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# Neuroinflammation and cell therapy for Parkinson's disease

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## 1. ABSTRACT

Cell therapy is a promising therapeutic alternative for Parkinson's disease, and one possible limiting factor may be that the pathological environment of PD is hostile for the process of neurogenesis, including grafted stem cells survival, proliferation, migration and dopaminergic neuronal fate specification along with maturation of the immature neurons and ultimately integration of the new neuronal progeny into functional neuronal circuits. Uncontrolled microglial activation and neuroinflammation contributes to neuronal damage in PD. Similarly, the microglia-derived inflammatory mediators may also influence grafted stem cells. Thus, we discuss reactive microgliosis and sustained, chronic neuroinflammation in PD, together with cytokine-dependent neurotoxicity and inflammation-derived oxidative stress on dopaminergic neuron in the substantia nigra pars compacta substantia nigra pars compacta (SNpc). Based on these, we further summarize the interaction between neuroinflammation and stem cells, and conclude that neuroinflammation acts as double-edged swords, instead of simply beneficial or detrimental, and stem cells display immunomodulatory functions beneficial for dopaminergic neurons via an anti-inflammatory action in PD.

## 2. INTRODUCTION

Parkinson's disease is a chronic and progressive neurodegenerative disease that affects approximately 1-3% of the population (1,2), characterized by the selective loss of dopaminergic neurons and the presence of Lewy bodies. The symptoms are only apparent when loss of at least 50% of the dopaminergic neurons in the SNpc occurs, which result in an over 80% reduction in dopamine (DA) levels in the striatum (2, 3). Because of the relative simplicity of the major pathology of PD with loss of a unifocal and phenotypically homogeneous neuronal population in SNpc, the anatomically well defined and easily accessible main target, namely the striatum with the relatively preserved downstream basal ganglia neurons, and well-characterized rodent and primate models of PD, PD has been thought to be particularly suitable for cell therapy to restore dopaminergic neurotransmission in the striatum (4, 5). It is proposed that the improved function depends on the number of continued survival and phenotypes of the grafted cells, and that a minimum of approximate 80,000 dopaminergic neurons-- about one fifth of the normal number of dopaminergic neurons in the human substantia nigra, may be required to obtain an ideal therapeutic effect (4).

Numerous stem cells or their derivatives (e.g. embryonic stem cells, fetal mesencephalic neurons, and neural stem cells) have been proposed to treat animal models of PD as well as patients with PD(6-11). Both some experimental animals and clinical patients of PD studies demonstrate that intrastriatal grafts of nigral DA neurons gains long-lasting and therapeutically valuable symptomatic relief (12, 13). Importantly, survival of the grafted dopaminergic neurons, reinnervation of the striatum, and formation of synaptic connections are also observed in autopsy (14,15), indicating that grafted dopaminergic neurons can functionally integrate into neuronal circuitries in the brain. However, experiments with transplants of rat and human mesencephalic dopamine neurons placed in the rat striatum have shown that most of the transplanted dopamine neurons die within the first 24 h post-transplantation (16), and only 5-20% of the dopamine neurons survive the implantation procedure, and the symptomatic relief is far from complete (17). Besides the loss and damage in the preparation of the tissue ahead of grafting, it is likely to a large extent due to the pathological environment that the grafted cells encounter. The PD microenvironment is prone to ongoing neuronal death, and can affect grafted cells in hosts with a similar pathogenesis as in the host dopaminergic neurons(18,19). Microglial activation and neuroinflammation is now considered to be instrumental to at least the progression if not the pathogenesis of PD (20-26). Microglial activation initiates or perpetuates neuronal loss by increasing cytotoxic molecules like superoxide, nitric oxide (NO), various pro-inflammatory cytokines, and prostaglandins (25,27, 28,29). Similar findings suggest that neuroinflammation inhibits neurogenesis in the adult hippocampus (30,31), suggesting the detrimental effects of neuroinflammation on stem cells. The blood-brain barrier (BBB) is also disrupted with intracerebral grafting and this may compromise the viability of the grafted cells through inflammatory mechanisms. Stem cells express receptors, and respond to trophic factors and cytokines, and the grafted stem cells can interact with the immune system. Hence, the effect of neuroinflammation and microglia activation on the grafted cells has turned out to be much complex.

Therefore, in this review we summarize cytokine-dependent neurotoxicity and inflammation-derived oxidative stress on nigrostriatal pathway degeneration in PD. More importantly, we focus on the multifunction of inflammatory mediators on grafted stem cells or their derivatives and the immunomodulatory properties of stem cells.

