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Editorial
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Immune-Inflammatory Modulation as the Therapeutic Strategy of Stem Cell Therapy for Amyotrophic Lateral Sclerosis

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Editorial

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease with no cure. The recent breakthroughs in pathogenic mechanisms of ALS and neurodegenerative diseases are summarized as follows: 1) Novel causative or associated genes not only expand the concepts on spectral paradigm of ALS from motor neuron disease to motor neural network syndrome or multisystem proteinopathy, but also emphasize the importance of RNA dysregulation and abnormal proteinostasis in neuronal death mechanisms [1-4]. 2) Importance of non-cell autonomous toxicity in neuronal cell death mechanisms in neurodegenerative disease [5,6]. 3) And diverse clinical study showing heterogeneity related with genetic backgrounds and multifactorial environmental factors [2].

Despite of all the advances in understanding the connection of clinical heterogeneity, genetic and molecular mechanisms of motor neuronal death in ALS, previously conducted clinical trials have failed. Most trials have been focused on single molecular target and not aiming multiple targets related to complex cell death mechanisms which could explain the failure of most clinical trials.

When focusing immune-inflammatory aspects in cell death mechanism of ALS, balance between pro-inflammatory and anti-inflammatory cytokines are not only important in onset but also disease progressive speed [7,8]. As shown in Figure 1, Proinflammatory cytokines including CCL2, IL-1 beta, CXCL10 are linearly increased as time is progressed from aymptomatic stage to advanced stage. However, anti-inflammatory cytokines such as TGF-beta, IL-4 and IL-10 are increased maximally to the time point of symptom onset, after that time point, these cytokines are rapidly dropped. And, the concepts on immune-inflammatory modulation are also accepted in other neurodegenerative diseases including Alzheimer and Parkinson disease. In molecular level, T-regulatory cell population number and dendritic transcriptional level have been characterized as a good biological marker for predicting progressive speed in ALS. In addition, activated subtype of microglia has been reported to be relevant in predicting disease progression [8,9].

Recently, mesenchymal stem cells (MSCs) therapy emerged as a potential therapeutic strategy for ALS and neurodegenerative disease because of having diverse effects. In addition to paracrine effects of MSCs releasing neurotrophic factors and stimulatory effect on intrinsic neurogenesis, MSCs are also known to regulate both innate and adaptive immune cells, through the release of soluble factors such as Prostaglandin E2 (PGE2), Indoleamine 2,3-dioxygenase (IDO), and TGF-β, resulting in switching patient's environment from a proinflammatory toxic to an anti-inflammatory, and neuroprotective condition [10,11].

In preclinical study, intrathecally delivered human MSCs into cerebrospinal fluid of SOD1G93A mice slowed disease progression in relation to increased lymphocyte infiltration into the spinal cord [12]. And, when MSCs are cultured along with peripheral blood mononuclear cells (PBMC) derived from ALS patients increased significantly proportion of regulatory T cells (Treg) and Th2 cells with enhanced production of anti-inflammatory cytokines including IL-4, IL-10 and transforming growth factor-beta (TGF-β) [11].

We reported immuno regulatory mechanisms for MSCs, such as elevation of regulatory T cells (Tregs) and T helper-2 cells (Th2 cells), play important roles in neuroprotective effect on motor neuronal cell death mechanisms in ALS, with secretion of neurotrophic factors, crucial aspects for the effectiveness of MSCs in ALS [10,11]. In addition, MSCs can modulate the functional properties of microglia via TGF-β secretion, switching roles from a classically activated phenotype to an

