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VIEWPOINT

Retargeting of Immature Oligodendrocytes Precipitates the Multiple Sclerosis Plaque

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Abstract. Disease developmental injury of oligodendrocytes compromises the maturational potential of these cells as they proliferate and attempt to reconstitute the myelin sheath of parent axons in multiple sclerosis. Involvement of injury is a sequential and also non-sequential form of activity that participates in the emergence of multiple forms of dynamic turnover within the multiple sclerosis plaque. The complex of inflammatory/demyelination earmarks such events in terms of ongoing injury to the oligodendrocyte in the first instance. The perivascular space remodelling invokes a gliotic response and a redistribution of injury to multiple other cellular components within encompassed confines of both neuronal axon and immune response. Macrophages attempt to reconstitute the microenvironment of the multiple sclerosis plaque within systems of redefined constitutional identity. Gliosis is a persistent overlapping series of systems in reconstruction of a perivascular space that proves irreversible inducer for further participation by systemic events in expansion and progression of the individual multiple sclerosis plaque.

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1. Introduction

Contrasting profiles of various activated stages of multiple sclerosis (MS) plaques indicate a driven and compromising phenomenon that targets the viability of oligodendrocytes. However, the role of autoantibody response in multiple sclerosis pathogenesis remains controversial (Aslam et al., 2010). The complex of inflammatory/demyelinating lesions is projected as terms of reference to the progression of an injury that encompasses delineated confines of the plaque margins. In this sense, the overall dimensionality of the individual MS plaque is contrasted with the relapsing/remitting nature of the demyelination of given sets of axons (Watzlawik et al., 2010). It is in such manner that the predominant characterization of injury in multiple sclerosis is a derived parameter of overwhelming proportions and one that indicates and further defines the micro-architecture of the individual MS plaque. Hyaluronan deposits, in particular, inhibit oligodendrocyte precursor cell maturation and remyelination (Sloane et al., 2010).

2. Component Participation

The development of significant component participation of multiple possible pathogenic pathways in multiple sclerosis is a real confrontational reflection of the acquired perturbations arising within contextual breakdown of the blood-brain barrier. In such context, CXCR2 signaling appears to protect oligodendrocyte lineage cells from apoptosis (Hosking et al., 2010) in virally induced demyelination.

One would consider the dynamics of demyelination as a primary consideration in terms of involvement of a variety of injuries that increasingly compromise the systematic repair of injured axons. It is particularly significant to view the terms of involvement as conditional targeting of myelin sheaths in a manner specifically offering further targets for immune response and for epitope spread. AlphaB-crystallin accumulates in oligodendrocytes and constitutes a major target for the adaptive immune response (van Noort et al., 2010).

The complex realization of injury within MS plaques is distinctively different from the involvement of normal appearing white matter and normal appearing grey matter in brains affected by multiple sclerosis.

In addition, the characteristically sparse inflammatory components in grey matter or cortical plaques attest to a range of projected involvements that further redefine the complexed inflammatory/demyelination phenomenon. Plaque formation may have some basis other than destructive cell-mediated immunity against a myelin or oligodendrocyte antigen (Henderson et al., 2009).

Insight of the underlying temporal sequence in acquisition of demyelinating lesions would implicate a further delineation of injury as forms of incremental severity and as consequential attributes of the targeted oligodendrocyte. CXCL12 signaling through CXCR4 directs migration and proliferation of oligodendrocyte precursor cells (Carbajal et al., 2010).

It is the failure of reconstitution of the oligodendrocyte population that allows for the emergence of a primary form of demyelination in patients with multiple sclerosis, particularly in view of a paucity of oligodendrocyte precursor cells (Jennings & Carroll, 2010).

3. Persistent Injury

The persistence of injury to the oligodendrocyte attests to the realization of a form of intervention that culminates in further progression of pathways in systemic involvement. CXCR4 promotes differentiation of oligodendrocyte precursor cells and hence remyelination (Patel et al., 2010).

