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Role of the innate immune system in the pathogenesis of multiple sclerosis

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INTRODUCTION

Being the earliest defense against pathogens, the innate immune system fights against infections and protects against self or innocuous antigens. Various cell types that compose the innate immune system share antigen recognition ability through their invariant receptors which do not undergo rearrangement and have no immunological memory. We might compare the components of the innate immune system not only to first line soldiers, but also to sentinels, who encounter the enemy and report to the “commanders”, the T and B lymphocytes, thus activating the adaptive immune response.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating autoimmune disease of the central nervous system (CNS) of unknown etiology and heterogeneous clinical symptoms & course (Weiner, 2004). Depending upon clinical presentation and course, MS is classified either as relapsing remitting (RR), primary progressive (PP) or secondary progressive (SP). About 87% of MS patients exhibit a RR course of disease (Weiner, 2008), characterized by acute attack (relapse) followed by partial or full recovery (remission) occurring at variable intervals (Debouverie et al., 2008). Of these RR-MS patients, about two-thirds transition to the secondary progressive phase where neurologic disability progresses in the absence of attacks (Runmarker and Andersen, 1993; Weiner, 2008). About 10% of MS patients have a primary progressive course manifested by progressive worsening from onset (Weiner, 2009).

Much has been done to understand the etiology of MS, with a major focus on the role of the adaptive immune system. It has been suggested that myelin-specific auto-reactive lymphocytes, mainly IFN- γ secreting T helper 1 (“Th1”) cells (Baker et al., 1991; Bettelli et al., 2004) and/or IL-17 producing “Th17” cells (Bettelli et al., 2008; Korn et al., 2007) are primed in periphery by unknown factors, after which they migrate to CNS, leading demyelination and axonal loss and subsequent neurological disability (Sospedra and Martin, 2005). Recent studies have suggested that the innate immune system also plays an important role both in the initiation and progression of MS by influencing the effector function of T and B cells (Weiner, 2008). The effector cells, in turn, express cytokines and activation markers that further activate innate immune cells (Monney et al., 2002). In this review, we will discuss the potential role of the innate immune system in the pathogenesis of MS and EAE (the murine

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model of MS); specifically, dendritic cells, microglial cells, natural killer cells, natural-killer T cells, mast cells and gamma-delta T cells.

DENDRITIC CELLS

Dendritic cells (DCs) are “professional antigen presenting cells” that play an important role in promoting activation and differentiation of naïve T cells. DCs are classified into different categories based on their surface markers. A widely accepted classification distinguishes human DCs into two categories: myeloid ($\text{Lin}^- \text{CD11c}^+$) and lymphoid/plasmacytoid ($\text{Lin}^- \text{CD11c}^{\text{dim}} \text{CD123}^+$) (Lipscomb and Masten, 2002; MacDonald et al., 2002). The interaction of DCs with T cells is crucial in determining T cell differentiation into either effector T cells (Th1, Th2 and Th17 cells) or regulatory T cells (natural Tregs and induced Tr1 cells) (Gilliet and Liu, 2002; Shortman and Heath, 2001). DCs can also affect NK cells function where they can either stimulate NK cell-mediated cytotoxicity (Fernandez et al., 1999) or “prime” NK responses toward viral and bacterial pathogens (Lucas et al., 2007). Myeloid dendritic cells (mDCs) can activate NK cells and selectively trigger the proliferation of the NK $\text{CD56}^{\text{bright}}$ cell subset (Vitale et al., 2004). Similarly, plasmacytoid dendritic cells (pDCs) can also interact with NK cells to stimulate their effector function and induce selective NK $\text{CD56}^{\text{bright}}$ cell expansion (Romagnani et al., 2005).