## 3. NEUROINFLAMMATION IN PD

### 3.1. Microglial activation in PD

The brain has been considered to be an immune-privileged organ but this is now undergoing a considerable reevaluation, for the unequivocal evidence that the permeability of the BBB can be regulated under normal conditions and may become dysregulated in chronic and acute neurodegenerative conditions. The hallmark of neuroinflammation is the activation of microglia, the resident brain immune cells (32), being kept in a resting state by intimate communication between neurons and microglia (33), and changing from their “resting” ramified state to an “activated” ameboid form, in order to migrate to areas of damage, proliferate and engulf invading organisms, apoptotic cells or cell debris (34,35). The density of microglia varies strongly by distinct brain regions from 0.5-16.5%, with the highest density of microglia within the hippocampus, olfactory telencephalon, basal ganglia, and substantia nigra (36).

As early as in 1988, McGeer and his colleague reported that large numbers of human leukocyte antigen-DR (HLA-DR) - positive reactive microglia were detected in the SN, particularly in areas of maximal neurodegeneration, namely the ventral and lateral portion of the SN (37), and the results is corroborated in 1-methyl-4-phenyl -1,2,3,6-tetrahydropyridine (MPTP) treated monkeys where activated microglia cells are found in the SN up to 14.5 years after the last exposure (38). Other animal models of PD, such as the rotenone (39) and 6-hydroxydopamine (40) models, have also been shown to activate microglia.

Moreover, excessive increased concentration of proinflammatory cytokines has been found in the SN, striatum and cerebrospinal fluid (CSF) in PD. For example, Interleukin-1β (IL-1β), interferon-γ (INF-γ) and tumor necrosis factor-α (TNF-α) are increased by 7- to 15-fold in the SN (41,42), and increased level of IL-1, IL-6, TNF-α is also observed in CSF (43,44). These data demonstrate that, besides an extensive loss of dopaminergic neurons in the mesencephalon, there exists neuroinflammation characterized by activation and proliferation of microglia, with excessive expression of inflammatory cytokines and inflammation-related factors in PD (45). A genome-wide association study of 2,000 individuals with PD demonstrates that PD is associated with a classical polymorphic HLA antigen and that rs3129882 is a proxy for this antigen. The evidence for genetic association of PD with the HLA region, lends strong and independent support to the involvement of neuroinflammation and humoral immunity in PD pathogenesis(46).

Epidemiological research and case reports reveal that the antecedent traumatic brain injury correlate closely with the development of PD in later life (47,48), and postencephalitic parkinsonism may occur in those exposed to infectious agents such as viruses and bacteria, even several decades later (49). Additionally, *In utero* bacterial endotoxin exposure may play a role in the later development of PD (50). Bacterial vaginosis is a fairly common condition in humans, occurring in pregnancy and associated with overgrowth of Gram-negative bacteria, a source of lipopolysaccharide (LPS). Given the higher sensitivity of the SN to LPS than other regions of the brain (51) and the relatively unformed state of the foetal BBB, this raises the possibility that prenatal neuroinflammation may predispose to a higher risk of PD in later life. It could partly explain the apparently random epidemiology of idiopathic PD that a prenatal cerebral infection with no symptomology at birth would be connected to the future development of PD. Indeed, prenatal infection in rats

results in a more prolonged response to inflammatory stimuli in the adult (52). Therefore, as a sequence of neuronal injury or infection, inflammation is a common feature of disease in the brain, and nigral microglial activation acts as a risk factor causing the developing degeneration of dopaminergic neurons (53).

Experimental models of PD in animals demonstrate that neuroinflammation appears to be a ubiquitous finding. Animal models of PD produced by supranigral and continuous infusion of nanogram quantities of LPS for 2 weeks further reveal that maximal activation of microglia in the SN occurs between 1 to 2 weeks after the start of LPS infusion, while degeneration of nigral dopaminergic neurons does not begin until 3 to 4 weeks after the occurrence of peak microglial activation (54). Critically, the damage to the dopaminergic neurons is still clearly evident 1 year postinjection, indicating that a transient exposure to a proinflammatory substance may initiate a sequence of events leading to apparently permanent neurodegeneration as occurs in PD itself (55). In addition, TLR4, the main receptor for LPS, is preferentially expressed on microglia compared to astrocytes, but expressed at very low or undetectable levels on neurons, confirming that microglia are much more responsive than astrocytes to LPS, whereas neurons are virtually unresponsive (56,57).

