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Review

Cell therapy for multiple sclerosis: a new hope

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Multiple sclerosis is a chronic demyelinating autoimmune disease with uncertain aetiology. Due to the heterogeneity of the disease, patients may present with a wide variety of neurological symptoms such as optic neuritis, sensory deficits or cerebellar dysfunction. It remains a disease showing little hope in terms of finding a cure. Although current therapies, such as interferon-β and glatiramer acetate, provide symptomatic relief and can delay the degenerative process, there is still a large impact on quality of life as these therapies lack an ability to reverse damage occurring prior to treatment. Recently, cell therapy has emerged as a promising treatment with signs of recovery both pathologically and clinically in a variety of animal models. Given the multifaceted capabilities of the various stem cells, including immunomodulation and neuroprotection, their potential use as a comprehensive therapy is much more promising than any pharmacological therapy to date. Here, the latest advances of cell therapy are discussed, in terms of potential efficacy, the various cell types that are used, their mechanisms of action and the obstacles that still need to be overcome for translation into a clinical setting.

Key words: neural stem cells, induced pluripotent stem cells, oligodendrocyte precursor cells, neurodegeneration, immunomodulation, remyelination

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Multiple sclerosis

What is multiple sclerosis?

Multiple sclerosis (MS) is an acquired chronic autoimmune disease that attacks myelin, oligodendrocytes and axons in the central nervous system (CNS) (Lassmann, 2007; Siffrin *et al.*, 2010). Its exact aetiology is unknown, but it appears to be multifactorial, encompassing both genetic (Olerup and Hillert, 1991; Sadovnick *et al.*, 1996) and environmental cues (Gale and Martyn, 1995; Buljevac *et al.*, 2002). It involves microglia, the resident macrophage of the CNS, T cells and macrophages (Muraro *et al.*, 2000; Li *et al.*, 2007). These release a variety of cytokines, such as tumour necrosis factor (TNF)-α and interferon (IFN)-γ (Li *et al.*, 2007), ultimately leading to demyelination (Metz *et al.*, 2014) and eventual axonal loss (Akassoglou *et al.*, 1998). These areas are known as lesions and are multifocal. The neurological signs of deterioration depend on their location and the extent of damage (Bitsch *et al.*, 2000). The disease typically begins between 20 and 30 years of age (Anderson *et al.*, 1992), with progressive deterioration with age (Siffrin *et al.*, 2010). While it has been shown that remyelination can occur in MS lesions (Albert *et al.*, 2007; Patani *et al.*, 2007), this does not prevent progression of the disease with most patients showing a reduced life expectancy of 7–14 years (Scalfari *et al.*, 2013). Quality of life is severely reduced in patients with MS due to problems with mobility, fatigue and bladder and bowel dysfunction.

Clinical progression of MS

There are four main types of MS: relapsing-remitting (RRMS), primary progressive (PPMS), secondary progressive (SPMS) and progressive-relapsing (PRMS). Relapses refer to new neurological symptoms experienced by the patient who have lasted for more than 24 h and without a change in core body

temperature or signs of infection. While relapses are due to acute inflammatory attacks, disease progression is due to neurodegeneration and cell death. Each type of MS follows a different clinical progression, and therefore, patients must be managed in a different manner.

RRMS is associated with relapses that are disseminated in time and space; i.e. the neurological symptoms must involve a different area of the cortex or be separated by a time of at least 30 days. Between relapses, the patient may recover completely; however, there can also be residual deficit upon recovery. There tends to be a lack of disease progression between relapses (Lublin and Reingold, 1996).

Patients with PPMS show disease progression from the onset. Although there may be plateaus in progression and some temporary improvements, patients usually have a gradual almost continuous decrease in baseline neurological function. There are no distinct relapses in patients with PPMS. PRMS shows a similar disease course, but it is distinct from PPMS in that there are acute relapses (Lublin and Reingold, 1996).

SPMS can be seen as the long-term outcome of RRMS as the majority of patients with this disease course begin with RRMS. Patients begin to show disease progression between relapses with a continuous decline in baseline neurological function. Relapses may continue to occur during this disease course (Lublin and Reingold, 1996).

