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Review

Immune cell trafficking across the barriers of the central nervous system in multiple sclerosis and stroke☆

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ABSTRACT

Each year about 650,000 Europeans die from stroke and a similar number lives with the sequelae of multiple sclerosis (MS). Stroke and MS differ in their etiology. Although cause and likewise clinical presentation set the two diseases apart, they share common downstream mechanisms that lead to damage and recovery. Demyelination and axonal injury are characteristics of MS but are also observed in stroke. Conversely, hallmarks of stroke, such as vascular impairment and neurodegeneration, are found in MS. However, the most conspicuous common feature is the marked neuroinflammatory response, marked by glia cell activation and immune cell influx.

In MS and stroke the blood–brain barrier is disrupted allowing bone marrow-derived macrophages to invade the brain in support of the resident microglia. In addition, there is a massive invasion of auto-reactive T-cells into the brain of patients with MS. Though less pronounced a similar phenomenon is also found in ischemic lesions. Not surprisingly, the two diseases also resemble each other at the level of gene expression and the biosynthesis of other proinflammatory mediators.

While MS has traditionally been considered to be an autoimmune neuroinflammatory disorder, the role of inflammation for cerebral ischemia has only been recognized later. In the case of MS the long track record as neuroinflammatory disease has paid off with respect to treatment options. There are now about a dozen of approved drugs for the treatment of MS that specifically target neuroinflammation by modulating the immune system. Interestingly, experimental work demonstrated that drugs that are in routine use to mitigate neuroinflammation in MS may also work in stroke models. Examples include Fingolimod, glatiramer acetate, and antibodies blocking the leukocyte integrin VLA-4. Moreover, therapeutic strategies that were discovered in experimental autoimmune encephalomyelitis (EAE), the animal model of MS, turned out to be also effective in experimental stroke models. This suggests that previous achievements in MS research may be relevant for stroke. Interestingly, the converse is equally true. Concepts on the neurovascular unit that were developed in a stroke context turned out to be applicable to neuroinflammatory research in MS. Examples include work on the important role of the vascular basement membrane and the BBB for the invasion of immune cells into the brain. Furthermore, tissue plasminogen activator (tPA), the only established drug treatment in acute stroke, modulates the pathogenesis of MS. Endogenous tPA is released from endothelium and astroglia and acts on the BBB, microglia and other neuroinflammatory cells. Thus, the vascular perspective of stroke research provides important input into the mechanisms on how endothelial cells and the BBB regulate inflammation in MS, particularly the invasion of immune cells into the CNS. In the current review we will first discuss pathogenesis of both diseases and current treatment regimens and will provide a detailed overview on pathways of immune cell migration across the barriers of the CNS and the role of activated astrocytes in this process. This article is part of a Special Issue entitled: Neuro Inflammation edited by Helga E. de Vries and Markus Schwaninger.

1. Multiple sclerosis

The first description of a patient with multiple sclerosis (MS) was possibly the case of Lidwina (1380–1433) from Schiedam (The Netherlands). Her disease began at the age of 16, soon after a fall while ice skating [1,2]. At the age of 19, both her legs were paralyzed

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and vision problems started. She developed symptoms consistent with MS, as we currently know it, as well as the age of onset and disease course, suggesting that the first MS diagnosis dates back to the 14th century. During the 19th century, other descriptions of patients with similar symptoms emerged. Jean-Martin Charcot, the "father of neurology", was an important figure in MS research, since he was the first to make the story of MS coherent. He examined the brain of a MS patient and found scars or "plaques" characteristic of MS. In 1868, he wrote "*La sclerose en plaques*" providing a full description of the disease and accompanying changes in the brain [1,2]. He was also the first to develop diagnostic criteria, known as the Charcot triad [1].

MS is seen as a heterogeneous disease since lesions are multifocal and the neurological signs are highly dependent on their location and extension resulting in a wide variety of clinical symptoms. MS lesions are usually located in the white matter around the ventricles, optic nerve, corpus callosum, cerebellum, spinal cord, brain stem or in subcortical gray matter regions [1]. Symptoms can include visual disturbance, muscle weakness, difficulties in coordination and balance, numbness or tingling, memory problems, or changes in bowel and bladder function. Less diagnostic but equally debilitating symptoms include cognitive changes, fatigue and mood alterations [3–5].

MS can be subdivided in several clinical forms: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS) and progressive relapsing MS (PRMS). The great majority of MS patients (approximately 85%) have RRMS which is characterized by acute attacks (relapses) which can last from a few days to weeks, followed by a period of partial or full recovery (remission) of the symptoms [1]. Usually patients with RRMS have no worsening of neurological function between relapses. SPMS is characterized by initial relapses followed by a more progressive phase with gradual deterioration of neurological function not associated with acute attacks. Patients might present occasional relapses or minor remissions [1]. Approximately 50% of RRMS patients convert to SPMS after 10 years and 90% after 25 years. Between 10-15% of MS patients develop PPMS, which is characterized by the lack of relapses, with increased functional decline from the onset of the disease. Patients occasionally show plateaus or temporary minor improvements. Like PPMS, PRMS is characterized by steady functional decline since onset, but in later stages patients present acute attacks, hence these two forms cannot be distinguished in early stages of the disease [1,3]. As the disease progresses severe disability may occur, with a median time of 10 years to reach walking impairment [3].

