

Review

Fragile privileges: autoimmunity in brain and eye

Hartmut WEKERLE^{1,*}, De-ming SUN^{2,*}

¹Max-Planck-Institute of Neurobiology, Martinsried 82152, Germany; ²Doheny Eye Institute, University of Southern California, Los Angeles, CA 90033, USA

Brain and eye tissues are subject to a reduced version of immune surveillance, which has evolved to protect the particularly sensitive tissues from accidental bystander damage created by regular inflammatory responses. Yet, there are autoimmune diseases in both organs. This review discusses the nature of immune reactivity in the healthy eye and brain tissues, and mechanisms that can overcome the protective barriers to create tissue specific disease.

Keywords: autoimmunity; autoantigenic strength; immune privilege; blood-brain barrier (BBB); blood-retina barrier (BRB); anterior chamber; T cells; experimental autoimmune encephalomyelitis (EAE); experimental autoimmune uveitis (EAU); central nervous system (CNS); eye

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Introduction

The immune system is programmed to continuously scan the body for potentially perilous microbial organisms. In doing so, elements of the immune system identify suspicious structures, and report the information to organized immune organs, where responses are mounted in order to neutralize the potential aggressors. However, immune surveillance is not absolute, and it does not function equally well in all organs. In particular, and on first sight against intuition, some of the most complex and vulnerable organs, including the central nervous system (CNS), the eye and the testis, seemed to be ignored by the immune system, a neglect euphemistically termed “immune privilege”^[1].

Unfortunately, the immune privileged status of the CNS and eye does not provide absolute protection against immune-mediated diseases. Multiple sclerosis (MS), the most important inflammatory brain disease among younger people in moderate climate zones, seems to be an autoimmune disease, caused by brain-autoreactive T lymphocytes. After being activated in the peripheral immune system, these T cells intrude into the brain, and there attack local tissue. This concept is not formally proven, but it rests on several lines of evidence. Indeed, besides signs of tissue degeneration, freshly active MS lesions show immune cell infiltrates, which suggest on-going

active autoimmune processes. In addition, the risk of disease is linked to a growing number of genes, so far all related to immune response and inflammation. Furthermore, the most efficient current therapies for MS are immunomodulatory, *ie*, they alter ongoing acute immune responses. Finally, in recent animal models, spontaneously developing autoimmune demyelinating CNS disease is clearly immune-mediated and resembles early phases of human MS.

Autoimmunity also occurs in the eye. Autoimmune inflammation of the middle layer of the eye, the uvea, is not uncommon in human populations. Uveitis is a sight-threatening, intraocular inflammatory disease in humans and is associated with a high visual morbidity. Like MS, there are diverse lines of evidence indicating an autoimmune pathogenesis in uveitis. Animal models of uveitis, collectively termed experimental autoimmune uveitis (EAU), have been developed in susceptible rodents, mostly by immunization with ocular self-antigens or by adoptive transfer with uveitogenic T cells^[2]. A number of uveitogenic molecules have been characterized, of which the interphotoreceptor retinal binding protein (IRBP) is uveitogenic for both mice and rats. Established animal models of acute, recurrent and chronic EAU provided us with the opportunity to examine differences in the mechanisms of disease, and determine the molecular and cellular properties that lead to disease progression.

In this brief review we shall discuss some structural and functional features that contribute to the immune privileged status of the CNS and eye, and how the privileged status can be lost, giving rise to local autoimmune disease.

* To whom correspondence should be addressed.

E-mail hwekerle@neuro.mpg.de (Hartmut WEKERLE);
dsun@doheny.org (De-ming SUN)

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Immune privileged tissues

The CNS and eye differ from other organs due to several structural peculiarities that profoundly affect local immune surveillance. In particular, the nervous tissues are secluded from the blood flow by a specialized, tight barrier comprising specialized endothelial cells that admit only a selected and tightly controlled set of circulating blood components into the CNS. Secondly, the CNS is less efficiently drained by lymphatic vasculature than other tissues. Hence the transport of antigenic material, either soluble, or transported by dendrite cells to peripheral immune organs is markedly reduced. Finally, CNS tissue lacks many of the functional cues, such as MHC molecules, cell adhesion molecules, chemokines and cytokines, which together create a hospitable milieu for T lymphocytes, allowing proper immune function and long-term survival.

