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Invited Review

Central nervous system: A modified immune surveillance circuit?

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ABSTRACT

Immune surveillance in the central nervous system (CNS) was considered impossible because: (i) the brain parenchyma is separated from the blood circulation by the blood–brain barrier (BBB); (ii) the brain lacks lymphatic drainage and (iii) the brain displays low major histocompatibility complex class II (MHCII) expression. In this context, the BBB prevents entry of immune molecules and effector cells to the CNS. The absence of lymphatic vessels avoids CNS antigens from reaching the lymph nodes for lymphocyte presentation and activation. Finally, the low MHCII expression hinders effective antigen presentation and re-activation of T cells for a competent immune response. All these factors limit the effectiveness of the afferent and efferent arms necessary to carry out immune surveillance. Nevertheless, recent evidence supports that CNS is monitored by the immune system through a modified surveillance circuit; this work reviews these findings.

1. Introduction

The immune system protects the organism by constant monitoring by specialized cells. These cells freely circulate between the lymphoid organs and other tissues searching for all kinds of potentially damaging agents of internal or external origin through a process known as immune surveillance (Wekerle, 1993). Immune surveillance occurs in most of the tissues, with few immune privileged exceptions that include the testicles, the anterior chamber of the eye and the central nervous system (CNS; Medawar, 1948; Barker and Billingham, 1977; Wekerle, 1993).

The CNS has structural properties that influence the immune reactivity. Among these features are the presence of the blood–brain barrier (BBB), the absence of lymphatic drainage and the reduced expression of Major Histocompatibility Complex Class II molecules (MHCII). The presence of the BBB interferes with the afferent arm of immune surveillance by preventing immune effector cells and molecules from entering the CNS, which in turn prevents an interaction between T cells and CNS antigens (Wekerle, 1993; Cserr and Knopf, 1990). The absence of lymphatic drainage restricts the efferent arm of the immune surveillance by preventing CNS antigens from reaching nearby lymphatic nodes (LNs), thus restricting the activation of lymphocytes. Finally, the low expression of the MHCII hinders antigen presentation and T cells re-activation. From this perspective, the immune privilege was regarded as a passive non-reactive state associated with the isolation of the CNS from the immune system. Nevertheless, these anatomical and structural elements are much more than passive barriers. For example, the physiological drainage of the cerebrospinal fluid (CSF) into the lymph and the blood circulation provides alternative routes for interstitial liquid antigens draining (Cserr and Knopf, 1990). Previous studies show that the BBB permits the selective access of some T cells (Ben-Nun et al., 1981; Naparstek et al., 1983). Finally, although under normal conditions CNS resident cells have a low or null expression of the MHCII, an inflammatory stimulus is capable of inducing rapidly its expression (Neumann, 2001; Carson et al., 2006).

For all these reasons, the concept of CNS immune privilege should be reassessed and rethought, especially because in the past the entry of immune elements into the CNS has been always associated with damage or disease development (Ransohoff et al., 2003; Bechmann, 2005).

2. CNS antigens draining routes

Adequate immune surveillance requires that both antigens and antigen-presenting cells (APCs) can reach the secondary lymphoid organs; this makes lymphatic drainage essential. In peripheral organs, resident APCs capture local antigens and migrate via afferent lymphatic vessels to the nearby LNs for antigen presentation

