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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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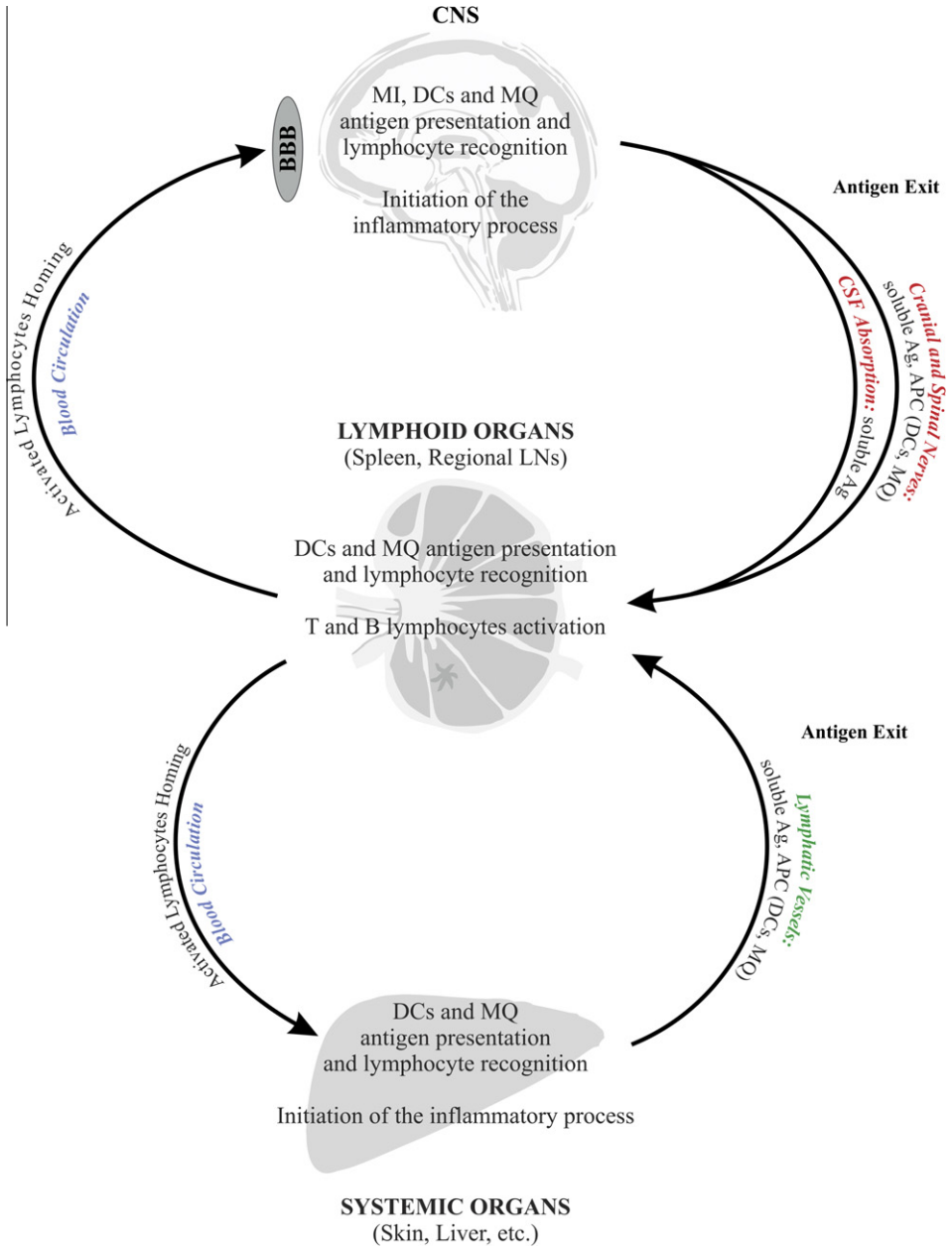

Fig. 1. Differences between systemic and CNS immune surveillance circuits. Antigen draining is normally executed by lymphatic vessels that communicate systemic organs with regional lymph nodes (LNs). Central nervous system (CNS) can drain antigens by alternate routes such as the physiological cerebrospinal 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