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Review Article

Translational Research in Stem Cell Treatment of Neuromuscular Diseases

Hakan Orbay[1] and Hiroshi Mizuno[2]

[1] *Department of Radiology, University of Wisconsin, Madison, WI 53792, USA*
[2] *Department of Plastic and Reconstructive Surgery, Juntendo University School of Medicine, Tokyo 1138421, Japan*

Correspondence should be addressed to Hiroshi Mizuno; hmizuno@juntendo.ac.jp

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Neuromuscular diseases are a heterogeneous group of diseases that lead to significant disability in effected individuals. Pharmacological treatments failed to provide any significant improvement to date. Recently, the introduction of stem cells into the field of health sciences raised the hopes for a new treatment for neuromuscular diseases. In theory, stem cells, owing to their multilineage differentiation capacity, could differentiate into myofibers and neurons and replace the degenerated cells leading to recovery of the patients. Results obtained from the preclinical studies supported this theory. However, clinical trials with stem cells could not meet the expectations mainly because of early mortality, limited migration, and differentiation of the implanted cells. Modification of the stem cells before implantation, such as introduction of deficient genes or commitment to a precursor cell line provided little improvement. The biggest barrier to overcome for a successful of stem cell treatment, which also should be the focus of the future studies, is to increase the functional integration of the donor cells with the recipient tissues. Understanding the underlying pathogenic mechanisms of the neuromuscular diseases is essential to achieve this goal.

1. Introduction

The term neuromuscular diseases define a wide range of conditions characterized by the weakness or wasting of the body muscles. Problems may primarily originate from the spinal cord, the peripheral nerves (neuropathies), the muscle fibers (myopathies), or the neuromuscular junction. Some of these diseases are hereditary, while others are acquired. The diagnosis is mainly done by clinical observation, electromyography, muscle biopsy, and in some instances molecular genetic studies. Some of the major types of neuromuscular diseases are amyotrophic lateral sclerosis (ALS), myasthenia gravis (MG), multiple sclerosis (MS), and muscular dystrophies (Duchenne's muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD)). Despite the long lasting research on the pathogenesis and the molecular mechanisms of neuromuscular diseases, no satisfactory treatment has been offered yet for these diseases [1].

Stem cell research is relatively new in the medical field but holds a great potential for the treatment of a variety of diseases that remained untreatable so far. Stem cells are believed to exist in all tissues in human body and may be totipotent, pluripotent, or multipotent, depending on tissue type. Neuromuscular degeneration itself seems to promote proliferation, migration, and transdifferentiation of autologous stem cells. Production of neurotropic and growth factors and stimulation of the regenerative processes by stem cells have been demonstrated in neurodegenerative diseases [2]. Therefore, human skeletal muscle tissue and nerve tissue have a limited regeneration capacity via the muscle stem cells, also called satellite cells and nerve derived stem cells, respectively [3]. However, this regeneration capacity is not enough to reverse the pathological process in case of neuromuscular diseases. Following the discovery of multilineage plasticity of the stem cells that can be obtained in large numbers from easily accessible tissues, several attempts have been performed to treat neuromuscular diseases via the local or systemic injection of the stem cells. Despite the promising results obtained from in vitro studies, these attempts have yielded limited success in vivo as well as in clinical trials.

This in part is due to the complexity of the microenvironment needed to ensure stem cell integration and function [3].

The aim of this paper is to summarize the translational research on the most common types of neuromuscular diseases.

2. Anatomy of Neuromuscular Unit

The formation of skeletal muscle begins during the fourth week of embryonic development by the rapid mitotic division of specialized mesodermal cells, termed myoblasts. By week nine of development, multinucleated skeletal muscle cells, termed muscle fibers, can be identified. By month five, the muscle fibers begin to accumulate protein filaments important in muscle contraction. Muscle fibers aggregate into bundles as the fetus grows, and by birth myoblast activity, so the formation of new muscle fibers stops. Muscle fibers contain longitudinally arranged myofilaments, named actin and myosin. Muscle contraction on a subcellular level is a complex interaction of myofilaments coupled with the influx and efflux of calcium ions following the excitation by nerve fibers. Each muscle fiber is bound to adjacent fibers to form bundles and accumulation of muscle bundles forms the muscle belly. Supporting connective tissue surrounding the individual fibers is named endomysium, the perimysium encloses the fascicles, and the epimysium surrounds the muscle belly [3].

Nerve fibers innervating the muscles originate from brain stem nuclei or the spinal cord and meet the muscle fibers in neuromuscular junctions. Neuromuscular junctions are composed of presynaptic nerve membrane, synaptic cleft, and postsynaptic muscle membrane. Myelinated motor nerve fibers enter their target muscles and they divide into 20–100 unmyelinated terminal fibers, each of which innervates a single muscle fiber. The terminal fiber from a motor axon and the muscle fiber it innervates are called a motor unit. The terminal nerve fibers contain the neurotransmitter acetylcholine (ACh) stored in synaptic vesicles. When the nerve fibers are stimulated by an action potential, ACh is released into the synaptic cleft and binds to the ACh receptors on the postsynaptic muscle membrane initiating the muscle contraction [6].

