BMB Reports - Manuscript Submission

Manuscript Draft

Manuscript Number: BMB-18-253

Title: In vivo Action of RNA G-quadruplex in Phloem Development

Article Type: Perspective (Invited Only)

Keywords: Phloem; Zinc-finger protein; RNA G-quadruplex; SMXL; Sucrose

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Immune inflammatory modulation as a potential therapeutic strategy of stem cell therapy for ALS and neurodegenerative diseases

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Keywords: ALS, neurodegenerative disease, BM-MSCs, immune modulation, biomarker,

Abbreviation:

ALS, Amyotrophic Lateral Sclerosis; BM-MSCs, Bone marrow originated mesenchymal stem cells; CSF, cerebrospinal fluid

Perspective to: Oh KW 2018, Repeated Intrathecal Mesenchymal Stem Cells for Amyotrophic Lateral Sclerosis. Annals of Neurology. 2018; 84(3):361-373. doi: 10.1002/ana.25302

Running title; Immune inflammatory modulation as a therapeutic strategy for stem cell therapy

Acknowledgements;

This work was supported by National Research Foundation (NRF) of Korea funded by Korea Ministry of Science (2018M3C7A1056512).And also supported by Korea Health Technology R&D Project through the Korea Health Industry, Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI16C2131).

Abstract

With emerging evidences on importance of non-cell autonomous toxicity in neurodegenerative diseases, therapeutic strategies targeting the modulation of key immune cells including microglia and Treg cells have been designed for treatment of ALS and other neurodegenerative diseases. The strategy switching the patient's environment from a pro-inflammatory toxic to an anti-inflammatory, and neuroprotective condition could be the potential therapy for neurodegenerative diseases. Mesenchymal stem cells (MSCs) regulate both innate and adaptive immune cells, through the release of soluble factors like TGF- β and elevation of regulatory T cells (Tregs) and T helper-2 cells (Th2 cells), would play important roles in the neuroprotective effect on motor neuronal cell death mechanisms in ALS. Single cycle of repeated intrathecal injections of BM-MSCs demonstrated a clinical benefit lasting at least of 6 months, with safety, in ALS patients. Cytokine profiles of CSF provided evidence that BM-MSCs have a role in switching from pro-inflammatory to anti-inflammatory conditions. The inverse correlation of TGF-β1 and MCP-1 level could be potential biomarker to responsiveness. Therefore, additional cycles of BM-MSC treatments are required to confirm the long-term efficacy and safety.

Among recent breakthroughs in understanding the pathogenic mechanisms of amyotrophic lateral sclerosis (ALS), important issues are summarized as follows: 1) knowledge of novel causative genes expand the concepts on ALS toward motor neural network syndrome or multisystem proteinopathy. 2) The concept of non-cell autonomous effect on motor neuronal cell death mechanisms supports further study of immune-inflammatory modulation as a clinical therapeutic strategy for neurodegenerative diseases. 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. Previous trials based on single molecular targets suggest the importance of integration with multiple molecular targets in the overall therapeutic strategy.

Mesenchymal stem cells (MSCs) therapy is the desired approach for addressing this issue. MSCs exert diverse actions, such as stimulating intrinsic neurogenesis, releasing diverse neurotrophic factors, and modulating immune-inflammatory processes. Traditional stem cell therapy has been promoted as potential strategy for ALS based on self-renewal and differentiation into multiple cell types with the final goal of repairing or replacing injured cells. However, simple replacement of injured cells and differentiation into motor neurons would be difficult to expect the new motor neurons reproducing the extensive connections from cortical neurons to brain-stem or spinal cord neuronal population. Moreover, new motor neurons, if integrated into a diseased network, might be subject to the same pathologic processes that brought about the demise of the original motor neurons (Appel et al (2016) Neurol 87:1-2)

Therefore, therapeutic strategy using stem cells should be switched toward the neuroprotective goals from the concept of neuronal replacement or reconstruction in neurodegenerative diseases. Repeated intrathecal MSCs therapy (Oh et al (2018) Ann Neurol

