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Review

Stem cell therapy for spinal cord injury: The use of oligodendrocytes and motor neurons derived from human embryonic stem cells

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ABSTRACT

Over the past few years, the understanding of stem cells as a potential therapeutic source has significantly evolved, and the previous concept of irreparable neural injury is being reconsidered. Stem cells are pluripotent cells with high differentiation potential. Induced proliferation and differentiation of these cells under optimal *in vitro* conditions has been used to generate different transplantable cells of various types and stages of development. For spinal cord injury recovery, the human embryonic stem cells and, recently, the human induced pluripotent stem cells are used as a main source, and two major types of cells are the target: the oligodendrocytes and motor neurons. The extensive experimental research efforts have focused on translating *in vitro* cellular regeneration of these cells to *in vivo* transplantation and survival of the transplants, in order to improve clinical outcomes. In this review, we will discuss the progressive development of the cellular generation protocols and the locomotor outcome of their transplantation at sites on spinal cord injury.

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1. Introduction

In 1908, Alexander Maksimov, a Russian histologist, proposed that all the blood cells and the process of hematopoiesis are derived from hematopoietic stem cells. However, it was not until 1963, when the Canadian scientists, James E. Till and Ernest A. McCulloch, for the first time, could demonstrate the presence of these stem cells, in mice bone marrow. Since then, research on the characteristics and therapeutic applications of these cells has initiated a new era of medicine.

2. Stem cells

Stem cells are non-differentiated cells that have the capability of proliferation, self-renewal, formation of large numbers of different types of cells, and regeneration of the already differentiated tissues. The potency of the stem cells can be determined depending on how many types of differentiated cells, and of what germ layers, the stem cells are capable to produce. This is defined as the 'differentiation potential'. The totipotential stem cells constitute the first line of cells during fetal development following fertilization, and may give rise to extraembryonic and embryonic cells. Following the separation of inner and outer cell masses, the cells of the inner cell mass (embryonic cells) are defined as pluripotential stem cells, and may give rise to any type of cells from the yet-to-be formed three germ layers: ectoderm, mesoderm, and endoderm. The cells of the outer cell mass form the trophoblast supporting the growth of the embryo. When the germ layers are separated, cells of each layer are classified as multipotent, oligopotent, or unipotent, depending on their differentiation potentials [4]. These higher levels of stem cells are defined as the adult stem cells (ASC), which are retained in most tissues during childhood and adulthood, and, under normal conditions, give rise to that specific line of cells of the retaining organ. However, some tissues, for unknown reasons, including brain, spinal cord, heart, and kidneys, with minor exceptions, do not maintain their stem cells, which limits their regenerative ability following injury [17].

Pluripotent stem cells have been an ideal source for cellular transplantation, due to their extensive proliferation and differentiation potential. Of these cells, embryonic stem cells (ESC), which are present during early stage of development, have drawn most attention. More than two decades of intense research on mouse ESC has provided insight into human ESC (hESC) research despite the differences between the two types of cells [13]. They have also provided the proper methods of differentiating mouse ESC into several clinically relevant neural and non-neural cell types [16]. Thomson et al. [33] were the first to isolate the hESC, using fourteen inner cell masses of *in vitro* fertilization (IVF)-produced embryos as a source. These blastocysts have since then constituted the major source of hESC. Other sources of ESC include nuclear transfer and therapeutic cloning. Nuclear transfer is achieved by transferring the nucleus of an adult differentiated egg (containing the DNA to be cloned) into an enucleated egg, which is then stimulated to form blastocysts, from which the ESC can be extracted. When nuclear transfer is performed for therapeutic purposes, using a nucleus of a somatic cell (e.g. skin cell), it is then called "therapeutic cloning" [4].

Following expansion, ESC are induced to form different cells of various stages of differentiation, including neuroepithelial cells, oligodendrocytes and their progenitors, as well as motor neurons and their progenitors. In this review, we will focus on the generation and transplantation of oligodendrocytes and motor neurons, and their progenitors.

A comparison between experimental generation of oligodendrocytes and motor neurons is summarized in Table 1 and Fig. 1.

3. hESC as a source of oligodendrocytes

Oligodendrocytes (OL) are one type of glial cells that provide support to the central nervous system (CNS), mainly by the formation of the myelin sheath. They extend into high numbers of branches and sub-branches expanding into sheets of myelin membranes that wrap around multiple neural axons. This myelin sheath facilitates the rapid saltatory conduction and insulation of the nerve cells [9,12]. It also promotes neuronal and axonal survival by secreting different types of neurotrophic factors [16,22].

Zhang et al. [35] studied the ability of the oligodendrocytes progenitor cells (OPC) derived from hESC to secrete neurotrophic factors. Of all the genes tested, 49 growth factors were significantly expressed by OPC. Of these factors, transforming growth factor (TGF)-β1, TGF-β2, activin A, vascular endothelial (VEGF), brain-derived neurotrophic factor (BDNF), midkine, and stem cell factor (SCF) proteins were of particular interests. These factors were found to play a remarkable role in neural regeneration and function restoration [35].

Following spinal cord injury (SCI), significant loss of OL and OPC adds to the deleterious effect of direct trauma and subsequent inflammation and vascular disruption. Therefore, replacement of these cells has been one of the promising treatment options that may preserve the axonal function and suppress their progressive loss.

3.1. Experimental generation of oligodendrocytes from hESC

Potential sources of human OL include aborted fetuses, olfactory biopsies of the neuroepithelium, and hESC. The latter may provide

Table 1
Characteristics and comparison between oligodendrocytes and motor neurons linages.

	Oligodendrocytes linage	Motor neurons linage
First use	[22]	[19]
Inducers	RA, Noggin, SHH, AA, EGF, PDGF, FGF, CNTF, IGF, HGF, T3, puromorphamine	RA, Noggin, SHH, puromorphamine, SAGA, dorsomorphin, BDNF, CNTF, GDNF, FGF, IGF1, AA, cAMP, NT-3, ROCK
Inhibitors	BMP	BMP
Expressed genetic markers	Sox8, Sox9, Sox10, Olig1, Olig2, Nkx2.2, Nkx6.2, A2B5, NG2, PDGF-R, PLP, Ngn3, Gli1, Gli2, OMG, MBP, GalC, RIP, O4, O1	Pax6, Sox1, Sox2, Sox3, Nestin, Otx2, NG2, HOXB1, HOXB4, HOXB6, HOXC5, HOXC8, HOXC10, HLBX9, Olig2, Nkx2.2, Nkx6.1, Irx3, GFP, HB9, Islet1, islet2, ChAT, MAP2, β III-tubulin, Musashi1, PTCH, Tuj1
Secreted factors	TGF-β1, TGF-β2, activin A, VEGF, BDNF, midkine, SCF	–
Integration and maturation after transplantation	Yes, at early and late stages	Yes
Locomotor improvement	Yes, only at early stage	Yes
Studies on humans	No	No