However, it should be noted that the immune privileged status of the CNS refers to a deficiency of the *adaptive* immune system. In marked contrast, the *innate* immune reactivity of CNS tissues is ensured by a tight network of microglia cells, bone marrow-derived phagocytes, which essentially cover the entire CNS tissue with fine processes that permanently seem to scan the surrounding microenvironment for alarming changes. Indeed, any unusual event, whether intrusion of a microbial agent, traumatic or spontaneous degeneration of parenchymal cells, or neoplastic transformation is sensed by the microglia cells and results in activation.

The blood brain barrier (BBB) tightly seals circulating blood from CNS tissues. It is a complex composite of diverse cells and basal laminae surrounding a specialized endothelial tube. In its simplest version, the capillary segment of the CNS vascular tree, the central part of the BBB, is formed by a vascular tube composed of endothelial cells tightly sealed by tight junctions. The endothelia further differ from other blood vessels by a relative deficiency in transcellular transport systems^[3]. These properties allow the BBB to keep most circulating blood cells and macromolecules from passing into CNS tissues.

The inner endothelial tube is surrounded by pericytes embedded in an inner basal lamina^[4]. This is followed by a concentric extracellular space, which is again surrounded by a second, parenchymal basal lamina that covers astrocytic end feet extending from the neighboring CNS parenchyma. This outer lamina differs from its central counterpart by its molecular composition, and thus presumably also by its functional properties^[5].

The immune privileged tissues of the CNS also differ from most other organs in their incomplete lymphatic drainage. In fact, in most organs, a steady stream of interstitial fluid clears subcellular material along with phagocytic antigen presenting cells (APCs) through specialized lymphatic vasculature to the nearest peripheral lymph organs, where immune responses against the imported antigens can be mounted. Such vascular drainage is incompletely developed in the CNS. In rodents, particle tracer studies showed CNS lymphatic drainage restricted to a rudimentary lymphatic flow that runs from the olfactory tissue to the deep cervical lymph node^[6].

Like most biological systems, the barrier function of the

BBB and blood retina barrier (BRB) is not absolute. As will be discussed below, a few immune cells pass through the endothelium and enter the tissue parenchyma. There, however, the new arrivals find a barren, hostile milieu. CNS tissue lacks most of the structures required by T lymphocytes to persist and respond properly. The spectrum of cytokines and chemokines is severely limited in the healthy CNS, and the same is true for cell-bound signaling structures, such as MHC molecules, co-stimulatory factors and cell adhesion molecules.

As has been shown, this particular milieu is stringently controlled by functionally active neurons. In fact, it is known that in conditions of neuronal degeneration, such as Alzheimer's, Parkinson's and Huntington's disease, the local CNS milieu shows signs of inflammatory reactivity. In such tissues, microglia cells, the immune sentinels of the CNS, are activated, cytokines and chemokines are upregulated, and often, but not always, inflammatory infiltrates are formed. Neurodegeneration thus shifts the immunologically barren CNS tissue into a friendlier environment for immune cells and immune reaction.

Experimentally, several set-ups support the neuronal control of CNS immune reactivity. A particularly informative system has been the unilateral axotomy of the rodent facial nerve^[7]. This operation results in degenerative changes in the facial nucleus, the location of the facial motor neuronal cell bodies, which become ensheathed with microglia cells that seem to crop off perisomatic synapses. Local cells produce and release soluble immune mediators, and upregulate MHC class I and class II molecules, as well as sets of co-stimulatory proteins. Perhaps most importantly, immune cells, among them T cells, spontaneously infiltrate the lesioned tissue, whereas the contralateral, unaffected nucleus remains completely free of any changes.

Immune infiltration of axotomized facial nuclei is particularly marked in animals with incipient EAE^[8]. Very similar changes are noted in rodents with EAE, where temperature trauma-induced lesions of CNS tissues become attractive for autoimmune inflammatory infiltrates, even if placed in regions commonly free of EAE inflammation.

In vitro studies of spontaneously forming neuronal circuits either in explants or dissociated cell cultures revealed that glia cells (microglia as well as astrocytes) near "firing" neurons lacking MHC molecules, although both cell types possess the relevant machinery in the absence of neurons. MHC molecules are also inducible in explants by inactivating local neurons, for example using the sodium channel blocker tetrodotoxin^[9].

