Published in final edited form as:
Physiol Rev. 2011 October ; 91(4): 1281–1304. doi:10.1152/physrev.00032.2010.

BRAIN REGENERATION IN PHYSIOLOGY AND PATHOLOGY: THE IMMUNE SIGNATURE DRIVING THERAPEUTIC PLASTICITY OF NEURAL STEM CELLS

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Abstract

Regenerative processes occurring under physiological (maintenance) and pathological (reparative) conditions are a fundamental part of life and vary greatly among different species, individuals, and tissues. Physiological regeneration occurs naturally as a consequence of normal cell erosion, or as an inevitable outcome of any biological process aiming at the restoration of homeostasis. Reparative regeneration occurs as a consequence of tissue damage. Although the central nervous system (CNS) has been considered for years as a "perennial" tissue, it has recently become clear that both physiological and reparative regeneration occur also within the CNS to sustain tissue homeostasis and repair. Proliferation and differentiation of neural stem/progenitor cells (NPCs) residing within the healthy CNS, or surviving injury, are considered crucial in sustaining these processes. Thus a large number of experimental stem cell-based transplantation systems for CNS repair have recently been established. The results suggest that transplanted NPCs promote tissue repair not only via cell replacement but also through their local contribution to changes in the diseased tissue milieu. This review focuses on the remarkable plasticity of endogenous and exogenous (transplanted) NPCs in promoting repair. Special attention will be given to the cross-talk existing between NPCs and CNS-resident microglia as well as CNS-infiltrating immune cells from the circulation, as a crucial event sustaining NPC-mediated neuroprotection. Finally, we will propose the concept of the context-dependent potency of transplanted NPCs (therapeutic plasticity) to exert multiple therapeutic actions, such as cell replacement, neurotrophic support, and immunomodulation, in CNS repair.

I. INTRODUCTION

Regeneration is a complex articulated process restoring the interrupted continuity of a missing organ or tissue mass, yielding new fully functional tissue (37). In both physiological (maintenance) and pathological (reparative) regenerative processes, stem cells are indeed major players. Thus the possibility to use these cells as therapeutic tools in transplantation

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DISCLOSURES No conflicts of interest, financial or otherwise, are declared by the authors.

Europe PMC Funders Author Manuscripts

settings is considered the holy grail of regenerative medicine (107). However, while a decade ago somatic stem and/or progenitor cells were unanimously thought of as a therapeutic tool to regenerate through cell replacement specific tissue elements lost as a consequence of disease processes (129, 195, 238), we are currently confronted with unexpected findings showing that somatic stem and progenitor cells possess the unique capacity to "oscillate" among multiple functional "therapeutic" states depending on the context in which they are transplanted.

In this review we first focus on the different mechanisms sustaining regenerative processes in health (constitutive renewal/plasticity) and in pathology (repair) (220, 249) while discussing in depth those occurring within the central nervous system (CNS) (226). Among CNS regenerative mechanisms, such as the regrowth of severed axons, cell renewal, synaptic plasticity, particular attention will be devoted to those sustained by the interactions occurring between the nervous and the immune systems. In the light of this, we will elaborate on when and how the cross-talk between neural stem/progenitor cells (NPCs) and CNS-resident and infiltrating blood-borne immune cells foster or hamper tissue repair. Here, we will use "NPCs" as a generic term encompassing the following stem and progenitor cells: *1*) adult CNS stem cells, referring to those cells that display cardinal features such as unlimited capacity for self-renewal, indefinite ability to proliferate in response to mitogens, and multipotency for differentiation, characterized by the ability to give rise to different neuroectodermal lineages of the CNS; *2*) multipotent progenitors of the adult brain, which are proliferative cells with only limited self-renewal that can differentiate into at least two different cell lineages; and *3*) lineage-specific precursors or progenitors, which are restricted to a single distinct lineage (such as neuronal, astroglial, or oligodendroglial). As we will see, not only NPCs residing within germinal niches but also some slowly cycling progenitors dispersed throughout the entire CNS parenchyma fulfill these criteria. We then focus on the role and potential application of NPC transplants in brain repair. We describe the local inflammation and tissue damage that generally occur concomitant with CNS disease, and the unique capacity of transplanted NPCs to adapt their migratory and therapeutic features towards damaged CNS areas. We conclude by discussing how transplanted NPCs might reestablish biologically relevant neuroimmune interactions to promote remarkable remodeling of the spared CNS tissue via several mechanisms, including cell replacement, immunomodulation, and neuroprotection. Dissection of the molecular and cellular events sustaining these alternative NPC-mediated "reparative" mechanisms will be presented as a conceptual framework to establish more efficacious therapies for neurological diseases.

II. PRINCIPLES OF REGENERATION

When generally speaking of regeneration, the natural replacement of extruded or worn out cells or body parts refers to a diverse set of biological events encompassing several different processes depending on the species, organ, tissue, and age. This concept can be easily grasped by looking at two simple facts: the changing regenerative capacities of different phyla in evolution and the uneven regenerative potential of different tissues and organs in individuals of the same species.

A growing number of comparative studies have been recently performed to understand the differences between regenerative capacities across the animal kingdom (225, 226). Regenerative strategies (TABLE 1) can be broadly classified into "epimorphic" regeneration, e.g., amphibian limb regeneration (161), and "morphallactic" regeneration, when a direct rearrangement of preexisting cells is observed, e.g., whole body regeneration in hydra (19, 23, 220, 237). These two main regenerative strategies are not mutually exclusive, and in several regeneration models, including planaria (4) and amphibians (230),

blastema formation is followed by the differentiation of the "regenerating" cells into the appropriate cell types, the so-called intercalary regeneration (3).

Regardless of the mode of action, regenerative processes can lead to either "perfect," complete, regeneration or "imperfect" regeneration (37, 140, 249), which is characterized by fibrotic reactions leading to scar formation (88). Several factors have been identified as promoting perfect versus imperfect regeneration. The type of tissue loss or injury (e.g., physiological, bioelectrical, chemical, traumatic) is important because it instructs the activation and proliferation of one versus another type of "renewable" cell. For instance, in humans, heart damage is followed by fibrosis and scarring, whereas heart regeneration with replacement of lost contractile tissue does occur in zebra fish and newt. In the fish, the new myocardium arises from undifferentiated progenitor cells (22), whereas in the newt cardiomyocytes have been shown to reenter the cell cycle. Several studies in simpler metazoan organisms (36, 108, 161, 226, 234) have indicated that also tissue architectural complexity is a crucial factor. Yet, complexity is not the only aspect involved, since limb regeneration occurs throughout life in newts and salamanders (urodele amphibians), whereas in frogs and toads (anuran amphibians) it is restricted to the developing larval limb (161) (see below).

The above-mentioned studies indicate that regeneration is possible only when the renewable cells, the stem cells, are present. Pluripotent stem cells called neoblasts [located throughout the body (3, 4, 201)] are involved in regeneration occurring in invertebrates and some vertebrates while tissue-associated stem/progenitor cells play a crucial role in the regeneration of most mammalian tissues (37). Thus a huge effort has been made in the last few years to characterize intrinsic cellular properties of stem cells, the nature of the niches allowing their survival in adult tissue, and their physiological and reparative regenerative capacities in different animal species (153, 236).

A. Role of Stem Cells in the Regeneration of Different Tissues

Stem cells are probably a basic feature of all multicellular organisms since they have been described for animals, fungi, and plants. They share the universal property of continuously replicating themselves and generate progeny of differentiated cells.

Stem cell activity is very much dependent on the niches in which they reside. The intrinsic characteristics of such niches are thought to be the consequence of stem cell "adaptation" to different maturing tissues (163). "Labile" tissues undergoing continuous cell renewal (e.g., skin, epithelia, cornea, blood) do contain multiple and disperse units of stem cell niches (e.g., intestinal crypts, hair follicle bulge in the skin) (153, 162, 247). In contrast, in some "stable" tissues (e.g., kidney and liver), stem cell niches have not been clearly characterized (118, 130). As a consequence of this, regeneration in labile tissues is favored by the persistence of undamaged stem cell niches, or of facultative niches (e.g., hematopoietic niches positioned in unconventional locations in the bone marrow, liver, and spleen). On the other hand, regeneration in stable tissue occurs mainly through compensatory cellular hyperplasia. Although stem-like cells are thought to be present in the periportal regions of the liver (72, 118), the bulk of "liver regeneration" takes place by proliferation of the existing mature cellular populations composing the intact organ (149).

B. Role of the Immune System in Regenerative Processes

Understanding the mechanisms hampering or favoring complete (perfect) regeneration compared with those promoting incomplete (imperfect) regeneration, via fibrotic scar formation, is still in infancy due to the fact that the distinction between the two processes is not an all-or-none phenomenon. The process of scar formation is an intermediate stage of

the regenerative process; imperfect regeneration occurs only when scar formed by is not replaced by regenerative tissue (192). Studies on fin regeneration in zebra fish show that a fish mutant devoid of blastema fails to regenerate the fin, but has normal wound healing responses (199, 240). On the other hand, some invertebrates (e.g., Oloturia) employ analogous cellular mechanisms during wound healing and organ regeneration (196, 199).

The effects of immune cells in promoting wound healing have been suggested to explain why persistence of scar leading to wound healing occurs during imperfect regeneration (88). Thus the different capacity for organ regeneration through phylogeny appeared to be correlated with the evolution of the immune system (88, 147, 148). The loss of regenerative capacity observed between urodele and anuran amphibians, the latter are capable of regenerative ability only at the larval stage, is an eloquent example since urodeles have lower immune competence with respect to anurans (231). The immune system of the anuran *Xenopus laevis* is ancestral at the larval stage, whereas it becomes similar to that of mammals in the adult (189).

However, it is now clear that the mere occurrence of the local inflammation driven by immune cells and of scar formation under injurious conditions are not the cause for the failure of regeneration, especially within the CNS, the topic of this review.

As a matter of fact, recent data show that the glial scar components [e.g., reactive astrocytes, microglia/macrophages and extracellular matrix molecules, especially chondroitin sulfate proteoglycans (CSPGs)] does not only act as growth inhibitors, but prevent damage spread and create favorable conditions for repair. Growth-promoting features were demonstrated for over-sulfated CSPGs (155). Astrocytes can contribute to immune regulation through their role in resealing of the blood-brain barrier (71) and have key roles in controlling multiple steps of adult neurogenesis (from proliferation and fate specification of NPCs to migration and integration of the neural progeny into preexisting neuronal circuits in the adult brain) (135). Macrophages and microglia were reported to support growth and survival of neurons (192). These and other results indicate that scar tissue and its components might have beneficial effects, at an early phase of the recovery process, and destructive effects, if not resolved in a timely manner. In the acute phase after injury, the glia scar seals the lesion site, restores homeostasis, preserves spared tissue, and modulates immunity; in the later periods, if these processes are timely resolved, they block subsequent stages that are pivotal to the overall repair. It is currently believed that what impairs recovery is not the scar formation itself, but the improper control of the timing of these two consecutive and intermingled early versus late glia scar-related processes (192).

