18

Cellular Based Therapies for the Treatment of Multiple Sclerosis

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS) and the primary cause of non-traumatic neurologic disability in the western world. Infiltration of myelin-specific effector T cells into the CNS is thought to cause demyelination and loss of axons resulting in deficient signal conduction and clinical onset of the disease. Although previously thought to be initiated by T helper 1 (Th1) cells, it has become evident that Th17 cells are also involved (Cua 2003). In addition, CD8+ T cells, macrophages, and B cells are also found in inflammatory infiltrates in the CNS of affected individuals. During the initial phases of the disease, once the myelin-specific peripherally activated T cells penetrate the CNS, they are re-activated by antigen presenting cells presenting their target antigen within the CNS and act to cause damage to axonal myelin through the activation of macrophages and the release of myelin toxic substances (Aktas, Waiczies et al. 2007).

One of the main obstacles to recovery and to the treatment of MS is the relatively low efficiency of spontaneous remyelination of axons by oligodendrocytes. In the majority of cases during the early phases of the disease a large amount of oligodendrocytes and their precursors are preserved within the characteristic demyelination plaques and retain the ability to remyelinate. Despite this resident population of remyelinating cells it has been shown that over time remyelination becomes incomplete and fails, resulting in the irreversible neurological damage associated with the disease (Franklin 2002).

The direct cause of MS remains unknown but it seems most likely to be a mixture of both genetic susceptibility and environmental factors. Genetic factors had been long suspected to affect the chances of an individual developing MS. It has been known for some time that there is a familial link to the disease with a sharp increase in disease probability if a family member has the disease (Dyment, Ebers et al. 2004), with a direct correlation between how closely related the affected individual is and the probability of developing the disease. The importance of genetic factors was underscored by the fact that adopted children have no statistically significant increase in there disease susceptibility compared to the general population, even if any of their adoptive family members have the disease. Other genetic factors such as gender and race have also been shown to have an effect (Sospedra and Martin 2005).

More recently environmental factors have been highlighted by an increase in MS cases in westernised society as opposed to that of other less developed areas of the world. It is thought this may be due to the lack of exposure to infection during adolescence and childhood and has been highlighted in places such as Japan (Li, Chu et al. 2007) where a strong link may exist between the number of MS cases and the increase in sanitation. Among infectious environmental factors, Epstein Barr and other human Herpes viruses have received most attention in recent years (Levin, Munger et al. 2010). Other non-infectious environmental factors, such as latitude and sun exposure have also been linked to the disease (Sospedra and Martin 2005).

Current treatments for MS include IFN-β, glatiramer acetate and mitoxantrone which show some degree of efficacy and have potential side effects (Markowitz 2010). New more effective treatments for MS are highly desirable, in particular those able to slow disease progression in addition to reducing the frequency of clinical exacerbations. Although several pharmacological therapies are in clinical trials or have recently been approved (such as the immunosuppressive drug Fingolimoid, (Cohen and Chun 2011)), cellular treatments are attractive alternatives. They may theoretically possess the ability to modulate the immune response but also enhance spontaneous remyelination of damaged axons and thus limit or even reverse the irreversible neurological damage associated with MS. The challenge is making this theoretical potential become a reality.

