T-Cells in Human Encephalitis

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Abstract

Encephalitis literally means inflammation of the brain. In general, this inflammation can result from a viral or bacterial infection in the brain itself or alternatively from a secondary autoimmune reaction against an infection or a tumor in the rest of the body. Besides this, encephalitis is present in (believed autoimmune) diseases with unknown etiology, such as multiple sclerosis or Rasmussen encephalitis (RE). This article summarizes the existing data on the role of T-cells in the pathogenesis of three types of human encephalitis: RE, paraneoplastic encephalomyelitis, and virus encephalitis. In all of them, T-cells play a major role in disease pathogenesis, mainly mediated by major histocompatibility complex class I-restricted CD8+ T-lymphocytes.

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Introduction

Inflammatory processes within the central nervous system (CNS) are mediated by three main effector systems: macrophages and microglial cells; B-lymphocytes and plasma cells and their effector products, antibodies; and T-lymphocytes. The T-cell system is the most strictly regulated and probably the most complex one among these. To perform an effective immune reaction, T-cells must patrol the CNS regularly and, on contact with a specific antigen in the context of the appropriate molecules, must expand clonally and enter the CNS in large numbers. Within the CNS, they have to perform their specific functions. CD4+ lymphocytes contribute to the activation of microglia/macrophages and B-cells, whereas CD8+ lymphocytes can act as cytotoxic effector cells, but also as regulatory cells. The brain milieu, on the other hand, does not explicitly favor these actions as evident from rapid apoptosis of T-cells in some disorders (Bauer et al., 1999).

In encephalitides, T-cells have been viewed primarily as “detrimental” for the CNS. However, they do also exert “beneficial” effects. This is particularly...
evident in cases of viral encephalitis. T-cells contribute to the clearance of infected cells (Hodgson et al., 1999; Liu and Chambers, 2001). On the other hand, people with numerically reduced or functionally impaired T-cells have an increased risk of succumbing to viral encephalitides. Also beyond viral diseases, T-cells may (down) regulate inflammatory processes and thereby prevent excessive damage to the CNS.

In this review, we attempt to summarize the existing knowledge on T-cell effects and—if available—potential ways of its therapeutic modification in Rasmussen encephalitis (RE), paraneoplastic encephalomyelitis (PEM), and virus encephalitides. Where appropriate, data from animal models of these human encephalitic diseases will be discussed.

### RE

RE is a chronic inflammatory brain disorder characterized by unihemispheric brain destruction, progressive impairment of neurological functions, and intractable seizures (Rasmussen et al., 1958; Bien et al., 2002b; 2005). The disorder mainly affects children with a peak of incidence at the age of 6–7 yr (Oguni et al., 1992). However, adolescent and adult patients with RE have been reported and probably account for about 10% of all cases (Hart et al., 1997). RE is an example of a disorder in which a humoral autoimmune genesis was proposed before the pathogenesis was linked to T-cells instead. The hypothesis of humoral autoimmunity at the core of RE pathogenesis was developed starting from a serendipitous observation: when four rabbits were immunized to raise antibodies against the subunit 3 of the ionotropic glutamate receptor (GluR3), two developed seizures. Histopathological examination of their brains showed bihemispheric inflammatory changes that were thought to mimic those of RE. Three out of four subsequently studied patients with RE, but none of the 21 controls, were found to harbor those GluR3 antibodies in their sera. One of the GluR3 antibody-positive patients was treated by plasma exchange and improved transiently (Rogers et al., 1994). However, recent studies of larger RE and control groups either did not find a difference between the number of GluR3 antibody-positive patients in RE and noninflammatory epilepsy groups (Wienfl et al., 2001; Mantegazza et al., 2002) or even concluded (on the basis of five different tests for GluR3 antibodies) that none of the tested patients with RE really harbored functional GluR3 antibodies (Watson et al., 2004).

