

● HIGHLIGHTS

Dental pulp stem cells for treating neurodegenerative diseases

The hippocampal formation, important for spatial learning and memory function, exhibits high level of plasticity in response to behavioral changes as well as injury. Dysfunction of the hippocampus is one of the hallmark features of neurodegenerative diseases like temporal lobe epilepsy (TLE) and Alzheimer's disease (AD) (Dhanushkodi and Shetty 2008). Excitotoxicity is one of the known mechanisms by which neurons undergo degeneration in neurodegenerative condition (Haglid et al., 1994; Doble et al., 1995). Brain regions such as hippocampus are more susceptible to excitotoxic damage. During excitotoxicity, the glutamate receptors are hyper-activated, resulting in an imbalance between inhibitory and excitatory function, disturbances in calcium homeostasis, mitochondrial function and enhanced production of free radicals that eventually cause the nerve cells to degenerate (Zheng et al., 2011). Most of the existing drugs for treating neurodegenerative diseases provide only symptomatic relief and do not affect the progression of the disease. Hence, there is a pressing need to identify alternate therapeutic approaches to treat neurodegenerative diseases.

Mesenchymal stem/stromal cells are better than embryonic stem cells: Stem cell therapy is evolving as a treatment option for many neurological and neurodegenerative diseases (Bjorklund and Lindvall 2000; Daniela et al., 2007). In this context, several studies have used embryonic stem cells to ameliorate the neurological and behavioural deterioration in animal models of neurodegenerative diseases. Nevertheless, due to difficulties in obtaining embryonic tissues, teratoma formation, immune rejection, and the ethical concerns associated with it, a significant portion of research have been focused on utilizing adult mesenchymal stem/stromal cells (MSCs) as a possible source for cell transplantation (Huang et al., 2009). Mesenchymal stem/stromal cells are plastic adhering fibroblast like cells first reported by Friedenstein et al. (1968). Adult derived MSC which can be obtained from bone marrow, placenta, adipose tissues, skin and dental pulps have generated remarkable interest in using these cells for treating neurological and non-neurological diseases (Wang et al., 2012). Mesenchymal stem/stromal cells from various tissue sources fit the criteria defined by the International Society for Cellular Transplantation (ISCT) to identify MSC, *i.e.*, plastic adherence property, expression of cell surface markers (positive for CD105, CD90 and CD73 and negative for hematopoietic markers like CD34, CD45, CD14 and human leukocyte antigen marker HLA-DR) and their ability to differentiate into osteocytes, adipocytes and chondrocytes (Dominici et al., 2006). Akin to embryonic stem cells, MSC can maintain

their replicative capacity for prolonged period *in vitro*. The advantages of using MSC over embryonic stem cells are that MSC could be from autologous sources, thereby bypassing ethical concerns as well as immune rejection. Further, due to their immunomodulatory potential, MSC can also be used in allogeneic and xenogeneic transplantation. Several pre-clinical and clinical studies have shown promising results with bone marrow mesenchymal stem/stromal cells (BM-MSCs) in treating neuronal and non-neuronal diseases (Derubeis and Cancedda, 2004; Bae et al., 2007; Wang et al., 2012).

Dental pulp stem cells are better than bone marrow mesenchymal stem/stromal cells for treating neurodegenerative diseases: Bone marrow mesenchymal stem/stromal cells are one of the thoroughly studied MSCs that were primarily considered as "Gold Standard" MSCs for treating a spectrum of diseases. Nonetheless, several disadvantages of using BM-MSCs are that bone marrow isolation is an excruciating surgical procedure with less yields of MSCs, lower proliferation rate and differentiation capacity that correlates with the age of the donor (Stenderup et al., 2003; Huang et al., 2009). Thus, there is a need to search for an alternate source of MSCs having therapeutic benefits similar to that of BM-MSCs. Furthermore, as systemic injections of MSCs are more feasible than direct transplantation, several pre-clinical studies conducted in the past concluded that only minor percentage of systemically injected MSCs home to CNS. Therefore, in order to achieve a clinically significant outcome using systemic injections of MSC for treating CNS diseases several factors need to be taken into consideration *i.e.*, the dynamics of blood-brain barrier (BBB) damage for a given neurodegenerative condition, tissue source of MSCs to be used and the expression pattern of homing factors like stromal cell derived factor-1 alpha (SDF-1 α), vascular cell adhesion molecule-1 (VCAM-1), hyaluronic acid, and their cognate receptors CXCR-4, very late antigen-4 (VLA-4/ α 4 β 1 integrin) and CD44 respectively (Lazarini et al., 2003; Stumm et al., 2003; Brooke et al., 2008; Li et al., 2012). Though MSC from various tissue sources fit the International Society for Cellular Therapy (ISCT) eligibility criteria they do differ in their migration potential (Brooke et al., 2008; Nystedt et al., 2013) and neuroprotective efficacy (Sakai et al., 2012) due to qualitative differences in their physiological niche. Thus, identifying MSCs with neurogenic potential and appropriate timing of systemic injection based on BBB damage would yield better CNS homing and engraftment. In this context, identification and successful isolation of dental pulp stem cells (DPSCs) with their inherent neurogenic potential have opened up an opportunity to explore a tailor made MSCs for treating nervous system diseases (Gronthos et al., 2000). Dental pulp stem cells originate from the migratory neural crest, thus possess both mesenchymal and neuronal characteristics and have been appropriately called as ectomesenchyme (Ranganathan and Lakshminarayanan,

2012). Dental pulp stem cells possess several advantages over BM-MSCs like less invasive procedure for isolation, better *ex vivo* expansion and neurogenic potential hold DPSCs as a suitable candidate for treating neurodegenerative diseases (Govindasamy et al., 2010; Ibarretxe et al., 2012). In line with this, DPSCs enhances the proliferation of endogenous neural stem/progenitor cells following intrahippocampal injection in naive mice (Huang et al., 2008). Furthermore, two recent studies demonstrated that DPSCs confer better neuroprotection than BM-MSCs in animal models of spinal cord injury and ischemia (Sakai et al., 2012; Yamagata et al., 2013). Interestingly, conditioned medium/secretome derived from DPSCs could also recapitulate the neuroprotective effects as that of direct DPSC cell transplantation (Inoue et al., 2013). Given their neural crest origin, the mRNA expression of various neurotrophic factors like glial derived neurotrophic factor, brain derived neurotrophic factor, ciliary neurotrophic factor and neurotrophic factor-3 are several folds higher in DPSC as compared to BM-MSC (Sakai et al., 2012).

Conclusion and future prospective: Neural crest originated DPSC could be an ideal stem cell candidate for treating neurological and neurodegenerative diseases. Dental pulp stem cells hold several advantages as oppose to BM-MSCs like less invasive isolation, superior *ex vivo* proliferation and inherent propensity to differentiate into neurons and glia. In future, several studies are warranted to explore the therapeutic potential of DPSCs as compared to the BM-MSC in treating various neurodegenerative diseases like Alzheimer's disease and temporal lobe epilepsy. Such studies should systematically investigate the neuroprotective effects of DPSCs and attempt to provide knowledge about the molecular, biochemical, and behavioral outcomes of DPSCs cell therapy. If the neuroprotective potential of DPSCs is relatively significant than that of BM-MSC, this would help basic researchers as well as clinicians to choose appropriate MSCs in preventing/treating patients with neurological/neurodegenerative diseases.

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