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Origins and significance of astrogliosis in the multiple sclerosis model, MOG peptide EAE

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Abstract

Astroglia, the most abundant cells in the human CNS, and even more prominent in multiple sclerosis patients, participate in CNS innate and adaptive immunity, and have been hypothesized to play an important role in multiple sclerosis progression. Experimental autoimmune encephalomyelitis elicited in mice by immunization with myelin oligodendrocyte glycoprotein peptide 35–55 provides a means by which to explore the genesis and disease significance of astrogliosis during a chronic immune-mediated CNS inflammatory/demyelinative disorder that, in its' pathological features, strongly resembles multiple sclerosis.

Keywords

multiple sclerosis; experimental autoimmune encephalomyelitis; astroglia

Introduction

Charcot, the first to publish a detailed description of multiple sclerosis, reported disseminated central nervous system (CNS) “sclerotic patches” in which “a certain number of axis-cylinders...still persist” as a defining pathological characteristic (1). Though more than a century has passed since Charcot’s lectures on this disease were published, unanswered questions remain about the origins and significance of the astrogliosis that causes the firmness (“sclerosis”) of multiple sclerosis plaques. Is the increase in astroglial prominence in and around these plaques entirely attributable to astroglial hypertrophy, or do numbers of astroglia increase as well? Is astrogliosis deleterious to oligodendroglial regeneration and axon survival? We will review what has been learned thus far about astrogliosis in a multiple sclerosis model, murine MOG peptide EAE.

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Myelin oligodendrocyte glycoprotein peptide experimental autoimmune encephalomyelitis (MOG peptide EAE)

Administration of MOG peptide emulsified in Freund's complete adjuvant, together with pertussis toxin, to adult C57BL/6 mice elicits hind limb weakness after a 10 to 14 day latent period. During this asymptomatic period, MOG peptide-specific Th17 and Th1 T cells accumulate in secondary lymphoid organs (2), and then, after passing through the lungs (3), traffic to CNS via choroid plexus and leptomeningeal blood vessels (2,4,5,6). The MOG peptide 35–55 immunization also elicits EAE in mice expressing human HLA-DR2 but no detectable mouse MHC class II (7), and immunization with an overlapping peptide (MOG peptide 34–56) elicits EAE in marmoset monkeys (8).

Histological examination of MOG peptide-immunized mice at the time-point at which weakness first appears demonstrates multifocal perivascular white matter inflammatory infiltrates, particularly in the spinal cord. Within these inflammatory infiltrates, myelin, and oligodendroglia, and damaged axons become fragmented and are ingested by macrophages. Over ensuing weeks, perivascular inflammatory infiltrates begin to clear, and newly formed oligodendroglia, derived from oligodendroglial progenitor cells (OPCs), remyelinate some of the axons that have survived within the lesions. However, CNS axon loss continues to progress (2).

How faithful a model for multiple sclerosis is MOG peptide EAE? The acute EAE lesions resemble "pattern 1" multiple sclerosis plaques (9), though neutrophils are more prominent in MOG peptide EAE (2) than in multiple sclerosis plaques. The prolonged persistence of neurological deficits in MOG peptide EAE, in conjunction with ongoing loss of CNS axons (2) which takes place despite a lack of new inflammatory lesions, simulates the progressive axon loss and non-remitting neurological deficits in patients with chronic multiple sclerosis (10,11).

The immunopathogenesis of MOG peptide EAE also resembles that of multiple sclerosis. CD4⁺ T cells responsive to MOG epitopes are increased in patients with multiple sclerosis as in mice with MOG peptide EAE (2,12), and Th1 and Th17 effector T cells invade the CNS in both disorders (2,13), and may be primarily responsible for CNS tissue injury (14). Both mice immunized with MOG peptide 35–55 and occasional patients with multiple sclerosis develop antibodies against MOG peptide, and, in children with acute disseminated encephalomyelitis, persistent expression of these antibodies suggests multiple sclerosis will eventually develop (15,16). However, anti-MOG antibodies are more commonly present in aquaporin-4 antibody-negative patients presenting with a neuromyelitis optica phenotype than in those with more typical forms of multiple sclerosis (17,18).

Astrogliosis in MOG peptide EAE

Astroglia are generated from radial glia during prenatal CNS development (19). Additional astroglia are formed postnatally by symmetric division of pre-existent astroglia (20), but in the normal adult, virtually all astroglia have become post-mitotic (21), with the exception that GFAP⁺/nestin⁺ neural stem cells in the adult subventricular zone and dentate nucleus, which undergo both symmetric and asymmetric division, the latter generating new neurons (22).

