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Review Article

Various strategies to improve efficacy of stem cell transplantation in multiple sclerosis: Focus on mesenchymal stem cells and neuroprotection

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) which predominantly affect young adults and undergo heavy socioeconomic burdens. Conventional therapeutic modalities for MS mostly downregulate aggressive immune responses and are almost insufficient for management of progressive course of the disease. Mesenchymal stem cells (MSCs), due to both immunomodulatory and neuroprotective properties have been known as practical cells for treatment of neurodegenerative diseases like MS. However, clinical translation of MSCs is associated with some limitations such as short-life engraftment duration, little in vivo trans-differentiation and restricted accessibility into damaged sites. Therefore, laboratory manipulation of MSCs can improve efficacy of MSCs transplantation in MS patients. In this review, we discuss several novel approaches, which can potentially enhance MSCs capabilities for treating MS.

1. Introduction

Multiple sclerosis (MS) is an inflammatory disease of central nervous system (CNS) with common neuropathology features such as neurodegeneration, demyelination, glial cell destruction, and eventually axonal loss (Dendrou et al., 2015; Vidal-Jordana & Montalban, 2017). MS affects up to 2 million individuals worldwide by involving predominately young adults undergo heavy socioeconomic burdens (Bin Ahmad, 2018; Negrotto & Correale, 2018). Integrity disturbance of axons and accumulation of irreversible sclerosis scars contribute to progressive phase of MS(Coclitu et al., 2016). Several hypotheses have elucidated to describe pathophysiology of MS. A recent concept proposed MS as a primary disease triggered by flawed function of oligodendrocytes that cause a myelin sheath damage and not as a result of immune cells attack into the CNS (Stys et al., 2012; Yamout & Alroughani, 2018). Other possible causes of MS are over-activating microglia cells, oxidative stress, neural cytoskeletal abnormalities, and ion channel dysfunction induced by mitochondrial injury and energy deficiency (Compston & Lassmann, 2006; Kidd, 2001). Conventional therapeutic modalities for MS mostly are restricted to symptomatic remedy and offer only short-term immunosuppressive effects while ignore neuroregeneration and just slow down progression of MS (Inglese & Petracca, 2015). These current disease-modifying therapies are commonly unable for long term remyelination and are insufficient for ameliorating progressive course of the disease (Torkildsen et al., 2016; Maarouf et al., 2018). Irreversible disabilities and little cell turnover of CNS in MS encourage researchers to focus on cell-based therapy as an alternative treatment for repairing damaged myelin. However, decisive curing of MS requires both inhibition of auto-reactive immune cells and rehabilitation of multifocal demyelinated lesions (Derwenskus & Lublin, 2014). Meanwhile, remyelination should involve quick restoration of defective myelin besides prevention from more axonal degeneration (Harlow et al., 2015; Zephir, 2018). In this paper, we review state-of-the-art approaches for renovating lost neurons, repairing disseminated myelin, and ameliorating vicious immune system in MS using stem cells.

2. Novel source of stem cells for regenerative application

To date, hematopoietic stem cells (HSCs) and embryonic stem cells

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(ESCs) have presented many advantages in clinical usage but their application is associated with some hurdles; hence scientists have been looking for other sources of stem cells for treatment of neurodegenerative diseases (Gratwohl et al., 2010; Atkins & Freedman, 2013; Racke & Imitola, 2017; Karussis et al., 2013; Yang et al., 2009a; Shirai et al., 2016; Chong et al., 2014). Each type of stem cells (embryonic, adult and IPS) or even stem cells of the same type but from different sources have distinguished characterizations. For example, MSCs from umbilical cord and adipose tissue have shown different inhibitory effects on lymphocyte activation (Pistoia & Raffaghello, 2017).

It has been shown that stem cells are prone to differentiate into tissue cells from which they have been originated. For instance, stem cells derived from nervous system are more talented to produce neuron lineage rather than other stem cells (Phinney & Isakova, 2014). Therefore, one of the suitable stem cells candidates for treatment of neurodegenerative disorders are neural stem cells (NSCs) and their derivatives. However, finding an ideal source of stem cell for treatment of MS is still under debate. Although ESCs are un-limited self-renewal cells with high plasticity for producing various cell lineages, but because of ethical problems risk of tumorigenicity, laborious availability, governmental restrictions and low pool of self-graft recourses, their application have been restricted (Gd & Mummery, 2003; Lee et al., 2013).

Oligodendrocyte progenitor cells (OPCs) derived from ESCs have been successfully utilized in patients with spinal cord injury for attenuating functional and histopathological deficits (Sharp et al., 2010). Albeit HSCs have been employed in a number of clinical studies for curing MS, but because of intensive chemotherapy prior to the HSCs administration and painful and invasive isolation procedure as well as infrequency of stem cells in bone marrow, other reservoirs of stem cells for treatment of MS have been pursued (Atkins & Freedman, 2013; Swart et al., 2017; Atkins et al., 2016; Rush et al., 2018).

2.1. Mesenchymal stem cells (MSCs)

The MSCs are multipotent stem cells presented in almost all tissues including bone marrow, fetal tissue, dental pulp, and even peripheral blood (Gao et al., 2016; Uccelli et al., 2011). Besides adipogenic, osteogenic and chondrogenic capacity, MSCs are capable to differentiate into even non-mesodermal lineages such as neural cells (Zemel'ko et al., 2013). In spite of great proliferative ability of MSCs, they are genetically stable in culture medium following high passages. Furthermore, MSCs are poor immunogen cells proper for alloraft transplanation without serious host immune rejection responses (Ding et al., 2011; Ullah et al., 2015).

Widely accepted positive surface markers for MSCs are CD105, CD166, CD73, CD90, CD29, octamer4, STRO-1 and negative markers are CD34, CD45, CD14, HLA-DR (Heathman et al., 2016). The MSCs have a wide range of immunomodulatory activities. In this context, MSCs inhibit B and T lymphocyte proliferation, reduce the inflammatory cytokines such as IFNγ, TNFα, IL6, IL17 while increase anti-inflammatory cytokines like IL10, TGF β and IL4 (Zhao et al., 2016; Yi & Song, 2012). The MSCs also enhance splenic and blood TCD4 + CD25 + FOXp3 + (Treg) population (Luz-Crawford et al., 2013). Some part of immunoregulatory effects of MSCs is through modulating the balance between Th1/Th2/Th17 and shifting from Th1/Th17 into Th2 (Qu et al., 2012; Duffy et al., 2011). Similarly, MSCs inhibit natural killer (NK) activity and suppress proliferation and activation of antigen-presenting cells (APCs) via downregulating co-stimulatory molecules on APCs (Spaggiari et al., n.d.; Machado & Telles PDdS, Nascimento ILO, 2013). Beneficial effect of MSCs is partly via their bioactive molecules or by direct contact of MSCs with surrounded cells. Since life duration of MSCs, following engraftment, is rather short (less than 90 days), immunoregulative features of MSCs maybe mediated by major soluble factors such as indoleamine-pyrrole 2,3-dioxygenase (IDO), transforming growth factor- β1 (TGF-β1), interleukin-10 (IL-10), nitric oxide (NO), prostaglandin E2 (PGE2), hepatocyte growth factor (HGF) (Mallucci et al., 2015). Moreover, neuroprotective effects of MSCs have been demonstrated in a number of studies using experimental autoimmune encephalomyelitis (EAE) as an animal model of MS (Zappia et al., 2005; Rafei et al., n.d.; Constantin et al., 2009; Glenn et al., 2015). Neurogenerative influence of MSCs is relatively mediated by secreting nerve growth factors (NGF), basic fibroblast growth factor (bFGF), BNDF, glial cell-derived neurotrophic factor (GDNF), hepatocyte growth factor (HGF), epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1) and IGF-2 (Gao et al., 2016). Parallel investigations have established neural growth promoting potential of MSCs suggesting their support in renovation of damaged myelin from both aspects of neurogeneration and immunomodulation. Additionally MSCs can release new mitochondria to destroyed cells thereby promote aerobic metabolism. Figu. 1 (Caicedo, 2017).

2.1.1. Gingiva and dental tissue-derived MSCs (GMSCs)

Although myelinogenic progenitor cells such as OPCs and Schwann cells (SCs) are perfect sources of cells for renovation of defective myelin, accessibility to these cell sources is limited and sometimes aggressive; therefore discovering more available pool of stem cells can be helpful in regenerative medicine. Gingiva-MSCs (GMSCs) are neural crest-derived cells with high potential for neural renovation besides facile and painless accessibility and obtainable even from discarded biological samples. GMSCs are multipotent nestin positive stem cells capable to differentiation into various progenitor cells along which simple extraction protocol from oral tissue have evolved new avenues for restorative medicine.(Rao et al., 2016) (Zhang et al., 2009). GMSCs have peculiar tolerogenic properties, which through their immunoregulatory and self-renewal characterizations participate in oral mucosal immunity. Of importance immunomodulatory effects of GMSCs can imply to polarization of macrophages toward anti-inflammatory M2 phenotype, stimulating Tregs proliferation, reducing T lymphocytes expansion and secreting high levels of IDO in inflammatory condition (Zhang et al., 2010; Wang et al., 2011).