### 3.2. Cytotoxic effects of activated microglia in PD

Microglial activation in PD is not limited to the SN, but is also observed in the putamen, hippocampus, transentorhinal cortex, cingulate cortex and temporal cortex. The pathological basis of PD confined to pars compacta of substantia nigra could be due to both the special sensitivity of dopaminergic neurons to oxidative action and the higher abundance of microglial cells in the SN (51,58). Activated microglia exert cytotoxic effects through two very different and yet complementary processes. First, they can act as phagocytes which involve direct cell-to-cell contact. Activated microglia phagocytose dopamine neuronal fibers at early stage of neuronal degeneration, suggesting that microglial phagocytosis of degenerating neurons is early occurring in neuronal degeneration. In addition, they phagocytose bystander dopamine neurons, suggesting that activated microglial participation in the progressive degeneration of dopamine neurons (59). Second, in response to immunologic stimuli, activated microglia produce proinflammatory and immune regulatory cytokines, as well as large variety of potentially noxious substances and growth factors, but the levels and timing of production of cytokines may greatly influence their overall effects, as overproduction of cytokines by microglia may lead to more deleterious and neurotoxic consequences as opposed to a merely defensive response, or may be neuroprotective in the initial and / or acute stage, and later become neurotoxic due to and prolonged production of cytokines in the chronic stage (60). For example, in transgenic mice with IL-6 overexpression in the brain, IL-6 enhances neuroprotection and neuroregeneration in models of brain insults (61,62). However, after the chronic exposure to the cytokine, features of neurodegenerative disease, consisting of neurodegeneration, blood–brain barrier breakdown, reactive gliosis, and impaired hippocampal neurogenesis are observed (63), confirming the possibility that the same inflammation can be beneficial in an acute situation but detrimental in a chronic condition, and that the degree and the specific profile of various factors present in the inflamed tissue might regulate brain degeneration or regeneration.

IL-1 and TNF-α are two main proinflammatory cytokines produced by activated microglia, and they are capable of promoting the development of the central nervous system (CNS) inflammation through the disruption of the BBB, the induction of adhesion molecules and chemokines from astrocytes and endothelial cells which facilitate the infiltration of leukocytes into the CNS (59, 64). TNF-α can also activate receptor-mediated proapoptotic pathways within the dopaminergic neuron, and the toxic effects of LPS are reduced by about 50% after the addition of neutralizing antibodies to TNF-α in rat primary dopaminergic neurons (65). Moreover, the proinflammatory cytokines TNF-α, IL-1β and IFN-γ cause potent activation of inducible nitric oxide synthase (iNOS) (66). However, a large body of evidence has supported the notion that microglia also produce cytokines with anti-inflammatory activity, such as transforming growth factor-beta (TGF-β) , IL-10, both of which inhibit microglial activation through their ability to inhibit antigen presentation and proinflammatory cytokines, chemokines and reactive oxygen intermediates (53).

Furthermore, via induction of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and iNOS, activated microglia release reactive oxygen species (ROS) such as superoxide and NO, which have the potential to harm cells and contribute to oxidative damage and neurodegeneration. ROS may accelerate the process of alpha-synuclein aggregation, and result in the formation of more ROS through toxic alpha-synuclein fibrils, therein generating a repetitive cycle of death for the DA neurons (67). NADPH oxidase is the major source of ROS, and NADPH-oxidase main subunit $gp91^{phox}$ is up-regulated in the SNpc of PD and MPTP mice, and in contrast, NADPH-oxidase inactivation attenuates MPTP neurotoxicity by mitigating inflammation-mediated oxidative attack on SNpc neurons, indicating that NADPH-oxidase-induced extracellular oxidative stress is instrumental in SNpc DA neurodegeneration caused by MPTP (68). Moreover, the activation of NADPH oxidase contributes to over 50% of the LPS-induced increase in intracellular ROS and that intracellular ROS is significant for the microglial activation and the production of proinflammatory mediators such as TNF-a (69) or prostaglandin E2 (PGE2) (70). Oxidative stress is the important mechanism through which microglia are toxic to neurons.

Chemokines such as macrophage inflammatory protein-1α (MIP-1α), MIP-1β, monocyte chemotactic protein-1 (MCP-1) and stromal cell derived factor-1 (SDF-1), produced by activated microglia, regulate rapid migration of microglia to the injury sites in CNS and amplify neuroinflammation (71).

### 3.3. Reactive microgliosis and sustained, chronic inflammation in PD

The immune system plays essential roles in the maintenance of tissue homeostasis and the response to infection and injury. Microglia are activated at a very early stage, which often precedes reactions of any other cell type in the brain(72), and thereby promote an inflammatory response that serves to further engage the immune system and initiate tissue repair. In most cases, the response is self-limiting, resolving once infection has been eradicated or the tissue damage has been repaired.

