Potential immunotherapy for Alzheimer disease and age-related dementia

Michal Schwartz, PhD; Michal Arad, PhD; Hila Ben-Yehuda, PhD

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 mechanism 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.

Keywords: Alzheimer disease; immune checkpoint; immunotherapy; macrophage; microglia

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),1-4 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.17-21

Here, we will discuss the role of the immune system in modulating disease. In addition, we will discuss if and how activating the immune system by immune checkpoint blockade can contribute to disease modification.
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. 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. 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. Additional studies revealed that systemic T cells not only participate in CNS repair, but are also needed for life-long brain plasticity.

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 and the blood-cerebrospinal fluid barrier (BCSFB) can serve as a key compartment for immune-brain crosstalk in health and disease. The BCSFB, which is comprised of the tightly connected choroid plexus (CP) epithelial cells, 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.

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, possibly together with additional immunoregulatory leukocytes, can modify AD pathology. Such cells can help remove misfolded protein including Aβ-plaques, balance the local inflammatory milieu, reduce gliosis, and protect synaptic structures.

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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), the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and the lymphocyte activation gene 3 (LAG-3). Inhibitory immune checkpoints are expressed on the surface of activated T cells and are engaged by their cognate ligands on the surface of antigen-presenting cells (APCs). This engagement leads to the inhibition of T cell proliferation and cytokine production, resulting in the suppression of immune responses. However, this suppression can be detrimental in the context of autoimmunity or cancer, where activated T cells need to be activated to fight off pathogens or tumor cells. Therefore, the manipulation of inhibitory immune checkpoints is a promising strategy for the treatment of autoimmune diseases and cancer.

Immune checkpoint blockade for mitigating Alzheimer disease pathology

Inhibitory immune checkpoints are crucial for the maintenance of immune homeostasis, but their dysregulation can lead to the pathogenesis of various diseases, including Alzheimer disease (AD). AD is a neurodegenerative disorder characterized by the accumulation of amyloid-β (Aβ) plaques and tau protein neurofibrillary tangles in the brain. The mainstay of current treatment is aimed at symptomatic relief and disease modification, but there is a pressing need for effective therapeutic strategies that can halt or reverse the disease process. Immune checkpoint blockade is a novel therapeutic approach that has shown promising results in preclinical and clinical studies. Immune checkpoint blockade targets the molecules expressed on the surface of immune cells that control their activation and function, such as PD-1, CTLA-4, and LAG-3, and prevents their engagement with their ligands. This leads to the reactivation of immune cells and enhanced immune responses against self-antigens and pathogens. Preclinical studies have shown that immune checkpoint blockade can improve neuroinflammation and cognitive function in AD models, suggesting that this approach may hold promise for the treatment of AD.

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. The results also suggest that immunosuppressive cells (such as FoxP3) must be used with caution, as their localization and kinetics play a critical role in the progression of AD.

Importantly, immunoregulatory T cells and anti-inflammatoryst 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.

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(PD-1), a member of the B7-CD28 family, expressed by a variety of activated effector memory immune cells, including CD4+ T cells. The PD-1 ligand is expressed by dendritic cells and regulatory T cells, as well as by non-immune cells such as endothelial and epithelial cells, and astrocytes. The interaction between PD-1 and PD-L1 suppresses memory T-cell responses, including proliferation, and cytokine production. Blocking the PD-L1/PD-1 pathway potentially results in an increase in T cell activation. 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. 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.

Notably, a single injection of antibody directed against either PD-1 or PD-L1 initiated a chain of events that started outside the brain, and, in synergy with inflammatory signals emerging from the diseased brain, restore the immune unlogical com munication between the brain and the immune system. The resulting modification of the immune 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.

Conclusion

In conclusion, results from animal studies suggest that treatment with PD-1/PD-L1 blockade evokes a series of immune events that start outside the brain, and, in synergy with inflammatory signals emerging from the diseased brain, restore the immune communication between the brain and the immune system. The resulting modification of the immune 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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References

1. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer’s disease. Lancet. 2011;377:1019-1031.
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science. 2002;297:353-356.
3. Glenner GG, Wong CW, Quaranta V, Eanes ED. The amyloid deposits in Alzheimer’s disease: their nature and pathogenesis. 1984; Appl Pathol 2:557-369.
4. Price DL, Whitehouse PJ, Struble RG. Alzheimer’s disease. Annu Rev Med. 1985;36:349-356.
5. Akiyama H, Barger S, Barnum S, et al. Inflammation and Alzheimer’s disease. Neurobiol Aging. 2000;21:383-421.
6. Wyss-Coray T. Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med. 2006;12:1005-1015.
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7. Wyss-Coray T, Mucke L. Inflammation in neurodegenerative disease—a double-edged sword. Neuron. 2002;35:419-432.
8. Schenk D, Barbour R, Dunn W, et al. Immuno-ination with amyloid-beta attenuates Alzheimer’s disease-like pathology in the PDAPP mouse. Nature. 1999;400:173-177.
9. Weiner HL, Lem et al. Maron R, et al. Nasal administration of amyloid-beta peptide decreases cerebral amyloid burden in a mouse model of Alzheimer’s disease. Ann Neurol. 2000;48:567-579.
10. Group AR, Martin BK, Szekely C, et al. Cognitive function over time in the Alzheimer’s disease-Animal model. J Neurosci. 2001;11:108-109.
11. Mocellin M, Leibowitz-Am it R, Yoles E, Mor F, Cohen IR, Schwartz M. Autoimmune T cells protect neurons from secondary degeneration after central nervous system atrophy. Nat Med. 1999;5:49-55.
12. Zhao W, Xie W, Xiao Q, Beers DR, Appel SH. Protective effects of an anti-inflammatory drug on monocytes and microglia in Alzheimer’s disease. J Neuroimmunol. 2006;99:1176-1187.
13. Shechter R, London A, Varol C, et al. Infiltrating brain cells play an anti-inflammatory role in recovery from spinal cord injury in mice. PLoS Med. 2009;6:e1000113.
14. London A, Itskovich E, Benhar I, et al. Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. J Exp Med. 2011;210:23-39.
15. Benowitz LL, Popovich PG. Inflammation: a pivotal resolution phase in spinal cord repair. PLoS One. 2011;6:e27969.
16. Cohen M, Matcovitch O, David E, et al. Chronic exposure to TGFbeta1 regulates myelin self-antigen presents to complete paralysis while avoiding autoimmune disease. J Clin Invest. 2001;108:591-599.
17. Moalem G, Leibowitz-Am it R, Yoles E, Mor F, Cohen IR, Schwartz M. Autoimmune T cells protect neurons from secondary degeneration after central nervous system atrophy. Nat Med. 1999;5:49-55.
18. Zhao W, Xie W, Xiao Q, Beers DR, Appel SH. Protective effects of an anti-inflammatory drug on monocytes and microglia in Alzheimer’s disease. J Neuroimmunol. 2006;99:1176-1187.
19. Shechter R, London A, Varol C, et al. Infiltrating brain cells play an anti-inflammatory role in recovery from spinal cord injury in mice. PLoS Med. 2009;6:e1000113.
20. London A, Itskovich E, Benhar I, et al. Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. J Exp Med. 2011;210:23-39.
21. Benowitz LL, Popovich PG. Inflammation: a pivotal resolution phase in spinal cord repair. PLoS One. 2011;6:e27969.
22. Cohen M, Matcovitch O, David E, et al. Chronic exposure to TGFbeta1 regulates myelin self-antigen presents to complete paralysis while avoiding autoimmune disease. J Clin Invest. 2001;108:591-599.
23. Moalem G, Leibowitz-Am it R, Yoles E, Mor F, Cohen IR, Schwartz M. Autoimmune T cells protect neurons from secondary degeneration after central nervous system atrophy. Nat Med. 1999;5:49-55.
24. Zhao W, Xie W, Xiao Q, Beers DR, Appel SH. Protective effects of an anti-inflammatory drug on monocytes and microglia in Alzheimer’s disease. J Neuroimmunol. 2006;99:1176-1187.
25. Shechter R, London A, Varol C, et al. Infiltrating brain cells play an anti-inflammatory role in recovery from spinal cord injury in mice. PLoS Med. 2009;6:e1000113.
26. London A, Itskovich E, Benhar I, et al. Neuroprotection and progenitor cell renewal in the injured adult murine retina requires healing monocyte-derived macrophages. J Exp Med. 2011;210:23-39.
27. Benowitz LL, Popovich PG. Inflammation: a pivotal resolution phase in spinal cord repair. PLoS One. 2011;6:e27969.
28. Cohen M, Matcovitch O, David E, et al. Chronic exposure to TGFbeta1 regulates myelin self-antigen presents to complete paralysis while avoiding autoimmune disease. J Clin Invest. 2001;108:591-599.
homeostatic process for replacing CNS myeloid cells. *Proc Natl Acad Sci U S A.* 2012;109:18150-18155.