Dental tissue MSCs (DT-MSCs) are harbored in dental pulp tissue. The DT-MSCs, by producing major growth factors and chemokines like GM-CSF, VEGF, RANTES, FLT-3, MCP-1 and fractalkine, have been shown to exert neuroprotective impacts on nearby cells that stimulate neuronal cell survival (Li et al., 2014a; Li et al., 2014b; Taşlı et al., 2016; Stanko et al., 2018). The DT-MSCs are multipotent stem cells which differentiate into many type of cells including neural lineages. They exhibit great proliferative valence along with simple accessible, low immunogenic and chromosome stability in high passages. Also, it has been demonstrated that DT-MSCs possess stronger immunomodulatory influence suggesting them as promising tools for stem cell therapy in MS (Liu et al., 2015).

2.1.2. Adipose-derived MSCs (AD-MSCs)

A growing body of evidence has demonstrated that adipose-tissue derived MSCs (AT-MSCs), owning to their unique properties such as easily accessible, abundance and simple harvesting protocols by minimally invasive procedure, are attractive candidate for CNS degenerative disorders (Marconi et al., 2013). The adipose tissue is a rich source of MSCs suitable for autologous transplantation. A large number of MSCs with high proliferative rate are obtained from liposuction (100,000 MSCs in each gram of fat). The AT-MSCs have a doubling time of about 60h and are genetically stable after at least 12 passages in culture medium while maintaining their telomere length and are less affected by donor age. Likewise, clinical administration of AT-MSCs is associated with less ethical concerns and are attainable in GMP manufacturing (Shalaby et al., 2016).

Different forms of adipose tissue including white, brown, bone marrow, mammary and mechanical exist in the body (Kolaparthy et al., 2015). The AT-MSCs owing to their low immunogenicity valence are proper cells for allogeneic graft (Ra et al., 2011). They are characterized

by presence of CD49e,CD49d, CD54, CD80, CD138, CD13, CD9, CD59, CD29, CD73, CD44, CD90, CD166, CD105, CD146, CD106 and STRO-1 and absence of CD34, CD19, CD144, CD11b,CD11c, CD146, CD56, CD14, CD31, CD45, CD133 and HLA-DR (Hamid et al., 2012). A study has proved that AT-MSCs are more resistant to apoptosis compared to BM-MSCs and are safe even at high doses (Ertas et al., 2012). These properties make AT-MSCs an appropriate alternative source for BM-MSCs.

The AT-MSCs produce angiogenic factors such vascular endothelial growth factor (VEGF), bFGF and IGF at a level more than BM-MSCs which help neovascularization (Li et al., 2015a; Kress et al., 2018). In comparison with BM-MSCs, AT-MSCs are more resistance to oxidative stress and hypoxia-induced apoptosis and have higher traveling speed with rotational direct (Kress et al., 2018; El-Badawy et al., 2016). Also, AT-MSCs produce high level of anti-inflammatory agents including IL-10, TGF-β and PGE2. Furthermore, AT-MSCs exhibit robust neuroregeneration phenomena by secreting neuroregulatory factors like NGF, BNDF and GDNF (Maumus et al., 2013). The HLA-G is one of the predominant players in attenuating of EAE severity in mice treated with AT-MSCs (Shalaby et al., 2016). The AT-MSCs also reduce Th17/Treg ratio by releasing leukemia inhibitory factor (LIF) resulting in abating EAE disabilities (Li et al., 2017a). Neuroprotective impact of AT-MSCs in EAE mice was represented in the growing number of clinical trials for treatment of MS patients (Constantin et al., 2009; Anderson et al., 2017; Meamar et al., 2016; Yousefi et al., 2016).

2.1.3. Fetus-derived MSCs (FD-MSCs)

Recently, neural stem cells (NSCs) derived from fetal tissue have attracted attentions for their usage in clinic. Fetal tissues including placenta, cord blood, Wharton's jelly and amniotic fluid contain high quantities of MSCs with similar characterizations to embryonic stem cells. The fetus-derived MSCs (FD-MSCs) are more desirable than ESCs due to their particular properties such as simple accessibility and less invasive isolation protocol from materials that used to be discarded (Shin et al., 2009). Similar to ESCs, FD-MSCs represent high self-renewal and differentiation capacity but, contrary to ESCs, FD-MSCs are stable genetically even in extremely proliferative condition and are less susceptible to be carcinogenic (O'Donoghue & Chan, 2006). Moreover, due to their enriched secretome containing BDNF, G-CSF, VEGF, TGF-β, IGF1 and GDNF, they are valuable candidates for healing neurological injuries (Brady et al., 2014; Arutyunyan et al., 2016).

The FD-MSCs express HLA-G on their surface or in the serum (La Rocca et al., 2009). The HLA-G is a tolerogenic molecule expressed in pregnancy which eliminates danger of immune rejection thereupon there is less possibility to be rejected by the host immune system (Ding et al., 2016). Additionally, MSCs from amniotic fluid, cord blood, and placenta have been shown to have significant immunomodulatory effects resemble to BM-MSCs in mitigating EAE severity (Kim et al., 2013; McDonald et al., 2015; Abumaree et al., 2017; Jiang et al., 2017; Giacoppo et al., 2017). Furthermore, Wharton Jelly-MSCs, a cell population belonging to connective tissue of umbilical cord, are easily achievable after spontaneous delivery without any invasive procedure. The WJ-MSCs are population with high proliferation valance alongside late senescence. The WJ-MSCs have been displayed to own profoundly neuroprotective effects on functional improvement in animal model of MS and therefore they are considered to be more practical in clinical translation relative to BM-MSCs. Interestingly, they express the chemokine receptors of CXCR4, CXCR3, and CXCR6, which conduct MSCs migration into the site of injury. The WJ-MSCs also can differentiate into neuro-glial commitment and release neurite guidance molecules such as ninjurin-2 and netrin (Joerger-Messerli et al., 2016).

Amniotic fluid MSCs (AF-MSCs) or WJ-MSCs combined with current therapies like growth factors can be more effective in neural regeneration. AF-MSCs produce a measurable amounts of BDNF and NGF suggesting AF-MSCs as promising tools for treating MS (Joerger-Messerli et al., 2016). Another study also has established that human derived umbilical MSCs, thanks to their several merits such as high proliferative valence and rich source of MSCs, are another suitable option for neurodegenerative diseases including MS (Zhang et al., 2011).

2.1.4. Olfactory ensheathing cells (OECs)

Olfactory ensheathing cells (OECs) are pluripotent glia cells that are present in olfactory bulb and mucosa in both peripheral nervous system (PNS) and CNS which shared properties of astrocytes and Schwann cells (Grosu-Bularda et al., 2015). The OECs are neural crest-derived cells with potential to cross the transitional zone between CNS and PNS (Azimi Alamouti et al., 2015). They, by secreting a variety of neuroregulatoy factors, have a supportive role in reviving damaged axons. The OECs are easily accessible and with their high valence for migration are capable to be localized in the axonal lesions and participate in myelination; therefore they can be a promising autologous source for lowering rate of progression in myelodegenerative diseases such amyotrophic lateral sclerosis (ALS) and MS (Li et al., 2015b; Chen et al., 2012). It is worth mentioning that OECs, in normal circumstances, are not able to generate myelin but after in vivo infusion and reaching the damaged sites they can take part in axonal remyelination in a manner like Schwann cells (Ekberg & St John, 2015). One of the remarkable OECs advantages is their migratory potential through long distances for cooperation in axonal remyelination (Anna et al., 2017; Ramón-Cueto et al., 2000).

2.1.5. Neural stem cells (NSCs)

Over recent decade, many researchers have concentrated on neural stem cells (NSCs) as a valuable source of stem cells for recovery of lesions in neurodegenerative diseases. The NSCs are self-renewal cells capable to differentiate into various neural progenitor cells (NPCs) such as oligodendrocytes, neurons and astrocytes (Gonzalez et al., 2016). They are multipotent stem cells distinguishable from other cells by expression of sox-2, nestin, prominin-1, CD56(NCAM), Notch2, oct4, ABCB1,ABCG2, HSPA4,9,14 and RBP1,2,7 while NPCs are unipotent cells located in forebrain with less capacity for self-renewal and commitment to generate the neurons characterized by expression of p75, neurotrophin receptor and PSNCAM.

Sub ventricular zone of the lateral ventricles, circumventricular organs (CVOs) and dentate gyrus of the hippocampus are naïve specific microenvironments for NSCs harboring (Gage Fred & Temple, 2013; Kornblum, 2007). The NSCs are obtained directly from embryonic, fetal or adult brain tissue or indirectly using in vitro differentiation from other stem cells (Kornblum, 2007; Temple, 2001).

Therapeutic potential of NSCs for alleviating of EAE has been indicated in a number of investigations (Li et al., 2017b; Ravanidis et al., 2015; Yang et al., 2009b; Nasri et al., 2018) in which neurological remission and immunological improvement in NSC-treated EAE mice have been demonstrated. The NSCs preferentially migrate along the normal pathway given by native NSCs and distribute rather in lesion sites than in the normal CNS parenchyma. Surprisingly, NSCs have been observed in the lymph nodes for 3 months from cell administration in EAE primate model (Jadasz et al., 2012).

The NSCs have similar origin as damaged neurons, are amenable in CNS milieu and habitude with neuronal circuitries. Thus, they can survive better in their natural niche and are more potent to share neural differentiation abilities (Vishwakarma et al., 2014). The ESC-derived OPCs did not survive more than one week after intraventricular administration into EAE mice whereas NSC-derived OPCs could survive more than 4 weeks in vivo and contributed in remyelination (Piao et al., 2015; Kuai et al., 2015; Liu et al., 2000; Grade et al., 2012).