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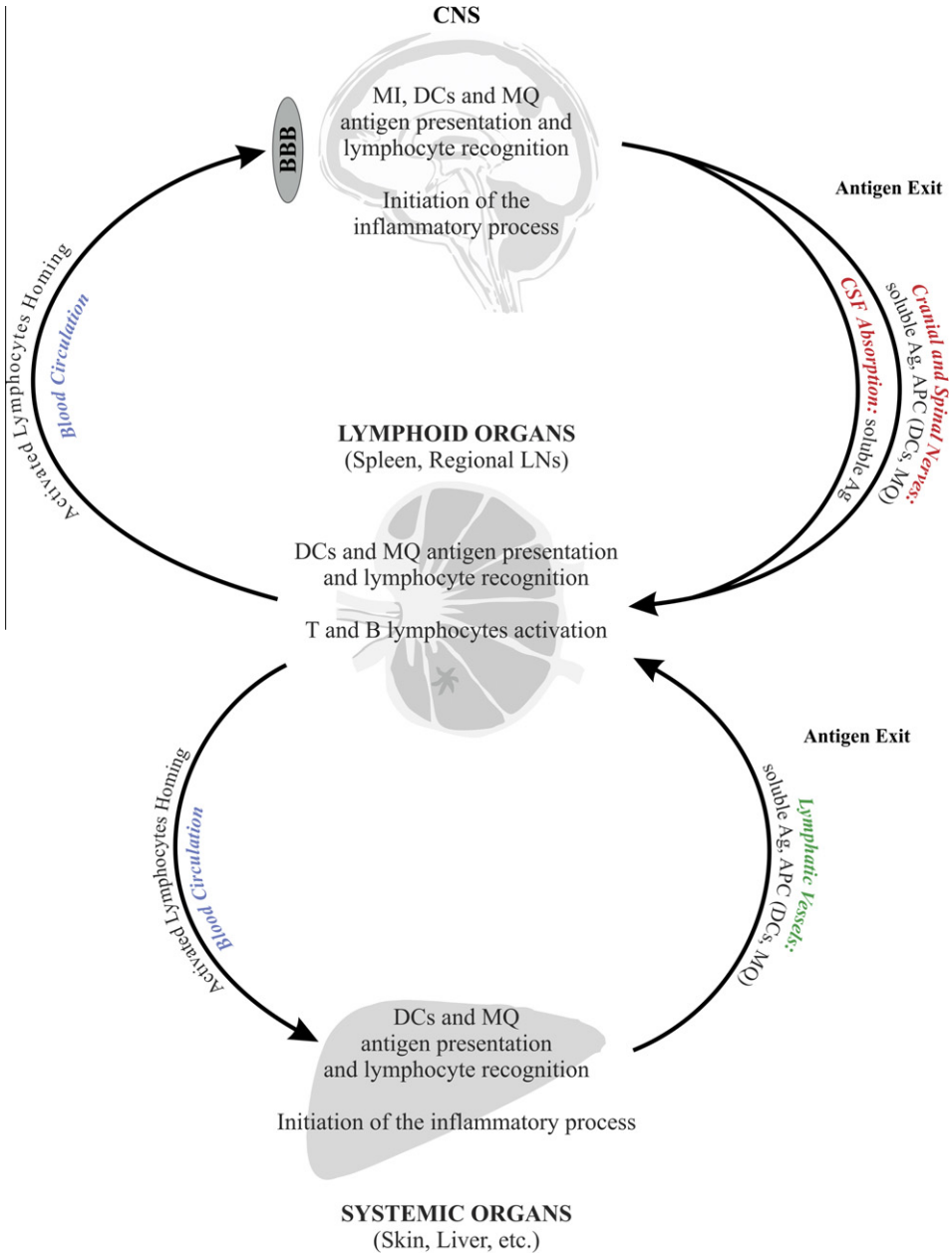

Fig. 1. Differences between systemic and CNS immune surveillance circuits. Antigen draining is normally executed by lymphatic vessels that communicate systemic organs with regional lymph nodes (LNs). Central nervous system (CNS) can drain antigens by alternate routes such as the physiological cerebrospinal fluid (CSF) circulation into the blood and via some cranial and spinal nerves roots into the lymph. Both surveillance circuits share antigen transport by antigen presenting cells (APC) or capture of lymph or CSF solubilized antigen by LNs APCs for further lymphocyte presentation and activation. In order to exert their function lymphocytes need to leave the LNs, home to the different organs and extravasate through a multistep process that involves adhesion molecules in both lymphocyte and endothelial cells. T and B cells must be activated to pass the blood–brain barrier (BBB) in the CNS. Systemic organs and CNS require an additional antigenic presentation to close the immune surveillance circuit. DCs, Dendritic cells; MI, Microglia; MQ, Macrophages.

(Oo et al., 2010; see Fig. 1). The CNS, however, lacks a traditional lymphatic system; consequently CNS antigens draining must occur through alternative routes.

One possible route is the physiological circulation and reabsorption of the CSF through the arachnoid villi towards the venous sinus, allowing CNS soluble antigens to reach the spleen via blood circulation (Harling-Berg et al., 1989; Cserr et al., 1992; Dickstein et al., 1999; also see Fig. 2). Another probable route is the outflow of CSF and interstitial liquid toward the head and neck's lymphatic vessels through the extensions of the subarachnoid space of the olfactory, optic, trigeminal and acoustic nerves (Dickstein et al., 1999). This route favors the arrival of CNS antigens to the deep and superficial cervical LNs (Table 1), thereby potentially promoting a high-level production of antibodies, which can be significantly abolished through surgical obstruction of these cranial nerves (Harling-Berg et al., 1989; Cserr et al., 1992; Gordon et al., 1992).

