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Lame Ducks or Fierce Creatures? - The Role of Oligodendrocytes in Multiple Sclerosis

T. Zeis · N. Schaeren-Wiemers

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Abstract In the pathogenesis of multiple sclerosis (MS), oligodendrocytes and its myelin sheaths are thought to be the primary target of destruction. The mechanism leading to oligodendrocyte injury and demyelination is still elusive. Oligodendrocytes are maintaining up to 50 internodes of myelin, which is an extraordinary metabolic demand. This makes them one of the most vulnerable cell types in the central nervous system (CNS), and even small insults can lead to oligodendrocyte impairment, demyelination, and axonal dysfunction. For this reason, oligodendrocytes are viewed as more or less the "lame ducks" of the CNS who can easily become victims. However, recent data demonstrate that this perception possibly needs to be revised. The latest data suggest that oligodendrocytes may also act as "fierce creatures," influencing the surrounding cells in many ways to preserve its own, as well as their function, allowing sustained functionality of the CNS upon an attack. In this review, the concept of "reactive or activated oligodendrocyte" is introduced, describing alterations in oligodendrocytes which are either protective mechanisms allowing survival in otherwise lethal environment or influence and possibly modulate the ongoing inflammation. Although "harnessed", oligodendrocytes might actively modulate and shape their environment and be part of the immune privilege of the brain.

Keywords Oligodendrocyte · Oligodendrocyte pathology · Normal-appearing white matter · Multiple sclerosis · Inflammation · Innate immunity

T. Zeis · N. Schaeren-Wiemers (✉)
Neurobiology, Department of Biomedicine,
University Hospital Basel,
Pharmacenter 7007, Klingelbergstrasse 50/70,
CH-4056 Basel, Switzerland
e-mail: Nicole.Schaeren-Wiemers@unibas.ch

Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). The pathological hallmark of the disease is the inflammatory plaque. Studies of its histopathology have revealed a wide heterogeneity at the cellular and molecular levels, which might partially reflect the diversity of the clinical disease course (Lucchinetti et al. 2000). There are several hypotheses to explain the immunological injury in MS. In the most prominent and most widely accepted hypothesis, MS is driven by a T cell-mediated immune response leading to secondary macrophage and microglia activation and demyelination (Compston et al. 2006). In a majority of MS cases, this immune response is further accompanied by antibodies or complement deposition (Lucchinetti et al. 2000). Other hypotheses implicate a viral pathogenesis to be the origin of MS (Kennedy and Steiner 1994) or intrinsic oligodendrocyte damage leading to subsequent MS disease (Lucchinetti et al. 2000).

One of the major features of an inflammatory plaque is demyelination and the loss of oligodendrocytes (Ozawa et al. 1994). Because of the fact that oligodendrocytes are highly specialized and have a high metabolic demand maintaining many myelin sheaths, oligodendrocytes are one of the most vulnerable cells in the CNS. There are many ways which lead to oligodendrocyte impairment and injury (for review see Ludwin 1997; Raine 1997; Merrill and Scolding 1999). Still, oligodendrocyte apoptosis and loss is not the major feature in MS, implicating that the major target of the destructive process is the myelin sheath (Ozawa et al. 1994). In particular cases, however, oligodendrocyte apoptosis might be a primary cause (Lucchinetti et al. 2000; Barnett and Prineas 2004). Studies from animal models showed that T cell infiltration and subsequent

inflammation in the CNS per se does not necessarily lead to extensive demyelination (for review see Gold et al. 2000; Gold et al. 2006). Furthermore, oligodendrocytes are able to resist at least to some extent to autoimmune-mediated demyelination (Ozawa et al. 1994). An important question arises: which mechanisms lead to or protect from potential harmful oligodendrocyte injury?

Oligodendrocytes - Lame Ducks?

Until now, many cell types have been shown to be potentially able to damage oligodendrocytes. In the first part of this review, we discuss some of these cell types and their mediators leading to oligodendrocyte injury or death. Figure 1 shows a schematic view of these cells and their possible oligodendrocyte harming mediators.