The most relevant data regarding T-cell pathology in RE have been obtained by studies on brain specimens that had been collected during epilepsy surgery procedures or diagnostic open brain biopsies. The first histopathological study using immunohistochemistry techniques showed that most of the inflammatory cells, apart from activated microglial cells, were T-lymphocytes (Farrell et al., 1995). In a subsequent study, RE brain tissue was analyzed by means of quantitative polymerase chain reaction (PCR) assessment of T-cell receptor (TCR) gene transcripts. A restricted (i.e., oligoclonal) BV family usage was not observed. However, the TCR Vβ families that were predominantly expressed, displayed a limited size heterogeneity and extensive repetition of inframe CDR3 nucleotide motifs compared with controls. The authors concluded that the local lymphocytic immune process in RE includes restricted T-cell populations that have likely expanded from a few precursor T-cells responding to discrete antigenic epitopes (Li et al., 1997). Another immunohistochemical study of RE brain specimens provided evidence of a granzyme B (GrB)-mediated cytotoxic T-lymphocyte (CTL) attack against neurons. The authors were able to document several relevant elements of such a reaction within the diseased brains: CD3+CD8+ T-cells containing GrB granules attached to neurons that expressed major histocompatibility complex class I (MHC I) as well as neurons dying by apoptosis (Bien et al., 2002a). Confirmatory observations have been provided by another recent histopathological study on a large hemidecortication series (Pardo et al., 2004). Further support for the T-cell concept of RE pathogenesis comes from a recent report on elevated numbers of CD8+ T-cells and increased levels of interleukin (IL)-6 in the blood of a group of untreated patients with RE that was compared to a healthy age-matched control cohort (Tekgul et al., 2005).

The only well-established way of RE therapy is functional hemispherectomy or deafferentation of the affected side of the cerebrum for treatment of the severe epilepsy. The results are excellent regarding seizure freedom, however, at the price of complete loss of all cortical functions of the affected hemisphere. That means that after this operation, spastic...
hemiplegia of the contralateral extremities, homonymous hemianopia, and—if performed on the language dominant side—aphasia will be inevitably present. Therefore, it has been common practice (Bien et al., 2005) to reserve hemispherectomy for non-seizure-free patients in whom further relevant deterioration of everyday functions is unlikely (because severe deficits have been brought about by the natural course of the disease and no relevant language functions reside on the affected brain hemisphere). During the last decade, case reports and small patient series have been published reporting on beneficial effects of different kinds of immunotherapies in patients not eligible for hemispherectomy. A recent open trial of the drug tacrolimus (a calcineurin inhibitor known to suppress the activation of T-lymphocytes) in comparison with a historical untreated control cohort showed a superior outcome of the treated patients regarding motor function and progression of hemiatrophy. The seizure outcome, however, was not superior in the tacrolimus group. These results were interpreted as suggesting a brain tissue and function protective effect of this drug (Bien et al., 2004). They provide indirect evidence for the concept of a T-cell-mediated tissue destruction in RE.

The above-described CTL mechanism in RE is suitable to explain the progressive brain tissue loss in this condition. However, it cannot directly account for the high-epileptic activity in RE brains. The most important limitation in the understanding of the pathophysiology of RE, however, is that the antigen/antigens against which the CTLs are directed is/are unknown. The solution of this issue, in other words is the elucidation of the etiology of RE will probably provide an explanation for the most awkward feature of this condition: the limitation of the inflammation to one of the cerebral hemispheres.

