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Is Expression of Mutational/ Deletional Genetic Lesions Determined Chiefly by Specifically Altered Myelin-axonal Interactions in Peripheral Neuropathy?

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Abstract: Simple pathways of interactive influence constituted by the Schwann cell and by a myelin sheath/axon complex might involve effective modes of induced expression of genetic lesions of a mutational or deletional type. Indeed, the Schwann cell itself would perhaps help characterize how such genetic lesions in hereditary peripheral neuropathy would be expressed in specific clinical forms of involvement that pathobiologically are demyelinative or axonal independent of actual distinction between dynamics of myelin deposition or axonal viability. In simple terms, one might perhaps realize paradoxical systems of expression and of progression of hereditary peripheral neuropathies inherent to disturbed control of genetic lesion expression. Indeed, disturbed gene expression as induced by mutation or deletion of genes would appear further modulated by essential attributes of myelin sheath and axonal interactions, as further reflected particularly in terms of Schwann cell participation. In terms of a range of types of peripheral neuropathies of hereditary and acquired type, mechanistic pathways of axonal and Schwann cell response would participate in actually creating various modulated forms of expression of gene interaction. Gene expression itself might itself constitute integrative interaction between neuronal axon and Schwann cell participation in peripheral neuropathies of both inherited and acquired type.

Key words: Deletional genetic, lesion, interaction, mutational, myelin-axonad

INTRODUCTION

A conceptual understanding related to the phenotypic variability arising from genotypic variability in patients with mutations of myelin protein zero, peripheral myelin protein 22 and early growth response 2 genes would appear central to an understanding of the organizational structural breakdown that results either in predominantly demyelinating neuropathy as seen in Charcot Marie-Tooth (CMT) neuropathy type 1 or in predominantly axonal neuropathy as seen in CMT-type 2 disorders. Also in terms of Wallerian degeneration of the distal axonal stump, lost axonal contact or input would appear to critically induce demyelination. Other factors would also perhaps operate in the case of the proximal axonal stump after injury[1]. In cases of peripheral myelin protein 22 alterations, for example, demyelination develops in association with activation of ubiquitin-proteosomal and lysosomal pathways leading to further characterization of the neuropathy as aggresome aggregation[2].

Of course, in a basic sense, particularly in view of the reported occurrence of mutations in peripheral myelin zero gene in some of the predominantly axonal forms (type 2)CMT patients, the actual validity in strictly dividing patients with Charcot Marie Tooth neuropathy into either a purely demyelinating or a purely axonal form of the disease appears questionable

It appears that indeed hereditary demyelinating and axonal neuropathies derive from variable clinical forms of involvement of a basically common pathogenesis. In this regard, for example, myotubularin-related 2 gene reacts with neurofilament light chain protein in both Schwann cells and neurons[3]. Also, a subset of mutations of the ganglioside-induced differentiation-associated protein 1 would relate to demyelination whereas others would induce axonal degeneration[4].

Certainly, the clinical designation of the Charcot Marie Tooth neuropathies under one single designation, admittedly mainly using clinical criteria, would perhaps be suggestive of an important degree of interdependence of the functions of the whole of the major genes mentioned in ensuring an integrally maintained organization of the myelinated axons as a whole cellular population within the peripheral nerve.For example, CMT4B1 as a demyelinating neuropathy would implicate abnormal membrane recycling or physiology that interrupts axon-Schwann cell

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interactions arising from loss of phosphatase activity of the myotubularin-related protein 2[5].In other words, it might actually be true that the myelinated peripheral axon is in fact one that normally would be divisible into both a myelin-investing sheath with its Schwann cell of origin on the one hand, and into an invested axon on the other, when a specific gene once mutated leads to demyelination. Distinctions between integral axonal components and integral myelin sheaths become less well-defined.

