The potential of immune checkpoint blockade for fighting against Alzheimer's disease

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Although the brain has been considered as an autonomous tissue that performs best without any assistance from the immune system, it is now widely accepted, much through our work, that circulating monocytes and CD4+ T cells are needed for supporting brain repair and functional plasticity. Over the years we demonstrated that brain's supporting leukocytes can get access to the brain territory through a unique interface located between the blood cerebrospinal fluid (CSF) and the blood vessels, remotely from the brain parenchyma, the epithelial layer that forms the blood-CSF-barrier, namely the choroid plexus epithelium (CP). This barrier serves as a gate that "ticketing" the leukocytes to allow their entry to the CNS, and its activity is controlled by its cytokine milieu, and specifically IFN-γ. 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, as opposed to the attempts that have been made over the years to use immunosuppressive drugs in AD, increased IFN-g 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. Immunosuppression could be achieved by blocking inhibitory immune checkpoints, regulatory pathways which maintain systemic immune homeostasis and tolerance. Among such inhibitory checkpoints is the PD-1/PD-L1. Using anti-PD-1 antibodies in several mouse models of AD was found to be effective in reversing cognitive loss, in removal of plaques, and in restoring brain homeostasis as determined by the inflammatory molecular profile. Such an approach is not meant to be directed against any disease-escalating factor in AD, but rather it empowers the immune system of the individual to drive the process of repair. Such an approach by directly targeting the immune system, rather than single disease risk factor in the brain, provides a comprehensive therapy that addresses numerous factors that go awry in the brain.