3. Stem Cells

Stem cells can be classified according to the way that they are derived and the source tissues. Embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), haemopoietic stem cells (HSCs), and induced pluripotent stem (iPS) cells are the major types of stem cells. Each one of these stem cell types possesses certain advantages and disadvantages which should be weighed carefully before the desired applications.

ESCs cells are derived from the inner cell mass of a developing blastocyst and are pluripotent, possessing the capacity to give rise to all 3 germ layers. Concerns about in vivo tumor formation and ethical concerns regarding their harvest have thus far restricted the use of ESCs [3]. MSCs and HSCs are multipotent, self-renewing cells derived from adult tissues that can form a number of cells or tissues that are usually restricted to a particular germ layer. The major advantages of the MSCs and HSCs over ES cells are the ease of harvest and lack of immunoreactivity since they are derived from autologous sources. However, they may be less desirable for the treatment of genetic diseases since they may possess the same genetic predisposition to the disease. For example, MSCs derived from ALS patients exhibit diminished growth and differentiation capacity [7].

Most recent advancement in the field of stem cell research is the development of iPS cells [8]. iPS cells are reprogrammed fibroblasts that are transfected by selected transcription factors delivered by vector-, virus-, protein-, or RNA-mediated approaches. Original protocol utilized transcription factors Oct 3/4, Klf, Sox2, and c-Myc; however multiple research groups have now accomplished successful reprogramming of fibroblasts using various combinations of factors [9–12]. These cells are not only an option for disease modeling but also provide a novel source for autologous cellular therapies [7].

Stem cells are used in two different ways in neurodegenerative diseases: direct differentiation and regeneration or paracrine anti-inflammatory activity. Moreover, stem cells might become eventually carriers of pharmacological and gene treatments [2].

4. Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease caused by the selective loss of both spinal and upper motor neurons [13]. It is the most common motor neuron disease in adults and usually diagnosed in the sixth decade of life. Initial presentation is limb weakness which progresses gradually to generalized muscle atrophy and paralysis. Respiratory muscle involvement leads to death usually within 5 years. The definitive treatment of the disease is the replacement of the lost motor neurons. Many pharmacologic agents have been tried for the treatment of ALS but none of them proved to be effective up to date.

Stem cells have been extensively experimented for the treatment of ALS in animal models and some provided significant benefit in preclinical level (Table 1). The types of stem cells that have been tested include neural stem and progenitor cells (NSCs, NPC), umbilical cord blood stem cells (UCBCs), bone marrow stem cells (BMCs), human glial restricted progenitors (hGRPs), embryonal stem (ES) cells, glial restricted progenitors (GRPs), and olfactory bulb neural progenitor cells (OB-NPCs). There are around ten clinical trials reported so far placing the amyotrophic lateral sclerosis to the top of the list of clinical trials for neurodegenerative disorders (Table 2). Even though some of these trials reported a limited success in terms of prolonged life span and functional improvement, the desired level of success has not been reached yet. Mazzini et al. reported the first clinical application of BMCs to the patients with ALS but mainly focused on the safety of the procedure in this preliminary

Table 1: Table summarizing the preclinical studies on the treatment of ALS with stem cells.

