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Interferon regulatory factor 1 regulation of oligodendrocyte injury and inflammatory demyelination

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Abstract

Oligodendrocyte injury and inflammatory demyelination are key pathological abnormalities of multiple sclerosis (MS), and its animal model, i.e., the experimental autoimmune encephalomyelitis (EAE). Traditionally, they are viewed as destructive processes secondary to a dysregulated autoimmune reaction. New evidence emerged over the last decade indicating that oligodendrocytes are not merely immune targets but rather active participants in the neuroimmune network and, in fact, can regulate the events leading to inflammatory demyelination. In this review, we are discussing the role of interferon regulatory factor 1 (IRF-1) as a master transcription factor orchestrating oligodendrocyte injury and inflammatory demyelination in MS and EAE. We are also discussing the significance of IRF-1 signaling in the induction of oligodendrocyte pyroptosis, a Caspase 1-dependent pro-inflammatory cell death, as a disease-enhancing mechanism. Finally, we are drawing attention to IRF-1 as a potential therapeutic target in MS and to the importance of investigating other oligodendrocyte-dependent disease mechanisms.

Keywords: Caspase 1; central nervous system (CNS) inflammation; demyelination; glial cells; interferon regulatory factor 1; IRF-1; multiple sclerosis; oligodendrocytes.

Introduction

Multiple sclerosis (MS) is the most common human demyelinating disease of the central nervous system (CNS) (Noseworthy et al., 2000). Pathologically, MS is characterized by perivascular inflammation, demyelination, oligodendrocyte and axonal injury, and astrogliosis (Lassmann, 2005). The etiology of MS is unknown, but it is believed to be an autoimmune disorder (Hafler, 2004). Autoimmunity in MS is attributed to failure of the peripheral immune tolerance and aberrant activation of self-reactive, myelin-specific T cells. Consequently, these T cells orchestrate and drive an inflammatory reaction against the CNS myelin and the myelin-producing oligodendrocytes (Steinman, 1996).

Oligodendrocyte injury and inflammatory demyelination are the hallmark of the MS lesion. Collectively, they represent a spectrum of processes rather than a single unified phenomenon. Demyelinating lesions in MS can appear not only as diffuse inflammatory tissue destruction but also as a subtle primary oligodendrogliopathy (degeneration of the periaxonal layers of the myelin) or oligodendrocyte apoptosis in the absence of significant inflammation (Lucchinetti et al., 2000). Furthermore, occurrence of isolated oligodendrocyte death/apoptosis or gene expression changes in the normal-appearing white matter (NAWM) are also described, implying that oligodendrocyte injury may occur very early in the disease process as a pre-lesional abnormality (Barnett and Prineas, 2004; Zeis et al., 2008).

Traditionally, oligodendrocytes and myelin are viewed as passive targets of uncontrolled inflammatory response. However, there are several lines of evidence indicating that this view is likely to be an oversimplification: (1) oligodendrocyte injury is an active process requiring intracellular signaling; (2) the injurious process can be prevented if its signaling mechanism is suppressed; (3) oligodendrocyte responsiveness to injury regulates the extent of CNS inflammation; (4) protecting oligodendrocytes against inflammatory injury results in protection against experimental autoimmune encephalomyelitis (EAE); (5) oligodendrocytes participate in the neuroimmune network by producing chemokines or other inflammatory molecules (Hisahara et al., 2000; Hovelmeyer et al., 2005; Balabanov et al., 2006, 2007; Kassmann et al., 2007; McGuire et al., 2010; Ren et al., 2011a). In this review, we will discuss the role of oligodendrocytes in CNS inflammation and the molecular mechanisms regulating oligodendrocyte injury and inflammatory demyelination.

