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Transforming Cellular Roles for Antigen Presentation and Immunoreactivity in Multiple Sclerosis

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Abstract: A simplified program operative during transition of lymphocytes and monocytes through cerebral endothelium and ependyma might provide an effective mechanism promoting reversal of roles of these two cell types with regard to antigen reactivity and antigen presentation. One might envision a role for the oligodendrocyte that mirror images injury to myelin-invested axons as an initiating mechanism in both presenting antigen and in determining the establishment of endless cycles of amplified demyelination. These appear paradoxically dictated by dynamics of the cyclical remyelination of such initially injured axons. Neuroinflammation with involvement of axons would progress as evolving demyelinative plaques scattered in random fashion in white matter. Macrophages appear to act as effector cells in demyelination of inflamed regions that propagate lymphocyte-induced effects in antigen presentation and immune response. Antigen presentation is implicated as a mechanism of progression of MS plaques. Demyelination depends on active phagocytosis of myelin lipid, in response to such antigen presentation. Transforming roles of lymphocyte antigen presentation and macrophage reactivity appear central to ongoing demyelination and remyelination cycles superimposed on an inflammatory axonopathy.

Key words: Immunoreactivity, antigen, presentation, lymphocytes

INTRODUCTION

A PREDETERMINING ROLE FOR AXONAL PATHOLOGY IN MULTIPLE SCLEROSIS DEMYELINATION

A heterogeneity of causes as active agents in pathogenesis of multiple sclerosis[1] would apparently go beyond just genesis of a well defined Multiple Sclerosis (MS) plaque. This may include in some cases a genetically induced increased susceptibility to demyelination secondary to inflammation. Autoimmunity may be linked in particular to overexpression of adhesion molecules and downregulation of heat shock proteins. Apoptosis and cell cycle activity are also affected[2]. In terms related particularly to inflammatory cell infiltrates with cytokine production in grossly uninvolved white matter, there would evolve a series of preliminary steps in production of a progressive lesion affecting myelin ensheathment and progressing usually as relapsing/remitting waves of demyelination..

Such additional myelin sheath pathology that is not directly linked to active demyelination would render the MS plaque only one process involving pathogenic events that induce patient symptomatology. Axonal injury is a major correlate of MS progression linked apparently to hyperphosphorylation and aggregation of microtubule-associated protein tau[3].

It is perhaps significant that multiple sclerosis progresses as a series of amplification steps arising concurrently with axonal myelin injury and with vascular wall damage, microglial reactivation, and macrophage-mediated phagocytosis. Multiple sclerosis, in particular, is increasingly being recognized as a form of neurodegeneration promoted or triggered by neuroinflammation[4,5], with subsequent attempts at remodeling of axonal connections[6].

The MS plaque represents mechanistic steps in induced axonal demyelination ranging from simple atrophy to complex pathways of dystrophy. Inflammatory axonopathy[7,8] would promote loss of myelin in cyclical waves involving remyelination . Axonal damage begins early in the disease course and modulates disease progression in terms more of degree of inflammation rather than of demyelination[9]. Inflammation appears at least partly responsible for the axonal damage in MS[10]. MS proves both demyelinative and remyelinative with regard to an inflammatory lesion that would apparently often primarily arise as an axonopathy[11] whose pathogenesis is difficult to determine[13].

INTERACTIVE AXONS AND MYELIN SHEATHS

Inflammatory reactivity drives the progression of multiple sclerosis plaques that involves interactivity of

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adhesion molecules between axons and their myelin sheaths.

Also, the very late antigen-4 (integrin alpha4beta1) is expressed on monocytes and T and B lymphocytes and is implicated in the massive recruitment of inflammatory cells[12]. Intravenous immunoglobulin interferes with alpha4 integrin-dependent leucocyte recruitment in multiple sclerosis[13].

Plaque evolutionary pathways would directly involve blood vascularity in plaque generation and maturation. Concomitant and sequential cycles of events amplify a host of potentially heterogeneous agents in genesis and evolution of white matter inflammation both outside plaques as well as within plaques. Microglia appear to secrete factors that induce liposaccharide-enhanced proliferation of oligodendrocyte progenitor cells implicating possibly Golli proteins[14]. Upregulated Tumor Necrosis Factor alpha and lymphotoxin-alpha around MS plaques appear involved in inflammation and demyelination[15].

Multiple scattered MS plaques would implicate the demarcation from myelinated white matter in eventual plaque progression at times of critical generation of these lesions.

Enlargement of MS plaques is linked to inflammatory amplification of multiple heterogeneous events involving both infectious or parainfectious and autoimmune mechanisms.

Chemokines interact to control T cell migration in neuroinflammatory tissues: CCR5 delta 32 deletion induces a poor prognostic outcome in MS patients[16].

