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NEUROLOGICAL LINEAGES AND NEUROLOGICAL DISEASES

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INTRODUCTION

While neuroglial cells have been regarded as "support cells" for neurons since the beginning of this century, it has been only in recent years that the nature of such "support" has begun to be appreciated. It is now clear that neuroglial cells provide neurons with essential substrates such as glutamine and remove or inactivate such toxic metabolic products as NH_{4+} (46,47,97,98), regulate activities of potassium and other ions in the extracellular space (56,57), and permit saltatory conduction of nerve impulses by forming myelin. In addition to these metabolic support functions, Schwann cells in the peripheral nervous system (PNS) synthesize many proteins necessary for neuronal development and survival; these include extracellular matrix constituents such as type IV collagen, fibronectin and laminin (5,6,14), cell adhesion proteins such as N-CAM and myelin associated glycoprotein (MAG) (51), and soluble proteins such as nerve growth factor (NGF) (2,29,30). Similar protein synthetic trophic functions are performed in central nervous system (CNS) by astroglia; these include the synthesis of extracellular matrix components and growth factors, for example insulin-like growth factor (1,13,20,21,58,65). It is now thought likely, as well, that neuroglia regulate the properties of the blood-brain barrier. CNS neuroglia, probably astroglia, induce brain capillaries to express the tight junction phenotype that is required for a competent blood-brain barrier (89) and it is possible that astroglia participate in the regulation of regional cerebral blood flow by modulating perivascular potassium concentrations (62).

This chapter will not focus on these "support" roles of neuroglia, but will address a closely related topic: how are the proliferation, differentiation, and metabolism of the various classes of neuroglia regulated under normal circumstances, and what are the consequences of perturbation of these regulatory mechanisms? We will review current information on the lineages of neuroglia of the peripheral and central nervous systems and their regulation and then briefly consider what is known about the functions and roles of these lineages in various human diseases.

S. U. Kim (ed.), *Myelination and Demyelination*

NEUROGLIAL LINEAGES

Peripheral Nervous System

The work of Le Douarin in chick-quail chimeras has been most valuable in documenting the differentiation of neural crest precursor cells into Schwann cells, autonomic and sensory neurons, neuroendocrine cells and melanocytes (42). Webster and coworkers employed classical electron microscopic observations to provide a clear picture of the subsequent segregation of Schwann cells into myelin-forming and non-myelinating adult phenotypes (93). Nerve cross-anastomosis experiments by several laboratories demonstrated plasticity of these Schwann cell phenotypes, with non-myelin forming Schwann cells capable of myelination if provided with an axon of appropriately large caliber. More recent immunohistological and molecular biological studies have provided further details on the effects of contact with axons of various caliber on the differentiation of Schwann cells. Schwann cells are induced by both large and small axons to express surface galactocerebroside and cytosolic proteolipid and to down-regulate surface expression of low affinity NGF receptors (86,88,95) but only by small axons to express a cytoskeletal protein resembling glial fibrillary acidic protein (18,35) and only by large axons to synthesize myelin (94).

The glial cells of the enteric nervous system were largely unstudied till the work of Jessen and Mirsky (34,35). Employing immunohistological methods, they demonstrated that these glia are irregular or multiprocess-bearing cells that express GFAP-like and glutamine synthetase immunoreactivity, in these respects resembling CNS astroglia.

Central Nervous System

Classical neuroanatomic techniques permitted identification of oligodendroglia, astrocytes, ependymal cells, and microglia in adult CNS and Muller cells in the retina. Astroglial foot processes were known to abut the basal lamina of CNS capillaries, and it was therefore presumed that astroglia regulate metabolite fluxes between bloodstream and neuropil. Ependymal cells were noted to be ciliated (50) and were thought to participate in absorption or secretion of CSF. Radial glia were suspected to be precursors of astroglia, and perhaps of oligodendroglia (8).

Immunohistological approaches to the identification of CNS neuroglia began with the work of Bignami, Dahl and Eng (3,15), who established GFAP as a "marker" for astroglia. Two types of astroglia were described: "protoplasmic", relatively poor in GFAP and located mainly in gray matter; and "fibrous", with more glial filaments and located mainly in white matter. It was initially unclear whether these were representatives of distinct astroglial lineages, different stages in differentiation along a single lineage, or simply different astroglial phenotypes dictated by their locale.

A decade ago, information on neuroglial lineages in CNS was very limited. It was assumed that divergence of oligodendroglial from astroglial lineages occurred early in development and in an irreversible fashion. Three successive stages in oligodendroglial maturation were delineated by combined microscopy and tritiated thymidine radioautography--immature light, transitional, and post-mitotic dark oligodendroglial. The relationship between small resting microglia and microglia "activated" by infection or other disease processes was appreciated. However, the ontogeny of microglia and the significance of microglial activation were unclear.