Stem cell	Animal model	Result	References
Mouse BMCs	$SOD1^{G93A}$ mouse	No effect	[48]
Mouse BMCs	$SOD1^{G93A}$ mouse	Prolonged life span and functional improvement	[49]
Mouse BMCs	$SOD1^{G93A}$ mouse	Prolonged life span and delayed disease onset	[50]
Mouse BMCs	$SOD1^{G93A}$ mouse	Functional improvement	[51]
Rat BMCs	$SOD1^{Leu126delTT}$ mouse	Prolonged life span in female mice only	[52]
Rat BMCs	hSOD1(G93A) rat	Prolonged life span, decreased motor neuron loss, and preserved motor functions	[53]
Rat BMCs	$SOD1^{G93A}$ rat	Prolonged life span and functional improvement	[54]
Human BMCs	$SOD1^{G93A}$ mouse	Prolonged life span and delayed disease onset	[55]
Human BMCs	$SOD1^{G93A}$ mouse	Prolonged life span functional improvement, and delayed disease onset	[56]
Human BMCs or Human BMC-derived NSCs	$SOD1^{G93A}$ mouse	No effect	[57]
Human BMCs	$SOD1^{G93A}$ mouse	Functional improvement	[58]
Human BMCs	$SOD1^{G93A}$ rat	Prolonged life span and functional improvement	[59]
Human UCBCs	$SOD1^{G93A}$ mouse	Prolonged life span	[60]
Human UCBCs	$SOD1^{G93A}$ mouse	Prolonged life span	[61]
Human UCBCs	$SOD1^{G93A}$ mouse	Prolonged life span and functional improvement	[62]
Human UCBCs	$SOD1^{G93A}$ mouse	Prolonged life span, functional improvement, delayed disease onset, and histological improvement	[63]
Human UCBCs	$SOD1^{G93A}$ mouse	No effect	[64]
Human UCBCs or Human UCBC-derived NSCs	$SOD1^{G93A}$ mouse	No effect	[57]
Human UCBCs	$SOD1^{G93A}$ mouse	Prolonged life span and amelioration of the symptoms	[65]
Human UCBCs	$SOD1^{G93A}$ mouse	Not mentioned	[66]
Human NPC	$SOD1^{G93A}$ rat	No effect	[67]
Human NPC	$SOD1^{G93A}$ rat	No effect	[68]
Human NSCs	$SOD1^{G93A}$ rat	Prolonged life span, functional improvement, and delayed disease onset	[69]
Human NSCs	$SOD1^{G93A}$ rat	Prolonged life span and functional improvement	[70]
Human NSCs	$SOD1^{G93A}$ mouse	Prolonged life span and delayed disease onset	[71]
Human NSCs	$SOD1^{G93A}$ rat	Prolonged life span	[69]
Human NSCs	$SOD1^{G93A}$ mouse	Improved neuromuscular transmission	[72]
Mouse NSCs	$SOD1^{G93A}$ mouse	Prolonged life span and delayed disease onset	[73]
Rat NSCs	$SOD1^{G93A}$ rat	Not mentioned	[74]
Mouse OB-NPCs	$SOD1^{G93A}$ mouse	Prolonged life span, functional improvement, and delayed disease onset	[75]
Mouse ESCs	$SOD1^{G93A}$ rat	No effect	[76]
Human GRPs	$SOD1^{G93A}$ mouse	Not mentioned	[77]

study [14]. They later on published larger patient series along with the long-term follow-up results [2, 15, 16], and in their final paper in 2012 they stated that BMC application does not improve the symptoms of ALS in the long term, however, stabilizes the symptoms of the disease thus prolonging the life span of the patients [17]. On the other hand, Nefussy et al. could not detect any benefit of stem cell treatment in case of ALS, but it should be mentioned that they mobilized the BMCs via injection of granulocyte colony stimulating factor (G-CSF) but did not carry out direct injection of the cells [18]. A common finding of these clinical trials was the lack of major side effects of intraspinal/intracerebral cell injection that makes the clinicians more comfortable in continuing their efforts for the refinement of the stem cell therapies for ALS [14, 15, 19, 20]. Therefore, more clinical trials are on the way and there are nine more in various stages listed in the NIH database for clinical trials.

Table 2: Table summarizing the clinical trials on the treatment of ALS with stem cells.

Phase	Stem cell	Followup	Results	Reference
—	BMCs		No adverse effects observed but final result not mentioned	[14]
—	BMCs	3 years	A significant slowing down of the linear decline of the forced vital capacity	[2]
—	BMCs	4 years	No adverse effects observed but final result not mentioned	[15]
—	G-CSF mobilized HSCs	6 months	No adverse effects observed but final result not mentioned	[19]
II	BM derived HSCs	1 year	9 patients showed clinical improvement confirmed by electroneuromyography. One patient was stabilized. No benefit observed in three patients	[78]
—	G-CSF mobilized HSCs	1 year	No adverse effects observed. Increased survival	[79]
I/II	BMCs	6 months	No adverse effects observed, disease symptoms stabilized	[80]
I-II	BMCs	6 months	Minor side effects were transient fever, headache. No major adverse effects were observed. Clinical improvement observed	[81]
—	G-CSF mobilized HSCs	—	No clinical benefit	[18]
—	G-CSF mobilized HSCs	—	No adverse effects but final result not mentioned	[20]
I	BMCs	1 year	No adverse effects observed but final result not mentioned	[16]
I	BMCs	9 years	No clinical benefit in long-term followup but the symptoms stabilized	[17]

5. Multiple Sclerosis

MS is a chronic inflammatory demyelinating disease of the central nervous system that leads to cumulative and irreversible damage. MS is characterized by self-reactive lymphocytes and demyelination. Therefore, any method for the treatment of MS, to be effective, should reverse the demyelination as well as suppressing self-reacting lymphocytes. Available drug therapies are only partially effective in these terms. However, stem cells, considering their immunosuppressive effects and multilineage differentiation capacity, may be applicable for meeting some of these goals. Preclinical data and ongoing clinical trials suggest that selected patients may respond positively to autologous stem cell transplantation. But it is still uncertain if adult stem cells can repair existing neurological deficits in patients with MS [21].