Likewise, as we will discuss below, the immune system does not impede regeneration unless the response is not well controlled. On the contrary, complex organisms are equipped with a fully formed immune system that supports perfect repair following tissue injury by taking advantage of their protective immune mechanisms.

III. NEURAL STEM CELLS

Owing to the fact that it is composed of postmitotic, life-long lasting cells whose number cannot increase after the end of embryonic neurogenesis, the CNS has been considered an hypertrophic but not hyperplastic tissue, a nonrenewable, “perennial” tissue [for review, see Goss et al. (84)]. As a consequence, mammalian CNS regeneration in terms of tissue reconstitution was thought to be simply impossible. To support this tissue “incompetence,” several impeding factors have been advocated (TABLE 2).

However, studies carried out in the last 20 years have challenged this dogma by showing the persistence of neural cell renewal (both neurons and glia), the so-called “adult

neurogenesis," within specific brain areas (80, 131). New neurons are produced throughout life in the forebrain and hippocampus of mammals, including rodents, rabbits, monkeys, and humans (49, 57, 68, 80, 113, 134, 179, 200). The source of the newly generated cells are NPCs which remain active within the subventricular zone (SVZ), in the forebrain, and the subgranular zone (SGZ) in the dentate gyrus (DG) of the hippocampus (80, 117). SVZ- and SGZ-derived adult neurogenesis ensures physiological cell renewal/addition within specific brain regions (olfactory bulb and dentate gyrus granule layer), and the SVZ can "regenerate" the whole system after cytotoxic removal of proliferating elements (ablation of proliferating cells with the antimetabolic agent Ara-C) (57).

However, due to the fact that generation of newly formed cells occurs only in very restricted areas, the CNS was still considered to be different from labile tissues, such as skin, blood (disperse, multiple stem cell niches), but also from hypertrophic/compensatory, stable organs such as liver, kidney (hyperplasia, ill-defined stem cell niches), and muscle (disperse stem/progenitor cells). These assumptions have been recently challenged by data showing that neurogenesis also occurs in several other regions of the CNS, such as neocortex, cerebellum, striatum, amygdala, and substantia nigra (51, 85, 94, 134, 159, 180) and more recently also in the hypothalamus (75, 85, 109, 110, 170) and in the spinal cord root ganglia (211). This evidence copes with that demonstrating the existence of slowly cycling multipotent local progenitors, dispersed throughout the whole CNS parenchyma and capable of differentiating into all neuroectodermal lineages, representing an important source of neural cell renewal particularly, but not exclusively, active in pathological conditions (25, 79, 96, 146, 257). The "perennial" state of the CNS can be now reassessed.

A. NPCs Persist Within the Healthy Adult Brain

As anticipated, NPCs mainly persist in restricted "niche" regions of postnatal and adult brains, both in rodents as well as in humans (7, 49, 80, 160, 181, 200).

In the SVZ of the lateral ventricles, a region highly related to the embryonic SVZ (49), neurons are born and feed into a network of chains of tangentially migrating neuroblasts that travel along the so-called rostral migratory stream (RMS) to reach the olfactory bulb (FIG. 1). The cellular composition and architecture of the adult mouse SVZ has been well characterized at the ultrastructural level. The SVZ contains a population of slowly dividing astrocytes, known as type B cells that are the primary precursors and act as bona fide CNS stem cells, both in vitro and in vivo. Type B cells give rise to actively proliferating (transit-amplifying) type C cells that function as the transit amplifying progenitors in the adult brain SVZ and which are scattered along the network of migrating neuroblasts (57). Type C cells, in turn, give rise to immature neuroblasts (type A cells), which migrate along the RMS to the olfactory bulb, where they terminally differentiate into various types olfactory bulb interneurons (56, 132). Recent studies indicate that type B cells in the adult CNS retain some important properties of radial glial cells (RG), the cells derived at E10–12, when cortical neurogenesis begins, from neuroepithelial cells (117). Adult SVZ type B cells, in fact, retain apical-basal polarity and are part of the ventricular epithelium, as are RG earlier in development. Type B cell bodies are generally located just under the ependymal cell layer but have short processes that extend through the ependymal layer with small apical endings that contact the ventricle (150, 215). These apical endings form junctional complexes among themselves, which are virtually identical to those that join RG earlier in development, and contain a single primary cilium. The function of this organelle in NPCs remains unknown, whereas recent works indicate that primary cilia are important sites for signal reception, particularly Sonic hedgehog homolog (Shh) (95, 216). Moreover, type B cells have relatively long basal processes, frequently oriented tangentially with specialized end feet on blood vessels (150), with which proliferating SVZ cells are frequently associated (227). Therefore, NPCs of the adult SVZ appear to maintain many epithelial characteristics that

allow them to bridge between blood vessels underlying the SVZ and the ventricular surface and are embedded within a population of cells classically considered as glial fibrillary acidic protein (GFAP)-expressing astrocytes.

Another major region that produces new neurons in the adult mammalian brain is the SGZ in the hippocampus, both in rodents (6, 68, 81, 86) and humans (61, 138). The new hippocampal neurons are born in the SGZ, which is located at the interface of the granule cell layer and the hilus, and in contrast to the extensive tangential migration undertaken by olfactory bulb neurons, hippocampal granule neurons move only a short distance into the granule cell layer (210). The SGZ contains two types of dividing cells: astrocytes (type B cells) and darkly stained small cells with small basophilic nuclei (type D cells) (6, 168). Consistent with observations in development and in the adult SVZ, radial astrocytes in the SGZ function as the primary precursors of the new neurons in the DG. Type B cells do not give rise to neurons directly but generate intermediate progenitors, which correspond to the small basophilic cells that are darkly stained by hematoxylin, referred to as type D cells or type II progenitors. Immature D cells appear to divide and function as the so-called intermediate progenitor cell (IPC) or basal progenitor (another type of neuronal progenitor appearing in the SVZ at the onset of neurogenesis), while more mature darkly stained D cells have a prominent process and have properties of neurons at different stages of maturation, characterized by the expression of doublecortin (DCX), poly-sialylated neural cell adhesion molecule (PSA-NCAM), collapsin response mediator protein 4 (CRMP-4, also known as TUC-4 or Ulip-1), neurogenic differentiation (NeuroD), prospero homeobox protein 1 (Prox1), and neuronal nuclei (NeuN) (209). These latter cells also progressively acquire electrophysiological characteristics of new mature granule neurons (73, 218). Retroviral lineage-tracing experiments in transgenic mice (G-tva) expressing the receptor for an avian leukosis retrovirus (93) specifically to target GFAP- or Nestin-expressing cells in the SGZ indicate that radial astrocytes not only divide but also generate the neurons in the adult DG (209). This and other studies support the interpretation that radial astrocytes function as primary progenitors (52, 101). In addition to their role as NPCs, radial astrocytes may also retain the classical astrocytic functions of supporting neuronal and synaptic activity in the granule and molecular layers of the DG. The electrophysiological properties of radial astrocytes are similar to those of other astrocytes in the brain (78).

Much like the RG in the developing cortex, SGZ RG are arranged in a regular array along the blades of the DG. Their progeny, the type D cells, are closely associated with the radial astrocytes creating regular clusters of young neurons along the SGZ of the postnatal DG (209). The prominent radial orientation of the processes of these astrocytes could play a fundamental role in the collection of signals that regulate their own proliferation as well as the proliferation and differentiation of D cells. A radial astrocyte could receive information along its main shaft, which is near the cell bodies of many granule neurons, as well as from endings of the radial process in the molecular layer where the DG receives internal and external input (117). Neurogenesis in the DG is therefore regulated by multiple physiological and environmental signals including adrenal steroids, glutamate receptor activation, seizures, enriched environmental conditions, exercise, inflammation, and antidepressants (117).

As previously discussed, stem cell niches are defined as local microenvironments that maintain and regulate stem cell features. Within these areas, the interactions between stem cells and their neighboring cells determine many vital properties of stem cells, including self-renewal, proliferation, and cell fate determination (55, 117).

Among neighboring cells, several lines of evidence indicate endothelial cells as exerting a pivotal role (38, 222). From an anatomical point of view, NPCs residing within the SGZ

form clusters with endothelial cells at the level of capillary tips (168) while the SVZ niche contains a planar vascular plexus and proliferating type B and type C cells that are apposed to blood vessels (150, 215, 227). Furthermore, SVZ type B cells are intercalated with ependymal cells, and their apical side is directly exposed to the ventricle. From a functional point of view, blood signals, such as vascular-endothelial growth factor (VEGF) and pigment epithelium-derived factor (PEDF), regulate the endothelial influence on NPCs. High levels of VEGF induce both hippocampal neurogenesis and angiogenesis while blockage of VEGF signaling abolished running- and enrichment-induced neurogenesis (34). PEDF stimulates neurogenesis once released from ependymal and endothelial cells through the activation of *Hes1* and *Hes5*, which are major mediators of the Notch pathway onto endothelial cells (98, 182, 214). All in all, these data indicate that endothelial cells are involved in the regulation of adult neurogenesis. Direct contact of NPCs with endothelial and ependymal cells (e.g., via laminin-integrin interactions) and secreted factors, such as VEGF or PEDF, are both required to support and mediate endothelial cell-NPC interactions.

B. Reparative Regeneration in the Brain: Role of the Germinal Versus Parenchymal NPCs

As for the other tissues of the body, the reparative regeneration capacities of the nervous system highly vary among different phyla. In the oldest living metazoans, such as the cnidarians polyp Hydra, the nervous system is capable of active regeneration; neurons are continuously produced in the body column and are constantly lost by sloughing at the extremities and into developing buds (108). Planarians possess a primitive brain structure and can perfectly regenerate a functional brain from almost any tiny body fragment (234). Among vertebrates, some fish (e.g., zebrafish, teleost) exhibit a great potential for structural and functional regeneration of brain and spinal cord after injury during adulthood (14, 100, 156, 263). Although imperfect, CNS regeneration occurs in reptiles, in urodele amphibians during adulthood, and in anuran amphibian at the larval stage (23, 41, 66, 74, 128, 164, 186).

