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Cross-talk between neural stem cells and immune cells: the key to better brain repair?

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Systemic or intracerebral delivery of neural stem and progenitor cells (NSPCs) and activation of endogenous NSPCs hold much promise as potential treatments for diseases in the human CNS. Recent studies have shed new light on the interaction between the NSPCs and cells belonging to the innate and adaptive arms of the immune system. According to these studies, the immune cells can be both beneficial and detrimental for cell genesis from grafted and endogenous NSPCs in the CNS, and the NSPCs exert their beneficial effects not only by cell replacement but also by immunomodulation and trophic support. The cross-talk between immune cells and NSPCs and their progeny seems to determine both the efficacy of endogenous regenerative responses and the mechanism of action as well as the fate and functional integration of grafted NSPCs. Better understanding of the dialog between NSPCs and innate and adaptive immune cells is crucial for further development of effective strategies for CNS repair.

The past decade has witnessed a revolution in our understanding of CNS inflammation, in particular regarding the involvement of immune cells in CNS maintenance and repair[1–4], their cross-talk with NSPCs in health[2] and disease[5–7], and the immunomodulatory capacity of NSPCs beyond their function in cell replacement[6,8–13]. Although an inflammatory response is known to be essential for healing throughout the body, inflammation in the CNS was until recently considered a synonym for a detrimental immune response that should be mitigated. Such a negative view evolved mostly owing to the unique structure and immunological features of the CNS as a tissue behind walls, lack of awareness of the complexity of the innate versus adaptive immune response and of the general heterogeneity of the participating immune cells and factors, and, above all, the lack of distinction between acute and chronic inflammatory conditions.

We now know that among innate immune cells, microglia and infiltrating monocyte-derived macrophages (hereafter called macrophages) are separate populations with distinct ontogeny[14] and different activities following injury[3] or in disease conditions[15]. Furthermore, it is now recognized that macrophages do not take part in microglial turnover in adulthood[3]. The critical task of macrophages following acute CNS injury lies in the resolution of the inflammatory response, mainly mediated by the activated microglia[3], and in the degradation of the glial scar[16], an interim stage in CNS repair that, if not properly resolved, is detrimental to healing. This new understanding of the role of microglia and macrophages in CNS repair is consistent with the current dogma of healing in non-CNS tissues, which involves both classically activated macrophages (M1 macrophages) and alternatively activated macrophages (M2 macrophages), albeit at different phases of recovery.

Emerging results indicate that cells mediating adaptive immunity, such as effector helper T cells and regulatory T cells, also contribute to CNS repair processes[1,5,17]. T cells recognizing CNS antigens have been implicated in the recovery from CNS injuries[1,17], a phenomenon that was collectively named "protective autoimmunity"[1,17]. In a model of acute injury[3] as well as in a model of Alzheimer's disease[15], self-reactive T cells facilitate recruitment of macrophages to the lesion site, though the underlying mechanism of such a recruitment is still under investigation. In addition, the entire process of recovery from injury does not involve a single type of immune cell; it is a network encompassing both effector and regulatory T cells at different stages and locations throughout the repair process.

In line with the new view of the role of innate and adaptive immunity in CNS repair, it has become clear that immune cells are capable of supporting CNS cell renewal[2]. In the healthy adult CNS, neurogenesis occurs almost exclusively from NSPCs located in two brain regions: the subventricular zone (SVZ) lining the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus. Neural stem and progenitor cells are both unspecialized, self-renewing cells with differentiation capacity within the neural lineage, progenitors having less self-renewal capacity and being more committed to neural differentiation. Both in animals and in humans, new dentate granule cells are continuously generated in the SGZ. Whether the NSPCs in SVZ of adult humans give rise to neurons reaching the olfactory bulb through the rostral migratory stream, as occurs in animals, is controversial[18,19]. The functional plasticity of the healthy CNS, including neurogenesis, depends on adaptive immunity[2,20,21] and on innate immunity of the NSPCs themselves, through, at least in part, their expression of Toll-like receptors (TLRs)[22]. In response to inflammatory reactions driven by microglia, macrophages and lymphocytes (mainly T and B cells), the multipotent, self-renewing NSPCs in the SVZ and SGZ may change their normal destiny and fate to interneurons in the olfactory bulb and granule cells in the hippocampal granule layer, respectively[23].

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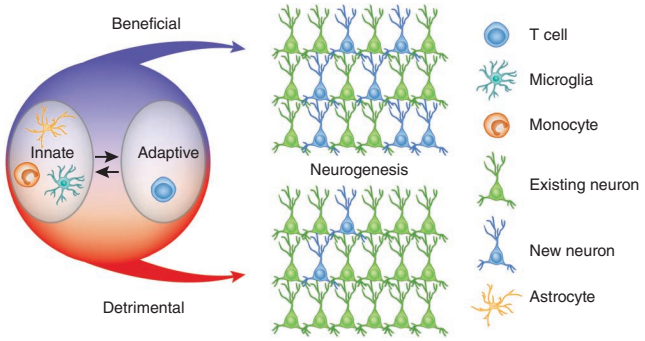

Figure 1 Cells of the innate (microglia, monocytes, monocyte-derived macrophages) and adaptive (T and B cells) immune arms have either detrimental or beneficial effects on neurogenesis both *in vitro* and *in vivo*. Although the precise cellular and molecular mechanisms regulating the interplay between these cells and NSPCs are still elusive, available data indicate that the effect is mainly mediated by soluble factors rather than by cell-to-cell contact. Among these factors, proinflammatory cytokines (for example, IL-1β, TNF-α, IL-6) seem to impair neurogenesis, whereas anti-inflammatory cytokines (IL-4, IL-15) and trophic factors (IGF-1, BDNF) are proneurogenic. The context in which secretion of these factors occurs is crucial: the amount and the timing of the release influence the net effect that the innate or adaptive immune cells, or both, exert on neurogenesis. The same cytokine or growth factor can be both pro- and antineurogenic depending on the microenvironment in which it operates. The interplay between innate and adaptive immune cells and NSPCs is a complex phenomenon in which cell-autonomous and non-cell-autonomous mechanisms operate concomitantly. See also **Table 1**.

Under pathological conditions associated with inflammation, the NSPCs and their progeny migrate into damaged areas to promote functional and structural repair[6]. Furthermore, transplanted NSPCs promote CNS tissue repair not only through cell replacement but also by immune modulation and trophic support, a phenomenon that was collectively named "therapeutic plasticity"[6,9], which opens up a promising avenue for therapies.

Here we summarize recent data supporting the idea that the extent of CNS repair by endogenous or grafted NSPCs depends on both cell-autonomous and non-cell-autonomous mechanisms, which are modulated by infiltrating circulating innate and adaptive immune cells and CNS-resident cells, such as activated microglia and astrocytes. Understanding the bidirectional relationships between the NSPCs and the immune cells will be critical for developing therapeutic strategies to enhance and/or regulate mechanisms of CNS repair.

Modulation of endogenous NSPCs by immune cells

With the progress in understanding of local CNS inflammation and the diversity of the immune response in general, it seems clear that poor spontaneous recovery from injury is not due to the mere presence of activated microglia or infiltration of macrophages or effector T and B cells, but to the non-optimal resolving response that could reflect incorrect timing of cell recruitment, excessive or insufficient numbers of recruited cells, and an inappropriate cell activation state (phenotype). The nature of the immune response driven by local and circulating immune cells also affects NSPC-driven tissue remodeling.