The stem cell types that have been used for the treatment of MS in animal models were BMCs, iPS, NSCs, NPCs, HSCs, ESCs, adipose-derived stem cells (ASCs), embryonal carcinoma cells, bone marrow transplantation (BMT), Schwann cells (SCs), Schwann cell precursors (SCPs), and oligodendrocyte progenitor (OCP) cells. It was Bonilla et al. who first used stem cells for the treatment of MS [22]. They have injected BM-derived HSCs into the mouse brain and obtained encouraging results. Numerous studies have followed and they are listed in Table 3. Oka et al. used primates for their experiments and injected monkey NPCs into the central nervous system of the monkeys to treat MS [4] (Figure 1). They have seen significant number of myelinating fibers in the transplantation zone. In another primate study it was reported that transplanted human NPCs decreased disability and increased survival of the animals [23]. The results of these two experiments were important in terms of the proximity of the animal model to human beings. The potential of iPS cells to differentiate into functional OPCs, as documented recently, is another milestone development that would ameliorate the stem cell donor site issues [24]. There is only one controversial study in the literature published by Reekmans et al. in which mouse NSCs were transplanted to a mouse MS model but no therapeutic effect or improvement in the disease state could be detected [25].

Clinical trials on the treatment of MS with stem cells are listed in Table 4. In the standard protocol, patients are first treated with a combination of immunosuppressive agents to eliminate all lymphocytes including self-reactive lymphocytes. Myeloablative treatment is followed by stem

Table 3: Table summarizing the preclinical studies on the treatment of MS with stem cells.

Stem cell	Animal model	Result	References
Mouse BM-derived HSCs	Neonatal mouse	Injected stem cells differentiated into oligodendroglial cells in vivo	[22]
Rat NPCs	Rat	Transplanted cells had migrated into white matter and acquired specific markers of the astroglial and oligodendroglial lineages	[82]
Mouse NPCs	Mouse	Significant numbers of donor cells entered into demyelinating areas of the central nervous system and differentiated into mature brain cells	[83]
Mouse NPCs	Mouse	The size of demyelinated areas and, extent of chronic axonal pathology were reduced in the transplanted brains	[84]
Mouse NPCs	Mouse	Decreased CNS inflammation and tissue injury and attenuated severity of EAE	[85]
Mouse NPCs	Mouse	Transplanted NPCs accumulated in inflammatory demyelinating lesions	[86]
Mouse NPCs	Mouse	Decreased inflammation in brain but no effect in spinal cord lesions	[87]
Mouse NPCs	Mouse	Reduced migration of transplanted cells in chronic disease	[88]
Mouse NPCs	Mouse	Enhanced remyelination	[84]
Mouse NPCs	Mouse	NPC differentiated into oligodendrocytes in vivo in long term	[87]
Mouse NPCs committed to glial lineage	Mouse	Migration of cells from the implantation site and remyelination of axons. Behavioral improvement	[89]
Mouse NPCs committed to glial lineage	Mouse	Remyelination of the axons was observed without alteration of T cells or macrophages within the CNS	[90]
Human NPCs	Monkey	Decreased disability and increased survival as well as long-term survival of implanted cells	[23]
Human ESC-derived NPCs	Mouse	Clinical improvement, cells migrated to the host white matter, attenuation of the inflammatory process	[91]
Monkey NPCs	Monkey	Significant number of myelinating profiles in the transplantation zone	[4]
BM transplantation	Mouse	Complete amelioration of the symptoms of MS	[92]
BM transplantation	Mouse	BM transplantation effectively blocked or delayed EAE development	[93]
BM transplantation	Mouse	Protection from disease development	[94]
NT2 embryonal carcinoma cell line, BM transplantation	Mouse	Both types of cells remained viable in the mouse brain and differentiated into neurons, astrocytes, and oligodendrocytes	[95]
Mouse NSCs	Mouse	NSCs migrated and differentiated into oligodendrocytes and stimulated remyelination	[96]
Mouse NSCs and mouse BMC-derived NSCs	Mouse	Both cell types suppressed the inflammatory process	[97]
Human BMCs	Mouse	Demyelination and the number of the lesions have decreased	[98]

Table 3: Continued.

Stem cell	Animal model	Result	References
Mouse NSCs	Mouse	Limited or no therapeutic potential	[25]
Mouse BMCs	Mouse	Antioxidant and neuroprotective activity for MSCs was documented	[99]
Mouse BMCs	Mouse	Decreased inflammation and decreased tissue levels of inflammatory mediators	[100]
Mouse BMCs	Mouse	BMCs enhanced recovery, prevented relapses, and promoted myelin repair	[101]
Mouse BMCs	Mouse	Transplanted cells decreased the inflammation but also formed demyelinating lesions in the brain parenchyma in some cases	[102]
Human BMCs	Mouse	Injected BMCs accumulated in the CNS, reduced the extent of damage, and increased oligodendrocyte lineage cells in lesion areas	[103]
Human BMCs differentiated into neurotrophic factor-producing cells	Mouse	Delay of symptom onset and increased animal survival	[104]
TREM2* -transduced BM-derived myeloid precursor cells	Mouse	Limited tissue destruction and facilitated repair	[105]
IFN-β** gene transfected mouse BMCs	Mouse	Inhibition of disease onset and decrease in clinical severity.	[106]
BDNF*** gene transfected mouse BMCs	Mouse	Delayed disease onset and a reduction in overall clinical severity	[107]
Mouse ASCs	Mouse	Bimodal therapeutic potential of ASCs was documented via suppressing the autoimmune response and via inducing local neuroregeneration	[108]
SC and SCPs	Rat	SCPs survived well, migrate through normal CNS tissue, interface smoothly and intimately with host glial cells, and myelinate extensively among the astrocytes of the retina	[109]
Mouse OPCs and BMCs	Mouse	BMCs increased OPC engraftment, migration, and maturation in myelinating oligodendrocytes	[110]
Mouse iPS derived OPC	Mouse	iPS cells could be differentiated into functional OPCs	[24]
OPC line CG-4	Rat	Transplanted cells migrated to inflammatory lesions and differentiated into oligodendrocytes	[111]