In the clinical setting, a complex net of ingredients including various cells, specialized niche and interplaying between cells and their milieu is demanded (Mallucci et al., 2015). Indeed, by manipulating each step of NPCs development including expansion, CNS migration to long distances, homing, NPC integration, survival and differentiation into

oligodendrocytes, NPC efficacy after grafting can be optimized. For example, migration capacity of NSCs from blood into inflammatory lesions is relatively limited but by upregulating chemotactic receptors on NSCs, using biotechnological methods, promising perspective in terms of NPCs usage in neuroregenerative medicine can be achieved. As another strategy, phosphatidylinositol-3-kinase (PI3K)/Akt signaling pathway is activated in neural progenitor cells after cell transplantation that triggers neurogenesis activities; therefore, by stimulating PI3K/Akt route using some mitogens neural regrowth can be promoted (Lee et al., 2016a). On the same line, NSCs engineered to produce neurotrophin3 have shown a substantial effect on improvement of functional outcomes in spinal cord injury in animals (Teng et al., 2014). Recently, elegant studies have shown that by modifying the culturing system in which the NSCs are grown can determine differentiation fate of NSCs into neurons, oligodendrocytes or astrocytes. Defining a certain culture system for NPCs by adding basic fibroblast growth factor (b-FGF-2) and epidermal growth factor (EGF) as important supplements for neural differentiation could generate various neural linage in vitro (Hu et al., 2013). Grafted NPCs attenuate deleterious effects of autoreactive responses also drive endogenous NPCs for participating in repair procedure and preparing a permissive milieu for neural regeneration and neural cell replacement (Vishwakarma et al., 2014).

Owning to limited accessibility of initial source (embryonic or fetal) for isolation of autologous NPCs, an allogeneic reservoir for NSCs isolation has attracted attentions. Nevertheless, immunological responses associated with graft–host interaction is still a serious limitation for allogeneic application of NPCs. Therefore, IPS-derived NPCs are becoming more attractive (Temple, 2001; Vishwakarma et al., 2014).

The NSCs therapy in neurodegenerative diseases such as ALS and Alzheimer's disease has been used successfully in terms of reducing destructive occurrences. To maximize beneficial therapeutic effects of NSCs in MS, NSCs should be tailored to reduce autoimmunity, enhance remyelination and increase their self-renewal potential to generating new NSCs. Inflammatory environment, reactive astrocytes and activated microglia represent two contrary performance in disease condition. That means inflammatory circumstance can harness ideal responses of NSCs and restrain activities of endogenous repair system or may stimulate integration of exogenous NSCs into native milieu and help neurogenesis (Imitola, 2007; Schäfer et al., 2016).

Time of NSCs transplantation is important for successful response in MS patients. In relapsing-remitting MS when the plaques are active, endogenous restoration system and injected NSCs are actively cooperated in reparative procedure while in progressive forms of MS because of gliosis and fibrosis scars, perfect function of reparative cells for rebuilding of lesions will be mitigated (Miller & Bai, 2012). There is no incisive document about fate of transplanted NSCs, whether they integrate into other neural cells, undergo trans-differentiation or collaborate in secreting systemic bioactive molecules such as TGF-b1 and TGF-b2.

2.1.6. Induced neural stem cells (iNSCs)

Despite self-renewal potential of NSCs, accessibility of the NSCs in the body is limited. The NSCs generated from somatic cells can be considered as a fairly patient-specific source for NSCs that compensate the shortcomings related to NSCs. Induced-NSCs (iNSCs) are pluripotent stem cells generated by introducing exogenous genes into somatic cells (fibroblasts, B cells, sertoli cells, liver cells, cord blood cells) via viral and non-viral transfection methods (Capetian et al., 2016). The iNSCs have similar pattern of phenotype, function, gene and epigenetic characterization as naive NSCs (Ruggieri et al., 2014). Contrary to NPCs and ESCs, starting cell source for generating iNSCs is easily attainable during which high level of NPCs with less ethical problems and difficult extraction procedure will be manufactured. Furthermore, iNSCs represent lower chromosome abnormality and less carcinogenic possibility with respect to ESCs and IPSs (Capetian et al., 2016; Ruggieri et al., 2014; Cairns Dana et al., 2016).

A substantial body of literature has produced viral-based iNSCs by direct transfection of fibroblast cells with several genes such as Sox2, Oct4, L-myc, Klf4 ,ZFP521, and Lin28 using lenti or retrovirus (Connor et al., 2015; Shahbazi et al., n.d.; Tian et al., 2017; Huang & Franklin, 2012). Other systems for iNSCs transfection are carrier molecules such as RNAs, proteins and non-insertion episomal vectors. Monolayer culture system and using a mixture of chemical agents such as repsox and valpronic are other strategies for iNSC production (Tang et al., 2017).

By overcoming some hurdles related to iNSC including hard control condition for differentiation of iNSCs into one of the neural lineages (neuron, astrocyte or oligodendrocytes) and supplying a homogenous population of iNSCs, a novel and applicable strategy for healing neurological diseases may be reachable.

2.1.7. Oligodendrocyte processor cells (OPCs)

Oligodendrocyte processor cells (OPCs) are major myelinating cells in CNS. The OPCs are originated from adult NSCs and are one of the promising cells for cell replacement in CNS neurodegenerative disorders. Oligodendrocytes are generated either from endogenous OPCs or by differentiation from other exogenous stem cells (Djelloul et al., 2017). The OPCs have been widely distributed in the CNS and are characterized by initial expression of NG2 and PDGF.Ra O4 expression in subsequent stage of its development (Douvaras et al., n.d.). Although OPCs are unipotent cells responsible to create oligodendrocytes, they may be multipotent in certain circumstances and differentiate into Schwann and neural cells (Imitola, 2007). By optimization of each step of OPCs development including culturing, expansion, migration, in vivo survival, and differentiation, an advancement in curing demyelinating diseases like MS can be achieved. In several studies, OPCs have been designated to restore myelin sheath in animal model of CNS demyelination (Rice et al., 2004; Prayoonwiwat & Rodriguez, 1993). At least four months for oligodendrocytes culturing is required. Therefore, discovering a method to shorten cultivating time to produce a large amounts of oligodendrocytes is of importance. Matured oligodendrocytes are unable to self-producing. Hence, finding a solution to eliminate this obstacle can be profitable in regenerative CNS engineering. This could be done via relevant mitogenic inducers or through manipulating the transcription factors genes or by engineering cell cycle and signaling molecules which take part in cell proliferation (Huang & Franklin, 2011). Some transcription factors (TFs) like Wnt, Notch and LINGO-1 suppress OPC differentiation while retinoid X receptors (RXRs) and Tcf4 are simulative nuclear receptors for OPCs evolution. Retinoic acid with inhibition of SMAD proteins, accelerates OPCs generation (Douvaras et al., n.d.). Therefore, culture medium of OPCs could enriched with agonist or antagonism agents which affect inhibitory or stimulative transcription factors (TFs) thereby a protocol to improve efficacy of OPCs prior to transplantation can be developed Hereupon, by inserting antagonism agents in OPCs culture for suppressing of inhibitory TFs and agonist factors for inducing stimulative TFs, a protocol to improve efficacy of OPCs prior to transplantation can be developed (Huang & Franklin, 2011).

2.1.8. Induced pluripotent stem cells (IPSs)

Induced pluripotent stem cells (IPSs) are synthetic pluripotent stem cells that are produced via introducing four embryonic transcription factors, i.e. sox2, oct4, c-myc and klf2, into somatic cells by viral (lenti or adeno virus) or non-viral (plasmid vectors, protein or nanoparticles) techniques (Gnecchi et al., 2017). The IPSs were discovered by Yamanaka and Takahashi by reprogramming the fibroblasts to generate ESCs-like processors named IPSs (Shi et al., 2017).

The IPSs have been employed for recognizing sporadic or familial diseases (Chen et al., 2013). They exhibit benefits of ESCs including high self-producing capacity and enhanced plasticity for differentiation into diverse types of cells and can be used as autograft cells in patients. They are able to generate a rich pool of autologous neurons for replacement of lost neurons and offer services for recognizing a newfound

Table 1
Novel candidate of stem cells for treatment of multiple sclerosis

Type of stem cell	Source	Advantages
GMSC	Neural crest cells in oral cavity	Easily accessible with non-aggressive procedure, easy extraction protocol, tolerogenic
AT-MSC	SVF, white, brown, bone marrow, mammary and mechanical adipose tissue	High abundance, easily accessible, simple laboratory manipulation, prolifrative capacity, genetically stable in high passages, poor immunogen
FD-MSC	Amnion, cord, blood, Wharton's jelly, placenta	Simple accessibility, less invasive isolation protocol from material that is routinely discarded, high self-renewal and differentiation capacity, chromosome stability tolerogenic due to HLA-G expression
NSC	Embryonic, fetal or adult brain	Similar origin with hurtful neurons, amenable in CNS milieu, habitude with neuronal circuitries thus better survival potential, more potent to share neural differentiation ability
iNPC	Somatic cells commonly fibroblast	Abundance of primary sources as well as merit points of NSCs
OPC	Endogenous NSCs	Major cell for myelination in CNS
OEC	Neural crest	Replaceable, Cross the transitional zone between CNS and PNS, remyelinataig of axons
IPS	Somatic cell mostly fibroblast	High self-renewal and differentiation potential, Abundance of primary sources
SKP	Dermis of skin	Accessible, potent to remyelinating by generating Schwann cells

drug targets for neurodegenerative condition and prepare several facilities for identifying of disease development (Grskovic et al., 2011).

