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Opinion

Type I/II Interferon Balance in the Regulation of Brain Physiology and Pathology

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Recent findings have revealed distinct roles for type I and II interferons (IFN-I and IFN-γ) in the recruitment of immune cells to the central nervous system (CNS) and highlighted the importance of this process for brain maintenance and protection/repair. Furthermore, manipulation of IFN-I and IFN-γ pathways in pathological contexts has yielded conflicting results. We discuss these findings, focusing on two distinct conditions; relapsing remitting multiple sclerosis (RRMS) and brain aging. Using these examples, we propose that regulation of immune cell entry to the CNS is a mechanism through which interaction between IFN-I and -II can affect brain function from its anatomical borders. Deviation from homeostatic IFN-I/-II balance may contribute to distinct brain pathologies, resulting from either insufficient immune surveillance of the CNS and loss of immune-dependent protection, or overwhelming leukocyte entry and immune-mediated destruction.

Trends

Homeostasis: IFN-γ signaling at the choroid plexus within the brain controls CNS immune surveillance important for brain maintenance.

Relapsing remitting multiple sclerosis: endogenously expressed as well as therapeutically delivered IFN-I ameliorates disease progression by indirectly attenuating IFN-γ signaling at the borders of the brain and restraining excess infiltration of pathological immune cells to the CNS.

Aging: excess expression of IFN-I by the CNS choroid plexus is associated with insufficient IFN-γ dependent CNS immune surveillance as well as with loss of cognitive function and neurogenesis.

Immunological Support of the CNS

In recent years it became apparent that the generalized perception of the brain and spinal cord as 'immune-privileged sites' needs to be revisited; circulating leukocytes were shown to play an indispensable role in maintenance and repair of the CNS. Accordingly, immune-deficient mice are more susceptible to mental stress, suffer from cognitive deficits, and show reduced hippocampal neurogenesis levels when compared to their wild-type counterparts [1–4], highlighting roles of systemic immunity in the day-to-day function of the CNS [5,6]. In addition, blood-derived monocytes were found to promote tissue recovery following acute CNS injury (spinal cord injury, SCI [7], optic nerve injury [8], or stroke [9]), support amyloid β (Aβ) clearance in Alzheimer's disease (AD) [10–16], and confer neuroprotection in neurodevelopmental Rett syndrome [17]. Moreover, specific T cell populations and T cell-derived cytokines were suggested to positively affect recovery from acute insults [18,19] and to mediate neuroprotective mechanisms in physiology [6,20–22] and in chronic neurodegenerative and inflammatory conditions (amyotrophic lateral sclerosis, ALS; Parkinson's disease, PD [23]; AD [24], and multiple sclerosis, MS [22]).

Whereas the blood–brain barrier (BBB) is impermeable under physiological conditions, recent studies strongly suggest that immune cells infiltrate to the CNS territory in a well-controlled manner via a specialized interface – the blood–cerebrospinal fluid barrier (BCSFB) formed by the choroid plexus (CP) of the brain [25] (Figure 1, Box 1). The CP is located in all four brain ventricles and comprises fenestrated blood capillaries surrounded by a monolayer of epithelial cells interconnected by tight junctions [26–28]. Under physiological conditions, the CP stroma, the space between endothelium of the blood vessels and the epithelial surface, is populated by various resident immune cell types [26], including $CD4^+$ T effector memory (T_{EM}) cells [29],