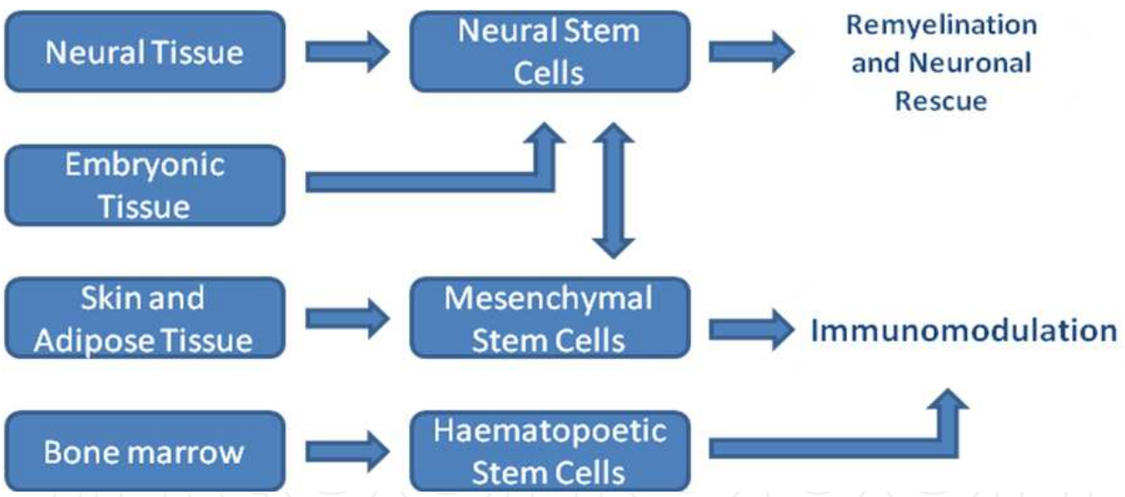

Fig. 1. Potential roles for different types of stem cells in the treatment of MS [Adapted from (Martino, Franklin et al. 2010)].

2. Stem cell therapies

Stem cells are the most promising treatment option in cellular therapy as they have the potential to differentiate into a multitude of cells. There are several types of stem cells which are isolated from different types of tissue which include embryonic, mesenchymal, hematopoietic and neuronal stem cells along with the relatively new discovery of fibroblast derived induced pluripotent stem cells (IPS). These different phenotypes of stem cells hold great potential in the treatment of a variety of different conditions and potentially have a

range of positive effects on MS and a range of other inflammatory, traumatic and neurodegenerative CNS conditions. The fact that stem cells possess the theoretical ability, under the right conditions, to differentiate into any type of cell in the body makes them a very desirable treatment option. However significant issues arise with their use including ethics, access to the cells, and their potential side effects.

2.1 Embryonic stem cells

Of all the different types of stem cells, embryonic stem cells (ESC) have the largest differentiating potential and are also the best categorised but despite this their use has come up against a variety of practical and ethical hurdles due to their embryonic source. Theoretically embryonic stem cells can provide an unlimited supply of cells with vast differentiation potential. In animal models and in the right environment, they can be directed into differentiating into oligodendrocytes and successfully undertaking remyelination (Nistor, Totoiu et al. 2005). This remyelination has been shown in a number of animal models following the infusion of ESC derived glial precursors leading to a significant degree of remyelination in both the spinal column and the brain (Brustle, Jones et al. 1999). It has also been noted that the time of infusion with these cells is crucial, with some studies showing that, in the case of spinal injury, remyelination is much more effective if the embryonic stem cell derived cells are introduced soon after the damage (7 days) as opposed to later after the event (10 months) (Keirstead, Nistor et al. 2005). This suggests that in the case of neurodegenerative disease these cells may be more effective if transplanted in the earlier stages of the condition.

Not only do embryonic stem cells show the potential to remyelinate but also have an effect on EAE through the modulation of the immune system, with a number of animal models showing a down regulation of the auto-immune T-lymphocyte response against self antigen (Fandrich, Lin et al. 2002). This immunomodulatory potential has been proposed to be through both contact-dependent mechanisms and the release of soluble factors. For example PGE_2 was identified as one of these factors in murine models in which embryonic stem cells had been used to dampen the immune response in organ transplantation (Imberti, Casiraghi et al. 2011).

Despite the promising potential of embryonic stem cells as a therapy for multiple diseases and conditions there are several hurdles which realistically may never be fully overcome. The first of these are the ethical ramifications of work involving embryonic stem cells. The fact that embryonic stem cells would most likely have to be sourced from human embryos has raised serious concerns about the use of sources of 'potential life' as a research tool. To date, much of the work in stem cell research has been conducted using unwanted embryos originally produced for IVF treatment. However, if this became a main stream treatment embryos would have to be produced for the specific purpose of producing appropriate stem cells, which many see as unethical (de Wert and Mummery 2003). Another ethical hurdle would be the production of autologus stem cells where the nucleus from the cell of the patient would be infused into a de-nucleated oocyte in order to create a strain of stem cells specific to the patient which would help to bypass the issue of rejection (de Wert and Mummery 2003). Many believe the specific use of embryonic stem cells is not the issue; it is the precedent it would set. The ethical debate surrounding ESC is unlikely to be easily resolved.