Current therapies

A full analysis of current therapies is not possible in the scope of this review. For a full review of current treatments of MS, see Filippini *et al.* (2013). However, to assess the need for cell therapy, it is necessary to understand how current therapies work and what their limitations are. Pharmacological treatments of MS work via either immunomodulation or immunosuppression.

IFN-β is a cytokine that works by increasing anti-inflammatory cytokines (Guo, Chang and Cheng, 2008; Ramgolam *et al.*, 2009; Zhang *et al.*, 2011) and reducing pro-inflammatory cytokines (Kozovska *et al.*, 1999; Ozenci *et al.*, 1999; Liu *et al.*, 2001). It has been shown to reduce relapse rates and prolong time between relapses in RRMS (Paty and Li, 1993; The IFNB Multiple Sclerosis Study, 1993) and can delay the time of conversion from clinically isolated syndrome (CIS) to clinical MS vs. placebo (Jacobs *et al.*, 2000; Kappos *et al.*, 2006; Comi *et al.*, 2012). It appears to have little to no effect on disease progression in PPMS (Leary *et al.*, 2003; Rojas *et al.*, 2009).

Glatiramer acetate is a polymer made up of four amino acids: alanine, lysine, glutamate and tyrosine. It is able to compete with self-antigens for binding to MHC II, thus diverting T cells away from myelin, increasing neuronal protection (Fridkis-Hareli *et al.*, 1994). It can also inhibit the production of IFN-γ, induce regulatory T cells and increase the production of anti-inflammatory cytokines (Gran *et al.*, 2000). It has been shown to reduce relapse rates in RRMS (Johnson *et al.*, 1995; Johnson *et al.*, 1998) and can delay conversion of CIS to clinical MS vs. placebo (Comi *et al.*, 2009). However, its effect on long-term disease progression is unclear, and it has been shown to have no effect in patients with PPMS (Wolinsky *et al.*, 2007).

Natalizumab is a humanized monoclonal antibody and a member of the α4β-integrin antagonists. These work by binding to these receptors on lymphocytes and preventing them from binding to vascular cell adhesion molecule, part of the process necessary for recruiting lymphocytes into tissue (Yednock *et al.*, 1992). This prevents them from crossing the blood–brain barrier (BBB). It has been shown to reduce the relapse rate and the risk of sustained progression of disability in patients with RRMS vs. placebo (Polman *et al.*, 2006). However, it has the possible side effect of progressive multifocal leukoencephalopathy, therefore making the benefit to risk ratio unclear, especially after prolonged use (Hirsch *et al.*, 2013).

Fingolimod is a member of the sphongosine-phosphate-1-receptor modulators. Sphingosine-1-phosphate type 1 receptors (S1P1Rs) are expressed on lymphocytes, and when fingolimod binds to these receptors, they are internalized (Brinkmann *et al.*, 2010). This prevents the release of lymphocytes from secondary lymphoid tissue, as it is S1P1R dependent (Matloubian *et al.*, 2004). It has been shown to reduce relapse rate and disability progression in RRMS vs. placebo (Kappos *et al.*, 2010) and is also more effective than IFN-β-1a (Cohen *et al.*, 2010).

Alemtuzumab is a monoclonal antibody against CD52, a receptor found on lymphocytes. When the antibody binds to CD52, it causes cell lysis, therefore depleting all CD52-positive cells (Coles *et al.*, 2006). This is a long-lasting effect, with T cells remaining reduced 12 months after initial treatment. It has been shown to reduce relapse rates and the risk of sustained disability in RRMS compared with IFN-β-1a (CAMMS223 Trial Investigators *et al.*, 2008; Bourdette and Yadav, 2009).

Why cell therapy?

Although these therapies are very effective at reducing relapses and can show some improvement in disease progression, there is still a large unmet need in treating patients with SPMS or PPMS. Disease progression in these clinical types is difficult to slow, and current therapies are unable to help patients with these conditions. Cell therapy may offer a new hope to such patients.

Current MS therapies focus on combating the inflammatory response with the hope of reducing CNS damage. However, they are unable to repair damage that has already occurred. Consequently, successful treatment of MS requires multiple considerations: neuroprotection, anti-inflammatory response and promotion of endogenous repair. Cell therapy is able to address a lot of these issues.