In EAE pathogenesis, several studies have suggested the involvement of DCs particularly, showing accumulation of these cells in CNS during inflammation (Bailey et al., 2007; Serafini et al., 2000), and in studies utilizing *in vitro* transfer models of activated antigen pulsed DCs (Dittel et al., 1999; Weir et al., 2002). These DCs activate encephalitogenic T cells and result in either induction of disease (Bailey et al., 2007; Dittel et al., 1999; Weir et al., 2002) or tolerance (Khouri et al., 1995; Xiao et al., 2004), depending upon the activation state of DCs and mechanism of antigen uptake (El Behi et al., 2005). DCs isolated from the CNS of R-EAE mice, induced by injection of PLP_{178–191}, are the most potent stimulators of naïve T cells or helper T cells in the presence or absence of endogenous peptide, suggesting the possible contribution of DCs in epitope spreading (spreading T cell reactivity to antigens in addition to initial disease inducing epitope), in the CNS during the disease (McMahon et al., 2005; Miller et al., 2007).

In humans, there are studies demonstrating altered DC phenotype/function in peripheral blood. In MS patients, DCs have an activated phenotype with an increased expression of activation markers and an aberrant secretion of proinflammatory cytokines. mDC-mediated inflammation is more pronounced in SP-MS patients than in RR-MS patients (Karni et al., 2006). These DCs show increased expression of the activation markers CD40 and CD80 in SP and RR patients whereas a decreased expression of programmed death ligand-1 (PDL1), an immunoregulatory molecule, was observed only in progressive patients. In the same study, mDCs isolated from SP-MS patients showed an enhanced production of IL-12 in response to IFN- γ and LPS (Karni et al., 2006). This activated phenotype of DCs in both RR- and SP-MS patients is accompanied by an enhanced pro-inflammatory T cell response as defined by increased secretion of TNF- α and IFN- γ . Similarly, it has been shown that monocyte-derived DCs differentiated from MS patients, secrete more pro-inflammatory cytokines such as IFN- γ , TNF- α (Th-1 bias cytokine) (Huang et al., 1999), IL-6 (Huang et al., 1999) and IL-23 (Th-17 bias cytokine) (Vaknin-Dembinsky et al., 2006; Vaknin-Dembinsky et al., 2008).

In addition to promoting MS pathology by secretion of pro-inflammatory cytokines, DCs also secrete the glycoprotein osteopontin, which is involved in chemotaxis, activation and differentiation of immune cells. Increased expression of osteopontin has been reported in brain lesions during EAE (Hur et al., 2007), as well as in DCs isolated from mice with EAE and from MS patients, which in turn may be related to skewed differentiation of Th1 and Th17 cells during the disease (Hur et al., 2007; Murugaiyan et al., 2008).

As discussed previously, plasmacytoid DCs (pDCs) represent another subset of DCs involved in both innate and adaptive immunity including protection from microbial infections and the generation of immunoregulatory immune responses (Siegal et al., 1999). pDCs isolated from peripheral blood of MS patients exhibit an altered phenotype with decreased or delayed expression of the activation markers CD86, CD83, CD40 and 4-IBBL, in addition to their altered functionality in terms of T cell proliferation and generation of regulatory T cells (Stasiolek et al., 2006).

Taken together, these studies suggest that DCs are important in promoting pro-inflammatory T cell responses in MS and are also linked to determine the RR and SP disease phases. Based on these observations, a number of DC-based therapies, both antigen-specific and non-specific, have been tested in EAE and other animal models with varied success. Multiple approaches have been used to modify DCs to treat EAE including the following: **a)** injection of either mature DCs (Zhang et al., 2002) or of IFN- γ treated DCs (Xiao et al., 2004) or of DCs treated with an autoantigenic peptide and matured in the presence of TNF- α (Menges et al., 2002), suppressed clinical severity of disease and inflammation in CNS; **b)** transfer of DCs transduced with SOCS-3 (suppressor of cytokine signaling inhibitor), could inhibit EAE by promotion of IL-10 and through inhibition of IL-12, IFN- γ and IL-23 secretion (Li et al., 2006); **c)** treatment of mice with *in vitro* stem cell derived DCs expressing death receptors like TRAIL or regulatory molecules like PDL-1 and treated with auto-antigens could prevent EAE (Hirata et al., 2005); **d)** Mitomycin C-treated DCs loaded with MBP (Terness et al., 2008) could inhibit the induction of disease or reduce severity of disease and extent of CNS inflammation.

