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Role of Stem cell therapy in spinal cord injuries

Essay

Submitted for partial fulfillment of Master Degree

In Anatomy

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Introduction

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. All stem cells regardless of their source have three general properties: capable of dividing and renewing themselves for long periods, unspecialized and can give rise to specialized cell types **(Galvin and Jones, 2002).**The two broad types of mammalian stem cells are: embryonic and adult stem cells **(Tuch, 2006).**

Just a decade ago, neuroscience textbooks held that neurons in the adult human brain and spinal cord could not regenerate. Once dead, it was thought, central nervous system (CNS) neurons were gone for good. Because rebuilding nervous tissue seemed out of the question, research focused almost entirely on therapeutic approaches to limiting further damage **(Bjorklund and Lindvall, 2000).**

Recent research into the regeneration mechanisms of the central nervous system, including the discovery of stem cells in the adult brain that can give rise to new neurons and neural support cells, has raised hopes that researchers can find ways to actually repair central nervous system damage. Research on stem cells in nervous system disorders is one of the few areas in which there is evidence that cell-replacement therapy can restore lost function **(Cao et al., 2009).**

The tiny number of stem cells in the adult spinal cord proliferates slowly or rarely, and fails to promote regeneration on their own. But recent experiments show that these same cells, grown in the lab and returned to the injury site, can restore some function in paralyzed rodents and primates **(Meletis et al., 2008).**

Neural stem cells can be cultured from the CNS of different mammalian species at many stages of development. Neural stem cells are multipotent since their differentiating progeny will give rise to the principal cellular phenotypes comprising the mature CNS: neurons, astrocytes and oligodendrocytes. Neural stem cells can also be derived from more primitive embryonic stem (ES) cells cultured from the blastocyst. ES cells are considered to be pluripotent since they can give rise to the full cellular spectrum and will contribute to all three of the embryonic germ layers: endoderm, mesoderm and ectoderm. Their progeny may also give rise to the multiple cellular phenotypes contributing to the CNS **(Ostenfeld and Svendsen, 2003).**

Although the hard bones of the spinal column protect the soft tissues of the spinal cord, vertebrae can still be broken or dislocated in a variety of ways and cause traumatic injury to the spinal cord at any level. The segment of the cord that is injured, and the severity of the injury, will determine which body functions are compromised or lost **(National Institutes of Health, 2009).**

Spinal cord trauma destroys numerous cell types, including the neurons that carry messages between the brain and the rest of the body. Even, the surviving axons no longer carry messages because oligodendrocytes, which make the axons' insulating myelin sheath, are lost **(Liu et al., 2000).**

In fact, it appears that neural stem cells move to create new cells in the event of injury, but only to create astrocytes. This is not enough to restore functioning because it is the death of oligodendrocytes that results in loss of myelin, which then halts communication between the brain and the rest of the body **(Steindler, 2007).**

The challenge has been to understand the signalling that would prompt neural stem cells (precursor cells) to differentiate into neurons and glial cells, and especially into the myelin-producing glial cells that can restore the protective sheath around the fibers and re-establish the connection to the brain **(Jones and Galvin, 2001).**Researchers have recently made progress to replenish these lost myelin-producing cells **(Liu et al., 2000).**

Aim of the work:

This essay aims at reviewing the possible sources of stem cells available for regeneration of the spinal cord in case of injury and the obstacles facing the regeneration process.

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مقدمة:

تتميز الخلايا الجذعية بقدرتها الفائقة علي أن تتطور إلى أنواع مختلفة وعديدة من الخلايا خلال وقت مبكر من الحياة وأثناء النمو. جميع الخلايا الجذعية بصرف النظر عن مصدرها تتميز بان لها ثلاث خصائص عامة و هي أنها قادرة علي الانقسام و تجديد نفسها لفترات طويلة كما أنها غير متخصصة لكنها قادرة علي أن تكون أنواع متخصصة من الخلايا.

الخلايا الجذعية تنقسم إلي نوعان الأول هو الخلايا الجذعية الجنينية و الثاني هو الخلايا الجذعية البالغة.

أقرت كتب علم الأعصاب منذ عقد مضي أن الخلايا العصبية في النخاع الشوكي ومخ الإنسان البالغ غير قادرة علي التجدد و بمجرد أن تموت هذه الخلايا فأنها لا تعود. و قد ركزت الأبحاث علي المنهج العلاجي للحد من المزيد من الأضرار للجهاز العصبي.

