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

1. Introduction . . . 27
2. Role of lymphocyte apoptosis in the CNS . . . 27
3. Mechanisms of T-lymphocyte apoptosis in the CNS . . . 28
   3.1. Activation-induced apoptosis . . . 28
   3.2. T-cell apoptosis due to impairment of costimulation and withdrawal of growth factor . . . 30
   3.3. Glucocorticoid-induced apoptosis . . . 31
   3.4. T-cell apoptosis induced by ligation of T-cell CD95 by CD95L expressed by astrocytes, microglia or neurons . . . 32
   3.5. Other possible mechanisms of T-cell apoptosis in the CNS . . . 32
4. Mechanisms of B-lymphocyte apoptosis in the CNS . . . 32
5. Strategies for promoting lymphocyte apoptosis in the CNS . . . 34
   5.1. Glucocorticoid-induced lymphocyte apoptosis . . . 34
   5.2. Soluble antigen administration . . . 34
   5.3. Intrathecal IFN-γ administration . . . 34
   5.4. Intrathecal CD95L administration . . . 34
   5.5. Transplantation of neural precursor cells . . . 34
   5.6. Administration of 1,25-dihydroxyvitamin D3 . . . 34
   5.7. Induction of B-cell apoptosis by anti-CD20 monoclonal antibody . . . 34

* 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

5.8. Targeting anti-apoptotic BCL-2 family members . . . 34
5.9. Targeting the Epstein–Barr virus in MS . . . 35
6. Conclusion . . . 35
References . . . 35

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

cells, there is accelerated and increased apoptosis of inflammatory cells in the spinal cord compared to that occurring in the first attack, indicating that previous CNS inflammation increases the level of inflammatory cell apoptosis (Gordon et al., 2001). Flügel et al. (2000) reported the remarkably rapid apoptotic elimination of MBP-specific T cells in the CNS in the vicinity of the axotomized facial nucleus. This indicates that noninflammatory insults to the CNS may also accelerate T-cell apoptosis.

T-cell apoptosis also occurs in the CNS in viral encephalomyelitis (Barac-Latas et al., 1994) and in human glioblastoma multiforme (Didenko et al., 2002; Walker et al., 2006) but the antigen specificity of the apoptotic T cells has not been determined. If T-cell apoptosis in glioblastoma multiforme involves tumour-specific T cells, this could contribute to the failure of the immune system to eliminate the malignant cells.

Little attention has been given by researchers to the potentially important role that apoptotic elimination of B cells plays in terminating immune attack on the CNS. B-cell apoptosis occurs in the CNS during spontaneous recovery from acute EAE (White et al., 2000) but the antigen specifity of the apoptotic B cells has not been determined.

3. Mechanisms of T-lymphocyte apoptosis in the CNS

The possible mechanisms of T-cell apoptosis in the CNS are summarized in Table 1.

3.1. Activation-induced apoptosis

Activation-induced apoptosis refers to the apoptosis of thymocytes or previously activated mature T cells, triggered by activation through the TCR (Smith et al., 1989; Russell et al., 1991b). The signalling pathways for activation-induced T-cell apoptosis are illustrated in Fig. 1. Activation-induced apoptosis of mature T cells is mediated through the activation of the Fas (CD95) pathway and related death receptor pathways, such as the tumour necrosis factor (TNF) receptor 1 (TNFR1) pathway (Alderson et al., 1995; Brunner et al., 1995; Dhein et al., 1995; Ju et al., 1995; Ashkenazi and Dixit, 1998). The CD95 pathway is activated by ligation of cell surface CD95 by CD95 ligand (CD95L; also known as Fas ligand) and can occur through the interaction of CD95 and CD95L on the same T cell (Brunner et al., 1995; Dhein et al., 1995). TCR ligation upregulates CD95 expression (Brunner et al., 1995; Ju et al., 1995) and induces the expression of CD95L (Alderson et al., 1995; Brunner et al., 1995; Ju et al., 1995). The intracellular signalling pathway for CD95 and related death receptors is dependent on the activity of cysteine proteases (caspases) (Ashkenazi and Dixit, 1998). Ligation of CD95 by the homotrimeric CD95L results in the clustering of CD95 and the recruitment of the adaptor protein Fas-associated death domain (FADD) to the clustered CD95 intracellular death domains. Pro-caspase-8 binds to FADD and is then cleaved to active caspase-8 by self-cleavage as a result of induced oligomerization. In T cells, interferon γ (IFN-γ) is required for

Table 1
Possible mechanisms of T-cell apoptosis in the CNS

Mechanism	Receptor activating (+) or inhibiting (−) apoptosis	Intracellular signaling molecules activating (+) or inhibiting (−) apoptosis	Requirement for antigen recognition
Activation-induced apoptosis (AICD)	CD95 and other death receptors such as TNFR1 (+)	Caspase-8 (+) FLIP (−) tBID (+) BIM (+) BAD (+) BCL-2 (−) BCL-X_L (−) BAX/BAK (+)	Yes
Cytokine withdrawal	CD28 (−) Cytokine receptor, e.g. IL-2R (−)	BIM (+) BAD (+) BCL-2 (−) BCL-X_L (−) BAX/BAK (+)	No
Glucocorticoids (GC)	GR (+)	BIM (+) BCL-2 (−) BAX/BAK (+)	No. GC inhibit AICD
Ligation of T-cell CD95 by CD95L expressed by microglia, astrocytes or neurons	CD95 (+)	Caspase-8 (+) FLIP (−) tBID (+) BIM (+) BAD (+) BCL-2 (−) BCL-X_L (−) BAX/BAK (+)	No
Regulatory T cells			
Reactive oxygen intermediates and NO			
Multifunctional proteins, e.g. osteopontin			

Abbreviations: AICD = activation-induced cell death; GC = glucocorticoids; GR = glucocorticoid receptor; NO = nitric oxide.

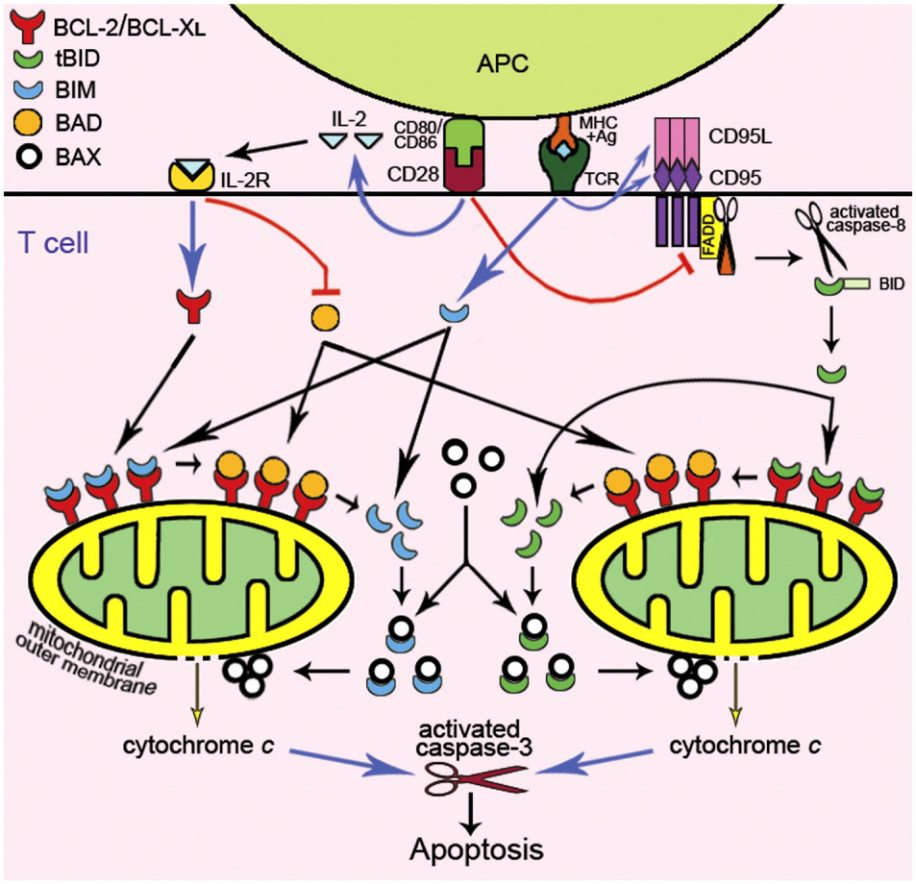

Fig. 1. Signalling pathways for T-cell apoptosis in the CNS. Activation-induced cell death is mediated through the CD95 pathway, which activates caspase-8, which cleaves BID to form truncated BID (tBID). If tBID is not sequestered by BCL-2/BCL-X_L, it activates BAX to permeabilize the mitochondrial outer membrane so that cytochrome *c* (which activates caspase-3) and other mediators of apoptosis are released from the mitochondria. CD95 can be activated by CD95 ligand (CD95L) expressed by the same T cell. TCR ligation induces the expression of CD95L, increases the expression of CD95 and increases the expression of BIM, which if not sequestered by BCL-2/BCL-X_L, will activate BAX/BAK. Costimulation through CD28 inhibits the CD95-mediated activation of caspase-8 and also induces the expression of IL-2, which in turn increases the expression of BCL-2//BCL-X_L and induces the phosphorylation and subsequent inactivation of BAD. Dephosphorylated BAD translocates from the cytoplasm to the mitochondria where it binds to BCL-2/BCL-X_L and displaces BIM and tBID, which can then activate BAX/BAK. Blue arrows indicate production or facilitation; red lines indicate inhibition; and black arrows indicate movement of molecules. Abbreviations: APC = antigen-presenting cell; IL-2R = IL-2 receptor; MHC = major histocompatibility complex molecule; Ag = antigen; FADD = Fas-associated death domain.

the production of caspase-8 and for activation-induced apoptosis (Liu and Janeway, 1990; Refaeli et al., 2002).