MICROGLIAL CELLS/ MACROPHAGES

Microglial cells comprise 10–20% of glial cells and are the most common immune cells in the CNS. Microglial cells are considered resident macrophages of the nervous system, being involved in phagocytosis, antigen presentation and production of cytokines (Benveniste, 1997). Microglial cells are rapidly activated in response to injury, neuro-degeneration, infection, tumors and inflammation. Until now, there are no unique markers distinguishing microglial cells from blood-derived macrophages in the CNS.

Microglial/macrophage cell activation contributes to MS and EAE pathology through antigen presentation and secretion of pro-inflammatory cytokines (Benveniste, 1997). Persistent activation of microglial cells has also been observed in the chronic phase of relapsing-remitting EAE and a correlation has been observed between activated microglial cells and loss of neuronal synapses (Rasmussen et al., 2007). Similarly, profound activation of microglial cells has been reported in MS, more frequently in progressive than in RR patients and specifically in association with inflammation of white matter (Kutzelnigg et al., 2005).

The role of microglial cells in antigen presentation is based on their expression of various molecules involved in antigen presentation such as MHC class II and costimulatory molecules CD83 and CD40 which are essential for interaction with effector T cells and B cells (Aravalli et al., 2007; Benveniste, 1997; Raivich and Banati, 2004). Microglial cells express all known TLRs (TLR 1–9) and expression of these receptors is pivotal for generation of neuroimmune responses (Aravalli et al., 2007; Jack et al., 2007; Lee and Lee, 2002). Several studies have shown the importance of TLRs in MS pathology. Expression of these receptors is increased in brain lesions in EAE and in MS (Andersson et al., 2008; Bsibsi et al., 2002). Induction of several models of EAE requires mycobacterium containing CFA (exhibiting PAMPs, Pathogen Associated Molecular Patterns, a ligand for TLRs). Mice that lack MyD88 (an important downstream molecule in TLR signaling), are resistant to EAE (Marta et al., 2008; Marta et al., 2009; Prinz et al., 2006).

In addition, macrophages and microglial cells are involved in demyelination and phagocytosis of the degraded myelin (Bauer et al., 1994), which results in augmentation of the expression of myeloperoxidases (Gray et al., 2008). The expression of these enzymes and reactive oxygen species cause neuronal damage (Benveniste, 1997; Raivich and Banati, 2004). The contribution of monocytic cells in epitope spreading is demonstrated by Theiler's virus infection model of EAE where virus-specific T cell response results in activation and recruitment of CNS resident APCs, which actively ingest and present myelin antigens to auto-reactive T cells leading to induction of auto-immune responses against myelin (Katz-Levy et al., 2000).

Microglial cells can also promote inflammation by secretion of molecules such as TWEAK (TNF like weak inducer of apoptosis), which is an inflammatory cytokine that can trigger various pathways including proliferation, angiogenesis, inflammation and induction of cell death. The expression of TWEAK is upregulated in MS lesions by the cytokine milieu in CNS (Serafini et al., 2008). TWEAK expressing microglial cells are involved in extensive loss of myelin, neuronal damage and vascular abnormalities in cortical lesions. Microglial cells also express IL-17 and the receptor for IL-17, which may worsen EAE by increasing production of IL-6, macrophage inflammatory proteins, nitric oxide, adhesion molecules and neurotropic factors by these cells in an autocrine manner (Kawanokuchi et al., 2008).