Thus, for example, there is solid evidence indicating that immune cells of the innate and adaptive response may influence phenotypic and functional characteristics of endogenous NSPCs. Activated microglia, which can acquire distinct phenotypes, can either support or interfere with processes of NSPC renewal needed for neurogenesis and oligodendrogenesis, depending on the timing of their presence in the injured microenvironment and their activity (**Fig. 1** and **Table 1**). On the one hand, activation of microglia induced by bacterial endotoxin, lipopolysaccharide (LPS), cranial irradiation, or in animal models of stroke and status epilepticus, is detrimental for the survival of newly formed hippocampal or striatal neurons[23–25]. The direct negative effect of LPS on NSPC proliferation through these cells' TLR-4 (ref. 22), the innate receptor for LPS, is in line with these findings. In addition, newly formed hippocampal cells undergoing apoptosis in intact and LPS-treated brain are cleared by phagocytic innate immune cells, and neurogenesis can be rescued by inhibition of these phagocytes[26]. Such phagocytic immune cells release proinflammatory cytokines including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α[25], which have a negative effect on NSPCs (**Table 1**). In this regard, we note that the ability of microglia to express the proneurogenic protein hormone insulin-like growth factor (IGF)-1 is inversely related to TNF-α[15], further supporting the contention that the phenotype of the activated immune cells determines their effect on healing in general and on cell renewal in particular. Similarly, TNF-α suppresses SGZ and SVZ progenitor proliferation through TNF receptor 1 signaling after status epilepticus and stroke[27,28]. On the other hand, new seizure-generated hippocampal neurons survive for at least 6 months despite a chronic local immune response characterized by increased numbers of activated phagocytic microglia[29]. Also, for several months after stroke, increased numbers of activated innate immune cells are located in the ipsilateral SVZ concomitant with the continuous production of new neuroblasts migrating into the striatum[30]. This latter effect has been, at least in part, attributed to the ability of a substantial proportion of these immune cells to express IGF-1. Furthermore, chronically activated microglia are permissive to neuronal differentiation and survival in adult mouse SVZ cultures[31], and microglia and microglia-conditioned media rescue the *in vitro* formation of neuroblasts from SVZ NSPCs, a property that is otherwise lost over the course of continued culture[32]. Moreover, IL-15, which is expressed by NSPCs in SVZ and produced by activated microglia, has been reported to promote proliferation and self-renewal of SVZ NSPCs, maintaining them in an undifferentiated state[33]. Finally, microglia activated by IL-4, which are reminiscent of alternatively activated macrophages, support neurogenesis[34].

Notably, innate and adaptive immunity in the CNS not only affect neurogenesis[23] but also oligodendrogenesis[34,35]. Innate immune cells activated by distinct cytokines have different effects on oligodendrogenesis; microglia activated by IL-4 and low-dose interferon (IFN)-γ support oligodendrogenesis, whereas microglia activated by high-dose IFN-γ impair oligodendrogenesis, though their effect can be partially reversed by IL-4 (ref. 34). Vaccination of mice suffering from experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis, with the immunomodulator glatiramer acetate increases oligodendrogenesis[35]. Immunomodulation with erythropoietin promotes oligodendrogenesis and attenuates white matter injury, concurrently with increased neurogenesis. These effects likely contribute to the functional improvement induced by this treatment[36]. However, inflammatory conditions associated with EAE, induced by encephalitogenic autoimmune T cells, differ from inflammation associated with acute injuries such as stroke or chronic neurodegenerative diseases. Recently, it was shown in a chronic EAE model in mice giving rise to elevated numbers of both microglia/macrophages and

Table 1 Factors mediating effects of immune cells on neural stem/progenitor cells

Soluble factor	Biological effect on NSPCs	Possible cell source in inflammatory conditions	Refs.
CCL5	Proliferation ↑	Reactive astrocytes, activated lymphocytes, microglia/macrophages	68
CXCL12	Migration ↑	Reactive astrocytes, activated endothelial cells, meningeal cells	69,70
CX3CL1	Proliferation ↑	Reactive astrocytes, activated lymphocytes, microglia/macrophages	68
CCL11	Proliferation ↓ Differentiation ↓	Reactive astrocytes, activated lymphocytes, microglia/macrophages	41
IFN-α	Proliferation ↓	Plasmacytoid dendritic cells, activated macrophages, endothelial cells, neurons	71
IFN-γ	Proliferation ↓	T cells (T_H1), natural killer cells	7,8
IL-1β	Proliferation ↓	Activated microglia/macrophages	72
IFN-γ	Proliferation ↑ Differentiation ↑	T cells (T_H1), through effect on microglia/macrophages	34
IL-4	Migration ↑ Differentiation ↑	T cells (T_H2), through effect on microglia/macrophages	34,73
IL-6	Proliferation ↓	Reactive astrocytes, activated lymphocytes, microglia/macrophages	25
IL-10	Migration ↑	Reactive astrocytes, activated lymphocytes, microglia/macrophages	73
IL-15	Proliferation ↑	Activated microglia	33
Osteopontin	Migration ↑	Activated microglia/macrophages	74
TNF-α	Proliferation ↓	Activated microglia/macrophages	28,31
BDNF	Survival↑ Differentiation ↑	Reactive astrocytes, monocytes, activated lymphocytes, activated microglia	75,76
CNTF	Survival↑ Differentiation ↑	Reactive astrocytes	77
Erythropoietin	Differentiation ↑	Reactive astrocytes, activated endothelial cells, microglia/macrophages	78,79
GDNF	Survival, differentiation ↑	Peripheral blood mononuclear cells	80
IGF-1	Proliferation ↑ Differentiation ↑	Peripheral blood mononuclear cells	30,81,82
PDGF-α	Proliferation ↑ Migration ↑	Reactive astrocytes, neurons	83,84
TGF-β	Differentiation ↑	Reactive astrocytes, microglia/macrophages, neurons	85
VEGF-α	Proliferation ↑ Migration ↑	Reactive astrocytes, activated endothelial cells	86,87

BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; GDNF, glial cell line–derived neurotrophic factor; IGF, insulin-like growth factor; IFN, interferon; IL, interleukin; LIF, leukemia inhibitory factor; PDGF, platelet-derived growth factor; SDF, stromal cell–derived factor; TGF, transforming growth factor; TNF, tumor necrosis factor; VEGF, vascular-endothelial growth factor.

T lymphocytes in the SVZ that the number of newly generated NSPCs is reduced[7], whereas there is an expansion of the pro-oligodendrogenic cell population[37]. This functional switch in the NSPC niche, induced by a multiple sclerosis–like inflammation, probably also occurs in humans, as a similar decrease in neuroblast number has been detected in the SVZ from patients with multiple sclerosis[37]. Nevertheless, in remitting-relapsing disease, fluctuations in cell renewal might reflect the stage of the local inflammatory pathology.

In the healthy CNS, T cells influence cell renewal, mostly from within the brain's borders, through a remote mechanism[20,38] (**Fig. 1**). Immune-deficient mice show impaired neurogenesis, and CNS-specific T helper cells promote hippocampal neurogenesis[2,21]. Under pathological conditions, the interaction between lymphocytes and NSPCs is even more complex. For example, T lymphocytes have been reported to be important in the abortive neuroregenerative response following stroke confined to the cerebral cortex in mice. Immunodeficient mice and mice selectively depleted of $CD4^+$ T lymphocytes exhibit reduced apoptosis and enhanced proliferation of NSPCs following cortical stroke[39]. Recently, it was shown that activated $CD4^+$ T cells expressing the glucocorticoid-induced TNF receptor (GITR) are responsible for the negative effect on NSPCs[40]. This complexity reflects the dynamics of the immune response following injury and, as a consequence, the continual changes in the needs for the repair; the same immune cells can be helpful or harmful at different stages in the response to injury.

Interestingly, age-related reduction in neurogenesis seems to be paralleled by aging of the immune system and elevation of circulating immune-related cells and molecules such as chemokines that have a negative effect on neurogenesis[41]. The chemokine CCL11, which was found to be elevated in both cerebrospinal fluid (CSF) and blood of aged mice, decreases adult neurogenesis and impaired learning and memory[41]. Other studies have indicated that chemokines in stem cell niches affect the migration and fate choice of the NSPCs and their viability; yet the repertoire of such chemokines is critically changing with age.

Neurogenesis seems to be controlled not only by immune cells but also by the neural cells that create the local microenvironment. For example, hippocampal astrocytes affect both proliferation and differentiation of NSPCs isolated from adult rat hippocampus. This effect is region-specific: whereas hippocampal astrocytes are effective, spinal cord astrocytes have no effect[42]. Interestingly, under similar conditions, neuron-enriched cultures promote oligodendrogenesis. Astrocytes also support neurogenesis from skin-derived stem cells[43] and from oligodendrocyte precursor cells[44].

Besides the effects on survival, renewal and fate decision of NSPCs by locally activated innate immune cells, there are also data indicating that these immune cells regulate the migration of neuroblasts toward injured brain regions through release of factors such as stromal cell–derived factor (SDF)-1 (ref. 45) and osteopontin[46], a phenomenon resembling the pathotropism of engrafted NSPCs, whose molecular and cellular characteristics will be discussed in detail below. Finally, microglial activation influences the development of the functional synaptic connectivity of adult-born neurons[47]. When new hippocampal neurons are produced in an environment characterized by status epilepticus–induced[48] or LPS-induced[47] microglial activation, they develop increased inhibitory drive at their afferent synapses. However, from these studies, it is not clear whether the claimed 'microglial' response reflects the action of resident microglial cells or encompasses the net outcome of both microglia and blood-borne CNS-infiltrating macrophages, possibly with non-redundant activities. Conversely, in a less severe seizure environment, without prominent microglial activation, this increase in inhibitory input is not observed[49]. Thus, it seems that, following insults to the adult brain, the pattern of synaptic alterations at afferent inputs to newly generated neurons also depends on cross-talk with immune cells in the pathological environment.

