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Induced pluripotent stem cells: Landscape for studying and treating hereditary hearing loss

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Abstract

Hearing loss (HL) is one of the most widespread sensory disorders, affecting approximately 1 in 500 newborns. Heritable diseases of the inner ear are the leading causes of prelingual HL. Treating of hereditary HL and understanding its underlying mechanisms remain difficult challenges to otolaryngologists. As stem cells are capable of self-renewal and differentiation, they are ideally suited both for disease modeling and regenerative medicine. Recently, description of induced pluripotent stem cells (iPSCs) has allowed the field of disease modeling and personalized therapy to become far more accessible and physiologically relevant, as iPSCs can be generated from patients of any genetic background. This review briefly describes the advantages of iPSCs technology and discusses potential applications of this powerful biological tool in studying and treating hereditary HL.

Keywords: IPSCs; Hereditary hearing loss; Disease modeling; Genetic correction

1. Introduction

Hearing loss (HL) is one of the most common birth defects and prevalent sensorineural disorders, affecting approximately 1 in 500 newborns with bilateral congenital sensorineural hearing loss ≥40 dB HL (Hilgert et al., 2009a). More than two-thirds of prelingual HL cases are attributed to hereditary factors, most of which are caused by mutations of a single gene that functions in the inner ear (Hilgert et al., 2009a; Morton and Nance, 2006). HL can be present in a non-syndromic form (70%), as a single disorder, or syndromic form (30%) associated with distinctive clinical features (Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss, 2002). More than 150 chromosomal loci and at least 80 genes have been identified to result in non-syndromic as well as syndromic forms of HL, and approximately 1000 causing mutations have been described (Hilgert et al., 2009a, 2009b). Due to unclear mechanisms underlying hereditary HL and the intricate microstructure of the inner ear, treatment of hereditary HL is still a huge challenge to otolaryngologists. Stem cells capable of self-renewal and differentiation are ideally suited both for generating disease models and for obtaining the large quantities of cells required for genetic correction and transplantation therapies. Three major types of stem cells have been adopted: embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs). Especially in recent years, significant advances have been made in the research of inherited disease by iPSC technology, opening an avenue to generate patient-specific pluripotent stem cells. With the presence of retroviral integration, human iPSCs are useful in understanding disease mechanisms, drug screening, and regenerative medicine

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(Takahashi et al., 2007). The iPSC technology have a broad application for neurodegenerative diseases, blood disorders and retinal degenerative diseases, but little is known for hereditary HL (Wiley et al., 2015; Ross and Akimov, 2014; Wang et al., 2012). In this review, we will briefly describe the advent of iPSCs technology and discuss potential applications of this powerful biological tool in studying and treating hereditary HL.

2. Comparison among three types of stem cells

All three types of stem cells contain two remarkable cellular characteristics that make them ideal candidates for regenerative medicine applications: the properties of "self-renewal" and "pluripotency". Self-renewal refers to the ability of these cells to make identical copies of themselves indefinitely, without developing chromosomal 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.

ESCs are harvested from the inner cell mass of the blastocyst of 5-day-old pre-implantation embryos. As ESCs can differentiate into the three germ layers, they are a popular tool used in regenerative medicine. ASCs are undifferentiated cells, found throughout the body after development that multiply by cell division to replenish dying cells and regenerate damaged tissues. These cells are suggested to be present in small numbers in most major organs, such as bone marrow, skin, brain and inner ear (Davanger and Evensen, 1971; Gage, 2000; Li et al., 2003). ESCs have played a substantial role in disease modeling and treatment studies in the past decades, however, harvesting ESCs from the inner cell mass of the blastocyst during development restricts their clinical practicality due to limited availability and ethical concerns. In addition, ESCs are by definition non-autologous, not derived from the patient for which they are destined, and for cell transplantation an additional obstacle of immune incompatibility exists (Wiley et al., 2015). Although the use of ASCs has no ethical issues and less concerns for immune rejection, limited potency and capacity for self-renewal hinders their further research.

Yamanaka and his colleagues revolutionized the stem cell field in 2006 when they demonstrated that murine fibroblasts could be reprogrammed into ESC-like pluripotent stem cells by transfecting four transcription factors, Klf4, Oct3/4, Sox2, and c-Myc (KOSM), termed induced pluripotent stem cells (iPSCs) (Takahashi and Yamanaka, 2006). One year later, Yamanaka's group successfully derived iPSCs also from human fibroblasts, thus making his work relevant to human disease and an incredibly promising potential resource for cellular transplantation studies (Takahashi et al., 2007). True pluripotency of iPSCs has been demonstrated by successful production of viable mice from iPSCs through tetraploid complementation (Zhao et al., 2009). However, in conventional transduction, retroviral vectors are randomly integrated into the host's genome, thus significantly increasing the risk of insertional mutagenesis and oncogenesis (Okita et al., 2013). In order to generate clinical-grade iPSCs, safer methods have become the main goal of development in reprogramming technology. The most promising are DNA-free and viral-free protocols. They include introduction of reprogramming-inducing molecules into cells such as: recombinant proteins, messenger RNA (mRNA), and mature microRNA (miRNA) (Kim et al., 2009; Warren et al., 2010; Miyoshi et al., 2011). The efficiency of non-integrating reprogramming methods is significantly enhanced by the use of low oxygen level conditions and small molecules such as histone deacetylase inhibitors and/or DNA methyltransferase inhibitors (Szablowska-Gadomska et al., 2011; Huangfu et al., 2008; Mikkelsen et al., 2008). The traditional methods of obtaining somatic cells requires harvesting skin specimens, which increases patient's discomfort. Some researchers have found that other human somatic cells derived from blood or urine samples also can be reprogrammed into iPSCs, which greatly facilitate their clinical applications (Zhou et al., 2012; Staerk et al., 2010).

The discovery of iPSC ushered in a new age in the field of disease modeling and regenerative medicine. Unlike ESCs, the human iPSCs are not constrained by ethical disputes, and, although not yet fully tested, they should be safer immunologically (Wiley et al., 2015). A key advantage of the iPSC technology is that these cells can be generated in large numbers using cells taken from the patients for which they are intended. Hence, iPSCs are patient-specific. Additionally, like ESCs, iPSCs are pluripotent and can be differentiated into any cell type of the three embryonic germ layers (Takahashi et al., 2007).

3. Contribution of IPSCs to hearing research

3.1. Hereditary hearing loss modeling

Most hereditary HL cases are caused by monogenic mutations (Angeli et al., 2012). They are usually manifested by functional defect of the organ of Corti – a structure of receiving, encoding and transmitting acoustic signals to higher auditory processing stations. Since the discovery of the first nonsyndromic deafness gene in 1993, more than 150 loci of deafness genes have been mapped and more than 80 genes have been implicated in nonsyndromic HL. These genes fall into four broad functional categories: hair bundle morphogenesis, ion homeostasis, extracellular matrix composition and transcription factors (Hilgert et al., 2009a; Yan and Liu, 2008). Spontaneous and induced mouse models of hereditary HL are routinely used for understanding of genesbiological relevance to auditory function. However, producing knockout, knock-in and conditional mutant gene-targeted mice is a high-cost and time-consuming process, especially knockout of certain genes such as BMP4 will cause the mouse to die before the inner ear is formed (Hogan et al., 1994). In addition, such models rarely mirror human disease pathological mechanisms, and the human response is often difficult to be predicted from these models (Blanton et al., 2002). It is assumed that patient-derived iPSCs can replace millions of animals currently