Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Apoptosis in brain-specific autoimmune disease

Jan Bauer, Hartmut Wekerle and Hans Lassmann

University of Vienna, Vienna, Austria and Max-Planck Institute for Psychiatry, Martinsried, Germany

Recent neuropathological studies of experimental autoimmune encephalomyelitis have focused attention on the high number of cells in the lesions that show typical morphological features of apoptosis. Surprisingly, it has turned out that the vast majority of apoptotic cells are T lymphocytes and that they actually represent the antigen-specific T-cell population responsible for the induction of the disease. Taken together, these data suggest that clearance of autoimmune inflammation in the nervous system is accomplished by the destruction of the antigen-specific T-cell population within the lesions. This may explain the low level of central nervous system specific T-cell memory formation, as well as previously unexplained phenomena of 'epitope spreading', in autoimmune inflammation of the nervous system.

Current Opinion in Immunology 1995, 7:839-843

Introduction

Cell death is a key event in physiological, as well as pathological, processes of the immune system. It can be mediated by two principally different mechanisms: apoptosis and necrosis. Apoptosis refers to a series of morphological changes that occur in dying cells and that are different from the changes seen in necrosis [1]. Unlike necrosis, which mediates cell death by disruption of the plasma membrane and lytic degradation of cytoplasmic organelles, a cell undergoing apoptosis loses volume, the cytoplasm condenses, and the nucleus shows condensation and clumping of the chromatin in parallel with DNA fragmentation. In the final stage, cell fragments pinch off forming so called 'apoptotic bodies'. Biochemically, activation of intracellular enzyme systems leads to primary DNA fragmentation, which is later followed by cell lysis [2]. Overall, the cell is lysed without liberation of proinflammatory degradation products. Before total degradation of apoptotic cells occurs, these cells are taken up by phagocytes thereby limiting the spilling of proinflammatory cytoplasmic contents into the surrounding tissue [3].

To date, many studies have focused on the role of apoptosis in physiological conditions of the immune system, such as positive or negative selection of T cells in the thymus [4]. However, relatively little is known about the patterns and mechanisms of cell death in immune mediated inflammatory lesions in target organs. In this review, we will discuss recent data, obtained from the well defined model of experimental autoimmune encephalomyelitis (EAE), that suggest that local cell death may play a major role in the regulation of the inflammatory process.

Basic principles of brain inflammation, as revealed by the study of EAE

The central nervous system (CNS) is continuously surveyed by the immune system. CD4+ T lymphocytes, which are activated in the circulation, can pass through the blood-brain barrier irrespective of their specific target antigens [5,6]. Yet, most of these T cells will not find the specific antigen in the nervous system and will therefore be rapidly cleared from the CNS parenchyma [6]. However, when T cells that are directed against an autoantigen of the CNS, such as myelin basic protein (MBP), confront their antigen on antigen-presenting cells (APCs) in the perivascular space, they will home and will be further activated in the nervous tissue (Fig. 1). This leads to a cascade of secondary events, such as the upregulation of the production of cytokines and chemokines [7,8,9], endothelial adhesion molecules [10-12], and further induction of the expression of MHC class II antigens on local APCs [13,14]. These events facilitate the entrance of a secondary wave of leukocytes into the CNS, leading to disease and local tissue damage. Acute EAE is a monophasic disease followed by spontaneous recovery, yet, in certain animal species, a chronic progressive or relapsing disease may develop.

Although the individual steps that operate in immune surveillance and the induction of brain inflammation are well understood, relatively little is known about the local mechanisms responsible for clearance of inflammation and the subsequent induction of tolerance. Recent evidence from both in vitro and in vivo studies of T-cell apoptosis, however, suggests that cell death in the CNS, besides playing a role in target-tissue destruction,
is an essential aspect of the local regulation of the inflammatory reaction.

