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Superantigen-Mediated Encephalitis

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1. Introduction

Encephalitis may result from the interaction between a pathogen and the host brain, such as in bacterial, viral or fungal infection of the CNS. There are, however, different states of aseptic encephalitis, which may be induced e.g. by way of (i) self-directed immune attacks as in experimental autoimmune encephalomyelitis or (ii) by certain substances like the copper chelating agent cuprizone (Torkildsen et al., 2008).
In fact, in encephalitis, infectious and non-infectious processes do not mutually exclude each other. Many pathogens such as bacteria or viruses encode for immune stimulating peptides, better known as superantigens for their enormous potency to stimulate immune cells (Kappler et al., 1989; Fleischer, 1991). T-cell superantigens have been developed twice during the evolution, namely independently by bacteria and by viruses. Not all bacteria or viruses do, however, possess a superantigen. - Superantigens act in a T-cell receptor V(beta) dependent manner (Figure 1). Thereby, up to 10% or even 20% of the T-cell repertoire may become activated, sometimes resulting in a fulminant inflammatory response. The latter depends also on the specific repertoire of the host's antigen-detection apparatus, e.g., the human-leucocyte-antigen (HLA) molecules.

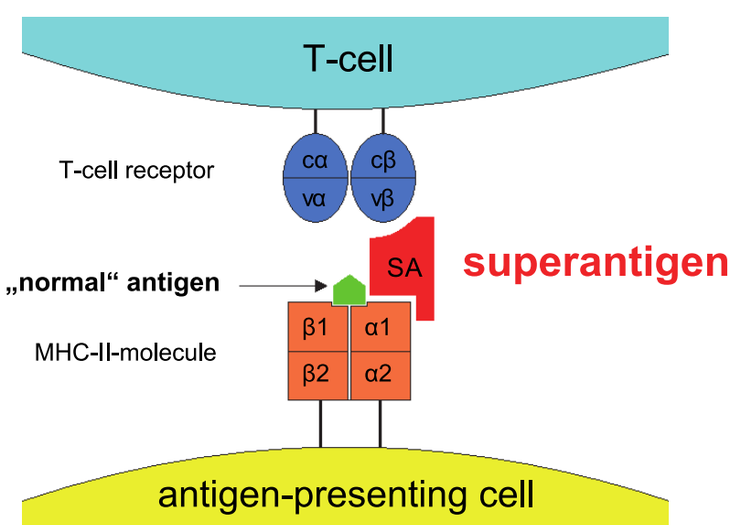

Fig. 1. Antigen and superantigen recognition via the MHC/T-cell receptor complex.

Taken together, superantigens are expected to take part in the inflammatory events induced by their pathogenic source. In florid bacterial or viral encephalitis, the detrimental effects that may be attributed to the pathogen or to its superantigen may be hardly discerned, while both may contribute to the final outcome. However, in case of slowly progressing encephalitides of e.g. viral origin, the superantigenic stimulus might be responsible for the initial and leading symptoms while the consequences of viral degeneration could be compensated for for a considerable time period and may become symptomatic later during the disease course. This is what has been suggested to happen in multiple sclerosis (MS) (Kornhuber et al., 2002, Kornhuber 2006, Emmer et al., 2008, 2010). In this respect, it may be of significance that the initial events of MS plaque generation seem to develop in the absence of tissue inflammation (Filippi et al., 1998; Barnett and Prineas, 2004). Although the etiology for slow progression in MS remains to be established, it has been speculated on a possible role e.g. for human endogenous retroviruses such as MSRV (Garson et al., 1998; Perron and Lang, 2010; Antony et al., 2010).

Our knowledge about the cerebral actions of T-cell superantigens, e.g. Staphylococcal enterotoxin A (SEA), relies on but a few experiments and, thus, is far from being comprehensive. Nevertheless, the results outlined below may be useful for future studies to further characterize the role of superantigens per se or in the context of bacterial or viral encephalitis, respectively.

2. Effects of intracerebral T-cell superantigen

Intracerebrally expressed superantigen induces a perivascular and periventricular inflammation (Kornhuber et al., 2002; Emmer et al., 2010). Fourty-microliter aliquots of superantigen or saline were slowly injected intracerebrally through a small burr hole in isoflurane-anesthetized male 300-g Lewis rats, 2.5 mm lateral from the midline at the bregma at a depth of 3.5 mm. Horizontal hematoxylin/eosin stained sections of the rat brains were investigated after fixing the brains with 4% buffered paraformaldehyde. Sections were obtained at the corpus callosum and at the level of the lateral ventricles. Cuffings of perivascular round cells were identified scattered around the injection canal. In the first 3 days, perivascular round cells could be observed in both hemispheres with a preponderance in the corpus callosum and the periventricular white matter. Thereafter perivascular round cells were confined to the injected hemisphere up to 12 days after SEA injection. Maximum response in the injected hemisphere was identified up to 8 days after injection (Fig. 1).

We wondered why the response to superantigen was relatively variable and usually low. It is well known that relapses in MS are often precipitated by some nonspecific immune stress such as infection. Furthermore, it is known that only activated immune cells are capable to invade the CNS (Wekerle et al., 1986). For these reasons we tried to imitate the stress by loading the blood with activated immune cells.

3. Activated splenocytes amplify superantigen encephalitis

Activated syngeneic splenocytes were injected in volumes of 0.5 ml through the penis vein of 300 g male Lewis rats on the third day after intracerebral injection of the superantigen SEA (see above). Activation of splenocytes was achieved in the following way under sterile

conditions: A syngeneic spleen was cut and the content passed through a sieve into isotonic NaCl-solution. Cells were washed three times and the pellet finally resuspended in RPMI-medium with 5 % heat-inactivated fetal calf serum and with a final concentration of 2 µg/ml concanavalin A (ConA). Cells were harvested and washed after 3 days in culture when they were maximally stimulated. They were kept in NaCl on crushed ice for injection purposes. Usually 10^7 cells were injected i.v. under brief general isoflurane anesthesia. The time course of the tissue reaction to 1 mg/ml SEA was investigated (Kornhuber et al., 2002). In general, perivascular round cell infiltrates were more numerous and more reproducible than without adding activated splenocytes. In the first up to 3 days after splenocyte injection, reactive vessels could be identified in both cerebral hemispheres with a preponderance on the injected side. Thereafter, inflamed blood vessels were confined to the injected hemisphere. The response was short-lived and could last for further 3 up to 12 days. Thereafter, no reactive vessels could be identified. On day 5 after i.v.-injection, on average 18.5±11.4 vessels with round cell cuffs were observed. When compared with the corresponding numbers obtained without i.v.-injection of activated splenocytes, the difference was statistically significant ($p < 0.05$; two-sided U-test). When the amount of activated splenocytes was kept constant at 10^7 per animal, the number of reactive blood vessels increased linearly with the concentration of SEA. When the injected SEA was kept constant at a concentration of 1 mg/ml, the number of reactive blood vessels increased linearly with the number of intravenously injected activated splenocytes.