In contrast, such regenerative capacity has been substantially lost in the mammalian CNS. This discrepancy is mainly attributed to the occurrence of widespread neurogenesis in the CNS of nonmammalian species, whereas in mammals a spontaneous, constitutive genesis of neurons and glia (“actual” neurogenesis) is confined in restricted, germinal layer-derived neurogenic sites (SVZ and SGZ) (FIG. 1). Local parenchymal progenitor cells dispersed throughout the remaining CNS parenchyma (including the rest of the brain, the cerebellum, and the spinal cord) are also shown to be unable to fully and spontaneously support neurogenesis in vivo (178, 217). On the whole, reactive neurogenesis from germinal mammalian NPCs is substantially though as a series of abortive/noncoordinated events which fail to provide nervous tissue regeneration or functionally integrated cell replacement.

However, recent data do challenge this view. As a matter of fact, reactive functional neurogenesis (and gliogenesis), occurring in both neurogenic and nonneurogenic CNS regions, has been shown in rodents in response to different types of acute versus chronic tissue injuries (217). Newborn NPCs, originally destined to migrate into the olfactory bulb, have been found terminally differentiated into medium spiny neurons within the injured area in rodent models of brain ischemia (9, 229). Active cell proliferation was observed in the SVZ from seven patients who died within 5–15 days of an acute ischemic stroke. This active proliferation coincides with an increased cell density within the SVZ, an enlargement of the cytoplasmic volume of astrocyte-like type B cells, and an increase of Ki-67-positive cells immunopositive for the neuronal markers Tuj-1 or PSA-NCAM (139). In experimental autoimmune encephalomyelitis (EAE), the animal model of multiple sclerosis (MS), it was shown an increased proliferation and mobilization of SVZ NPCs differentiating into oligodendrocyte precursor cells (OPCs) in the corpus callosum (154, 171). This is considered to be a very early reactive phenomenon since chronic inflammation, such as that

occurring during EAE, leads to a sharp reduction of the proliferative and migratory capacities of SVZ NPCs and to a significant accumulation of nonmigratory type A cells within the caudal SVZ (174). Finally, neurogenesis in response to CNS injury has been also reported in nonneurogenic regions of the mouse CNS parenchyma [e.g., striatum (9), hippocampus (157), corticospinal system (40), spinal cord (146), subcortical white matter (77)] (FIG. 1). This ectopic neurogenesis seems to be sustained by a largest class of cycling local parenchymal progenitors, variably named as pericytes, $NG2^+$ glia (also known as OPCs, polydendrocytes, or synantocytes), and reactive astrocytes, sharing some similarities but maintaining some differences (188). All of them act, in defined experimental conditions, as multipotent progenitor cells but differ in their origin: reactive astrocytes are of the astroglial origin, pericytes are either mesodermal or neural crest-derived, and NG2 glia are derived from the neuroectoderm (18, 25, 30, 51, 58, 59, 94, 158, 257). Owing to their morphological and functional phenotype, these cells are thought to be particularly suited to elicit neural repair in brain regions far away from zones of adult neurogenesis (188).

In mice suffering from stab wound lesion within the right neocortex, tamoxifen-inducible recombination induced in the astrocyte-specific glutamate aspartate transporter (GLAST) locus revealed that astrocytes exposed to injury may resume properties of glia present at earlier developmental stages. Four weeks after injury, the vast majority of the $reporter^+$ proliferating cells were $S100\beta^+$ and high-affinity glutamate transporter 1 $(GLT1)^+$. Although most of the proliferating astrocytes remain in vivo within their lineage, and share hallmarks with NPCs and developmental radial glia, the very same cells, in a more favorable in vitro environment, showed multipotency and capacity for self-renewal (25).

In chemically induced demyelinated lesions, genetic fate mapping approach using Cre-lox technique to label platelet-derived growth factor receptor $(PDGFR)\alpha/NG2^+$ cells showed that the reconstruction of the damaged myelin in the adult white matter was due to new remyelinating oligodendrocytes and Schwann cells mainly derived from adult OPCs (257). To establish whether OPCs differentiated into remyelinating oligodendrocytes, tissue sections from 21-day-old lesions (when remyelination is complete) were examined by using CC1 or transferrin as markers of differentiated oligodendrocytes. Abundant $CC1^+$ and $transferrin^+$ cells were evident within the outer rim of the lesion, where oligodendrocyte-mediated remyelination could be detected by histology. These results provide evidence that adult $OPCs/NG2^+$ cells have a wider differentiation potential than previously thought, exhibiting the capacity to differentiate into Schwann cells of neural crest lineage as well as all three neuroepithelial lineages (neurons, astrocytes, and oligodendrocytes).

The normally very limited proliferation capacity of spinal cord central canal ependymal cells dramatically increases after experimental injury (146). In contrast to the uninjured spinal cord, 4 days after injury genetically labeled cells migrated outside the ependymal layer. The ependymal progeny migrated towards the injury, lost its ependymal phenotype, and started expressing astrocytic markers such as the transcription factor Sox9 and the GFAP. Ten months later, the majority of the ependyma-derived progeny had contributed to the formation of the glial scar at the injury site, but a certain number of them were distributed in the intact-appearing gray and white matter bordering the lesion. Most of these latter cells were positive for the oligodendroglial transcription factor Olig2 and displayed mature oligodendrocyte morphology with myelin basic protein (MBP)-positive processes ensheathing axons (146).

IV. NEUROIMMUNE CELL INTERACTIONS

The evidence described above supports the notion that in mammals the adult CNS possesses endogenous potential for reparative (cellular) regeneration, such as axonal regrowth and cell

replacement. The latter is induced by tissue injuries and occurs via germinal layer-dependent and -independent (e.g., parenchymal progenitors) processes (142). However, in most types of CNS diseases, both neurogenesis and axonal regrowth are either insufficient or suboptimal to promote efficient tissue regeneration. This "imperfect" regeneration has been often attributed to local inflammatory events, reactive gliosis, and cell death. Yet, as hinted to above and discussed below, immune-mediated processes are actually required to eliminate dangerous substances or degenerating tissue, and to create a local milieu within the damaged tissue supporting neuroprotection, axonal regeneration, and cell renewal; however, for this immune response to be beneficial, it requires fine regulation. This dual effect of the immune system reflects the fact that while playing a pivotal role in CNS function, the immune response escapes regulation in the CNS under certain disease conditions. This view is schematically presented in FIGURE 2. According to this model, immune-mediated reactions exert a beneficial effect if well controlled but detrimental if control is lost. Thus the effects of the immune system depend of the type of injury, the time following injury, the phenotype of the cells, or the specific disease conditions (190). Understanding molecular and cellular mechanisms underlying both protective and detrimental immune mediated processes should lead to novel strategies to foster protective responses while diminishing detrimental ones. Ultimately, such fine tuning should provide a permissive milieu for an effective repair process (206).

Within the protective capabilities of the immune system, one of the striking observations is related to stem cells. It has become clear that both endogenous and transplanted NPCs engage in cross talk with immune cells to instruct reparative strategies. Before further explaining this issue, we will first describe how the protective immune system operates within the CNS. We will emphasize first that local inflammation and scar formation are both essential for survival, repair, and renewal, but that their regulation is often suboptimal (190, 212). In addition, we will discuss how these new notions affect our view of the interactions occurring between immune cells and stem cells, and their relevance for CNS repair following acute and chronic conditions.

A. A Paradigm Shift in Understanding Neural-Immune Interactions: Protective Immunity and Brain Plasticity

The concept of the CNS as an immune privileged site originates from studies showing that *1*) foreign grafts are not strongly rejected in the brain; *2*) there are no lymphatic vessels leaving the brain; *3*) under normal conditions there are no infiltrating blood immune cells detectable in the CNS (67); *4*) the interpretation of the role of the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier (1), and the constitutive neural expression of ligands which induce death of immune cells by apoptosis (43); and *5*) findings demonstrating spatial and temporal association between the appearance of various inflammatory markers and the course of neurodegenerative processes. All these lines of evidence contributed to the common belief that the CNS functions better in the absence of any immune-cell activity.

Accumulating evidence from recent studies suggests that this perception of immune privilege is overly simplistic.

First, it is now known that immune cells survey the healthy CNS (106). T lymphocytes can enter the CNS territory via the choroid plexus of the noninflamed brain and move within the CSF. It is estimated that the CSF of healthy individuals contains ~150,000 cells, of which 80% are memory T cells (67).

Second, although the CNS lacks lymphatic drainage, brain-derived antigens, which are substances (usually proteins) that are recognized by cells of the adaptive immune system,

can exit the CNS and are identified by the immune system in the periphery. There is now evidence that antigens from the CNS are processed locally by professional antigen presenting cells, such as dendritic cells (DCs), which migrate from the CSF to cervical lymph nodes (99). Under normal conditions, when host defense mechanisms are intact, no foreign antigens (such as bacterial proteins) enter the CNS. Thus the antigens that are encountered and processed by DC are predominantly peptides derived from CNS self-proteins. These CNS proteins can be recognized by CNS-specific T cells, which interact with local DCs (13). Therefore, it is not completely surprising that most of the T cells found in the CSF recognize self-antigens. While this phenomenon has been used as an explanation for how immune disease begins in a noninflamed brain (184), it has been proposed that this immune response against autologous antigens actually supports the functions of the brain, unless it gets out control, a phenomenon that was named “protective autoimmunity” (205). According to this view, immune surveillance by autoimmune T cells provides protection needed for brain maintenance and repair, brain pathologies emerge when such surveillance either loses control, leading to autoimmune disease, or exhibits insufficient activity, leading to neurodegeneration (205).

The first demonstration of protective autoimmunity originates from studies, performed 10 years ago, showing that blood mononuclear cells, including macrophages and T cells, are needed for CNS repair (185, 204). Originally, it was shown that for the blood macrophages to be effective, they must first be driven to an “alternatively” activated state (185, 207). In these initial studies, it was proposed that spontaneous recovery is often poor because recruitment of blood cells with such a phenotype is not sufficient (121), but it was not clear why this was the case. Subsequent to this finding, it was demonstrated that monocyte recruitment to the injured CNS is limited and that T cells recognizing CNS facilitate monocytes’ recruitment (212). Such T cells were found to play a crucial role in recovery from CNS insult (89, 151, 254), a phenomenon that supports the concept of “protective autoimmunity” (151, 203). Notably, the CNS-specific T cells that confer neuroprotection can potentially be the self-same T cells that can induce autoimmune disease (e.g., MS, EAE), if their response is not well regulated (105, 151). The capacity to contain CNS-specific T cells was suggested to represent an evolutionary compromise between the need for these cells to mediate repair versus the risk of developing autoimmune disease (166, 204). The activity of self-reactive T cells is tightly regulated by various mechanisms. One of these mechanisms involves $CD4^+CD25^+$ regulatory T cells, which suppress autoimmune activity by default, but can be transiently inactivated (103, 105) by a “danger signal” such as Toll-like receptor (TLR) activation (169). In this regard it is important to note, as opposed to the initial contention (198), TLRs respond not only to foreign compounds but also to endogenous molecules that can convey a message of urgency or danger. These receptors are expressed in the CNS by microglia, perivascular DCs, and NPCs (235) and can respond to endogenous molecular signals such as matrix proteins, fragmented DNA, RNA, heat-shock proteins, lipid degradation, and others.

