Activation-Induced Apoptosis of Auto-reactive and Alloreactive T Lymphocytes in the Target Organ as a Major Mechanism of Tolerance

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Abstract

Normal individuals have mature T lymphocytes that are capable of reacting to self-antigens and can be activated by cross-reacting environmental antigens. The mechanism that maintains immune tolerance and prevents these activated autoreactive T cells from causing autoimmune disease is unclear. We have previously hypothesized that activation-induced apoptosis of previously activated autoreactive T cells in the target organ is a major mechanism for maintaining tolerance. Here I review the current evidence to support this hypothesis. It is proposed that when activated autoreactive T cells enter the target organ, they are reactivated mainly by non-professional antigen-presenting cells (APC) and deleted by activation-induced apoptosis through the Fas (CD95) pathway before producing significant target organ damage. This apoptosis occurs because the reactivated T cells do not receive sufficient costimulation from the non-professional APC to up-regulate their expression of Bcl-2-related anti-apoptotic proteins, which inhibit the CD95 pro-apoptotic pathway. This is in contrast to the situation in peripheral lymphoid organs, where reactivation of T cells by professional APC results in sufficient costimulation-induced up-regulation of Bcl-2-related proteins to inhibit the CD95 pathway and allow T cell proliferation and survival as memory T cells. Activation-induced apoptosis of alloreactive T cells in allografts can similarly account for spontaneous allograft acceptance, as occurs after MHC-mismatched liver transplantation.

Keywords: apoptosis, autoimmunity; CD95 (Fas); experimental autoimmune encephalomyelitis; immune tolerance; T lymphocyte; transplantation.

Introduction

Tolerance

All normal individuals have T lymphocytes capable of reacting to self-antigens. Because there is increasing evidence that T cells are much more cross-reactive than previously thought, it is likely that these autoreactive T cells are often primed by exposure to cross-reacting environmental antigens. Why then do normal individuals not develop autoimmune disease? The question of the mechanism of immune tolerance is an old one, but the evidence that T cells are highly cross-reactive emphasizes the importance of immune tolerance in allowing normal function and survival of the body and its organs. Some definitions of immune tolerance make assumptions about the mechanism of tolerance and lead to confusion. In the present article, tolerance will be defined as the survival of the normal structure and function of a tissue or organ in the presence of an activated immune response against components of the tissue or organ. Immune tolerance applies not only to self-tolerance, but also to the spontaneous tolerance that develops after organ
transplantation, particularly of the liver. Explanations for immune tolerance that depend on sequestration of tissue-specific antigens are inadequate to account for immune tolerance, in view of the high level of T cell cross-reactivity. Autoreactive T cells activated by cross-reacting environmental antigens will enter any organ, including those with blood–tissue barriers such as the brain, and will eventually encounter their target antigen.

A number of mechanisms have been proposed to maintain immune tolerance through the regulation of activated T cells. These include T cell anergy, regulatory T cells producing immunosuppressive cytokines and activation-induced T cell apoptosis in undefined sites. The present article will review the current evidence supporting our previously proposed hypothesis that activation-induced T cell apoptosis in the target organ is a major mechanism of immune tolerance.

**Activation-induced T cell apoptosis**

The term ‘activation-induced apoptosis’ refers to the apoptosis of thymocytes or previously activated mature T cells, triggered by activation through the T cell receptor (TCR). The CD95 pathway and related death receptor pathways are mediated through the activation of the Fas (CD95) pathway and related death receptor pathways. The CD95 pathway is activated by the ligation of cell surface CD95 by CD95 ligand (CD95L; also known as Fas ligand) and can occur by the interaction of CD95 and CD95L on the same T cell. T cell receptor ligation up-regulates CD95 expression and induces the expression of CD95L. The intracellular signalling pathway for CD95 and related death receptors is dependent on the activity of a number of cysteine proteases (caspases).

