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# Commentary

## Connections between the immune system and the nervous system

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The nervous system and the immune system are connected anatomically (1) and physiologically (2, 3). In this issue of the *Proceedings*, Pham-Dinh *et al.* (4) confirm that myelin/oligodendrocyte glycoprotein (MOG) is a member of the immunoglobulin gene superfamily (5) and demonstrate that the gene encoding MOG maps to the major histocompatibility complex (MHC). These observations extend our view of the interrelationships between the nervous system and the immune system.

The interactions between the nervous system and the immune system are extensive. The basic mechanism underlying fever is a prime example of this interplay between immunity and the brain. Infection causes macrophages to produce interleukin 1, which enters the hypothalamus through a breach in the blood–brain barrier in the preoptic area. There it triggers a rise in body temperature. Other factors, including infection, trauma, and stress, can act through the hypothalamic–pituitary axis to influence the immune system. Inflammation stimulates the release of cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6, which can trigger the release of corticotropin-releasing factor by the hypothalamus (6, 7). Corticotropin-releasing factor can stimulate the pituitary to produce adrenocorticotropin, ACTH, which circulates to the adrenal glands and stimulates the release of cortisol. Cortisol in turn may suppress immune responses and cause thymic involution. Corticotropin-releasing factor also has a paradoxical effect on lymphocytes at the site of inflammation, where it heightens inflammatory responses. In experimental animals, failure to release normal levels of corticotropin-releasing factor in response to stress is correlated with susceptibility to experimentally induced autoimmunity (8). Recently Wilder, Chrousos, and colleagues (39) have demonstrated that corticotropin-releasing factor is present in the synovial fluid and tissues of patients with rheumatoid arthritis.

Immune mediators such as γ-interferon have been known for some time to induce the expression of immune system-related molecules, such as MHC class I and class II molecules, on neurons, glial cells, and even muscle (9). The response to γ-interferon allows glial cells, myocytes, and perhaps even neurons to present antigens to T lymphocytes of the immune system.

The connections between the nervous system and the immune system include not only the effect of circulating hormones and cytokines, but also involve "hard wiring." Pioneering work by Felten *et al.* (10) demonstrated that lymphoid organs are innervated. Granstein and colleagues (11) have shown that nerves are intimately associated with Langerhans cells in the skin. These nerves release calcitonin gene-related peptide, a neuropeptide that can inhibit the ability of Langerhans cells to present antigen to the immune system. These observations may provide an explanation for why psoriasis and atopic dermatitis worsen with anxiety. Perhaps in these diseases neuronal inhibition of Langerhans cells is defective.

The findings of Gardinier, Pham-Dinh, and colleagues (4, 5) add further evidence for a major association between the nervous system and the immune system. They studied the molecular genetics of a minor component of the myelin sheath in the central nervous system, MOG. MOG is located on the external surface of oligodendrocytes and may play a role in the later stages of myelination and in the maintenance of myelin homeostasis (4).

Gardinier *et al.* (5) had reported the MOG, sequenced from a rat cDNA clone, is a unique member of the immunoglobulin gene superfamily. Pham-Dinh *et al.* (4) confirmed these findings with MOG from bovine, mouse, and rat cDNAs. The sequence included a potential glycosylation site, as well as an N terminus suitable for its location on the extracytosolic side of the membrane and two membrane-spanning domains (a unique occurrence in the immunoglobulin superfamily). The developmental expression of MOG was studied, and it was first detected in rat brain at 10 days after birth. Expression of MOG coincided with the later phases of myelinogenesis.

Two findings about MOG stimulate further speculation about immune system–nervous system interactions: First, MOG has significant sequence homologies with other members of the immunoglobulin gene superfamily. Second, MOG maps within the MHC.

The N-terminal extracellular domain of MOG was most homologous with two non-myelin proteins: bovine butyrophilin, expressed in the mammary gland during lactation (4, 5, 12), and the B-G antigens of the chicken MHC (4, 5, 13). MOG, butyrophilin, and the B-G antigen have characteristics of an immunoglobulin variable-region-like domain, including an invariant tryptophan, two cysteines spaced 73 amino acids apart (for MOG and butyrophilin) or 71 amino acids apart (for B-G), and several conserved amino acid residues. Interestingly, MOG is not the first myelin gene to be included in the immunoglobulin gene superfamily. Myelin-associated glycoprotein (MAG), present in the central and peripheral nerve myelin sheath, and protein zero (P0), the principal peripheral nerve myelin glycoprotein, also belong to the immunoglobulin gene superfamily (14–17). Indeed, several molecules found in the central nervous system are also members of the immunoglobulin gene superfamily, including neural cell adhesion molecule (N-CAM; ref. 18), L1 (19), transiently expressed axonal glycoprotein 1 (TAG-1; ref. 20), contactin (21), neuroglian (22), fasciclins II and III (23), Thy-1 (24), and CD4 (25). Gardinier, Pham-Dinh, and colleagues (4, 5) speculate that the immunoglobulin-like extracellular domain of MOG implies a role in adhesion and cell surface interactions in myelinogenesis, and perhaps even in axonal outgrowth.

