Regenerative Medicine: From Basic Research to Clinical Application in Physical Medicine and Rehabilitation

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Abstract

The present paper aims to report the aspect of physical medicine and rehabilitation in regenerative medicine.

First, description the conceptual of rehabilitation. Secondly, briefly review the regenerative studies related with cases in the field of rehabilitation. Thirdly, suggestion for integrating regenerative therapy into rehabilitation strategies.

The function status associated with physical activity is a health indicator and is the domain of quality of life. The effectiveness of rehabilitation interventions to restore physical functioning can be enhanced by the use of regenerative therapies. To investigate the potential of cellular therapy for the successful improvement of functional status, a paradigm shift of rehabilitation treatment and research is required. The vertical integration of rehabilitation and regeneration since the onset of therapeutic intervention allows the goal to be faster and more effective. The translation of stem cell therapy to a positive clinical change depends on the micro or niche environment for life control of stem cells, proliferation and regeneration. Rehabilitation strategies such as exercise and neuromuscular electrical stimulation (NMES) is required to optimize stem cell transplantation.

Biosciences and human functioning research in rehabilitation as a core component of future rehabilitation strategies in regenerative therapies.

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A CONCEPTUAL DESCRIPTION OF REHABILITATION

Rehabilitation is the health strategy which, based on WHO's integrative model of functioning, disability and health (ICF) applies and integrates approaches with the goal to enable persons with health conditions experiencing or likely to experience disability to achieve and maintain optimal functioning.[1] The goal of Physical and Rehabilitation Medicine (PMR) to reduce impairment due to disease, degeneration process, injury and congenital diseases, prevent complications, improve function and activity so as to enable to social participate, contributing to minimization of the experience of disability in the population.[2] Rehabilitation program starts with the onset of an illness or injury as effectively and as early as possible, to reduce the potential for complications. Acute rehabilitation is important in order to utilize new concepts of plasticity and motor learning.[2] It is clear evidence that an intensive period of rehabilitation after an acute event produces clear, short-term functional gains even where full recovery does not occur. There is now considerable evidence that rehabilitation produces real benefits and improved functional performance and participation outcomes but there is also evidence that short-term gains are lost unless longer-term support is available.[2] The function status associated with physical activity is a health indicator and is the domain of quality of life. Functional evaluations can be used to assess many physical aspects and a variety of measures and tools available to carry out functional evaluations which involve different domains.[2,3,4] Human functioning is a major target of the rehabilitation program, but it takes a long period of time to contact with the persons with disabilities to provide rehabilitation so that the

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cost of rehabilitation services increases. The effectiveness of rehabilitation interventions to restore physical functioning can be enhanced by the use of cellular therapy or other regenerative therapies. To investigate the potential of cellular therapy for the successful improvement of functional status and clinical outcome of positive function status, a paradigm shift is required. Research area in rehabilitation ranging from cell (biosciences) to society (human functioning) based on the International Classification of Functioning, Disability and Health (ICF).[5,6] Evidenced-based medicine promotes the translation of research into practice. Research in rehabilitation largely neglect mechanotransductive principles guiding cellular and molecular behavior. Conversely, research in regenerative medicine have target modulation of molecular, cellular, and histological properties, so rehabilitation research now start and prepare specific, science-based protocols for patients.7 Rehabilitation technology is one of the most important and promising research fields today and in the future.

