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Demyelinating diseases and potential repair strategies

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Abstract

Demyelination is associated with a number of neurological disorders including multiple sclerosis (MS), spinal cord injury and nerve compression. MS lesions often show axon loss and therefore reparative therapeutic goals include remyelination and neuroprotection of vulnerable axons. Experimental cellular transplantation has proven successful in a number of demyelination and injury models to remyelinate and improve functional outcome. Here we discuss the remyelination and neuroprotective potential of several myelin-forming cells types and their behavior in different demyelination and injury models. Better understanding of these models and current cell-based strategies for remyelination and neuroprotection offer exciting opportunities to develop strategies for clinical studies.

Keywords

demyelination; remyelination; peripheral myelin forming cells; transplantation

1. Introduction

Demyelination in the central nervous system (CNS) occurs due to a variety of pathophysiological conditions. Perhaps the most notable is demyelination associated with multiple sclerosis (MS). MS is thought to be an autoimmune disease characterized by inflammatory lesions throughout the brain and the spinal cord. MS lesion sites can present with both distinct demyelination and with axonopathy [1]. Impulse conduction is either blocked or slowed in these lesion sites resulting in neurological symptoms. Demyelination can also occur in traumatic spinal cord injury and in cerebral infarction. In contusive spinal cord injury the spinal cord often presents with a central necrotic core, but areas of demyelinated axons are present outside of this region. Apoptotic oligodendrocytes have been observed in experimentally induced spinal cord injury models at considerable distances of the injury sites [2]. Thus, interventional approaches to encourage CNS remyelination have relevance to a number of immunologic and traumatic CNS disorders.

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2. Experimental models of demyelination

Experimental models of demyelination are an important tool to study prospective therapeutic strategies. A well-established model to study a MS-like disease in animals is experimental autoimmune encephalomyelitis (EAE). Rodent EAE is induced by immunization with an appropriate myelin antigen and can take the form of a monophasic or chronic relapsing disease. While this model system in many ways mimics MS in humans, it represents a distinct experimental pathophysiological condition. Advantages of the EAE model include its similarity to MS by its inflammatory nature and its multifocal lesion distribution. Disadvantages for experimental studies include the unpredictability of lesion location and the variability with time of lesion pathology. Other model systems for demyelinating lesions are genetic or chemically induced. The genetic models are not truly demyelinating lesion models, but amyelinating or dysmyelinating models; congenital absence of myelin and poor myelin formation, respectively. However, these genetic mutant models do have representation in human pathophysiology. Unlike MS or EAE, lesions in the areas of poor myelination in the genetic mutant models are noninflammatory. Pelizaeus-Merzbacher disease is a congenital disease where myelin does not form appropriately in the CNS of children. This disease is genetically related to a defect in the proteolipid protein (PLP) [3]. It is thought that PLP is essential for compact myelin formation in the CNS. A rat mutant model, the myelin-deficient (*md*) rat, has a point mutation in the PLP gene. These animals have virtually no central myelin, although peripheral myelin is normal. An advantage of this model system as opposed to EAE for cell transplantation studies for remyelination is the certainty and stability of lesion site for CNS cell injection. Therefore, presence of myelination after cell transfer into the *md* rat clearly demonstrates the contribution of donor cells [4]. Indeed the first demonstration of restoration of conduction velocity by cell transplantation in myelin-deficient CNS was observed in this model system [4]. Another commonly used dysmyelinating mutant model is the shiverer (*shi*) mouse, which has a defect in the myelin basic protein (MBP) gene that results in no or poor CNS myelination[5].

The first demonstration of myelination by cell transplantation was in the shiverer [6]. A number of cell types including neural precursors can remyelinate the shiverer brain after intraventricular injection or direct injection into the brain [7–10]. A recent study demonstrated extensive remyelination in the shiverer following transplantation of human oligodendrocyte progenitors [10]. While important in demonstrating the potential of transplanted myelin-forming cells to repair white matter of genetically dysmyelinated axons, these genetic dysmyelinating model systems do not provide direct information on the potential of transplanted cells to repair adult demyelinated CNS. An alternative approach to study demyelination in the adult CNS is to employ chemically mediated demyelination. In order to control the site of demyelination, demyelinating agents, such as diphtheria toxin, lysophosphatidylcholine (LPC) or ethidium bromide (EB) have been injected directly into CNS tissues to induce focal sites of demyelination. Cuprizone intoxication is a commonly used model of experimental demyelination and remyelination. An advantage of this model is that oral dosing of cuprizone can be used to induce predictable demyelination in the corpus callosum and superior peduncles [11–13]. While all of these toxin models initially lead to destruction of myelin, rodents show endogenous remyelination after several weeks. In order to significantly delay this endogenous remyelination process, a model has been developed using focal x-irradiation prior to chemically induced remyelination by EB; the x-irradiation blocks mitosis and proliferation of endogenous myelin-forming progenitor cells [14]. Thus, this model system (X-EB) allows for prolonged (6–8 weeks) focal demyelination in the adult rodent spinal cord. In this model system the ethidium bromide chelates nucleic acid and kills cells preserving axons. Thus, when central white matter is targeted, all glia cells including astrocytes and oligodendrocytes are killed. While this aglial lesion is unique and does not represent a naturally occurring process, it does provide an important experimental environment to study first