Activated caspase-8 mediates apoptosis by cleaving the pro-apoptotic molecule BID into a truncated form (tBID) that promotes cytochrome *c* release from mitochondria, with the resultant activation of downstream effector caspases such as caspase-3 (Li et al., 1998; Luo et al., 1998). BID is a member of the BCL-2 family, the members of which play a crucial role in the regulation of apoptosis (Kim et al., 2006). The BCL-2 family contains anti-apoptotic and pro-apoptotic members and is divided into three groups which are defined by the homology shared within four conserved BCL-2 homology domains (BH1–4). The classification and roles of the BCL-2 family members are summarized in Table 2. The anti-apoptotic molecules, which include BCL-2 and BCL-X_L, display sequence conservation through BH1–4. The pro-apoptotic members are divided into: (i) more fully conserved multidomain members (BAX and BAK) which have homology in the BH1–3 domains; and (ii) members which have homology only in the BH3 domain (BH3-only molecules). In viable cells, the multidomain pro-apoptotic molecules exist as inactive monomers in the cytosol (BAX) or at the mitochondria (BAK). Following activation, BAX inserts into the mitochondrial outer membrane as homo-oligomers, and BAK also homo-oligmerizes, resulting in the permeabilization of this membrane and release of intermembrane space proteins, including cytochrome *c*. The BH3-only pro- apoptotic members are further subdivided into: (a) activators (e.g. tBID and BIM) which directly activate BAX/BAK and which are prevented from doing so by being bound to, and sequestered by, the anti-apoptotics BCL-2/BCL-X_L; and (b) 'inactivators' (e.g. BAD) which do not directly activate BAX/BAK but inactivate the anti-apoptotics by preventing their sequestration of the activators, for example BAD displaces tBID/BIM from BCL-2/BCL-X_L to activate BAX/BAK (Kim et al., 2006).

It has previously been thought that in some T cells, the CD95-mediated death pathway occurs independently of the activation of BID, the translocation of BAX to the mitochondria and the release of cytochrome *c*, if a large amount of caspase-8 is activated (Scaffidi et al., 1998). However, recent studies indicate that the activation of BID, the translocation of BAX to

Table 2
Members of BCL-2 family and roles in apoptosis

	Group			
	Anti-apoptotic	Pro-apoptotic		
		Multidomain	Activator BH3-only	Inactivator BH3-only
Domains of BCL-2 homology (BH)	BH1 BH2 BH3 BH4	BH1 BH2 BH3	BH3	BH3
Members	BCL-2 BCL-X_L BCL-W MCL-1	BAX BAK	BID BIM PUMA	BAD BIK HRK NOXA BMF
Function	Sequestering the activators (BID, BIM and PUMA)	Permeabilization of mitochondrial outer membrane with release of cytochrome *c*	Direct activation of BAX and BAK	Inactivation of the anti-apoptotics by preventing their sequestration of the activators

the mitochondria and release of cytochrome *c* are essential for CD95-triggered apoptosis in all cell types (Tafani et al., 2006). TCR ligation also upregulates the expression of the activator BIM (Sandalova et al., 2004), in addition to upregulating CD95 expression and inducing CD95L expression. Thus, in vivo, BIM and tBID may act synergistically to induce apoptosis following TCR ligation.

Several studies have attempted to examine the role of the CD95 pathway and TNFR1 pathway in T-cell apoptosis in the CNS by using mice which are genetically deficient in the expression of CD95, CD95L or TNFR1 (reviewed by Pender and Rist, 2001). However, because deficiency of these molecules generally inhibits the induction and/or effector phase of EAE, the effect on T-cell apoptosis is difficult to interpret, with the exception of SJL mice where the CD95 pathway does not play a major role in the induction/effector phase. In CD95-deficient SJL mice, the severity of EAE is increased in association with decreased apoptosis of inflammatory cells in the CNS, indicating that the CD95 pathway is involved in lymphocyte apoptosis in the CNS (Suvannavejh et al., 2000). An alternative experimental approach analyzing the expression of CD95 and CD95L by T cells in the CNS has indicated that the CD95 pathway is involved in T-cell apoptosis in the CNS during recovery from EAE in the rat (White et al., 1998b). T cells, particularly Vβ8.2$^+$ T cells (representing the encephalitogenic MBP-specific T cells), express CD95 and CD95L in the CNS of rats with acute EAE (White et al., 1998b; Kohji and Matsumoto, 2000). During spontaneous recovery from acute EAE induced by immunization with MBP, Vβ8.2$^+$ T cells expressing CD95 or CD95L are much more vulnerable to apoptosis in the CNS than Vβ8.2$^+$ T cells not expressing these proteins (White et al., 1998b). The susceptibility of Vβ8.2$^+$ T cells expressing these molecules is further increased by the intraperitoneal administration of soluble MBP which reduces the severity of EAE (Ishigami et al., 1998). The vulnerability of CD95L-expressing T cells to apoptosis suggests that ligation of CD95 by CD95L on the same T cell contributes to T-cell apoptosis in the CNS. Administration of anti-CD95L antibody to Lewis rats after the clinical peak of EAE decreases the apoptosis of inflammatory cells in the CNS, increases the severity of inflammation in the CNS and delays clinical recovery (Wildbaum et al., 2000). The importance of death receptor-mediated lymphocyte apoptosis in the CNS for recovery from EAE has also been demonstrated by the finding that overexpression of FLIP, which inhibits apoptosis mediated through CD95 and related death receptors by preventing the activation of procaspase-8, decreases the clearance of T cells and B cells from the CNS and exacerbates EAE in DBA/1 mice (Djerbi et al., 2003).

In human glioblastoma multiforme, T cells expressing CD95L are eight times more vulnerable to apoptosis than those not expressing CD95L, suggesting that T-cell apoptosis is induced by overactivation of the TCR (Walker et al., 2006).

3.2. T-cell apoptosis due to impairment of costimulation and withdrawal of growth factor

Impairment of costimulation and withdrawal of growth factor are two related mechanisms that contribute to T-cell apoptosis in the CNS. The signalling pathways whereby costimulation modulates T-cell apoptosis are illustrated in Fig. 1. Costimulation of previously activated T cells influences their survival by two mechanisms: (i) inhibiting CD95-mediated activation-induced cell death; and (ii) increasing the production of growth factors (particularly interleukin-2 [IL-2]), withdrawal of which can induce T-cell apoptosis through a CD95-independent mechanism. Compared with peripheral lymphoid organs, the normal CNS has few professional antigen-presenting cells (APC) but many non-professional APC such as microglia and astrocytes, which can express MHC molecules and present antigen to T cells but which do not provide costimulatory signals. It has been suggested that CNS-reactive T cells are vulnerable to activation-induced apoptosis in the CNS because of a lack of costimulatory survival signals in the CNS (Pender et al., 1992; Tabi et al., 1994; Pender, 1999). This could explain why soluble antigen therapy induces apoptosis of autoreactive T cells preferentially in the CNS rather than in the peripheral lymphoid organs (Ishigami et al., 1998).

Costimulation by professional APC (Liu and Janeway, 1990; Groux et al., 1993) or by the direct ligation of the T-cell costimulatory receptor CD28 (Collette et al., 1997) inhibits

activation-induced apoptosis of previously activated T cells. Costimulation through CD28 can inhibit CD95-mediated T-cell apoptosis by several mechanisms: (i) preventing the induction of CD95L expression in T cells (Collette et al., 1997); (ii) inhibiting the CD95-mediated activation of caspase-8 (Jones et al., 2002); and (iii) increasing the expression of IL-2 which (a) upregulates the expression of the anti- apoptotic molecules, BCL-2 and BCL-X_L, and (b) inactivates the pro-apoptotic molecule BAD by phosphorylation. Costimulation of previously activated T cells increases their expression of IL-2 (Schweitzer and Sharpe, 1998), which inhibits activation-induced T-cell apoptosis (Groux et al., 1993; Ford et al., 1996). IL-2 increases the expression of BCL-2 (Deng and Podack, 1993; Akbar et al., 1996; Mor and Cohen, 1996; Mueller et al., 1996) and BCL-X_L (Akbar et al., 1996; Mueller et al., 1996). The inhibitory effect of BCL-2 and BCL-X_L on activation-induced T-cell death can be accounted for by their sequestration of tBID and subsequent inhibition of the CD95-mediated death pathway, as discussed above in Section 3.1, summarized in Table 2 and illustrated in Fig. 1. IL-2 also induces the phosphorylation of BAD so that it is retained in the cytoplasm and does not translocate to the mitochondria (Ayllón et al., 2000), where it can displace tBID from BCL-2/BCL-X_L to activate BAX/BAK (Kim et al., 2006) (Table 2). This displacement of tBID by BAD can account for the ability of BAD to augment CD95-triggered apoptosis in thymocytes (Mok et al., 1999).

Growth factor withdrawal can also trigger apoptosis through a pathway not dependent on CD95 or related death receptors (Strasser, 2005). It has been shown that, following the withdrawal of superantigen from superantigen-activated T cells, the T cells undergo apoptosis through a CD95-independent pathway that is mediated by the pro-apoptotic molecule BIM and inhibited by BCL-2, the level of which decreases just before the occurrence of T-cell apoptosis (Hildeman et al., 2002). It was suggested that the reduction in BCL-2 expression was at least partly due to cytokine withdrawal because cytokines including IL-2, IL-4, IL-7 and IL-15 that signal through the common γ chain of the IL-2 receptor can induce BCL-2 expression, as well as BCL-X_L expression (Akbar et al., 1996). Withdrawal of IL-2, IL-4 or IL-7 from T cells results in the dephosphorylation of BAD (Ayllón et al., 2000; Fleischer et al., 2004; Li et al., 2004), which then translocates from the cytoplasm, where it is bound in its phosphorylated form to 14-3-3 proteins, to the mitochondria where it can displace BIM and tBID from BCL-2/BCL-X_L to activate BAX/BAK (Kim et al., 2006) (Table 2). As mentioned in Section 3.1, TCR ligation also upregulates the expression of BIM (Sandalova et al., 2004), so that whether a T cell undergoes apoptosis or not upon cytokine withdrawal will be influenced by its recent history of TCR ligation.