Linking inflammatory overactivity to persistence, recurrence and intensity of an infectious or parainfectious process would necessarily implicate inflammatory reactivity as an amplified pattern of injury primarily involving the integral axon/myelin unit. Local proinflammatory cytokine production results in widespread autoimmune inflammatory activity in the CNS in experimental autoimmune encephalomyelitis[17]. Transforming cellular injury would arise as interactions between the neuron (and its axon) and multiple oligodendrocytes in development of the MS plaque.

A non-infectious basis for evolving myelin injury would implicate cytokines and inflammatory reactivity and also the establishment of oligodendrocyte pathology as a specifically induced demyelination. Inflammatory processes acutely injure axons and myelin involving an interplay of plasticity and remyelination and also loss of trophic support for axons[18]. Neurons may variably interact with multiple oligodendrocytes in promoting susceptibility to further episodes of demyelination.

DEMYELINATION

Demyelination of the axon appears a cascade-like series of events primarily arising from interactions with oligodendrocytes.

Demyelinative waves of injury evolve as plaque enlargement and maturation as predetermined by pathology initially arising in the affected myelin sheath and in the supplying oligodendrocytes. Initial inflammation is replaced by a predominant demyelination possibly maintained by humoral mediators[19].

MS plaque maturation is a distinct process in development of serial axonal injuries that progress somewhat independently of oligodendrocytic and myelin sheath injury. Progressively active lesions of the MS process implicate inflammation in axons that reflect a multiplicity of events arising from progression of neuronal membrane reactivity and injury. Membrane turnover due to demyelination and remyelination, gliosis, inflammation, and attempted remyelination may contribute to increased creatine and choline levels in white matter lesions that are isointense on MR imaging[20].

T lymphocyte reactions and antibody reactions compromise remyelination of seriously injured axonal segments.

WHITE MATTER INVOLVEMENT

Mononuclear/microglial cell infiltration of the white matter progresses as evolving plaque genesis. Plaque genesis in multiple sclerosis implicates sequentially inflicted lesions in its own right. Myelin sheaths may fail to fully invest the demyelinated axonal segments.

Myelin sheaths would dysfunctionally implicate remyelination as recurring waves of injury. The axon constitutes a large number of myelinated segments that promote participation of multiple supplying oligodendrocytes in progression of the demyelinating MS plaque.

Pathways of generic transformation in initial plaque formation would predetermine subsequent evolving progression in genesis, enlargement and maturation of the MS plaque. Cyclooxygenase-2 in particular may possibly be associated with pro-inflammatory states and may be expressed by many cell types including microglia in response to cytokines, growth factors, and proinflammatory molecules[21].

A demyelinating lesion primarily arises as inflammation of successive axon segments supplied by multiple oligodendrocytes.

A T lymphocyte helper role would operate in conjunction with a cytokine reactivity involving both

chemotaxis and chemical injury in a context of activated transcription pathways.

Pathways of injury arise from a potentially highly varied group of sources that specifically disrupt myelin/axon interactivity. Increased free radical generation and decreased reparative/degradative activity affecting in particular proteolysis, may contribute. Heat shock proteins may enhance cytoprotection in states of neuroinflammation[22]. Demyelination would promote axonal segment injury as a possible principal determinant of subsequent remyelinating dynamics accounting for a phasically active MS disease process.

Preservation of axons in demyelinating MS plaques would attest to reproducible events linked to sequential plaque evolution. An axonal demyelination of multiple segments progresses as precipitating causes of subsequent evolving injury to the axon.

An induced demyelination may arise as a predetermined lesion of the axon, with perhaps subsequent evolution as maturation of the axonal lesion itself. Cytokine-mediated events might allow for apparent preservation of axonal structure in the face of reactive transformation of injury to the myelin sheath.

MULTIPLICITY OF EVENTS IN LYMPHOCYTE/MICROGLIAL INTERACTION IN MULTIPLE SCLEROSIS

Multiplicity of foci of sclerosis would underlie a system process of evolving injury related particularly to enhanced susceptibility to a variety of agents.

It might be significant that conversion pathways of progressive damage to the myelin sheath would reflect biochemical change arising in and sustained by kinetics of microglial activation. It is in terms of relationships between T and B lymphocytes on the one hand, and microglia on the other, that multiple foci of sclerosis also develop as centerpoints of involvement of a myelin sheath network involving expression of adhesion molecules and interactions between lymphocytes and the blood brain barrier in the presence of chemokines and chemokine receptors[23].

System injury is a means for intensely progressive transformation of myelin sheaths enwrapped around axonally damaged segments of the neuron.

An initial participation of system networks as multiple MS plaques would render demyelination only one aspect of a disease process that culminates in events segmentally transforming the axon.

