to only require one or two reprogramming factors, but it was not feasible to obtain neural stem cells from most patients (12,13). Keratinocytes were reported to be non-invasive and easily obtainable from patients by plucking hairs, but the establishment of keratinocyte cultures from the hair follicle samples proved to be challenging, and the reprogramming was difficult to reproduce early on (14). Eventually, peripheral blood mononuclear cells (PBMCs) were shown to be both easily obtained from patients and easily reprogrammed, largely solving the somatic cell source problem (15). Recent reports even demonstrated the

It has been 10 years since Shinya Yamanaka rocked the scientific community by reporting the first derivation of induced pluripotent stem cells (iPSCs). This review highlights some of the accomplishments made in iPSC models of genetic disorders, focusing mainly on neural and cardiac disease.
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ability to reprogram renal epithelial cells from urine (16) and dental pulp stem cells from deciduous teeth (17).

Improvements to the delivery of the reprogramming factors also quickly followed. The field quickly replaced retroviral vectors, which required replication to transduce somatic cells, with lentiviral vectors (11). Worry about insertional mutation due to viral integration led to the development of the STEMCCA vector in which all reprogramming factors were included on a single lentiviral vector that could be excised using Cre-recombinase (18). Provision of the reprogramming factors as mRNAs (19) or proteins (20,21) was a non-integrating answer to the viral integration issue. These approaches were not adopted widely due to the difficulty of generating sufficient quantities of high-quality mRNAs or proteins and/or the difficulty delivering them into somatic cells. Finally, Sendai virus vectors (22) and episomal vectors (23) have met widespread adoption because they meet the criteria of being both non-integrating and easy to use. Both reprogramming systems are commercially available, making the process accessible to many labs and reproducible.

The Promises and Pitfalls of iPSC Disease Models

The promise of iPSCs as a clinical and research tool was apparent in two different ways. First, translational research applications for pluripotent stem cells were rooted in regenerative medicine with the idea that stem cells could be differentiated and implanted into individuals to cure injury or disease. Thus, one immediate application for iPSCs was autologous stem cell transplants. If one could generate pristine iPSCs from any given patient, then they could provide their own tissue to repair/replace injured ones. Second, many recognized that the genetics of the iPSCs reflected the genetics of the patient. Thus, iPSCs could be used to model human genetic disorders. Since it was still relatively difficult to use homologous recombination in hESCs, iPSCs provided a more direct way to study cells harbouring a particular genetic disorder, including those difficult to generate by homologous recombination.

Early studies of iPSCs focused on identifying differences between hESCs and iPSCs to identify *bona fide* iPSCs and/or ascertain the quality of individual iPSC clones (24). These studies turned toward epigenetic analyses, since the difference between the iPSCs and their somatic counterparts were known to be epigenetic and variances were suspected to lie somewhere in between those extremes. Indeed, one study reported that iPSCs retained the epigenetic signature of their starting somatic cells, which in turn, affects their differentiation potential (25). Another study reported a realm of pluripotency, in which hESCs occupied a small niche, and iPSCs occupied a larger, but overlapping niche (26).

While these epigenetic studies focused on distinguishing iPSCs from hESCs, they also pointed to larger epigenetic changes that distinguish somatic cells from pluripotent stem cells. This has an impact on the use of iPSC for disease modelling. The altering of epigenetic states between somatic cells and iPSCs may obscure the retention of disease state for disorders that involve epigenetic modification (i.e. imprinting disorders or X-linked disorders in females) (27) or for disorders with mixed aetiology in which other factors such as the environment or epigenetic alterations may play a role. This possibility remains a warning for those using iPSCs to model disorders with unknown aetiologies. With this limitation aside, iPSCs are beginning to hit their stride at models for human disease.

iPSC Models of Human Neural Disorders

The earliest iPSC models of human disease were reported from patients with neurological disorders. This may have been due to the fact that the earliest hESC differentiation protocols were focused on neurons. Early differentiation protocols utilized developmental principles to differentiate and pattern neurons (28). They usually involved embryoid body (EB) intermediates, which emulates gastrulation to direct some tissue down the ectodermal lineage (2,29). More recent neural differentiation protocols capitalized on dual SMAD inhibition using a combination of Noggin or the small molecule LDN193189 along with SB431542 or Noggin alone to restrict differentiation to ectodermal tissues (30). Serum-free media formulated to encourage the growth of neural cell types and substrates required for neural cell adhesion were used to preferentially encourage the growth and expansion of neural ectoderm in both approaches. Morphogens such as retinoic acid and sonic hedgehog are used to caudalize and ventralize the neural ectoderm, respectively.

