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Editorial
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The Transitioning from Stem Cells to Stem Cell-Derived Exosomes for Treatment of Neurodegenerative Conditions

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Editorial

Arguably, the therapeutic application of stem cells is one of the most exciting advancements in the field of neurodegenerative diseases. The advancement in research of the stem cell biology has significantly improved our basic knowledge of the mechanism of stem cell functioning and repair mechanisms. The stem cells are well known for their self-renewal capacity, and ability to transform into virtually all types of cells and thereby making up the neuronal loss in the neurodegenerative conditions. The stem cells also provide extensive trophic support to the damaged brain and modulate the microenvironment to enhance survival of neurons and neurogenesis. Following transplantation, stem cells transmigrate through the blood-brain barrier to home in the injury sites where they promote tissue repair and initiate neurogenesis [1,2]. In the injury or inflammation site, stem cells either get transformed to different cell types depending on the microenvironment or release several paracrine factors e.g., Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF) and Vascular Endothelial Growth Factor (VEGF) which promote repair and/or regeneration of the neurons [3-5]. They have the capacity to overcome the human leukocyte antigen barrier and can also reprogram pro-inflammatory microglia (M1) to their anti-inflammatory phenotype (M2) [6,7]. But, all these good things don't come without a price. There is a good chance of infection of these cells by contaminating bacteria, viruses, fungi or even PRIONs which can transmit diseases to the recipients [8,9]. Not only contamination issues, cell age, viability, proliferative capacity or differentiation status of a particular batch of cells can influence the success of the cell transplantation. Handling methods, storage, transport etc. can modify the stem cell characteristics that may affect the success rate of the treatment [10]. Transplanted stem cells may undergo uncontrolled proliferation forming unwanted tissue mass resembling primitive neural structure [11]. Tumorigenesis and mutagenesis are other important issues which should be considered in the stem cell therapy [12]. Moreover, many pluripotent stem cells including Induced Pluripotent Cells (iPSCs) were reported to induce teratoma and teratocarcinoma which further questions the safety of stem cell therapy [13]. Also, immune suppression evoked by transplanted hMSCs may lead to several unwanted effects in the recipient body. Another common complication of allogeneic stem cell transplantation is Graft-Versus-Host Disease (GVHD) in an attempt to reject the graft tissue by the donor body. This effect can be overcome by donor-recipient matching, immunological sequestration or by using immunosuppressive drugs. All these approaches have their own drawbacks and together they make the stem cell therapy questionable (Figure 1) [14]. The literature has accumulated substantial evidence to suggest that MSCs exert their therapeutic effect with the help of soluble factors as well as by producing Exosomes (EVs). EVs are nano-sized vesicles (30 nm to 100 nm) of endocytic origin and play a pivotal role in intercellular communication. Their therapeutic effect depends on the content they carry e.g., proteins, mRNA, miRNA etc. [15]. They are released by every cell in the extracellular fluid. EVs have a potential role in carrying and delivering neurodegeneration related factors such as β-amyloid associated with Alzheimer's disease, α-synuclein in Parkinson's disease, huntingtin in Huntington's disease or miRNA e.g., miR-27a-3p in Amyotrophic Lateral Sclerosis, each of which has a potential to be used as a biomarker for the corresponding diseases [16,17]. It has been shown that MSC-derived exosomes were able to exert therapeutic effect like MSCs [18]. MSC derived exosomes have been shown to reduce cognitive deficiency caused by TBI in mouse and have the potential for treatment of TBI [15,19,20]. Exosomes carrying functional miRNA induced neurite remodeling and functional recovery following stroke in rats and mice [21,22]. While in general EVs are basically lipid envelops, recently a non-enveloped EV composed of virus-like capsids have been discovered. These EVs carry the Arc mRNA responsible for synaptic plasticity and long-term potentiation in metazoan brains including mammals. Although their

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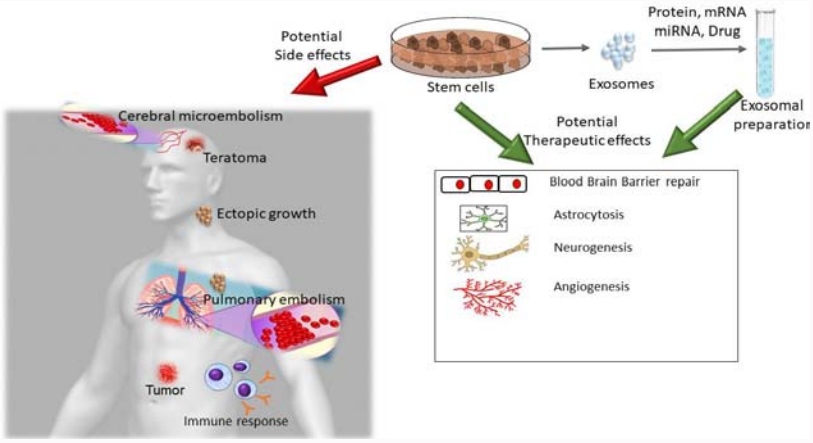

Figure 1: Benefits and risks of cell based therapeutics of the neurodegenerative conditions.

detailed functions in the nervous system in health or diseases is yet to be identified, these EVs are implicated in one directional intercellular communication in the nervous system [23-25]. The EV- mediated drug delivery approach is also promising. The lipid composition, the major component of EVs enhances their stability while circulating in the body [26]. On the other hand, the protein components of EVs inhibit the complement and phagocytosis; thereby reduce the clearance [27,28]. EVs safely and successfully carry the payloads like miRNA or siRNA which would otherwise easily degrade in the serum, to the target tissues crossing the blood-brain barrier [29]. Both hydrophobic and hydrophilic drugs can be loaded into the EVs [30]. The advancement of therapeutic approaches from the cell-based to subcellular exosomes based therapy has potential advantages. While exosomes can deliver therapeutic effects at least equivalent to that of MSCs, the exosomes have a longer shelf-life and in vivo half-life and thus can be available to patients more readily while needed [15]. Probably the biggest advantage of using exosomes is the safety. All the safety issues related to using MSCs can be avoided by the use of MSC derived exosomes without compromising the efficacy [15,31,32]. Thus, exosomes, especially, the MSC- derived exosomes can solve several issues associated with MSC therapy and bring a new era in the therapeutics of neurodegenerative conditions including stroke and TBI.

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