Another issue surrounding embryonic stem cells is safety. The use of heterologus embryonic stem cells carries the risk of the formation of teratoma (tumour) within the specific organ of transplantation (Bjorklund, Sanchez-Pernaute et al. 2002; Blum and Benvenisty 2008). Altering the cells to reduce this risk may prove very difficult and may also have a detrimental effect on the cells' ability to exert the therapeutic purpose for which they are intended. This issue can be avoided with the use of autologus stem cells (mentioned above) but this leads to not only ethical but also practical issues, with every patient being treated having to be cloned to produce the stock of autologous cells for treatment.

2.2 Adult neuronal stem cells

Adult neural stem cells (aNSC) do not carry the same ethical burden as embryonic stem cells and have shown the ability to both remyelinate demyelinated axons and modulate the autoimmune response. These cells are generally isolated from the adult mammalian sub ventricular zone (SVZ), which makes them difficult to extract and use for clinical purposes. They can be maintained for extended periods in vitro and still retain the ability to differentiate and proliferate (Nunes, Roy et al. 2003). In EAE it has been documented that aNSC can act to aid the disease both through remyelination and through an immunomodulatory effect. In terms of remyelination, aNSC have been proposed as treatments for a multitude of different conditions such as neurodegenerative disorders including MS (Magalon, Cantarella et al. 2007), CNS traumas (Iwanami, Kaneko et al. 2005) and malignant tumours. Transplanted cells have been shown to migrate from the area of infusion to the area of inflammation (Ben-Hur, Einstein et al. 2003) especially within the white matter of the CNS, with the labelling of infused cells showing that 80% of lesions contain labelled cells within 24 hours of infusion (Politi, Bacigaluppi et al. 2007). aNSC are also seen to be durable within the body with labelled cells still detected within lesions 20 days after infusion (Politi, Bacigaluppi et al. 2007). Along with the detection of aNSC presence and migration visualised by cell labelling, remyelination and cell replacement have also been visualised in EAE with the use of electron microscopy (Pluchino, Quattrini et al. 2003). aNSC's have been shown to migrate to areas of demyelination (and not to areas of normal looking brain and CNS matter) and differentiate into oligodendrocytes capable of remyelination and thus attenuate the clinical symptoms of EAE within the tested animals.

In terms of the immunomodulatory effects of aNSC on neurodegenerative diseases such as MS there has been some debate. It has been shown that animals given an IV injection of aNSCs in the early stages of EAE show a significant immunosuppressive effect. Animals treated with aNSCs were shown to have a gathering of the infused cells at the spleen and lymph nodes and here had a profound effect on the immune response to self CNS antigen through their interaction with the T-cell populations in these areas (Einstein, Fainstein et al. 2007). T-cells isolated from the lymph nodes of mice that had been infused with aNSC's showed no activation in the presence of either CNS specific antigens or other non-specific stimulus (Einstein, Fainstein et al. 2007). It is evident that these cells, when injected intravenously at the early stages of the disease, do not penetrate the CNS or get attracted to areas of inflammation like aNSC's injected at the height of the disease but travel to areas of immune regulation such as the spleen and lymph nodes where they have an dampening effect on the peripheral immune response (Ben-Hur 2008).

The key to the use of aNSC's in therapy will be optimising the technique to allow both the immunomodulatory and the remyelinating features of the treatment to work in tandem and thus have a greater effect on the symptoms of the disease. aNSCs have several advantages

over other forms of stem cells, including fewer ethical burdens, maintaining differential and proliferative ability over long periods of time, and having both immunomodulatory and remyelinating potential. Therefore, they are one of the more promising avenues of investigation into MS treatments. They also seem to pose little risk of tumour formation, which is in stark contrast to a number of other stem cell types. In all the aNSC transplant studies in both healthy and diseased animals there have been no instances of tumour formation which suggests that the potential use of this treatment in vivo would carry little if any risk in the way of tumour development.