84:361-373) empathized not only the importance of ethical issue and concept of enriched model for stratified medicine, but also the significance of diverse biological markers as a predicting tool for the effectiveness and responsiveness of autologous MSCs treatment. Moreover, autologous MSCs have multiple advantages in clinical practice, especially in relation to ethical concerns, lack of possible tumorigenesis or graft rejections. MSCs 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, thereby switching the patient's environment from a proinflammatory toxic to an anti-inflammatory, and neuroprotective condition. Recently, we reported that immunoregulatory mechanisms for MSCs, such as elevation of regulatory T cells (Tregs) and T helper-2 cells (Th2 cells), would play important roles in the neuroprotective effect on motor neuronal cell death mechanisms in ALS, similar to the secretion of neurotrophic factors that are crucial to the effectiveness of MSCs in ALS. In addition, MSCs can modulate the functional properties of microglia via TGF- β secretion, switching them from a classically activated phenotype to an inflammation-resolving phenotype. These modes of action mechanisms published in previous our data are summarized in Diagram. These effects of MSCs could be an important therapeutic strategy to inhibit toxic neuroinflammatory processes in the symptomatic stage of ALS.

Data of our previous phase 1 clinical trial have shown that repeated intrathecal autologous bone marrow-derived mesenchymal stem cells (BM-MSCs) therapy is a promising therapeutic strategy, however, reliable biological markers predicting prognosis and/or delineating mechanisms on protecting cell death in ALS have not yet fully described. Furthermore, we reported that factors such as TGF-β, angiogenin (ANG), and vascular endothelial growth factor (VEGF), cytokines secreted by BM-MSCs, play crucial roles in the ALS patient's response to intrathecal autologous BM-MSCs injection. Based on the known action mechanisms of MSCs and findings from an in vivo transgenic mouse study, we

hypothesized that repeated intrathecal BM-MSCs administration could be a valuable therapeutic strategy for ALS. After completion this first randomised, controlled trial designed to evaluate the safety and efficacy of repeated intrathecal BM-MSC therapy in ALS patients, post-hoc analysis of candidate biological markers, genetic and clinical features have been conducted. Repeated intrathecal injections of MSCs demonstrated a possible clinical benefit on functional decline with safety in ALS patients. Cytokine profiles of CSF provided evidence that BM-MSCs have a role in switching from pro-inflammatory to anti-inflammatory conditions. The inverse correlation of TGF-β1 and MCP-1 level could be potential biomarker to responsiveness.

This study was enriched in that it considered clinical findings but also genetic aspects by excluding known common mutations that might be seen even in sporadic ALS. Furthermore, relevance of CSF biomarkers was evaluated for depth of understanding underlying immunomodulatory mechanism of BM-MSCs

Post-hoc survival analysis did not show a significant difference between the two groups. Despite the positive effect on ALSFRS-R lasting at least 6 months, the lack of long-term survival benefit may be associated with the number of treatment of MSC with two limited injections of this trial protocol. The potential therapeutic effect of BM-MSCs would not persist long-lasting because BM-MSCs gradually disappear over time in CSF. Considering the immune modulatory effect of BM-MSC treatment using less-invasive procedures, serial additional BM-MSC treatments after 6 months might improve long-term efficacy.

