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2018 Yearbook of Neurorestoratology

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REVIEW ARTICLE

2018 Yearbook of Neurorestoratology

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ABSTRACT

The Neurorestoratology discipline is getting worldwide attention from the clinicians, basic scientists, students and policy makers alike. Accordingly, this year too, the discipline has made profound advances and great achievements for the benefit of the mankind. In this report, of the 2018 Neurorestoratology Yearbook, salient features of new developments are summarized. This Yearbook consists 3 key themes namely (i) the new findings on pathogenesis of neurological diseases or degeneration; (ii) the new mechanisms of neurorestorative aspects; and (iii) the achievements and progresses made in the clinical field of neurorestorative therapies. The new trend has emerged in clinical studies that are based on greater levels of evidence-based medical practices both in clinical therapies and clinical trials based on standard designs.

1 Introduction

Little drops of water, little grains of sand, make the mighty ocean and the pleasant land. —Julia Carney.

The Neurorestoratology is one of the frontiers of neuroscience and neuro-medicine disciplines. To make readers aware and to follow the developments in the field every year, we have initiated publishing the Yearbooks recently that is acclaimed among the neurorestorative communities worldwide. Accordingly, the 2018 Neurorestorative Yearbook summarizes the major progresses and achievements of the year focusing on pathogenesis of neurological diseases, mechanisms of neurorestorative function, and clinical therapies based on neurorestorative principals.

2 New findings on pathogenesis of the diseases or degeneration in the nervous system

Several studies support the cholinergic system failure hypothesis in the development of Alzheimer's disease (AD) pathogenesis because cholinergic therapy either slowed down or partially restored brain atrophy [1]. In addition, the tau pathology strongly connected with the pathologic processes of AD. The tau deposition could damage the intrinsic neuronal network

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connectivity and spread further within the brain to damage synaptic connection. With the increasing tau burden in AD, the functional impairment and weakening of the neuronal connectivity occurs in a progressive manner leading to loss of function and development of the disease [2]. Musi et al. found a strong association between the presence of neurofibrillary tangle (NFTs) and cellular senescence in the brain causing neurodegeneration [3]. This pathological process may be implicated for a new neurorestorative therapy for suitable AD treatment. The study by Wei et al. demonstrated that exacerbating oxidation of the voltage-gated K^+ channel subfamily B member 1(KCNB1) channels might be another key factor in the pathogenesis of AD [4]. Gatt and coworkers reported that patients with dementia associated with Lewy bodies (DLB) in AD and/or in Parkinson disease dementia (PDD) exhibited 2-fold increase in cortin-positive cells in the subgranular zone as compared to non-demented controls subjects. They also found that treatment with selective serotonin reuptake inhibitors was associated with increased hippocampal neurogenesis and preservation of cognition in DLB/PDD patients [5].

Hu et al. showed that the T-lymphocyte levels in the peripheral blood were lower in Parkinson's disease (PD) than in healthy subjects. Treatment with L-DOPA in PD patients resulted in higher levels of T-lymphocytes in the peripheral blood as compared to placebo. This is well known that the immune function of T cells in patients with other severe neurological disease are also lower in plasma [6].

Through integrating genomic fine mapping with brain expression and chromosomal conformation data, Pardiñas and colleagues identified the genes within 33 loci was responsible for the pathogenesis of schizophrenia [7].

Shi et al. showed that reducing chromosome 9 open reading frame 72 (C9ORF72) expression by repeating its expansion could trigger motor neurons' degeneration in patients with amyotrophic lateral sclerosis (ALS) through accumulation of glutamate receptors that lead to excitotoxicity and/or impaired clearance of neurotoxic dipeptide repeat proteins derived from the repeat expansion [8].

There are discrepancies in discoveries about neurogenesis in human. Sorrells et al. reported that neurogenesis in the dentate gyrus does not continue, or is extremely rare, in adult humans. The number of proliferating progenitors and young neurons in the dentate gyrus declines sharply during the first year of life until 13 years of age [9]. One report by Boldrini et al. demonstrates that similar numbers of intermediate neural progenitors and neurons are present in the dentate gyrus across the ages. On the other hand, healthy older subjects without cognitive impairment or neuropsychiatric disease keep neurogenesis and sustained human-specific cognitive function throughout the life [10]. These discrepancies in results suggest that pathogenesis of neurodegenerative and psychological diseases might be of different origin.

3 New mechanisms of neurorestorative therapy

Intranasal mesenchymal stromal cell (MSC) treatment significantly improved sensorimotor and mechanosensory function after 21 days of subarachnoid hemorrhage (SAH) associated with a sharp decline in SAH-induced activation of astrocytes and microglia/macrophages in the affected hemisphere. This suggests that SAH induced activation of microglia and microphages could be reduced by treatment of stem cells and indicates one of the functional neurorestorative mechanisms [11].

