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Modeling rare diseases with induced pluripotent stem cell technology

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ABSTRACT

Rare diseases, in totality, affect a significant proportion of the population and represent an unmet medical need facing the scientific community. However, the treatment of individuals affected by rare diseases is hampered by poorly understood mechanisms preventing the development of viable therapeutics. The discovery and application of cellular reprogramming to create novel induced pluripotent stem cell models of rare diseases has revolutionized the rare disease community. Through developmental and functional analysis of differentiated cell types, these stem cell models carrying patient-specific mutations have become an invaluable tool for rare disease research. In this review article, we discuss the reprogramming of samples from individuals affected with rare diseases to induced pluripotent stem cells, current and future applications for this technology, and how integration of genome editing to rare disease research will help to improve our understanding of disease pathogenesis and lead to patient therapies.

1. Rare diseases - background

In what can be viewed as a misnomer, rare diseases are not appreciably “rare” when considered collectively. Commonly classified by prevalence, definitions and estimates vary across regions and are often complicated by unclear diagnosis and unique presentations [1]. A rare disease is defined as a condition affecting fewer than 5 in 10,000 people in Europe and fewer than 200,000 people total within the United States, according to the Orphan Drug Regulation 141/2000 and Orphan Drug Act of 1983, respectively. It is estimated that between 8 and 10% of the population are affected by a rare condition [2]. This translates to > 30 million affected individuals in the United States alone and approximately 350 million worldwide [3]. Based on epidemiological and genomic data, estimates from the US National Institutes of Health suggest approximately 7000 unique rare diseases are present worldwide. However, less than 10% of rare disease patients are treated, reflecting a significant need for development of medical interventions and increased studies to understand disease pathogenesis [2].

Over 80% of rare diseases are considered genetic in origin [2]. A majority of these conditions including neurofibromatosis I, achondrophasia, Friedrich's ataxia, and many inborn errors of metabolism, are monogenic diseases defined by defects in a single gene. In polygenic disorders, including Fanconi anemia and muscular dystrophies, multiple genes contribute to a single disease. The importance of disease modifiers at additional genetic loci, such as allelic variants of α1-antitrypsin antiprotease (or SERPINA1) associated with portal hypertension in cystic fibrosis or defects arising in regulatory regions of the genome, have also been recognized [4]. Further, approximately half of rare diseases manifest in children and result in developmental malformations accounting for 20% of infant deaths, a leading cause of mortality in this age group [5].

Rare disease research relies heavily upon the modeling of genetic changes and developmental pathways to recapitulate the unique aspects of human disease pathology. Induced pluripotent stem cells (iPSCs) derived from human samples have developed into a viable and complementary biological model to overcome some of the challenges associated with traditional approaches, such as animal models and immortalized cell lines. In this brief review, we discuss the values and challenges in the use of iPSCs for the study of rare diseases, as well as potential uses for iPSCs in translational applications. Due to the many significant publications within this rapidly maturing field, we are forced to limit our discussions to a selected number of publications. We apologize to any authors whose excellent work was not specifically cited here.

2. Induced pluripotent stem cells for modeling rare diseases

The *in vitro* modeling and analysis of human diseases was revolutionized by the discovery of reprogramming mature cells to pluripotency by Kazutoshi Takahashi and Shinya Yamanaka in 2006. The

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induction of four transcription factors, KLF4, MYC, POU5F1, and SOX2, was found to allow derivation of embryonic stem cell-like pluripotent cells, now referred to as iPSCs, from mouse and later human somatic cells [6,7]. The simplicity of these experiments was surprising given the complexity of reprogramming experiments leading up to its discovery. The use of somatic cell nuclear transfer (SCNT) demonstrated in *Xenopus laevis* by Sir John Gurdon in 1958 and later in mammals with the cloning of "Dolly" the sheep by Wilmut et al., in 1996 suggested complex mechanisms encompassing genetic and epigenetic changes controlled cellular de-differentiation [8,9]. Therefore, the ability of a quartet of transcription factors to yield pluripotent cells largely indistinguishable from human ES cells was remarkable. This seminal work also opened up new possibilities for the use of iPSCs in disease and gene-specific applications. The Yamanaka studies and subsequent publications from other labs also helped alleviate some of the ethical debates surrounding human pluripotent stem cells by avoiding stem cell isolation from the embryonic inner cell mass.

Since their initial discovery, iPSCs have shown great potential in modeling the pathogenesis of rare diseases. Traditional approaches have often relied upon primary or patient-derived immortalized cell lines to study the etiology and physiology of rare conditions. While primary cell types are readily available from blood or tissue biopsies, disease relevant cell types are not always easily isolated nor may they be propagated indefinitely. Moreover, immortalized cell lines are often not an accurate reflection of their primary culture counterparts, limiting their reliability in functional studies. Similarly, despite being an irreplaceable tool to date for *in vivo* validation, animal models do not always recapitulate human pathogenesis [10]. There are considerable anatomic, embryonic, and metabolic differences between mice and humans which may reflect difficulties in translating therapeutic discoveries to clinical trials [11].