* Triggering receptor expressed on myeloid cells 2, ** interferon-β, *** brain-derived neurotrophic factor.

cell transplantation. However, direct intrathecal injection of stem cells as well as nonmyeloablative stem cell transplantation has also been tried with favorable results [26, 27]. The largest series published so far includes 183 patients that are recorded in the database of the European Blood and Marrow Transplantation Group [28]. All these patients were treated with HSCs, and overall transplant-related mortality was 5.3% with an improvement or stabilization of neurological conditions in 63% of patients during a median followup of 41.7 months. The only reported serious side effect of stem cell treatment of MS was the Epstein-Barr virus-associated posttransplantation lymphoproliferative disorder [29]. In summary, both myeloablative or nonmyeloablative stem cell applications seem to be safe and both provide a certain level of clinical benefit to the patients.

6. Muscular Dystrophies

DMD is characterized by a progressive degeneration of the whole body musculature due to a deficit in the dystrophin gene. Dystrophin is a large protein of skeletal muscle tissue that is expressed under the sarcolemma and contributes to the stability of the giant syncytial muscle fibers. Natural course

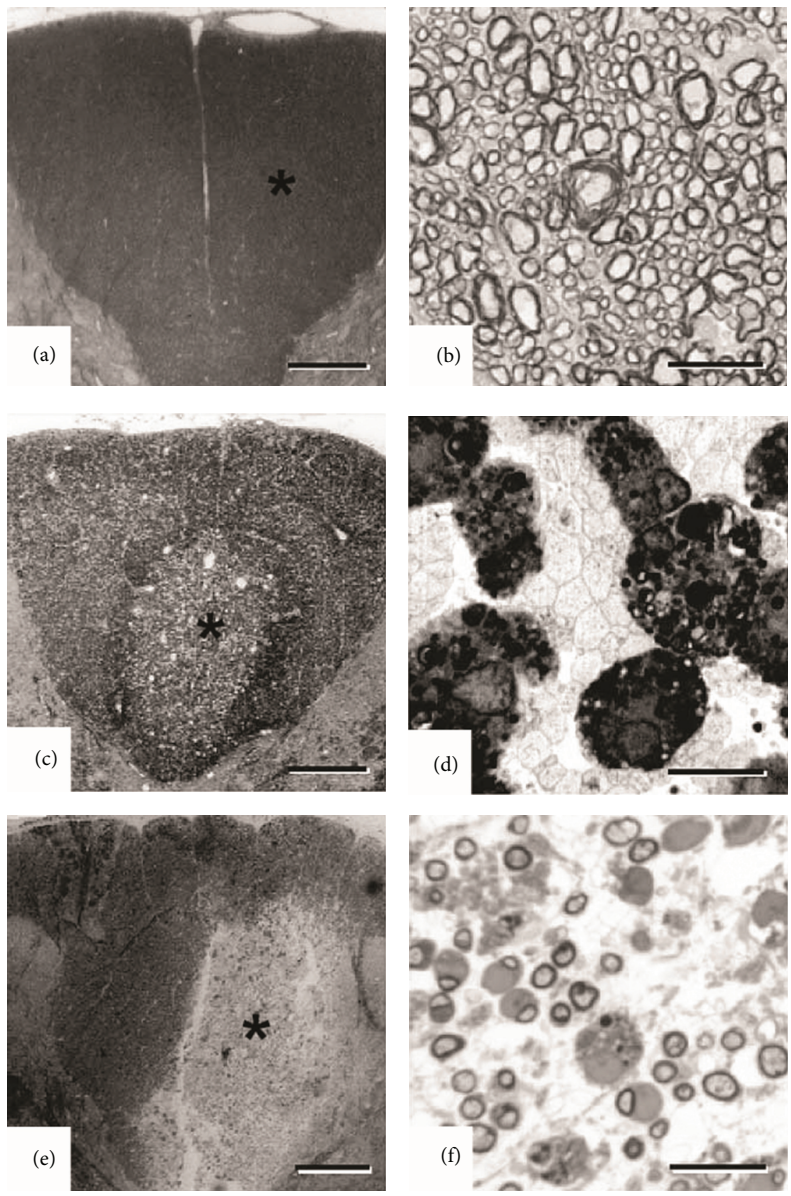

Figure 1: Remyelination of the marmoset spinal cord following transplantation of adult marmoset precursor cells. Normal (a), demyelinated (c), and remyelinated (e) axons of the dorsal column in the marmoset. (b), (d), and (f) are highpower magnification of the area around the asterisk in (a), (c), and (e), respectively. The anatomical pattern of myelination was similar to that produced by the Schwann cells (scale bar, for (a), (c), and (e) = 250 Am, for (b), (d), and (f) = 10 Am). Adapted from [4].