The mechanisms used by neurons to suppress MHC molecules in surrounding glia cells remain unclear, although there is evidence that neurotrophins may be involved. Addition of nerve growth factor, for example, at least partly restores suppression to tetrodotoxin paralyzed neurons^[10]. Another structure that might function in neuronal regulation of the CNS immune milieu is fractalkine, a chemokine present in the CNS both bound to (neuronal) cell surfaces and in a soluble form. Fractalkine acts on glia cells expressing the specific receptor by repressing activating signals, dampening neurotoxic effects by

activated microglia^[11].

The immune privilege of ocular tissues is maintained by most of the structural specializations described above that act in the CNS. For example, the blood vessels form a largely impermeable BRB by interconnecting endothelial cells with dense arrays of tight junctions^[12]. However, the eye uses additional mechanisms to prevent potentially pathogenic inflammatory responses.

In this context, the anterior chamber (AC) of the eye is a particularly immune-privileged site^[13]. Introduction of antigen into the AC triggers a deviant systemic immune response, resulting in the generation of antigen-specific regulatory T cells and suppression of delayed type-hypersensitivity (DTH), rather than an overtly inflammatory response. This phenomenon was initially described as F1 lymphocyte-immune deviation^[14-16] and subsequently termed “anterior chamber associated immune deviation” (ACAID)^[16]. The antigenic signal delivered to the AC is carried into the circulation and delivered to the spleen^[16, 17] where regulatory T cells are generated^[18]. CD-1 reactive natural killer T cells are required for the inhibition of DTH after the AC injection of antigen^[19]. DTH is a form of T cell-mediated immunity that plays an important role in protection against pathogens.

Inhibition of DTH (after intraocular injection) has been reproduced *in vitro*^[17, 20], revealing that several immunosuppressive factors are important in the induction of tolerance to antigen^[21], including complement (C) of the innate immune system^[22]. Suppression of DTH (identical to ACAID) can also be evoked by the intravenous injection of APC pulsed *in vitro* with soluble antigen in the presence of immunosuppressive factors found in the ocular microenvironment^[23].

Recent studies found that cells leaving the eye after antigen exposure traffic to the marginal zone (MZ) of the spleen and that two types of APC promote tolerance in the MZ - F4/80⁺ APC and MZ B cells. Both communicate with iNKT cells via the CD1d molecule expressed on their cell membranes and result in the generation of CD8⁺ Treg cells^[24-26].

Autoantigenic strength

In his Clonal Selection Theory, Burnet postulated that immune cell clones with receptors for self-antigens are deleted from the immune repertoire, thus ensuring immunological self-tolerance. This concept has been substantiated in its basic tenets by an overwhelming body of experimental data. Indeed, the immune system depends on the thymus, a central immune organ, where naïve, diverse T cells are generated, and where most self-reactive clones are removed by various complementary mechanisms. However, at the same time, it has become clear that the deletion machinery is less than perfect. Peripheral T cell populations in both primates and rodents abound with T cells specifically responding to tissue-specific autoantigens, including antigens from the CNS and eye.

Numerous theories have been proposed to explain the failed functions allowing autoreactive T cells to pass through the thymus, and whether autoreactive T cells could have a positive, physiological role in the body. We will not discuss these

questions here, but instead consider another, rarely treated aspect of autoimmunity, namely “autoantigenic strength”.

It is long known that most, if not all CNS and eye molecules qualify as potential autoantigens, *ie* that practically all protein structures may be recognized by a complementary T cell clone preexisting in the healthy immune repertoire. Yet, there are certain tissue specific proteins that stand out due to their particularly high degree of immunogenicity, making them targets for pathogenic T cell responses in autoimmune diseases (Table 1). Furthermore, the linear sequences of such known autoantigens are not all equally autoimmunogenic; the autoantigenic determinants of an autoantigen are commonly restricted to particular, characteristic molecular determinants.

There are numerous factors influencing the autoantigenicity of a self-protein, such as availability, processing, binding to MHC class II molecules, affinity of peptide/MHC complexes to TCR, *etc*, potentially dictating the pathogenic potential of a given self-protein.

