International Journal of Molecular Medicine and Advance Sciences 1 (3): 255-261, 2005

Mirror Images of Contact Inhibitionversus Reactive Responsiveness Between Axon and Myelin Sheath In Peripheral and Central Nervous System

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Abstract: Mirror image systems of influence between reactive responsiveness and contact inhibition pathways might help better delineate relationships between axon and its enwrapping myelin sheath. Indeed, a single integral system of axon with its myelin might implicate close analogous forms of influence between the Schwann cell or the oligodendrocyte and its related axon in a manner specifically involving gene expression as patterns of pathobiology in either peripheral or central demyelinative disorders. Indeed, in terms of a conceptual system that would go beyond simple myelin subcomponent constituent deficiency arising from gene deletion or gene mutation, one might perhaps conceive axonal participation in terms of anomalous gene expression as referable specifically in terms of interactive pathobiologic effects of disturbed contact inhibition and disturbed reactive responsiveness of Schwann cell or oligodendrocyte with its related axon.It is perhaps in terms particularly of a structured superimposition of multiple myelin subcomponents both in peripheral nerves and also in central white matter that one might better conceptualize a strict mirror image series of pathways of analogous influence in determining particularly pathobiologic patterns of evolving peripheral neuropathy and of central white matter injury. In simple terms, a single mechanism of axonal participation that predetermines oligodendrocyte or Schwann cell reactivity or contact inhibitory influence would essentially help account for demyelination as primarily an integral expression of genetic influence implicating also axons.

Key words: Mirror images, reactive, responsiveness axon, myelin

INTRODUCTION

ARE THE NEUROTROPHIC LIGAND AND ITS RECEPTOR COUNTERPARTS OF THE SAME ESSENTIAL ENTITY?
IS AXON AND SCHWANN CELL INTERACTION A MUTUAL RELATIONSHIP WITHIN ONE BASIC BIOLOGIC PRECURSOR UNIT?

The most common forms of inherited demyelinating neuropathy are due to mutation in genes encoding protein zero (PO), peripheral myelin protein 22 (PMP22) and connexin 32 (Cx 32) as expressed by Schwann cells and as components of the myelin sheath[1]. Mechanisms acting on Schwann cells include contact phenomena (with the axon, with other Schwann cells and with fibroblasts), neurotrophic factors and their respective receptors, and particularly in the special context of the myelin sheath and matrix components such as integrins and adhesion molecules in general. Also, B6 and B12 vitamin deficiencies have been associated with peripheral neuropathy[2]. All these phenomena act on a particularly labile transcriptional series of mechanisms that are apparently inducible by particularly interacting series of neurotrophic factors on the one hand and by contact stimuli on the other.

Myelination by the Schwann cell would appear essentially to fulfill further this specialization characterization of the Schwann cell leading to a situation that would additionally add substantially to the biologic stability of a cell that otherwise would tend to respond in an intrinsically labile fashion. In this regard, for example, a dystroglycan-dystrophin-related protein 2 complex at the surface of myelin forming Schwann cells would cluster and interact with L-periaxin--disruption of this DRP2-dysroglycan complex promotes hypomyeliantion and destabilization of the Schwann cell and axon unit in Prx (-/-) mice; indeed, DRP2-dystroglycan complex appears important in terminal stages of peripheral nervous system myelinogenesis and regulation of myelin thickness[3].

Hence, it might very well be true that the Schwann cell rather than the axon or neurofilaments is the center stage player in most forms of peripheral neuropathy or of peripheral nerve injury. For example, even in cases of Charcot Marie Tooth-disease Type (CMT) IA with peripheral myelin protein 22 gene duplication, axonal attenuation appears possibly present in association with impaired Schwann cell effect on myelinated axons[4]. Indeed, PMP22 duplicating causes more severe distal axonal disorganization of the cytoskeleton that PMP22 deletion in Schwann cells in CMTIA[5].

