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Neuroimmune Pharmacological Control of EAE

Kalipada Pahan

Department of Neurological sciences, Rush University Medical Center, Cohn Research Building, Suite 320, 1735 West Harrison St, Chicago, IL 60612, USA

Kalipada Pahan: Kalipada_Pahan@rush.edu

Experimental allergic encephalomyelitis (EAE) is an experimentally induced autoimmune disorder of the central nervous system (CNS). Although it serves as an animal model for multiple sclerosis (MS), its discovery was not associated with MS. In the early 1930s, Rivers et al. (1933) were wondering about encephalomyelitis in humans upon rabies vaccination and that led to the induction of encephalomyelitis in animals after repeated injections of dehydrated spinal cords from rabbits infected with rabies. Since then it remains the best animal model to study the neuroimmunology of encephalomyelitis. Eventually, different studies have improved EAE and established EAE as a suitable one to model many aspects of MS. Despite active induction by the injection of whole spinal cord preparations or proteins derived from myelin (commonly myelin basic protein (MBP) or proteolipid protein (PLP)), EAE could be passively transferred by encephalitogenic MBP- or PLP-specific T cells. However, in all the described models, disease is characterized by the disruption of blood-brain barrier (BBB), perivascular infiltrates within the CNS, and paralysis.

The proinflammatory molecules secreted by infiltrating macrophages, T cells, and activated glial cells interact with the CNS to determine the outcome of the inflammatory process leading to the destruction of myelin and oligodendrocytes. Therefore, the disease could be regulated at various stages—antigen priming, generation of encephalitogenic T cells, disruption of BBB, inflammation, and loss oligodendroglia. Although there is no effective therapy against MS, studies on these neuroimmunological regulatory steps in EAE have led to the discovery many pharmacological interventions in MS that include interferons, copaxone, mitoxantrone, statins, tysabri, cyclophosphamide, glucocorticoids, etc. Recent discoveries of many new players in various branches of immunity have significantly broadened our understanding of the broad-spectrum crosstalk among innate immunity, adaptive immunity, inflammation, and demyelination in EAE, which may lead to new and effective pharmacological interventions in MS. Therefore, we have devoted this special issue to highlight some of the recent discoveries on EAE and explain these discoveries in the light of neuroimmune pharmacology.

The development of defined, predictable, and reproducible ways to alter the disease process of EAE may lead to a greater understanding of the pathogenesis of the disease and to treatments for EAE that may be translated into treatments to prevent exacerbations of MS. Accordingly, one comprehensive review by Libbey et al. (2010) describes how modulation of EAE could be achieved through vaccination or DNA immunization with molecular mimics of self-CNS proteins. Furthermore, they have presented exciting data to demonstrate that EAE can be modulated through the administration of curdlan, a linear extracellular polysaccharide produced by *Agrobacterium sp.* It is interesting because curdlan administration switches relapsing-remitting EAE into primary progressive EAE in mice.

It is well-established that thymic clonal deletion of autoantigen-reactive T cells plays a central role in preventing the development of any autoimmune disorder. During clonal selection, only those T cell clones that receive sufficient stimulation by foreign antigenic peptide/major histocompatibility complex complexes are activated and expand. In a far-reaching review, Sabatino et al. (2010) have delineated how ligand strength contributes to the degree of T cell activation and how this is dependent on the extent and quality of T cell signaling. They have proposed that autoreactive T cells are not all equal, and therefore tolerance induction strategies must incorporate ligand strength in order to be successful in treating EAE and ultimately the human disease MS.

One of the approaches for regulating Ag-specific T cell responses to encephalitogenic peptides is to induce non-responsiveness using TCR ligands containing extracellular domains of MHC class II linked to specific peptide targets. Therefore, Sinha et al. (2010) have examined the therapeutic efficacy of recombinant TCR ligand (RTL)551, a partial agonist specific for T cells reactive to mMOG-35–55 peptide, on EAE. Here, they describe that RTL551 therapy can reverse disease progression and reduce demyelination and axonal damage induced by rhMOG without suppressing the anti-MOG antibody response. These results suggest that successful regulation of T cell activation by RTL restricts potential damage by demyelinating antibodies and that RTL therapy may be used for the treatment of MS subjects.

Although MS is an inflammatory T cell-mediated autoimmune disorder, which subset of helper T (Th) cells is most critical for the pathogenesis of EAE is still a matter of debate. It has been widely accepted that interferon-gamma (IFN- γ)-producing Th1 cells are pathogenic in MS and EAE and that switching of Th1 to a Th2 phenotype is a way to ameliorate the disease process. However, this correlation is now brought into question after the discovery of interleukin (IL)-23 because IL-23 in collaboration with TGF- β and IL-6 generate and sustain a distinct set of CD4⁺ cells, known as Th17 cells, which release IL-17, IL-21, and IL-22. Here, El-Behi et al. (2010) have made a bold attempt to describe how both Th1 and Th17 cells contribute to CNS autoimmunity, albeit through different mechanisms. A better understanding of the roles that Th1 and Th17 cells play in autoimmune inflammation will be helpful in developing new therapeutic approaches.