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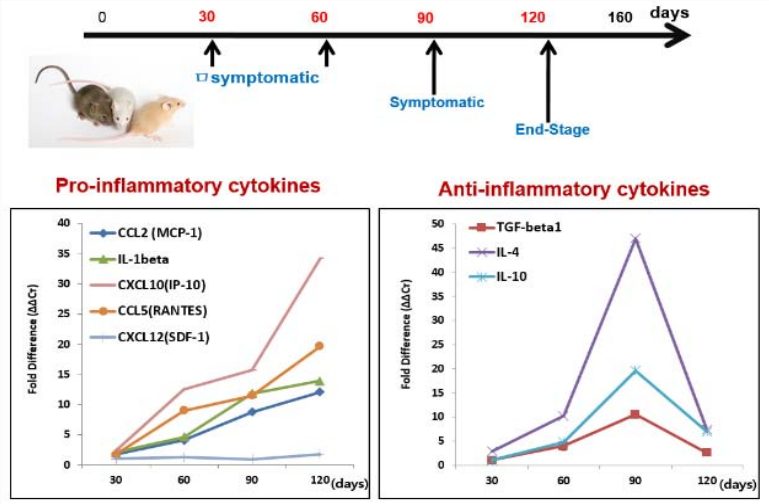

Figure 1: Temporal Patterns of Inflammatory Cytokine Level in ALS Tg Mice. Proinflammatory cytokines are linearly increased as time is progressed from aymptomatic stage to advanced stage. However, anti-inflammatory cytokines are reached at high level until symptom onset, after that these level are rapidly decreased.

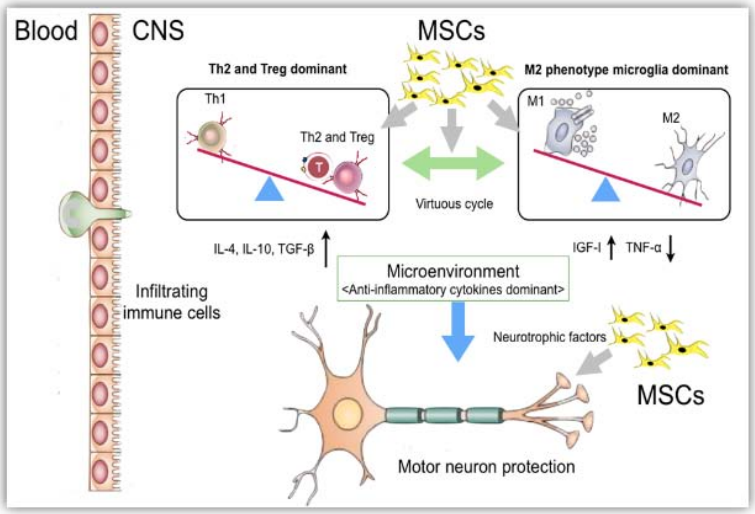

Figure 2: Conceptual Hypothesis; Effect of Mesenchymal Stem Cells (MSCs) therapy in ALS; MSCs injected into cerebrospinal fluid space might change the pro-inflammatory environments into anti-inflammatory conditions, that is, converting Th1/M1 dominant environment into Th2 /Tregand M2 dominant condition.

inflammation-resolving phenotype. The role switching effect may be associated with the inhibition of neuroinflammatory processes in ALS [10]. Analyzing recent clinical trials, effect of MSCs on clinical response suggest strongly that properties of MSCs secreting VEGF, TGF-beta, and Angiogeninare related to good responders to MSC treatment. And when measuring the levels of CSF pro and anti- inflammatory cytokines after MSC treatment, IL-10, TGF-β and IL-6 levels were increased while monocyte chemo attractant protein 1 (MCP-1) levels decreased [13,14]. These findings suggest that immune-inflammatory modulation is an important therapeutic strategy for stem cell therapy for ALS, which is schematically summarized in Figure 2.

However these preclinical and clinical studies are still at preliminary stage, well designed clinical studies are essential with inclusion of post-hoc analysis and systematic analysis of reliable biological markers related to immune-inflammation. Recently published draft of guidelines for Clinical Trials in ALS/MND released from ALS Clinical Trials Workshop which took place at Airlie Conference in Warrenton, Virginia (March 2016) emphasized the importance of excluding the genetic and clinical heterogeneity when enrolling subjects and requirements for post-hoc analysis on biological markers to identify subgroup of patients which appear to respond better to the specific treatment [15].

Therefore, more appropriate therapeutic strategies including optimal selection criteria of patients and quantitative measurement of reliable biological markers related immune-inflammatory cytokines would be important when evaluating the strategy of stem cell therapy aiming immune-inflammatory modulation.

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