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Review Article

Stem Cells in PMR Practices

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Abstract

Stem cells are one of the most fascinating areas of biology today. But like many expanding fields of scientific inquiry, research on stem cells raises scientific questions as rapidly as it generates new discoveries. Stem cell therapy presents the potential promise to heal the defective systems in the body and the field is witnessing some path breaking research currently. The technology is provocative and promising, but the future is far from certain. Nevertheless, the science that is unfolding about neural and muscular development, autoimmune diseases especially Rheumatoid Arthritis is exciting in its potential implications. This article contains current information derived from internet searches on their use in some common conditions in Physical Medicine and Rehabilitation practices.

Keywords: Stem cell, Stem cell therapy, Spinal cord injury, Stroke, Myopathy, Rheumatoid arthritis

Introduction

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division (self renewal). The second is that under certain physiologic or experimental conditions, they can be induced to become cells with special functions (potency). Therefore, when a stem cell divides, each new cell has the potential to either remain a stem cell or become another type of cell with a more specialized function, such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas, a muscle cell, a red blood cell, or a brain cell etc.

Sources

Stem cells are derived from three main sources: embryo, adult and the umbilical cord.

Embryonic stem cells: These stem cells are derived from the epiblast tissue of the inner cell mass of the earliest stages of development of the embryo called blastocyst before it would implant on the uterine wall. These cells can self replicate and are pluripotent. Because of their combined abilities of unlimited expansion and pluripotency, embryonic stem cells remain a theoretically potential source for regenerative medicine and tissue replacement after injury or disease.

Adult stem cell: The term adult stem cell refers to any cell which is found in a developed organism that has two properties: the ability to divide and create another cell like itself and also divide and create a cell more differentiated than itself. Sources of adult stem cell have been found in bone marrow, blood stream, cornea and retina of the eyes, dentine, liver, skin, pancreas and gastro intestinal tract. In contrast to the embryonic stem cells, these are not capable of forming all the cells of the body, i.e. they are not pluripotent. Adult stem cells are dispersed throughout the body of a mature animal and behave very differently depending on the local milieu. Also, the adult stem cells share no common features and thus have no means of characterization; as opposed to these the embryonic stem cells can be defined by their origin, i.e. the inner cell mass of blastocyst. The origin of the adult stem cells remains a controversy till date.

Umbilical cord stem cells: These are cells harvested from the cord blood. Cord blood is rich in stem cells, and after appropriate human leukocyte antigen [HLA] matching, it may be used to treat a variety of conditions. Characteristics of these cells are identical to adult stem cells except that they are not derived from adults and that their concentration is far more in umbilical blood as compared to adults.

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The intermediate cell is called a precursor or progenitor cell. Precursor or progenitor cells in fetus or adults are partly differentiated cells and eventually divide and give rise to mature differentiated cells. These cells are often committed which means that they tend to differentiate only along a particular cellular development pathway; however, some recent studies have shown that this may not be as definitive as was once thought.

Neurological diseases

Until recently, the inability of the adult brain cells to regenerate after sustaining damage was an accepted scientific dogma. However, evidence has accumulated over the last decade that neurons and astrocytes can be generated from isolated cells of the adult mammalian central nervous system. On the basis of this phenomenon of adult CNS plasticity, or neurogenesis, stem cell-based therapies have been developed for various CNS diseases, including stroke, traumatic brain injury, spinal cord injury and neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease.

The reasons for these stem cells receiving such attention for the treatment of neurological disorders relates to their:

1. Capacity to proliferate in culture with the prospect that large numbers of cells can be derived from a limited source.

2. Potential to be harvested from patients themselves.

3. Ability to migrate and disseminate following implantation within the adult CNS.

4. Possible tropism for areas of pathology.

5. Ease of manipulation using viral and non-viral gene transfer methods.

6. Ability to better integrate into normal brain cytoarchitecture with the potential for physiologically regulated release of substances.[1]

It also seems likely stem cell implants stimulate endogenous host repair mechanisms or provide a degree of neuro protection which limits the effects of ongoing damage rather than replace lost neurons and repair the damaged neural architecture.