2.3 Mesenchymal stem cells

Mesenchymal stem cells are stromal stem cells which can be isolated from a variety of adult tissues but predominantly from the bone marrow. The therapeutic effect of these cells on neurodegenerative diseases has previously been based mainly on immunomodulation, but recently it has been proposed that these cells may be able to induce axon remyelination. However, this is yet to be unequivocally proven. In terms of immunomodulation, bone marrow isolated mesenchymal stem cells are known to have a dampening effect of the autoimmune response to CNS self antigens in EAE. The mesenchymal cells are shown to have an inhibitory effect on the activation of encephalitogenic T cells primed against self CNS antigen, thus reducing disease severity (Kassis, Grigoriadis et al. 2008). T-cells isolated from MSC-treated animals show a reduced ability to produce inflammatory cytokines (such as IFN-γ and TNF-α) and do not proliferate in the presence of the EAE-inducing CNS self antigen (Gerdoni, Gallo et al. 2007). In addition to reducing T-cell function, MSCs can also modulate the proliferation and maturation of antigen presenting cells (APC) (Beyth, Borovsky et al. 2005), which in turn affect T-cell priming to self antigens.

The potential for the infusion of mesenchymal bone marrow derived stem cells to induce a degree of remyelination in animal models of MS has been reported in a few studies. Such cells removed from the bone marrow of donor mice and cultured in vitro were infused into damaged EAE spinal cords and induce both central and peripheral myelination (Akiyama, Radtke et al. 2002).

Bone marrow stem cells can also be used as a source of neural cells, bone marrow-derived neural stem cells. These cells are phenotypically identical to aNSC isolated from the SVC and express the neural stem cell marker nestin. Like aNSC's and unlike other stem cells isolated from the bone marrow, these cells show the ability to migrate into the CNS and differentiate into both oligodendrocytes and neurons at sites of CNS damage, such as inflammatory CNS lesions in MS (Kabos, Ehtesham et al. 2002). However, their differentiation into cells capable of remyelination is not the only way these cells are said to act in the repair of damaged axons. They may also promote remyelination by pre-existing cells through the release of growth factors. Bone marrow derived neuronal cells also seem to have significant immunomodulatory properties, such as in vitro suppression of T cells, B cells and natural killer (NK) cells.

2.4 Haematopoietic stem cells

Hematopoietic stem cells (HSC) have been extensively studied for immune replacement therapy in aggressive forms of MS. There are a number of advantages to this form of stem cell which is why research into it has been so thorough. The isolation process compared to that of other stem cells is less invasive and more ethically acceptable as the CD34+ cells can be easily isolated from peripheral blood. HSC transplantation (HCST) may be one of the

most potent available forms of immunotherapy; however issues of safety have limited the advance of this approach into clinical use. Useful predictors of good therapeutic outcomes after HSCT include rigorous selection of the most suitable patients for this type of treatment and the specific treatment protocol. Patients with low to intermediate level of disability experiencing active relapses despite treatments with IFN-beta or with more potent immunosuppressive drugs, such as mitoxantrone, may show a better risk/benefit ratio than those with advanced, secondary progressive disease with higher disability (Muraro, Cassiani Ingoni et al. 2003; Burt, Cohen et al. 2005). The regime of treatment is also vital to the success of the treatment with early studies, which used myeloblative transplantation regimes, suffering high levels of toxicity and mortality (Burt, Cohen et al. 2005). The use of revised, non myeloblative HSCT conditioning protocols, seems to have had a positive effect on the mortality rates associated with the previous treatment regimes.