Several studies have examined the effects of BCL-2/BCL-X_L expression or CD28 costimulation on T-cell apoptosis in the CNS in EAE. In Lewis rats with EAE, Vβ8.2$^+$ T cells expressing BCL-2 are less vulnerable to apoptosis in the CNS than Vβ8.2$^+$ cells not expressing BCL-2 (White et al., 1998b). In mice, the transgenic overexpression of BCL-X_L in T cells decreases the apoptosis of inflammatory cells in the CNS and increases the severity of EAE (Issazadeh et al., 2000). Similarly, transgenic overexpression of BCL-2 in T cells decreases the apoptosis of T cells in the CNS and increases the severity of EAE (Okuda et al., 2002). In contrast, the transfer of encephalitogenic T cells to mice deficient in the costimulatory molecules CD80 and CD86 resulted in increased apoptosis of inflammatory cells in the CNS and decreased the severity of EAE (Chang et al., 2003). Taken together, these studies in EAE indicate that the levels of T-cell costimulation and T-cell expression of BCL-2 and BCL-X_L in the CNS are important modulators of T-cell apoptosis in the CNS. However, they do not reveal whether this modulation is occurring by modifying CD95-mediated activation-induced T-cell death or by modifying the CD95-independent apoptotic response to growth factor, for example IL-2, withdrawal. The first of these processes would involve only T cells recognizing their antigen within the CNS, whereas the second could effect any T cell in the CNS. It is possible that some CNS-reactive T cells are deleted by the first process and some by the second. It is also possible that the fate of each individual CNS-reactive T cell is influenced by synergy between both apoptotic pathways. Thus, whether TCR reactivation in the CNS results in T-cell death or survival depends on the balance between pro-apoptotic and anti-apoptotic factors affecting each T cell.

3.3. Glucocorticoid-induced apoptosis

Another possible mechanism for T-cell apoptosis in the CNS is glucocorticoid-induced apoptosis. Glucocorticoids exert their many effects on the immune system by binding to the glucocorticoid receptor (GR), a ligand-dependent transcription factor. Although it has long been known that glucocorticoids can induce T-cell apoptosis (Nieto and López-Rivas, 1989), the mechanism for this remains unclear. Glucocorticoids inhibit the production of IL-2 (Boumpas et al., 1991), which can induce the expression of BCL-2 and BCL-X_L and protect T cells from glucocorticoid-induced apoptosis (Nieto and López-Rivas, 1989; Mor and Cohen, 1996). At least in T-cell acute lymphoblastic leukemic cells, glucocorticoid-induced apoptosis depends on the induction of the pro-apoptotic molecule BIM (Lu et al., 2006), which directly activates BAX/BAK unless sequestered by BCL-2/BCL-X_L.

Glucocorticoids are endogenously released during spontaneous recovery from acute EAE (MacPhee et al., 1989). Adrenalectomy, which prevents the production of glucocorticoids, reduces the level of T-cell apoptosis in the CNS in EAE, suggesting that glucocorticoids may contribute to the T-cell apoptosis (Smith et al., 1996). However, glucocorticoid release is not solely responsible for the T-cell apoptosis because T-cell apoptosis occurs in the CNS during recovery from mild EAE without glucocorticoid release (Smith et al., 1996). It should also be noted that adrenalectomy not only prevents the increased glucocorticoid production that occurs in EAE but also abrogates basal glucocorticoid production, which itself could modulate the levels of cytokines and pro-apoptotic and anti-apoptotic molecules in the CNS and thereby influence activation-induced T-cell apoptosis and cytokine-withdrawal apoptosis. Therefore, it not known whether the increased endogenous release of glucocorticoids in EAE is sufficient to increase T-cell apoptosis above that which might occur with basal glucocorticoid secretion.

Furthermore, glucocorticoid-induced apoptosis cannot explain the selective apoptotic elimination of CNS-reactive T cells in the CNS in EAE (Tabi et al., 1994, 1995) because the administration of exogenous glucocorticoids actually inhibits the selective apoptosis of Vβ8.2$^+$ cells representing MBP-specific T cells in the CNS (McCombe et al., 1996b). This inhibition can be accounted for by the ability of glucocorticoids to antagonize activation-induced cell death (Zacharchuk et al., 1990), by reducing the expression of CD95L (Yang et al., 1995; Baumann et al., 2005), and possibly by also directly inhibiting the CD95 pathway (Zipp et al., 2000).

3.4. T-cell apoptosis induced by ligation of T-cell CD95 by CD95L expressed by astrocytes, microglia or neurons

In addition to activation-induced T-cell apoptosis, where activation of the TCR drives the T cell through the CD95-mediated death pathway, there is another possible pathway for CD95-mediated T-cell death in the CNS, where CD95L expressed by astrocytes, microglia or neurons might interact with T-cell CD95 in an antigen-independent manner. In Lewis rats with EAE, apoptotic inflammatory cells associate with astrocytes (Kohji et al., 1998), and astrocytes express CD95L, leading to the suggestion that CD95L-expressing astrocytes induce T-cell apoptosis in the CNS by ligating T-cell CD95 (Kohji and Matsumoto, 2000). Astrocytes expressing CD95L can induce apoptosis in target cells in vitro (Bechmann et al., 1999; Choi et al., 1999). Similarly, microglia can express CD95L and can induce apoptosis in CD95-expressing target cells in vitro (Frigerio et al., 2000). However, it remains unclear whether, in vivo, CD95L expressed by astrocytes and microglia plays a role in inducing T-cell apoptosis. Because such a mechanism does not depend on antigen recognition by T cells, it could affect any T cell in the CNS. An alternative role for astrocytes and microglia in inducing T-cell apoptosis is that astrocytes and microglia present CNS antigens to T cells but fail to provide costimulation, and thereby lead to activation-induced T-cell apoptosis through the interaction of CD95L and CD95 on the same T cell (Pender, 1999). This is consistent with the finding that antigen presentation to MBP-specific T cells by microglia in vitro results in T-cell apoptosis, which can be prevented by the addition of IL-2 (Ford et al., 1996). The fact that microglia express considerably higher levels of class II MHC molecules than astrocytes in rats with EAE and that this increases during the disease course (Matsumoto et al., 1986) indicates that microglia are more likely than astrocytes to present antigens to CD4$^+$ T cells in vivo. The association of apoptotic inflammatory cells with astrocytes in the CNS (Kohji et al., 1998) might be the effect rather than the cause of apoptosis, as astrocytes can phagocytose apoptotic lymphocytes in EAE (Nguyen and Pender, 1998).

Neurons can also express CD95L (Bechmann et al., 1999; Flügel et al., 2000) and can induce apoptosis of MBP-specific T cells in vitro (Flügel et al., 2000). Because MBP-specific T cells rapidly undergo apoptosis in the immediate vicinity of CD95L-expressing neurons of the axotomized facial nerve in vivo, it has been concluded that the T-cell apoptosis is due to the direct ligation of T-cell CD95 by neuronal CD95L (Flügel et al., 2000). However, microglia express class II MHC molecules following axotomy (Streit et al., 1989), and it is possible that the apoptotic elimination of MBP-specific T cells after axotomy is dependent on antigen presentation by microglia and represents activation-induced cell death through interaction of CD95 and CD95L on the same T cell. The close association of apoptotic T cells with, and their internalization by, neurons (Flügel et al., 2000) may be the result rather than the cause of apoptosis, if neurons can phagocytose apoptotic lymphocytes in the same way as oligodendrocytes and astrocytes can (Nguyen and Pender, 1998).

3.5. Other possible mechanisms of T-cell apoptosis in the CNS

It has been suggested that reactive oxygen intermediates and nitric oxide released by macrophages in the CNS may be responsible for T-cell apoptosis in the CNS in EAE (Zettl et al., 1997). However, Bachmann et al. (1999) found that the level of T-cell apoptosis in the CNS in mice with EAE was not altered by deficiency of inducible nitric oxide synthase and concluded that nitric oxide does not have a major role in inducing T-cell apoptosis in the CNS.

Another possible mechanism for T-cell apoptosis in the CNS is that induced by regulatory T cells. T cells specifically targeted against encephalitogenic T cells can kill the latter cells in vitro (Sun et al., 1988). γδ T cells expressing CD95L can induce apoptosis in encephalitogenic T cells in vitro, and mice deficient in γδ T cells have decreased apoptosis of encephalitogenic T cells in the CNS and fail to recover from EAE (Ponomarev and Dittel, 2005).

Given the complexity of apoptotic signalling pathways, it is likely that many, as yet unstudied, endogenous proteins are able to modulate T-cell apoptosis in the CNS. Recently it has been shown that the multifunctional protein, osteopontin, inhibits the apoptosis of activated T cells in vitro, promotes survival of inflammatory cells in the CNS and worsens the disease course in mice with EAE (Hur et al., 2007).