The development of cell type-specific antibodies in addition to anti-GFAP (eg. anti-galactocerebroside [anti-galC]) to identify mature oligodendroglia; the anti-ganglioside monoclonal antibody A2B5, which, in the rat, binds to the plasma membrane surface of precursor cells in the oligodendroglial lineage (10,59,60,71,74); and anti-glutamine synthetase, which binds to the interior of mature astroglia (61), permits identification of various neuroglial types and description of their stages of differentiation. These immunohistologic reagents, when combined with advances in tissue culture that allow serial observation on neuroglia in the presence or absence of neurons and growth factors (38), selective killing of single classes of neuroglia by complement and antibody dependent cytolysis, tritiated thymidine radioautography to identify cells undergoing mitosis, and retrovirus-mediated gene transfer techniques to identify all the descendants of single infected cells (69), have permitted more critical analysis of neuroglial lineages.

Application of these new techniques has permitted a number of important advances in our understanding of CNS glial lineage relationships. Miller et al were able to demonstrate the existence of at least two non-interconvertable classes of astroglia. "Type 1" astrocytes are abundant in gray matter, appear in rat brain before birth, maintain processes that abut brain capillaries, and are responsible for the astroglial reaction to various forms of brain injury (52). The immunohistological phenotype of these cells in the rat is GFAP + A2B5-. The lineage relationships of type 1 astroglia are not understood, but it is clear that type 1 astroglial progenitors diverge from progenitors within the oligodendroglial lineage very early in CNS development. "Type 2" astroglia, which are abundant in optic nerve and white matter, appear only postnatally in the rat, contribute to the glial limiting membrane of optic nerve and send processes to abut nodes of Ranvier. The immunohistological phenotype of these cells in the rat is GFAP + A2B5+. At the same time, Raff's group (59,91) and others (23) described the characteristics of an immediate precursor for both the type 2 astrocyte and the oligodendrocyte: the oligodendrocyte-type 2 astrocyte ("O2A") cell. In the rat, this O2A cell has the immunophenotype A2B5 + galC-GFAP-. Cells of this phenotype are small, round, bi- or multi-polar, and are both actively motile and actively mitotic. Their migration through optic nerve, and possibly other regions of immature CNS, serves to seed the neuropil with precursors for mature oligodendroglia and type 2 astroglia (81). Unfortunately, the monoclonal antibody A2B5 fails to mark such common precursor cells in species other than the rat, and there is a great need for a more generally applicable histological means for identification of this branch point in the oligodendroglial lineage.

Herndon et al (28) and Ludwin (49) clearly documented that oligodendroglia in mature brain of experimental animals are capable of mitosis following demyelination induced by viral or other diseases, thus indicating that the persistent nature of demyelination. These observations suggest that the irreversible demyelination observed, for example, in multiple sclerosis, cannot be ascribed simply to an irreversibly post-mitotic state for oligodendroglia in adult brain.

Price and Cepko showed that lineage relationships in brain and retina can be worked out by retrovirus-mediated transfer of the bacterial gene for beta-galactosidase, a convenient marker for the descendants of cells infected with this retroviral construct (68,69). This technology has shown that precursor cells common to glial and neuronal lineages persist in brain and retina to a developmental stage much later than previously suspected.

Several laboratories have demonstrated that CNS microglia derive from the systemic monocyte lineage and have many of the properties of macrophages in non-neural tissues. These include phagocytosis, display of MHC class II antigens and production of various monokines (22,27,63,100). At least two conclusions can be drawn from these observations. First, brain microglia have the capacity to act both as antigen-processing cells and effector cells during the evolution of immune disorders of the CNS. Second, it should be possible to repopulate brains of patients with inherited lysosomal or peroxisomal disorders with cells containing the missing or inactive protein by marrow transplantation, though one cannot necessarily assume that expression of such a protein in microglia would be of therapeutic value.

Linser and Moscona showed that the activity of glutamine synthetase, an enzyme vital for ammonia detoxification, is induced in Muller cells by axonal contact and repressed by axotomy (46,47). This is one of the better documented examples of an effect of neuronal contact on neuroglial phenotype.