Due to the complex and changing nature of MS, it is possible that it will be necessary to apply different cell types to

different stages and forms of the disease. Determining which cells would be most appropriate to resolve inflammatory or neurodegenerative components of the disease will allow for targeted therapy ensuring that patients receive the most beneficial therapy. However, it must be mentioned that due to the large number of available treatments for RRMS, current ethical guidelines restrict stem cell trials on these patients.

While initially it was assumed that stem cells exerted their therapeutic effect by replacement of lost cells, it is now becoming clearer that this is not the case. Although many cells transplanted have the capacity to differentiate into the required cells, many of the beneficial effects seen in animal models occur too rapidly for this to be the direct cause of therapy. This has led to the concepts of 'functional multipotency' and 'therapeutic plasticity' to describe the observed effects seen by stem cells *in vivo* (Martino and Pluchino, 2006; Teng *et al.*, 2011). These terms suggest that rather than replacing cells, transplanted stem cells exert therapeutic effects in other ways, such as immune modulation. The effects of stem cells can be split into their ability to regulate and modulate the immune system, their ability to enhance endogenous progenitors and in some cases their ability to actively replace lost cells.

Many of the stem cells that are described in this review are able to release neurotrophins. These proteins are able to increase the proliferation and maturation of oligodendrocyte precursor cells (OPCs), thus enhancing the endogenous progenitors' ability to repair the CNS. Neurotrophins also improve axonal growth, increase neuroprotection and have been shown to inhibit the migration and reactivation of immune cells (Kerschensteiner *et al.*, 2003; Lykissas *et al.*, 2007).

These stem cells are also able to influence the immune system. There is evidence that they can attenuate inflammation by reducing the amount of pro-inflammatory cytokines while increasing the production of anti-inflammatory cytokines. They can inhibit T-cell activation and reduce their encephalitogenicity, as well as reducing B-cell activation and thus the production of antibodies. In some cases, they are also able to regulate dendritic cells.

Examples of all of the effects seen will be examined within the discussion of the individual cell types.

Clinical application

Although the various cell therapies have shown promise in animal models, translating them into a clinical option has been less successful. The main problem with neural stem cells (NSCs), induced pluripotent stem (iPS) cells and oligodendrocyte precursors has been producing a large number of clinical grade cells that are considered safe. Novel methods of producing these cells are coming into practice, as will be discussed later in the article. Once these have been described in detail, they could allow for the large-scale production of viable neural and oligodendrocyte precursors. Hopefully as these are advanced, we will begin to see more clinical trials involving these cell types. Embryonic stem (ES) cells carry an ethical burden and are tumourogenic.

Mesenchymal stem cells (MSCs) on the other hand have already been used in clinical trials. This has allowed transplantation of these cells in MS in Phase I/II clinical trials (Karussis *et al.*, 2010; Bonab *et al.*, 2012; Connick *et al.*, 2012). These trials have demonstrated that injection of MSCs is safe and clinically feasible. There is also evidence that they induce their immunomodulatory effects and that there is some improvement physiologically and functionally (Connick *et al.*, 2012).

Animal models of MS

As multiple sclerosis does not exist in other species, various animal models have been generated to study the disease and test therapies. Many models exist for non-inflammatory demyelination, including cuprizone, a copper chelator, which is fed to mice for 4–6 weeks. It causes apoptosis of oligodendrocytes and is a model for lesions in which demyelination and remyelination coincide (Skripuletz *et al.*, 2011). Another model for demyelination involves injecting lysolecithin, a phospholipase A_2 activator, into the spinal cord. Again, the demyelination is not immune mediated as it occurs even in immune-deficient mice (Bieber, Kerr and Rodriguez, 2003).

Viral-induced demyelination has also been described (Lipton, 1975) and has demonstrated that it is possible to maintain inflammatory demyelination following clearance of any pathogen gene expression, which may help with the understanding of MS. More recently, the Theiler's murine encephalomyelitis virus (TMEV) model has been described (Zoecklein *et al.*, 2003). This is a very useful model as it is chronic and lasts the entire lifespan of the mouse. It also closely follows the disease progression and has several characters of MS (Lipton, 1975; van Engelen *et al.*, 1994), including some MRI features (Pirko *et al.*, 2004a,b, 2009).

