

Multiple Sclerosis and Experimental Allergic Encephalomyelitis

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Multiple sclerosis (MS) is the most common human demyelinating disease of the CNS. The etiology of MS is poorly understood, however, it is widely believed as a T cell-mediated autoimmune disease that ultimately targets the CNS [1,2]. Experimental allergic encephalomyelitis (EAE) is the animal model for MS. Although it is an animal model for MS, when we look at the history of EAE, we find that its discovery was not associated with MS. In the early 1930s, while Rivers et al. [3] were wondering about encephalomyelitis in humans upon rabies vaccination, he found encephalomyelitis in animals after repeated injections of dehydrated spinal cords from rabbits infected with rabies. Since then it is being used as a model to study the disease process of encephalomyelitis.

Nowadays, EAE is actively induced by the injection of whole spinal cord preparations or proteins derived from myelin (commonly myelin basic protein (MBP) or proteolipid protein (PLP)). Activated T cells isolated from the spleen and lymph nodes of actively immunized animals can also be used to transfer disease to naive recipients [2,4]. In both models, neuroantigen-specific autoimmune T cells first contact a naive intact BBB and are able to extravasate through the BBB due to their activated status [5]. These cells are retained in the CNS due to presentation of appropriate antigen and undergo further activation. This is followed by the recruitment of non-antigen-specific lymphocytes and activated macrophages from the blood into this site, accompanied by the activation of resident glial cells and further disruption of the BBB [6-10].

Recent studies have discovered many new players in various branches of neuroimmunology. Such discoveries help us to broaden our understanding of the broad-spectrum crosstalk among innate immunity, adaptive immunity, inflammation, and demyelination in EAE, which may lead to new and effective therapeutic interventions in MS. Therefore, we have devoted this special issue to highlight some of the recent discoveries on MS and EAE.

Since autoimmune T cells play a key role in demyelination in MS, scientists have been investigating for several decades whether antibodies to myelin protein antigens contribute to the diagnosis and pathogenesis of MS. Accordingly, numerous myelin antigen have been identified that are assumed to play a role in MS. However, a few recent developments are challenging this dogma, particularly when studying the neurodegenerative phase of MS. Here, in authoritative review, Levin et al. [11] have compiled evidences to highlight how both T-cell and antibody responses to various non-myelin targets (e.g. osteopontin, α B crystalline, contactin-2, neurofilaments, neurofascin etc) also contribute to the neurodegenerative facet of MS. Because MS is a complex disease, a comprehensive understanding of underlying mechanisms is important for designing better treatment option for this disease.

In addition to being an integral part of human metabolism, lipids play diverse and critical roles in the immune system. Accordingly, significant insight into the role of lipid-reactive T cells has been gained over the past few decades. However, little is known about invariant NKT (iNKT) cells that represent a specialized subset of innate-like T lymphocytes. These iNKT cells recognize mainly glycolipid antigens

presented by the MHC class I-related protein CD1d. Interestingly, this cell type is emerging as a promising target for immunotherapy in MS and other autoimmune disorders. Here, in a well-crafted review, Hogan et al. [12] have provided an overview of mechanism of this important area in CNS autoimmunity. They have also delineated immunological crosstalk between glycolipid and iNKT cells in relation to MS, defining the mechanisms of (NK) T cell activation in autoimmune diseases.

Citrullination is basically the conversion of arginine into citrulline by an enzyme called peptidylarginine deiminase. Although citrullination of proteins has many physiological functions, aberrant citrullination however, can play a role in pathophysiology of various human diseases. Citrullinated proteins usually serve as autoantigen in autoimmune disorders. Accordingly, citrulline residues are found in myelin basic protein (MBP), which is a major autoantigen in MS, and an increased level of citrullinated MBP has been reported in the brains of MS patients. Here, Raats et al. [13] delineate how citrullination modulates various aspects of autoimmune disorders and discuss the possibility to target the citrullination process as a therapeutic approach to treat MS and other autoimmune and inflammatory disorders.

Although NO alone is beneficial, once NO is produced in excess, it is known to react with superoxide to form peroxynitrite, the most reactive derivative of NO known to date. NO and peroxynitrite, together with reactive oxygen species, damage different biomolecules in cells, causing nitrosative stress. Several studies indicate an important role for nitrosative stress in the pathogenesis of MS. Here, in an elegant review [14], Dr. Sha has delineated how nitrosative stress contributes to various aspects of MS and EAE, including inflammation, oligodendrocyte injury, changes in synaptic transmission, axonal degeneration, and neuronal death. Furthermore, this review highlights the need to investigate S-nitrosylated transcriptional factors and the protein targets of S-nitrosylation in MS, thus providing newer insights into therapeutic modulation of MS based on nitrosylation.