The dimensions of injury to the central nervous system myelin are integral to ongoing change in constitutional identity of the oligodendrocyte in early stages of inception of the multiple sclerosis plaque. Areas within expanding plaques may show marked oligodendrocyte

loss and apoptosis without a component of infiltrating lymphocytes (Henderson et al., 2009). In this sense, there is a determined identification of the targeted oligodendrocyte within scope of operability of such events as replication, developmental maturation and incremental evolution of the myelin-synthesizing cells. Axon-oligodendrocyte interactions determine both myelination and also pathophysiology of demyelination (Piaton et al., 2010). It is in such manner that primary progressive MS and secondary progressive MS contrast with the commoner variety of clinical course seen as relapsing/remitting disease.

Within indices of reproducible identity, the further contrasting involvement in MS patients is a delimited gain and subsequent loss of identity of the initially targeted oligodendrocyte population. Neural precursor cells induce proliferation of oligodendrocyte precursor cells and promote differentiation to mature oligodendrocytes (Einstein et al., 2009).

The individual characterization of the MS plaque is a very distinctive profile component within systems of potentially reversible demyelination and as subsequent involvement of given subsets of oligodendrocytes, as evidentially identified within the MS plaque. In such manner, the component systems of involvement indicate a characterization that strictly redefines the dynamics of the multiple sclerosis process in terms of inducible response. Primary loss and dysfunction of astrocytes and autoantibodies targeting aquaporin on astrocytes may trigger demyelination at an early stage of plaque formation (Sharma et al., 2010).

In such manner, further onset and subsequent ongoing progression are strictly characterizations of the pathogenic mechanisms applicable beyond simple enumeration of other components of the MS plaque (Sato et al., 2010).

4. Reconstitution

In real terms, the distinction of macrophages that directly strip myelin sheaths from axons and also the recognition of loosened inner myelin sheaths immediately surrounding axons are interacting profiles of an injury that is secondary to oligodendrocyte cell damage and loss.

In such manner, the reconstitution of oligodendrocyte subpopulations would indicate the maintenance of a state of constitutional recovery in the face of events resembling in many ways the active apoptosis of such cells. 17-beta estradiol partially ameliorates loss of oligodendrocytes and demyelination (Taylor et al., 2010).

It is within the further developmental stage of depletion of oligodendrocyte subpopulations that there evolves incremental injury to the stage of complete demyelination of the involved axons.

There is a high frequency of autoreactive T cells during multiple sclerosis, with ability for homing to tissues (Bahbauhi et al., 2010). It is significant that various stages in inflammatory/demyelination prove indices of activity of the oligodendrocyte subsets. Cyclooxygenase- 2 expression is related to dying oligodendrocytes and to demyelination (Carlson et al., 2010). In such manner, the progression of injury in multiple sclerosis is inherently progressive as a result of recurrent and also progressive depletion of oligodendrocyte cell populations within the MS plaque.

The margins of the active chronic plaque indicate a restorative imbalance in the supply and also depletion of restitution indices in oligodendrocyte replication and maturation. In a real sense, progression of MS plaque demyelination arises within contextually progressive lack of maturation of oligodendrocyte subpopulations bordering and defining the MS plaque. Theiler's murine encephalomyelitis virus infects early stages of oligodencrocyte lineage and blocks oligodendrocyte maturation (Pringproa et al., 2010).

5. Profile Characterization

Significance of injury to the myelin sheath is a profile characterization of the injury in terms of

a primary depletive phenomenon.

It is in such terms that multiple sclerosis arises and progresses in direct reference to a reduced potential for oligodendrocytes to both proliferate and also reach significant maturational status within plaque regions of involved white and grey matter of the central nervous system. Increased expression of Insulin-like growth factor binding protein-1 activates migration of oligodendrocytes (Chesik et al., 2010).

