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REVIEW

Effects of neuroinflammation on the regenerative capacity of brain stem cells

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Abstract

In the adult brain, neurogenesis under physiological conditions occurs in the subventricular zone and in the dentate gyrus. Although the exact molecular mechanisms that regulate neural stem cell proliferation and differentiation are largely unknown, several factors have been shown to affect neurogenesis. Decreased neurogenesis in the hippocampus has been recognized as one of the mechanisms of age-related brain dysfunction. Furthermore, in pathological conditions of the central nervous system associated with neuroinflammation, inflammatory mediators such as cytokines and chemokines can affect the capacity of brain stem cells and alter neurogenesis. In this review, we summarize the state of the art on the effects of neuroinflammation on adult neurogenesis and discuss the use of the lipopolysaccharide-model to study the effects of inflammation and reactive-microglia on brain stem cells and neurogenesis. Furthermore, we discuss the possible causes underlying reduced neurogenesis with normal aging and potential anti-inflammatory, pro-neurogenic interventions aimed at improving memory deficits in normal and pathological aging and in neurodegenerative diseases.

Keywords: aging, brain, inflammation, lipopolysaccharide, neurogenesis.

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Adult neurogenesis

In the adult mammalian brain, neural stem cells are localized in two areas: the subventricular zone (SVZ), a layer extending along the lateral wall of the lateral ventricle (Doetsch and Scharff 2001), and the subgranular zone of the dentate gyrus (DG) of the hippocampus (Limke and Rao 2002), a thin cell layer between the granule cell layer and dentate hilus (Seri *et al.* 2001). Hippocampal neurogenesis plays a role in the maintenance of normal hippocampal function, learning and memory (Gould *et al.* 1999; Shors *et al.* 2001). Several hippocampus-dependent learning tasks increase the proliferation of neuronal progenitors in the SGZ and promote the survival of newly generated neurons (Gould *et al.* 1999; Drapeau *et al.* 2007).

Like hippocampal progenitor cells, SVZ stem cells are tightly controlled under physiological conditions (Morshead *et al.* 1994, 1998), and in addition to their role in maintaining brain homeostasis, are involved in neuronal replacement in response to aberrant conditions. Although little is known about the exact molecular mechanisms that regulate neural stem cells niche, several factors are known to affect neurogenesis. Self-renewal, proliferation, differentiation and migration of these cells vary, depending on the local microenvironment characterizing the different types of brain injury.

By mechanisms as yet unknown, brain stem cells become 'activated' after neuronal injury and preferentially migrate at

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Abbreviations used: BDNF, brain-derived neurotrophic factor; DG, dentate gyrus; IFN, interferon; IL, interleukin; iPSC, induced pluripotent stem cells; LPS, lipopolysaccharide; MSC, mesenchymal stem cells; NO, nitric oxide; NOS, nitric oxide synthase; NSC, neural stem cells; SVZ, subventricular zone; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α.

the sites of pathology, indicating that mediators at the injury site can guide the migration of precursor cells (Arvidsson *et al.* 2002; Nakatomi *et al.* 2002). The recently discovered potential of cellular regeneration in the diseased brain has gained a lot of interest among basic and clinical neuroscientists, and further studies are required to understand the mechanisms of neurogenesis and the potential therapeutic use of stem cells in pathological conditions of the CNS.

Effects of neuroinflammation on neurogenesis

Until fairly recently, the brain was considered an immunologically privileged site, not susceptible to immune activation due to the presence of the blood brain barrier (Lucas *et al.* 2006). However, it became increasingly clear that the CNS is immunologically specialized, and immune cells and mediators are found in the CNS under both normal and pathological states, while neurons are interacting with and regulating immune cells (Lucin and Wyss-Coray 2009).