In other words, in peripheral neuropathies, it might actually be misleading to distinguish between a purely or predominantly demyelinating type from an axonal type of pathology, especially since pathogenic mechanisms would tend to proceed as a neuropathic form of pathologic involvement. Indeed, even in the spontaneously occurring feline form of diabetes mellitus, although Schwann cell injury and myelin loss are prevalent, in severe cases, axonal degeneration develops[6]. Conversely, mutation of proteolipid protein (as a major myelin constituent) but not of alternatively spliced isoform DM20, would induce Pilizarus-Merzbacher disease, a form of leukodystrophy associated at times with a peripheral neuropathy[7].

Indeed, point mutations in PMP22, PO and EGR2, besides causing CMT1, would also cause two more severe, early-onset forms of peripheral neuropathy, Dejerine-Sottas syndrome and congenital hypomyelinating neuropathy. In addition, mutations of connexin 32 can also cause a CMT1 of X-linked dominant type.

Hence, within a context of an apparently highly variable relationship between genotype and phenotype as a whole group of peripheral neuropathies, any form of classification of peripheral neuropathies centered on either a demyelinating or axonal form of pathology would fail to account for a combined variability of genetic defects in the context of clinical diversity. Such a situation might be further compounded by the fact that myelin would depend on an intact axon in a manner whereby this myelin in turn is also necessary for integrity of the invested axon.

Hence, it would appear that a situation of unrelated degeneration of myelin and axon would evolve in terms of mutation of the myelin and other genes. Indeed, mutational and deletional genetic lesions might determine consequences of myelin and axonal degeneration events in a paradoxical context of induced progression of expression of such mutational and deletional genetic lesions.

Indeed, interactions between neuron and Schwann cells would appear to critically determine expression of peripheral myelin protein 22 both in health and disease[8].

Certainly, perhaps, a better understanding of the mutually related dependence of the myelin and of the axon would implicate dynamics and modes of development and of maintenance of a fully myelinated axon. A simple concept of superimposed investment of an axon by a myelin sheath would fail to account for such mutual interdependence in terms particularly of developmental maintenance of axon/myelin viability. One perhaps cannot legitimately speak of the myelin sheath and of the axon as apparently two distinct components of a nerve fiber, even beyond simple concepts of production of the myelin sheath from a distinct glial type of cell, the Schwann cell.

In other words, it would perhaps be valid to consider the neuronal axonal process, and the accompanying investing Schwann cell as actually constituting an integral system of pathogenesis independent of actual interactive pathways of induced progression of either demyelination or of axonal degeneration.

In purely developmental terms, the Schwann cell and the neuronal body with its axonal process would better be considered a single entity of induced genetic defects that both arise and evolve in terms of reciprocal expression and of mutual interdependence.

In this regard, for example, various mitochondrial DNA mutations may be associated with axonal degeneration and also in some cases with primary myelin damage[9].

It is this apparent paradox of the peripheral neuropathic lesion both as a target and as effective inducer of genetic lesions or of their expression leading to demyelination and axonal injury that one might recognize the Schwann cell as a central mediator of expression of genetic lesions in hereditary neuropathy. In a sense, the combined axon and its myelin sheath within the peripheral nerve would go beyond any concept of classification of the peripheral neuropathy as either simply demyelinating or axonal in type.

Such a view might perhaps explain for example the highly variable phenotypic expression in terms of a peripheral neuropathy that would involve a correlative genetic mutation/deletion on the one hand with a symptomatology and severity of such symptomatology on the other.

The peripheral myelinated axon as a combined composite structural and physiologic entity would simply constitute an integral expression of Schwann cell biology that evolves as genetic progression of induced and of inducing influence.

These would be reflected, for example, in forms of Schwann cell dysfunction and injury as seen in diabetic neuropathy[10]. The integral axon/investing myelin sheath would assume biologic and pathobiologic attributes beyond simple distinctions of characterization of axon and

myelin on the one hand and of an integral system of genetic mutational events in peripheral neuropathies on the other.

