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Review

Disease modeling using human induced pluripotent stem cells: Lessons from the liver ☆

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ABSTRACT

Human pluripotent stem cells (hPSCs) have the capacity to differentiate into any of the hundreds of distinct cell types that comprise the human body. This unique characteristic has resulted in considerable interest in the field of regenerative medicine, given the potential for these cells to be used to protect, repair, or replace diseased, injured, and aged cells within the human body. In addition to their potential in therapeutics, hPSCs can be used to study the earliest stages of human development and to provide a platform for both drug screening and disease modeling using human cells. Recently, the description of human induced pluripotent stem cells (hIPSCs) has allowed the field of disease modeling to become far more accessible and physiologically relevant, as pluripotent cells can be generated from patients of any genetic background. Disease models derived from hIPSCs that manifest cellular disease phenotypes have been established to study several monogenic diseases; furthermore, hIPSCs can be used for phenotype-based drug screens to investigate complex diseases for which the underlying genetic mechanism is unknown. As a result, the use of stem cells as research tools has seen an unprecedented growth within the last decade as researchers look for *in vitro* disease models which closely mimic *in vivo* responses in humans. Here, we discuss the beginnings of hPSCs, starting with isolation of human embryonic stem cells, moving into the development and optimization of hIPSC technology, and ending with the application of hIPSCs towards disease modeling and drug screening applications, with specific examples highlighting the modeling of inherited metabolic disorders of the liver. This article is part of a Special Issue entitled Linking transcription to physiology in lipodomics.

1. Introduction

1.1. Stem cells and the era of regenerative medicine Introduction

1.1.1. Degenerative disease

Western society has seen a dramatic increase in life expectancy over the last century due to the development of vaccines, antibiotics, improved sanitation, and increased general public health awareness. This increase in life expectancy due to decreased occurrence and severity of infectious disease has now unmasked an increase in debilitating illness and morbidity due to degenerative diseases. Degenerative disease is characterized as a progressive deterioration of the structure and/or function of an organ or tissue over time. These diseases are recognized as major health problems that are either currently affecting or will affect the general population in the near future. Additionally, increased incidence of degenerative disease is also of major economic concern as patient management and care, as well as the associated costs of infrastructure, can deliver a high financial burden. Diseases such as Alzheimer's and Parkinson's disease, motor neuron disease, multiple sclerosis, diabetes, kidney, liver, and heart disease, as well as blindness and cancers of many types, are all, at their most basic level, due to loss of environmental and cellular homeostasis of the resident stem cell pools in these tissues. This loss of stem cells ultimately leads to hypoplasia, a gradual loss of a population or populations of cells that is unable to be replaced, leaving the organ or tissue structurally and functionally deficient. Unfortunately, current treatments for many degenerative diseases simply address symptoms, reducing their severity or the speed of their onset. Presently, there are no reliable preventative or curative treatments for degenerative diseases other than whole organ transplantation, which often has limited success and use due to immune rejection and insufficient supply of suitable donor organs compared to demand.

1.1.2. Self-renewal and pluripotency

Human pluripotent stem cells (hPSCs) possess two remarkable cellular characteristics that set them apart from all other stem cells and make them an ideal candidate for regenerative medicine applications: the properties of “self-renewal” and “pluripotency” (Fig. 1). Self-renewal refers to the ability of these cells to make identical copies of themselves indefinitely, without developing chromosomal

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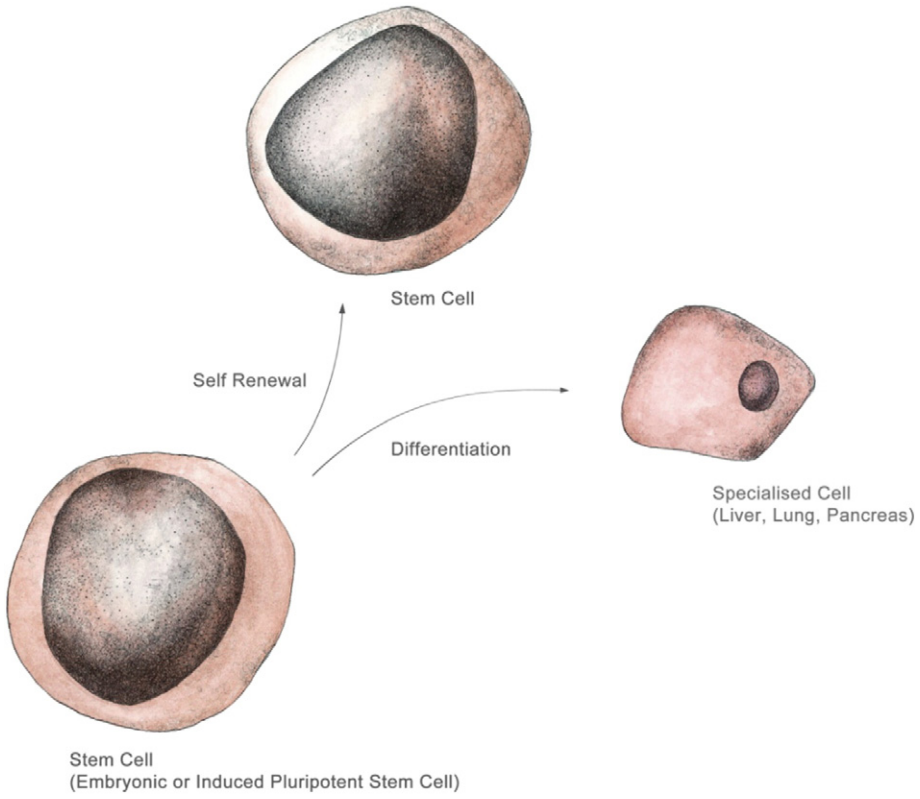