52. El Khoury J, Toft M, Hickman SE, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer’s disease. *Nat Med.* 2007;13:432-438.

53. Beers DR, Henkel JS, Zhao W, Wang J, Appel SH. CD4+ T cells support glial neuroprotection, slow disease progression, and modify glial morphology in an animal model of inherited ALS. *Proc Natl Acad Sci USA.* 2008;105:15558-15563.

54. Kunis G, Baruch K, Miller O, Schwartz M. Immunization with a myelin-derived antigen activates the brain’s choroid plexus for recruitment of immunoregulatory cells to the CNS and attenuates disease progression in a mouse model of ALS. *J Neurosci.* 2015;35:6381-6393.

55. Wisniewski HM, Barcikowska M, Kida E. Phagocytosis of beta/A4 amyloid fibrils of ALS. *PLoS One.* 2008;105:15558-15563.

56. Baruch K, Deczkowska A, Rosenzweig N, et al. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. *Science.* 2014;346:89-93.

57. Baruch K, Deczkowska A, Rosenzweig N, et al. PD-1 in m one checkpoint blockade reduces pathology and improves memory in m ouse m odels of Alzheimer’s e r’s disease. *Nat Commun.* 2016;22:135-137.

58. Baruch K, Rosenzweig N, Kertser A, et al. Breaking immune tolerance by targeting Foxp3 regulatory T cells mitigates Alzheimer’s disease pathology. *Nat Commun.* 2015;6:7967.

59. Marsh SE, Abud EM, Lakatos A, et al. The adaptive immune system restrains Alzheimer’s disease pathogenesis by modulating microglial function. *Proc Natl Acad Sci USA.* 2016;113:E1316-1325.

60. Rosenzweig N, Dvir-Sternfeld R, Tsitsov-Kamil e, et al. PD-1/PD-L1 checkpoint blockade harnesses monocyte-derived macrophages to combat cognitive impairment in a mouse model of Alzheimer’s disease. *Proc Natl Acad Sci U S A.* 2019;116:1185-1192.

61. Baruch K, Deczkowska A, David E, et al. The programmed death-1 (PD-1) pathway regulates autoimmunity in nonobese diabetic (NOD) mice. *J Exp Med.* 2013;198:63-69.

62. Yang W, Li H, Chen PW, et al. PD-L1 expression on human ocular cells and its possible role in regulating im mune m ediated s econdary infl amm ation m ation. *Invest Ophthalmol Vis Sci.* 2009;50:273-280.

63. Carter L, Fouser LA, Jussif J, et al. PD-1/PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. *Eur J Immunol.* 2002;32:634-643.

64. Freem an G, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med.* 2002;192:1027-1034.

65. Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. *Nat Immunol.* 2009;10:1185-1192.

66. El Khoury J, Toft M, Hickman SE, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer’s disease. *Nat Med.* 2007;13:432-438.

67. Ansari MJ, Salama AD, Chitnis T, et al. The programmed death-1 (PD-1) pathway regulates autoreactive m one diabetes in nonobese diabetic (NOD) mice. *J Exp Med.* 2013;198:63-69.

68. Yang W, Li H, Chen PW, et al. PD-L1 expression on human ocular cells and its possible role in regulating immune-mediated secondary inflammation. *Invest Ophthalmol Vis Sci.* 2009;50:273-280.

69. Carter L, Fouser LA, Jussif J, et al. PD-1/PD-L inhibitory pathway affects both CD4+ and CD8+ T cells and is overcome by IL-2. *Eur J Immunol.* 2002;32:634-643.

70. Freem an G, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med.* 2002;192:1027-1034.

71. Fife BT, Pauken KE, Eagar TN, et al. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal. *Nat Immunol.* 2009;10:1185-1192.

72. Karwacz K, Bricogne C, MacDonald D, Arce F, Bennett CL, Collins M, Escors D. PD-L1 co-stimulation contributes to ligand-induced T cell receptor down-modulation on CD8+ T cells. *EMBO Mol Med.* 2011;3:581-592.

73. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer’s disease: assessing sex and gender differences. *Clin Epidemiol.* 2014;6:37-48.

74. Alzheimers D. 2013 Alzheimer’s disease facts and figures. *Alzheimers Dement.* 2013;9:208-245.

75. Deczkowska A, Schwartz M. Targeting neuro-immune communication in neurodegeneration: Challenges and opportunities. *J Exp Med.* 2018;215:2702-2704.