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Apoptosis of Inflammatory Cells in Immune Control of the Nervous System: Role of Glia

Michael P. Pender and Michael J. Rist

Abstract

Normal individuals have T lymphocytes capable of reacting to central nervous system (CNS) antigens such as myelin basic protein (MBP) (Martin et al., [1990]). In view of recent evidence indicating that T cells are much more cross-reactive than previously thought (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 autoreactive 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 has been proposed to be an important mechanism for controlling autoimmune attacks on the CNS (Pender et al., [1992]; Schmied et al., [1993]). Although other mechanisms, such as immune deviation (Wenkel et al., [2000]), may possibly also contribute to the control of the immune response in the CNS, this review will focus on T-cell apoptosis in the CNS and the role of glia in this process.

Keywords

T cell; microglia; astrocyte; experimental autoimmune encephalomyelitis; multiple sclerosis

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]). In view of recent evidence indicating that T cells are much more cross-reactive than previously thought (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 autoreactive 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 has been proposed to be an important mechanism for controlling autoimmune attacks on the CNS (Pender et al., [1992]; Schmied et al., [1993]). Although other mechanisms, such as immune deviation (Wenkel et al., [2000]), may possibly also

contribute to the control of the immune response in the CNS, this review will focus on T-cell apoptosis in the CNS and the role of glia in this process.

Role Of T-Cell 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. EAE can be induced by active immunization with myelin antigens and complete Freund's adjuvant or by the passive transfer of T cells sensitized to myelin antigens. It may follow either an acute monophasic course or a chronic relapsing-remitting course. T-cell apoptosis occurs in the CNS in acute EAE and has been proposed to contribute to the spontaneous recovery from disease (Pender et al., [1991], [1992]; Schmied et al., [1993]). It is maximal at the time of spontaneous clinical recovery (Schmied et al., [1993]; Tabi et al., [1994]; McCombe et al., [1996a]). 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]). It should also be noted that other inflammatory cells, such as macrophages/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. The occurrence of T-cell apoptosis is consistent with the relative lack of T-cell proliferation in the CNS in acute EAE (Ohmori et al., [1992]) and with the suggestion that T-cell loss from the CNS is responsible for remission of EAE (Zeine and Owens, [1993]).

An important question concerns the specificity of the T cells undergoing apoptosis in the CNS, as this may shed light on both the significance and mechanisms of T-cell apoptosis. If T-cell apoptosis involves autoreactive T cells, it would mean that it could control the disease process by eliminating the disease-causing encephalitogenic T cells. If T-cell apoptosis in the CNS selectively affects T cells reactive to CNS antigens, this would indicate that an antigen-specific mechanism, such as activation-induced cell death (i.e., cell death triggered by activation through the T-cell receptor (TCR)), is responsible. On the other hand, if T-cell apoptosis nonselectively involves any T cell in the CNS, it would indicate that the mechanism of apoptosis was unlikely to be activation-induced cell death, as only T cells encountering their specific antigen would be reactivated in the CNS. 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]; Tabi et al., [1995]; Bauer et al., [1998]), but there is controversy regarding the selectivity of the process for CNS-reactive T cells. One study found that Vβ8.2$^+$ 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 Vβ8.2$^+$ 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 specific genetic markers, Bauer et al. ([1998]) have shown 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, one involving specific antigen recognition and one not.

The occurrence of T-cell apoptosis in the CNS of bone marrow chimeras with EAE induced by the passive transfer of encephalitogenic T cells with a different major histocompatibility complex (MHC) 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 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]).

Apoptosis of inflammatory cells also occurs in the CNS in chronic relapsing EAE, especially during relapses (Pender et al., [1991]; Bonetti et al., [1997]; Malipiero et al., [1997]; Kohji et al., [1998]; Suvannavejh et al., [2000]), but the types of inflammatory cells have not been identified, except in the study by Bonetti et al. ([1997]) who reported apoptosis of $CD4^+$ T cells and macrophages/microglia. When EAE is reinduced in Lewis rats by active immunization after recovery from passively induced EAE there is accelerated and increased apoptosis of inflammatory cells in the spinal cord compared to that occurring in the first attack, suggesting that previous CNS inflammation may increase the level of inflammatory cell apoptosis (Gordon et al., [2001]). Flügel et al. ([2000]) have 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. In viral encephalomyelitis, T-cell apoptosis occurs in the CNS (Barac-Latas et al., [1994]) but it has not been determined whether this affects virus-specific T cells.

