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Invited Review

Olfactory ensheathing cells: potential for glial cell transplantation into areas of CNS injury

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Summary. Ensheathing cells are the glial cells that ensheath olfactory axons within both the PNS and CNS portions of the primary olfactory pathway. These glial cells express a mixture of astrocyte-specific and Schwann cell-specific phenotypic features, support axonal growth by olfactory as well as by non-olfactory neurons, and survive transplantation into injured areas of the CNS.This review article focuses on those phenotypic features that are expressed by ensheathing cells that make them ideal candidates for transplantation into wound cavities in the damaged spinal cord of humans. Although much work remains to be done before such a therapeutic approach can be tried, the likelihood that ensheathing cells could simultaneously perform the roles of both astrocytes and Schwann cells following transplantation is the justification for developing such a therapeutic approach using animal models of spinal cord injury.

Key Words: Ensheathing cells, Olfactory bulb, Phenotype, Transplantation

Introduction

Axons inside fiber tracts of the central nervous system (CNS) are intimately associated with either astrocytes or oligodendrocytes, whereas in peripheral nerves the axons are ensheathed by Schwann cells. The transition in this glial cell ensheathment occurs abruptly inside spinal cord and nonolfactory cranial nerve rootlets as the axons cross the PNS-CNS transitional zone (Fraher, 1992). Axons are the only structures that pass through the glia limitans of this transitional region (Fraher, 1992). The histology of the PNS-CNS transitional region of the first cranial nerve, however, is very different from that just described. Most importantly, there is no abrupt transition between the tissue of the PNS (i.e. the rootlet) and CNS (i.e. the nerve fiber layer of the olfactory bulb), such as one sees in other nerve rootlets (Doucette, 1991). In fact, the same type of glial cell ensheaths the olfactory axons, all of which are unmyelinated, on both sides of this transitional zone. These glial cells, which are referred to as ensheathing cells (Doucette, 1984, 1990), possess a highly malleable phenotype, express a mixture of astrocyte-specific and Schwann cell-specific phenotypic features, and perform the roles of both astrocytes and Schwann cells (Doucette, 1990, 1993a; Doucette and Devon, 1993). As a result, there has been much debate as to whether they belong to the astrocyte or the Schwann cell family (Barber and Lindsay, 1982; Norgren et al., 1992; Pixley, 1992; Ramon-Cueto and Nieto-Sampedro, 1992; Doucette, 1993b) or whether they may even represent a novel glial cell type (Barnett et al., 1993; Doucette and Devon, 1993). Regardless of the outcome of this debate, the transplantation of ensheathing cells into areas of spinal cord injury should be pursued as part of a therapeutic approach to treating paralysis.

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Olfactory ensheathing cells perform astrocyte-specific and Schwann cell-specific functions

Ensheathing cells have a highly malleable phenotype, most likely as a result of their co-expressing phenotypic features of astrocytes and Schwann cells (see Doucette and Devon, 1993 for a review). Thus, they probably have the ability to become more astrocyte-like or more Schwann cell-like as the need arises. Devon and Doucette (1992) recently demonstrated just how malleable the phenotype of ensheathing cells could be. They co-cultured ensheathing cells with dorsal root ganglion (DRG) neurons and showed that these glial cells myelinated the DRG neurites, assembling peripheral type myelin in the process. These myelinating ensheathing cells were each surrounded by their own basal lamina covering, a situation that was identical to the manner in which Schwann cells myelinate axons. It is not known whether the expression of a myelinating phenotype by ensheathing cells precludes the expression of astrocyte-specific phenotypic features, such as contributing to the formation of the glia limitans (Berger, 1971; Barber and Lindsay, 1982; Doucette, 1984;

Doucette, 1990, 1993a; Valverde and Lopez-Mascaraque 1991) or the expression of central type glial fibrillary acidic protein (Barber and Dahl, 1987). It also remains to be determined whether ensheathing cells, like Schwann cells (Eldridge et al., 1987; Eldridge et al., 1989), must be apposed to a basal lamina covering in order to assemble a myelin sheath.

For brain areas outside of the olfactory bulb, the formation of a glia limitans is the exclusive domain of astrocytes (Peters et al., 1990). In the olfactory bulb, however, astrocytes share this role with ensheathing cells (Berger, 1971; Barber and Lindsay, 1982; Doucette 1984, 1990, 1993a; Valverde and Lopez-Mascaraque, 1991). These two cell types share this role everywhere except at the PNS-CNS transitional zone of the first cranial nerve, where it is ensheathing cells that have the exclusive role of forming the glia limitans (Doucette, 1991, 1993a). This situation arises as a result of the developmental sequence of events that occur during the formation of the nerve fiber layer of the olfactory bulb in mammalian embryos (Doucette, 1989; Marin-Padilla and Amieva, 1989). The culmination of this sequence of events is a gradual reduction in the ensheathing cell contribution to the glia limitans of the olfactory bulb and a concurrent increase in the astrocyte contribution as one progresses distally from the nerve root entry zone (Doucette, 1991, 1993a). It has been noted that olfactory nerve rootlets do not always immediately fuse with the ventral surface of the bulb, but may travel within the subarachnoid space for quite a distance prior to piercing the glia limitans along the lateral, medial or dorsal surfaces of the bulb (Doucette, 1991, 1993a). At these bulbar surfaces it is common to find olfactory nerve rootlets that are in the process of entering the nerve fiber layer of the bulb, thus explaining why ensheathing cells continue to form part of the glia limitans at locations other than the ventral surface of the bulb. The functional significance of this unique glial cell arrangement at the PNS-CNS transitional zone of the olfactory nerve is that it may play a vital role in the regenerative ability of olfactory receptor neurons to extend their axons into and within the CNS of adult mammals.