Activated caspase-8 can mediate apoptosis via two pathways: (i) direct activation of downstream effector caspases (such as caspase-3) by direct cleavage; or (ii) indirect activation of downstream effector caspases by causing the release of cytochrome c from mitochondria. Bcl-2 and Bcl-xL block downstream caspase activation and apoptosis mediated by the indirect CD95 signalling pathway, but not by the direct pathway. The contributions of these two pathways vary among different cell types, probably owing to different levels of activated caspase-8 and its downstream substrates. It appears that some T cells use the direct pathway whereas other T cells use the indirect pathway. In the direct pathway, a large amount of caspase-8 is activated following CD95 cross-linking and this directly cleaves and thereby activates downstream caspases such as caspase-3, which mediate the final destruction of the cell including DNA cleavage and the morphological changes of apoptosis. In the indirect pathway, a small amount of activated caspase-8 cleaves BID, a Bcl-2-interacting protein, into a truncated form that promotes cytochrome c release from mitochondria, with the resultant activation of the downstream effector caspases such as caspase-3. It is also possible that truncated BID may activate downstream caspases by a cytochrome c-independent pathway. BID contains the Bcl-2 homologous domain 3 (BH3 domain), through which it interacts with Bcl-2-related proteins that can inhibit the apoptotic changes induced by truncated BID. The interaction of BID with Bcl-2-related proteins can explain the inhibition of CD95-mediated apoptosis by Bcl-2 and Bcl-xL.

There is evidence that costimulation of previously activated T cells influences their survival. Costimulation by professional APCs or by the direct ligation of CD28 inhibits activation-induced apoptosis of previously activated T cells. Interleukin (IL)-2, expression of which is increased by co-stimulation of previously activated T cells, increases the expression of Bcl-2 and inhibits activation-induced apoptosis of previously activated T cells. Furthermore, CD28 costimulation enhances the expression of Bcl-xL, which can inhibit activation-induced T cell apoptosis. The inhibitory effect of Bcl-2-related proteins on activation-induced T cell death may be accounted for by their interaction with BID and their inhibition of the CD95 pathway (see earlier). CD28 costimulation may also prevent the induction of CD95L expression. Therefore, whether TCR reactivation results in T cell death or survival depends on the balance between pro-apoptotic and anti-apoptotic factors. Repeated TCR activation promotes the CD95 pro-apoptotic pathway, whereas costimulation promotes the Bcl-2-related anti-apoptotic pathway. It is probable that effector T cells are like other previously activated T cells in their dependence on costimulation for survival. Thus, the reactivation of effector T cells in the absence of costimulation may lead to final effector function and cell death, whereas the reactivation of effector T cells in the presence...
of costimulation may allow ongoing effector function and eventual persistence as memory T cells. This would be consistent with the linear differentiation pathway model of memory T cell differentiation, in which memory T cells are derived directly from effector cells.28 Effector T cells may differ from other previously activated T cells only by having a shorter time interval since last being activated.

The inhibitory action of IL-2 on activation-induced T cell apoptosis22,27 appears to contradict the observation that previous exposure to IL-2 increases the susceptibility to activation-induced apoptosis.25 This discrepancy can be explained by differences in the timing of IL-2 exposure. The increased susceptibility to activation-induced cell death of T cells previously exposed to IL-2 may be due to the IL-2-induced up-regulation of CD95L expression and suppression of the expression of FLICE (caspase-8)-inhibitory protein (FLIP), an inhibitor of CD95 signalling.30 Thus, previous activation through the TCR and IL-2 increases the susceptibility to activation-induced apoptosis, which can be overcome by further IL-2 at the time of reactivation of the TCR. The outcome of TCR reactivation is determined by the balance between proapoptotic and anti-apoptotic factors, which are influenced by the circumstances of previous and present T cell activation.

The site of activation-induced apoptosis of previously activated T cells also needs to be considered. For autoreactive and all reactive T cells, the target organ is likely to be the site of activation-induced apoptosis for two reasons. First, the target organ contains the greatest amount of antigen recognized by the T cells. Second, it also contains non-professional APC, which can present this antigen to the TCR in the context of class I or class II major histocompatibility complex (MHC) molecules, but which fail to provide sufficient costimulation to inhibit activation-induced apoptosis. We have previously hypothesized that activation-induced apoptosis of autoreactive T cells in the target organ following reactivation by non-professional APC is a general mechanism for maintaining T cell tolerance and protecting against autoimmune disease.5,6 A model for T cell tolerance depending on the lack of costimulation in the target organ has also been proposed by Matzinger.31 T cell apoptosis will now be considered in the various target organs in which it has so far been reported or implicated.