Interferon-gamma (IFN-γ), interferon regulatory factor 1 (IRF-1), and MS

IFN-γ is a pleiotropic inflammatory cytokine implicated as a deleterious factor in MS (Steinman, 2001). Elevated levels of IFN-γ are detected in serum, cerebrospinal fluid, and brain lesions of MS patients, and are found to correlate with disease activity and neurological disability (Hirsch et al., 1985; Vartanian et al., 1996; Calabresi et al., 1998; Killestein et al.,

2001; Moldovan et al., 2003). Most importantly, administration of IFN-γ to patients with MS leads to disease exacerbation, whereas blockade of this cytokine with neutralizing antibodies leads to clinical improvement (Panitch et al., 1987; Skurkovich et al., 2001). IFN-γ is produced by T cells and it is involved in the regulation of virtually every step of the autoimmune response (Hirsch et al., 1985; Steinman, 2001). In the effector stage, IFN-γ provides a link between inflammation and oligodendrocyte injury. IFN-γ-stimulated oligodendrocytes upregulate the expression of major histocompatibility complex (MHC) class I molecules, Fas (CD95), and tumor necrosis factor-α receptor (TNF-αR), which function as receptors for cell-mediated cytotoxicity (Turnley et al., 1991; Torres et al., 1995; Agresti et al., 1998; Pouly et al., 2000). The latter also involves T cells and macrophages, and represents the most common pattern of inflammatory demyelination in MS (Lucchinetti et al., 2000). Independently, IFN-γ also inhibits the proliferation and differentiation of oligodendrocyte lineage cells, and causes their cell death in transgenic animal models and cell cultures (Corbin et al., 1996; Vartanian et al., 1996; Baerwald et al., 2000; Chew et al., 2005; Lin et al., 2005; Balabanov et al., 2006; Horiuchi et al., 2006; Wang et al., 2010).

A single nucleotide polymorphism of *IRF-1* gene is found to be associated with progressive MS (Fortunato et al., 2008). The molecular mechanisms beneath this association are still unknown, but there are several important activities of IRF-1 that can be considered. IRF-1 is an interferon-induced transcription factor with pro-inflammatory and pro-injurious functions. Absence of IRF-1 as demonstrated in IRF-1 knockout (KO) mice, while it does not produce any gross anatomical abnormalities, results in abnormal IFN-γ responses (Matsuyama et al., 1993). The mice are also protected against EAE, i.e., the animal model of MS (Tada et al., 1997; Buch et al., 2003). A number of IFN-γ-dependent genes, including *MHC class I* molecule, *Fas*, *TNF-αR*, and *Caspase 1*, contain an IRF-1 binding element (IRF-E), and are transcriptionally regulated by IRF-1 (Agresti et al., 1998; Ming et al., 2002; Ren et al., 2011a, b) (Figure 1).

