MIGRATION OF SCHWANN CELLS

REQUIREMENTS FOR SCHWANN CELL MIGRATION WITHIN CNS ENVIRONMENTS: A VIEWPOINT

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Abstract—Schwann cells are able to migrate into the CNS and myelinate CNS axons in a number of developmental and pathological situations. Morphological studies based on normal, mutant, and experimentally-lesioned tissue have indicated that Schwann cells are only able to enter the CNS when the integrity of the astrocytic glia limitans is disrupted. The significance and subtlety of the interactions between Schwann cells and astrocytes have been further explored by glial cell transplantation studies. These studies support in vitro observations on Schwann cell behaviour in highlighting the importance of extracellular matrix for both migration and myelin sheath formation. The failure of Schwann cells to intermix with astrocytes is an important aspect of glial cell biology which will have a bearing on efforts to remyelinate demyelinated axons by Schwann cell-transplantation.

Key words: Schwann cells, astrocytes, Schwann cell-transplantation, migration, demyelination, PNS-CNS interface, glia limitans.

The central nervous system can be defined as that part of the nervous system enclosed within an environment of neuroectoderm-derived astrocytes. Its boundaries are defined by the glia limitans, the basal lamina-covered layer of astrocyte processes which lies beneath the pia mater and next to blood vessels. Although Schwann cells can occasionally be found associating with axons within the normal central nervous system, they are not a normal cellular component of the undamaged central nervous system. However, Schwann cells can migrate into areas of damaged CNS where they remyelinate axons that were once myelinated by oligodendrocytes and enclosed within the astrocytic environment of the CNS. This review will examine the circumstances under which Schwann cells enter the CNS in normal and pathological situations in order to identify the rules by which this invasion and migration are governed.

Central to an understanding of what influences migration of Schwann cells into and within the CNS are the answers to the following three questions: what attracts the Schwann cells into the CNS in pathological situations where they are found myelinating CNS axons, what prevents or limits their entry in normal and pathological situations, and what substrates do the cells need for movement? By reviewing the behaviour of Schwann cells under normal and pathological circumstances, and testing hypotheses arising from such studies by glial cell transplantation, it is possible to provide some of the answers to these questions.

SCHWANN CELL-ASTROCYTE INTERACTIONS IN NORMAL ANIMALS AND MYELIN MUTANTS

At the transition zone between PNS and CNS, where cranial and spinal nerve roots join the neuraxis, there is an orderly transition from Schwann cell myelination to oligodendrocyte myelination of axons, which is accompanied by the appearance of astrocytes at the node of Ranvier where the transition takes place. At this point of transition the astrocyte surface abutting the Schwann cell is invariably covered by a basal lamina which is continuous with that of the glia limitans. This sharp demarcation is even seen in situations where CNS axons are not myelinated, such as the myelin-deficient rat and the jimpy mouse. A similar demarcation is also seen in rare situations close to the root transition zone where “islands” Schwann cells are occasionally found myelinating CNS axons or where “islands” of central glial cells occur in nerve roots in normal animals, where Schwann cells are occasionally found myelinating CNS axons in normal animals, and more extensively in mutants such as the Browman-Wyse rat. Thus, in situations where there has been no pathological alteration to astrocytes there is a sharp transition from Schwann cell to central glia.
ensheathment of axons. The central glia ensheathment may be by astrocytes alone, or by oligodendrocytes and astrocytes. Intermixing of oligodendrocyte and Schwann cell myelination of axons is never seen in normal animals.

OBSERVATIONS ON THE BEHAVIOUR OF SCHWANN CELLS IN PATHOLOGICAL SITUATIONS WITHIN THE CNS

There are a number of pathological situations in which Schwann cell myelination of CNS axons occurs, and they are invariably associated with disturbance to the integrity of the glia limitans. Almost without exception, Schwann cell invasion only occurs when axons which should or could be myelinated by oligodendrocytes are present.

