Original article

Potential immunotherapy for Alzheimer disease and age-related dementia

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Emerging results support the concept that Alzheimer disease (AD) and age-related dementia are affected by the ability of the immune system to contain the brain's pathology. Accordingly, well-controlled boosting, rather than suppression of systemic immunity, has been suggested as a new approach to modify disease pathology without directly targeting any of the brain's disease hallmarks. Here, we provide a short review of the mechanisms orchestrating the cross-talk between the brain and the immune system. We then discuss how immune checkpoint blockade directed against the PD-1/PD-L1 pathways could be developed as an immunotherapeutic approach to combat this disease using a regimen that will address the needs to combat AD.

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Introduction

Alzheimer disease (AD) is a devastating age-related neurodegenerative disorder, and the most frequent cause of senile dementia.[1] The appearance of cognitive decline is associated with accumulation of misfolded proteins, as well as the presence of several additional toxic agents.[2] Among the common neuropathological features found in AD are synaptic and neuronal loss, intracellular neurofibrillary tangles, elevated levels of the toxic form of amyloid beta (Aβ),[1-42] and the accumulation of extracellular senile plaques containing misfolded Aβ peptide.[2-4] Local inflammatory responses as well as uncontrolled astrocyte reactivity are often observed in the brains of AD patients and in animal models; these processes are not necessarily the primary causes of the disease, but are considered to be key factors in disease progression and escalation.[5-7] The accumulated misfolded proteins and the neuroinflammatory response have led to numerous attempts over the years to arrest disease progression, either using treatments that are directed against the misfolded proteins to arrest plaque burden,[8,9] or using systemic anti-inflammatory drugs to arrest the brain inflammation. Inconsistent and even conflicting results were obtained, and none of the drugs tested thus far have proven effective in reversing or arresting cognitive loss in patients.[10-16]

The failure of treatments directed at Aβ to arrest or reverse cognitive loss could reflect the fact that by the time Aβ plaque burden is high, removal of plaques, while still important, may be insufficient to modify disease because numerous collateral disease-escalating factors enter into a vicious cycle and continue even after the plaques are removed. Such factors might include immune-related molecules and cells. In apparent support of such a view are, recent results demonstrating that resolution of inflammation is an active mechanism mediated by recruitment of circulating immune cells to sites of brain pathology.[17-19]

Here, we will discuss the role of brain immune communication in brain homeostasis and repair. In addition, we will discuss if and how activating the immune system by immune checkpoint blockade can contribute to disease modification.

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Systemic leukocytes are essential players in central nervous system repair

For decades, it was commonly assumed that the brain is unable to tolerate immune cell entry, mainly due to the belief that it is a tissue behind barriers, and considered an immune privileged site.[20] In animal models of acute central nervous system (CNS) injuries, both monocyte-derived macrophages and $CD4^+$ T cells recognizing brain antigens, are needed for coping with and helping heal parenchymal damage.[21-28] Moreover, T cells present in the periphery facilitate recruitment of monocyte-derived macrophages to the CNS. Such macrophages play a role in supporting neuronal survival and axonal regrowth, by resolving the local inflammatory response and facilitating local scar removal.[25-27,29-32] Additional studies revealed that systemic T cells not only participate in CNS repair, but are also needed for life-long brain plasticity.[33-35]

Independent attempts were made to understand how T cells support healthy brain plasticity while they are excluded from the brain parenchyma, how they facilitate recruitment of monocyte-derived macrophages, and how such monocytes can gain access to the CNS without breaching the blood-brain-barrier (BBB). Such attempts have suggested that the brain's barriers, including the meningeal barrier[36,37] and the blood-cerebrospinal fluid barrier (BCSFB) can serve as a key compartment for immune-brain crosstalk in health and disease.[19,38,39] The BCSFB, which is comprised of the tightly connected choroid plexus (CP) epithelial cells,[40-43] along with the accumulated evidence that immune cells are needed for brain maintenance and repair, led us to suggest that the CP is a physiological gateway that enables selective immune cell access, depending on the needs of the CNS.[19,38]

The paradoxical fate of the "leukocyte gate" to the brain in Alzheimer disease models

Several independent studies in animal models have shown that recruitment of circulating monocyte-derived macrophages,[44-52] possibly together with additional immunoregulatory leukocytes, can modify AD pathology.[31,53,54] Such cells can help remove misfolded protein including Aβ-plaques,[48,55,56] balance the local inflammatory milieu,[46,47,57] reduce gliosis,[58] and protect synaptic structures.[46,57,59]