Possible Mechanisms Of T-Cell Apoptosis In The CNS

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

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

CD95-CD95L interaction on the same T cell (activation-induced apoptosis)
Interaction of astrocytic, microglial, or neuronal CD95L with T-cell CD95
Activation of T-cell TNFR1 pathway
Deficiency of IL-2 leading to passive cell death or disinhibition of T-cell CD95 pathway
Glucocorticosteroid-induced apoptosis
Production of nitric oxide or reactive oxygen intermediates by macrophages or glia
Interaction with regulatory T cells

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., [1991]). 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 tumor necrosis factor (TNF) receptor 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 signaling pathway for CD95 and related death receptors is dependent on the activity of a number of cysteine proteases (caspases) (Ashkenazi and Dixit, [1998]).

There is evidence that costimulation of previously activated T cells influences their survival. Costimulation by professional antigen-presenting cells (APC) (Liu and Janeway, [1990]; Groux et al., [1993]) or by the direct ligation of CD28 (Collette et al., [1997]) inhibits activation-induced apoptosis of previously activated T cells. Interleukin-2 (IL-2), expression of which is increased by costimulation of previously activated T cells (Schweitzer and Sharpe, [1998]), increases the expression of the anti-apoptotic protein Bcl-2 (Deng and Podack, [1993]; Mor and Cohen, [1996]; Mueller et al., [1996]) and inhibits activation-induced apoptosis of previously activated T cells (Groux et al., [1993]; Ford et al., [1996]). Furthermore, CD28 costimulation enhances the expression of the anti-apoptotic protein Bcl-x (Boise et al., [1995]; Mueller et al., [1996]), which can inhibit activation-induced T-cell apoptosis (Boise et al., [1995]). The inhibitory effect of Bcl-2 and the related Bcl-x on activation-induced T-cell death may be accounted for by their interaction with Bid, a pro-apoptotic protein involved in the CD95 death pathway (Li et al., [1998]; Luo et al., [1998]). CD28 costimulation may also prevent the induction of CD95L expression on T cells (Collette et al., [1997]). Therefore, whether TCR reactivation results in T-cell death or survival depends on the balance between pro-apoptotic and anti-apoptotic factors.

Several studies have examined the role of the CD95 pathway in T-cell apoptosis in the CNS. One approach has involved the use of mice which are genetically deficient in the expression of CD95 or CD95L (Malipiero et al., [1997]; Sabelko et al., [1997]; Waldner et al., [1997]; Okuda et al., [1998]; Bachmann et al., [1999]; Dittel et al., [1999]; Sabelko-Downes et al., [1999], Suvannavejh et al., [2000]). However, in some systems, deficiency of CD95 or CD95L interferes with the induction and/or effector phase of EAE (Malipiero et al., [1997]; Sabelko et al., [1997]; Waldner et al., [1997]; Okuda et al., [1998]; Bachmann et al., [1999]; Dittel et al., [1999]; Sabelko-Downes et al., [1999]). Sabelko et al. ([1997]) found that CD95 deficiency decreased the clinical signs of actively induced EAE and decreased the proportion of inflammatory cells undergoing apoptosis in the CNS but did not affect the degree of CNS inflammation. Bachmann et al. ([1999]) found that CD95L deficiency reduced inflammation and demyelination but did not reduce the proportion of T cells undergoing apoptosis in the CNS in actively induced EAE. The effect of CD95 or CD95L deficiency on the induction/effector phase of EAE makes it difficult to interpret the effect of such deficiency on T-cell apoptosis in the CNS. In an attempt to overcome this problem, the passive transfer model of EAE has been used. If the ligation of CD95 by CD95L on the same T cell is necessary for T-cell apoptosis in the CNS, it would be predicted that the passive transfer of encephalitogenic T cells deficient in CD95 or CD95L would result in decreased T-cell apoptosis and aggravation of EAE. However, CD95 or CD95L deficiency in the transferred T cells decreases disease severity in recipient B10.PL mice (Dittel et al., [1999]; Sabelko-Downes et al., [1999]), rendering these experiments difficult to interpret from the point of view of T-cell apoptosis. Interestingly, when encephalitogenic T cells from normal donors were transferred into CD95L-deficient mice the severity of EAE was increased, suggesting that recipient-derived CD95L contributes to the regulation of EAE (Dittel et al., [1999]; Sabelko-Downes et al., [1999]). This suggestion was supported by the finding of clusters of $CD4^+$ T cells surrounded by $CD11b^+$ macrophages/microglia in the spinal cords of CD95L-deficient recipients with a prolonged course of EAE (Sabelko-Downes et al., [1999]). Sabelko-Downes et al. ([1999]) proposed that CD95L expressed by host cells resident in, or recruited into, the CNS may ligate T-cell CD95 and thereby induce T-cell apoptosis in the CNS.