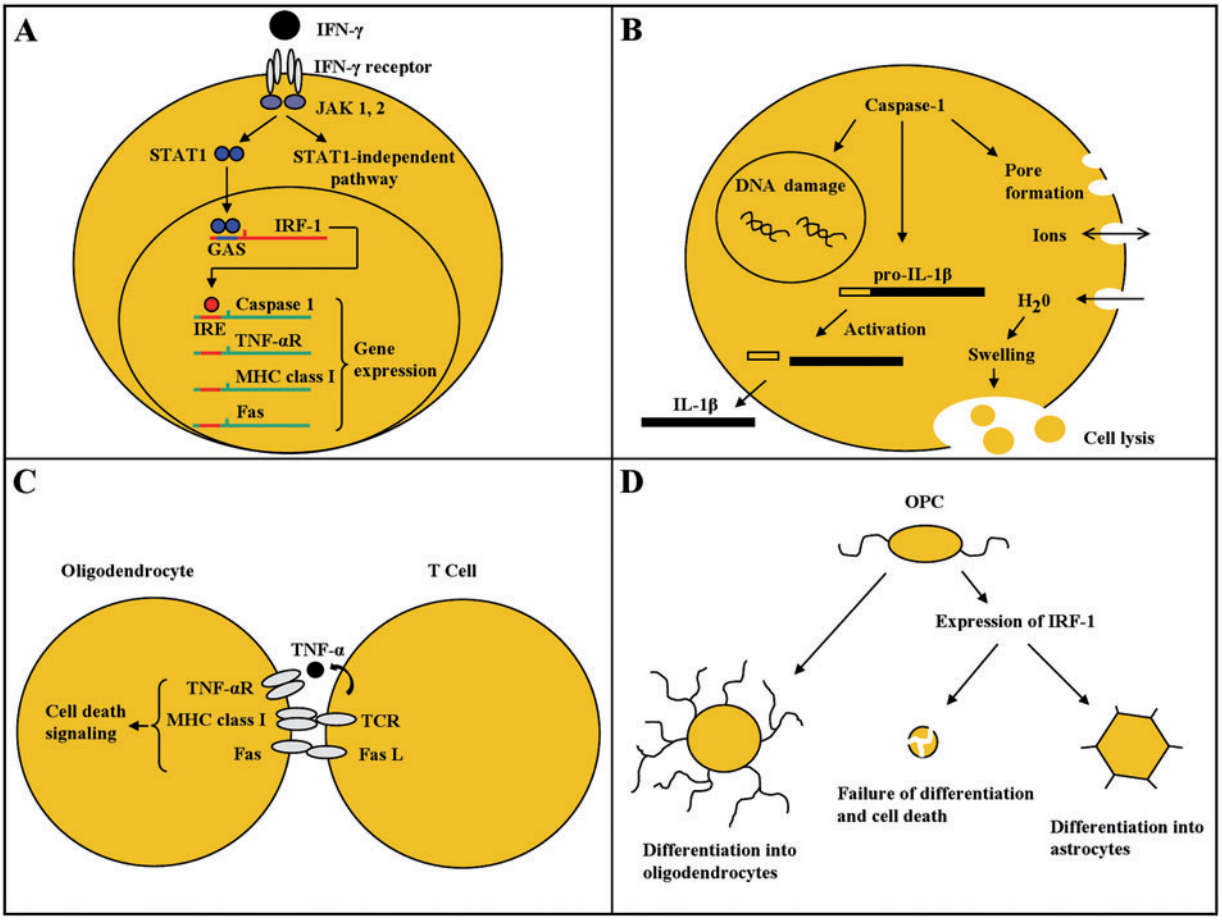

Figure 1 IRF-1 regulation of oligodendrocyte injury.
(A) IFN-γ induces the expression of IRF-1via the Jak/STAT1 signaling pathway. In turn, IRF-1 upregulates the expression of genes with pro-inflammatory and pro-injurious functions. (B) Caspase 1 initiates pyroptosis in oligodendrocytes, a pro-inflammatory cell death, associated with DNA damage and release of IL-1β and cellular contents in the extracellular space. (C) TNF-α, MHC class I molecule, and Fas serve as receptors for cell-mediated cytotoxicity, and trigger cell death signaling in oligodendrocytes. (D) Expression of IRF-1 in OPC interferes with their proliferation and differentiation, and leads to cell death and in some instances to differentiation into astrocytes.

As we mentioned above, these genes are expressed by oligodendrocytes in MS lesions and involved in cell-mediated cytotoxicity (Gobin et al., 2001; Ming et al., 2002; Höftberger et al., 2004; Lassmann, 2005; Ren et al., 2011b). IRF-1 also interacts with NF-κB (a transcription factor that mediates the cellular effects of TNF-α), suggesting a molecular basis for pro-inflammatory cytokine synergism (Agresti et al., 1998). Finally, IRF-1 mediates the injurious effect of IFN-γ on oligodendrocyte progenitor cells (OPC) and in certain settings promotes their differentiation into astrocytes (Wang et al., 2010; Horiuchi et al., 2011; Tanner et al., 2011) (Figure 1).

Recently, we reported on the expression of IRF-1 in active and chronic-active MS lesions (Ren et al., 2011b). Such expression was detected at the margins of the demyelinating lesions co-localizing predominantly with microglia and oligodendrocytes, and to a lesser extent with astrocytes. Additionally, IRF-1 expression was observed in some of the perivascular and infiltrating immune cells. During the specimen examination, we also found *Caspase 1*, an IRF-1 regulated gene (see below), to be also highly expressed. The cellular pattern of Caspase 1 expression was rather similar; microglia and oligodendrocytes localized in the perilesional areas are the main immunopositive cell populations. NAWM obtained from the same human brains did not demonstrate any appreciable immunopositivity for either molecule. Thus, IRF-1 appears to be directly involved in the pathogenesis of MS, oligodendrocyte injury, and inflammatory demyelination.

