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Review

# Multiple sclerosis: Lessons from molecular neuropathology

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, which leads to widespread focal lesions of primary demyelination with variable axonal, neuronal and astroglia injury. The mechanisms responsible for tissue injury in the MS brain and spinal cord are only incompletely understood. In this review we discuss that the formation of confluent subpial cortical lesions is the most specific type of tissue damage, which is exclusively present in MS patients. Current data suggest that subpial demyelination is triggered by a soluble factor, which is produced in meningeal inflammatory infiltrates and diffuses into the cortical parenchyma, where it destroys myelin either directly or indirectly through microglia activation. The presence of demyelinating activity in sera and cerebrospinal fluid of MS patients is known for decades, but the molecular nature of the possibly underlying demyelinating factor is still unclear. Destruction of myelin sheaths and oligodendrocytes as well as neurodegeneration in MS are associated with massive oxidative stress and mitochondrial injury. Oxidative stress appears to be driven in early MS by activated microglia and oxidative burst and is, in the progressive stage of the disease, amplified by additional factors related to the age of patients and accumulation of pre-existing brain damage. Thus, the demyelinating factor in MS patients may either be a currently unknown cytokine or an inflammatory mediator or, alternatively, a mixture of cytokines. It may activate microglia towards uncontrolled oxygen radical production. Alternatively, the demyelinating factor may by itself trigger demyelination, which is then amplified by oxidative injury. The molecular characterization of the demyelinating factor may provide an important clue for the understanding of MS pathogenesis in the future.



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## Introduction

Despite extensive research efforts performed during the last decades, key aspects of multiple sclerosis etiology and pathogenesis still remain unresolved. One reason for this unsatisfactory situation is that our knowledge on the mechanisms involved in brain inflammation and immune-mediated tissue injury are largely based on data obtained in experimental models, while direct studies on brain lesions of multiple sclerosis patients are sparse. This is due to the limited availability of suitable biopsy and autopsy tissue from patients and from lesions with active demyelination and neurodegeneration. Nevertheless, neuropathological research performed during the last century has set the ground for our understanding of the disease process in MS, and the results of these investigations are recently re-evaluated on the basis of our knowledge of modern neurobiology and immunology. The aim of this review is to summarize the author's view regarding current knowledge and to define areas where future efforts are necessary.

*Abbreviations:* MS, multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; MOG, myelin oligodendrocyte glycoprotein.

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## Widespread plaque-like demyelination is the specific hallmark of multiple sclerosis

Multiple sclerosis is a chronic inflammatory disease of the central nervous system, which leads to the formation of large confluent plaques of demyelination in the white and gray matter (Lassmann et al., 2007). During the acute phase of myelin destruction, axons degenerate in an extent that is variable between patients and even between plaques from the same patient (Ferguson et al., 1997; Kornek et al., 2000; Trapp et al., 1998). Furthermore, astrocytes are also affected within active lesions (Brosnan and Raine, 2013). They lose their polarity resulting in a disturbance of the perivascular and subpial glia limitans, and reduce their expression of molecules involved in tissue water homeostasis, glutamate buffering and energy coupling with oligodendrocytes (Matsushita et al., 2011; Parratt and Prineas, 2010; Sharma et al., 2010). Thus, astrocyte injury may amplify demyelination and neurodegeneration in active lesions. With lesion maturation, fibrillary gliosis is induced which not only is responsible for scar formation but also inhibits remyelination. Active tissue injury in all stages of multiple sclerosis is associated with inflammation, the inflammatory infiltrates being composed of T lymphocytes, B lymphocytes and plasma cells (Frischer et al., 2009). Furthermore active demyelination and axonal or neuronal damage occur at sites of microglia activation and macrophage infiltration of the tissue, and activated microglia express pro-inflammatory cytokines and enzymes involved in the production of oxygen and nitric oxide radicals (Fischer et al., 2012, 2013). Most of the immune mechanisms which are associated with demyelination and tissue damage in multiple sclerosis are also present in other inflammatory and neurodegenerative diseases of the central nervous system, and it is thought that these potential mechanisms converge into a final common pathway of tissue damage in all these diseases. It has, however, to be emphasized that widespread primary demyelination with preservation of axons is highly specific for MS, as it is not present in other conditions of brain damage with the exception of virus infection of oligodendrocytes (Denic et al., 2011) or the presence of specific toxins affecting myelin and/or oligodendrocytes (Van der Star et al., 2012). Thus, a major prerequisite for the understanding of the pathogenesis of MS is to identify the mechanism that specifically affects myelin and oligodendrocytes and leads to widespread primary demyelination.