4. Mechanisms of B-lymphocyte apoptosis in the CNS

The possible mechanisms of B-cell apoptosis in the CNS are summarized in Table 3. Apoptosis can be induced in mature B cells by hyper-crosslinking the B-cell antigen receptor (BCR) (Hartley et al., 1991; Russell et al., 1991a); this does not involve the interaction of CD95 and CD95L (Peter et al., 1995; Lens et al., 1996). The degree of cross-linking of surface immunoglobulin (sIg) receptors on mature B cells determines whether the B cells proliferate or are deleted; weak sIg cross-linking induces B cells to proliferate, whereas strong sIg cross-linking by multivalent antigens such as cell membrane antigens eliminates B cells by apoptosis (Parry et al., 1994; Tsubata et al., 1994). BCR ligation increases the expression of BIM (Craxton et al., 2005), which, if not sequestered by BCL-2/BCL-X_L, induces apoptosis by directly activating BAX/BAK. B-cell activating factor (BAFF) blocks BCR-induced apoptosis by downregulating the expression of BIM and by inducing the

Table 3
Possible mechanisms of B-cell apoptosis in the CNS

Mechanism	Receptor activating (+) or inhibiting (−) apoptosis	Intracellular signaling molecules activating (+) or inhibiting (−) apoptosis	Requirement for antigen recognition by B cell
Hyper-cross-linking of BCR	BCR (+) BAFF-R (−) IL-4R (−) CD40 (−)	BIM (+) BAD (+) BCL-X_L (−) BCL-2 (−) BAX/BAK (+)	Yes
Ligation of B-cell CD95 by CD95L expressed by: (i) T cells (ii) same B cell (iii) microglia, astrocytes or neurons	CD95 (+) BCR (−) IL-4R (−)	Caspase-8 (+) FLIP (−) tBID (+) BAD (+) BCL-X_L (−) BCL-2 (−) BAX/BAK (+)	No
Cytokine withdrawal	IL-4R (−)	BIM (+) BAD (+) BCL-X_L (−) BCL-2 (−) BAX/BAK (+)	No
Glucocorticoids	GR (+)	BIM (+) BCL-2 (−) BAX/BAK (+)	No

Abbreviations: BAFF = B-cell activating factor; BAFF-R = BAFF receptors (BR3, BCMA and TACI); GR = glucocorticoid receptor.

phosphorylation of BIM, which promotes its ubiquitination and subsequent degradation by the proteasome (Craxton et al., 2005). At least in immature B cells, BCR ligation results in the dephosphorylation of BAD (Malissein et al., 2003), which then translocates from the cytoplasm to the mitochondria where it can displace BIM from BCL-2/BCL-X_L to activate BAX/BAK. BCR-triggered apoptosis is dependent on the absence of T-cell signals, because it can be inhibited by IL-4 (Parry et al., 1994) and ligation of CD40, which is constitutively expressed on B lymphocytes (Valentine and Licciardi, 1992; Tsubata et al., 1993; Lens et al., 1996). The anti-apoptotic effect of IL-4 is explained by its ability to increase the expression of BCL-X_L (Wurster et al., 2002) and, at least in chronic lymphocytic leukemic B cells, BCL-2 (Dancescu et al., 1992). It is also likely that IL-4 inhibits B-cell apoptosis by promoting the phosphorylation and subsequent inactivation of BAD, as it does in T cells (Fleischer et al., 2004), as discussed above in Section 3.2. The anti-apoptotic action of CD40 ligation is due to its ability to upregulate the expression of BCL-X_L (Craxton et al., 2005).

Another mechanism of apoptosis in mature B cells is mediated through CD95, the expression of which is upregulated by the ligation of B-cell CD40 by activated T cells expressing CD40L (Garrone et al., 1995; Rothstein et al., 1995). This CD40L-triggered CD95-mediated apoptosis can be overcome by BCR ligation (Rothstein et al., 1995) which inhibits the CD95-mediated activation of caspase-8 (Hinshaw et al., 2003), although antigen-specific B cells that have been activated for a prolonged period can become sensitive to CD95-mediated cell death (Wang et al., 1996). CD40 signalling can also inhibit the CD95-induced activation of caspase-8 (Benson et al., 2006). IL-4 also inhibits CD95-mediated apoptosis in B cells (Foote et al., 1996; Wurster et al., 2002), which can be explained by its ability to increase the expression of BCL-X_L (Wurster et al., 2002) and BCL-2 (Dancescu et al., 1992) and to inactivate BAD (Fleischer et al., 2004). The CD95-mediated pathway is postulated to result from the ligation of B-cell CD95 by T-cell CD95L (Rathmell et al., 1996). However, activated B cells express functional CD95L (Hahne et al., 1996) as well as CD95 (Wang et al., 1996), which raises the possibility that the interaction of CD95L and CD95 on the same B cell may mediate apoptosis.

Cytokine withdrawal is another mechanism of B-cell apoptosis. IL-4 can rescue B cells from spontaneous apoptosis in vitro (Illera et al., 1993) by increasing the expression of BCL-2/BCL-X_L and by inactivating BAD, as discussed above. In the IL-3-dependent B-cell line Ba/F3, IL-3 induces phosphorylation of BIM, which promotes its ubiquitination and subsequent degradation by the proteasome (Qi et al., 2006) so that it can no longer activate BAX/BAK.

Apoptosis can also be induced in mature B cells by glucocorticoids (Andréau et al., 1998), which, at least in chronic lymphocytic leukemic B cells, upregulate the expression of BIM (Iglesias-Serret et al., 2007), as they do in T-cell acute lymphoblastic leukemic cells (Lu et al., 2006). Another possible mechanism of B-cell apoptosis in the CNS is ligation of B-cell CD95 by CD95L expressed by microglia, astrocytes or neurons, as suggested for T-cell apoptosis in Section 3.4.

During spontaneous recovery from acute EAE, B cells expressing CD95 and B cells expressing CD95L are highly vulnerable to apoptosis in the CNS, whereas B cells expressing BCL-2 are protected from apoptosis (White et al., 2000). The vunerability of B cells expressing CD95L to apoptosis in the CNS suggests that B-cell apoptosis is mediated by the interaction of CD95L and CD95 on the same B cell. White et al. (2000) hypothesized that CD95-mediated apoptosis occurs in CNS B cells that are expressing low levels of BCL-2 because of cytokine withdrawal following activation-induced apoptosis of encephalitogenic T cells. A role for CD95 in mediating B-cell apoptosis in the CNS is also suggested by the finding that overexpression of

FLIP, which inhibits CD95-mediated apoptosis, reduces the clearance of B cells from the CNS in EAE (Djerbi et al., 2003). It is also possible that some B cells are being deleted in the CNS by non-CD95-dependent mechanisms, such as BCR hyper-cross-linking or by the action of endogenous glucocorticoids, which are released during spontaneous recovery from acute EAE (MacPhee et al., 1989). Further studies are warranted to investigate the role and mechanisms of B-cell apoptosis in the CNS.

5. Strategies for promoting lymphocyte apoptosis in the CNS

5.1. Glucocorticoid-induced lymphocyte apoptosis

Glucocorticoids exert a variety of immunomodulatory activities on inflammation in the CNS (Reichardt et al., 2006), and high-dose intravenous glucocorticoid therapy is widely used to treat relapses of MS. The administration of exogenous glucocorticoids increases the level of T-cell apoptosis in the CNS in EAE (McCombe et al., 1996b; Nguyen et al., 1997; Schmidt et al., 2000, 2003). However, the beneficial effect of glucocorticoid therapy in EAE does not depend on the induction of increased T-cell apoptosis in the CNS because EAE can be inhibited by low doses of dexamethasone which do not increase T-cell apoptosis in the CNS (Nguyen et al., 1997). It should also be noted that, although higher glucocorticoid doses increase the overall level of T-cell apoptosis in the CNS (McCombe et al., 1996b; Nguyen et al., 1997), they actually inhibit the selective apoptosis of encephalitogenic T cells in the CNS in EAE (McCombe et al., 1996b). This may contribute to the relapses of EAE that occur after cessation of glucocorticoid therapy (Nguyen et al., 1997). It is likely that glucocorticoid therapy also increases the level of B-cell apoptosis in the CNS but this has not yet been investigated.

5.2. Soluble antigen administration

The parenteral administration of high doses of soluble myelin antigen increases T-cell apoptosis in the CNS and reduces the severity of EAE (Ishigami et al., 1998; Weishaupt et al., 2000; Tischner et al., 2007). It is possible that soluble antigen therapy also increases B-cell apoptosis in the CNS but this has not yet been studied.

5.3. Intrathecal IFN-γ administration

The intrathecal delivery of IFN-γ by an IFN-γ-gene-containing vector increases the apoptosis of lymphocytes in the CNS and reduces the severity of EAE (Furlan et al., 2001). Because this therapy increases the expression of TNFR1 by inflammatory cells in the CNS, it has been suggested that the augmentation of apoptosis is mediated through TNFR1 (Furlan et al., 2001). However, because the therapy also increases the expression of class II MHC molecules in the CNS, increased T-cell apoptosis may occur through CD95-mediated activation-induced apoptosis resulting from increased antigen presentation to $CD4^+$ T cells, in the absence of costimulatory signals.

5.4. Intrathecal CD95L administration

The intrathecal infusion of recombinant CD95L greatly increases the apoptosis of inflammatory cells in the CNS and reduces the severity of EAE in Lewis rats (Zhu et al., 2002). Although CD95 expression was observed on neurons, astrocytes and oligodendrocytes in the CNS there was no detectable damage to these cells or to the myelin structure after the infusion of CD95L.

5.5. Transplantation of neural precursor cells

When adult neural precursor cells are injected intravenously into mice with EAE, the transplanted cells lodge in the perivascular areas of the CNS where they lead to increased apoptosis of T cells within the CNS and decreased severity of EAE (Pluchino et al., 2005). The mechanism for the increased T-cell apoptosis is unclear but a possible explanation is increased activation-induced cell death driven by CNS antigens presented by the transplanted cells or by the increased number of microglia, in the absence of costimulatory signals.

5.6. Administration of 1,25-dihydroxyvitamin D3

The administration of 1,25-dihydroxyvitamin D3 increases the level of apoptosis of inflammatory cells in the CNS and decreases the severity of EAE (Spach et al., 2004). The mechanism for the increased apoptosis of inflammatory cells is unclear but may involve the pro-apoptotic proteins, calpain-2 and caspase-8-associated protein 2, the CNS expression of which is increased by the administration of 1,25-dihydroxyvitamin D3. On the other hand, 1,25-dihydroxyvitamin D3 can inhibit activation-induced T-cell apoptosis by reducing the expression of CD95L (Cippitelli et al., 2002).

