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Review article

Abnormal Tr1 differentiation in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). In the recent years, accumulating evidence has supported an immunosuppressive role for regulatory T cells (Tregs). Most studies in the context of autoimmunity have focused on the defects of the $CD4^+CD25^{high}$ Tregs. However, we recently demonstrated an altered function of Tr1 Treg cells in MS, characterized by a lack of IL-10 secretion. Therefore, several major regulatory T cell defects are involved in human autoimmune disease. Hence, the induction of Tregs or the stimulation of Treg activity may be beneficial for the treatment of such diseases.
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Keywords: Multiple sclerosis; Tr1 regulatory T cells; IL-10; CD46

Contents

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1. Introduction

Despite advances in the understanding of the mechanisms regulating T cell activation, T cell-mediated autoimmune diseases are still not well understood. Among them, multiple sclerosis (MS) is a complex genetic disease with inflammation in the central nervous system (CNS) white matter mediated by activated autoreactive lymphocytes (Feldmann and Steinman, 2005; Hafler and De Jager, 2005; Hafler et al., 2005; Hohlfeld and Wekerle, 2004). Once in the CNS, these autoreactive T cells target the myelin basic protein on the myelin sheath, and recruit more inflammatory immune cells to the site of attack (Bruck, 2005; Liu et al., 2006; McQualter and Bernard, 2007). The pathology of the inflammatory reaction is consistent with a T cell-mediated immune response, leading to tissue damage through activated macrophages and microglia. This repeated inflammation and subsequent demyelination will then instigate nerve impulses to be slowed or stopped, causing the symptoms of MS. Therefore, the understanding of the factors controlling T cell activation, inflammation and migration within the brain is of crucial importance (Adorini, 2004; Hohlfeld and Wekerle, 2004). Worldwide, MS may affect 2.5 million individuals including 400,000 subjects in the US, and 80,000 individuals in the UK and it is the most common disease affecting young adults. Hence, new approaches need to be developed in treating this disease.

In the recent years, the characterization of regulatory T cells (Tregs) and of their role in controlling the immune response has been highlighted. Indeed, the loss of Treg function seems to be a critical factor in the pathogenesis of human autoimmune diseases (Kretschmer et al., 2006; Paust and Cantor, 2005; Wraith et al., 2004). Several classes of Tregs have now been identified, including the naturally occurring $CD4^+CD25^{high}$ Tregs, as well as induced Tregs such as Tr1 and Th3 cells. Most studies of these cells in the context of autoimmunity have focused on the defects of the $CD4^+CD25^{high}$ Tregs. However, we also recently demonstrated an altered function of Tr1 regulatory T cells in MS, characterized by a lack of IL-10 secretion. Therefore, several major regulatory T cell defects that encompass the various sorts of Tregs are involved in human autoimmune diseases. This suggests that therapies aiming at enhancing or inducing Treg responses might be beneficial for such diseases.

2. Regulatory T cells and multiple sclerosis (MS)

In the past years, a resurgence of interest in regulatory T cells has emerged. Such T cells have been shown to regulate the immune response by turning off the signals initiated during the immune response. A variety of lymphocyte populations with suppressive capabilities have been reported in both animals and humans. Shimon Sakaguchi first described Tregs as the major contributors in controlling autoreactive T cells and maintaining a state of peripheral tolerance to a range of self-antigens (Sakaguchi et al., 1985, 1995). An early observation on suppressive activity that was lessened in patients with MS was published in 1986 (Antel et al., 1986). The absence or depletion of Tregs cells leads to autoimmune destruction of a wide range of target organs (Fontenot et al., 2003; Hori et al., 2003; Khattri et al., 2003).

2.1. $CD4^+CD25^{high}$ regulatory T cells

2.1.1. Characterization

$CD4^+CD25^{high}$ regulatory T cells contribute to the maintenance of peripheral tolerance by active suppression and require cell contact *in vitro* to exert their negative regulation. These cells were initially characterized in mice by expression of CD25 on $CD4^+$ T cells (Sakaguchi et al., 1995), and the expression of FoxP3 transcription factor is crucial to their development and function (Hori et al., 2003; Khattri et al., 2003). Several groups demonstrated that Tregs also exist in humans and that they are very similar in phenotype and function to their murine counterparts (Baecher-Allan et al., 2001; Dieckmann et al., 2001; Jonuleit et al., 2001; Stephens et al., 2001; Taams et al., 2001; Taylor et al., 2001). However, while CD25 is a useful marker to identify murine Tregs, only high CD25 expression should be considered as Tregs in human, as intermediate CD25 expressing T cells do not exhibit suppressive activity (Baecher-Allan et al., 2001, 2003; Roncador et al., 2005). They also expressed FoxP3, although again activated human T cells also express low amounts of FoxP3 albeit in lower amounts than Tregs (Roncador et al., 2005; Walker et al., 2003). They are anergic when stimulated by T cell receptor (TCR) cross-linking *in vitro*, and suppress T cell activation in a non-HLA-restricted, contact-dependent manner. IL-2 signaling is required for maintaining the homeostasis of Treg cells *in vivo* (Fontenot et al., 2005; Maloy and Powrie, 2005). Additional phenotypic characterizations include CD62L expression that is downregulated on effector T cells, no expression of CCR7 (Hoffmann et al., 2004; Noma et al., 2005), the exclusion of cells expressing the early activation marker CD69 (Gray et al., 2003; McNeill et al., 2007), and high-level expression of glucocorticoid-induced TNFR family-related gene/protein (GITR) (Ono et al., 2006). Finally, the expression of E3 ubiquitin ligase, GRAIL, is upregulated in $CD4^+CD25^+$ Tregs, and its forced expression induces a regulatory phenotype (Mackenzie et al., 2007).

2.1.2. $CD4^+CD25^+$ T cells in MS

A role of these $CD4^+CD25^{high}$ regulatory T cells has first been shown in regulating autoimmune diseases in animal models, including EAE (Kohm et al., 2002; Nishibori et al., 2004). In MS patients, the levels of circulating $CD4^+CD25^+$ T cells and $CD4^+CD25^{high}$ Treg cells are not altered (Putheti et al., 2004). However, we and others have reported a decrease of $CD4^+CD25^{high}$ regulatory T cell function in patients with MS (Haas et al., 2005; Huan et al., 2005; Viglietta et al., 2004). Indeed, a significant decrease in the suppressive activity of $CD4^+CD25^{high}$ regulatory T cells from peripheral blood of patients with MS as compared with healthy donors was observed (Viglietta et al., 2004). Interestingly, only patients in the relapsing–remitting phase exhibit impaired Treg function, characterized by a reduction in proliferation and interferon-gamma production of $CD4^+CD25^-$ responder T cells (Venken et al., 2006). Secondary progressive patients have normal $CD4^+CD25^+$ Tregs. Furthermore, consistently with their suppressive capacity, $CD4^+CD25^+$ Tregs from secondary progressive MS patients have normal levels of FoxP3 expression while FoxP3 expression was decreased in relapsing–remitting MS patients.

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