Local antigens also exit the CNS by APCs such as macrophages or dendritic cells (DCs). These cells uptake and process local antigens and leave the CNS following the same routes as CNS antigens to reach the cervical LNs (Kuhlmann et al., 2001; de Vos et al., 2002; Karman et al., 2004). Although under physiological conditions these cells are absent from the cerebral parenchyma, they are usually present in structures that produce or transport CSF, such as ventricles, meninges and choroid plexuses (Matyszak

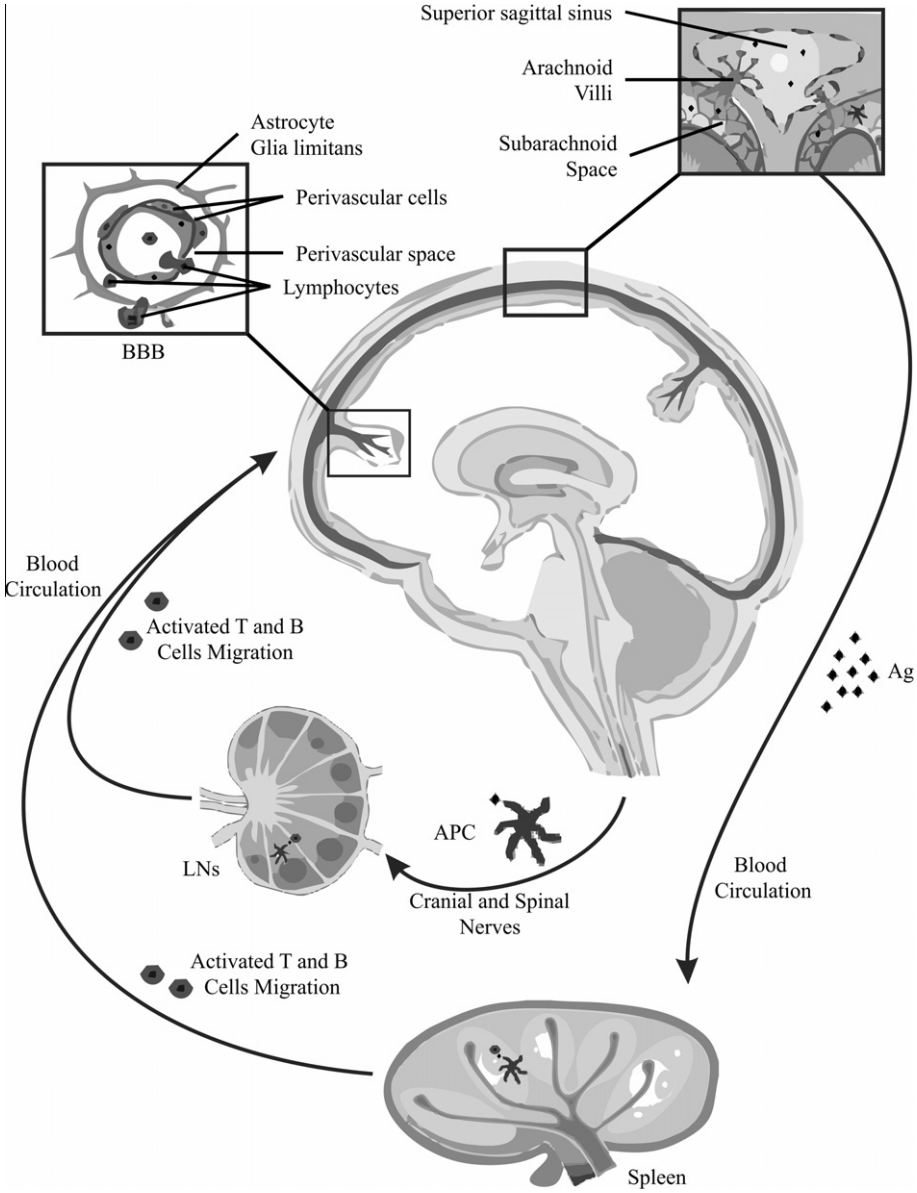

Fig. 2. Modified immune surveillance circuit in the Central Nervous System. Proposed immune surveillance circuit through antigen (Ag) exit, either solubilized in the cerebrospinal fluid or transported by antigen-presenting cells (APC) for its presentation to lymphocytes in the cervical lymph nodes (LNs) and/or the spleen, thus forming the efferent arm of surveillance; and with the subsequent arrival of activated lymphocytes in the central nervous system (CNS) through the blood–brain barrier (BBB), constituting the afferent arm.

