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# Regeneration and repair in multiple sclerosis: The role of cell transplantation

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ABSTRACT

Physiological (*spontaneous*) and reactive (*reparative*) regenerative processes are fundamental part of life and greatly differ among the different animals and tissues. While spontaneous regeneration naturally occurs upon cell attrition, reparative regeneration occurs as a consequence of tissue damage. Both spontaneous and reparative regeneration play an important role in maintaining the normal equilibrium of the central nervous system (CNS) as well as in promoting its repair upon injury. Cells play a critical role in reparative regeneration as regenerating structures (cells or tissues) depend on the proliferation without (de)differentiation of parenchymal cells surviving to the injury, proliferation of stem (progenitor) cells resident in the injured tissue, dedifferentiation of mature cells in the remaining tissue, or by the influx of stem cells originating outside the damaged tissue. Considering the central role of stem and progenitor cells in regeneration, a spur of experimental stem cell-based transplantation approaches for tissue (e.g. CNS) repair has been recently generated. This review will focus on the therapeutic efficacy of different sources of somatic stem cells – and in particular on those of neural origin – in promoting CNS repair in a chronic (auto)immune-mediated inflammatory disorder such as multiple sclerosis.



Since the first observation of reparative regeneration in a limb – via blastema formation in the crayfish – made in 1712 by Rene-Antoine Ferchault de Reaumur, the scientific community had to wait for Francisco Tello's work, in the early 20th century, to have preliminary evidence that also the central nervous system (CNS) has the ability to regenerate after an injury [32]. The potential value of this observation was first recognized by Ramon y Cajal who defined "*curious and significant*" the experiment carried out by Tello. '*When a piece of the distal stump of a sectioned nerve is introduced in a cerebral wound of a rabbit* – wrote Ramon y Cajal – *a regenerative capacity appears in the apathetic [axons] of the white substance. This demonstrates that the impotence of the central [axons] to restore the peripheral stump is neither fatal nor irremediable*' [29]. The seminal work of Tello has been recently rejuvenated by detailed *in vitro* and *in vivo* mechanistic evidence supporting the existence of an intrinsic (innate) self-maintenance program, '*the brain repair system*' [18], sustaining either CNS homeostasis or CNS repair via reparative (cellular or tissue) regeneration (Fig. 1).

Inflammation and degeneration are the typical reactive pathological processes occurring in the CNS upon tissue injury. They are only apparently distinct processes. Inflammation and degeneration have, in fact, the tendency to become strictly interrelated as soon as they turn into a chronic phase. As such, primary neurodegeneration triggers secondary inflammatory reaction(s), while primary inflammatory reactions lead to neurodegenerative phenomena. Several molecular and cellular events sustaining intrinsic brain repair mechanisms (*reparative regeneration*) occurring within the CNS as a consequence of chronic inflammatory and/or degenerative processes have been described so far. They can be divided into three distinct – although strictly interrelated – categories: inflammation-driven processes, CNS plasticity and neuro(glio)genesis (see for review [18]). By one hand, humoral and cellular inflammatory components shift sense (*function*) over time from a tissue-damaging mode to a mode promoting tissue repair (e.g. neurotrophic support from inflammatory cells) (see for review [19]). By the other hand, the recruitment of alternative "non-damaged" functioning neuronal pathways (cortical maps) – occurring mainly via axonal branching and synaptogenesis – takes place 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 matter of investigation. Finally, endogenous neural stem/precursor cells (NPCs) – the self-renewing and multipotent cells of the CNS – may adapt targeted migration into damaged areas and promote repair via several mechanisms of action (e.g. neuro and gliogenesis, immunomodulation, neuroprotection) [21]. It is still a matter of investigation whether (or not) equally robust brain repair/protection can occur following the recruitment within the CNS of trans-differentiating stem cells of a different embryonic origin (e.g. developmental plasticity vs. cell fusion).