principles of axo-glial interactions. The relatively long time window of persistent and locally defined demyelination in the adult rodent spinal cord in this model system allows the study of the remyelinating potential of transplanted cells in the adult CNS.

As important as these chemically induced models of demyelination are for studying axo-glial interactions in vivo and the potential for engrafted cells to form myelin, the fate of transplanted cells into an inflammatory lesion such as EAE, which is more representative of MS, is not well understood. EAE typically shows disseminated inflammation in the CNS which makes it difficult to target a consistent lesion site for cell transplantation. Kerschensteiner et al. [15] developed a model to induce a focal or targeted EAE inflammatory lesion in the dorsal funiculus of the rat spinal cord making this model amenable to cell transplantation and electrophysiological analysis. Lewis rats were immunized with rMOG (1–125) at subclinical levels that did not induce disseminated disease. About three weeks later, intraspinal injections of proinflammatory cytokines (TNF- α and IFN- γ) were microinjected into the dorsal funiculus of the spinal cord. The resulting focal inflammatory white matter lesion was similar to those observed in disseminated EAE. The inflammatory infiltrate in the focal EAE lesion is primarily composed of macrophages (ED1⁺-cells) and to a lesser extent perivascular and parenchymal T cells (CD3⁺-cells) [15]. Both ascending dorsal column (sensory) and descending corticospinal tract (motor) axons are affected by the dorsal funiculus lesion. While extensive demyelination is observed in dorsal column axons in this model system, severe axon loss occurs in the corticospinal tract. Thus, potential effects of cell transplantation on axotomy and demyelination can be studied separately in this inflammatory lesion model. This group also developed a focal EAE model in the cortex [16]. This cortical demyelination model is of particular interest because of recent studies indicating cortical demyelination in MS patients [17,18]. Fundamental questions in terms of the viability of cells implanted into an inflammatory lesion and the potential of transplanted cells to repair chronic demyelination lesions, which are gliotic, may be addressed using these focal models and have important implications for cell-based therapies in MS.

3. Endogenous myelin repair and potential stimulation of endogenous progenitors

Spontaneous or endogenous remyelination occurs in most rodent models of demyelination. When rat spinal cord white matter is chemically demyelinated, substantial endogenous remyelination occurs by about three weeks [19]. The remyelinated spinal cord axons show patterns of both central- and peripheral-like myelin. The origin of cells responsible for this endogenous repair of myelin is thought to derive from spinal cord progenitor cells and invasion of peripheral Schwann cells. However, recent work suggests that Schwann cells can be derived from central progenitor cells and at least some of the peripheral-like myelin observed in spinal cord may be centrally derived [20–22].

In contrast to rodents endogenous repair of myelin in humans and non-human primates is much more limited. Pathological studies on CNS in demyelinating diseases indicate the potential of limited regions of endogenous remyelination [23]. These areas of remyelination in MS patients are observed in the outer margins of an MS lesion site. They are characterized by thinly myelinated, oligodendrocyte-like myelinated axons in non-inflammatory stable lesions. These putative areas of remyelination in MS patients are referred to as shadow plaques. Thus, while rodents have a robust endogenous remyelination potential in the CNS, this process is much more limited in humans. However, a recent study indicates that a subpopulation of MS patients has extensive remyelination [24]. This difference of the endogenous repair potential between rodents and humans presents an experimental challenge. Rodent model systems must be carefully employed for interventional studies if they are to be extrapolated to humans.

Pharmacological approaches, such as application of neurotrophic factors and mitogens (e.g. bFGF and EGF) to enhance remyelination in humans are limited; they have not achieved extensive myelin repair. If stimulation of endogenous cells to remyelinate the human CNS cannot be achieved, an alternative approach may be to isolate and expand human myelin-forming progenitor cells in vitro, and to reintroduce them into the demyelinated human CNS via cell transplantation approaches. Thus, while myelin-forming cells in the form of progenitors may be present in the adult CNS, in vitro manipulation, expansion and reintroduction into the CNS (cell transplantation) of these cells may be required to achieve an appropriate therapeutic outcome [25].