**Mechanisms of apoptosis induction in T cells in vitro**

A number of mechanisms have been found to induce apoptosis of T cells in vitro. Early studies by Wyllie [15] revealed that corticosteroids are strong inducers of apoptosis in T cells. This also occurs in encephalitogenic (MBP-specific) T cells, which can be synchronously driven into apoptosis when glucocorticosteroids are added in vitro at a late stage after antigen-specific stimulation (R. Gold, M Schmied, U Tontsch, H-P Hartung, H Wekerle, unpublished data). A second mechanism responsible for T-cell death is so-called 'propriocidal regulation' [16], implying that T cells become apoptotic when they encounter a strong antigenic challenge. Unlike apoptosis induced by glucocorticoids, antigen-induced apoptosis occurs preferentially in the S phase of the cell-cycle progression of T cells [17]. Moreover, apoptosis of T-cell hybridomas triggered by antigen engagement of the TCR seems to happen irrespective of the presence of glucocorticoids. This only occurs at moderate doses of these stimuli, whereas a high dose of either antigen or glucocorticoids overrides the antagonism, and induction of apoptosis proceeds [18]. A third way to drive T cells into apoptosis in vitro is by the addition or withdrawal of certain cytokines. An important factor in the induction of apoptosis is IL-2 [19]. The presence of IL-2 is not important for apoptosis induced by corticosteroids [20], but is essential for antigen-induced apoptosis, probably because it causes T cells to enter the S phase or later stages of the cell cycle, where they are susceptible to apoptosis [16]. Although the presence of IL-2 is required for antigen-induced apoptosis under certain conditions, its deprivation may also drive T cells dependent on IL-2 into apoptosis [21]. Another interesting cytokine is transforming growth factor (TGF)-β. This cytokine belongs to a family of peptides with potent immunosuppressive effects. It

![Fig. 1. Hypothetical view of clearance of brain inflammation by apoptosis of T cells during autoimmune disease in CNS. During surveillance of the CNS, activated antigen-specific T cells (Tag) enter the CNS and locally recognize their antigen (Ag). This results in the release of Th1 cytokines, which is followed by entrance of a secondary wave of T cells (T) and macrophages (M). During the inflammatory response, the antigen-specific T cells undergo apoptosis, possibly by combined influences of corticosteroids, antigen and cytokines. CSF, cerebrospinal fluid.](image-url)
inhibits the proliferation of T cells [22] and is able to downregulate interferon (IFN)-γ induced by MHC class II expression [23]. Studies by Weller et al. [21] revealed that exposure to TGF-β in both IL-2-dependent and IL-2-independent (IL-4-dependent) T-cell lines induced apoptosis.

**Clearance of inflammation by apoptosis of T cells in EAE**

In 1991, Pender et al. [24] described that besides oligodendrocytes, in being target cells in the tissue destruction in EAE, T cells in the lesions were also destroyed by apoptosis. With this description, the authors raised, for the first time, the possibility that local apoptosis of T cells in the target tissue could be a way of downregulating inflammation and installing tolerance. This initial observation of the presence of apoptotic T cells in the CNS of animals with EAE was followed by a more detailed study from Schmied et al. [25] who used in situ nick translation in combination with immunocytochemistry to show that, at least in acute monophasic EAE, mainly T lymphocytes and not the cells of the CNS parenchyma were undergoing apoptosis. Furthermore, in this study, quantitation suggested that apoptosis is a very efficient mechanism of T-cell elimination in the lesions. At the time of recovery from the disease, up to 49% of all T cells present showed nuclear changes. These data also indicated that within a 24 hour period, two to sixfold more than the total T-cell population present in the inflammatory infiltrates were destroyed by apoptosis and, thus, that active inflammation could only be maintained by the recruitment of new T cells from the circulation or by local proliferation. More recently, it became clear that the local destruction of T cells is not restricted to EAE, but can also be found in other inflammatory diseases of the nervous system. For example, apoptotic T cells are present to a similar extent in the lesions of experimental allergic neuritis, an autoimmune mediated inflammatory disease of peripheral nerves [26], and demyelinating encephalomyelitis induced by coronavirus [27]. In addition, T-cell apoptosis is frequently encountered in active lesions of multiple sclerosis [28].

Several mechanisms may operate in the elimination of T cells. During EAE, a strong corticosteroid response is generated, which leads to the generation of high serum levels of glucocorticoids at the onset of remission (Fig. 1). Adrenalectomy aggravates EAE, an effect that can be abolished by steroid replacement [29]. Furthermore, the peak of apoptosis within lesions coincides with the peak of serum glucocorticoid levels. In EAE, however, only T cells that have infiltrated the CNS undergo apoptosis, whereas T cells in meninges and perivascular space virtually completely escape apoptotic destruction [25], thus making a sole corticosteroid effect unlikely to operate in vivo.