Kunath et al. showed that the focal nature of PARKIN-mediated neurodegeneration and lack of active synucleinopathy in most young-onset cases could make patients to be the ideal candidates for dopaminergic cell replacement therapy. This is in the line of a new neurorestorative mechanism using genetically engineered grafts that are resistant to synucleinopathy. It appears that this will improve the outcome of cell replacement therapies for sporadic PD cases [12].

Data of da Silva et al. showed that manipulations of dopamine neuronal activity of the substantia nigra pars compacta after initiation of motor activity did not affect the ongoing motor functions [13]. Liu et al. revealed that fast release of dopamine could provide molecular machinery for functional regulations. These findings will definitely advance the therapeutic strategies for the patients of PD in future [14].

A study by Konermann et al. demonstrated that

CasRx as a programmable RNA-binding module for efficient targeting of cellular RNA in a neuronal model of frontotemporal dementia. This enabled a general platform for transcriptome engineering, which could be a new neurorestorative mechanism for exploration of future therapeutic strategy [15].

Pignatelli et al. reported that unknown transient enhancement of context recognition was based on the plasticity of engram cell excitability. This is a recall of contextual memory that is influenced by previous but recent activation of the same engram. The state of excitability of engram cells mediates differential behavioral outcomes upon memory retrieval. This suggests that promoting adaptive behavior may be important for survival [16].

Bussian et al. found cleaning up senescent astrocytes and microglia could prevent gliosis, hyperphosphorylation of both soluble and insoluble tau, and degeneration of cortical and hippocampal neurons. This could be the basis of preserving cognitive function [17].

Data by Bedrosian et al. elucidates that increasing the amount of maternal care can block the accumulation of long interspersed nuclear element-1 (L1). This early life experience drives somatic variation in the genome via L1 retrotransposons. This discovery implicates to treat certain disease of the children such as Autism through mothers' more love and care [18].

4 New achievements and progresses in clinical neurorestorative therapies

4.1 Cell therapy

Levi et al. conducted a multi-center single blind, randomized clinical study of human neural stem cell transplantation into the cervical spinal cord in patients with chronic C5-7 tetraplegia. They found that after 1-year post-transplantation, the procedures of cell therapy were safe, well tolerable, and feasible and resulted in a trend towards motor sensibility gains in the treated subjects [19]. Further research by Guadalajara et al. showed that a 58-year-old man with an incomplete spinal cord injury (SCI) secondary to L1 vertebral fracture, presented gait disorder with neurogenic bowel and bladder dysfunction. He received autologous mesenchymal stromal cells in the subarachnoid space by lumbar puncture. This patient had significant improvement in almost every functional scale of SCI [20]. Vaquero et al. reported a phase 2 clinical trial in patients with chronic SCI that received three intrathecal administrations of MSCs. In this study, patients showed varied clinical improvement in sensitivity, motor power, spasms, spasticity, neuropathic pain, sexual function and/or sphincter dysfunction during the follow-up [21]. This treatment was also well tolerated without any adverse event-related to MSC administration. Vaquero et al. further presented a phase 2 clinical trials that has six paraplegic patients with post-traumatic syringomyelia that received MSCs inside the syrinx [22]. These patients achieved reduction of syrinx and clinical improvements in motor function, sensation, neurogenic urodynamic and bowel dysfunction and spasticity with a follow-up for 6 months in different degrees of improvements. Vaquero et al. reported that intrathecal administration of autologous MSCs could improve progressively or relieve neuropathic pain intensity in SCI patients during 10 months' follow-up [23]. Data by Santamaría et al. showed results in a female subject with complete C2 SCI who received bone marrow derived MSC through intrathecal infusions. After 14 months' post-injury, she exhibited deep inspiratory maneuvers triggered respiratory-like EMG bursting in the biceps and several other muscles [24]. Gustavo et al. reported that the combination of immune and regenerative cell therapy could restore chronic muscular atrophy in clinical and histological examination in patients with severe muscular atrophy because of chronic complete SCI [25]. Al Kandari et al. followed up nine patients with chronic SCI that underwent cell transplantation therapies from China, Egypt, Germany, India, and Iran; but didn't find clinical useful improvements in sensorimotor, autonomic, or functional status in individuals after cell therapy [26].

Liem et al. reported that bone marrow-derived mononuclear cells transplantation could improve bowel function in 2 children with spina bifida after myelomeningocele repair [27].