of the disease is confinement to wheelchairs around the age of 12 and death ensues in the later stages due to cardiomyopathy. During the course of the disease, effected skeletal muscle tissue regenerates to a limited extend through the activation of satellite cells but multiple cycles of degeneration-regeneration eventually lead to exhaustion of the myogenic reservoir. Replenishment of the myogenic reservoir is the principle of the stem cell transplantation to the skeletal muscle in muscular dystrophies. BMD is very similar to DMD except that it gets worse at a much slower rate and it is less common [30].

DMD and BMD are the most extensively studied diseases in the group of neuromuscular disorders. Therefore it would be overwhelming to cite all the experimental papers on treatment of muscular dystrophies in this paper. Instead, a general summary of the preclinical studies is given in Table 5. The most commonly used cell type in preclinical studies was myoblasts that originate from myogenic progenitors (MPCs), and the main MPCs in skeletal muscles are satellite cells. These normally quiescent cells are located beneath the muscle fiber basal lamina, and upon activation they either differentiate into committed progenitors (myoblasts) or self-renew by asymmetric division [3, 30, 31]. However, the first experimental report by Ferrari et al. utilized BM-derived MPCs in a mouse model of muscle degeneration [32]. Lafreniere et al. carried out the only primate study

Table 4: Table summarizing the clinical trials on the treatment of MS with stem cells.

Phase	Stem cell	Followup	Results	Reference
I/II	HSCs	15 months	The number of lesions decreased on MRI. Clinically, patients improved slightly or remained stable	[112]
—	HSCs	1–1.5 years	A fall in intensity of motor and coordination disorders. No recovery of cranial nerve function was observed	[113]
I/II	HSCs	16 months	Positive early results	[114]
II	HSCs	12 months	EDSS improved in some patients. Only two patients had relapses Disappearance of enhanced T1 lesions on MRI	[115]
II	HSCs	24 months	Important clinical issues in the use of HDIT and stem cell transplantation for MS were identified	[116]
II	HSCs	36 months	All patients showed clinical stabilization or improvement. Quality of life improved	[117]
—	HSCs	2 years	Long-term suppression of inflammatory activity in MS patients who received HSCs is associated with profound qualitative immunological changes	[118]
—	HSCs	3 years	HSCs can reduce BDNF levels to values associated with lower activity	[119]
—	HSCs	41.7 months	Improvement or stabilization of neurological conditions in 63% of patients. HSCs was shown as a promising procedure to slow down progression in a subset of patients affected by severe, progressive MS	[28]
—	BMCs	19 months	Some degree of improvement in the sensory, pyramidal, and cerebellar functions noted	[120]
I/II	HSCs	37 months	All patients were free from progression (no deterioration in EDSS), and 16 were free of relapses. Significant improvements were noted in neurological disability	[27]
I	BMCs	12 months	EDSS improvement in 5/7, stabilization in 1/7, and worsening in 1/7 patients. Hints of clinical but not radiological efficacy and evidence of safety with no serious adverse events	[26]
—	HSCs	48.92 months	Confirmed relapse-free survival rate was 62.9% and progression-free survival rate was 83.3%	[121]
I/II	BMCs	≤25 months	Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects	[81]
—	BMCs	—	Expression of FoxP3 at 6 months after intrathecal injection of MSC was significantly higher than the levels prior to treatment. Such significant enhanced expression of FoxP3 associated with clinical stability	[122]
—	BMCs	12 months	Improvement of EDSS by 0.5–1 points in 6/8, stabilization in 1/8, and progression in 1/8 patients	[123]
IIa	BMCs	10 months	There were no safety issues of stem cell application. The evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection	[124]

Table 5: Table summarizing the preclinical studies on the treatment of muscular dystrophies with stem cells.

Stem cell	References
Mouse BMCs (as a vehicle for gene delivery)	[34, 35]
Mouse BMCs	[39, 125–128]
Mouse HSCs	[40]
Dog HSCs	[129]
Human HSCs	[130]
Human BMCs	[131, 132]
Mouse MDSCs (as a vehicle for gene delivery)	[36]
Mouse MDSCs	[133–135]
Dog MDSCs	[136]
Human MDSCs	[137, 138]
Mouse mesoangioblasts (as a vehicle for gene delivery)	[5]
Mouse mesoangioblasts	[139–142]
Canine mesoangioblasts	[143]
Mouse iPS	[144–146]
Human ASCs	[147–152]
Mouse myoblasts/MPCs	[135, 153–165]
Dog myoblast/MPCs	[166]
Porcine myoblast/MPCs	[167]
Monkey myoblasts/MPCs	[33]
Human myoblast/MPCs	[168–172]
Human UCBCs	[148, 173, 174]
Human SSCs*	[175, 176]
Mouse ESCs	[177, 178]
Mouse ESC-derived myogenic precursors	[179]
Mouse BMC-derived myogenic precursors	[32, 180]
Mouse satellite cells	[38]
Human primordial germ cells	[181]
Human IDPSC**	[182]
Human primary fetal skeletal muscle cells	[183]
hfMSCs***	[184, 185]
BM transplantation (in mice)	[186]
Mouse side population cells (as a vehicle for gene delivery)	[37]