PEM

In the 1960s, a series of clinico-pathological studies reported on the coexistence of encephalitis and myelitis with malignant diseases (Brierley et al., 1960; Henson et al., 1965; Corsellis et al., 1968). Later on, the term PEM was coined for this constellation. Besides this, paraneoplastic peripheral neuropathies were encountered. The predilection sites for the inflammation in the CNS (and the resulting clinical syndromes) are cerebellum (resulting in ataxia); mediotemporal structures (resulting in “limbic” symptoms like disturbance of recent memory, temporal lobe seizures, and psychiatric abnormalities); brainstem (bulbar dysfunction); anterior horn cells in the spinal cord (resulting in motor impairment). The above quoted early pathological studies on autopsy tissue (Brierley et al., 1960; Henson et al., 1965; Corsellis et al., 1968) revealed encephalitis with round cell (lymphocytic) perivascular cuffs and parenchymal infiltration plus microglial activation (but relatively low numbers of macrophages). Later on, immunohistochemical histopathological studies showed that the infiltrating lymphocytes mainly are CD3+CD8+ T-cells (Graus et al., 1990b; Panegyres et al., 1993; Bernal et al., 2002). A major breakthrough was the identification and antigenic characterization of serum autoantibodies in those patients during the 1980s and 1990s (to mention only the earlier reports: Jaeckle et al., 1985; Cunningham et al., 1986; Graus et al., 1986; Dalmau et al., 1990; 1991). This led to the proposal of antibody-defined neurological syndromes. Even though there is no absolute correlation of antibody, type of neurological syndrome and type of underlying malignancy, several typical constellations have been observed over the years (Table 1). Further research led to the demonstration that these autoantibodies do not only react with distinct structures of human and rodent brains (one of the standard test procedures for these antibodies does make use of this property) but also with cells from the underlying tumor. Based on this observation, it was hypothesized that the neurological syndromes result from those antibodies, which were thought to be primarily directed against the tumor and (“unfortunately”) get access to the brain in which they cross-react with brain epitopes (Furneaux et al., 1990). However, any further attempt to prove this hypothesis failed: Most of the antigens were found to reside mainly within the cytoplasm or even the nuclei of brain cells (thereby being “out of reach” of antibodies); removal of antibodies from patients’ circulation by plasma exchange or immunoabsorption did not consistently improve these patients’ clinical symptoms (Graus et al., 1990a; Cher et al., 1995; Gultekin et al., 2000); and passive transfer and immunization studies failed to induce disease in animals (SillevisSmitt et al., 1995; Tanaka et al., 1995).

Today, PEM is viewed as T-cell mediated. This assumption is based on the neuropathological findings of elements of a cytotoxic T-cell attack...
within the brains of affected people (Bernal et al., 2002) but also on some other observations regarding anti-Yo, anti-Hu, and anti-Ma syndromes and their respective antigens, cerebellar degeneration-related protein 2 (cdr2), HuD, and PNMA1.

The most prominent evidence for a pathogenetically relevant contribution of T-cells to PEM comes from studies on patients with anti-Yo positive paraneoplastic cerebellar degeneration. The related antigen, called cdr2, is present in the cytoplasm of Purkinje cells and binds to c-Myc thereby downregulating its activity. This antigen is also expressed in some gynecological cancers (Corradi et al., 1997; Okano et al., 1999; Darnell et al., 2000). In blood and cerebral spinal fluid of anti-Yo-positive patients, circulating cdr2-specific CTLs were detected that were directed against the tumor and in addition against Purkinje cells (Albert et al., 1998; 2000). The results from these studies suggest that cdr2-specific CTLs are the pathogenetically relevant, “crossreactive” link between tumor immunity and the disease process within the nervous system. It must be stressed that despite earlier observations of a lack of Purkinje cells in the absence of inflammatory infiltrates, such infiltrates have been readily observed within the cerebellum of an anti-Yo-positive patient (Verschuuren et al., 1996). It appears likely that the T-cells disappear after the destruction of the Purkinje cells and are not seen during later disease stages.

The protein, HuD, is normally restricted to neurons, but it is ectopically expressed in small cell lung cancer cells. It is an intranuclear RNA-binding protein, probably involved in the regulation of the cell cycle (Szabo et al., 1991). Two anti-Hu antibody positive patients but not control patients harbored T-cells reacting to stimulation with HuD in their blood (Benyahia et al., 1999). Activated CD8+ T-cells from a patient with paraneoplastic anti-Hu positive neuropathy lysed her own fibroblasts after incubation with interferon-γ (for MHC I induction) and after injection of recombinant HuD protein into the cells (Tanaka et al., 1999). As in the case of cdr2, these reports are highly suggestive of a T-cell response against HuD. The results of an immunohistochemical and PCR