The effect of CD95 deficiency on T-cell apoptosis in the CNS may be easier to interpret in SJL mice in which the CD95 pathway does not play a major role in the induction/effector phase of EAE. In CD95-deficient SJL mice the severity of actively induced EAE is increased in association with decreased apoptosis of inflammatory cells in the CNS (Suvannavejh et al., [2000]). In intact SJL/J mice with chronic relapsing EAE, T cells in the CNS express CD95 and CD95L (Bonetti et al., [1997]).

Studies in the Lewis rat have also indicated roles for CD95 and CD95L in T-cell apoptosis in the CNS during recovery from acute EAE. 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, 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 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. Recently, Wildbaum et al. ([2000]) showed that the administration of anti-CD95L antibody to Lewis rats after the clinical peak of EAE decreases mononuclear cell apoptosis and increases mononuclear infiltration in the CNS, and delays clinical recovery.

Bachmann et al. ([1999]) proposed that the TNF-receptor-1 (TNFR1) pathway, not the CD95 pathway, is involved in T-cell apoptosis in the CNS. They found decreased T-cell apoptosis in the CNS when EAE was actively induced in TNFR1-deficient mice or in mice deficient in both TNF and lymphotoxin. However, interruption of the TNFR1 pathway also reduced the amount of CNS demyelination. It is therefore possible that the reduction in T-cell apoptosis was due to a decrease in the amount of soluble myelin antigen available to trigger activation-induced apoptosis rather than indicating direct involvement of the TNFR1 pathway in the T-cell apoptotic process. K¨orner et al. ([1995]) also found that TNF blockade reduced the rate of T-cell loss from the CNS in EAE and suggested that this might represent delayed T-cell apoptosis, but again the TNF blockade probably reduced CNS demyelination as it prevented the development of neurological signs. It has also been reported that the administration of anti-TNF-α antibody decreases the proportion of T cells undergoing apoptosis in the CNS of rats with EAE treated with soluble MBP (Weishaupt et al., [2000]).

Glucocorticosteroid-Induced Apoptosis

Another possible mechanism for T-cell apoptosis in the CNS is glucocorticosteroid-induced apoptosis. Glucocorticosteroids can induce T-cell apoptosis in vitro (Nieto and Lopez-Rivas, [1989]) and are endogenously released during spontaneous recovery from acute EAE (MacPhee et al., [1989]). Adrenalectomy, which prevents the production of glucocorticosteroids, reduces the level of T-cell apoptosis in the CNS in EAE, indicating that glucocorticosteroids may contribute to the T-cell apoptosis (Smith et al., [1996]). However, glucocorticosteroid release is not solely responsible for the T-cell apoptosis because T-cell apoptosis occurs in the CNS during recovery from mild EAE without glucocorticosteroid release (Smith et al., [1996]). Furthermore, glucocorticosteroid-induced apoptosis can not explain the selective apoptotic elimination of CNS-reactive T cells. Although the administration of exogenous glucocorticosteroids increases the level of T-cell apoptosis in the CNS in EAE (McCombe et al., [1996b]; Nguyen et al., [1997]; Schmidt et al., [2000]), it actually inhibits the selective apoptosis of MBP-specific T cells (McCombe et al., [1996b]). This inhibition can be accounted for by the ability of glucocorticosteroids to antagonize activation-induced cell death (Zacharchuk et al., [1990]), probably at least in part by reducing the expression of CD95L (Yang et al., [1995]), and possibly by also directly inhibiting the CD95 pathway (Zipp et al., [2000]). Thus in mild EAE, activation-induced cell death may be the predominant mechanism of T-cell apoptosis in the CNS, whereas in more severe EAE there may be superimposed glucocorticosteroid-induced nonselective T-cell apoptosis.

