Mechanisms of Schwann Cell Damage in Inflammatory Neuropathy

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Inflammatory demyelination of nerve in Guillain-Barré syndrome is triggered in most patients by prior infection with one of a series of organisms, including Campylobacter jejuni. The resulting inflammatory cascade, involving T cells, macrophages, complement, and cytokines, disrupts physiologic function of the peripheral nerve in part by targeting Schwann cells, the multipotential glial cells that synthesize multilamellar, compacted myelin and secrete growth factors. In vitro evidence suggests that the Schwann cell may itself be able to modulate the cascade by serving as an antigen-presenting cell and by producing cytokines and other acute-phase reactants.

Demyelination of Schwann cell internodes and blocking of peripheral nerve conduction are the consequences of a cascade of immune events that underlie the monophasic subacute paralysis of Guillain-Barré syndrome (GBS). It is suggested that a preceding infection triggers both cellular and humoral immune responses against antigen epitopes on viral or bacterial organisms that cross-react with shared epitopes on Schwann cells, myelin, or axons (or all three). The infections most frequently linked to the development of GBS include those caused by cytomegalovirus, Epstein-Barr virus, mycoplasma, and certain serotypes of Campylobacter jejuni.

C. jejuni is reported to be associated with both the acute motor axonal and the demyelinating varieties of GBS [1]. This review is limited to mechanisms by which Schwann cells, the principle myelinating glial cells of peripheral nerves, may contribute to the development of endoneurial inflammation and nerve damage. Most reports have focused on peripheral nerve myelin (PNM) as the target of immune-mediated attack since histochemical and ultrastructural studies of peripheral nerve of GBS patients demonstrated focal destruction of the myelin with preservation of the myelin-producing Schwann cell (reviewed in [2]). The ability of the Schwann cell to resist cytolysis and potentially mediate endoneurial pathophysiology through the release of cytokines and acute-phase reactants is the subject of current interest.

Schwann Cell Phenotype Expression

Schwann cells differentiate from progenitors derived from neural ectoderm. Schwann cell phenotypes with diverse biologic functions express different sets of genes regulated by axonal contact through increases in growth factors, including heregulin, a member of the Neu differentiation factors, and cAMP (reviewed in [3]). Immature, premyelinating Schwann cells express p75 NGFr (a low-affinity receptor for nerve growth factor), N-CAM (neural cell adhesion molecule), and S-100β (a Ca++-binding protein). A subgroup of Schwann cells in contact with smaller-diameter axons express a species of glial fibrillary acid protein.

The myelinating Schwann cell phenotype in human nerves is induced by contact with axons >2.5 μm in diameter and expresses myelin-associated proteins, including the principal glycoprotein (P0), PMP-22, basic proteins (P1 and P2), the myelin-associated glycoprotein, and CNPase. This phenotype is negative for NGFr and N-CAM but continues to express S-100β and CR1 (complement receptor type 1), which binds activation fragments (C3b and C4b) of the complement cascade. Contact of the myelin internode stimulates axonal neurofilament phosphorylation and segregation of ion channels in the axolemma. Axolemmal Na+ channels are limited to the nodes of Ranvier, whereas K+ channels occur under the internode [4]. This segregation contributes to electrophysiologic characteristics of nerve, allowing saltatory conduction. Demyelination unmasks the internodal K+ channels, decreasing the efficiency of conduction of the ion impulse, blocking the spread of passive depolarization, and leading to failure of impulse propagation. Injury to and degeneration of the distal axon through either trauma or inflammation cause Schwann cells to lose the myelinating phenotype and leads to myelin vesiculation and complement-dependent phagocytosis of myelin by macrophages [5, 6].

After axonal degeneration, residual columns of Schwann cells are proposed to express adhesion molecules (e.g., N-CAM) and bind growth factors to surface p75 NGFr, which provides pathways for the regrowth of motor and sensory fibers [7]. Schwann cells secrete trophic factors, such as nerve growth factor, ciliary nerve trophic factor, and glial-derived neurotrophic factor, which contribute to axonal out-growth and sprouting and to neuronal survival.

Schwann Cells Secrete Inflammatory Mediators

Experimental evidence provides support that Schwann cells have the ability to secrete cytokines with the potential to either
Schwann cells, which serve as targets of immune-mediated demyelination, can potentially modulate multiple aspects of inflammatory cascade by serving as secondary antigen-presenting cells and by producing cytokines and acute-phase reactants. Ag = antigen, IL = interleukin, MHC = major histocompatibility complex, γ-IFN = γ-interferon, Ab = antibody, NGF = nerve growth factor, CNTF = ciliary neurotrophic growth factor, GDGF = glia-derived growth factor, TGFβ = transforming growth factor-β, C3 = 3rd component of complement.

Figure 1. Schwann cells, which serve as targets of immune-mediated demyelination, can potentially modulate multiple aspects of inflammatory cascade by serving as secondary antigen-presenting cells and by producing cytokines and acute-phase reactants.

Antigen Presentation

Chimera studies in experimental allergic neuritis, an animal model for GBS, have established clearly that bone marrow–derived macrophages are the primary antigen-presenting cells for naive T cells in disease induction [11, 12]. However, the ability of rat Schwann cells to secrete IL-1β and express MHC class II antigen in response to IFN-γ theoretically would allow the cells to act as local endoneurial antigen-presenting cells to initiate and augment inflammation by T lymphocytes previously sensitized in the systemic circulation [13–15]. MHC expression by Schwann cells of class II and class I molecules also bears direct relevance as to whether they can serve as cytotoxic targets for Th1, CD4+, or CD8+ autoreactive T lymphocytes. There is no clear evidence of Schwann cell cytolyis by T cells in GBS. Enhanced T cell proliferative responses in the circulation of GBS patients are directed against peptides of P0 and P2 [16], both of which are expressed on peripheral myelin and not on Schwann cells. Since a Schwann cell antigen has not yet been defined and expression of Ia by human Schwann cells in vivo is still a matter of some debate [17], the role of CD4+ T cells in mediating Schwann cell damage remains to be clarified.

