What about the host? A possible answer using iPSCs

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Recently, with the 2019/2020 pandemic science has been the subject of major interest and discussion. From medicine, to virology or statistics, scientists of various fields collaborated towards a common cause, adapting and working in areas outside their comfort zones. Through collaboration, inventiveness, solidarity, open sharing and self-discipline; teams, people and institutions reassembled around objectives rather than around leaders.

Presently, society and science are reinventing themselves. In the past few years, through an externally financed project (FCT PTDC/BIM-MEC/4762/2014), a new line of work emerged in the department of human genetics.
The technology to generate autologous-induced pluripotent stem cells (iPSCs) by nuclear reprogramming of patient's somatic cells raises several possibilities. Thus, the use of iPSCs became a long term objective with the collaboration of PhD students, grantees and others. Efforts were carried out to generate differentiated cells from Gaucher (Duarte et al., 2019) and Fabry disease (Duarte et al., 2020). The aim of this line of work was to establish cell models for the study of Lysosomal Storage Disorders (LSDs).

Cell models are one of the best applications of iPSCs as they can be an alternative to animal models while bearing the donor's genetic background. However, their use in the study of pathogenesis of rare diseases is also complemented by their use in toxicity studies, regenerative medicine and even clinical trials. Considering the, aforementioned, urgent need for reinvention, it is easy to see that once the pandemic is under control there will be a multitude of aspects that will urge societal and scientific intervention.
In this particular presentation, focusing on the helpfulness of iPSCs, it is possible to envisage new projects of wider application, going beyond genetic disease studies, and being quickly applied to the study of infectious diseases, cell-group susceptibility, individual susceptibility and hastening clinical trials. Using iPSCs to study the host's response to infection will certainly become an important application of iPSCs.

Introduction

From Genetics of human disease to pathophysiology of human hosts in infectious diseases, iPSCs can be used at different levels of studies.
Currently, researchers examine the SARS-CoV-2 viral genome to follow the spread of infection and phylogenetic variability around the world (1), while others are studying the human genome to identify the causes in the outlier cases and determine whether the causes of increased or decreased susceptibility to infection, severity of symptoms and immune status (2).
Genetics and the genetic study of patients and populations, provided important data concerning the cause of inherited diseases and the risk of specific populations. The lack of good models, that mimic the human cell target of diseases, hinders R&D and the understanding of the human pathophysiologic mechanisms. Through iPSC (3) it is possible to create promising cell-based models and cell-based assays and therapeutic studies (Table 1).

LSD as rare genetic diseases vs infectious diseases	Common applications for iPSC studies	Commonly affected cells/tissues
Fabry disease	Pathophysiology; cell models	Cardiac; renal; cerebrovascular; skin
Gaucher disease	Pathophysiology; cell models; test of chemical compounds	Bone; neuronal; macrophage; cardiac; liver; spleen; lung
Other genetic diseases	Pathophysiology; cell models; test of chemical compounds; clinical trials; cell therapy; cell assays	Cardiac; renal; cerebrovascular; bone; liver; cartilage; neuronal; multiple systems.
Infectious diseases	Pathophysiology; host interaction; test of chemical compounds; clinical trials; cell therapy; cell assays	Cardiac; renal; neuronal; cerebrovascular; liver; lung; immune system; multiple systems.

Table 1: Genetic diseases and infectious diseases as targets for iPSC studies

Main objectives:

Establish hiPSCs models that can be used for better comprehension of the disease mechanisms and for the testing of various therapeutic approaches.

Materials and Methods

Our biological material of choice has been human skin fibroblasts. These cells are easy to acquire, to transport, to adapt and are amenable to different methods for delivery of the Yamanaka factors, in our case the different delivery vectors were successfully chosen for forcing the fibroblasts into stem-like cells.

Results

As seen with the recent events, approaches using iPSCs can have widespread application, their utility to study humans as "hosts" of genetic diseases or hosts of infectious diseases overlaps.

Conclusion: Human iPSCs (hiPSCs) derived cells and that they can be used to study mechanisms of infection and provide ideal platforms for drug screening (4). Hence our aim is to contribute with the presently installed capacity and establish new collaborations with interested parties in order to provide more insights into genetic or acquired diseases.

References: 1. https://nextstrain.org/ncov/global; 2. https://www.covid19hg.org/ ; 3.Takahashi K, et al., *Cell*, 2006; 4. Bose B. *Stem Cell Rev Rep*,. 2020

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