The most commonly used model for MS is experimental autoimmune encephalomyelitis (EAE) as its histopathology is similar to that of MS (Waksman and Adams, 1962). Animals are immunized with a component of myelin, such as myelin basic protein or myelin oligodendroglial glycoprotein, resulting in demyelination and in some cases axonal loss (Zamvil *et al.*, 1985). No single model is able to cover all the aspects involved in MS due to its complex nature; therefore, it is important to assess the benefit of any treatment using multiple models. However, the models are extremely useful for learning more about the biology of remyelination (Blakemore and Franklin, 2008).

Cell types and applications

In recent years, much attention has been focused on cell therapy as an option to treat MS due to its complex pathophysiology involving degenerative changes in a pro-inflammatory environment. Ever since Blakemore (1977) demonstrated that myelination could be achieved using transplanted cells,

an intensive research has been conducted into cell therapy as a treatment for MS. It is now widely accepted to be a promising approach as many studies have shown its ability to promote CNS regeneration and modulate the immune aspect of the disease. Both are essential for any meaningful therapy for MS. The main cell types and how they exert their therapeutic effects are described below, and a full summary is provided in Table 1.

Neural stem cells

NSCs are a population of cells found in the subventricular zone (SVZ) and subgranular zone (SGZ) (Alvarez-Buylla and Lim, 2004). The SVZ is a structure located on the lateral walls of the lateral ventricles and has been shown to have a higher cell density and proliferation in active MS compared with controls (Nait-Oumesmar *et al.*, 2007). The SGZ is found in the dentate gyrus, part of the hippocampus. The hippocampus is found in the medial temporal lobe of the brain and plays an important role in memory. Mouse NSCs are able to differentiate into the three neuroectodermal lineages: neurons, astrocytes and oligodendrocytes (Davis and Temple, 1994). In the adult brain, they are involved in learning and memory (Pan, Storm and Xia, 2013). In addition to this, mouse NSCs have been shown to aid the remyelination process in lesions close to the cellular niche via the formation

Table 1 . Advantages and disadvantages of different cell types

Cell type	Advantages	Disadvantages
NSCs	• Remyelinating potential	• Difficult to generate a large number of cells
	• Migrate to lesions	• Difficult to isolate
	• Immunomodulatory effects	
	• Neuroprotective (release neurotrophins)	
	• Reduce glial scar formation	
	• May be able to form directly from fibroblasts for autologous transplant	
MSCs	• Autologous transplant	• Not neural tissue
	• Migrate to lesions	• Might not maintain effects long term
	• Immunomodulatory effects	
	• Enhance progenitor proliferation and remyelination	
	• Neuroprotective (release neurotrophins)	
	• Already in clinical trials	
	• Easy to isolate	
OPCs	• Can migrate to lesions and remyelinate	• Difficult to isolate
	• May be able to form directly from fibroblasts for autologous transplant	• Different cell stage changes myelination and migration potential
		• Adult cells less capable of remyelination and migration
ES	• Can differentiate into all cell types	• Ethical barriers
	• Can be effective in remyelinating	• Require immunosuppression
iPS	• Can differentiate into NSCs and OPCs	• Tumourogenic
	• No ethical barriers	• Still in early stages
	• Autologous transplant	• Tumourogenic
		• Long differentiation process

ES, embryonic stem cells; iPS, induced pluripotent stem cells; MSCs, mesenchymal stem cells; NSCs, neural stem cells; OPCs, oligodendrocyte precursor cells.

of oligodendrocyte precursors (Picard-Riera *et al.*, 2002), and in some cases, they outnumber the recruitment of cells further differentiated down the oligodendrocyte lineage, suggesting that they play an important role in remyelination (Xing *et al.*, 2014). NSCs cannot be obtained directly from the patient, as this would cause extensive brain damage. However, methods of producing them will be discussed later.

