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Full Length Research Paper

Transplantation of olfactory ensheathing cells for treatment of inflammatory demyelinating diseases in the central nervous system

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Demyelinating diseases are typical responses of the white matter of the central nervous system to detrimental factors such as infection, poisoning, degeneration and malnutrition. Of them, inflammatory demyelinating diseases including multiple sclerosis and acute disseminated encephalomyelitis are most commonly found. The current paper discusses the pathomechanism of inflammatory demyelinating diseases and experimental as well as clinical possibilities of olfactory ensheathing cells (OECS) for their treatment, and compares OECS with Schwann cells and oligodendroglias in clinical use. Renewed research efforts are required to investigate the molecular biology of OECS regarding the existing disadvantages of OECS transplant.

Key words: Demyelinating diseases, nerve regeneration, functional recovery.

INTRODUCTION

Demyelinating diseases of the central nervous system (CNS), such as multiple sclerosis (MS) still lie in the focal attention of clinicians in terms of treatment, as they pose heavy financial burdens and mental stress to patents as well as their families. The only possible approach is to regenerate myelin sheath at the affected sites. Over the past few years, researchers have investigated the possibility of cell replacement in which transplant cells with capacities of migration, differentiation, transformation and regeneration of myelin sheath safely reach the target areas without tumor-causing tendency.

Recently, researchers at home and abroad have turned their attention to the olfactory ensheathing cells (OECS), the cells from olfactory mucosa for treatment of these diseases. OECS is taken from the lining of the nose. When the olfactory cells are added to a solution containing a scar reducing compound, and the combined solution is added to a damaged spinal cord in rats, the spinal cord was shown to regenerate resulting in a recovery of sensation and movement. The olfactory ensheathing cells provide an environment that promotes axon growth. The goal of this paper was to discuss the pathomechanism of inflammatory demyelinating diseases and experimental as well as clinical possibilities of olfactory ensheathing cells (OECS) for their treatment, and compare OECS with Schwann cells and oligodendroglias in clinical use.

CONCEPTS RELEVANT TO THE INFLAMMATORY DEMYELINATING DISEASES OF CNS

Myelin sheath functions to protect CNS neuraxons and aid the transmission of nerve impulse as well as insulation. The formation and structural maintenance of myelin sheath rely on oligodendroglias and intact neuraxons, as well as blood supply. Thus the demyelinating diseases can be observed in cases of neuron diseases such as amyotrophic lateral sclerosis, cerebral ischemic attacks, and CNS lesions. MS in most cases is considered to be

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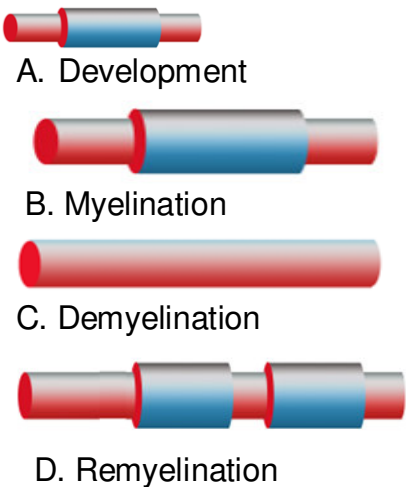

Figure 1. The relationship between thickness/length of myelin sheath and size of axons during myelination and remyelination. A: myelin sheath formed by oligodendrocytes in the developmental stage; B: the thickness/length of myelin sheath change following axonal grow; C: demyelination of axons, and D: Spontaneous remyelination caused by oligodendrocytes.

an autoimmune disease, that is, a typical inflammatory demyelinating disease.