Other observations argue in favour of antigen-induced apoptosis in EAE. MBP-specific T cells in rodents preferentially express the Vß8.2+ TCR [30-32]. In EAE, these Vß8.2+ T cells predominantly localize in the CNS parenchyma [33,34]; furthermore, in EAE lesions, apoptosis is highest in the Vß8.2+ MBP-specific T-cell population [35], indirectly suggesting that antigen-specific cells in particular are susceptible (Fig. 1). Preliminary experiments performed in our laboratories studying the behaviour of prelabeled encephalitogenic T cells in vivo indeed suggest that it is predominantly the antigen-specific T-cell population that is eliminated by apoptosis in situ.

Liberation of MBP during the course of inflammatory mediated tissue damage may finally lead to a concentration of the specific antigen in the brain extracellular space (Fig. 1) that is sufficient for the induction of T-cell apoptosis in situ [36]. Besides the antigen concentration, the kind of APC may also play a role in antigen-induced apoptosis. During EAE, perivascular cells, infiltrating macrophages, microglial cells and astrocytes may act as APCs. For the latter, in recent years, evidence has been obtained that points to a downregulatory role in EAE [37]. These in vivo observations are in line with the in vitro finding that apoptosis of T lymphocytes at late post-activation stage is pronounced when astrocytes are used as APCs, whereas apoptosis is marginal or absent when antigen presentation is accomplished by APCs from the thymus (R. Gold, M. Schmied, U. Tontsch, H-P. Hartung, H. Wekerle, unpublished data). However, the rate of T-cell apoptosis during EAE in radiation bone marrow chimeric rats is similar to normal rats with EAE, in spite of the inability in these chimeras to present antigen to the transferred T lymphocytes by local astrocytes or microglial cells [38].

As part of the probable multifactorial induction of T-cell apoptosis, a third mechanism involved in T-cell elimination during the course of EAE may be cytokine-mediated apoptosis. In particular TGF-β may be of importance (Fig. 1). When administered during EAE, this cytokine has been shown to improve the clinical course of this disease [39,40]. As seen in the in vitro studies by Weller et al. [21], TGF-β may also affect EAE by inducing apoptosis in T cells. TGF-β in brain lesions is not only made by inflammatory cells, such as macrophages [41], but can also be produced by astrocytes [42].

**Conclusions**

Recent evidence shows that the disposal of autoreactive T cells during EAE is a very effective mechanism for clearance of CNS inflammation. Apoptosis of T cells might occur through an increase in the production of corticosteroids, the presence or absence of cytokines, through antigen induction, or through combinations of these. Whatever the mechanisms are that finally lead to apoptosis of T lymphocytes in the lesions of EAE, the elimination of these cells in the target organ has profound immunological consequences and may explain characteristics of CNS autoimmunity, which...
so far have remained enigmatic. For instance, it may explain why Ohmori et al. [43] found that in CNS lesions, proliferation of T cells is discontinued rapidly. Moreover, it is generally known that rodents that have gone through one episode of EAE are protected against attempts to induce a relapse by a second immunization. This is against intuition because, in general, primary immunization leads to the expansion of antigen-specific lymphocyte clones and to differentiation of memory cells.

Although a variety of phenomena (i.e. hormonal conditioning and immunological network interactions) play a role in the resistance to reinduction of EAE, deletion of primary encephalitogenic T cells is definitely an additional contributing factor. This has been best shown in Lewis rats and H-2d mice where, initially, most encephalitogenic (MBP-specific) T cells use the VB8.2+ gene for their antigen receptors. During the course of disease, however, these originally dominant T-cell clones are progressively lost [44]. This process is accompanied by the gradual loss of reactivity against the dominant encephalitogenic epitopes. MBP sequence 68–88 in Lewis rats [33,45] and Ac1–10 in H-2u mice [31,32], and a redirected response against additional secondary epitopes [46,47], a phenomenon termed (intramolecular) ‘epitope spreading’ [48]. We propose that both the low MBP-specific T-cell memory formation, as well as epitope spreading, are a direct result of local death (apoptosis) of the encephalitogenic T cells within the target parenchyma. Accordingly, in the Lewis rat, the first wave of VB8.2+ (MBP peptide 68–88) specific T cells, which are responsible for the clinical EAE episode, would be eliminated from CNS by apoptosis. T cells specific for secondary, ‘cryptic’ epitopes would be expanded instead. It will have to be established in the future whether the effective elimination of T cells as seen in both EAE as well as in experimental autoimmune neuritis (EAN), is a unique mechanism in nervous system immune reactivity or if it is a general mechanism which also functions in autoimmune or infectious diseases of other organs.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Cohen JJ: Apoptosis. Immunol Today 1993, 14:126–130.
2. Peitsch MC, Mannherz HG, Tschopp J: The apoptosis endonucleases: cleaning up after cell death? Trends Cell Biol 1994, 4:37–41.
3. Savill J, Fadok V, Henson P, Haslett C: Phagocyte recognition of cells undergoing apoptosis. Immunol Today 1993, 14:131–136.
4. Marrack P, Hugo P, McCormack J, Kappler J: Death and T cells. Immunol Rev 1993, 133:119–129.
5. Wekerle H, Linting C, Lassmann H, Meyermann R: Cellular immune reactivity within the CNS. Trends Neurosci 1986, 9:271–277.
6. Hickey WF, Hsu BL, Kimura H: T lymphocyte entry into the central nervous system in experimental allergic encephalomyelitis. J Neurosci Res 1991, 28:254–260.
7. Merrill JE, Konno DH, Clayton J, Ando DG, Hinton DR, Holman FM: Inflammatory leukocytes and cytokines in the peptide induced disease of experimental allergic encephalomyelitis in SJL and P19.PL mice. Proc Natl Acad Sci USA 1992, 89:574–578.
8. Olsson T: Role of cytokines in multiple sclerosis and experimental autoimmune encephalomyelitis. Eur J Neurol 1994, 1:7–19.