Oligodendrocyte Injury Mediated by Immune Cells

In acute MS lesions, $CD4^+$ and $CD8^+$ T lymphocytes are present. These cells can recognize their antigen if presented by major histocompatibility complex (MHC) molecules expressed on target cells, and be subsequently activated. Under normal conditions, MHC expression in the CNS does either not occur or is below detection levels (Redwine et al. 2001). In vitro experiments showed, however, that oligodendrocytes can be induced to express MHC class I (Grenier et al. 1989; Kim 1985) and MHC class II molecules (Bergsteindottir et al. 1992). Also in vivo, it has been shown that oligodendrocytes are expressing MHC class I molecules in a murine model of CNS inflammation and demyelination (Redwine et al. 2001) and in MS lesions (Hoftberger et al. 2004). This suggests that under pathological conditions, oligodendrocytes induce MHC I expression and can thereby directly activate T cells and consequently be damaged by them.

$CD8^+$ T Lymphocytes

By the interaction of the $CD8^+$ T cell receptor together with the MHC class I peptide complex, $CD8^+$ T cells are activated and are directly cytotoxic to cells presenting their specific antigen (Parkin and Cohen 2001). The activation of $CD8^+$ T cell by recognition of their specific antigen is then followed by clonal expansion. In MS, this was shown by analyzing lesions, blood, and cerebral spinal fluid (CSF) for clonal composition and T cell receptor repertoire (Babbe et al. 2000; Skulina et al. 2004). These results suggested that $CD8^+$ T cells might have recognized their specific antigen within the lesion and might have been activated. It