Although, the above-mentioned studies emphasize the negative contribution of microglial/macrophage cells in MS or EAE pathology, there is evidence indicating a potential beneficial role of these cells. For example, microglial cells are capable of secreting anti-inflammatory cytokines (IL-10 and TGF- β) depending upon the inflammatory milieu in CNS (Napoli and Neumann, 2009a; Napoli and Neumann, 2009b). Microglial cells are also capable of secreting neurotrophic factors such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1) and neurotrophin 3 (NT3) and thus may contribute in promoting neurogenesis (Napoli and Neumann, 2009b). Along a similar line, TREM2 (Triggering receptor expressed on myeloid cells-2), is a microglial/macrophage specific membrane-bound receptor involved in reducing inflammation and promoting phagocytosis (Piccio et al., 2007). The soluble form of TREM2 is increased in the CSF of both progressive and RRMS patients and might be responsible for inhibiting regulatory function of surface-bound TREM-2 on myeloid cells (Piccio et al., 2008). Thus, during disease, microglial cells may act as "double edged sword" performing both neuro-destructive and neuro-protective functions (Aravalli et al., 2007). Switching their function from neuro-destructive to neuro-protective may be beneficial in preventing chronic demyelination and axonal loss and thus preventing progression or relapse of disease (Weiner, 2008).

NATURAL KILLER CELLS

Natural Killer (NK) cells contribute to both effector and regulatory functions of the innate immune system via their cytotoxic activity mainly against viral infected cells or tumor cells and through their ability to secrete different cytokines (Moretta et al., 2008). These two functions are differently implemented by the two main subsets of NK cells that have been identified in the human. The CD56^{dim} NK cell subset has primarily cytotoxic function, whereas the CD56^{bright} NK cell subset secretes abundant quantities of anti-inflammatory cytokines which perform "regulatory" function (Cooper et al., 2001a). According to another classification, based on their cytokine pattern, NK cells can be distinguished into NK1 (secreting IFN- γ and IL-10) and NK2 (secreting IL-5 and IL-13) (Peritt et al., 1998). Several reports have highlighted the importance of NK-DC interactions during the early stages of the immune responses (Della Chiesa et al., 2003; Ferlazzo et al., 2002; Fernandez et al., 1999; Gerosa et al., 2002; Moretta et al., 2006; Walzer et al., 2005). NK cells can stimulate DC maturation (Vitale et al., 2005) and increase the amount of DC-produced cytokines (Della

Chiesa et al., 2006; Piccioli et al., 2002). Moreover, NK cells can mediate cytotoxicity against immature DCs, whereas mature DCs are protected (Piccioli et al., 2002; Wilson et al., 1999).

NK cells can induce the surface expression of IL-15 in mDCs, which in turn is important in CD8⁺ T cell activation and NK cells can also interact with Foxp3⁺ regulatory T cells (Tregs). Tregs can inhibit NK cell proliferation and effector function, whereas NK cells can inhibit the expression of the Foxp3 marker (in humans and mice) and the peripheral conversion of CD4⁺CD25⁺Foxp3⁺ into Tregs (Zimmer et al., 2008).

Although the involvement of NK cells in the pathophysiology of autoimmune diseases has been studied for many years (Matsumoto et al., 1998; Zhang et al., 1997), the actual role of NK cells in CNS autoimmunity is still not clear (Morandi et al., 2008). *In vitro* NK cells show cytotoxic activity towards oligodendrocytes and other glial cells, such as astrocytes and microglial cells (figure 2) during inflammation. This cytotoxic interaction is mediated between the activating NKG2D receptor, expressed by NK cells, and its ligands, such as MHC Class I chain-related molecules A and B (MICA/B) and UL16-binding proteins 1, 2 and 3 (ULBPs) expressed by oligodendrocytes and fetal astrocytes (Saikali et al., 2007), and also between other molecules, such as lymphocyte function-associated antigen 1 receptors (LFA-1) and CD54 on astrocytes (Darlington et al., 2008). These interactions result in a caspase-dependent cleavage of astrocyte intermediate filaments (Darlington et al., 2008). NK cells can kill microglial cells by release of perforin by interactions involving NKG2D and NKP46 receptors on NK cells (Lunemann et al., 2008).