4. Immunohistochemical characterization of round cell cuffing

Immunohistochemical investigations of the SEA-encephalitis were performed using shock-frozen brains fixed at -80 °C. Six µm kryocut sections were made at -14 °C. Neighboring tissue sections that showed both, the cerebral ventricles and the stitch canal were taken for further evaluation. The avidin–streptavidin–biotin (ABC)-method was used throughout for immunohistochemical staining purposes. All used antibodies were ordered by BD Biosciences Pharmingen. After preincubation with goat serum for 20 min, incubation with the primary antibody (1:50, 1 h) was followed by incubation with the secondary antibody (1:50, 30 min). After 30 min in the pre-diluted streptavidin–horseradish–peroxidase (HRP) all tissue sections were finally incubated with diaminobenzidine (DAB) solution until the desired colour intensity was obtained. Sections were dehydrated three times on increasing grades of alcohol and covered with Roti-Histokit. Spleen tissue slices served as the positive controls. All used primary antibodies were highly specific for their target antigen. Negative controls included substitution of primary antibodies by antibodies of the same isotype with specificities against non-host antigens.

12 h after i.v. injection of ConA-activated spleen cells (i.e. 3 days after intracerebral injection of SEA), relatively high numbers of immunoreactive CD3+, CD4+ and CD8+ T-cells were present in a perivascular distribution and also scattered in the parenchyma around the stitch canal of the injected hemisphere (Fig. 3). The perivascular cuffs consisted of several layers of round cells. The amount of immunoreactive cells within the perivascular infiltrates, i.e. CD3+, CD4+ and CD8+ T-cells decreased gradually thereafter (Figs. 3 and 4) and amounted merely to usually 1 complete layer of immunopositive cells 3 days after i.v. injection of splenocytes and some loosely grouped perivascular cells after 5 days. Thus, the

inflammatory response was less large than in the previous experiments (see above). Among the different T-lymphocyte subsets, CD8+ T-cells were generally the most numerous ones (Figs. 3 and 4). The number of CD3+ T-cells within slices of the injected right hemisphere made up only about one quarter of the sum of the T-cells found to express CD8 or CD4 (Figs. 3 and 4). The relative numbers of reactive blood vessels remained more or less constant within the investigated time period (not shown). In the non-injected left hemisphere, the inflammatory activity was generally less prominent (Fig. 4). In fact, notable numbers of CD4+ and CD8+ T-cells within perivascular cuffs were identified only 3 days after i.v. injection of ConA-activated spleen cells (Fig. 4). In the brains of control animals, T-cells expressing CD4, CD8 or CD3 were not detected except for isolated immunopositive cells in the area of the stitch canal 0.5 days after the i.v. injection of ConA-activated splenocytes (not shown). Five days after the i.v. injection, no stained T-cells were found in the investigated brain slices of both control animals.

The cerebral inflammatory reaction was short-lived, presumably due to the rapid disappearance of the injected superantigen, e.g. by non-specific binding to cell surfaces. Differences in the duration of the inflammation in the order of several days may be due to different preparations of the superantigen, which may impact the immunostimulatory potency of the SEA reagent.

The cerebral inflammation induced by SEA was most prominent within the injected hemisphere and consisted initially mainly of CD8+ T-cells, which made up about 65% of the perivascular round cell population (Fig. 4). As no similar inflammatory response could be identified in the brains of the control animals that had received saline intracerebrally, the results do not appear to be due to the stitch trauma. Furthermore, only relatively small numbers of T-cells were found within the non-injected left hemisphere 0.5 days after i.v. injection of the ConA-activated splenocytes. As the number of the perivascular round cells detected in the left hemisphere peaked after 3 days following the i.v. injection of the ConA-activated splenocytes (Fig. 4), migration from the injected right hemisphere via the corpus callosum is the presumable reason for their occurrence contralateral to the injection site as has been suspected previously (Kornhuber et al., 2002). How does the superantigen expressed in the brain tissue lead to local recruitment and activation of T-cells? Presumably, the unprocessed superantigen was presented by MHC molecules on the surface of perivascular cells, microglial cells or dendritic cells, which are known to express MHC-class II constitutively within the CNS (Sedgwick et al., 1993; Stoll, 2002). By way of contrast, MHC-class I is not present on cell surfaces in the cerebral parenchyma unless its expression is specifically induced (Sedgwick et al., 1993; Redwine et al., 2001). When the injected ConA-activated cells appear in the circulation in high numbers after i.v. injection, namely 3 days after the intracerebral SEA-injection, free superantigen seems unlikely to be present in the cerebral extracellular fluid. Therefore, direct binding of SEA to the T-cell receptor (TCR) of ConA-activated splenocytes that come to traverse the blood–brain barrier does not seem to play a major role for T-cell activation in the present case (Fleischer, 1991; Herrmann et al., 1990; Yagi et al., 1990). However, only relatively small numbers of T-cells migrate through the cerebral blood vessels as part of a surveillance process, unless specific stimuli force them to stay on the abluminal side (Wekerle et al., 1986). The persistence of T-cells within the parenchyma after intracerebral injection of SEA may be taken as evidence that a specific stimulus forced them to stay within the CNS, therefore. After local expression of SEA, the

majority of the T-cells detected within the intracerebral perivascular infiltrates was CD8+, while a minority was CD4+ (Figs. 1 and 2). Although superantigens presented via MHC II are well known to stimulate CD4+ T-cells, it has been demonstrated that SEA may activate CD8+ T-cells in a TCR-dependent manner (Müller-Alouf et al., 2001; Stinissen et al., 1995). Results obtained by gene expression analysis for the SEA encephalitis are in line with a CD8+ T-cell driven immune response (see below; Emmer et al., 2008). At a first glance it seemed to be curious that the numbers of T-cells expressing CD8 or CD4 detected within the right hemisphere in sum outnumbered the CD3+ ones at each investigated time point. The immunostaining for CD3 like that for CD4 and CD8 was of sufficient quality to allow a clear distinction between positive and negative cells (Fig. 3). Therefore, it does not seem likely that the mismatch between the results for CD3 and CD8 was artificial in nature. Actually, a diminished expression of CD3 but not of CD4 or CD8 has been reported previously for T-cells that had been challenged by superantigen (Damle et al., 1993; Niedergang et al., 1995; Makida et al., 1996; Von Essen et al., 2004). Therefore, the finding of a lower expression of CD3 in comparison to CD8 on T-lymphocytes like in the present investigation can be taken as evidence for the presence of a previous superantigenic stimulus.