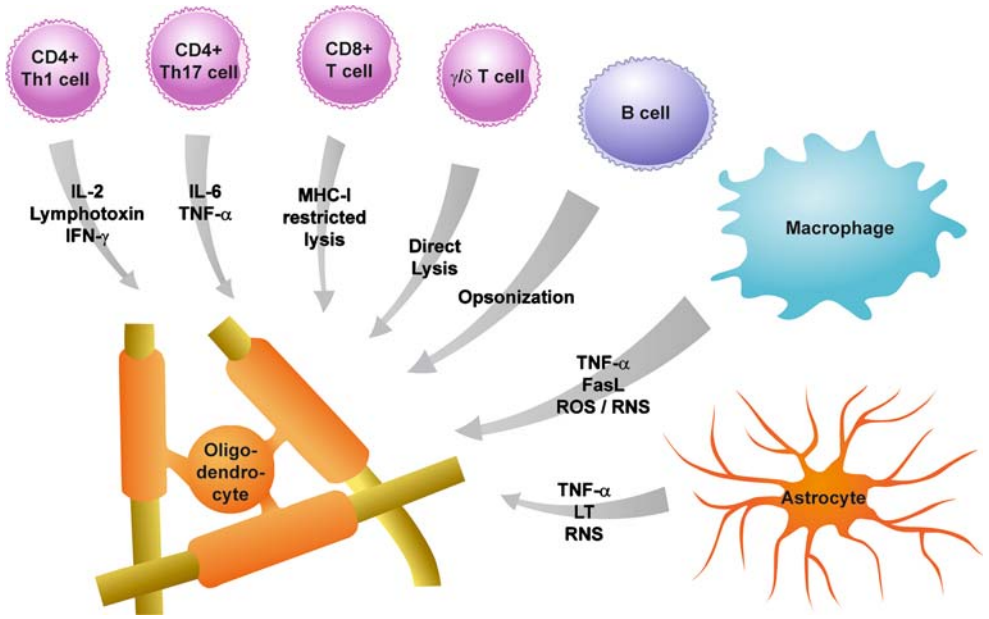

Figure 1 Cells mediating oligodendrocyte injury in the course of MS. Many different cell types have the potential to damage oligodendrocytes. In this figure, some of these cells and their potential oligodendrocyte-damaging mediators are summarized. $CD4^+$ Th1 T cells have been shown to induce oligodendrocyte damage among others through IL-2, LT, and IFN-γ, whereas oligodendrocyte-damaging mechanisms of Th17 T cells involve IL-6 and TNF-α. $CD8^+$ T cells can induce oligodendrocyte damage directly by MHC class I-restricted cell lysis. Furthermore, γ/δ T cells were also shown to have the potential of damaging oligodendrocytes by direct lysis. By secreting antibodies, B cell-mediated damage to oligodendrocytes through opsonization was demonstrated. Macrophages are one of the main cell types inducing oligodendrocyte damage by TNF-α, FasL, ROS/RNS, and other mechanisms. Furthermore, astrocytes were shown to be potentially harmful to oligodendrocytes by mechanisms involving TNF-α, LT, and RNS

has been shown that oligodendrocytes are susceptible to cytolysis by $CD8^+$ T lymphocytes (Jurewicz et al. 1998; Ruijs et al. 1990). Furthermore, an involvement of $CD8^+$ cytotoxic T lymphocytes in autoimmune demyelination was shown in experimental autoimmune encephalomyelitis (EAE) (Huseby et al. 2001; Sun et al. 2001). Altogether, this suggests that $CD8^+$ T lymphocytes might contribute to oligodendrocyte injury in MS.

$CD4^+$ T Lymphocytes

$CD4^+$ T helper cells recognize their cognate antigen exclusively in the context of MHC class II molecules. In contrast to MHC class I molecules, the expression of MHC class II molecules by oligodendrocytes could not be demonstrated in MS (Lee and Raine 1989). MHC class II expression is restricted to professional antigen-presenting cells such as microglia/macrophages and dendritic cells (Becher et al. 2000; Greter et al. 2005). It is easily conceivable that $CD4^+$ T helper cells induce oligodendrocyte damage by secreting cytokines and promoting activation of nearby macrophages and microglia. Studies in EAE suggest that $CD4^+$ T cells of the Th1 and Th17 lineage play a major role in disease pathology (Gutcher et al. 2006; Langrish et al. 2005; Lassmann and Ransohoff 2004; Sospedra and Martin 2005; Weaver et al. 2006). Th1 cells are characterized by the predominant secretion of IFN-γ whereas Th17 cells are shown to secrete IL-17A, IL-17F, and IL-22 (Iwakura and Ishigame 2006; Kreymborg et al. 2007; McGeachy et al. 2007). It was shown that oligodendrocytes express TNF-α receptors (Cannella et al. 2007; Raine et al. 1998) and other cytokine receptors such as IFN-γ receptor (Cannella and Raine 2004), and treatment of oligodendroglial cell lines with IFN-γ induces apoptosis (Buntinx et al. 2004). Oligodendrocytes were also shown to be susceptible to TNF-α-induced cell death (D'Souza et al. 1996; Jurewicz et al. 2005; Selmaj and Raine 1988). Taken together, activated $CD4^+$ T lymphocytes do contribute to some extent, directly or indirectly, to oligodendrocyte injury in MS.

γ/δ T Lymphocytes

Another cell type found in MS lesions are γ/δ T lymphocytes (Wucherpfennig et al. 1992). γ/δ T cells are a T cell subpopulation showing a different T cell receptor structure than α/β T cells (Li et al. 1998). The role of γ/δ T lymphocytes in MS is still unclear. Nevertheless, depletion of γ/δ T lymphocytes during EAE has been shown to ameliorate disease severity during the acute phases of the disease (Rajan et al. 1996). Furthermore, γ/δ T cells were shown to enhance adoptive transfer of EAE by promoting antigen presentation and IL-12 production (Odyniec et al. 2004). As lysis of oligodendrocytes by γ/δ T cells has been demonstrated in vitro (Freedman et al. 1991), a possible impact on oligodendrocyte injury in MS might not be ruled out.