Following brain injury or exposure to pathogens, an inflammatory response is driven by the activation of resident microglia, local invasion of circulating immune cells, and production of cytokines, chemokines, neurotransmitters, and reactive oxygen species. These inflammatory components are essential to recruit cells of the immune system to the compromised area. Microglia, the resident macrophages of brain parenchyma, play a central role in the inflammatory response. In healthy brain, microglia are present in a resting state, but they can rapidly react to subtle microenvironmental alterations by changing morphology and acquiring an array of functions, including phagocytosis and secretion of inflammatory mediators (Liu and Hong 2003; Perry 2004). Reactive microglia migrate along a chemotactic gradient to reach the site of injury and phagocytose cellular debris or foreign materials. Reactive microglia can release chemokines to attract more microglia and secrete inflammatory factors to further propagate neuroinflammation. A variety of cytotoxic substances released by activated microglia can cause neuronal damage by enhancing oxidative stress and activating cell-death pathways (Choi *et al.* 2009). Over-activation of microglia cells can result from a variety of injury signals, such as oxidative stress molecules, β-amyloid peptide oligomers, ischemia, brain trauma, which all promote erroneous signaling cascades in microglia cells and induce proinflammatory cytokine production (Fernandez *et al.* 2008; Morales *et al.* 2010). Morales and colleagues postulated that neuroinflammation induced by activation of the innate immune system is a major driving force in Alzheimer's disease pathogenesis. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, which are activated in Alzheimer's disease, signal through different neuronal receptors, thus activating protein kinases involved in tau hyperphosphorylation (Morales *et al.* 2010).

Although a well-regulated inflammatory process is essential for tissue repair, an excessive or protracted inflammatory response can result in a more severe and chronic neuroinflammatory cycle that is thought to play an important role in the development and/or progression of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's disease and multiple sclerosis (Hemmer *et al.* 2004; Gao and Hong 2008; Stolp and Dziegielewska 2009).

Several findings support a role for inflammation in the pathogenesis of neurodegenerative disorders. Specifically, in postmortem brain from Alzheimer's disease patients activated microglia surrounding amyloid plaques (Rozemuller *et al.* 2005) and/or injured neurons (Klegeris *et al.* 2007), increased levels of proinflammatory cytokines and complement activation (Rozemuller *et al.* 2005) have been reported. Supporting a role for inflammation in the pathogenesis of Alzheimer's disease, epidemiological studies indicate that long-term use of non-steroidal anti-inflammatory drugs has a protective effect and significantly lowers the risk of developing Alzheimer's disease later in life (Klegeris and McGeer 2005; Rozemuller *et al.* 2005; McGeer and McGeer 2007). Furthermore, genetic polymorphisms for several inflammatory cytokines and their receptors modulate the risk of disease (Bossu *et al.* 2007), and animal and cell culture models show that modulation of inflammation is effective in curbing the disease process (Rozemuller *et al.* 2005). These evidences are not specific to Alzheimer's disease, since neuroinflammation significantly contributes to the pathogenesis of many neurodegenerative diseases (Klegeris *et al.* 2007). Innate immune response associated with gliosis, in particular microglial cell activation, is an important neuropathological feature of Parkinson's disease in humans and in animal models of the disease. Activated microglial cells might contribute to dopaminergic cell death by releasing cytotoxic inflammatory compounds such as proinflammatory cytokines [TNF-α, IL-1β, and interferon (IFN)-γ] (Hirsch and Hunot 2009). The link between inflammation, oxidative stress and Parkinson's disease is supported by an overwhelming number of studies that implicate inflammatory processes in the progressive loss of nigral dopaminergic neurons. However, despite the promising data on neuroprotective effects of anti-inflammatory agents in animal models, it remains to be determined whether anti-inflammatory therapy in humans could have a beneficial effect in preventing or slowing down progression of Parkinson's disease (Tansey and Goldberg 2010). Therapeutic intervention aimed at prevention or down-regulation of immune-associated mechanisms represents a promising approach to stop disease progression. With the available knowledge of the cellular and molecular network implicated in the immune-associated damage to dopaminergic neurons, several immunotherapeutic approaches are possible, some of which have already been

applied or tested in other neurological disorders (Hirsch and Hunot 2009).

Damaged neurons can be repaired by the activation of endogenous neuronal stem cells, which migrate to regions of brain injury, differentiate into neuronal cells, and integrate into neuronal circuits (Belmadani *et al.* 2006). The potential of stem cells has been demonstrated *in vitro* and *in vivo* using animal models of brain inflammation and disease (Gage 2002; Abrous *et al.* 2005). However, it is important to emphasize that the inflammatory environment may influence the temporal and spatial relationship in the neural stem cell niche and thus, alter self-renewal, survival, migration and neuronal differentiation of stem cells (Martino and Pluchino 2006).

