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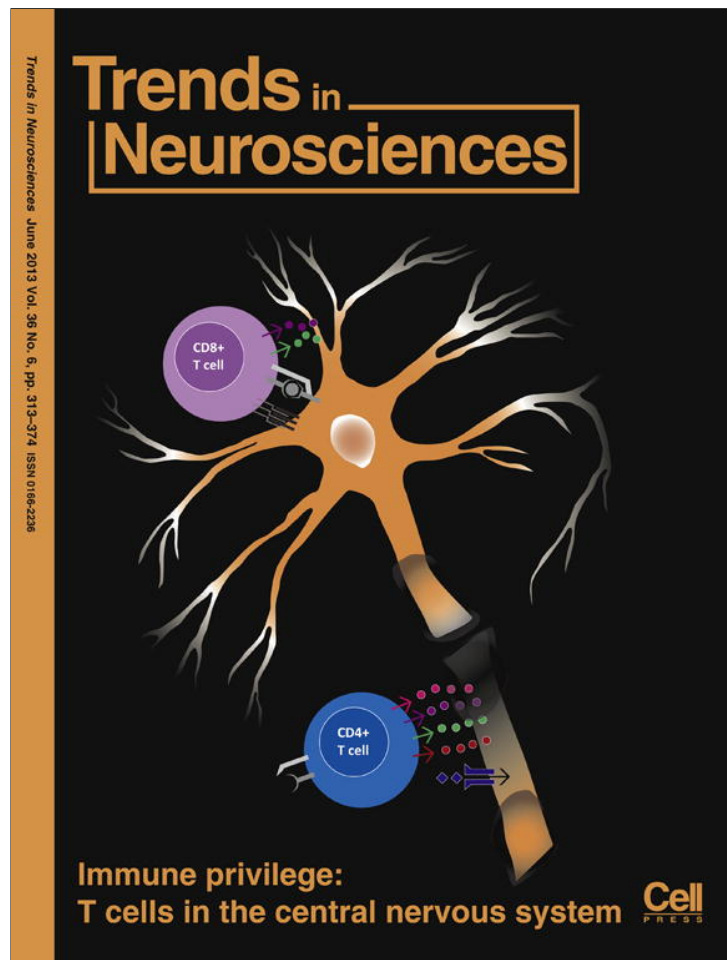
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Neurons as targets for T cells in the nervous system

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Accumulating evidence shows that T cells penetrate the central nervous system (CNS) parenchyma in several autoimmune, infectious, and degenerative neurological diseases. The structural and functional consequences for CNS neurons of their encounter with activated T cells have been investigated in several experimental systems, including *ex vivo* co-cultures, electrophysiology, and *in vivo* imaging. Here, we review the modalities of neuron/T cell interactions. We substantiate the contention that T cells are directly responsible for neuronal damage in a large number of neurological diseases and discuss mechanisms of neuronal damage mediated by distinct T cell subsets, the impact of which differs depending on the disease. Finally, we describe how a better understanding of the mechanisms at play offers new possibilities for therapeutic intervention.

Introduction

Interactions between the CNS and the immune system must be carefully balanced to allow the immune system to fight invading pathogens, while preventing excessive inflammatory damage to this organ, given its vital functions and poor regenerative capacity. A series of mechanisms, collectively dubbed ‘immune privilege’, ensure that immune reactions are kept to a minimum in the CNS. However, this immune privilege is relative, and there is a crucial need for constant surveillance [1,2]. This is supported by observations that treatments aimed at preventing CNS access by circulating immune cells have led to uncontrolled viral infection of the CNS [3].

Accumulating evidence shows that T cells actively penetrate the CNS parenchyma in numerous inflammatory, infectious, and degenerative diseases. Moreover, T cells are also able to enter the CNS under non-pathological conditions [4–6]. The consequence for CNS resident cells, and more specifically for neurons, of their encounter with activated T cells is a major issue. This review summarizes current knowledge on immune–neuronal crosstalk in the CNS, its mechanisms, functional consequences, and

implications for therapeutic intervention. The physiological influence of T cells on steady state neurogenesis has been recently reviewed [7] and will not be discussed here.

Modalities and consequences of neuron/T cell interactions

T cell entry in the CNS

Entry into the CNS occurs either directly across the blood–brain barrier from capillaries and post-capillary venules, or indirectly through the choroid plexus and the subarachnoid space via the cerebrospinal fluid [2,8,9]. Regardless of their route of entry, the penetration of T cells into the CNS relies on a number of molecular interactions involving integrins, selectins, and chemokines [2]. The interaction between $\alpha 4\beta 1$ integrin expressed by T cells and its ligands, vascular cell adhesion molecule (VCAM)-1 and fibronectin, appears essential for efficient penetration of both CD4 and CD8 T cells in the subarachnoid space [10–12]. However, the requirements for migration into the CNS differ significantly for these two T cell subsets. For example, cerebral endothelial cells constitutively express MHC class I, but not MHC class II, molecules, thereby allowing antigen-specific transendothelial traffic into the brain for CD8 T cells only [13]. Additionally, evidence indicates that CD4 T cells that have gained access to the subarachnoid space need to be reactivated by resident antigen-presenting cells (APCs) to access the neuropil [2], an issue that remains undetermined for CD8 T cells.