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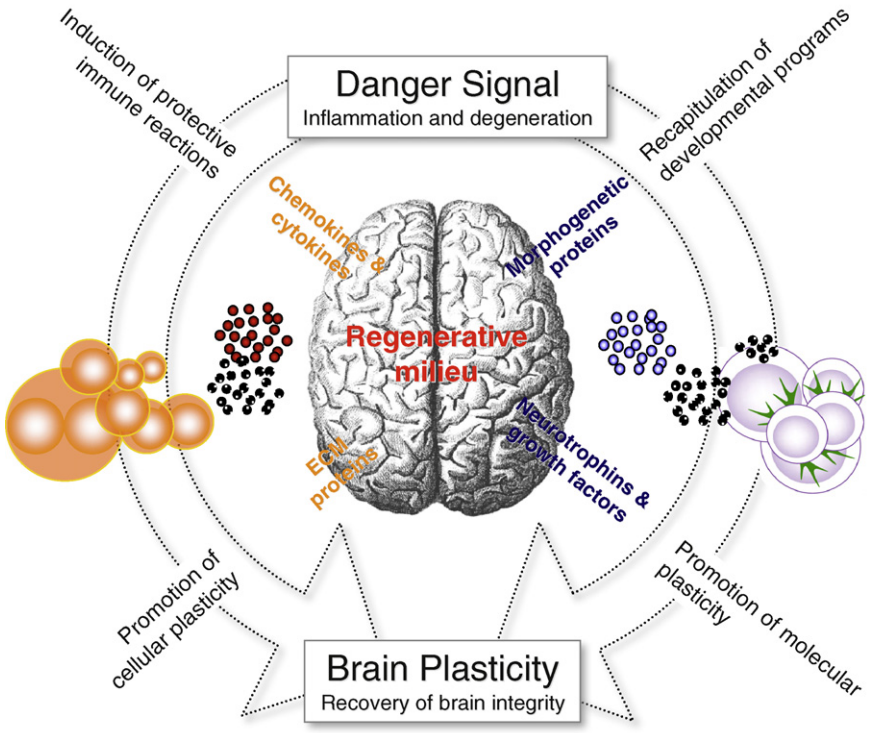


**Fig. 1.** The brain repair system. Inflammation and degeneration trigger molecular and cellular events sustaining intrinsic brain repair mechanisms which act via the stimulation of inflammation-driven processes and the recruitment of alternative "non-damaged" functioning neuronal pathways. These processes – which are modulated by a milieu of 'regenerative' molecules secreted by both inflammatory and neural cells – stimulate molecular and cellular mechanisms promoting 'activation' of endogenous stem/precursor elements with homeostatic and repairing capabilities (adapted from Ref. [18]).

The dissection of the molecular and cellular events sustaining reactive brain repair might provide an attractive conceptual framework to foresee more efficacious therapies for neurological diseases. Indeed, fostering and/or resetting 'spontaneous' regenerative process may lead to 'natural' therapies characterized by more efficacy and less toxicity. Being stem cells an integral part of the underlying mechanisms orchestrating the brain repair processes, we will focus this review on the role of stem cell transplantation in multiple sclerosis (MS), an inflammatory (auto)immune-mediated disease of the CNS characterized by multifocal demyelination leading to irreversible axonal loss and degeneration [20]. Particular emphasis will be put on the use of NPCs, though also other sources of somatic stem cells will be discussed.

While neurodegeneration occurring in MS is predominantly viewed as the consequence of an uncontrolled – and still undiscovered – pathogenic alien, there is also accumulating evidence suggesting that the failure of the *brain repair system* may be considered as one of the contributing factors leading to irreversible neurodegeneration. As a matter of fact, spontaneous remyelination occurs in MS lesions but its extent is often incomplete, limited, and variable among cases [6,17]. In a correlative radiological–pathological study in post-mortem human MS brains, remyelinated areas were found in 42% of the lesions studied; partial remyelination was observed in 19% of the lesions, while 23% of the lesions were completely remyelinated 'shadow' plaques [3]. In a more recent study performed on 51 autopsies of MS patients with different clinical courses and disease durations, the extent of remyelination was variable between cases. In 20% of patients – both relapsing and progressive patients – the extent of remyelination was extensive with 60–96% of the global lesion area remyelinated [23]. Although it is still unknown which is the ultimate reason why spontaneous remyelination fails over time in MS, the most likely causes can be summarized as follows (see for review [6]): (i) quantitative reduction of oligodendrocyte precursors (OPCs) as well as scarce ability of these cells to differentiate into myelinating oligodendrocytes; (ii) failure of OPCs to 'respond' to demyelination; (iii) selective depletion of myelinating cells around demyelinating areas over years; (iv) inhibition of remyelination as result of a "critical" balance between pro-inflammatory and pro-remyelinating effects of cytokines; (v) limitation of endogenous OPCs migration to sites of injury by reactive astrocytic scar formation; and (vi) acute and/or chronic loss of axons.