Mature neurons also can be fabricated via direct reprogramming of fibroblasts by insertion of several transcription factor such as ascl1. Although this technique is in infancy stage of its development, it can eliminate ethical and tumorigenic risks accompanied with IPSs (Xiao et al., 2015). There are high throughput techniques to enhance efficiency of reprograming protocols in a no-integrating and non-viral manner. Genome editing system can rectify genetic errors in host cells after IPS transplantation. Nevertheless, abnormality may be generated even after IPS injection for the diseases with genetic causes. Conserved epigenetic profile of somatic cells and risk of tumor formation are other concerns of IPS therapy (Payne et al., 2015).

A well-executed study produced iPSCs from primary progressive MS (PPMS) patients using non-viral method. Then, they have generated functional IPS-derived OPCs to produce functional myelin and engraftment in injury site of brain after transplantation into a mice model of demyelination (Ardhanareeswaran et al., 2017). Efficacy of IPS-derived OPCs from PPMS was similar to the IPS-OPCs from healthy people also OPC from IPS-PPMS patients had the same functionality as primary OPCs. Another research examined influences of IPS-NPC in mice model of MS in which they showed that IPS-NPCs promote remyelination and activate endogenous OPCs (Douvaras et al., 2014).

The IPSs also were applied as a vehicle for modeling pathophysiology of neurodevelopmental diseases besides for modeling monogenic disorders. Another interesting capability of IPSs is in vitro mimicking of a certain aberrant phenotype of the brain development whilst compensate the limitation of ESCs such as poor availability of a genetically abnormal embryos. The IPSs provide an opportunity for identifying genetic programs that are actively participating in the prenatal brain. Furthermore, IPSs could be used for inquiring brain abnormalities CNS contexture and neural connection in postmortem brain along with function, phenotype and gene expression of neurons (Ardhanareeswaran et al., 2017). The IPSs have ability to reconstruct all steps of the brain development from embryogenesis to final maturity. Although IPSs simulate in vivo brain development but due to complex neural connections and complicated synaptic occurrences in central and peripheral nervous system, IPSs are unable to fully resemble in vivo situation. A model of IPSs which is generated in a special environment in presence of defined chemicals, toxin and other challenging environmental additives, helps to anticipating the growing pain likely to happen in future (Ardhanareeswaran et al., 2017). It has been shown that seeding of IPSs in an appropriate mini-scaffold, preferentially hydrogel material, could give rise to a personalized IPS that proliferates and differentiates into special lineages (Lin et al., 2017). Bioprocessing of this miniature system culture could be automated in favor of MS curing.

2.1.9. Skin derived stem cells (SKPs)

Another category of adult stem cells is skin-derived processors (SKPs), which are resident in dermis of skin. The SKPs are multipotent stem cells demonstrating properties of embryonic neural crest precursors and allocate several transcription factor similar to NSCs including Pax3, Snail, Twist, Sox9 and slung. Whisker follicles and dermal papillae of hair are niche for SKPs (Giacoppo et al., 2017; Fernandes et al., 2008).

The SKPs are accessible autologous source of cells potent to convert into peripheral neural progenitor or Schwann cells; therefore participate in axonal remyelination and cell replacement even in CNS tissue following oligodendrocyte injury (Fernandes et al., 2008). The SKPs are also located in olfactory epithelium capable to migrate into peripheral organs using peripheral nerves and assist in distribution of SKPs in many peripheral tissues (Fernandes et al., 2004).

Although adult stem cells from each tissue are talented to produce similar lineage to tissue cells that reside in, SKPs are potent to generate more lineage cells in a less bias manner. The SKPs are distinguishable from MSCs due to non-adherent spheroid shape and differentiation capacity into non-mesodermal lineage including neural cells. Moreover, they are greatly accessible and maintain their stemness and differential potential even one year after consecutive passages in culture without karyotype abnormality. Separated colonies of SKPs are more flexible for differentiation into different embryonic processor cells and each colonies of SKPs creates a more homogenous population than other adult stem cells (see Table 1) (Giacoppo et al., 2017). (See Figs. 1 and 2.)

3. MSCs and multiple sclerosis

Stem cell therapy for MS initiated from the idea that MSCs might integrate into CNS-derived cells and differentiate into neural cells. Beneficial effects of MSCs have been demonstrated in a number of preclinical studies using EAE as an animal model for multiple sclerosis (Zappia et al., 2005; Rafei et al., n.d.; Shalaby et al., 2016). They have shown effectiveness of MSCs in decreasing clinical severity of EAE as well recapitulating damaged neurons. In this regards, the therapeutic potential of MSC transplantation and its optimized protocol for treating MS was reported by international stem cells transplantation study group (IMSCTSG) in 2010 (Freedman et al., 2010).

In a pilot study 10 PPMS patients were intrathecally injected by autologous BM-MSCs in which preventive effects of MSCs in related to MS progression with no serious side effects were reported. (Bonab et al., 2007). This investigation was tested in 20 progressive MS patients, as an open-label study, with the same safety results (Bonab et al., 2012a). Another open-label phase I clinical trial used autologous NPCs derived from MSCs in 20 progressive MS patients. The MSC-NPCs were infused intrathecally during 3 doses of every 3 months. The study has demonstrated feasibility and tolerability of MSC-NPCs (Harris et al., 2016). In another study by Karusiss et al. MSCs were used in MS and ALS patients both intravenously and intrathecally. Findings of the study have indicated no differences in MSC function between intravenous and intrathecal routes and tracing results confirmed existence of MSC in CNS

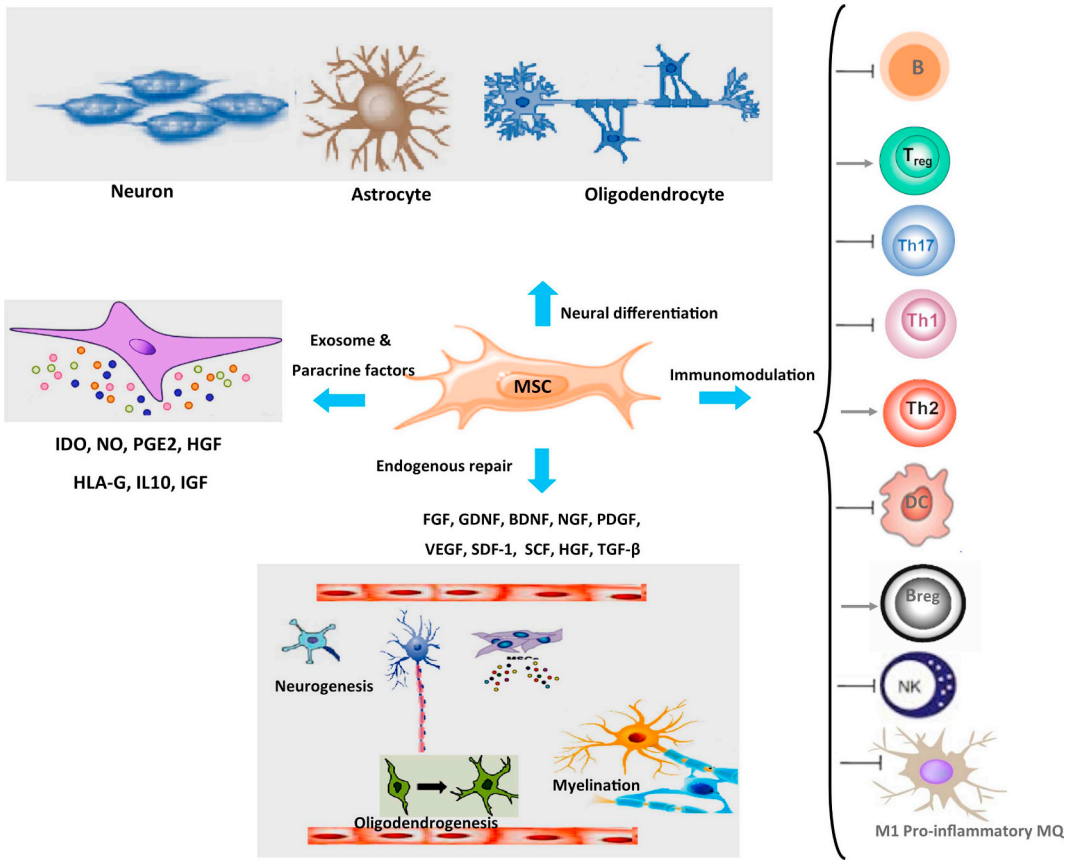

Fig. 1. Different mechanisms by which mesenchymal stem cells collaborate in neuroregeneration.
MSC = Mesenchymal Stem Cell, Th = T helper cell, DC = Dendritic cell, Breg = B regulatory cell, NK = Natural Killer, FGF = Fibroblast Glial Factor, GDNF = Glial Cell Derived Neurotropic factor. BDNF = Brain-Derived Neurotropic Factor, NGF = neural Growth Factor, PDGF = Platelet Derived Growth Factor, VEGF = Vascular Endothelial growth factor, SDF1 = ,Stromal Cell-derived Factor, SCF = Stem Cell Factor, HGF = Hepatocyte Growth Factor, TGFβ = Transforming Growth Factor, PGE2 = Prostaglandin E2, HLAG2 = Human Leukocyte Antigen G2, IDO = Indole 2,3 dioxygenase, IL10 = Interleukin 10, IGF = Insulin Like Growth Factor, NO = Nitrite Oxide

besides immunomodulatory effects of MSCs and reasonable safety of the procedure (Karussis et al., 2010a). Connick et al., in another open-label study, administrated autologous MSCs into 10 SPMS patients with optic neuritis history. Results verified safety of MSCs in MS patients also proved their efficacy on optic nerve (Connick et al., 2012a). Recently, a placebo-controlled phase II trial with 1 year follow up was carried out that involved 9 MS patients who were infused by 2×10^6 MSCs/Kg. Results showed a significant reduction in inflammatory cells and cytokines resulting in reduced MS severity (Dulamea, 2015). Very recently, a triple-blind, placebo-controlled research was performed in which low doses (1×10^6 MSCs/ Kg) and high doses (4×10^6 MSCs/ Kg) of AT-MSCs were administrated into progressive MS patients followed for 12 months. The results demonstrated safety, and feasibility of AT-MSCs in MS patients (Fernandez et al., 2018). Table 2 summarizes clinical trials using MSCs in MS patients.

