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.
Synergistic interaction between measles virus infection and myelin basic protein peptide-specific T cells in the induction of experimental allergic encephalomyelitis in Lewis rats

Uwe G. Liebert and Volker ter Meulen
Institut für Virologie und Immunbiologie, Universität Würzburg, Würzburg, Germany
(Received 17 February 1993)
(Revision received 1 April 1993)
(Accepted 15 April 1993)

Key words: Autoimmunity; Measles virus; Central nervous system; Experimental allergic encephalomyelitis; Myelin basic protein

Summary

The questions how a viral infection induces cellular autoimmune reactions (CMAI) and which components of both virus and auto-antigen play part in this process were addressed in our animal model of measles virus (MV)-induced CMAI against myelin basic protein (MBP) during subacute measles encephalitis (SAME). In an attempt to define whether cellular or humoral immune responses are involved in the occurrence of the autoimmune based disease process, Lewis rats were treated with different combinations of antibodies and T cells reactive with either MV and its structural proteins or MBP and MBP-peptides. The only treatment combination after which experimental allergic encephalomyelitis (EAE)-like disease and pathology developed was when non-encephalitogenic T cells reactive against residues 69-81 of MBP were adoptively transferred into MV-infected Lewis rats. The results of the study show that T cells which are non-encephalitogenic in the normal central nervous tissue are capable of inducing an allergic encephalomyelitis in animals with a viral infection involving the brain.

Introduction

Autoimmune reactions have been observed to occur in acute and chronic RNA and DNA virus infections (Ter Meulen, 1989). The pathogenetic significance of such autoimmunity, however, is not well understood in most circumstances. Particularly autoantibodies disappear usually when the virus has been eliminated from the body. In contrast, cell-mediated autoimmune reactions (CMAI) may persist in the absence of the causative infectious agent, for example in postinfectious encephalomyelitis or after antiviral vaccination (Johnson, 1987). That CMAI do play a pathogenetic role has been shown by inducing clinical disease and neuropathological changes following the adoptive transfer of myelin basic protein (MBP) autoantigen-specific CD4+ T cells and subsequent induction of experimental allergic encephalomyelitis (EAE) in rats and mice (Zamvil et al., 1985; Sedgwick et al., 1987). In order to elucidate the mechanisms of virus-induced autoimmunity, an animal model has been established in which in the course of persistent infection, measles virus (MV) induced T lymphocytes with autoreactivity for CNS antigens were detected (Liebert et al., 1988, 1990). Evidence for a pathogenetic role of the observed autoreactivity is based on: (1) adoptive transfer of EAE-like disease with MBP-reactive CD4+ T cells derived from infected rats; (2) fine specificity of encephalitogenic T cells in animals with EAE and subacute measles viral encephalitis (SAME); and (3) substitution of sequences from the encephalitogenic region of MBP by measles virus in the induction of EAE. Previously we have shown that immunization of Lewis rats with a peptide comprising residues 69–81 (GSLPOKSORSQ) of guinea pig MBP sufficed to lead to the development of EAE in MV infected rats. The
peptide 69–81 represents 11 of the 14 amino acid sequence (residues 69–84: GSLPQKSQRSQDEN) which form the major encephalitogenic region of MBP and are required to induce EAE in unprimed Lewis rats (Hashim et al., 1986).

The purpose of this study was to define the nature of the immune response against the MBP-peptide 69–81 as well as to search for components of the Nv or regions on its proteins which are essential for the complementation between MBP and MV in the induction of EAE. The results show that autoreactive T cells against peptide 69–81 become encephalitogenic in the MV-infected CNS although they were not sufficient to induce allergic encephalitis in an uninfected animal. Antibodies to either MBP or MV as well as MV-reactive T cells apparently play a minor role if any in the pathogenesis of the MV-induced autoimmune disease process and they do not complement peptide 69–81 to induce EAE.