How can one interact effects that are neurotrophic in the form of ligands and receptors with a whole host of

contact phenomena, to specifically colocalize on the Schwann cell membrane cytoplasm and nucleus?

Of course, it would appear that ligand-receptor interactions themselves essentially contact phenomena and that in the final analysis Schwann cell biology would evolve in terms of contact inhibition and of contact stimulation. It is this essential aspect of the biology of Schwann cells that would help explain the essential pathobiology of regeneration of peripheral nerves and of their axons after axotomy.

It is especially the nature of the mutual interactions between axon and its Schwann cell or cells that would underlie the essential pathobiology of Schwann cell responsiveness or unresponsiveness when the peripheral axon or nerve is transected. Indeed, disorders causing demyelination as Charcot Marie Tooth type 1 or axonal loss as Charcot Marie Tooth type 2 would tend both to disturb axon-myelin relationships; as a consequence, also, a "myelin" gene mutation can at times induce electrophysiologic features of Charcot-Marie Tooth type 2[6]. PMP22 as a component of compact myelin produced by Schwann cells appears involved not only as a structural component in peripheral nerve development, myelin stability and axonal maintenance, but also appears to regulate Schwann cell proliferation and differentiation[7].

In fact, duplications, deletions or point mutations of the PMP22 gene are responsible for most common forms of hereditary peripheral neuropathy including hereditary neuropathy with liability to pressure palsies and also Charcot-Marie-Tooth type IA and a subtype of Dejerine-Sottas syndrome.

Whether in fact retrograde flow of neurotrophic factors is a central basic phenomenon in recovery from peripheral neuropathy is still perhaps an unknown parameter to some extent; however, much of neurotrophic phenomena in nerve injury might essentially progress in terms of biology of Schwann cells themselves, in a context also of influences exerted by locally accumulating macrophages. Peripheral myelin protein 22 itself appears to function in the initiation of myelination and probably is involved in Schwann cell ensheathment of the axon and also with subsequent extension of this cell along the axon[8].

What about the nature of disturbances of contact phenomena that would so dramatically affect Schwann cells? In this regard, for example, an absence or abnormal functioning of laminin alpha 2 chain might alter the feed-back control during myelinogenesis, leading to an over-ensheathment of axon. Alternatively, a compensatory up-regulation of other laminins might induce the hyperproduction of myelin sheaths[9].

Perhaps, Schwann cells as migratory, mitotically active cells, are capable, on the one hand, of undergoing myelination and demyelination, and also apoptosis, and on the other hand, of evolving as highly responsive cells. In a final analysis, indeed, direct cell-cell interaction during developmental progression between that Schwann cell and axon would constitute systems of basic unique relationships between specific neurotrophic ligands and corresponding receptors.

Indeed, integral axon/Schwann cell, and integral ligand/receptor relationships as both system components would perhaps essentially constitute relationships as counterparts of one process that are related as patterns of thesis and antithesis. In simple basic terms of analogous extension, indeed, in terms especially of a neurotrophic ligand and its corresponding receptor, one might envisage mirror image pathways of interaction that are basically models of conceptually considering even integral relationships of an axon and its various myelin related determinants in peripheral neuropathy.

ARE LARGE CALIBER AND CONSIDERABLE LENGTH OF INDIVIDUAL AXONS DETERMINANT OF DEGREE OF AXONAL PRESERVATION AFTER SEGMENTAL DEMYELINATION IN PERIPHERAL NEUROPATHY?

Are large axons more susceptible to an axonopathy after an episode of demyelination? Certainly, myelination provides extrinsic trophic signals that influence normal maturation and long term survival of axons. Myelin-associated glycoprotein and proteolipid proteins appear essential for mediating myelin-derived trophic signals to axons. Indeed, axonal damage appears an integral part of myelin disease as seen in patients with inherited peripheral neuropathy Charcot-Marie-Tooth disease type 1[10,11]. Certainly, there would appear to evolve interacting associations of mutually influencing factors as determinants of pathobiology of segmental demyelination in terms of a diminution in the number of large axons in cases of peripheral neuropathy, and also particularly as associated features of genetic disorders involving Schwann cells. Certainly, the strictly segmental patterns of the demyelination process itself would directly implicate individual Schwann cell involvement in these disorders, leading to a concept of strict cellular individuality as a phenomenon of progression of infliction of injury in several patterns of evolving peripheral neuropathy.