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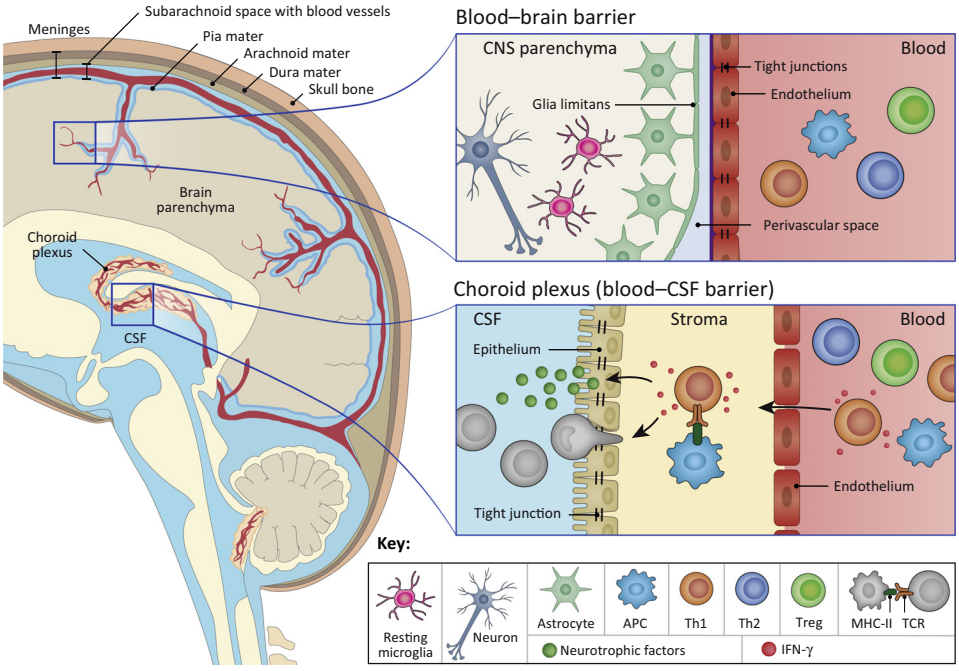

Figure 1. The Central Nervous System (CNS) Borders. The blood–brain barrier (BBB) (at the parenchymal vasculature and the meninges) consists a layer of endothelial cells (interconnected by tight junctions) and glia limitans (a surface made of astrocyte foot processes). The blood–CSF barrier (BCSFB) at the choroid plexus (CP) is a structure located in brain ventricles, and comprises an endothelial wall of fenestrated blood capillaries and a monolayer of tight junction-connected epithelial cells. Whereas the BBB remains impermeable to immune cells under physiological conditions, the CP is viewed as a site of constant brain–immune dialogue, which supports CNS function by controlling leukocyte trafficking to the CNS territory and maintains the production of neurotropic factors from the CP epithelium. Abbreviations: IFN, interferon; TCR, T cell receptor; Th1/2, type 1/2 T helper cell; Treg, regulatory T cell.

Box 1. Endothelial Barriers and Epithelial Gates of the CNS

The CNS is separated from circulating immune cells by a complex system of barriers; however, some level of communication between the CNS and peripheral immunity must be maintained. Indeed, various blood-derived immune cells reside within the CNS territory, mostly in the CSF and at the borders of the brain (the CP and CSF-filled meningeal and perivascular spaces), but not in the brain parenchyma, which is dominated by long-lived resided myeloid cells, the microglia. Importantly, the phenotype of CNS-infiltrating cells was shown to modulate brain maintenance, repair, and protection (reviewed in [5,6]).

Based on current understanding of the structure of the brain borders, and studies of the CSF cellular composition, several (often contradicting) mechanisms have been proposed regarding the site through which immune cells enter the CNS territory [36,100–102]. Recent experimental data have suggested that the barriers of the brain, the BBB and the meningeal layers, which are based on endothelial tight junctions, do not normally allow immune cell passage, and that breaching these barriers by leukocytes should be considered as a sign of pathology. By contrast, epithelium-based barriers, such as the CP, are immunologically active surfaces, strategically positioned to sense and respond to signals from compartments that they separate (the blood and the CSF, in the case of the CP), and well-equipped to mediate controlled immune cell trafficking [5,36]. In addition, although often overlooked, circumventricular organs (CVOs) with an epithelium-based structure similar to the CP may also provide a gate for leukocyte trafficking to the CNS [36,100]. Overall, this hypothesis is supported by the fact that the distinction between 'endothelial barriers' and 'epithelial gates' can also be observed at the borders of other immune-privileged organs [36]. Advances in research tools, especially the development of *in vivo* live imaging that would enable long-term observation of the brain borders, will be necessary to further address this question in the future.

frequently found adjacent to antigen-presenting cells (APCs) [29,30] (Figure 1). Sequencing of the CP $CD4^+$ T cell receptor (TCR) repertoire revealed significant enrichment of CNS-specific clones [29] associated with 'protective autoimmunity' (Box 2) [19]. These findings suggest there is ongoing presentation of CNS-derived antigens and continuous stimulation of the local T_{EM}