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Review

Immunomodulatory effects of stem cells: Therapeutic option for neurodegenerative disorders

Martin Caprnda[a,1], Peter Kubatka[b,c,1], Katarina Gazdikova[d,e,**], Iveta Gasparova[f], Vanda Valentova[b], Nadezda Stollarova[g], Giampiero La Rocca[h], Nazarii Kobyliak[i], Jozef Dragasek[j], Ioana Mozos[k], Robert Prosecky[l], Dario Siniscalco[m], Dietrich Büsselberg[n], Luis Rodrigo[o], Peter Kruzliak[p,q,*]

[a] 1st Department of Internal Medicine, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia
[b] Department of Medical Biology, Jessenius Faculty of Medicine, Comenius University, Martin, Slovakia
[c] Division of Oncology, Biomedical Center Martin, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia
[d] Department of Nutrition, Faculty of Nursing and Professional Health Studies, Slovak Medical University, Bratislava, Slovakia
[e] Department of General Medicine, Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia
[f] Institute of Biology, Genetics and Medical Genetics, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovakia
[g] Catholic University in Ružomberok, Faculty of Pedagogy, Department of Biology and Ecology, Ružomberok, Slovakia
[h] Human Anatomy Section, Department of Experimental Biomedicine and Clinical Neurosciences, University of Palermo and Euro-Mediterranean Institute of Science and Technology (IEMEST), Palermo, Italy
[i] Endocrinology Department, Bogomolets National Medical University, Kyiv, Ukraine
[j] 1st Department of Psychiatry, Faculty of Medicine, Pavol Jozef Safarik University and University Hospital, Kosice, Slovakia
[k] Department of Functional Sciences, Discipline of Pathophysiology, "Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
[l] Department of Internal Medicine, Merciful Brothers' Hospital, Brno, Czech Republic
[m] Department of Experimental Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy
[n] Weill Cornell Medical College in Qatar, Qatar Foundation – Education City, Doha, Qatar
[o] University of Oviedo, Central University Hospital of Asturias (HUCA), Oviedo, Spain
[p] Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic
[q] 2nd Department of Surgery, Faculty of Medicine,St. Anne's University Hospital, Brno, Czech Republic

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ABSTRACT

Stem cells have the capability of self-renewal and can differentiate into different cell types that might be used in regenerative medicine. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS) currently lack effective treatments. Although stem cell therapy is still on the way from bench to bedside, we consider that it might provide new hope for patients suffering with neurodegenerative diseases. In this article, we will give an overview of recent studies on the potential therapeutic use of mesenchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and perinatal stem cells to neurodegenerative disorders and we will describe their immunomodulatory mechanisms of action in specific therapeutic modalities.

Contents

* Corresponding author at: University of Veterinary and Pharmaceutical Sciences, Palackeho 1/1946, 612 42 Brno, Czech Republic.
** Corresponding author at: Department of Nutrition, Faculty of Nursing and Professional Health Studies, Slovak Medical University, Limbova 12, 833 03 Bratislava, Slovakia.
E-mail addresses: katarina.gazdikova@szu.sk (K. Gazdikova), kruzliakpeter@gmail.com (P. Kruzliak).
[1] Co-first/equal authorship.