IRF-1, oligodendrocytes, and EAE

EAE is an animal model of MS that replicates many of the key pathogenic steps of the human disease (Steinman and Zamvil, 2006). The experimental disease can be induced in mice by an active immunization with myelin peptides or by an adoptive transfer of myelin-specific T cells (Swanborg, 1988). The role of IRF-1 in EAE was initially investigated using IRF-1 KO mice. In these studies, the KO mice (C57BL/6J strain background) were found to be resistant to EAE upon immunization with MOG_{35-55} compared to wild-type (WT) mice (Tada et al., 1997; Buch et al., 2003) (Figure 2). This phenotypic characteristic was associated with impaired Th1 cell differentiation and biased development toward Th2 cell phenotype, implying that IRF-1 plays a disease susceptibility role in EAE (Buch et al., 2003; Lohoff and Mak, 2005). These initial studies, however, did not investigate whether IRF-1 is expressed in the CNS, nor did they address the effect of such expression on the natural course of EAE. The issues above are pertinent as we found that IRF-1 is expressed by glial cells in MS lesions, whereas other investigators reported that the levels of IRF-1 expression in peripheral immune cells of MS patients to be decreased compared to those in healthy individuals (Feng et al., 2002; Ren et al., 2011b).

We examined the CNS expression of IRF-1 in MOG_{35-55} induced EAE (Ren et al., 2011b). IRF-1 was detected in the areas of CNS inflammation and co-localized with the perivascular mononuclear cells as well as with microglia and oligodendrocytes. In contrast, no such expression was detected in the control mice. In an effort to separate the central (glial)

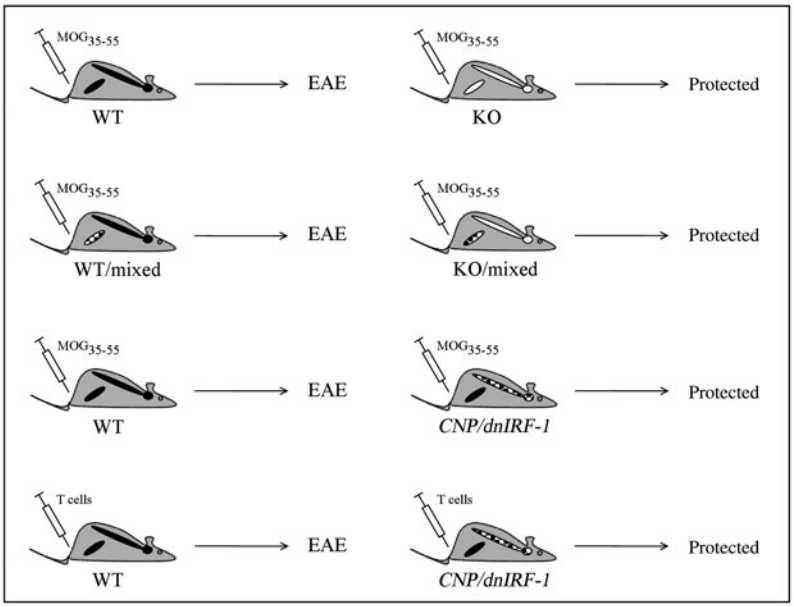

Figure 2 IRF-1 expression in oligodendrocyte-regulated EAE.
IRF-1 KO, compared to WT mice, were protected against active (immunization with MOG_{35-55}) EAE (first row). Bone-marrow chimera mice which lack IRF-1 expression in the CNS (KO/mixed), in contrast to mice which express it (WT/mixed), were also protected against active EAE (second row). Transgenic mice with suppressed IRF-1 signaling in oligodendrocytes (*CNP/dnIRF-1*) were protected against active as well as adoptive (T cell transfer) EAE (third and forth rows).

and peripheral immune effects of IRF-1, we generated bone-marrow chimera mice which differentially express IRF-1 in the CNS (Ren et al., 2010, 2011b). Four bone-marrow chimera mice were generated – WT/WT and KO/KO mice (WT and KO mice transplanted with identical bone-marrow cells), and WT/mixed and KO/mixed mice (WT and KO mice transplanted with a mixture of WT and KO bone-marrow cells at equal ratios). By design, the WT/mixed and the KO/mixed chimera mice had a comparable percentage of IRF-1-expressing T cells and CD4(+) cells in the periphery, but differed in their capacity to express IRF-1 in the CNS.