Inflammation is a complex process that, depending on the conditions, can either enhance or suppress neurogenesis. The discrepancies between the pro-neurogenic and anti-neurogenic properties of inflammation may depend on how microglia, macrophages and/or astrocytes are activated and on the duration of inflammation (Fig. 1). Although the effects of brain inflammation on neuronal injury and neurogenesis in various CNS disorders have been a matter of intense investigation in recent years, the mechanisms, function and significance of the modulation of neurogenesis during inflammatory processes remain to be elucidated. It has been suggested that activated microglia in inflammatory settings can inhibit neurogenesis (Butovsky *et al.* 2006). Indeed, mediators released by the immune cells, like cytokines and nitric oxide (NO), negatively regulate adult neurogenesis (Vallieres *et al.* 2002; Monje *et al.* 2003; Liu *et al.* 2006). However, recent evidence suggests that activated microglia are not always detrimental for neurogenesis, but, under certain conditions, can be beneficial (Hanisch and Kettenmann 2007). For instance, both neurogenesis and oligodendrogenesis are induced by microglia activated by IL-4 or low level of IFN-γ [59]. IFN-γ also enhanced neuronal differentiation when directly administered to neural stem cells (NSC) or neuronal cell lines (Wong *et al.* 2004; Song *et al.* 2005), and IFN-γ transgenic mice exhibited increased NSC proliferation and differentiation in the adult DG, which was associated with neuroprotection and improved spatial cognitive performance (Baron *et al.* 2008).

Exercise has been demonstrated as another positive factor that stimulates plasticity, neurogenesis and enhances cognitive functions by reducing pro-inflammatory conditions and increasing growth factor levels (Cotman *et al.* 2007). Supporting a positive effect of exercise on neurogenesis during inflammation, treadmill exercise has been shown to counteract the suppressive effects of peripheral lipopolysaccharide (LPS) on hippocampal neurogenesis, learning and memory (Wu *et al.* 2007).

Environmental enrichment also stimulates hippocampal neurogenesis in adult mice and increases the number of dendritic spines, extent of branching, and number of synapses per neuron (van Praag *et al.* 2000). The beneficial effects of environmental enrichment may be due to the inhibition of the expression of pro-inflammatory genes in the brain (Dong *et al.* 2007).