Beginning in 2010, Marius Wernig and Thomas Sudhof published a series of papers reporting the direct conversion of mouse and human fibroblasts into neurons using transcription factors. Combinations of BRN2, ASCL1 and MYT1L plus NEUROD1 in humans were used to convert fibroblasts into neurons. Ultimately, the addition of only one transcription factor, NGN2, was shown to convert hESCs and human iPSCs into neurons. Following neural induction, in vitro-derived human neurons require maturation to develop synaptic activity and mature action potentials. This process seems to take approximately 7 weeks, except for iN cells, which are reported to take a week. Studies of dendritic spine morphology and densities may take even longer. Nonetheless, *in vitro* differentiated neurons demonstrate typical electrophysiological properties, and may even be amenable to studies of synaptic plasticity.

Neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) (31–38), Huntington disease (39–41), Parkinson's disease (PD) (42–47), and Alzheimer disease (48–50) are among the most studied disorders using iPSCs. iPSC-derived neurons from these disorders have been reported to have altered neuronal morphology, including neurite degeneration, reduced soma size, and disturbed mitochondrial morphology. Protein aggregate formation has been observed in neurons, as has increased cellular stress. The ability of *in vitro*-derived neurons to recapitulate cellular phenotypes is remarkable since these disorders usually present in aged individuals, and the neurons represent fetal neurons. A neurodegenerative disorder that affects young children, spinal muscular atrophy (SMA), has also been modelled by using iPSCs by multiple groups (51–53). Cellular phenotypes associated with this disorder include hyperexcitability, smaller soma size, incomplete synapses, and a reduction in cytoplasmic and nuclear aggregate structures, called gems. iPSCs from individuals with familial dysautonomia, a fatal peripheral neuropathy, have also been made (54). Upon differentiation into neural crest precursors and peripheral neurons, differentiation and migration defects were observed. Table 1 summarizes many of the neural disorders that have been modelled using iPSCs and lists the neural phenotypes identified for each disorder.

Tremendous progress has also been made modelling neurodevelopmental disorders using pluripotent stem cells. Induced pluripotent stem cells have been derived from individuals with Rett (55–57), Fragile X (58–60), Timothy (61,62), Dravet (63,64), Prader-Willi (65–67), Angelman (65), Dup15q (68), 15q11.2 microdeletion (69), and Phelan McDermid syndromes (70). For many

Table 1. iPSC models of neural disorders

Disorder	Genes involved	Neural phenotypes	Refs
Neurodegenerative			
ALS	*TDP43, SOD1, C9ORF72, VAPB, FUS*, sporadic	Neuronal death, neurite degeneration, reduced soma size, and disturbed mitochondrial morphology, altered excitability	(31–38)
SMA	*SMN1*	Increased apoptosis, altered axonal transport, hyperexcitability	(51–53)
Parkinsons' Disease	*PARKIN1, PARKIN2, PINK, SNCA, LRRK2*	α-synuclein aggregates, increased nitrosative stress, increased endoplasmic reticulum associated degradation products	(42–47)
Huntington Disease	*HTT*	Elevated glutamate evoked responses, higher lysosomal activity, increased caspase activity	(39–41,99,100)
Alzheimer Disease	*APP, PS1, PS2*	Increased Aβ40, phosphorylated Tau, and active GSK3β	(48–50)
Familial Dysautonomia	*IKBKAP*	Defective differentiation, migration	(54)
Neurodevelopmental			
Rett syndrome	*MECP2*	Reduced dendritic spine density, smaller soma size, altered electrophysiology, alterations in Ca^{2+} influx and fewer synapses	(55–57,101)
Fragile X syndrome	*FMR1*	Fewer synapses, reduced neurite length, increased Ca2+ transients	(58–60)
Angelman syndrome	*UBE3A*, 15q11.2-q13 deletion	Neural phenotypes not studied other than gene expression	(65)
Prader-Willi syndrome	15q11.2-q13 deletion	Neural phenotypes not studied other than gene expression	(65–67,102)
Dup15q syndrome	15q11.2-q13 duplication	Neural phenotypes not studied other than gene expression	(68)
Idiopathic autism	*TRPC6, CHD8, CNTNAP2*	Altered neuronal migration, reduced dendritic length/branching, reduced dendritic spine density	(79,80)
Dravet syndrome	*SNC1A*	Altered Na+ current density, spontaneous activity	(63,64)
Timothy syndrome	*CACNA1*	Altered Ca2+ signaling, dendritic retraction	(61, 62,103)
Phelan-McDermid syndrome	*SHANK3*	Fewer synapses, altered electrophysiology	(70)
Schizophrenia	22q11 deletion, *DISC1*, sporadic	Aberrant migration, altered WNT signaling, and increased oxidative stress in neural progenitor cells, increased catecholamine expression in neurons	(72–76,104)
Bipolar disorder	Sporadic, but familial	Decreased proliferation of neural stem cells, mitochondrial defects, hyperexcitability	(77,78)
15q11.2 deletion syndrome	*CYFIP, TUBGCP5, NIPA1, NIPA2*	Altered dendritic morphology	(69)
Hereditary spastic paraplegia	*SPAST, ATL1, SPG11*	Motor neurons, forebrain glutamatergic neurons	(81–83)