Materials and methods

Animals and experiments

Inbred Lewis rats were obtained from the Zentralinstitut für Versuchstierzucht, Hanover, Germany, and were certified pathogen-free by the supplier. Every 6–8 months, the breeding colony was rechecked serologically for pathogens. Animals were kept in a barrier system with light negative pressure (150 mPA) and a 12-h day (artificial light) and were fed and watered ad libitum. Room temperature (22 ± 2°C) and humidity (50 ± 5%) were regulated by air conditioning. Immunization with MBP and MBP peptides was done in 6–8-week-old rats, infection with MV in animals aged 3–4 weeks. T cells were adoptively transferred by injection into the tail vein (0.5–20 x 10^6). Passive transfer of antibodies or immunoglobulins was done according to the schedule published by Linnington and Lassmann (Lassmann et al., 1988; Linnington et al., 1988). MV antibodies were prepared by immunization of rats or rabbits with gradient purified measles virions as well as MBP, or peptides 69–81 and 69–84 respectively. Rabbit immunoglobulin specific for MBP peptide 75–84 was kindly provided by Dr. George Hashim, Columbia University, New York. The MV-specific antibodies neutralize measles virus at titers above 1:5000 and precipitate all major MV proteins in Western blot experiments. Monoclonal anti-H and anti-N antibodies were described previously (Ter Meulen et al., 1981, Carter et al., 1982).

The clinical severity of EAE-like disease was assessed using a scale of 0 to 5 (Lassmann, 1983). Histological examination was done on hematoxylin and cosin (H & E) and Luxol fast blue (LFB)-stained paraformaldehyde-fixed and paraffin-embedded sections of spinal cord (longitudinal and transverse) and brain (coronal sections) as described previously (Liebert and ter Meulen, 1987).

Virus and antigens

The neurotropic rodent-adapted CAM/RB strain of measles virus was used in all experiments as described previously (Liebert et al., 1987). For T lymphoproliferation assays, measles virions were disrupted by sonication and remaining infectivity was inactivated by exposure to UV light (12 W/5 min) and heat (55°C/30 min). Recombinant MV nucleocapsid (N), phospho (P) and matrix (M) proteins expressed from Escherichia coli were purified by urea extraction and used as described (Reich et al., 1992). Haemagglutinin (H) and fusion (F) protein were used in a microparticulate form suitable for T cell stimulation as DMSO dissolved nitrocellulose-bound protein (Abou-Zaid et al., 1987; Körner et al., 1991). MBP was prepared from spinal cord according to standard procedures (Eylar et al., 1979). Peptides comprising the major Lewis rat encephalitogenic region of MBP (residues 69–84) as well as two overlapping non-encephalitogenic peptides (residues 69–81 and 75–84, respectively) were prepared by the solid-phase method and purified to homogeneity as described previously (Hashim et al., 1986).

T cell lines, proliferation assay and phenotypic characterisation of T cells

The assays were done as described previously (Liebert et al., 1988, Reich et al., 1992). Briefly, cell lines were isolated from lymph nodes and spleen by adding antigen in optimal concentrations to single cell suspensions. After 48–72 h, T cell blasts were separated by BSA gradient centrifugation, followed by expansion in IL-2-containing RPMI 1640 medium for 3–5 days. T cell lines were established by alternating cycles of restimulation with antigen together with irradiated (3000 rad) thymocytes and splenocytes from donor animals (6–8 weeks old) as source of antigen-presenting cells (APC) and expansion with II-2. Specificity of cell lines was tested in a lymphoproliferation assay with 2 x 10^4 T cell blasts, 1 x 10^6 APCs and antigen (2–30 µg ml^-1) in a final volume of 200 µl in flat-bottomed microtiter plates, in which uptake of ^3Hthymidine (^3HdT) was determined. Stimulation indices (ratio of uptake with and without antigen) were calculated. Phenotypic characterization was done by FACScan. Antibodies used were W3/25 and OX8 for rat CD4 and CD8, R73 for rat a/βT cell receptor (kindly provided by Dr. Thomas Hünig, Institut für Virologie und Immunobiologie, Universität Würzburg; Hünig et al., 1989), OX6, OX17 and OX18 for rat MHC class I and class II antigens. Antibodies reactive for Vβ gene products were R78 (Vβ 8.2-specific), B73 (Vβ 8.5), G101 (Vβ 10), HIS42 (Vβ 16) and L180/1 as a negative control.
Results