Immunization of WT/WT and KO/KO mice with MOG_{35-55} produced expected results; the former developed significant disease, whereas the latter were protected. WT/mixed mice also developed significant disease, which in terms of clinical severity and inflammatory demyelination, was comparable to the one observed in the WT/WT mice. In contrast, the KO/mixed mice were protected against EAE, displaying, pathologically, only minimal inflammatory demyelination and oligodendrocyte cell death (Figure 2). These results indicate that IRF-1 is expressed in the CNS and it regulates the severity of EAE independently of its expression in the peripheral immune system. In addition, inflammatory demyelination and oligodendrocyte cell death in EAE appear to be dependent on IRF-1 as well.

In order to further dissect the regulatory mechanisms related to IRF-1, we generated a transgenic mouse line with impaired IRF-1 signaling specifically in oligodendrocytes (*CNP/dnIRF-1* line on C57BL/6J background) (Ren et al., 2011a). As designed, *CNP/dnIRF-1* mice were phenotypically normal with the exception of their inability to upregulate the expression of IRF-1-dependent genes, such as *MHC class I* molecule and *Caspase 1*, in oligodendrocytes. The latter was achieved by transgenic expression of the dominant negative form of IRF-1 (dnIRF-1) in these cells. dnIRF-1 lacks the transcription activation domain of IRF-1 and has the capacity to bind genomic DNA at IRE-E without inducing a transcriptional response (Bouker et al., 2005). In effect, dnIRF-1 functions as a competitive inhibitor of IRF-1-dependent gene expression.

EAE experiments with *CNP/dnIRF-1* mice generated a number of new, and to some extent, unexpected findings. The primary result of these experiments was that the *CNP/dnRIF-1* mice, in contrast to the WT mice, were protected against EAE (Figure 2). Their disease induced by active immunization with MOG_{35-55} was significantly milder compared to WT mice, i.e., the transgenic mice never became paralyzed, and associated with a minimal inflammatory reaction in the CNS. Adoptive method of EAE induction was also employed and it yielded similar clinical results, i.e., transfer of activated MOG_{35-55}-specific T cells from immunized WT into naïve transgenic mice failed to induce severe disease. Pathologically, the inflammatory infiltrates in the *CNP/dnIRF-1* mice were mainly perivascular and did not invade the CNS parenchyma or the myelin sheaths. This was strikingly different from the diffuse inflammatory demyelination and axonal injury observed in the WT mice. In fact, very little oligodendrocyte cell death and axonal injury were detected in the *CNP/dnIRF-1* mice. In conclusion, suppression of IRF-1 signaling protects oligodendrocytes, which translates into protection against EAE and reduction of demyelination, and axonal injury. Implicitly, it also appears that IRF-1 utilizes a signaling mechanism, intrinsic to oligodendrocytes, which can affect both oligodendrocyte injury/death and the extent of CNS inflammation.

IRF-1, cell-mediated cytotoxicity, and pyroptosis

Oligodendrocyte protection studies imply the existence of a process which can link oligodendrocyte injury or death to the regulatory mechanisms of EAE. We, as well as others, have shown that IRF-1 regulates the expression of a number of genes involved in cell-mediated cytotoxicity, including MHC class I molecule, Fas, and TNF-αR (Agresti et al., 1998; Ren et al., 2011a). Transgenic mice lacking some of these receptors or their downstream adoptive molecules specifically in oligodendrocytes also appear to be protected against EAE (Hovelmeyer et al., 2005; McGuire et al., 2010). Oligodendrocyte apoptosis, assessed by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) positivity, was reported to be decreased in these studies as well. Therefore, increased oligodendrocyte resistance against inflammatory injury results in protection against EAE (Figure 1A,C). However, there is still a question of how do injured oligodendrocytes enhance inflammation. In addition, there is a theoretical conflict in associating oligodendrocyte apoptosis and inflammation in a causative relationship as by definition the former is a non-inflammatory form of cell death; occurrence of oligodendrocyte apoptosis during normal brain development is not associated with an inflammatory reaction (Fink and Cookson, 2005; Balabanov et al., 2006).

