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Editorial

Peripheral Blood Mononuclear Cells and Growth Factor Therapy for Cerebral Palsy

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▸ See the article "Serial Changes of Cytokines in Children with Cerebral Palsy Who Received Intravenous Granulocyte-colony Stimulating Factor Followed by Autologous Mobilized Peripheral Blood Mononuclear Cells" in volume 33, e102.

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Perinatal hypoxic-ischemic brain injury is a main cause of cerebral palsy, the most representative disability during childhood. The developing brain differs from the adult brain in response to damage, which is defined as a "tertiary mechanism of injury" characterized by persistent inflammation and epigenetic changes that induce injury-prone status and hinder regeneration.[1] To resolve the pathophysiology, various approaches have been investigated including infusion of peripheral blood mononuclear cells and administration of growth factors. In the past, stem cell therapy was expected to exert efficacy by replacing lost tissue with regenerated cells. However, an increasing number of reports show the importance of cytokines as part of the therapeutic mechanism in stem cell therapy. Growth factors have been used in stem cell therapy to modulate pathophysiological changes after the injury. Growth factors added to culture or secreted by stem cells are often potent on cell fate, cell to cell contact in cell tracking, proliferation and lineage induction. Among candidate growth factors revealed as efficacious in preclinical experiments, erythropoietin and granulocyte-colony stimulating factors (G-CSF) were used in clinical trials. A previous clinical study of intravenously introduced cord blood cells and erythropoietin combination therapy showed positive effects in motor improvement.[2] It was also reported that infusion of cord blood cells elevated systemic levels of interleukin (IL)-8, pentraxin 3, and toll-like receptor 4, which were known as pro-inflammatory, however, later found to be associated with neurogenesis and angiogenesis. The changes occurred within 12 days after the therapy and were significantly correlated with long-term functional outcome, while fluorodeoxyglucose positron emission tomography (FDG-PET) revealed anti-inflammatory response in the brain tissue.[3] Therefore, administration of stem cells seems to induce systemic changes that ultimately affect brain plasticity through anti-inflammatory and immune modulatory actions.

In this issue, Koh et al.[4] reported changes of cytokines after autologous transfusion of mobilized peripheral blood mononuclear cells which was induced by administrating G-CSF in children with cerebral palsy. The cytokines vascular endothelial growth factor (VEGF), IL-6, and IL-10 all increased in similar pattern one month after peripheral blood mononuclear cell injection. The levels of IL-6 and G-CSF increased significantly in therapy responders who showed more improvement than non-responders. IL-6, known as pro-inflammatory, has been investigated as a therapeutic target in inflammatory conditions which revealed its

anti-inflammatory properties.[5] Meanwhile, IL-10 functions as a critical anti-inflammatory mediator. Defective IL-10 promoted accumulation of damaged macrophages and exacerbated inflammatory signals.[6] Administration of mesenchymal stem cells in septic condition leads to more production of IL-10 in macrophages of host organs including the lungs and spleen and improved organ function, suggesting host immune response involved in the therapeutic mechanism.[7]

The G-CSF has been used in many studies targeting restoration from brain injury or dysfunction including stroke, brain hemorrhage, myelopathy, and Parkinsonism to mobilize stem cells into the brain. In an experimental ischemia model, G-CSF exerted neuroprotection against stress-induced endoplasmic reticulum apoptosis, resulting in attenuation of pro-apoptotic proteins and potentiation of anti-apoptotic proteins.[8] The G-CSF augments IL-10-producing regulatory T cells, and high dose G-CSF attenuates monocyte infiltration in the brain tissue after stroke in an IL-10-dependent manner.[9] In a meta-analysis of randomized controlled trials, evidence of safety for G-CSF in stroke was confirmed, however, the efficacy was only supported by improvement of Barthel index.[10] Since stroke shows complicated local responses depending on post-injury duration, phase, and stroke subtypes, specific brain conditions may influence the neuroprotective efficacy of G-CSF. Likewise, the neurodevelopmental outcomes in children with cerebral palsy differ by age and the severity of motor function. Therefore, the application of G-CSF or intravenous infusion of autologous mononuclear cells in children with cerebral palsy needs to be investigated further with stratification of patients according to the age, duration after the onset of injury, type of lesion, and degree of severity. Further study with larger populations and consideration of brain injury pathophysiology will confirm the efficacy and may suggest adequate indication of cell or growth factor therapy including autologous mononuclear cell therapy induced by G-CSF administration for children with cerebral palsy.

In conclusion, by analyzing salient host response as possible therapeutic mechanisms, the optimal therapeutic method utilizing blood mononuclear cells and growth factors can be addressed for different brain pathology.

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