B Cells and Antibodies

In the CSF of MS patients, abnormal oligoclonal immunoglobulin bands are detected, which supports the clinical diagnosis of MS (Compston et al. 2006). Autoantibodies against myelin components were reported to be present in the serum, CSF, and lesions of MS patients (Genain et al. 1999; Reindl et al. 1999). In line with this, IgG isolated from inflamed CNS tissue from MS patients were shown to recognize MOG (O'Connor et al. 2005). Recently, meningeal B cell follicles were reported to associate with early onset of disease and severe cortical pathology in secondary progressive MS (Magliozzi et al. 2007). Therefore, antibody-producing B cells may have potential impact on oligodendrocyte injury and demyelination. For example, injection of antibodies augmented demyelination during the course of a T cell-mediated transfer EAE (Linington et al. 1988). Further, it has been shown that by opsonizing the myelin - oligodendrocyte surface, antibodies can stimulate oligodendrocyte lysis of macrophages through their Fc receptors (Scolding and Compston 1991). Also, another demyelinating mechanism by antibodies was shown to involve membrane attack complex (MAC) deposition, which finally leads to complement-mediated cytolysis (Mead et al. 2002; for review see Sospedra and Martin 2005). Altogether, direct antibody-mediated injury of oligodendrocytes in MS might play an important role, although its impact on MS pathogenesis could not be determined yet.

Oligodendrocyte Injury Mediated by Activated Macrophages/Microglia

Activated macrophages and microglia may play an important role in inducing oligodendrocyte injury during acute inflammation in MS. It has been shown that disease severity in EAE correlates best with macrophage infiltration (Berger et al. 1997). Activated macrophages and microglia were shown to have incorporated myelin products and express a large variety of different oligodendrocyte-deleterious compounds, such as TNF-α, reactive oxygen species (ROS), reactive nitrogen species (RNS), and Fas ligand (FasL). TNF-α is a potent cytotoxic molecule capable of inducing oligodendrocyte cell death (D'Souza et al. 1996; Jurewicz et al. 2005; Selmaj and Raine 1988). The production of ROS and RNS by activated macrophages and microglia can lead to various types of damage such as lipid

peroxidation, tyrosine nitrosylation, and DNA strand breaks (van der Veen and Roberts 1999; Willenborg et al. 1999; Zhang et al. 1994). High expression of inducible nitric oxide synthase (iNOS) and neuronal nitric oxide synthase (nNOS) has been reported in activated macrophages and microglia within active lesions in MS (De Groot et al. 1997; Hill et al. 2004), and RNS-mediated damage in oligodendrocytes has also been demonstrated (Jack et al. 2007; Li et al. 2005; Merrill et al. 1993). Oligodendrocytes were also reported to express Fas in MS lesions (D'Souza et al. 1996). FasL was shown to induce oligodendrocyte damage (Li et al. 2002), and as microglia express FasL in MS lesions (Becher et al. 1998), they might, therefore, induce oligodendrocyte apoptosis. Furthermore, it has been shown that activated macrophages and microglia are capable of damaging oligodendrocytes in an antibody-dependent mechanism (Griot-Wenk et al. 1991). Altogether, activated macrophages and microglia might be one of the major mediators of oligodendrocyte injury in MS.

Oligodendrocyte Injury Mediated by Astrocytes

Astrocytes are known to maintain physiological glutamate levels in the brain. Therefore, malfunctioning or too slow glutamate uptake might lead to an enhancement of oligodendrocyte excitotoxic damage (Newcombe et al. 2007). In addition, astrocytes are also known to express TNF-α and LT-α. Thus, astrocytes might also be a potential inducer of oligodendrocyte injury via TNF-α- and LT-α-dependent mechanisms (for review see Williams et al. 2007). An expression of all three isoforms of NOS by astrocytes was also reported (for review see Gibson et al. 2005). In MS plaques, high levels of constitutively expressed NOS were detected to be expressed by astrocytes and macrophages (De Groot et al. 1997). In contrast to astrocytes, oligodendrocytes are shown to be much more susceptible to NO-induced oxidative stress (Mitrovic et al. 1995). This is explained by the high iron load stored in oligodendrocytes (Connor and Menzies 1995; Roskams and Connor, 1994; Thorburne and Juurlink 1996) and their low content of reduced glutathione (GSH) (Juurlink et al. 1998; Thorburne and Juurlink 1996). Iron (Fe^{2+}) was reported to be involved in the formation of hydroxyl radicals (Gutteridge and Halliwell 1989), whereas glutathione peroxidase activity, using GSH as an electron donor, scavenges hydrogen peroxide and thus inhibits hydroxyl radical formation (Juurlink et al. 1998). A production of NO through NOS expressed by astrocytes might, therefore, lead to oxidative stress and damage in oligodendrocytes. Taken together, activated astrocytes might also be involved in damaging oligodendrocytes during the disease course of MS.

