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Invited Review

CNS-specific T cells shape brain function via the choroid plexus

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ABSTRACT

Adaptive immunity was repeatedly shown to play a role in maintaining lifelong brain function. Under physiological conditions, this activity was associated with $CD4^+$ T cells specific for brain self-antigens. Nevertheless, direct interactions of T cells with the healthy neuronal parenchyma are hardly detectable. Recent studies have identified the brain's choroid plexus (CP) as an active neuro-immunological interface, enriched with CNS-specific $CD4^+$ T cells. Strategically positioned for receiving signals from both the central nervous system (CNS) through the cerebrospinal fluid (CSF), and from the circulation through epithelium-immune cell interactions, the CP has recently been recognized as an important immunological compartment in maintaining and restoring brain homeostasis/allostasis. Here, we propose that CNS-specific T cells shape brain function via the CP, and suggest this immunological control to be lost as part of aging, in general, and immune senescence, in particular. Accordingly, the CP may serve as a novel target for immunomodulation to restore brain equilibrium.

1. Introduction

The mammalian central nervous system (CNS) is an immune-privileged site, shielded behind barriers from direct interaction with circulating immune cells. Based on its anatomical features, and the fact that CNS inflammation is detrimental to the neural parenchyma under certain pathological conditions, the healthy brain was long considered to ideally function when protected from circulating immunity. Accordingly, neuroinflammation was repeatedly shown to impair brain function, inhibiting hippocampal neurogenesis, disrupting cognitive ability, and contributing to illness and depression (Dantzer et al., 2008; Monje et al., 2003; Raison et al., 2006).

For the past two decades, however, abundant data have suggested adaptive immunity as a key regulator of brain cell renewal, behavior, learning and memory; immune deficiency was linked to impaired brain plasticity, and when adaptive immunity was boosted brain function was restored or even enhanced (Kipnis et al., 2004, 2012; Wolf et al., 2009; Yirmiya and Goshen, 2011; Ziv et al., 2006). Yet, how can we reconcile these two opposite consequences of immune activation within the brain's territory? Dissecting CNS-immune cell interactions across different models of acute CNS trauma, neurodegeneration and behavioral paradigms, has begun to reveal the complex nature of these interactions, in which type, extent, timing and location of the immune response, all critically determine the outcome (thoroughly reviewed in (Kipnis et al., 2012; Rook et al., 2011; Schwartz and Shechter, 2010)). Nevertheless, as T cells can barely be found in the CNS parenchyma under healthy conditions, the mechanism by which they affect the brain remained a mystery.

Here we propose a possible novel underlying mechanism by which adaptive immunity shapes brain function and plasticity, and suggest the choroid plexus (CP) as a site through which immunological control of these processes is maintained, or eventually lost, throughout life.

2. CNS-specific adaptive immunity shapes brain function

Over the past decades, circulating lymphocytes, and particularly $CD4^+$ T cells specific for brain self-antigens, were shown to have a pivotal role in supporting brain plasticity, both in health and in response to CNS trauma (Hauben et al., 2001; Hendrix and Nitsch, 2007; Hofstetter et al., 2003; Olsson et al., 2003; Wolf et al., 2009; Ziv et al., 2006), a phenomenon established by our group and termed "protective autoimmunity" (Moalem et al., 1999).

At the time, the findings suggesting a neuroprotective role for CNS-specific T cells were surprising, as autoreactive T cells were considered synonymous with autoimmune diseases; the possibility of benign autoimmunity was not considered. Examining the potential mechanism by which these cells exert a neuroprotective role in models of CNS trauma and neurodegeneration has highlighted their ability to indirectly control CNS inflammation. In the case of acute CNS trauma, such as spinal cord injury (SCI), vaccination with a CNS-specific antigen, but not an irrelevant antigen, was found to support the recovery process (Hauben et al., 2001). The underlying mechanism was later shown to be dependent on a well-orchestrated adaptive immune response,

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where CNS-specific T cells augment the beneficial recruitment of anti-inflammatory monocyte-derived macrophages to the injured spinal cord (Shechter et al., 2009).

Similar neuroprotective effects of CNS-specific immune cells were also observed under neurodegenerative conditions of the CNS. Active immunization with Copolymer-1 (Copaxone®; glatiramer acetate) administered with adjuvant, inducing an autoreactive-like response against CNS antigens (Kipnis et al., 2000), was shown to protect motor neurons in ALS (Angelov et al., 2003), and dopaminergic neurons are protected in an animal model of Parkinson's disease following passive Copolymer-1 immunization (Benner et al., 2004). Under such conditions, where the collaborative activity of innate and adaptive immunity support is needed to suppress of neuroinflammation, boosting of autoimmunity was suggested as a possible remedy for neurodegenerative diseases (Schwartz and Kipnis, 2004).

Perhaps more intriguing, the beneficial role of CNS-specific T cells was found to go beyond the context of CNS trauma and neurodegeneration. In the case of higher cognitive functions, it was shown that $CD4^+$ T cells recognizing specific CNS antigens support hippocampal neurogenesis, spatial learning and memory performance (Ziv et al., 2006; Wolf et al., 2009). The first evidence for a role of adaptive immunity in brain function came from experiments that examined cognitive ability in immune compromised mice, demonstrating that these animals display impairments in hippocampal function (Kipnis et al., 2004). Subsequently, it was shown that T cells that recognize specific CNS antigens are active participants in such immune-dependent cognitive function, affecting brain-cell renewal and spatial learning and memory (Ziv et al., 2006). These cognitive impairments were later found to be amenable to partial rescue following various forms of immunomodulation (Baruch et al., 2013; Ron-Harel et al., 2008). Moreover, when naive mice were depleted of adaptive immune cells, and specifically of their $CD4^+$ cells, they experienced impairments in spatial-memory (Derecki et al., 2010; Ron-Harel et al., 2008; Wolf et al., 2009), supporting the notion that CNS-specific circulating immunity has a life-long role in maintaining brain function.