Table 1
Onconeural Antibodies, Their Antigens, Associated Neurological Syndromes, and Typical Underlying Malignancies

| Name            | Antigen       | Function                   | Neurological syndromes                  | Most frequently associated tumors |
|-----------------|---------------|----------------------------|-----------------------------------------|----------------------------------|
| ANNA-3          | 170 kD        | Unknown                    | Neuropathy, PCD, PLE                    | SCLC                             |
| Anti-amphiphysin| Amphiphysin    | Unknown Vesicles/endoptosis| Stiffman syndrome; PLE                   | Mamma; SCLC                       |
| Anti-CV2 (anti-CRMP5) | CRMP5         | Neuronal development       | Encephalitis                            | SCLC, Thymoma                     |
| Anti-Hu (ANNA-1)| Hu Proteins   | RNA binding                | Encephalomyelitis, neuropathy            | SCLC, Neuroblastoma               |
| Anti-Ma          | Ma Proteins   | Unknown                    | Brainstem encephalitis, PLE             | Mamma, diverse Lung               |
| Anti-Recoverin   | Recoverin     | Unknown Phototransduction  | POMA                                    | Mamma, SCLC                       |
| Anti-Ri (ANNA-2)| NOVA          | RNA binding                | PLE, brainstem encephalitis             | Testis                           |
| Anti-Ta/Ma2      | Ma proteins   | Unknown Muscle filament    | Myasthenia gravis                       | Thymoma                          |
| Anti-Titin       | Titin         | Unknown DNA binding        | PCD                                     | M. Hodgkin                       |
| Anti-Tr (PCA-Tr)| Unknown       | Unknown                    | Encephalitis, LEMS, neuropathy          | Ovary, Mamma, Uterus SCLC         |
| Anti-Yo (PCA-1)  | cdr2, cdr62   | Unknown DNA binding        |                                        |                                  |
| PCA-2            | 280 kD        | Unknown DNA binding        |                                        |                                  |

ANNA, antineuronal nuclear antibody; cdr2, cerebellar degeneration-related protein 2; CRMP, collapsin response mediator protein; LEMS, Lambert Eaton myasthenic syndrome; PCA, Purkinje cell antibody; PCD, paraneoplastic cerebellar degeneration; PLE, paraneoplastic limbic encephalitis; POMA, paraneoplastic opsoclonus myoclonus ataxia syndrome; SCLC, small cell lung cancer.
study on TCR Vβ families of T-lymphocytes within the brains of anti-Hu positive patients (autopsy specimens) providing evidence for an oligoclonal expansion of CD8+ T-cells are concordant with this concept (Voltz et al., 1998). The induction of a (subclinical) brain inflammation by adoptive transfer of T-cells specific for the autologous onconeural antigen PNMA1 (the antigen of anti-Ma antibodies) in DA rats (Pellkofer et al., 2004) provides further, at least provisional, evidence for a T-cell mediated pathogenesis for this subform of PEM.

The results of therapeutic efforts directed against the inflammatory brain attack in PEM have in general been rather disappointing. Usually, patients deteriorate or remain on a low level of function despite immunosuppressive or immunomodulatory treatment. Most patients die rapidly as a consequence of the neurological disorder rather than by the tumor itself. Only an effective tumor treatment seems to be associated with an improved neurological outcome (Keime-Guibert et al., 1999; 2000). For further information on PEM, see the recent review literature (Voltz, 2002; Bataller and Dalmau, 2004; Roberts and Darnell, 2004).

**Virus Encephalitis**

Recently anti-inflammatory “Tysabri” trials (natalizumab, given in combination with β-interferon) in patients with multiple sclerosis (MS) were stopped as a result of development of progressive multifocal leuкоencephalopathy (PML) in several cases (Sheridan, 2005; Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gold et al., 2005). Natalizumab is a selective adhesion-molecule inhibitor that acts by binding to cell surface receptors known as α4β1 (VLA-4) and α4β7 integrins. α-4 integrins are important in mediating the migration of lymphocytes from the bloodstream to sites of inflammation in the tissues. It is likely that blockage of lymphocyte migration into the brain in combination with the immunosuppressive action of β-interferon, has predisposed those patients for the opportunistic infection. This unfortunate development of PML shows that a certain degree of immune surveillance by T-lymphocytes is needed to counteract virus proliferation in brain.