Fig. 1. Self-renewal and pluripotency. Human pluripotent cells are characterized by their unique ability to self-renew, making unlimited identical copies of themselves while retaining their pluripotency, the capacity to differentiate into more specialized cells.

abnormalities or undergoing growth arrest. Pluripotency refers to the ability of these cells to differentiate into any cell of the human body, following the natural path of human embryonic development, when given the appropriate signals to do so. Since hPSCs were first isolated in 1998, numerous studies have shown that these cells are indeed able to form extraembryonic tissues such as trophectoderm [1,2], the three primary germ layers; ectoderm, mesoderm and endoderm [3], and a myriad of cell types derived from these primary germ layers, including from ectoderm neurons [4], keratinocytes [5], retinal epithelium [6], from the mesoderm skeletal muscle [7], cardiomyocytes [8], hematopoietic cells [9], vascular smooth muscle [10,11], osteoblasts [12], chondrocytes [13], and cells of the kidney [14], and from the endoderm liver [15], lung [16], and pancreas [17]. Therefore, it is self-evident that hPSCs represent a viable source of cells to combat degenerative disease in society.

2. A brief history of pluripotent stem cells

The concept of a "stem cell" is not a new one. Work in the hematopoietic system identified populations of stem cells that were capable of producing all of the cells that comprise the human blood system [18]. Following this discovery, many other stem cell populations have been identified and are implicated in replenishing various tissues over the lifetime of an organism [19]. However, it was observations within the tissue mass of a certain type of rare tumor known as a teratoma that gave researchers the first hint that a stem cell capable of producing *all* of the tissues found in an adult organism might exist.

2.1. Teratomas and teratocarcinomas

A teratoma is a rare tumor that forms in the gonads of a wide number of vertebrates including mice and humans [20]. Teratomas contain cells representative of all three germ layers that are arranged within the tumor mass in a random and disorganized manner. These tumors can be either benign or malignant, the latter known as a teratocarcinoma [21]. The cells that comprise the differentiated population of the teratocarcinoma are generally not malignant; however, certain cells responsible for the malignant properties of the tumor, *i.e.* the ability to initiate new tumor formation and repopulate the entire mass of the tumor, are called embryonic carcinoma (EC) cells and represent a dysregulated form of cancerous stem cells [22].

Both human and mouse EC cells have subsequently been isolated and cultured *in vitro*, each with their own unique and shared growth and differentiation characteristics [20]. It has been demonstrated in the mouse that EC cells can be isolated from teratocarcinomas, cultured *in vitro*, and transplanted back into mice to form new teratomas [23]. These cells are able to be cultured *in vitro* using methodologies reserved for other malignant cell lines, demonstrate a loss of contact growth inhibition, can be established as permanent cultures, and most importantly demonstrate the ability to self-renew and differentiate into a wide variety of cell types [24,25] (Table 1). Extensive studies of EC cells led to the development of culture methodologies that would eventually result in the isolation and culture of mouse embryonic stem cells (mESCs), which in turn would lead to the isolation of the first human embryonic stem cells (hESCs).

Table 1
List of human and mouse embryo carcinoma lines and their differentiation potential.

Cell line	Species	Pluripotent	Ectoderm	Endoderm	Mesoderm
F9	Mouse	N	N	N	N
P19	Mouse	Y	Y	Y	Y
PCC4	Mouse	Y	Y	Y	Y
PCC3/S640	Mouse	N	Y	Y	N
OTT650	Mouse	Y	Y	Y	Y
NTERA2	Human	Y	Y	Y	Y
NCCIT	Human	Y	Y	Y	Y
TERA2	Human	Y	Y	Y	Y
NCRG3	Human	Y	Y	Y	Y
NTERA2.cl.D1	Human	Y	Y	Y	Y
TERA2.cl.SP12	Human	Y	Y	Y	Y