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1. Introduction

Neurodegeneration and neurodegenerative disorders are considered as a serious global health problem affecting the aging population. Neurodegeneration is linked with the loss of neurons in the brain or spinal cord, which is characterized as the loss of a particular neuronal subtype or generalized loss of neuronal populations. In the brain, Alzheimer's disease (AD) results in widespread loss of neurons, while Parkinson's disease (PD) involves the specific and localized loss of dopaminergic neurons in the substantia nigra. In the brainstem and spinal cord, amyotrophic lateral sclerosis (ALS) involves the degeneration and loss of motor neurons [1]. Multiple sclerosis (MS) is a demyelinating disease that affects the nerve cells in the brain and spinal cord. Stem cells (SCs) have the capability of self-renewal and to differentiate in different cell types. These properties could be used to become part of powerful clinical techniques. An example is the use of hematopoietic stem cells (HSCs) from bone marrow transplants to treat leukaemia, hemophilia, and anemia. Although novel therapeutic approaches have been developed over the past 50 years, the treatment for a number of neurodegenerative disorders are still limited to conventional approaches that primarily address symptoms. On the other hand applications where stem cells are used to treat neurodegenerative are increasing (Table 1). Moreover, stem cells can lead to functional improvements in nervous tissue that could be clinically beneficial through mechanisms other than cell replacement, for example, immunomodulation. In this regard, SCs and SCs-derived cells have been shown to possess broad immunoregulatory activities and are capable of influencing both adaptive and innate immune responses [2]. These cells can migrate to the sites of inflammation and exert the immunomodulatory and anti-inflammatory effects through interactions with lymphocytes or production of cytokines. SCs and SCs-derived cells demonstrate hypoimmunogenic (HLA system class I and II), and modulation effects on the activity of T cells, natural killer cells, dendritic cells, B cells, neutrophils, monocytes or macrophages as observed in a wide spectrum of experiments in vitro, in vivo, and ex vivo [3].

Stem cell transplantation is regarded as a potentially perspective modality for the treatment of neurodegenerative disorders. In a few past years, advances in stem cell biology have changed the current status of neurodegenerative disease modelling, diagnosis, and transplantation therapy [4]. There are various types and sources of stem cells utilized in research of neurodegenerative disorders [5]. In this regard, among the most investigated SCs belong: mesenchymal stem cells (MSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and perinatal stem cells. MSCs and iPSCs derived precursor cells can modulate the autoimmune response in the central nervous system and promote endogenous remyelination and repair process in animal models [6]. NSCs have the potential to generate both neurons and glia of the developing brain and they also account for the limited regenerative potential in the adult brain [7]. Finally, ESCs' and perinatal stem cells' transplants have been widely suggested in several neurodegenerative disorders or brain injuries [8]; however, in ESCs major limitation is the ethical issue regarding their origin. Various types and sources SCs for the therapy in neurodegenerative disorders summarises.

This article gives a brief overview of research involving above mentioned five SC types that have potential therapy applications in

Table 1
Application of stem cell in neurodegenerative diseases.

Type of cell therapy	Potential Application	Advantage	Disadvantage	New tools and technologies
Mesenchymal stem cells (MSCs)	MS (Cristofanilli et al., 2011); AD (Yun et al., 2013); ALS(Forostyak et al., 2014));	wide range of tissue sources; broad immunoregulatory properties	low efficacy; formation of tumors	non-integrating vectors (Banasik and McCray, 2010); suicide gene strategies (Di Stasi et al., 2011); Phage display and cell sorting (Daquinag et al., 2011)
Neural stem cells (NSCs)	Stroke (Popa-Wagner et al., 2014); ALS (Mitrecic et al., 2010); AD (Wu et al., 2008); PD (Xu et al., 2010).	Less of a risk for tumor formation	difficulty to purify; limited supply; restricted potential	TALEN(Cerbini et al., 2015)
Embryonic stem cells (ESCs)	Stroke (Pignataro et al., 2007); AD (Moghadam et al., 2009); PD (Kim et al., 2007)	Immune rejection; high proliferation capability	difficulty to pure ES cell-derived neuronal progenitor cells; formation of tumors; ethic conflict	iPS(Takahashi and Yamanaka, 2013) Phage display and cell sorting (Daquinag et al., 2011)
Induced pluripotent stem cells (iPSCs)	Stroke (Jiang et al., 2011); PD (Rhee et al., 2011)	resistance to immune rejection	reduced efficiency and higher variability in neural differentiation; high medical costs; long term to get the iPS cell	TALEN(Cerbini et al., 2015); New vectors for gene delivery (Warren et al., 2010);