Indeed, Schwann cells with nuclear cyclin D1 expression as well as proliferating Schwann cells are both associated with demyelinated axonal segments[12] in a model of Charcot-Marie-Tooth type IA disease.

Certainly, demyelination might involve processes that start and end simply in breakdown of the myelin sheath but is only in an essential additional context of processes likely to lead directly to significant axonopathy,

particularly affecting larger rather than smaller axons. Indeed, aging mice deficient for myelin associated glycoprotein have been reported to exhibit axonal degeneration and neuropathy with minimal signs of demyelination[13]. In this regard, for example, L-Periaxin, a PDZ-domain protein localized to the plasma membrane of myelinating Schwann cells, appears to play a key role in the stabilization of mature myelin in peripheral nerves. Indeed, mutations affecting L-Periaxin would predispose to demyelinating peripheral neuropathy in some patients consistent with a disruption of L-Periaxin function in terms of nerve injury. Anti-Periaxin antibodies in patients with IgG monoclonal gammopathy of unknown significance or in patients with diabetes also appear to promote sensory nerve conduction defects[14].

Indeed, large axons might constitute systems of susceptibility especially more vulnerable to injury after loss of investing Schwann cells, a phenomenon that would in addition implicate pathways of segmental pathology of the axon itself as a consequence of complete breakdown of several integral components of neuronal injury. In this sense, it might be true to consider the axon, as simply dependent on systems of integrity as applicable to continually sustained vitality throughout its length, a phenomenon indeed that would particularly render susceptible the axon to forms of to injury arising from lack of trophic factor and loss of the investing Schwann cell and its myelin sheath but expressed pathobiologcally as an essential loss of larger axons.

Even the dying back phenomenon seen so commonly in many cases of peripheral neuropathy would constitute expressions of a basic form of axonopathy that would tend to progress and to prove persistent in terms of essentially evolving lack of trophic effect. Indeed, the actual dimensions of large caliber and of actual constitutive length of an axon would evolve as systems of susceptibility specifically implicating the axon as pathways of lost integrity in terms of loss of integrity of Schwann cells or of myelin sheath referable specifically as segmental axonal or nerve involvement.

Indeed, for example, in cases of Machado-Joseph disease, there would tend to develop a loss of large myelinated fibers and distal axonopathy with relative hypomyelination in peripheral nerves (Lin & Soong, 2002).

THE NORMAL SUPERIMPOSED SERIAL SYNTHETIC SEQUENCE OF INCORPORATION OF MYELIN CONSTITUENTS IS ESSENTIALLY DISTURBED IN MANY HEREDITARY PERIPHERAL NEUROPATHIES

The active process or demyelination as seen particularly in certain cases of hereditary peripheral neuropathies would constitute a broad generic group of disorders not necessarily related specifically to deficient gene function or expression. In this regard, for example, also, optic neuropathy at times is associated with several types of inherited mitochondrial disorders whereby the fine balance between energy demand and nerve tissue function would be disturbed[15]. Indeed, mitochondrial toxicity as induced by antiretroviral drugs is a new cause of acquired neuropathy as seen in AIDS patients treated with 2'3'-dideoxycytidine[16]. Also, nitric oxide would appear to constitute a critical factor in degeneration and regeneration of peripheral nerve, implicating regular Wallerian degeneration in terms of fiber regeneration[17].

In fact, it might be true that specific gene overexpression, as referable for example to myelin-associated glycoprotein, would result in a clinical peripheral neuropathy with features suggestive of the Charcot-Marie-Tooth phenotype. On the other hand, no unique genes have been found for Charcot-Marie-Tooth type 2 and both Cx32 and PO would appear to contribute to the phenotype. Indeed, Charcot-Marie-Tooth Type 2 is probably genetically much more heterogeneous than CMT1[18].