What could be the best approach to suppress Th17 cells in EAE both pharmacologically and physiologically? Nath et al. (2010) delineate for the first time the immune regulation of CD4⁺ Th17 cells in EAE by a compound, which is physiologically available in mammalian cells. S-nitrosoglutathione (GSNO) is a physiological nitric oxide molecule that regulates biological activities of target proteins via S-nitrosylation. Interestingly, GSNO attenuates the disease process of EAE by reducing the production of IL17 (from Th₁ or Th17 cells) and the infiltration of CD4⁺ T cells into the CNS without affecting the levels of Th1 (IFN- γ) and Th2 (IL-4) immune responses. STAT3 and ROR γ are positive regulators of Th17 signaling. They have also demonstrated that GSNO suppresses the phosphorylation of STAT3, but not STAT4 (Th1) and STAT6 (Th2), and attenuates the expression of ROR γ , but not T-bet (Th1) and GATA3 (Th2). These exciting results enhance the possibility of treating Th17-mediated autoimmune disorders with GSNO as a primary or an adjunct therapy.

In addition to Th1, Th2 and Th17 cells, another subset of Th cell is recently making headlines as a possible player in autoimmune disorders. This is Th9 cells, which are driven by the collaborative efforts of TGF- β and IL-4. Th9 cells produce large amounts of IL-9 and IL-10. It is puzzling because IL-9 together with TGF- β can contribute to Th17 cell differentiation and alternatively Th17 cells themselves can also produce some IL-9. A better understanding of IL-9 will have important consequences in the field of immune regulation. In an encyclopedic review, Li and Rostami (2010) describe biology and functions of IL-9 and IL-9 receptor in normal physiology and autoimmune pathophysiology. Although IL-9 has largely been regarded

as a Th2 cytokine, either neutralization of IL-9 or deficiency of IL-9 receptor attenuates EAE suggesting that this cytokine may also be considered as a therapeutic target for MS.

It has been demonstrated that infectious agents contribute to the development of autoimmune diseases including MS. However, there is evidence indicating that infection may have a protective effect on autoimmunity as well via suppression of Th17 response and increase in regulatory T cell (Treg) response. In particular, it has been shown that mycobacterial infection and mycobacterium components can modulate EAE. The promising results from BCG vaccination clinical trials validate research on mycobacteria-induced suppression in human autoimmune diseases and strengthen the rationale for future trials in MS patients. Here, Lee et al. (2010) have reviewed these exciting results on immunomodulatory role of mycobacteria in both MS and EAE. In addition, they have summarized some of the possible mechanisms by which mycobacterial infections suppress Th17 response and augment Treg response for providing protection against autoimmune diseases.

Even though inflammation is not the only mechanism underlying MS pathogenesis, proper control of neuro-inflammation is an important therapeutic step in MS. Simonini et al. (2010) have used an effective way to attenuate neuroinflammation via modulation of the level of noradrenaline (NA), an endogenous neurotransmitter, in the CNS. First, they have demonstrated that depleting brain NA using locus ceruleus-specific neurotoxin *N*-(2-chloroethyl)-*N*-ethyl-2 bromobenzylamine aggravates EAE without altering peripheral T cells. Second, a synthetic NA precursor L-threo-3,4-dihydroxyphenylserine (L-DOPS) significantly suppresses the progression of EAE. While L-DOPS attenuates glial activation, it has no effect on Th1 and Th17 cells suggesting that the primary target of this drug is the CNS and that increasing central NA levels pharmacologically may provide benefit in patients with MS.

In EAE and MS, inflammation is present in the periphery as well as the CNS. To understand the role of peripheral vs. CNS inflammation in the disease process of EAE, Ren et al. (2010) have used bone marrow chimeric technology. Interferon regulatory factor 1 (IRF-1) is one of the proinflammatory transcription factors that participates in the transcription of various proinflammatory molecules including inducible nitric oxide synthase, IL-12p35, RANTES/CCL5, TNF- α receptor, MHC class I, protein kinase R, caspase-1, Fas, etc. They have provided direct evidence that CNS IRF-1 regulates the inflammatory process and the disease severity in EAE. These findings are relevant to the pathogenic mechanisms of MS disease progression and may provide a basis for the development of anti-IRF-1 therapy against MS.

Finally, all therapies that ameliorate MS suppress EAE in rodents. However, all therapies that ameliorate EAE in rodents do not suppress MS. Had all rodent results been translated to humans, MS would have been cured long back. The wide immunological disparity between inbred rodent strains and the heterogeneous human population is probably the single most important factor, which hampers the translation of rodent results into effective therapies for MS. On the other hand, common marmosets are new world monkeys. The marmoset (*Callithrix jacchus*) and human (*Homo sapiens*) are thought to have diverged from a common ancestor, a primitive anthropoid, approximately 30 million years ago. It has been shown that immunization of common marmosets with human myelin and/or myelin proteins leads to a form of EAE that resembles MS. Kap et al. (2010) have summarized these exciting studies in marmosets. Neuropathological features of marmoset EAE, including inflammation, demyelination, and axonal injury, are strikingly similar to findings in the human disease. Therefore, in certain situations, where it is desirable, but impossible, to study human immune responses in vivo, common marmoset monkey provides an acceptable alternative.

We understand that a short special issue like this one cannot cover all recent developments on EAE, but it may offer a visionary framework. Identification and characterization of various

neuroimmunological pathways regulating the disease process of EAE is important for designing new therapeutic strategies for MS. Therefore, we believe that this exciting collection of review and research articles clearly highlighting emerging aspects of EAE may pioneer and steer future research efforts aimed to reveal further secrets of EAE and provide promising therapeutic strategies for MS patients.

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