DISEASE MECHANISMS IN MS

Informing tactics to combat MS

"Know your enemy, and know yourself, and you can win a hundred battles." So says Sun Tzu in *The Art of War*, an ancient Chinese text on military strategy that continues to find applications in diverse aspects of life today. In the case of multiple sclerosis (MS)—a debilitating neuroimmunological disorder that commonly begins in early adulthood and affects 2.5 million people worldwide—the difficulty of knowing the enemy represents a major challenge to development of curative therapies.

The precise cause of MS and the immunological targets remain obscure, and the clinical course is highly heterogeneous between patients. Moreover, relapsing–remitting MS (RRMS)—the most common form of the disease—involves alternating periods of clinical worsening and abatement, commonly followed by sustained deterioration during secondary progressive MS (SPMS). Each of these stages involves numerous disease mechanisms and, as such, MS represents a multifaceted adversary. On the other hand, endogenous neuroreparative and functional recovery mechanisms are activated during remission, highlighting an area where "knowing oneself" could provide clues to inform therapeutic strategies.

In this focus issue on disease mechanisms in MS, we present five Review articles covering key facets of MS neurobiology—not only mechanisms underlying pathology, but also those involved in remission and recovery. A complete understanding of the disease process, including the patient's capacity for compensatory responses, should be a cornerstone of therapeutic efforts.

To begin, Alberto Ascherio and colleagues discuss possible causes of MS, including genetic, environmental, lifestyle and dietary factors. The concordance rate for MS of 25% among identical twins illustrates not only the extent of the genetic influence on disease susceptibility, but also the contribution of nongenetic factors. Notably, mounting evidence from clinical and epidemiological studies supports a causative role for infection with Epstein–Barr virus, low serum levels of vitamin D, and smoking. As the last two factors can be easily addressed with increased sunlight exposure and/or vitamin D supplementation, and by avoidance or cessation of smoking, they represent important targets in preventive strategies that could be implemented at the population level.

T cells have long been recognized as effectors in MS pathology. In their Review, Edgar Meinl *et al.* argue that the role of B cells should not be overlooked. The authors point to the most common immunodiagnostic feature of MS—oligoclonal bands—as evidence of B-cell involvement, and discuss the efficacy of B-cell-targeting therapies and recent successes in identification of autoantibody targets, such as the potassium channel KIR4.1.

Two articles in this issue focus on mechanisms underlying recovery in MS. Robin Franklin and colleagues describe the many pathways that lead to axonal damage in inflammatory white matter lesions, including oxidative damage and energy insufficiency, before discussing the capacity for remyelination during lesion resolution, and potential strategies to encourage this process. They highlight the need for tools to assess remyelination status as an important next step forward. Valentina Tomassini and colleagues approach recovery at the functional level, reviewing evidence to support adaptive changes in brain network activity that restore function despite damage at the cellular level. Together, these two forms of recovery during MS remission highlight key processes that could be stimulated or augmented to reduce lesion burden and possibly even prevent disease progression.

10–20% of patients with MS have the primary progressive form, in which periods of remission are absent and disease steadily worsens from the outset, and most patients with RRMS eventually transition to SPMS. This stage of disease presents a particular challenge in the clinic as—unlike in RRMS, for which treatments to slow disease and improve symptoms are available—therapies for progressive MS are lacking. In the final Review of this issue, Hans Lassmann *et al.* describe pathological changes and disease mechanisms accompanying conversion from RRMS to SPMS, including 'trapping' of inflammation behind the blood–brain barrier and expansion of existing lesions. They discuss the multiple mechanisms that characterize disease progression, such as exhaustion of functional compensation, and mitochondrial damage. The authors highlight several possible therapeutic targets for progressive MS, noting the potential for translational research between studies in other neurological disorders that share some MS disease mechanisms, such as stroke and Parkinson disease.

At the heart of the MS armamentarium is a complexity that continues to hold mysteries after decades of research. However, as ongoing studies unravel the multiple disease mechanisms and inform the development of promising therapeutic strategies, we find perhaps that warfare is as much a science as an art.

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Competing interests
The author declares no competing interests.