These considerations might implicate precise pathogenic pathways potentially central to involvement of axons and myelin sheath as integrated by a viable Schwann cell sheath primarily targeted in peripheral demyelinating neuropathy. In this connection, for example, mutations of the gene encoding myotubularin-related protein 2 cause autosomal recessive Charcot-Marie-Tooth disease type 4B1, with severe motor and sensory neuropathy, focally folded myelin sheaths and demyelination. Indeed, malfunction of neural membrane recycling, membrane trafficking and/or endocytic or exocytotic processes would develop in association with altered axon and Schwann cell interactions[19].

The sustainment or resynthesis of myelin might evolve as systems of viability or as systems of susceptibility impaired due to an essential imbalance between various genes such as HMSN1a and HNPP (peripheral myelin PMP22), HMSN1b (myelin zero MPZ, PO), HMSNX (connexin 32, Cx32), HMSN type 1 or hypomyelination neuropathies (early growth response 2 gene, EGFR 2, Knox 20). Indeed, it might be reasonable to implicate that particularly pathways of long-term sustainment in the form of normal myelin sheath enwrappment around axons of peripheral nerves especially as an essential balance of production and participation of the various myelin protein constituents and related myelin components. In this connection, for example, IgM anti-myelin-associated glycoprotein paraproteinemia would cause myelin-sheath outfolding and infolding, myelin degeneration and multiple increased concentric loops in a context of apparently disturbed adhesion functionality in terms of axon-myelin

relationships[20]. Such a balance would be particularly jeopardized in certain autosomal recessive hereditary peripheral neuropathies whereby a single gene would induce for example patterns of combined motor and sensory neuropathy to evolve simply as constitutive disturbances or myelin-axon disruption involving operative contact phenomena.

In terms of apparently primary hypomyelination neuropathies, it might indeed be valid to suppose the existence of a certain sequential chains in the formation and deposition of peripheral myelin constituents based on the pre-existing presence of a specific myelin-associated protein. In general terms, the formation of myelin itself might necessitate essentially strict sequences of biochemical events involving the progressive incorporation of various myelin constituents in a likewise specific sequential pattern of evolving systems of response and functionality.

INTERACTING SCHWANN CELL AND ENDONEURAL STROMAL CELLS AFTER PERIPHERAL NERVE TRANSECTION

It appears conceivable that distally directed sprouting of axons following transection of a peripheral nerve would be dictated by stimuli arising in the distal nerve stump. Certainly, neurotrophic effect would account for axonal outgrowth distally in terms specifically arising form idealized concepts of evolving influence as patterned by neurotrophic factors concurrent with axonal-myelin sheath and Schwann cell interactions of predominantly contact type. Also, glial cell line-derived neurotrophic factor would tend to rescue nonpeptidergic unmyelinated primary afferents in streptozotocin-treated diabetic mice[21].

Such a phenomenon would perhaps intimately relate to endoneural fibrosis and vascularization, phenomena that might actually arise in relation to the production and localization of neurotrophic factors in the distal axonal and neural stump. Certainly, a progressive system of anterograde Wallerian degeneration would essentially characterize the pathobiology of the distal stump, as an integral process linked intrinsically to subsequent neurotrophic factor production and localization as essential endoneural reactive vascular phenomena and involving also macrophages as in chronic inflammatory demyelinating polyneuropathy[22]. Certainly, trophic effects might determine specificity of endoneural reactive phenomena, especially in term of consequent Wallerian degeneration of axons and of their enveloping myelin sheath. For example, the voltage-gated "glial" sodium channel (NaG) would appear to play a role in Schwann cell-axon interactions and NaG immunoreactivity is particularly increased in distal nerve after Wallerian degeneration[23].