There are many issues when using hematopoietic stem cells as a treatment option in MS involving both ethics and safety. The risk involved in HSCT is relatively high although safety has increased over recent years. An example is the drop in mortality rate in patients suffering from autoimmune conditions treated with autologus hematopoietic stem cell transplantation, which was 7.3% between 1995 and 2000 and dropped to 1.3% in the period from 2001-2007 (Schippling, Heesen et al. 2008). The direct effect of the hematopoietic stem cells in giving rise to malignant tumours is an obvious risk but another major issue is the level of immunosupression needed during a stem cell transplantation, which leaves the patient particularly vulnerable to infections. The risk factors in this type of immunosuppressive therapy make it a last resort, with patients and treating physicians having to assess and discuss the risk/benefit ratios of such a treatment before undertaking it. Considering that many patients with MS live for many years and can, to some degree, manage and slow the progression of their illness with pharmaceutical treatments, it may be hard to justify a therapy such as AHSCT. However, as the methods and techniques involved in AHSCT improve and the favourable outcomes seen in animal models are translated into human studies (this has already been seen in the limited number of humans successfully treated with the method), this treatment could in time become a key immunomodulation technique in treating MS. As these issues are overcome large scale, long term, controlled studies will be necessary to test the true efficacy of the treatment (Mancardi and Saccardi 2008) after which HSCT treatment may be deemed safe for larger scale use.

2.5 Induced pluripotent stem cells

Induced pluripotent stem cells (IPS) are possibly the most exciting development in the field of stem cell therapy for the last few years. A group in Japan has shown that it is possible to generate pluripotent stem cells from fibroblast cultures with the addition of just 4 transcription factors (Oct 3/4, Sox2, Klf4 and c-Myc) under ESC culturing conditions (Takahashi, Tanabe et al. 2007). These cells represent a significant step forward as they share the morphology and many functional properties with ESCs but can be generated from fibroblasts in the laboratory. The accessibility of fibroblasts, the comparatively straight forward techniques involved in generating IPS and the removal of important ethical burdens suggests an enormous treatment potential for such a type of stem cells. These cells could become a valid treatment option in regenerative medicine not only in MS but a variety of other inflammatory, neurodegenerative, and traumatic diseases including spinal cord injury, juvenile diabetes (Thomson, Itskovitz-Eldor et al. 1998) and potentially many others.

Despite their enormous potential, IPS do raise a number of safety concerns which must be overcome before they are considered as a valid treatment in humans. Due to a large number of retroviral integration sites (retroviruses are used to insert the relevant transcription factors into target cells to induce IPS) on IPS for each of the stimulating factors they may be prone to tumourigenesis. Mouse studies showed around 20% rate of tumour formation which is thought to be due to the reactivation of the c-Myc oncogene by retrovirus (Okita, Ichisaka et al. 2007). Tumour formation caused by retroviral integration is a serious issue which must be solved before this treatment is considered in the clinic.

Other problems must be resolved as well. The yield of IPS cells from human fibroblast cultures is very low, which could represent a practical obstacle to the development of IPS as a treatment. The precise nature of IPS and their origin is still a matter of debate. Different theories suggest that the cells induced into IPS are actually undifferentiated stem cell-like cells within the fibroblast cultures. It is also possible that undetectable genetic alterations in the cells of origin may be required for IPS induction (Takahashi, Tanabe et al. 2007). For now these cells are a very useful tool within the process of understanding disease mechanisms and toxicology ex-vivo however the ultimate goal must be to develop this therapy to a point where it can be used to treat human conditions. Considering that these cells were only discovered in 2007, research into this form of pluripotent cells is still at an early stage. As time progresses it is likely some of the issues surrounding these cells will be overcome, and along with a better understanding of the mechanisms behind these cells they may become a valid treatment option in human medicine.

In summary, stem cells treatments are, and have been for some time, one of the most promising and exciting potential treatment options within human medicine. Thus far, they have failed to fulfil this immense promise having been held back by many ethical, practical and safety related hurdles. Nevertheless, stem cell research is constantly moving forward. With the discovery of new treatment protocols and new types of promising cells, such as IPS, the time when stem cells become a front line treatment for immunomodulation and neural regeneration in MS may be closer than ever.