Mouse NSCs have the potential to differentiate into myelinating oligodendrocytes (Yandava, Billinghurst and Snyder, 1999) as demonstrated by transplantation of NSCs, obtained from the SVZ of adult mice, intraventricularly into EAE mice resulting in functional recovery (Pluchino *et al.*, 2003; Einstein *et al.*, 2007). This is a benefit as it means that they do not require *in vitro* programming before transplantation. Mouse NSCs also have the ability to promote remyelination by enhancing endogenous progenitors (Einstein *et al.*, 2009). Mouse NSCs release multiple neurotrophins, including nerve growth factor, ciliary neurotrophic factor, brain-derived neurotrophic factor and neurotrophin-3 (Lu *et al.*, 2003; Pluchino *et al.*, 2003) and therefore can increase the proliferation and maturation of OPCs both *in vivo* and *in vitro* (Einstein *et al.*, 2009) and improve axonal growth (Lykissas *et al.*, 2007). Importantly, mouse NSCs have been shown to reduce astrogliogenic factors and glial scar formation (Pluchino *et al.*, 2003). Glial scars are formed by activation of astrocytes, changing their phenotype, becoming more fibrous. This involves increased production of the intermediate filament glial fibrillary acidic protein (GFAP) and extracellular deposition of chrondroitin sulphate proteoglycans (CSPGs) (Fawcett and Asher, 1999). These cells help form a barrier that contains the inflammatory milieu, thus protecting the surrounding brain tissue from unnecessary damage. However, they also express many inhibitory factors for axon growth and remyelination, such as CSPGs (Fawcett and Asher, 1999), and therefore reduce the capacity for regeneration.

Interestingly, mouse NSCs also appear to reduce acute axonal injury, chronic axonal loss and demyelination (Pluchino *et al.*, 2003). It is thought that this may occur via their ability to regulate the immune system. It has been shown that rat NSCs can attenuate inflammation (Ben-Hur *et al.*, 2003). They can inhibit T-cell activation, both locally and peripherally, and induce T-cell apoptosis (Einstein *et al.*, 2009). Following intravenous transplantation, NSCs were found in the lymph nodes and the spleen. Here both human and rat NSCs could inhibit activation of myelin-specific T cells, prevent their proliferation and reduce their encephalitogenicity (Einstein *et al.*, 2003; Pluchino *et al.*, 2009a). It is likely that these effects are due to the neurotrophins released. Mouse NSCs have also been shown to impede dendritic cell functions via a bone morphogenic protein-4 mechanism (Pluchino *et al.*, 2009b). Together these aspects could play a large role in their ability to improve animals in EAE models, both clinically and pathologically (Pluchino *et al.*, 2003; Einstein *et al.*, 2007).

Both rat and mouse NSCs, when injected intravenously, are able to cross the BBB and enter the CNS (Ben-Hur *et al.*, 2003; Einstein *et al.*, 2003; Pluchino *et al.*, 2003). It has been suggested that they are able to do this by following environmental cues created by inflammation at the lesions (Picard-Riera *et al.*, 2002). These cells express multiple cell adhesion molecules and cytokine receptors that enable them to adhere to endothelial cells and transmigrate across the BBB into the CNS (Imitola *et al.*, 2004; Rampon *et al.*, 2008; Pluchino *et al.*, 2009a). This is an important factor as direct transplantation into the CNS can cause further inflammation and damage. Although NSCs appear to have this capacity, it is thought that the majority of their beneficial effects are mediated by their immunomodulatory capabilities (Pluchino *et al.*, 2009a).

Mesenchymal stem cells

MSCs are a population of stem cells found in bone marrow (Friedenstein, Chailakhjan and Lalykina, 1970). They are involved in the regulation of haematopoietic stem cells. They have the capacity to generate cells of mesenchymal lineage such as bone (Kuznetsov, Friedenstein and Gehron Robey, 1997), adipose tissue (Dennis *et al.*, 1999), cartilage (Pereira *et al.*, 1995), tendons (Young *et al.*, 1998), muscle (Ferrari *et al.*, 1998) and even neural tissue (Kopen, Prockop and Phinney, 1999).