In this connection, Schwann cells would actually be responsive elements in much of the reactive and neurotrophic phenomena arising directly from pathobiologic consequence of peripheral nerve transection.

Such a postulate might account for a more pronounced reactivity in terms of active features evolving after injury to peripheral nerves as induced injury of neural fiber tracts in patterns inherent to oligodendrocyte and Schwann cell systems of comparative or analogous systems of responsive impairment.

In simple terms, a set of basic biologic differences would exist between oligodendrocytes and Schwann cells. However, Schwann cells would be closely linked to reactive and vascular proliferative changes in forms of patterned impairment of responsiveness analogous to those affecting oligodendrocytes. In fact, one particular problem after peripheral nerve transection as an often-florid fibrous tissue response would contribute significantly in impaired alignment of axonal sprouts to the distally affected axonal stumps in patterns of evolving loss of contact phenomena and in terms of loss of responsiveness to neurotrophic factors that might also apply in various ways to patterned anomalous involvement of distal axonal segments in the central nervous system but where oligodendrocytes rather than Schwann cells are primary systems of contact phenomena of interaction.

Such a situation might constitute conflicts of interest pathobiologically between the reactive microenvironment for regrowth of the axons on the one hand with a mechanical barrier processes of influence on the other in the accurate alignment of axons as distal stump responsive systems of anomalous or equivocal axonal regeneration as seen particularly in central nervous system pathology of white matter injury.

A significant part of this difficulty would appear determined as disturbed distributions of the Schwann cells in terms of enwrapping sheaths of the individual axon—in fact, malalignment of axons might evolve itself as maldistribution patterns in terms of a combined loss of contact inhibition and contact expressiveness influencing Schwann cells in distal stump site of transformation subsequent to axonal or neural transection. Also, beta1 integrin appears to link laminin in the basal lamina to the cytoskeleton in order for Schwann cells to ensheath axons, and alteration of this linkage would contribute to the peripheral neuropathy of congenital muscular dystrophy[24].

The neurotrophic effects as a concomitant phenomenon of perhaps both the Wallerian degeneration

and the Schwann cell participation in reactive proliferation at the site of injury and more distally would perhaps alsohelp account for much of the distinctive nature of both contact inhibition and contact responsiveness between axonal and enwrapping myelin in both peripheral nerve and central nervous system white matter injury.17

In this regard, for example, in terminal AIDS patients a multifocal immunologically mediated inflammatory neuropathy may characteristically develop with increased density of macrophages and T cells at all levels of the peripheral nervous system with segmental demyelination and axonal loss[25] .

In addition, the common occurrence of Schwannomas and neurofibromas would testify to a well-developed series of system pathways involving proliferative capabilities of Schwann cells in terms particularly of the intimate biologic interrelationship between nerve sheath elements and of endoneural cell-stromal elements.

In fact, neurofibromas, being lesions that essentially involve the substance of the nerve trunk, would in contrast to Schwannomas, tend to incorporate a phenomenon of participation of both endoneural stroma and Schwann cell-type elements within pathways of integral neurotrophic effect best understood as mutually influencing mirror image patterns of contact and responsive phenomena of axon and enwrapping myelin.

It is interesting that by light microscopy it is not possible to distinguish Schwann cells from endoneural fibroblasts, a phenomenon in fact whereby Schwann cells would perhaps constitute proliferative elements of response that however sequentially implicate systems of endoneural stromal reactivity in giving rise to minifascicle-like contact and responsive phenomena of interaction as seen also in neuroma formation[26].

It might very well be valid to consider the original derivation of Schwann cells as simply closely related to endoneural stromal cells and that these cells become progressively more specialized in terms specifically of capability in producing segmental sleeves of myelin sheath around axons. Such possible derivation of the Schwann cell from endoneural stromal cell elements would perhaps actually allow for a regression to stromal type cells on the part of such Schwann cells that would develop in peripheral nerve transection as a system of loss of interactions of mirror image influences between contact and responsive pathways of interaction.