Reactive or Activated Oligodendrocytes - Pure Defensive or Even Fierce Creatures?

As discussed before, immune cells and brain resident cells are able to produce a variety of potentially harmful factors for oligodendrocytes. These "attacks" are occurring either directly via lysis or indirectly via toxic mediators or via an imbalance of the surrounding environment. As demyelination is a major feature in MS and loss of oligodendrocyte during the chronic disease process is also evident, oligodendrocytes can be regarded as "poor victims" in the pathogenic process of MS. Still, the question arises if oligodendrocytes are really "lame ducks" passively allowing disease progression or if they attempt to defend themselves in one way or another, which could even influence disease progression?

Studies characterizing oligodendrocytes in MS lesions, in primary oligodendrocyte cultures, and in analysis of normal-appearing white matter (NAWM) MS tissue, which is mostly devoid of immune infiltrates - therefore suitable to study prelesional activities of oligodendrocytes - have recently disclosed a view of oligodendrocytes being potential immune-modulating in MS. Furthermore, oligodendrocytes were shown to successfully protect themselves during pathogenesis of Balo's concentric sclerosis (Stadelmann et al. 2005). Altogether, these findings might lead to a view of oligodendrocytes being at least capable to defend themselves or even be a reactive - to some extent active cell type - part of the immune privilege of the brain. In this study, we discuss the capacity of oligodendrocytes to react against certain insults for their own protection, and how they might modulate their environment by influencing disease progression.

Activation of Endogenous Protective Mechanisms

In the last few years, growing evidence suggest an involvement of hypoxia-like pathogenic mechanisms in MS (Lassmann 2003). Especially, in the so-called pattern III of the lesion patterns identified recently (Lucchinetti et al. 2000), hypoxia-like tissue injury may play a pathogenetic role (Aboul-Enein et al. 2003). Hypoxic tissue injury can be induced in many ways. As already mentioned above, ROS and RNS are known to induce cellular damages and proposed to be involved in the demyelinating processes (Smith et al. 1999). For example, NO can impair respiratory chain function in mitochondria, and by that can cause axon conduction block (Redford et al. 1997). In particular, oligodendrocytes are vulnerable to NO-mediated damage (Smith et al. 1999; Smith and Lassmann 2002), and therefore, activation of mechanisms protecting oligodendrocytes from oxidative stress inducing damage would be highly

beneficial. A recent study of subcortical NAWM from MS cases has shown the upregulation of several genes involved in ischemic preconditioning (Graumann et al. 2003). In particular, HIF-1α has been shown to be an important regulator of hypoxic preconditioning (Bergeron et al. 2000; Bernaudin et al. 2002; Sharp et al. 2001) and is activated by hypoxia, growth factors, NO, and others (for review see Brune and Zhou 2007; Semenza 2002). HIF-1α and some of its downstream genes were shown to be elevated in MS NAWM (Graumann et al. 2003) and in situ hybridization experiments of MS NAWM (Zeis et al. 2008), and examinations of Balo's concentric sclerosis identified oligodendrocytes expressing this transcription factor (Stadelmann et al. 2005), suggesting that oligodendrocytes mount ischemic protective mechanisms during the disease course (Fig. 2). Furthermore, oligodendrocytes were also shown to express heat shock protein 70 (HSP70) (Stadelmann et al. 2005) and HSP32 (Stahnke et al. 2007). In the case of HSP70, a protective role has been shown in brain ischemia (for review see Christians et al. 2002), whereas HSP32 was shown to exert a protective role against oxidative stress in an oligodendroglial cell line (Stahnke et al. 2007).