NK cells may also play a role in CNS protection and repair, as these cells have the ability to produce neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) as reported in mice with EAE (Hammarberg et al., 2000). Studies of the role of NK cells in EAE have shown contradictory results: Zhang (Zhang et al., 1997), Matsumoto (Matsumoto et al., 1998), Xu (Xu et al., 2005), Galazka (Galazka et al., 2007) and Huang (Huang et al., 2006) described a beneficial role of NK cells in mouse or rat EAE. On the contrary, Winckler-Pickett (Winkler-Pickett et al., 2008) observed a milder form of EAE in NK-depleted mice and Vollmer (Vollmer et al., 2005) demonstrated a worsening effect of IL-21 on EAE which was dependent on the presence of NK cells. These discrepancies may be due to the heterogeneity of NK cells, which are composed of distinct subsets of NK cells performing different functions and thus having different influences on the immune response.

The absence of common markers, for instance CD56, among human and mouse NK cells makes it complicated to translate mouse EAE into human MS biology. Studies in humans suggest a more beneficial effect of various subsets of NK cells in multiple sclerosis. NK cells are present in demyelinating lesions of patients with MS (Traugott, 1985). A decreased cytotoxic activity of circulating NK cells has been described in patients with MS during clinical relapses (Kastrukoff et al., 2003; Kastrukoff et al., 1998). An increase of the “NK2” NK cell subpopulation was observed in MS patients in remission compared to patients in relapse suggesting that the NK2 subpopulation may have a beneficial role in maintaining the remission phase (Takahashi et al., 2001). The same subset of NK cells seemed to negatively regulate the activation of antigen-specific autoreactive T cells (Takahashi et al., 2004). Recently, another subpopulation of NK cells characterized as CD8^{dim}CD56⁺CD3⁺CD4⁺ have been shown to be reduced in untreated subjects with MS as well as clinical isolated syndrome (Ebers et al.) (De Jager et al., 2008).

Many studies have suggested a beneficial effect of the CD56^{bright} NK cell subset in MS patients during treatment, as their number is increased by immunomodulatory and immunosuppressant therapies, such as daclizumab (Bielekova et al., 2006), interferon- β (Saraste et al., 2007) and cyclophosphamide (Rinaldi, 2007). In the study of daclizumab-treated patients, the increased

number of CD56^{bright} NK cells correlated with a decreased number of Gad⁺ lesions on MRI (Bielekova et al., 2006). The role of CD56^{bright} NK cells in modulating the autoimmune response is likely mediated by their cytokine secretion pattern (Cooper et al., 2001b) but can also be mediated by their cytotoxic properties. In the above-mentioned study on daclizumab, *in vitro* cultures of NK cells with daclizumab showed that inhibition of T cell proliferation and T cell suppression was completely abrogated by the removal of the NK cells from total peripheral cells (Bielekova et al., 2006). The increased ability of total NK cells from daclizumab-treated patients to kill activated T cells *in vitro* was correlated with an increase of blood CD56^{bright} NK cells and a decreased number of circulating CD4⁺ and CD8⁺ T cells in the MS patients undergoing therapy. Another study showed that CD56^{bright} NK cells may be involved in the well-known decrease of MS relapse rate during pregnancy, as an increase of this subset and a decrease of CD56^{dim} NK cells was observed in pregnant MS patients (Airas et al., 2008). Taken together, these data show that NK cells, and especially certain subpopulations, may play a regulatory role in multiple sclerosis by modulating the activation and the survival of autoreactive T cells, microglial cells and astrocytes through cytokine production and direct cytotoxicity.

