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Review Article

STEM CELLS: A CASE STUDY OF NOVEL INNOVATIONS TO ACCELERATE DRUG DISCOVERY

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ABSTRACT
Pharmaceutical companies are facing increasing costs in their drug discovery programs. Poor mouse models and the lack of supply of patient-specific human tissue have inhibited progress in drug discovery for many diseases. However, recent innovations in pluripotent stem cell technology may be able to alleviate this bottleneck and thereby offer a major paradigm shift in the way pharmaceutical companies conduct drug discovery. This present review attempts to overview the general understanding of induced pluripotent stem cell biology and explores its possible application in drug discovery for Cystic Fibrosis.
KEYWORDS: Drug discovery, drug screening, stem cells, induced pluripotent stem cells, reprogramming

INTRODUCTION

Drug discovery programs have been increasingly expensive; costing nearly an average of $1.8 billion dollars per drug approval in the United States.[1] Current efforts for drug discovery have been hampered by a lack of supply of human tissue bearing the mutation of interest. Another limitation is that mouse models of human diseases do not faithfully phenocopy human physiology (e.g. Cystic Fibrosis). Because of these limitations current methods for drug discovery often involve drug screening in cell lines that do not faithfully mimic the relevant indication and could partly account for the high rate of failure. Thus, a more predictive model for preclinical phase screening can be cost reducing.

The emergence of pluripotent stem cell technology has made it possible to obtain a variety of cell types in vitro. Pluripotent stem cells may offer a novel platform to more predictably interrogate the effects of drug candidates in humans. It is therefore possible that pluripotent stem cell technology will play a large role in preclinical drug screening for diseases like Cystic Fibrosis.

Induced Pluripotent Stem Cells

Stem cells are classically defined by their ability to self-renew and differentiate to more specialized cell types. Different types of stem cells have the varying differentiation potentials (potency). By definition, embryonic stem cells have the potential to give rise to all the specialized cell types of the three germ lineages, the endoderm, the mesoderm, and the ectoderm. On the other hand, adult stem cells are typically more limited in potency and can typically only give rise to cells within a single lineage.

Because of the ethical and immunological limitations of embryonic stem cells, induced pluripotent stem (iPS) cells offer a novel source of patient-specific pluripotent stem cells. Shinya Yamanaka first derived pluripotent stem cells from adult mouse fibroblasts in 2006 through the viral transfection of the transcriptional factors *Oct4*, *Sox2*, *Klf4*, and *c-Myc*, an experiment that awarded him the Nobel Prize for Physiology or Medicine in 2012.[2] Soon after, iPS cells were derived from human fibroblasts.[3] These discoveries helped shape the field of regenerative medicine today as the having a virtually unlimited supply of reprogrammed patient-specific cells is now theoretically possible. With a seemingly unlimited supply of patient-specific cells, several groups have used this model to screen for potential drug candidates in diseases such as Cystic Fibrosis.

Current Challenges in Cystic Fibrosis

Cystic Fibrosis (CF) is monogenic disease that primarily affects Caucasians of Northern European ancestry. Currently, it is estimated that 30,000 children and adults in the United States have Cystic Fibrosis. One in 29 people of Caucasian ancestry are unaffected carriers of the CF gene mutation. Between 900-1,000 new cases are diagnosed each year and the predicted median age of survival for a person with CF is in the late 30s.[4] The disease affects the ability of cells to transport of salt and water across their membrane in many organs, but lung disease is responsible for the majority of the symptoms. Most people are diagnosed with CF at birth through genetic newborn screening test or a low-cost sweat test, which measures the amount of chloride in the sweat. Since early diagnosis has been shown to reduce symptoms, all newborns born in the United States are now required to undergo screening for cystic fibrosis.[5]

