Advances in Progressive MS

Peter A. Calabresi, MD
Director, Division of
Neuroimmunology
Professor of Neurology
Johns Hopkins University
Medical Center
Baltimore, MD

Multiple sclerosis (MS) is a heterogeneous disease with an unpredictable course and a wide range of severity; some individuals rapidly progress to a disabled state while others experience only mild symptoms. While many people with MS appear clinically stable, especially during the first decade of illness, research studies suggest progression of disease related tissue damage ensues from the onset and reaches a critical threshold at which the person can no longer compensate due to accumulated pathology and loss of plasticity with age. While relapsing MS is characterized by new immune cell infiltrates into the CNS, progressive MS is thought to be related more to compartmentalized inflammation with leptomeningeal lymphoid aggregates and parenchymal neurotoxic glial cell activation.

We have sought to understand if there is genetic susceptibility to a more severe tissue response to inflammation that may render some people with MS more likely to have rapid progressive disease. Previous genetic studies have identified variants that are associated with an increased risk of developing MS; no variants have been consistently associated with MS severity, in part because of the inherent limitations of clinical rating scales that are insensitive to early degenerative changes that underlie disease progression. Retinal ganglion cell loss is well documented in MS. We and others have shown that longitudinal measures of optical coherence tomography (OCT) imaging of the retinal ganglion cell layer can detect atrophy that correlates with and predicts both clinical and imaging-based neurodegenerative disease progression in MS. Therefore, we hypothesized that OCT measures of ganglion cell layer thinning may serve as a sensitive phenotype to discover genetic predictors of disease course. We conducted a set of genome-wide association studies (GWAS) of longitudinal structure and functional visual pathway phenotypes in MS combining parameters of disease progression and OCT and found a highly significant association between complement component C3 pathway gene variants and more rapid and severe ganglion cell layer atrophy in people with MS. These results from unbiased analyses are strongly supported by several prior reports that mechanistically implicated early complement factors in neurodegeneration, and more specifically, C3 in neurotoxic astrocytes, as described below.

The mechanisms underlying progressive MS likely involve phenotypic changes in subsets of activated microglia and astroglia that result in failed endogenous remyelination and neurotoxicity. In 2017, a seminal paper was published by the Barres Laboratory at Stanford describing for the first time a subset of neurotoxic astrocytes (A1 phenotype) that were shown to mediate damage in rodent brains as compared to their trophic counterparts (A2 phenotype) (Liddelow et al. 2017). Specifically, A1 astrocytes inhibited OPC differentiation and caused OL and retinal ganglion cell (RGC) cell death, whereas A2 astrocytes helped to maintain neuronal health. Remarkably, the A1 neurotoxic profile is characterized by high expression of C3 potentially linking C3 with a CNS pathogenic cell type. Indeed, C3+ astrocytes and microglia have been described in a number of neurodegenerative diseases and data from C3 knockout mice reveal neuroprotection.