*Synovial stem cells, **human immature dental pulp stem cells, ***human fetal mesenchymal stem cells.

and reported that the grafted cells fused only with the recipient fibers at the injection site but did not migrate for so long distances limiting the success of the treatment [33]. Gene delivery methods using stem cells as vehicles proved some improvement [5, 34–37]. Tedesco et al. transplanted genetically corrected mesoangioblasts in SCID/mdx mice intramuscularly [5]. They have successfully documented the dystrophin production and amelioration of morphological defects in tibialis anterior muscle of SCID/mdx mice following cell transplantation (Figure 2). While most of the other studies documented the limited success of stem cell treatment in muscular dystrophies, some others reported no benefit [38–40].

Despite the high number of preclinical studies and encouraging data, clinical trials have been hampered by poor survival and limited migratory ability of the cells (Table 6). Neumeyer et al. reported no positive effect of myoblast transplantation into the tibialis anterior muscles of the patients with BMD [41]. Skuk et al. could detect fusion of the donor and recipient muscle fibers and subsequent synthesis of donor dystrophin following MPC allotransplantation; however this observation was limited to the injection sites [42]. Zhang et al. reported similar results following the transplantation of allogeneic human UCBCs [43]. Oxidative stress, fusion inability, and some administration methodologies are the suspected causes of poor cell survival following transplantation. Intramuscular administration was the preferred method of cellular delivery in most of the clinical studies since many cell types are not able to cross the endothelial barriers of the skeletal muscle tissue. The migration of the injected cells was generally restricted to short distances from the injection site. The resultant large intramuscular pockets of cells subsequently lead to cell death due to inefficient nutrient supply in vivo. Currently, there is only one ongoing clinical trial on stem cell treatment of muscular dystrophies in the NIH database. In this study the researchers aim to treat DMD by human UCBC transplantation.

7. Myasthenia Gravis

MG is an Ach receptor antibody-mediated autoimmune neuromuscular disease. The pathogenesis of MG involves the hyperactivity of T lymphocytes, activation of complement system, deficiency of immunomodulation, and impairment of immune homeostasis.

MSC has got the potential to correct impaired immune homeostasis in diseases like MG because they express intercellular adhesion molecule (ICAM)-1, ICAM-2, lymphocyte function-associated antigen (LFA) 3, fibronectin, lamin, and collagen, which are involved in the process of immune reaction. Moreover MSCs can modulate the T lymphocyte function via direct physical contact through the cell adhesion molecules [44, 45]. However, there are a just a few experimental studies on the application of stem cells for the treatment of MG. The first study was published by Yu et al. [44]. In this study BMCs were applied intravenously to a mouse model of MG. The authors noted a significant decrease in the circulating levels of Ach receptor IgG antibody and a significant functional improvement. The same group injected human UCBCs to mouse model of MG in another experiment and obtained similar results [46]. Sheng et al. injected granulocyte macrophage colony stimulating factor (GM-CSF) to a mouse model of MG and noted a decreased immune response against the Ach receptors through the mobilization of tolerogenic precursor cells [47]. The results