4. Transplantation of myelin-forming cells for axonal repair

Remyelination and improvement in conduction has been demonstrated following transplantation of oligodendroglial lineage cells [4,26,27] Schwann cells [28], olfactory ensheathing cells (OECs) [29,30] and various types of stem cells [20,31–33]. Given the success of cell transplantation to form functional myelin in animal models, myelin-forming cell transplantation has been suggested as a potential repair strategy for demyelinated CNS axons [19,27,28,34].

One of the cell types mentioned above, the OEC, has attracted much recent attention as a candidate for cell therapy. OECs can remyelinate central [29,34,35] and peripheral [36] axons. Moreover, they can be harvested from biopsy of the nasal mucosa which offers the possibility of autologous cell transplantation. Several clinical studies are ongoing using OECs [37–40].

Adult olfactory neurons continually undergo turnover from an endogenous progenitor pool, and their nascent axons grow through the olfactory nerves and cross the PNS-CNS interface, where they form new synaptic connections in the olfactory bulb [41]. OEC, associates with olfactory receptor neurons from their peripheral origin to their central projection in the outer nerve layer of the olfactory bulb [42]. This putative support role of OECs in axonal growth within the adult CNS has spawned extensive research to study the potential of OEC transplants to encourage axonal regeneration and functional recovery in spinal cord injury models [43–48]. Transplantation of OECs into injured spinal cord is associated with axonal regeneration and functional improvement even when transplantation is delayed [49,50]. In these animals, myelinated axons spanning the lesion site display a characteristic peripheral pattern of myelination similar to that of Schwann cells myelination [34,44–48]. Moreover, engrafted OECs provide an environment that supports the development and maturation of nodes of Ranvier and the restoration of impulse conduction in central remyelinated axons [51].

While the precise mechanism responsible for functional recovery after OEC transplantation is not fully understood, several mechanisms including remyelination, plasticity associated with novel polysynaptic pathways and recruitment of endogenous Schwann cells have been suggested to contribute [52–54]. The apoptotic cell death of M1 cortical neurons is reduced and cortical neuronal density is increased following OEC transplantations [55]. Enhanced levels of BDNF were observed in the OEC transplanted lesion site. Locomotor function was also improved in the OEC transplanted group. Since axonopathy can be profound in MS lesions, it will be interesting to determine in experimental models of EAE whether cellular transplantation can reduce axonopathy.

5. Conclusions

Cell-based therapeutic approaches are being considered for a number of neurological diseases. Improved neurological function in EAE has been reported following intravenous infusion and neurosphere-derived multipotent precursors [56,57] and bone marrow-derived stem cells [58]. Suggested mechanisms include reduction of inflammatory infiltration

(immunomodulation), thus reducing demyelination and axon loss, and elevation of trophic factors that may be neuroprotective or stimulate endogenous oligodendroglial cells. Extensive research indicates the potential of oligodendrocytes and their precursors, Schwann cells, OECs and a number of stem cell types to remyelinate axons. Following spinal cord injury transplantation of OECs results in considerable functional improvement. Indeed, OECs are being used in clinical studies for spinal cord injury [37–40]. While experimental studies demonstrate that myelin-forming cell transplantation into acute sites of demyelination leads to remyelination, the repair potential of cell transplantation into chronic gliotic lesions is unknown. Future work to study the behavior and reparative potential of cell transplantation into acute and chronic inflammatory CNS lesion will certainly be important in terms of evaluating cell transplantation for MS.

List of Abbreviations

BDNF	brain-derived neurotrophic factor
bFGF	basic fibroblast growth factor
CNS	central nervous system
EAE	experimental autoimmune encephalomyelitis
EB	ethidium bromide
EGF	epidermal growth factor
IFN-γ	interferon-gamma
LPC	lysophosphatidylcholine
M1	primary motor cortex
MBP	myelin basic protein
<i>md</i>	myelin-deficient rat
MS	multiple sclerosis
OECs	olfactory ensheathing cells
PLP	proteolipid protein
PNS	

	peripheral nervous system
rMOG	recombinant myelin oligodendrocyte glycoprotein
<i>shi</i>	shiverer mouse
TNF-α	tumor necrosis factor-alpha
X-EB	X-irradiation and ethidium bromide injection

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