POTENTIAL IMPACT REGENERATIVE MEDICINE ON THE REHABILITATION PRACTICE

Rehabilitation strategies rarely have been utilized to maximize regenerative medicines therapeutic benefit. Regenerative medicines provide modern therapeutics mainly to enable tissue repairing, restoration of damaged or diseased cells or tissues.8 The goal of regenerative medicine is to restore tissue and organ function lost as a result of aging, injury, or disease.9 Regenerative medicine cover a broad spectrum including methods for promotion of self-healing, cell-based therapies, tissue engineering, and neo-organogenesis. Any disease, trauma, and degenerative conditions or condition (acquired or genetic) that results in damaged failing or malfunctioning tissue may be amenable to regenerative medicine technologies.7 However, after regeneration functional restoration of lost or damaged tissues and organs become possible. Given the rapid technological progress in regenerative medicine, future rehabilitation treatment paradigms may significantly shift. Rehabilitation clinicians now care for patients with previously unimaginable recovery from massive multitrauma orthopedic injuries and a number of patients with previously unimaginable survival achieves by organs or tissues regenerated with engineered contructs. For making tissue and organ transplantations successful few promising candidates such as immune-modulators, adhesions, integrins and new biological scaffold materials and bioactive molecules are essentially used to replace injured or missing tissues. It essentially needs a microenvironment or niche for induction of regeneration because microenvironment affects and influences the cell behavior during development.8 However, various bio-molecules such as inducers, transcription factors, healers and molecules are essentially required for regeneration of cells which also assist growing new organs in vitro mainly in cell culture. Stem cell and direct gene therapy have been explored in animal models and in a few clinical settings to generate damaged or diseased tissues in spinal cord (SCIs), brain injuries, myocardial infarction, bone, and joint diseases. Therefore regenerative medicine technologies have potential impact on the practice of rehabilitation.10 Mesenchymal stem cells (MSCs) respond to a variety of stimuli, including hormonal, chemical, and mechanical factors to differentiate into a variety of specialized cell types including bone, tendon, muscle, and cartilage but they do not have the plasticity of embryonal stem cells.8,10,11 After trauma, soluble factors within the perivascular space cause the release of pericytes from microvessels. Pericytes have been described as “medicinal signaling cells” once released, where they can be activated into mesenchymal stem cells, exhibiting their homing, trophic and immunomodulatory roles.12 One major advantage of using human MSCs for in vivo therapy is that they are nonimmunogenic, make them an attractive candidate for clinical applications.8,13 Adult stem cells are of interest, have been the subject of the most investigations in musculoskeletal research. Relationship between symptomatic or functional changes and cell therapy is still a question and ongoing clinical trials, and explore the challenges to making this a realistic treatment option for the future.

Spinal cord injury

Spinal cord injury (SCI) results in severe neurological damage, results in paralysis, which severely affects quality of life. The physiopathology of spinal cord trauma is determined by 2 basic conditions: the trauma

itself, involving either cellular death or electrolyte, metabolite, and enzyme release, and the cascade of acute inflammation with swelling, ischemia, and reperfusion as a secondary neuronal injury.[14] Recovery from SCI is difficult because the injured spinal cord loses its ability to regenerate lost or damaged cells and re-establish functional neural connections.[15] Because there is no effective medical therapy available, several studies have been carried out in animal models, which have included rehabilitation, pharmacological treatment, and cell therapy.[10] Cell transplantation has become the most promising treatment for neurodegenerative diseases or central nervous system injuries such as spinal cord trauma. Adult stem cells can be used as an ideal alternative of Schwann cells (SCs) that are transplantable cells in bio artificial nerve grafts. Adipose tissue has proven one of the most primary ASCs (Adipose Schwann cells) that can be used in nerve repairing. It focuses on replacing the lost or damaged cells with progenitor or stem cells, leading to further axonal growth, remyelination of axons, and reduction of neuronal degeneration. The question of how rehabilitation treatment might benefit SCI patients receiving stem cell transplantation will be an important area for future investigation. In animal model, bone marrow stromal cells and bone marrow mononuclear cells (BMMNCs) have been found to replace white and gray matter, with neuronal and axonal regeneration, proliferation, myelination, and neovascularization of astrocytes, leading to further functional improvements.[16]