Inflammatory demyelinating diseases are probably T-cell mediated autoimmune diseases targeted at the myelin antigen of CNS (Merson et al., 2010). Histologically, MS is characterized by random lesions in CNS, active MS features in acute and chronic demyelinating lesions, apoptosis of oligodendrocytes at different degrees, activation of microglias, and invasion of active astrocytes, as well as change to neuraxons (Irvine and Blakemore, 2008). Automatic regeneration of myelin sheath is sometimes observed when a thin myelin sheath surrounds neuraxons and the interval between neuraxon segments shortens. Regrettably, the automatic regeneration of myelin sheath is changeable and it may be incomplete or absent under many conditions. Lack of myelin sheath regeneration not only damages the transmission of electrical signals, but also leads to secondary lesions due to loss of neuraxons caused by lasting demyelination (Ziehn et al., 2010; Soulika et al., 2009).

AUTOMATIC REGENERATION OF MYELIN SHEATH IN THE DEMYELINATING DISEASES OF CNS

The major cell mechanism of myelin sheath regeneration is that some premature oligodendrocyte precursor cells (OPCs) proliferate, migrate and differentiate into oligodendroglias that form myelin sheath coating the neuraxons (Einstein et al., 2009; Rosenbluth and Schiff, 2009). Basically, the regeneration of myelin sheath is

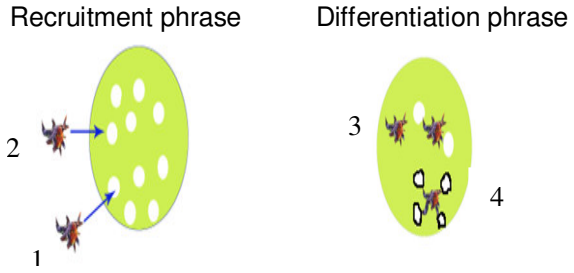

Figure 2. Process of myelin sheath formation. 1: Proliferation of oligodendrocyte precursors; 2: Migration of oligodendrocyte precursors; 3: Oligodendrocytes wrap up axons, and 4: Myelin sheath formation.

similar to the development of myelin sheath, during which some major myelin proteins are expressed in the same sequence (Slavin et al., 2008), regulated by seemingly the same transcriptional factors. However the regeneration and formation of myelin sheath differ in some aspects. As the diameter and the length of neuraxons increase during the development, those of myelin sheath also increase, while the diameter and the length of neuraxons stay unchanged during regeneration because myelin sheath during demyelination is mature. Thus the neuraxons following regeneration of myelin sheath have myelin sheath shorter and thinner than the normal (Dubois-Dalcq et al., 2008) (Figure 1).

Another cell origin of automatic myelin sheath repair is the precursor cells in the subventricular zone (SVZ) (Menn et al., 2006; Zhao et al., 2008), which originate from the nerve stem cells expressing GFAP. Induced by the cytokines produced in inflammation and demyelination, the precursor cells rapidly transform into oligodendroglias when spreading from SVZ (Delaunay et al., 2008) (Figure 2).

Schwann cells (SCs) are recently identified among the cells involved in regeneration of myelin sheath. In some cases of MS, SCs are detected in spinal cord and cerebella, and produce peripheral nervous system (PNS) myelin surrounding demyelinating neuraxons. SCs migration to CNS is a natural repair mechanism (Compston et al., 2006).

The regeneration of myelin sheath following MS is complicated, and interwoven with the inflammatory response. The natural immune microglias play a critical role in the regeneration. In the acute or chronic MS lesions, the active microglias form a cytotoxic inflammatory environment. This accelerates MS progression due to tissue damages on the one hand; clears the apoptotic inflammatory immune cells, oligodendroglias, and myelin debris, and thus inhibits inflammation to create a favorable environment for regeneration of myelin sheath and neuraxons, induced by IFN-γ, M-CSF, GM-CSF and IFN-β on the other hand (Neumann et al., 2009). Existing data demonstrate that tissue recovery as well as regeneration of myelin sheath is accompanied with

inflammation, and several steps during inflammation are indispensable to maturation of oligodendroglias and regeneration of myelin sheath (Wolswijk, 2002; Totoiu et al., 2004). Microglias also directly promote regeneration of myelin sheath through excretion of some cytokines (Merson et al., 2010; Setzu et al., 2006).

