Role of Stem Cells in Neurological Disorders, with Special Reference to Cerebral Palsy in Children

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Stem cells seem to be the new exciting topic in many of today's scientific studies. While there is great progress in this area of study, there is just as much controversy surrounding the use of stem cells in clinical therapy. Stem cells are the building blocks of our bodies. They are versatile cells that can become many different forms of tissues. Their proliferative capacity combined with the ability to become specialized make stem cells unique. Their potential for saving lives can revolutionize the treatment of diseases previously thought incurable.

Stem cells have been isolated from embryonic, fetal and adult tissues and, more recently, also from extra-embryonic adnexa such as umbilical cord, placenta, fetal membranes and amniotic fluid. Each different stem cell population carries particular features, values and limitations.

In the past decade, there have been profound changes in our understanding of the mechanisms of injuries to the CNS. Simultaneously, new insights into the regenerative potential of neural cell lines have provided a glimmer of therapeutic hope. Neuronal loss may not be as irretrievable as once assumed.

As the nerve cells are incapable of regenerating after damage, stem cell therapy is emerging as a potentially revolutionary new way to treat diseases and injuries, with

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List of Abbreviations

Aβ	Beta- amyloid
AD	Alzheimer's disease
AFMS	Amniotic fluid mesenchymal stem cells
AFS	Amniotic fluid stem cells
ALS	Amyotrophic lateral sclerosis
ASCs	Adult stem cells
APP	Amyloid Precursor Protein
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
bFGF	Basic fibroblast growth factor
CB	Cord blood
CNS	Central nervous system
CP	Cerebral Palsy
CSCs	Cardiac stem cells
CT	Computed tomography
DA	Dopaminergic
EGF	Epidermal growth factor
EPO	Erythropoietin
ESCs	Embryonic stem cells
FGF	Fibroblast growth factor
G-CSF	Granulocyte colony-stimulating factor
GABA	Gamma-aminobutyric acid
GDNF	Glial cell line derived neurotrophic factor
GFAP	Glial fibrillary astrocytic protein

List of Abbreviations (Cont.)

GRP	Glial restricted precursors
GPCs	Glial precursor cells
GSCs	Germ line stem cells
HBOT	Hyperbaric oxygen therapy
HD	Huntington's disease
HLA	Human leukocyte antigen
hNGF	Human neural growth factor
HSCs	Hematopoietic stem cells
IL	Interleukin
IPSCs	Induced pluripotent stem cells
L-DOPA	L-3,4 dihydroxyphenylalanine
LSCs	Limbal stem cells
MCAO	Medial carotid artery occlusion
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells or Multipotent stem cells
NGF	Nerve growth factor
NPCs	Neural precursor cells
NRP	Neural restricted precursor
NSCs	Neural stem cells
NT-3	Neurotrophin-3
6-OHDA	6-Hydroxydopamine
OPCs	Oligodendrocyte progenitor cells

List of Abbreviations (Cont.)

PD	Parkinson's disease
PEDF	Pigment epithelium derived factor
PNS	Peripheral nervous system
PSA-NCAM	Polysialylated neural cell adhesion molecule
PT	Physiotherapy
RMS	Rostral migratory stream
SCI	Spinal cord injury
SDF-1	Stromal cell-derived factor 1
SDF-1α	Stromal-derived factor 1α
SGZ	Sub-granular zone
SNpc	Substantia nigra pars compacta
SVZ	Sub-ventricular zone
TGF- α	Transforming growth factor-α
TH	Tyrosine hydroxylase
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
UCB	Umbilical cord blood
UCBSCs	Umbilical cord blood stem cells
VEGF	Vascular endothelial growth factor
Online *	"Online" denotes that the reference used is a website and "*" is its number in the list of online websites grouped in the reference section of this essay

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Introduction

Regenerative medicine is an interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause ***(Daar and Greenwood, 2007).*** In recent decades, major advancements in this field have been facilitated by the discovery of 'stem cells'. Stem cells are distinctive and versatile type of cells that can divide indefinitely and have a unique capacity to renew themselves and to give rise to specialized cell types ***(De Coppi et al., 2009).***

Today there are more than six hundred known disorders and conditions that affect the nervous system; and for many of them treatment options are extremely limited. In addition to the physical and mental toll these conditions take on patients, their families and caregivers, they also have an enormous economic impact due to medical expenses and lost productivity ***(Online [1]).***

The adult central nervous system (CNS) was long thought to be largely post-mitotic, with very limited ability to regenerate ***(Filbin, 2003).*** Thus, it came as a surprise when the existence of neural stem cells (NSCs) in the adult CNS was discovered ***(Temple, 2001).*** These adult NSCs can be amplified *in vitro* through many passages without losing their multipotentiality, being capable of giving rise to neurons, astrocytes, and oligodendrocytes, both in culture and after transplantation to specific regions *in vivo* ***(Anderson, 2001).***

Rapid advances in adult NSC biology have raised great expectations that these cells can be used as potential resources for neuronal replacement therapy after neuro-degenerative diseases or cerebral injury as cerebral palsy ***(Alessandri et al., 2004)***.