REGULATION OF NEUROGLIAL LINEAGES

To what extent is the program for proliferation and differentiation of neuroglia controlled by mechanisms intrinsic to the differentiating precursor cells themselves, and to what extent by exogenous signs (eg. hormones, growth factors, cell contact-dependent phenomena)? That which is known can be summarized in a few sentences. Survival and initial proliferation of the O2A precursors of mature oligodendroglia and type 2 astroglia is dependent upon intimate contact with neurons (9), but later development of oligodendroglia, including the timely appearance of the various myelin-specific proteins can proceed in the absence of neurons (39,99). A protein in serum, not yet fully characterized, induces O2A cells to differentiate toward type 2 astroglia; in its absence, the oligodendroglial phenotype is favored (60). Proliferation of cells of the O2A lineage is enhanced by type 1 astroglia (59), and this appears to be accomplished by means of the secretion by these astrocytes of platelet-derived growth factor and insulin-like growth factor (1,10,71,74). Basic fibroblast growth factor also stimulates proliferation of cells of the oligodendroglial lineage (12). Proliferation of type 1 astrocytes appears to be inhibited by neuronal contact (26,84), and phenotypic and metabolic maturation of type 1 astroglia to be enhanced by contact with endothelial cell basal lamina (25).

In contrast to the behaviour of type 1 astroglia in CNS, proliferation of Schwann cells in PNS is enhanced by axonal contact (76,84). Schwann cell mitosis is also unstimulated by agents which increase Schwann cell intracellular adenosine 3',5'-monophosphate (85) and by fibroblast growth factor, glial growth factor, and PDGF (67) (Hardy and Pleasure, submitted for publication). Axonal contact induces Schwann cells to down-regulate surface expression of NGF receptors and neural cell adhesion molecules (N-CAM), but to upregulate synthesis of galactolipids such as galC and glycoproteins such as P_o (36,37,43,51,53,88). One of the signals involved in this neuronal modulation of Schwann cell phenotype appears to be an elevation in Schwann cell cyclic AMP content (43,53,80,86).

The recent application of methods for in situ hybridization to localize NGF mRNA has demonstrated that Schwann cell levels of this mRNA are high in the immature animal, diminish in the adult, and rise early during Wallerian degeneration; this rise in Schwann cell synthetic

capacity for this protein is due to the action of macrophages which invade the degenerating nerve and release interleukin-1 (2,29,30,45).

NEUROGLIA IN DISEASE

This is a very brief summary of a large body of data. Only selected references are provided, and the reader is urged to consult standard texts (eg. Dyck et al, Peripheral Neuropathy, 1984) for further details.

Inherited Disorders of Oligodendroglia and Schwann Cells

A number of genetic defects affecting the synthesis of proteins required for normal function of myelin-forming cells have been recognized (87). Mutation of the X chromosome affecting the gene for proteolipid, the principal structural protein of CNS myelin, causes sex-linked dysmyelination in the mouse (the "jimpy" strain), in "myelin-deficient" rats, and Pelizaeus-Merzbacher disease in man (54). An autosomal mutation affecting the myelin basic protein gene also causes CNS demyelination in the mouse (66), but no human analogue has yet been recognized.

Autosomal mutations affecting either lyosomal arylsulfatase A or galactocerebrosidase interfere with metabolism by oligodendroglia and Schwann cells of myelin galactosphingolipids, causing dysmyelinative encephalopathy and neuropathy. A mouse analogue of human galactocerebrosidase deficiency has also been recognized (the "twitcher" strain). Metabolism of myelin lipids is also impaired and the integrity of myelin is compromised in human inherited peroxisomal disorders affecting the PNS (phytanic acid oxidase deficiency or Refsum's disease) or both CNS and PNS (adrenoleukodystrophy).

Neurofibromatosis (NF, von Recklinghausen's disease) is a dominantly inherited predisposition to tumors containing Schwann-like cells (64). NF is one of the most frequent inherited disorders affecting the nervous system. The existence of two distinct forms of NF, long suspected on clinical grounds, has now been verified by genetic analysis. Systemic NF, characterized by cafe au lait spots and axillary freckles, Lisch nodules of the iris, malformations of the sphenoid, vertebrae and tibia in addition to subcutaneous and plexiform Schwann cell tumors, is due to a mutation on chromosome 17, in the neighborhood of but not in the gene for NGF receptor (79). The much rare central form of NF, characterized by bilateral acoustic neurinomas and a paucity of cutaneous manifestations, is carried on chromosome 22 (78), and appears to result from inactivation of an anti-oncogene (40,78). The genetic defects in these two forms of neurofibromatosis are expressed primarily in neural crest-derived cells, especially in Schwann cells, but there is an increased incidence of tumours in neural tube-derived cells as well, for example optic gliomas.

Acquired Disorders of Oligodendroglia and Schwann Cells

Immune mechanisms compromising the survival or function of myelin forming cells play a role in the pathogenesis of multiple sclerosis (MS) and the Guillain-Barre syndrome (GBS) (31,32,92), and both cell-mediated and serologically mediated immune processes involving sensitization to such myelin components as myelin basic protein, P_2 basic protein, and galactocerebroside participate in the pathogenesis of experimental models that simulate some of the clinical and pathological features of MS and GBS. For example, rabbits immunized repeatedly with galC develop antibody-mediated PNS demyelination, and Lewis rats sensitized to P_2 PNS

myelin protein develop T-lymphocyte-mediated PNS demyelination (75). Both microglia and astroglia may play roles in the pathogenesis of these immune-mediated disorders by presenting antigens and secreting monokines and thereby facilitating lymphocyte-mediated damage to myelin and to myelin synthesizing cells (4,22,27,63,100).