The Schwann Cell as Only a Specialized Form of a Basic Cell-type Capable Particularly of Flexibility in Responsive Adaptation Biologically and Morphologically Around an Axon: A central point of interest concerns the status of the Schwann cell as a distinct specialized cell type with the neuron or the fibrocyte or even perhaps the oligodendrocyte.

However, postulating a specialization role for both the Schwann cell and the oligodendrocyte would incorporate particularly the expression of distinct morphologic features as a strict pathobiologic pathway in its own right. Realization of a full series of pathobiologic dimensions related to genetic lesion expression might actually help account for an essential myelin-axon interdependence as reflected in Schwann cell ensheathment of the axon.

It may be particularly true for the Schwann cell that the ensheathing biologic functions of this cell type would largely determine the characteristically distinctive features of the cell both structurally and in terms of subsequent biologic specialization.

In a sense perhaps the Schwann cell should be considered a prime example of biologic specialization based apparently largely on contact phenomena. Also, in this regard, for example, mechanical stimuli as seen in cases of chronic nerve compression would directly induce Schwann cell proliferation[11] .

The specialized status of the Schwann cell as distinct from for example the perineurial cell is largely a result of such a phenomenon of contact-induced differentiation.

In other words, perhaps, it may be more appropriate to consider the fully differentiated S100-protein-positive Schwann cell as essentially an extreme example of flexibility potentiality in terms of reversible differentiation, specialization and adaptation of a cell type common to Schwannomas, neurofibromas and peripheral nerve sheath tumors in general

Hence, perhaps, the essential quality of Schwann cell types is their ability to respond to distinct morphologic consequences of contact axonal phenomena, with subsequent expression of a developed basement membrane, strong S100-protein-positivity and innumerable other features involving a well-developed reactive proliferation to injury.

Infact, it would appear perhaps that the well-developed proliferative potential of Schwann cells as evidenced not only in response to injury to nerves and in peripheral neuropathies of many types, but also in the common occurrence of Schwannomas, neurofibromas and peripheral nerve sheath tumors in general, would parallel closely ability of the Schwann cell to subsequently adapt both morphologically and biologically to a role of ensheathment around the axon.

And it is particularly with this view of the Schwann cell not as a specific cell type but as a morphologic and biologic expression of a series of induced processes of specialization and adaptation that one would consider the relationship of the Schwann cell with the perineurial cell in terms of the differences between Schwannomas and neurofibromas and with other lesions such as malignant Schwannomas and plexiform neurofibromas. Also, it may be significant to note that bone marrow stromal cells subsequent to injection in a damaged peripheral nerve can differentiate into Schwann cells[12].

The extraordinarily flexible responsiveness of the Schwann cell in terms of adaptability would appear tied up with a susceptibility to neoplastic transformation and proliferation, particularly as evidenced by the development of several multiple nerve sheath tumors in patients with neurofibromatosis and malignant transformation. Also, peripheral neuropathy would appear to occur commonly in patients with Neurofibromatosis Type 2 in particular because of possible pathology affecting endoneural cells or axonal ensheathment[13] .

Certainly, it would seem true that neurofibromatosis with the whole gamut of meningiomas, Schwannomas, neurofibromas, bilateral and/or multiple sites of involvement, the elephantiasis itself of excess skin folds, all would attest to an excessive trophic effect beyond even recognized expression of growth factor induction. It is in terms of an exuberance of trophic effect" that one might better account for particularly distinctive components of neurofibromatosis clinically, pathobiologically and morphologically.

The endoneural fibroblast and the schwann cell as two fundamental promotors in axonal sprouting, together essentially constituting a single biologic unit after peripheral nerve injury: It would appear that contact-induction and contact-inhibition phenomena would play a fundamental role in regulated axonal growth and remyelination after nerve transection or crush injury and in Wallerian degeneration of the distal stump. In this regard, it would seem that Schwann cells in particular are mainly involved in enhancing contact-related phenomena leading to and enhancing axonal sprouting. In this regard, Src tyrosine kinases would appear to enhance Schwann cell response and axon-Schwann cell interactions in promoting also axonal outgrowth as seen after nerve crush injury[14].