Cerebral palsy is the term for a range of non-progressive syndromes of posture and motor impairment that result from an insult to the developing central nervous system (CNS), which can occur in utero, during delivery, or during the first 2 years of life ***(Cans, 2000)***.It is the most common cause of severe physical disability in childhood ***(Kuban and Leviton, 1994)***. The overall reported prevalence in children aged 3–10 years is 2.4 per 1000 children ***(Stanley et al., 2000)***.During the past 20 years, there have been increases in the incidence and prevalence of cerebral palsy related to improved documentation of cases by national registries, advances in neonatal care and higher survival for very-low-birth weight infants ***(O'Shea et al., 1998)***.

There is currently no cure for cerebral palsy and no standard therapy that works for all patients. This has lead many researchers to believe that regenerative stem cell therapies provide an option to regenerate nerve tissue and repair damage to the brain ***(Lee et al., 2007)***. Their success in an adult stroke model led the researchers to explore the potential for helping babies recover from hypoxic ischemia, a loss of blood and oxygen that can result in cerebral palsy ***(Baker et al., 2008)***.

Due to the complexities involved in harvesting human neural cells, easily-accessible, alternative stem cells - like those found in umbilical cord blood - are being researched as potential sources for cellular therapies to treat neurological diseases, such as cerebral palsy ***(Online [2])***.

Aim of The Work

Stem cell research indicates that there is a real possibility for restoring function to the areas of damaged brain; therefore, the present study aims at exploring the role of stem cells in regeneration of damaged brain cells in different neurological conditions with special reference to cerebral palsy.

Chapter 1

Stem Cells

The term ‘stem cells’ first appeared in the research literature at least 140 years ago. It was originally used by embryologists to describe germ line cells, and by hematologists to describe blood-forming cells ***(Ramalho-Santos and Willenbring, 2007). Till and McCulloch (1961),*** established the spleen colony assay to define the mouse hematopoietic stem cells (HSCs) with its ability to self-renew. Since then, the term ‘stem cells’ is used to identify cells that share the dual ability to proliferate indefinitely (i.e. self-renewal) and to differentiate into one or more types of specialized cells (i.e. potency) ***(Mimeault and Batra, 2006).***

Properties of Stem Cells:

There are five minimal functional states of stem cells **‘SMART’** (**S**elf-renewal, **M**aturation, **A**poptosis, **R**esting mode and **T**rafficking) that constitute an interesting model for maintaining stem cell homeostasis *in vivo***.** The lack of any of these ‘**SMART**’ features would make stem cells much less physiological and particularly useless in therapeutics ***(Meissner et al., 2007) (Fig. 1).***

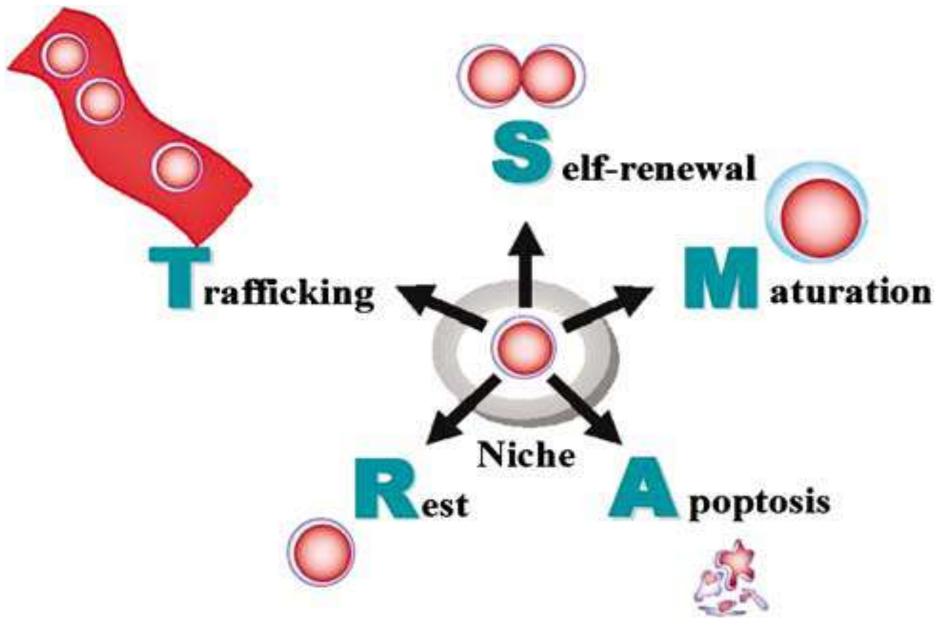

Fig. (1): A diagram illustrating the **'SMART'** physiological features of stem cells *in vivo* ***(Cheng, 2008).***

1-Self-Renewal:

It is a common misconception that all stem cell self-renewal occurs in the same way that general cells proliferate. In fact, stem cells show two different methods of self-renewing: one is symmetrical (stochastic differentiation) which divides into two daughter stem cells, and the other is asymmetrical (obligatory asymmetric replication) that gives one daughter stem cell and one differentiated cell. Embryonic stem cells (ESCs) can only undergo symmetrical self-renewing division, whereas adult stem cells (ASCs) [for example, hematopoietic stem cells (HSCs) and neural stem cells (NSCs)] are thought to undergo asymmetrical self-renewing division under homeostatic conditions ***(Morrison and Kimble, 2006).***