Microglial activation plays an important role in the pathogenesis of MS and other neurodegenerative disorders. Here, Roy and Pahan [15] delineate that T helper 2 (Th2) cells, which have been shown to be beneficial for different autoimmune disorders including MS and EAE, suppress microglial activation via cell-to-cell contact. Interestingly, Th2 cells express higher levels of α V (α_v) and β 3 (β_3) integrins as compared to Th1 cells, and functional blocking antibodies against α V

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Received September 15, 2013; **Accepted** September 16, 2013; **Published** September 23, 2013

Citation: Pahan K (2013) Multiple Sclerosis and Experimental Allergic Encephalomyelitis. J Clin Cell Immunol 4: e113. doi:10.4172/2155-9899.1000e113

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and $\beta 3$ integrins impair the ability of Th2 cells to suppress microglial activation. Furthermore, this study also shows that microglia express the beta subunit of PDGF receptor (PDGFR β) and that neutralization of PDGFR β abrogates the ability of Th2 cells to suppress microglial inflammation. This study highlights the importance of $\alpha V\beta 3$ and PDGFR β in guiding the anti-inflammatory activity of Th2 cells via activation of CREB, which may be responsible for beneficial effect of Th2 cells in MS.

Although MS is an autoimmune disorder, metabolism is altered in numerous human disorders including MS. Therefore, if effectively harnessed, metabolic alterations can provide enormous insights into the underlying mechanisms that give rise to aberrant energy metabolism of immune cells and resident brain cells in MS. However, such information was not known. Using cutting-edge metabolomics approach, Giri et al. [16] have profiled the plasma metabolites at the chronic phase of disease utilizing relapsing remitting experimental autoimmune encephalomyelitis (RR-EAE) model in SJL mice. They have identified a 44 metabolite signature drawn from various metabolic pathways (bile acid biosynthesis, taurine metabolism, tryptophan and histidine metabolism, linoleic acid and D-arginine metabolism), which correlated well with severity of the EAE disease, suggesting that these metabolic changes could be exploited as biomarkers for EAE/MS progression and to design new therapeutic options for MS.

Rescuing and sustenance of oligodendrocytes and myelin in MS patients is of high priority for developing effective therapies. Several studies have shown that demyelination in MS is caused by proinflammatory mediators and nitric oxide (NO), which is released by perivascular infiltrates and/or activated glial cells. However, the molecular mechanism of NO-mediated oligodendroglial death is poorly understood. Here Jana and Pahan [17] have explored the role of NO in modulating the expression of myelin-specific genes [myelin basic protein (MBP), 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP)] that ultimately leads to oligodendroglial death. They have demonstrated that both exogenous and endogenous NO down-regulates the expression of myelin genes (MBP, PLP, CNPase, and MOG) in primary human mixed glial cells and oligodendrocytes, which is probably an early event before the oligodendrocytes death.

Estrogen has very intimate relationship with the progression of MS. Disease remission is very common during pregnancy when estrogen level is high. In rodents, relatively low doses of 17 β -estradiol (E2) and estriol confer potent protection against clinical and histological signs of EAE. However, the molecular and cellular mechanisms by which estrogens regulate MS and EAE have not yet been well characterized. Here, Offner et al. [18] have delineated a novel mechanism behind estrogen-mediated protection of EAE in mice. Using B cells from MOG-immunized PD-L1^{-/-} and PD-L2^{-/-} donor mice and estrogen-preconditioned B-cell deficient μ MT^{-/-} recipient mice, they have demonstrated that PD-1 and PD-L1 play important roles in determining the E2-mediated EAE susceptibility and in controlling chronic disease progression. According to them, PD-1 interaction with PD-L1, but not PD-L2, on B cells is crucial for estrogen-mediated protection in EAE. This study may help in designing a new therapeutic strategy for MS and EAE via enhanced co-operation among estrogen, PD-1 and PD-L1.

Although despite intense investigations, there is no effective drug against MS, studies on neuroimmunological regulations of EAE have led to the discovery of many pharmacological interventions in MS. These include interferons, copaxone, tysabri, statins, glucocorticoids, mitoxantrone, cyclophosphamide, fingolimod etc.

Metformin and lovastatin are FDA-approved drugs for diabetes and hypercholesterolemia, respectively. Here, Singh et al. [19] have demonstrated that a combination of suboptimal levels of metformin and lovastatin attenuates the disease process of EAE by reducing the infiltration of myelin reactive T cells (CD4 and CD8) and macrophages (CD68) as well as the expression of their signatory cytokines in the spinal cords of EAE animals. These results suggest that the oral administration of a combination of these FDA approved drugs in suboptimal doses has potential to suppress MS pathogenesis.

Clinical application of adult neural stem cells (aNSCs) in neurodegenerative and neuroinflammatory diseases is limited because of difficulties in delivery into the CNS. These cells do not readily diffuse across the blood-brain barrier (BBB) or ventricular lining. Although delivery of aNSCs by stereotactic injection is definitely an option, it has several limitations. Here, Zhang et al. [20] have used the intranasal route to deliver stem cells into the CNS of EAE mice. It is a potential strategy to overcome the obstacles created by the BBB and is a promising option because of its non-invasiveness. They have shown that after intranasal administration, aNSCs move into olfactory bulb, cortex, and spinal cord and induce earlier functional recovery, and exhibit anti-inflammatory and remyelination effects in the CNS of EAE mice. These results may delineate an effective and non-invasive stem cell-based therapeutic approach for MS and other neurological disorders.

Understanding underlying neuroimmune pathways regulating the disease process of EAE is important for designing new therapeutic strategies for MS. Therefore, this provocative collection of research and review articles clearly highlighting emerging aspects of MS and EAE may provide promising therapeutic strategies for patients.

Acknowledgement

This study was supported by National Institutes of Health grant (AT6681) and Veteran Affairs Merit Award (I01BX002174).

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