Conversely, a self-propelling cycle of sustained, chronic inflammatory process exists in the brain of PD, which is particularly damaging to the SN dopaminergic neurons. First, exposure to infectious agents such as viruses and bacteria or certain environmental toxicants such as rotenone, can directly lead to the activation of microglia. Second, a variety of soluble factors such as neurotransmitters or its metabolites, released from injured neurons, have proved to be the potential stimulators of reactive microgliosis (73). Third, Lewy bodies containing a-synuclein exist in brain of PD (74). The accumulation of a-synuclein results in the formation of intermediate state oligomers, leading to neuronal cell death with release of protein aggregates into the extracellular space (75). Microglia phagocytose extracellular released a-synuclein, and aggregated, nitrated, and oxidized forms of a-synuclein and neuronal death itself induce additional microglial activation (76). The internalization of a-synuclein by microglia is followed by activation of NADPH oxidase and production of ROS (77). Forth, neurons are able to negatively regulate the reactivity of glial cells through a potential dimerization of the neural cell adhesion molecules expressed on the surface of both cell types, therefore, loss of cell–cell contact between neurons and glial cells may also result in microglial activation (78, 79). Therefore, regardless of the nature of the initiating factors, a cycle may exist: Microglial activation leads to neurodegeneration; neuronal injury, in turn, leads to reactive microglial activation, which further exacerbates neurodegeneration. Over time the continuing presence of this cycle results in the distinct, eventually self-perpetuating neurodegenerative process in the SN.

Considering the presence of sustained, chronic inflammation in PD and cytotoxicity induced by activated microglia, a warning regarding the long-term viability of transplanted stem cells is raised. Stem cells carry receptors for many cytokines and chemokines, suggesting an active crosstalk between the immune and stem cells. Modulating the inflammatory response, particularly the microglial activation, could improve the survival of transplanted cells in patients with PD, and increase the likelihood of a successful outcome.

## 4. NEUROINFLAMMATION MODULATES THE FATE OF GRAFTED CELLS

### 4.1. Role of inflammation on cell survival and stem cell proliferation

Experiments with transplants of rat and human mesencephalic DA neurons in the rat striatum have shown that only 3-20% of grafted dopamine neurons survive the procedure (16,17,79, 81). The reasons for the high death rate of grafted neurons may be features in the environment surrounding a graft that are toxic to DA neurons. Mediators produced by activated microglia such as TNF-α and IL-1β activate astrocytes (56), and the combination of factors that are produced by activated microglia and astrocytes in turn may promote neurotoxicity. Specially, these factors are preferentially toxic to DA neurons. In order to improve the survival of DA neurons in grafts, Lazaroids are applied to inhibit free radical generation, and the yield of surviving DA neurons increases significantly (17).

The vigorous inflammatory and immune reaction associated with activated microglia at the lesion sites of PD might be key to the decreased survival of neural stem or progenitor cells long term. It is demonstrated that a negative correlation of cell survival of the grafted neural stem cells (NSC) to IB4-positive cells, suggesting that inflammatory cytokines are detrimental to the transplanted cells(82). However, the proinflammatory cytokines show differential effects on the proliferation of stem cells. Ben Hur *et al.* found that neural progenitor cells (NPCs) expressed the receptors of TNF-α and IFN-γ, and both TNF-α and IFN-γ inhibited NPCs proliferation. Additionally, IFN-γ increased NPCs apoptotic cell which was partially blocked by TNF-α.(83). Contrary to their findings, others prove that TNF-α triggers apoptotic cell death of NPCs through TNFRI (84). And moreover, recent findings reveal that exposure of SVZ cultures to 1 ng/ml TNF-α induces cell proliferation, whereas 10 and 100 ng/ml TNF-α induces apoptotic cell death (85).

Sasaki T *et al.* investigated the postischemic proliferation of progenitor cells in the subgranular zone (SGZ) after administering cyclooxygenase (COX) inhibitors with various specificities and postischemic neurogenesis in COX-2 knockout mice, and found that the postischemic enhanced proliferation of NPCs was attenuated by COX inhibitors and in COX-2 knockout mice, and thus they thought that COX-2 was an important modulator in enhancement of proliferation of NPCs after ischemia (86). On the contrary, recent studies reveal that COX-2 mediates the impairment of the survival of newly generated cells derived from the NSCs in the dentate gyrus by LPS, and it is suggested that the ameliorating effects of COX-2 inhibitor against LPS action might be exerted by suppressing the cytokine production involved in neuroinflammation, but further experiments should be required to confirm this possibility(87).

