Complex relationships

This issue of Neurology® Neuroimmunology & Neuroinflammation (N2) contains articles on a variety of interesting topics demonstrating the complexity of the relationships of the immunologic system with diseases beyond autoimmunity such as neurodegenerative disorders. I have highlighted a few of these studies below.

Immunologic profiling is central to the study of autoimmune diseases and the development of personalized medicine. In this issue of N2, several immune profiling studies provide novel observations. Dooley et al.1 performed multiplex flow cytometry to identify immunologic signatures in untreated and treated patients with multiple sclerosis (MS). They describe systemic immune differences between untreated patients with MS and healthy controls and found that immunomodulatory treatments (interferon-β, glatiramer acetate, natalizumab, fingolimod) induced unique alterations in the immune profile of the patients. Of note, there were only 2 significant effects shared across treatments and these were B cell–related changes occurring with interferon-β and fingolimod. This appears to support recent evidence of the importance of B cells in MS pathogenesis and treatment. Additional studies explored cytokine measurements and a comparison of results to those of a cohort of subjects with autoimmune thyroid disease. The findings showed that despite shared genetic risk factors, the immunologic changes in MS and autoimmune thyroid disease were different, suggesting complex gene–immune relationships to be elucidated.

The relationship of the immunologic system with neurodegenerative processes is complex and ranges from protective to pathogenic. In amyotrophic lateral sclerosis (ALS), early protective immune responses are replaced by destructive responses with some immune cells playing both sides of the fence at different times. Murdock et al.2 used flow cytometry to profile the leukocyte populations in patients with ALS and correlate the findings with clinical metrics of ALS. They found a significant increase in the percentage of neutrophils and a significant decrease in the percentage of CD4 T cells and CD16− monocytes in patients with ALS compared to controls. To evaluate this relationship further, the authors calculated a neutrophil to CD16− monocyte ratio for each patient and found that it was significantly elevated in patients with ALS and increased as the ALS Functional Rating Scale score decreased, suggesting that this ratio may have utility as a biomarker of ALS. In another ALS-focused study, Lu et al.3 examine the relationship between inflammatory markers and neuromuscular markers as well as ALS disease stages over time demonstrating longitudinal changes for some markers that may prove useful for prognosis and evaluation of treatment responses.

Another neurodegenerative disorder in which autoimmune mechanisms have been implicated is Parkinson disease. This is supported by the finding that some patients with Parkinson disease develop antibodies against α-synuclein. Having previously demonstrated that antibodies to Epstein-Barr virus (EBV) latent membrane protein 1 (LMP1) cross-reacted with α-synuclein, in this issue of N2, Woulfe et al.4 determined the target α-synuclein epitope using a commercial LMP1 antibody and then studied several human cohorts with EBV antibodies (none with Parkinson disease) for the presence of cross-reactivity with the α-synuclein epitope. They demonstrate that a majority of patients with EBV infection develop these antibodies and speculate that molecular mimicry induced by EBV LMP1 may underlie the development of the α-synuclein autoantibodies in patients with Parkinson disease. These results provide the basis for conducting epidemiologic studies of EBV infection and risk of Parkinson disease as well as prospective studies of the presence of these cross-reactive antibodies in patients with Parkinson disease.

The topic of molecular mimicry is also addressed in the study by Rühl et al.5 that provides insight into mimicry involving CD8+ T cells in MS. The authors studied a human leukocyte antigen (HLA)-A3–restricted human myelin-reactive CD8+ T cell receptor, called 2D1, that had been isolated from a patient

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with MS. Using a novel antigen-search technology developed by their group, the authors identified and validated a cross-reactive peptide that was recognized by this clone in the context of HLA-A2. The authors cautiously note that demonstration of mimicry between 2 different HLA class I molecules that present different peptides does not prove clinical relevance. However, this study demonstrates the utility of this method that can be applied to identify candidate antigens of CD8\(^+\) T cells from MS lesions.

The diagnostic uncertainty that results from the inability to demonstrate an infectious organism in a patient with an inflammatory CNS disorder can lead to suboptimal treatment. In a pilot study, Salzberg et al.\(^6\) performed next-generation sequencing of the microbiome in brain or spinal cord biopsies from 10 patients with suspected infections in whom conventional studies were negative or inconclusive. Analyses of the sequencing results identified infectious agents in 3 patients with the pathogen confirmed by other methodologies and in 5 cases clarified the noninfectious nature of the inflammatory process. This is an important study demonstrating the direct clinical utility of next-generation sequencing. More details about the study can be found in the accompanying editorial by Drs. Berger and Wilson.\(^7\)

In addition to these articles, this issue of N\(^2\) contains a consensus paper by Benjamin et al.\(^8\) aimed at defining and classifying the etiology of arterial ischemic stroke in patients with HIV for which many etiologies are likely inflammatory; a case report by Ikumi et al.\(^9\) of a patient with MS treated with fingolimod who developed HSV-2-related hemophagocytic lymphohistiocytosis; and 2 patients reported by Lioger et al.\(^10\) who experienced successful treatment with rituximab of cerebral cryoglobulinemic vasculitis associated with Sjögren syndrome.

I hope you will find these and the other articles in this issue of N\(^2\) to be of interest and I welcome your comments.

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