Stroke

Stroke is a leading cause of death and disability worldwide. Thrombolysis with tissue plasminogen activator is now a well-established treatment for acute ischemic stroke and is associated with significant improvements in outcomes. However, its use is limited to a narrow time window of only 4.5 hours from symptom onset. Stem cell therapy is an emerging therapeutic modality with evidence of significant benefits in preclinical stroke models. Preclinical studies have shown benefits of stem cell therapy in both acute and chronic models of stroke.[17] Translation to the bedside, however, remains distant, and there are many questions that remain unanswered. Targets for stem cell therapy include neuroprotective approaches aimed at protecting at-risk tissue during the acute phase of stroke, as well as neuroreparative approaches which may involve direct replacement of damaged brain tissue, or alternatively promotion of the brain's endogenous repair processes. Neural stem cells (NSCs) have the capacity to differentiate into neurons, astrocytes, and oligodendrocytes. There are a number of proposed mechanisms that have been investigated in preclinical stroke models such as : Formation of new neuronal circuitry, reduced apoptosis, reduced inflammation, promotion of angiogenesis, promotion of neurogenesis, promotion of other endogenous repair processes or amplified endogenous plasticity responses.[17] One study demonstrated that adult NSCs derived from the subventricular zone of young adult rats could survive and migrate towards the lesion in rats with an ischemic stroke following intracisternal administration. Electron microscopy examination also suggested that the transplanted cells showed signs of neuronal differentiation.[7] In one study, CD34+ cell transplantation delivered intravenously resulted in increased perilesional angiogenesis and subsequent neurogenesis in mice at 48 hours poststroke.[18] A further animal study investigating direct intracerebral implantation of CD34+ cells 1 week after induced stroke was also able to show evidence of neurogenesis and angiogenesis, with differentiation of transplanted cells into cells expressing markers for neurons, glial cells, and vascular endothelial cells.[19] Two trials utilising BMMNCs have been reported in chronic stroke patients. There were no treatment-related adverse events up to 6 months follow-up. All patients showed improvements in their National Institutes of Health Stroke Scale scores by 6 months.[20] Ischemic stroke is known to increase levels of CD34+ cells (mobilized from the bone marrow) in the peripheral blood. There is evidence that increased CD34+ mobilisation into the peripheral blood in patients with acute ischemic stroke correlates with neurological recovery, with higher counts associated with better recovery.[21]

Ligamen, cartilage and bone

The titers of MSCs at various tissue locations naturally decrease with age, may affect the musculoskeletal system and may become a target of therapies in the future. This decrease is primarily due to decreases in vascular density, which is not only the source of local MSCs but also the cause of poor wound repair in older

adults.[11] Through paracrine activity, mesenchymal stem cells exhibit a secretory or "trophic" function, with anti-inflammatory, immunomodulatory, pro-angiogenic, anti-apoptotic, anti-fibrotic, and wound-healing properties that have proliferative effects. The "trophic" effects of MSCs establish a regenerative microenvironment at the site of injury by (1) inhibiting ischemia-related apoptosis, (2) inhibiting scar formation, (3) stimulating angiogenesis by secreting large amounts of Vascular Endothelial Growth Factor (VEGF) and by transforming some of the MSCs back into pericytes that function to stabilize the fragile, newly forming capillaries, and (4) secreting tissue progenitor-specific mitogens so that the slow process of tissue regeneration is enhanced . Thus MSCs serve as "drug stores" for sites of injury.[22] Cytokines and mechanical environments play a role in stimulating MSCs into bone, tendon, and cartilage precursors.[11] The poorly vascularised ligaments and tendons have a limited capacity for healing and, even if healing has occurred, the biomechanical properties of the healed structures are usually inferior to normal tissue.[22] In the case of the anterior cruciate ligament (ACL), however, the thin synovial sheath of ACL is disrupted, and blood dissipates in the synovial fluid, making the formation of a localized hematoma difficult. With such a lack of supply of cytokines and growth factors and a low supply of reparative cells at the injury site, the ability for a torn ACL to heal becomes limited. In addition, its torn ends retract significantly because of the high residual strain existed in the intact ACL, making the bridging of the gap even more difficult.[23] Biologically, it is also found that the properties of ACL fibroblasts are different from those derived from other ligaments and exhibit higher matrix metalloproteinases (MMPs) activities and poor adhesive strength.[24,25] The ACL of knee has limited capability to heal, and the results of nonsurgical management of its midsubstance rupture have been poor.[26] For ligaments, it is particularly important to consider development of novel functional tissue engineering (FTE) approaches including the use of growth factors, gene transfer/gene therapy, cell therapy, and extracellular matrix bioscaffolds.[27,28] The use of MSCs has further benefits such as osteointegration at the tendon-bone interfaces. In one study, partial ACL tears were treated in 2 separate rat models by injecting MSCs into the joints after surgical lesions were created. Both studies demonstrated nearly normal strength and ligament healing compared with control subjects.[29] In an RCT of 50 patients in 2 equal groups undergoing hamstring ACL reconstruction, the intervention group received thrombin-activated platelet rich plasma (PRP)-soaked grafts and demonstrated improved anterior-posterior instrumented knee stability via a KT 2000 arthrometer at 6 months.[30]