Other Possible Mechanisms

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]). Chu et al. ([2000]) found that interferon-γ (IFN-γ) deficiency increases the severity of EAE and decreases the apoptosis of activated T cells in the CNS. They proposed that the decrease in T-cell apoptosis was due to a lack of IFN-γ-induced nitric oxide production by macrophages and microglia in the CNS. However, another study 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 (Bachmann et al., [1999]). In a review of nitric oxide and its role in apoptosis, Brüne et al. ([1998]) detail how nitric oxide can have both anti-apoptotic and pro-apoptotic properties.

Issazadeh et al. ([2000]) have proposed that T-cell apoptosis in the CNS may result from passive cell death due to deprivation of growth factors such as IL-2. To investigate this they used mice that transgenically express the anti-apoptotic protein Bcl-x_L, which can inhibit T-cell apoptosis due to growth factor deprivation. They found that the over-expression of Bcl-x_L in T cells increases the severity of EAE and decreases the apoptosis of inflammatory cells in the CNS (Issazadeh et al., [2000]). However, inhibition of T-cell apoptosis by Bcl-x_L does not necessarily indicate that the apoptosis is due to passive cell death because Bcl-x_L can also inhibit activation-induced T-cell apoptosis (Boise et al., [1995]). In Lewis rats with EAE, Vβ 8.2^+ T cells expressing the anti-apoptotic protein Bcl-2 are protected against apoptosis in the CNS, which might be explained by inhibition of CD95-mediated activation-induced T-cell apoptosis (White et al., [1998b]). It is possible that passive cell death and activation-induced cell death both contribute to T-cell apoptosis in the CNS. There is also some overlap in the mechanisms of glucocorticosteroid-induced apoptosis and passive cell death due to IL-2 deprivation, as IL-2 induces the expression of Bcl-2 and rescues T cells from glucocorticosteroid-induced apoptosis (Mor and Cohen, [1996]).

Other possible mechanisms for T-cell apoptosis in the CNS include interaction with regulatory T cells (Sun et al., [1988]), an effect of gangliosides (Irani, [1998]), and the T-cell expression of the pro-apoptotic protein Bax (Bonetti et al., [1997]; Kohji and Matsumoto, [2000]).

Role Of Glia And Neurons In T-Cell Apoptosis In The CNS

T cells may interact with glial cells and neurons in the CNS and thereby receive signals that influence their susceptibility to apoptosis. These signals include TCR ligation, costimulatory signals and apoptosis-inducing signals. If a glial cell expresses class II MHC molecules it can present antigenic peptides to $CD4^+$ T cells. As discussed above, TCR ligation upregulates CD95 expression and induces CD95L expression by the T cell and can thus lead to activation-induced apoptosis. If a glial cell expresses costimulatory molecules such as CD80 or CD86, it may provide a costimulatory signal to the T cell through CD28 and thereby induce the production of anti-apoptotic proteins. By contrast, if the glial cell expresses CD95L it may ligate T-cell CD95 and induce apoptosis. Glial cells may also produce other pro-apoptotic signals such as nitric oxide, which might also induce T-cell apoptosis. Recent studies have implicated astrocytes, microglia, and neurons as CNS residents that can influence the susceptibility of T cells to apoptosis. Glial cells also participate in the phagocytosis of apoptotic lymphocytes in the CNS (Nguyen and Pender, [1998]). Phagocytosis of apoptotic cells is a general mechanism for clearing these cells from tissues and may have an important role in preventing the leakage of noxious contents from the dying cells (Ren and Savill, [1998]).