Systemic indicators of how multiple sclerosis relapses and remits might specifically incorporate induced myelin breakdown linked inherently to a lymphocyte/microglial inter-reactivity.

Antigen preservation appears only a preliminary step in immune response effecting evolving systems based on consumption of complement and on cellular and antibody reactivity inducing demyelinaton. In addition, P2X(7)R mediated signaling may modulate astrocytic response to neuroinflammation by inducing pore formation, altered cell permeability, cytokine release and apoptosis. ATP and ADP modulate purinergic P2 receptors that are either of metabotropic P2Y or of ionotropic P2X receptor family[24].

Subunit complexity in the derived system pathways of demyelination would render neuroinflammation a manifested process of disease evolution largely characterized as pathways of axonal subunit damage.

Modes of interaction between lymphocytes and microglia might centrally implicate a response of both types of cell as an ongoing demyelination initiated as a chemical-toxic or virally induced disorder.

Demyelination activates ongoing interactivity between lymphocytes and microglia that endresult in a macrophage-induced phagocytosis of myelin. Also, macrophages are in particular a major source of metalloproteinase-12 involved in inflammatory cell infiltration in the pathogenesis of multiple sclerosis and this remains raised during periods of remission[25].

It is in terms of a phagocytic dysfunction as activated macrophages invade myelin sheaths that there would also evolve a segmental axonal disorder linked largely to loss of oligodendroglial viability.

A remitting/relapsing series of events in multiple sclerosis originates as multiple foci of sclerosis and ends up as demyelination of axons with eventual loss of oligodendrocytes.

Distinctive macrophage-directed reactivity to the myelin sheath might progress hand in hand with renewed replacement of the myelin lipid. Multiple sclerosis generally proves relentlessly progressive to form burnt-out demyelinated plaques.

Vascular patterns of interaction and axonal segment demyelination implicate immune response, monocyte migration and homing as a series of evolved effects resulting in both effective and ineffective phagocytosis of myelin lipid. Calcium influx via voltage gated calcium channels may significantly contribute to neurological disability[26].

A REVERSAL OF ROLES FOR LYMPHOCYTES AND MICROGLIA/MACROPHAGES SECONDARY TO AXONAL NEUROINFLAMMATION

A proliferating lymphocyte cell pool that cycles through the central nervous system and peripheral blood without involving the peripheral nervous system appears a function of the CNS endothelium.

The actual actively dividing lymphocyte and monocyte cell pool would further implicate a change in reactivity tied up with reactivity of the resident microglia in a manner that promotes in some way selective oligoclonal expansion. T cells and B cells might segregate in a manner that would encourage persistent reactivity towards antigens presented both as endothelial and microglial cells of the central nervous system (CNS).

The actual homing and migration of lymphocytes and monocytes might in a sense recapitulate events that transform reactivity of these cells as strictly dictated by myelin sheath determinants based on antigenic expression by endothelial cells.

Realized pathways might implicate in particular a sharply outlined system of participation between circulating pools of lymphocytes and monocytes on the one hand and a series of activated systems ranging from oligodendrocytes, astrocytes and microglia. Cytokines appear to render oligodendrocytes more susceptible to cell death pathways in an inflammatory background[27].

The oligodendrocytes would appear targeted to evolve in terms of how microglia do in fact constitute an effective endpathway in such realized selectivity in response to circumscribed foci of myelin sheath damage around axons.

Multiple sclerosis plaques would, in effect, constitute foci of selectively cloned lymphocytes and monocytes that are promoted towards subsequent targeting of the oligodendrocytes as dictated by vascular endothelium and microglial cell pools. It might be significant that a vascular core to MS plaques is only a representation of pathways and modes of inter-reactivity between circulating and cycling proliferative pools of lymphocytes and monocytes as driven by oligodendrocytes in particular. Driven systems that paradoxically act as targeting systems on oligodendrocytes would constitute transformed mechanistic pathways dictated by endothelial interaction. Increased white matter perfusion contrasts with decreased grey matter perfusion in MS patients, the latter implicating neuronal and axonal loss secondary to neuroinflammation[28].

Antigen-presentation would appear a powerful inducing pathway that strongly promotes selective subclones of cycling lymphocytes and monocytes and one that selectively produces intrathecal oligoclonal antibody.

In a system of amplification promoting pathways of antigen presentation and also of selective lymphocyte/monocyte subcloning, there might be generated an interactivity between these two cell types that is directed by vascular endothelium.

Inducible nitric oxide synthase appears to play an important role in pathogenesis and is localized to ependymal cells, inflammatory cells and occasionally in astrocytes[29].

Microglially presented antigen might variably constitute both an initiator and a subsequent modeling system in promoting selective reactivity to the myelin sheath.