At the onset of clinical deficits in C57BL/6 mice with MOG peptide EAE, some astroglia within and bordering white matter inflammatory infiltrates begin to express immunoreactive nestin and vimentin as well as proteins indicative of entry into the cell cycle (23). Soon thereafter, the cell bodies and processes of many astroglia within both white and gray matter

enlarge, become intensely glial fibrillary acidic protein (GFAP) immunoreactive, express cytoskeletal vimentin (21), and synthesize and secrete chemokines that attract systemic immune cells to the CNS. Apoptosis of these activated astroglia is rarely demonstrable, and astrogliosis remains prominent in most areas of the CNS for months after the onset of MOG peptide EAE (21,23) (Figure 1).

Autoantibodies against astroglial aquaporin-4 are useful biomarkers for neuromyelitis optica, and may compromise astroglial water homeostasis (24). Aquaporin-4 protein expression is induced in chronic multiple sclerosis plaques (25). Adaptive immune responses to aquaporin-4 may also contribute to astrogliosis in EAE: passive transfer of human anti-aquaporin-4 IgG to mice given complete Freund's adjuvant and pertussis toxin enhances astroglial process formation (26); and the severity of MOG peptide EAE is markedly diminished in aquaporin-4 knockout C57BL/6 mice (27).

Some astroglia, particularly in gray matter, do not express immunohistologically demonstrable GFAP. In fact, no single protein "marker" permits immunohistological identification and enumeration of all astroglia. However, all astroglia in mice that carry a GFAP promoter-green fluorescent protein (GFP) transgene (28) do express immunohistologically detectable GFP. By eliciting MOG peptide EAE in these transgenic mice, we observed that numbers of astroglia in spinal cord white matter have increased by approximately 75% by day 35 post-MOG peptide 35–55 immunization, but have not changed significantly in spinal cord gray matter (21). Thus, the astrogliosis in MOG peptide EAE is a consequence of both astroglial proliferation and hypertrophy in white matter, but solely of astroglial hypertrophy in gray matter.

Are the additional astroglia that accumulate in white matter derived only from pre-existent white matter astroglia that mitose during the acute phase of the illness? Or are some of these new astroglia formed from OPCs, the major pool of proliferating cells in the normal adult mammalian CNS (29), which have the capacity to assume an astroglial phenotype when maintained in an appropriate medium in vitro (30)? Or, alternatively, are astroglia recruited from ependymal cells during MOG peptide EAE, as they are after spinal cord trauma (31)? We genetically fate-mapped astroglia, OPCs, and ependyma using cell type-specific tamoxifen-inducible cre transgenes. Results indicated that neither OPCs nor ependyma contribute to astrogliosis in adult mice with MOG peptide EAE, and that the increase in astroglial numbers is attributable solely to proliferation of pre-existent astroglia in white matter (21).

Astroglial modulation of CNS inflammation in MOG peptide EAE

Astroglia influence the entry of systemic immune cells into the CNS in two principal ways: by participating, with CNS endothelial cells and pericytes in the maintenance of an intact blood-brain barrier (32) that limits inflammatory cell entry (33); and by synthesizing and secreting chemokines that attract myeloid and lymphoid cells into the CNS (34). Messenger RNAs encoding two of these chemokines, CCL2 (MCP-1), which attracts CCR2+ monocytes and other myeloid cells, and CXCL10 (IP-10), which attracts CXCR3+ lymphocytes, are induced more than 100-fold during the acute phase of MOG peptide EAE (21), and this induction occurs principally in astroglia (Figure 2). The severity of MOG peptide EAE is diminished in mice constitutively lacking CCL2 signaling (35,36), presumably because CNS homing of inflammatory monocytes is diminished (37). Somewhat surprisingly, the severity of MOG peptide EAE is increased in mice constitutively lacking CXCL10 or CXCR3 gene expression. It has been suggested that this is attributable to sequestration by astroglial CXCL10 of CXCR3+ lymphocytes that do enter the CNS to the perivascular space, thus preventing their penetration into the parenchyma of the CNS (38).

Does astrogliosis contribute to demyelination, remyelination failure, and axon loss in MOG peptide EAE?

Astroglia secrete inhibitors of OPC differentiation to myelin-forming oligodendroglia, including bone morphogenic proteins and hyaluronan. These macromolecules accumulate in demyelinating lesions, and may impair remyelination (39,40).