Taken together, it has been demonstrated that the round cells that take part in perivascular cuffing of the encephalitis induced by the superantigen SEA are primarily composed of T-cells, especially of CD8+ T-cells. This result may be of importance with respect to the pathogenesis of inflammatory diseases of the central nervous system. The fact that upon the superantigenic stimulus T-cells become CD3-negative in significant numbers, leaving the expression of e.g. CD8 unaltered, may be used to demonstrate the involvement of a superantigenic stimulus in different states of encephalitis.

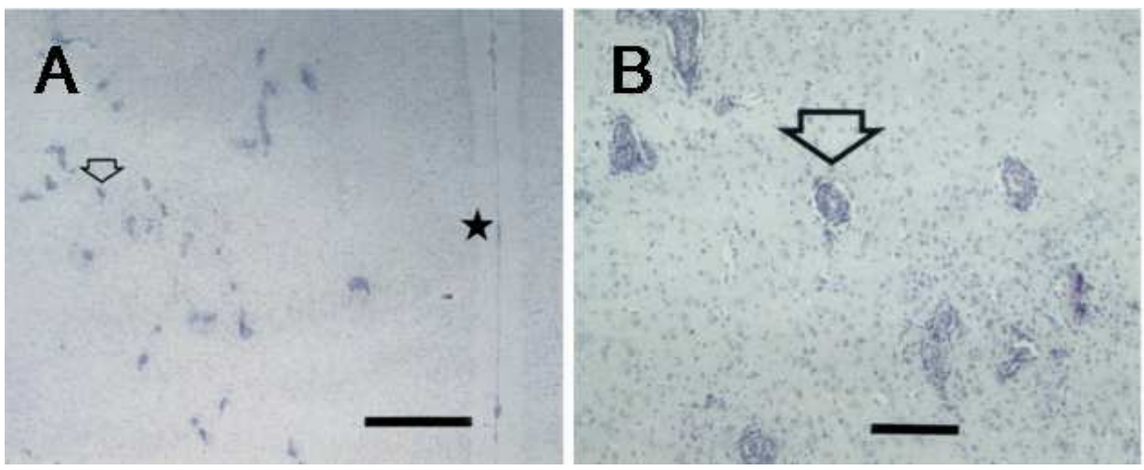

Fig. 2. The figure illustrates the effect of intracerebral superantigen. Frontal sections of the rat brain at the level of the corpus callosum, hematoxylin and eosin stain. The interhemispheric cleft has been marked by a star. (A) Five days after intracerebral SEA-injection and 8 days after i.v. injection ConA-activated splenocytes. (B) Part A at a higher magnification.

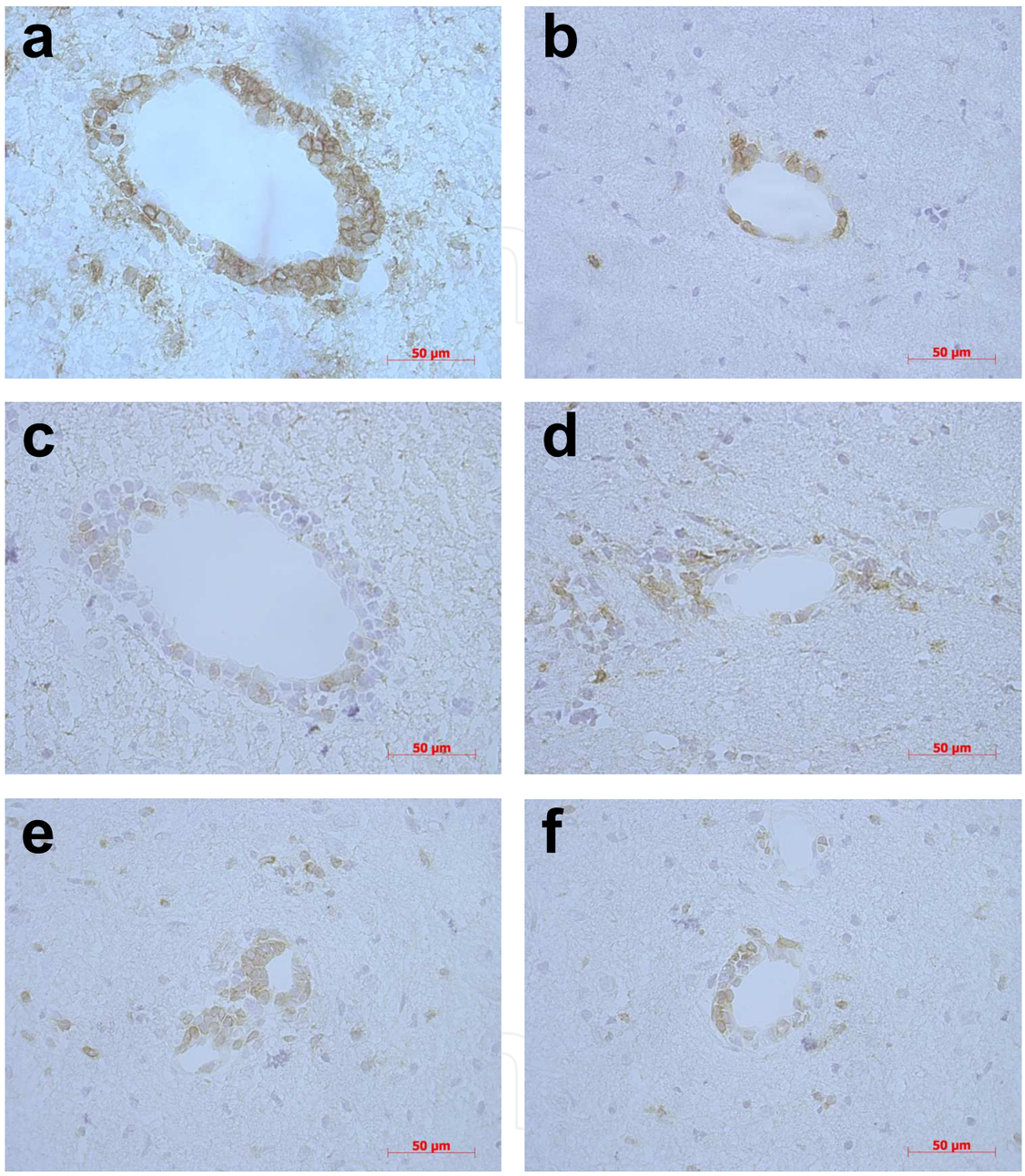

Fig. 3. Representative immunohistochemical stains of rat brain slices of the right hemisphere (streptavidin–biotin-method) after intracerebral injection with Staphylococcal enterotoxin A (SEA). Slices obtained 0.5 and 3 days after i.v. injection of ConA-activated splenocytes show expression of the antigens CD8 (a, day 0.5; b, day 3), CD4 (c, day 0.5; d, day 3), and CD3 (e, day 0.5; f, day 3). Note the special preponderance of CD8+ T-cells (a) in comparison with CD4+ T-cells (c). With time, the perivascular round cell count decreased as exemplified by the T-cells expressing CD8, CD4 or CD3, 3 days after i.v. injection of ConA activated splenocytes (b, d, f) compared with those detected after 0.5 days (a, c, e) (Emmer et al., 2010).