It is widely thought that NS/PCs are very sensitive to increases of ROS and result in apoptosis. In consistent with this, it is demonstrated that DMNQ-induced excessive oxidative stress causes p53 accumulation and consequently caspase-2 activation, which in turn initiates apoptotic cell death via the mitochondria-mediated caspase-dependent pathway in NSCs (88). $H_2O_2$ induces acute cell apoptosis in NS/PCs in concentration- and time-dependent manners (89). Similarly, endogenous NO is proved to exert a negative control on the proliferation rate of undifferentiated precursors (90). Contrariwise, it is

proposed, that the cellular response to small changes in the level of ROS has beneficial effects on cell growth and viability under normal conditions (91,92), and a recent research reveals that endogenous ROS and NO are essential for the proliferation of embryonic NS/PCs (93).

### 4.2. Role of inflammation on stem cell migration and homing

Previous works have demonstrated that stem cells including both NSCs and mesenchymal stem cells (MSCs) transplanted systemically or intracerebrally could migrate selectively to the sites of lesion areas (94-98), and it is suggested that inflammation attracts stem cells to the appropriate place for repair purposes via the regulation of growth factor signaling and the secretion of a number of chemoattractant cytokines(99,100).

Activated microglial cells have been shown to produce several chemokines such as SDF-1, MIP-1α, MIP-1β, MCP-1, and Regulated upon Activation Normal T cell Expressed and Secreted (RANTES) (71). Correspondingly, NPCs express a wide range of proinflammatory chemokine receptors, including CCR1, CCR2, CCR5, CXCR3 and CXCR4, but no CCR3 or CCR7(101-103). The chemokines or chemoattractant cytokines via their receptors regulate the migration of stem cells to the sites of neuroinflammation, and very similar results are observed in MSCs(104,105). In addition, human neural progenitor cells express many adhesion molecules involved in inflammation such as α2, α6 and β1 integrins(106), and CD44 (107).

Stem cell homing is defined as the arrest of stem cells within the vasculature of a tissue followed by transmigration across the endothelium, and engrafting into the tissue where they exert local, functional effects. Both MSCs and NSCs have proved to be capable of homing into inflamed areas of the CNS selectively after intravenous or intraarterial injection (95-97). The proposed mechanism of homing that sustains this phenomenon includes two ways: the active way that stem cells actively home to tissues using leukocyte-like cell-adhesion and transmigration and/or the passive way that stem cells become passively entrapped in small-diameter blood vessels (105). The active process consists of tethering, rolling and firm adhesion to inflamed endothelial cells, and extravasation into inflamed CNS areas, which is sequentially mediated by the constitutive expression of functional cell adhesion molecules (such as CD44), integrins (such as α4, β1) and chemokine receptors (such as CCR1, CCR2, CCR5, CXCR3 and CXCR4) on the surface of stem cells. In addition to chemokines and adhesion molecules, MSCs secrete proteases that regulate transmigration and invasion of the basement membrane of endothelium and degrade extracellular matrix during chemotaxis (105,108). Moreover, the transendothelial migration is reduced by both blocking antibodies toward matrix metalloproteinase-2 (MMP-2) and SiRNA knockdown of MMP-2 in MSCs (109). Therefore, inflammation, as the common feature of disease in the brain (110, 111) although alterations in the extracellular milieu during disease or injury are distinct for each pathology, is a key player in the homing and recruitment of stem cells to sites of CNS injury where factors such as SDF-1α, leukaemia inhibitory factor (LIF) and interleukin-6, are overexpressed (112).

### 4.3. Role of inflammation on stem cell differentiation and integration

Studying inflammatory effects on stem cells differentiation, embryonic rat striatal cells transplanted into the excitotoxic striatum lesion shows that the majority of grafted NSCs exhibit glial-like morphology and only a very small fraction develop into neuron-like characteristics (113). Surprisingly, it has been shown that, even in the quiescent form, microglial cells promote astrogliogenesis and maintenance of NSCs through their paracrine effects and that their effects are caused by activation of Stat3 function(114).

Considering the proinflammatory cytokines released by activated microglia, it is demonstrated that IL-6 and LIF released by activated microglia promote astrocytic differentiation of NS/PCs via the activation of the JAK/STAT and MAPK pathways (115). IL-6 promotes both astrogliogenesis and oligodendrogliogenesis and diverts stem cells into a glial program, suggesting that IL-6 inhibition of neurogenesis is primarily due to reduced neuronal differentiation rather than selective influences on cell death or proliferative activity (116). Several studies indicate that exposure of hippocampal NPCs to TNF-α when they are undergoing differentiation but not proliferation has a detrimental effect on their neuronal lineage fate, which may be mediated through increased expression of Hes1 (117,118). However, it is proved that low concentrations (1 ng/ml) of TNF-α promote axonogenesis and neuronal maturation of subventricular zone (SVZ) cell cultures (119).