Taken together, these studies suggest that there is no scientific basis to attribute any uniform role to innate and adaptive immunity in modulating endogenous NSPCs in the healthy or diseased CNS. Rather, the origin of innate immune cells (microglia or macrophages), the subtype of adaptive immune cells (effector or regulatory T cells), the nature of the pathology and whether the inflammatory condition is acute or chronic will determine the outcome.

Modulation of inflammation by transplanted NSPCs

Transplantation of NSPCs of human origin has been proposed as a potential therapy in several acute and chronic CNS disorders[50]. After implantation, the grafted NSPCs are exposed to host immune cells, including both those that are part of the pathological environment

and those that have been induced by the transplantation procedure. Thus, it is conceivable that the immune mechanisms regulating cell genesis from endogenous NSPCs under pathological conditions that we have discussed above will operate similarly on grafted NSPCs in terms of their homing, survival and modes of action. This is particularly relevant if one considers the recent evidence that transplanted NSPCs not only can promote replacement of damaged cells but also exert immunomodulatory and neuroprotective effects preventing tissue damage and/or rescuing degenerating host cells (**Fig. 2**)[9,12,51]. Better understanding of the cellular and molecular mechanisms regulating the cross-talk between transplanted NSPCs and immune cells will be crucial to promote functional repair and avoid side effects or toxic effects of NSPC transplantation.

Homing of NSPCs after transplantation depends on their constitutive expression of an armamentarium of membrane receptors (chemokine receptors, cell adhesion molecules, integrins, TLRs) enabling them to follow gradients of chemoattractants, such as proinflammatory cytokines and chemokines[12,13] and danger signals[22]. Hence, independently of the route of their administration—local, intravenous (i.v.), intrathecal (i.t.) or intracerebroventricular (i.c.v.)—injected NSPCs exhibit pathotropism toward inflamed CNS areas (**Fig. 2**). Nevertheless, the route of cell delivery might still represent a major factor affecting outcome since the therapeutic efficacy of NSPCs greatly varies depending on the number of cells homing to areas of pathology. To maximize NSPC pathotropism, direct local (intralesional) cell transplantation may be preferable in focal CNS disorders (such as Parkinson's disease, spinal cord injury (SCI), Huntington's disease or stroke)[11,50,52]. Systemic or CSF delivery should be reserved for multifocal and/or widespread disseminated CNS diseases (for example, multiple sclerosis, spinocerebellar ataxia, amyotrophic lateral sclerosis (ALS))[9].

When transplanted NSPCs reach the areas of injured CNS in sufficient numbers, their mode of therapeutic action—cell replacement versus neuroprotective or immunomodulatory effect—depends on both cell-autonomous (intrinsic) and non-cell-autonomous (microenvironment-dictated) factors (**Figs. 2** and **3**). Although the precise molecular and cellular mechanisms sustaining each mode of action are far from being fully elucidated, it is becoming clear that the type of transplanted NSPCs and the degree of tissue inflammation are crucial. When cellular degeneration is caused by intrinsic cellular defects operating in a discrete CNS area (ALS, Parkinson's disease, Huntington's disease) and reactive inflammatory processes bear a resolving phenotype, cell-autonomous programs prevail over microenvironmentally dictated cues. In this case, lineage-restricted

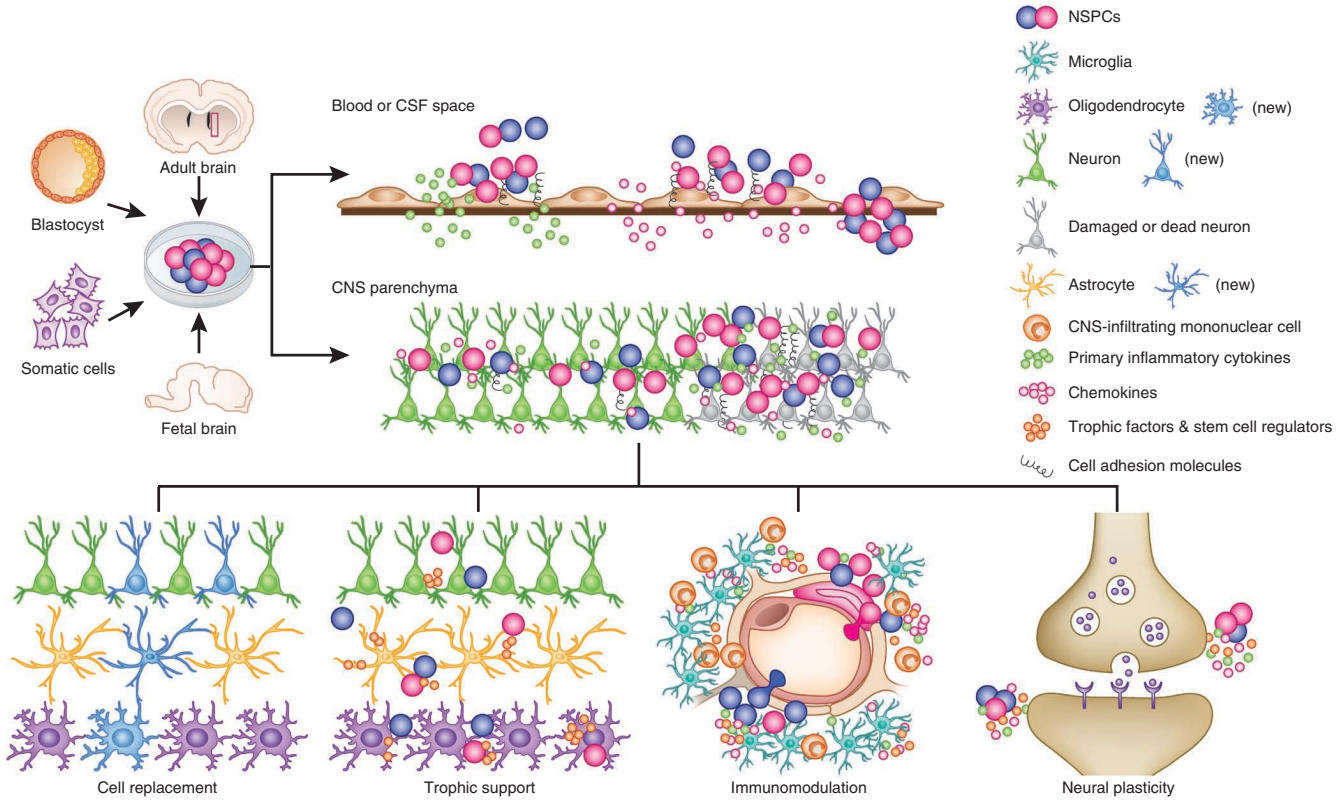

Figure 2 After transplantation, NSPCs derived from different sources (embryonic stem cells, fetal and adult brain, reprogrammed somatic cells) promote CNS repair using several mechanisms collectively named stem cell therapeutic plasticity. Whatever the route of administration (local, intrathecal, i.v., i.c.v.), transplanted NSPCs do show pathotropism; that is, ability to home to injured sites. This homing occurs because transplanted NSPCs display on their surface an array of sensor molecules (for example, adhesion molecules, chemokine receptors) capable of responding to a milieu of chemoattractant substances (for example, chemokines and cytokines) released at the site of CNS injury by both activated resident microglia and blood-borne infiltrating immune cells. Once reaching the site of injury, transplanted NSPCs interact with the microenvironment and adapt their fate and function(s) to specific environmental needs occurring as a result of different pathological conditions. This interaction is also affected by the degree of tissue inflammation, as the cross-talk between CNS-resident and infiltrating immune cells and transplanted NSPCs shapes the therapeutic mechanisms of the transplantation. Therapeutic mechanisms vary from cell replacement to anti-inflammatory effects, neurotrophic support leading to rescue of host neural cells, and neuronal plasticity. The reason one mechanism prevails over the other is poorly understood. Nevertheless, the different mechanisms are not mutually exclusive. Whatever the therapeutic mechanism of action of transplanted NSPCs, the final outcome is to promote recovery by preventing tissue damage and/or sustaining the reestablishment of appropriately functioning neuronal circuits.