Most of what we know about the role of T-lymphocytes in virus encephalitis comes from experimental models. Susceptible (immunological knock-out) mouse and rat strains have been infected with a large number of viruses such as measles, polio, herpes simplex, and Theiler’s (picorna). The immunological mechanisms induced on virus infections are extremely complex since both the properties encoded by the virus as well as the hosts immunological reaction, which may differ strongly between different strains of a certain species, determine the outcome of the disease (Liebert and ter Meulen, 1987; Watanabe et al., 1987). Nevertheless, a number of basic processes have been delineated. After infection of CNS cells, surveilling T-cells may enter the brain and initiate various processes such as upregulation of cytokines like IL-1α, IL-2, IL-6, tumor necrosis factor-α, and interferon (IFN)-γ (Frei et al., 1988; Schneider-Schaulies et al., 1993; Morris et al., 1997), upregulation of adhesion molecules (Soili-Hanninen et al., 1997), and upregulation of MHC expression (Brankin et al., 1995). This is the start of inflammation, which in susceptible animals and depending on the type of virus used, may lead to chronic demyelination or neuronal damage. CD8+ lymphocytes may play an important role in virus-encephalitis by elimination of the virus. In this respect, one study showed that elimination of borna disease virus by virus-specific CD4+ T-cells is achieved via induction of cytotoxic CD8+ T-cells (Noske et al., 1998). As for demyelination, in Thielers’ virus encephalomyelitis (TMEV) this may not be CD8-mediated (Pullen et al., 1993; Murray et al., 1998b) but seems to depend strongly on the balance between persistent virus infection and the immune cells (Rodriguez et al., 1996). Here, the extent to which CD4+ or CD8+ cells are responsible for the neurological deficits is unclear. Studies of TMEV induction in β2-microglobulin-deficient transgenic mice, which therefore lack functional CD8+ T-cells, develop a high-level virus-specific CD4-mediated inflammation. Although clinical deficits in these animals were absent, they could be induced after further subcutaneous immunization with the virus. This suggested that CD8+ T-cells appear to be primarily involved in downregulation of a potentially damaging CD4+ T-cell response in resistant animals (Pullen et al. 1993). On the other hand, studies by Murray et al. (1998a,b), which induced Thielers’ encephalitis in CD4 and CD8 knockout animals, showed that in the absence of CD8+ cells neurological deficits were lacking, whereas the absence
of CD4+ cells resulted in severe neurological deficits. A comparable situation is found in acute CNS infection of mice by the neurotropic JHM strain of mouse hepatitis virus (JHMV). Although demyelination in JHMV correlates well with T-cell infiltration (Houtman and Fleming, 1996), contrary results regarding the role of CD4 and CD8 T-cells are found (Wang et al., 1990; Wu et al., 2000; Pewe and Perlman, 2002). In herpes simplex virus (HSV), influenza A, and borna virus-induced demyelination, an important role of CD8+ cells has been consistently shown (Hudson and Streilein, 1994; Stevenson et al., 1996). A more recent paper (van der Most et al., 2003) shows that CD8+ T-lymphocytes play a role beyond the immediate cytotoxic function. Dengue virus-specific CD8+ cells, displaying an effector-memory phenotype, remained in the CNS for a long time (up to 56 d) after infection. Unfortunately, the authors did not present data demonstrating that persistence of inflammation here was accompanied by perseverance of virus antigen such as demonstrated in human HSV encephalitis (see the following paragraph).