Interactions of T Cells With Astrocytes

Antigen presentation by astrocytes from Lewis rats inhibits MBP-specific T-cell proliferation (Matsumoto et al., [1992]., [1993]) and primes MBP-specific T cells for apoptosis in vitro

(Gold et al., [1996]). In Lewis rats with EAE, apoptotic inflammatory cells associate more closely with astrocytes than with microglia (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]). Such a mechanism would not necessarily depend on antigen presentation by astrocytes. Astrocytes expressing CD95L can induce apoptosis in target cells in vitro (Bechmann et al., [1999]; Choi et al., [1999]). Another possible role for astrocytes in Lewis rats with EAE is that astrocytes 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]). It is possible that the association of apoptotic inflammatory cells with astrocytes in the CNS (Kohji et al., [1998]) is the effect rather than the cause of apoptosis, as astrocytes can phagocytose apoptotic lymphocytes in EAE (Nguyen and Pender, [1998]). It should be noted that astrocytes from SJL mice can express the costimulatory molecule CD80 (B7-1) and, in contrast to astrocytes from Lewis rats, induce the proliferation of myelin-specific T cells in vitro (Tan et al., [1998]). This difference may contribute to the chronic relapsing course of EAE in SJL mice as opposed to the acute monophasic course in Lewis rats.

Interactions of T Cells With Microglia

In vitro experiments have shown that interactions of T cells with microglia can lead to either proliferation or apoptosis of the T cells. The outcome of the interaction may be influenced by the activation states of the microglia and T cells and by variations in the sources of microglia.

Exposure of murine microglial cells to IFN-γ in vitro results in efficient antigen presentation to, and proliferation of, antigen-specific T cells (Frei et al., [1987]). Aloisi et al. ([1998]) have reported that IFN-γ increases the expression of class II MHC molecules, CD54 and CD40 by murine microglia but that, unless it is combined with lipopolysaccharide, it does not induce the expression of the costimulatory molecule CD86.

By contrast, antigen presentation to MBP-specific T cells by rat microglia in vitro results in T-cell apoptosis, which can be prevented by the addition of IL-2 (Ford et al., [1996]). These findings may be explained by the induction of activation-induced T-cell apoptosis through interaction of CD95L and CD95 on the same T cell, in the absence of sufficient costimulation to inhibit the CD95 pathway. 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 clinical course (Matsumoto et al., [1986]) indicates that microglia are more likely than astrocytes to present antigens to T cells in vivo. An alternative mechanism for the microglial induction of T-cell apoptosis is the direct ligation of T-cell CD95 by microglial CD95L. Human microglia can express CD95L and can induce apoptosis in CD95-expressing target cells in vitro (Frigerio et al., [2000]). Antigen presentation by microglia is not necessary for this mechanism to operate. Microglia also appear to play a role in the phagocytosis of apoptotic lymphocytes in the CNS in EAE (Nguyen and Pender, [1998]) and are able to phagocytose apoptotic encephalitogenic T cells in vitro (Chan et al., [2001]).

Interactions of T Cells With Neurons

It has also been proposed that neurons induce T-cell apoptosis in the CNS. Neurons 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]). Furthermore, MBP-specific T cells rapidly undergo apoptosis in the immediate vicinity of CD95L-expressing neurons of the axotomized facial nerve in vivo, and 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 rapid apoptotic elimination of MBP-specific T cells after axotomy is dependent on antigen presentation by microglia. It may also be possible that the close association of apoptotic T cells with, and their internalization by, neurons (Flügel et al., [2000]) are the result rather than the cause of apoptosis, if neurons can phagocytose apoptotic lymphocytes in the same way as can oligodendrocytes and astrocytes (Nguyen and Pender, [1998]).

Apoptosis Of Microglia, Macrophages, And B Cells In The CNS

In comparison with T-cell apoptosis, considerably less attention has been given to the mechanisms and significance of apoptosis of microglia, macrophages and B cells in the CNS. Microglia express CD95 and undergo apoptosis in vitro when incubated with CD95L-expressing cells (Lee et al., [2000]). However, the expression of CD95 or CD95L by microglia and macrophages in the CNS of rats with EAE was not found to increase their susceptibility to apoptosis, suggesting that microglial and macrophage apoptosis may not be mediated through the CD95 pathway in vivo (White et al., [1998a]). In contrast, the expression of CD95 and CD95L by B cells in the CNS of rats with EAE increases their vulnerability to apoptosis, whereas the expression of Bcl-2 is associated with their protection from apoptosis (White et al., [2000]). This suggests that B cell apoptosis in the CNS may be mediated through the CD95 pathway. Apoptosis of B cells, microglia, and macrophages in the CNS may contribute to the termination of immune responses in the CNS, as does T-cell apoptosis.

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