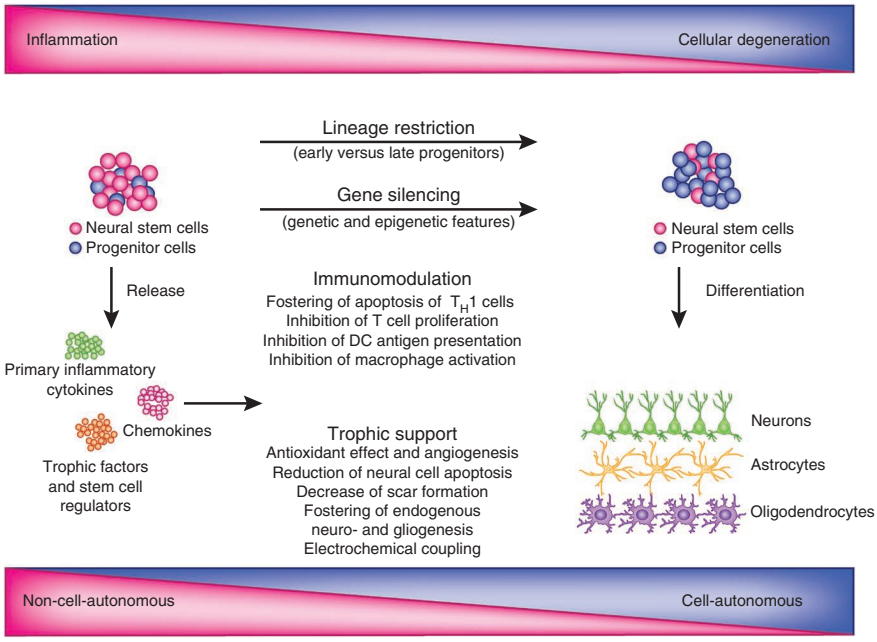

Figure 3 The extent of tissue regeneration *in vivo* driven by grafted multipotent NSPCs depends on the efficacy of the different activities such cells adopt after transplantation. Both cell-autonomous and non-cell-autonomous mechanisms affect the final fate and behavior of grafted NSPCs. Blood-borne infiltrating or resident immune cells, which are always present in the injured CNS whatever the primary cause of tissue damage, can drive intrinsic versus environmentally induced processes occurring in grafted NSPCs. Whereas cell-autonomous mechanisms driving terminal differentiation of transplanted NSPCs tend to prevail in pathological conditions characterized by neuronal degeneration and mild reactive inflammation, mainly driven by CNS-resident microglia, induced mechanisms supporting other effects of transplanted NSPCs tend to prevail in acute or chronic unresolved inflammation. The beneficial effects besides cell replacement occur because transplanted NSPCs sense the inflammatory environment and, in such an environment, promote tissue homeostasis and repair by releasing, at the site of tissue damage, a plethora of constitutively expressed molecules (chemokines, cytokines, growth factors, stem cell regulators) capable of immunomodulation and trophic support. Cell-autonomous mechanism driving terminal differentiation mainly operate in lineage-committed progenitors owing to epigenetic restriction of transcriptional circuits; this, in turn, also limits the amounts of neuroprotective substances released by transplanted cells. In contrast, non-cell-autonomous mechanisms are expected to mainly operate in early progenitors whose fate and behavior strongly depend on environmental needs. DC, dendritic cell.

progenitors show better functional integration properties than early progenitors. One possible explanation of this phenomenon might rely on the progressive gene silencing occurring during lineage restriction: genes active in earlier progenitors are gradually silenced at developmentally later stages, and subsets of cell type–specific genes are turned on[53]. In animal models of genetically induced dysmyelination or hypomyelination (for example, the shiverer mouse) or chemically induced demyelination[54], local transplantation of many different types of glial restricted progenitors extensively remyelinates denuded axons. In animal models of Parkinson's disease, intrastriatal grafts of dopaminergic neuronal progenitors derived from different species, including humans, and from cellular sources can survive, reinnervate the striatum and ameliorate behavioral deficits[55].

For optimal recovery from many brain diseases, cell replacement by NSPC-derived cells and at least partial reconstruction of neural circuitry should probably be the long-term goal. Although clinical trials with NSPCs are planned or in progress in stroke, ALS, Pelizaeus-Merzbacher disease, Batten's disease, brain tumors and SCI (http://www.clinicaltrials.gov/), it is unlikely that these grafts will replace dead neurons and/or glial cells, and whether they will lead to any recovery of function is unclear. In fact, survival and integration of transplanted NSPC-derived neurons into remaining circuitry have so far not been demonstrated in any human brain disorder. Efficacious cell replacement will require the generation of the correct neuronal phenotype. This is particularly challenging in, for example, Alzheimer's disease and stroke because the NSPCs would have to be predifferentiated *in vitro* to several different types of neuroblast for subsequent implantation. The evidence that neuronal replacement can work in the diseased human brain comes from trials in which human fetal mesencephalic tissue (not NSPCs), rich in primary dopaminergic neuroblasts, was transplanted to the striatum in patients with Parkinson's disease: the dopaminergic neurons survived for more than a decade, reinnervated denervated areas and became functionally integrated, released transmitter and improved symptoms in some patients[50].

For successful NSPC transplantation in the clinic, we need to expand our knowledge of how immune cells influence the function of the grafted NSPCs and their neuronal progeny in the host tissue. In patients with Parkinson's disease who survive many months after transplantation, activated innate immune cells, T cells and B cells surrounding allogeneic grafts of fetal mesencephalic tissue were proposed to be responsible for functional impairment of the graft and possibly for adverse effects such as induction of involuntary movements[56]. Furthermore, allogeneic grafts of embryonic stem cell–derived NSPCs implanted into intact mouse brain cause an immune response characterized by activated innate immune cells and lymphocytes, which suppress neuronal differentiation and promote glial cell fate, probably through release of IL-6 (ref. 57). In similar allogeneic grafts, blockade of the accumulation of $CD8^+$ T cells, as well as reduction of the levels of IL-6, results in an increased percentage of neurons.

Available data suggest that cell replacement may not be the prevailing mechanism when NSPCs are transplanted in a persistently unfavorable chronic inflammatory environment. Transplanted NSPCs (from several sources) show some degree of functional integration and terminal differentiation (for example, to neurons or oligodendrocytes) in animal models of such disorders, but undifferentiated NSPCs also promote tissue regeneration and functional recovery through their immunomodulatory and trophic effects (**Figs. 2** and **3** and **Table 2**). The lack of functional integration can, at least in part, be explained by the fact that primary proinflammatory cytokines (for example, TNF-α, IL-1β, IFN-γ) render transplanted NSPCs unable to fully differentiate by increasing the expression of inhibitors of the cell cycle[7]. Whether the immunomodulatory effect can be simply attributed to the microenvironmental cues regulating factor secretion by the transplanted NSPCs is not fully understood. Whatever the underlying mechanism,

Table 2 Transplantation of NSPCs in animal models of CNS disorders characterized by acute or chronic inflammation