Certainly, much of the pathobiology of nerve transection and crush injury would revolve around

interruption of the individual axon, and on how such neuronal discontinuity could be re-established. For example, a 27-kDa heat shock protein would appear to critically induce axonal outgrowth by influencing cytoskeletal dynamics in Schwann cells[15].

Certainly, in large measure, the clinical outcome of a peripheral nerve injury would depend mainly on re-establishment of axonal and myelin sheath continuity, with specific reference to matching of the proximal stump with a corresponding distal Schwann cell sheath. Remyelination of the re-established axon would constitute a regulated mechanism determining clinical recovery and effective establishment of axonal continuity as constituted also by an intact investing Schwann cell sheath.

Infact, in view of the myelin derivation from such Schwann cells, Schwann cells would play a central role in re-establishing axonal continuity, a phenomenon essentially concerned with physical electrophysiological continuity and also in contact facilitation and inhibition between terminal sprouts. In this regard, galactin-1, that is endogenous to neurons, axons and Schwann cells, would appear to relate Schwann cell migration to subsequent axonal regeneration[16].

Schwann cells and adjacent axonal sprouts and myelin sheaths would probably operate with endoneural fibroblasts and other cell elements facilitating or inhibiting axonal sprouting as a system specifically inherent to axonal continuity and active maintenance of such axonal continuity. In addition, the peripheral Schwann cell/myelin sheath might paradoxically constitute the effective expression biologically of such maintained axonal continuity and of dynamics of axonal sprouting.

Certainly, the tendency often of formation of a neuroma at the site of injury of a peripheral nerve would attest to the central role played by endoneural fibroblasts; such a phenomenon would also be possibly suggestive of a close biologic relationship between Schwann cells and endoneural fibroblasts. A relationship whereby Schwann cells determine development of laminin and basal laminar components, macrophage activity and an essential ability to synthesize myelin would implicate the laying down of a structural and functional ensheathment around the axons in terms of interactive influences of Schwann cells based on membrane contact.

Certain physical contact phenomena would implicate a mechanism whereby distal axonal continuity could be re-established. Determining the degree of success of such axonal sprouting in establishing a longstanding clinical recovery would relate particularly to motor or sensory regain of function as a functionality of Schwann cell membrane interactions in a context of axonal continuity

That a whole array of cytokines but not T-lymphocytes or neutrophils are essentially involved indicates the part played by macrophages not simply as scavengers of broken down myelin but also with regard to their integrative function in orchestrating a whole series of highly complex phenomena leading to physical induction and inhibition of growing axonal sprouts in a micro-environment rich in neurotrophic factors and cytokines. On the other hand, immune mediated demyelination might constitute a common pathogenetic pathway in many forms of CMT-type neuropathies[17]. Indeed, apoptosis of Schwann cells would appear a central event in peripheral nerve regeneration after axotomy, mediated via nerve growth factor and the low affinity neurotrophin receptor[18].

In fact, nerve regeneration might constitute the expressed regeneration in terms particularly of specific biologic properties of Schwann cells as distinct from those of oligodendrocytes. Certainly, it would seem that the endoneural fibroblast would represent the effector cell type promoting peripheral nerve axonal regeneration, a cell type capable also of assuming other essential functions in peripheral nerve regeneration in terms of specialized Schwann cell functionality.

In this context, however, fibrin deposited at sites of nerve injury, would appear to alter extracellular matrix and inhibit Schwann cell migration[19].

Such a situation and particularly the micro-environmental operating conditions of regeneration in peripheral neuropathies in contrast to axotomy would essentially be a radically distinct sequence of events in terms of a more limited dynamic role played by endoneural fibroblasts.