Interestingly, CNS-recognizing T cells are not only needed for neuroprotection following acute CNS insults, but are also needed for the maintenance of the healthy CNS. This maintenance is manifested by support of cognitive ability, which is impaired in immune compromised animals (54, 123, 194, 260), the ability to cope with stress (124), the ability to maintain normal attention (35), and the ability to display normal neurogenesis in health and disease (125, 260). Moreover, under chronic neurodegenerative conditions, it was suggested (208, 262), and subsequently proven experimentally (11, 15, 42), that onset of chronic disease reflects the inability of circulating T cells to contain these threats (206). Insight into the mechanism of T-cell activity following acute injury or under chronic conditions has recently emerged from several studies, all of which suggest that T cells facilitate recruitment of monocytes that locally control the microglial response (26, 115, 212). These findings

corroborate those of others suggesting that blood monocytes are needed for CNS repair (255). It remains an open question whether T cells and monocytes are similarly activated and recruited under normal conditions, and in pathological situations (205, 206).

B. Immune Cells Are Needed to Support Adult Neurogenesis

The findings described above support the notion that the endogenous protective autoimmune response observed following injury could in fact be an extreme manifestation of the physiological supportive autoimmune activity that takes place in normal brain function (261). Consequently, the influence of immune activity on cell renewal from adult stem/progenitor cells was examined, as these processes occur constantly, but are increased following injury.

It was then discovered that immune-deficient mice that are devoid of mature T cells (SCID and nude) exhibit impaired hippocampal neurogenesis, which could be partially restored upon reconstitution of the immune system (260). Importantly, the association between adult neurogenesis and the integrity of the adaptive immune system is also reflected by performance in tests of hippocampal-dependent spatial learning [e.g., in the Morris water maze (MWM)] (54, 104). Immune-deficient mice perform poorly in a MWM task relative to genetically matched wild-type mice. As in the case of neurogenesis, this impairment in spatial learning and memory can be remedied by immune reconstitution (54, 104, 244). While these results attributed to T cells a role in maintaining neurogenesis and spatial learning abilities, they did not reveal whether T-cell specificity to CNS antigens is required for the observed effects. The question of antigenic specificity was addressed using two lines of T-cell receptor transgenic mice. Transgenic mice in which the majority of their T-cell pool is specific for an irrelevant antigen (ovalbumin) were found to have impaired hippocampal neurogenesis and spatial learning abilities, while transgenic mice in which the majority of T-cell pool is specific for the abundant CNS antigen, myelin basic protein (T_{MBP}-transgenic mice), exhibit increased hippocampal neurogenesis and are superior to their wild-type controls in their spatial learning abilities. Thus the T-cell contribution to hippocampal neurogenesis and learning/ memory ability under nonpathological conditions requires specificity to CNS-derived antigens. The mechanism by which T cells affect these properties of hippocampal plasticity seems to involve the regulation of brain-derived neurotrophic factor (BDNF) production, and cytokine milieu that are apparently connected (29, 54, 259). The production of BDNF by neurons in the dentate gyrus is correlated with neurogenesis and improved spatial learning and memory; BDNF levels are reduced in immune-deficient mice and elevated in T_{MBP}-transgenic mice (259). However, BDNF, which is known to be important for various aspects of hippocampal plasticity including neurogenesis and spatial memory (90, 116, 202), is not the only mediator of the effects of T cells on the hippocampus. Under nonpathological conditions, the supportive effects of T cells are mediated, through a remote mechanism by cytokines that control the behavior of microglia, astrocytes, and neurons (53, 54, 193, 205, 206). Interestingly, housing of rats in an enriched environment (containing opportunities for physical activity), a paradigm known to increase neurogenesis, also induces a dramatic increase in the number of activated microglia seen in the dentate gyrus (260). Importantly, many of these microglia secrete insulin-like growth factor (IGF)-I, a growth factor known to be important for neurogenesis and neuroprotection (39, 233).

C. Conditions Under Which Activated Immune Cells Are Detrimental to Adult Neurogenesis

Interestingly, and not unexpectedly, as much as the integrity of the immune system is important for maintaining adult neurogenesis under normal conditions, immune-cell activity was also shown to be a negative regulator of neurogenesis under inflammatory conditions. Several studies have demonstrated that local inflammation, mediated by proinflammatory

microglia/macrophages, could have detrimental effects on neurogenesis (65, 152, 174). A decrease of neurogenesis was, for instance, observed following intrathecal or systemic injection of the bacterial compound lipopolysacharide (LPS), a potent activator of innate immunity (83). The decreased neurogenesis was associated with robust microglial/macrophage activation in the hippocampus and was restored following treatment with anti-inflammatory drugs, thus confirming that inflammatory mediators were indeed the cause of the reduced neurogenesis (65, 152). Among inflammatory mediators, primary inflammatory cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and IL-6, seem to play a major role. IL-1β promotes the decrease of proliferating cells in the SGZ when induced by acute stress or ectopically expressed within the brain (by means of a recombinant adenoviral vector) (111, 145). Exposure to recombinant IL-6 or to TNF-α decreased in vitro neurogenesis by ~50%, and addition of neutralizing anti-IL-6 antibody was able to fully restore in vitro neurogenesis (152). Finally, IFN-γ is able to restrict NPC cell cycle progression to the G_0 phase in vitro and to impair proliferation of SVZ cells in vivo (174).

The beneficial versus detrimental contribution of immune factors to neurogenesis is substantiated by additional in vitro evidence. A series of in vitro experiments in which microglia were cocultured with adult NPCs were carried out, leading to the observation that unlike LPS-activated microglia that impair neurogenesis, microglia that encounter moderate levels of T-cell derived cytokines (such as IL-4 and IFN-γ) acquire a phenotype supportive of neurogenesis, characterized by production of IGF-I and MHC class II expression, coupled with production of low levels of TNF-α (28, 29). Furthermore, injection of such IL-4 and IFN-γ-activated microglia into the CSF of healthy animals increases the number of newly formed neurons in the hippocampus. Other experiments showed that activation of microglia by IL-4 before exposure to LPS maintains the microglia in a noninflamed state, thus suggesting a role for adaptive immunity in regulating homeostasis of local brain immune activity.

These findings also support the notion that activation of microglia by mediators of adaptive immunity (e.g., T-cell derived cytokines), leading to a classical activation (by IFN-γ) or to alternative activation (by IL-4), has distinctive consequences for neurogenesis compared with activation of microglia by mediators of the innate immune response (such as LPS). However, a high dose and prolonged exposure to T-cell derived cytokines, such as IFN-γ, can also lead to severe microglia-mediated inflammation, which can impair neurogenesis (27). Corroborating the observations that LPS or LPS-induced microglia impaired neurogenesis are observations that NPCs express TLRs, and that TLR4-deficient mice express high levels of neurogenesis (191).

Thus immune cell activity seems to have multiple effects on neurogenesis depending on the exact nature and extent of immune cell activation and consequently the phenotype that the innate immune cells acquires (141).

V. NPC TRANSPLANTS AND BRAIN REPAIR

The discovery of adult neurogenesis has fostered the development of regenerative therapies based on stem cell transplantation for acute and chronic neurodegenerative disorders. Motivated by the ambitious expectation to achieve CNS regeneration via functional neuronal replacement, those studies have already evidenced a potential benefit of NPC grafts in animal models of several neurological diseases. Nevertheless, growing evidence suggests that the effects orchestrated by transplanted NPCs, in most experimental cases, are not associated only with the generation of new neurons or glial cells (177) and that the context in which these cells are transplanted critically determines the outcome. Cell replacement is

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not the sole way for transplanted NPCs to foster regeneration; a more complex therapeutic scenario can be envisaged. The concept of therapeutic plasticity is now emerging; NPCs adapt their fate and functions to the tissue context in which they are transplanted, and within this context they may exert different therapeutic functions going from cell replacement, neurotrophic support, to immunomodulation. We will show below that the interplay between the immune and the stem cells systems represent the crucial event sustaining therapeutic plasticity because it promotes the formation within damaged tissue of atypical ectopic niches and this, in turn, sustains conditions (e.g., recapitulation of developmental programs) necessary for fostering regeneration. The concept of therapeutic plasticity will also help to explain why transplantation may promote tissue repair while endogenous NPCs do not.

A. Sources of Transplantable NPCs

The choice of the cell source for transplantation strategies is based on their intrinsic capacity to adapt their specification fate to different environmental needs. In principle, both embryonic stem cells (ES), including induced pluripotent stem cells (iPS), and adult NPCs can meet this criterion. Nevertheless, it is important to note that although adult NPCs can by definition give rise to all three neural lineages, their potential for cell replacement is very limited since they cannot be directed efficiently to most types of neuronal lineages, as these had differentiated during development from earlier NPCs. Regarding ES, we have learned that the various types of neurons are generated at different stages of development and that once the ES-derived NPCs had exited a certain time window, they are not able to generate any more of that specific type of neurons, although they remain multipotential in regard to their ability to give rise to all three neural lineages.

ES are pluripotent cells derived from the inner cell mass of blastocyst-stage embryos and possess two unique characteristics: an indefinite self-renewal capacity and pluripotency and the ability to generate all tissues of the body that are products of the epiblast lineage. ES cells remain genetically normal even after 140 cycles of division (221). Improvements regarding the ES culturing protocols to generate large-scale numbers of transplantable ES as well as ES-derived CNS-specific NPCs have been recently described. Feeder-independent growth of human ES (e.g., using protein components solely derived from recombinant sources or purified from human material) can be achieved as well as the in vitro propagation of ES cell-derived CNS-specific stem cells without accompanying differentiation. Furthermore, firm differentiation paradigms with selection protocols for avoiding in vivo teratocarcinoma formation after ES (or ES-derived cells) cell transplantation, which is thought to be the main impeding factor for ES transplantation, have been recently developed (45).

iPS are a new source of pluripotent stem cells recently obtained by genetic reprogramming of somatic cells (e.g., fibroblasts) (92, 97, 224). Since then, somatic cells of different origin can be reprogrammed into iPS cells by viral (or protein)-mediated expression of four transcription factors (Myc, Oct4, Sox2, and Klf4). iPS are relatively indistinguishable from ES as morphology, growth ability, chromatin state, gene expression profiling, and potential to differentiate into any cell type (137, 165, 239). The opportunity to derive pluripotent stem cells directly from a patient's own cells to produce autologous stem cells including NPCs is thought to be one major advantage for stem cell transplantation therapies due to the lack of any concern for the patient immune-response.