4. Route

To date, stem cell transplantation has been administrated via different routes in animal models and humans. According to the nature of the disease, optimal route for stem cell injection can be different. MS is a multifocal and systemic disease; therefore, IV route as an easy and safe way can modulate immune aggressive responses in peripheral lymphatic tissue. However, due to the trapping of stem cell in systemic organs, only small number of stem cells can reach the damaged sites (Li et al., 2015c; Liu et al., 2016). Moreover because most inflammatory foci in MS are in vicinity of subarachnoid spaces in spinal cord and brain ventricles, indeed direct injection via intrathecal or intra ventricular can be more effective (Liu et al., 2016; Lavoie & Rosu-Myles, 2013; Payne et al., 2008). Direct injection into cerebrospinal fluid can be helpful in case of spinal cord lesions. However, Karusiss et al. have indicated no differences between IV and IT routes in terms of MSCs efficacy in MS and ALS patients (Karussis et al., 2010a).

Intranasal (i.n) administration is a novel non-invasive and quick delivery route for MSC transplantation (Lavoie & Rosu-Myles, 2013). Special anatomic position of nose maximizes cell entry into CNS and overcomes some concerns related to the direct delivery such as safety, cerebral ischemia and micro emboli. Moreover, large number of cell accessibility into CNS is achievable with respect to the IV pathway. Therefore, i.n administration is a suitable way for MSC delivery. The MSCs can pass through olfactory area in nasal space and reach olfactory bulb, CSF and spinal cord in less than 2h and distribute in inflammatory sites in CNS via perivascular and perineuronal outlet. Pretreatment with hyaluronidase can improve i.n efficacy by weakening nasopharyngeal mucosa connections (Li et al., 2015c; Payne et al., 2008; Kurtz, 2008; Kean et al., 2013). Remedial effects of MSCs will be enhanced in MS if MSCs are delivered in a more targeted manner instead of just one route.

5. Allogeneic or autograft MSCs

As mentioned previously MSCs from MS and healthy donors have similar immunosuppressive potential also same differentiation, proliferation and morphological traits (Mallam et al., 2010; Auletta et al., 2012; Kassis et al., 2013). Of elementary benefits of healthy allogenic

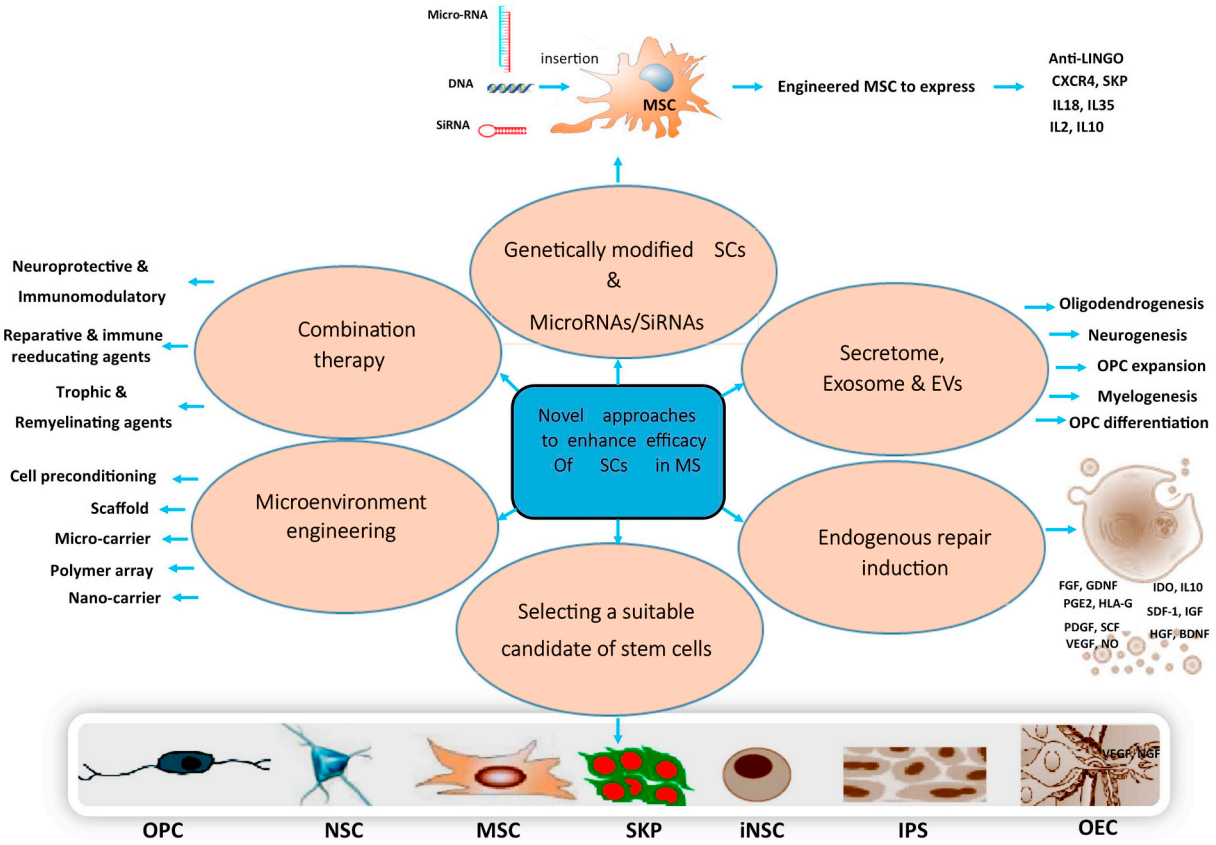

Fig. 2. Novel strategies to improve MSC efficacy before or after transplantation in MS patients.
SCs = Stem Cells, OPC = Oligodendrocye Progenitor Cell, NSC = Neural Stem Cell, MSC = Mesenchymal Stem Cell, SKP = Skin Progenitor Cells, iNSC = induced Neural Stem Cell, IPS = Induced Pluripotent Stem Cells, OEC = Olfactory Ensheating Cells, FGF = Fibroblast Glial Factor, GDNF = Glial Cell Derived Neurotrophic factor, PGE2 = Prostaglandin E2, HLAG2 = Human Leukocyte Antigen G2, IDO = Indole 2,3 dioxygenase, IL10 = Interleukin 10, SDF1 = ,Stromal cell-Derived Factor, IGF = Insulin Like Growth Factor, PDGF = Platelet Derived Growth Factor, SCF = Stem Cell Factor, VEGF = ,Vascular Endothelial growth factor, NO = Nitrite Oxide, HGF = Hepatocyte Growth Factor,BDNF = Brain-Derived Neurotrophic Factor

source of MSCs is exclusion of defective genes which may be present in genetic susceptible MS individuals. Of importance, risks of allogen MSC transplantation can imply graft-versus-autoimmunity and pre-conditioning with immunosuppressive drugs for non-MHC match MSCs (Uchida et al., 2016). An earlier study demonstrated no difference between autologous, syngeneic and allograft MSCs in prevention of relapses in EAE model. Moreover, inflammatory circumstances in EAE did not impose serious destructive effects on practical characterization of MSCs (Gao et al., 2016). Unexpectedly, it has been revealed that MSCs from animal model of ALS fail in having an appropriate neuroprotective effect that is suggestive of a universal allogenic bank of MSCs for stem cell therapy in future (Kassis et al., 2013).