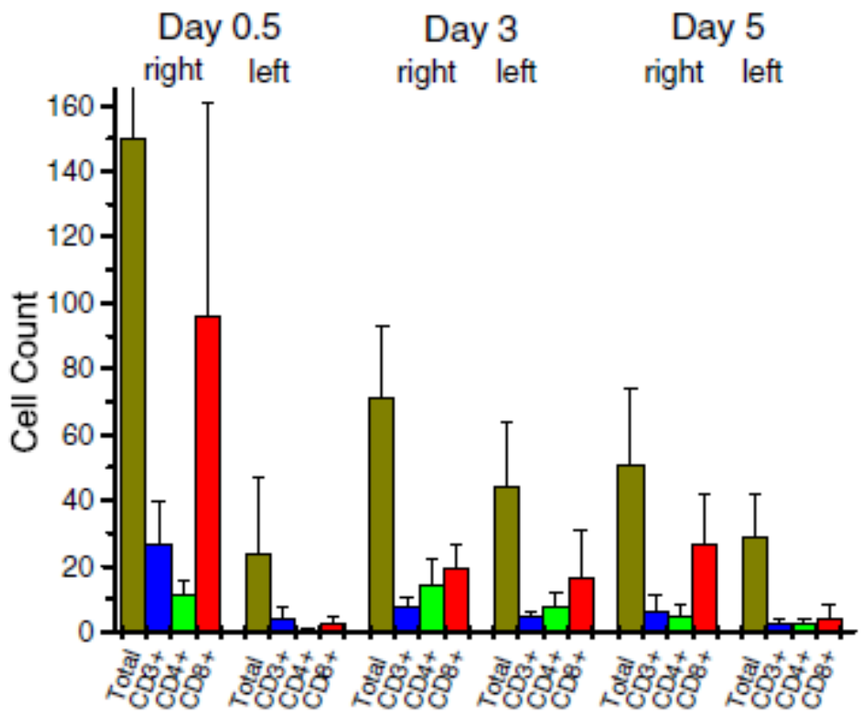

Fig. 4. Summary of the perivascular round cell counts (columns) are given together with the standard deviation (bars) for the entirety of the cells per tissue slice and hemisphere (olive green) and for the cells positively stained with CD3 (blue), CD4 (green) and CD8 (red), after injection of the superantigen Staphylococcal enterotoxin A (SEA) into the right hemisphere followed by intravenous loading of ConA-activated splenocytes 3 days later. The bar of the first left-sided column has been cut. Its value amounts to 58 cells. The 3 investigated time points, i.e. 0.5 days, 3 days and 5 days, refer to the interval between intravenous splenocyte injection and sacrification of the animals (Emmer et al., 2010).

5. Gene expression profile of superantigen encephalitis

Of 5 male 300 g Lewis rats, two animals received 50 µl of 1 mg/ ml SEA and two animals were injected with saline into the right brain hemisphere during deep anaesthesia. Injections were placed 2.5 mm lateral to the midline and 2 mm behind the bregma. One rat was sham operated. Three days after this procedure, $1.5*10^7$ ConA-activated splenocytes (see above), were injected into the penis vein of each animal. Eight days after the initial surgical procedure, brains were taken from all Lewis rats. A coronar disk (2 mm) including the injection channel was prepared and divided into an injected half and a non-injected half. The samples were snap frozen in isopropanol and stored at -80 °C. Microarray analysis was performed as described previously (Staege et al., 2004). Data analyses were performed by using Statistical Analysis of Microarrays (SAM) (Tusher et al., 2001). Results from the 4 rat brain hemispheres of the two 'SEA' animals were compared with the 4 hemispheres of the 2 'saline' animals. Furthermore, the differential gene expression after saline injection versus sham operation was calculated. Due to the small sample size, a relatively conservative approach was followed with $\Delta = 0.75$, a false discovery rate of 0.099 and a minimum change factor of three. To be acceptable, the signal intensities had to be above 30. Validation of

microarray data was done by real-time PCR. To validate the results of the microarray analysis, the transcriptional regulation of nine genes [CCL5 (RANTES), TIMP-1, osteopontin, CD74, RT1-Da, complement component 3, tenascin C, CD8 and CCL2 (MCP-1)] that showed significant differential expression in rat brains with SEA encephalitis was measured also using real-time PCR. Total RNA was extracted from brain tissue using Trizol (Invitrogen, Karlsruhe, Germany) or the RNeasy kit (Qiagen, Hilden, Germany). Quantitative RT-PCR (qRT-PCR) was performed by using the QuantiTect SYBR Green RT-PCR Kit (Qiagen) using the following conditions: 94 °C, 45 s; 62 °C, 45 s; 72 °C, 60 s. Each reaction was subjected to melting temperature analysis to confirm presence of the expected products. Specific gene amplification was normalized to GAPDH. Target genes and GAPDH were amplified with 40 cycles using a ROTOR GENE RG-3000 (Corbett Research, Sydney, Australia) and ROTOR GENE 6 software. The threshold cycle (CT) value was defined as the fraction cycle number and set at 10 times the standard deviation above the mean baseline fluorescence calculated from cycles 3 to 15. The fold changes in the target genes normalized to actin 22 (as house keeping gene) and relative expression of controls (1 uninjected rat brain) was calculated by using standard ΔΔCT method.

Of the 8800 investigated genes, 106 were at least 3-fold increased with SEA over saline, while 29 genes were decreased at least 3-fold. The respective microarray data of differentially overexpressed *genes* are summarized in Table 1. Genes with increased expression were grouped in the following order: antigen presentation, lymphocytes, chemokines / chemokine receptors, microglial reaction / macrophages, phagocytosis / opsonization, extracellular matrix / cell adhesion, anti-inflammatory reaction and miscellaneous/ compound to inflammation. Some of the genes with decreased expression (not shown) presumably belong to cerebral cell elements such as neurons or astrocytes, e.g. genes encoding for neurotransmitter receptors or ion channels. In fact, the expression for the genes encoding for CCL5 (RANTES), TIMP-1, osteopontin, CD74, RT1-Da, complement component 3, tenascin C, CD8 and CCL2 (MCP-1) in relation to the house keeping gene for actin 22 as measured by real-time PCR showed a high level of conformity in comparison with the results obtained by using microarrays. Differential gene expression after saline injection versus sham operation revealed at least 3-fold overexpression of six genes and underexpression of 40 genes (not shown). The relatively mild differences observed in the gene expression between both conditions may reflect the consequences of the injection trauma and are considered of minor relevance for the SEA encephalitis.