3. Non-stem cell cellular therapies

It is not only stem cells which have been identified as a potential treatment option for patients suffering from MS. There are a range of possible cellular treatments which involve the infusion of cells isolated from the body with aims varying from halting the progression of the disease through immunomodulation to the active re-myelination of affected axons. Non-stem cell treatments would include the infusion of peripheral nervous system myelinating Schwann cells into the CNS as well as the use of ex vivo cultured oligodendrocytes, olfactory ensheathing cells and even cells isolated from the body's immune system such as T-cells.

3.1 Oligodendrocyte and oligodendrocyte precursor cells

Myelination of axons within the CNS is typically the task of oligodendrocytes and their precursors during development and in response to damage, however it has been shown that a significant proportion of these cells are lost or are deemed functionally inactive in MS, particularly in chronic phases of disease. It has been suggested that the reason for this decrease in numbers of oligodendrocytes is due to either the lack of differentiation of precursor cells into mature oligodendrocytes or the death of the oligodendrocytes once they reach a certain point within the developmental process (Wolswijk 2000).

There is a degree of debate over the stage at which oligodendrocyte precursor cells (OPC) are most effective at myelinating axons along there maturation process. It is thought that oligodendrocyte progenitor cells are responsible for generating the largest amount of myelin over the widest area and are more proficient than mature oligodendrocytes (Franklin 2002; Wolswijk 2002). There is evidence that mature oligodendrocytes when infused into a demyelinated CNS environment are less capable of migration and division at the site of demyelination than the more motile and proliferative oligodendrocyte progenitor cell. Another advantage of OPCs is their ability to react to their microenvironment. The path of maturation of these cells is affected by cytokines, chemokines and growth factors causing their maturation to a cell with remyelinating potential "in the right place at the right time", which is also aided by enhancement of the signalling matrix and removal of phagocytic debris by inflammatory cells (Zawadzka and Franklin 2007).

3.2 Schwann cells

Schwann cells, typically responsible for myelination within the peripheral nervous system, are seen as an alternative to oligodendrocytes and OPCs in the cellular treatment of MS and have been shown to be capable of a significant degree of axonal remyelination within the CNS of MS patients (Lavdas, Papastefanaki et al. 2008). Despite the issues surrounding the use of these cells, such as their inability to interact with astrocytes and limited survivability within the CNS, their ability to remyelinate axons and improve axonal conduction in damaged axons is not in doubt. The question is whether they can do so to such a degree that it is an effective and worthwhile treatment option for patients with MS. Schwann cells have been proposed as a treatment for CNS damage not only for MS but for other pathological conditions including the repair of spinal cord injury (Oudega 2007) where their proposed function to aid the remyelination of damaged axons remains the same. There are many positive and negative aspects to Schwann cells as a potential cellular treatment option in MS, with the main advantage being the ease of accessibility from peripheral nerve biopsies and thus the relatively simple task of culturing autologus populations of these cells. Another positive aspect is that they are less likely than oligodendrocytes to be prone to MS related autoimmune attack as this tends to be against the CNS myelinating cells due to being targeted towards mature oligodendrocyte antigens (Kohama, Lankford et al. 2001). On this note, the myelin they produce is also less likely to be susceptible to autoimmune attack due the slight differences in its make up as compared with the myelin produced by oligodendrocytes. Due to the autoimmune attack in the CNS being focused against antigens within the oligodendrocyte produced myelin, the subtle differences in the makeup of Schwann cell myelin makes it a less likely target.