Adult NPCs are multipotent cells obtainable from embryonic, fetal, neonatal, and adult CNS tissue. In serum-free cultures with EGF and fibroblast growth factor (FGF)-II, NPCs proliferate almost indefinitely and form multicellular free-floating spheres (neurospheres), which spontaneously differentiate into CNS postmitotic daughter cells (neurons, astrocytes, oligodendrocytes) after growth factor with-drawal. Nevertheless, human NPCs have limited

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proliferation capacity over serial passaging in vitro due to decreasing telomerase activity (and telomere length). However, recent evidence indicates that NPCs grown in monolayer and in serum-free media can be propagated in homogeneous cultures and can be unlimited expanded (46).

B. Injection Routes

The route of cell administration represents a major issue for NPC transplantation and appears to be very much dependent on the location and number of CNS lesion site(s) (focal vs. multifocal). The anatomo-pathological features of focal CNS disorders [Parkinson's disease (PD), Huntington's disease (HD)] might suggest that direct local (intralesional) cell transplantation would facilitate tissue regeneration, while the multifocality of certain others CNS disorders, e.g., demyelinating disorders such as MS, would represent a major limitation for intralesional cell-transplantation approaches. Directly targeting individual lesions would restrict the approach to a handful of the most clinically articulate of lesions.

Following the first observation in experimental brain tumors (2), the systemic (e.g., intravenous, intrathecal) transplantation of NPCs can be therapeutically efficacious in multifocal CNS disorders. In EAE, systemically transplanted cells are capable to follow, once travelling into either the bloodstream or the CSF, a gradient of chemoattractants (e.g., proinflammatory cytokines and chemokines) occurring at the site of inflammatory lesions (143, 177). Tethering, rolling, and firm adhesion to inflamed endothelial cells and then transendothelial migration across the BBB into the inflamed CNS areas are sequentially mediated by the constitutive expression of functional cell adhesion molecules (CAM) (e.g., CD44) (183), integrins (e.g., α4, β1), and chemokine receptors (e.g., CCR1, CCR2, CCR5, CXCR3, CXCR4) on NPC surface (143, 177).

C. Transplantation Aiming at Cell Replacement: The Issue of Cell Differentiation and Integration

The mere ability of NPCs to adopt specific phenotypic traits does not guarantee that, once transplanted, those cells actually differentiate in the correct cell type and incorporate into the recipient tissue. Such a challenging goal requires complex developmental processes, such as directed migration and long-distance neurite growth, which, as we will see, are not easily accomplished in the adult CNS environment, either in healthy or disease-affected conditions. In addition, donor cells must be able to cope with the specific pathological conditions (e.g., excitotoxicity, inflammation, hemorrhage, degeneration) that are presented by different acute and chronic neurodegenerative diseases.

In the case of neuronal cell degeneration, the success of cell replacement depends on the complexity and precision of the pattern of connectivity that needs to be restored. In PD, a disease characterized by an extensive loss of dopamine (DA) neurons in the substantia nigra pars compacta and their terminals in the striatum (24), donor cells are transplanted directly into the target region (the striatum) to circumvent the problem of long-distance neuritic growth in the adult CNS (20, 129, 172, 228). Since the late 1980s, transplantation of human fetal ventral mesencephalic tissues into the striatum of PD patients has been adopted as therapy for patients with advanced disease. After many encouraging open-label studies of fetal cell transplantation for PD, three randomized, double-blind, placebo-controlled studies found no net benefit. In addition, patients in two of the studies developed dyskinesias that persisted despite reductions in medication (87). Interestingly, recent reports have shown that as early as 14 years after transplantation into the striatum of individuals with PD, grafted nigral neurons are found to have Lewy body-like inclusions that stained positively for α-synuclein and ubiquitin and to have reduced immunostaining for DA transporter (112, 126). These pathological changes suggest that PD is a real ongoing process that can affect grafted

cells in the striatum (host-to-graft disease transfer) in a manner similar to host DA neurons in the substantia nigra. These recent findings are going to have implications for (stem) cell-based therapies and for understanding the causes of PD.

Efficient cell replacement is even more demanding when more precise restoration of connectivity is needed; for example, in motor and sensory pathways, the function of which relies on topographically arranged projection maps. In cases in which specific cell populations are affected, such as HD, amyotrophic lateral sclerosis (ALS), or cerebellar degeneration, successful transplantation requires both selective replacement of lost phenotypes and the reestablishment of the original connection patterns with local and distant host partners. Transplantation in experimental models, such as mutant mice with Purkinje cell degeneration, has shown that fetal cerebellar cells have a remarkable capacity for specific integration into host circuits (219), and mild behavioral improvement has been observed (258). Nevertheless, significant recovery of motor function is hampered by the inability of most transplanted Purkinje cells to rewire efferent connections with host cerebellar nuclei (219). In the case of HD, in which a mutant gene causes the selective death of striatal neurons (102), functional recovery requires at least partial reconstruction of a complex cortico-striato-pallidal circuit. However, the selective cell death, and the vicinity and accessibility of host pallidal targets for donor axons originating in the striatum, together with the genetic nature and slow progression of the disease, make it a good candidate for cell transplantation.

Further requirements have to be met when cell replacement is designed to treat focal lesions that cause global neuronal degeneration, such as traumatic or vascular injuries. In these cases, transplanted cells should be able to generate multiple phenotypes in appropriate relative numbers, develop local circuits, and reestablish long-distance connections with host partners.

In the case of glial cell degeneration, grafted cells have to develop specific phenotypes to reestablish proper relationships with host elements at the single-cell level. Among these disorders, CNS diseases characterized mainly by myelin damage, such as genetic dysmyelinating and acquired inflammatory demyelinating diseases, are especially attractive targets for cell-based therapeutic strategies. These diseases are in fact caused by the loss of a single cell type (e.g., oligodendrocytes), and the complete reconstruction of the original anatomical organization is not necessarily required to obtain functional recovery (76, 77).

In genetically transmitted dysmyelinating diseases, hereditary defects lead to either a failure of myelination during development, or to premature myelin breakdown. Here, large regions are demyelinated and depleted of competent glial cells and OPCs. Since the resident local glial progenitor cell population is incapable of producing myelin in these conditions, the transplantation of gene defect-free myelin-forming cells is the only possible strategy for achieving anatomic and functional myelin restoration (82). To achieve this end, transplanted progenitors cells should be insufficient numbers, competent for broad dispersal and extensive myelination, and capable to integrate into the highly permissive, normal developmental program of the CNS. Experimentally, the transplantation of various cell types, including multipotent precursors such as OPCs, olfactory en-sheating cells (OECs), and both adult and embryonic NPCs have been performed in different animal models (such as shiverer mice, myelin-deficient rats, and the shaking pup canine myelin mutant) (17). Although all these cell types have been shown to promote remyelination, OPCs are the most efficient cells at remyelinating demyelinated axons (77). When transplanted directly into areas of CNS demyelination, OPCs are able to myelinate focal demyelinated areas in the neonatal and adult canine mutant (8), in the myelin-deficient rat (69), and in shiverer mice (241, 242). In this very last study, donor-derived (human) myelin effectively ensheathed

host shiverer axons, and confocal microscope analysis revealed the presence of nodes of Ranvier with an appropriate nodal architecture. Most importantly, the transplanted shiverer mice lived significantly longer compared with the controls, and a fraction of mice appeared to be completely rescued (241).

In acquired inflammatory demyelinating diseases, the most common of which is MS, the complex issues of cell therapy involve not only the optimal transplantable cell type, but also the manipulation of the host CNS to allow the therapeutic actions of transplanted cells. In these disorders, a close interplay between environmental factors and susceptibility genes (91, 120) triggers a cascade of events that engage the immune system, resulting in acute inflammatory injury of axons and glia, accompanied by frank demyelination (114, 119, 232). This leads to highly heterogeneous, chronic inflammatory, demyelinating multifocal CNS lesions (44, 60, 243). Given the complexity of the pathological environment, the efficacy of cell therapy in inflammatory demyelinating disorders cannot rely solely on regeneration of the myelin sheath. Transplanted cells need to target the specific sites of disease, migrate and integrate in the host tissue, and survive in the CNS environment inflicted with inflammation and/or degeneration. This adds crucial issues of timing, route of cell delivery, as well as long-term survival of grafted cells in the “inhospitable” adult CNS environment. Embryonic and adult SVZ-like NPCs are the only stem/precursor cells of the CNS capable of being consistently therapeutically efficacious in experimental models of multifocal inflammatory demyelinating diseases (5, 16, 17, 62–64, 70, 143, 173–177, 248). This is because they have been shown to be capable of reaching the injury site, modifying the inhospitable microenvironment, and triggering a cascade of events, the so-called “bystander” effect, leading to the rescuing of the regenerative potential of endogenous progenitors.

D. Transplantation Aiming at Rescuing Endogenous Regenerating Cells: The Bystander Effect and the Atypical Niche

The perspective of cell replacement (neuronal or glial) from transplanted NPCs has received at first predominant attention and thus eclipsed a variety of other benefits potentially offered by NPCs. As a matter of fact, irrespective of the characteristics of experimental disease, which include disease course (acute vs. chronic), neuropathological features (focal vs. multifocal), and the type of inflammation (primary vs. reactive), functional recovery obtained by NPC transplantation does not always correlate with absolute numbers of transplant-derived, terminally differentiated neuronal/glial cells. NPCs transplanted into rodents with experimental PD or HD very scarcely differentiate into tyrosine hydroxylase (TH)-immunoreactive neurons despite significant behavioral improvement (143). Similarly, mice with SCI show remarkable locomotor recovery, despite the pathological evidence of preferential astroglial fate of transplanted NPCs (143). On the other hand, the large majority of NPCs injected intravenously into mice with experimental cerebral hemorrhage or with acute ischemic stroke retain expression of undifferentiation markers (e.g., nestin) at the boundaries of the ischemic brain tissue (10). Also in both mouse and monkey EAE, the very low differentiation of transplanted NPCs (e.g., into oligodendrocytes) is in apparent contrast to the evidence of significant axonal protection at a neurophysiological level. More than 20% of transplanted NPCs accumulate (and survive for months) at the level of perivascular inflammatory CNS areas while retaining undifferentiated morphological and phenotypic characteristics (173, 177). Interestingly, the NPC accumulation within perivascular CNS areas induces the formation of new anatomical and functional entities, named atypical ectopic (perivascular) niches, which are functionally similar to prototypical germinal niches but differ in the cellular components and in the regional tropism. Such atypical ectopic niches are found within both the CNS (e.g., brain and spinal cord) and secondary lymphoid organs and contain transplanted NPCs, blood-borne (*encephalitogenic*) inflammatory cells,

and CNS-resident cells (e.g., inflammation-reactive astrocytes and microglia). The dynamic secretion of soluble inflammatory mediators, growth factors, and stem cell regulators by the different cells of the atypical ectopic niche, in response to environmental cues, pivotally contributes to the maintenance and long-term therapeutic efficacy of (proliferating vs. quiescent) transplanted NPCs. Although the molecular mechanisms underlying formation and survival of atypical niches have not been yet elucidated, the recapitulation of developmental programs via the secretion by immune as well as neural cells of stem cell regulators [e.g., bone morphogenetic protein (BMP) 4, Noggin] and the establishment of vascular-NPC interactions within the niche can be advocated as crucial.