It is interesting to note that sublethal doses of inflammatory cytokines such as IFN-γ and TNF-α were reported to induce protective mechanisms in target cells (Fig. 2). The induction of HSP70 in oligodendrocytes was shown in vitro by treatment of oligodendrocyte cultures with a mix of cytokines (D'Souza et al. 1994). Furthermore, treatment of oligodendrocyte cultures with IFN-γ led to an increase in the expression of genes involved in protection against oxidative stress (Balabanov et al. 2007). In line with this, treatment of mice with IFN-γ before the onset of EAE led to an amelioration of the disease through activating the integrated stress response (Lin et al. 2007). Altogether, oligodendrocytes are able to induce and express endogenous protective mechanisms allowing them to survive in an otherwise potentially lethal environment.

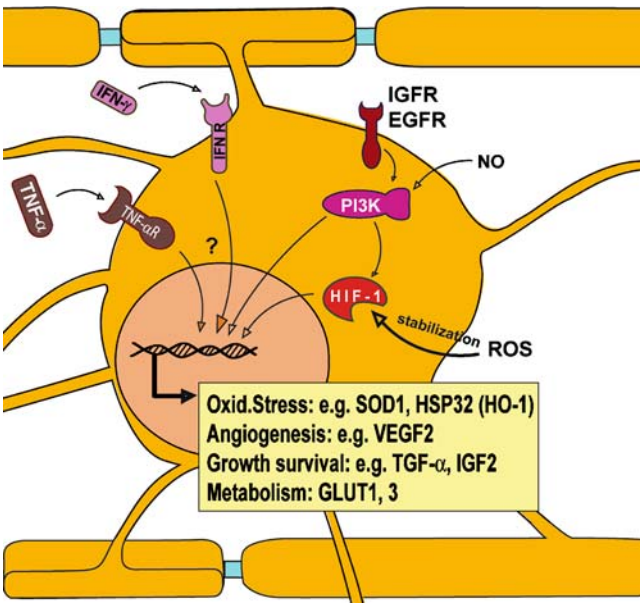

Figure 2 Ischemic preconditioning pathways in oligodendrocytes. Recent studies showed that oligodendrocytes can mount ischemic preconditioning mechanisms upon different stimuli. Treatment of oligodendrocytes with sublethal doses of IFN-γ and TNF-α led to the upregulation of genes involved in ischemic tolerance. Protective genes were also shown to be upregulated in oligodendrocytes after stimulation with growth factors. Furthermore, low levels of RNS/ROS were reported to lead to a stabilization of HIF-1α, which in turn activates the transcription of protective genes such as for example VEGFR, GLUT1, and GLUT3

Growth Factors

Changes in growth factors and growth factor receptors expression were demonstrated in MS. Several growth factors such as nerve growth factor (NGF), insulin-like growth factor (IGF), and transforming growth factor β (TGF-β) were reported to be expressed by oligodendrocytes (for review see Du and Dreyfus 2002). By expression of these factors, oligodendrocytes might influence the survival and/or function of neighboring cells. NGF can bind to the tyrosine kinase receptor A (TrkA) and to the low-affinity nerve growth factor receptor ($p75^{NTR}$). By binding to TrkA, NGF promotes cell survival whereas binding to $p75^{NTR}$ under some circumstances might also modulate susceptibility to programmed cell death or apoptosis (Casaccia-Bonnefil et al. 1999; Yoon et al. 1998). In EAE, the expression of TrkA was detected on neurons, astrocytes, and oligodendrocytes (Oderfeld-Nowak et al. 2003; Oderfeld-Nowak et al. 2001), whereas $p75^{NTR}$ was detected on neurons, microglia, astrocytes, and oligodendrocytes (Nataf et al. 1998; Villoslada et al. 2000). In EAE, NGF was shown to have beneficial effects, as NGF-deprived rats display more severe neurological deficits during disease course. Furthermore, treatment of marmoset monkeys with NGF prevented the full development of EAE lesions and delayed the onset of clinical EAE (Micera et al. 2000; Villoslada et al. 2000). Another growth factor expressed by oligodendrocytes is IGF-1, which was reported to ameliorate TNF-α-induced demyelination in transgenic mice (Ye et al. 2007). Furthermore, IGF-1 was also reported to reduce demyelination in EAE (Liu et al. 1995), although this beneficial effect is still under debate (Cannella et al. 2000). The expression of TGF-β by oligodendrocytes was also reported, which is discussed in the next chapter. Altogether, by expressing several growth factors, oligodendrocytes are able to influence their own function and survival, and also the function and survival of nearby cells.