Many cytokines produced during demyelination are dependent on contexts to environments in terms of biological activities. The factors such as IFN-γ, TNF-α, IL-1β, IL-2, IL-6, and IL-12 mediate the tissue damages, and are also dispensable in the regeneration of myelin sheath (Arnett et al., 2001; Arnett et al., 2003; Selvaraju et al., 2004). Some other cytokines such as IFN-β as an immunoregulating factor control the level of autoimmunity and, or even switch the inflammation process to the anti-inflammation process to protect nerve tissues (Weinstock-Guttman et al., 2008).

TGF-β secreted by active microglias and macrophages is also a multi-functional factor that plays a key role in inducting immunotolerance. TGF-β is a potent inhibitor for inflammation, and also promotes differentiation of OPCs (Herrera-Molina and von Bernhardi, 2005; Qian et al., 2008). Homogeneous IGF-1 together with TGF-β inhibits late proliferation of OPCs and advances differentiation and formation of myelin sheath (Kotter et al., 2005).

Semaphorins are a group of molecules for signal transduction for the neuron development. *In vitro* experiments find that semaphorins 3A and 3F respectively repulse or attract embryonic OPCs. Research results demonstrate that these two semaphorins are differentially expressed in the peripheral gliacytes in the active MS lesions and the neurons with demyelinating neuraxons, and that the high expression of semaphoring 3F in the lesions attracts OPCs and contributes to regeneration of myelin sheath (Spassky et al., 2002; Williams et al., 2007).

There is evidence showing that small molecules distributed on the surface of neuraxons may control the thickness of the regenerated myelin sheath during regeneration of myelin sheath (Hu et al., 2006), e.g. lack of Tag1 leading to a thin myelin sheath. Some other factors on the surface of the demyelinating neuraxons are even more important: The high expression of Nrg1 and Laminin2 in the damaged neuraxons appears in the acute MS lesions and they aid identification of neuraxons by OPCs and thus mediate production of myelin sheath (Colognato et al., 2007).

LIMITATIONS OF AUTOMATIC MYELIN SHEATH REGENERATION IN THE INFLAMMATORY LESIONS

Though the regeneration of myelin sheath begins in the early stage of the inflammatory demyelinating diseases, this process is inadequate considering functional recovery requirements. The adequacies are:

1. Inflammatory factors such as TNF, IFN-γ, and IL-1β are highly expressed in the MS lesions. Many cytotoxic molecules are produced by activated microglias and macrophages including protease, lipolytic enzyme, active oxygen, glutamic acid, inflammatory factors (Lassmann, 2008; Ransohoff and Perry, 2009), astrocytes concentration, and opening of the blood-brain barrier that induces inflammatory cell invasion. These factors directly damaging myelin-forming cells result in a low level of OPCS and effective action cells are thus lacked.
2. Fas is highly expressed by OPCs in the lesions and thus the lesions are easily affected by apoptosis mediated by Fas1 (Aktas et al., 2006).
3. OPCs has a poor ability to migrate and only covers a small area, whereas OPCs migrating to the demyelinating areas are attacked by secondary demyelination (Mothe and Tator, 2008; Sher et al., 2009).
4. Proliferation of astrocytes in the lesions inhibits regeneration of myelin sheath by OPCs. This reactively proliferated strocytes lack regulators for expression of neu, that is, the effective promoters of myelin sheath regeneration (Stangel and Hartung, 2002).
5. The disorderly demyelination is different from the myelination during the development: When the demyelinating neuraxons are wreathed by densely degenerated myelin, the neuraxons maintain demyelination or slow regeneration.
6. The regulators for formation of myelin sheath during development are re-expressed in the MS patients to inhibit regeneration of myelin sheath. PSA-NCAM is re-expressed in demyelinating neuraxons, FGF2 is expressed, and Lingo-1 expressed in oligodendroglias and neurons (Zhou et al., 2006; Mi et al., 2005; Lee et al., 2007).
7. In chronic lesions of MS, chondroitin sulfate proteoglycans and glycosaminoglycans abnormally concentrate to inhibit repair of lesions (Sherman and Back, 2008).
8. The lesions lack growth factors and nutrition factors, leading to inhibition of proliferation and migration of OPCs.