Adult articular cartilage exhibits little capacity for intrinsic repair, and thus even minor injuries may lead to progressive damage and osteoarthritic joint degeneration, resulting in significant pain and disability, characterised by progressive degenerative changes in the articular cartilage, subchondral bone, menisci, synovium and most other joint tissues. Magnetic Resonance Imaging (MRI) and arthroscopy studies show a high incidence of cartilage lesions are present in asymptomatic joints.[31] The great majority of approaches for cell-based or tissue-engineered repair of articular cartilage defects have focused on the treatment of focal chondral defects.[32.] Adipose-derived MSCs also have potential application in cartilage regeneration and have been shown to have superior proliferative potential compared with other types of MSCs.[12,22] Within a rabbit model, adipose derived MSC applied in a fibrin glue scaffold illustrated excellent rates of subchondral bone healing.[33] Saw and his coworkers (2013) reported in an RCT, the intervention group underwent postoperative injections of PBSCs and hyaluronan, whereas the control group underwent injections of hyaluronan alone. Clinical outcome scores at 24 months did not illustrate a statistical difference. Cell-based strategies for fracture repair in cases of nonunion are currently receiving considerable attention. Autologous bone marrow–derived MSCs were expanded in culture, loaded onto ceramic cylinders, and implanted into 8-mm segmental defects in rat femoral with successful bone formation 8 weeks later.[11,34,35] More recent investigation has demonstrated possible synergism of combined MSC and endothelial progenitor cells (EPC) therapy for the repair and regeneration of bone, with the combined application of the two cell types demonstrating improved efficacy over the delivery of either cell type alone.

Wound Healing

Burn patients are the most common patient population with extensive skin loss. These wounds are stopped in the inflammatory phase due to an imbalance between the production of growth factors, which stimulate the cell proliferation, and proteases, generally produced by fibroblasts, that stimulate migration to the wound site. The causes of this imbalance vary and are associated with the excessive presence of pro-inflammatory cytokines, decreased growth factors, abnormal deposition of collagen and other proteins of the extracellular matrix, alteration of cell proliferation and protein synthesis, and also an increased apoptosis. Stem cells regulate these processes in adult tissues because they have high self-renewal capacity, the ability to produce undifferentiated progenies throughout the whole lifetime of the individual, and the ability to differentiate into different functional cell types.[36]

Myocardial Infarction

Study in animal model of myocardial infarction (MI) have demonstrated migration of MSCs to the injured heart with subsequent improvement in left ventricular function.[37] A clinical study of post-MI patients showed that intracoronary injection of radiolabeled autologous bone marrow cells resulted in only 1.3% to 2.6% engrafment.[38] Migration and subsequent engraftment of MSCs in the heart is mediated by homing/chemokine factors, monocyte chemotactic protein-3 (MCP-3) and stromal cell derived factor-1 (SDF-1).[10]

Muscular Dystrophy

Duchenne muscular dystrophy (DMD) arises due to either spontaneous mutations or inherited nonsense point mutations in the dystrophin gene. Dystrophin, an important cytoskeletal protein, and a major component of the dystrophin–glycoprotein complex (DGC), is responsible for the maintenance of cell integrity, mediation of cytoplasmic signaling and muscle cell function. Patients afflicted with DMD rapidly exhaust their satellite cell reserves due to continuous cycles of muscle injury and regeneration, and as such lose their ability to regenerate, resulting in compromised muscle function and degeneration.[37,39] Muscle satellite cells cannot replace the cells with the malfunctioning dystrophin protein. Currently stem cell therapy to treat muscular dystrophia is being heavily researched. Price *et al.* saw there were positive results of restoring dystrophin function three weeks after injection, a promising start to a possible long term treatment.[40,41]