Spinal Cord Injury[2]

Injury to neural tissue results in a permanent deficit as neurons do not have the ability to repair or regenerate. Isolation and preparation of specific population of adult stem cells have evolved to the point of a stable, long term culturing with capacity to differentiate into neural phenotypes from all three neural lineages: neurons, astrocytes and oligodendrocytes. Major strategies in stem cell therapy in spinal cord injury are based upon activation of endogenous neural stem cells and exogenous stem cell transplantation[3]. In animal experiments, different varieties of adult stem cells viz olfactory ensheathing cells, cultured spinal cord stem cells, bone marrow derived stem cells and dermis-derived stem cells have been implanted in a rat model of spinal cord injury. And although no definite conclusions were reached on which of them is best for neural injuries, each of these showed ability to incorporate into spinal cord, differentiate and improve the locomotor capability[4]. The presence of neural stem cells (NSC) in the adult mammalian spinal cord suggests the latent capacity of regeneration of injured spinal cord if the NSC are activated properly. In this situation it is crucial to understand the underlying mechanisms of maintenance, activation and differentiation of neural stem cells and subsequent process, including the migration, survival and functional maturation of differentiated cells which may be possible by further studies[5,6]. Experiments involving the use of human umbilical cord blood, a rich source of non-embryonic stem cells, showed that cord blood derived stem cells migrate and participate in the healing of neurological defects caused by traumatic assault.

Human experiments involving persons with paraplegia are being conducted in many centres in the world. Ravinovich et al. [7] implanted human neural stem cells from the foetal brain and haematopoietic liver tissue into the injured human spinal cords 1 month to 6 years following injury. Contraction of some muscles and partial recovery of sensitivity was observed in 40% of the patients. Unpublished human adult stem cell therapies for spinal injury revealed that many of the centres are using olfactory bulb cells extracted from the spinal injury patient's upper nose. Also, certain reports that have originated from mainland China and Portugal has concurred with results of animals experiments in terms of improvement in neurological recovery following stem cell infusions. Where there is no cure for the local and distant damage sustained in spinal cord injury, current research in the field of stem cells, shows great promise.

Stroke

Several new therapies are under investigation to address the long-term disability of stroke survivors. Growth factors, amphetamines, cortical stimulation, and new approaches to physical therapy (e.g., constraint-induced therapy) offer the possibility of improving neurologic deficits months or years after the recovery process has reached a plateau. Stem cell therapy offers hope for stroke patients, especially for those who have missed the narrow 3- hour window for administration of tissue plasminogen activator. Borlongan CV and Hess DC[8] provided preclinical evidence that neuroteratocarcinoma (NT2N)

cells, a clonal cell line, considered to be neural progenitor cells, significantly attenuated motor and cognitive deficits when transplanted to adult rats 4 weeks after middle cerebral artery occlusion. It is possible that transplanted cells secrete trophic factors that help to maintain marginally surviving cells or otherwise enhance the local environment sufficiently to improve function. Transplantation might also conceivably produce a host reaction that could include sprouting of new axons and synapse formation.

It remains uncertain which type of cell would be most appropriate for transplantation into stroke patients. Various cell types (e.g., porcine foetal cells, embryonic stem cells, and immortalized neuronal cells and bone marrow stromal cells) are being investigated. Recent experimental studies raised the possibility of using mesenchymal stem cells (MSCs) as stroke therapy. There is increasing evidence that MSCs promote functional recovery in animal models of ischemic stroke. In specific culture conditions, human MSCs can differentiate into cells that express markers of neuronal progenitor cells and can engraft and migrate along paths that resemble those of neuronal progenitor cells. It is still controversial, however, whether spontaneous cell fusion or true differentiation was the primary cause for these unexpected cell outcomes. MSCs are eminently suitable for human trials because these cells can be obtained readily from bone marrow under local anesthesia, are easily expanded by culture, and potentially could be delivered to injured brain tissue without the need for invasive stereotaxic operations. Moreover, the use of patients' own bone marrow cells should circumvent the problems of host immunity and graftversus-host disease. Bang et al. [9] reported that in patients with cerebral infarcts, the intravenous infusion of autologous MSCs appears to be feasible and a safe therapy that may improve functional recovery.