Assessment of MV antibodies and MV T cells in the induction of EAE

In order to determine the role of immune responses against MV in the pathogenesis of measles encephalitis in Lewis rats, a series of experiments were carried out. First, different MV-reactive hyperimmune sera or purified immunoglobulin from monoclonal antibody-secreting hybridomas were intravenously administered into rats that were immunized with MBP peptide 69–81. This treatment was ineffective as neither clinical nor histological changes were observed (Table 1). For a second set of experiments, T cell lines were established by immunization of rats with MV (lines MV1L, MV3L, MV4L) or bacterially expressed recombinant nucleocapsid (N) protein (line MVN1L). All lines proliferate with MV antigen added to cultures. Lines MV1L, MV3L and MV4L recognized the N as well as the haemagglutinin (H) protein of MV. Additional reactivity to matrix (M) or fusion (F) protein was detected in line MV4L, and for line MV1L a minor reactivity was seen against M protein (Table 2). Line MVN1L was induced by immunizing rats with recombinant N protein, selected in vitro from bulk cultures by addition of inactivated measles virions during the first two restimulation cycles and maintained with the alternating addition of either MV or N protein. This line was reactive only with N protein and showed no proliferation with any of the other MV structural proteins (Table 2). The four cell lines did not proliferate (3HdT uptake) when MBP or MBP peptides were added to cultures. From the third restimulation cycle, the four T cell lines expressed the α/β T cell receptor and were CD4+ as determined by FACS analysis. Experiments where OX6 and OX18 monoclonal antibodies were added in the lymphoproliferation assay showed that MV recognition by the T cell lines is MHC class II restricted (data not shown). Each of the four MV-reactive cell lines were administered intravenously into rats that were either simultaneously or 10 days earlier immunized with MBP peptide 69–81. This combination of peptide immunization with adoptive transfer of MV-reactive cell lines was also ineffective and did not lead to the occurrence of EAE (Table 1).

Passive transfer of antibodies against MBP or MBP peptides

In a third experimental approach, antibodies directed against MBP and MBP peptides were injected into intracerebrally MV-infected Lewis rats (Table 3). The virus dose (10−2.5−10−3) was chosen carefully so that no fatal MV-encephalitis occurred and most animals did not exhibit clinically apparent disease. None

---

**Table 1**  
Effect of MV-specific antibodies or T cells in rats immunized with MBP-peptide 69–81

| Treatment of peptide 69–81 | Number of rats with EAE-like lesions/total number of rats |
|---------------------------|----------------------------------------------------------|
| RaMV serum                | 0/4                                                      |
| raMV serum                | 0/3                                                      |
| MAb anti-N Ig             | 0/3                                                      |
| MAb anti-H Ig             | 0/4                                                      |
| MV1L-T cells              | 0/6                                                      |
| MV3L-T cells              | 0/3                                                      |
| MV4L-T cells              | 0/4                                                      |
| MVN1L-T cells             | 0/8                                                      |

6–8-week-old Lewis rats were subcutaneously immunized with 100 µg MBP peptide 69–81. 10–12 days later, anti MV sera from rabbit (RaMV serum, 1 ml) or rat (raMV serum, 0.5–1 ml), mouse immunoglobulin (lg, 500 µg) directed against the MV nucleocapsid (N) or haemagglutinin (H), protein A column-purified from hybridoma supernatant were given intraperitoneally for 5 days. In other experiments, MV-reactive CD4+ T cells (5 or 20×10⁶, see Table 2) were adoptively transferred by tail vein injection. Histological examination was carried out 16–20 days after immunization with MBP-peptide.

---

**Table 2**  
MV-specific CD4+ T cell lines

| Cell line designation | ³HdT (cpm/μl) uptake in the presence of | Medium | MV | pBD2 | N | P | M | F | H |
|-----------------------|----------------------------------------|--------|----|------|---|---|---|---|---|
|                       |                                        |        |    |      |   |   |   |   |   |
| MV1L                  |                                        | 836    | 28775/34.4 | 1790 | 24301/13.5 | 4340/2.4 | 9534/5.3 | 1550/1.9 | 8720/10.4 |
| MV3L                  |                                        | 735    | 8427/11.5  | 894  | 15228/17.0 | 1245/1.4  | 971/1.1  | 596/0.8  | 6244/8.5 |
| MV4L                  |                                        | 312    | 14448/63   | 486  | 8815/18.1  | 1034/2.1  | 8446/17.4 | 2992/9.6 | 1367/4.4 |
| MVN1L                 |                                        | 623    | 18793/30.2 | 687  | 27481/40.0 | 813/1.2   | 744/1.1  | 578/0.9  | 667/1.1 |

