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Transplantation Options for Therapeutic Central Nervous System Remyelination

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Persistent demyelination, in addition to being the major pathology of multiple sclerosis and the leucodystrophies, is also a feature of spinal cord trauma where there is evidence that it contributes to the functional deficit. In experimental animals it is possible to remyelinate demyelinated CNS axons by transplanting cultures containing central or peripheral myelinogenic cells. Using functional testing we have been able to show that transplant-mediated remyelination results in restoration of function lost as a consequence of demyelination. Glial cell transplantation may therefore provide a therapeutic strategy for remyelinating areas of chronic demyelination. This article reviews issues that have to be addressed before glial transplantation can be undertaken in humans. These include: what cells to use, where would the cells come from, and can we predict how much remyelination will be achieved? It concludes that the most promising approach will be to use neural multipotential stem cells isolated from embryonic CNS, expanded in vitro as neurospheres and then committed to oligodendrocyte lineage differentiation prior to implantation. However, even with such preparations, which have considerable myelinating potential, the extent of remyelination that will be achieved cannot currently be predicted with any degree of certainty.

Key words: Oligodendrocytes; Schwann cells; Transplantation; Demyelination; Remyelination

INTRODUCTION

Persistent demyelination, in addition to being the major pathology of multiple sclerosis and the leucodystrophies, is also a feature of spinal cord trauma where there is evidence that it contributes to the functional deficit (11,36). In experimental animals it is possible to remyelinate demyelinated CNS axons by transplanting cultures containing central or peripheral myelinogenic cells (8). Myelin sheaths made by transplanted glial cells enhance action potential conduction (20,21,39) and we have been able to show that both normal and transplant-mediated remyelination results in restoration of function lost as a consequence of demyelination (22). In addition, Schwann cell and olfactory ensheathing cell transplantation, in the form of "bridges," provides a means of stimulating regeneration of CNS axons (19,32). Glial cell transplantation may therefore provide a therapeutic strategy for remyelinating areas of chronic demyelination and stimulating axon regeneration. However, before glial transplantation can be undertaken in humans as a treatment in situations where endogenous remyelination has failed, a number of issues have to be resolved. The most important of these are: will the procedure be safe, and will it be effective in restoring function lost as a consequence of chronic demyelination?

WILL INTRODUCTION OF GLIAL CELLS INTO AREAS OF DEMYELINATION BE SAFE?

The experience gained from human and xenogenic tissue grafting for the treatment of Parkinson's disease indicates that the introduction of exogenous cells into the human brain is not an inherently hazardous procedure providing donor tissue is monitored for potentially harmful pathogens. It has been our experience that the injections of suspensions of glial cells into areas of acute demyelination does not damage axons provided the suspensions do not have very high numbers of astrocytes and that they contain some cells that have the capacity to generate myelin sheaths (unpublished observations). The injection of embryonic tissue that has the potential to generate neurons leads to the development of classical neural grafts that can act as space-occupying lesions in the context of white matter tracts (unpublished observations). However, if the transplant is prepared in such a way that avoids this outcome then injection of myelinogenic cells would appear to be a sufficiently safe proce-

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dure to proceed to clinical trials that primarily involve assessment of safety and also the feasibility of detecting remyelination (Phase I clinical trials).

A central issue to be addressed prior to such clinical trials is whether transplanted glial cells are able to remyelinate large areas of demyelination. In order to resolve this issue we need to know the answers to three related questions: what cells to use, where would the cells come from, and can we predict how much remyelination there will be following the introduction different types of cells?

WHAT CELLS WOULD BE MOST APPROPRIATE TO TRANSPLANT?

The main animal models in which transplant-derived remyelination has been demonstrated are: (i) naturally occurring myelin mutants (rats, mice, and dogs) where a mutation, duplication, or deletion of a major myelin protein gene prevents the formation of normal myelin in the CNS, and (ii) focal areas of gliotoxin-induced demyelination in the spinal cord of adult rodents. Remyelination in these animal models can be effected by transplantation of tissue fragments containing a mixture of cell types or by purified populations of cells expanded in vitro. Oligodendrocyte lineage cells, Schwann cells, and olfactory bulb ensheathing cells all remyelinate axons following transplantation. Within the oligodendrocyte lineage, the oligodendrocyte progenitor cell has been the focus of much attention, partly because it is the cell responsible for endogenous remyelination and partly because it was shown to produce more myelin over a larger area than later stages of the lineage when transplanted into the myelin-deficient shiverer mouse (40). This last observation was to be expected given the greater capacity for division and migration of the immature cell in vitro (31). Recent data suggest that cells earlier in the oligodendrocyte lineage than the A2B5+ progenitor may have an even greater capacity for extensive transplantation-derived remyelination (2,12,23,43).