Such an event might actually be part of a whole series of mechanisms whereby neurotrophic effects together with mitotic ctivity and a full range of other reactive phenomena of a fibrovascular nature would create microenvironments promoting the stimulation of responsiveness of proximal axonal sprout.

Indeed, axonal sprouting in a distal direction might relate topographically to systems of receptivity of the distal axonal stump in a manner analogous to basic conceptual forms of interaction of responsive reactivity and of contact inhibition in controlling regenerative axonal sprouting in a contextual framework of a resulting intact axon. Indeed, macrophages appear involved as a widespread phenomenon in genetically determined demyelination, as seen with deficiency of gap junction protein connexin 32[27]. Cx 32 possibly functions as a channel forming protein in facilitating comnunication between the abaxonal and additional aspects of Schwann cell cytoplasm[28].

MUTATIONS OF THE SAME GENE PRODUCING DIFFERENT CLINICAL PERIPHERAL NEUROPATHIES.--ANINTEGRALAXONAL/MYELIN SUBUNIT BIOLOGICALLY AND PATHOBIOLOGICALLY

The production pathologically of either an axonal or a demyelinating form of peripheral neuropathy associated with mutations of the same gene would indicate fundamentally integral relationships in development and maintenance of both axons and peripheral myelin in nerves.

In this regard, for example, apparent loss-of-function mutations in the periaxin gene would tend to cause autosomal recessive Dehjerine-Sottas neuropathy or severe demyelinating Charcot-Marie-Tooth disease. Indeed, the carboxyl terminal domain of the periaxin protein would appear particularly important in stabilizing of the myelin sheath[29].

Such a situation would, for example, be suggestive of an essentially structured form of developmental relationship of axon with myelin. Indeed, for example, mutations in Cx32 gap junction protein can impair Schwann cell-axon interactions with subsequent pathology in both myelin and axon[30]. Myelin presumably cannot be produced unless the axon has developed, as presumably in cases of congenital neuropathy showing absence of large myelinated fibers[31].

Also, the myelin constituents themselves might be essentially structured as one component related to another in terms of pathways of deposition, and of subsequent normal physiologic and pathobiologic sustainment. A particularly critical problem clinically would actually evolve as potential disruptions of the whole myelin framework in terms of either development or maintenance of pathways of influence as arising from absence or anomalous effect of myelin component involvement.

In this regard, for example, periaxin-null mice not only develop more hypermyelinated axons than their wild-type counterparts, but they tend to recapulate this hypermyelination during regeneration. Indeed, regulation of peripheral myelin thickness appears disrupted in peripheral nerve regeneration; this might be related to the fact that L-periaxin is a constituent of the dystroglycan-dystrohin-relaed protein 2 complex linking the Schwann cell cytoskeleton to the extracellular matrix[32].

These considerations might not necessarily be limited to chemical reactivity, but particularly also relate to the actual structural organizational deposition of the myelin in specific relation to the axon. Indeed, myelin-associated glycoprotein would appear to control neurofilament phosphorylation and axon caliber[33].

Hence, a rather complex situation might arise whereby each clinical category or "disorder" of peripheral nerve demyelination/axonopathy would comprise a whole heterogeneous group of possible component disturbance or pathology involving singly or multiple ways mutations of the same gene. Indeed, different basic forms of neuropathy might actually be related to precise genetic mutations in that gene in terms however arising from modes of formation and deposition of other myelin components at a particular stage in development of the myelin sheath and nerve.

Indeed, the Neuregulin signaling system would appear to function during multiple stages of Schwann cell development and would be essential for correct myelination. Furthermore, myelin sheath thickness would determine axonal diameter and trophic signaling would perhaps determine the number of Schwann cell enwrappings around an axon[34].

Indeed, theoretically, one should consider the interaction of specific genetic mutations in myelin formation simply as specific pathways leading to patterned effects of infection or trauma that would be significant pathobiologically as different specific disturbances of gene expression affecting especially myelin or Schwann cell.

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