It has been shown that human MSCs are able to enter the CNS when injected intravenously, whether there are signs of inflammation or not (Gordon *et al.*, 2010). There is also evidence that certain cytokines commonly expressed in lesions of MS guide migration of these cells (Rice and Scolding, 2010). Once they arrive in the CNS, mouse MSCs are able to exert their immunomodulating and immunosuppressive actions (Gerdoni *et al.*, 2007). Mouse MSCs can prevent B cells from accessing the CNS and reduce the production of antibodies against myelin (Gerdoni *et al.*, 2007). Human MSCs can regulate dendritic cells by impeding their development and function (Jiang *et al.*, 2005). They have been shown to increase the number of anti-inflammatory cytokines and T cells and to reduce the number of inflammatory T cells and cytokines (Bai *et al.*, 2009). Importantly, human MSCs can reduce cell oxidative damage via the release of superoxide dismutase-3, which can also promote neuronal survival (Kemp *et al.*, 2010). These changes to the immune response may explain why these cells are able to reduce demyelination in EAE model mice (Munoz *et al.*, 2005).

In addition to their immunomodulating properties, human MSCs can also enhance the endogenous neural progenitors by stimulating their proliferation (Munoz *et al.*, 2005) and their differentiation into mature myelinating oligodendrocytes (Bai *et al.*, 2009). NSCs co-injected with rat MSCs were more likely to differentiate into oligodendrocytes (Rivera *et al.*, 2009). Additionally, rat MSCs exhibit neuroprotective and neurogenic properties (Isele *et al.*, 2007). This is likely due to their release of neurotrophins such as neurotrophic factor-3/4/5, nerve growth factor-β and platelet-derived growth factor (Jaramillo-Merchan *et al.*, 2013). Interestingly, human MSCs can reduce the formation of glial scars and

increase axon growth via the release hepatocyte growth factor (Bai *et al.*, 2012; Jeong *et al.*, 2012).

Oligodendrocyte precursor cells

OPCs, first described by Ffrench-Constant and Raff (1986), are the cells that mediate spontaneous remyelination of the CNS (Lucchinetti, Parisi and Bruck, 2005). In mice and rats, they are activated following changes in microglia and astrocytes that occur during injury in response to the cytokines, chemokines and growth factors released (Glezer, Lapointe and Rivest, 2006; Rhodes, Raivich and Fawcett, 2006). These chemical cues also recruit OPCs to sites where remyelination is needed. Here they differentiate into functional oligodendrocytes that are able to remyelinate axons. The inflammatory cells help provide a remyelinating environment by removing myelin debris and by secreting cytokines and chemokines that promote OPC recruitment and survival (Dziembowska *et al.*, 2005). At different stages of their development, these cells have different migratory and remyelinating capacities; earlier progenitors have been shown to produce more myelin over a larger area of the brain (Rosenbluth *et al.*, 1990; Warrington, Barbarese and Pfeiffer, 1993).

ES cells and reprogrammed stem cells

ES cells are derived from the inner cell mass of the blastocyst. They are self-renewing and are able to differentiate into endoderm (Mfopou *et al.*, 2014), mesoderm (Oeda *et al.*, 2013) and ectoderm (Surmacz *et al.*, 2012). Human ES cells can differentiate into oligodendrocytes and myelinate axons in animal models of demyelination (Nistor *et al.*, 2005). Rat ES cells exhibit some immunomodulatory properties (Fandrich *et al.*, 2002). They can differentiate into an oligodendrocyte precursor prior to transplantation to aid with myelination (Brüstle *et al.*, 1999; Keirstead *et al.*, 2005). However, there are many issues surrounding these cells, such as their ability to form teratomas *in vivo* (Bjorklund *et al.*, 2002); the ethical issues about using cells from an embryo; and the problems surrounding rejection of tissue formed from these cells.

To overcome some of these issues of using ES cells, pluripotent cells have been derived from somatic cells. These cells are known as iPS cells and were first described by Yamanaka and Takahashi (2006). They are able to form tissues from all three germ layers (Liu *et al.*, 2010; Sakurai *et al.*, 2012; Veraitch *et al.*, 2013). Although they overcome the ethical problems associated with ES cells, because the conversion of iPS cells to differentiated cells is not entirely efficient, they still carry a risk of forming teratomas.

