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Review

Neuro-immune interactions of neural stem cell transplants: From animal disease models to human trials

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ABSTRACT

Stem cell technology is a promising branch of regenerative medicine that is aimed at developing new approaches for the treatment of severely debilitating human diseases, including those affecting the central nervous system (CNS).

Despite the increasing understanding of the mechanisms governing their biology, the application of stem cell therapeutics remains challenging. The initial idea that stem cell transplants work in vivo via the replacement of endogenous cells lost or damaged owing to disease has been challenged by accumulating evidence of their therapeutic plasticity. This new concept covers the remarkable immune regulatory and tissue trophic effects that transplanted stem cells exert at the level of the neural microenvironment to promote tissue healing via combination of immune modulatory and tissue protective actions, while retaining predominantly undifferentiated features.

Among a number of promising candidate stem cell sources, neural stem/precursor cells (NPCs) are under extensive investigation with regard to their therapeutic plasticity after transplantation. The significant impact in vivo of experimental NPC therapies in animal models of inflammatory CNS diseases has raised great expectations that these stem cells, or the manipulation of the mechanisms behind their therapeutic impact, could soon be translated to human studies.

This review aims to provide an update on the most recent evidence of therapeutically-relevant neuro-immune interactions following NPC transplants in animal models of multiple sclerosis, cerebral stroke and traumas of the spinal cord, and consideration of the forthcoming challenges related to the early translation of some of these exciting experimental outcomes into clinical medicines.

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Introduction

The discovery of adult neurogenesis and the development of protocols that allow in vitro growth and significantly large scale-up of stem and precursor cells of the brain (Reynolds and Weiss, 1992) have fostered the development of innovative therapies aimed at stem cell transplantation for acute and chronic disorders of the nervous system (Cossetti et al., 2012). Motivated by the expectation of achieving CNS repair and/or regeneration via functional neural cell replacement, these studies have demonstrated a potential benefit of neural stem/precursor cell (NPC)-based experimental treatments in animal models of several neurological diseases (Martino et al., 2011). However, mounting evidence suggests that the effects orchestrated by transplanted NPCs are

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not only associated with the generation of new neurons or glial cells but also that the pathological setting in which these cells are transplanted critically determines the outcome (Cossetti et al., 2012). Cell replacement is therefore only one of the multiple ways in which transplanted NPCs promote tissue repair, and a much more complex therapeutic scenario should be foreseen. The concept of stem cell therapeutic plasticity (Martino and Pluchino, 2006) (or functional multipotency) (Teng et al., 2011) has therefore emerged, as it describes the multiple way(s) grafted NPCs which mediate systemic homeostasis, e.g. by the secretion of tissue trophic factors, as well as interaction with tissue-resident vs. -infiltrating immune cells, at the level of the inflammatory tissue context in which they are either transplanted or to which they migrate after transplantation.

The newest picture is therefore that stem cell therapies, contrary to single-molecule-based pharmaceutical interventions, hold the potential to deliver a complex series of information to a multitude of targets in the diseased microenvironment (Cossetti et al., 2012). While no final mechanisms (or direct evidence) of stem cell-to-host immune system interaction is yet available, a number of studies are now focussing on the cellular signalling that exists between grafted stem cells and endogenous target cells, with the aim of clarifying its physiological or circumstantial nature, and elucidating its molecular signature and therapeutic potential.

Here we will review the most recent evidence of immune modulation following syngeneic NPC transplants in animal models of multiple sclerosis, spinal cord injury and stroke, and discuss the next challenges related to the translation of some of these exciting experimental outcomes into clinical medicines.

Multiple sclerosis

Multiple sclerosis (MS) is a complex, highly debilitating CNS autoimmune disease that constitutes the most common cause of neurological disability in young adults (Compston and Coles, 2002). The main pathological hallmark of MS is the presence of highly heterogeneous, chronic inflammatory and demyelinating perivascular lesions within the CNS (Compston and Coles, 2002; Dyment and Ebers, 2002; Flugel et al., 2001; Lucchinetti et al., 2000; Noseworthy et al., 2000; Wingerchuk et al., 2001). Most of the demyelinated regions undergo partial remyelination and show structural repair and recovery of function (Barkhof et al., 2003; Chang et al., 2002; Compston, 1996, 1997; Prineas et al., 1993; Raine and Wu, 1993). However, remyelination in MS is typically patchy and incomplete, and ultimately fails (Blakemore et al., 2002; Franklin, 2002; Franklin and Ffrench-Constant, 2008). The failure of remyelination in MS has multiple causes:

(i) Inadequate provision of OPCs (recruitment failure) (Chari et al., 2003) or a failure of recruited OPCs to differentiate into remyelinating oligodendrocytes (differentiation failure) (Jepson et al., 2012; Syed et al., 2011);
(ii) Ageing of the perilesional microenvironment where recruited OPCs show impaired differentiation into oligodendrocytes (Ruckh et al., 2012);
(iii) Inhospitable environment generated by pro-inflammatory Th1/Th17 cells and cytokines (Steinman, 2007); and
(iv) Anatomical barriers around chronic lesions impeding the recruitment of OPCs (Franklin, 2002).