and Perry, 1996; McMenamin et al., 2003). In fact during neuro-inflammatory conditions, DCs accumulate in the CSF, as well as in perivascular spaces. These findings suggest that the CSF might be a major route for transporting DCs from the CNS to the lymphoid organs (Hatterer et al., 2008). Additionally, it has been reported that DCs injected into the CSF preferentially migrate to B cell follicles within the cervical LNs; suggesting that under neuro-inflammatory conditions, specific mechanisms direct the DCs migration to this location (Hatterer et al., 2006).

Therefore CNS antigens probably access lymphoid tissues rapidly through the CSF or APC transport for subsequent processing and appropriate presentation, in order to stimulate specific antigen responses in immature and memory T cells (Ransohoff et al., 2003).

3. Peripheral stimulation in the lymphatic nodes

Lymphoid organs present a functional specialization for distinct anatomical sites for carrying out immune responses with particular characteristics against local antigens (Wolvers et al., 1999; Kraal et al., 2006). For instance, ileal Peyer's patches provide oral tolerance to many dietary antigens and commensal bacteria. In order to induce tolerance, local DCs capture antigens, migrate to the mucosa-draining LNs and generate antigen-specific suppressive T cells (Fig. 1). The failure to induce tolerance leads to food allergy or celiac disease (Kraal et al., 2006).

In contrast, the CNS does not normally possess any structurally-defined lymphoid tissue. The peripheral immune response to CNS antigens commonly occurs at the cervical LNs and is characterized by a predominant antibody response, a Th2 type response (Harling-Berg et al., 1989; de Vos et al., 2002; Mojtahedi, 2005). One factor that may influence the immature T helper lymphocytes to acquire a Th2 profile in the cervical LNs is the relatively high concentration of antigens in APCs. It could also be induced through the secretion of CNS immune-regulating molecules draining toward the cervical LNs, where these molecules could influence antigen presentation by modulating APC activity (Mojtahedi, 2005). Finally,

Table 1
Reported routes for CNS antigens draining.

Antigen	CNS leaving mechanism	CNS off-site detection	References
MBP	Macrophages Dendritic cells CSF	Cervical lymph nodes Spleen Serum	Massaro et al. (1985), Thompson et al. (1985), Lamers et al. (1998), Liu et al. (2001), de Vos et al. (2002), Ohta et al. (2002) and Fabriek et al. (2005)
PLP	Macrophages Dendritic cells	Cervical lymph nodes	de Vos et al. (2002), Ohta et al. (2002) and Fabriek et al. (2005)
HTLV-I	CSF Lymphocytes CSF cells	Serum Peripheral blood monocytes	Bhagavati et al. (1988), Moritoyo et al. (1999) and Cartier and Ramirez (2005)
HIV	CSF CSF cells	Lymph nodes Spleen Peripheral blood cells Serum	Cashion et al. (1999) and Chiodi et al. (1988, 1992)
VZV	CSF	Serum	Sotelo et al. (2008)
Taenia solium	CSF	Serum	Garcia et al. (2000), Pardini et al. (2001) and Bobes et al. (2006)
Toxoplasma gondhi	CSF	Serum	Requejo et al. (1997), and Chaves-Borges et al. (1999)

MBP, Myelin basic protein; HTLV-I, Human T-lymphotropic virus type I; HIV, Human immunodeficiency virus; VZV, Varicella zoster virus.

DCs preferential migration from CSF to B cell follicles in the cervical LNs could also contribute to an active antibody response (Hatterer et al. 2006). These types of immune responses contribute to less damage than Th1 immune responses, which are usually associated with CNS inflammatory pathologies (Chavarria and Alcocer-Varela, 2004).

4. Lymphocytes migration to CNS

Although it was believed that leukocytes were excluded from the CNS by the BBB making immune surveillance impossible, it is now known that BBB does not prevent CNS leukocyte trafficking. Indeed, T, B and NK lymphocytes as well as cells of the macrophage/monocyte lineage have been detected in the CNS under normal conditions (Hickey, 1999), CNS perivascular macrophages are continually replaced (Hickey and Kimura, 1988) and lymphocytes can gain access to CSF either by traversing BBB to the perivascular space or the choroid plexus (Seabrook et al., 1998; Kivisäkk et al., 2003; Ransohoff et al., 2003).