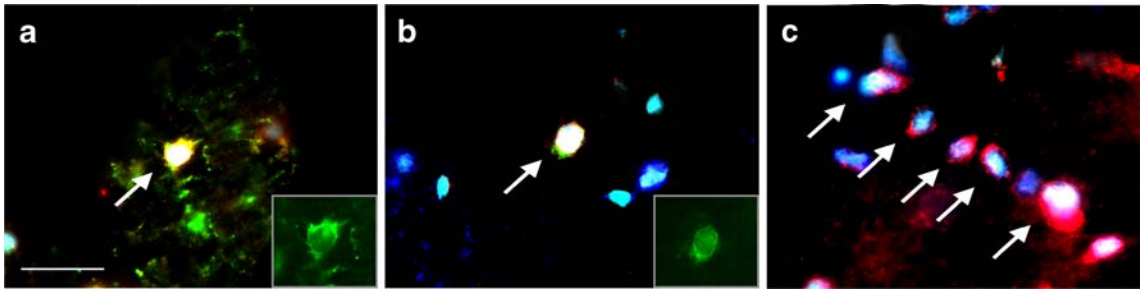

Figure 3 STAT6 signaling pathway expression in oligodendrocytes. Recently, oligodendrocytes were shown to be able to express immune mechanism relevant genes. Immunofluorescence colocalization analysis of proteins from the STAT6 signaling pathway in MS patients revealed the expression of IL-4R (**a**), IL-13R (**b**), and STAT6 (**c**) in oligodendrocytes (Olig2 positive) in subcortical normal-appearing white matter brain tissue. **a** Colocalization of STAT6 (*red*), IL-4R (*green*, *inset*), OLIG2 (*blue*), and DAPI (*cyan*); **b** colocalization of STAT6 (*red*), IL-13R (*green*, *inset*), OLIG2 (*blue*), and DAPI (*cyan*); **c** colocalization of STAT6 (*red*), OLIG2 (*blue*), and DAPI (*cyan*) in oligodendrocytes arranged in interfascicular rows, which is typical for myelinating oligodendrocytes (for more detailed pictures see Zeis et al. 2008). Scale bar=25 μm

Potential Immune-modulating Ability of Oligodendrocytes

Immunohistochemical analysis of proteins expressed by oligodendrocytes revealed that oligodendrocytes are able to express cytokine receptors and members from the JAK/STAT family (Cannella and Raine 2004; Zeis et al. 2008). In a recent study, we have shown that genes from the STAT6 signaling pathway are upregulated in MS NAWM and that STAT6 and its members JAK1/3, IL-4R, and IL-13R are expressed by oligodendrocytes (Figs. 3 and 4)