T cell lines were isolated from MV-infected (MV1L, MV3L, MV4L) or from recombinant N protein-immunized (MVN1L) Lewis rats. Antigens added to T cell cultures (after at least two cycles of in vitro restimulation with MV) were: disrupted measles virions (MV), recombinant viral N, P or M protein or protein extract from E. coli not containing measles sequences (pBD2, Reich et al., 1992), affinity column-purified viral haemagglutinin (H) or fusion (F) protein bound to nitrocellulose microparticles. ³HdT uptake in the presence of pure nitrocellulose did not exceed the control uptake without antigen (medium control).
TABLE 3
Effect of autoantibodies to MBP in MV-infected rats

| Antibody injected   | Number of rats infected | Number of rats developing EAE |
|---------------------|-------------------------|------------------------------|
| Anti MBP (rat)      | 4                       | 0                            |
| Anti MBP (rabbit)   | 6                       | 0                            |
| Anti 69–84 (rat)    | 6                       | 0                            |
| Anti 75–84 (rat)    | 3                       | 0                            |
| Anti 75–84 (rabbit) | 6                       | 0                            |
| Anti 69–81 (rat)    | 4                       | 0                            |
| Anti 69–81 (rabbit) | 6                       | 0                            |

4-week-old animals were infected intracerebrally with neurotropic rodent adapted CAM/RB \((1 \times 10^3 \text{TCID}_{50})\) and antibodies \((500 \mu\text{g})\) were injected intravenously every 2nd day, starting 3 days following MV infection. Histological examination was done between 12 and 15 days post infection.

of the antibody-treated rats showed inflammatory cell infiltrations in the CNS, particularly lumbar or sacral spinal cord, and demyelination was also not discovered in H&E/LFB-stained paraffin sections.

TABLE 4
In vitro characteristics of MBP peptide 69–81-specific CD4\(^+\) T cell lines

| Antigen added \(^a\) | Antibody added \(^b\) | \(^3\)HdT incorporation in S67-1 cell line | \(^3\)HdT incorporation in S67-2 cell line |
|---------------------|----------------------|------------------------------------------|------------------------------------------|
|                     |                      | cpm | % response | cpm | % response |
| Medium -            | -                    | 1237 | 5.0        | 577 | 1.1        |
| Peptide 69–81 -     | -                    | 24815 | 100       | 52059 | 100       |
| MBP -               | -                    | 1450 | 5.8        | 1226 | 2.4        |
| Peptide 69–84 -     | -                    | 3802 | 15.3       | 845  | 1.6        |
| MV -                | -                    | 978  | 3.9        | n.d. | n.d.       |
| N -                 | -                    | 1427 | 5.8        | 887  | 1.7        |
| P -                 | -                    | 1192 | 4.8        | n.d. | n.d.       |
| M -                 | -                    | 1569 | 6.3        | n.d. | n.d.       |
| F -                 | -                    | 1226 | 4.9        | n.d. | n.d.       |
| H -                 | -                    | 898  | 3.6        | 613  | 1.2        |
| Peptide 69–81 W3/25 | n.d.                 | 17752 | 34.1       |
| Peptide 69–81 OX8   | n.d.                 | 49196 | 94.5       |
| Peptide 69–81 OX6   | 2965                 | 2655 | 5.1        |
| Peptide 69–81 OX17  | n.d.                 | 53152 | 102.1      |
| Peptide 69–81 OX18  | n.d.                 | 46385 | 89.1       |

\(^a\) Antigen concentration added to T cell cultures was \(10 \mu\text{g ml}^{-1}\).
\(^b\) Antibody was added in a concentration of \(1 \text{mg ml}^{-1}\).
\(^c\) n.d., not done.

TABLE 5
V\(\beta\)-gene repertoire of T cell lines

|                       | V\(\beta\)10 | V\(\beta\)8.5 | V\(\beta\)16 | V\(\beta\)8.2 | CD4 | CD8 | \(\alpha/\beta\) TCR |
|-----------------------|-------------|---------------|-------------|--------------|-----|-----|---------------------|
| MBP                   | 1.0         | 2.4           | 1.0         | 2.3          | 97.1| 91.8| 3.1                 |
| S67-1                 | 4.8         | 3.4           | 2.9         | 8.5          | 92.5| 90.5| 2.8                 |
| S67-2                 | 2.8         | 1.4           | 2.1         | 1.7          | 94.3| 95.4| 0.4                 |
| MVIL                  | 0.8         | 1.3           | 1.5         | 3.1          | 89.4| 96.1| 0.6                 |
| MV44L                 | 1.6         | 23.6          | 3.4         | 4.8          | 14.5| 94.2| 1.8                 |