Interference of IRF-1 signaling with the mechanisms of pro-inflammatory cell death, aka pyroptosis (Greek: *pyro* – fire/fever, *ptosis* – falling, falling in fire), can be hypothesized. Pyroptosis is exclusively dependent on the presence of Caspase 1 expression in cells, and similar to apoptosis involves enzymatic digestion of the genomic DNA – the pyroptotic cells are also TUNEL positive – but unlike apoptosis, it would result in an inflammatory reaction (Bergsbaken et al., 2009) (Figure 2B). This is due to the ability of Caspase 1 to activate cytoplasmic IL-1β (Caspase 1, aka interleukin 1 beta-converting enzyme) and to create pores in the cell membrane, allowing leakage of cellular contents. Thus, pyroptosis can create a pro-inflammatory environment in the CNS, enriched with self-antigens and 'danger' signals, which can stimulate T cell chemotaxis and antigen presentation. As the induction of EAE is dependent on *de novo* antigen presentation in the CNS and Toll-like receptor signaling, one can consider that injured oligodendrocytes can indeed enhance the inflammatory process (Tompkins et al., 2002; Marta et al., 2008) (Figure 3). In contrast, suppression of the mechanisms of pyroptosis may diminish the inflammatory response in the CNS despite the presence of activated T cells in the periphery. Experimentally, overexpression of baculovirus p35 Caspase inhibitor in oligodendrocytes provides not only cell protection against cell death *in vitro* but also against EAE; Caspase 1 is also targeted by p35 (Hisahara et al., 2000).

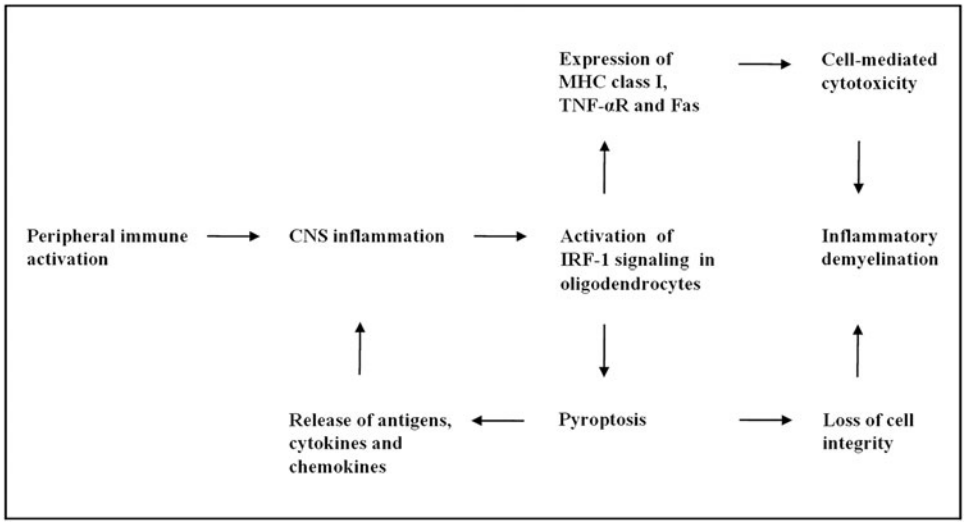

Figure 3 Model of IRF-1 regulation of inflammatory demyelination.
In response to CNS inflammation, oligodendrocytes upregulate IRF-1 expression and signaling. Induction of pyroptosis serves as a positive feedback for the inflammatory process. Oligodendrocyte death either by pyroptosis or cell-mediated cytotoxicity results in myelin destruction.