When data were first analysed, it became obvious that after intracerebral SEA injection versus saline injection, expression of several genes was markedly increased in the injected hemisphere and also displayed considerable overexpression in the non-injected contralateral hemisphere as well. This finding might correspond to the bilateral perivascular inflammatory reaction observed by using histology in the first days of SEA encephalitis (see above). Due to this finding, it was decided to analyse both hemispheres together. This approach certainly reduces absolute values of differential gene expression and at the same time it might reduce detection of false-positive data, e.g. resulting from the small number of samples. The results are in conformity with the light microscopy findings of a perivascular inflammation.

Among the genes with elevated expression, there was a considerable number of genes encoding for MHC class II molecules, which are constitutively expressed on microglial cells in the brain. In a state of encephalitis, they may be detected on astrocytes as well.

Superantigen is presented in the context of MHC class II. However, 8 days after intracerebral injection of the superantigen, it might be doubted whether the elevated expression of genes for MHC class II molecules is still a direct consequence of the superantigenic stimulus. Antigen-presenting cells present in the inflammatory area may comprise microglial elements, monocytes and astrocytes [elevated expression of genes for: Serping1, CD53 antigen, CCAAT/ enhancer binding protein (C / EBP) delta, glial fibrillary acidic protein (GFAP) and calcium binding protein S100A4]. T lymphocytes seem to play a major role among the hematogenous cellular infiltrates of the SEA encephalitis. While the genes for CD3 and CD8 were found to be significantly elevated, this was not the case with the gene for CD4. This fits to immunohistochemical results showing that the perivascular round cell cuffs are dominated by CD8+ T lymphocytes on days 3.5, 6 and 8 after intracerebral SEA injection (see above). This finding was unexpected as usually CD4+ T cells are activated by T-cell superantigen presented in the context of MHC class II molecules (Fields et al., 1996). By way of contrast, CD8+ T cells are predominantly stimulated in the context of MHC class I molecules (Jelonek et al., 1998). As the latter ones are not constitutively presented in the brain, it seems unlikely that these molecules play a major role in the induction of the SEA encephalitis. Rather SEA may have been presented in the context of MHC class II. Previously, a similar stimulation of CD8+ T cells via superantigen bound to MHC class II as found in the present investigation has been reported (Fraser, 1989). Of interest, there exists a parallel to MS, where CD8+ T cells have been reported to predominate among perivascular inflammatory infiltrates (Liu et al., 2007; Jilek et al., 2007). Further proteins involved in antigen presentation or in signalling cascades were significantly overexpressed with SEA comprise sialoprotein CD43, cathepsin C, and CD 72. Similar to other states of cerebral inflammation such as in MS or EAE, there was a profound increase in the expression of the genes for the following proteins involved in chemotaxis after SEA injection: RANTES (CCL5), osteopontin, MCP-1 (CCL2) and CXCL10. Furthermore, the gene for the receptor of MCP-1 (CCR2) showed a significantly increased expression. In contrast to the elevated chemokine levels, cytokines, such as interleukin-2, tumour necrosis factor alpha or interferon gamma, did not reveal significantly increased differential expression levels. As these cytokines belong to the group of substances which are released early in the course of an inflammation, it is quite plausible that the genes for these cytokines are not expressed any more differentially 8 days after injection of SEA. Intracerebral injection of SEA was followed by an enhanced expression of genes encoding different complement factors such as C3, C4a, C1q, B, D (adipsin) and serping 1. These factors may be released from microglial cells (Raivich and Banati, 2004) or from macrophages. Complement factors were suggested to play a role in opsonization and phagocytosis. Complement factors 1q, 3 and 4a showed a high expression in microarray studies in EAE and MS (Tajouri et al., 2003; Lock et al., 2002). Actually, increased expression was detected for genes that are also related to phagocytosis. These were Fc-gamma receptor, Vav1, galectin 3 (Wilkinson et al., 2006; Rotshenker, 2003). These genes were previously shown to display increased expression in EAE (Lock et al., 2002; Reichert and Rotshenker, 1999; Carmody et al., 2006). A number of genes with increased expression levels after SEA injection were related to the extracellular matrix. These were lysyl oxidase, tenascin C, alpha-1- collagen type III, syndecan 1, alpha-1-collagen, alpha-1- procollagen type I, vimentin, matrix-gla-protein, periostin, oxidized LDL-receptor-1 and alpha-tubulin. The

gene for tenascin C was measured with elevated expression in EAE and in MS (Lock et al., 2002, Carmody et al., 2006), while a similar increase for the gene of alpha-tubulin was present in MS (Carmody et al., 2006). Not all of the above summarized genes that showed enhanced expression after intracerebral superantigen injection did so in EAE or MS. Furthermore, the gene for integrin alpha M was detected with elevated expression in the present study. Integrin alpha M mediates cellular adhesion to the extracellular matrix (Friedl and Brocker, 2000). It is also upregulated in EAE and in MS (Lock et al., 2002, Carmody et al., 2006). Whether the enhanced gene expression of components of the extracellular matrix reflects alterations in the context of the encephalitis or reflects reparative activity remains to be established. Increased expression of the following genes may be regarded as part of an anti-inflammatory tissue reaction: alpha-2-macroglobulin, metallothionein, heat shock protein 27 (HSP27), haeme oxygenase-1, C/ EBP-related transcription factor beta, coeruloplasmin and pleckstrin. The gene products take part in the inactivation of proteolytic enzymes (alpha-macroglobulin), in the reduction in oxidative stress (methallothionein, haeme oxygenase 1, coeruloplasmin) or in the apoptosis induction (HSP27). Several of these genes have been observed with increased expression in EAE or in MS (Table 3), such as metallothionein (Tajouri et al., 2003; Lock et al., 2002; Penkowa and Hidalgo, 2003; Espejo et al., 2005; Espejo and Martinez-Caceres, 2005), haeme oxygenase 1 (Levine and Chakrabarty, 2004; Tan et al., 2004) and HSP27 (Tajouri et al., 2003). Furthermore, there was a significant increase for the genes of the metalloproteinase 9 (MMP9) and its inhibitor, the tissue inhibitor of metalloproteinase 1 (TIMP-1). Both genes were reported to be upregulated in EAE and in plaque tissue from patients with MS (Steinman, 1999; Pagenstecher et al., 1998). While MMP9 is e.g. required for the migration of lymphocytes through the basilar membrane and thus for invading the CNS, the much more pronounced upregulation of TIMP-1 may be regarded as an anti-inflammatory response. Other genes with increased expression levels in the SEA encephalitis are genes encoded for different cytochromes (P450 type 1b1, b558 and b245), granulin, lipocalin and STAT1. The role of the proteins during the course of the SEA encephalitis is not entirely clear. At least the elevated gene expression for STAT1 was noted previously in EAE (Jee et al., 2001) and in MS (Frisullo et al., 2006). Furthermore, the gene for granulin was observed with elevated expression in MS (Tajouri et al., 2003).