A reversal of roles in terms of both antigen presentation and reactivity might involve lymphocytes and monocytes during their active migration through CNS endothelium; this may be dictated by a selective vulnerability of perivascular zones of grouped oligodendrocytes and microglia. Expression of VCAM-1 adhesion molecule as induced by Tumor Necrosis Factor receptor-1 on astrocytes is centrally involved in T cell entry into inflamed CNS parenchyma[30]. Reversal of roles would induce an amplified expansion of microglial cell pools concurrent with antigen presentation by oligodendrocytes.

ANTIGEN PRESENTATION

The oligodendrocyte comes to fulfill a role as an antigen-presenting cell with macrophages attacking the myelin sheath in strict contextual frameworks of evolving lymphocyte turnover.

It is peculiar to multiple sclerosis that selected MS foci of plaque activity promote further activity in these same plaque foci rendering disease progression a strictly cyclical and amplified process of the classically remitting/relapsing disease.

A graduated antigen presentation and lymphocyte/monocyte reactivity to the myelin sheath would progress as systems arising from active proliferation of migrating and homing pools of lymphocytes. Macrophage inflammatory protein-1alpha is expressed by lymphcytes and monocytes and induces chemotaxis and proinflammation[31]. It is in such terms that targeting novel antigens presented by microglia and the oligodendrocytes would interactively amplify each other. The endothelium would act as a selector in such a process[32] in affecting lymphocyte turnover between the circulation and the perivascular plaque regions with progressively damaged myelin sheaths. Estrogen receptor alpha signaling may possibly implicate endothelial cells or microglia in estrogen-mediated neuroprotection observed in experimental autoimmune encephalomyelitis[33]. Estrogen may skew TH-1 to TH-2 type response through suppression of TH1 and potentiation of TH2-mediated disease with exacerbation or suppression of inflammatory disease states[34].

The actual breakdown of myelin sheaths might dictate attributes of myelin replacement subsequent to antigen presentation on oligodendrocytes.

The multiple sclerosis process involves depletion of oligodendrocytes in the burnt-out MS plaque. Myelin sheaths come to represent a reactive antigenic site promoting a reversal of roles of lymphocytes and the microglial/macrophage system, and in a manner that effectively substitutes antigenically the endothelial cell for the oligodendrocyte.

Endothelium would correlate with plaque populations of oligodendrocytes in a manner that is essentially heterogeneous in any given MS plaque. Elevated plasma endothelial microparticles occur during exacerbations of MS and conjugate with monocytes and activate these through CD54[35]. Polyclonality of homing and cycling proliferative pools of lymphocytes would prove a determining factor as strictly heterogeneous reactivity patterns involving microglia, monocytes and macrophages that are directed against the myelin sheath. CD14 memory T cells traversing cerebral microvasculature are characterized by CXCR3 surface marker[36].

Further selectivity in the homing of lymphocytes would promote ongoing activity of the demyelinating plaque and subsequent remyelination.

Such a paradoxical system of remyelination dictating a selective vulnerability to further cycles of demyelination might prove a main determinant driving the lymphocyte and macrophage systems as progressive plaque evolution. "Resetting" of the immune system may prove an effective possible mechanism in treatment of MS patients, including after stem cell transplantation[37]. A continuous realignment in the immune and inflammatory response occurs in MS[38].

Initiation of cycles of demyelination and remyelination might be particularly influenced by transected axons early in the course of the disease.

Actual selective sites of MS plaque formation would constitute a function of the cerebral endothelium and ependyma in a process attributing an antigen-presenting role to oligodendrocytes. Lymphocytes arising as cell-mediated and complement-fixing antibody systems of production would relegate a macrophage role in the actual stripping of the myelin sheath.

Changes in gap junction intercellular communication may develop in neuroinflammatory states, and accompanied by astrocytic hypertrophy and proliferation of both astrocytes and microglia[39].

Axonal transection has been an observed feature in evolving MS plaques that might present antigen to oligodendrocyte cell pools surrounding activated endothelium; this process may progress as reactivity of circulating lymphocytes and monocytes.

The strict roles played by enwrapped axons would account for a heterogeneous lymphocyte reactivity resulting in oligoclonal antibody production in cerebrospinal fluid. The proximity of many multiple sclerosis plaques to the ventricular surface may implicate ependyma in inducing cycling and proliferating lymphocytes and macrophages that subsequently react to oligodendrocytes and myelin sheaths.

CONCLUSION

Only in terms of a reversal of roles between lymphocytes and the microglial/macrophage system can one account for progression of an MS process that evolves in terms of a remyelination of axons and dictating further waves of demyelination. It is in terms of CNS endothelium and of ventricular ependyma that such a reversal of roles would evolve. The actual initiation of cycles of remyelination promoting demyelination might lie with injured axons exposed to a neuroinflammation affecting axonal segments as globally distributed in the brain and spinal cord.

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