1. X-irradiation of the neonatal rat spinal cord

Following X-irradiation of the neonatal spinal cord, Schwann cells can be observed passing through the glia limitans and myelinating CNS axons. X-irradiation of the developing spinal cord just prior to myelination not only prevents the generation of myelin-forming oligodendrocytes but will also compromise the generation of astrocytes needed to accommodate the increase in size of the spinal cord which results from the rapid increase in axon diameter which precedes myelination. This failure of astrocytes to maintain the integrity of the CNS environment allows Schwann cells to enter the CNS and myelinate axons. It is useful to compare the X-irradiation situation to the myelin-deficient rat. In the MD rat there is a similar failure of myelination, due to degeneration of myelinating oligodendrocytes. However, in contrast to the X-irradiated neonatal cord, there is no compromise to the astrocytes. This means that the glia limitans remains intact throughout development, and hence there is no Schwann cell invasion (Fig. 1). The importance of the intact glia limitans in preventing this invasion is best illustrated by the observation that Schwann cells will myelinate CNS axons following X-irradiation of the spinal cord of MD rat neonates.

Fig. 1. i—This figure illustrates the surface of the spinal cord of the myelin-deficient rat at the point of entry of the nerve root (NR). In this mutant, the axons of the PNS, including the nerve roots, are normally myelinated by Schwann cells, but the axons comprising the CNS white matter tracts are unmyelinated due to the premature degeneration of oligodendrocytes. The presence of an intact astrocytic environment around these axons, including the basal lamina-coated glia limitans, prevents these axons from being myelinated by Schwann cells, in spite of their close proximity to the nerve roots. ii—Following transplantation of Schwann cells into the white matter of the myelin-deficient rat, Schwann cell myelination of the axons is limited. Moreover, it is localized to the point of injection where the astrocytes have been damaged by the trauma associated with the injection procedure itself.
Schwann cell migration

2. Trauma

Disruption of the glia limitans and demyelination of CNS axons are both consequences of spinal cord trauma. Schwann cell myelination of CNS axons is frequently seen following naturally occurring and experimentally induced spinal cord trauma. The axons of retinal ganglion cells of the rat are normally not myelinated. However, following trauma to the retina and choroid, Schwann cell myelination of these axons can be observed and it is of particular interest that the extent of Schwann cell myelination is influenced by the animals age. There are several possible explanations for this observation: (1) the recruitment signal for attracting Schwann cells is greater in developing animals; (2) Schwann cells become less responsive to these signals with age; or (3) the ability of astrocytes to exclude Schwann cells increases with age. When Schwann cells are found myelinating axons in the retina in this and other situations, the areas of myelination are restricted, indicating that factors other than the presence of axons available for myelination play a significant role in controlling Schwann cell myelination of CNS axons.

The tendency for Schwann cells to myelinate CNS axons in situations where astrocytes are compromised following trauma occurs in vertebrate classes other than mammals. Following crush lesions of the goldfish optic nerve there is a local loss of astrocytes. As the severed retinal ganglion cells regenerate through this region, the regenerated axons are myelinated by Schwann cells. Where the axons pass back into an astrocyte-containing area they are myelinated by oligodendrocytes.

3. Injection of gliotoxins into white matter tracts

When substances which kill glial cells (gliotoxins) are injected into white matter tracts of the spinal cord, there is a clear association between loss of astrocytes, the presence of demyelinated axons and the myelination of CNS axons by Schwann cells (Fig. 2). Thus, injections of ethidium bromide
and 6-aminonicotinamide into the dorsal columns of rats, substances which intoxicate both oligodendrocytes and astrocytes, results in extensive Schwann cell myelination of CNS axons, while lysolecithin, which is more selectively toxic to oligodendrocytes, results in Schwann cell remyelination being limited to the central parts of the area of demyelination. In the cat, for example, it is possible to produce Schwann cell myelination across almost the entire transverse area of the dorsal funiculus by the injection of 2 μl of 0.05% ethidium bromide. Results obtained with 6-aminonicotinamide are particularly interesting because they reveal how Schwann cells behave when they gain access to grey matter. In this location they relate to neurons and synapses in a manner similar to that seen in peripheral ganglia. Similar observation can be made following X-irradiation of the neonatal rat spinal cord and following systemic intoxication with a number of agents which show selective gliotoxicity.

4. Inflammatory demyelination

Schwann cell myelination of demyelinated axons can occur in some MS plaques, notably those in the spinal cord. It is most prevalent in Japanese MS patients who suffer a more fulminating form of the disease. It is also a feature of some experimentally-induced virus infections in experimental animals and certain forms of experimental allergic encephalomyelitis. Again, an association between astrocyte loss and Schwann cell remyelination is observed.