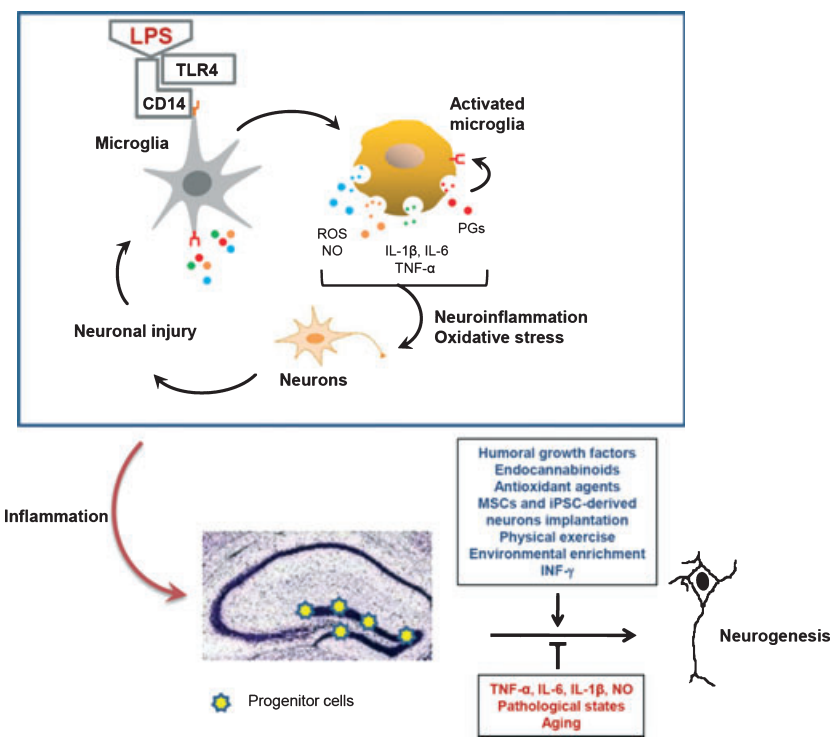

Fig. 1 Effects of neuroinflammation on neurogenesis lipopolysaccharide (LPS)-induced neuroinflammation causes reactive microgliosis, which contributes to neuronal dysfunction and degeneration by releasing inflammatory and neurotoxic factors [interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-1β, nitric oxide (NO), reactive oxygen species (ROS)]. These pro-inflammatory mediators can alter the 'neural stem cell' niche, leading to decrease in proliferation and neuronal differentiation of progenitor cells, which results in inhibition of neurogenesis. In contrast, other factors such as humoral growth factors, endocannabinoids, antioxidant agents, mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSC)-derived neurons implantation, interferon (IFN)-γ, physical exercise and environmental enrichment can stimulate neurogenesis.

Lipopolysaccharide-induced neuroinflammation and effects on neurogenesis

In the CNS, LPS binds to a CD14 receptor, a glycosyl-phosphatidylinositol-linked membrane protein, and together with the extracellular adaptor proteins MD-2 binds to the toll-like receptor 4 (TLR4) expressed by microglia (Beutler 2004), causing a direct activation of brain innate immunity (Montine *et al.* 2002; Aid *et al.* 2008). TLR-4 is the key transmembrane receptor for LPS effect because mice with either a point or null mutation in the TLR4 gene are insensitive to LPS (Rosenberg 2002; Palsson-McDermott and O'Neill 2004). Transduction through TLR-4 results in a cascade of intracellular events that leads to the transcription of inflammatory and immune response genes (Bonow *et al.* 2009).

Lipopolysaccharide induces an increase in the synthesis of inflammatory mediators, like cytokines, primarily IL-1, IL-6, and TNF-α, chemokines, products of arachidonic acid metabolism, free radicals generated by NADPH oxidase, myeloperoxidase and inducible nitric oxide synthase (NOS) (Quan *et al.* 1994; Montine *et al.* 2002). Cytokines and chemokines, in turn, mediate the recruitment of polymorphonuclear leukocytes and monocytes from the bone marrow.

Lipopolysaccharide-induced neuroinflammation has been shown to severely affect CNS cognitive function, length and spine density, dopaminergic cells, learning, memory, and neurogenesis (Quan *et al.* 1994; Shaw *et al.* 2001; Monje *et al.* 2003). A recent study showed that soluble factors released from microglia can direct the migration of neural precursor cells (Shapiro *et al.* 2008), and several reports demonstrated migration and regeneration of neural cells to sites of brain injury (Snyder *et al.* 1997; Arvidsson *et al.* 2002; Nakatomi *et al.* 2002).

The link between brain inflammation and neurogenesis, and the role of microglia in the modulation of neurogenesis under pathological conditions are under intense investigation. To study the effects of inflammation on the regenerative capacity of brain stem cells, several studies have focused on the microglia reaction after an acute injury and after administration of LPS (Ekdahl *et al.* 2003; Monje *et al.* 2003). TLR4 is abundantly expressed by neural stem/progenitor cells and LPS decreases the proliferation of cultured neural stem/progenitor cells *via* a nuclear factor-kappa B-dependent mechanism (Rolls *et al.* 2007). Indeed, the absence of TLR4 results in enhanced proliferation and neuronal differentiation (Rolls *et al.* 2007). Additional studies *in vitro* indicate that TLR4 directly modulates self-renewal and the cell-fate decision of neuronal progenitor cells (Rolls *et al.* 2007).

Activated microglia have been identified as the putative candidate responsible for down-regulating hippocampal neurogenesis after LPS-induced neuroinflammation (Ekdahl *et al.* 2003; Monje *et al.* 2003). Activated microglia were localized in close proximity to the newly formed cells, and there was a negative correlation between the number of activated microglia in the neurogenic zone and the number of surviving new hippocampal neurons (Ekdahl *et al.* 2003). This hypothesis is supported by a number of *in vitro* studies demonstrating that the survival of new hippocampal neurons is reduced when they are co-cultured with microglial cells activated by LPS, or exposed to their conditioned medium (Monje *et al.* 2003; Liu *et al.* 2005; Cacci *et al.* 2008). Because an IL-6 antibody selectively restored hippocampal neurogenesis, this effect was likely mediated by IL-6 (Monje *et al.* 2003; Nakanishi *et al.* 2007). Supporting this concept, transgenic mice with chronic astroglial expression of IL-6 show a substantial decrease in the production of new neurons (Vallieres *et al.* 2002).