T cell apoptosis in the central nervous system

Experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) is a T cell-mediated autoimmune demyelinating disease of the central nervous system (CNS) that is widely studied as a model of the human demyelinating disease multiple sclerosis.32 T cell apoptosis occurs in the CNS in rats with acute EAE and has been proposed to contribute to the spontaneous recovery from acute EAE and the development of tolerance.5,33,34 It is maximal at the time of spontaneous clinical recovery34–36 and is a major mechanism for eliminating encephalitogenic T cells from the CNS.35–38 This T cell apoptosis is consistent with the relative lack of T cell proliferation in the CNS in acute EAE.39 It should be noted that macrophages,40–42 microglia41,42 and B cells (CA White et al., unpubl. obs., 1999) also undergo apoptosis in the CNS in EAE. To study T cell apoptosis in the target organ, it is therefore essential to demonstrate apoptosis of cells expressing T cell markers rather than simply demonstrating apoptosis in an unlabelled inflammatory cell infiltrate.

It has been proposed that the apoptotic deletion of auto-reactive T cells in the CNS is due to activation-induced apoptosis following reactivation by CNS non-professional APC, such as astrocytes or microglia, which fail to deliver the co-stimulatory signal needed to inhibit activation-induced apoptosis.5,35,37 This is supported by studies showing that the T cell apoptotic process in the CNS selectively affects CNS-reactive T cells, whereas the activated non-CNS-reactive T cells that accumulate in the CNS in EAE recirculate to the peripheral lymphoid organs.35,37 It is also supported by the following additional in vivo observations. First, the apoptosis of auto-reactive T cells in the CNS in EAE is inhibited by the administration of glucocorticoid,43 which is known to antagonize activation-induced apoptosis in vitro, probably at least in part by reducing the expression of CD95L.44,45 Second, autoreactive T cells expressing CD95 or CD95L are highly vulnerable to apoptosis in the CNS in EAE, whereas autoreactive T cells expressing Bcl-2 are relatively protected from apoptosis.36 Third, the intraperitoneal administration of the soluble target antigen, myelin basic protein, markedly increases the level of CD95-dependent autoreactive T cell apoptosis in the CNS, but not in the peripheral lymphoid organs, and ameliorates the disease in rats with EAE.45 Given that the systemic administration of soluble myelin basic protein should
result in its distribution throughout lymphoid and non-lymphoid organs including the CNS, this finding indicates that the environment in the CNS is more conducive to activation-induced T cell apoptosis than the environment of the spleen or the lymph node draining the site of inoculation with myelin basic protein and adjuvants. One possible explanation is that professional APC in the peripheral lymphoid organs provide high levels of costimulation with resultant high T cell levels of anti-apoptotic proteins, such as Bcl-2, which inhibit CD95-mediated activation-induced apoptosis, whereas the predominantly non-professional APC in the CNS are unable to provide sufficient costimulation to inhibit this apoptosis. Autoreactive T cells in the CNS may also have higher levels of CD95 and CD95L expression than those in the peripheral lymphoid organs, because they are more likely to have been repeatedly activated by antigen.

In vitro studies have implicated astrocytes and microglia as CNS non-professional APC that induce T cell apoptosis by their interactions with autoreactive T cells. Antigen presentation by astrocytes inhibits T cell proliferation and primes T cells for apoptosis. Antigen presentation to autoreactive CD4+ T cells by microglia results in T cell apoptosis which can be prevented by the addition of IL-2. The finding that apoptotic cells are more closely associated with astrocytes than with microglia in the CNS in EAE has been interpreted as indicating that astrocytes, rather than microglia, induce T cell apoptosis. However, the fact that microglia express considerably higher levels of class II MHC molecules than astrocytes in EAE and that this increases during the clinical course indicates that microglia are more likely than astrocytes to present antigen to T cells in vivo.