INTEGRATING REGENERATIVE THERAPY INTO REHABILITATION STRATEGIES

While regenerative medicine approaches have been widely investigated for use in populations commonly seen by rehabilitation professionals, rarely have rehabilitation strategies been utilized to maximize regenerative medicines therapeutic benefit. Maximal functional benefits in the treatment of skeletal muscle injuries may be best achieved when regenerative medicine and rehabilitation approaches are simultaneously applied.[9] Mechanical stimulation is a promising method for communicating with cells following transplantation and may enhance the regenerative potential of donor and host cells. The mechanical stimulation in a fracture environment also stimulates the migration and differentiation of MSCs at a fracture site and is now known to be an integral part of fracture healing.[11] Ambrosio (2009) reported that a combination therapy comprised of stem cell transplantation and neuromuscular electrical stimulation significantly increases the force-generating capacity of injured skeletal muscle when compared with the administration of electrical stimulation alone. In preliminary murine finding have demonstrated that the application of targeted muscle contraction protocols enhances molecular, cellular, and tissue functioning.[9]

Regarding table 1. electrical stimulation (ES) may be a selective non-drug approach for mobilizing NSCs in the central nervous system.[42] Xiang and his coworkers reported that Functional Electrical Stimulation (FES) increases the number of NPCs in the known neurogenic niches in acute stroke rats.[43] One study in aged mice, running significantly increases neural stem cell (NSC).[44] A retrospective analysis of a clinical study in which a nonrandomized sample of 110 patients with thoracolumbar SCI underwent autologous bone marrow-derived mononuclear cell (BMMNC) transplantation intrathecally and subsequent neurorehabilitation, with a mean follow-up of 2 years ± 1 month. There were statistically significant beneficial effects, both symptomatic and functional, from intrathecal autologous BMMNC and rehabilitation. This was a safe and viable therapeutic option with no long-

term side effects at 2 years.15 One study was to evaluate the functional effects of autologous bone marrow stem cell (CD45_/CD34_) transplantation in acute spinal cord injury in exercise training and in sedentary Wistar rats.

Author	Subjects Characteristics	Stem Cell Therapy	Rehabilitation intervention	Dependent Variable	Results
Inoue et al. (2016)	25-week-old SAMP10 mice		running on the treadmill	Plasma adiponectin & the numbers of BM-derived circulating CD34+/integrin-α, MuSCs	Increased levels of plasma adiponectin & the numbers of BM-derived circulating CD34+/integrin-α, MuSCs
rycz et al (2016)	4-week-old C57BL mice human healthy volunteer 20-28 year old		mice:endurance exercise on treadmill 3d/wk for 5wk exercise on rotating wheels 45- min for days human: running at a distance of 9-10km/day,speed 0,2km/min,6x/wk,for 5wk	VSEL HSPCs	Both mice and human, exercise mobilizes VSEL and HSPCs into PB
Xiang et al. (2014)	rat model of stroke		FES,paralyzed right forelimbs	NPCs	Increases the number of NPCs
Sharma et al (2013)	human:TH-L SCI	aulogous BMMNC	neurorehabilitation :exercise protocol, occupational therapy, psychological therapy	ASIA scale FIM ADL ambulation bladder management spasticity sensory	91% showed symptomatic, investigational, and functional improvement
Blackmore et al. (2009)	old mice (≥18 month)		21 days running	NSC	Significantly increased NSC
Carvalho et al. (2008)	adult male Wistar rats	BM stem cells CD45+, CD34-	60-min swimming session 6x/week, 6 week	BBB locomotor rating scale	The combination group resulted in significant improvement locomotor rating scale
Laufts et al. (2004)	C57/B16, 129/SV, eNOS -/- male mice patients with stable CAD		mice: running wheel human: bicycle ergometer training 15 to 20 min, 60-80% VO2peak-	EPCs histology from blood vessel :angiogenesis, neointima formation	Both mice and human, exercise increase in circulating EPCs Mice: reduced neointima formation, enhanced neoangiogenesis

Table 1. Studies evaluating rehabilitation intervention with and without stem cell therapy.