Obviously, availability to APCs is a critical feature. Indeed, this is not a trivial prerequisite. Recent studies of APCs isolated from the CNS without severing the parenchyma indicate that the level of local autoantigen presented is remarkably low, too low to trigger T cell proliferation, but sufficient to reactivate numerous pro-inflammatory cytokine and chemokine genes and genes involved in T cell migration^[27]. Addition of exogenous autoantigen by intrathecal infusion of soluble MBP promptly exacerbates a nascent response, but ultimately leads to premature T cell apoptosis via activated cell death^[28].

Very recently, a phenomenon called cumulative immunity was recognized that could well determine the autoantigenic power of a tissue specific self-antigen. Krishnamoorthy *et al* studied immune reactivity in a transgenic mouse expressing a MOG-specific T cell receptor on a large proportion of its CD4⁺ T cells. About 5%-10% of these mice spontaneously develop autoimmune inflammation affecting the optic nerve and spinal cord. Surprisingly, when crossed into a MOG-deficient background, *ie*, in the absence of the nominal autoantigen, spontaneous EAE was noted with a similar frequency. A detailed proteomic investigation revealed that the MOG-specific TCR co-recognized a particular epitope on the middle neurofilament (NF-M18-30), a component of the axonal cytoskeleton. Transfer studies confirmed that MOG/NF-M double reactive T cells transferred to MOG-deficient mice induced EAE with a delayed onset compared to wildtype, MOG sufficient recipients, whereas double knock-out mice lacking both MOG and NF-M remained completely resistant^[29].

Is the unexpected cross-reactivity between MOG35-55 and NF-M18-30 the “private” reaction pattern of one particular T cell clone, namely 2D2, or is it commonly found among I-Ab restricted, MOG35-55 reactive T cells? The latter seems to be true. In fact, among a series of MOG35-55, I-A^b restricted T cell clones freshly selected from a primed C57BL/6 mouse, a substantial number, but not all, cross-reacted against NF-M18-30.

The findings might indicate that when recognizing epitopes in the same tissue at the same time, although the epitopes

Table 1. Selected rodent and primate EAE (and EAU models) and their indications representing aspects of MS^[37].

Strain	Antigen	Induction	Clinical course	Pathology
MOUSE-EAE/EAU				
C57BL6 (H-2 ^b)	Spinal cord homogenate	Active	Resistant	CNS demyelination, acute inflammation, axonal damage Ocular inflammation
	MOG (aa 35–55)	Active, passive	Severe, chronic-progressive, non-relapsing	
	IRBP (aa 1–20)	Active	Mild, acute disease	
	PLP	Passive	Severe disease	
B10RIII	IRBP (aa 161–180)	Active	Severe	Ocular inflammation
		Passive	Severe	
C3H.SW (H-2 ^b)	MOG (aa 35–55)	Active	Severe, chronic non-relapsing	Inflammation, demyelination
SJL (H-2 ^s)	Spinal cord homogenate	Active	Relapsing-relapsing, Progressive (SCH, MBP)	Demyelination, inflammation
	MBP	Active, passive	Relapsing-relapsing	Demyelination, inflammation
	PLP	Active, passive	Relapsing-relapsing	Demyelination, inflammation
	MOG (aa 92–106)	Active, passive	Severe acute	Inflammation and demyelination
	MAG (myelin-associated glycoprotein) (aa 97–112)			
	MOBP (myelin-associated/ oligodendrocyte basic protein) (aa 37–60)	Active	Non-relapsing	Inflammation
	CNPase (2',3'-cyclic nucleotide 3'-phosphodiesterase)			
	OSP (oligodendrocyte-specific glycoprotein)			
(B6 x SJL) F1 (H-2 ^{b/s})	MOG	Active	Relapsing-relapsing	Inflammation, demyelination
B10.S (H-2 ^s)	CNS homogenate	Active	Resistant	
ASW (H-2 ^s)	MOG	Active	Resistant	Acute inflammation, demyelination
	MOG (aa 92–106)	Active	Depending on Bordetella pertussis application: +secondary progressive (SP)-primary progressive (PP)	
Biozzi AB/L (H-2 ^s)	Brain homogenate		Resistant	
Biozzi AB/H (H-2 ^{dq1})	Spinal cord homogenate	Active	Relapsing-relapsing	Inflammation, demyelination in relapse phase
	MBP (aa 12–26; 21–35)	Active	Native MBP: resistant, MBP 12–26 and MBP 21–35: mild acute	Inflammation
	MOG (aa 1–22; 43–57; 134–148)	Active	Chronic relapsing (MOG 1–22) Chronic acute (MOG 35–55)	Inflammation, no demyelination Native MOG: demyelination
	PLP (aa 56–70)	Active	Chronic relapsing	Inflammation, demyelination
	Ab-crystallin (aa 1–16)	Active	Acute mild	Inflammation
	GFAP (glial fibrillary acidic protein)	Active	Acute severe	Inflammation
ABH (H-2A ^{g7})	MAG (aa 97–112)			
	OSP			
	CNPase			
NOD/Lt (H-2 ^{g7})	rMOG, MOG (aa 35–55)	Active	CREAE	Demyelination with peptide
NOD congenic strain III (H-2 ^{g7})	MOG	Active	Resistant	