The intrinsic complex nature of MS – in particular its chronicity and multifocality – poses great challenges for cell-based remyelinating therapies. Two major requirements have to be satisfied: (i) an unlimited source of cells; and (ii) the possibility to access several CNS damaged areas at the same time.

Since early seventies, several experimental transplantation approaches aimed at restoring the myelin architecture within CNS demyelinated areas have been developed. Different types of myelin-forming cells have been variably transplanted into rodent models of either genetic, chemical or autoimmune CNS demyelination. These approaches show serious limitations. In particular, lineage-restricted myelin-forming cells – either OPCs, Schwann's Cells or Olfactory Ensheathing Cells – posses limited growth and expansion characteristics *in vitro* and drive remyelination only within restricted CNS areas close to the transplantation site *in vivo* [7].

The functional and morphological properties of stem cells – of either embryonic or adult origin – might overcome such limitation so to represent a promising alternative for transplantation approaches in MS (Fig. 2) [21]. The therapeutic use of embryonic stem (ES) cells is still constrained by some key issues – such as feeder-independent growth (expansion) and *in vivo* teratocarcinoma formation – which need to be solved before proposing any ES cell-based therapy for human applications. On the other hand, adult (or somatic) stem cells might represent a ready-to-use

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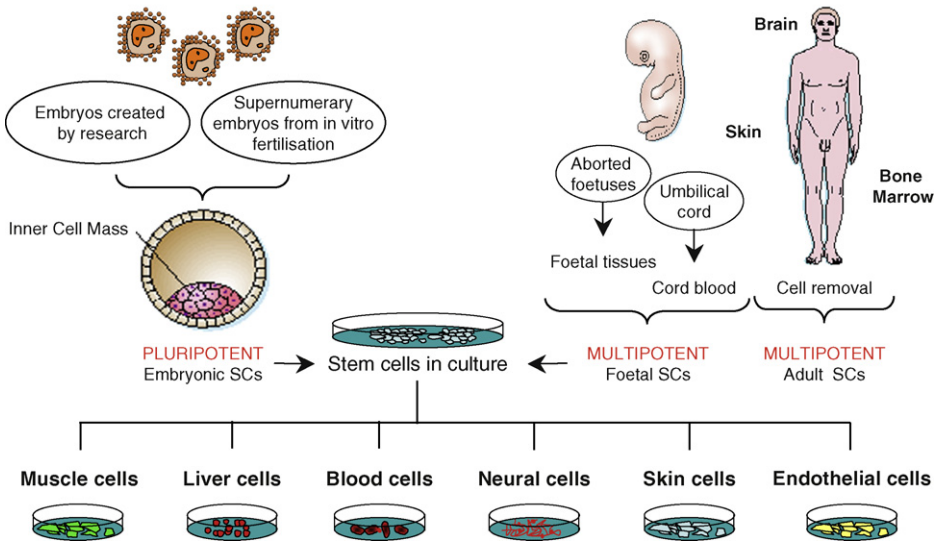


**Fig. 2.** Sources of stem cells (SCs) for therapeutic use. Pluripotent (namely embryonic) stem cells (SC) can be obtained from early stage embryos while somatic (or adult) stem cells – which are multipotent in nature and already partially committed into a certain types of cell lineages – can be virtually obtained from all tissue belonging to embryos, foetuses and adults. The therapeutic use of embryonic SC cells is limited by the unlimited growth, the tumorigenic potential, and the undetermined differentiation. The therapeutic use of somatic (or adult) SCs is restricted by the limited growth potential.

cell source for cell-based therapies, since they can be obtained by different tissues (e.g. bone marrow, brain, etc.) and have been widely used in experimental and clinical settings *in vivo* without causing tumour formation and overt toxic/side effects [21].