The common theme that emerges for all of these examples is the clear relationship between destruction of the astrocytes which constitute the glia limitans, the presence of demyelinated axons and Schwann cell myelination of CNS axons. The technique of glial cell transplantation has enabled this relationship to be studied in greater depth.

Fig. 3. The manner in which Schwann cells migrate within a glia-free area of demyelination becomes apparent when Schwann cells are transplanted into the sub-arachnoid space above an X-irradiated ethidium bromide lesion. Schwann cells enter the lesion along blood vessels (BV), using the perivascular extracellular matrix as a substrate. This same matrix enables the Schwann cells to remyelinate those demyelinated axons immediately adjacent to the blood vessel. Subsequently, remyelination proceeds in a stepwise manner away from the blood vessel, migrating Schwann cells using the basal lamina around established myelinating Schwann cells to reach an available length of demyelinated axon and then invest it with a new myelin sheath. The absence of an extracellular matrix within glia-free areas of demyelination means that Schwann cells are unable to migrate through areas containing only demyelinated axons. The absence of extensive Schwann cell remyelination at the edges of the lesion indicate that the extracellular matrix associated with astrocyte surfaces is a minor route of entry into the lesion from the sub-arachnoid space compared with the blood vessel route.
THE BEHAVIOUR OF SCHWANN CELLS PLACED NEAR TO OR INTO AREAS OF GLIA-FREE DEMYELINATION

If spinal cord white matter is subjected to 40 Grays of X-irradiation prior to inducing demyelination by the injection of gliotoxins, the normal repair response which follows such an injection does not take place (Fig. 2i). Consequently, the demyelinated axons remain demyelinated and the lesion can be used as a “test-bed” to examine how transplanted cells interact with demyelinated axons and each other in glia-free area of demyelination.

When a source of Schwann cells, in the form of a segment of predegenerated peripheral nerve, is placed over such areas of demyelination, Schwann cells migrate into the lesion and remyelinate the demyelinated axons.® With small species such as the rat, the remyelination is rapid and extensive. If, however, the experiments are undertaken in the cat and the transplantation is carried out 14 days after induction of demyelination, the larger size of the lesion together with the absence of inflammatory responses associated with the intraspinal injection, means that the routes by which this migration takes place can be more readily appreciated (Fig. 3). In this situation, the restriction of Schwann cell myelination to the perivascular region is striking. When such perivascular clumps of Schwann cells are examined in detail it can be seen that myelination is most advanced adjacent to the blood vessel, with earlier stages of remyelination (engagement, engulfment, spiralling etc) occurring at increasing distances away from the blood vessel. This pattern of remyelination indicates that the perivascular space represents an important avenue of migration for Schwann cells into the CNS, a conclusion supported by a number of other studies. Moreover, it also provides information on the manner in which Schwann cells move away from the blood vessel into areas of the lesion containing demyelinated axons. These areas contain no glial cells and the Schwann cells move through the axon environment in a stepwise fashion, engaging demyelinated axons only where they can maintain contact with an established Schwann cell. There was no evidence that Schwann cells could migrate along demyelinated axons which lay in an environment that was both glia-free and devoid of extracellular matrix. Thus, movement of Schwann cells through an environment consisting solely of demyelinated axons is very much more cautious than that through collagen containing areas where one observes multiple Schwann cells interacting with single axons so that remyelination...
of a lesion proceeds rapidly. These in vivo observations are entirely consistent with those made in vitro, where it was observed that Schwann cells would not myelinate along suspended fascicles of neurites, but were able to do so if they could maintain contact with a collagen-coated surface. In vivo the surface may be provided by extracellular matrix or cells, in particular those coated in basal lamina. A further important point to arise from these studies is that Schwann cells respond to a diffusible chemotactic signal, indicated by the migration of Schwann cells from a remote source in response to a lesion containing demyelinated axons. These signals have yet to be identified but the demyelinated axon itself seems a probable source.