of these disorders, forebrain glutamatergic neurons have been generated, although other neuronal subtypes are also being investigated. As these disorders are thought to influence synaptic activity, electrophysiology and morphological analyses of iPSC-derived neurons have been employed to study these disorders. Morphological cellular phenotypes observed have included small soma size, fewer synapses, lower synaptic protein levels, and reduced neurite length. Electrophysiological and functional phenotypes observed have included abnormal calcium signalling, altered sodium current density, prolonged action potential patterns, and altered excitatory synaptic activity (Table 1). These phenotypes are likely the tip of the iceberg for neurodevelopmental disorders. Our understanding of neural development and neuronal subtype specification is increasing and is being translated into differentiation protocols. This will enable the dissection of cell autonomous and non-cell autonomous phenotypes, as well as cellular phenotypes that require a precise balance of neuronal subtypes. Furthermore, the development of assays adapted for cultured neurons—for instance, chemically induced synaptic plasticity—is expanding. Thus, we can expect a reciprocal expansion of electrophysiological phenotypes.

Other neural disorders that have been modelled using human iPSCs include the psychiatric disorders, schizophrenia (71–76) and bipolar disorder (77,78); idiopathic autism spectrum disorder (79,80); and hereditary spastic paraplegia (81–83). Although schizophrenia and autism spectrum disorder do not have known genetic causes in most affected individuals, they have high heritability. iPSCs have been derived either from one of the rare known genetic subtypes of these disorders, from families with a clear autosomal dominant inheritance pattern, or from an individual with severe early onset disease. Thus illustrating the ability of iPSCs to model disorders of unknown genetic etiologies. iPSCs derived from individuals with a few different forms of hereditary spastic paraplegia are chipping away at the variety of different cellular phenotypes associated with several phenotypically similar disorders.

iPSC Models of Inherited Heart Disease

Like their neural counterparts, differentiation of iPSCs into cardiomyocytes follows embryonic developmental pathways. Also like their neural counterparts, cardiomyocyte differentiation can be accomplished using embryoid body-mediated and

Table 2. iPSC models of cardiac disorders

Disorder	Genes	Cardiomyocyte phenotypes	Ref
Classic cardiomyopathies			
HCM	*MYH7, MYBPC3*	Cellular enlargement, contractile arrhythmia, dysregulated Ca2+ cycling, increased expression of HCM genes, Cellular enlargement, myofibrillar disarray	(84–86)
DCM	*TNNT2, DES, TTN, RBM20*	Altered Ca2+ handling, impaired response to β-adrenergic stress, decreased contractility, disorganized sarcomeres, abnormal α-actinin distribution in sarcomeres, Abnormal aggregation of DES, Abnormal aggregation of DES	(87–91)
ARVC	*PKP2*	Cellular enlargement, altered Ca2+ handling, increased adipogenicity, reduced localization of cell surface desomosomic proteins, metabolic defects, and abnormal (PPAR-γ) activation	(92–94)
Channelopathies			
Long QT syndrome	*KCNH2, KCNQ1, CACNA1C*	Prolonged action potentials, early afterdepolarizations, susceptibility to arrhythmias, altered Ca2+ handling,	(103,105–110)
CVPT	*RYR2, CASQ2*	Delayed afterdepolarizations, altered Ca2+ handling, disorganized myofibrils, contractile arrhythmia	(111,112)
Mitochondrial disorders			
Barth syndrome	*TAZ*	Sparse/irregular sarcomeres, contractile abnormalities	(113)
Friedrich's ataxia	*FXN*	Impaired Ca2+ handling, cellular enlargement, impaired β-adrenergic response	(114)
CPT II	*CPT2*	Not determined	(115)
Other cardiac disease-associated rare genetic disorders			
LEOPARD syndrome	*PTPN11*	Cellular enlargement, increased sarcomeric organization, nuclear NFATC4 localization	(116)
Pompe disease	*GAA*	Glycogen-filled lysosomes	(117–120)
Lamin A/C mutations	*LMNA*	Accelerated senescence and apoptosis	(121)

monolayer-based protocols. In both cases, iPSCs are first coaxed into accepting a mesodermal identity, and then specified and matured into cardiac cells. BMP, TGFB/activin/NODAL, WNT, and FGF signalling are all important for differentiation into myocardial cells. Differentiated cardiomyocytes express *TNNT2* and *MEF2C* and exhibit intact sarcomeres and spontaneous rhythmic contraction. iPSC-derived cardiomyocytes also require *in vitro* maturation, and despite best efforts, still display phenotypes and gene expression profiles most similar to fetal cardiomyocytes. Continued improvement to differentiation protocols, including 3D tissue engineering strategies will benefit these *in vitro* models of cardiac development.