Source Cells Species	Route of cell administration	Disease model Species	Human disease	Presumed mechanism(s) of efficacy: Differentiation of transplanted cells	Presumed mechanism(s) of efficacy: Other actions	Functional outcome	Ref.
Neonatal striatum NSPCs Rat	I.c.v.	Acute EAE Rat	Multiple sclerosis	Not tested	Inhibition of MOG-specific lymphocyte proliferation	Improvement of locomotor activity (EAE score)	58
Adult SVZ NSPCs Mouse	I.c.v. and i.v.	Chronic EAE Mouse	Multiple sclerosis	Oligodendroglial and neuronal differentiation	Rescue of endogenous OPCs and modulation of neurotrophic and/or growth factors	Improvement of locomotor activity (EAE score and neurophysiological tests)	12
Adult SVZ NSPCs Mouse	I.v.	Relapsing EAE Mouse	Multiple sclerosis	Not tested	Induction of apoptosis of CNS-infiltrating T lymphocytes	Improvement of locomotor activity (EAE score)	13
Fetal brain NSPCs Human	I.c.v. and i.v.	Chronic EAE Non-human primate	Multiple sclerosis	No neuronal or glial differentiation	Inhibition of dendritic cell activation and lymphocyte proliferation	Improvement of locomotor activity (EAE score and neurophysiological tests)	61
Adult SVZ NSPCs (IL-10 producing) Mouse	I.c.v. and i.v.	Chronic EAE Mouse	Multiple sclerosis	Oligodendroglial and neuronal differentiation	Inhibition of peripheral and CNS-confined inflammation; induction of apoptosis of CNS-infiltrating T lymphocytes	Improvement of locomotor activity (EAE score)	88
Adult SVZ NSPCs Mouse	I.v.	Chronic EAE Mouse	Multiple sclerosis	No neuronal or glial differentiation	LIF-mediated inhibition of encephalitogenic T_H17 cell differentiation	Improvement of locomotor activity (EAE score)	63
Fetal brain NSPCs Human	Intracerebral (cortex)	MCAO (60 min) Rat	Ischemic stroke	50% neuronal and 15% astroglial differentiation	Less macrophage and microglial cell infiltration at lesion borders	Not tested	89
Fetal brain NSPCs Human	Intracerebral (cortex)	Distal MCAO (permanent) Rat	Ischemic stroke	Not tested	Enhanced blood-brain barrier integrity, tight junctions and neovascularization; fewer $Iba1^+$ monocytes and macrophages	Bimodal pattern of functional recovery. Early: independent of neovascularization Delayed: VEGF-dependent, coincident with neovascularization.	90
Adult SVZ NSPCs Mouse	I.v.	MCAO (45 min) Mouse	Ischemic stroke	No neuronal or glial differentiation	Rescue of endogenous striatal medium spiny neurons; suppression of inflammation and glial scar formation	Improvement in modified neurological severity score and grip strength	10
Neonatal cerebellum (c17.2) NSPCs Mouse	Intracerebral (cortex)	MCAO (60 min) Rat	Ischemic stroke	No long-term survival of graft	Not tested	Improved fMRI and trend toward better behavioral performance	91
Fetal brain NSPCs Human	I.v. and intracerebral	Collagenase-induced intracerebral hemorrhage Mouse	Hemorrhagic stroke	No neuronal or glial differentiation	Attenuated cerebral and splenic expression of TNF-α, IL-6 and NF-κB; reduced brain edema, inflammatory infiltrate (OX-42 signal, myelo-peroxidase) and apoptosis	Improvement in modified limb-placement test	59
Fibroblasts iPS-derived NSPCs Human	Intracerebral (striatum)	MCAO (30 min) Mouse	Ischemic stroke	79% HuD^+ neurons and 13% DCX^+ neuroblasts	Increased production of VEGF in astrocytes and blood vessels	Improvement in forelimb function, staircase test	92
Fetal brain NSPCs (immortalized) Human	I.v.	MCAO (90 min) Mouse	Ischemic stroke	20% neuronal and 60% astroglial differentiation	Decreased hemispheric atrophy	Improved sensorimotor function (Rotarod test, modified limb-placement test, ability to turn in an alley)	93
Neonatal cerebellum NSPCs (immortalized) Mouse	Intraspinal (using NSPC-seeded scaffold)	Hemisection (lateral thoracic, T9–T10) spinal cord injury Rat	Acute spinal cord injury	Most cells immunoreactive for nestin	Trophic support	Improved sensorimotor deficits (BBB scale, ability to maintain body position on an inclined plane, hindlimb withdrawal to pain)	94

(continued)

Table 2 Transplantation of NSPCs in animal models of CNS disorders characterized by acute or chronic inflammation (continued)

Source Cells Species	Route of cell administration	Disease model Species	Human disease	Presumed mechanism(s) of efficacy: Differentiation of transplanted cells	Presumed mechanism(s) of efficacy: Other actions	Functional outcome	Ref.
Neonatal cerebellum NSPCs (immortalized) Mouse	Intraspinal	Microwire knife (dorsal cervical, C3) spinal cord injury Rat	Acute spinal cord injury	No evidence of differentiation	*In vivo* secretion of NGF, BDNF, GDNF	Not tested	95
Adult SVZ NSPCs Mouse	I.c.v.	Weight drop (dorsal thoracic, T12) spinal cord injury Mouse	Acute spinal cord injury	Not tested	*In vivo* secretion of BDNF and Noggin	Improved locomotor activity (BMS scale)	5
Adult SVZ NSPCs Mouse	Intraspinal	Weight drop (dorsal thoracic, T12) spinal cord injury Mouse	Acute spinal cord injury	Not tested	Inhibition of spinal cord recruitment of classically activated (M1-like) macrophages	Improved locomotor activity (BMS scale)	11
Neonatal cerebellum NSPCs (immortalized) Mouse	Intracerebral (substantia nigra, VTA)	MPTP injection Mouse	Parkinson's disease	10% neuronal differentiation	Rescue of endogenous TH^+ neurons; increased GDNF	Decrease of amphetamine-induced rotation	96
Fetal SVZ NSPCs Mouse	Intracerebral (striatum)	6-OHDA injection Rat	Parkinson's disease	No neuronal differentiation; 12.5%–31% increased neuronal survival, decrease of caspase-3^+TH^+ neurons	Increased Shh?	Decrease of amphetamine-induced rotation	97
Fetal ventricular germinal zone NSPCs Human	Intracerebral (striatum and substantia nigra)	MPTP injection Monkey	Parkinson's disease	Small number of TH^+ and DAT^+ cells in substantia nigra, no neurons in striatum	Hypertrophy of host TH^+ neurons in substantia nigra; decrease of α-synuclein aggregations	Improvement in Parkinson's factor score	98
Fetal brain NSPCs Human	Intracerebral (striatum)	Quinolinic acid injection Rat	Huntington's disease	1% NeuN immunoreactivity, 3.5% GFAP immunoreactivity	Greater striatal volume (26%); increased CNTF, BDNF, GDNF	Improvement of motor function in cylinder test	99
Fetal brain NSPCs Human	Intracerebral (striatum)	3-NP injection Rat	Huntington's disease	Predominant nestin immunoreactivity, low NeuN and GFAP immunoreactivity, certain calbindin and GAD immunoreactivity	Extensive survival of striatal neurons; increased BDNF	Improvement of motor function in Rotarod test	100

Table summarizes evidence for mechanisms other than cell replacement underlying the functional recovery in different disease models after transplantation of NSPCs. Studies demonstrating behavioral improvement mainly due to neuronal replacement, such as those using transplantation of predifferentiated NSPCs in models of Parkinson's disease, are not included. 3-NP, 3-nitropropionic acid; 6-OHDA, 6-hydroxydopamine; BBB, Basso-Beattie-Bresnahan scale; BDNF, brain-derived neurotrophic factor; BMS, Basso mouse scale; c17.2, an immortalized neural progenitor cell line derived from neonatal mouse cerebellum; CCAO, common carotid artery occlusion; CNTF, ciliary neurotrophic factor; DAT, dopamine transporter; DCX, doublecortin; EAE, experimental autoimmune encephalomyelitis; fMRI, functional magnetic resonance imaging; GAD, glutamic acid decarboxylase; GDNF, glial cell line–derived neurotrophic factor; GFAP, glial fibrillary acidic protein; i.c.v., intracerebroventricular; i.v., intravenous; MBF, medial basal forebrain; MCAO, middle cerebral artery occlusion; MOG, myelin-oligodendrocyte glycoprotein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NeuN, neuronal nuclear antigen; NGF, nerve growth factor; NSPCs, neural stem and progenitor cells; OPCs, oligodendrocyte progenitor cells; OX-42, an antibody to CD11b; PGA, polyglycolic acid; Shh, sonic hedgehog; SVZ, subventricular zone; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

it is now established that transplanted NSPCs—while remaining undifferentiated—can express and produce *in situ* a wide array of constitutive transmembrane and secreted immunomodulatory and trophic molecules capable of promoting tissue repair[9].

In inflammatory disease such as EAE, transplantation (i.v., i.c.v. or i.t.) of NSPCs inhibits proliferation[58] and/or promotes apoptosis of encephalitogenic CNS-infiltrating T cells[13]. This last effect has been attributed to either the expression of death receptor ligands (FasL, TRAIL and Apo3L) or the production of soluble mediators (nitric oxide, IFN-γ, glial cell line–derived neurotrophic factor (GDNF) and leukemia inhibitory factor (LIF)) involved in mitochondria-mediated apoptosis. In the post-acute phase of ischemic or hemorrhagic stroke, i.v. delivery of NSPCs inhibits local activation of innate immune cells and recruitment to the CNS of more blood-borne inflammatory cells[10,59]. In the subacute phase of a response to spinal cord contusion, either i.t. or local transplantation of NSPCs results in an immunomodulatory effect, manifested in a change in the cytokine profile and fewer proinflammatory cells at the lesion site[5,11].