Peripheral nerve inflammatory infiltrates in both GBS and experimental allergic neuritis are principally Ia+ macrophages, the primary effectors of demyelination. Macrophages interact with opsonized targets through surface receptors for the Fc portion of IgG, IgA, and complement activation fragments. Interaction enhances the release of proteases capable of cleaving structural myelin proteins and cytokines (TNF-α and IL-1β), which may contribute to down-regulation of myelin gene expression and stimulate Schwann cell proliferation [18]. Unlike the oligodendrocytes, TNF-α by itself does not cause Schwann cell apoptosis [19], but the combination of TNF-α in association with other cytokines, such as TGF-β, has not been investigated.
Complement as an Effector of Endoneurial Damage

The development of demyelination in GBS correlates with the detection of C-fixing antibody against carbohydrate epitopes of a variety of gangliosides and neural glycolipids, some of which are expressed on the core sugars of C. jejuni lipopolysaccharide [20, 21]. In GBS patients, the presence of IgM anti-PNM antibody and anti-Schwann cell antibody correlates with the clinical course and with the complement-activation products in cerebrospinal fluid and serum (C3a, C5a, and sC5b-9) and in peripheral nerve (C5b-9). Antibody to PNM can directly mediate complement-dependent demyelination in vitro through formation of channel-forming terminal complexes of complement, C5b-8 and C5b-9. These channels facilitate Ca ++ influx and activation of endogenous neutral proteases capable of cleaving structural myelin proteins, including P0 and MBP, to cause splitting of myelin lamellae and vesiculation [21].

Increasing evidence suggests that one of the earliest detectable effectors in the peripheral nerve in GBS is the transient deposition of C3d and C5b-9 on the Schwann cell internode [22] or at the nodes of Ranvier. This can occur as early as 4 days after the development of neurologic symptoms, prior to infiltration of mononuclear cells. Vesiculation of the superficial myelin lamellae is associated with C5b-9 deposition on the Schwann cell internodes followed by association with macrophages containing phagocytosed myelin membrane expressing C5b-9. Despite the evidence of high levels of circulating complement-fixing antibody capable of binding Schwann cells in GBS patients [23] and immunohistologic evidence of C5b-9 insertion in Schwann cell plasma membrane in GBS patients, Schwann cells are resistant to complement-mediated attack [24]. This in part reflects the expression of molecules that prevent or enhance degradation of complement-activation products [24, 25].

Complement cascade activation on target membranes is down-regulated by membrane proteins. CR1 (CD35), as a cofactor for factor I, enhances C4b and C3b breakdown. Decay-accelerating factor (CD55) and membrane cofactor protein (CD46) inhibit C3 and C5 convertase formation. CD59 and C8-binding protein can inhibit C8/C9 incorporation and C9 polymerization during assembly of the terminal complement-activation complexes. The human phosphatidylinositol-based glycosyl phosphatidylinositol–anchored proteins CD55, CD59, and C8-bp are widely expressed on a variety of cells, including those of hematopoietic lineage, on which they inhibit autologous complement activation. The expression deficiency of these membrane proteins, especially CD55 and CD59, produces episodic hemolysis in patients with paroxysmal nocturnal hemoglobinuria, due to enhanced lytic susceptibility of their erythrocytes to autologous complement activation.

Human Schwann cells express CD35, CD46, CD55, and CD59 [25]. Increased CD59 expression between postnatal days 1 and 6 is a significant factor in the resistance of rat Schwann cells to complement-mediated lysis [24]. Surprisingly, compact human and rat myelin membrane, an extension of Schwann cell plasma membrane, expressed only CD59 [25]. The lack of C3 convertase regulation allows C3 fragments, C3b and iC3b, to efficiently deposit on myelin membrane during anti-body-mediated complement activation, and it likely contributes to activation of the alternative pathway of complement by PNM in the absence of specific antibody [26]. Such distribution of complement regulatory proteins could contribute to Schwann cell survival while enhancing myelin opsonization and phagocytosis by macrophages through complement surface receptors CR1 and CR3.

Sublytic terminal complement complex insertion causes oligodendrocytes to down-regulate myelin protein gene expression, inhibits apoptosis in vitro, and drives the cell into S phase [27, 28]. It is therefore possible that sublytic C5b-9 insertion into myelinating Schwann cells enhances myelin devestment by inducing expression of the premyelinating phenotype and stimulating cell division, thereby ultimately contributing to repair and remyelination. Terminal activation products of the complement cascade may also increase interaction between Schwann cells and macrophages through up-regulation of Schwann cell intercellular adhesion molecule, a ligand of CR3 on macrophages.

C. jejuni is one of a series of infectious organisms implicated in triggering GBS in some patients. It is proposed that through antigenic mimicry, the immune response against the infectious agents induces endoneurial inflammation, some of which is directed toward the Schwann cell. This multipotential glial cell, vital for the normal physiologic function of peripheral nerve, is hypothetically capable of contributing to the inflammatory process through production of cytokines, acute-phase reactants, and growth factors. Much of this work has been done in in vitro systems. The extent to which such factors contribute to the in vivo process remains a subject of investigation.

References