An appreciation of how the Schwann cells' dependence on contact with a stable extracellular matrix will affect the cells' behaviour in the CNS is readily appreciated following the injection of Schwann cells into glia-free areas of demyelination in the cat (Fig. 4). When cells are injected into such a lesion they will come to rest next to demyelinated axons in association with one of three structures: (1) other demyelinated axons; (2) collagen relating to blood vessels or meningeal surfaces; or (3) astrocyte processes, which extend into the edges of the lesion from the adjacent normal tissue (compare Figs 3 and 4). As Schwann cell myelination is only observed in perivascular areas and adjacent to astrocyte surfaces, and was never seen around axons lying free in extracellular space, it can be concluded that in the CNS the stable surface which Schwann cells require to initiate myelination can be provided not only by collagen, but also by the surface of astrocytes. Where Schwann cells are observed myelinating demyelinated axons next to astrocyte processes the surface of these cells is invariably coated by a basal lamina.

Thus, Schwann cells can migrate towards demyelinated axons from a distant source and their major route of migration is along collagen-containing perivascular spaces. Within a lesion environment, migration occurs in association with cells coated in basal lamina such as astrocytes and myelinating Schwann cells.

Collagen is a key component of the extracellular matrix which permits Schwann cell migration and myelination. The extracellular space of the normal CNS contains no collagen, but it can be deposited during inflammation, especially when the integrity of the CNS is breached so that pial cells and Schwann cells gain entry into the CNS. Under such circumstances collagen is deposited in the extracellular space and on the surface of astrocytes. Thus in the absence of collagen deposition Schwann cells migration and myelination will be limited.

THE RELATIONSHIP BETWEEN ASTROCYTES AND SCHWANN CELLS IN AREAS OF DEMYELINATION AS REVEALED BY GLIAL CELL TRANSPLANTATION

The observations described thus far reveal a paradoxical role for astrocytes with regard to Schwann cell myelination in the CNS. While on the one hand the study of normal and pathological material suggested that the presence of astrocytes prevents Schwann cells entering the CNS, on the other hand, the transplantation studies so far examined indicate that the surface of astrocytes may promote Schwann cell behaviour by providing a surface for migration and myelination. Thus, it appears that astrocytes can play both an inhibitory and facilitatory role with regard to Schwann cell myelination. This apparent paradox has been resolved by glial transplantation studies which have indicated that the role played by astrocytes can be directly related to the arrangements they adopt within a repairing lesion.

Some years ago a series of transplantation studies were undertaken to formally test the hypothesis that astrocytes restrict Schwann cell access to CNS axons. These studies made use of the both the non-X-irradiated and X-irradiated ethidium bromide lesion in the rat spinal cord. Central to understanding these experiments are two observations. Firstly, the normal ethidium bromide lesion is mainly repaired by Schwann cells, with oligodendrocyte remyelination limited to astrocyte containing areas around the edges of the lesion next to normal white matter. Secondly, all glial cell cultures prepared from the CNS are contaminated by Schwann cells. This point was first established when cultures, ostensibly of CNS glia, were transplanted into non-repairing X-irradiated ethidium bromide lesions and resulted in areas of Schwann cell remyelination. Careful examination of the cultures revealed the presence of small numbers of Schwann cells (<5%), identified as cells co-expressing S100 and laminin or L1. Unless specific steps are taken to remove these cells, they have been identified in all subsequently prepared cultures of CNS glia. Thus,
following transplantation into the non-irradiated lesion, Schwann cells are of both host origin and transplant origin, whereas, in the X-irradiated lesion they are exclusively of transplant origin.

The predominantly Schwann cell-repaired ethidium bromide lesion can be changed to one where most remyelination is by oligodendrocytes by transplanting mixed CNS cultures. If the proportion of astrocytes within the transplant is reduced this change does not occur, and the majority of axons are remyelinated by Schwann cells despite the increased number of central myelinating cells. Taken together, these two results indicate that the presence of astrocytes is necessary to prevent extensive Schwann cell remyelination and is consistent with an inhibitory role for astrocytes. Interestingly, the shift towards oligodendrocyte remyelination is not as great if astrocytes alone are transplanted, a result which suggests that the ability of astrocytes to control the invasion of Schwann cells may be related to the availability of oligodendrocyte lineage cells. Following transplantation of a mixed culture, these cells are in abundance. However, following transplantation of astrocytes alone, the host is the only source of oligodendrocyte-lineage cells.

