Harnessing systemic immunity to help the mind: The potential of immune checkpoint blockade for fighting against Alzheimer's disease

Abstract:

Although the brain was considered an autonomous tissue that performs optimally without any assistance from the immune system, it is now widely accepted, in great part through our work, that circulating monocytes and CD4+ T cells are needed to support brain repair and functional plasticity. Over the years, we demonstrated that brain’s supporting leukocytes can gain access to the brain’s territory through a unique interface located between the blood cerebrospinal fluid (CSF) and the blood vessels, remote from the brain parenchyma. This barrier, the choroid plexus epithelium (CP), forms the blood-CSF- barrier, and serves as a gate controlling leukocyte entry to the CNS. In analyzing how the activity of this interface determines the fate of the brain, we discovered using immunogenomics and immunohistochemistry, that in aging and in mouse models of Alzheimer’s disease (AD) this interface is suppressed with respect to its ability to allow communication between the brain and the circulating leukocytes. We found that transiently reducing systemic immune suppression activated the CP to express trafficking molecules, and in turn led to recruitment of immune regulatory cells to sites of brain pathology. Lifting of suppression could be achieved by blocking inhibitory immune checkpoints, regulatory pathways that maintain systemic immune homeostasis and tolerance. Among such inhibitory immune checkpoints is the PD-1/PD-L1 receptor/ligand.
pair. We found that treatment with anti-PD-1 antibodies was effective in reversing cognitive loss, in removal of plaques, and in restoring brain homeostasis in several mouse models of AD. Such an approach is not meant to be directed against any single disease-escalating factor in AD, but rather, empowers the immune system to drive the process of repair, which comprehensive addresses numerous factors that go awry in this disease.

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