This review focuses on the role of cytokines (IFN-γ, IL-4, IL-10, IL-12, tumor necrosis factor and TGF-β) in T-cell mediated immunity in multiple sclerosis and EAE.

9. Glabinski AR, Tani M, Aras S, Stoler MH, Tuohy VK, Ransohoff RM: Regulation and function of central nervous system chemokines. Int J Dev Neurosci 1995, 13:153–165.
10. Wilcox CE, Ward AMV, Evans A, Baker D, Rathlein R, Turk JL: Endothelial cell expression of the intercellular adhesion molecule-1 (ICAM-1) in the central nervous system of guinea pigs during acute and chronic relapsing experimental allergic encephalomyelitis. J Neuroimmunol 1990, 30:43–51.
11. Cannella B, Cross AH, Raine CS: Adhesion-related molecules in the central nervous system. Upregulation correlates with inflammatory cell influx during relapsing experimental autoimmune encephalomyelitis. Lab Invest 1991, 65:23–31.
12. Wyllie AH: The apoptosis endonuclease. Nature 1980, 284:535–536.
13. Boehme SA, Lenardo MJ: Ligand-induced apoptosis of mature T lymphocytes (propriocidal regulation) occurs at distinct stages of the cell cycle. Leukemia 1993, 7:545–549.
14. Boehme SA, Lenardo MJ: Propriocidal apoptosis of mature T lymphocytes occurs at S phase of the cell cycle. Eur J Immunol 1992, 23:1552–1560.
15. Zacharchuk CM, Mercep M, Chakraborti PK, Simons SS, Ashwell JD: Programmed T lymphocyte cell death. Cell activation- and steroid-induced pathways are mutually antagonistic. J Immunol 1990, 145:4037–4045.
16. Lenardo MJ: Interleukin-2 programs mouse αβ T lymphocytes for apoptosis. Nature 1991, 353:858–861.
17. Weller M, Constam DB, Malipiero U, Fontana A: The authors show that thymocyte apoptosis in vitro, without down-regulating bcl-2 mRNA expression. Proc Natl Acad Sci USA 1992, 89:1293–1300.
18. Glabinski AR, Tani M, Aras S, Stoler MH, Tuohy VK, Ransohoff RM: Regulation and function of central nervous system chemokines. Int J Dev Neurosci 1995, 13:153–165.
19. Wilcox CE, Ward AMV, Evans A, Baker D, Rathlein R, Turk JL: Endothelial cell expression of the intercellular adhesion molecule-1 (ICAM-1) in the central nervous system of guinea pigs during acute and chronic relapsing experimental allergic encephalomyelitis. J Neuroimmunol 1990, 30:43–51.
20. Zubiaga AM, Munoz E, Huber BT: IL-4 and IL-2 selectively rescue Th cell subsets from glucocorticoid-induced apoptosis. J Immunol 1992, 149:107–112.
21. Weller M, Constam DB, Malipiero U, Fontana A: Transforming growth factor-β induces apoptosis of murine T cell clones without down-regulating bcl-2 mRNA expression. Eur J Immunol 1994, 24:1293–1300.
22. Kehrl JH, Wakefield LM, Roberts AB, Jakowlew S, Alvarez-Mon M, Derynck R, Sporn MB, Fauci AS: Production of transforming growth factor β by human T lymphocytes and its potential role in the regulation of T cell growth. J Exp Med 1986, 163:1037–1050.
23. Schlüsener HJ: Transforming growth factors type β1 and β2 suppress rat astrocyte autoantigen presentation and antagonize hyperinduction of class II major histocompatibility complex
24. Pender MP, Nguyen KB, McCombe PA, Kerr JFR: Apoptosis in the nervous system in experimental allergic encephalomyelitis. / Neurosci 1991, 104:81–87.

