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Therapeutic stem cell plasticity orchestrates tissue plasticity

In ischaemic stroke, recanalizing and neuroprotective therapeutic strategies have failed, so far, adequately to prevent or reverse tissue damage. The sudden and unpredictable onset (Roger *et al*., 2011) and the local tissue complexity (Lo, 2008) are the main limiting factors. Nevertheless, tissue damage and loss of function can—for a definite period after stroke—be constrained by a 'plastic' reaction that the brain is capable of setting in place, which acts to reconstruct neuronal circuits.

The fundamental premise of the idea of brain plasticity in stroke was inferred by Paul Broca (1824–80) in 1865. While studying autoptic cases of aphasic patients, he hypothesized that a lost cortical function (namely speech) can be sustained by another brain area, even localized in the contralateral hemisphere (Broca, 1865). Since then, many scientists have investigated, at both macroscopic and microscopic levels, the mechanisms underlying CNS remodelling after injury and, nowadays, there is no uncertainty that the nervous tissue is endowed with a very considerable degree of plasticity (Payne and Lomber, 2001). The rapid and massive structural changes occurring at synaptic (e.g. strength of connectivity, synaptogenesis), dendritic and axonal levels (e.g. sprouting, branching), during both physiological and pathological conditions, are the most striking examples of this phenomenon.

In recent years, the possibility that the nervous system can also achieve change in structures that alter networks of functional connectivity (Paillard, 1976) has been reinforced by the discovery of another adaptive mechanism termed neurogenesis (Altman and Das, 1965). The adult CNS naturally replaces extruded or worn out cells through generation of new elements of neuronal and glial lineages from neural stem and progenitor cells. The discovery of adult neuro(glio)genesis has fostered the development of therapies based on neural progenitor cell transplantation for acute and chronic neurodegenerative disorders, including stroke (Lindvall and Kokaia, 2010). However, it is still not clear to what extent transplantation of these cells impacts on nervous system endowed plasticity following ischaemic damage (Zhang and Chopp, 2009).

In this issue of *Brain*, Andres and colleagues (page 1777) show that perilesional transplantation of human neural progenitor cells significantly improves functional outcome in experimental cortical stroke in rats. Although the efficacy of this type of transplantation in stroke has previously been reported (Kelly *et al*., 2004), the authors make the intriguing observation that transplanted human neural progenitor cells that survive for at least 5 weeks in the perilesional milieu are capable of reducing white matter atrophy, but not the overall lesion volume. Moreover, dendritic arborizations of layer V pyramidal neurons increase in both hemispheres, but only persist over time (at 4 weeks after treatment) ipsilesionally in human neural progenitor cell-treated mice. Contralateral corticocortical, corticostriatal and corticospinal axonal projections are also increased in transplanted rodents. The next step in the investigation was to show whether or not functional recovery is due to the direct influence of human neural progenitor cells on the processes of plasticity. Using *in vitro* co-cultures of human neural progenitor cells and cortical neurons, the authors observed an increase in neuronal sprouting, dendritic branching and axonal length. These findings are attributed to the secretion by human neural progenitor cells of guidance molecules (i.e. slit, thrombospondin 1 and 2) and vascular endothelial growth factor α.

The ability of transplanted neural progenitor cells to protect the CNS from diverse injuries using multifaceted 'bystander' effects—the concept of therapeutic plasticity (Martino and Pluchino, 2006)—has already been substantiated in several experimental neurological diseases, including stroke (Bacigaluppi *et al*., 2009). Neural progenitor cells may adapt their fate and functionality to the tissue context in which they are transplanted and, within this context, exert different therapeutic neuroprotective effects (e.g. cell replacement, neurotrophic support, immunomodulation, angiogenesis: Ourednik *et al*., 2002; Einstein *et al*., 2003; Pluchino *et al*., 2003, 2005; Hayase *et al*., 2009). However, the demonstration by Andres and colleagues that human neural progenitor cell transplantation may promote the formation of new local circuits is of particular interest owing to the fact that such an effect can mainly be attributed to undifferentiated human neural progenitor cells releasing neurotrophic growth factors and stem cell regulators at the site of tissue damage. Although the holy grail of replacing endogenous damaged neurons with transplanted functional cells has not been achieved here, the possibility that human neural progenitor cells foster plastic abilities endowed in the CNS using molecules constitutively expressed during development and adulthood is noteworthy.

While a further level of complexity regarding neural progenitor cells-based therapies in stroke is emerging, whether or not these

cells are capable of changing the electrical and/or molecular micro-environment, directly or via local production of soluble molecules (in one or both hemispheres), remains to be investigated. The interhemispheric electrical cross-talk is known to be important in stroke recovery, as suggested by previous studies showing spontaneous re-mapping in the ipsi- and contralesional hemispheres (Nudo, 2006). Endogenous post-stroke plasticity has variably been shown to be constrained by the upregulation over time of growth inhibiting genes that limit the initial pro-plasticity period sustained by the growth promoting genes (critical period) (Carmichael *et al*., 2005; Murphy and Corbett, 2009; Southwell *et al*., 2010; Reitmeir *et al*., 2011).