In order to be capable of passing through the BBB lymphocytes must be activated, independently of their antigenic specificity and MHCII compatibility(Richert et al., 1979; Wekerle et al., 1986; Hickey, 1999). Their retention and participation in CNS inflammation depend on the common patterns of antigen presentation and T cell recognition (Hickey et al., 1991; Knopf et al., 1998; Hickey, 1999). Systemic memory and activated lymphocytes also reach the CNS, thus contributing to the immune surveillance of the CNS (Silva et al., 1999; Kwok et al., 2002; Kivisäkk et al., 2006).

BBB lymphocyte crossing occurs by similar mechanisms described for endothelial transmigration in other tissues; it follows a sequential process of cellular rolling, adhesion and diapedesis; and is mediated and guided by adhesion molecules and chemokines (Drevets and Leenen, 2000). Adhesion molecules are expressed in lymphocytes and endothelial cells (Table 2), and are regulated by immune system and glia cell molecules. Astrocytes and microglia also modulate BBB permeability, increasing or decreasing lymphocyte recruitment (McCarron et al., 1993; Male et al., 1994; Hickey, 1999, 2001). Additionally, adhesion molecules participate in the differential recruitment of several types of lymphocytes and determine lymphocyte final CNS locations, such as parenchyma, meninges or choroid plexus (Baron et al., 1993; Hickey, 1999, 2001).

5. Antigen presentation in the CNS

In physiological conditions, CNS presents low expression of MHCII molecules. Therefore, resident brain cells would be unable to present specific antigens to T lymphocytes. The absence of professional APCs in brain parenchyma could prevent the initiation and propagation of immune responses (Neumann, 2001). Nevertheless, pre-activated T lymphocytes in the immune organs may migrate to the brain parenchyma and release pro-inflammatory cytokines (IFN-γ, TNF-α) inducing MHCII molecules into almost all CNS residing cells (Neumann, 2001; Carson et al., 2006). Also, monocytes/macrophages are recruited and infiltrate the perivascular space as sentinels (Neumann, 2001). Consequently, infiltrated T lymphocytes recognize the antigens presented by these APCs and act as effector cells (Neumann, 2001; Prat et al., 2001).

6. CNS modified immune surveillance: multiple sclerosis as an example

Traditionally immune surveillance involves well-coordinated events between the focus of inflammation and the local lymphoid organs(Fig. 1; Oo et al., 2010).

Despite its structural properties CNS can be monitored by a modified immune surveillance circuit (Fig. 2). Multiple sclerosis clearly shows that immune surveillance is possible in the CNS, though with particular characteristics of its own.

Multiple sclerosis is an autoimmune disease characterized by inflammation, demyelinization and axonal degeneration (Glass et al., 2010). This disease presents characteristic pathological changes such as: an important perivascular infiltration of lymphocytes and plasma cells in the white substance of brain and spinal cord, loss of BBB integrity, astrocyte and microglia activation, and demyelinization (Wekerle, 1993; Glass et al., 2010). Auto-reactive T and B cells are fundamental for disease development. These cells require antigenic presentation of myelin antigens by APCs such as DCs, macrophages and microglia (Fig. 2) in order to activate and differentiate into effector cells (Glass et al., 2010). Several studies have demonstrated that DCs and macrophages can leave the CNS transporting myelin antigens and reach the cervical LNs for antigen presentation to auto-reactive T and B lymphocytes (Fig. 2; Kuhlmann et al., 2001; de Vos et al., 2002; Karman et al., 2004; Fabriek et al., 2005). Also it is probable that CSF and serum soluble myelin antigens could reach cervical LNs and the spleen to be captured there by local APCs and presented to the respective specific lymphocytes (Massaro et al., 1985; Thompson et al., 1985; Lamers et al., 1998). Once activated, the auto-reactive lymphocytes would be able

Table 2
Molecules involved in lymphocyte transmigration to the CNS.