Furthermore, recurring inflammation may have profound consequences on the health of anatomically intact axons, resulting in progressive and irreversible damage/dysfunction that accounts for the degenerative nature of MS (Franklin and Ffrench-Constant, 2008; Patrikios et al., 2006). The sequential involvement of most of the above processes underlies the clinical course of MS, which is characterised by recurrent episodes of relapses that eventually leave temporary or persistent deficits, to finally deteriorate into a secondary chronic progressive phase (Compston and Coles, 2002).

The issue of (stem) cell therapies for MS has therefore gained in complexity as its success relies on the capacity of transplanted (stem) cells to target the specific sites of disease, integrate into the host tissue and eventually differentiate into neural functional cells (neurons and glia), while surviving in the chronically inflamed CNS environment. This adds crucial concerns of identification of cell source, its constitutive vs. reactive immunogenicity, window of opportunity, route of cell delivery, as well as ways in which to help the integration and long-term survival of grafted cells in the 'inhospitable' inflammatory CNS environment. All these are critical aspects of stem cell therapies that must be critically considered when envisaging therapeutic cell transplants for MS (Martino et al., 2011).

The route of cell administration has always been a major constraint for stem cell transplantation in CNS diseases and appeared to be very much dependent on the presence of focal vs. multifocal lesions to target. With MS being a multifocal disease, it is unrealistic to propose lesion-targeted injection of cells (Pluchino and Martino, 2008). This is also complicated by the fact that it is generally difficult to determine which of the multiple lesions identified by magnetic resonance imaging (MRI) would underscore clinical significance, and whether they would eventually be amenable to effective (therapeutically relevant) remyelination upon (stem) cell therapy (Chen et al., 2007).

Following a number of successful proof-of-concept in vivo remyelination studies with focally-transplanted glial progenitor cell types, including oligodendrocytes (Blakemore and Crang, 1988), OPCs (Groves et al., 1993; Windrem et al., 2004, 2008) and Schwann cells (Blakemore, 1977; Zujovic et al., 2012), NPCs were the very first candidate stem cells for systemic cell treatment of experimental autoimmune encephalomyelitis (EAE), as an animal model of MS [reviewed in Pluchino et al. (2004) and Goldman et al. (2012)]. During the last decade, rodents and non-human primates with acute, relapsing and chronic EAE (Martino and Pluchino, 2006) have been treated with NPCs injected intracerebroventricularly (icv), intrathecally (it) or intravenously (iv). These studies have shown that systemically injected NPCs enter the CNS where they survive for months in perivascular inflammatory areas while retaining mostly undifferentiated features, and remarkably reduce the clinical and pathological burden of the disease (Martino and Pluchino, 2006). Interestingly, the majority of these reports have substantially failed to show convincing differentiation and integration of transplanted NPCs in vivo, but rather contributed to the provocative idea that NPC transplants would work through mechanisms other than direct cell differentiation that imply the interaction between NPCs and immune cells (Cossetti et al., 2012; Martino and Pluchino, 2007).

The first evidence that NPCs possess immune-like features came from the observation that systemically injected NPCs use functional leukocyte-specific cell adhesion molecules (such as CD44 and very late antigen [VLA]-4) and inflammatory chemokine receptors (e.g. CCR2, CCR5 and CXCR4) to interact with activated ependymal and endothelial cells and ultimately enter the brain (Ben-Hur et al., 2003; Einstein et al., 2003; Pluchino et al., 2003). Once into the CNS, NPCs are found around inflamed blood vessels, in close contact with endogenous neural cells (e.g. astrocytes and neurons) and CNS-infiltrating blood-borne $CD45^+$ immune cells, while creating niche-like areas that are ultrastructurally and molecularly reminiscent of the prototypical stem cell niches from which NPCs were derived (Pluchino et al., 2005). NPC transplants are also associated with significantly reduced glial scar formation (Pluchino et al., 2003) and local inflammatory response (Ben-Hur et al., 2003; Einstein et al., 2006; Pluchino et al., 2005, 2009a, 2009b), which in turn lead to the increased survival and recruitment of endogenous neural cells (e.g. oligodendroglial progenitor cells) participating in the brain's intrinsic reparative response upon myelin damage (Einstein et al., 2009; Pluchino et al., 2005). The underlying molecular mechanisms by which transplanted NPCs confer this broad tissue protection were first indirectly linked to the increased