The scarce and inappropriate terminal differentiation, the propensity for maintaining an undifferentiated phenotype within the host tissue, and the colocalization of transplanted NPCs with immune cells within perivascular atypical niches suggested that transplanted NPCs might be therapeutically efficacious through bystander (paracrine) mechanisms alternative to cell replacement (143) (FIG. 3).

First, transplanted cells might significantly reduce scar formation and/or increase the survival and function of endogenous glial and neuronal progenitors that have survived to the pathological insult. This neuroprotective effect is usually accompanied by increased in vivo bioavailability of main neurotrophic factors such as nerve growth factor (NGF), BDNF, ciliary neurotrophic factor (CNTF), and glial-derived neurotrophic factor (GDNF) (143). By interacting with their cognate receptors, neurotrophic factors generate survival signals in neuronal cells. In addition, these factors may also directly interfere with cell mechanisms responsible for neuronal death through the upregulation of antiapoptotic and antioxidative stress proteins (136, 252). For example, NPCs injected into the spinal cord after traumatic injury were shown to promote axon sprouting by secreting NGF, BDNF, GDNF, and neurotrophin-3 (NT-3) (133). In neurodegeneration models such as PD, NPCs appeared to efficiently decrease PD symptoms by rescuing dopaminergic neurons through production of stem cell factor (SCF) (253) or GDNF (167). Likewise, transplantation of NPCs into the lumbar spinal cord of ALS rodents was shown to postpone the disease onset, to preserve the viability of motor neurons, and to prolong animal survival (48, 246). In these studies, molecular and histological analyses of the spinal cord of grafted animals revealed a significant neuroprotection that correlated with increased levels of VEGF, IGF-I, GDNF, and BDNF. Moreover, several neurotrophins that may be released by NPCs were shown to inhibit EAE. IGF-I and glial growth factor (GGF)-2 are neurotrophic factors that promote survival and proliferation in the oligodendrocyte lineage (12, 32, 33, 144). Treatment with these factors was beneficial clinically and pathologically in animals with EAE (31, 250, 251).

Second, undifferentiated transplanted NPCs might promote bystander immune modulation, as they can release soluble molecules (such as chemokines and cytokines) and express immune-relevant receptors (such as chemokine receptors and CAMs), which are able to profoundly change inflammatory environment (143). The first indication of a novel (anti-inflammatory) effect of NPCs was obtained when neurospheres were transplanted intracerebrally in acute spinal cord homogenate (SCH)-induced EAE Lewis rats (64). These EAE rats show acute, reversible paralytic disease that is the result of disseminated CNS inflammation without demyelination or axonal injury (223). NPC transplantation in EAE Lewis rats attenuated the inflammatory brain process and clinical severity of disease (64). Follow-up studies examined the effect of NPC transplantation on either intra-cerebral or intravenous cell injection, in the myelin oligodendrocyte glycoprotein (MOG)35–55-induced EAE in C57BL/6 mice. In this model, there is an acute paralytic disease due to a T cell-mediated autoimmune process that causes severe axonal injury and demyelination. Subsequently, the mice remain with fixed neurologic sequel, the severity of which is

correlated with the extent of axonal loss (245). NPC transplantation in EAE mice attenuated the inflammatory process, rescued the endogenous pool of oligodendrocyte progenitor cells, reduced acute and chronic axonal injury and demyelination, and improved the overall clinical and neurophysiological performance of the mice (63, 175).

However, the exact mechanisms by which transplanted NPCs attenuate CNS inflammation are not yet clear. NPCs might induce apoptosis of proinflammatory (Th1), but not anti-inflammatory (Th2), T helper cells selectively, via the inflammation-driven upregulation of membrane expression of functional death receptor ligands (e.g., FasL, TRAIL, Apo3L) on NPCs (177). Alternatively, it has been suggested that NPCs inhibit T-cell activation and proliferation by a nonspecific, bystander immune suppressive action (62). This notion emerged from coculture experiments that showed a striking inhibition of the activation and proliferation of EAE-derived, as well as naive, T cells by NPCs, following stimulation by various stimuli (63, 64). The suppressive effect of NPCs on T cells was accompanied by a significant suppression of proinflammatory cytokines, such as IL-2, TNF-α, and IFN-γ (62). Moreover, NPCs inhibited multiple inflammatory signals, as exemplified by attenuation of T-cell receptor-, IL-2-, and IL6-mediated immune cell activation and/or proliferation (70). Finally, recent attention to the complement cascade's role in proliferation and regeneration has challenged the view that it is solely injurious to the CNS; instead, the complement cascade maintains a somewhat paradoxical role as it has been implicated in both injury pathogenesis and protection. In addition to promotion and participation in neuroinflammation following injury, in vitro and in vivo experiments have revealed that complement proteins influence stem cell maturation, cellular migration, synaptogenesis, growth factor induction, activation of anti-apoptotic and pro-survival signaling molecules, and neuroprotection from cytotoxic agents (197).

Whatever is the exact mechanism, this plastic behavior of transplanted NPCs has revealed the capacity of such cells to engage multiple mechanisms of action within specific inflammatory microenvironments in vivo (143). Supporting this statement is the recent evidence showing the remarkable immune modulatory capacities of transplanted NPCs not only within specific CNS areas (5, 63, 64, 173, 175, 177) but also in non-CNS areas (62, 176). NPC-mediated bystander immune regulation may, in fact, take place in the CNS at the level of the "atypical perivascular niches" (177) but also in secondary lymphoid organs, such as the lymph nodes (62, 176) or the spleen (122). In these "peripheral" immune relevant sites, NPCs display remarkable capacity to target (and synergize with) immune cells so to stably change the perivascular microenvironment. This "peripheral" NPC/T-cell interaction was first suggested when NPCs intravenously injected prior to EAE disease onset (e.g., at 8 days after the immunization) were transiently found in peripheral lymphoid organs, where they interacted with T cells to reduce their encephalitogenicity (62). In this setup of intravenous NPC injections at an early time point, transplanted cells did not cross the BBB, and their entire effect was mediated by peripheral immune suppression, resulting in reduced immune cell infiltration into the CNS and consequently milder CNS damage. To corroborate this latter finding, it was later shown that NPCs surviving in lymph nodes of EAE mice do hamper the activation of myeloid DCs, which in turn led to the steady restraint of the expansion of antigen-specific (encephalitogenic) T cells (176). Interestingly, the ultrastructural analysis of lymph nodes from NPC-injected EAE mice showed the presence of numerous large-size NPCs, which were frequently found to establish consistent anatomical contacts with lymph node cells through either polarized nanotubes, membrane-derived microvesicles, cytoplasmic expansions, or elongated intercellular junctions. Recent studies have started addressing the role of individual molecular candidates in regulating this novel immunomodulatory (or regulatory) capacity of transplanted NPCs in EAE. NPCs hinder the activation of myeloid DC via a BMP-4-dependent mechanism, which is completely reverted by the BMP antagonist Noggin (176). Concurrently, other reports have

begun to elucidate some of the paracrine factors that are responsible for mediating the immune suppressive versus prosurvival capacity of other nonhematopoietic somatic stem cell sources; these include chemokines and the inducible nitric oxide synthase (187) as well as stanniocalcin-1 (STC-1), a peptide hormone that modulates mineral metabolism (21).

VI. CONCLUSIONS: NPC THERAPEUTIC PLASTICITY

The CNS is not simply a “mass” of organized cells but a complex set of circuits, a remarkable portion of which is composed of “cables” and synaptic contacts with delicate spatial organization. This delicate organization has led to the common view that the only mechanism whereby the brain maintains its plasticity at adulthood is at the synaptic levels; no new neurons are formed, and no regrowth can occur. Research over the last few decades has dramatically changed this perception. Axonal growth does take place in the adult CNS (50), and the potential for cell renewal exists (80). The emerging question now is why such regenerative processes do not occur to an extent that allows functional restoration? The identification of a number of mechanisms modulating brain repair, ranging from protective adaptive immunity to infiltrating monocytes, glial scar, and stem-cell driven neurogenesis and gliogenesis, has led to the conclusion that the rate-limiting factors are spatial and temporal synchrony. This has stimulated a new avenue of research aimed at identifying the precise reciprocal relationships between the different operating parties. In this article, three commonly believed dogmas concerning CNS repair, NPCs are capable of tissue regeneration only via cell replacement, CNS-infiltrating immune cells are only detrimental, and glial scar formation impairs CNS regeneration, have been challenged, and particular attention has gained the functional response of NPCs (self-renewal and multipotency) to inflammation.

Experimental evidence strongly supports the contention that NPCs are capable of engaging a deterministic interaction with immune cells that are either beneficial or detrimental (29, 65, 152, 175, 177, 191, 213, 260). Taken together, these results concur to challenge the common view that the immune system is hostile to neural stem cell-mediated regeneration. As a consequence, the dogma that the adaptive immune system is hampering appropriate organ regeneration while favoring repair via scar formation is no longer globally applicable when discussing about CNS regeneration. It is suggestive, based on existing data, that NPCs should be considered, not only as standby replacing cells but also as bona fide immune relevant cells of the brain. Is this a remnant of an early developmental mechanism that regulates tissue (re)generation in the embryo, or is it a mere question related to the promiscuous and serendipitous expression of molecules playing an immune-relevant function? While, at first sight, the immune and the neural stem cell systems appear quite separate in their aims and modes of action, a thorough reevaluation of published data warrants the hypothesis that interactions between the two systems might actually have important consequences for health.