Ensheathing cells are apposed to a basal lamina only where these glial cells contribute to the formation of the glia limitans (Berger, 1971; Barber and Lindsay, 1982; Doucette, 1984, 1990, 1993a; Valverde and Lopez-Mascaraque, 1991). Throughout the nerve fiber layer of the bulb, the plasma membranes of ensheathing cells within the olfactory fascicles come into close contact with the astrocytes that occupy the spaces between the fascicles. The absence of an intervening basal lamina at such locations indicates just how well the ensheathing cell is integrated into the CNS. In other words, astrocytes recognize the ensheathing cell as a normal constituent of the CNS.

The peripheral type myelin that is assembled by ensheathing cells when co-cultured with DRG neurons contains galactocerebroside and myelin basic protein (Devon and Doucette, 1992), but it is not yet known which additional myelin associated molecules are also present. Ensheathing cells would actually be expected to express a nonmyelinating phenotype when grown in vitro, because these cells only ensheath unmyelinated axons in vivo and thus would not have expressed myelin associated molecules at the time of plating. In neuron-free cultures, ensheathing cells do indeed fail to express myelin associated molecules, even when examined within the first few days after plating (Barnett et al., 1993; Doucette and Devon, 1994a,b; however, see Ramon-Cueto and Nieto-Sampedro, 1992). Like Schwann cells, the full expression of a myelinating phenotype by ensheathing cells is heavily dependent on their making contact with appropriately sized axons. Even growth media that are known to promote the expression of a myelinating phenotype by oligodendrocytes (Doucette and Devon, 1994a), or the partial re-expression of such a phenotype by Schwann cells (Doucette and Devon, 1994b), were ineffective on ensheathing cells. It would appear that in ensheathing cells the synthesis of myelin associated molecules and their assembly into a myelin sheath is under a different regulatory control than it is in either oligodendrocytes or Schwann cells. Clearly, this is an area that is ripe for further investigation.

Manipulating the cellular environment of lesion cavities

The cellular environment of a lesion cavity in the brain or spinal cord is one of the big obstacles encountered by regenerating axons in the CNS of adult mammals. Numerous attempts have been made to manipulate this cellular environment to create one more conducive to supporting axonal growth. These manipulations have included the transplantation of Schwann cells or immature astrocytes (Kromer and Cornbrooks, 1985, 1987; Smith et al., 1986; Silver, 1988; Neuberger et al., 1992), both of which provide excellent support for growing axons, and of genetically modified cells that synthesize and secrete large amounts of specific growth factors (Cunningham et al., 1991; Kawaja et al., 1992). Other manipulations have been aimed at altering the phenotype of the glial cells that contribute to the formation of scar tissue at the site of injury (Kiernan, 1979; Tator and Fehlings, 1991). Although these attempts have achieved some degree of success in promoting the survival of injured neurons and/or in encouraging axonal growth into and through the lesion, a number of problems remain to be solved (see Tator and Fehlings, 1991; Reier et al., 1992 for reviews). For example, although it is desirable to alter the astrocytic response to brain injury so that the host astrocytes facilitate rather than hinder axonal growth, these glial cells must still be allowed to reestablish the glia limitans, which separates neural and non-neural tissues, and to promote the establishment of a functional blood-brain barrier upon the restoration of a blood supply to the injured area. Furthermore, the glial cells

must also be able to phagocytose necrotic material, to encourage and sustain the growth of axons into the lesion cavity, to promote the growth of axons into distal regions of brain tissue, to reconstitute the ionic milieu, and to remyelinate the larger axons to allow for the proper conduction of action potentials.

In effect, none of the cell types that have been used thus far to manipulate the cellular environment of the lesion cavity are able to perform all of these functions. Schwann cells can myelinate axons, and either Schwann cells or genetically modified fibroblasts have the capacity to promote extensive axonal growth, but neither cell type will contribute to the restoration of the glia limitans or the blood-brain barrier nor will either of them become incorporated into the CNS (Kromer and Cornbrooks, 1985, 1987; Berry et al., 1988; Chen et al., 1991; Kawaja et al., 1991; Franklin et al., 1992; Montero-Menei et al., 1992; Neuberger et al., 1992). Astrocytes, on the other hand, if isolated from the cerebral hemispheres of fetuses, support axonal growth, control scar formation, and become integrated into the host CNS (Smith et al., 1986; Smith and Miller, 1991), but cannot remyelinate axons.