Other pro-inflammatory cytokines could contribute to the inhibition of neurogenesis. For instance, IL-1β can reduce neurogenesis in the DG (Goshen *et al.* 2008; Spulber *et al.* 2008), whereas TNF-α seems to play a detrimental role in neural survival/differentiation (Monje *et al.* 2003; Liu *et al.* 2005). When added to adult hippocampal progenitor cell cultures, TNF-α decreased neurogenesis by 50% (Monje *et al.* 2003). Increased production of TNF-α by microglial cells during hippocampal inflammation could contribute to the death of new hippocampal progenitor cells (Vezzani *et al.* 2002).

Another inflammatory mediator, NO, is a negative regulator of neurogenesis. A significant increase in SVZ cell proliferation has been demonstrated in neuronal NOS deficient mice (Sun *et al.* 2005), or after inhibition of neuronal NOS activity (Cheng *et al.* 2003; Moreno-Lopez *et al.* 2004). Furthermore, pathological concentrations of NO *in vitro* have a skewing effect on NSC differentiation, diverting a pro-neuronal to a pro-astroglial fate (Covacu *et al.* 2006).

Neuroinflammation inhibits neurogenesis by a variety of mechanisms, including an alteration in the relationship between progenitor cells and cells of the neurovasculature, a direct effect of activated microglia on the precursor cells, or stimulation of the hypothalamic-pituitary-adrenal axis (Monje *et al.* 2003). However, little is known on how a pathological environment with reactive-microglia affects the differentiation of precursor cells. An invariant feature of damage to the CNS is the migration of microglia cells to the site of injury and their subsequent activation. There is some evidence that newborn neurons generated from stem cells could partially replace dead cells following brain injury (Nakatomi *et al.* 2002; Thored *et al.* 2006). Therefore, the identification of suitable tools to direct microglial state towards a pro-neurogenic phenotype could represent a new strategy to promote brain regenerative processes (Nakatomi *et al.* 2002; Thored *et al.* 2006).

'Aging brain': a matter of hot debate

Evidence of morphological alterations of microglia with normal aging led to the hypothesis that microglia become dysfunctional in the aged brain (Streit *et al.* 2004). Senescence may impair the ability of microglia to function and respond to stimuli normally and increase the vulnerability to neurodegenerative diseases. The most prominent and early feature of microglia senescence is a morphological alteration characterized by deramification, cytoplasmic beading/spheroid formation, shortened and twisted cytoplasmic processes, and partial or complete cytoplasmic fragmentation (Streit *et al.* 2004).

Markers of inflammation and microglia and astrocytes activation are significantly increased in the hippocampus of aged mice (Kuzumaki *et al.* 2010), rats (Aid and Bosetti 2007; Kuzumaki *et al.* 2010) and humans (David *et al.* 1997; Sheffield and Berman 1998). These age-associated changes may underlie the alteration of microglial function and their responses to injury.

Microglia isolated from aging brains have increased basal levels of IL-6, which could exacerbate cognitive deficits associated with neuroinflammation (Sparkman *et al.* 2006). Furthermore, increased IL-6, IL-1β, and TNF-α production in response to LPS stimulation when compared with microglia derived from young brains, suggesting that aging microglia are over-responsive to inflammatory stimuli (Ye and Johnson 1999; Xie *et al.* 2003).

Memory deficits seen during normal or pathological aging may be linked to alterations in neurogenesis. Decreased neurogenesis in the hippocampus has been recognized as one of the mechanisms of age-related brain dysfunction (Kuzumaki *et al.* 2010). However, the molecular mechanisms underlying the decrease in neurogenesis with aging remain unclear.

It has been suggested that the age-related deficit in hippocampal-dependent learning is in part due to an increase in IL-1β (Gemma and Bickford 2007). Indeed, the up-regulation of IL-1β expression coupled with a down-regulation of IL-4 expression in the aging brain is associated with impaired long term potentiation, one of the major cellular pathways involved in learning and memory (Nolan *et al.* 2005). A key anti-inflammatory action of IL-4 results from its ability to antagonize the effects of IL-1β or to inhibit the synthesis of IL-1β mRNA and protein; in fact co-treatment of LPS-stimulated hippocampal neurons with IL-4 abrogated the increased expression of IL-1β (Nolan *et al.* 2005).