It is the persistence of incremental compromise of injured oligodendrocytes that allows for emergence of profiles of progression as MS plaques enlarge and encroach on the adjacent white matter. Presence and activation of neuronal nitric oxide synthetase in oligodendrocytes may reduce viability of these cells (Yao et al., 2010). The significance of overlapping pathogenic mechanisms in inducing a targeted oligodendrocyte subset to become depleted is borne out by the concomitant myelin sheath loss and the injury to the parent axon.

Transforming growth factor beta-1 induces activated Jagged1-Notch1 signaling to regulate oligodendrocyte progenitor differentiation, myelin formation in development and remyelination in the adult central nervous system (Zhang et al., 2010). Neurons are significant as component systems in reproducible further compromise of the injured oligodendrocytes, as well exemplified by lack of growth factors such as Platelet derived growth factor and Nerve growth factor (Einstein et al., 2009).

It is within such systematic depletion of oligodendrocytes that the true nature of multiple sclerosis increasingly induces a series of restorative attempts involving the myelin synthesizing events. Incremental severity is a central trait characteristic of multiple sclerosis pathophysiology in a manner that is terminated only with total depletion of the given subset of targeted oligodendrocytes. Notch1 signaling is one mechanism regulating oligodendrocyte precursor cell differentiation during CNS remyelination (Zhang et al., 2009).

6. Injury Definition

Particular relevance has to be considered in the definition of an injury that is cellular from inception, and also incremental at outset. In such setting, the oligodendrocyte appears a reproducible model for the pathogenesis of further cellular injury as reflected subsequently in the demyelination of the axons of supply and of the neurodegeneration that arises. A strictly non-sequential series of injuries encompasses the incremental involvement as reflected by the end-stage chronic MS plaque that is predominantly acellular and gliotic. ADAM12 is expressed by astrocytes and is not a suitable marker for oligodendrocytes; it is present in brain lesions affected by oligodendrocyte loss (Baertling et al., 2010).

Developmental realization of the vasogenic edema surrounding early MS plaques and the widening of the perivascular spaces allow for the systemic interventional involvement of the individual MS plaque in a manner specifically conducive towards further incremental disease activity. Loss of balance between extracellular forces and intracellular contractions might possibly account for failed remyelination by oligodendrocytes (Bauer & ffrench Constant, 2009).

7. Heterogeneity

A heterogeneity of involvement in realization of injury to various components of the active MS plaque seems to target in particular manner the margins of the plaque as this encroaches on normal appearing surrounding white matter. In such manner, the lesions present in Normal Appearing White Matter reflect the systemic factors in pathogenesis and also as indicated by Wallerian degeneration of the constituent axons.

The specific interpretation of injury as elucidated by depletion of fully mature oligodendrocytes would indicate a series of confounding influences that activate proliferation at the expense of maturation of the individual myelin-synthesizing cell (Fancy et al., 2010).

The remyelinated axon is one that shows generally a thinner myelin sheath and shorter internodes in a manner that reflects the progressive loss of synthesizing potential of the oligodendrocytes (Nakahara et al., 2009). The deliberate involvement as specific targeting of a given subset of such oligodendrocytes would indicate a particular predilection for injury that is concurrently acquired with a global and also focal loss of function of the blood-brain barrier.

In such manner, a phenomenal restitution of the injurious event is paramount to the progressive depletion of oligodendrocytes. It is in this sense that actual loss of these cells is index parameter for progression of a demyelination of axons in the first instance. The involvement of the parent neuron is incrementally an injury to the axon with often transection of this structure component.

Development of injury in multiple sclerosis is hence a persistent overlapping of various forms of pathogenic pathways within the further complex of an inflammatory reaction that promotes the remodelling of the adjacent matrix.

Extracellular matrix proteases and intracellular proteases would appear to both contribute to a significant remodelling of the injurious agent as further indicated by progressive gliosis of the MS plaque.

The involvement of astrocytes indicates a tissue response in terms of the significant injury to multiple components of the MS plaque and as further illustrated by the perivascular or perivenular aggregation of immune and inflammatory cells within plaques.