Interestingly, CNS-specific T cells were also shown to affect adult neurogenesis in unexpected niches of the healthy CNS parenchyma, such as in the adult spinal cord. Our team recently identified a novel neurogenic niche in the adult spinal cord, in which mechanosensory stimuli control GABAergic neuronal differentiation and survival, suggested to play a local inhibitory role in managing pain sensation (Shechter et al., 2011). This neurogenic niche was shown to be impaired in T and B cell-deficient SCID mice and enhanced in transgenic mice overexpressing a T-cell receptor for myelin basic protein (MBP) (Shechter et al., 2007), suggesting that the involvement of autoimmune T cells in supporting CNS plasticity goes beyond the constitutively active neurogenic niches, shaping the CNS response to sensory inputs.

3. Immune–dependent maintenance from the brain's borders

Though, as briefly summarized above, CNS-specific adaptive immunity was shown across different models to protect and support the CNS, both in health and disease, direct interactions of T cells with the neuronal parenchyma, in particular the healthy one, are hardly detectable. This led us and others to consider the possibility that this T-cell dependent supportive effect is either indirect, or that it is mediated from outside the neuronal tissue (Kipnis et al., 2012; Schwartz and Shechter, 2010).

In the healthy brain, T cells are mainly found at the cerebrospinal fluid (CSF), or at the "borders" of the CNS: the CP at the brain's ventricles, and the meningeal membranes that cover the brain (Engelhardt and Ransohoff, 2005). It is at these sites that T cells were suggested to encounter their cognate antigen, presented to them by tissue-resident APCs (Anandasabapathy et al., 2011; Kivisakk et al., 2009). Importantly, T cells were shown to accumulate at these compartments upon potential need of the CNS for support – in experimental paradigms of mental stress (Lewitus et al., 2008) and the performance of cognitive tasks (Derecki et al., 2010).

The first line of evidence suggesting the importance of these sites in mediating immune–dependent restoration or homeostasis/allostasis of the brain came from studies of immunological response to mental stress (Lewitus et al., 2008, 2009; Lewitus and Schwartz, 2009). Following a stressful episode, T cells were found to traffic to the CP, along with the elevation of the adhesion molecule ICAM-1 by the CP epithelium (Lewitus et al., 2008). Immunization with CNS-specific peptide results in enhanced recruitment of lymphocytes to the CP, which correlates with improved ability of the animals to cope with stress, and the restoration of hippocampal brain-derived neurotrophic factor (BDNF) to pre-stress levels (Lewitus et al., 2009).

The anatomical location of the CP within the brain ventricles supports its potential role in regulating brain plasticity and in turn, brain function (Fig. 1). In close proximity to the CP, the ependymal cells lining the ventricles were shown to serve as a reservoir of neural stem cells that is activated following CNS damage (Carlen et al., 2009; Mirzadeh et al., 2008), and the adjacent subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus–hippocampus are two constitutively active niches of adult neurogenesis (Gage, 2000). In models of brain injuries, the CP was shown to respond by synthesizing and secreting into the CSF various growth factors and other peptides that are of trophic benefit to the CNS, promoting repair, tissue remodeling and neurogenesis (Chodobski and Szmydynger-Chodobska, 2001; Johanson et al., 2000). Such growth factors and neurotrophins, when directly injected into the CSF, can stimulate adult neurogenesis (Lehtinen and Walsh, 2011; Perez-Martin et al., 2010). Importantly, the expression levels of these factors, particularly BDNF and insulin-like growth factor (IGF)-1, were shown to be upregulated in the CP in response to chronic stress (Sathyanesan et al., 2012), further substantiating the CP role in maintaining brain plasticity and homeostasis.

Another evidence for the importance of immune–dependent maintenance from the brain's borders came from the examination of the meningeal spaces of the brain following the performance of cognitive tasks. In this experimental paradigm, $CD4^+$ T-cells were shown to accumulate in the meninges and were demonstrated to locally produce the cytokine interleukin (IL)-4 (Derecki et al., 2010). Preventing accumulation of these cells in the meninges (by the administration of the immune modulator, FTY720) or preventing their production of IL-4 (by using IL-$4^{-/-}$ bone-marrow (BM) chimeric mice) result in impaired cognitive ability. Interestingly, both of these manipulations prompted a phenotypic switch of the meningeal myeloid cells to a proinflammatory subtype, suggesting that $CD4^+$-derived IL-4 indirectly affects cognition by modulating the phenotype of additional cell lineages (Butovsky et al., 2006b; Zhao et al., 2006).

Taken together, it is suggestive that immune–dependent orchestration of maintenance of the CNS occurs at the brain's borders, and that T cells may exert their effects on the healthy CNS from afar, without directly interacting with the neuronal parenchyma.

4. Immunological control of brain function from the choroid plexus

Located within the brain ventricles, the CP is a villous structure, comprised of a continuous single layer of epithelium that surrounds an inner stroma, which is vascularized by blood vessels