The ability of transplanted NSPCs to act as immunomodulatory cells is also supported by recent studies showing that NSPCs, similarly to other stem cell types, such as mesenchymal stem cells, can exert such effects outside the CNS as well after i.v., subcutaneous or intraperitoneal injection. In mouse models of EAE or following experimental stroke, i.v. NSPCs may inhibit the initiation and maintenance of the inflammatory events occurring in the secondary lymphoid organs (lymph nodes and spleen)[59–62]. Dendritic cell antigen presentation and antigen-specific T cell proliferation[60] are impaired after i.v. or subcutaneous injection of NSPCs into EAE mice. This has been recently attributed to the secretion by the NSPCs of LIF, which antagonizes the IL-6–mediated phosphorylation of signal transducer and activator of transcription 3 (STAT3), both required for encephalitogenic T_H17 cell differentiation[63]. Finally, the immunomodulatory properties of NSPCs seem to be a constitutive, and possibly an evolutionarily conserved, signature. Human fetal NSPCs constitutively express around 18% of the total number of immune-related genes and inhibit T lymphocyte proliferation, as well as dendritic cell maturation, *in vitro*[61,64]. It is also worth noting that, along with immunomodulatory molecules, undifferentiated NSPCs persisting in inflamed CNS areas secrete a plethora of trophic factors capable of protecting endogenous neural cells from programmed cell death, preventing glial scar formation, re-establishing neuron-glia functional interactions and enhancing endogenous remyelination[9,12,50].

Therapeutic perspectives

Accumulating evidence indicates that immune cells and NSPCs share several molecular and cellular developmental and immune regulatory pathways (for example, production of chemokines, trophic factors, cytokines, TLRs and stem cell regulators) that together render these cells able to interact in response to tissue damage. This is not entirely unexpected, given that the function of both the inflammatory reaction and the mobilization of endogenous NSPCs, occurring in the CNS in response to danger signals, is to limit the extent of the tissue damage and, possibly, to promote repair. Thus, a continuous cross-talk between immune cells and NSPCs (endogenous or grafted) is probably crucial for homeostasis in CNS and for survival and preserved function of its cellular components after damage. These interactions might constitute a developmental relic, as innate immune cells home to the CNS before neurogenesis occurs[14] and brain architecture becomes perturbed postnatally in microglia-depleted mice[65].

Taken together, data so far reported suggest that intrinsic (cell autonomous) mechanisms operating in endogenous NSPCs might prevail under conditions characterized by acute neurodegeneration associated with a transient, mild, reactive, self-limiting inflammation. Under conditions of severe unresolved, chronic inflammation, cell renewal is impaired. Such conditions are amenable to modulation by boosting the numbers of cells with resolving activity; for example, by recruitment of IL-10–expressing macrophages[16,66]. The underlying mechanism favoring one or the other mode of action, although still far from being fully elucidated, can be partly attributed to the capacity of immune cells and stem cells to cross-talk by means of horizontal communication strategies[11]. Further studies are needed to understand whether, when and how endogenous NSPCs can take over and locally manifest an immunomodulatory effect. It is possible that such an activity is acquired only by grafted cells and reflects the *in vitro* manipulations of these cells during their isolation.

It is now clear that the interactions between immune cells and NSPCs and their progeny must be considered when developing transplantation strategies. Accumulated results do support the notion that committed NSPCs with limited differentiation options and high integrating ability are the most appropriate cellular sources for transplantation in diseases in which cell replacement is the most desirable effect and inflammation is only a self-limiting reaction to the graft. However, in chronic inflammatory diseases (such as multiple sclerosis) or in acute inflammatory responses following traumatic injuries (such as SCI, stroke), undifferentiated NSPCs mediate their beneficial effects by secreting neuroprotective molecules in response to microenvironmentally dictated cues. In these cases, however, we still need to understand how to guide the undifferentiated NSPCs to produce neuroprotective molecules in a timely manner and with a certain degree of specificity to avoid unwanted side effects. Human fetal NSPCs are less tumorigenic than embryonic stem cells and, importantly, in the clinical trial with human NSPCs in Batten's disease, no tumors were detected in five patients 2 years after transplantation (http://www.stemcellsinc.com/announcements/stemcells-inc-s-phase-i-batten-trial-data-featured-at-american-association-of-neurological-surgeon?A=SearchResult&SearchID=2128330&ObjectID=10251&ObjectType=7). However, human embryonic stem and probably also induced pluripotent stem (iPS) cell–derived NSPCs are associated with a risk of tumor formation in response to microenvironment-mediated signals[67]. Seminatore *et al.*[67] concluded that the effect of an ischemic environment on the formation of tumors by transplanted human embryonic stem cell–derived NSPCs is limited to early differentiation stages. In contrast, hyperproliferation observed at later stages of differentiation corresponds to an intrinsic activity. Thus, a tight control of the transplantation timing and route of cell administration is required to avoid side effects and foster reparative properties of transplanted NSPCs. An early window for NSPC transplantation seems to be the most appropriate because soon after CNS damage the expression of genes encoding molecules supporting tissue growth predominates over that of genes encoding molecules opposing plasticity[10,48,51]. Although introducing large numbers of autologous committed precursors (for example, iPS cells) might be optimal for cell replacement strategies, the discovery of factors governing the NSPC-mediated neuroprotective effect is required to optimize the treatment and avoid unwanted side effects. However, the identification of factors involved in the effect mediated by the transplanted cells is still in its infancy, thus representing the greatest challenge to be solved before envisaging translation of NSPC-based therapies to routine use at the bedside. Some such molecules have been described (LIF, BMP-4, trophic factors), but the environmental stimuli and the timing, as well as the best administration route, to promote the appropriate secretion of such molecules in the target tissue remain elusive.

Conclusions

Scientific advancements during the last few years have lead to a shift in our view on immune responses in the CNS and their action in neural degeneration, plasticity and repair. The diversity of immune responses is now well appreciated, as is the lack of redundancy between microglia and infiltrating monocyte-derived macrophages. We now know that local inflammation does not reflect a single type of process; it could be an outcome of failure of resolution of local innate immunity or an overall adaptive uncontrolled immunity. Immune-related factors that impair neuronal survival and induce neuronal death also inhibit regeneration; therefore, immunomodulation should benefit stem cell therapy. Both *in vitro* and after transplantation *in vivo,* NSPCs not only form neural cells for replacement but also exert immunomodulatory and trophic effects, so-called "therapeutic plasticity"[9]. Whether endogenous NSPCs in their native location have similar capacities has not been documented. The challenge now is to determine in more detail the cross-talk between different populations of immune cells and endogenous and grafted NSPCs at different phases in acute and chronic brain disease.

Optimum regeneration and therapeutic efficacy will require that the timing and mode of modulation of immune responses and delivery of exogenous NSPCs and stimulation of endogenous NSPCs be carefully chosen.