8. Inflammatory / Demyelination

The full complex of inflammatory/demyelination constitutes a tissue response that further compromises the involvement of injured oligodendrocyte subsets. It is with particular reference to such system components as microglia, macrophages, T-lymphocytes, complement and edema that the nature of injury in multiple sclerosis is a triggered complicating form of inducible depletion of most components as evidenced in the end-stage chronic MS plaque.

The integration of various proposed pathogenic pathways in the constitutional reconstruction of the MS plaque is one that is fundamentally reactivating. Mild hypoxia favors neural stem cell proliferation and neuronal and oligodendroglial differentiation (Santilli et al., 2010).

In a sense, the gliosis is paramount feature of the progressive plaque in a manner that is symptomatic of further incremental injury to multiple components of such plaques. It is this integral targeting of oligodendrocytes that further spreads to involve other cellular components as well-illustrated by the macrophage-induced phagocytosis of myelin lipid and also the matrix remodelling of the perivascular space.

It is within confines of the plaque and also beyond such plaque margins that the persistence of the injurious events further promotes a systemization of involvement that incorporates epitope spread of antigenicity.

The prominence of the immune response that primarily involves T-lymphocytes, but also the ingress of antibodies and complement within the perivascular space of the central nervous system, would indicate a compromised viability of multiple cell types within the MS plaque. It is in such setting that the initial onset of the MS disease process allows for the establishment of an injury that propagates as oligodendrocyte depletion and subsequently as gliosis. Apoptosis of oligodendrocytes and post-translational modifications of myelin basic protein are implicated early in multiple sclerosis (Artemiadis & Anagnostouli, 2010).

Gliosis is a marker and also active participant in the development of injury to multiple cell component systems ranging from myelin sheath to axonal atrophy or transection, and also neurodegeneration that is secondarily responsible for compromised synaptic function and atrophy (Siffrin et al., 2010).

9. Portal of Entry

Portal of entry in MS plaques denotes a systemic integration of the injury that is spread within the system confines of white and grey matter irrespective of subsequent dynamics of the inflammatory/demyelination complex of events. It is in terms defining such systemic spread of the injurious agent that multiple sclerosis proves both persistent and progressive in spite of an overall often relapsing-remitting disease course.

The incipient lesion in early stages of definition of the individual MS plaque indicate a breakdown of the blood-brain barrier in a manner that allows participation of oligodendrocytes within astrocytic subfields. In such manner, the incremental nature of the injury is one based primarily on persistent antigenicity of the injured cells and myelin sheath.

10. Concluding Remarks

The centrality of involvement of the oligodendrocyte in MS plaques correlates with a gliotic response that is developmentally related closely to subsequent dynamics of remodelling of the perivascular space.

The participating astrocyte is allied to immature forms of oligodendrocytes in a manner that allows the creation of a permissive environment conducive to active impairment of the micro-architecture of the enveloping myelin sheath and to active injury or transection of axonal segments. Neurodegeneration of the parent neuron is consequential and also original focus in a manner that is consonant with the dynamics of turnover of immature oligodendrocytes that are incapable of constituting a fully mature myelin sheath around the axon.

It is within defining contexts of an impaired blood-brain barrier that various ill-defined immature stages of oligodendrocyte biology contribute directly to potentialities of turnover and repeated waves of breakdown of the myelin sheaths.

Given the dimensions of systemic participation, there is an enhancement of immune responsiveness arising particularly from intra-thecal proliferation of plasma cells in particular.

Various forms of multiple sclerosis plaque mechanics range from inflammatory/demyelination complexing, T-cell immune response, antibody-complement interaction, distal oligodendrogliopathy, and direct depletion of oligodendrocyte subpopulations by apoptosis.

Remodelling of the perivascular space proves, therefore, a platform for integrative combination of multiple foci of involvement that permit emergence of immature forms of oligodendrocytes within dimensions specifically of a gliotic response.

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