In addition, neurogenesis is downregulated when NSCs are exposed to NO, and the decreased ability to generate neurons is also found to be transmitted to the progeny of the cells, whereas astroglial differentiation is instead upregulated. But it is suggested that endogenous NO contributes to the maturation of neurons that recently arrive to the olfactory bulb (90).

However, Aarum J. *et al* studied microglial effects on differentiation, and found that precursor cell cultures from both the embryonic and the adult brain, grown in conditioned media from activated microglia, contained a higher proportion of neurons than would be expected from their spontaneous differentiation alone. It is speculated that microglia cells play a purely instructive role in inducing the precursor cells to be committed for a neuronal fate, instead of selectively promoting the survival of neuronal cells e.g., by providing neurotrophins or producing factors that are toxic to astrocytes (99). Further studies have revealed that hippocampal neurogenesis is associated with the recruitment of T cells and the activation of microglia, and is markedly impaired in immune-deficient mice (120), implying that microglial cells play an important role in neurogenesis (121,122). Therefore, the regulation of the immune-cell activity is crucial: too little immune activity (as in immune deficiency syndromes) or too much immune activity (as in severe inflammatory diseases) can

result in impaired neurogenesis (123), and the excessive glial scar formation would prohibit the new generated neurons from integrating morphologically into normal tissue (124).

## 5. GRAFT REJECTION AND ALLOGENEIC/XENOGENEIC STEM CELLS

Not only will transplanted cells encounter an inflamed environment, but they may contribute to it, because allogeneic/xenogeneic stem cells would not be immunologically matched to the host and induce some level of the immune rejection response. It is proved that *in vitro* cultured NSCs before differentiation exhibit low MHC molecule expression that then increases especially in differentiated astrocytes (125, 126). Isolated NSCs express also the costimulatory molecules CD80 and CD86. The exposure to proinflammatory cytokines such as IFN-γ and TNF-α enhances the expression of CD80, CD86 and MHC class I (but not class II) molecules (127, 128**)**. This renders the NSCs recognizable by T cells or natural killer (NK) cells *in vitro*, leading to classical immune-mediated cytolysis (129). NSCs transplanted in a rat model of spinal cord injury were ultimately rejected after an extended period of growth and maturation (130). Even when grafts survive, numerous CD45+ cells are observed around the allograft in patients receiving grafts of fetal nigral tissue to treat PD (131). Compared with autologous NSCs transplantation, allografts not only show decreased survival, but also decreased migration away from the transplant site and decreased differentiation of neurons (132, 133).

Embryonic stem cells (ES) express low levels of HLA class I molecules which are up-regulated by IFN-γ stimulation or after differentiation (134, 135). Human MSCs express low-intermediate level of HLA-class I and LFA-3, but do not express the co-stimulatory molecules CD80, CD86, CD40 or CD40L (136, 137). In addition, human MSCs express HLA-G, a non-classical MHC class I antigen that may prevent the immune response against MSCs (138).

Although the graft is proved to survive well with marked clinical benefit to PD, T cells have been observed in the site of the graft after cessation of cyclosporin A(131, 139). Moreover, in patients with Huntington's disease who underwent neural transplantation containing striatal anlagen in the striatum a decade earlier, activated microglia, within and surrounding those components of the grafts containing striatal markers, are found periodically engulfing neuronal elements of the graft, suggestive of potential phagocytosis (124). These data indicate that chronic rejection events may take place, and the chronic inflammatory reactions may theoretically play a role in the reported development of abnormal movements (dystonia and dyskinesias) seen in the double-blind U.S. transplant trials (140).

## 6. IMMUNOMODULATORY EFFECTS OF STEM CELLS

Traditionally, neuroinflammation plays an important role in the fate of endogenous and grafted stem cells, and the initial purpose of stem cell transplantation for neurodegenerative disease is cell replacement therapy, which aims at promoting structural and functional repair of damaged tissues. However, experimental studies reveal that grafted stem cells display immunomodulatory functions that promote neuroprotection (141,142), and now most of such studies focus on the treatment of multiple sclerosis (MS), a chronic inflammatory neurodegenerative disease with loss of axons and myelin sheaths.