و قد اكتشفت الأبحاث الحديثة وجود خلايا جذعيه في مخ الإنسان البالغ قادرة علي تكوين خلايا عصبية جديدة مما أعطى الأمل للباحثين في إيجاد طرق لإصلاح إصابات الجهاز العصبي المركزي. ويعتبر دور الخلايا الجذعية في علاج إصابات الجهاز العصبي إحدى المجالات القليلة التي أثبتت فعاليتها في العلاج بالخلايا الجذعية.

الخلايا الجذعية العصبية من الممكن استنباتها من الجهاز العصبي المركزي لمختلف أنواع الثدييات في معظم مراحل التطور. كما يمكن استنباتها من الخلايا الجذعية الجنينية الأصلية التي لديها القدرة علي الانقسام المتعدد لإعطاء أي نوع من أنواع خلايا جسم الإنسان.

ويتعرض النخاع الشوكي للإصابة إذا حدث كسر في عظم الفقرات. وتتحرك الخلايا الجذعية العصبية إلي مكان الإصابة لتكوين الخلايا النجمية فقط و التي تكون غير كافية لاستعادة الوظائف المفقودة.

التحدي في هذا المجال هو إيجاد الحاف للخلايا الجذعية لتكوين خلايا عصبية و التي من شانها استعادة الوظائف المفقودة في أماكن الإصابة بالجهاز العصبي و إعادة اتصال الحبل الشوكي بالمخ.

الغرض من هذا البحث هو استعراض المصادر الممكنة للخلايا الجذعية القادرة علي إعادة تجديد الحبل الشوكي في حالة اصابتة مع استعراض المعوقات التي تواجه عملية التجديد.

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Contents

List of Abbreviations

- **ALS** : Amyotrophic lateral sclerosis.
- **ASIA** : American Spinal Injury Association.
- **bFGF** : Basic fibroblast growth factor.
- **BMSC** : Bone marrow stem cell.
- **CNS** : Central nervous system.
- **EB** : Embryoid body.
- **ECMs** : Extracellular matrices.
- **EGF** : Epidermal growth factor.
- **ESC** : Embryonic stem cell.
- **FGF** : Fibroblast growth factor.
- **GABA** : γ-aminobutyric acid.
- **hESC** : Human embryonic stem cell.
- **HSC** : Hematopoietic stem cell.
- **ICM** : Inner cell mass.
- **iPSC** : Induced pluripotent stem cell.
- **IV injection**: Intravenous injection.
- **MAG** : Myelin associated glycoprotein.
- **MEF** : Mouse embryonic fibroblast.
- **mESC** : Mouse embryonic stem cell
- **MHC** : Major histocompatibility complex.
- **MSC** : Mesenchymal stem cell.
- **NCSC** : Neural crest stem cell.
- **NPC** : Neural precursor cell.
- **NSC** : Neural stem cell.
- **NSCISC** : National Spinal Cord Injury Statistical Center.
- **OEC** : Olfactory ensheathing cell.
- **OMgp** : Oligodendrocyte myelin glycoprotein.
- **PGC** : Primordial germ cell.
- **RA** : Retinoic acid.
- **SCI** : Spinal cord injury.
- **SVZ** : Subventricular zone.
- **UCB** : Umbilical cord blood.

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Acknowledgment

First of all, I would like to thank ***God*** *for allowing me to perform this study.*

My profound thanks and deep appreciation to ***Prof. Dr.Kariman Mohamed Abd El-Fattah Al Gohari,*** *Head of Anatomy Department, Faculty of Medicine, Ain Shams University. It was an honor to me to carry out this work under her continuous guidance and expert supervision.*

I would like to express my profound gratefulness and sincere appreciation to ***Prof. Dr. Azza Salah El-Din Soliman Yonis,*** *Professor of Anatomy, Faculty of Medicine, Ain Shams University, for her support, valuable remarks and suggestions.*

I wish to express my thanks to ***Dr. Haidy Farid Abd El-Hamid,*** *Assistant Professor of Anatomy, Faculty of Medicine, Ain Shams University, for her supervision, patience and encouragement.*

I would like to express my deepest thanks and gratitude to every member of my family, especially my husband who Did a lot for me, my professors and colleagues who stood beside me throughout this work, giving me their support, sympathy and guidance.