The combination of bone marrow stem cell therapy (CD45_/CD34_) and exercise training resulted in significant functional improvement in acute spinal cord injury. This observation may be explained by release of factors from exercising muscles that stimulate neuronal outgrowth such as neurotrophin. Nevertheless, the mononuclear fraction of bone marrow stem cells also had progenitors of anti-inflammatory cells since anti-apoptotic molecules are produced by mesenchymal stem cells (MSC).[14]

Physical exercises provokes a number of stimuli: mechanical, metabolic and hypoxic results in induction of molecular adaptations that improve physical performance, fitness and/or health. It also induces the release of various growth factors, cytokines and hormones. A number of studies have shown that exercise improves the function and regeneration of the cardiovascular system and skeletal muscle by activating and mobilization organ-resident stem cells or by recruiting bloodcirculating stem or progenitor cells. Beside improves the function of the vascular and skeletal muscle, physical exercise has been associated with a number of beneficial effects such as enhanced memory and learning, improved executive function, the prevention and treatment of depression, and a reduction in the risk of developing neurodegenerative disorders such as Alzheimer's disease. The rodent studies have demonstrating that voluntary running in both young and aged mice increases hippocampal neurogenesis, resulting in improved performance in water and radial arm mazes, and in object recognition. However, growth hormone receptor signaling regulates that exercise-induced stimulation of endogenous NSCs.[44]

A numbers of clinical and experimental studies showed that exercise training also helped prevent muscle wasting in aged humans and animals. Study in a senescence-accelerated mouse prone 10 (SAMP10) model suggest that ET can improve aging-related impairments of BM-derived MuSC (muscle stem cell) regenerative capacity and muscle metabolic alterations via an AMPK-dependent mechanism that is mediated by an adiponectin/AdipoR1 axis.[43]

Evidence has also accumulated that hematopoietic stem/progenitor cells (HSPCs) and endothelial progenitor cells (EPCs) expand in bone marrow (BM) in response to endurance exercise and are subsequently mobilized into peripheral blood (PB).[46,47] Stem cells mobilized during strenuous exercise act as "circulating paramedics," with a role in repairing microscopic damage in skeletal muscles as well as in other tissues. Marycz and his coworkers (2016) performed an endurance exercise experiment in which mice were subjected to forced running on a treadmill for 5 days or 5 weeks, that not only are very small embryonic like stem cells (VSELs) released from BM into PB in response to physical exercise but there is also a positive effect of exercise on the expansion of this primitive pool of stem cells in BM. Several factors triggered by exercise, such as insulin-like growth factor 1, VEGF, platelet-derived growth factor, hepatocyte growth factor, and hormones such as androgens, mediate this effect. Other non-peptide-based regulators of cell growth, such as bioactive phosphosphingolipids and alarmines released from hypoxic tissues, may play an important role as well.[48] In vitro research proved that not only

does an enabling environment improve releasing and increasing cells proliferation but both mechanical and physical stress, are associated with mechanisms controlling cellular functions. These findings provide evidence that endurance training may play modulating role in regulation of cellular functions and VSELs releasing.[47,49,50]

In animal study, Carvalho and his coworkers reported that the combination of BM stem cell therapy (CD45+ /CD34-) and exercise training resulted significant functional improvement in acute spinal cord injury.[14] "Stem Cell patients Ongoing Recovery through Exercise" (SCORE) is a RCT of pediatric cancer patients undergoing autologous hematopoietic stem cell transplantation (SCT). The first phase of the exercise program will be an inpatient intervention, beginning when the child is hospitalized undergoing conditioning therapy and continuing until discharge. Assessments include measures of QOL, fatigue, health related fitness (HRF), physical activity levels and hematological and immunological reconstitution. This study expect to find improvements in immunological recovery and quality of life, and decreased acquisition of sedentary behavior and fitness deconditioning.[51]

Conclusions

Rehabilitation strategies integrates regenerative technologies will developing innovative and effective methods that promote the restoration of function and quality of life. The successful integration of this regeneration medicine approach into clinical practice is dependent on a better understanding of physiological process of regeneration and how rehabilitation strategies may be able to optimize those responses in a patient-specific manner. Rehabilitation strategies play a critical role in facilitating tissue function not only after regeneration has occurred but also during the regenerative process. Combining research of rehabilitation medicine and regenerative medicine opens up unique and forward-looking opportunities to expand the scientific basis of rehabilitation medicine. Biosciences and human functioning research in rehabilitation as a core component of future rehabilitation strategies in regenerative therapies.

Declaration of Interest

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