Experimental autoimmune encephalomyelitis (EAE) is an animal model of MS (143,144). The systemically-injected NPCs selectively enter the inflamed CNS, survive in perivascular CNS areas, and exert immune-like function effects that promote long-lasting neuroprotection by inducing programmed cell death of blood-borne, CNS-infiltrating pro-inflammatory TH1 (but not anti-inflammatory TH2) cells (101,145). Other studies demonstrate that both intraventricular and intravenous NPCs transplantations attenuate brain inflammation in acute and chronic EAE. Especially, neural precursors grafted intravenously enter lymph nodes and spleen instead of CNS, inhibit the activation and proliferation of T cells, and markedly reduce their encephalitogenicity, indicating that NPCs exert an immunomodulatory effect by peripheral immunosuppression (146,147). Additionally, subcutaneously injected NPCs also accumulate and survive within draining lymph nodes for over two months, but not in the CNS, where a permissive ectopic germinal niche-like micro-environment in perivascular lymph node area is established. Within this context, surviving NPCs hamper the activation of myeloid dendritic cells (DC) via the release of major developmental stem cell regulators, including the morphogens bone morphogenetic protein (BMP)-4, sonic hedgehog (Shh), the extracellular matrix protein tenascin C, and the BMP antagonist Noggin. This BMP-4-dependent mechanism that hinders the DC maturation is highly specific for immune regulatory NPCs, and, in turn, leads to the steady restraint of the expansion of antigen-specific (encephalitogenic) T cells (148). Furthermore, NSCs genetically modified to overexpress IL-10, an effective anti-inflammatory cytokine (IL-10–NSCs), significantly enhance both the ability of these cells to suppress autoimmune responses in the periphery and in inflammatory foci of the CNS and the ability of transplanted NSCs to differentiate into more neurons and oligodendrocytes but fewer astrocytes. Importantly, via reduced local inflammation and increased debris clearance, IL-10–NSCs convert a hostile environment into a supportive one, which promotes endogenous remyelination and neuron/oligodendrocyte repopulation (149).

Aiming at investigating the effect on acute cerebral and peripheral inflammation after intracerebral haemorrhage (ICH) of NSCs, it is found that NSCs injected intravenously at 2 after collagenase-induced ICH results in fewer initial neurologic deteriorations and reduced brain oedema formation, inflammatory infiltrations and apoptosis in perihematomal areas, and that NSCs modulate the splenic inflammatory pathway to reduce the cerebral inflammation. Additionally, NSCs inhibit *in vitro* macrophage activations after LPS stimulation in a cell-to-cell contact dependent manner. Therefore, intravenous NSCs administration during the hyperacute stage in stroke

modulates innate cerebral inflammatory responses with interacting with peripheral inflammatory systems, and protects the brain via a bystander mechanism rather than via any direct cell replacement (150).

MSCs have been proved to have a number of unique immunological properties, and it is demonstrated that the MSC-mediated immunosuppression is exerted nonselectively on virtually all the cells of the immune system. Besides the suppression of proliferation of T, B (151,152), and dendritic cells through the induction of cell division arrest, MSCs are able to inhibit proliferation of NK cells and impair dendritic cell maturation, as well as antigen presentation (152,153). The immunomodulatory properties of MSCs in cell transplantation as a protective mechanism have also successfully been exploited in *in vitro* and in a number of disease models including autoimmune encephalomyelitis, PD, renal ischemia-reperfusion injury, toxic-induced hepatic failure, diabetes, rheumatoid arthritis and graft-versus host disease (108,152). Gerdoni E and his colleagues injected intravenously MSCs to treat EAE, and a significantly milder disease and fewer relapses, with decreased number of inflammatory infiltrates, reduced demyelination, and axonal loss were observed. Moreover, proliferation of T cells from the lymph nodes and the spleen of MSC-treated mice was significantly impaired, and total antigen specific IgG production, as well as that of each IgG subclass, was significantly inhibited, suggesting that MSCs could effectively ameliorate relapsing-remitting EAE through the inhibition of pathogenic T- and B-cell responses directed against the immunizing antigen. MSCs entered the central nervous system but did not transdifferentiate into neural cells (142,153). In contrast, Kassis I and colleagues' study demonstrated that the intravenously and intraventricularly injected MSCs were attracted to the areas of central nervous system inflammation and expressed neuronal, astrocytic, and oligodendrocytic markers, and the direct injection of MSCs into the ventricles of the brain led to a more pronounced reduction in infiltrating lesions, indicating an additional and possibly more important local *in situ* immunomodulatory effect (154).