The bystander effect, which was initially shown as a peculiar feature of transplanted neural progenitor cells (Martino and Pluchino, 2006), has recently been advocated to explain the therapeutic effect in CNS disorders exerted by other stem cells, such as mesenchymal stem cells, displaying very low capabilities of neural (trans) differentiation (Li *et al*., 2002; Prockop, 2007; Uccelli *et al*., 2008). Although mechanistic evidence sustaining the bystander effect of mesenchymal stem cells in stroke has not entirely been dissected, it still represents the theoretical background on which Honmou and colleagues planned the phase I safety trial reported on page 1790. A single intravenous infusion of autologous mesenchymal stem cells ($0.6–1.6 \times 10^8$ cells per patient) was delivered to 12 patients (41–73 years old) during the subacute or chronic phase of stroke (from 36–133 days after the acute event). Neurological and neuroradiological analyses, carried out for 1 year after cell infusion, did not show any side and/or toxic effect and revealed some hints of efficacy. Neurological improvement, measured with the National Institutes of Health Stroke Scale, was observed in 4 (33%) out of 12 patients within the first 7 days after mesenchymal stem cell infusion and was maintained for 1 year. In seven patients, there was a 15% reduction in lesion volume at 7 days after cell infusion. Finally, mesenchymal stem cell efficacy was shown to correlate inversely with the time interval between stroke and cell infusion: patients receiving transplantation soon after stroke (24–38 days) had an increased neurological improvement compared with patients receiving cells in the subacute/chronic phase (42–92 days).

Even though the study by Honmou *et al*. was designed mainly for safety, and the number of stroke patients treated with mesenchymal stem cells was very limited, it is tempting to speculate on some of the preliminary efficacy results. In particular, the time window used for transplanting mesenchymal stem cells is of interest: cells transplanted into patients soon after stroke showed a more favourable outcome. An early time window for neural progenitor cell transplantation was also used by Andres *et al*. to promote recovery from stroke in rats. Together, these results can, at least partially, be explained by recent evidence suggesting the existence of a pro-regenerative inflammatory microenvironment supporting transplanted cell survival at early time points after stroke (Darsalia *et al*., 2011). This resonates with recent data showing that, shortly after stroke, expression of growth promoting genes (e.g. growth associated protein 43, brain abundant membrane attached signal protein 1, myristoylated alanine rich protein kinase C substrate and small proline-rich protein 1A) predominates over growth inhibiting genes (e.g. semaphorin 3a, ephrin receptors A5 and B1: Carmichael *et al*., 2005; Murphy and Corbett, 2009) and anti-plasticity extracellular molecules (e.g. versican, neurocan and aggrecan: Yiu and He, 2006).

The way seems now open for stem cell treatment in incurable neurological disorders such as stroke. Although there are still more open questions than answers, some preliminary considerations can be offered. If stem cell plasticity is the main therapeutic mechanism we are aiming at, an early time window for treatment seems to be required to maximize efficacy. Mesenchymal stem cells are a ready-to-use source because they are of autologous origin, simply available and easy to grow *in vitro*. Thus far, the only available neural progenitor cells are of allogenic origin (e.g. foetuses), requiring the concomitant use of immunosuppressant agents, which in stroke patients is best avoided due to the increased frequency of infections. It is still unrealistic to regulate exogenously the different effects transplanted stem cells may exert *in vivo,* in response to environmental signals, in order to foster bystander therapeutic effects while avoiding unwanted and/or toxic side effects. Recently, it has been shown that various sources of stem cells may form tumours in response to microenvironment-mediated signals, particularly when heterotopically implanted (Fazel *et al*., 2008; Amariglio *et al*., 2009; Melzi *et al*., 2010; Thirabanjasak *et al*., 2010; Jeong *et al*., 2011); thus, homotopic should be preferred to heterotopic transplantation procedures. Finally, we still need to develop *in vivo* imaging technologies to supervise stem cell effects upon transplantation. Although MRI has proven to be capable of monitoring the fate (Politi *et al*., 2007) and clinical efficacy (Jiang *et al*., 2006) of transplanted stem cells in preclinical models, there are no available techniques to label stem cells permanently *in vivo* without any safety concerns.

While apprehensions exist about the possibility of an extensive 'unregulated' use of stem cells in neurological disorders, in the near future cogent answers to the still pending questions will be provided only by well-designed preclinical experimental approaches and randomized clinical trials.

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Inherited peripheral neuropathies: a myriad of genes and complex phenotypes

Inherited peripheral neuropathies form a sizable group of disorders that are known for their remarkable clinical and genetic heterogeneity. A common feature is the progressive length-dependent neurodegeneration in the peripheral nervous system (PNS). As a group, inherited peripheral neuropathies are the most common hereditary neuromuscular disorders with an estimated prevalence of one in every 2500 individuals. The inherited peripheral neuropathies are subdivided in hereditary motor and sensory neuropathy