● PERSPECTIVE

By using either endogenous or transplanted stem cells, which could you prefer for neural regeneration?

Neural regeneration by stem cells transplantation: Tissue regeneration and homeostasis are principally dependent on tissue stem cells which possess abilities of self-renewal and differentiation into multidirectional specialized cell types. In general, stem cells are critical for normal tissue renewal as well as repair after tissue injury. For example, mesenchymal stromal cells and endothelial progenitor cells identified in bone marrow could express several markers of pluripotent stem cells including Nanog and Oct-4. Such cells are also found in peripheral blood as well as in umbilical cord blood which might contribute to neural tissue-repair. Consequently, stems cells could constitute an asset for neural regeneration (**Figure 1**). Many studies have engaged different techniques for employing the neural stem cells into specific lineages such as neurons and glial cells, which may promote specific functional recovery through neurogenesis (Nystedt et al., 2006). In addition, preceding studies have revealed the recovery following transplantation of pluripotent stem cells in spinal cord injury models demonstrated the therapeutic potential of this approach, meaning that pluripotent stem cell-derived neural stem cells promote the functional recovery of motor neuron following stem cells transplantation into the damaged neural tissues. Amazingly, the motor function in a non-human primate animal model has been restored by transplanting human stem cells (Iwanami et al., 2005). The functional improvement seems to be associated with the grafted neuronal stem cells (Abematsu et al., 2010). Synaptogenesis between graft-derived neurons and host-derived neurons may be possible contributing to the functional recovery. In addition, re-myelination of the de-myelinated axons is a key mechanism in the regeneration of the injured spinal cord neurons (Kawabata et al., 2016). So, neural stem cells need to primarily differentiate both into neurons and into oligodendrocytes. Axonal growth supported by astrocytes derived from transplanted stem cells may be another foundation for the observed recovery. A previous study had indicated that transplanted stem cells-derived astrocytes in an injured spinal cord promote the outgrowth of serotonergic axon fibers. Oligodendrocytes derived from transplanted stem cells may also play an essential role in promoting the neural recovery by re-myelination of axons.

Several weeks after the injury are the optimum time period for the stem cells transplantation. In addition, inflammation has beneficial and harmful both effects on the transplanted stem cells, which may promote the survival of stem cells by inducing the secretion of trophic factors. Actually, it has been shown that the recovery of neurotrophin level in ischemic brain damage is important for neuronal survival (Lee et al., 2006). Animal study has showed estrogens may also reduce ischemic neuronal damage. In addition, estrogen replacement therapy may improve cognitive function and reduce neurodegeneration in Alzheimer's disease. On the other hand, the release of pro-inflammatory cytokines from active microglia could hurt engrafted stem cells. Challenges remaining to be addressed are the precise management/regulation of transplanted stem cells and the efficacy of them. Transplantation of stem cells may be sometimes an invasive procedure associated with several risks. Signaling pathways that may support the stem cells for self-renewal are often dysregulated leading to carcinogenesis. Furthermore, reduced ability of self-renewal might bring the host into age-related pathologies such as neurodegenerative diseases. Therefore, regeneration tissues should depend on a careful management/regulation of stem cells for the healthy homeostasis. Moreover, time trouble might exist. At present, it takes about a few months to establish pluripotent stem cells. It takes another several months to induce them into neural stem cells. Troublesomely, it would be obligatory to keep fine quality until the use of stem cells for transplantation.

Dietary approach for neural regeneration: Due to the absence of authentic effective treatments for the neural regeneration without using those stem cells transplantation, however, many neuronal degenerative dysfunctions are now public health concern. Therefore, a number of preventive and therapeutic features including modifiable lifestyle factors such as diet and exercise have been proposed mainly by epidemiological research. During exercise, for example, it has been reported that normal quiescent stem cells in muscle proliferate and undergo myogenic differentiation, leading to the regeneration of skeletal muscle (Yin et al., 2013). Although many lifestyle factors could affect brain function, some involvements of foods may be promising in the prevention of neural dysfunction. In particular, diet may also be an important regulator of stem cells. It has been described that a multi-nutrient preparation has a striking therapeutic potential in spinal cord injury. In addition, dietary selections can play a certain role in the neuroprotection of Alzheimer's disease. So, diet could biologically be a major modulator of stem cells in the host. As stem cells may respond to signs from their environment, dietary signals and nutrients could influence them. However, the relation between nutrient consumption and neural regeneration is fairly complex. In addition, the convolution of the human diet makes it difficult to examine their distinct effects of neural regeneration. Indeed, human diet usually consists of complex combinations of lipids, peptides, vitamins, and/or another nutrients that might act synergistically or antagonistically. Anyway, many properties of foods could have some protective potentials for cells including stem cells, which could be facilitated through efficient modulation of the phosphatidylinositide 3-kinase/protein kinase B/phosphatase and tensin homolog deleted on chromosome 10 (PI3K/AKT/PTEN) signaling pathway (Matsuda et al., 2018a). Accordingly, dietary intake might be crucial for keeping health of stem cells.