MSCs can also inhibit the activation of microglia and have a protective effect on the dopaminergic system through an anti-inflammatory mechanism. In co-cultures of LPS-stimulated microglia and MSCs using a Transwell culture chamber system to physically separate LPS-stimulated microglia and MSCs in order to inhibit cell-cell contact, the MSC treatment significantly decreases LPS-induced microglial activation, TNF-α, iNOS mRNA expression, and production of NO and TNF-α, while significantly increases expression of anti-inflammatory cytokines (IL-6, IL-10, and TGF-β). In the animal study, the MSCs treatment in rats via the tail vein reveals that tyrosine hydroxylase-immunopositive (TH-ip) neuronal loss induced by LPS stimulation is considerably decreased in the SN and is clearly accompanied by a decrease in microglial activation, as well as expression of TNF-a and iNOS mRNA and production of TNF-a (155). Additionally, intravenous transplantation of MSCs into the MPTP-induced PD model can also lead to repairing of BBB, reduction of mannose-binding lectin (MBL) infiltration at SNpc and MBL expression in the liver, suppression of the activation of microglia, together with prevention of dopaminergic neuron death. But no MSCs are observed to differentiate into dopaminergic neurons, while the MSCs migrate into the SNpc and release TGF-β1 there (156). A common feature of these studies is that the therapeutic effect of MSCs does not seem to be associated with differentiation into neural cells but mainly to be the result of anti-inflammatory activity coupled with a protective effect on the surrounding neural tissue, suggesting that MSCs have a neuroprotective effect on dopaminergic neurons through anti-inflammatory actions mediated by the modulation of microglial activation.

Taken together, several types of stem cells have shown to possess immunomodulatory properties, including NSCs, bone marrow stromal cells, hematopoietic stem cells, and embryonic stem cells (141). Although it is yet to be determined whether various types of stem cells share common immune characteristics, and the mechanisms by which these cells exert their immunosuppressive function are still unclear, it is likely that both cell-to-cell contact and soluble factors are involved in anti-inflammatory activity of stem cells (108). Therefore, the neuroprotective effect of stem cells in PD may be mediated not only by their differentiation into dopaminergic neurons and trophic factors secreted, but also by their ability of immunosuppression that may contribute to functional recovery.

## 7. CONCLUSIONS AND PERSPECTIVES

Reactive microgliosis and sustained, chronic neuroinflammation play an important role in the pathogenesis of PD, and activated microglia form a vicious self-perpetuating neuronal degeneration cycle resulting in the long-term progressive neurodegeneration. Neuroinflammation acts as double-edged swords, simultaneously beneficial and detrimental, on modulating neurogenesis and biology of endogenous / exogenous stem cells including cell survival, proliferation, homing, migration, differentiation and integration in response to brain pathology, and in return, stem cells display immunomodulatory functions which are beneficial for dopaminergic neurons via an anti-inflammatory action. In order to improve cell therapy and optimize immune modulatory treatments for PD, further works as followings should be done in the future. First, given the multiple functions of inflammatory and immune molecules, much more needs to be learned about their more detailed and special functions in PD and stem cell biology. Second, in order to promote the beneficial effects and reduce or inhibit the detrimental effects of inflammation on neurogenisis of stem cells, measures to direct and instruct instead of simply suppress the inflammatory machinery should be taken. Third, measures to enhance the immunomodulatory capacities of stem cells should be researched.

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Feng Li and Shaowei Zhu, contributed equally to this work and should be considered co-first authors. This

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**Abbreviations:** PD: Parkinson's disease, SN: substantia nigra, SNpc: substantia nigra pars compacta, DA: dopamine/dopaminergic, NO: nitric oxide, BBB: blood-brain barrier, HLA: human leukocyte antigen, MPTP: 1-methyl-4-phenyl -1,2,3,6-tetrahydropyridine, CSF: cerebrospinal fluid, IL-1β: Interleukin-1β, INF-γ: interferon-γ, TNF-α: tumor necrosis factor-α, LPS: lipopolysaccharide, CNS: central nervous system, iNOS: inducible nitric oxide synthase, TGF-β: transforming growth factor-beta, NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase, ROS: reactive oxygen species, PGE2: prostaglandin E2, MIP-1α: macrophage inflammatory protein-1α , MCP-1: monocyte chemotactic protein-1, SDF-1: stromal cell derived factor-1, NS/PCs: neural stem/progenitor cells, SVZ: subventricular zone (SVZ), SGZ: subgranular zone, COX: cyclooxygenase, MSCs: mesenchymal stem cells, RANTES: Regulated upon Activation Normal T cell Expressed and Secreted, MMP-2: matrix metalloproteinase-2, LIF: leukaemia inhibitory factor, ES: Embryonic stem cells, MS: multiple sclerosis, EAE: experimental autoimmune encephalomyelitis, DC: myeloid dendritic cells, BMP: bone morphogenetic protein, Shh: sonic hedgehog, ICH: intracerebral haemorrhage

**Key Words:** Parkinson's disease, Neuroinflammation, Cell therapy, Microglia, Stem cells, Anti-inflammatory, Review

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