T cells also exhibit differences in terms of migration depending on their activation status. Except during the perinatal period [6], naïve CD4 or CD8 T cells do not readily penetrate the CNS because they do not express the appropriate adhesion molecules and chemokine receptors [4]. Conversely, activated T cells [9–12] and regulatory CD4 T cells [5] can enter the CNS, but with regional preferences depending on the functional subset considered (Box 1). For example, T helper (Th)1 cells preferentially infiltrate the spinal cord. By contrast, when Th17 cells are more numerous than Th1 cells, inflammation in the brainstem, cerebellum, and cerebrum predominate. This may result from the fact that Th1 cells rely on the $\alpha 4\beta 1$ integrin to penetrate the spinal cord, whereas Th17 cells are dependent on the $\alpha L\beta 2$ integrin to enter the brain parenchyma [14]. Th17 cells are also more sensitive than Th1 cells to

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Box 1. T cells: three main subsets, each with different flavors

The thymus-derived T cells constitute key players of antigen-specific immune responses. They are characterized by surface expression of T cell receptors (TCRs). Each TCR is composed of two highly variable chains involved in antigen recognition, associated with invariant signal transduction molecules. Each T cell expresses ~30 000 identical TCRs. Most T cells (~97%) express TCRs composed of variable α and β chains, which recognize short antigenic peptides bound to MHC molecules at the surface of antigen-presenting cells (APCs). They are divided into three main functional subsets:

- (i) **CD8 T cells** are characterized by the surface expression of CD8 molecules. Their TCRs recognize antigenic peptides associated with MHC class I molecules on nearly all nucleated cells. Following activation, they produce cytotoxic factors, such as perforin and granzymes, compartmentalized into secretory lysosomes called lytic granules. These granules traffic rapidly to the contact zone between cytotoxic CD8 T cells and target cells and their content is released in this confined area. This leads to the formation of transmembrane pores, allowing entry of granzyme molecules within the target cell. Consequently, local accumulation of Ca^{2+} and activation of proteases and caspases may occur. CD8 T cells also release cytokines such as TNF, Fas ligand, and IFN- γ . Thus, the main function of CD8 T cells is to destroy infected or tumor cells and to activate innate immune cells such as macrophages. More diverse functions have been reported for CD8 T cells, owing to their ability to secrete chemokines and other cytokines.
- (ii) **Helper CD4 T cells** express CD4 molecules on their surface and are activated when their TCR recognize antigenic peptides associated with MHC class II molecules, which are expressed on the surface of professional APCs only, namely dendritic cells, macrophages, and B cells. Their main function is to promote activation and differentiation of both innate (macrophages) and adaptive (B cells, cytotoxic CD8 T cells) immune cells. This function is carried out through the release of cytokines. Depending on the specific conditions of their initial activation, helper CD4 T cells can differentiate into various functional subsets differing in the cytokines they synthesize. For instance, helper CD4 T (Th)1 cells produce IL-2, TNF, and IFN- γ that enhance, among others, the killing potential of macrophages and CD8 T cells. Th2 cells produce IL-4, IL-5, IL-13, and promote activation and maturation of B cells. T follicular helper cells are specialized in the secretion of IL-21 and promote antigen-specific B cell immunity. Th17 cells release IL-17, IL-21, and IL-22 and are involved in the activation and recruitment of neutrophils. Myelin-specific Th17 cells are highly encephalitogenic upon transfer into non-immunized animals. However, the role played by individual Th17 cytokines and by plasticity towards the Th1 lineage *in vivo* is still debated.
- (iii) **Regulatory CD4 T cells** are key in the prevention of autoimmune responses, the limitation of immune responses in tissues exposed to foreign antigens, and terminating immune responses. The main regulatory CD4 T cell type stably expresses the Foxp3 transcription factor. Their ablation leads to rapid multi-organ inflammation.

kinin receptor-1 agonists, thereby inhibiting their migration into the CNS [15]. Finally, it was recently reported that other adhesion molecules, in particular Ninjurin 1, play an important role for activated T cell crawling along the endothelium and for their transmigration into the CNS [16].

It should also be noted that Th17 cell entry might result from the disruption of blood–brain barrier tight junctions by inflammatory cytokines. Such cytokines could target local endothelial cells, which are known to express IL-17 and IL-22 receptors [17].

Expression of MHC class I molecules and antigen presentation by neurons

T cells are activated, proliferate, and acquire effector functions in response to an antigen-specific signal transmitted by surface T cell receptors (TCRs), which recognize short peptide fragments associated with MHC molecules at the surface of APCs (Box 1).

Because neurons do not express MHC class II molecules, they cannot interact in an antigen-specific way with effector CD4 T cells. By contrast, strong evidence indicates that CNS neurons can express MHC class I molecules, either constitutively or during infection or inflammation. There are, however, differences according to the neuronal subsets or the developmental stages. For instance, adult cerebellar Purkinje neurons express detectable levels of MHC class I [18], whereas cortical neurons, which constitutively express MHC class I molecules during development, exhibit a progressive reduction of expression after postnatal day 23 [19,20]. MHC class I expression has also been demonstrated *in situ*, appearing in association with synaptic structures at steady state [18–20], and has been clearly documented in inflammatory conditions or during neurodegeneration [21–23]. Intriguingly, some neuronal populations, such as the hypothalamic magnocellular neurons, appear more

easily inducible for MHC class I expression upon inflammation [24].