Self-renewing multipotential neural stem cells that can differentiate into neurons, astrocytes, and oligodendrocytes can be isolated from both the embryonic and adult rodent brain and can be expanded in vitro as clusters of cells in serum-free medium containing EGF or FGF-2. A more restricted differentiation develops when these multipotential neural stem cell clusters are expanded under the influence of medium conditioned by the B104 neuroblastoma cell line (2,43). Such clusters are termed oligospheres, and it is significant that implantation of oligospheres into the spinal cord of the myelin-deficient rat results in larger areas of myelination than implantation of neurospheres (26,42).

AVAILABILITY OF HUMAN MYELINOGENIC CELLS

Although oligodendrocytes can be obtained from the adult human CNS in relatively large numbers, these cells fail to generate myelin sheaths when transplanted into demyelinated rat CNS (38). On the other hand, implantation of fetal human CNS tissue into the developing rodent brain results in the generation of myelination-competent cells (35). Until recently, this implied that if glial cell transplantation using CNS cells was to be developed clinically, it would be necessary to use human fetal tissue. This posed a major problem. Not only would the ethical issues and availability of human fetal tissue have to be confronted, it would also be necessary to develop methods to generate large numbers of oligodendrocyte progenitors from such tissue. Although some oligodendrocytes can be generated in vitro from early human embryonic CNS tissue (29,34), injection of such cultures into areas of demyelination in immunosuppressed rats is not followed by extensive remyelination (S. Chandran and W. F. Blakemore, unpublished observations). The requirement for large amounts of human fetal CNS tissue to develop ways of generating significant numbers of oligodendrocyte progenitors has recently been resolved by the demonstration that myelination-competent cells can be generated from human multipotential neural stem cells expanded in vitro as neurospheres (9) or as immortalized cell lines (13). In addition, in vitro conditions have been established for the generation of tissue-specific embryonic stem cell lines from human blastocytes (39). This ability to generate large numbers of neural stem cells from a single aborted fetus or a blastocyte removes one of the major obstacles to considering oligodendrocyte progenitors as the cell of choice for developing glial cell transplantation as a clinical therapy in humans. However, unlike the situation in the rodent, the in vitro conditions required for commitment of human neural multipotential stem cells to the oligodendrocyte lineage have yet to be established. Recent experience with implanting porcine tissue rich in neural precursors into areas of acute demyelination in immunosuppressed rats has indicated that significant oligodendrocyte remyelination can only be achieved if the cell preparation is manipulated in vitro to remove its potential to generate neuroblasts. In the absence of such treatment, space-occupying neural grafts develop (P. M. Smith, C. Svendson, R. Barker, and W. F. Blakemore, unpublished observations). The demonstration of such potential warrants caution and, taken with the superior remyelinating potential of oli-

gospheres over neurospheres, strongly suggests that in vitro manipulation to achieve commitment to oligodendrocyte differential will be essential if neural multipotential cells are to find a place in the treatment of chronic demyelination.

Obtaining human Schwann cells presents far fewer problems. In vitro purification and expansion of human Schwann cells has already been achieved (25,28) and thus cells from a nerve biopsy could provide an autologous source of cells for transplantation. A greater number of cells could be obtained from a split-fascicle biopsy of a larger nerve or allogeneic cells could be generated from peripheral nerves of cadaveric organ donors. Much less work has been done on human olfactory ensheathing cells, but there is little reason to doubt that they can be isolated and grown in vitro from a biopsy using protocols similar to those used in the rat (3).

REMYELINATING CAPACITY OF DIFFERENT CELL TYPES

To date most transplantation studies have been conducted either in developing animals or using models of acute demyelination in adult animals in which the area available for myelination by the transplanted cells is small, approximately 1–2 mm^3. These situations do not mimic the situation found in potential target situations in humans. Here the areas of demyelination are chronic and/or the areas to be myelinated are large. MS is characterized by multiple areas of chronic demyelination with axons set within an astrocyte environment while in the leucodystrophies there is loss of myelin throughout the neuraxis. Thus, if extensive remyelination, a requirement for restoration of function, is to be achieved, implanted cells will have to migrate widely. Our ability to predict whether this will be achieved depends on the cell type to be used. In the case of Schwann cells we can predict that myelination will be limited for reasons discussed in the next section. However, the extent of remyelination that may be achieved following the introduction of oligodendrocyte progenitors is more difficult to predict because of our incomplete knowledge of CNS remyelination and limitations imposed by the models currently used for transplantation experiments.