Viral infections of neuroglia are increasingly recognized (7,11,90). Ependymal cells express surface binding sites for herpes simplex, mumps, measles and other viruses, which may participate in the pathogenesis of viral encephalitides. In some instances (eg. coronavirus in mice, papova virus in humans), oligodendroglial infection leads to CNS demyelination. Both direct cytolytic effects of the infection on myelin-forming cells and the triggering by the viral infection of an inflammatory process consequent to a delayed hypersensitivity mechanism play roles in these disorders. Neuroglia can serve as reservoirs for latent virus (eg. herpes simplex within gasserian ganglion Schwann cells) or for chronic viral infections (eg. HIV) (7,19). In some instances (eg. simian sarcoma viral infection), growth factors encoded by the viral genome (eg. v-sis) induce tumors (eg. glioblastoma).

Bacterial infections of neuroglia also occur. The most common example is the accumulation of Hansen's bacilli within the Schwann cells of subcutaneous nerve twigs in lepromatous leprosy, resulting in the loss of pain and temperature perception that is a characteristic feature of this disease.

Neuroglia are affected by various endocrine diseases. Myelination is delayed in infantile hypothyroidism, and some adults with hypothyroidism develop a demyelinative neuropathy. Diabetes mellitus also predisposes to PNS demyelination, perhaps due in part to the presence of aldose reductase within Schwann cells, but axonal degeneration is more common and more severe.

Toxins known to selectively affect neuroglia are far less numerous than those injuring neurons. Perhaps the best example is the protein exotoxin secreted by C. diphtheriae, which inhibits Schwann cell protein synthesis and induces a delayed demyelinative polyneuropathy in patients with pharyngeal or wound diphtheria.

Examples of the intermediary metabolism by neuroglia of toxins affecting primarily neurons are also now recognized. Neuroglia play a protective role in some instances, for example the detoxification of ammonia and of excitatory neurotoxins by astroglia (97,98), while in other cases, a non-toxic precursor is converted to a toxic product by neuroglia (eg. MPTP to MPP+).

Secondary Responses of Neuroglial Cells

Astrogliosis occurs in CNS in response to many types of injury, and appears to be primarily a response of type 1 astrocytes (52). In most instances, the relative contributions of astroglial proliferation, astroglial hypertrophy, and accumulation of GFAP+ fibrils to this astroglial reaction have not been worked out. An even more glaring lacune in our knowledge is the lack of information on the functional significance of astrogliosis--is it a reparative process, or instead, an impediment to regeneration (17,48,77). Perhaps the answer is that either is true, depending on age and species (82).

Retinal Muller cells also respond to injury by accumulation of GFAP (16). In addition, when maintained in culture in the absence of neurons, these cells can assume a lenslike phenotype, including the expression of antigens characteristic of lens cells (55).

Schwann cells respond to axotomy caused by Wallerian degeneration by upregulation of expression of NGF receptor and N-CAM (51,80,88) and increased synthesis of NGF--all events likely to enhance subsequent axonal regeneration. Schwann cell mitosis is transiently, but dramatically augmented during the early stages of Wallerian degeneration (76) and the Schwann cells form columns ("bands of Bungner") through which the regenerating axonal sprouts then propagate. Whether this Schwann cell proliferation is induced by the exposure to axonal fragments (84), to myelinic fragments (96), or both, remains to be established. Schwann cells also evince a mitogenic response to demyelination (24), but in this instance do not up-regulate NGF receptor expression (86).

Microglia are activated by CNS infections and immune disorders to a macrophage-like phenotype, becoming actively phagocytic, expressing MHC components necessary for antigen presentation, and secreting monokines (22,27,100).

Oligodendroglial proliferation also occurs in mature brain in response to many types of injury (28,49) and is followed by accelerated synthesis of myelin constituents (41). The relative contributions of mature oligodendroglial and residual precursor cells to this proliferation are unclear. Invasion of CNS by nerve root Schwann cells also occurs in response to CNS demyelination, and can lead to considerable remyelination, for example of MS spinal cord lesions (33). Such aberrant remyelination is recognizable by the presence of basal lamina encircling the myelinating cell (which occurs normally in PNS but not CNS) and by immunohistological techniques which detect myelin constituents normally restricted to PNS (eg. P_2, P_o). The functional consequences of such Schwann cell remyelination of CNS have not been established.

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