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EDITORIAL

Global Neurology

Benefits and Circumspections of Cell-Based Therapy of Stroke

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"If one way be better than another, that you may be sure is nature's way." Aristotle

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For proceeding in regenerative therapy of heart disease, in 2014 Japan has organized an approving system for stem cells application relying on their safety and effectiveness. In this case, a team from Osaka University utilized induced pluripotent stem cells (iPSCs)-derived heart-muscles on thin sheets attachable to attenuated heart muscle aiming to its recovery. This system made some problems as provided conditions for marketing unverified treatments to the patients. In spite of risk factors patients were received, such as immunosuppression, surgery, and side effects of product itself, however, no guarantee for effectiveness of this therapeutics has been observed. Hence, a number of physicians asked to cease selling out of this treatment until the results of performed remedies analyzed whether they are effective or not [1].

Currently, stroke is the second leading cause of death and disability globally [2-4]. Since existing treatments are inefficient for complete functional recovery, the survivals from stroke usually needs to be cared which is a burden to society. As a promising curing strategy, the aim of cell-therapy of stroke is to restore brain homeostasis through anti-inflammatory mechanisms after acute ischemia or renewing injured brain tissue through releasing growth factors, neuronal replacement, and bio-bridge development following chronic ischemia [5].

From applicational aspect, cell-based therapy categorized in two parts of: 1) Directly utilizing cultured cells; or 2) Indirectly usage of their products, indicatively exosomes. However, for enhancement of transplanted cells efficacy, they might be integrated inside biomaterials and/or usage of factors and drugs [6]. In addition to constructive role of biomaterials in refilling empty space of degenerated tissue, also it establishes regeneration through supporting cellular survival and localizing their zone of action on target area of injury [7]. Stem cells-derived exosomes contain cellular neuroprotective factors acting through paracrine signaling without risks of cell transplantation such as immunoreactivity and vascular obstruction. Interestingly, by adjusting microRNA content of exosomes, it is possible to exploit their regulatory role in neurovascular restoration [8].

A notable issue in cell therapy is balancing the view to stem cells efficacy based on their types. As embryonic stem cells [ESCs] studied more extensively than adult stem cells [ASCs], the potential capabilities of adult stem cells in curing diseases has been overlooked which needs to be deciphered by designing aimful studies [9]. Probably, this vision originates from ESCs history in stem cells research. The other reason attributed to intricacy of ASCs slower growth rate comparing to ESCs. However, in addition to application of ASCs for transplantation, also, targeting ASCs study would be promising for deeper understanding of endogenous ASCs behavior for manipulating them in provoking endogenous neuro-angiogenesis. As, endogenous neural stem cells [NSCs] population and their capacity declines by aging process and stroke quickens this procedure, supporting endogenous NSCs in old patients would be critical for maintaining their brain function [10]. Therefore, ASCs are not only a choice for transplantation after stroke but also their application might be a simulation of endogenous NSCs restorative behavior that exploited by regulatory factors after neurodegenerative diseases.

Another hopeful cellular product is iPSCs and NSCs cell line. iPSCs are capable of differentiation into neuronal precursor cells [NPCs] that after transplantation achieve regional identity of the host tissue and integrates to resident neurons through spreading axons to other parts of brain even in contralateral cortex [11,12]. The advantage of iPSCs comparing to ESCs is their non-controversial identity from ethical facet and minimal need for immunosuppression. Presently, Japan is pioneer in planning for banking various lines of iPSCs for allograft transplantation based on human leukocyte haplotypes for providing needs of its population until 2022 [11]. In addition, NSCs are good choice for transplantation as they own neuroprotective capability, but their application has some restrictions as their expansion numbers in culture is limited and the other one is their genetic instability in vitro. Accordingly, NSCs line has been developed by ReNeuron, a stem cell research company, called as CTX cell line for overcoming these limitations [13,14].

The need for establishing certain treatments for stroke highlights the feasible as well as careful strategic plans for introducing cell products to the clinics. This view emphasizes on the vitality of obtaining accurate analyzed data before clinical stage. Thereby, animal modeling and especially large animal models will be helpful for elevating confidence of safer treatment, in the basis of: 1) similar hematoma volume comparing to humans which is much bigger than rodents which takes longer time to be eliminated; 2) availability of stereotaxic techniques for delicate targeting of injury site for transplantation with higher accuracy; 3) probably one the substantial reasons of large animals modeling necessity is revealing high inconsistencies in result of stroke treatment similar to which is observable in human patients. The importance of the latter one is lower variability in rodent ischemia modeling. Therefore, this complexity would be neglected by generalizing the promising findings of cell therapy in rodents to the human. Using large animal models could help to fill unknown gaps before planning for clinical trials [7].

After achieving convincing results, cell products might be utilized in clinical trials. Considering companies interest in accelerating the time from lab to clinic, it is reasonable to regulate strict rules as well as auxiliary for serving patients by high certitude of safety [9,15]. These kind of translational approaches for generalizing benefits of cell therapy in clinics is noteworthy movement, but long-term risks of cell products should not be neglected by short-term merits of cell therapy. Collectively, developing stringent preclinical studies and clinical trials needs to be the mandatory provision for product license acquisition.

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