Mouse iPS cells can be differentiated into neural progenitors and once implanted have been shown to improve clinical and pathological features of EAE. They did not exert their effects via cell replacement, but rather via the secretion of leukaemia inhibitory factor (LIF) (Laterza *et al.*, 2013). LIF promotes the survival and differentiation of endogenous OPCs and enhances the remyelination potential of both OPCs and mature oligodendrocytes (Laterza *et al.*, 2013).

NSCs can be differentiated further into OPCs, meaning that iPS cells can form OPCs (Kanakasabai *et al.*, 2012). On two occasions, OPCs derived from human iPS cells transplanted into the shiverer mouse strain led to engraftment and myelination, resulting in prolonged survival, equivalent to the use of primary OPCs (Windrem *et al.*, 2004; Windrem *et al.*, 2008).

These results suggest that iPS cells may offer a way of generating both OPCs and NPCs for autologous transplantation into patients. However, it should be noted that the process of differentiation takes a long time and therefore may not be clinically viable.

Recent evidence has shown that it is possible to differentiate fibroblasts into multipotent tissue-specific stem cells, including NSCs (Thier *et al.*, 2012). Once obtained, they can be maintained *in vitro* and are able to proliferate extensively without losing their ability to differentiate (Iwanami *et al.*, 2005). This allows for a small number of cells to be taken from the patient to be expanded in culture providing a large number of cells for transplantation. This method has also been used to obtain OPCs, offering a viable method of generating these cells for therapeutic use (Yang *et al.*, 2013). These novel methods are very promising, giving the best opportunity to create tissue-specific, non-tumourigenic stem cells for clinical application.

Hurdles still to confront

Despite the huge advance in potential therapeutics using cell replacement therapies, there are still many technical and ethical issues to overcome. First of these is what type of cell to use. All cell types described previously have their own advantages and disadvantages. Certain cell types are better able to migrate to lesions in the CNS, while others have better remyelinating abilities. Some cells appear to migrate to and remain in the lung, whereas others are more capable of entering the CNS. It is not clear yet which cell type has the most therapeutic benefit. It will be necessary to conduct trials to test how well these therapies translate into clinical practice and how best to address the problems associated with each cell type. It may also be necessary to consider co-transplantation of different cell types.

The best route of transplantation is also up for debate. While the best signs have been shown with transplantation close to the lesion (Franklin and Ffrench-Constant, 2010), this is often impractical with patients due to the multifocal pathology of multiple sclerosis and as this would require surgery. Both intravenous and intracerebroventricular injection have shown promise in animal models (Pluchino *et al.*, 2003, 2009a), although there is evidence that 90% of these cells remain in the lungs (Fischer *et al.*, 2009).

The timing of treatment is also important. Whether it is necessary to transplant cells early during the acute lesion or whether there is some leeway is still uncertain. Further to this, it is necessary for the cells to be able to survive for a long

time, as the disease is progressive. If patients require multiple injections, then the cost of such a therapy may not be viable. Some cells may lose their capacity to remyelinate or exert immunomodulatory effects over time (Fainstein *et al.*, 2013).

Perhaps the biggest issue to overcome is the environment of the CNS. The cells of the CNS express many factors that inhibit both remyelination and axon regeneration. Whether these cells are capable of changing the environment enough to help contribute to recovery from the disease is yet to be seen. Cells may require treating prior to transplantation to help change the environment to a pro-remyelinating state.

Conclusion

Despite the best efforts, current treatment methods are insufficient to prevent the progression of MS. Although cell therapy is just beginning to be explored as a possible therapeutic option, it is clear that it offers a lot of potential. The wide-ranging effects of these cells mean that they can realistically target all aspects of the disease, unlike current therapies that only address the inflammatory aspects and are not neuroprotective. There are still many issues to resolve, however, with various trials already showing their safety; we will hopefully be able to observe their efficacy in due course.

Author biography

S.H. is a fifth-year medical student at Imperial College London who has completed an intercalated BSc in Neuroscience and Mental Health. He is interested in Neuroscience, with a particular focus on regeneration in the central nervous system. In 2013, he was awarded one of four WR Henderson Scholarships. This allowed him to get an experience of research first hand. He hopes to continue in the field of Neuroscience as a Clinical Fellow and is keen to undertake a PhD in the future.

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