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Review article

Stem cell therapy in amyotrophic lateral sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a rare and lethal neurodegenerative disease for which there is no effective medical treatment. Although riluzole, an *N*-methyl-D-aspartate receptor antagonist, has been shown to be reasonably safe for patients with ALS, the drug has been demonstrated to prolong median survival by only 2–5 months. There is mounting evidence that stem cell-based gene therapy is a promising treatment modality for patients with ALS. In this review, we focus on the types, sources, and doses of stem cells that have been shown to be effective for ALS patients, the differences in cytokines or chemokines secreted from these various stem cells, and the immune-modulation activity of stem cells as treatment for ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is an incurable, degenerative neurological disease. The clinical characteristics of ALS include muscle weakness and atrophy, spasticity, and eventual paralysis due to the progressive loss of spinal and brainstem motor neurons. Death typically occurs 3–5 years after symptoms begin [1,2]. The disease currently affects an estimated 350,000 people worldwide, and there are no effective treatments. Although riluzole, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, is the only drug approved by the US Food and Drug Administration for ALS, it has been shown to offer only a modest improvement in symptoms and to prolong median survival by a maximum of 3–5 months. Therefore, an effective treatment for ALS is urgently needed. This review article focuses on the emergence of stem cell-based gene therapy in ALS.

2. Molecular mechanisms mediating the development of ALS

It is still not fully understood why specific neuronal populations are selectively vulnerable in ALS. Mutations in several genes have been shown to be related to the development of the disease, including mutations in the *SOD1*, TARDBP

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(*TDP-43*), *FUS/TLS*, *FIG4*, and chromosome 9 open reading frame 72 (*C9orf72*) genes. A hexanucleotide repeat expansion of the *C9orf72* gene has been identified as the underlying genetic cause of chromosome 9p21-linked frontotemporal lobar degeneration and ALS [3–5].

In addition, about 20% of cases of inherited ALS are caused by mutations in the superoxide dismutase-1 (*SOD1*) gene, particularly mutations that cause misfolding of the protein product [6]. Studies have shown that mutant *SOD1* transgenic mice with loss of *SOD1* function show phenotypic characteristics of motor neuron disease, including progressive deterioration of the brainstem and a functional loss of spinal motor neurons, resulting in weakness, loss of muscle function, and premature death. Interestingly, studies have shown that epigenetic factors, such as aging, are possible causes of ALS in more than 90% of patients with the disease [7].

3. Superoxide dismutases

In vivo, superoxide dismutases are responsible for peroxidation reactions in cells. These enzymes are divided into several species based on their intracellular locations. SOD1 (Cu/ZnSOD) is located in the mitochondrial intermembrane space and cytosol, while SOD2 (MnSOD) is found in the mitochondrial matrix. Although these dismutases are located in different intramitochondrial locations, these enzymes have the same catalytic functions.

4. Other molecular mechanisms of ALS

Excitotoxicity of motor neurons has also been implicated in the pathogenesis of ALS. Most patients with sporadic ALS express reduced levels of synaptosomal high-affinity glutamate uptake and glutamate transporters such as excitatory amino acid transporter 2 (EAAT2 or GLT1) in the motor cortex and spinal cord, resulting in apoptosis of motor neurons due to elevated extracellular glutamate concentrations [8,9]. The NMDA receptor antagonist riluzole effectively minimizes the overexcitation of motor neurons caused by elevated levels of extracellular glutamate and has been shown to have a good safety profile in patients with ALS; however, the drug only extends the lifespan of ALS patients by several months [10–14].

5. Pathology of mutant SOD1 transgenic mice

In 1994, Gurney et al established strains of transgenic mice that express mutant human SOD1 (mSOD1) in order to study the impact of overproduction of mutant SOD1 protein and its accumulation on motor neuron function in ALS [15,16]. Of these mSOD1 transgenic mice, a strain of hemizygous mice harboring human SOD1 with the G93A mutation in high copy number has been shown to be an appropriate model for studying ALS in mice with a short lifespan because these mice become completely paralyzed and die within 16–18 weeks of age. On the other hand, G93A-mSOD1 mice with a low transgene copy number are used to study ALS in mice with longer lifespans. These mice demonstrate much slower disease progression and die within 8–9 months of age [16]. The results of pathological studies of these mutant SOD1 mice have revealed accumulation of mutant SOD1 in the brainstem and spinal motor neurons, marked inflammation around the dying neurons, and overexpression of cytokines such as tumor necrosis factor alpha and interferon gamma in spinal lesions [17,18].

6. Stem cell therapy as treatment for ALS

Stem cells have the ability to continuously divide and differentiate into a number of different types of cell. Stem cells also secrete various cytokines, chemokines, and trophic factors that are known to modulate inflammation, attract other stem cells to sites of injury, enhance cell survival, and participate in angiogenesis and neurogenesis [19,20]. Tables 1 and 2 provide a review of clinical trials in ALS patients and animals.

Table 1 – Clinical trials of stem cell therapy as treatment for amyotrophic lateral sclerosis (ALS).

Humans	Stem cell source	Conditioning regimen	Delivery method	Dose	Outcome
sALS patients	$CD34^+$ HSCs	Total body irradiation (450 cGY); tacrolimus (0.3 mg/kg/d IV) and methotrexate (5 mg/m^2 IV)	IV injection	Absolute neutrophil count $>5 \times 10^8$/L	No clinical benefit
ALS patients	Autologous MSCs	None reported	Multiple intraspinal thoracic subcutaneous injections	Approximately 5.7×10^7 cells total	Decelerated linear decline of forced vital capacity
ALS patients	Autologous $CD133^+$ cells	None reported	Bilateral injection into frontal motor cortex	$2.5–7.5 \times 10^5$ cells/site	Survived more than 47 months

IV = intravenous; HSC = hematopoietic stem cells; MSC = mesenchymal stem cells; sALS = sporadic amyotrophic lateral sclerosis.