The conclusion that the T cell apoptotic process in the CNS in EAE selectively affects CNS-reactive T cells has recently been challenged by the finding that non-CNS-reactive T cells also undergo apoptosis in the CNS in acute EAE. However, the level of non-CNS-reactive T cell apoptosis appeared to be considerably less than the level of CNS-reactive T cell apoptosis and may be explained by the effects of the endogenous release of corticosterone, which occurs during spontaneous clinical recovery from moderate to severe EAE but not from mild EAE. This is supported by the fact that adrenalectomy reduces T cell apoptosis in the CNS in EAE and that the administration of the glucocorticoid dexamethasone increases apoptosis of non-CNS-reactive, but not CNS-reactive, T cells. Thus, the T cell apoptosis in the CNS in EAE may be due to a combination of activation-induced apoptosis of CNS-reactive T cells and glucocorticoid-induced apoptosis of non-CNS-reactive T cells. 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 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. However, the TCR of the encephalitogenic T cells may still interact with the MHC–peptide complex 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 (see later). Bauer et al. have suggested that CNS-infiltrating T cells of any specificity are eliminated by apoptosis through an as yet undetermined mechanism. This concept has major implications for the maintenance of T cell memory for any antigen, as activated T cells (including memory cells) of any specificity can enter the normal or inflamed CNS and would be deleted there. This would lead to a progressive loss of memory T cells, particularly if the same process also occurred in other organs such as the testis and eye (see later). Such a non-specific deletion of all activated T cells would seem to be a poorly controlled waste of useful T cells that would not be favourable for the long-term survival of the whole animal.

The earlier discussion has dealt with spontaneous recovery from acute EAE. Lewis rats that have recovered from acute EAE induced by immunization with myelin basic protein and adjuvants develop tolerance to myelin basic protein, as evidenced by the resistance to re-induction of EAE by active immunization. It has been suggested that ongoing activation-induced T cell apoptosis in the CNS may contribute to this tolerant state. The proportions of auto-reactive T cells expressing CD95 and CD95L in the CNS increase during the late recovery phase of EAE, raising the possibility that activation-induced apoptosis is enhanced in the previously inflamed CNS compared to the normal CNS because of the increased availability of myelin antigens following demyelination and the increased class II MHC expression by microglia. Increased activation-induced apoptosis of T cells in previously inflamed regions of the CNS may account for the redistribution of lesions in subsequent milder or subclinical episodes of EAE induced by rechallenge, a phenomenon termed target organ resistance. Further studies are needed to determine to what extent activation-induced T cell apoptosis contributes to the tolerant state that develops after recovery from acute EAE.
**Multiple sclerosis**

Multiple sclerosis is a chronic inflammatory demyelinating disease of the CNS that results in recurrent attacks, or sometimes a progressive course, of neurological dysfunction. There is increasing evidence that multiple sclerosis is an autoimmune disease.\(^{38,59}\) Apoptotic T cells have been found in the CNS of patients with multiple sclerosis,\(^{60,61}\) but these may have been non-CNS-reactive T cells dying by glucocorticoid-induced apoptosis. One study found that T cell apoptosis was strikingly infrequent.\(^{61}\) In these studies, apoptosis has been investigated by the detection of DNA fragments in situ using the terminal deoxyribonucleotidyl transferase-mediated dUTP-digoxigenin nick end-labelling (TUNEL) assay. This technique does not discriminate among apoptosis, necrosis and postmortem autolysis.\(^{62,63}\) The problem can be overcome if it has already been determined by electron microscopy of well fixed tissue that cell death is occurring by apoptosis rather than by necrosis. However, it remains a potential problem for suboptimally fixed human tissue obtained post-mortem, where autolysis may lead to false-positive results for apoptosis.