In the course of our studies, we demonstrated that IRF-1 positively regulates the expression of Caspase 1. We identified the presence of IRE in the Caspases 1 gene promoter and demonstrated its transcriptional significance in a number of promoter reporter assays and electrophoretic mobility shift assay (Wang et al., 2010; Ren et al., 2011b). In corroboration, we also showed that glial cells lacking IRF-1 cannot upregulate Caspase 1 expression upon stimulation with IFN-γ (Ren et al., 2011b). Most importantly, we demonstrated in our EAE experiments that KO/mixed and *CNP/dnIRF-1* mice did not express Caspase 1 in the CNS, including in the oligodendrocytes, a finding which correlated with the fact that these mice were protected against the disease. In contrast, WT, WT/WT, and WT/mixed mice significantly upregulated Caspase 1 expression in their oligodendrocytes. They developed severe EAE associated with significant perivascular and parenchymal inflammation (Ren et al., 2011a,b). Finally, increased oligodendrocyte expression of IRF-1 and Caspase 1 was detected at the leading edges active of MS lesions and not in the NAWM (Ming et al., 2002; Ren et al., 2011b).

Concluding remarks

There is a growing interest in developing a treatment strategy focused on oligodendrocyte and myelin protection in MS. One can appreciate the emergence of experimental approaches based on delivery of oligodendrocyte growth/trophic factors, receptor agonists, and neural stem cells to the CNS (Butzkueven et al., 2002; Linker et al., 2002; Mi et al., 2007; Martino et al., 2010). Commonly, such efforts are facing the enormous complexities of the disease pathogenesis and the pleiotropic nature of the potential therapeutic targets. In our opinion, successful development of an oligodendrocyte protective strategy is dependent on identification of a cell-specific mechanism with differential significance to injury or survival. Suppression of IRF-1 signaling, as described above, resulted in a dramatic protection against EAE without any appreciable adverse effects. Correspondingly, such suppression had no negative impact on oligodendrocyte development, but provided oligodendrocyte and axonal protection against injury. Perhaps, pharmaceutical targeting of IRF-1 or its function, e.g., IRF-1/Caspase 1 signaling, can be of clinical utility in controlling the disease activity in MS and the extent of CNS injury. Gene silencing of IRF-1 may be of use in pre-transplant manipulation of neuronal stem cells for the purpose of increasing their survival and reparative potential in MS lesions.

Virtually all transgenic manipulations of oligodendrocytes associated with successful protection against EAE have targeted the IFN-γ's STAT1-dependent signaling pathway (STAT1, IRF-1), its downstream gene targets (TNF-αR, Fas), and adoptive/associated functional molecules (Fas-associated protein with death domain, Caspases) (Hisahara et al., 2000; Hovelmeyer et al., 2005; Balabanov et al., 2007; McGuire et al., 2010; Ren et al., 2011a). Hypothetically, this signaling pathway may function as a common-end mechanism of oligodendrocyte injury and inflammatory demyelination. Further studies, however, are needed in this direction, specifically: (1) establishing whether the STAT1-dependent pathway is a default oligodendrocyte response to injury or a result of signaling dysbalance; (2) identification of negative regulators of this signaling pathway, which can be further explored *in vivo*; (3) examining for STAT-1-independent pathways in oligodendrocytes, as they may account for some of the observed cell protective effects; and (4) synergism with other transcription factors and signaling pathways. It will be also of clinical interest to investigate whether activation of IFN-γ's STAT1-dependent signaling pathway has any prognostic significance in MS or relationship to failure of therapy. In addition, there is a number of other important questions related to how oligodendrocyte response to IFN-γ or injury contribute

to the autoimmunity in MS, and whether there are peripheral markers that can be used for their elucidation.

In summary, IRF-1 is a master transcription factor that regulates oligodendrocyte injury and inflammatory demyelination. IRF-1 studies support the 'active' role of oligodendrocytes in CNS inflammation and underscore the need for further investigations of oligodendrocyte-dependent disease mechanisms. They also provide an important prospective on the pathogenesis of MS, as well as potential therapeutic targets of the disease.

Acknowledgments

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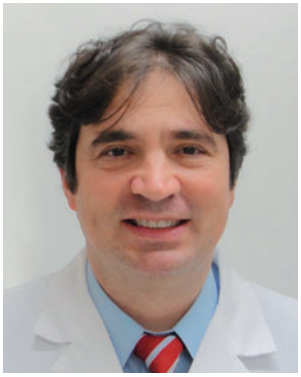

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