Might MOG also have some unforeseen immunological status within the central nervous system? Could MOG conceivably serve as a co-receptor or antigen presented for T-cell recognition? Chicken B-G antigens are strong immune adjuvants, and like MOG, B-G molecules themselves elicit strong immune responses (4, 26).

What are the implications of mapping the MOG gene within the MHC? MHC molecules are poorly expressed in the central nervous system, unless induced. Oldstone and colleagues (27) demonstrated that neurons evade immune surveillance by failing to express MHC molecules constitutively on their surfaces. This characteristic of low MHC expres-

Abbreviations: MHC, major histocompatibility complex; MOG, myelin/oligodendrocyte glycoprotein; MS, multiple sclerosis.

sion provides a form of stealth for the neuron and prevents killer T cells from attacking intraneuronal virus (27). Indeed viral persistence (in some cases) is preferential to immune-mediated virus eradication, at least from the perspective of neuronal function. Bystander injury to neurons during an immunological confrontation with virus could result in irreparable damage to mature neurons, which cannot divide. Similarly, oligodendroglial cells express virtually no MHC molecules unless induced by cytokines such as γ-interferon. T cells damage virally infected oligodendroglial cells, when the MHC is induced. During some states of persistent infection of oligodendroglial cells, myelin can survive quite well, and can even regenerate if damaged (28). Most molecules encoded within the MHC have immune functions, although a few genes interspersed within the MHC have no role in antigen presentation or the immune system (29). Perhaps MOG might provide some rudimentary molecular framework for presentation of pathogens to the immune system. MOG, like the B-G proteins in poultry, might stimulate the immune system without invoking traditional cellular inflammation within the central nervous system, an attack that would be deleterious to the host or hostess. T cells and B cells recognize and respond to B-G molecules quite differently than they do to conventional MHC molecules.

MOG might play a role in the pathogenesis of multiple sclerosis (MS), a demyelinating disease of the central nervous system, where an inflammatory response to myelin is apparent. MS is a chronic disease involving an inflammatory reaction within the white matter of the central nervous system mediated by T cells, B cells, and macrophages. The target of the inflammatory response in MS has been elusive. Analysis of the T-cell-receptor gene rearrangements in the MS lesion has indicated that at least one of the major immune responses in the MS lesion is directed to myelin basic protein (30, 40). Immune responses to other myelin components might be important (30). It is known that induction of immunity to MOG in experimental animals can result in paralysis and demyelination (31–33).

Might a defect in the metabolism of MOG lead to an inflammatory response against myelin? Indeed, even a response to an aberrantly processed myelin component such as MOG might kindle an immune response to other myelin components. It is known, for example, that in some degenerative diseases of white matter, termed leukodystrophies, an inflammatory response to myelin can occur as a consequence of dysmyelination. Indeed, many genetic disorders are associated with a profound immune response in the affected tissue (34). For example, in adrenoleukodystrophy, extensive perivascular infiltration of the white matter with lymphocytes and macrophages occurs. Adrenoleukodystrophy is an X chromosome-linked disease, caused by a mutation in very-long-chain-fatty acyl-CoA synthetase, an enzyme critical in peroxisome biogenesis, belonging to the ATP-binding-cassette superfamily of transporters (35). TAP1 and TAP2 are two other members of the ATP-binding-cassette family of transporters, and the genes encoding these peptide transporters map in the class II region of the human MHC (29, 36).

Polymorphic variants of MOG may be pathogenic. Recently genetic susceptibility to MS was linked to a polymorphism in the myelin basic protein gene, in an analysis of Finnish MS patients (37). This finding was not confirmed in a study of multiplex families in the western United States (38). Given the high degree of polymorphism of many genes mapped within the MHC, it would be worthwhile to perform such an analysis, looking for linkage of susceptibility to MS with alleles of MOG.

Both hard wiring and molecular interactions link the immune system and the nervous system. Some of the molecules used in one system share structural motifs with molecules of the other. Our understanding of neurological memory and the generation of the diversity of connections in the nervous system is rudimentary. It is tempting to speculate that some of the strategies employed to provide immunological memory and to elaborate immunological diversity might be reiterated (with modifications) in the design of neurological memory and neuronal diversification.

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