6. Biotechnological approaches to improve MSCs efficacy

6.1. Microenvironment engineering

Differentiation potential of MSCs is affected by stiffness of surrounded extracellular matrix. Stem cell fate can change by modification of environmental cues and growth factors in culture medium. Bio mimicry is printing of in vivo extracellular matrix molecules (ECM) along with their interactions with nearby cells on a scaffold or biomaterial. Biomimicry could be a key approach for delineating MSCs destination. Cell-encapsulation using nanoparticles is a novel strategy capable to delivery of stem cells in targeted area for a demanded time (Mao et al., 2016). Hydrogel and amyloid fibrils are biomaterials with high flexible modulus that provide physical and biochemical support for neuronal differentiation in which stem cells can remain in target site for long time (Yang et al., 2015). Hydrogels have been shown to be suitable scaffold for neural tissue engineering (Onoe et al., 2016). Collagen scaffold and graghene foam also can increase stem cell survival and promote concentration of stem cells in transplanted site and support neuron growth (Guan et al., 2013)

Temperature, stiffness, modules elasticity, precise compounds of biomaterial and spatiotemporal signals of cell niche can determine stem cell destination (Das et al., 2016). Another approach is a thermo-sensitive system able to regulate stem cell-ECM interactions (Bianchi et al., 2017). Designing a MSCs-biomaterial system to regular release of growth factors and post-translational enzymes such as matrix metalloproteinase (MMP) can recapitulate ECM architecture and enhance MSC migration rate and even local delivery of MSCs into desired site. Selecting a scaffold with special ECM can maintain stemness valence of MSCs during culture (Chen & Liu, 2016). The MSCs after replacing in neural milieu can produce an extracellular matrix similar to natural ECM of neurons and subsequently, by decellularization of this ECM, a natural scaffold for neural differentiation will be achievable (Ban et al., 2017).

Different types of bioreactors have been invented for expansion and differentiation of stem cells. Bioreactors using mass transporting and diffusion of nutrients in a circulative form provide a homogenous niche for producing a large scale of stem cells in a short period of time (Stephenson & Grayson, 2018). In these bioreactors nutrient levels, oxygen regime, pH and ROS can be monitored in situ. Bioreactors also allow cultivation of cells on scaffold and three-dimensional (3D) system to promote expansion and differentiation potential of stem cells (Sart & Agathos, 2016; Sart et al., 2014; Petry et al., 2018). Additionally,

Table 2
Clinical trials using mesenchymal stem cells (MSCs) in multiple sclerosis (MS) patients

Study	Source of SCs & type of MS	Route and follow-up endpoint	Mean doses of SCs and number of patients	Results
Yamout et al , Lebanon, 2010 (Yamout et al., 2010)	BM-MSC SPMS, RRMS	IV 12 months 12months	30×10^6 cells/patient N = 10	Clinical improvement with no serious adverse events and no radiological change.
Karusiss, et al, Israel, 2010 (Karussis et al., 2010b)	BM-MSC SPMS,PPMS	IV,IT 25 months	60-70 $\times10^6$ cells/injection/patient N = 15	Safety of MSC, MSC existence in CNS, neurological improvement
Odinak, et al, Russia, 2011 (Odinak et al., 2011)	BM-MSCs All MS types	IV 24 months	2×10^6 MSCs/kg N = 8	Safety, improve/stabilize MS progression
Mohyeddin et al, Iran, 2012 (Bonab et al., 2012b)	BM-MSC SPMS, PPMS	IV 12 months	29.5×10^6/patients N = 22	improve/stabilize the progression of the disease ,safety of IT MSC transplantation
Connick et al, UK, 2012 (Connick et al., 2012b)	BM-MSC SPMC with optic neuritis	IV 12 months	1-2 × 106 MSCs/ Kg N = 10	Physiological and functional improvement in visual symptoms
Liufriu et al, Spain, 2014 (Llufriu et al., 2014)	BM-MSC RRMS	IT 12 months	1-2 × 106 MSCs/ Kg N = 9	Reducing Th1, IFN-c, Th17 &Th1/ Th17 ratio, lower the mean number of GEL no AE reports
Lublin et al, USA and Canada, 2014 (Lublin et al., 2014)	Placenta derived-MSCs RRMS, SPMS	IV 12 months	Low doses = 150×10^6/patients High doses = 600×10^6/patients N = 16	Patients were progression free on EDSS and GEL images
Harris et al, New York, 2016 (Harris et al., 2016)	MSC-NPC SPMS,PPMS	IT 12 months	10×10^6/injection, three doses spaced three months apart N = 20	Safety and tolerability
Cohen et al, USA, 2018 (Cohen et al., 2018)	BM-MSC RRMS, SPMS	IV 12 months	1-2 $\times10^6$/MSCs/kg N = 24	Safety, feasibility and tolerability
Fernandez et al, Spain, 2018 (Fernandez et al., 2018)	AT-MSCs SPMS	IV 12 months	low doses (1×10^6 MSCs/ Kg) high doses (4×10^6 MSCs/Kg) N = 34	Safety and feasibility

SCs = Stem cells, BM-MSCs = Bone marrow mesenchymal stem cells, NPCs = Neural processor cells, IV = Intravenous, IT = IT = Intrathecal, SPMS = Secondary progressive multiple sclerosis, PPMS = Primary progressive multiple sclerosis, RRMS = Relapsing remitting MS

bioreactors decrease cost and extremely hard labor while are more practical.

Micro carriers are another system with numerous advantages to compensate limitations of bioreactors to expand and differentiation of stem cells. Micro carriers are a micro-solid suspension at a high surface/volume ratio with an automated slow agitation for culture flow that makes easy scale up, facile perfusion and cell harvesting with high potential possible to control cell condition and to provide a homogenous environment for growth medium distribution (Chen et al., 2013; Ashok et al., 2016). Biocompatible micro carriers can be administrated in vivo and used as a scaffold for 3D culturing of stem cells in live systems (Chen et al., 2013; Tra et al., n.d.). The 3D microfluidic array is an impressive co-culture technology for preparing a proper niche for injected stem cells and managing endogenous neural behavior in CNS (Yang et al., 2015).

There is a closed whole automated miniature device for stem cell culture with high yield of bio manufacturing as well as minimal cost which reduces laboratory variation related to same assays. In this miniature system all biological processes including cell expansion, differentiation and purification happens in one tube leading to saving time and decreasing the labor-intensive work (Huebsch et al., 2016).

Polymer array is a high throughput novel technology to identifying cell-scaffold physiochemical interactions which anticipate appropriate substrate for stem cell progenitors. This polymer can switch intracellular molecular cascade into a specific pathway (Coyle et al., 2016). In this scenario, robotic-based technology with rich liquid environment is a great hope for stem cells engineering in future (Coyle et al., 2016).

Using MSCs preconditioning approach using growth factors subsequently cultivating pretreated cells on a relevant 3D material such as acellular spinal cord scaffold or pre-vascularized scaffold neuronal lesions in CNS can be repaired (Kress et al., 2018; Hu et al., 2017a). Acellular spinal cord scaffold is non-immunogenic and biocompatible with same algorithm to natural environment in CNS (Hu et al., 2017a). Co-culturing of MSCs and pre-activated Schwann cells in conduits polymer can promotes neural differentiation of MSCs and exert dramatic influence on renovating spinal cord (Liao et al., 2010).

Nanocarriers (1-1000nm) conjugated with small molecules such as siRNA/miRNAs can affect stem cell destination and induce neuronal differentiation. Moreover, previous studies have demonstrated nanoparticles can alter gene expression of growth factors' receptors and cytoskeleton proteins (Andre et al., 2016).

6.2. Modifying secretome, exosome and extracellular vesicles

Recently many scientific reports have indicated therapeutic effects of MSCs that may be substantially attributed to their paracrine soluble factors (Paul & Anisimov, 2013; Estrada et al., 2009). Since trans-differentiation and cell fusion of MSCs in injury site is a rare phenomenon, the importance of secretome-derived MSCs, as a cell free treatment, will be highlighted in curing of diseases. The secretome is encoded by only 10% of the genome while contain a complex set of proteins, growth factors, enzymes, major peptide, lipids, miRNA and many other macromolecules with neurogenesis, anti-inflammatory, angiogenesis and anti-apoptosis activities (Maumus et al., 2013). Interestingly, secretome can eliminate the hurdles of cell therapy including tumorigenicity, immune rejection, high cost and time-consuming manufacturing. Another advantage of secretome is its applicability even as an allogeneic material, off-the-shelf, quick accessibility and availability in a large scale (Drago et al., 2013; Ranganath et al., 2012).

Exosomes and extracellular vehicles (EVs) play a key role in therapeutic effects of MSCs. Several literatures have indicated that neurogenesis, immunoregulation and angiogenesis properties of exosomes are as effective as parented MSCs (Robbins & Morelli, 2014). Owing to neuroprotective, immunoregulative and tolerogenic properties of exosomes, they can be applied as a vaccine for neurogeneration in autoimmune diseases like MS (Tran & Damaser, 2015).

Exosomes are round-shaped extracellular vesicles (10-100nm) evolved by shedding from cell surface membranes or by integration of plasma membrane and endoplasmic micro vesicles. They are produced by many nucleated cells and are distinguishable from other vacuoles with specific membranous compartments involved in biogenesis

activities of exosomes. Exosomes are released in body fluids and transfer biological information to the cells and tissues at the long distance (Wen et al., 2016; Alejandra Lopez-Verrilli et al., 2016). Isolation of exosomes is performed by ultracentrifugation or ultrafiltration technique. Exosomes have exceptional compounds based on their cell context, cell lineage, stage of cell activation (mature or immature) and cell circumstance (inflammation, immunosupresion or tumorigenic). Intra-vesicular contents of exosomes are employed for vesicle membrane, antigen presenting, macromolecule transporting, cell trafficking, receptor-ligand attachment, apoptosis, cytoskeleton system and other cell activities (Robbins & Morelli, 2014; Tsao et al., 2014). Surprisingly, the content and amount of secretome/exosome is highly sensitive to any small change in surrounded microenvironment; therefore pretreatment of MSCs with selective growth factors or biomaterial can change secretory profile of MSCs for a special demand. Several literatures have proved that MSCs following incubation with ischemic brain extract can produce exosome with enhanced level of fibroblast growth factor II (FGF-II), glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), hepatocyte growth factor (HGF), granulocyte colony-stimulating factor (G-CSF), platelet-derived growth factor (PDGF) insulin growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), stromal cell-derived factor (SDF-1), transforming growth factor beta (TGF-β) and stem cell factor (SCF) (Maumus et al., 2013; Casado et al., 2017; Tang, 2015; Lee et al., 2016b; Drommelschmidt et al., 2017). Administration of these preconditioning exosomes into ischemic brain has improved severity of disabilities in animals (Manuel et al., 2017). Beneficial effects of exosomes contribute to a complex net of secretome-derived soluble factors as well as interactions between them.