It has been hypothesized that multiple sclerosis is due to a genetically determined failure of activation-induced apoptosis of autoreactive T cells in the CNS.\(^{64}\) Activation-induced T cell apoptosis may fail in the CNS because of two broad types of abnormality. First, there may be an abnormality in CNS APC with increased costimulatory ability or possibly decreased CD95L expression by these APC. Second, there may be an abnormality in the T cells leading to underactivity of the pro-apoptotic CD95 pathway or overactivity of the anti-apoptotic Bcl-2-related protein family. Further studies are needed to determine whether there is a failure of T cell apoptosis in the CNS in multiple sclerosis.

**T cell apoptosis in the peripheral nervous system**

Experimental autoimmune neuritis is a T cell-mediated autoimmune demyelinating disease of the peripheral nervous system. T cell apoptosis occurs in the peripheral nervous system of rats with acute experimental autoimmune neuritis.\(^{65,66}\) It is maximal at the time of spontaneous clinical recovery and has been suggested to contribute to the recovery process and monophasic clinical course. The intravenous administration of the target antigen, P2 protein, markedly increases the level of T cell apoptosis in the peripheral nervous system and ameliorates the disease, indicating that the apoptosis is due to activation-induced cell death of autoreactive T cells.\(^{67}\) The administration of glucocorticoid also increases the level of T cell apoptosis in the peripheral nervous system in experimental autoimmune neuritis\(^{68}\) but it has not been determined whether this involves the autoreactive or non-autoreactive T cells.

**T cell apoptosis in the liver**

**Autoreactive T cells**

Apoptotic inflammatory cells are present in the liver of irradiated transgenic mice that express H-2K\(^b\) in the liver and have been injected with lymph node cells from transgenic mice expressing in their T cells a K\(^b\)-specific TCR.\(^{69}\) It has been suggested that these apoptotic cells are autoreactive (K\(^b\)-specific) CD8\(^+\) T cells that have been deleted in the liver.\(^{69}\) It has also been proposed that naïve autoreactive CD8\(^+\) T cells circulate to the liver and undergo apoptosis after being activated by hepatocytes which act as non-professional APC.\(^{70}\) However, an alternative explanation is that the K\(^b\) transgene is processed in the draining lymph nodes (as can occur with other self-antigens\(^{71}\)), where it activates the K\(^b\)-specific T cells in the context of the background class I MHC (H-2\(^d\)) molecules and the activated K\(^b\)-specific T cells then enter the liver, where they are reactivated and deleted after interacting with hepatocytes or other non-professional APC presenting K\(^b\) in the context of the background H-2\(^d\) molecules.

**Alloreactive T cells**

Major histocompatibility complex-mismatched liver allografts are often accepted spontaneously, in contrast to the rejection of other MHC-mismatched organs, such as the skin, heart and kidney.\(^{72}\)
Apoptosis of inflammatory cells is prominent in spontaneously accepted liver allografts and is associated with a decline in the cytotoxic T lymphocyte activity of the graft-infiltrating cells. The administration of IL-2 inhibits the apoptosis, increases the cytotoxic T lymphocyte activity of the graft-infiltrating cells and induces acute graft rejection. On the basis of these results, it has been suggested that T cell apoptosis in the liver may be responsible for spontaneous liver allograft acceptance. These findings are consistent with activation-induced apoptosis of alloreactive T cells in the liver, following interaction of the T cells with MHC-expressing hepatocytes that fail to provide the costimulation required to up-regulate the T cell levels of antiapoptotic Bcl-2-related proteins. The administration of IL-2 would increase the T cell levels of these anti-apoptotic proteins and inhibit the T cell apoptosis, with resultant rejection of the allograft. The spontaneous rejection of other transplanted organs, such as skin and heart, may be related to the smaller size and lower antigen load (from parenchymal cells and passenger leukocytes) of these organs. Thus, in small allografts the alloreactive T cells may destroy the transplanted organ before the majority of these T cells have been deleted by activation-induced apoptosis. The spontaneous acceptance of multiple heart and kidney grafts in a single recipient that would rapidly reject these organs if they were transplanted singly is consistent with this concept.