As we have explained, the fact that Schwann cells are not usually resident within the CNS has its advantages in terms of not being recognised in an autoimmune attack, however the fact that these cells are out of their usual environment also has some negative ramifications. Schwann cells do not tend to migrate to areas of inflammation within the white matter of the CNS due to the inhibitory effect that astrocytes have on them. Schwann cells and astrocytes cannot coexist which poses huge problems in the treatment of MS as the majority of demyelinated plaques contain large numbers of astrocytes. Astrocytes have a number of detrimental effects on Schwann cells, effecting both their successful migration into the CNS white matter (Iwashita, Fawcett et al. 2000) and their ability to remyelinate and survive (Shields, Blakemore et al. 2000) within damaged astrocyte rich areas. It is proposed that this negative effect on Schwann cells in mediated by the release of soluble factors from the

astrocytes (astrocyte conditioned medium reduced Schwann cell proliferation and remyelination (Guenard, Gwynn et al. 1994)) such as Ephrins (Afshari, Kwok et al. 2010) and also through a prolonged contact interaction between Schwann cells and the astrocytes mediated by N-Cadherin (Wilby, Muir et al. 1999). This limited ability to function within the CNS is a major drawback for the use of Schwann cells as a remyelinating treatment as any effect they do have will be short lived due to the short time span they can survive within the appropriate system. If Schwann cells are to become a widely used remyelinating treatment option in the treatment of MS work will have to be done to produce a Schwann cell-based therapy capable of migrating to sites of CNS inflammation and able to survive in the presence of astrocytes. Efforts are being made to improve the chances of Schwann cells surviving interaction with astrocytes through methods such as genetically altering the cells (Papastefanaki, Chen et al. 2007).

3.3 Olfactory ensheathing cell

Another type of cell that has been proposed for the remyelination of axons in multiple sclerosis is the olfactory ensheathing cell (OEC). These are a form of unique glial cell found only in the olfactory system close to the first cranial nerve. These cells are favourable over other cell based therapies for a number of properties, one of which is their ability to survive in the presence of astrocytes. Astrocytes are found around areas of MS induced CNS inflammation and as previously discussed are a major problem for Schwann cell therapy. OEC's can survive in conjunction with astrocytes and can also make the environment around the CNS inflammation more hospitable to the migration and survival of endogenous Schwann cells (Boyd, Lee et al. 2004).

Despite this ability to survive and retain function in the presence of astrocytes there are also some disadvantages to the OEC in the treatment of MS. Despite their ability to remyelinate axons and partially regenerate nerve fibres (Richter and Roskams 2008) they do not seem to have a great deal of the ability to cross the MS associated lesion and or to reconnect with neurons on the opposite side of the lesion. It is thought that due to this process of repair not being overly apparent most of the benefit for the use of OEC comes from the promotion of the growth of intact fibres. However, in the case of spinal injury it has been shown that, to at least some degree, these cells have the ability to stimulate neuroprotection, activate angiogenesis and stimulate axon re-growth as well as remyelination (Richter and Roskams 2008). Another benefit of these cells is that in some cases they have been suggested to restore a degree of functions lost due to the CNS lesions. However, there is very little immunological data to support this conclusion, which was derived mainly from behavioural tests (Barnett and Riddell 2004). It is thought that the most useful way to utilise this type of cells may be to use them in parallel with other synergistic treatments. This would produce a combination treatment with the potential to regenerate axons but also reconnect the damaged connections across the compromised areas of the CNS which OEC alone are unable to do (Barnett and Riddell 2007).

3.4 T-cell therapy

Another cellular treatment for MS which differs from all the previous treatments as it does not involve remyelinating cells is T-cell therapy. When thinking of ways to tackle autoimmunity one of the most obvious candidates for cellular therapy has to be regulatory T-cells due to their role in maintaining immunological self tolerance within the body. This CD4+CD25+ cell surface marker positive family of cells within the body is in part to control

the immune response and therefore seem an obvious choice for cellular therapy for MS. It is known that in the peripheral blood of patients with MS there is a significant decrease in the functionality of T-regulatory cells (Viglietta, Baecher-Allan et al. 2004) when compared to healthy controls, which shows this may be a causative mechanism behind the disease and readdressing this balance may go some way to alleviating autoimmunity.

It has been shown in animal models that adoptive transfer of such T-regulatory cells has a positive effect on models of autoimmune disease (Jiang, Lechler et al. 2006), in some cases offering a significant degree of protection from the disease (Kohm, Carpentier et al. 2002) and therefore poses a degree of therapeutic potential in the treatment of MS. The therapeutic potential of these cells is based on their ability to suppress the function of auto reactive T helper cells in-vitro and to show a significant potential for in-vivo treatment as well. There is also the possibility of targeting these cells in-vivo with other drugs in an attempt to expand an antigen specific population of these cells to tackle the autoimmune response in the MS patients.