Sung et al. examined the effects of transfusion of circulatory-derived autologous CD34+ cells into the intra-carotid artery of the ipsilateral brain infarct area in old ischemic stroke patients. Their results showed that procedure of CD34+ cell therapy was safe and

might offer some benefits to old ischemic stroke patients [28]. A study by Savitz and coworkers revealed that delivering autologous bone marrow derived ALD-401 through internal carotid artery infusion for patients with disabling middle cerebral artery subacute stroke was safe, but didn't show significant functional improvement compared to sham-harvest with sham-infusion [29]. Laskowitz et al. conducted a phase I open-label trial, which showed that a single i.v. dose of allogeneic non-HLA matched human umbilical cord blood cells was safe and improved some of the neurological functions in 10 patients with acute middle cerebral artery ischemic stroke [30].

van Horne et al. reported that peripheral nerve graft within the substantia nigra at the time of deep brain stimulation (DBS) surgery was feasible, safe and had some clinical benefits for patients in PD [31].

Nguyen et al. reported that the autologous bone marrow mononuclear cells improved quality of life in 30 children with cerebral palsy (CP) after 6 months of transplantation through intrathecal infusions [32]. This was accompanied with improvements in gross motor function and muscle tone. Elena et al. showed that cell therapy based on M2 macrophages was safe and significantly improved neurologic functions in patients with severe CP [33].

da Cruz et al. successfully delivered the retinal pigment epithelium patch for two patients with age-related macular degeneration. The epithelium patch survived well and associated with patients' visual acuity improvement during 12 months' follow-up study [34].

Mao et al. showed their clinical study of a multicenter, randomized, double-blinded, placebo-controlled trial of olfactory ensheathing cells and Schwann cells to test two kinds of neurorestorative effect for patients with sub-acute and chronic ischemic stroke [35]. Phan et al. report their design of phase 1 trial of human amniotic epithelial cells (hAECs) for ischemic stroke that assesses the safety of allogeneic hAECs [36]. Deng et al. publish their design of a prospective, randomized, controlled, observer-blinded phase II trial to assess the clinical safety and feasibility of allogenic bone marrow-derived MSCs by intrathecal infusion in patients with ischemic stroke due to cerebral infarction within the middle cerebral artery [37]. Osanai et al. report the design, which is a randomized, double-blind, placebo-controlled, multicenter for MultiStem®-one kind of allogenic cell products cell products in patients with acute (within 18–36 h of stroke onset) ischemic stroke. Its aim is to obtain stronger evidence and to show the efficacy of MultiStem® for treatment of ischemic stroke [38].

Garitaonandia et al. report that International Stem Cell Corporation's (ISCO's) will conduct a single-center, open label, dose escalating 12-month study with a 5-year follow-up evaluating the safety and efficacy of a novel human parthenogenetic derived neural stem cell in PD patient [39].

Loring reports that an autologous cell therapy is entering the regulatory approval process in 2018 with the U.S. Food and Drug Administration, and will begin to transplant the cells within 1 to 2 years [40].

4.2 Neurostimulation/neuromodulation and the brain-computer interface (BCI)

Cichoń et al. reported extremely low-frequency electromagnetic field therapy could improve the effectiveness of rehabilitation for post-stroke patients through significantly increased growth factors, cytokine levels and gene expression on the mRNA level. This could be another new mechanism of functional neurorestoration [41].

Implanted electrodes for electrical stimulation with intensive neurorehabilitation could partially restored standing and walking abilities in patients with complete chronic SCI [42,43]. In such cases, improved reflexive voiding efficiency [44], enhanced cardiovascular fitness and body composition [45], better neurological recovery [46] that supported the activities of daily living [47], and reduced that elevated blood pressures to normal ranges from a chronic hypotensive state [48] were observed.

Poiani and colleagues report that a design of a randomized double-blinded trial of photobiomodulation using low-level laser therapy (LLLT) could be an effective low-cost treatment for patients with traumatic brain injury (TBI). The results were evaluated to see whether LLLT could improve or restore cognitive sequel after TBI [49]. Santos et al. published a design of a double-blinded, randomized, controlled trial of patients with diffuse axonal injury due to a severe TBI in an acute stage. They evaluated whether early and delayed effects of transcranial light-emitting diodes

therapy could improve or restore the cognitive function and promote beneficial hemodynamic changes in cerebral circulation [50].

da Silva et al. presented a design of a randomized, controlled, double-blind, clinical trial for photobiomodulation in the sublingual region for multiple sclerosis (MS). The neurorestorative mechanisms for photobiomodulation may include neurogenesis, reducing nitric oxide levels, and regulating the cytokine IL10 and thereby inducing neuroprotection [51].

