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Review Article

Advances in translational inner ear stem cell research

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ABSTRACT

Stem cell research is expanding our understanding of developmental biology as well as promising the development of new therapies for a range of different diseases. Within hearing research, the use of stem cells has focused mainly on cell replacement. Stem cells however have a broad range of other potential applications that are just beginning to be explored in the ear. Mesenchymal stem cells are an adult derived stem cell population that have been shown to produce growth factors, modulate the immune system and can differentiate into a wide variety of tissue types. Potential advantages of mesenchymal/adult stem cells are that they have no ethical constraints on their use. However, appropriate regulatory oversight seems necessary in order to protect patients from side effects. Disadvantages may be the lack of efficacy in many preclinical studies. But if proven safe and efficacious, they are easily translatable to clinical trials. The current review will focus on the potential application on mesenchymal stem cells for the treatment of inner ear disorders.

Contents

1. Introduction

Research and application of mesenchymal stem cell technology

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has rapidly emerged in most areas of medicine (Bianco et al., 2013). Despite this rapid progress in other fields, only few publications concentrate on the use of mesenchymal stem cells in the inner ear (Lee et al., 2012; Kasagi et al., 2013; Tan et al., 2014; Zhou et al., 2011; Choi et al., 2012). Mesenchymal stem cells are a readily available population of cells that can be used both for cell replacement strategies but also for modulation of inflammatory injury and production of growth factors. They have the potential for rapid translation into clinical applications since for the most part these cells can be autologously obtained from adipose tissue or bone marrow prior to transplantation. This review will give an overview on mesenchymal stem cells and their potential application in otology. Application of stem cells for regenerative treatment and cell replacement has been previously reviewed (Pettingill et al., 2007; Shi and Edge, 2013; Almeida-Branco et al., 2015; Santaolalla et al., 2013; Hu et al., 2009; Kohrman and Raphael, 2013; Rubel et al., 2013; Mallick et al., 2012; Gillespie et al., 2014; Müller and Barr-Gillespie, 2015; Devarajan et al., 2011; Richardson et al., 2008; Martinez-Monedero and Edge, 2007; Pauley et al., 2008; Okano and Kelley, 2012; Géléoc and Holt, 2014).

2. Classification of stem and progenitor cells

Stem cells are characterized by their ability to proliferate extensively (self-renewal capacity), by the fact that they usually arise from a single cell (clonality) and by their potency, i.e., their ability to differentiate into different cell types (Kolios and Moodley, 2013) (Table 1). Based on their potency to differentiate, they can be further subdivided into toti- or omnipotent (Condic, 2014), pluripotent (Tesar, 2016), multipotent, oligopotent and unipotent cells. Toti- or omnipotent cells are able to differentiate into embryonic and extraembryonic tissue (Kolios and Moodley, 2013). Thus, they are able to give rise to a complete organism (Condic, 2014). Only the zygote and the cells after the first division are totipotent, i.e., they possess the ability to produce an orchestrated developmental sequence being reflected in the development of the embryo and the placenta (Condic, 2014). Pluripotent stem cells are able to differentiate into cells arising from the ectoderm, endoderm, and mesoderm (Tesar, 2016) a feature that is unique for embryonic stem cells derived from the inner cell mass of the blastocyst (Condic, 2014). However, pluripotency can be induced in somatic cells by reprogramming (Takahashi and Yamanaka, 2006). These cells are termed induced pluripotent stem cells (iPSCs) and have revolutionized the field of regenerative medicine (Zomer et al., 2015).

By contrast, multipotent stem cells are found in most tissues and differentiate into cells from a single germ layer (Kolios and Moodley, 2013). The best defined example of this category is the mesenchymal stem cell (Krampera et al., 2007). Initially isolated only from the bone marrow, these cells are now known to be present in various tissue types such as adipose tissue, bone, Wharton's jelly, umbilical cord and peripheral blood, amnion, skin, hair follicles and dental tissues. They are characterized by their adhesion to cell culture dishes and by the presence of specific surface markers (Dominici et al., 2006). These cells have the capacity to differentiate into adipose tissue, bone, cartilage, and muscle, however, they are also able to transdifferentiate into cell types from other germ layers, such as neuronal tissue (ectoderm) (Chang et al., 2013).

Oligopotent stem cells retain their self-renewal capacity and are able to differentiate into at least two or more cell types within a specific tissue (Kolios and Moodley, 2013). Such cells have been identified on the ocular surface (Majo et al., 2008). Another example of oligopotent stem cells are hematopoietic stem cells since they typically differentiate into myeloid and lymphoid cells (Marone et al., 2002). Although unipotent stem cells can self-renew, they differentiate into only one specific cell type and form a single lineage such as the satellite cells that reside in the muscle (Dumont et al., 2015). They also have been identified in the skin, maintaining the Merkel cell population (Wright et al., 2015). Based on their self-renewal capacity and their differentiation ability, stem cells should be distinguished from progenitor cells. Whereas stem cells retain an unlimited capacity for self-renewal, this capacity is limited in progenitor cells.

2.1. Endogenous stem cells in the ear

Endogenous adult stem cells reside all tissues, and are important for tissue homeostasis and remodelling processes (Kolios and Moodley, 2013; Klimczak and Kozlowska, 2016). They originate during ontogenesis and remain in a quiescent state until local stimuli activate their proliferation, differentiation or migration (Marone et al., 2002). Usually, they reside in a stem cell niche under specific environmental conditions (Kiefer, 2011). The function of tissue-resident stem cells depends on intrinsic and extrinsic signals from their microenvironment (Dumont et al., 2015). During injury, they proliferate in order to induce reparative processes (Kolios and Moodley, 2013; Dumont et al., 2015). In the inner ear, stem or progenitor cells can be isolated from neonatal tissue. Advanced lineage tracing techniques have suggested that supporting cells can proliferate and expand after injury to promote repair (Wang et al., 2015).

Sphere generating cells from the inner ear were first identified by Li et al. (2003). These endogenous progenitor cells have been isolated successfully from neonatal tissue (Coleman et al., 2007). Once formed, cells within spheres show mitosis, apoptosis, necrosis and phagocytosis (Rak et al., 2011; Bez et al., 2003). With sphere generating cells isolated from the utricular epithelium, Li et al. generated hair cell-like cells (Li et al., 2003) which may to be able to repair tissue after inner ear trauma *in vivo* (Li et al., 2004). Rask-Anderson et al. expanded this method and identified progenitor cells in human cochleae (Rask-Andersen et al., 2005). Mouse cochlear stem cells have the ability to transform into inner ear hair cell-like cells (Li et al., 2003; Diensthuber et al., 2009; Yerukhimovich et al., 2007; Savary et al., 2008) as well as glia-like cells (Yerukhimovich et al., 2007). The utricular macula and

Table 1
Classification of stem cells.

Stem Cell Type	Characteristics	Applications
Embryonic (ESC)	Pluripotent, can form all tissue types	Replacement of tissue, disease modelling
Induced pluripotent (iPSC)	Same characteristics as embryonic stem cells but induced from differentiated cells such as fibroblasts	Disease modelling, drug screening, investigation of epigenetics
Endogenous stem cells	Present in all tissues with capacity to replace tissue in which they reside to different degrees	Potential modulation of repair within a tissue
Mesenchymal Stem Cells (MSC)	Multipotent, present in most tissue; easily isolated	Tissue replacement, modulation of inflammation, modulation of apoptosis, induction of angiogenesis

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