Indeed, a setting of more preserved physical continuity of much of the endoneural stroma and other constituents of the peripheral nerves in hereditary neuropathies and neuropathies of vascular origin would perhaps account for much of the distinctive persistence and progression of many cases of hereditary peripheral neuropathy both clinically and pathologically. In this regard, also, for example, in diabetic neuropathies, down regulation of Caveolin-1 expression might promote Schwann cell responsiveness to neuregulins[20]. Also, greater sensitivity to Endothelin –1 or platelet derived growth factor might be implicated in Schwann cell response to hyperglycemia[21].

Certainly, in specific reference to axonal sprouting, this would appear that the lack of more direct participation of the endoneural fibroblasts as part of regenerative phenomena would be counterbalanced by the better preservation of much of the nerve trunk substance in peripheral neuropathies when contrasted with the physical disruption of axonal continuity in cases of axotomy.

The schwann cell and schwann cell basal lamina as critical in the pathogenesis of demyelinating neuropathy in paraproteinemia: It would appear that IgM antibodies causing the paraproteinemia of Waldenstrom's macroglobulinemia would induce peripheral demyelinating polyneuropathy in terms of a series of disturbed Schwann cell-axonal interactions.

Such a view might implicate the myelin sheath around the peripheral nerve axon in terms of how the Schwann cell, and possibly also the endoneural elements, might constitute a progressive pathway mechanism in induced damage of axonal/myelin conduction and as specifically disturbed by MAG antibodies or even by anti-L-periaxon antibodies[22]. In actual fact, IgM deposits on Schwann cell basal lamina as an early target of autoimmune response does not involve epitope specificity[23].

Certainly, ultrastructural study and immunohistochemical stains would demonstrate both disincompaction of the myelin with widening especially of the outer lamellae of the myelin, together with deposition of the IgM antibody in the axon itself.

Indeed, the MAG antibody would probably be polyclonal or monoclonal, and uniformly expressed as a demyelinating polyneuropathy.

A largely physical series of phenomena might largely explain much of the demyelination in cases of MAG-antibody related cases of peripheral neuropathy. That it tends to occur particularly distally would be consistent perhaps with a purely physical form of disturbance involving interactions between the Schwann cell basal lamina and the axon in small nerve trunks.

Certainly, a concept involving physical phenomena might be more clearly implicated in cases of peripheral neuropathy associated with mixed cryoglobulinemia, whereby increased viscosity of blood and superimposed thrombosis would reduce vascular flow and induce ischemia of nerve trunks. Also, in cases of hereditary gelsolin amyloidosis, impaired actin modulation might underlie both neuronal and Schwann cell dysfunction in terms of axonal transport and of myelin deposition[24].

Certainly, a general association between an inflammatory response and a basic physical series of phenomena might be particularly associated with osteosclerotic myeloma causing extensive demyelination and disincompaction of myelin and resulting in a lesion resembling chronic inflammatory demyelinating polyneuropathy[25]. A simple concept recognizing the Schwann cell basal lamina as the central focus of involvement in many cases of demyelinating peripheral neuropathy would appear suggestive of a disruption of contact interactions that directly results in a tendency for breakdown of myelin as seen in cases of Waldenstrom's macroglobulinemia. The axonal involvement would tend to appear as a secondary phenomenon in such cases.

The implication of vasculature in cases of mixed cryoglobulinemia, and of the inflammatory features of the polyneuropathy associated with osteosclerotic myeloma, would involve the endoneural stromal vasculature; this micro-environment might critically concern a whole series of mechanisms affecting viability of Schwann cells and consequently of myelin sheaths as an extension of the basal lamina of such Schwann cells.

Demyelination as seen in many or most cases of peripheral neuropathy of paraproteinemic type would seem to revolve around a compromise of viability of the Schwann cell and a disruption of its interactions with the myelinated axon.

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