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1. Moalem, G. *et al.* Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat. Med.* **5**, 49–55 (1999).
2. Ziv, Y. *et al.* Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nat. Neurosci.* **9**, 268–275 (2006).
3. Shechter, R. *et al.* Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Med.* **6**, e1000113 (2009).
4. Martino, G. How the brain repairs itself: new therapeutic strategies in inflammatory and degenerative CNS disorders. *Lancet Neurol.* **3**, 372–378 (2004).
5. Ziv, Y. *et al.* Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proc. Natl. Acad. Sci. USA* **103**, 13174–13179 (2006).
6. Martino, G. *et al.* Brain regeneration in physiology and pathology: the immune signature driving therapeutic plasticity of neural stem cells. *Physiol. Rev.* **91**, 1281–1304 (2011).
7. Pluchino, S. *et al.* Persistent inflammation alters the function of the endogenous brain stem cell compartment. *Brain* **131**, 2564–2578 (2008).
8. Ben-Hur, T. *et al.* Effects of proinflammatory cytokines on the growth, fate, and motility of multipotential neural precursor cells. *Mol. Cell. Neurosci.* **24**, 623–631 (2003).
9. Martino, G. & Pluchino, S. The therapeutic potential of neural stem cells. *Nat. Rev. Neurosci.* **7**, 395–406 (2006).
10. Bacigaluppi, M. *et al.* Delayed post-ischaemic neuroprotection following systemic neural stem cell transplantation involves multiple mechanisms. *Brain* **132**, 2239–2251 (2009).
11. Cusimano, M. *et al.* Transplanted neural stem/precursor cells instruct phagocytes and reduce secondary tissue damage in the injured spinal cord. *Brain* **135**, 447–460 (2012).
12. Pluchino, S. *et al.* Injection of adult neurospheres induces recovery in a chronic model of multiple sclerosis. *Nature* **422**, 688–694 (2003).
13. Pluchino, S. *et al.* Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. *Nature* **436**, 266–271 (2005).
14. Ginhoux, F. *et al.* Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* **330**, 841–845 (2010).
15. Butovsky, O. *et al.* Glatiramer acetate fights against Alzheimer's disease by inducing dendritic-like microglia expressing insulin-like growth factor 1. *Proc. Natl. Acad. Sci. USA* **103**, 11784–11789 (2006).
16. Shechter, R. *et al.* The glial scar-monocyte interplay: a pivotal resolution phase in spinal cord repair. *PLoS ONE* **6**, e27969 (2011).
17. Hauben, E. *et al.* Vaccination with a Nogo-A-derived peptide after incomplete spinal-cord injury promotes recovery via a T-cell-mediated neuroprotective response: comparison with other myelin antigens. *Proc. Natl. Acad. Sci. USA* **98**, 15173–15178 (2001).
18. Curtis, M.A. *et al.* Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. *Science* **315**, 1243–1249 (2007).
19. Sanai, N. *et al.* Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* **478**, 382–386 (2011).
20. Derecki, N.C. *et al.* Regulation of learning and memory by meningeal immunity: a key role for IL-4. *J. Exp. Med.* **207**, 1067–1080 (2010).
21. Wolf, S.A. *et al.* Adaptive peripheral immune response increases proliferation of neural precursor cells in the adult hippocampus. *FASEB J.* **23**, 3121–3128 (2009).
22. Rolls, A. *et al.* Toll-like receptors modulate adult hippocampal neurogenesis. *Nat. Cell Biol.* **9**, 1081–1088 (2007).
23. Ekdahl, C.T. *et al.* Inflammation is detrimental for neurogenesis in adult brain. *Proc. Natl. Acad. Sci. USA* **100**, 13632–13637 (2003).
24. Hoehn, B.D., Palmer, T.D. & Steinberg, G.K. Neurogenesis in rats after focal cerebral ischemia is enhanced by indomethacin. *Stroke* **36**, 2718–2724 (2005).
25. Monje, M.L., Toda, H. & Palmer, T.D. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* **302**, 1760–1765 (2003).
26. Sierra, A. *et al.* Microglia shape adult hippocampal neurogenesis through apoptosis-coupled phagocytosis. *Cell Stem Cell* **7**, 483–495 (2010).
27. Iosif, R.E. *et al.* Suppression of stroke-induced progenitor proliferation in adult subventricular zone by tumor necrosis factor receptor 1. *J. Cereb. Blood Flow Metab.* **28**, 1574–1587 (2008).
28. Iosif, R.E. *et al.* Tumor necrosis factor receptor 1 is a negative regulator of progenitor proliferation in adult hippocampal neurogenesis. *J. Neurosci.* **26**, 9703–9712 (2006).
29. Bonde, S., Ekdahl, C.T. & Lindvall, O. Long-term neuronal replacement in adult rat hippocampus after status epilepticus despite chronic inflammation. *Eur. J. Neurosci.* **23**, 965–974 (2006).
30. Thored, P. *et al.* Long-term accumulation of microglia with proneurogenic phenotype concomitant with persistent neurogenesis in adult subventricular zone after stroke. *Glia* **57**, 835–849 (2009).
31. Cacci, E., Ajmone-Cat, M.A., Anelli, T., Biagioni, S. & Minghetti, L. *In vitro* neuronal and glial differentiation from embryonic or adult neural precursor cells are differently affected by chronic or acute activation of microglia. *Glia* **56**, 412–425 (2008).
32. Walton, N.M. *et al.* Microglia instruct subventricular zone neurogenesis. *Glia* **54**, 815–825 (2006).
33. Gómez-Nicola, D. *et al.* Interleukin-15 regulates proliferation and self-renewal of adult neural stem cells. *Mol. Biol. Cell* **22**, 1960–1970 (2011).
34. Butovsky, O. *et al.* Microglia activated by IL-4 or IFN-γ differentially induce neurogenesis and oligodendrogenesis from adult stem/progenitor cells. *Mol. Cell. Neurosci.* **31**, 149–160 (2006).
35. Skihar, V. *et al.* Promoting oligodendrogenesis and myelin repair using the multiple sclerosis medication glatiramer acetate. *Proc. Natl. Acad. Sci. USA* **106**, 17992–17997 (2009).
36. Cho, Y.K. *et al.* Erythropoietin promotes oligodendrogenesis and myelin repair following lysolecithin-induced injury in spinal cord slice culture. *Biochem. Biophys. Res. Commun.* **417**, 753–759 (2012).
37. Tepavčević, V. *et al.* Inflammation-induced subventricular zone dysfunction leads to olfactory deficits in a targeted mouse model of multiple sclerosis. *J. Clin. Invest.* **121**, 4722–4734 (2011).
38. Ron-Harel, N., Cardon, M. & Schwartz, M. Brain homeostasis is maintained by "danger" signals stimulating a supportive immune response within the brain's borders. *Brain Behav. Immun.* **25**, 1036–1043 (2011).
39. Saino, O. *et al.* Immunodeficiency reduces neural stem/progenitor cell apoptosis and enhances neurogenesis in the cerebral cortex after stroke. *J. Neurosci. Res.* **88**, 2385–2397 (2010).
40. Takata, M. *et al.* Glucocorticoid-induced TNF receptor-triggered T cells are key modulators for survival/death of neural stem/progenitor cells induced by ischemic stroke. *Cell Death Differ.* **19**, 756–767 (2012).
41. Villeda, S.A. *et al.* The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature* **477**, 90–94 (2011).
42. Song, H., Stevens, C.F. & Gage, F.H. Astroglia induce neurogenesis from adult neural stem cells. *Nature* **417**, 39–44 (2002).
43. Joannides, A. *et al.* Efficient generation of neural precursors from adult human skin: astrocytes promote neurogenesis from skin-derived stem cells. *Lancet* **364**, 172–178 (2004).
44. Gaughwin, P.M. *et al.* Astrocytes promote neurogenesis from oligodendrocyte precursor cells. *Eur. J. Neurosci.* **23**, 945–956 (2006).
45. Thored, P. *et al.* Persistent production of neurons from adult brain stem cells during recovery after stroke. *Stem Cells* **24**, 739–747 (2006).
46. Yan, Y.P. *et al.* Osteopontin is a mediator of the lateral migration of neuroblasts from the subventricular zone after focal cerebral ischemia. *Neurochem. Int.* **55**, 826–832 (2009).
47. Jakubs, K. *et al.* Inflammation regulates functional integration of neurons born in adult brain. *J. Neurosci.* **28**, 12477–12488 (2008).
48. Jakubs, K. *et al.* Environment matters: synaptic properties of neurons born in the epileptic adult brain develop to reduce excitability. *Neuron* **52**, 1047–1059 (2006).
49. Wood, J.C. *et al.* Functional integration of new hippocampal neurons following insults to the adult brain is determined by characteristics of pathological environment. *Exp. Neurol.* **229**, 484–493 (2011).
50. Lindvall, O. & Kokaia, Z. Stem cells in human neurodegenerative disorders–time for clinical translation? *J. Clin. Invest.* **120**, 29–40 (2010).
51. Darsalia, V. *et al.* Cell number and timing of transplantation determine survival of human neural stem cell grafts in stroke-damaged rat brain. *J. Cereb. Blood Flow Metab.* **31**, 235–242 (2011).
52. Bachoud-Lévi, A.C. *et al.* Motor and cognitive improvements in patients with Huntington's disease after neural transplantation. *Lancet* **356**, 1975–1979 (2000).
53. Li, E. Chromatin modification and epigenetic reprogramming in mammalian development. *Nat. Rev. Genet.* **3**, 662–673 (2002).
54. Blakemore, W.F. & Franklin, R.J. Remyelination in experimental models of toxin-induced demyelination. *Curr. Top. Microbiol. Immunol.* **318**, 193–212 (2008).
55. Lindvall, O. & Kokaia, Z. Prospects of stem cell therapy for replacing dopamine neurons in Parkinson's disease. *Trends Pharmacol. Sci.* **30**, 260–267 (2009).
56. Kordower, J.H. *et al.* Functional fetal nigral grafts in a patient with Parkinson's disease: chemoanatomic, ultrastructural, and metabolic studies. *J. Comp. Neurol.* **370**, 203–230 (1996).
57. Gomi, M. *et al.* Single and local blockade of interleukin-6 signaling promotes neuronal differentiation from transplanted embryonic stem cell-derived neural precursor cells. *J. Neurosci. Res.* **89**, 1388–1399 (2011).
58. Einstein, O. *et al.* Intraventricular transplantation of neural precursor cell spheres attenuates acute experimental allergic encephalomyelitis. *Mol. Cell. Neurosci.* **24**, 1074–1082 (2003).
59. Lee, S.T. *et al.* Anti-inflammatory mechanism of intravascular neural stem cell transplantation in haemorrhagic stroke. *Brain* **131**, 616–629 (2008).