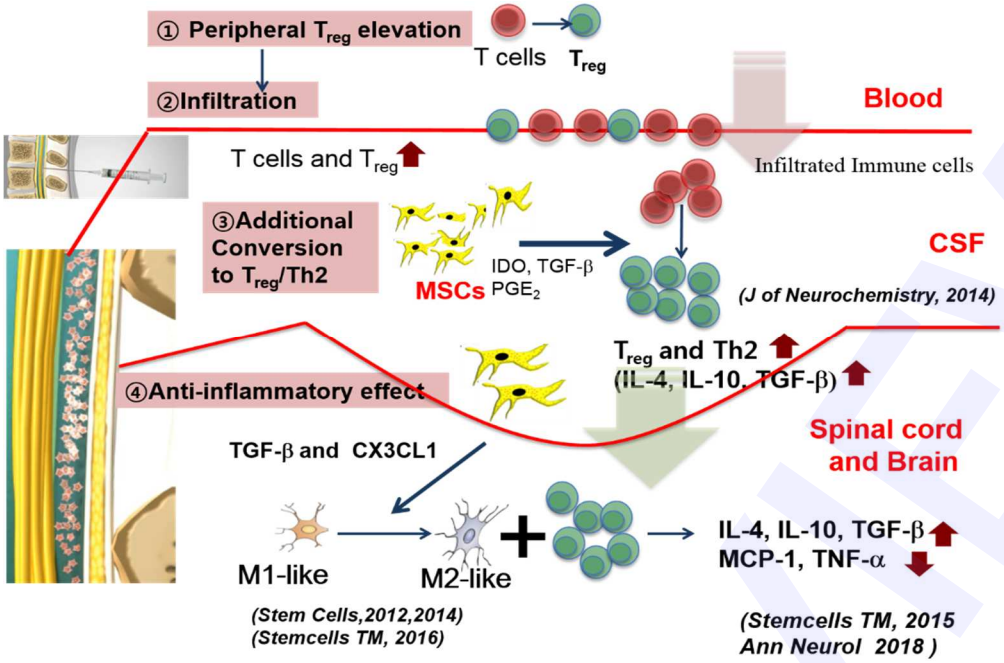

Diagram 1. Summary of plausible mechanisms of intrathecally injected BM-MSCs in ALS

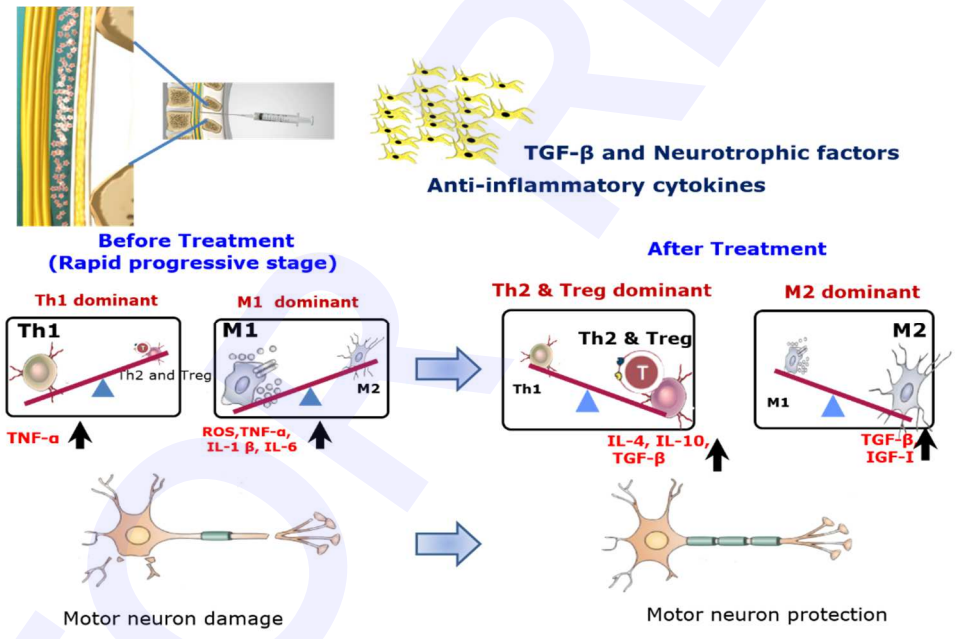

Diagram 2. Hypothesized mechanisms of repeated intrathecal autologous MSCs therapy for ALS when focused on the changes from pre-treated state to post-treated one of key immune-inflammatory cells