Another form of T cell therapy which has been proposed is the use of inflammatory CD4+ T cells. These cells have long been thought to have little therapeutic potential in CNS autoimmunity but it has been proposed by a group in Israel that a lack of CD4+ immune cells recruited to the CNS may affect the immunological balance in the CNS further and exacerbate inflammation within the system (Schwartz and Shechter 2010). Their theory is that these CD4+ T cells must be recruited to the CNS to modify areas of local inflammation and also to aid the protective process through the recruitment of blood-borne monocytes (Schwartz, London et al. 2009). Many current therapies for MS involve treatment with immunosuppressive drug regimes which will strongly inhibit the ability of these inflammatory T cells to perform the proposed protective function and it has thus been proposed that a boost of such a T cell response to carefully chosen CNS proteins may act to improve and not hinder the immunological response against the localised inflammation.

In summary, although cellular therapies for MS are often focused around stem cells, it is evident that non stem cell therapies have an important role to play. They do in most cases provide a safer, more ethical and more practical option of treatment compared to stem cells but may not posses as much treatment potential. However, this is not to say they are less effective than the treatments currently available. Like stem cells, the different types of these cells give non stem cell cellular therapies both remyelination and immunomodulatory potential. These cells have the potential to be used on their own or in combination with other therapies. With steps being taken to improve their efficacy (such as genetic alteration in the case of Schwann cells), they could become mainstream treatments in the fight against MS.

4. Conclusion

The devastating effect MS has on the lives of affected individuals and those close to them demands that this field of research be at the forefront of treatment development. The lack of current effective and curative therapies for this disease makes the advancement of cellular treatments all the more important as a new more effective line of treatment. The outstanding potential of cellular therapies to cover all bases in terms of treatment of MS including immunomodulation, neuroprotection and remyelination makes them impossible to ignore as they realistically have the most potential of any field of treatment currently available. Their potential is almost limitless with the variety of different effects the different cellular

treatments can have on the disease and how these could fit the needs of individual patients and their specific disease circumstances.

The challenge to take these cellular therapies from being full of potential to being effective treatment options is one thousands of researchers around the world are working on every day. They strive to remove the issues which at the moment are holding back the clinical potential of these 'shining light' treatments in order to be able to offer patients diagnosed with MS hope that it may be possible to restore the myelin architecture within their CNS and to overcome the disease. The treatment options for MS are currently insufficient but the encouraging point is that the field is constantly moving forwards. With cellular based therapies at the forefront of this advancement it will give sufferers of the disease hope that better treatments and better prognosis may be just around the corner.

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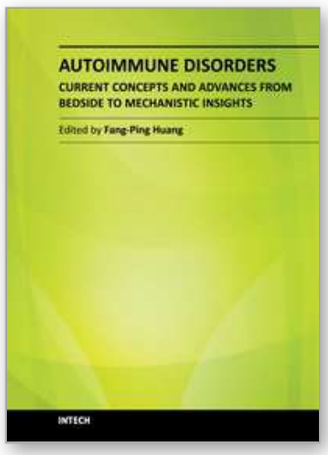

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Autoimmune disorders are caused due to break down of the immune system, which consequently fails in its ability to differentiate "self" from "non-self" in the context of immunology. The diseases are intriguing, both clinically and immunologically, for their diversified clinical phenotypes and complex underlying immunological mechanisms. This book offers cutting-edge information on some of the specific autoimmune disease phenotypes, respective diagnostic and prognostic measures, classical and new therapeutic options currently available, pathogenesis and underlying mechanisms potentially involved, and beyond. In the form of Open Access, such information is made freely available to clinicians, basic scientists and many others who will be interested regarding current advances in the areas. Its potential readers will find many of the chapters containing in-depth analysis, interesting discussions and various thought-provoking novel ideas.

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