The distribution of the T cell receptor V\(\beta\)-genes was determined by FACScan analysis.
that the immunization of intracerebrally MV-infected

Discussion

Previous experiments in our laboratory have shown

TABLE 6
Adoptive transfer of MBP-peptide 69--81-specific T cells

| Number of T cells transferred | Recipient animals | Mean clinical score | Incidence of EAE |
|-------------------------------|-------------------|--------------------|------------------|
| (×10^-6)                      |                   |                    | Clinical Histological |
| 0.5                           | Post infection b  | 0                   | 0/5              |
| 1                             | Post infection b  | 0                   | 0/3              |
| 2                             | Post infection b  | 1.0                 | 1/3              |
| 4                             | Post infection b  | 2.5                 | 2/4              |
| 8                             | Post infection b  | 3.2                 | 5/5              |
| 8                             | Post infection with inactivated MV b | 0 | 0/4 |
| 4                             | Mock-infected c   | 0                   | 0/4              |
| 8                             | Mock-infected c   | 0                   | 0/4              |
| 16                            | Mock-infected c   | 0                   | 0/3              |

T cell line S67-2 was used in all experiments within 48 h after antigen restimulation in vitro. Adoptive transfer was carried out by injection into the tail vein of 5--6-week-old Lewis rats. Recipient animals were pretreated at the age of 3--4 weeks by intracerebral injection with CAM/RB (a) or UV and heat-inactivated MV (b) or were mock-infected with PBS (c).

added, while OX8 as well as OX17 and OX18 were ineffective. Hence, the results confirm the FACS results and further reveal MHC class II restriction of the cell line (Table 4). The use of monoclonal antibodies directed against V3-gene products showed that both MBP peptide 69--81-reactive cell lines, similar to a MBP cell line expressed predominantly (line S67--1) or exclusively V3 8.2 (Table 5). One of the two peptide-reactive T cell lines (line S67--2) was used for adoptive transfer experiments. 0.5--16 × 10^6 T cells were intravenously injected into rats 28--42 days after intracerebral MV infection. At this time point, the blood--brain barrier is intact and measles virus can not be recovered from the CNS. In some rats, however, viral antigen is present in isolated cells of neuronal type in the cortex and basal ganglia as well as thalamus. Within 4--6 days of transfer of a minimum of 2 × 10^6 S67--2 T cells, an EAE-like disease occurs. In all rats with clinical signs of encephalomyelitis and in some without clinical symptoms, the characteristic perivascular inflammatory infiltrates of lympho-mononuclear cells were seen in transverse and longitudinal sections through the spinal cord. In contrast, no lesions were detected in sections from rats that were mock-infected or infected with inactivated MV, even when cell numbers as high as 16 × 10^6 were transferred intravenously (Table 6).

Lewis rats with MBP peptide 69--81 leads to EAE in about 40% of animals. In contrast, immunization with the peptide after mock-infection or UV inactivation of the virus was ineffective (Liebert et al., 1990). It was concluded that in MV-infected Lewis rats the immunological response to viral antigen probably complements the T cell responsiveness to a normally non-encephalitogenic MBP epitope and that additional factors may be involved in the development of virus-induced autoimmune reactions against brain tissue. It has also been reported that the immunological expression of either of two epitopes of MBP residues 75--84 and 69--81, which cover the entire. major encephalitogenic site, does not lead to the development of EAE in Lewis rats (Offner et al., 1987; Hashim and Day, 1988). Here we show that T cells specific for MBP peptide 69--81 acquire encephalitogenic potential when adoptively transferred into MV infected animals. Transfer of these cell lines into mock-infected rats or rats that were intracerebrally injected with inactivated MV was ineffective and lead to neither clinical nor histological signs of EAE. These results correlate well with earlier observations in animals immunized with the peptide 69--81 (Liebert et al., 1990).

