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Immune interactions at the blood–brain barrier

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The blood-brain barrier (BBB) is constituted by the cerebral microvascular endothelium which is characterized by the presence of a continuous network of complex tight junctions, lack of fenestrations and vesicular transcytosis, expression of asymetric transport systems and specific enzymes. Under the control of surrounding astrocytes, the cerebral endothelium selectively and efficiently limits the exchanges between blood and brain of soluble substances such as hormones, growth factors, or immune mediators, as well as cells of the immune system. On the basis of the existence of the BBB, the central nervous system (CNS) has often been considered as an 'immunologically privileged organ', not normally accessible to leukocyte traffic. However, we know now that activated T cells can adhere to the cerebral endothelium and enter the brain during demyelinating diseases and it has been proposed that HIV-1 might gain entry into brain tissue by infiltration of infected monocytes.

A complex communication network likely appears in brain between infiltrated leukocytes and CNS cells in the course of neuropathological disorders like Multiple Sclerosis or HIV-1 encephalitis. Cerebral endothelial cells, when activated by inflammatory mediators, appear to be actively involved in the process of leukocyte infiltration into the brain by expressing adhesion molecules (E-selectin, vascular and intercellular adhesion molecules: VCAM-1 and ICAM-1, respectively) and secreting a number of cytokines, chemokines and vasoactive factors. Microglia and brain macrophages, in addition to the fact that they constitute the major site of productive viral replication during HIV-1 encephalitis, more generally speaking play a central role in the neuropathological manifestations of inflammatory and infectious diseases of the CNS: this is due to their strong capacity of secretion of a variety of factors, such as TNF-α, platelet-activating factor, nitric oxide or eicosanoids, which affect both BBB permeability or integrity and neuronal survival. Astrocytes, which generally play a neuroprotective role by maintaining cerebral homeostasis, appear to modulate the secretory activity of brain macrophages and constitute themselves a major source of inflammatory cytokines. Moreover, astrocytes and microglial cells can express major histocompatibility complex and adhesion molecules and thus contribute to the immune activation of infiltrated leukocytes. Finally, even neurons may have the capacity to produce cytokines such as IL-1α and TNF-α and directly interact with infiltrated leukocytes through the expression of adhesion molecules.

In conclusion, the evolution of an inflammatory or infectious process in the CNS may depend on the balance between positive and negative immunoregulatory roles played by the different resident cell types, in interaction with infiltrated leukocytes. Unraveling of the molecular mechanisms involved in these interactions should provide new therapeutic strategies for neuropathological diseases.