The content of vesicle-derived MSCs can be used as a biomarker for anticipating disease and also employed in antigen carrying for tumor suppression because they reflect the characterizations of the cells from which they are originated (Tran & Damaser, 2015). These vesicles could protect genetic materials from nuclease attack and therefore can be used as a potent particle in gene therapy (Mathiyalagan & Sahoo, 2017).

Extracellular vesicles are patient specific vesicles meaning that MSCs in traumatic condition produce the relevant exosome for repairing lesions. Patients with identified diseases have therapeutic vesicles with preferential agents to cure their disease. The MSC-derived EVs contain immunomodulatory factors such as IL-10, TGFβ1, indoleamine 2,3-dioxygenase (IDO) and PGE2 which are able to cross blood brain barrier; recently they have been shown to reduce severity of autoimmune diseases such as graft-versus-host disease (Robbins & Morelli, 2014).

Neuroregulatoy platform of MSC-derived secretome can be modified by dynamic culturing of MSCs in computer-controlled bioreactors. This Dynamic system is able to up-regulate NOTCH1 and miR-16 expression that both are incorporated in neural differentiation (Teixeira et al., 2016). MSC-derived vesicles are capable to stimulate NPCs proliferation and neural survival as well take part in neural differentiation and remyelination. These vesicles also have been shown to inhibit astroglia cells and therefore are prevented from destructive effects of inflammatory cytokines in autoimmune condition. Furthermore exosomes with carrying tolerogenic antigens (tolerosome) can induce immunotolerance or even immunosuppression in autoimmune diseases including MS (Robbins & Morelli, 2014). Some limitations should be overcome before secretome therapy finds its way to clinical routine. First, interplay between secretome compounds in vesicles and their characterization should be precisely identified. second, standard protocols for MSC-derived vesicle treatment, vesicle concentration and vesicle qualification should be defined. Third, to determine if repetitive doses of exosomes are essential and whether secretomes have equivalent outcomes as MSCs. Altogether, identifying precise molecular mechanisms for achieving desired protective effect of MSCs-derived exosomes is demanding to evolve novel therapeutic strategies for cell-free based therapies.

6.3. Stimulation of endogenous repair system

Following MS-related inflammation, indigenous oligodendrocyte precursor cells (OPCs) trigger spontaneous remyelination resulting in remitting of the disease but because of the progressive nature of MS and dispersed localization of lesions in MS, this endogenous correction system is not able to fully restore demyelinated foci. In non-pathological situation naive NPCs repopulate CNS by generating new neurons whereas in pathological condition instinct neural stem cells are incompetent for fully replacement of lost neural cells (Hollingsworth et al., 2017). Endogenous regenerative medicine (ERM) is a new avenue in clinical settings inspired by in vivo spontaneous mechanism for wound healing in which resident reparative (stem) cells are encouraged to humming into damaged sites (Wu et al., 2018).

Aptamers are novel driving cues and rapidly developing nucleic acid vehicles for cell immobilization, adherence and differentiation. Aptamers are non-immunogenic/toxic single-strand oligonucleotids (30-80 base pairs) with secondary or tertiary conformational structures to binding into special targets for certain purposes (Röthlisberger et al., 2017).

Extent of endogenous remyelination in different MS patients is dependent on CNS cell texture, OPCs properties and location of plaques in white and gray matter. Each step of OPC development such as proliferation, differentiation or recruitment of OPCs in lesions may be defective in MS due to poor microenvironment or incompetence nature of OPCs in these patients (Jadasz et al., 2012). In initial phase of MS myelin sheath is generated by proliferating OPCs performance but new myelin is more fragile and thinner (Dubois-Dalcq et al., 2005). However, after axonal loss and generating sclerosis scars, reparative machinery of CNS is unable to restore lost cells (Yong, 2009).

Stem cell therapy in early stage of MS is more efficient because sclerosis scars and residual derbies in late phase of MS, after emerging chronic lesions, result in inhibition of OPC recruitment and hamper endogenous repair (Jennings & Carroll, 2010). The ECM density and astrogliosis are key players to providing a permissive microenvironment for OPC movement into lesions. Therefore, by restraining some inhibitory chemokines and provocation other chemotactic agents which are participated in OPC employment can promote native reparative remyelination system (Zhao et al., 2008; Domingues et al., 2016).

Certain growth factors such as bFGF, PDGF, retinoid X receptor g (RXRg) and some signaling molecules like Ascl-1 and Sox17 can affect several activities belonging to OPC such as myelination, and axonal encompassing (Huang et al., 2011; Wang et al., 2014).

Inflammatory condition in MS acts as a two-edged sword. That is, pro inflammatory cytokines promote tissue regeneration by recruiting reparative cells and help to migration, cell adherence and homing capability of healing cells (Schäfer et al., 2016). For example, macrophages account for secreting both inflammatory and neuroregulatory factors; therefore by precise controlling of CNS inflammation in injurious niche can afford useful results in rehabilitating intrinsic repair system in lesions (Mallucci et al., 2015). The MSCs by secreting neurotrophic factors, scavenging oxidants and reducing neurocytotoxity can encourage endogenous neuronal restoration (Gao et al., 2016).

6.4. Genetically modified MSC

Projecting of MSCs to overexpress or down regulate chosen genes is considered as a novel biotechnology trick for improving efficacy of MSCs. For example, MSCs engineering for over expression of CCR7 can develop MSC homing (Li et al., 2014c). Likewise, suppression of hostile genes in MSCs could promote MSC capability for desired purposes (Gao et al., 2016) The MSCs are feasible candidate for gene delivery due to their exceptional traits. Laboratory manipulation can increase neural differentiation capacity of MSCs. for instance, MSCs can be designed for

immensely expression of notch intracellular domain (NICD), noggin and brain-derived neurotrophic factor (BDNF) as fateful genes for neural development (Glavaski-Joksimovic & Bohn, 2013). Genetically manipulated MSCs to overexpress CXCR4 result in neuroprotection and MSC fusion into target site (Yu et al., 2012).

The MSCs genetically modified to overexpress nerve growth factor (NGF), BDNF and other growth factors that can be employed in curing a variety of neurological diseases.

Gene insertion in MSC can be achieved by viral or non-viral techniques. Viral method have high output for transfection and provoke long-lasting gene expression in host cells whereas non-viral system typically is suitable for managing gene insertion in host cells. Most common viral vectors for gene integration and cytoengineering belong to adeno virus and lentivirus families (Madeira et al., 2010; Peister et al., 2000; Wang et al., 2013; Huang et al., 2012a).

Nanocarries with prolonged release potential and specific cell targeting specially on surface of the cells also are considered as non-viral vectors for MSCs engineering (Tenkumo et al., 2016).

Modifying of MSCs to express a particular surface antibody against a non-viral gene-transporting system is regarded as another non-viral gene transporting systems (Huang et al., 2012b). The 3D biomaterial is a further transfection model with high efficacy for gene delivery particularly in neurodegenerative diseases.

Adipose derived mesenchymal stem cells (AD-MSCs) have been genetically engineered to express beta interferon which presented an impressive immunomodulatory impact on reducing EAE severity (Mohammadzadeh et al., 2016).

Genetically designed MSCs for cytosine deaminase expression are able to cross the blood-brain-barrier with a dramatic competence for selective homing into deleterious tissue of CNS (Huang et al., 2012a). The MSCs engineered to expressed sphingosine kinase 1 (SPK1) gene are able to reduce neurological impairments in the EAE mice receiving transduced-MSCs by enhancing of Tregs and shifting from Th1/Th17 into Th2 (Wang et al., 2018).

Cell encapsulation is a high efficient innovative technique for functional improvement and sustained release of remedial molecules with homogenous distribution in a defined area of CNS as well as long cell survival time (Muslimov et al., 2017).

Injectable cell-capsule is a reticular porous structure consist of a membrane, anchoring system and ECM surrounded with cells. The capsule is permeable for nutrients, biocompatible, replaceable, removable and simultaneously inhibits host deleterious cells from entering into the capsule and prevents immune rejection. Encapsulation system has been applied in clinical trials e.g. to deliver NGF and GDNF to Alzheimer's and Parkinson's patients (Emerich et al., 2014).

The CXCL12–CXCR4 axis has an important role in NSC-mediated remyelination and recruitment of endogenous NPCs; therefore engineering of NSCs or MSCs to express CXCR4 can improve neurological functions by reviving of oligodendrocyte, NPC migration and inducing neural endogenous repair system (Li et al., 2012a).

The MS lesions express an extraordinary amount of LINGO-1. Therefore, by suppressing of LINGO-1in MSCs, remyelination and OPC differentiation can be controlled (Rudick et al., 2008; Satoh et al., 2007).