(Continued)

Strain	Antigen	Induction	Clinical course	Pathology
BALB/c (H-2 ^d)	Spinal cord homogenate MBP (aa 59–76) PLP (aa 178–191)	Active Passive Active	Resistant aEAE resistant, tEAE: acute Relatively resistant, atypical EAE	Inflammation, demyelination
B10.PL (H-2 ^u)	MBP (aa Ac1–9)	Active, passive		
PL/J (H-2 ^u)	MBP (aa 89–169) MBP (aa 1–37) MOG (aa 35–55) PLP (aa 43–64)	Active, passive Active, passive Active, passive	CREAE CREAE and chronic persisting paralysis Relapsing-remitting CREAE	Demyelination, acute inflammation Demyelination, acute inflammation Demyelination, acute inflammation
DBA/1 (H-2 ^q)	Spinal cord homogenate MOG (aa 79–96)	Active Active	Resistant Acute	Inflammation, demyelination
SWR/J (H-2 ^q)	Spinal cord homogenate PLP	Active Active		
C3/HEJ (H-2 ^k)	PLP	Active	Atypical EAE	Inflammation
RAT-EAE/EAU				
Lewis (RT1-l)	Spinal cord homogenate MBP (aa 68–88) PLP MOG (aa 35–55) S100 β (aa 76–91) GFAP IRBP (aa 177–1091) S-antigen	Active Active and passive Active and passive Active and passive Passive Passive Active Passive Active	Acute Acute, relapses after cyclosporine Weak acute Weak acute, after native MOG chronic progressive Weak acute Weak acute Acute, severe Chronic, severe Acute, modest	CNS inflammation CNS inflammation CNS inflammation CNS inflammation, demye- lination with native MOG CNS inflammation CNS inflammation Ocular inflammation Ocular inflammation
Dark Agouti (DA) (RT1-av1)	Spinal cord homogenate MBP (aa 62–75) MOG BTN (Butyrophilin) (aa 74–90)	Active in incomplete FA Active and passive Active and passive Active	CREAE Acute Chronic, relapsing-remitting No disease	CNS inflammation and demyelination CNS inflammation CNS inflammation and demyelination CNS inflammation
Brown Norway (BN) (RT1-n)	MBP Rat spinal cord MOG	Passive Active Active	Acute Acute Chronic progressive	CNS inflammation CNS inflammation CNS inflammation, demyelination CNS inflammation
PVG (RT1-c)	MBP	Active resistant, passive susceptible	Acute	CNS inflammation
NON-HUMAN-PRIMATE-EAE				
Macaca mulatta (Rhesus monkey) (Mamu-DPB1*01)	Rabbit brain extract Brain extract with adjuvant MOG (aa 4–20, 35–50, 94–116)	Active Active Active	Acute and chronic progressive Acute and chronic Acute and chronic	CNS inflammation and demyelination CNS inflammation with necrosis CNS inflammation with necrosis

(Continued)

Strain	Antigen	Induction	Clinical course	Pathology
	MBP (aa 61–82, 80–105, 170–186)	Active and passive	Acute and chronic	CNS inflammation with necrosis
Macaca fascicularis (Cynomolgus monkey)	Brain homogenate	Active	Acute and CREAE	CNS inflammation, necrotic lesions
	MBP	Active	Acute and CREA	CNS inflammation, necrotic lesions
Macaca nemestrina	Brain homogenate and MBP	Active	Relatively resistant	
Common marmoset (Calithrix jacchus)	Myelin homogenate	Active	Acute – chronic progressive	CNS inflammation, demyelination, necrotic lesions
Caja-DRB*W1201	MBP	Active and passive	Mild acute	CNS inflammation, no demyelination
	PLP	Active	Mild acute	CNS inflammation, no demyelination
	MOG (aa 1–124, 14–36)	Active	RR, secondary progressive	CNS inflammation and demyelination

came from distinct protein structures and derived from different cell sources, T cell could add up both response components into a particularly strong cumulative autoimmune response. Obviously, this concept has to be validated in independent autoimmune situations.