UNIQUE FEATURES OF OECS AND THE EFFECT ON DEMYELINATION

The olfactory epithelium of mammalians has a capacity of regeneration in all the life. Regarding different species, the olfactory epithelium upgrades every 4 to 8 weeks. The neural precursor cells originating from the deep layer of the olfactory epithelium migrate to the apical part of the epithelium and grow the neuraxons that are accompanied by OECs from the olfactory epithelium. The neuraxons permeate the sieve plates and project to the direction of olfactory tubercles over the PNS-CNS interface and connect to the neurons inside the olfactory tubercles (Zhu et al., 2010; Rela et al., 2010). OECs wreathe the olfactory channel centered by the olfactory nerves, preventing their contact to other peripheral gliacytes.

Even after the olfactory nerves are severed, they can be connected to the targets inside the olfactory tubercles under the guidance of OECs.

OECs have characteristics of both SCs and astrocytes. Though OECs in normal conditions cannot promote formation of myelin sheath for neuraxons of the olfactory nerves, some animal experiments show that they facilitate myelin sheath regeneration for demyelinating neuraxons (Mothe and Tator, 2008; Sher et al., 2009; Franklin, 2003; Shi et al., 2010). If they are transplanted to the demyelinating spinal cord, they form myelin, similar to the peripheral PO formed by SCs (Franklin, 2003; Shi et al., 2010). Other experiments demonstrate that transplanted OECs recover the transduction rate of CNS neuraxons and improve frequency response, thus overcoming the signal transduction blocking due to demyelination of neuraxons.

COMPARISON BETWEEN OECS AND OLIGODENDROGLIAS AND SCS AS TRANSPLANTED CELLS IN TREATMENT

Earlier research (Herrera et al., 2001) demonstrated that the oligodendroglia replacement repaired the CNS damages due to demyelination. However MS lesions executed self immunity towards oligodendroglias and thus oligodendroglias were subjected to secondary immune attack, not like OECs and SCs as peripheral nerve cells expressing different antigens thus avoiding attacks. Moreover, compared with OECs and SCs, it is difficult to collect oligodendroglias, while the former two theoretically may be collected from the patients themselves.

Other studies demonstrate that though SCs transplant alone induces remyelination and myelination for neuraxons without myelin sheath, transplant of SCs and astrocytes causes a wider regeneration area and evidently improve the transduction from neuraxons with myelin sheath regeneration (Shields et al., 2000; Oudega and Xu, 2006), indicating that SCs transplant is inadequate for treatment of demyelinating diseases and astrocytes induce cell signal transduction for SCs migration (Mothe and Tator, 2008; Sher et al., 2009). Compared with OECs, SCs only cause a limited regeneration area, while OECs form myelin sheath centering the transplant receiving area expanding to a millimeter-radius range. Additionally, SCs repulse astrocytes when coculturing: Transplanted SCs only form myelin sheath in areas short of astrocytes, and they are unable to promote regeneration of neuraxons wrapped by process of astrocytes through promoting astrocytes circling the neuraxons. Thus SCs are not a good choice for repair of damages to myelin sheath (Franklin, 2003).