Astroglia facilitate normal glutamatergic neurotransmission by glutamate transporter-mediated uptake of L-glutamate from the CNS extracellular milieu, and by its' conversion to L-glutamine via astroglial glutamine synthetase. Astroglial glutamate transporter and glutamine synthetase activities are diminished during EAE (41,42), thus possibly contributing to excitotoxic injury to the oligodendroglial lineage and axons (43,44,45). In addition to maintaining CNS glutamate and water homeostasis and ensuring the integrity of the blood-brain barrier, astroglia play a central role in CNS innate immunity (see reference 46 for a review of this topic).

There have been several genetically based explorations of the effects of reactive astrogliosis on the severity of MOG peptide EAE. Diminishing astroglial production of chemokines and other inflammatory mediators by transgenic inhibition of astroglial NF- κ B (47) by lentivirus-mediated knockdown of astroglial Act1 (48), or by conditional ablation of astroglial TrkB, which selectively suppressed BDNF-mediated astroglial production of nitric oxide (49), diminishes severity of MOG peptide EAE, whereas killing reactive astroglia by targeted deletion of astroglial gp130, a receptor required for signaling by members of the IL-6 cytokine family heightens MOG peptide EAE severity (50). These studies argue that suppressing production of proinflammatory mediators by astroglia diminishes EAE severity, but that apoptosis-mediated depletion of reactive astroglia enhances EAE severity, probably, at least in part, to disruption of the blood-brain barrier (32).

Summary and Conclusions

Astrogliosis is a prominent, but still poorly understood, feature of multiple sclerosis. Analysis in the robust multiple sclerosis model, MOG peptide EAE, shows that astrogliosis is a consequence of both astroglial hypertrophy and astroglial proliferation in CNS white matter, but only of astroglial hypertrophy in CNS gray matter (Figure 3). Though normal astroglia help to restrict entry of systemic immune cells into the CNS, hypertrophic astroglia synthesize chemokines that enhance immune cell homing to the CNS during MOG peptide EAE. Establishing the significance of persistent astrogliosis with respect to incomplete remyelination and ongoing axon loss in MOG peptide EAE, and more systematic analyses of astrogliosis in acute and chronic multiple sclerosis plaques, may suggest more effective ways than are currently available to prevent progression in patients with multiple sclerosis.

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Figure 1.

Spinal cord white matter astrogliosis and monocyte/microglia-derived macrophage infiltration 60 days post-MOG peptide immunization of Emx-cre/Rosa-STOP-EYFP transgenic mice with genetically tagged corticospinal tracts (CSTs). Longitudinal spinal cord sections through the dorsal CSTs of normal (Panel A) and MOG peptide EAE (Panels B and C) Emx-cre/Rosa-STOP-EYFP transgenic mice. Note the infiltration by Iba1+ monocyte/microglia-derived macrophages (white) into the EAE dorsal CST in Panel B. Also note the partial loss of CST axons (green) in the EAE CST in Panels B and C, in comparison to normal, in Panel A. In Panel C, hypertrophic astroglial processes (red) border the dorsal CST, but, in comparison to macrophages, fewer astroglia penetrate into the CST itself. Also in Panel C, and to a lesser extent in Panel B, note the frequent segmental enlargements (“blebs”) along the course of surviving axons. Blue = DAPI nuclear staining. The horizontal bar indicates 20µm, and the magnification is the same in the 3 panels.

Figure 2.

Induction of astroglial CCL2 (MCP-1) in MOG peptide EAE

Spinal cord cross-section from a mouse immunized with CFA without MOG peptide (“CFA control”, 3 upper panels) and a mouse given MOG peptide in CFA (“EAE”, 3 lower panels) 21 days prior to sacrifice. The panels on the left show CCL2 immunoreactivity (green), those in the center show GFAP immunoreactivity (red), and the colors are overlaid in the panels on the right. Note that most astroglia in the lower right panel are yellow, thus demonstrating induction of immunoreactive CCL2 expression in astroglia in EAE. Blue = DAPI nuclear staining; vertical bars = 100µm.

Figure 3.

Cartoon showing the genesis of astrogliosis in MOG peptide EAE. In CNS white matter (WM), astroglia both proliferate and enlarge, whereas astroglia in gray matter (GM) enlarge, but do not proliferate. Neither oligodendroglial progenitor cells (OPCs) nor ependymal cells contribute to astrogliosis in MOG peptide EAE, and ependymal cells do not generate either OPCs or neuronal lineage cells. The figure is reproduced from reference 21, with permission of the Journal of Neuroscience. The innate immune functions of reactive astroglia are reviewed in reference 46.