MAST CELLS

Mast cells are a crucial component of allergic responses through the release of large quantities of histamine from their cytoplasmic granules upon binding of IgE to their FcR1 receptor expressed on the surface. Their granules contain several molecules including histamine, that are involved in inflammatory and antimicrobial response and can secrete cytokines and other mediators through mechanisms independent from degranulation. Thus, their involvement in the immune response is not limited to allergy. Through these secretory molecules, they influence different cell types of the innate and acquired immune system including DCs, neutrophils, T and B lymphocytes. They can activate lymphocytes and also drive T cell differentiation into a Th1, Th2 and also Th17 phenotype through the secretion of cytokines such as IL-4, IL-10, IL-13, TGF- β , TNF- α and IL-6 (Christy and Brown, 2007; Malaviya et al., 1996; Stelekati et al., 2007).

Mast cells are present in the normal brain in the parenchyma and at the blood-brain barrier (Silver et al., 1996) and can interact with myelin (Medic et al., 2008; Theoharides et al., 1993). *In vitro*, myelin proteins stimulate mast cell degranulation and release of proteases, which in turn degrade myelin basic protein (MBP) (Johnson et al., 1988). In rats, mast cells can adhere to myelin and release the content of their granules through a mechanism that involves the scavenger receptors A expressed by mast cells (Medic et al., 2008). Furthermore, these cells can phagocytose myelin vesicles and can interact with oligodendrocytes (Medic et al., 2008). Mice that lack mast cells develop a milder form of EAE (Secor et al., 2000) and show reduced autoreactive T cell responses (Gregory et al., 2005). Fc receptors expressed on the surface of these mast cells also contribute to EAE severity (Robbie-Ryan et al., 2003). However, recent studies have described a severe EAE course in mast cell-deficient mice (Bennett et al., 2009). In addition, interactions between mast cells and other cells of the immune system in the secondary lymphoid organs might also contribute to disease severity in EAE (Tanzola et al., 2003).

In MS, histopathological analysis showed an accumulation of mast cells in MS plaques and normal appearing white matter (Olsson, 1974; Toms et al., 1990). In addition, the mast cell specific enzyme, tryptase, was elevated in the cerebrospinal fluid (CSF) of MS patients (Rozniecki et al., 1995), along with other mast-cell specific genes in MS plaques (Lock et al., 2002). In conclusion, mast cells may play multiple roles in MS pathogenesis. They influence immune cells both in periphery and in CNS itself. These observations make mast cells a potential target for designing therapeutic strategy against MS. The use of anti-histaminic drug,

hydroxyzine (Logothetis et al., 2005), or flavonoid luteolin which can block the activation of mast cells by MBP and subsequent stimulation of T cells by them (Kempuraj et al., 2008; Theoharides et al., 2008), may be of benefit in MS.

INVARIANT NK T CELLS

NK-T cells are a particular subset of T cells that share properties of NK cells and T cells and that recognize lipid antigen presented by CD1d, a lipid monomorphic glycoprotein, by a T cell receptor of limited diversity (Tupin and Kronenberg, 2006). These cells can be either CD4⁺ or CD8⁺ or can be CD4⁻ CD8⁻. These cells are considered part of the innate rather than adaptive immune system cells due to: 1) their limited TCR diversity; and 2) because these cells affect cytotoxicity and cytokine production without a need for cell division/differentiation similar to other cells of innate immune system. These cells are known to play an important role in fighting infection as suggested by various mouse knockout models (Tupin et al., 2008; Tyznik et al., 2008). NK-T cells are capable of producing cytokines such as IFN- γ , IL-10, IL-4, IL-13 and TGF- β , all implicated in prevention of autoimmunity (Araki et al., 2003; El Behi et al., 2005; Furlan et al., 2003; Illes et al., 2000). IL-10 produced by NK-T cells have shown to be essential for induction of regulatory T cells (Sonoda et al., 2001). In addition to their role in host defense, NK-T cells are also linked to inflammation and autoimmune diseases. For instance, over expression of invariant TCR by NK-T cells in NOD mice leads to protection from EAE mediated by decreased IFN- γ production (Mars et al., 2002). In addition, activation of NK-T cells using α -GalCer can also modulate disease by induction of Th2 cytokines (Mars et al., 2002; Pal et al., 2001; Singh et al., 2001). In contrast, other reports suggest that protection under these conditions might be mediated via secretion of Th1 cytokines like IFN- γ (Furlan et al., 2003). During MS, the number of total NK-T cells decreases with a prominent decrease of CD4⁻ cell population and a modest decrease of CD4⁺ NK-T cell subpopulation (Araki et al., 2003; Illes et al., 2000). Long term cell lines derived from NK-T cells isolated from MS, showed an enhanced secretion of IL-4 and no differences in IFN- γ secretion: this “Th2 bias” of NK-T cells might be involved in mediating the remission phase of MS, highlighting the “immunoregulatory” role of these cells in MS (Araki et al., 2003).