5.7. Induction of B-cell apoptosis by anti-CD20 monoclonal antibody

Monoclonal antibodies against CD20, which is expressed by B cells, induce B-cell death by several mechanisms (Cragg and Glennie, 2004). Rituximab and 1F5, which redistribute CD20 into membrane rafts, are bound efficiently by complement C1q, deposit C3b, and result in complement-dependent cytotoxicity, which is important for their in vivo efficacy. They also induce B-cell apoptosis but to a lesser degree than the B1 anti-CD20 monoclonal antibody, which does not redistribute CD20 into membrane rafts, bind C1q, or cause efficient complement-dependent cytotoxicity. Rituximab reduces the numbers of B cells and T cells in the cerebrospinal fluid of patients with MS (Cross et al., 2006), but its therapeutic efficacy has not yet been determined.

5.8. Targeting anti-apoptotic BCL-2 family members

It has previously been suggested that targeting of antisense BCL-2 oligonucleotides to T cells in the CNS might increase T-cell apoptosis there and be beneficial in MS (Pender, 1998), but a major limitation of this approach is the problem of drug

delivery. Another means of antagonizing BCL-2/BCL-X_L is provided by ABT-737, a recently developed potent small-molecule inhibitor of the anti-apoptotic proteins BCL-2, BCL-X_L and BCL-W (Oltersdorf et al., 2005). This compound induces lymphopenia in vivo (Oltersdorf et al., 2005), although normal lymphocytes are much less sensitive than chronic lymphocytic leukemic cells (Del Gaizo Moore et al., 2007). In chronic lymphocytic leukemic cells, ABT-737 displaces BIM from the BH3-binding pocket of BCL-2 so that the displaced BIM can activate BAX and induce apoptosis (Del Gaizo Moore et al., 2007). ABT-737 has the potential to increase apoptosis of B cells and T cells in inflammatory CNS lesions, although it is unknown whether it can cross the blood–brain barrier.

5.9. Targeting the Epstein–Barr virus in MS

A potential approach to augmenting lymphocyte apoptosis in the CNS in MS is to target the Epstein–Barr virus (EBV), which has been strongly implicated in the pathogenesis of MS and other human chronic autoimmune diseases such as systemic lupus erythematosus (Pender, 2003). It has been hypothesized that patients with MS have a genetic susceptibility to the effects of B-lymphocyte infection with EBV, resulting in EBV-infected autoreactive B cells, which could not only produce pathogenic autoantibodies but also provide costimulatory survival signals in the CNS to CNS-reactive T cells, that would otherwise be deleted there by activation-induced apoptosis (Pender, 2003). Therefore, therapies that induce apoptosis in EBV-infected B cells in the CNS might disinhibit activation-induced T-cell apoptosis in the CNS in MS by reducing the costimulatory anti-apoptotic signals available to the T cells. Therapeutic approaches to eliminating EBV-infected B cells include: rituximab, which deletes EBV-infected B cells as well as other CD20-expressing B cells; the transfer of autologous EBV-specific cytotoxic T cells (Savoldo et al., 2006); and targeting small interfering RNA to the EBV-encoded latent membrane protein 1 (Mei et al., 2006), which plays a key role in EBV infection of B cells by mimicking an activated CD40 receptor.

6. Conclusion

The elimination of autoreactive T cells and B cells from the CNS by apoptosis plays an important role in switching off autoimmune attack. Augmenting lymphocyte apoptosis in the CNS is a potential strategy for treating autoimmune CNS diseases such as MS. These strategies involve enhancing the physiological pro-apoptotic pathways and blocking the physiological anti-apoptotic pathways that normally control the fate of lymphocytes in the CNS.

References

Akbar, A.N., Borthwick, N.J., Wickremasinghe, R.G., Panayiotidis, P., Pilling, D., Bofill, M., Krajewski, S., Reed, J.C., Salmon, M., 1996. Interleukin-2 receptor common γ-chain signaling cytokines regulate activated T cell apoptosis in response to growth factor withdrawal: selective induction of anti-apoptotic (bcl-2, bcl-x_L) but not pro-apoptotic (bax, bcl-x_S) gene expression. Eur. J. Immunol. 26, 294–299.

Alderson, M.R., Tough, T.W., Davis-Smith, T., Braddy, S., Falk, B., Schooley, K.A., Goodwin, R.G., Smith, C.A., Ramsdell, F., Lynch, D.H., 1995. Fas ligand mediates activation-induced cell death in human T lymphocytes. J. Exp. Med. 181, 71–77.

Andréau, K., Lemaire, C., Souvannavong, V., Adam, A., 1998. Induction of apoptosis by dexamethasone in the B cell lineage. Immunopharmacology 40, 67–76.

Ashkenazi, A., Dixit, V.M., 1998. Death receptors: signaling and modulation. Science 281, 1305–1308.

Ayllón, V., Martínez-A, C., García, A., Cayla, X., Rebollo, A., 2000. Protein phosphatase 1α is a Ras-activated Bad phosphatase that regulates interleukin-2 deprivation-induced apoptosis. EMBO J. 19, 2237–2246.

Bachmann, R., Eugster, H.-P., Frei, K., Fontana, A., Lassmann, H., 1999. Impairment of TNF-receptor-1 signaling but not Fas signaling diminishes T-cell apoptosis in myelin oligodendrocyte glycoprotein peptide-induced chronic demyelinating autoimmune encephalomyelitis in mice. Am. J. Pathol. 154, 1417–1422.

Barac-Latas, V., Wege, H., Lassmann, H., 1994. Apoptosis of T lymphocytes in coronavirus-induced encephalomyelitis. Reg. Immunol. 6, 355–357.

Bauer, J., Bradl, M., Hickey, W.F., Forss-Petter, S., Breitschopf, H., Linington, C., Wekerle, H., Lassmann, H., 1998. T-cell apoptosis in inflammatory brain lesions: destruction of T cells does not depend on antigen recognition. Am. J. Pathol. 153, 715–724.

Baumann, S., Dostert, A., Novac, N., Bauer, A., Schmid, W., Fas, S.C., Krueger, A., Heinzel, T., Kirchhoff, S., Schutz, G., Krammer, P.H., 2005. Glucocorticoids inhibit activation-induced cell death (AICD) via direct DNA-dependent repression of the CD95 ligand gene by a glucocorticoid receptor dimer. Blood 106, 617–625.

Bechmann, I., Mor, G., Nilsen, J., Eliza, M., Nitsch, R., Naftolin, F., 1999. FasL (CD95L, Apo1L) is expressed in the normal rat and human brain: evidence for the existence of an immunological brain barrier. Glia 27, 62–74.

Benson, R.J., Hostager, B.S., Bishop, G.A., 2006. Rapid CD40-mediated rescue from CD95-induced apoptosis requires TNFR-associated factor-6 and PI3K. Eur. J. Immunol. 36, 2535–2543.

Boumpas, D.T., Anastassiou, E.D., Older, S.A., Tsokos, G.C., Nelson, D.L., Balow, J.E., 1991. Dexamethasone inhibits human interleukin 2 but not interleukin 2 receptor gene expression in vitro at the level of nuclear transcription. J. Clin. Invest. 87, 1739–1747.

Brunner, T., Mogil, R.J., LaFace, D., Yoo, N.J., Mahboubi, A., Echeverri, F., Martin, S.J., Force, W.R., Lynch, D.H., Ware, C.F., Green, D.R., 1995. Cell-autonomous Fas (CD95)/Fas-ligand interaction mediates activation-induced apoptosis in T-cell hybridomas. Nature 373, 441–444.

Chang, T.T., Sobel, R.A., Wei, T., Ransohoff, R.M., Kuchroo, V.K., Sharpe, A.H., 2003. Recovery from EAE is associated with decreased survival of encephalitogenic T cells in the CNS of B7-1/B7-2-deficient mice. Eur. J. Immunol. 33, 2022–2032.

Choi, C., Park, J.Y., Lee, J., Lim, J.-H., Shin, E.-C., Ahn, Y.S., Kim, C.-H., Kim, S.-J., Kim, J.-D., Choi, I.S., Choi, I.-H., 1999. Fas ligand and Fas are expressed constitutively in human astrocytes and the expression increases with IL-1, IL-6, TNF- α, or IFN-γ. J. Immunol. 162, 1889–1895.

Cippitelli, M., Fionda, C., Di Bona, D., Di Rosa, F., Lupo, A., Piccoli, M., Frati, L., Santoni, A., 2002. Negative regulation of CD95 ligand gene expression by vitamin D3 in T lymphocytes. J. Immunol. 168, 1154–1166.

Collette, Y., Razanajaona, D., Ghiotto, M., Olive, D., 1997. CD28 can promote T cell survival through a phosphatidylinositol 3-kinase-independent mechanism. Eur. J. Immunol. 27, 3283–3289.

Cragg, M.S., Glennie, M.J., 2004. Antibody specificity controls in vivo effector mechanisms of anti-CD20 reagents. Blood 103, 2738–2743.

Craxton, A., Draves, K.E., Gruppi, A., Clark, E.A., 2005. BAFF regulates B cell survival by downregulating the BH3-only family member Bim via the ERK pathway. J. Exp. Med. 202, 1363–1374.

Cross, A.H., Stark, J.L., Lauber, J., Ramsbottom, M.J., Lyons, J.A., 2006. Rituximab reduces B cells and T cells in cerebrospinal fluid of multiple sclerosis patients. J. Neuroimmunol. 180, 63–70.

Dancescu, M., Rubio-Trujillo, M., Biron, G., Bron, D., Delespesse, G., Sarfati, M., 1992. Interleukin 4 protects chronic lymphocytic leukemic B cells from death by apoptosis and upregulates Bcl-2 expression. J. Exp. Med. 176, 1319–1326.

Del Gaizo Moore, V., Brown, J.R., Certo, M., Love, T.M., Novina, C.D., Letai, A., 2007. Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737. J. Clin. Invest. 117, 112–121.