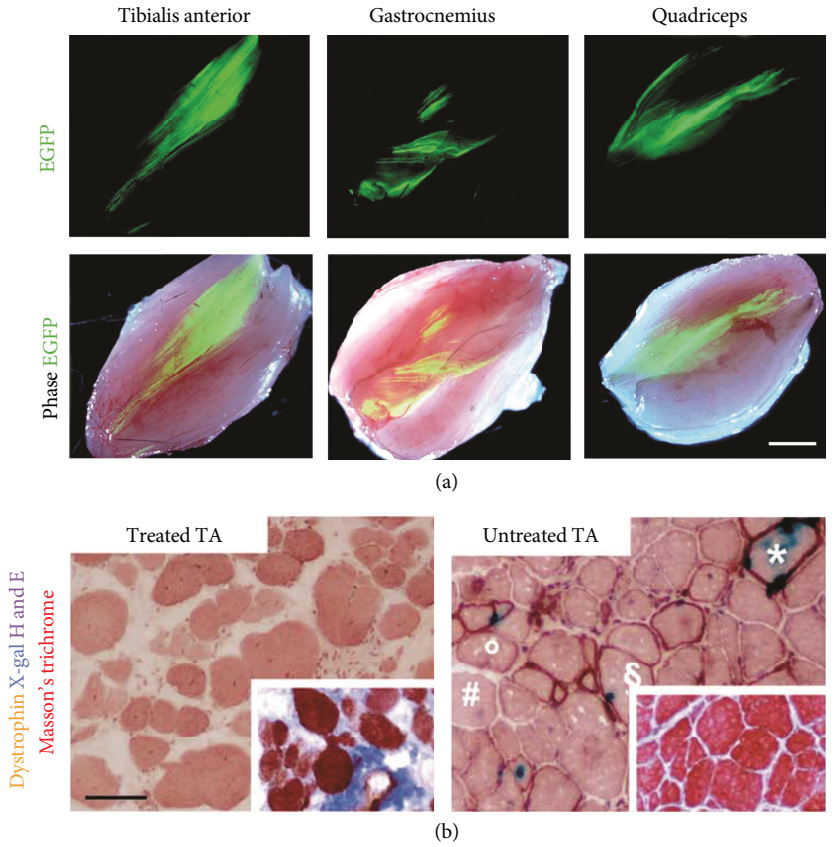

Figure 2: Intramuscular transplantation of genetically corrected mesoangioblasts in SCID/mdx mice. (a) Representative images showing the tibialis anterior (TA), gastrocnemius, and quadriceps muscles that received three intramuscular injections of 10^6 corrected mesoangioblasts. Images show engraftment of donor cells demonstrated by EGFP fluorescence (green) 3 weeks after the last injection (scale bar, 2 mm). (b) Donor cell engraftment, dystrophin production, and amelioration of morphological defects in tibialis anterior muscle from a treated SCID/mdx mouse compared with an untreated SCID/mdx mouse. Insets show Masson trichrome staining. ∗, §, ∘, and # indicate strong, intermediate, weak, and no dystrophin positivity, respectively (scale bar, 100 mm). Adapted from [5].

Table 6: Table summarizing the clinical trials on the treatment of muscular dystrophies with stem cells.

Phase	Stem cell	Followup	Results	Reference
—	Myoblast/MPCs	1 year	No improvement in muscle strength.	[41]
—	Myoblast/MPCs	4 weeks	Allotransplantation of normal MPCs induced the expression of donor-derived dystrophin, however this expression was restricted to the sites of injection.	[42]
I	MDSCs	7 months	No local or systemic side effects were observed. Treated patients had an increased ratio of capillary per muscle fibers with a switch from slow to fast myosin-positive myofibers.	[187]
	UCBCs	100 days	Restoration of the dystrophin in muscles, and improvement of the locomotive function.	[43]

of these experiments were encouraging in terms of clinical application, and a phase I clinical trial is already on the way (ClinicalTrials.gov identifier: NCT00424489). The purpose of this study was stated as to assess the toxicity/feasibility of autologous hematopoietic stem cell transplantation for refractory MG cases in the NIH database. Several other studies are required to assess the feasibility of stem cell therapy for MG, and the concerns about the safety of the stem cell application in case of MG should be further investigated.

8. Discussion and Conclusions

Stem cells are the regenerative reservoirs of the body. They are located in niches in the tissues and become active in case of tissue injury to replace the degenerated cells. There

are two possible mechanisms for the therapeutic effects of the stem cells: differentiation into different cell types or paracrine secretion. Some neuromuscular diseases like MS, ALS, and MG have got an inflammatory component, and in this case anti-inflammatory and immunomodulatory effects of stem cells could provide a treatment. In case of muscular dystrophies, the mechanism is the degeneration of muscle fibers rather than autoimmune destruction so the differentiation capacity of the stem cells comes forward.

Currently there is a gap between animal and human applications of stem cells in neuromuscular disorders so as the promising results obtained in animal studies have not been reproduced in clinical trials yet. The reasons for this failure can be summarized as limited differentiation of stem cells into required cell types, short survival times of transplanted cells, and lack of widespread effect due to the limited migration of the cells away from the injection site. In case of neuromuscular diseases, the preferred way for the delivery of the cells should be direct injection to the target tissues since the biological barriers may limit the migration of stem cells to the target tissues thus decreasing the efficacy of the treatment. Nevertheless lack of long distance migration of the stem cells in the tissues is still a major obstacle in front of cellular therapies as mentioned above. Ideas like corrective gene delivery via stem cells are theoretically brilliant, however, despite some improvement, they have not reached the desired clinical effectiveness yet. One single common result of stem cell trials is the safety of the procedure. Therefore further research can safely be carried out to overcome the current obstacles. Moreover, introduction of new stem cell types such as iPS cells will help to overcome donor site and ethical issues and increase the availability of stem cells.

In conclusion, stem cells still hold a great promise for the treatment of traditionally untreatable diseases. Continuing research will enable the clinicians to understand the biological processes of the neuromuscular diseases better and allow the modification of current treatment protocols accordingly. However the expectations from clinical applications should be kept realistic, and more importantly best effort should be done to prevent the worsening of the pathologies by cellular treatments.

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