The presence of MBP-reactive CD4^+ T cells to MBP is one of the requirements for the induction of EAE. Furthermore, it was shown that demyelination may occur when antibodies enter the CNS as a consequence of blood--brain barrier disturbance caused by small numbers of encephalitogenic T cells (Lassman et al., 1988). On the basis of our complementation experiments with peptide 69--81 and MV infection, we tried to define a region on measles virus carrying the required sequences for either humoral or cellular immune responses responsible for EAE in peptide 69--81-primed rats. However, all attempts failed and we did not succeed so far to substitute the active MV infection by either humoral or cellular immune responses against MV or its proteins. A possible explanation could be that the peptide-reactive T cells in contrast to MBP-specific T cells are incapable in disturbing the integrity of the blood--brain barrier. This interpretation, however, is unlikely, since we detected increased levels of both albumin and anti-MV antibodies in the cerebrospinal levels of both albumin and anti-MV antibodies (when MV antibodies were administered intravenously, data not shown). No increased immunoglobulin level was detected in the CSF of control rats which received no peptide-reactive T cells but equivalent amounts of MV antibodies. This indicates increased permeability of the barrier for immunoglobulins in recipients of peptide-specific T cells. Taken together, the inability to induce EAE with isolated immune responses, either humoral or cellular, against MV or MV proteins, and the synergistic interaction between MBP peptide-reactive T cells and MV infec-
tion in the induction of EAE in Lewis rats indicate that complementation for EAE requires the active infection and replication of MV in brain cells. The mechanism of EAE induction in the measles-infected animals does apparently not involve cross-reactivity of MBP or MBP peptide-reactive T cell lines with MV components. Sequence comparison between the 69–84 sequence of MBP and MV proteins has not revealed homology or the presence of common T cell epitope motifs (Liebert et al., 1990). A possible explanation for the synergism between MV infection and MBP peptide T cell response may be a modification of cyto- and lymphokine expression in brain cells after viral infection (Frei et al., 1991; Moskophidis et al., 1991; Shankar et al., 1992) which ultimately may upregulate MHC class II or adhesion molecules in the CNS (Dörries et al., personal communication). It is conceivable that these changes could facilitate the interaction between T cells and the CNS. Moreover, processing and presentation of MBP peptides may be altered in the infected CNS so that additional peptides not present in an immunological form are seen by the immune system. One such peptide could represent the 69–81 sequence of MBP. This hypothesis is supported by the lack of peptide 69–81 reactivity in all analysed MBP-specific T cell lines isolated from rats suffering from EAE and the failure to isolate peptide 69–81-reactive T cells from MBP-primed rats (Liebert et al., 1990). Additional investigations including peptide rescue experiments from virus-infected brain cell cultures are necessary to investigate this possibility. It is tempting to speculate that autoimmune diseases may develop on the basis of similar phenomena and ultimately lead to chronic inflammatory CNS processes which perpetuate even in the absence of the triggering agent. Further investigations will hopefully elucidate mechanism(s) of virus-induced autoimmunity and provide therapeutic approaches to prevent the initiation of autoimmune disease processes.

Acknowledgements

We acknowledge Drs. George Hashim, St. Luke’s-Roosevelt Hospital Center, and Thomas Hünig and Nora Torres-Nagel for providing peptides and antibodies. This work was supported by the Deutsche Forschungsgemeinschaft.

References

Abou-Zeid, C., Filley, E. Steel, J. and Rook, G.W.A. (1987) A simple new method for using antigens separated-by polyacrylamide gel electrophoresis to stimulate lymphocytes in vitro after converting bands cut from Western blot into antigen bearing particles. J. Immunol. Methods 98, 5–11.

Carter, M.J., Willcocks, M.M., Löffler, S. and ter Meulen, V. (1982) Relationships between monoclonal antibody binding sites on the measles virus haemagglutinin. J. Gen. Virol. 63, 113–120.

Eylar, E.H., Kniskern, P.J. and Jackson, J.J. (1979) Myelin basic protein. Methods Enzymol. 32B, 323.

Hashim, G.A. and Day, E.D. (1988) Role of antibodies in T cell-mediated experimental allergic encephalomyelitis. J. Neurosci. Res. 21, 1–5.

Hashim, G.A., Day, E.D., Fredane, L., Intintila, P. and Carvalho, E. (1986) Biological activity of region 65–102 of the myelin basic protein. J. Neurosci. Res. 16, 467–478.

Häning, T., Wallny, H.J., Hartley, J.K., Lavezky, A. and Tiefenthaler, G. (1989) A monoclonal antibody to a constant determinant of the rat T cell antigen receptor that induces T cell activation. J. Exp. Med. 169, 73–78.

Johnson, R.T. (1987) The pathogenesis of acute viral encephalitis and postinfectious encephalomyelitis. J. Infect. Dis. 115, 359–364.