Deng, G., Podack, E.R., 1993. Suppression of apoptosis in a cytotoxic T-cell line by interleukin 2-mediated gene transcription and deregulated expression of the protooncogene bcl-2. Proc. Natl. Acad. Sci. U. S. A. 90, 2189–2193.

Dhein, J., Walczak, H., Bäumler, C., Debatin, K.-M., Krammer, P.H., 1995. Autocrine T-cell suicide mediated by APO-1/(Fas/CD95). Nature 373, 438–441.

Didenko, V.V., Ngo, H.N., Minchew, C., Baskin, D.S., 2002. Apoptosis of T lymphocytes invading glioblastomas multiforme: a possible tumor defense mechanism. J. Neurosurg. 96, 580–584.

Djerbi, M., Abdul-Majid, K.-B., Abedi-Valugerdi, M., Olsson, T., Harris, R.A., Grandien, A., 2003. Expression of the long form of human FLIP by retroviral gene transfer of hemopoietic stem cells exacerbates experimental autoimmune encephalomyelitis. J. Immunol. 170, 2064–2073.

Fleischer, A., Ghadiri, A., Dessauge, F., Duhamel, M., Cayla, X., Garcia, A., Rebollo, A., 2004. Bad-dependent rafts alteration is a consequence of an early intracellular signal triggered by interleukin-4 deprivation. Mol. Cancer Res. 2, 674–684.

Flügel, A., Schwaiger, F.W., Neumann, H., Medana, I., Willem, M., Wekerle, H., Kreutzberg, G.W., Graeber, M.B., 2000. Neuronal FasL induces cell death of encephalitogenic T lymphocytes. Brain Pathol. 10, 353–364.

Foote, L.C., Howard, R.G., Marshak-Rothstein, A., Rothstein, T.L., 1996. IL-4 induces Fas resistance in B cells. J. Immunol. 157, 2749–2753.

Ford, A.L., Foulcher, E., Lemckert, F.A., Sedgwick, J.D., 1996. Microglia induce CD4 T lymphocyte final effector function and death. J. Exp. Med. 184, 1737–1745.

Frigerio, S., Silei, V., Ciusani, E., Massa, G., Lauro, G.M., Salmaggi, A., 2000. Modulation of Fas-Ligand (Fas-L) on human microglial cells: an in vitro study. J. Neuroimmunol. 105, 109–114.

Furlan, R., Brambilla, E., Ruffini, F., Poliani, P.L., Bergami, A., Marconi, P.C., Franciotta, D.M., Penna, G., Comi, G., Adorini, L., Martino, G., 2001. Intrathecal delivery of IFN-γ protects C57BL/6 mice from chronic-progressive experimental autoimmune encephalomyelitis by increasing apoptosis of central nervous system-infiltrating lymphocytes. J. Immunol. 167, 1821–1829.

Garrone, P., Neidhardt, E.M., Garcia, E., Galibert, L., van Kooten, C., Banchereau, J., 1995. Fas ligation induced apoptosis of CD40-activated human B lymphocytes. J. Exp. Med. 182, 1265–1273.

Gold, R., Hartung, H.P., Lassmann, H., 1997. T-cell apoptosis in autoimmune diseases: termination of inflammation in the nervous system and other sites with specialized immune-defense mechanisms. Trends Neurosci. 20, 399–404.

Gordon, F.L., Nguyen, K.B., White, C.A., Pender, M.P., 2001. Rapid entry and downregulation of T cells in the central nervous system during the reinduction of experimental autoimmune encephalomyelitis. J. Neuroimmunol. 112, 15–27.

Groux, H., Monte, D., Plouvier, B., Capron, A., Ameisen, J.-C., 1993. CD3-mediated apoptosis of human medullary thymocytes and activated peripheral T cells: respective roles of interleukin-1, interleukin-2, interferon-γ and accessory cells. Eur. J. Immunol. 23, 1623–1629.

Hahne, M., Renno, T., Schroeter, M., Irmler, M., French, L., Bornand, T., Robson MacDonald, H., Tschopp, J., 1996. Activated B cells express functional Fas ligand. Eur. J. Immunol. 26, 721–724.

Hartley, S.B., Crosbie, J., Brink, R., Kantor, A.B., Basten, A., Goodnow, C.C., 1991. Elimination from peripheral lymphoid tissues of self-reactive B lymphocytes recognizing membrane-bound antigens. Nature 353, 765–769.

Hemmer, B., Fleckenstein, B.T., Vergelli, M., Jung, G., McFarland, H., Martin, R., Wiesmüller, K.-H., 1997. Identification of high potency microbial and self ligands for a human autoreactive class II-restricted T cell clone. J. Exp. Med. 185, 1651–1659.

Hickey, W.F., Hsu, B.L., Kimura, H., 1991. T-lymphocyte entry into the central nervous system. J. Neurosci. Res. 28, 254–260.

Hildeman, D.A., Zhu, Y., Mitchell, T.C., Bouillet, P., Strasser, A., Kappler, J., Marrack, P., 2002. Activated T cell death in vivo mediated by proapoptotic Bcl-2 family member Bim. Immunity 16, 759–767.

Hinshaw, J.A., Mueller, C.M., Scott, D.W., Williams, M.S., 2003. B cell receptor signaling mediates immediate protection from Fas-induced apoptosis upstream of caspase activation through an atypical protein kinase C isozyme and de novo protein synthesis. Eur. J. Immunol. 33, 2490–2500.

Hur, E.M., Youssef, S., Haws, M.E., Zhang, S.Y., Sobel, R.A., Steinman, L., 2007. Osteopontin-induced relapse and progression of autoimmune brain disease through enhanced survival of activated T cells. Nat. Immunol. 8, 74–83.

Iglesias-Serret, D., de Frias, M., Santidrian, A.F., Coll-Mulet, L., Cosialls, A.M., Barragan, M., Domingo, A., Gil, J., Pons, G., 2007. Regulation of the proapoptotic BH3-only protein BIM by glucocorticoids, survival signals and proteasome in chronic lymphocytic leukemia cells. Leukemia 21, 281–287.

Illera, V.A., Perandones, C.E., Stunz, L.L., Mower Jr., D.A., Ashman, R.F., 1993. Apoptosis in splenic B lymphocytes. Regulation by protein kinase C and IL-4. J. Immunol. 151, 2965–2973.

Ishigami, T., White, C.A., Pender, M.P., 1998. Soluble antigen therapy induces apoptosis of autoreactive T cells preferentially in the target organ rather than in the peripheral lymphoid organs. Eur. J. Immunol. 28, 1626–1635.

Issazadeh, S., Abdallah, K., Chitnis, T., Chandraker, A., Wells, A.D., Turka, L.A., Sayegh, M.H., Khoury, S.J., 2000. Role of passive T-cell death in chronic experimental autoimmune encephalomyelitis. J. Clin. Invest. 105, 1109–1116.

Jones, R.G., Elford, A.R., Parsons, M.J., Wu, L., Krawczyk, C.M., Yeh, W.-C., Hakem, R., Rottapel, R., Woodgett, J.R., Ohashi, P.S., 2002. CD28-dependent activation of protein kinase B/Akt blocks Fas-mediated apoptosis by preventing death-inducing signaling complex assembly. J. Exp. Med. 196, 335–348.

Ju, S.-T., Panka, D.J., Cui, H., Ettinger, R., El-Khatib, M., Sherr, D.H., Stanger, B.Z., Marshak-Rothstein, A., 1995. Fas (CD95)/FasL interactions required for programmed cell death after T-cell activation. Nature 373, 444–448.

Kim, H., Rafiuddin-Shah, M., Tu, H.-C., Jeffers, J.R., Zambetti, G.P., Hsieh, J.J.-D., Cheng, E.H.-Y., 2006. Hierarchical regulation of mitochondrion-dependent apoptosis by BCL-2 subfamilies. Nat. Cell Biol. 8, 1348–1358.

Kohji, T., Matsumoto, Y., 2000. Coexpression of Fas/FasL and Bax on brain and infiltrating T cells in the central nervous system is closely associated with apoptotic cell death during autoimmune encephalomyelitis. J. Neuroimmunol. 106, 165–171.

Kohji, T., Tanuma, N., Aikawa, Y., Kawazoe, Y., Suzuki, Y., Kohyama, K., Matsumoto, Y., 1998. Interaction between apoptotic cells and reactive brain cells in the central nervous system of rats with autoimmune encephalomyelitis. J. Neuroimmunol. 82, 168–174.

Lens, S.M.A., Tesselaar, K., den Drijver, B.F.A., van Oers, M.H.J., van Lier, R.A.W., 1996. A dual role for both CD40-ligand and TNF-α in controlling human B cell death. J. Immunol. 156, 507–514.

Li, H., Zhu, H., Xu, C.-J., Yuan, J., 1998. Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. Cell 94, 491–501.

Li, W.Q., Jiang, Q., Khaled, A.R., Keller, J.R., Durum, S.K., 2004. Interleukin-7 inactivates the pro-apoptotic protein bad promoting T cell survival. J. Biol. Chem. 279, 29160–29166.

Liu, Y., Janeway Jr., C.A., 1990. Interferon γ plays a critical role in induced cell death of effector T cell: a possible third mechanism of self-tolerance. J. Exp. Med. 172, 1735–1739.

Lu, J., Quearry, B., Harada, H., 2006. p38-MAP kinase activation followed by BIM induction is essential for glucocorticoid-induced apoptosis in lymphoblastic leukemia cells. FEBS Lett. 580, 3539–3544.

Luo, X., Budihardjo, I., Zou, H., Slaughter, C., Wang, X., 1998. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. Cell 94, 481–490.

MacPhee, I.A., Antoni, F.A., Mason, D.W., 1989. Spontaneous recovery of rats from experimental allergic encephalomyelitis is dependent on regulation of the immune system by endogenous adrenal corticosteroids. J. Exp. Med. 169, 431–445.