It has been suggested that the expression of Schwann cell-specific phenotypic features by ensheathing cells facilitates the growth of olfactory axons into and within the CNS of adult mammals (Doucette, 1990) and that ensheathing cells could simultaneously perform the roles of both astrocytes and Schwann cells (Doucette and Devon, 1993). Admittedly, the expression of a mixed phenotype makes it difficult to decide exactly where to place ensheathing cells in the different families of glial cells, but it is consistent with the hypothesis (Doucette, 1984, 1990; Raisman, 1985; Ramon-Cueto and Nieto-Sampedro, 1994) that ensheathing cells make the primary olfactory pathway more hospitable to growing axons. Their malleable phenotype thus makes them an ideal candidate for glial cell transplantation into areas of CNS injury. Ensheathing cells normally reside within the CNS and thus would probably not be extruded from non-olfactory areas of the CNS, as may happen with Schwann cells and genetically-modified fibroblast cell suspensions. In fact, due to their ability to express astrocyte-specific phenotypic features, ensheathing cells could contribute to the reconstitution of the glia limitans and of the blood brain barrier in the injured area. Admittedly, these roles can also be performed by immature astrocytes when transplanted into a lesion cavity, but such glial cells, being obtained from aborted human fetuses, would be more difficult to obtain.

Ensheathing cells could not only promote the growth of regenerating axons but could also remyelinate the larger of these axons, possibly even in the presence of astrocytes. Doucette (1990) presented preliminary evidence that some ensheathing cells extend processes to envelop scattered myelinated (non-olfactory) axons of the olfactory nerve fiber layer and suggested that they might be responsible for myelinating these axons. Of significance here is the fact that there are no oligodendrocytes in the nerve fiber layer of the bulb (Doucette, 1990, 1993a). Neurites of an appropriate diameter can be myelinated by ensheathing cells (Devon and Doucette, 1992), which is consistent with their being the cells responsible for myelinating axons in vivo in the olfactory nerve fiber layer. Schwann cells, on the other hand, not only fail to become integrated into the CNS, but astrocytes somehow perturb the neuron-Schwann cell interactions that lead to myelination (Franklin et al., 1992; Guenard et al., 1994).

Conclusion

Schwann cells are good promoters of axonal growth, and under certain conditions even astrocytes have been shown to possess growth-promoting properties (Smith et al., 1986; Ard et al., 1987; Ard and Bunge, 1988; Neugebauer et al., 1988; Silver, 1988; Bahr and Bunge, 1989; Hatten et al., 1991; Kawaja and Gage, 1991). However, promoting axonal growth in the injured spinal cord of adult mammals is only one of many problems that must be overcome in the treatment of spinal cord injury (Collins and West, 1989). Although it is unlikely that any one glial cell type can correct all of these problems, what is sorely needed is a cell that can adopt several different roles as the need arises. This is exactly what ensheathing cells appear to do (Doucette and Devon, 1993), being able for example to switch their phenotype from that resembling an astrocyte to one more like that of a myelinating Schwann cell (Devon and Doucette, 1992). It is very likely that ensheathing cells will be able to combine the roles of astrocytes and Schwann cells when transplanted into a lesion cavity, due to their having a highly malleable phenotype (Doucette and Devon, 1993).

Ensheathing cells possess the necessary molecular mechanisms to facilitate axonal growth (Doucette, 1990, 1993c; Devon and Doucette, 1992) and were found to support the regeneration of DRG axons in vivo when they were placed inside semipermeable polymer tubes (Lustgarten et al., 1991) or transplanted into the dorsal root entry zone of the spinal cord (Ramon-Cueto and Nieto-Sampedro, 1994). Ensheathing cells also support the growth in vitro of dopaminergic neurons from the substantia nigra of fetal rats (Denis-Donini and Estenoz, 1988) and of retinal ganglion neurons from chick embryos (Goodman et al., 1993). These findings are mentioned not to imply that ensheathing cells will promote axonal growth better than either Schwann cells or immature astrocytes. Rather, it is hypothesized that they will differ from Schwann cells in reconstituting the glia limitans and blood brain barrier and in allowing maximal re-entry of axons into the host tissue on the caudal side of the lesion. Furthermore, they will differ from astrocytes in being able to remyelinate the regenerating axons. As we learn more about their cellular phenotype, a fluorescent activated cell sorter could be used to obtain purified populations of ensheathing cells from an autologous nasal mucosal

biopsy (Lanza et al., 1993). Such a procedure is likely to yield a sufficient number of viable cells, given the fact that Ramon-Cueto and Nieto-Sampedro (1994) obtained their ensheathing cells from the olfactory bulbs of adult rats and used them for transplantation experiments involving the dorsal root entry zone of the spinal cord. Due to the high proliferative rate of ensheathing cells in serum-containing media it will be relatively easy to expand cultures initiated from mucosal biopsies to increase the cell yield and/or to genetically modify them to further enhance their axonal growth-promoting ability.

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