Genes with decreased expression: The number of genes with significantly and at least threefold decreased expression was small (n = 29), in comparison with the number of genes showing an increased expression (n = 106). Among the former genes, there was a number of genes related to cerebral cellular functions such as neurotransmitter receptors, ion channel proteins, ion pumps or growth factor receptors: retinoid-X-receptor gamma, cholinergic receptor (nicotinic, alpha polypetide 2, neuronal), potassium voltage-gated channel, subfamily H member 8 (ATPase), proton pump (H+ transporting, V1 subunit G, isoform 3 and H+/K+ ATPase), calbindin and oncomodulin. Expression of these genes was not observed to be decreased in EAE or MS. Nevertheless, in EAE and MS, genes with decreased expression levels were observed to encode proteins with similar functions. These included myosin VIIA, phosphatidylinositol 4- kinase (Tajouri et al., 2003), TGF beta 3, cadherin-7 (Lindberg et al., 2004), somatostatin and kinesin (Lock et al., 2002). Taken together, the gene expression data in the present study support previously reported light microscopy findings of the encephalitis developing after superantigen injection into the rat brain (Kornhuber et

al., 2003). The peculiar gene expression pattern found 8 days after superantigen injection is compatible with a CD8+ T lymphocyte driven process leading to different cerebral inflammatory and anti-inflammatory reactions. As superantigens were implicated in the pathogenesis of human autoimmune diseases, such as MS, the comparison of the presented data with those gathered with EAE or MS may be of general interest. Actually, there is considerable conformity between the gene expression profile of the SEA encephalitis and EAE or MS (Table 2). This accordance between the three different states of inflammation may be due to the fact that a T-cell-driven pathogenesis is common to all of them.

Accession no.	Description	SEA	NaCl	Ratio
Antigen presentation				
X13044	MHC-II (CD74 antigen)	3542	130	27.2
X14254	MHC-II (invariant chain)	1209	45	26.9
X07551	MHC-II B-alpha gene	1384	113	12.2
X56596	MHC-II B-1 beta chain	1014	168	6.0
X53054	MHC-II (protein complex)	1322	219	6.0
M64795	MHC-I (CRT 1-u)	620	106	5.8
U31599	MHC-II (DM beta)	433	82	5.3
M36151	MHC-II A-beta gene (RT1 class II locus Bb)	794	154	5.2
K02815	MHC-II (locus Ba)	1982	387	5.1
M15562	MHC-II	1180	231	5.1
X57523	TGF-beta (activated)	310	83	3.7
AI171966	MHC-II (DM beta)	1619	440	3.7
X67504	MHC-I (locus Aw2)	205	61	3.3
U31599	MHC-II	215	69	3.1
Lymphocytes				
X03015	CD8 antigen (alpha chain)	282	35	8.1
S79711	CD3 gamma-chain	68	14	4.9
X14319	T-cell receptor (beta chain)	282	61	4.6
M10072	CD45 antigen	130	32	4.1
U24441	Matrix metallopeptidase 9	198	49	4.0
D90404	Cathepsin C	476	148	3.2
AI045440	Sialophorin	75	24	3.1
Chemokine / chemokine receptor				
M14656	Secreted phosphoprotein 1 (osteopontin)	1694	94	18
AI009658	CCL5 (RANTES)	1345	88	15.3
AA892854	CXCL13	442	63	7
X17053	CCL2 (MCP-1)	226	38	5.9
AA945737	CXCR4	60	11	5.5

Accession no.	Description	SEA	NaCl	Ratio
U17035	CXCL10	175	40	4.4
X52498	TGF beta1	414	132	3.1
Microglial reaction/macrophages				
U18729	Cytochrome b558 alpha subunit	985	169	5.8
U09540	Cytochrome P450 type 1b1	223	40	5.6
AF028784	GFAP (alternatively spliced form)	4474	1030	4.3
AI176856	Cytochrome P450 (Cyp1b1)	289	70	4.1
AA800318	Serping1	1085	285	3.8
M57276	CD53 antigen	537	158	3.4
M65149	CCAAT/enhancer binding protein (C/EBP)	257	77	3.3
M24067	Serpin E1	180	59	3.1
U10894	Allograft inflammatory factor 1	669	219	3.1
Phagocytosis/opsonization				
J02962	IgE-binding protein (Galectin 3)	1220	87	14.0
M29866	Complement component 3	1358	122	11.1
X52477	Pre-pro-complement component 3	935	103	9.1
X71127	Complement C1q beta chain	3632	649	5.6
M92059	Adipsin	138	25	5.5
X73371	Fc gamma-receptor	209	41	5.1
AA892775	Lysozyme	4526	919	4.9
AA891576	Complement component 1q	98	20	4.9
AA893280	Adipose differentiation related protein	563	135	4.2
AI639117	Complement factor B	268	65	4.1
AI639117	Complement factor B	268	65	4.1
M32062	Fc-gamma-receptor 3	433	117	3.7
M32062	Fc gamma-receptor II beta	597	173	3.5
U42719	Complement component 4a	1453	416	3.5
D10757	Proteosome (macropain) subunit, beta type 9	277	80	3.5
U39476	Vav 1 oncogene	106	31	3.4
D88666	Fatty acid-binding protein (adipocyte)	131	40	3.3
Extracellular matrix/cell adhesion				
S66184	Lysyl-oxidase; fibroblast	140	16	8.8
U15550	Tenascin-C	61	10	6.1
S61865	Syndecan 1	105	20	5.3
X70369	Collagen type III alpha 1	862	165	5.2
U59801	Integrin alpha M	84	18	4.7