Directed differentiation of somatic cells into neural stem cells or matured neuron is applicable by expression of a series of transcription factors such as c-Myc, Sox2, Klf4, Myt1l, Brn2, Ascl1 and E47/Tcf3. However, this technology needs to be furthered studied (Hou & Lu, 2016).

In a study, adipose tissue-derived MSCs were biotechnologically manipulated for expression of interleukin 35 which were then transplanted in EAE mice. As a result, clinical score of EAE and disability severity were decreased in IL35 transfected-MSC EAE mice (Zhao et al., 2017). Another study has introduced IL10 into adipose-derived MSCs after which they were administrated interaperitoneal into EAE mice in early stage. The results indicated that pathological symptoms of EAE were significantly reduced in MSC-IL10 animals by down regulation of proinflammatory pattern of cytokines and stimulating immunosuppressing responses (Payne et al., 2013).

The MSCs can differentiate into oligodendrocytes or Schwann cells at presence of chemical defined medium, genetically handling or by seeding in a certain scaffold. These differentiated cells are proficient for treating neurodegenerative diseases such MS. It has been indicated that peripheral blood-derived MSCs with laboratory manipulation can generate Schwann cells with specific and functional markers of SCs and thereby compensate limited numbers of Schwann cells for repairing peripheral neurodegenerative diseases (Keilhoff et al., 2006).

To date, several genes including IL18, IL12, IL2 and tyrosine hydroxylase have been inserted into MSCs for different purposes (Hodgkinson et al., 2010). Similarly, MSCs have been genetically modified to express a myelin MOG-specific receptor that remains in brain and for a continuous beneficiary effects in CNS tissues.

6.5. Micro RNAs for augmenting stem cell efficacy

Micro RNAs (miRNAs) are non-coding small-molecule RNAs with ability to regulate

gene expression. The miRNAs are very conserved posttranslational molecules (20-25 nucleotides) which are highly expressed in nervous system (Rupaimoole & Slack, 2017). Differentiation pattern of OPCs is conducted by genetic and epigenetic programs including miRNAs15 (Siegel et al., 2012). The miRNAs associate in principal activities of stem cells such as proliferation, survival, apoptosis and differentiation. They act by knocking down or overexpression of pivotal genes. A single miRNA can manage the activities of a copious number of genes that cooperate in producing same product. The miRNAs profile in MS is exceptional and different from other diseases. For example, miRNA21 and miRNA146 are present in relapsing remitting MS patients (Guerau-de-Arellano et al., 2012). Thus, miRNA targeting may partly manage neuropathology course of MS. The miRNAs attach to the complementary nucleotide position in their target mRNAs and then by digesting or neutralizing gene expression and consequently protein translation machinery can regulate a cascade of cellular reactions. For example, during traumatic injury miR-124 is overexpressed in CNS resulting in functional repair of defective neurons (Hu et al., 2017b). It has been shown that BM-MSCs can be gene-engineered to express miR-124 and then such transduced-MSCs can be employed for reducing neurological damages in spinal cord injury and promoting BM-MSCs differentiation into neurons. The miRNA218 in combination with FGF2 accelerates AT-MSC differentiation into neurocytes by affecting Wnt signaling route (Hu et al., 2017b).

Meanwhile, miR-146a has been established to exert an important role in regulating stem cell survival by modification of Fas signaling pathway therefore can compensate limited number of OPCs in CNS lesions.

The miRNA-124 also conducts retention of neurons in primary state causing prolonged neuron survival. Similarly, up regulation of miRNA-9 proceeds neural differentiation by modulating Tlx1 transcription factor. The miRNA-125a and miRNA-125b have a serious duty in conversion of pluripotent stem cells into neural lineage by binding to Fyn and inhibiting its expression, promote axon-glial signal transduction and eventually led to maturation of oligodendrocytes (Hu et al., 2017b).

The siRNAs are short synthetic double stranded interfering RNA (21-23 nucleotides) potent to down-regulate mRNA in a wide range of cells. They are capable to silencing the gene with truncated protein production. Although siRNAs are a novel technology for genome editing, they face some challenges such as rapid clearance, low cellular uptake and enzymatic digestion. By selecting a proper lipid carrier for siRNA transporting one may overcome such problems. The siRNAs are produced by bio-processing of longer RNA hairpin transcripts. They, unlike LINGO-1 in OPC, can increase maturation of oligodendrocyte.

Antibody against LINGO-1 has been indicated to promote remyelination in EAE mice (Sun et al., 2015). There are various strategies for delivering siRNA/miRNA into target cells among which nanocarriers are high-throughput vehicles for RNA delivery with overcoming the obstacles of siRNA/miRNA transporting. Furthermore, internalization, release, and distribution of siRNA/miRNA need to be optimized. It has been demonstrated that miR-219 regulates the differentiation of ESC-NPC into OPCs and subsequently into oligodendrocytes and elevates endogenous NPCs numbers thereby remyelination (Fan et al., 2017).

7. Combination of stem cells and other therapeutic agents

A very encouraging aspect of MS treatment using MSCs is combinatorial therapy using neuroprotective and immunomodulatory agents. Ideally, these combined treatments disrupt sclerosis scars to capitalize entry of stem cells into lesions. Thus, stem cell therapy for MS is more advantageous if applied in conjugated with other therapeutic agents tailored to neuroprotection and immunoregulation. For example, activity of LINGO -, an inhibitory surface molecule on neural cell, can be suppressed by a proper antagonism such as an antibody or miRNA/siRNA. Therefore, stem cells combined with LINGO antagonism can exert a synergism effect on neural repair and remyelination (Yong, 2009). another combined strategy is preconditioning of culture medium of cells with certain agents in favor of neural regrowth. In this scenario, the MSCs preconditioning with bFGF in a hypoxia condition results in faster expansion rate of MSCs (Caroti et al., 2017).

In vitro and animal studies have revealed that glatiramer acetate (GA) in inflammatory condition can exert its neuroprotective effects by stimulating other immune cells to generate neuroprotective factors such as BDNF, IGF-1 and PDGF, and have a satisfactory outcome in maturation of OPCs and rebuilding myelin sheath. Accordingly, stem cells conjugated with GA would offer more therapeutic effects. It is now evidenced that two kind of stem cells is more effective than each of them alone. For instance, MSCs and Schwann cells in collaboration with each other or mixture of MSCs in differentiated and un-differentiated state have demonstrated to be more beneficial (Mantovani, 2011). Conventional herbs with immunoregulatory properties combined with stem cells can exhibit a synergic effect in MS therapy. In this regard, one study has shown that curcumin as an anti-inflammatory and antioxidant herb loaded in a nanoparticle in combination with MSCs has been used for repairing lesions in CNS that resulted in more striking outcomes in reducing functional deficits in neurodegenerative diseases including MS and ALS (Attari et al., 2015; Jinfeng et al., 2016). Mixture of nanocurcumin and MSCs can protect curcumin from enzymatic digestion to reach target tissue easily and rapidly and improve bioavailability and solubility of curcumin (Tripodo et al., 2015).

Rehabilitation, vitamin compounds, growth factors and biomaterials with specialized ECM enriched in laminin and fibronectin have a booster effects for stem cell therapy. In vivo differentiation of stem cells is influenced by several factors in serum (Li et al., 2012b). In this regard,

Combination of bFGF/IGF-1 or retinoic acid/neurotrophins or bFGF/retinoic acid has an additive effect in neurogenesis process (Rao et al., 2016). Several components such as selenium, transferrin, insulin, BMP2 and fibronectin can also collaborate in raising neuroprotective effect of MSCs. When neurovax, rituximab and alemtuzumab combine with stem cells may exhibit an extra beneficial outcome in MS treatment. Also, recombinant human erythropoietin that is a neurokine with diverse neurotrophic consequences potentially can maximize competence of MSCs in curing of MS. Moreover, rHIgM22 is a novel neuroprotecive antibody which combined with MSCs is capable to exert a synergism influence on neuropathology symptoms of MS (Fig. 2) (Villoslada, 2016).

8. Conclusions

In summary, stem cell transplantation offers novel approaches for treatment of multiple sclerosis patients. However, there are still many open questions that are needed to be answered before making it into clinical routine. Exploring a strategy to reeducating immune system of MS individuals by stem cell will be an elegant step forward in therapeutic implication. Other prerequisite consideration for MSC therapy in MS is accessibility of stem cells into multifocal lesions and excluding the inhospitable effects of inflammatory environment in CNS. Another limitation is remarkable variation in methodological approaches in the fields of MSCs culture, culture reagents, cell expansion, cryopreservation, thawing, inconsistency pathological appearance of experimental model and variable nature of MS in different patients; therefore, need to identical standard protocols for laboratory management of MSCs to avoid inconsistency. Discovering advanced methods to monitoring MSCs fate in vivo is another important necessity in future studies. Finally, cell efficacy will be more useful if transplantation be accomplished in early stage of MS preferentially in RRMS stage. Furthermore, fresh MSCs is better than cryopreserved MSCs. Combination therapy using neuroprotective/immunomodulatory mediators or remyelinative/trophic components or reparative/immune reeducating factors can also hold great promises for treatment of MS. Remyelination is achievable in a narrow time before axonal damage and prior to emerging sclerosis scaring. Altogether, in vitro manipulation of MSCs and cell preconditioning approaches can hold great hopes in neuroregenerative medicine although more research in order to get them into clinical routine is warranted.

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