Interleukin-1β in the hippocampus (Murray and Lynch 1998; Kuzumaki *et al.* 2010; Lynch 2010) has been proposed to contribute to the anti-neurogenic effect by suppressing hippocampal neurogenesis in the aging brain (Koo and Duman 2008) *via* epigenetic modifications (Kuzumaki *et al.* 2010). Indeed, aging induces a significant increase in histone H3-lysine 9 trimethylation at the promoter of a neural progenitor cell marker (NeuroD) in the hippocampus (Kuzumaki *et al.* 2010). Overall, these data suggest that IL-1β, which levels are increased with aging, can exert an epigenetic modulation of neural progenitor cells.

The reasons for decreased neurogenesis with aging may be related to an intrinsic inability to respond to the proliferative stimulation in the neurogenic niche, a reduction of proliferative stem cells number, or activated microglia and neuroinflammation. Neural stem cells therapy has considerable potential to repopulate damaged areas of the adult and aging brain. Understanding the basis for reduced neurogenesis in the aging brain is necessary to determine the functional importance of new neurons and the potential therapeutic use of neural stem cells for repair.

Stem cell technology: a potential regenerative strategy for aging and disease

Neurogenesis by endogenous brain stem cells cannot fully compensate for the neuronal loss observed in aging and, particularly, in neurodegenerative diseases. One reason for this limited response is the lack of trophic support and inhibitory signals within the brain microenvironment (Croft and Przyborski 2009), indicative of oxidative stress (Kelly *et al.* 2010) and age-related neuroinflammation. These observations stimulated a search for agents that could increase neurogenesis and enhance neuroprotection.

A number of humoral growth factors have been shown to modulate the mitotic expansion and the neuronal stem cells differentiation. To promote the integration of newly formed neurons into the mature brain circuit, several groups have focused on brain-derived neurotrophic factor (BDNF) (Cho *et al.* 2007). Decreased levels of BDNF have been reported in normal aging (Hattiangady *et al.* 2005) and neurodegenerative diseases, where discrete brain regions affected by loss of neurons have decreased levels of BDNF, which can contribute to lack of trophic support for neurons and to subsequent neurodegeneration (Hock *et al.* 2000). There is evidence that BDNF can promote survival and neuronal differentiation of hippocampal progenitor cells and improve learning and memory (Shetty *et al.* 2004; Hattiangady *et al.* 2005). Thus, exogenous BDNF could potentially promote the formation of new neurons in the aged or diseased brain (Pencea *et al.* 2001). In addition to BDNF, studies have shown that intracerebroventricular infusion of fibroblast growth factor-2 or nerve growth factor can also enhance neurogenesis and improve learning and memory deficits in the aged brain (Fischer 1994; Shetty *et al.* 2005; Rai *et al.* 2007). Insulin-like growth factor-1 is another promising candidate to regulate and restore neurogenesis in the aging brain since it influences neuronal production during development and then decreases with age (Lichtenwalner *et al.* 2001). Antioxidant agents (Lim *et al.* 2005; Lynch

et al. 2007; Kelly *et al.* 2010), and endocannabinoids (Marchalant *et al.* 2009) have an anti-inflammatory effects and improve age-related deficits in spatial learning during normal and pathological aging.

An alternative approach for restoring function following neuronal loss is implantation of stem progenitor cells (Prockop *et al.* 2003; Munoz *et al.* 2005). Progenitor cells can be generated from several sources and show great promise for many clinical applications, including disease modeling, drug screening, and regenerative medicine (Marchetto *et al.* 2010). Recently, it has been shown that forced expression of some transcription factors, in human fibroblasts and adipose cells can reprogram the cells to a pluripotent state. These induced pluripotent cells (iPSC) exhibit similar properties of human embryonic cells, can self-renew, and are capable to give rise to all cells types including neurons (Liu *et al.* 2010). Cell reprogramming and successful generation of iPSC-derived neurons that became functionally intergrated after transplantation has been reported for several neurodegenerative diseases like Parkinson's and Huntington' diseases (Park *et al.* 2008; Soldner *et al.* 2009; Marchetto *et al.* 2010). Mouse iPSC-derived precursors were differentiated into dopamine neurons and transplanted into a rat model of dopamine neurons depletion, in which they were functionally integrated in the striatum and improved Parkinson-like symptoms (Wernig *et al.* 2008). Promising results were obtained by Aubry and collegues also with human embryonic stem cells, which after transplantation matured into striatal neurons in a rat model of Huntington's disease (Aubry *et al.* 2008).