iPSC models of the three major classes of pure genetic cardiomyopathies have been developed: hypertrophic cardiomyopathy (HCM; 84–86), dilated cardiomyopathy (DCM; 87–91), and arrhythmogenic right ventricular cardiomyopathy (ARVC; 92–94). These three types of cardiomyopathy typically affect the whole beating heart, presenting unique challenges for these disorders. Additionally, iPSC models of other genetic disorders resulting in heart disease have been created. These include channelopathies such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT; 103,105–110); mitochondrial disorders such as Barth syndrome (113), Friedrich's ataxia (114), and carnitine palmitoyltransferase II deficiency (CPT II; 115); and other rare genetic conditions associated with cardiac disease, such as LEOPARD syndrome (116), Pompe disease (117–120), and laminopathies (121). Significant progress has been made, and iPSC models have contributed to an understanding of the mechanistic underpinnings of cardiac disease. Table 2 summarizes the iPSC models of cardiomyopathies or cardiac associated disorders as well as their cellular phenotypes.

Genetic forms of HCM, DCM, and AVRC can be caused by mutations in structural proteins that make up cardiac muscle. Genetic forms of HCM have been modelled by iPSCs derived from individuals with mutations in *MYH7* and *MYBPC3* (84–86). iPSCs have been derived from patients with DCM caused by mutations in *TTN, DES*, *TNNT2* and *RBM20* (87–91). AVRC has been modelled using iPSCs harbouring mutations in *PKP2* (92–94). iPSC-derived cardiomyocytes from individuals with these disorders show structural abnormalities such as cellular enlargement, sarcomere and/or myofibrillar disorganization, and mislocalized or aberrantly aggregated structural proteins. Importantly, they also show functional deficits such as dysregulated calcium (Ca2+) handling, contractile dysfunction, and impaired responses to β-adrenergic or mechanical stress (Table 2).

Studies in cardiomyocytes generated from iPSC models of other genetic disorders involving cardiac dysfunction (i.e. Barth syndrome, Friedrich's ataxia, CPT II, LEOPARD syndrome, and Pompe disease) show many overlapping features with HCM, DCM, and AVRC, including cellular enlargement, altered Ca2+ handling, and contractile abnormalities (Table 2). As expected, each of these disorders also frequently show phenotypic features unique to their genetic etiologies, as well as non-cardiac features in other iPSC-derivatives.

Other Genetic Disorders

Many other genetic disorders have been modelled using patient-specific iPSCs in the past 10 years. iPSC models of Duchenne's Muscular Dystrophy (41,95) have been generated and differentiated into myocytes and myotubes. iPSCs from individuals with juvenile diabetes have been differentiated into insulin producing cells (41). Hepatocytes derived from an individual with familial hypercholesterolemia were deficient in LDL-C uptake and had elevated secretion of a lipidated protein (96–98). Kotton *et al.* even generated more that 100 disease-

specific iPSC lines from individuals with a variety of different diseases that affect the lung, including cystic fibrosis, a-1 antitrypsin deficiency, scleroderma, and sickle-cell disease (18). Furthermore, they were able to differentiate them into definitive endoderm, a developmental progenitor to lung tissue. Although there may be some disorders that are difficult to model through this epigenetic reprogramming (i.e. some imprinting disorders), the technology is broadly applicable to almost any human genetic disorder, limited mainly by the ability to readily differentiate the cells into disease-relevant cell types.

Looking Forward

In the 10 years since the first discovery of epigenetic reprogramming into iPSCs, work has been done by many different groups to model a variety of genetic disorders, in part because of its ease, accessibility, and commercialization. With many such disease models in existence, new technologies such as direct conversion to differentiated cell types, 3D culture systems, and clustered regularly interspersed repeats (CRISPR) further expand the possibilities for iPSC-based disease modelling. For example, direct lineage conversion of iPSCs into neurons as described above, circumvents the slow pace of neural development. While this might not be the most developmentally correct differentiation strategy, it may facilitate the use of iPSC-derived neurons for high-throughput drug screening. 3D cultures enable the study of phenotypes that are inaccessible or undetectable in monolayer or colony-based cultures. For instance, 3D cardiac microtissues harbouring mutations in TTN were required to uncover the disease-related deficits in contractile function (90). Using CRISPR or related technologies, causative mutations have been genetically corrected for ALS, Parkinson's disease, and many other disorders. This enables comparison of isogenic control samples and greater confidence in cellular phenotypes of disease.

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The author regrets that not all iPSC models of human disease could be discussed here. Overlooked papers or findings were not intentional.

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