The route of cell administration represents a major constrain for stem cell transplantation and appears to be very much depending on the CNS lesion site(s) (focal vs. multifocal).

The anatomo-pathological features of focal CNS disorders, such as Parkinson's disease (PD) or acute spinal cord injury (SCI) (but also stroke, and brain trauma) might suggest that direct local (*intralesional*) cell transplantation might facilitate tissue regeneration, while the multifocality of certain CNS disorders – such as MS and epilepsy – would represent a major limitation for *intralesional* cell-transplantation approaches. In multifocal CNS disorders, systemic (e.g. intravenous, intrathecal) transplantation of stem cells can be therapeutically efficacious owing to the ability of transplanted cells to follow, via the blood stream or cerebrospinal fluid circulation, a gradient of chemoattractants (e.g. pro-inflammatory cytokines and chemokines) occurring at the site of inflammatory lesions [21,26,27].

Specific homing of transplanted NPCs – as well as of hematopoietic (HSCs) and mesenchymal stem cells (MSCs) – into CNS damged areas can be achieved as it has been shown in the experimental model of MS [namely experimental autoimmune encephalomyelitis (EAE)] [10,21,26,35], SCI [1,11], epilepsy, and stroke [25]. The constitutive expression of functional cell adhesion molecules (CAM) and chemokine receptors [21,26] – which represent part of a common immune signature (Fig. 3) – is the supposed mechanism underlying the capacity of stem cells to tether, roll, and firmly adhere to inflamed endothelial (and leptomeningeal) cells and to migrate into inflamed CNS areas.

In the adult CNS, proliferating neural cells represent an heterogeneous population of mitotically active, self-renewing and multipotent cells showing complex patterns of gene expression that vary in space and time [12]. The categorization of NPCs is used as a generic term encompassing both stem and progenitor cells and includes '*bona fide*' CNS stem cells, (intermediate stage) multipotent neural progenitors and lineage-oriented neural precursors. CNS stem cells display cardinal features such as (virtually) unlimited capacity for self-renewal and ability to proliferate in response to mitogens, and multipotency for the different neuroectodermal lineages of the CNS (e.g. astrocytes, oligodendrocytes and neurons). Multipotent progenitors are proliferative cells with only limited self-renewal that can differentiate into at least two different cell lineages [34], while lineage-oriented precursors are cells with restriction to one distinct neural lineage.

Although NPCs have been successfully transplanted in several pre-clinical models of neurological disorders (e.g. disease course [acute vs. chronic], neuropathological features [focal vs. multifocal] and type of inflammation [primary vs. reactive], functional recovery obtained upon NPC transplantation scarcely correlates with absolute numbers of transplant-derived newly generated terminally differentiated neuronal cells (see for review [21]). Irrespective from the characteristics of the experimental disease model, NPCs transplanted in rodents with experimental PD or Huntington's disease (HD), very scarcely differentiate into tyrosine hydroxylase (TH)-immunoreactive neurons despite significant behavioural improvement. Similarly, mice with SCI, acute stroke and intracerebral hemorrage do improve despite pathological evidence of preferential astroglial fate of transplanted NPCs. The large majority of NPCs injected into mice with experimental cerebral hemorrage or with acute ischemic stroke, express markers of undifferentiation, such as nestin, when surrounding damaged CNS areas. In EAE, very low differentiation of transplanted NPCs into myelin forming oligodendrocytes is accompanied by neurophysiological evidence of axonal protection and remyelination.