Accession no.	Description	SEA	NaCl	Ratio
U75405UTR#1	Alpha-1 collagen mRNA	2804	624	4.5
M27207	Procollagen, type 1, alpha 1	2070	568	3.6
X62952	Vimentin	2652	763	3.5
AI012030	Matrix Gla protein	1932	561	3.4
AA894092	Periostin, osteoblast specific factor (predicted)	47	14	3.4
AI231472	Procollagen, type 1, alpha 1	999	308	3.2
AI071531	Oxidized low density lipoprotein receptor 1	63	20	3.2
AA892333	Tubulin, alpha 6	1662	553	3.0
Antiinflammatory reaction				
AI169327	Tissue inhibitor of metalloproteinase 1	940	20	47.0
M22670	Alpha-2-macroglobulin	219	9	24.3
AI045030	CCAAT/enhancer binding protein delta	118	22	5.4
AA998683	Heat shock 27-kDa protein 1	1386	273	5.1
AA817854	Ceruloplasmin	183	39	4.7
AI169327	TIMP-1	1671	362	4.6
S77528	NF-IL6 (C/EBP-related transcription factor beta)	74	16	4.6
L33869	Ceruloplasmin	391	92	4.3
AI176456	Metallothionein	11045	2980	3.7
M86389	Heat shock 27-kDa protein 1	1563	444	3.5
AA799323	Pleckstrin	99	29	3.4
M65149	CCAAT/enhancer binding protein delta	257	77	3.3
J02722	Haeme oxygenase (decycling) 1	194	58	3.3
M23566	Alpha-2-macroglobulin	3153	989	3.2
AA900582	Alpha-2-macroglobulin	1000	330	3.0
Miscellaneous/compound to inflammation				
L07114	Apolipoprotein B complex	378	23	16.4
AA946503	Lipocalin 2	629	45	14.0
M80367	Guanylate nucleotide binding protein	132	25	5.3
X06916	Protein p9Ka, (S100 calcium binding Prot. A4)	774	153	5.1
AA892553	STAT-1	261	54	4.8
D26393	Hexokinase II	143	33	4.3
X62322	Granulin	4118	1048	3.9
AA946044	Yamaguchi sarcoma viral (v-yes-1) oncogene	79	21	3.8
D21215	Coagulation factor 10	44	12	3.7
AA894029	Cytochrome b-245 beta polypeptide)	116	31	3.7

Accession no.	Description	SEA	NaCl	Ratio
L13192	Forkhead box D1	114	32	3.6
M18349	Protein tyrosine phosphatase, receptor type, C	80	22	3.6
J02869	Cytochrome P450 (Cyp2d9)	153	43	3.6
S66024	CAMP responsive element modulator	68	19	3.6
K03039	Leukocyte common antigen	35	10	3.5
X61381	Interferon-induced trans-membrane protein 3	2347	671	3.5
AI233219	Endothelial cell-specific molecule 1	38	11	3.5
M33648	Coenzyme A synthase 2	192	56	3.4
M19257	Retinol binding protein 1, cellular	653	199	3.3
D30649	Ectonucleotide pyrophosphatase 3	56	17	3.3
E00903	Natriuretic peptide precursor type A	362	112	3.2
J05495	Macrophage galactose lectin 1	88	28	3.1
S67722	Prostaglandin-endoperoxide synthase 2	595	192	3.1
U77038	Protein tyrosine phosphatase type 6	68	22	3.1

Table 1. Absolute and relative signal intensities measured with Affymetrix Rat Genome U34A are given for individual genes that exhibited significantly and at least 3-fold increased differential expression after intracerebral (i.c.) SEA injection compared with saline injection.

Description	MS	EAE	SEA encephalitis
MHC-II	↑ [Lock et al., 2002]	↑ [Carmody et al., 2006]	↑
MHC-I	↑ [Tajouri et al., 2003]		↑
Matrixmetallopeptidase 9	↑ [Steinman, 1999]		↑
CD8 antigen alpha chain	↑ [Liu et al., 2007]		↑
T-cell receptor beta chain	↑ [Lock et al., 2002]	↑ [Carmody et al., 2006]	↑
CD3 gamma-chain	↑ [Liu et al., 2007]		↑
CD 45 antigen	↑ [Liu et al., 2007]		↑
Leukocyte common antigen	↑ [Liu et al., 2007]		↑
Cathepsin C (dipeptidyl peptidase I)		↑ [Carmody et al., 2006]	↑
Sialophorin (CD43)		↑ [Ford et al., 2003]	↑
Secreted phosphoprotein 1 (osteopontin)	↑ [Lock et al., 2002] ↓ [Lindberg et al., 2004]	↑ [Kim et al., 2004]	↑
Chemokine (C-C-motiv ligand) 5, RANTES	↑ [Boven et al., 2000]	↑ [Dos Santos et al., 2005]	↑
Early response JE gene (chemokine C-C motiv ligand 2 (MCP-1)	↑ [Tanuma et al., 2006]	↑ [Hofmann et al., 2002]	↑
Chemokine (C-X-C motif) ligand 10 (CXCL10)	↑ [Tajouri et al., 2003]	↑ [Tajouri et al., 2003]	↑
Transforming growth factor,	↓ [Lindberg et al., 2004]	↑ [Carmody et al., 2006]	↑

beta 1 (TGF beta1)	↑ [Lock et al., 2002]		
CD53 antigen		↑ [Carmody et al., 2006]	↑
IgE-binding protein (Galectin 3)		↑ [Reichert, 1999]	↑
Vav 1 oncogene		↑ [Carmody et al., 2006]	↑
Fc gamma-receptor	↑ [Lock et al., 2002]		↑
Lysozym	↑ [Lock et al., 2002]		↑
Complement C1q	↑ [Tajouri et al., 2003]		↑
Complement component 3	↑ [Lock et al., 2002]		↑
Complement component 4a		↑ [Tajouri et al., 2003]	↑
Fatty acid-binding protein (adipocyte)		↑ [Carmody et al., 2006]	↑
Integrin alpha M	↑ [Lock et al., 2002]	↑ [Carmody et al., 2006]	↑
Tenascin-C	↑ [Lock et al., 2002]	↓ [Carmody et al., 2006]	↑
Collagen type III alpha 1	↓ [Tajouri et al., 2003]	↓ [Tajouri et al., 2003]	↑
Tubulin, alpha 6	↑ [Tajouri et al., 2003]	↓	↑
Haeme oxygenase 1		↑ [Tan et al., 2004]	↑
TIMP-1		↑ [Steinman, 1999]	↑
Alpha 2 macroglobulin		↑ [Hunter et al., 1991]	↑
Heat shock 27-kDa protein 1		↑ [Tajouri et al., 2003]	↑
NF-IL6(C / EBP-related transcription factor beta);	↑ [Lock et al., 2002]		↑
Metallothionein	↑ [Tajouri et al., 2003]	↑ [Espejo et al., 2005]	↑
GFAP (alternatively spliced form)		↑ [Tani et al., 1996]	↑
Granulin	↑ [Tajouri et al., 2003]		↑
STAT-1	↑ [Frisullo et al., 2006]	↑ [Carmody et al., 2006]	↑
Coagulation factor 10		↑ [Carmody et al., 2006]	↑
Hexokinase II		↑ [Carmody et al., 2006]	↑
Protein tyrosine phosphatase, receptor type, C		↑ [Carmody et al., 2006]	↑
Guanylate nucleotide binding protein		↑ [Carmody et al., 2006]	↑

Table 2. Comparison of the differential expression of individual genes for which data were available for the SEA encephalitis (present investigation) and from EAE and MS.