These experimental studies may give a general idea how in virus encephalitis these immunological mechanisms function. The situation in human encephalitis may, however, differ, depending on the human virus type and specific human genetic/immunological factors. Although virus encephalitis is not uncommon, the knowledge about the contribution of cellular immunity in eliminating virus and to the CNS damage is remarkably fragmented (Booss and Esiri, 2003). Overall, there are several lines of evidence that suggest that especially MHC I-restricted CD8+ T-lymphocytes also play an important role in human virus encephalitis. First of all, in virus encephalitis as in PML, RE and in MS (Booss et al., 1983; Woodroffe et al., 1986; Hayashi et al., 1988; Gay et al., 1997), detailed quantification of inflammatory cells show that CD8+ cells generally outnumber CD4+ cells in the tissue infiltrates. Furthermore, CD4+ cells are more restricted to the perivascular inflammatory cuffs, whereas CD8+ cells tend to diffusely infiltrate the parenchyma of the lesions (Gay et al., 1997; Babbe et al., 2000; Anlar et al., 2001), although some studies result the opposite (Nagano et al., 1991). More specific studies reveal a role of CTL in virus encephalitis. As an example, in PML, JC-specific T-lymphocytes can be found in the blood of affected patients. These specific CTLs were detected in 10 out of 11 PML patients who survived vs only 1 out of 11 PML patients who progressed. These data suggest that the presence of JC-specific cytotoxic T-lymphocytes is indicative for a favorable outcome (Du Pasquier et al., 2004a,b). A role for T-lymphocytes in virus elimination was also suggested in HIV encephalitis; immunopathological studies reveal the presence of both CD4+ as well as CD8+ T-lymphocytes surrounding hippocampal neurons suggesting that these cells are in the process of eliminating these virus-infected neurons. A problem with these specific studies is that, in situ, neurons have not been found to be infected by HIV and thus a HIV-specific T-cell-mediated response against these neurons cannot be proven (Petito et al., 2003). Also in West Nile Fever (WNF) encephalitis a role of cytotoxic T-cells has been shown. Primary or memory CD8+ T-cells from patients with WNF that were generated in vivo efficiently killed target cells that displayed West Nile viral antigens in a class I MHC-restricted manner suggesting that CD8+ T-cells have an important function in clearing infection from tissues and preventing viral persistence (Shrestha and Diamond, 2004). Case studies of patients with HSV encephalitis reveal that infiltrating lymphocytes can remain in the brain for a very long time (3–10 yr) after clinical recovery. Persistent HSV DNA could be recognized by PCR even though immunohistochemical stainings for HSV proteins were negative (Nicoll et al., 1991a,b; 1993). As mentioned earlier, one important aspect in T-cell cytotoxicity, but also in the cellular defense against viruses, is the presence of MHC I and II expression in neural (virus-infected) cells of the CNS. The expression of MHC II antigens in brain, predominantly on microglia, has been shown in a large number of studies (Kennedy et al., 1990; Achim et al., 1991; Nagano et al., 1991; An et al., 1996). Detection of MHC I antigens have been shown only in a very small number of publications (Achim and Wiley, 1992; Gogate et al., 1996). Interestingly in PML, MHC I expression was seen on JC virus-infected oligodendrocytes, suggesting that these oligodendrocytes can be targets for a MHC I-dependent cytotoxic T-cell response (Achim and Wiley, 1992). In subacute sclerosing panencephalitis, MHC I upregulation was found in neurons of which a small number were double-labeled for measles virus, suggesting that here virus-infected cells could be the target for a cytotoxic cellular response, too (Gogate et al., 1996). It is known that IFN-γ is an important
factor in upregulation of MHC I (Linda et al., 1998; Parra et al., 1999; Bergmann et al., 2003; 2004). To what extent neural MHC class I expression is upregulated by the virus infection itself is unclear. It is, however, well known that viruses can actively downregulate this MHC class I expression, a function that is one of the many ways in which viruses limit the immune response, something that is also called immune evasion (Ploegh, 1998; Lieberman et al., 2002; Basta and Bennink, 2003).

Summary

In the described forms of human encephalitis, most of the existing (still highly fragmentary) knowledge about the role of T-cells basically comes from studies of human brain tissue obtained by autopsies, diagnostic brain biopsies, or epilepsy surgery procedures and from studies of peripheral blood lymphocytes and soluble factors of the immune system. Animal studies have provided additional insights into T-cell function in some instances. It is obvious that most often CD8\(^+\) T-cells play a role as MHC I restricted cytotoxic effector cells directed against brain cells. The antigens involved in this process are only rarely known. Regulatory functions of CD8\(^+\) cells are, however, also conceivable. Up to now, T-cell studies have not become diagnostic routine procedures in those disorders. At least in RE, insights into the T-cell pathogenesis of this disorder have guided the first promising anti-T-cell treatment approaches.

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