Failed immune privilege: Invasion of privileged tissues by autoimmune T cells

Nevertheless, the immune privilege in the CNS and eye is by no means perfect. In fact, there are rare, but spectacular instances where the immune privileged status is abandoned, and lymphocytes and other inflammatory cells seemingly gain free access to the shielded tissues. As expected, such inappropriate inflammation can have devastating consequences. In human MS, for example, the influx of autoimmune T cells responding to CNS autoantigens sets off a pathological chain of reactions that can lead to a patient suffering severe neuronal dysfunction and disability. Similarly, immune privilege of the eye may be lost, with similarly severe consequences, namely loss of vision.

Fortunately, notwithstanding the considerable number of peoples suffering from autoimmune CNS or eye disease, loss of immune privilege in either organ remains a relatively exceptional event. This is explained partly by the complex barrier function of CNS and eye blood vessels, which allows only a very few specialized immune cells to pass into the surrounding tissue.

It has been known for a long time that contrary to traditional concepts of immune reactivity, the healthy immune repertoire is by no means depleted of self-reactive immune cells. In fact, the peripheral blood of healthy people contains an amazing proportion of T cells with receptors recognizing CNS autoantigens^[30]. However, to break through the blood-tissue barrier, an autoimmune T cell has to acquire a very particular set of functional properties. First of all, as demonstrated by transfer experiments in rodents, CNS reactive T cells only transfer EAE to recipients if they had been maximally activated before

injection^[31]. Resting autoimmune T cells would not cause disease, even if transferred in enormous numbers, and activation of autoimmune T cells *per se* is not sufficient to open the way through the blood-tissue barriers. It has been known ever since the first transfers of myelin specific T cell lines that clinical disease and histological lesions do not arise directly after T cell injection, but that clinical EAE develops after a latency period of 3 or more days after transfer. Until recently, it remained unknown where the transferred cells first reside in the recipient's body, and why they enter the CNS only after a protracted period of time.

A study using genetically modified encephalitogenic effector T cells expressing the green fluorescent protein (GFP)^[32] showed that indeed, the transferred activated T cells travel through the peripheral immune system up to day 3–4 after transfer when they enter the CNS. After initially infiltrating the lung vasculature, the T cells settle in peripheral immune organs, first in perithymic lymph nodes and subsequently in the spleen.

Within the immune milieu, the migrant T cells undergo remarkable changes in their gene expression profile, which prove to be indispensable for enabling the T cells to reach the target organ and invade it. Changes in gene expression are in both directions: A microarray analysis comparing the transcriptomes of *in vitro* activated effector T cells (the cells transferred to recipient rats) with T cells resident in the spleen (the T cells ready to invade the CNS) identified an estimated 600 down-regulated, and about 300 up-regulated genes in the spleen milieu. The down-regulated genes include numerous T cell activation markers, such as CD25, whereas a series of genes involved in cell migration (chemokines and receptors, etc) were induced^[33]. Intriguingly, KLF-2, a master gene controlling T cell migration and quiescence^[34] was among the elevated genes, suggesting a regulatory role for this gene. Interestingly, KLF-2 controls the transcription of sphingosin-1-phosphate receptors, which are not only centrally involved in regulating T cell egress from lymphoid organs, but have also

become promising targets in immunomodulatory therapies for human autoimmunity^[35]. In fact, although without experimental proof so far, the KLF-2/sphingosin-phosphate receptor axis may contribute to the signals triggering the mass exodus of reshaped migratory effector T cells from the spleen 3–4 days after transfer.