Analyzing the fate of the CP with respect to its ability to support leukocyte trafficking revealed that its activity is impaired in animal models of brain aging and AD.[60,61] It was further discovered that reducing systemic immune suppression in AD animal models, by transiently depleting peripheral $Foxp3^+$ regulatory T cells has a beneficial effect in mitigating disease pathology.[62] These results are consistent with an independent observation, showing that the adaptive immune system plays an important role in the progression of AD in animal models. For example, it was demonstrated that genetic ablation of B, T, and natural killer cells in the 5xFAD mouse model by crossing these mice with Rag2/Il2rc double knockout animals (Rag-5xFAD), resulted in increased plaque load and increased soluble Aβ levels.[63]

> AD is a devastating age-related neurodegenerative disorder, and the most frequent cause of senile dementia

Importantly, immunoregulatory T cells and anti-inflammatory cells are needed in the brain as a source of anti-inflammatory cytokines for reducing the inflammatory response. Homing of such immunomodulating cells requires well-controlled boosting, rather than suppression of systemic immunity. Accordingly, special care must be taken when viewing immunosuppressive cells (such as FoxP3) as uniformly beneficial or harmful in neurodegenerative diseases, without considering their localization and kinetics.

Taken together, the results summarized above created the basis for our approach of empowering the systemic immune system, by transiently blocking inhibitory immune checkpoints, to drive a cascade of immune events that starts outside the brain, induces activation of the CP, and culminates in immune-dependent brain repair processes.[61,64]

Immune checkpoint blockade for mitigating Alzheimer disease pathology

Inhibitory immune checkpoints restrain the activity of memory T cells, mainly those directed against self-compounds, to avoid autoimmune diseases. Among such checkpoints are the programmed cell death protein 1

(PD-1), a member of the B7-CD28 family, expressed by a variety of activated effector memory immune cells, including CD4+ T cells.[65] The PD-1 ligand is expressed by dendritic cells and regulatory T cells,[66] as well as by non-immune cells such as endothelial and epithelial cells,[67,68] and astrocytes.[66] The interaction between PD-1 and PD-L1 suppresses memory T-cell responses, including proliferation, and cytokine production.[65,69] Blocking the PD-L1/PD-1 pathway potentially results in an increase in T cell activation.[70-72] Based on our new understanding, we envisioned that targeting systemic PD-1/PD-L1 might be a way to activate such a protective/reparative immune response.

Our studies using anti-PD-1 or anti-PD-L1 antibody in the 5xFAD mouse model of AD, as well as in a dementia model of tau pathology, revealed that such treatments are effective in helping and even reversing cognitive impairments and reducing disease pathology. This process was associated with monocyte-derived macrophages homing to the brain.[61,62] These macrophages locally express numerous molecules including scavenger receptors for removal of dead cells as well as misfolded or aggregated proteins, anti-inflammatory cytokines, and growth factors.[61,64]

Importantly, a single injection of antibody directed against either PD-1 or PD-L1 initiated a chain of events that started outside the brain, and led to alterations in several processes within the brain that together resulted in disease modification.[64]

Notably, in most mouse models of AD, disease symptoms begin earlier in females than in males. In humans there is no clear scientific consensus regarding gender differences in AD, though most studies have shown that men and women exhibit differences in the development and progression of the disease.[73] Generally, women are considered at greater risk and show more rapid progression.[74] Notably, both female and male mice of tau-driven models of dementia and amyloid β-driven pathology similarly responded to treatment with immune checkpoint blockade directed to PD-1 or PD-L1.[64]

Conclusion

In conclusion, results from animal studies suggest that treatment with PD-1/PD-L1 blockade evokes a series of immunological events that start outside the brain, and, in synergy with inflammatory signals emerging from the diseased brain, restore the immunological communication between the brain and the immune system.[75] The resulting modification of the immunological milieu of the brain culminates in reduction of cognitive deficits and disease pathological manifestations. The treatment protocol going forward to clinical trials will require intermittent administration of the antibody. Such a protocol is likely to reduce adverse immunological effects. Moreover, since the treatment is not directed against a single factor within the brain that contributes to disease escalation, but rather affects common immunological pathways, it is expected to have a higher efficacy than past attempts, and to overcome disease heterogeneity and some translational obstacles. ■

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