Multiple sclerosis generally starts with bouts of disease followed by phases of remission (Lublin and Reingold, 1996). In this relapsing and remitting stage of the disease (RRMS) anti-inflammatory or immunomodulatory treatments are effective, suggesting inflammation as the major driver of clinical disease and tissue injury (Wiendl and Hohlfeld, 2009). Pathologically, RRMS is mainly reflected by focal demyelination in the white matter. Lesions in the gray matter, in particular in the cerebral cortex, are present already in early stages of the disease (Lucchinetti et al., 2011), but their number and size is small (Kutzelnigg et al., 2005). After several years of RRMS, when the extent of neurological disability reaches a certain threshold, the disease converts into secondary progressive MS (SPMS). In these patients, relapses become rare or absent, while they suffer from slow and continuous deterioration of their neurological status. About 10 to 20% of MS patients develop progressive disease from its onset (primary progressive MS, PPMS; Lublin and Reingold, 1996). Disease conversion to progressive MS is related to the age of the patient and the disease-related accumulation of disability and brain damage (Leray et al., 2010). In pathology, inflammatory demyelinating lesions in the white mater are still seen, though most of these lesions do not develop *de novo* in the white matter but, when active, rather expand at the outer edges of pre-existing plaques (Frischer et al., 2009; Prineas et al., 2001). In addition, extensive demyelination affects the gray matter, in particular the cerebral and cerebellar cortex. Furthermore, there is profound diffuse inflammation and neurodegeneration in the normal appearing white matter. These processes result in extensive tissue loss reflected by atrophy of the entire gray and white matter (Kutzelnigg et al., 2005). Thus, in the progressive stage there is besides the disease-specific demyelinating process a generalized neurodegeneration affecting the entire brain. The association of the neurodegenerative process with patient's age and accumulation of disease burden suggests that additional amplification mechanisms promote global CNS damage.

As mentioned above, demyelination and neurodegeneration in MS is associated with inflammation at all stages of the disease, including SPMS and PPMS, consistent of infiltrates with T-cells and B-cells as well as with activated macrophages and microglia. Furthermore, in patients with long-lasting disease inflammation may decrease to levels seen in age matched controls and in these patients no active demyelination is present and acute axonal injury is similar to that seen in the respective controls (Frischer et al., 2009). These data indicate that also in the progressive stage of MS demyelination and neurodegeneration is at least in part driven by the inflammatory process. This view is in disagreement with clinical observations, showing that enhancing lesions in MRI are sparse in the progressive stage of MS and that current immunomodulatory or immunosuppressive treatments largely have failed in clinical trials (Wiendl and Hohlfeld, 2009). However, inflammation in the progressive stage of MS is in part trapped within the central nervous system behind a closed or repaired blood brain barrier (Hochmeister et al., 2006) and may form lymph follicle like aggregates within the meninges (Serafini et al., 2004). Thus, potentially effective immunosuppressive treatments in MS have to be based on drugs, which reach the central nervous system through an intact blood brain barrier. Furthermore, the specific nature of the inflammatory response within the brain and spinal cord of patients with progressive MS has to be defined in detail regarding its response to anti-inflammatory therapeutic strategies.

## Subpial cortical lesions provide clues for the understanding of MS pathogenesis

For a long time MS has been regarded as a demyelinating disease affecting the white matter. Although demyelination in the cerebral cortex was already noted decades ago in some pathological studies (Brownell and Hughes, 1962; Kidd et al., 1999; Lumsden, 1970), only the application of immunohistochemistry for myelin proteins uncovered the extent of demyelination present in the gray matter of the MS brain (Bo et al., 2003; Peterson et al., 2001). Cortical lesions in MS may appear in three forms: cortico-subcortical lesions, small intra-cortical lesions and subpial lesions (Bo et al., 2003). The latter dominate cortical pathology. Subpial cortical demyelination appears to be exquisitely specific for MS, since it is not present in any other inflammatory, neurodegenerative or metabolic disease affecting the cortex and meninges (Fischer et al., 2013; Moll et al., 2008). This holds true even for virus-induced demyelinating diseases such as progressive multifocal leukoencephalopathy (PML) or subacute sclerosing panencephalitis (SSPE), where only cortico-subcortical or small intra-cortical lesions are found (Moll et al., 2008).

In comparison to cortical lesions much less is known regarding demyelinating lesions in the deep gray matter. Their occurrence has been described in several pathological studies, but information regarding their presence in different disease stages is limited (Brownell and Hughes, 1962; Cifelli et al., 2002; Gilmore et al., 2009; Huitinga et al., 2004; Lumsden, 1970; Vercellino et al., 2009). Importantly, however, deep gray matter nuclei are affected not only by focal plaques of demyelination, but also by diffuse neuronal loss in the absence of demyelinated lesions (Cifelli et al., 2002; Vercellino et al., 2009).

Subpial cortical demyelination is associated with inflammation in the meninges, while T- or B-cell infiltrates in the cortical parenchyma or around cortical vessels are sparse or absent (Brink et al., 2005; Choi et al., 2012; Howell et al., 2011; Kutzelnigg et al., 2005). Demyelination expands from subpial into deeper cortical layers, where active demyelination occurs at sites of microglia activation. Subpial cortical lesions mainly arise in the cortical sulci and deep invaginations of the outer brain surface such as the insular cortex, the cingulate cortex, or the