Upon reaching the CNS blood vessels, the migratory T cells face a highly sophisticated barrier system. Indeed, as shown by recent real-time imaging studies using two-photon microscopy, the T cell use extremely elaborated strategies to overcome this barrier^[27]. Freshly arriving T cells attach to the luminal surface of BBB vessels, and instead of immediately crossing the vascular wall, they first crawl over the surface, preferentially against the blood flow. Actual extravasation occurs only after an extensive period of scanning. On the abluminal side of the BBB vessel, the T cells continue their crawling locomotion until they contact one or more of the local phagocytes surrounding the blood vessel. Although these phagocytes are distinct from classical macrophages and dendritic cells, they are able to productively present antigen to T cells. In particular, the BBB associated phagocytes present locally produced autoantigens, although apparently at low doses. Autoantigen recognition is sufficient to partially activate incoming encephalitogenic T cells by inducing a set of immune mediators and their receptors, but does not trigger full activation with cell proliferation. Rather, serial contacts of encephalitogenic effector T cells with local autoantigen-presenting phagocytes appear to guide the T cells to the surface of the CNS and ultimately into the parenchyma (Figure 1).

Within the CNS white matter, myelin specific effector T cells initially migrate through the dense parenchyma at remarkably high speed. They are stopped by local antigen presenting cells, either activated microglia or intruded peripheral macrophages, which express high levels of MHC class II proteins. The effector T cells dock onto these cells and form immune synapses, juxtaposing T cell receptor-enriched membrane areas with MHC class II containing membranes of the antigen presenting cells. As a result of these contacts, the T

cells become highly activated, producing high levels of pro-inflammatory cytokines and chemokines^[36]. Either directly or indirectly via recruitment and activation of accessory cells, this activation process is responsible for the functional and structural changes underlying clinical EAE.

Implications

Immune privilege has evolved particularly elaborate structural organization in certain tissues, such as the CNS or eye, in order to avoid unacceptable collateral damage connected with inflammatory responses routinely triggered by immune surveillance. However, the immune privilege of the CNS and eye does not mean complete lack of protection. First, elements of innate immune responsiveness provide some defense; and second, a specialized subset of T cells is able to overcome the vascular barriers to enter the shielded tissue. These cells have a beneficial function in screening the CNS and eye for microbial agents, but they are pathogenic if they respond to local self-antigens. Detailed insights into the mechanisms of tissue invasion by autoimmune migrant T cells could provide a basis for specific treatments of autoimmune diseases in immune privileged organs.

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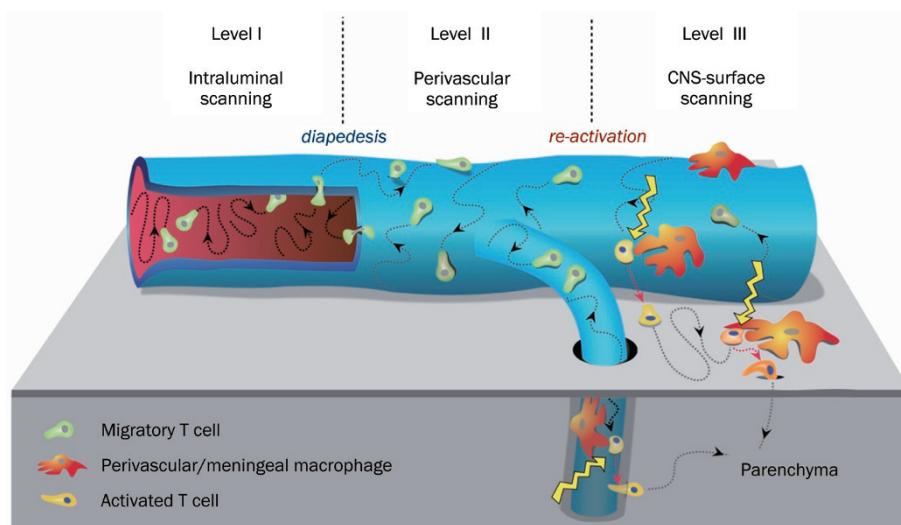


Figure 1. Three-level interaction of migratory autoimmune T cells with the blood-brain barrier. Blood-borne T cells attach to the inner surface of a CNS associated blood vessel, where they crawl randomly, but mainly against the blood stream (Level I). The T cells cross the vessel wall and continue crawling on the outer surface (Level II), until they make contact with local perivascular phagocytes. These phagocytes present local autoantigens and signal the migratory T cells to enter the CNS parenchyma (Level III). [Adapted from ^{27]}

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