GAMMA-DELTA T CELLS

Gamma-delta T cells are a unique subset of lymphocytes that recognize non-MHC restricted antigens through invariant gamma-delta T-cell receptors. They are present in abundance in epithelium, particularly intestinal epithelium, rather than in peripheral blood (Hayday, 2000). A subset of gamma-delta T cells that express Fc-gamma receptor, CD16, has cytotoxic properties (Angelini et al., 2004). The exact role of gamma-delta T cells in MS pathology is not clear. In EAE, they have been shown to play a diverse role. They can either aggravate EAE (Odyniec et al., 2004; Olive, 1995; Rajan et al., 1996; Rajan et al., 1998; Spahn et al., 1999), or show a protective effect (Kobayashi et al., 1997; Ponomarev and Dittel, 2005; Ponomarev et al., 2004), or may show no effect on disease (Matsumoto et al., 1998). In MS patients, several groups have reported an increase in gamma-delta T cells in the CSF (Mix et al., 1990; Shimonkevitz et al., 1993), which correlates with their increased number in peripheral blood (Stinissen et al., 1995). Importantly, the increased number of gamma-delta T cells was identified in a group of MS patients with high MRI activity (Rinaldi et al., 2006). Another study showed expansion of CD16⁺ cytotoxic gamma-delta T cells in MS patients mainly during the progressive phase of disease (Chen and Freedman, 2008). Gamma-delta T cells are present in MS lesions (Selmaj et al., 1991), and are expanded by glial cells (Freedman et al., 1997b). They may lyse oligodendrocytes (Freedman et al., 1991), through a mechanism that involves either heat-shock proteins expressed by oligodendrocytes (Freedman et al., 1997a), or release of perforin or interaction between Fas and Fas ligand (Zeine et al., 1998), or via NKGD2-ligand interaction (Saikali et al., 2007). In conclusion, the gamma-delta T cell population increases

in MS patients with “active” or progressive disease, and might contribute to disease pathology by exerting a direct cytotoxic effect on oligodendrocytes.

In summary, cells of the innate immune system can act in either a beneficial or detrimental fashion in MS. On one hand, they can prevent autoimmunity by differentiation of regulatory T cells and by secretion of neurotrophic growth factors. On the other hand, the innate immune system can play an immuno-pathogenic role by promoting the differentiation of Th1 and Th17 cells which drive acute inflammatory events associated with relapses in MS (figure 1). Furthermore, the progressive phase of MS is now believed to be mediated by innate immune system as reflected by their activated phenotype in periphery which might be directly responsible for neurodegenerative changes in secondary progressive MS (figure 2). Until now, there are no specific therapies to target innate immune cells in MS. As the role of innate immune system in MS becomes better defined, it will be possible to design therapy to transform immuno-pathogenic innate immune cells to a more immuno-regulatory innate immune cells.

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Figure 1.

Potential contribution of cytokines secreted by innate immune cells in MS and their role in T cell differentiation: effector or regulatory T cells. Inflammatory cytokines (in red) secreted by innate immune cells lead to differentiation of effector T cell populations such as Th1, Th2 and Th17 involved either in mediating inflammation or in immunomodulation. Whereas anti-inflammatory cytokines (in green) secreted by innate immune cells play an important role in induction of regulatory T cells that are capable of mediating tolerogenic function during disease.