6. B-Cell superantigens and oligoclonal bands

When the role of superantigens is considered with respect to encephalitis, B-cell superantigens have to be taken into consideration in addition T-cell superantigens. A prominent representative for B-cell superantigens is gp120, which forms part of the envelope of the human immune-deficiency virus (HIV) (Neshat et al., 2000; Patke and Shaerer, 2000; Zouali, 2007). Like T-cell superantigens, B-cell superantigens stimulate their target cells in a clonal manner (Müller and Köhler, 1997; Goodyear and Silverman, 2005). As more than 1 B-cell clone is expected to be stimulated by a B-cell superantigen, it may be speculated whether this type of stimulus would result in the presence of oligoclonal IgG

bands on isoelectric focussing. Indeed, oligoclonal IgG bands have been identified in various encephalitic diseases in the cerebrospinal fluid (CSF), including e.g. different forms of viral or bacterial encephalitis. Usually, all the antibodies forming oligoclonal bands in these diseases are directed against proteins of the encephalitogenic pathogen. However, there are states of encephalitis like in MS, where the presence of oligoclonal bands cannot be attributed to a certain pathogen. In fact, the antigen specificities present in MS oligoclonal bands comprise almost any antigen that has been tested. Therefore, these oligoclonal antibodies in MS have been termed as "nonsense antibodies" (Mattson et al., 1980). Among this nonsense-spectrum of antigen specificities, frequently an intrathecal antibody sythesis against measles, rubella, varizella zoster virus, herpes simplex virus, Epstein-Barr virus, and Chlamydia pneumoniae have been found (Reiber et al., 1998; Skorstad et al., 2009; Franciotta et al., 2010; Fainardi et al., 2009). It may be interesting to mention here, that antibodies specific for myelin proteins form only a small part of the oligoclonal IgG antibodies in MS (Owens et al., 2009). If nonsense antibodies like in MS would be due to a B-cell superantigenic stimulus, experimental proof should be available. Therefore, we tested in vitro, whether B-cell superantigens were capable to induce the formation of oligoclonal IgG bands on isoelectric focussing. In fact, after stimulation of peripheral blood mononuclear cells in vitro with the B-cell superantigen gp120, we detected IgG-bands by isoelectric focussing of the supernatant (Figure 5; Emmer et al., unpublished). This IgG-production

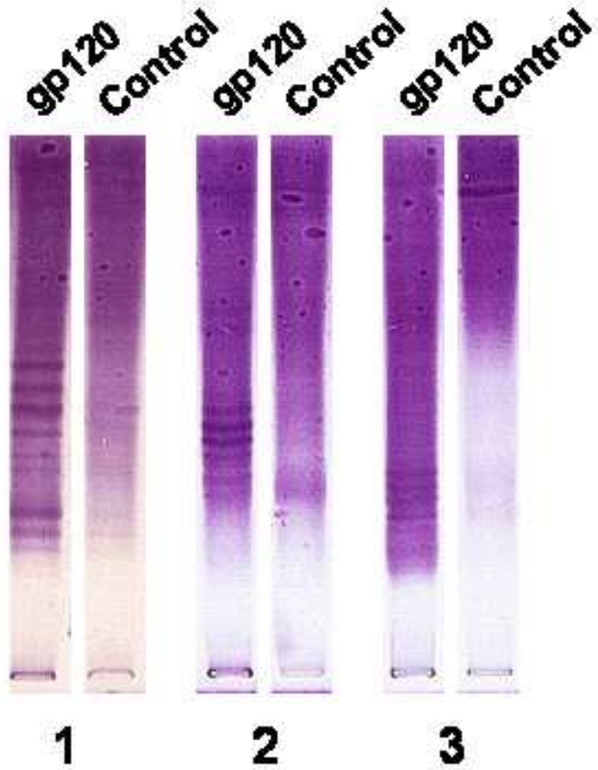

Fig. 5. Representative results obtained by isoelectric focussing after stimulation of peripheral blood mononuclear cells from 3 healthy human donors in vitro with gp120 (8 µg/ml) and without gp120 (control). The numbers underneath the images denote the different subjects.

depended on the concentration of the B-cell superantigen. The detected oligoclonal bands were quite similar to those found by isoelectric focussing in the cerebrospinal fluid of MS-patients. Our results suggest that B-cell superantigens may play a role in the pathogenesis of the inflammatory response of multiple sclerosis.
The expression of oligoclonal IgG in the CSF of MS-patients per se could have a detrimental influence, e.g. by opsonization of central nervous system components and subsequent phagocytosis by macrophages. In fact, the progress of the disease has been reported to be unfavourable if multiple oligoclonal bands are detected in the CSF of MS-patients (Joseph et al., 2009).

7. Conclusion

The present review focusses on the encephalitogenic effects of the intracerebrally expressed T-cell superantigen SEA. It has been demonstrated that SEA is capable to induce a perivascular inflammatory response, which was short lived after a single intracerebral injection. In the context of a pathogen residing within the CNS, a T cell superantigen is, however, expected to be expressed for prolonged periods of time and could, therefore, induce a longer lasting inflammatory response. The latter might add to the noxious response of the pathogen itself. Furthermore it was demonstrated that B-cell superantigens are able to stimulate B-cells to produce IgG which is detected as oligoclonal bands by isoelectric focussing. These oligoclonal bands resemble those found in the CSF of MS-patients.
Beside bacterial infections, the presented findings could be of special relevance for viral encephalitis and possibly for multiple sclerosis.

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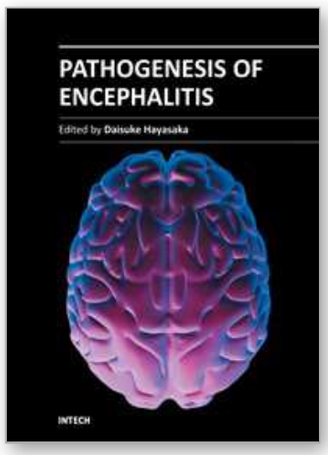

Pathogenesis of Encephalitis
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Many infectious agents, such as viruses, bacteria, and parasites, can cause inflammation of the central nervous system (CNS). Encephalitis is an inflammation of the brain parenchyma, which may result in a more advanced and serious disease meningoencephalitis. To establish accurate diagnosis and develop effective vaccines and drugs to overcome this disease, it is important to understand and elucidate the mechanism of its pathogenesis. This book, which is divided into four sections, provides comprehensive commentaries on encephalitis. The first section (6 chapters) covers diagnosis and clinical symptoms of encephalitis with some neurological disorders. The second section (5 chapters) reviews some virus infections with the outlines of inflammatory and chemokine responses. The third section (7 chapters) deals with the non-viral causative agents of encephalitis. The last section (4 chapters) discusses the experimental model of encephalitis. The different chapters of this book provide valuable and important information not only to the researchers, but also to the physician and health care workers.

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