Expression of MHC class I molecules can also be induced in primary cultures of CNS neurons by viral infection or inflammatory stimuli such as IFN- γ but not TNF- α [25,26]. The MHC class I inducing property of IFN- γ is dramatically increased by blockade of sodium channels by tetrodotoxin [26,27]. Likewise, IFN- α/β is induced in neurons upon triggering of membrane-bound Toll-like receptors and cytosolic sensors for viruses such as retinoic acid-inducible gene (RIG)-like receptors and promotes MHC class I expression in an autocrine and/or paracrine manner [25,28]. Additionally, ionotropic glutamate receptor stimulation leads to potent nuclear factor (NF)- κ B activation and strong MHC class I protein expression in rat cerebellar granule cells [29].

Most antigenic peptides are derived from cytosolic proteins upon their degradation by the immunoproteasome. Transporters translocate the cytosolic peptides to the endoplasmic reticulum where they associate with the nascent MHC class I molecule. Importantly, neurons can express the different components of this molecular machinery under inflammatory or degenerative situations [26,30,31], thereby expressing functionally relevant MHC class I–peptide complexes [25].

These observations led to the concept that, in an inflammatory context, functionally impaired neurons may become targets for CD8 T cell cytotoxicity. A systematic analysis of the propensity of CNS neurons to express MHC class I molecules and of the underlying molecular mechanisms is, however, warranted.

Consequences for neurons of their antigen-dependent interactions with CD8 T cells

Interactions between neurons and CD8 T cells have been mostly studied *in vitro* using confocal imaging [27] and

time-lapse videomicroscopy [25,32]. Much less information is currently available on the *in vivo* consequences of such antigen-specific neuron/CD8 T cell contacts, although intravital microscopy will undoubtedly soon provide novel information [33,34].

Experimental evidence on the mechanisms whereby effector molecules of cytotoxic CD8 T cells disturb the electrical excitability of neurons is sparse, but this has been extensively studied in ventricular cardiomyocytes [35]. Both cell types share features on electrical excitability. Because most of the pathways involved in cardiomyocytes are also present in neurons [36], it seems conceivable that similar mechanisms will be used in both cases. Indeed, analysis of the molecular consequences of cytotoxic granule release using cardiomyocytes has provided insights into mechanisms most likely also operational in neurons [36]. In addition, whole-cell patch clamp recordings revealed an immediate impairment of electrical signaling in MHC class I-expressing, peptide-loaded hippocampal neurons upon contact with antigen-specific CD8 T cells. Electrical silencing was due to massive shunting of the membrane capacitance, following insertion of channel-forming perforin, which was paralleled by an increase of intracellular Ca^{2+} . These effects were mediated by perforin *per se* and could not be induced by granzymes alone [32].

Importantly, cytokines released from T cells might also contribute to direct and collateral disturbances of electrical signaling in neurons. For instance, IFN- γ secreted by both CD4 and CD8 T cells was shown to induce neuronal excitotoxicity by intracellular trans-signaling between the IFN- γ receptor and a Ca^{2+} -permeable neuronal AMPA/kainate receptor [37]. The impact of cytotoxic CD8 T cells on neuronal electrical excitability might have functional consequences in patients, for example, conduction blocks or paroxysmal neurological symptoms.

Once effector CD8 T cells are arrested, they establish stable contacts with axons, dendrites or more rarely neuronal somata in an antigen- and MHC class I-dependent manner [25,27]. These stable contacts rapidly cause segmental damage of neurites in the form of spheroids or beads, independent of detectable morphological changes of somata (Figure 1a). Localized transection of neurites was also detected at contact sites with effector CD8 T cells [27]. The molecular mechanisms whereby CD8 T cells inflict structural damage to neurites are not fully understood, although it probably results from the transfer of cytolytic granule content [38]. It seems that cytokines such as IFN- γ and TNF- α are not able to promote direct localized damage of neurites [27]. The contribution of other T cell mediators such as Fas ligand, metalloproteinases, or reactive oxygen species [39] is currently unknown.

Antigen-specific lysis of target cells by activated CD8 T cells also applies to neurons, although peculiarities have been described (Figure 1b). Indeed, despite the rapid formation of stable conjugates between CD8 T cells and neurons *in vitro*, neuronal apoptosis is not observed before 3–4 hours [25,40]. The delayed kinetics as well as experiments using gene-deficient animals are consistent with cytotoxicity mediated by the triggering of Fas on the neuron by Fas ligand expressed by CD8 T cells, rather than by release of preformed lytic granules [32,40,41]. As neurons can upregulate

surface expression of Fas upon incubation with IFN- γ [40], a plausible scenario involves a dialog between CD8 T cells and neurons at the contact zone. Recognition of specific MHC class I-peptide complexes by T cells would promote the polarized release of IFN- γ , which would in turn enhance neuronal Fas expression and susceptibility to apoptosis. In addition, impairment of neuronal electrical activity would enhance MHC class I expression on neurons and their subsequent CD8 T cell-mediated killing [26].

Antigen-independent interactions between T cells and neurons

These aspects have classically been discussed in autoimmune CNS diseases, in particular multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE), its main animal model. Activation of T cells and APCs within the CNS leads to a local release of inflammatory cytokines and cytotoxic molecules (perforin, granzyme, death ligands, nitric oxide, reactive oxygen species, glutamate). Moreover, damage to glial cells may result in indirect axonal degeneration through the lack of trophic support. In demyelinated neurons, an altered distribution and expression of various ion channels and transporters leads to local enhanced activity and intracellular calcium accumulation with subsequent neuronal cell death [42].