Magnus, T., Chan, A., Savill, J., Toyka, K.V., Gold, R., 2002. Phagocytic removal of apoptotic, inflammatory lymphocytes in the central nervous system by microglia and its functional implications. J. Neuroimmunol. 130, 1–9.

Malissein, E., Verdier, M., Ratinaud, M.H., Troutaud, D., 2003. Changes in Bad phosphorylation are correlated with BCR-induced apoptosis of WEHI-231 immature B cells. Biochimie 85, 733–740.

Martin, R., Jaraquemada, D., Flerlage, M., Richert, J., Whitaker, J., Long, E.O., McFarlin, D.E., McFarland, H.F., 1990. Fine specificity and HLA restriction

of myelin basic protein-specific cytotoxic T cell lines from multiple sclerosis patients and healthy individuals. J. Immunol. 145, 540–548.
Mason, D., 1998. A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol. Today 19, 395–404.
Matsumoto, Y., Hara, N., Tanaka, R., Fujiwara, M., 1986. Immunohistochemical analysis of the rat central nervous system during experimental allergic encephalomyelitis, with special reference to Ia-positive cells with dendritic morphology. J. Immunol. 136, 3668–3676.
McCombe, P.A., Nickson, I., Tabi, Z., Pender, M.P., 1996a. Apoptosis of $V\beta8.2^+$ T lymphocytes in the spinal cord during recovery from experimental autoimmune encephalomyelitis induced in Lewis rats by inoculation with myelin basic protein. J. Neurol. Sci. 139, 1–6.
McCombe, P.A., Nickson, I., Tabi, Z., Pender, M.P., 1996b. Corticosteroid treatment of experimental autoimmune encephalomyelitis in the Lewis rat results in loss of $V\beta8.2^+$ and myelin basic protein-reactive cells from the spinal cord, with increased total T-cell apoptosis but reduced apoptosis of $V\beta8.2^+$ cells. J. Neuroimmunol. 70, 93–101.
Mei, Y.P., Zhu, X.F., Zhou, J.M., Huang, H., Deng, R., Zeng, Y.X., 2006. siRNA targeting LMP1-induced apoptosis in EBV-positive lymphoma cells is associated with inhibition of telomerase activity and expression. Cancer Lett. 232, 189–198.
Mok, C.-L., Gil-Gómez, G., Williams, O., Coles, M., Taga, S., Tolaini, M., Norton, T., Kioussis, D., Brady, H.J.M., 1999. Bad can act as a key regulator of T cell apoptosis and T cell development. J. Exp. Med. 189, 575–586.
Mor, F., Cohen, I.R., 1996. IL-2 rescues antigen-specific T cells from radiation or dexamethasone-induced apoptosis: correlation with induction of Bcl-2. J. Immunol. 156, 515–522.
Mueller, D.L., Seiffert, S., Fang, W., Behrens, T.W., 1996. Differential regulation of bcl-2 and bcl-x by CD3, CD28, and the IL-2 receptor in cloned $CD4^+$ helper T cells: a model for the long-term survival of memory cells. J. Immunol. 156, 1764–1771.
Nguyen, K.B., Pender, M.P., 1998. Phagocytosis of apoptotic lymphocytes by oligodendrocytes in experimental autoimmune encephalomyelitis. Acta Neuropathol. (Berl.) 95, 40–46.
Nguyen, K.B., McCombe, P.A., Pender, M.P., 1994. Macrophage apoptosis in the central nervous system in experimental autoimmune encephalomyelitis. J. Autoimmun. 7, 145–152.
Nguyen, K.B., McCombe, P.A., Pender, M.P., 1997. Increased apoptosis of T lymphocytes and macrophages in the central and peripheral nervous systems of Lewis rats with experimental autoimmune encephalomyelitis treated with dexamethasone. J. Neuropathol. Exp. Neurol. 56, 58–69.
Nieto, M.A., López-Rivas, A., 1989. IL-2 protects T lymphocytes from glucocorticoid-induced DNA fragmentation and cell death. J. Immunol. 143, 4166–4170.
Okuda, Y., Okuda, M., Bernard, C.C.A., 2002. The suppression of T cell apoptosis influences the severity of disease during the chronic phase but not the recovery from the acute phase of experimental autoimmune encephalomyelitis in mice. J. Neuroimmunol. 131, 115–125.
Oltersdorf, T., Elmore, S.W., Shoemaker, A.R., Armstrong, R.C., Augeri, D.J., Belli, B.A., Bruncko, M., Deckwerth, T.L., Dinges, J., Hajduk, P.J., Joseph, M.K., Kitada, S., Korsmeyer, S.J., Kunzer, A.R., Letai, A., Li, C., Mitten, M.J., Nettesheim, D.G., Ng, S., Nimmer, P.M., O'Connor, J.M., Oleksijew, A., Petros, A.M., Reed, J.C., Shen, W., Tahir, S.K., Thompson, C.B., Tomaselli, K.J., Wang, B., Wendt, M.D., Zhang, H., Fesik, S.W., Rosenberg, S.H., 2005. An inhibitor of Bcl-2 family proteins induces regression of solid tumours. Nature 435, 677–681.
Parry, S.L., Holman, M.J., Hasbold, J., Klaus, G.G.B., 1994. Plastic-immobilized anti-μ or anti-δ antibodies induce apoptosis in mature murine B lymphocytes. Eur. J. Immunol. 24, 974–979.
Pender, M.P., 1998. Genetically determined failure of activation-induced apoptosis of autoreactive T cells as a cause of multiple sclerosis. Lancet 351, 978–981.
Pender, M.P., 1999. Activation-induced apoptosis of autoreactive and alloreactive T lymphocytes in the target organ as a major mechanism of tolerance. Immunol. Cell Biol. 77, 216–223.
Pender, M.P., 2003. Infection of autoreactive B lymphocytes with EBV, causing chronic autoimmune diseases. Trends Immunol. 24, 584–588.
Pender, M.P., Rist, M.J., 2001. Apoptosis of inflammatory cells in immune control of the nervous system: role of glia. Glia 36, 137–144.
Pender, M.P., Nguyen, K.B., McCombe, P.A., Kerr, J.F.R., 1991. Apoptosis in the nervous system in experimental allergic encephalomyelitis. J. Neurol. Sci. 104, 81–87.
Pender, M.P., McCombe, P.A., Yoong, G., Nguyen, K.B., 1992. Apoptosis of αβ T lymphocytes in the nervous system in experimental autoimmune encephalomyelitis: its possible implications for recovery and acquired tolerance. J. Autoimmun. 5, 401–410.
Pender, M.P., Csurhes, P.A., Greer, J.M., Mowat, P.D., Henderson, R.D., Cameron, K.D., Purdie, D.M., McCombe, P.A., Good, M.F., 2000. Surges of increased T cell reactivity to an encephalitogenic region of myelin proteolipid protein occur more often in patients with multiple sclerosis than in healthy subjects. J. Immunol. 165, 5322–5331.
Peter, M.E., Dhein, J., Ehret, A., Hellbardt, S., Walczak, H., Moldenhauer, G., Krammer, P.H., 1995. APO-1(CD95)-dependent and -independent antigen receptor-induced apoptosis in human T and B cell lines. Int. Immunol. 7, 1873–1877.
Pluchino, S., Zanotti, L., Rossi, B., Brambilla, E., Ottoboni, L., Salani, G., Martinello, M., Cattalini, A., Bergami, A., Furlan, R., Comi, G., Constantin, G., Martino, G., 2005. Neurosphere-derived multipotent precursors promote neuroprotection by an immunomodulatory mechanism. Nature 436, 266–271.
Ponomarev, E.D., Dittel, B.N., 2005. γδ T cells regulate the extent and duration of inflammation in the central nervous system by a Fas ligand-dependent mechanism. J. Immunol. 174, 4678–4687.
Qi, X.-J., Wildey, G.M., Howe, P.H., 2006. Evidence that Ser^{87} of Bim_{EL} is phosphorylated by Akt and regulates Bim_{EL} apoptotic function. J. Biol. Chem. 281, 813–823.
Qian, S., Lu, L., Fu, F., Li, Y., Li, W., Starzl, T.E., Fung, J.J., Thomson, A.W., 1997. Apoptosis within spontaneously accepted mouse liver allografts: evidence for deletion of cytotoxic T cells and implications for tolerance induction. J. Immunol. 158, 4654–4661.
Rathmell, J.C., Townsend, S.E., Xu, J.C., Flavell, R.A., Goodnow, C.C., 1996. Expansion or elimination of B cells in vivo: dual roles for CD40- and Fas (CD95)-ligands modulated by the B cell antigen receptor. Cell 87, 319–329.
Refaeli, Y., Van Parijs, L., Alexander, S.I., Abbas, A.K., 2002. Interferon γ is required for activation-induced death of T lymphocytes. J. Exp. Med. 196, 999–1005.
Reichardt, H.M., Gold, R., Lühder, F., 2006. Glucocorticoids in multiple sclerosis and experimental autoimmune encephalomyelitis. Expert Rev. Neurother. 6, 1657–1670.
Rothstein, T.L., Wang, J.K.M., Panka, D.J., Foote, L.C., Wang, Z., Stanger, B., Cui, H., Ju, S., Marshak-Rothstein, A., 1995. Protection against Fas-dependent Th1-mediated apoptosis by antigen receptor engagement in B cells. Nature 374, 163–165.
Russell, D.M., Dembić, Z., Morahan, G., Miller, J.F.A.P., Bürki, K., Nemazee, D., 1991a. Peripheral deletion of self-reactive B cells. Nature 354, 308–311.
Russell, J.H., White, C.L., Loh, D.Y., Meleedy-Rey, P., 1991b. Receptor-stimulated death pathway is opened by antigen in mature T cells. Proc. Natl. Acad. Sci. U. S. A. 88, 2151–2155.
Sandalova, E., Wei, C.-H., Masucci, M.G., Levitsky, V., 2004. Regulation of expression of Bcl-2 protein family member Bim by T cell receptor triggering. Proc. Natl. Acad. Sci. U. S. A. 101, 3011–3016.
Savoldo, B., Goss, J.A., Hammer, M.M., Zhang, L., Lopez, T., Gee, A.P., Lin, Y.F., Quiros-Tejeira, R.E., Reinke, P., Schubert, S., Gottschalk, S., Finegold, M.J., Brenner, M.K., Rooney, C.M., Heslop, H.E., 2006. Treatment of solid organ transplant recipients with autologous Epstein Barr virus-specific cytotoxic T lymphocytes (CTLs). Blood 108, 2942–2949.
Scaffidi, C., Fulda, S., Srinivasan, A., Friesen, C., Li, F., Tomaselli, K.J., Debatin, K.M., Krammer, P.H., Peter, M.E., 1998. Two CD95 (APO-1/Fas) signaling pathways. EMBO J. 17, 1675–1687.
Schmidt, J., Gold, R., Schönrock, L., Zettl, U.K., Hartung, H.-P., Toyka, K.V., 2000. T-cell apoptosis in situ in experimental autoimmune encephalomyelitis following methylprednisolone pulse therapy. Brain 123, 1431–1441.
Schmidt, J., Metselaar, J.M., Wauben, M.H., Toyka, K.V., Storm, G., Gold, R., 2003. Drug targeting by long-circulating liposomal glucocorticosteroids increases therapeutic efficacy in a model of multiple sclerosis. Brain 126, 1895–1904.