Nan and associates[10] reported that intravascular infusion of cord stem cells provides neurological improvement in rats with brain haemorrhage. They suggested that cord blood cells may not need to penetrate into the midbrain since they also release growth factors such as brain-derived neurotrophic factor (BDNF), neurotrophin-3(NT3) and Nerve growth factor (NGF) that can stimulate the growth of endogenous stem cells in the brain.

Amplification of endogenous stem cells provides an alternative way of re-innervating the damaged brain and correcting neurological impairments. Among the many stem cells mobilization agents, granulocyte colony-stimulating factor (G-CSF) received much attention. G-CSF exerts an apoptotic effect on neurons possibly through its receptors and implicates neurogenesis by stimulating the progenitor cells as a mechanism underlying G-CSF's therapeutic recovery. Shyu and colleagues[11] explored the therapeutic potential of G-CSF therapy in ischemic stroke in a phase I study. The assessment of functional score at 12 months revealed significant improvement in fluorodeoxyglucose in the cortical areas surrounding the ischemic core in G-CSF patients compared with control patients over and above improvement in motor scale score. Since G-CSF may act primarily on neurons, it is likely that earlier the treatment, the more potent the neuroprotective effects. G-CSF may hold as an important therapeutic probability of stroke management in the future.

Cerebral Palsy

The similar logistics of stem cell therapy in ischemic stroke also applies for the management of Cerebral palsy. However study in this population is sparse.

Mueller et al. [12] examined whether human neural stem cells (hNSCs) replace lost cells in a newborn mouse model of brain damage. Mice received brain parenchymal or intraventricular injections of hNSCs derived from embryonic germ (EG) cells. The locations of hNSCs within the mouse brain were determined through DiD fluorescence and immunodetection of human-specific nestin and nuclear antigen. The stem cells migrated away from the injection site and were found at sites of injury within the striatum, hippocampus, thalamus and white matter tracts and at remote locations in the brain. Subsets of grafted cells expressed neuronal and glial cell markers. hNSCs restored partially the complement of striatal neurons in brain-damaged mice. They concluded that human EG cell-derived NSCs can engraft successfully into injured newborn brain, where they can survive and disseminate into the lesioned areas, differentiate into neuronal and glial cells and replace lost neurons. Another data available from the centre of immunotherapy who had subjected 125 severely brain injured patients with cerebral palsy to a stem cell transplantation therapy via a lumbar puncture (subarachnoidally) showed apparent neurological improvement in 85% of cell grafted cerebral palsy patients.

The Department of Neurology, All India Institute of Medical Sciences undertook the project on Intra-arterial infusion of autologous bone marrow stem cells in patients with static encephalopathy including cerebral palsy to test the hypothesis that intra-arterial infusion of autologous bone-marrow derived stem cells in patients with non-progressive (static) encephalopathy, with special reference to cerebral palsy, and hypoxic-ischemic encephalopathy is feasible, safe and improves neurological functional outcome[1]. The outcome is awaited.

Rheumatoid Arthritis[13]

Haemopoietic stem cell transplantation (HSCT) is a new

therapeutic measure for some severe auto immune diseases[14,15]. The rational of the therapy is to're-set' the immune system and induce tolerance. Support to this treatment modality has been provided by the coincidental observation, that in patients who had both an autoimmune disease and a haematological malignancy, treatment of the malignancy with bone marrow transplantation (BMT), also resulted in a 'cure' of the autoimmune disease. HSCT is different from the conventional BMT, in that the individual's own stem cells (autologous) are removed, his or her bone marrow is ablated and stem cells are then re-infused into the individual. Thus, autologous HSCT following haematoimmunoablation is more a support or rescue event, rather than BMT in the clinical sense. Recent developments in HSCT have brought a level of safety, which allows it to be considered as a therapeutic opinion for autoimmune diseases. The European Blood and Bone Marrow Transplantation (EBMT) approve autologous HSCT in patients with severe, active rheumatoid arthritis with no other significant end-organ disease. Autologous bone marrow stem cell transplantation requires a skilled team effort and is associated with an approximate mortality risk of about 6.5%. However, the benefit risk ratio of HSCT in autoimmune disease appears to justify the initiation of prospective controlled comparative studies. Other methods like autovaccination and chemo-stem cell therapy are also attempted in the treatment of rheumatoid arthritis.