Remyelination by Transplanted Schwann Cells

Schwann cells myelinate CNS axons most extensively when there is a combination of disruption of the glia limitans and the presence of axon that should be myelinated (16). For example, following the injection of ethidium bromide into white matter tracts—a procedure that results in death of both astrocytes and oligodendrocytes, leaving demyelinated axons in an astrocyte-depleted environment—there is widespread remyelination by Schwann cells (4). This Schwann cell remyelination can be prevented if astrocytes are introduced into the subarachnoid space to reconstruct the glia limitans (17), or when mixtures of oligodendrocyte progenitors and astrocytes are transplanted into the area to reconstruct a normal CNS environment (7). Because astrocytes prevent Schwann cells from gaining access to demyelinated axons, would it be possible to achieve remyelination by transplanting Schwann cells into areas depleted of astrocytes? Such a situation can be created in the cat spinal cord by injection of ethidium bromide into white matter exposed to 40 Gy of x-irradiation to prevent spontaneous remyelination. When Schwann cells are introduced into such lesions, where demyelinated axons cross a fluid-filled cystic cavity, it is apparent that in the absence of astrocytes and an extracellular matrix the transplanted cells are prevented from engaging and myelinating axons. Schwann cell remyelination is only observed near to the injection point, either in association with blood vessels or adjacent to basal lamina-covered astrocytes, both of which are situations where an extracellular matrix is present (5,6). Moreover, transplanted cells that make contact with axons away from either blood vessels or astrocytes can be observed associating with axons but failing to form myelin sheaths, mimicking their inability to myelinate axons in vitro in the absence of a stable extracellular matrix (10). Thus, there is a curious paradox that the ability of transplanted Schwann cells to gain access to demyelinated axons is impaired by the presence of astrocytes, while their ability to myelinate may require the production of an extracellular matrix that astrocytes are able to provide. The nature of the complex interactions between astrocytes and Schwann cells places serious limitations on their potential usefulness as therapeutic cells for chronic demyelinating diseases. It should be pointed out that all studies so far conducted have used adult animals and/or cells expanded in vitro as Schwann cells and thus the repair potential of embryonic Schwann cells has not been evaluated.

Remyelination by Transplanted Oligodendrocyte Lineage Cells

Most of the studies that have demonstrated the oligodendrocyte-generating potential of mutipotential neural stem cells and extensive migration of transplanted myelinogenic cells have been conducted in the immature nervous system. It is clear from our own work that progenitor cells behave very differently when introduced into the adult CNS. Thus, despite their capacity to migrate in vitro, during development and after implantation into the developing nervous system, supernumerary oligodendrocyte progenitors do not survive following implantation into normal adult white matter and are there-

fore unable to migrate (15,30). They do, however, survive and differentiate into oligodendrocytes when implanted into areas of demyelination and will migrate in normal white matter if it has been subjected to doses of x-irradiation sufficient to deplete the tissue of endogenous precursors (15,24,30). This latter observation demonstrates that although the adult CNS cannot support oligodendrocyte progenitor survival and migration in its native state, it is amenable to modification to enable it to do so.

Although numerous studies have now shown that transplanted oligodendrocyte progenitors can myelinate demyelinated axons, there have been only a very limited number of studies that give an indication of the extent of remyelination achievable following the introduction of a given number of cells into an area of chronic demyelination in adult individuals. This paucity of information arises for three reasons. First, although the total number of cells implanted is always given for individual transplantation experiments, the precise composition of the culture from which the transplant is obtained is often not known. In most instances the cell preparations represent cultures enriched for cells of the oligodendrocyte lineage. Second, the survival time following transplantation is usually short because the animals into which they have been introduced do not live long. Most experiments using the myelin-deficient rat have to be terminated after 2–3 weeks and animals subjected to the x-irradiated ethidium bromide protocol are killed after 1 month because of the potential for developing radiation necrosis. This lack of data is important, as it is now clear from studies on endogenous remyelination that, contrary to our previous understanding, remyelination can be a protracted process (18,37,42). Third, the environments into which cells have been implanted may have a beneficial effect on the remyelinating ability of the transplanted cells compared with environments containing chronically demyelinated axons. For example, when cells are introduced into young animals they are being introduced into a situation where myelination is or would normally be occurring. Similarly, when cells are transplanted into acute demyelinating lesions they are being introduced into a situation undergoing endogenous remyelination. These situations do not resemble potential clinical situations in humans, where cells would be introduced into situations where endogenous remyelination has failed and where axons are set in a matrix of astrocyte processes. It is clear from in vitro studies that astrocytes have an inhibitory effect on movement of oligodendrocyte progenitors (14), can influence process formation by oligodendrocytes (27), and in some experiments actually inhibit myelination by reducing oligodendrocyte numbers (33). Thus, despite the knowledge that one can remyelinate areas of demyelination and restore function by transplantation, and that the cells with the greatest remyelinating potential are cells at the pre-oligodendrocyte progenitor stage of development, we lack the quantitative information that would allow us to predict the extent of remyelination that might be achieved following transplantation of a given number of cells of a particular phenotype into an area of chronic demyelination. However, exciting results from Ian Duncan's laboratory indicate that when the right cells are used and animals are allowed to survive long enough remyelination can be very extensive (1).

PROSPECTS FOR CLINICAL APPLICATION

The recent progress with human multipotential neural stem cells means that human therapy would not require excessive amounts of human embryonic tissue. Although it may take some time to define the in vitro conditions necessary to obtain oligodendrocyte pre-progenitors from human multipotential neural stem cells, serious consideration should be given to the practicalities of clinical trails.

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