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Editorial

Achievements and Challenges in Current Multiple Sclerosis Research

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Editorial

The inauguration of a journal on multiple sclerosis (MS) and neuroimmunology warrants a perspective view of the current research directions of this disease, which is the most prevalent disabling neurological disorder among young adults. Since the 19th century, when MS was differentiated as an identifiable entity [1], intensive studies attempted to elucidate the pathology and discover a therapy for this heterogeneous multifaceted disease. Animal models, in particular various forms of experimental autoimmune encephalomyelitis (EAE), have been highly valuable for both investigating disease pathology and for drug development. Traditionally, MS has been considered an autoimmune disease, in which the immune system reacts against the body's own constituents, in this case against the myelin in the CNS [2]. However, novel technologies such as advanced imaging systems, as well as systematic analysis of CNS biopsies and postmortem samples, have greatly progressed our understanding of the disease. Consequently, in addition to the sclerotic demyelinated lesions (plaques) in the white matter, which are the hallmark of his disease, diffused molecular and cellular changes in "normal-appearing" white matter and grey matter pathology have been recognized as important components of MS pathology [3].

Despite of the substantial progress, there are fundamental unsolved aspects and controversial issues in MS research [4]. In particular, controversy surrounds the precise nature of the inflammatory and the neurodegenerative processes mediating MS, and the interplay between them at the different disease stages. Inflammation is widely considered the primary process in MS, involving multiple interactions of immune cells of both the adaptive and innate systems that occur either focally or diffusely throughout the white and grey matter [2,5]. Thus, pro-inflammatory T-cells of the T-helper (Th)1 and Th17 subtypes, cytotoxic T-cells, B-cells and macrophages, enter the CNS through the blood brain barrier (BBB) and the plexus choroideus. The resident immune cells, the microglia, are subsequently activated and further stimulate the T-cells by presenting CNS antigens. The immune attack results in destruction of the myelin sheaths and impairment of the nerve fiber conductivity. Demyelinated axons are prone to degeneration due to lack of trophic support by the myelin sheaths and increased vulnerability to the immune attacks. Moreover, with disease development, neurodegenerative mechanisms take place and can further cause direct axonal loss, synaptic damage and neuronal cell death [6]. Importantly, significant axonal injury has also been detected in patients with short disease durations, supporting the recognition in the neurodegenerative aspects of MS [7]. Accordingly, diffused brain damage and progressive axonal and neuronal loss are currently regarded as key factors in determining the long-term irreversible neurological impairment and decline that most MS patients endure, as well as in the conversion to a progressive disease. Whether neurodegeneration occurs as a distinct phenomenon or as a consequence of the inflammatory process was a matter of substantial controversy. At present, most opinions agree that the inflammation, manifested at all the disease stages, is the driving force of MS, and neurodegeneration occurs on an inflammatory background [8,9]. Even in the progressive disease stage, when extensive neurodegeneration prevails, axonal damage is either immediate or subsequent to inflammatory infiltrations. However, the inflammatory response at the progressive disease occurs, at least in part, behind an intact BBB, separately from peripheral regulation [10].

These findings were instrumental in the development of effective therapies attempting to restrain the pathological processes, enhance protective routes and prevent disease progression. The fundamental role of the inflammatory processes in MS pathology provided the rational for immunomodulatory disease-modifying treatments (DMT) that have attempted to shift the immune system from pro-inflammatory to anti-inflammatory pathways. A growing understanding of the immune system's cellular and molecular mechanisms together with modern biotechnology engendered promising treatment strategies with novel mechanisms of actions, such as inhibitory molecules, monoclonal antibodies, and cell therapies [11,12]. Various specific therapies that target exclusively the encephalitogenic response are under study. But, thus far, the MS treatments that demonstrated robust clinical effects are relatively broad-based, targeting and even depleting certain cell populations, or obstructing their migratory pathways. Indeed several drugs have already demonstrated efficacy in phase II and III clinical trials by reducing disease activity and disability accumulation, and have been approved as first or second line treatments. However, along with the advent of potent treatments, rare but severe adverse effects, such as infections and malignancies, have occurred. The balance between efficacy and long-term safety, namely the risk-benefit-ratio, is therefore a central consideration in MS therapy.

The essential challenge for MS therapy is to target not only the inflammatory aspect of the disease but also the neuronal pathology, aiming towards neuroprotection and repair. The functional elements of the CNS, the neurons and the myelinating oligodendrocytes, are terminally differentiated cells with a limited capacity to respond to injury. They depend for renewal on the availability of their precursors, the neuronal and the oligodendrocyte progenitor cells, that must undergo proliferation, migration and differentiation into

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defined progeny. Moreover, in the case of MS, to be effective in repair, they need to survive the hostile conditions within the inflamed lesion. The brain has a certain ability to repair neurological damage, and subsequent to the pathological damage, opposing neuroprotective routes are stimulated [4,13]. However, self-repair mechanisms are characteristic to the early disease phases. With time, repair processes decline, exposing the neuronal population to impairments. Recent findings indicate that immunomodulatory treatments can induce neuroprotective consequences and provide a supportive milieu for repair processes [12,13]. Whether these effects result from genuine neuroprotective mechanisms or from their anti-inflammatory properties remains to be established. Regardless, the feasibility of resolving the whole spectrum of neurological damage involved in MS by immunomodulatory treatments is doubted, particularly in the progressive phase, when inflammation occurs independently of peripheral regulation and neurodegeneration prevails [10].

Intensive efforts are therefor currently devoted to develop strategies that will target the neurodegenerative aspect of MS by promoting neuroprotection, remyelination and repair of the CNS functional elements [14]. These include blocking myelin associated components that negatively regulate oligodendroglial differentiation as well as obstructing ion-channels. The capability of up-regulating growth promoting molecules that support the development and survival of oligodendrocytes and neurons is being tested. Stem cell therapy is a very promising strategy to repair CNS damage by introducing pluripotent cells with differentiation and proliferation potential [11,15]. The efficacy of such approaches was shown in the EAE model and in animal models of neurodegenerative diseases, and some of them have also shown beneficial effects in human neurodegenerative pathologies. However, potential obstacles, such as short half-lives, delivery to the CNS, and adverse side effects are still unsolved. MS and neuroimmunology remains a very active field of research. The challenge is to combine effective immunomodulatory therapies with novel neuroprotective approaches to obtain control over this disease and substantially prevent disease progression.

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