This scarce and inappropriate terminal differentiation and the propensity of maintaining an undifferentiated phenotype within the host tissue, suggest that transplanted NPCs might be therapeutic efficacious via a bystander mechanism(s) alternative to cell replacement. On one hand, transplanted NPCs might reduce the scar formation and/or increase survival and function(s) of endogenous glial and neuronal progenitors surviving to the pathological insult. This neuroprotective effect is accompanied by increased *in vivo* bioavailability of major neurotrophins (e.g. nerve growth factor [NGF], brain-derived growth factor [BDNF], ciliary neurotrophic growth factor [CNTF], glial-derived neurotrophic growth factor [GDNF]). On the other hand, transplanted NPCs promote bystander immunomodulation – via the release of soluble immunomodulatory molecules (e.g. cytokines and chemokines), and the expression of immune-relevant receptors (e.g. chemokine receptors, CAMs) – so to profoundly down-regulate effector functions of inflammatory

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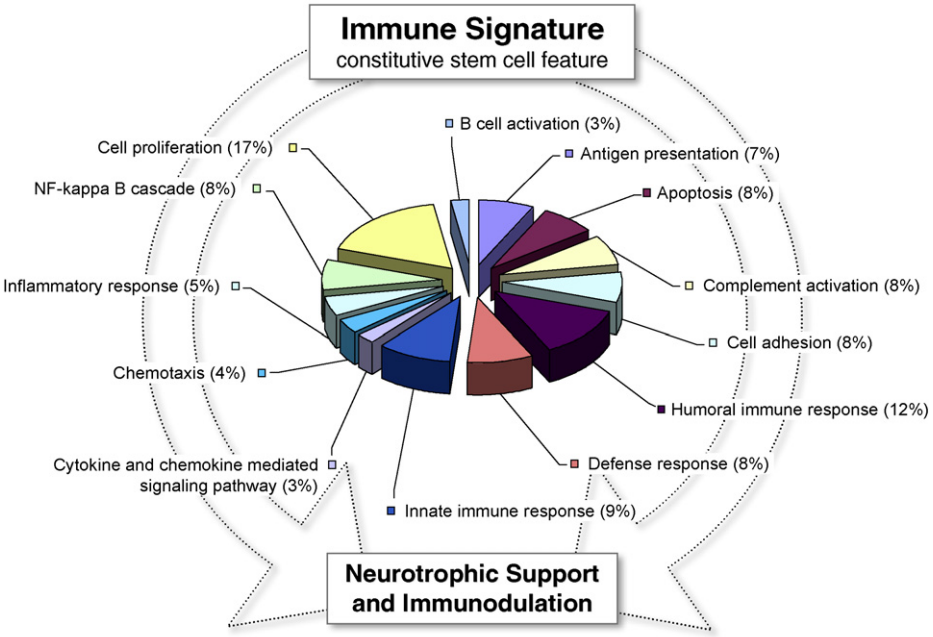


**Fig. 3.** The immune signature of human foetal neural stem cells. Using a HGU133A Affymetrix® chip (GO:0006955) a 22.215-probe set has been screened. Among these probe sets, 637 were referring to the immune response genes. Out of 637 immune response genes, 117 (18.3%) were found expressed by NPCs (obtained from the diencephalon and telencephalon of a 10.5 weeks post-conception human foetus). In the figure the percentage of the different categories of immune genes expressed by human NPCs is represented.

T cells and macrophages (Fig. 3) [27]. It is interesting to note that recent evidence show that transplanted NPCs might also exert immunomodulatory functions within peripheral lymphoid organs [5].