Regeneration of myelin sheath following OECs transplant is like sheath formation after combined transplantation of SCs and astrocytes (Shields et al., 2000; Oudega et al., 2006). Following OECs transplant, a relatively thick myelin is formed, accompanied with a large amount of cytoplasm and nucleus surrounding the demyelinating neuraxons, a result from a single OECs forming myelin sheath for a single neuraxon segment. As a unique type of cells in the neurogliacytes, OECs are the only gliocytes that can cross the PNS-CNS interface. As they show the phenotypes of astrocytes, after transplant to the CNS lesions, they only cause astrocyte transformation in the recipient, and evidently adapt to the recipient environment ((Zhu et al., 2010; Rela et al, 2010; Richter et al., 2005).

IMMUNITY AND INTERVENTION FOR OECS TRANSPLANT

It was thought that the MHC antigen level was low because CNS lacked a complete lymphatic system and the blood-brain barrier existed. Thus CNS was considered as an immune privileged site. Additionally, the brain tissues locally produced immune suppression factors including TGF-β and lymph-related factors that had functions such as local anti-inflammation, anti-mitosis, and downregulation of cytokines (Li et al., 2006). Though inflammation causes change to internal environment in MS, the brain tissues are still immunetolerant and non-responsive. This immune privilege, however, is limited, and complete immune action mechanism still exists in the brain. Despite a slower rejection reaction in CNS than in other systems, CNS still produces immune-globulins, and MHC related to immune response are expressed on the neuron surface.

Currently, OECs in clinical practice are often collected from the embryonic olfactory tubercles as embryo express low MHC thus with low immunity. However in experiments on mice and monkeys (Hudson et al., 1994), homeotransplantation of embryo induced anti-transplant immune response in the recipient, indicating that neuron transplant requires HLA matching to relieve rejection reaction, like other organ transplants, to enable long-term survival and function of transplant cells. Monoclonal anti-bodies such as anti-IL-2 receptor as immune regulators also prolong OECs survival following transplant.

Many international institutions are trying to apply autotransplantation of OECs to cure CNS lesions. Researchers in Australia use olfactory mucosa autograft to treat advanced paraplegia (Mackay-Sim et al., 2008). In Portugal, autotranplantation of olfactory mucosa is applied to treat spinal cord lesions (Feron et al., 2005). Follow-up for years demonstrate nerve function recovers at certain degrees. Autotransplantation prevents immune rejection and risks in ethics.

PROSPECT OF OECS AND EXISTING PROBLEM

Generally speaking, demyelinating diseases such as MS are treated in the following approaches: (1) Activation of

endogenous repair mechanism; (2) Provision of exogenous myelinating cells; and (3) Inhibition of detrimental factors that damage myelin-forming cells. The increase of endogenous regeneration of myelin sheath fails in clinical practice (Stangel and Hartung, 2002), and the third approach to inject intravenous immunoglobulins achieves no desired results. Researchers thus turn their attention to cell transplant to cure the demyelinating diseases, especially OECs transplant likely to be put into clinical practice. Currently, global efforts are made to advance autotransplantation of OECs in clinical practice. Genetic modification for heterograft has also paved a road for this technique into clinical practice.

As there is lack of understanding of the biology of OECs, there are also weaknesses for the application of OECs. Firstly, the cell source is inadequate, and autotransplantation of OECS still requires investigation. Besides autotransplantation, immunosuppressants are necessitated. Secondly, purification of transplant cells is still in debate. Delucia et al. (2003) and Santos-Benito and Ramon-Cueto, (2003) stressed cell purification, considering that primary culturing achieved no desired results due to cell pollution. Franklin et al. (2003) and Lakatos et al. (2003) thought OECs transplant mixed with some meningocytes promote regeneration of myelin sheath by OECs. Thirdly, the timing is difficult to control. Whether to transplant OECs in the acute phase or in the chronic phase is still uncertain. Fourthly, in what degree the transplant environment and components of the transplant determines the phenotype of OECs is not decided yet. Fifthly, transplanted OECs only show phenotype of myelination to some extent. How to optimize the phenotype of myelination to promote regeneration deserves renewed efforts. Sixthly, there is lack of understanding of exogenous OECs in terms of immune regulation for the inflammatory demyelinating disease.

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