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Clinical Neurology and Neurosurgery 110 (2008) 889–896

Clinical Neurology and Neurosurgery

www.elsevier.com/locate/clineuro

Review

The potential use of stem cells in multiple sclerosis: An overview of the preclinical experience

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Received 28 December 2007; received in revised form 2 February 2008; accepted 7 February 2008

Abstract

The reported neurodegeneration process in multiple sclerosis may explain the lack of efficacy of the currently used immunomodulating modalities and the irreversible axonal damage, which results in accumulating disability. Efforts for neuroprotective treatments have not been, so far, successful in clinical studies in other CNS diseases. Therefore, for MS, the use of stem cells may provide a logical solution, since these cells can migrate locally into the areas of white matter lesions (plaques) and have the potential to support local neurogenesis and rebuilding of the affected myelin. This may be achieved both by support of the resident CNS stem cells repertoire and by differentiation of the transplanted cells into neurons and myelin-producing cells (oligodendrocytes). Stem cells were also shown to possess immunomodulating properties, inducing systemic and local suppression of the myelin-targeting autoimmune lymphocytes. Several types of stem cells (embryonic and adult) have been described and extensively studied in animal models of CNS diseases. In this review, we summarize the experience with the use of different types of stem cells in the animal models of MS (EAE) and we describe the advantages and disadvantages of each stem cell type for future clinical applications in MS.

Keywords: Stem cells; Embryonic stem cells (ESC); Neuronal stem cells (NSC); Neurospheres; Mesenchymal stromal cells (MSC); Experimental autoimmune encephalomyelitis (EAE); Multiple sclerosis (MS); Neurodegeneration; Neuroprotection; Immunomodulation

Contents

Abbreviations: CNS, central nervous system; MS, multiple sclerosis; BM, bone marrow; MSC, mesenchymal stem cells; NSC, neuronal stem cells; EAE, experimental autoimmune encephalomyelitis; ALS, amyotrophic lateral sclerosis; ESC, embryonic stem cells.

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doi:10.1016/j.clineuro.2008.02.008

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory multifocal demyelinating disease of the central nervous system (CNS) that affects predominantly young adults. While its pathogenesis is still obscure, and multiple (genetic, environmental and infectious) factors seem to be involved in it, it is widely accepted that the final pathogenetic pathway is that of an autoimmune attack against myelin components. Additional mechanisms have been lately under covered, including a damage of the axons in the CNS and a degenerative process, which is probably the result of inflammation, and which causes accumulating and irreversible damage with time [1,2]. Naturally, treatment approaches for MS are targeting the immune system, either in a non-specific way (systemic immunosuppression with cytotoxic agents) or through immunomodulation (to specifically down-regulate the myelin-reactive autoimmune lymphocytes or to enhance the regulatory immune networks) in order to control the inflammatory process which – as mentioned – causes the demyelination [1,2]. Unfortunately, the currently existing treatments for MS (both the immunosuppressive ones and the immunomodulating, i.e. Glatiramer acetate and interferon beta, are only partially effective, probably due to their limited ability to exert a significant in situ immunomodulation in the areas of lesions in the CNS, paralleled by a deficiency in growth factors production and insufficient numbers or mobilization of the resident CNS stem cells [3].

It is therefore obvious that, in order to improve treatment outcome in MS, innovative approaches are required for immune regulation rather than non-selective immunosuppression, as well as therapeutic interventions which may offer effective in situ immunomodulation and neuroprotection.

Extensive studies have provided strong evidence for neurodegeneration in MS, including the finding of amyloid precursor protein (APP) accumulation in neurons [4], a reduction in NAA/Cr ration in MR spectroscopy (MRS) which correlates well with the degree of disability [5], the finding of axonal ovoids/transected axons at the edge and the core of active lesions [6] and of oxidative damage in mitochondrial DNA and impaired activity of mitochondrial enzyme complexes [7], the reduction in axonal density in normally appearing white matter (NAWM) early in MS and a more prominent reduction of axonal density in spinal cord NAWM in progressive MS patients [8,9].

A logical treatment approach to enhance neuroprotective mechanisms and to induce neuroregeneration in MS is with stem cell transplantation.

Stem cells are a diverse group of multipotent cells. In general these cells are relatively undifferentiated and unspecialized and they can give rise to the differentiated and specialized cells of the body. All stem cells exert two characteristic features: (1) the capacity for self-renewal and (2) the potential to produce various differentiated cells types. There are different kinds of stem cells which can be isolated from embryonic and adult tissues. Embryonic stem cells (ESC) are cells derived from the inner cell mass of embryos [10,11] at the blastocyte stage (5–9 days after fertilization). The only source for human stem cells is from embryos obtained from in vitro fertilization (IVF). The adult or non-embryonic stem cells are more differentiated than ESC, however not yet fully differentiated. Theoretically, the usage of ESC and adult NSC might represent the optimal source for cell-replacement therapies in CNS disorders like multiple sclerosis.

In the current review, the various types of stem cells, which were mainly studied in animal models, will be reviewed as a potential therapeutic approach for multiple sclerosis. The main and common mechanisms of action of all stem cells, include induction of neuroregeneration and remyelination, through the activation of resident stem cells or production of new CNS cell lineage progenitors, paralleled by local and systemic immunomodulating effects.

2. Experience with various types of stem cells in animal models of multiple sclerosis ANS CNS demyalination

2.1. Embryonic stem cells

Mentioned ESC derived from the inner cell mast of the blastocyte are capable to give rise to cells from all three germ layers. ESC were shown to be able to differentiate in vitro into several cell types of the body including neural cells; the actual fate of their differentiation is controlled through manipulation with growth factors, chemical agents and neurotrophic factors like, EGF, FGF-2, BDNF, and retinoic acid [12–16]. ESC express distinct surface markers such as Oct-4, Sox-2, and SSEA-1/2/3/4. Several studies showed the ability of these cells to differentiate into myelin-producing cells (oligodendrocytes) [17–20] and neurons [21–26], becoming therefore ideal candidates for neuroregeneration and remyelination in diseases like multiple sclerosis. In a recent study it was found that neurospheres derived from ESC obtained from ILRIL6 chimeras (soluble interleukin-6 receptor fused to interleukin-6) exhibit an enhanced differentiation into oligodendrocytes with more branches and peripheral accumulation of myelin basic protein (MBP) in myelin membranes [27]. Transplantation of differentiated oligodendroglial progenitors derived from ESC into the shiverer mouse model of dysmyelination resulted in integration, differentiation into oligodendrocytes, and compact myelin formation demonstrating that these cells display a functional phenotype [18]. When transplanted in rodent models of induced demyelination, embryonic stem cells were shown able to differentiate into glial cells and re-ensheath demyelinated axons in vivo [20,28].

Researchers have underlined that ESCs could be a "double-edged sword" since they may cause the formation of a non-homologous implant and teratomas within the organ of transplantation [20,29,30]. Immune rejection by the host immune system has been considered to be one of the greatest hurdles for cellular transplantation