The adult bone marrow contains a non-haematopoietic cell lineage, which is by default capable of differentiating into osteoblasts, adipocytes, and chondrocytes. Due to their preferential capacity of differentiating into cells of the mesodermal lineage, these cells are currently defined as "mesenchymal" stem cells (MSCs). MSCs constitute the stromal scaffold providing the appropriate microenvironment for maturation and differentiation of blood-derived progenitor cells possibly by means of the release of survival factors [9]. In addition to the marrow, MSCs also reside in other tissues, such as the adipose tissue (adipose derived stem cells; ADSC) and the muscle (muscle derived stem cells; MDSC). The MSC niche is not completely characterized, though it would be very likely that – whatever the tissue – MSC-like cells lie in intimate contact with blood vessels. A number of tissue-specific cells, such as the pericytes, are found in close association with MSCs at the level of the MSC niche. MCS transplantation have been recently proposed as an alternative cell-based therapy for several diseases including neurological disorders such as MS. However, the mechanism(s) sustaining the therapeutic effect of such cells is still under scrutiny. (i) MSCs can be used as tolerogenic cells – as it has been shown in humans suffering from malignancies undergoing HSC transplantation [16] – possibly because they can affect dendritic cell maturation and, in turn, generate tolerogenic antigen presenting cells (APCs) [33]. (ii) MSCs can be used as bystander regulator of the immune response since they intrinsically synthesize and secrete very large amounts bioactive factors (the so-called "*trophic activity*") that inhibit scarring and apoptosis, and stimulate angiogenesis and mitosis of tissue intrinsic stem or progenitor cells *in vitro* and *in vivo* [4]. As a consequence of the trophic signature, MSCs arrest cell division (by inhibition of T cell proliferation), induce T cell anergy [33], induce $CD4^+$ T cell subsets with a regulatory phenotype, affect B lymphocyte proliferation and maturation to antibody secreting cells [33], and migrate to inflammatory areas using both cell adhesion molecules and receptors for inflammatory chemokines (e.g. CXCR4) [33]. (iii) MSCs can contribute to cell replacement in an injured CNS since in principle they can (trans)differentiate into cells of the neuroectodermal lineage [14,24]. Cells with biochemical, anatomical, and electrophysiological characteristics of neuronal cells can be obtained *in vitro* from MSCs [9]. Upon intravenous injection, MSCs engraft into different tissues – including the brain – where they escape immune surveillance and differentiate into cells expressing some microglial and astroglial markers [33].

Despite MSCs can exert multifaceted therapeutic effects, data accumulated so far support the concept that transplantation of such cells protect the CNS from autoimmune demyelination via a mechanism alternative to cell replacement and/or cell transdifferentiation [33]. The observed therapeutic effect is though to be mainly due to the intrinsic capacities of such cells to (i) secreting a large number of cytokines and chemokines (*trophic activity*), the pattern of secretion changing as early as transplanted MSCs encounter new (micro)environment *in vivo* (e.g. within the CNS); (ii) suppressing inflammation, both by cell-to-cell contact as well as through the release of anti-inflammatory molecules (e.g. soluble IL-1R antagonists inhibiting the production of TNFα by activated macrophages); and (iii) enhancing the proliferation, migration and differentiation of endogenous stem/progenitor cells [28].

HSCs retain the ability throughout adult life to self-renew and differentiate into cells of all blood lineages. The transplantation of HSCs – obtained from autologous or allogeneic bone marrow, umbilical chord or peripheral blood – is a widely utilized therapy for patients with haematopoietic malignancies and solid tumours. In addition, autologous HSC transplantation has been also successfully utilized to target the autoimmune response in several autoimmune diseases including MS [8,30]. In the latter case, the efficacy of HSC transplantation (following intense chemotherapy) is likely to be based on the intense immune suppression which ends up in the eradication of most autoimmune cells followed by the successful engraftment of the transplanted stem cells which, in turn, reconstitute the immune system and promote self-tolerance [33]. We cannot exclude additional benefits of such therapy since it has

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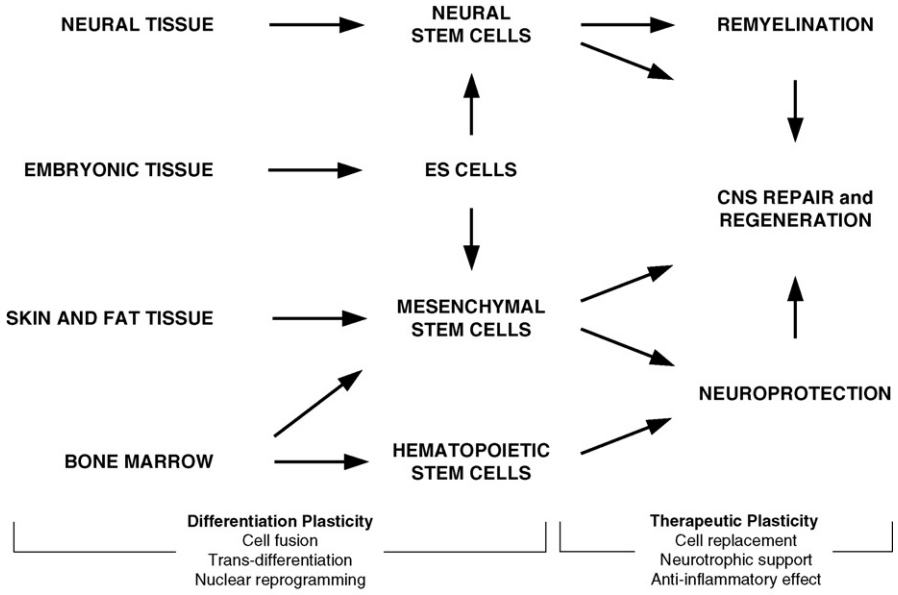