As a consequence of the immune signature, NPCs can exert immunomodulatory functions once transplanted in CNS inflammatory environment. As discussed before, cell replacement is no longer the exclusive therapeutic mode of action of transplanted NPCs. This is the second dogma we have been challenging in this review. We have shown that NPC transplantation does promote CNS repair via intrinsic neuroprotective bystander capacities, mainly exerted by undifferentiated stem cells producing, at the site of tissue damage, a milieu of neuroprotective molecules once temporally and spatially orchestrated by environmental needs. This milieu contains molecules (e.g., immunomodulatory substances, neurotrophic growth factors, and stem cell regulators), some of which are constitutively expressed by NPCs for maintaining tissue homeostasis both during development and adult life (127). The intrinsic nature (pleiotropism and redundancy) of these molecules as well as

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their "constitutive" expression may help explain the evidence that other sources of somatic stem cells (e.g., mesenchymal stem cells), endowed with negligible transdifferentiation capability, play a profitable role in CNS repair (47, 256). Thus cell plasticity can also be viewed as the capacity of somatic stem cells to adapt their fate and function(s) to specific environmental circumstances resulting from multiple pathological conditions (therapeutic plasticity).

The capacity of stem cells to release immunoregulatory substances as well as growth factors and their ability to cross-talk with immune-relevant cells has opened a new stem cell-based therapeutic scenario encompassing combination therapies resorting to both stem cells and immune relevant cells. Experiments aimed at cotransplanting different types of stem cells with other immunomodulatory cells, e.g., monocytes, mesenchymal stem cells, and T cells, have been already performed, and the overall results do indicate that stem cell therapeutic activity can be boosted by immune relevant cells capable of cross-talking with stem cells (259). The acquisition of a deeper knowledge into the molecular and cellular mechanisms sustaining the interactions between resident (e.g., microglia) versus blood-borne immune cells (T and B lymphocytes) and endogenous NPCs is a prerequisite to better investigate the challenging ability of transplanted NPCs to protect the brain from several types of injuries using different and/or articulated bystander strategies. The exact knowledge and the potential impact of articulated interactions between immune and stem cells explaining the nonconventional stem cell-mediated therapeutic mechanisms might result, in the long run, in more efficacious therapeutic alternatives. In turn, this would lead to a more instructive confrontation with still unsolved and demanding questions regarding the best way to tightly control and regulate in vivo the different/articulated, but also potentially divergent, therapeutic stem cell-mediated functions. Nevertheless, a futuristic therapeutic scenario can be envisaged in which we will have the possibility to exogenously regulate the different (conventional vs. nonconventional) somatic stem cell-mediated therapeutic effects to more productively treat, without any relevant side/toxic effects, still incurable neurological disorders.

Acknowledgments

We are grateful to Melania Cusimano and Giulia Tyzack for critically discussing the manuscript.

GRANTS This work was supported in part by Italian Multiple Sclerosis Foundation (FISM) Grants 2004/R/15 (to S. Pluchino) and 2002/R/37 (to G. Martino), National Multiple Sclerosis Society (NMSS) Partial Grants RG-4001-A1 (to S. Pluchino) and RG 3591-A-1 and RG 3762-A-1 (to G. Martino), the Italian Ministry of Health Young Investigator Award 2009 (to S. Pluchino), the European Research Council Starting Independent Researcher Grant (to S. Pluchino) and Advanced Research Award 2008 (to M. Schwartz), the BMW Italy Group (BMW 2008 MART to G. Martino), Wings for Life Grant SE-013/09 (to S. Pluchino), Banca Agricola Popolare di Ragusa (BAPR) Unrestricted Grant (to S. Pluchino), Compagnia di San Paolo Progetto NEUROTRANSPLANT 2004.2019 and 1553 IT/CV and Regione Piemonte Sanità finalizzata 2008 (to L. Bonfanti), NARSAD Distinguished Investigator Award (to M. Schwartz), the Glaucoma Research Foundation (to M. Schwartz), and The Israel Research Foundation (ISFlegacy), awarded to M. Schwartz. S. Pluchino holds a John and Lucille van Geest University Lecturership in Brain Repair at the Cambridge Centre for Brain Repair, University of Cambridge (Cambridge, UK).

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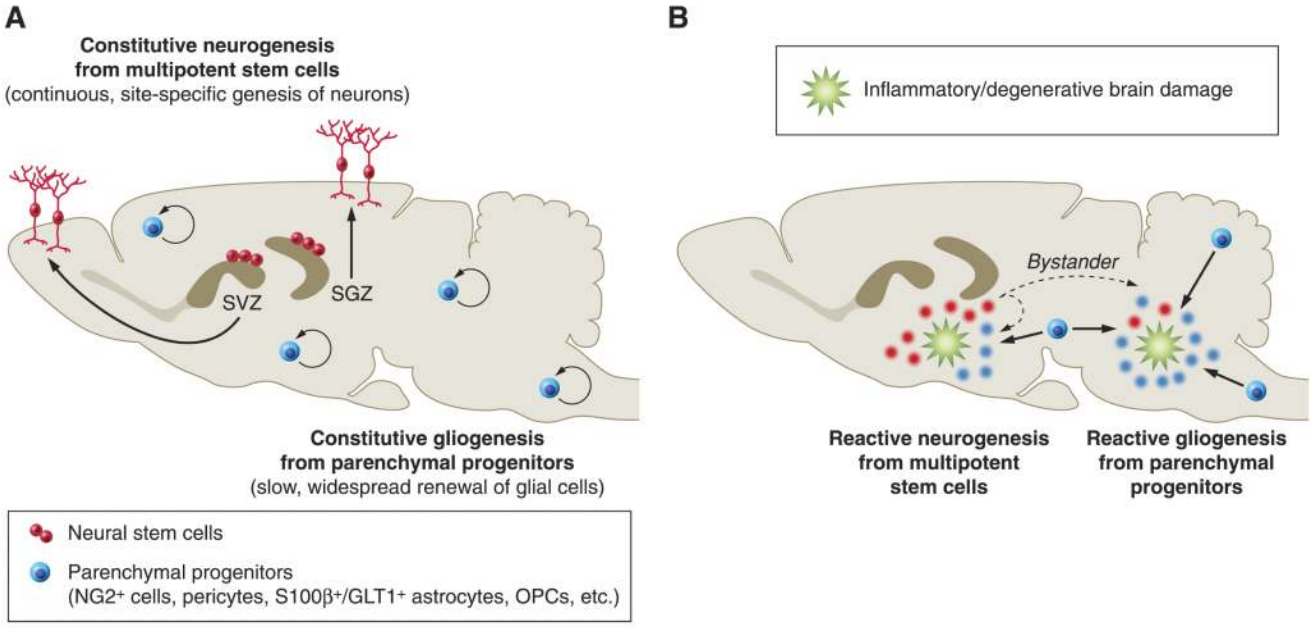

FIGURE 1.

Schematic representation of constitutive (physiological) adult neuro(glio)genesis and reactive neuro(glio)genesis occurring as a consequence of a CNS-restricted inflammatory/degenerative lesion. *A*: constitutive neurogenesis, granting continuous renewal of specific neuronal populations, is restricted to germinal layer-derived neurogenic sites (subventricular zone, SVZ; subgranular zone, SGZ). Although retaining some multipotency, local progenitors, widespread within the parenchyma, mainly contribute to the slow renewal of glial cells. *B*: as a result of a CNS-restricted lesion (e.g., inflammatory, degenerative), both NPCs within neurogenic niches and parenchymal progenitors are activated and might migrate toward damaged tissue. The final fate of both NPCs and parenchymal progenitors is very much depending of the type of CNS insults they are reactive to and the microenvironment they have to confront with. In particular, the cellular components of such pathological microenvironment - blood-borne mononuclear cells, CNS-resident activated microglia, degenerating neurons and glial cells - play a major role (see also FIG. 2). Reactive neuro(glio)genesis can be abortive (not ensuring a proper tissue healing), detrimental (promoting reactive astrogliosis), but also regenerating. If the latter is the case, newly generated undifferentiated NPCs and parenchymal progenitors (e.g., OPCs, $NG2^+$ cells, $S100\beta^+/GLT1^+$ astrocytes, pericytes) can provide tissue protection by cell replacement or by releasing trophic factor or anti-inflammatory molecules (bystander effect). Replacement of neurons mainly occurs when the damage occurs closely to neurogenic areas (e.g., middle cerebral artery occlusion stroke) while replacement of glial cells might occur in parenchymal areas close or not to neurogenic niches (e.g., OPCs in demyelinating disorders).

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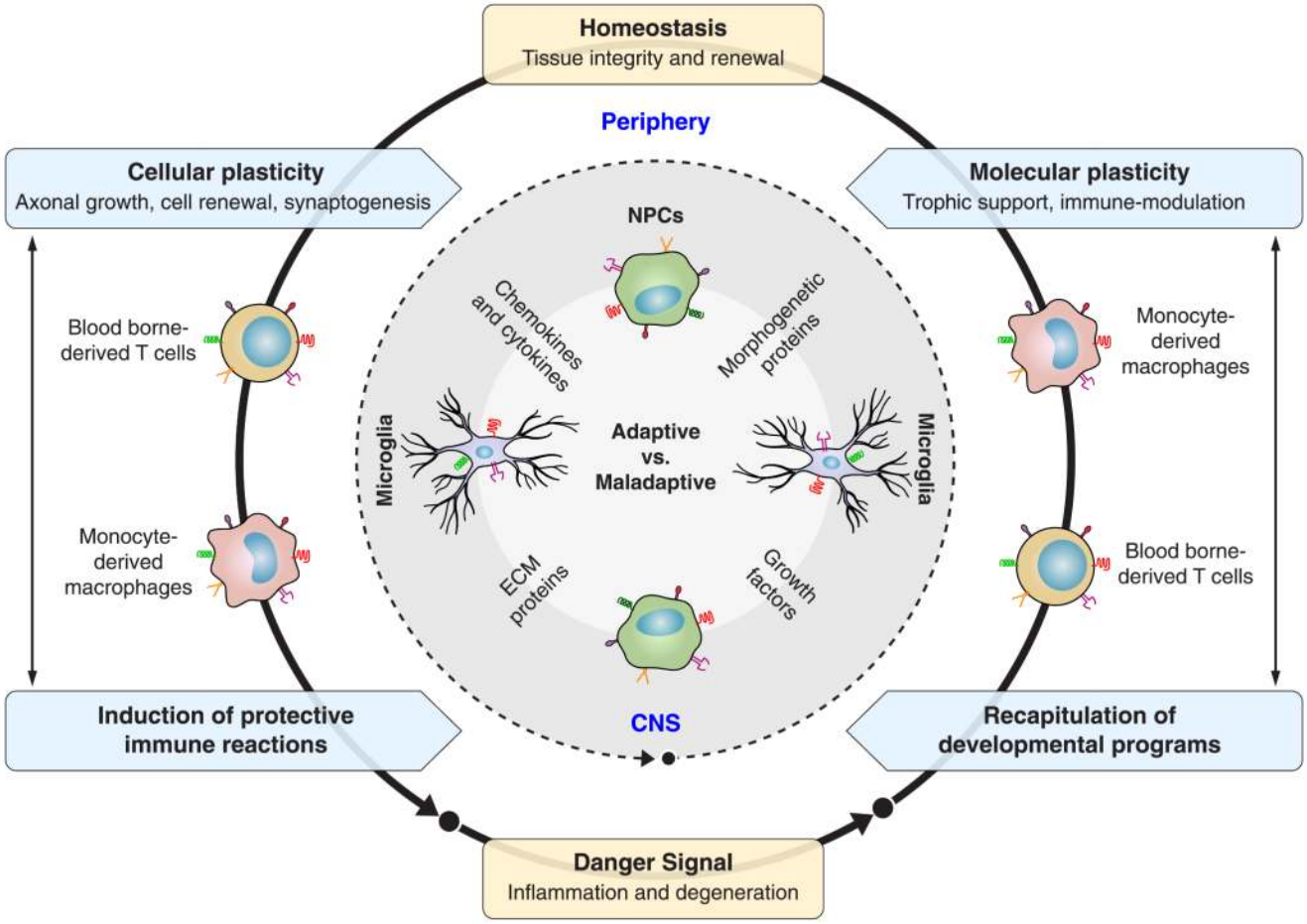