CD4 T cells, which cannot recognize antigens on neurons due to lack of expression of MHC class II molecules, have nevertheless a major impact on neurons, eventually causing apoptosis, in particular through the TNF-related apoptosis-inducing ligand (TRAIL) pathway [43,44] (Figure 2a,b). In brain slice/T cell co-cultures, activated T cells induce oscillatory calcium alterations in neurons [45], leading to calcium overload and death of neurons, which can, however, be blocked by NMDA/AMPA/kainate antagonists or inhibition of perforin. Among CD4 T cells, Th17 cells exhibit a preferential ability to engage sustained contacts with neurons [33]. In EAE, it was also shown that neuron/Th17 cell contacts induce localized Ca^{2+} oscillations and neuronal injury, which could be reversed by the NMDA receptor antagonist MK801. Importantly, this damage was reversible, even during full-blown inflammatory attack, offering a window of opportunity for therapeutic intervention [33]. Interestingly, blockade of AMPA/kainate receptors ameliorates the neurological sequelae in EAE [46,47]. Reactive oxygen and nitrogen species produced by macrophages during neuroinflammation also trigger mitochondrial pathology and initiate focal axonal degeneration, a phenomenon reversible upon neutralization of these mediators [48].

Paradoxically, the end result of neuron/T cell interaction can even be beneficial. In co-culture experiments, activated human CD8 T cells inhibit neurite outgrowth without detectable neuronal apoptosis in a contact-dependent but antigen-independent manner, whereas activated CD4 T cells promote neurite outgrowth [49]. Interestingly, activated T cells can produce neurotrophins [50], notably brain-derived neurotrophic factor (BDNF), which may contribute to axonal protection following T cell-directed therapeutic strategies [51–53]. Collectively, these observations support the concept that some T cells have neuroprotective and/or neuroregenerative properties [50,54]. However, the