Schmied M, Breitschopf H, Gold R, Zischler H, Rothe G, Wekerle H, Lassmann H: 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 1993, 143:446–452.

26. Zettl UW, Gold R, Hartung H-P, Toya KV: Apoptotic cell death of T-lymphocytes in experimental autoimmune neuritis of the Lewis rat. Neurosci Lett 1994, 176:75–79.

This study shows for the first time that apoptosis of inflammatory T cells is not unique to the CNS, but operates in the peripheral nervous system as well.

27. Barac-Latas V, Wege H, Lassmann H: Apoptosis of T lymphocytes in coronavirus induced encephalomyelitis. Reg Immunol 1995, 6:355–357.

The study shows that, similar to autoimmune encephalomyelitis, apoptosis is also a major mechanism to eliminate T lymphocytes in brain inflammatory lesion encephalomyelitis induced by coronavirus.

28. Oszawa G, Suchanek G, Breitschopf H, Brück W, Budka H, Jellinger K, Lassmann H: Patterns of oligodendroglia pathology in multiple sclerosis. Brain 1994, 117:1311–1322.

This paper deals with patterns of inflammation, demyelination and cell death in multiple sclerosis. Of importance here is that, by combination with simultaneous surface labeling revealed that in the CNS parenchyma. In contrast, infiltrated cells in meninges and inflammatory lesion of T cells from the CNS during the course of EAE. DNA analysis in situ nick translation, it is shown that besides oligodendrocytes, T lymphocytes also undergo acute cell death.

29. MacPhee IA, Antoni FA, Mason DW: Spontaneous recovery of rats from experimental allergic encephalomyelitis is dependent on regulation of the immune system by endogenous adrenal corticosteroids. J Exp Med 1989, 169:431–445.

30. Acha-Orbea H, Mitchell DJ, Timmermann L, Wraith DC, Taucsh GS, Waldow D, Zanmili SS, McDevitt HO, Steinman L: Limited heterogeneity of T cell receptors from lymphocytes mediating autoimmune encephalomyelitis allows specific immune intervention. Cell 1988, 54:263–273.

31. Urban Jl, Kumar V, Kono DH, Gomez C, Hovath SJ, Clayton J, Ando DG, Sercarz EE, Hood L: Restricted use of T cell receptor V genes in murine autoimmune encephalomyelitis. Nature 1988, 341:541–544.

32. Chluba J, Steeg C, Becker A, Wekerle H, Epplen JT: T cell receptor β chain usage in myelin basic protein-specific rat T lymphocytes. Eur J Immunol 1989, 19:279–284.

33. Tsuchida M, Matsumoto Y, Hanawa H, Tsuchida M, Abo IF. Limited heterogeneity of T cell receptors from lymphocytes mediating autoimmune encephalomyelitis allows specific immune intervention. Cell 1988, 54:263–273.

34. Lannes-Vieira J, Gehrman J, Kreutzberg GW, Wekerle H: The inflammatory lesion of T-cell line transferred experimental autoimmune encephalomyelitis of the Lewis rat: distinct nature of parenchymal and perivascular infiltrates. Acta Neuropathol 1994, 87:335–442.

This study confirms earlier studies that activated T cells enter the CNS rapidly, irrespective of their antigen specificity. Furthermore, it shows that MBP-specific Vβ8.2+ T cells during EAE are localized predominantly in the CNS parenchyma. In contrast, infiltrated cells in meninges and perivascular space were seen to use Vβ genes randomly.

35. Tabi Z, McCombe PA, Pender MP: Apoptotic elimination of Vβ8.2+ cells from the central nervous system during recovery from experimental autoimmune encephalomyelitis induced by passive transfer of Vβ8.2+ encephalitogenic T cells. Eur J Immunol 1994, 24:2609–2617.