Schmied, M., Breitschopf, H., Gold, R., Zischler, H., Rothe, G., Wekerle, H., Lassmann, H., 1993. Apoptosis of T lymphocytes in experimental autoimmune encephalomyelitis: evidence for programmed cell death as a mechanism to control inflammation in the brain. Am. J. Pathol. 143, 446–452.

Schweitzer, A.N., Sharpe, A.H., 1998. Studies using antigen-presenting cells lacking expression of both B7-1 (CD80) and B7-2 (CD86) show distinct requirements for B7 molecules during priming versus restimulation of Th2 but not Th1 cytokine production. J. Immunol. 161, 2762–2771.

Smith, C.A., Williams, G.T., Kingston, R., Jenkinson, E.J., Owen, J.J.T., 1989. Antibodies to CD3/T-cell receptor complex induce death by apoptosis in immature T cells in thymic cultures. Nature 337, 181–184.

Smith, T., Schmied, M., Hewson, A.K., Lassmann, H., Cuzner, M.L., 1996. Apoptosis of T cells and macrophages in the central nervous system of intact and adrenalectomized Lewis rats during experimental allergic encephalomyelitis. J. Autoimmun. 9, 167–174.

Spach, K.M., Pedersen, L.B., Nashold, F.E., Kayo, T., Yandell, B.S., Prolla, T.A., Hayes, C.E., 2004. Gene expression analysis suggests that 1,25-dihydroxyvitamin D3 reverses experimental autoimmune encephalomyelitis by stimulating inflammatory cell apoptosis. Physiol. Genomics 18, 141–151.

Strasser, A., 2005. The role of BH3-only proteins in the immune system. Nat. Rev. Immunol. 5, 189–200.

Streit, W.J., Graeber, M.B., Kreutzberg, G.W., 1989. Expression of Ia antigen on perivascular and microglial cells after sublethal and lethal motor neuron injury. Exp. Neurol. 105, 115–126.

Sun, D., Qin, Y., Chluba, J., Epplen, J.T., Wekerle, H., 1988. Suppression of experimentally induced autoimmune encephalomyelitis by cytolytic T–T cell interactions. Nature 332, 843–845.

Suvannavejh, G.C., Dal Canto, M.C., Matis, L.A., Miller, S.D., 2000. Fas-mediated apoptosis in clinical remissions of relapsing experimental autoimmune encephalomyelitis. J. Clin. Invest. 105, 223–231.

Tabi, Z., McCombe, P.A., Pender, M.P., 1994. Apoptotic elimination of $V\beta8.2^+$ cells from the central nervous system during recovery from experimental autoimmune encephalomyelitis induced by the passive transfer of $V\beta8.2^+$ encephalitogenic T cells. Eur. J. Immunol. 24, 2609–2617.

Tabi, Z., McCombe, P.A., Pender, M.P., 1995. Antigen-specific down-regulation of myelin basic protein-reactive T cells during spontaneous recovery from experimental autoimmune encephalomyelitis: further evidence of apoptotic deletion of autoreactive T cells in the central nervous system. Int. Immunol. 7, 967–973.

Tafani, M., Karpinich, N.O., Serroni, A., Russo, M.A., Farber, J.L., 2006. Re-evaluation of the distinction between type I and type II cells: the necessary role of the mitochondria in both the extrinsic and intrinsic signaling pathways upon Fas receptor activation. J. Cell. Physiol. 208, 556–565.

Tischner, D., Weishaupt, A., van den Brandt, J., Ip, C.W., Kerkau, T., Gold, R., Reichardt, H.M., 2007. Antigen therapy of experimental autoimmune encephalomyelitis selectively induces apoptosis of pathogenic T cells. J. Neuroimmunol. 183, 146–150.

Tsubata, T., Wu, J., Honjo, T., 1993. B-cell apoptosis induced by antigen receptor crosslinking is blocked by T-cell signal through CD40. Nature 364, 645–648.

Tsubata, T., Murakami, M., Nisitani, S., Honjo, T., 1994. Molecular mechanisms for B lymphocyte selection: induction and regulation of antigen-receptor-mediated apoptosis of mature B cells in normal mice and their defect in autoimmunity-prone mice. Phil. Trans. R. Soc. Lond. 345, 297–301.

Valentine, M.A., Licciardi, K.A., 1992. Rescue from anti-IgM-induced programmed cell death by the B cell surface proteins CD20 and CD40. Eur. J. Immunol. 22, 3141–3148.

Walker, D.G., Chuah, T., Rist, M.J., Pender, M.P., 2006. T-cell apoptosis in human glioblastoma multiforme: implications for immunotherapy. J. Neuroimmunol. 175, 59–68.

Wang, J., Taniuchi, I., Maekawa, Y., Howard, M., Cooper, M.D., Watanabe, T., 1996. Expression and function of Fas antigen on activated murine B cells. Eur. J. Immunol. 26, 92–96.

Weishaupt, A., Jander, S., Brück, W., Kuhlmann, T., Stienekemeier, M., Hartung, T., Toyka, K.V., Stoll, G., Gold, R., 2000. Molecular mechanisms of high-dose antigen therapy in experimental autoimmune encephalomyelitis: rapid induction of Th1-type cytokines and inducible nitric oxide synthase. J. Immunol. 165, 7157–7163.

Wekerle, H., Linington, C., Lassmann, H., Meyermann, R., 1986. Cellular immune reactivity within the CNS. Trends Neurosci. 9, 271–277.

White, C.A., McCombe, P.A., Pender, M.P., 1998a. Microglia are more susceptible than macrophages to apoptosis in the central nervous system in experimental autoimmune encephalomyelitis through a mechanism not involving Fas (CD95). Int. Immunol. 10, 935–941.

White, C.A., McCombe, P.A., Pender, M.P., 1998b. The roles of Fas, Fas ligand and Bcl-2 in T cell apoptosis in the central nervous system in experimental autoimmune encephalomyelitis. J. Neuroimmunol. 82, 47–55.

White, C.A., Nguyen, K.B., Pender, M.P., 2000. B cell apoptosis in the central nervous system in experimental autoimmune encephalomyelitis: roles of B cell CD95, CD95L and Bcl-2 expression. J. Autoimmun. 14, 195–204.

Wildbaum, G., Westermann, J., Maor, G., Karin, N., 2000. A targeted DNA vaccine encoding Fas ligand defines its dual role in the regulation of experimental autoimmune encephalomyelitis. J. Clin. Invest. 106, 671–679.

Wucherpfennig, K.W., Strominger, J.L., 1995. Molecular mimicry in T cell-mediated autoimmunity: viral peptides activate human T cell clones specific for myelin basic protein. Cell 80, 695–705.

Wurster, A.L., Rodgers, V.L., White, M.F., Rothstein, T.L., Grusby, M.J., 2002. Interleukin-4-mediated protection of primary B cells from apoptosis through Stat6-dependent up-regulation of Bcl-x_L. J. Biol. Chem. 277, 27169–27175.

Yang, Y., Merćep, M., Ware, C.F., Ashwell, J.D., 1995. Fas and activation-induced Fas ligand mediate apoptosis of T cell hybridomas: inhibition of Fas ligand expression by retinoic acid and glucocorticoids. J. Exp. Med. 181, 1673–1682.

Zacharchuk, C.M., Merćep, M., Chakraborti, P.K., Simons, S.S., Ashwell, J.D., 1990. Programmed T lymphocyte death: cell activation- and steroid-induced pathways are mutually antagonistic. J. Immunol. 145, 4037–4045.

Zettl, U.K., Mix, E., Zielasek, J., Stangel, M., Hartung, H.-P., Gold, R., 1997. Apoptosis of myelin-reactive T cells induced by reactive oxygen and nitrogen intermediates in vitro. Cell. Immunol. 178, 1–8.

Zhu, B., Luo, L., Chen, Y., Paty, D.W., Cynader, M.S., 2002. Intrathecal Fas ligand infusion strengthens immunoprivilege of central nervous system and suppresses experimental autoimmune encephalomyelitis. J. Immunol. 169, 1561–1569.

Zipp, F., Wendling, U., Beyer, M., Grieger, U., Waiczies, S., Wagenknecht, B., Haas, J., Weller, M., 2000. Dual effect of glucocorticoids on apoptosis of human autoreactive and foreign antigen-specific T cells. J. Neuroimmunol. 110, 214–222.