Körner, H., Shleiphake, A., Winter, J., Zimprich, F., Lassmann, H., Sedgwick, J., Siddel, S. and Wehe, H. (1991) Nucleocapsid or spike protein-specific CD4 + T lymphocytes protect against coronavirus-induced encephalomyelitis in the absence of CD8 + T cells. J. Immunol. 147, 2317–2323.

Lassmann, H. (1983) Comparative neuropathology of chronic experimental allergic encephalomyelitis and multiple sclerosis. Springer Verlag, Berlin-Heidelberg-New York-Tokyo.

Lassmann, H., Brunner, C., Bradl, M. and Linnington, C. (1988) Experimental allergic encephalomyelitis: the balance between encephalitogenic T lymphocytes and demyelinating antibodies determines size and structure of demyelinated lesions. Acta Neuropathol. Berl. 75, 566–576.

Liebert, U.G. and ter Meulen, V. (1987) Virological aspects of measles virus induced encephalomyelitis in Lewis and BN rats. J. Gen. Virol. 68, 1715–1722.

Liebert, U.G., Schneider-Schaulies, S. and ter Meulen, V. (1988) Measles encephalitis in rats: a model for virus induced autoimmune reactions. In: C. Confavreux, G. Aimard and M. Devic (Eds.), Trends in European Multiple Sclerosis Research, Elsevier, Amsterdam, pp. 133–139.

Liebert, U.G., Hashim, G. and ter Meulen, V. (1990). Characterization of measles virus-induced cellular autoimmune reactions against myelin basic protein in Lewis rats. J. Neuroimmunol. 29, 139–147.

Linnington, C., Bradl, M., Lassman, H., Brunner, C. and Vass, K. (1988) Augmentation of demyelination in rat acute allergic encephalomyelitis by circulating mouse monoclonal antibodies directed against a myelin/oligodendrocyte glycoprotein. Am. J. Pathol. 140, 443–454.

Moskophidis, D., Frei, K., Löhler, J., Fontana, A. and Zinkernagel R. (1991) Production of random classes of immunoglobulins in brain tissue during persistent viral infection paralelly by secretion of interleukin-6 (IL-6) but not IL-4, IL-5 and gamma interferon. J. Virol. 65, 1364–1369.

Offner, H., Hashim, G. and Vandenbark, A.A. (1987) Response of rat encephalitogenic T lymphocyte lines to synthetic peptides of myelin basic protein. J. Neurosci. Res. 17, 344–348.

Piani, D., Frei, K., Quang Do, K., Cuenoid M and Fontana, A. (1991) Murine brain macrophage induce NMDA receptor mediated neurotoxicity in vitro by secreting glutamate. Neurosci. Lett. 133, 159–163.

Reich, A., Erlewine, O., Niewiesk, S., ter Meulen, V. and Liebert U.G. (1992) CD4 + T cells control measles virus infection of the central nervous system. Immunology 76, 185–191.

Sedgwick, J., Brostoff, S. and Mason, D. (1987) Experimental allergic encephalomyelitis in the absence of a classical delayed-type hypersensitivity reaction. Severe paralytic disease correlates with the presence of interleukin 2 receptor-positive cells infiltrating the central nervous system. J. Exp. Med. 165, 1058–1075.
Shankar, V., Kao, M., Hamir, A.N., Sheng, H., Koprowski, H. and Dietzschold, B. (1992). Kinetics of virus spread and changes in levels of several cytokine mRNAs in the brain after intranasal infection of rats with Borna disease virus. J. Virol. 66, 992–998.

Ter Meulen, V. (1989) Virus-induced cell-mediated autoimmunity. In: A. Notkins and M.B.A. Oldstone (Eds.), Concepts in Viral Pathogenesis, Springer Verlag, Berlin, pp. 297–303.

Ter Meulen, V., Löffler, S., Carter, M. and Stephenson, J.R. (1981) Antigenic characterization of measles and SSPE virus haemagglutinin by monoclonal antibodies. J. Gen. Virol. 57, 357–364.

Torres-Nagel, N.E., Gold, D.P. and Hünig, T. (1993) Identification of rat Tcrb-V8.2, 8.5 and 10 gene products by monoclonal antibodies. Immunogenetics 37, 305–308.

Zamvil, S.S., Nelson, P.A., Mitchell, D.J., Knobler, R.L., Fritz R.B. and Steinman, L. (1985). Encephalitogenic T cell clones specific for myelin basic protein. An unusual bias in antigen recognition. J. Exp. Med. 162, 2107–2124.