Myopathy

Cell transplantation is believed to be an attractive technique among the various prospective methods of healing muscle wasting and other degenerative diseases. Cell-based therapies involve the delivery of normal cells to the dystrophic muscle, with the hope that the delivered cells will fuse or repopulate the dystrophic muscle, thereby improving muscle pathology and function. An initial study using grafting a normal muscle into a dystrophic recipient muscle bed approach showed nearly normal contractile properties in adult dystrophic hosts after implantation of a muscle graft, suggesting that muscle transplantation may indeed be a viable treatment[16]. However, some ethical issues make this form of treatment difficult to pursue particularly the required use of newborn muscle in order to overcome problems seen with adult tissues, including appropriate reinnervation and revascularization.

A second, more promising cell-based approach is myoblast transfer, a procedure that involves injecting or transplanting donor muscle precursor cells (myoblasts) into a dystrophic host. Injected myoblasts can indeed fuse into host *mdx* myofibers and can result in dystrophin expression at 30–40% of normal levels. Despite some promising results, myoblast transfer has many obstacles which include attaining sufficient distribution and fusion of donor cells with host muscle fibers, extending the donor myoblast survival period (since many cells die soon after transplantation), and eliminating the immune response to donor myoblasts or newly synthesized dystrophin protein[17]. In human clinical studies, even with multiple injection sites, the efficiency of myoblast transfer was very low and failed to improve muscle strength in the Duchene muscular dystrophy patient group[18,19, 20].

An alternative cell-based method to myoblast transfer is the systemic delivery of precursor cells with myogenic potential. These multipotential cells, referred to as side population (SP) cell (progenitor cell), can be derived from different tissues including bone marrow and muscle. SP cells demonstrate a clear plasticity to myogenic and hematopoietic lineages[21]. In initial studies, intravenous injection of isolated SP cells from marrow and muscle into *mdx* mice, led to the incorporation of donor nuclei within existing muscle fibers and to the expression of dystrophin[21]. Unfortunately, the frequency of incorporation of donor nuclei and the level of dystrophin expression were rather low and did not result in major therapeutic benefits. Although the idea of isolating multipotent progenitor cells that can give rise to myogenic progeny is quite appealing, a great deal of work is still required to further characterize these cells before clinical trials can be envisioned.

Recently, attention has turned to the adult mesenchymal stem cell[22]. A variety of protocols have been developed to isolate the rare cells that are capable of many cell divisions and of generating several alternative types of cells. One type of these stem cells, called the mesoangioblast because of its apparent derivation from endothelial cells, has generated particular interest, because it offers both a means of dispersing myogenic cells and a total yield of muscle sufficient for use in therapy. When injected intra-arterially, mesoangioblasts become lodged in capillary beds downstream in the muscle. From these diffuse sites, the cells invade and progressively repair fibres in large, disparate regions of muscle. This procedure provides hope for the broad distribution of myogenic cells, but the intra-arterial delivery must be repeated in order to treat a chronic disease such as muscular dystrophy[23].

Cord Blood Banking

Cord blood banking is considered by many as "biological insurance", as stem cells are being used to treat a variety of cancers and blood disorders and that research shows possible value against Alzheimer's disease, Parkinson's disease, and heart disease. Therefore, saving your baby's cord blood may one day possibly help your baby, siblings, or other family members should they ever need it. Though cord blood banking has some legitimate uses but appears

to be a poor investment except for people who (a) have a relative with a disease for which cord blood effectiveness has been demonstrated or (b) are wealthy enough to afford betting more than $3,000 per year on a long shot. In India, it is believed that the practice of cord blood banking exists in Mumbai and Chennai.

Challenges

Some issues remain at the forefront of the controversy involving stem cell research -legislation, ethical issues related with use of human embryos or stored cord blood, allotransplantation and xenotransplantation, enrolment of participants for stem cell study, astronomical cost, standardisation, insurance and unintended outcomes. The period between laboratory experimentation and clinical treatment can be decades long. Researchers directly treating patients with experimental therapies can be subject to the disciplinary bodies of their institutions, rather than outside entities. Also, the risks of forming unwanted tissues and teratocarcinomas by stem cells require further evaluation and long term follow ups.

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