Emerging new understanding of brain immune surveillance in combating neurodegenerative diseases

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Immunosureveilence is needed for supporting brain repair and functional plasticity. It involves the microglia, the brain resident immune myeloid cells, circulating and monocytes and CD4+ T cells. The blood-cerebrospinal fluid-barrier (BCSFB), namely the choroid plexus epithelium (CP) was identified as an immune-brain interface, and as a gate that "ticketing" the leukocytes to allow their entry to the CNS. In analyzing how the activity of this interface determines the fate of the brain, we discovered by immunogenomic and by immunohistochemistry that in aging and in Alzheimer's disease (AD) mouse this interface is suppressed with respect to its ability to allow communication between the brain and the circulating leukocytes. We further found that by transiently reducing systemic immune suppression, increased IFN-γ availability at the CP, thereby activated the CP to express trafficking molecules, and in turn led to recruitment of immune regulatory cells to sites of brain pathology. Immune activation could be achieved by blocking inhibitory immune checkpoints, regulatory pathways which maintain systemic immune homeostasis and tolerance. Among such inhibitory checkpoints, PD-1/PD-L1 pathway has been tested. Antibodies directed to this pathway, in several mouse models of AD, was found to be effective in reversing cognitive loss, restoring immunological brain homeostasis as determined by the inflammatory molecular profile, and reduced disease pathology. Our emerging new understanding on the fate of microglia in AD, suggest that microglial are also kept under tightr regulation by brain checkpoint mechanisms, manipulation of which could be an additional target.