ELSEVIER

Journal of Neuroimmunology 191 (2007) 26–38

Journal of Neuroimmunology

www.elsevier.com/locate/jneuroim

Review article

Treating autoimmune demyelination by augmenting lymphocyte apoptosis in the central nervous system

Michael P. Pender *

Neuroimmunology Research Centre, School of Medicine, The University of Queensland, Australia

Received 29 August 2007; accepted 7 September 2007

Abstract

The elimination of autoreactive T cells from the central nervous system (CNS) by apoptosis plays an important role in switching off autoimmune attack. B-cell apoptosis in the CNS probably also has a key role in downregulating autoimmunity. Augmenting lymphocyte apoptosis in the CNS is a potential strategy for treating autoimmune CNS diseases such as multiple sclerosis. These strategies involve modulation of the physiological pro-apoptotic and anti-apoptotic pathways that control lymphocyte fate in the CNS. In the case of T cells, apoptosis can be augmented by enhancing activation-induced T-cell apoptosis through the CD95 (Fas) pathway and by inhibiting costimulation-induced anti-apoptotic pathways mediated through BCL-2 and BCL-X_L.

Keywords: Multiple sclerosis; Experimental autoimmune encephalomyelitis; T cell; B cell; CD95; BCL-2

Contents

* Department of Medicine, Clinical Sciences Building, Royal Brisbane & Women's Hospital, Queensland 4029, Australia. Tel.: +61 7 33655218; fax: +61 7 33655462.
E-mail address: m.hawes@uq.edu.au.

0165-5728/$ - see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneuroim.2007.09.015

1. Introduction

Normal individuals have T lymphocytes capable of reacting to central nervous system (CNS) antigens such as myelin basic protein (MBP) (Martin et al., 1990). Given the high level of cross-reactivity of T cells (Mason, 1998), it is likely that these autoreactive T cells are often primed by exposure to cross-reacting environmental antigens. Indeed it has been shown that viral and bacterial peptides can activate myelin-reactive human T cells (Wucherpfennig and Strominger, 1995; Hemmer et al., 1997). Furthermore, normal healthy subjects experience surges of increased frequencies of circulating myelin-reactive T cells that might be driven by cross-reactive environmental antigens (Pender et al., 2000). Such activated myelin-reactive T cells would be expected to enter the CNS in healthy individuals, because activated T cells of any specificity, including autoreactive T cells, enter the normal CNS parenchyma (Wekerle et al., 1986; Hickey et al., 1991). If CNS-reactive T cells survive in the CNS, they have the potential to attack the CNS, either directly or through the recruitment of other inflammatory cells, and thus lead to CNS damage such as demyelination. Therefore, the physiological control of auto-reactive T cells in the CNS is likely to have an important role in preventing the development of autoimmune CNS disorders such as multiple sclerosis (MS) (Pender, 1998). T-cell apoptosis in the CNS is an important mechanism for controlling autoimmune attack on the CNS (Pender et al., 1991, 1992; Schmied et al., 1993; Tabi et al., 1994, 1995; Gold et al., 1997; Pender and Rist, 2001). B-cell apoptosis in the CNS may also be important in terminating autoimmune attack on the CNS (White et al., 2000). Thus one potential therapeutic approach for treating and preventing autoimmune CNS diseases such as MS is to augment the apoptotic elimination of autoreactive T cells and B cells in the CNS. This review will focus on the regulation of neuroinflammation by lymphocyte apoptosis in the CNS.

2. Role of lymphocyte apoptosis in the CNS

T-cell apoptosis in the CNS has been studied mainly in experimental autoimmune encephalomyelitis (EAE), a T-cell-mediated inflammatory demyelinating disease of the CNS that is widely studied as a model of MS. T-cell apoptosis occurs in the CNS in acute EAE and plays an important role in the spontaneous recovery from disease (Pender et al., 1991, 1992; Schmied et al., 1993; Tabi et al., 1994, 1995; McCombe et al., 1996a; Bauer et al., 1998). The main site of T-cell apoptosis is the CNS parenchyma rather than the perivascular space or meninges (Schmied et al., 1993; Bauer et al., 1998). The apoptotic T cells are phagocytosed by macrophages, microglia, astrocytes and oligodendrocytes (Nguyen and Pender, 1998; Magnus et al., 2002). It should be noted that other inflammatory cells, such as macrophages and microglia (Nguyen et al., 1994, 1997; White et al., 1998a; Kohji and Matsumoto, 2000) and B lymphocytes (White et al., 2000), also undergo apoptosis in the CNS in acute EAE. To study T-cell apoptosis in the CNS, it is therefore essential to demonstrate apoptosis of cells expressing T-cell markers rather than simply to demonstrate apoptosis in an unlabelled inflammatory cell infiltrate.

An important question concerns the antigen specificity of the T cells undergoing apoptosis in the CNS, as this is relevant to both the significance and mechanisms of T-cell apoptosis (Pender and Rist, 2001). It is clear that encephalitogenic T cells are rapidly eliminated from the CNS by apoptosis during spontaneous recovery from acute EAE (Tabi et al., 1994, 1995; McCombe et al., 1996a; Bauer et al., 1998), but there is controversy regarding the selectivity of the process for CNS-reactive T cells. One study found that $V\beta8.2^+$ MBP-specific T cells were selectively eliminated from the CNS by apoptosis in rats recovering from EAE induced by the passive transfer of an encephalitogenic $V\beta8.2^+$ MBP-specific T-cell clone, whereas T cells specific for the non-CNS antigen ovalbumin survived in the CNS and recirculated to the peripheral lymphoid organs (Tabi et al., 1994, 1995). This study could not exclude the possibility that some ovalbumin-reactive T cells also underwent apoptosis in the CNS. Using T cells carrying a specific genetic marker, Bauer et al. (1998) demonstrated that ovalbumin-specific T cells and MBP-specific T cells both undergo apoptosis in the CNS in EAE. They concluded that T-cell apoptosis occurs in a nonselective manner and is not dependent on antigen recognition in the CNS. However, in their study the level of ovalbumin-specific T-cell apoptosis appeared to be considerably less than the level of MBP-specific T-cell apoptosis, suggesting that there may be two mechanisms for T-cell apoptosis in the CNS in EAE, one involving specific antigen recognition and one not.

The occurrence of T-cell apoptosis in the CNS of bone-marrow chimeric rats with EAE induced by the passive transfer of encephalitogenic T cells expressing different major histocompatibility complex (MHC) genes than the resident CNS cells has been interpreted as indicating that T-cell apoptosis is not dependent on antigen presentation by CNS parenchymal glial cells (Bauer et al., 1998). However, the T-cell receptors (TCR) of the encephalitogenic T cells may still interact with the MHC–peptide complexes of the CNS parenchymal cells in an alloreactive response because of the MHC mismatch, and the encephalitogenic T cells may be deleted in the same way as T cells are deleted by apoptosis in liver transplants (Qian et al., 1997).

When EAE is reinduced in Lewis rats by active immunization with MBP and complete Freund's adjuvant after recovery from EAE induced by passively transferred MBP-specific T