For example, reduction in caloric intake is generally associated with the benefits of body health including reduced cancer incidence, extended lifespan, and reversal of age-related effects (Fontana et al., 2010). In contrast, obesity is associated with cardiovascular disease, diabetes, and increased cancer incidence (Must et al., 1999). Studies suggest that ketogenic diets defined as high fat, moderate protein and low carbohydrate contents could protect against loss of neurons after brain damage (Neal et al., 2008). Interest in ketogenic diets is increasing due to potential neuroprotective benefits against neural disorders such as Alzheimer's and Parkinson's diseases. The diet may be partly associated with improved mitochondrial metabolism (Matsuda et al., 2018b). All the consequences on the possible induction of stem cells by dietary approach could function on the improvement of neural regeneration (**Figure 1**). Caloric restriction might be beneficial to the function of stem cells, while high fat diets impair the stem cells and/or could even bring in carcinogenesis. Those are plausible, as obesity has been recognized as a risk factor for the development of cancer. Ketogenesis may encourage the stress-resistance against DNA damage, which may improve the function of stem cells. In addition, several fatty acids may directly support the progenitor of stem cells. With a fatty acid, stem cells may acquire several features of more stemness including the competency of oncogenic transformation. Stem cells are susceptible to the inflammatory signals through activation of inhibitor of nuclear factor kappa-B kinase β/nuclear factor kappa B (IKKβ/NFκB) pathway. In this situation,

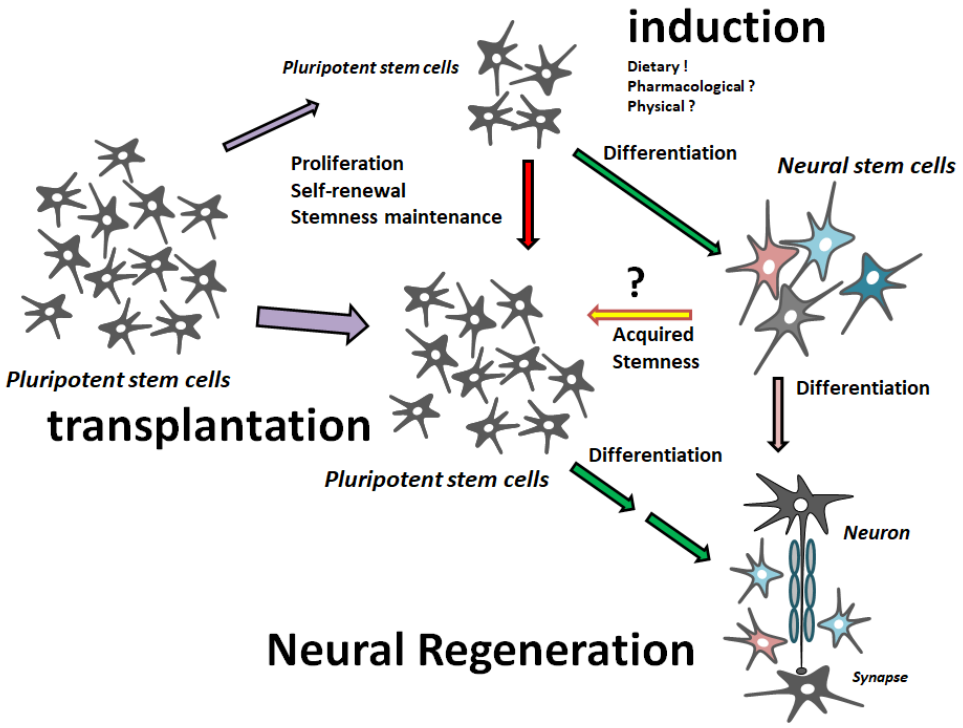

Figure 1 Hypothetical schematic image of the neuronal regeneration pathway.
Stem cells might proliferate and/or differentiate in response to the extracellular growth factor and/or differentiation factor stimulations. In order to accomplish to get neural regeneration, supplementation of stem cells should be required either by stem cells transplantation or by induction of endogenous stem cells. The model shows several triggers for proliferation and/or differentiation could affect the destinations of neural stem cells. Note that some critical routes have been omitted for clarity.

the number of stem cells may diminish due to the apoptosis, resulting in the loss of neurons. On the contrary, a short-term treatment with high fatty acids may improve the proliferation of neural stem cells, suggesting that the response to fatty acids may differentially adjust neural stem cells. Dietary n-3 polyunsaturated fatty acids appear to enhance neurogenesis suggesting that dietary approaches might have the potential to rescue neuronal loss. Taken together, neuro-protection could be achieved by certain diets. Some nutrients might control the capabilities of self-renewal/differentiation of stem cells. However, diet is a modifiable lifestyle factor that influences good health as well as underwrites to diseases such as cancer for the incidence and progression. Further studies focusing on endogenous stem cells in different conditions of diets would help to identify nutritional factors crucial for the population as well as activity/pluripotency of stem cells. In addition, more studies will be mandatory to determine the precise mechanisms in molecular biology.

Satoru Matsuda*, Yukie Nakagawa, Kumi Amano, Yuka Ikeda, Ai Tsuji, Yasuko Kitagishi
Department of Food Science and Nutrition, Nara Women's University, Kita-Uoya, Nishimachi, Nara, Japan
***Correspondence to:** Satoru Matsuda, MD, PhD, smatsuda@cc.nara-wu.ac.jp.*
***orcid:** 0000-0003-4274-5345 (Satoru Matsuda)*
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