2.1. Advantages of iPSCs for disease modeling

Patient-derived iPSCs offer an invaluable alternative for modeling rare diseases, directly addressing some of the challenges associated with traditional methods (Fig. 1). Along with the capacity to propagate indefinitely, iPSCs have the potential to differentiate into virtually any human cell type given the proper environmental stimuli. By utilizing this pluripotent capacity in iPSCs carrying specific pathogenic mutations, patient-specific iPSCs can model the molecular mechanisms underlying disease pathophysiology. The hope for iPSCs in regenerative medicine and cell therapy applications are further fueled by the potential immune compatibility of iPSC derivatives in autologous settings, suggesting a lessened risk for graft rejection compared to more common allogeneic stem cell-based therapies [12]. Indeed, ongoing clinical studies utilizing iPSCs as a source for transplantable cellular derivatives, such as retinal pigment epithelium for treatment of age-related macular degeneration, have demonstrated tissue engraftment > 1 yr post-transplantation to patients, providing hope for the continued success of regenerative therapies [13].

Stem cell-based models have been successfully used to study disorders of varying genetic origin. Monogenic-based rare disorders are, thus far, the most widely studied using iPSC approaches, particularly when a clear cellular phenotype has been established [14]. Given the genetic basis for most rare disorders, iPSCs are particularly well adapted for this purpose. Additionally, rare childhood diseases of developmental origin can be robustly modeled using directed differentiation assays [15]. However, recapitulating mature cell defects of late onset disorders has proven to be more challenging as some differentiation protocols better reflect immature rather than adult cell types [16,17]. Several studies have utilized cell stressors, such as hydrogen peroxide or antibiotics, to generate ROS promoting mitochondrial stress to induce cellular aging [11,18]. A more physiologically relevant approach recently developed involves small molecule inhibition of telomerase activity that demonstrated classical features of aging, including increased DNA damage, ROS, and downregulation of tyrosine hydroxylase [19]. iPSC models of premature aging syndromes, such as Hutchinson-Gilford progeria syndrome, have not only successfully modeled rapid differentiation and stem cell aging, but have also facilitated identification of age-related markers utilized in the understanding of more common, late onset diseases such as Parkinson's disease [20,21]. Complex diseases involving multiple or unknown genes, as in Autism spectrum disorder and schizophrenia, have also been successfully developed and modeled using iPSCs [22,23]. In particular, the study of rare monogenic disorders displaying phenotypic elements of poorly understood polygenetic diseases, holds much promise for mechanistic insight into these complex disorders. For example, a role for brain-specific L1 retrotransposon activity, traditionally associated with Rett syndrome, was recently demonstrated within a schizophrenia derived iPSC model [24].

A principle advantage of iPSC modeling is the ability to construct a model within the context of an individual's genome, allowing a robust approach to disorders involving unknown loci. Conceivably, patient-

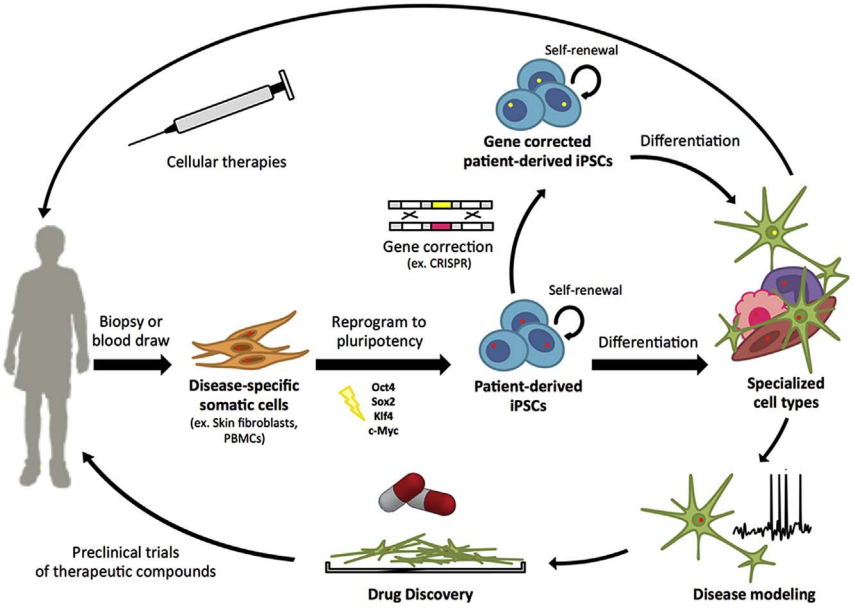

Fig. 1. iPSC generation and potential uses of iPSC-derivatives for rare disease studies.

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