Finally, I would like to dedicate this work to the spirit of my father.

Introduction

Few survivable injuries are comparable with the devastating physical and psychological consequences of the paralysis that result from trauma to the spinal cord. Each year, over 10,000 North Americans, most below the age of thirty, sustain SCI **(Nobunaga et al., 1999).**

Thirty years ago, patients with such injury and their families were told "nothing can be done". Once the acute phase of SCI is over, the focus of care shifts to rehabilitation and development of strategies to cope with the residual function of the patient. However few options exist to improve a patient's neurological status, as cells in the CNS had a limited ability to regenerate and glial scar formation occurs. This produces a barrier to axonal growth. In addition, local myelin proteins, such as myelin associated glycoprotein, are released and inhibit axonal growth **(Campos et al., 2004).**

Therapies to enhance neurological function after SCI are urgently needed. This need has sparked great interest in the neuroscience community, and many exciting experimental strategies have emerged **(Stripling, 1990).**

Despite advances in medical and surgical care, current clinical therapies for SCI are limited. During the last two decades, the search for new therapies has been revolutionized by the discovery of stem cells, inspiring scientists and clinicians to search for stem cell-based reparative approaches for many disorders, including neurotrauma. Cell-based therapies using embryonic and adult stem cells in animal models of these disorders have provided positive outcome results **(Salewski et al., 2010).**

Aim of The Work

This essay aims at reviewing the possible sources of stem cells available for regeneration of the spinal cord in case of injury and the obstacles facing the regeneration process.

Stem cells

The stem cell is the origin of life. As stated first by the great pathologist Rudolph Virchow "All cells come from cells" .The ultimate stem cell, the fertilized ovum, is formed from fusion of the haploid progeny of germinal stem cells **(Sell, 2004).**

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. All stem cells regardless of their source, have general properties: they are capable of, dividing and renewing themselves for long periods, are unspecialized and give rise to specialized cell types such as those of the brain, heart, kidney and muscle **(National Institutes of Health, 2009)**.

Unlike muscle cells, blood cells, or nerve cells which do not normally replicate themselves, stem cells may replicate many times, or proliferate. One of the fundamental properties of a stem cell is that it does not have any tissue-specific structure that allows it to perform specialized functions. When unspecialized stem cells give rise to specialized cells, the process is called differentiation **(National Institutes of Health, 2009).**

In a broad sense, stem cells are a population of cells capable of indefinite self-renewal that give rise to "daughter" cells committed to specific differentiation lineages through asymmetrical cell division. Their ability to control proliferation, differentiation, and apoptosis distinguishes them from neoplastic cells **(Yu and Silva, 2008).**

To ensure self-renewal, stem cells undergo two types of cell division. Symmetric division gives rise to two identical daughter cells. Asymmetric division, on the other hand, produces only one stem cell and a progenitor cell with limited

self-renewal potential. Progenitors can go through several rounds of cell division before terminally differentiating into a mature cell **(Beckmann et al., 2007).**

The normal function of stem cells includes the maintenance of homeostasis mediated by providing trophic support, as well as serving as a reservoir for replacing dysfunctional and senescent cells throughout the lifetime of the organism **(Yu and Silva, 2008).**

Classification of stem cells according to their differentiation potential:

Stem cells could be classified into totipotent, pluripotent, multipotent, oligopotent and unipotent stem cells based on their differentiation potential **(Wagers and Weissman, 2004).**

Totipotent stem cells are found in early embryos (2 cell stage). Each cell could differentiate into embryonic and extraembryonic cell types. Such cells could form a complete organism (e.g., identical twins) **(Scholer, 2007).**

Pluripotent stem cells are the descendants of totipotent cells and can differentiate into nearly all cell types found in the body. Such cells exist in the differentiated inner cell mass of the blastocysts **(Passier and Mummery, 2003).**

Induced pluripotent stem cells (iPSCs) are a type of pluripotent stem cell artificially derived from a non-pluripotent cell, typically an adult somatic cell, by inducing a "forced" expression of certain genes. Mouse iPSCs were first reported by **Takahashi and Yamanaka (2006)**, and human iPSCs were first reported by **Takahashi et al. (2007) and Yu et al.(2007).** These are not adult stem cells, but rather reprogrammed cells (e.g. epithelial cells) given pluripotent capabilities. Using genetic reprogramming with protein transcription factors,