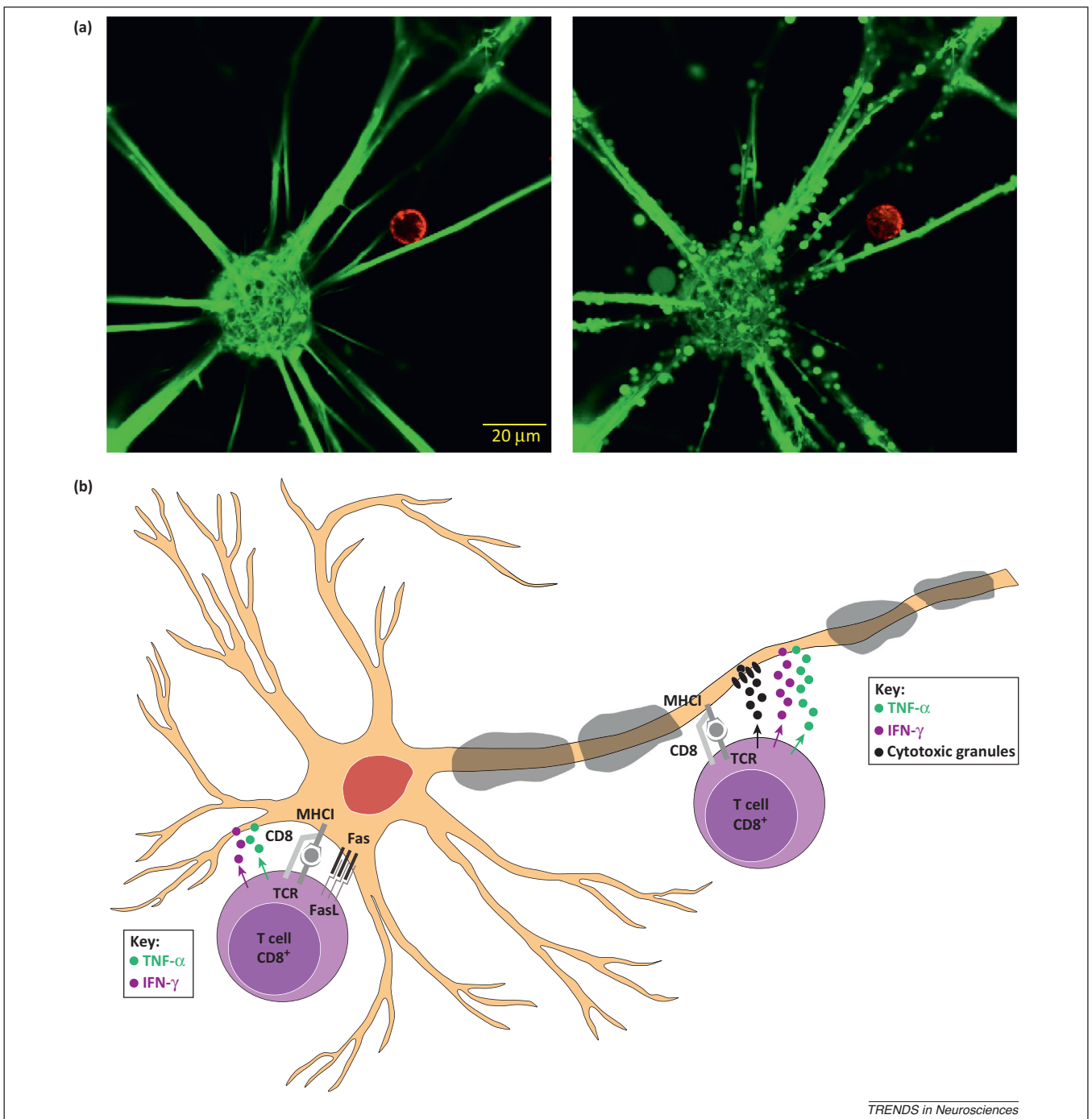


Figure 1. Interaction of neurons with cytotoxic CD8 T cells. **(a)** Morphological changes of infected neurons following contact with Borna disease virus (BDV)-specific CD8 T cells. In mammals, BDV replicates in central nervous system (CNS) neurons without damaging the host cells. BDV-induced encephalitis develops with preferential accumulation of CD8 T cells within lesions, which play a central role in neuronal destruction [96]. CD8 T cells freshly purified from the brains of rats infected with BDV were labeled with PKH-26 (red) and added to calcein-loaded (green) cultures of BDV-infected neurons [25]. The figure in the left panel is taken at the onset of neuron/CD8 T cell interaction. The figure in the right panel, taken after 45 minutes of stable neuron/CD8 T cell contact, shows calcein leakage throughout the culture, affecting both neurites and neuronal somas. After longer neuron/CD8 T cell interaction (4–6 hours), neuronal apoptosis and progressive disaggregation of the neuronal network were noted [25]. **(b)** Schematic illustration of the consequences of antigen-specific CD8 T cell interactions with neurons. Upon recognition of antigenic peptides associated with major histocompatibility complex (MHC) class I molecules through their specific T cell receptors (TCRs), cytotoxic CD8 T cells release lytic granules containing perforin and granzyme A and B in a polarized manner towards the target structure, here an axon [41]. Cytokines such as interferon (IFN)- γ and tumor necrosis factor (TNF)- α are also released and will affect the biology of the neurons that express their receptors, sensitizing them to apoptosis [26,37]. Fas ligand at the cell surface of the CD8 T cells can engage Fas expressed by neurons and initiate an apoptotic cascade [40]. Other mediators may be involved in the dialog between neurons and CD8 T cells including other cytokines, chemokines, neuromediators, reactive oxygen species, and metalloproteinases.

nature of the T cells involved and the modalities of action remain controversial [55–57].

It should be mentioned that several studies have demonstrated that T cells exert beneficial effects not only

during pathological situations, but also under physiological situations such as neurogenesis, learning and memory, or responses to stress [7,58]. Of particular note, regulatory CD4 T cells have been demonstrated to contribute to CNS