4.3 Neurorestorative surgery

Falci et al. performed dorsal root entry zone lesion of the spinal cord caudal to the level of complete spinal cord transection could completely or near-completely relieve all below-level neuropathic pain in 3 patients but failed to relieve their SCI induced central pain [52].

Intramedullary decompression under microscope and decompression laminectomy with duroplasty can benefit for patients with acute complete SCI in improving their neurological functions. But these procedures need to be confirmed by clinical trial of a multicenter, randomized, double blind placebo-control of intramedullary decompression. The design of a clinical trial of intramedullary decompression will explore the safety and neurorestorative effects in patients with acute complete spinal cord contusion injury [53].

4.4 Pharmaceutical neurorestorative therapy

Evidence from Ko et al. demonstrated that acidic fibroblast growth factor directly applied to the injured spinal cord in 48 patients with chronic SCI was safe, feasible, and could yield modest functional improvement after 48 months of follow-up study [54].

Granulocyte-colony stimulating factor (GCSF) had some benefits in cases of incomplete subacute and chronic SCI in some studies of double-blind randomized controlled clinical trials [55, 56].

McDonald et al. reported placebo-controlled phase 2 trial of Drisapersen for Duchenne muscular dystrophy. They found that Drisapersen 6 mg/kg/week resulted in a treatment benefit of 6-minute walking distance that is largely maintained up to 24 weeks after discontinuation of the therapy [57].

Panza et al. showed the trial design to evaluate whether solanezumab and gantenerumab could prevent AD in its early onset for people with autosomal-dominant AD or cognitively healthy subjects at risk of developing sporadic AD [58].

4.5 Bioengineering and tissue engineering therapy

Strauss et al. reported that intrathecal antisense oligonucleotide (nusinersen) therapy was relatively safe and well tolerated in spinal muscular atrophy (SMA) patients with advanced disease and spinal fusion [59].

Eckstein et al. described that rituximab was used to treat 8 patients with langerhans cell histiocytosis and neurologic dysfunction resulted in some clinical improvement that included gait abnormalities, tremors, proprioceptive deficits, dysarthria/dysphagia and intellectual/behavioral/psychological symptoms [60].

Kucher et al. found that human anti-Nogo-A antibody was well tolerated in patients with acute complete SCI through intrathecal administration and showing some efficacy [61].

4.6 Other therapies

Hubscher et al. found that locomotor training could improve bladder, bowel and sexual function in patients with chronic SCI [62]. Sandroff et al. published a design of a single-blind, randomised controlled trial of exercise training for managing learning and memory impairment and evaluated whether this therapy could improve cognition in patients with multiple sclerosis [63].

4.7 Guidelines

Trento et al. showed large heterogeneity regarding product specification, particularly in the markers used for phenotypical characterization and their threshold of expression. Thus, use of potency assays to MSC functionality, and karyotyping aside from variations in the culture method is needed in order to standardize the MSC product as a clinical therapeutic tool. For this, it is needed to set up the standard of cell culture and quality control to keep cells more homogeneous that may reduce variability and could be easier to interpret results in clinical trials from different centers [64].

It should be noted that several authors often misused this identification standard of MSCs to that

of mesenchymal stem cells. The criteria of MSCs developed by the International Society for Cellular Therapy include (1) MSC must be plastic-adherent when maintained in standard culture conditions; (2) MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules; and (3) MSC must differentiate to osteoblasts, adipocytes and chondroblasts in vitro [65–67].

In this regards, Chinese Association of Neurorestoratology sets the standards of the culture and quality control of umbilical cord MSCs and neural progenitor/precursor cells that were used in neurorestorative clinical application in 2017 [68, 69].

International Association of Neurorestoratology and the Chinese Association of Neurorestoratology proposed clinical cell therapy guidelines for neurorestoration, which included items of cell type nomenclature, cell quality control, minimal suggested cell doses, informed patients consent, indications and contraindications for undergoing cell therapy, documentation of procedure and therapy, safety & efficacy evaluations, policy of repeated treatments, no cost to patients for unproven therapies, basic principles of cell therapy, and publishing responsibility [70].

Based on established medical, engineering and scientific principles, Bikson et al. outlined a robust and transparent technical framework for ensuring limited output transcranial electrical stimulation devices, which are designed to minimize risks, while also supporting access and innovation could be a new beginning in neurorestorative therapy for the benefit of patients [71].

5 Summary

In 2018, the trend in global clinical research revealed that there are rigorous and high levels of evidence-based medical practice in ongoing or completed clinical trials and/or upcoming clinical trial designs. This will undoubtedly provide greater benefits to patients from neurorestorative therapies.

Disclosure

The authors declare that they have no competing interests.

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