Patients with CF have a reduction of water in the fluid lining of the respiratory airways. Symptoms of CF include coughing, wheezing and shortness of breath.[6] The diminished water content is primary causes respiratory mucus secretion to become thicker and, ultimately, clogs the small airway.[7] The lungs can then be highly susceptible to persistent infection and chronic inflammation. As a result, many CF patients suffer from pneumonia and bronchitis. The vicious cycle of excess mucous, inflammation, and recurrent infections eventually causes respiratory failure and ultimately death.[8]

The vast majority of CF is caused by a homozygous single base pair deletion in the Cystic Fibrosis Transmembrane Regulator (CFTR).[9] The CFTR protein is found in cells that line various organs such as the lung. CTFR controls the movement of chloride and thiocyanate ions across epithelial cell membranes and with a defective protein the salt balance of the body is disturbed. There are over 2,000 kinds of CFTR mutations. The CFTRΔ508 mutation is the most common and accounts for about 70% of CF cases.[10]

The cost of treating CF can be staggering. The average cost of outpatient care for a person with CF living in the United States is just over $48,000.[11] Patients with CF often must take pancreatic enzymes and insulin to properly digest food. Each

year, one in three CF patients are hospitalized, mostly from complications caused by infections requiring intravenous antibiotics.

Currently there is no direct cure for cystic fibrosis, and treatments and therapies vary from patient to patient. Drug discovery efforts have been hampered by the lack of access to disease tissue and the lack of transgenic mice that faithfully phenocopy human CF. Recently, Kalydeco by Vertex Pharmaceuticals (VX-770/ivacaftor) was reported to be a clinically effective drug in patients with the CFTR mutation G551D which is characterized by poor chloride conductance.[12] This is the first drug ever to directly correct the CFTR gene and increases the chloride channel activity of the CFTR-G551D protein.[13] Unfortunately, this subset of CFTR mutation occurs in about 1% of CF patients. Therefore, therapeutics for the other 99% of CF cases have yet to be identified and remain a significant unmet medical need.

VX809 and VX661 are drug candidates manufactured by Vertex Pharmaceuticals to target the more common CFTRΔ508 mutation and therefore are designed to restore the proper folding and/or trafficking of CFTRΔ508. These compounds are currently undergoing clinical trial to meet this unmet medical need. Current Phase II data indicates that these drugs have shown a marginal improvement in sweat chloride only when taken in combination with Kalydeco.[14] Therefore, better drug candidates to directly target the more common CFTRΔ508 mutation remain a significant challenge.

Stem Cells as a Cystic Fibrosis Disease Model

A lack of access to human airway epithelium and appropriate disease models has hampered the access to novel drug candidates for CF to target the more common CFTRΔ508 mutation. As a result, transgenic mouse fibroblasts and epithelial cell lines that poorly recapitulate the cellular machinery normally responsible for the proper processing and trafficking of CFTR were used to identify both VX809 and VX66 (although they work well to recapitulate the ion channel's gating properties).[15] These cell lines do not reflect real biology of CF in the airway and likely account for why these drugs failed to replicate in vitro results in patient clinical trials.[16] In fact, many previous hit compounds that caused CFTRΔ508 to be appropriately localized in the plasma membrane of fibroblasts or cell lines proved to be ineffective when tested on the limited quantity of available human airway epithelium.

iPS cells have the potential to bypasses the major bottleneck by generating a nearly limitless supplies of CF airway epithelium from CF patient-derived iPS cells. So far, three groups have been able to generate lung epithelial progenitors from human iPS cells including human iPS cells derived from CF patients and are currently using their technology to screen for drug candidates.[17-19] These findings offer a radical paradigm shift in drug screening and open the possibility of patient-specific iPS cells, providing a new platform for CF drug discovery and offer unprecedented insights to CF pathogenesis.

CONCLUSION

The promise of iPS cells may offer a paradigm shift in the way pharmaceutical companies conduct preclinical drug discovery. Creating a robust system of patient-specific cell lines for drug screening may have far reaching consequences in drug discovery and personalized medicine. Such progress may be able to better predict preclinical drug candidates for clinical trial and thereby represent a significant advance in pharmaceutical innovation.

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