Here, using fluorescence-activated cell sorter (FACS) analysis, the authors show that there is selective disappearance of disease inducing Vβ8.2+ T cells from the CNS during the course of EAE. DNA analysis in combination with simultaneous surface labeling revealed that in the apoptotic T-cell population, the frequency of Vβ8.2+ cells was about sevenfold higher than in the normal (non-apoptotic) T-cell population. Furthermore, after decrease of Vβ8.2+ T-cell numbers in the CNS, the authors could not detect Vβ8.2+ cells in lymphoid organs, indicating that elimination of these autoreactive T cells in CNS by apoptosis is complete and that the decrease in number of these cells is not due to recirculation to lymphoid organs.

36. Critchfield JM, Racke MK, Zünkiga-Pflucker JC, Cannella B, Raine CS, Goveman J, Lenardo MJ: T cell deletion in high antigen dose therapy of autoimmune encephalomyelitis. Science 1994, 263:1139–1143.

It is shown that in vitro, T cells die by apoptosis during IL-2 stimulated cell cycling and TCR engagement at high doses of antigens (including MBP and peptide Ac1–11). In vivo, repeated treatment with soluble MBP is seen to improve the clinical course of EAE probably due to eradication of disease-causing T cells.

37. Matsumoto Y, Hanawa H, Tsuchida M, Abo T: In situ inactivation of infiltrating T cells in the central nervous system with autoimmune encephalomyelitis. The role of astrocytes. Immunology 1993, 79:381–390.

38. Hickey WF, Kimura H: Perivascular microglial cells of the CNS are bone-marrow derived and present antigen in vivo. Science 1988, 239:290–292.

39. Racke MK, Dhib-Jalbout S, Cannella B, Albert PS, Raine CS, McFarlin DE: Prevention and treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-β1. J Immunol 1991, 146:3012–3017.

40. Racke MK, Sirram S, Carlino J, Cannella B, Raine CS, McFarlin DE: Long-term treatment of chronic relapsing experimental allergic encephalomyelitis by transforming growth factor-β2. J Neuroimmunol 1993, 46:175–184.

41. Kiefer R, Streit WJ, Toya KV, Kreutzberg GW, Hartung H-P: Transforming growth factor-β1: a lesion-associated cytokine of the nervous system. Int J Dev Neurosci 1995, 13:331–339.

42. Wahl SM, Allen JB, McCarty-Francis N, Morganti-Kossmann MC, Kossmann T, Ellsworht L, Mwat UE, Megenhagen SE, Orenstein JM, Macrophage- and astrocyte-derived transforming growth factor-β as a mediator of central nervous system dysfunction in acquired immune deficiency syndrome. J Exp Med 1991, 173:981–991.

43. Ohmori K, Hong Y, Fujiwara M, Matsumoto Y: In situ demonstration of proliferating cells in the rat central nervous system during autoimmune encephalomyelitis. Evidence suggesting that most infiltrating T cells do not proliferate in the target organ. Lab Invest 1992, 66:54–62.

44. Offner H, Buenafe AC, Vainieri M, Celnik B, Weinberg AD, Gold DP, Hashim G, Vandenbark AA: Where, when, and how to detect biased expression of disease-relevant Vβ genes in rats with experimental autoimmune encephalomyelitis. J Immunol 1993, 151:506–517.

45. Burns FR, Li X, Shen N, Offner H, Chou YK, Vandenbark AA, Heber-Katz E. Both rat and mouse T cell receptors specific for the encephalitogenic determinant of myelin basic protein use similar Vα and Vβ chain genes even though the major histocompatibility complex and encephalitogenic determinants being recognized are different. J Exp Med 1989, 169:27–39.

46. Lehmann PV, Forshuber T, Miller A, Sercarz EE: Spreading of T-cell autoimmunity to cryptic determinants of an autoantigen. Nature 1992, 358:155–157.

47. Mor F, Cohen IR: Shifts in the epitopes of myelin basic protein recognized by Lewis rat T cells before, during and after the induction of experimental autoimmune encephalomyelitis. J Clin Invest 1993, 92:2199–2206.

48. Lehmann PV, Sercarz EE, Forshuber T, Dayan CM, Gammon G: Determinant spreading and the dynamics of the autoimmune T cell repertoire. Immunol Today 1993, 14:203–208.