Due to its heterogeneous nature, there is no single test or specific clinical feature diagnostic for MS. However, analysis of the cerebralspinal fluid (CSF) may support the clinical diagnosis since more than 90% of MS patients shows increased immunoglobulin load and two or more oligoclonal bands in the CSF. A way to detect and demonstrate MS lesions is by using magnetic resonance imaging (MRI). It is usually used to support the diagnosis, estimate lesion load and their location, disease activity, atrophy level of the brain and axonal loss [1].

MS is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) characterized by the presence of lesions or plaques in the brain [6]. These demyelinating lesions are composed of perivascular infiltrates of namely $CD4^+$ and $CD8^+$ T cells, monocyte-derived macrophages and occasionally plasma cells [7]. In these so-called active lesions, immune cells further traffic to the brain parenchyma initiating an autoimmune response against myelin antigens leading to cell and tissue damage. As the disease progresses to the chronic phase, gradual lesion expansion is observed, together with myelin-laden macrophages present in the lesion edge, demyelinated axons and neurodegeneration, oligodendrocyte injury or death, microglia activation and astrogliosis [8–10]. Due to the importance of the immune system in disease progression, MS was for a long time considered an autoimmune disease.

Much of what we know so far results from experiments in the animal model for MS — Experimental Autoimmune Encephalomyelitis (EAE). The acute mouse model of EAE is induced in susceptible mouse strains by active immunization of the animals with CNS homogenates, myelin or myelin-derived antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG) or myelin proteolipid protein (PLP) emulsified in adjuvant [11]. Upon immunization, antigen presenting cells mature in the lymph nodes where they present myelin-derived peptides to naïve T cells [12]. During this process, upregulation of co-stimulatory molecules such as CD80, CD86 and CD40 which interact with CD28 and CD40 ligand, as well as secretion of pro-inflammatory cytokines mediate the activation and differentiation of T cells. In mice, differentiation of $CD4^+$ T helper cells into pro-inflammatory interferon-gamma (IFN-γ) or interleukin-17 (IL-17)-producing Th1 and Th17 cells, respectively, has been shown essential for EAE induction [13]. Therefore, active EAE is a T cell-driven autoimmune disease where pathogenic auto-reactive Th1 and Th17 cells mediate the disease process [13]. Furthermore, differentiation of naïve T cells into T cells with a suppressive function (regulatory T cells — Tregs) is also present in EAE and has been shown important for disease recovery [12]. Importantly, this model allows the study of T cell mediated processes of disease. In humans, the role of specific T helper subtypes is not as clear as it is in EAE. It has been shown in the early 90s that, instead of being completely deleted by negative selection in the thymus, myelin-reactive $CD4^+$ T cells are present in the peripheral blood of MS patients as well as healthy individuals [14]. However, a recent study has shown that myelin-reactive T cells from MS patients produced high levels of IFN-γ, IL-17 and granulocyte-macrophage colony-stimulating factor (GM-CSF), compared to healthy controls, which mainly produced IL-10 [15]. Although the frequency of myelin-specific T cells is unchanged between MS patients and controls, it has been shown that Treg cells from RRMS patients had a decreased suppressor function when compared to Treg cells from healthy controls or SPMS patients [16,17]. On the other hand, it has been suggested that effector T cells from RRMS patients are actually resistant to suppression by Treg cells [18]. These results suggest that the mechanism for tolerance failure in MS is complex but might have an important contribution in MS pathogenesis.

Although MS was for a long time considered an autoimmune disease, it is nowadays clear that the pathogenesis of MS is more intricate than initially thought, with progressive neurodegeneration in addition to inflammatory processes [1]. The autoimmune model of MS has been challenged by the "inside-out" hypothesis of MS etiology, where it is argued that an initial degenerative event begins in the CNS, with an autoimmune response as a secondary event [19]. Some reports have provided evidence for this model. One study has described early MS lesions with few or any infiltrated lymphocytes, but with oligodendrocyte loss and microglia activation in a RRMS patient that had died right after a relapse. This intriguing report suggests that oligodendrocyte death could be the trigger of the adaptive immune response and underlies the possibility of other processes contributing for lesion formation in MS [20,21]. Other studies have observed myelin damage beyond areas of inflammation, suggesting that myelin injury could precede inflammatory events [22]. Importantly, it is known that anti-inflammatory drugs used by RRMS patients have no effect in PPMS [23,24] suggesting that a degenerative mechanism could be the primary initiating event.

Most of the currently used disease-modifying treatments (DMTs) immunosuppressive or immunomodulatory [25] and include interferon-beta (IFN-β) (*Avonex*, *Rebif*, *Betaseron* and *Extavia*), glatiramer acetate (*Copaxone*), Natalizumab (*Tysabri*) [3] and the new oral drugs fingolimod (*Gilenya*), teriflunomide (*Aubagio*) and dimethyl fumarate (*Tecfidera*) [26] [3,27–30]. IFNβ and glatiramer acetate are usually used as a first line treatment [31]. If patients do not respond to these DMTs, other treatment options are considered. Natalizumab is a monoclonal antibody which prevents the entry of immune cells into the brain by blocking the interaction of the integrin very late antigen-4 (VLA-4) on immune cells with vascular cell adhesion molecule-1 (VCAM-1) present on the