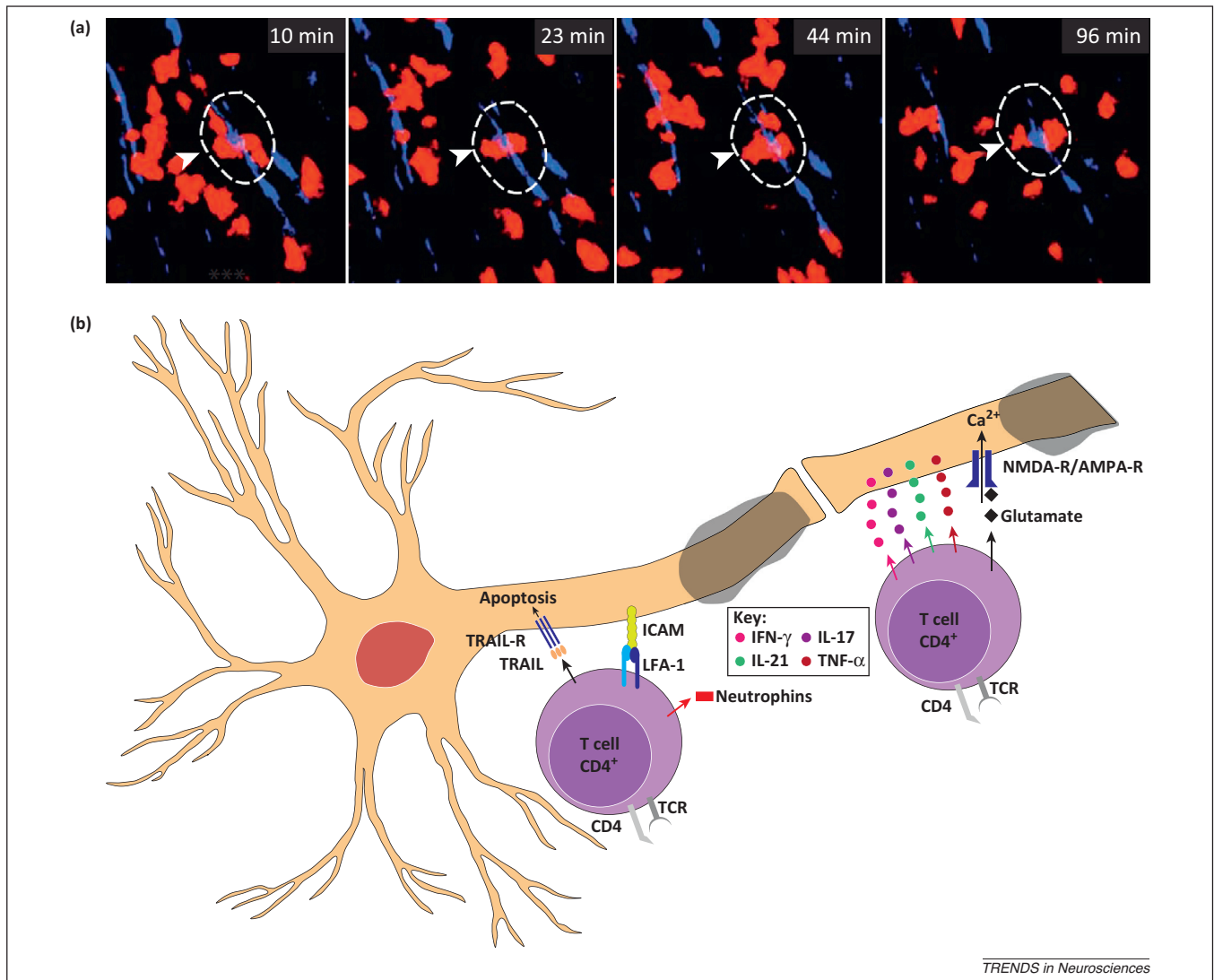


Figure 2. Interaction of neurons with helper CD4 T cells. (a) Interaction of T helper (Th)17 CD4 T cells (tdRFP-red) with neuronal processes (EGFP-blue) in the brainstem of a mouse suffering from experimental autoimmune encephalomyelitis, as assessed by two-photon laser scanning microscopy. Areas of close proximity at neuronal process varicosities (blue, dotted area) were identified through the colocalization channel (white). Reproduced, with permission, from [33]. (b) Schematic illustration of antigen-independent interactions between helper CD4 T cells and neurons. Due to the lack of expression of major histocompatibility complex (MHC) class II molecules by neurons [21,23], T cell receptors (TCRs) cannot bridge CD4 T cells with neurons. Rather, adhesion molecules may be at play, such as lymphocyte function-associated antigen-1 (LFA1) on T cells interacting with intercellular adhesion molecules (ICAM) on the neuron surface [33]. Th1 cells, and even more so Th17 cells, have demonstrated a propensity to contact axons *in vivo*, promoting increase in intraneuronal Ca^{2+} concentration that precedes axonal and neuronal injury [33]. Candidate molecules that might be involved in these processes include neuromediators, in particular glutamate, the array of cytokines and chemokines produced by the different CD4 T cell subsets, reactive oxygen species, and matrix metalloproteinases. Some CD4 T cells, notably Th1 cells, also produce cytotoxic mediators such as granzymes or perforin. TNF-related apoptosis-inducing ligand (TRAIL), Fas ligand, and other members of the tumor necrosis factor (TNF) family as well as interferon (IFN)- γ are also important candidates for the deleterious effects of CD4 T cells on neurons, acting either directly to induce neuronal apoptosis or through sensitization to excitotoxic molecules [37,43–47].

homeostasis and to counterbalance inflammation [59,60]. The potential of CNS resident cells to induce regulatory CD4 T cells, and in particular of neurons through their production of TGF- β , thereby contributing to a local anti-inflammatory environment, has attracted considerable attention [61].

The influence of neurotransmitters in the dialog between neurons and immune cells is just beginning to be recognized and much remains to be explored [62,63].

Neuron/T cell interactions under pathophysiological conditions

The *in vitro* and *in vivo* data summarized in the previous section stress the multiple modalities and consequences of

antigen-specific and antigen-independent interactions of neurons with T cells. Consequently, the concept that neurons may serve as targets for T cells has emerged in a variety of neurological disorders (Box 2). Specific examples of how neurons interact with T cells during disease are detailed below.

Non-infectious diseases associated with antigen-dependent interactions of neurons with CD8 T cells

These recent years, neurons have been identified as targets of adaptive immune responses in a growing number of autoimmune CNS disorders [64–66]. In diseases associated with antibodies to synaptic and extra synaptic neuronal cell surface antigens, the antibody-mediated disturbance of

Box 2. What is the range of immune-mediated disorders targeting neurons?

Immune-mediated disorders targeting neurons can be triggered by local infection, for instance by neurotropic viruses [72,75,96]. These diseases can also be triggered by distant infection (e.g., Sydenham's chorea), vaccination (post-infectious/-vaccinal encephalomyelitis), and a variety of malignancies (paraneoplastic encephalomyelitis) [64–67]. They also can occur without an as yet identifiable cause (autoimmune encephalomyelitis). Indeed, many neurological diseases are associated with autoantibodies specifically targeting neurotransmitter receptors involved in excitatory (AMPA-, NMDA-, mGluR1, and mGluR5 receptors) and inhibitory (GABA_B and glycine receptors) synaptic transmission, or in the regulation of neuronal excitability (voltage-gated potassium channels) [64,65,67]. Recently, diseases in which a given subset of neurons is damaged or destroyed, such as idiopathic central diabetes insipidus or narcolepsy, have also been shown to have an immune-mediated origin, with plausible involvement of CD8 T cells [97–99]. CD8 T cell-mediated pathology is also highly suspected in encephalitis associated with autoantibodies specific for intracellular neuronal antigens (Hu, Ma2, glutamic acid decarboxylase) [67]. Immune targeting of CNS neurons/axons in MS has recently emerged as a likely mechanism [44,87]. Intriguingly, neurodegenerative diseases such as PD are also associated with focal T cell inflammation [78]. T cells are also postulated to play a role in amyotrophic lateral sclerosis [100].

synaptic transmission and neuronal excitability is often reversible, accounting for a generally good response to immunotherapy. In diseases associated with antibodies to intracellular neuronal antigens, CD8 T cell-mediated neurotoxicity seems to be the prevailing pathogenic mechanism, causing progressive neuronal cell death and neurological decline with poor response to immunotherapy [67]. For instance, selective loss of Purkinje neurons in paraneoplastic cerebellar degeneration (PCD) might be mediated by cytotoxic CD8 T cells recognizing the onconeural antigen Cdr2, a cytoplasmic antigen expressed by both tumor cells and Purkinje neurons. Indeed, T cell infiltration in the cerebellum can be detected in PCD [68,69] and Purkinje neurons can express MHC class I molecules [18].