60. Einstein, O. *et al.* Neural precursors attenuate autoimmune encephalomyelitis by peripheral immunosuppression. *Ann. Neurol.* **61**, 209–218 (2007).
61. Pluchino, S. *et al.* Human neural stem cells ameliorate autoimmune encephalomyelitis in non-human primates. *Ann. Neurol.* **66**, 343–354 (2009).
62. Payne, N.L. *et al.* Comparative study on the therapeutic potential of neurally differentiated stem cells in a mouse model of multiple sclerosis. *PLoS ONE* **7**, e35093 (2012).
63. Cao, W. *et al.* Leukemia inhibitory factor inhibits T helper 17 cell differentiation and confers treatment effects of neural progenitor cell therapy in autoimmune disease. *Immunity* **35**, 273–284 (2011).
64. Pluchino, S. *et al.* Regeneration and repair in multiple sclerosis: the role of cell transplantation. *Neurosci. Lett.* **456**, 101–106 (2009).
65. Erblich, B. *et al.* Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits. *PLoS ONE* **6**, e26317 (2011).
66. London, A. *et al.* Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. *J. Exp. Med.* **208**, 23–39 (2011).
67. Seminatore, C. *et al.* The postischemic environment differentially impacts teratoma or tumor formation after transplantation of human embryonic stem cell-derived neural progenitors. *Stroke* **41**, 153–159 (2010).
68. Krathwohl, M.D. & Kaiser, J.L. Chemokines promote quiescence and survival of human neural progenitor cells. *Stem Cells* **22**, 109–118 (2004).
69. Reiss, K. *et al.* Stromal cell-derived factor 1 is secreted by meningeal cells and acts as chemotactic factor on neuronal stem cells of the cerebellar external granular layer. *Neuroscience* **115**, 295–305 (2002).
70. Imitola, J. *et al.* Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1α/CXC chemokine receptor 4 pathway. *Proc. Natl. Acad. Sci. USA* **101**, 18117–18122 (2004).
71. Moriyama, M. *et al.* Complement receptor 2 is expressed in neural progenitor cells and regulates adult hippocampal neurogenesis. *J. Neurosci.* **31**, 3981–3989 (2011).
72. Koo, J.W. & Duman, R.S. IL-1β is an essential mediator of the antineurogenic and anhedonic effects of stress. *Proc. Natl. Acad. Sci. USA* **105**, 751–756 (2008).
73. Guan, Y. *et al.* Upregulation of chemokine receptor expression by IL-10/IL-4 in adult neural stem cells. *Exp. Mol. Pathol.* **85**, 232–236 (2008).
74. Yan, Y.P. *et al.* Persistent migration of neuroblasts from the subventricular zone to the injured striatum mediated by osteopontin following intracerebral hemorrhage. *J. Neurochem.* **109**, 1624–1635 (2009).
75. Ahmed, S., Reynolds, B.A. & Weiss, S. BDNF enhances the differentiation but not the survival of CNS stem cell-derived neuronal precursors. *J. Neurosci.* **15**, 5765–5778 (1995).
76. Batchelor, P.E. *et al.* Activated macrophages and microglia induce dopaminergic sprouting in the injured striatum and express brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. *J. Neurosci.* **19**, 1708–1716 (1999).
77. Emsley, J.G. & Hagg, T. Endogenous and exogenous ciliary neurotrophic factor enhances forebrain neurogenesis in adult mice. *Exp. Neurol.* **183**, 298–310 (2003).
78. Bernaudin, M. *et al.* A potential role for erythropoietin in focal permanent cerebral ischemia in mice. *J. Cereb. Blood Flow Metab.* **19**, 643–651 (1999).
79. Shingo, T. *et al.* Erythropoietin regulates the *in vitro* and *in vivo* production of neuronal progenitors by mammalian forebrain neural stem cells. *J. Neurosci.* **21**, 9733–9743 (2001).
80. Roussa, E. & Krieglstein, K. GDNF promotes neuronal differentiation and dopaminergic development of mouse mesencephalic neurospheres. *Neurosci. Lett.* **361**, 52–55 (2004).
81. Åberg, M.A. *et al.* IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. *Mol. Cell. Neurosci.* **24**, 23–40 (2003).
82. Hsieh, J. *et al.* IGF-I instructs multipotent adult neural progenitor cells to become oligodendrocytes. *J. Cell Biol.* **164**, 111–122 (2004).
83. Erlandsson, A., Enarsson, M. & Forsberg-Nilsson, K. Immature neurons from CNS stem cells proliferate in response to platelet-derived growth factor. *J. Neurosci.* **21**, 3483–3491 (2001).
84. Kondo, T. & Raff, M. Oligodendrocyte precursor cells reprogrammed to become multipotential CNS stem cells. *Science* **289**, 1754–1757 (2000).
85. Stipursky, J. & Gomes, F.C. TGF-β1/SMAD signaling induces astrocyte fate commitment in vitro: implications for radial glia development. *Glia* **55**, 1023–1033 (2007).
86. Schänzer, A. *et al.* Direct stimulation of adult neural stem cells in vitro and neurogenesis in vivo by vascular endothelial growth factor. *Brain Pathol.* **14**, 237–248 (2004).
87. Schmidt, N.O. *et al.* Brain tumor tropism of transplanted human neural stem cells is induced by vascular endothelial growth factor. *Neoplasia* **7**, 623–629 (2005).
88. Yang, J. *et al.* Adult neural stem cells expressing IL-10 confer potent immunomodulation and remyelination in experimental autoimmune encephalitis. *J. Clin. Invest.* **119**, 3678–3691 (2009).
89. Kelly, S. *et al.* Transplanted human fetal neural stem cells survive, migrate, and differentiate in ischemic rat cerebral cortex. *Proc. Natl. Acad. Sci. USA* **101**, 11839–11844 (2004).
90. Horie, N. *et al.* Transplanted stem cell-secreted vascular endothelial growth factor effects poststroke recovery, inflammation, and vascular repair. *Stem Cells* **29**, 274–285 (2011).
91. Ramos-Cabrer, P. *et al.* Stem cell mediation of functional recovery after stroke in the rat. *PLoS ONE* **5**, e12779 (2010).
92. Oki, K. *et al.* Human induced pluripotent stem cells form functional neurons and improve recovery after grafting in stroke-damaged brain. *Stem Cells* **30**, 1120–1133 (2012).
93. Chu, K. *et al.* Human neural stem cells improve sensorimotor deficits in the adult rat brain with experimental focal ischemia. *Brain Res.* **1016**, 145–153 (2004).
94. Teng, Y.D. *et al.* Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. *Proc. Natl. Acad. Sci. USA* **99**, 3024–3029 (2002).
95. Lu, P. *et al.* Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. *Exp. Neurol.* **181**, 115–129 (2003).
96. Ourednik, J. *et al.* Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. *Nat. Biotechnol.* **20**, 1103–1110 (2002).
97. Rafuse, V.F. *et al.* Neuroprotective properties of cultured neural progenitor cells are associated with the production of sonic hedgehog. *Neuroscience* **131**, 899–916 (2005).
98. Redmond, D.E. Jr. *et al.* Behavioral improvement in a primate Parkinson's model is associated with multiple homeostatic effects of human neural stem cells. *Proc. Natl. Acad. Sci. USA* **104**, 12175–12180 (2007).
99. McBride, J.L. *et al.* Human neural stem cell transplants improve motor function in a rat model of Huntington's disease. *J. Comp. Neurol.* **475**, 211–219 (2004).
100. Ryu, J.K. *et al.* Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. *Neurobiol. Dis.* **16**, 68–77 (2004).