FIGURE 2.

In vitro and in vivo mechanistic evidence supporting the existence of an intrinsic (innate) self-maintenance program sustaining either CNS homeostasis during adaptive (physiological) conditions, or CNS repair during maladaptive (pathological) conditions. Several molecular and cellular events sustaining this phenomenon have been described so far. They can be divided into three distinct, although strictly interrelated, categories: immune-mediated processes (sustained by blood-borne T cells and monocyte-derived macrophages as well as CNS-resident microglia), axonal and synaptic plasticity, and neuro(glio)genesis. Depending on the context (microenvironment), humoral and cellular components supporting immune-mediated processes may shift sense (function) over time from a tissue-damaging mode to a mode-promoting tissue homeostasis (e.g., neurotrophic support from inflammatory cells). Axonal branching and synaptogenesis are plastic mechanisms maintaining tissue integrity as well as driving the recruitment of alternative "nondamaged" functioning neuronal pathways (cortical maps) as a consequence of brain damage. Whether or not (and to what extent) the recapitulation of precise developmental pathways underlies the whole phenomenon of brain plasticity is still a matter of investigation. Finally, endogenous neural stem/precursor cells (NPCs), the self-renewing and multipotent cells of the CNS capable of driving neurogenesis and gliogenesis in adult life, may promote physiological replacement of neural cells as well as adapt targeted migration into damaged areas to promote repair via several mechanisms of action encompassing neuro(glio)genesis, immunomodulation, and neuroprotection. In this complex interplay, the interaction between cells (e.g., microglia, NPCs) resident within the CNS and

those (T cells, monocyte-derived macrophages) derived from the bloodstream, but infiltrating the CNS, is crucial to sustain the adaptive (homeostatic) control of the brain during physiological condition as well as to instructing brain repair during maladaptive (pathological) conditions.

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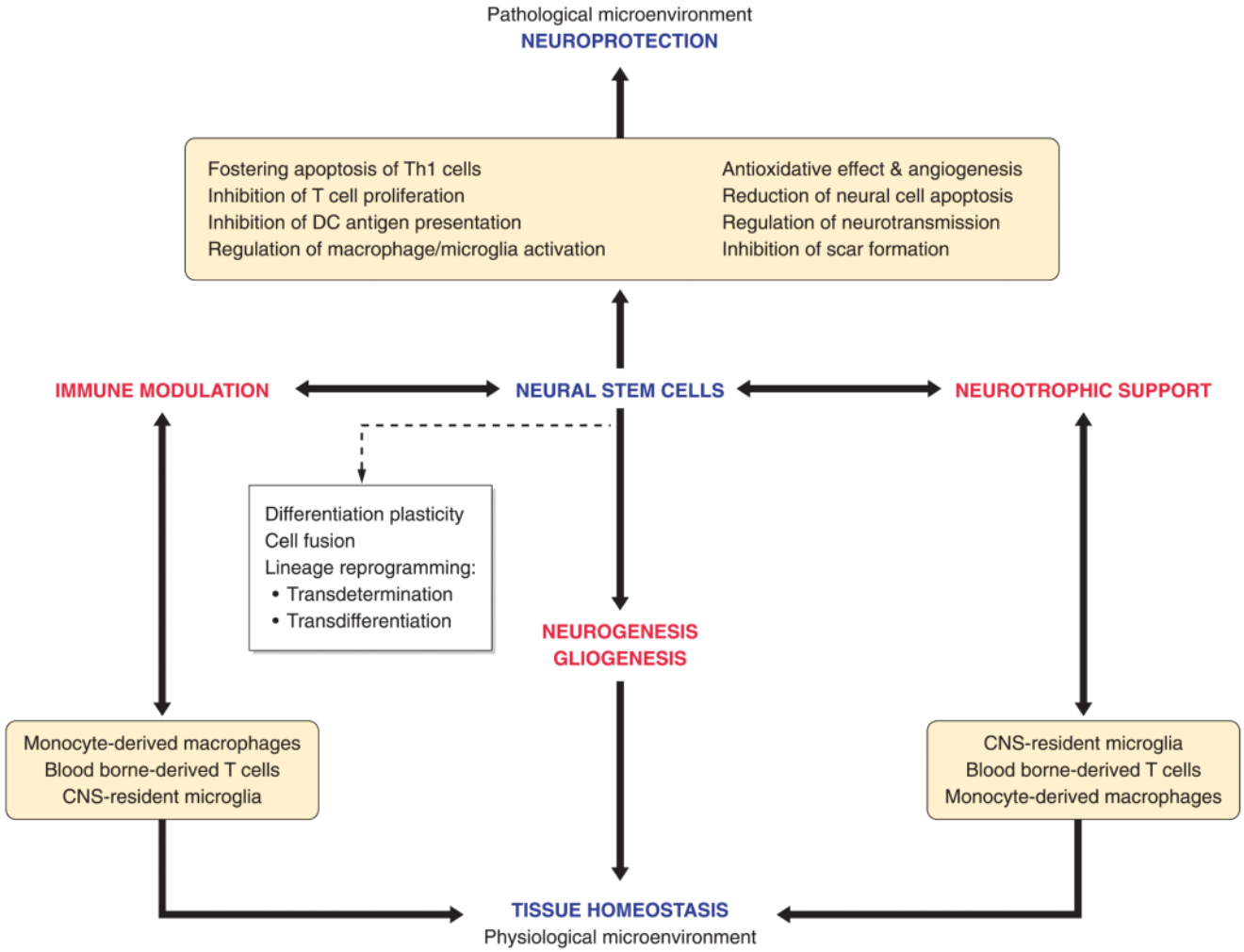

FIGURE 3.

The results so far obtained using NPCs as a therapeutic weapon for neurological disorders consistently challenge the sole and limited view that those cells therapeutically work exclusively throughout cell replacement. As a matter of fact, transplantation of NPCs may also promote CNS repair via intrinsic neuroprotective "bystander" capacities, mainly exerted by undifferentiated NPCs releasing, at the site of tissue damage, a milieu of neurotrophic (e.g., growth factors, stem cell regulators) and immunomodulatory (e.g., cytokines, chemokines, complement components) molecules whose release is temporally and spatially orchestrated by environmental needs, and the net final effect is neuroprotection. Thus the concept of stem cell therapeutic plasticity is emerging and can be viewed as the capacity of these somatic cells to adapt their fate and function(s) to specific environmental needs occurring as a result of different pathological conditions. This is just a recapitulation of the homeostatic control exerted by NPCs in normal conditions (FIG. 2). As such, the molecules sustaining the therapeutic plasticity mechanism are pleiotropic and redundant in nature and are "constitutively" secreted by stem cells; they are the very same molecules capable to perform the homeostatic control of CNS integrity by sustaining an interplay between blood-borne immune cells (T cells, monocyte-derived macrophages) surveying the brain and CNS resident neural and nonneural cells (e.g., microglia).

Table 1

Tissue damage and loss ignites several different regenerative processes depending on the species, organ, tissue, and age

Type of Regeneration	Characteristics	Subtype of Regeneration
Physiological regeneration	The natural replacement of extruded or worn out cells or body parts	
Reparative regeneration		Tissue regeneration: replacement of damaged tissues without the mediation of a blastema
		Epimorphic regeneration: replacement of complex structures through the mediation of a blastema
		Cellular regeneration:* reconstitution of a damaged cell
		Intercalary regeneration: blastema formation is followed by differentiation of cells into the appropriate types
Morphallaxis	Reconstitution of form after severe damage by remodelling the body	
Hypertrophy		Compensatory:+ increase in size of a paired organ after its pair has been lost or damaged
		Regenerative: restoration of mass of damaged internal organs

*Axonal regeneration, the regrowth of axons from spared cell bodies of injured neurons, can be categorized within “cellular regeneration” phenomena. Axonal growth is mostly abortive in the CNS but not in the peripheral nervous system.

+Collateral sprouting from spared axons is encompassed among compensatory mechanisms.

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Table 2

Factors involved in the decrease of CNS regenerative capacity through phylogeny

Point	Factor
1	Increasing tissue architectural complexity *
2	Progressive restriction of spontaneous adult neurogenesis (location of stem cell niches/progenitors) *
3	Loss of nonspecialized glial cells (radial ependymoglia) and their replacement with more specialized ones (astrocytes) *
4	Reaccess to embryonic developmental programs (reactivation of periventricular germinal layers) *
5	Occurrence of inhibitory factors for axonal growth/cell migration
6	Increase of necrosis leading to inflammation at the site of the injury, instead of elimination of debris by apoptosis and microglia/macrophages *
7	Lack of timely resolution of the local inflammatory response following clearance of dead cells and cell debris *
8	Activation of reactive/reparative processes (e.g., astrogliosis) instead of regeneration *
9	Failure of timely resolution of the glial scar *
10	Acquirement of strong immune surveillance
11	Increase of time necessary for growth of axons and cells resulting in a temporal mismatch in which the biologic factors enabling repair are active for too short time frames

* Some of these points *1–2*, *3–4*, *6–7*, *8–9* are strictly linked.