Rasmussen's encephalitis (RE) is considered a paradigm of a MHC class I restricted CD8-mediated epilepsy syndrome. This intractable focal epilepsy is associated with spreading inflammation affecting only one hemisphere. The pronounced T cell infiltrate is predominantly composed of CD8 T cells, leading to substantial loss of neurons and astrocytes [22,70]. Lytic granules in T cells exhibit a polar orientation towards the neuronal plasma membrane in the absence of notable Fas ligand expression. Neurons display impaired axonal transport as well as signs of apoptosis [22]. CD8 T cells found in RE lesions exhibit a restricted TCR diversity, suggesting that they expanded from few precursors locally responding to as yet unidentified antigens [71].

Neuron/CD8 T cell interactions during viral encephalitis
Virus-specific CD8 T cells play a central role in the control of many neurotropic viruses, such as West Nile virus (WNV), or herpes simplex virus type 1 (HSV-1). However, their pathological impact differs according to the virus studied, with CD8 T cells either clearing infection through killing of infected cells or maintaining viral latency without destroying the infected neurons.

WNV, a mosquito-transmitted neurotropic flavivirus, leads to severe meningoencephalitis in humans. Mouse models have unambiguously revealed that CD8 T cells control viral infection in the CNS through both perforin and Fas/Fas ligand pathways [72]. Interestingly, infection favors a productive interaction between antiviral CD8 T cells and neurons. Indeed, infected neurons rapidly produce the CXCL10 chemokine that promotes recruitment of CXCR3-expressing CD8 T cells into the CNS [73]. Moreover, WNV infection induces TRAIL-R2 and Fas expression on neurons, thereby inhibiting viral replication and favoring neuronal killing by WNV-specific CD8 T cells [72,74].

In both mice and humans, HSV-1 enters a lifelong latent state within infected sensory neurons in the trigeminal ganglia. Strikingly, activated CD8 T cells are found in direct contact with infected neurons [75] and frequently polarize their TCR to the interface between T cells and neurons without causing overt cell lysis. In mice, these CD8 T cells are largely virus-specific and use at least two non-cytolytic mechanisms to maintain HSV-1 latency. The first one involves the secretion of IFN- γ , which inhibits expression of HSV-1 gene products required for viral reactivation. The second involves release of granzyme B-containing lytic granules, which curiously does not activate neuronal caspases but rather degrades the HSV-1 immediate early protein ICP4, while sparing the infected neurons [76]. Of note, CD8 T cells residing in the infected trigeminal ganglia are not renewed by the circulating T cell pool, and resemble the tissue-resident memory CD8 T cells found in the brain following viral elimination [77].

Pathogenic contribution of CD4 T cells in neurodegenerative disorders

CNS infiltration and neuronal killing by T cells are also observed in prototypical neurodegenerative disorders such as Parkinson's disease (PD), or amyotrophic lateral sclerosis. The mechanisms responsible for the loss of dopaminergic neurons in PD are not fully deciphered, but immunohistochemical studies have revealed a localized infiltration by both CD4 and CD8 T cells in the substantia nigra [78]. In addition, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication model of PD applied to gene-deficient mice revealed that CD4, but not CD8, T cells contribute to loss of dopaminergic neurons [78]. The deleterious CD4 T cells appear to act on dopaminergic neurons in a Fas ligand-dependent manner. Moreover, immunization with nitrated α -synuclein activates specific Th1 and Th17 cells that enhance the loss of dopaminergic neurons in the MPTP model [79]. Conversely, regulatory CD4 T cells were shown to provide neuroprotection, through attenuation of microglial activation [79,80].

Neuron/T cell contribution to MS

Genetic studies and data from animal models have long suggested the key contribution of CD4 T cells in MS pathogenesis. However, the importance of CD8 T cells in the disease process has recently emerged. Indeed, CD8 T cells by far outnumber CD4 T cells in white matter lesions. Moreover, CD8 T cells are frequently found in the parenchyma, whereas CD4 T cells display a more perivascular

distribution [81]. CD8 T cells are frequently found in close apposition to oligodendrocytes, and destructed myelin and axonal damage in white matter lesions correlates with the number of CD8⁺ T cells [82]. Further, CD8 but not CD4 T cells show oligoclonal expansion within the CNS, suggesting local activation by antigens [83]. Along with the clear MHC class I expression by neurons and all other CNS cell types in inflammatory MS lesions [23], these findings suggest that CD8 T cells could contribute as effector cells to the damage of both oligodendrocytes/myelin and axons in white matter and possibly gray matter lesions.

Gray matter MS lesions display much lower T cell infiltration compared to white matter [84]. However, gray matter lesions show a pronounced preponderance of CD8 T cells [85]. In these lesions, demyelination and oligodendrocyte death is accompanied by axonal and dendritic transection, reduced synaptic density, and apoptotic changes within neuronal perikarya [84].

It should be reminded, however, that CD4 T cells are still considered as important pathogenic effectors in MS. Indeed, the predominance of CD4 T cells in active MS lesions [86] and a predominance of CD4 T cells in chronic active lesions in the spinal cord gray matter when compared to chronic inactive disease have been described [44]. Recently, perivascular CD3 T cell infiltration was seen in 82% of cortical plaques [87]. CD8 T cells were present in 77% of these plaques. Owing to limited tissue availability, CD4 T cells were not investigated. Thus, it is most likely that CD4 together with CD8 T cells contribute to neuron/axon injury in MS.

