**SELECTED CIRCULATING IMMUNE CELLS PART OF THE FUNCTIONING BRAIN AND LINKS PHYSIOLOGY TO PATHOLOGY**

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For decades, the central nervous system (CNS) was viewed as an autonomous unit preserved behind a wall, and shielded from immune cells and from pathogens present in the circulation. Based on extensive experimental evidence, we propose that the central nervous system (CNS) is critically dependent on circulating immune cell support (by self-reactive T cells and monocytes) for its normal functioning and repair. Breakdown of the dialogue between the brain and circulating immune cells may occur at any level, starting from the immune cell composition in the circulation, the nature and the number of immune cells recruited cells to the borders of the CNS, the phenotypes acquired by the recruited cells, and their location and time of arrival within the CNS territory; defects in these processes can impact cognitive performance, resilience to stress, emergence of developmental neuropsychological disorders, onset and progression of neurodegenerative diseases, and repair following acute injury. This concept unifies our understanding of the role of immune cells in the healthy brain (as manifested by their function in neurogenesis, expression of brain-derived neurotrophic factors, expression of growth factors and synapse-associated proteins) and explains their role in 'protective autoimmunity'. The dialogue between the CNS tissue and the circulating immune cells may occur in different immunological compartments, a finding that calls for re-definition of the brain as an immune privileged site, and suggests a common pathway potentially amenable to immune-based interventions in supporting recovery from injury, and coping with stress, depression, aging or neurodegenerative conditions.