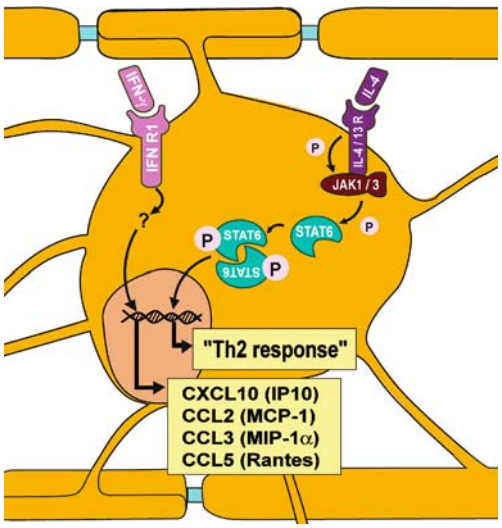

Figure 4 Immune response-mediating pathways in oligodendrocytes. Analysis of proteins expressed by oligodendrocytes revealed that oligodendrocytes are able to express immune mechanisms-related proteins. Members of the STAT6 signaling pathway, such as IL-4R, IL13R, JAK1, and STAT6, were shown to be expressed by oligodendrocytes. This might indicate an anti-inflammatory "Th-2"-like response by oligodendrocytes. Furthermore, treatment of oligodendrocytes with a sublethal dose of IFN-γ and TNF-α led to the secretion of chemokines such as CXCL10 (IP-10), CCL2 (MCP-1), CCL3 (MIP-1α), and CCL5 (Rantes). Altogether, this indicates that oligodendrocytes might play an immune-modulating role MS

(Zeis et al. 2008). The STAT6 signaling pathway is known from $CD4^+$ T helper cells type 2, and it has been shown that STAT6 is critically required for differentiation into Th2 cells (Kaplan et al. 1996). Although still debated, cytokines of the Th2 type such as IL-4 and IL-10 are thought to be mostly beneficial in MS and EAE (Cannella and Raine 2004; Sospedra and Martin 2005). In EAE, it has been shown that STAT6 knockout mice develop a more severe disease than wild-type mice (Chitnis et al. 2001). This might be because of the lack of Th2 cells and of the inability of oligodendrocytes to modulate their environment in an anti-inflammatory way. The expression and activation of an anti-inflammatory response by oligodendrocytes might be crucial for them to compensate for the upregulated proinflammatory environment and to limit the inflammatory response and damage (Zeis et al. 2008). The expression of different cytokine receptors on oligodendrocytes in active and silent lesions may further suggest an active role in innate immunity of the CNS (Cannella and Raine 2004). Oligodendrocytes were also shown to express TGF-β in vitro (da Cunha et al. 1993; McKinnon et al. 1993), which can suppress immune and inflammatory responses (for review see Pratt and McPherson 1997), and might promote myelination and remyelination (Setzu et al. 2006).

In vitro experiments suggested that, upon stimulation by INF-γ, oligodendrocytes express protective genes against oxidative stress and a number of chemokines, including CXCL10, CCL2, CCL3, and CCL5 (Fig. 4) (Balabanov et al. 2007). CXCL10, CCL2, and CCL5 were also found to be upregulated in MS NAWM (Graumann et al. 2003). Furthermore, mice with oligodendrocytes with suppressed responsiveness to IFN-γ showed higher oligodendrocyte apoptosis in EAE and an accelerated disease onset, but milder perivascular inflammation and minimal parenchymal infiltration and demyelination (Balabanov et al. 2007). This effect of IFN-γ on oligodendrocytes demonstrates that oligodendrocytes are capable to react on external immune

challenges by induction of protective mechanisms and that they can modulate inflammatory responses. The expression of cytokine receptors and members from the anti-inflammatory STAT6 signaling pathway and the possibility of chemokine expression might point to oligodendrocytes playing a role in the innate immunity by actively modulating their environment and interacting with cells of the immune system.

Conclusions

Oligodendrocytes as the myelinating cell type in the CNS are the major targets in MS. Many studies have shown that oligodendrocytes are easily damaged by various mechanisms. Therefore, oligodendrocytes might be seen as "lame ducks" of the CNS. However, growing evidence indicate that oligodendrocyte are far more than a passive presence in the CNS during MS. Oligodendrocytes are either constitutively expressing or inducing various molecules able to influence inflammatory reactions and prevent cell death to conserve the functionality of the CNS. It seems that oligodendrocytes in MS have a rather active or reactive phenotype, preventing fatal damage and modulating their surrounding. Therefore, oligodendrocytes may even act as "fierce creatures," influencing innate immunity and being an active part in the formation of the immune privilege of the brain.

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