To date, the underlying mechanisms of tissue injury can only be postulated from rather indirect evidence. In MS tissue, axons undergo pathology eventually leading to transection and neuronal cell bodies are reduced in numbers [88]. Evidence for apoptotic neuronal death was provided [84], possibly resulting from retrograde degeneration or direct injury. It should, however, be noted that axonal injury does not necessarily lead to subsequent death of the parent cell body [89]. A primary role for T cell-mediated neuronal cell death is also conceivable. In fact, progressive gray but not white matter atrophy, observed within 3 months of the first relapse in people with MS [90], suggests a direct insult to neurons rather than a retrograde mechanism subsequent to axonal pathology. Whole brain MR spectroscopy studies also indicate gray matter involvement early in the disease [91].

Therapeutic implications

From all we have described, it is perspicuous that blockade of T cell entry and T cell effector function appears as a highly effective approach to limit CNS damage. In fact, one strategy based on blocking the $\alpha 4$ integrin [10] has already led to the therapeutic development of Natalizumab, a monoclonal antibody that inhibits transmigration via the blood–brain barrier. Future strategies aimed at blocking leucocyte trafficking should take into account the T cell subsets involved in the disease process, which differ in their molecular and topographical requirements [14]. It has also to be kept in mind that the pathologic processes are already ongoing when the patients consult for the first time, thereby limiting the potential efficacy of T cell transmigration blocking

strategies. Thus, a focus of inflammation in the CNS may increase in size as a result of a 'driving force' for pathology arising from the lesion itself and no longer from outside the CNS.

Another alternative therapeutic approach lies in trying to disrupt local neuron/T cell interactions. The first step of direct neuron/T cell crosstalk is adhesion of the cells, for which lymphocyte function-associated antigen-1 (LFA-1) seems to play a major role [33]. However, Efalizumab, an LFA-1 blocking antibody, was withdrawn from the market due to increased risk of viral opportunistic infections. Importantly, any intervention directed towards processes within the CNS will require sufficient levels of the modulating agent on site. Despite relative leakiness of the blood–brain barrier in chronic neuroinflammation, size and lipophilic properties will be important parameters to consider for local availability.

Downstream events in inflammatory neuronal injury involve NMDA/AMPA and ion channels, mitochondrial alterations, nitrogen or oxygen species, excitotoxicity, cytotoxicity, calcium upregulation, and apoptosis [88,92]. Therapeutic interventions targeting these pathways range from AMPA and sodium channel/release blockers to anti-oxidative strategies or anti-apoptotic concepts.

Due to their proinflammatory and cell death-inducing properties, TNF/TNF receptor family members were also considered as therapeutic targets. Indeed, TNF- α blocking agents are already used in clinical practice to treat several autoimmune diseases. However, a phase II trial applying a neutralizing soluble TNF receptor to MS patients had to be stopped because of disease exacerbations [93]. This apparent discrepancy may be explained by the nerve growth promoting properties of TNF- α in the CNS. Interestingly, a genetic polymorphism associated with MS [94], but not with other autoimmune diseases, leads to expression of a soluble form of TNF receptor-1 that can block TNF- α and thus mimics the effect of TNF-blocking drugs [95]. Other members of the TNF family, such as TRAIL and Fas ligand, were also investigated as potential therapeutic targets. It became clear, however, that these death pathways are double-edged swords, making them unsuitable for treatment purposes in neuroinflammatory diseases such as MS.

Concluding remarks

Given its major pathological consequences, the impact of T cells on neuronal biology has been very actively investigated in recent years. However, much remains to be understood about how the various T cell subsets affect neuronal function and survival (Box 3). The other side of the equation, how neurons modify T cell functions and viability, has been much less investigated but is equally important to consider.

We have focused on diseases for which recent data have documented the often deleterious effects of CD4 and/or CD8 T cells on neurons. These examples likely represent only a fraction of the pathological conditions in which T cells contribute to functional or structural neuronal CNS tissue alteration. It is our contention that an increasing number of neurological and psychiatric illnesses will turn out to be, at least in part, immune mediated. Understanding the specific

Box 3. Outstanding questions

- What are the various routes and the molecular requirements for CNS trafficking of immune cells under basal and inflammatory conditions?
- Are there major differences in the route and molecular pathways involved in entry of T cells into the gray vs. white matter?
- Can T cells have a beneficial effect on neuronal functions, either at steady state or during pathological conditions?
- Can the negative impact of T cells on neuronal function be reversible?
- What are the molecular bases of the interaction of neurons with the various T cell subsets (cytotoxic CD8, helper CD4, and regulatory CD4 T cells)?
- What is the contribution of the different T cell subsets in neuronal damage observed in MS and in other inflammatory neurological disorders?
- Can we therapeutically interfere with T cell entry into the CNS or with their deleterious action on CNS parenchyma without compromising their functions in systemic and CNS immune surveillance?
- Can the action of T cells be manipulated to promote their potential neuroprotective properties?

contribution of T cells in these ailments could provide drastic shifts in therapeutic care.

Currently, the most efficient approach to inhibit T cell-mediated damage within the CNS is to block T cell entry. Very efficient drugs approved for MS patients, such as Natalizumab and Fingolimod, are based on this concept. The use of these molecules may well be extended to other inflammatory diseases of the CNS, provided that the therapeutic benefits outweigh the rare but severe infectious side effects. However, more targeted approaches aimed at blocking specific T cell functions in the CNS or their consequences in neurons/axons are still needed.

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