Possible role of T cell apoptosis in other organs

Eye
Apoptosis of inflammatory cells occurs in the anterior chamber of the eye infected by herpes simplex virus. This apoptosis is not observed in mutant mice lacking CD95 or CD95L expression, indicating that it is mediated through the CD95 pathway. Studies on radiation bone marrow chimeras have suggested that CD95L expression by resident cells of the eye inhibits inflammation and, by inference, is involved in the apoptotic process, although the role of CD95L expression by T cells was not examined. It was concluded that an interaction between CD95L-expressing cells of the eye and CD95-expressing lymphocytes is responsible for this apoptosis and for the ‘immune privilege’ of the eye.

Testis
One study has reported that testicular grafts expressing CD95L survive, whereas those not expressing CD95L are rejected when transplanted into allogeneic mice. Although apoptosis was not assessed, the authors concluded that an interaction between CD95L on testicular cells and CD95 on infiltrating T cells resulted in apoptosis of alloreactive T cells and graft acceptance and was responsible for the ‘immune privilege’ of the testis. Another study found that CD95L expression did not protect the testis from rejection. Further studies are needed to determine whether T cell apoptosis occurs in the testis, particularly in experimental autoimmune orchitis.

Ovary
Experimental autoimmune oophoritis is an autoimmune CD4+ T cell-mediated ovarian disease that is studied as a model of human premature ovarian failure. As in the case of acute EAE, mice immunized with a peptide of ZP3, a major glycoprotein in the zona pellucida, together with adjuvants, spontaneously recover from the disease and become resistant to disease reinduction. Interestingly, although the previously inflamed endogenous ovaries are resistant to reinduction of disease, ovaries implanted after disease recovery are susceptible to oophoritis, indicating target organ resistance. The mechanism of target organ resistance has not been determined, but one possible explanation is that there is increased activation-induced apoptosis of autoreactive T cells in the previously inflamed ovary as a result of increased availability of ovarian antigen and increased parenchymal class II MHC expression. It should be noted that the impact of activation-induced apoptosis in the ovary on the peripheral lymphoid pool of ovary-reactive T cells may be considerably less than the impact of this process in the CNS on the peripheral lymphoid pool of
CNS-reactive T cells, because the smaller size of the ovary would result in it being a less effective ‘sink’ for the elimination of ovary-reactive T cells.

**Salivary glands in primary Sjögren’s syndrome and synovia in rheumatoid arthritis**

Primary Sjögren’s syndrome is a chronic autoimmune disease characterized by T cell infiltration of the exocrine glands, including the salivary and lacrimal glands. One study found a low level of lymphocyte apoptosis in the periductal inflammatory foci of the salivary glands, compared with that in the interstitium. The authors suggested that impaired T cell apoptosis in the salivary gland may explain the chronic nature of the lesions. It has also been reported that there is a lack of T cell apoptosis in the inflammatory infiltrates in the synovia of patients with rheumatoid arthritis.

How does activation-induced apoptosis of antiviral T cells in the infected organ not prevent viral clearance?

It would be expected that T cells directed against infectious agents would be deleted by activation-induced apoptosis in infected organs. Apoptosis of inflammatory cells occurs in the virally infected CNS, eye and liver, although it has not been determined whether antiviral T cells are involved. How does activation-induced apoptosis of antiviral T cells in the infected organ not prevent viral clearance when the same apoptotic process in autoreactive T cells prevents autoimmune disease? The most obvious explanation is the difference in antigen load. In the virally infected organ the total amount of viral antigen is likely to be much less than the total amount of individual major self-antigens. Thus, the antiviral T cells would be expected to clear the virus from the organ before a significant proportion of these T cells is eliminated by activation-induced apoptosis; once virus is cleared the antiviral T cells would continue to recirculate as memory cells. It is also possible that viral infection induces the expression of costimulatory molecules on normally non-professional parenchymal APC and that the costimulation up-regulates the levels of anti-apoptotic Bcl-2-related proteins in the antiviral T cells and thus inhibits T cell apoptosis.

**Conclusion**

In conclusion, there is increasing evidence that activation-induced apoptosis of previously activated autoreactive T cells in the target organ maintains immune tolerance and prevents autoimmune disease. Similarly, activation-induced apoptosis of alloreactive T cells in allografts can account for spontaneous allograft acceptance.

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