The interaction between oligodendrocyte-lineage cells and astrocytes in controlling Schwann cell invasion can be investigated further using the X-irradiated ethidium bromide lesion, where the presence of Schwann cells can be confined to the small contaminating population within the transplant. When a mixed population of central glia is transplanted into a non-irradiated lesion, all but a few axons are remyelinated by oligodendrocytes. However, as the proportion of transplanted oligodendrocytes is reduced, a level is reached below which the astrocytes within the transplant are unable to prevent the co-transplanted Schwann cells from becoming the dominant myelinating cell within the lesion. Thus, oligodendrocyte lineage cells are required in order for astrocytes to contain the small population of Schwann cells. When astrocytes are transplanted with a small contaminating population of Schwann cells and no oligodendrocyte lineage cells, the failure of astrocytes to control the Schwann cells again becomes evident. In this latter situation, transplanted astrocytes are confined to small, basal-lamina bound islands or clumps of cells that contain a few axons. The majority of axons remain outside these small islands and are remyelinated by Schwann cells, which presumably make use of the basal lamina associated with the astrocyte to migrate and myelinate (Fig. 4iii).

The arrangement adopted by transplanted astrocytes when oligodendrocyte-lineage cells are present or absent is therefore quite different. When oligodendrocytes are present the two cell types combine to reconstruct an extensive glial environment containing many oligodendrocyte remyelinated axons contained within a glia limitans. Schwann cell remyelination is restricted to those axons that are “outside”. Thus, the normal relationship between CNS and PNS is re-created by the transplanted cells. In the absence of oligodendrocytes, although a glia limitans is established by transplanted astrocytes most of the demyelinated axons lie “outside”. What is interesting to note is that when astrocytes are transplanted without Schwann cells, the tendency of astrocytes to aggregate so as to exclude demyelinated axons is not pronounced, suggesting that it is the Schwann cells that induce this behaviour in the transplanted astrocytes.

THE INTRODUCTION OF SCHWANN CELLS INTO A NORMAL CNS ENVIRONMENT

The ability of an established astrocytic environment to contain and limit the behaviour of Schwann cells within the CNS is most obviously revealed when Schwann cells are introduced directly into astrocyte containing areas. When Schwann cells are injected into the normal CNS, few if any cells can be detected 1 month after transplantation. Moreover, an astrocytosis is detected around the implantation site that appears to be induced by the Schwann cells. Thus, when Schwann cells are transplanted into the developing CNS, it appears that the Schwann cells are not merely confined to the area around the point of injection but are actively extruded by astrocytes when they do establish within the substance of the CNS. Attempts to introduce Schwann cells into areas containing large diameter unmyelinated axons and astrocytes, such as occurs in the retina, results in very little Schwann cell remyelination despite there being axons available to be myelinated. The same is also true of Schwann cell transplants into the myelin deficient rat (Fig. 1). It would therefore appear that not only are Schwann cells unable to gain entry into astrocytic environments in mature animals, but their presence also stimulates an astrocytic response.
CONCLUSIONS

In this review we have described a number of examples which support the notion that Schwann cell migration and remyelination within the CNS can be related to the presence or absence of an intact astrocytic environment. In essence, there is a “mutual exclusion” between the two cell types, a phenomenon which can be related to the epithelial properties manifested by both cells. A feature of epithelial cells is their association with a basal lamina along one surface, a feature also exhibited by both axon-associated Schwann cells and astrocytes of both the normal or reconstructed glia limitans. It is a basic principle of development that basal lamina formation separates non-compatible tissue elements and there is a sharp transition between one type of epithelial cell and the next when they share the same basal lamina, as occurs for instance in the respiratory and digestive systems. In these latter systems, if one cell type should degenerate, the territory previously occupied by that cell type can be taken over by its neighbour. This process will continue until viable epithelium is reached, when the invasion ceases and a new boundary is established. It would appear, therefore, that in their interactions astrocytes and Schwann cells manifest all the basic behaviour of epithelial cells. With this appreciation it is possible to predict what would happen if one tried to remyelinate multiple sclerosis plaques by transplanting Schwann cells without first removing the astrocytes which surround the demyelinated axons.

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