Mesenchymal stem cells (MSCs) of adult bone marrow and amniotic fluid (Tsai *et al.* 2006; Cipriani *et al.* 2007) are also regarded as potential candidates for regenerative medicine. Recent reports have shown that adult bone marrow and amniotic fluid contain a subpopulation of mesenchymal stem cells that can be isolated and have the capacity to differentiate into multiple lineages (Pittenger *et al.* 1999; Woodbury *et al.* 2000), including neurons, and are capable of replacing damaged neuronal tissue (Cipriani *et al.* 2007; Kim *et al.* 2009). The neuroprotective effect of MSCs may be mediated by their differentiation into neuron-like cells, but also their ability to produce various trophic factors that may contribute to functional recovery, neuronal cell survival, and stimulation of endogenous regeneration (Barry and Murphy 2004; Kim *et al.* 2009).

Experimental evidence from transplant studies indicates an amplification of the endogenous neurogenic response to injury in MSC-treated animals (Cicchetti *et al.* 2002; Barry and Murphy 2004; Mahmood *et al.* 2005), suggesting that one therapeutic benefit of MSCs is to promote the formation and survival of new neurons in the adult brain from resident neuronal stem cells in the SVZ (Chen *et al.* 2001; Chen and Swanson 2003) and in the hippocampal DG (Munoz *et al.* 2005; Ben-Shaanan *et al.* 2008). MSCs-implanted cells also have the remarkable ability to migrate to sites of tissue damage and stimulate repair either by differentiating into tissue-specific cells or by creating a milieu that enhances the repair of endogenous cells (Alvarez-Buylla *et al.* 2002; Cipriani *et al.* 2007). These effects on brain plasticity are thought to be mediated primarily by the release of cytokines and growth factors produced by MSCs, which activate endogenous restorative and regenerative processes within the host brain (Biebl *et al.* 2000; Chen *et al.* 2005).

Several studies *in vitro* and *in vivo* showed that MSCs implantation has protective, anti-inflammatory effects (Gerdoni *et al.* 2007; Guo *et al.* 2007), and can dramatically decrease neural damage (Dong *et al.* 2007; Gao and Hong 2008; Kim *et al.* 2009). Human MSCs inhibited LPS-stimulated microglial activation and the production of pro-inflammatory mediators (Zhou *et al.* 2009). Furthermore, MSCs inhibited T-cell proliferation, decreased IFN-γ production, and increased IL-4 production, indicating a shift in T cells from a pro-inflammatory (IFN-γ-producing) state to an anti-inflammatory (IL-4-producing) state (Aggarwal and Pittenger 2005). Nevertheless, the potential immunomodulatory effects of MSCs on primary microglia remain to be fully evaluated. MSCs may respond to inflammatory cues and significantly increase production of neurotrophic factors, which may be involved in anti-inflammatory mechanisms (Zhou *et al.* 2009).

Recently, Lee and colleagues showed that intracerebral transplantation of MSCs into double-transgenic Alzheimer's mice significantly reduced amyloid beta plaques, inflammation and improved cognitive functions (Lee *et al.* 2010). Furthermore, a first clinical pilot study with MSCs transplanted into the striatum of patients with advanced Parkinson's disease showed some clinical improvements without any adverse events during the observation period (Venkataramana *et al.* 2010). Thus, stem cells could be a viable therapeutic approach to return the brain to homeostasis, enhance or induce neurogenesis, and represent ideal candidates for the treatment of neurodegenerative diseases.

In summary, the presence of neuronal progenitor cells in adult human and rodent brain, the regenerative capacity of stem cells, and the recent development of stem cells technology open new areas of research aimed at stimulating neuronal regeneration in the brain during aging, neuroinflammation and neurodegenerative diseases. A better understanding of the mechanisms that modulate the inhibition versus the stimulation of neurogenesis during neuroinflammation, and the integration of stem cells transplanted in diseased brain could help to develop novel therapeutic approaches with a potential application in neurodegenerative diseases with a strong inflammatory component.

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