Molecule	Other names	Cell expression	Ligand	Expression	Function	References
Selectin family						
P-selectin	CD62P	CNS endothelial cells	PSGL1	Constitutive Inducible	Rolling Adhesion	Kerfoot and Kubes (2002), Piccio et al. (2002), Kivisäkk et al. (2003), Coisne et al. (2006) and Döring et al. (2007)
E-selectin	CD62E	Activated CNS endothelial cells	PSGL1	Inducible	Rolling Adhesion	Wong et al. (1999), Piccio et al. (2002), Omari and Dorovini-Zis (2003) and Coisne et al. (2006)
PSGL1	CD162	Circulating activated, effector and memory lymphocytes	E-selectin P-selectin	Constitutive Inducible	Rolling	Piccio et al. (2002, 2005) and Kivisäkk et al. (2003)
Integrin family						
LFA-1	CD11a/CD18 α1β2 integrin	Circulating activated, effector and memory lymphocytes	ICAM-1 JAM	Constitutive Inducible	Adhesion Transmigration	Archelos et al. (1993), Piccio et al. (2002) and Yang et al. (2008)
VLA-4	CD49d/CD29 α4β1 integrin	Circulating activated, effector and memory lymphocytes	VCAM-1 Fibronectin	Constitutive Inducible	Adhesion Transmigration	Yednock et al. (1992), Baron et al. (1993), Piccio et al. (2002) and Roffê et al. (2003)
Inmmunoglobulin superfamily						
PECAM-1	CD31	CNS endothelial cells Lymphocyte	PECAM-1	Constitutive	Adhesion Transmigration	Wong et al. (1999), Qing et al. (2001), Graesser et al. (2002), Greenwood et al. (2002) and Coisne et al. (2006)
ICAM-1	CD54	Activated CNS endothelial cells	LFA-1	Constitutive Inducible	Adhesion Transmigration	Archelos et al. (1993), Wong et al. (1999), Piccio et al. (2002, 2005), Greenwood et al. (2002), Kivisäkk et al. (2003), Omari and Dorovini-Zis (2003) and Yang et al. (2008)
VCAM-1	CD106	Activated CNS endothelial cells	VLA-4	Constitutive Inducible	Adhesion Transmigration	Yednock et al. (1992), Baron et al. (1993), Wong et al. (1999), Greenwood et al. (2002), Piccio et al. (2002), Omari and Dorovini-Zis (2003) and Roffê et al. (2003)
JAM-A		Activated CNS endothelial cells	LFA-1	Constitutive Inducible	Adhesion	Del Maschio et al. (1999), Padden et al. (2007), Yeung et al. (2008), Alvarez et al. (2011)
TNF superfamily						
CD40L	CD154	Activated T CD4 lymphocyte	CD40	Constitutive Inducible	Adhesion	Omari and Dorovini-Zis (2003) and Vowinkel et al. (2006)
TNF-R superfamily						
CD40		Endothelial cells	CD40L	Constitutive Inducible	Adhesion	Omari and Dorovini-Zis (2003), Vowinkel et al. (2006) and Ramirez et al. (2010)

ICAM-1, Intercellular adhesion molecule 1; JAM-A, Junctional adhesion molecule A; LFA- 1, Lymphocyte function associated molecule 1; PECAM-1, Platelet-endothelial cell adhesion molecule 1; PSGL-1, P-selectin glycoprotein ligand 1; VCAM-1, Vascular cell adhesion molecule 1; VLA-4, Very late antigen 4.

to home to the CNS and enter the perivascular space of the BBB (Fig. 2; Seabrook et al., 1998; Silva et al., 1999). Still these lymphocytes require an additional specific antigen signal to enable them to migrate from the perivascular space to the cerebral parenchyma in order to begin an inflammatory process in the CNS (Archambault et al., 2005); therefore completing the CNS immune surveillance circuit (Fig. 2).

7. Conclusions

Active immune surveillance in the CNS is integrated by a modified immune circuit resulting in protection from possible brain damage (Baron et al., 1993). This implies a dynamic communication between the CNS and the secondary lymphoid organs. Based on the CNS physiology, three characteristics emerge that are immunologically relevant to the circulation of CNS antigens and their drainage. First, the movement of interstitial fluid and CSF through the subarachnoid space allows antigen access to immune cell sentinels and to lymphatic vessels via cranial and spinal nerves. Second, the drainage of interstitial fluids and CSF makes it possible for antigens to reach at a relatively high concentration a large number of cervical LN APCs. Subsequently, activated lymphocytes migrate to the CNS through the BBB. Third, CNS antigens quickly reach the subarachnoid space to be drained; however, some residual antigens are retained at various sites within the cerebral tissue. This retention presents an opportunity for small but immunologically significant quantities of antigens to interact with recirculating antigen-specific lymphocytes that have been previously activated in the cervical LNs (Harling-Berg et al., 1989).

Conflict of interest statement

All authors declare that there are no conflicts of interest.

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