**Fig. 4.** Therapeutic plasticity of stem cells. Stem cell transplantation may promote CNS repair and regeneration via different modes of action (the concept of *therapeutic plasticity*) mainly encompassing cell replacement and bystander activity (neurotrophic support and immunomodulation). This therapeutic behaviour – which is plastic in its essence – is environmental-dictated and represents a common *stem cell signature* (NPCs, MSCs, HSCs). Although differentiation plasticity cannot be a priori excluded, the bystander therapeutic activity of stem cells might also reconcile data showing that somatic stem cells (e.g. HSCs, MSCs), with very low capabilities of neural (trans) differentiation, may efficiently promote CNS repair.

been recently demonstrated that thymic output generates a new and diverse T cell receptor (TCR) repertoire after autologous HSC transplantation in MS patients [22].

Apart from the effect(s) on the immune system, there are data showing that transplanted HSCs may also have the capacity to differentiate into other specific cell types (e.g. muscle, skin, liver, lung) including neural cells both in rodents and humans [25]. HSCs, peripherally injected in humans affected by haematological malignancies enter the brain and produce new neural cells (e.g. neurons, microglia), as demonstrated by detection of Y-chromosome-positive Purkinje cells in the cerebellum of female patients who have undergone bone marrow transplantation from male donors [15,31]. Other results indicate that, in rats suffering from a demyelinated lesion of the spinal cord, intravenous or intraparenchimal HSC transplantation results in varying degrees of remyelination which appears proportional to the number of injected cells [1,2,11].

Although HSCs may theoretically contribute to generate new neurons as well as myelin-forming cells in the adult brain by means of (i) trans-differentiation (direct conversion of transplanted cells into neurons), or (ii) cell fusion (assimilation of transplanted cells or their progeny into existing neural cells and formation of heterokaryons), the efficacy of HSC transplantation for CNS-confined autoimmune diseases is still considered to be mainly due to the immunomodulatory capacities of such cells to depleting autoaggressive (circulating) cells. However, we cannot exclude that an HSC-mediated mechanism alternative to peripheral immunomodulation might occur upon transplantation as it has recently shown that mature cells of the lymphoid lineage may not only secrete growth factors [13,36] but also dedifferentiate (nuclear reprogramming) *in vivo* back to early uncommitted progenitors in the bone marrow [35].

All together the results so far obtained using stem cells as a therapeutic weapon for neurological disorders consistently challenge the sole and limited view that stem cells therapeutically work exclusively throughout cell replacement. As a matter of fact, transplantation of different sources of stem cells (e.g. NPCs, HSCs, MSCs) may also promote CNS repair via intrinsic *neuroprotective* bystander capacities, mainly exerted by undifferentiated stem cells releasing, at the site of tissue damage, a milieu of *neuroprotective* and *immunomodulatory* molecules whose release is temporally and spatially orchestrated by environmental needs. Since these molecules, acting in a paracrine fashion, are *pleiotropic and redundant in nature* and '*constitutively*' secreted by stem cells – thus representing a sort of *stem cell signature* – we can easily explain data showing that several different sources of somatic stem cells (e.g. HSCs, MSCs), other than NPCs, with very low capabilities of neural (trans) differentiation may efficiently promote CNS repair. Thus, stem cell *therapeutic plasticity* (Fig. 4) can be viewed as the capacity of somatic these cells to adapt their fate and function(s) to specific environmental needs occurring as a result of different pathological conditions.

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