



Commentary: CD22 blockade restores homeostatic microglial phagocytosis in ageing brains

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A Commentary on

CD22 blockade restores homeostatic microglial phagocytosis in ageing brains

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Recently, a ground-breaking study on microglia being a potential target for immunotherapy in neurodegenerative diseases was reported in *Nature* (1). Pluvinage et al. combined CRISPR–Cas9 knockout screens with RNA sequencing analysis to identify approximately 3,000 genes. They finally discovered that CD22, a canonical receptor typically expressed on B-cells (2), was significantly upregulated in microglia of the central nervous system (CNS) of an aged mouse, and approximately three times more in aged microglia than young microglia. Interestingly, the authors showed that CD22 was a negative regulator of microglial phagocytosis, and blocking CD22 in CNS either by specific antibody or by genetic ablation promoted the clearance of extracellular oligomeric amyloid- β [A β , neuropathological hallmark of Alzheimer's disease (AD)] and α -synuclein fibrils (pathological hallmark of Parkinson's disease) *in vivo*, and improved hippocampal-dependent learning and memory performance. Furthermore, they found that the mechanism underlying microglial CD22-blocking-mediated neuroprotection may involve an increase in the number of hippocampal dentate granule neurons expressing c-FOS and phospho-cAMP response element-binding protein. The research represents a breakthrough in the field of treatment for neurodegenerative diseases. The immunotherapy conducted by microglial CD22 may be a potential therapeutic strategy to restore and improve age-related cognitive impairment.

Perioperative neurocognitive disorder, an age-related neurodegenerative disease, is a highly prevalent condition with significant effects on the prognosis of elderly individuals undergoing anesthesia and surgery, including acute post-operative delirium and long-lasting post-operative cognitive dysfunction (POCD) (3, 4). The incidence of POCD was reportedly between 25 and 40% among elderly patients at the point of discharge, and it could lead to a significantly higher mortality rate (5). The exact mechanism of POCD remains elusive and there is no agreement on the efficiency of current treatments such as anti-inflammatory, antioxidant and neuroprotective agents (6). A β and phosphorylation of tau protein, secondary to anesthesia and surgery, are believed to be pathological hallmarks of POCD (7). Normal microglia engulf and degrade A β and tau protein by

phagocytosis; however, the change in engulfment of microglia is associated with age and the aged microglia become more proinflammatory and less phagocytic (1, 8). Therefore, we speculated that the age-related deterioration of microglial phagocytosis could be the potential mechanism underlying POCD. Immunotherapy mediated by the restoration of microglial phagocytosis could provide a new path in preventing and treating POCD.

Immunotherapy induced by selective blockade of some immune checkpoints, such as PD-1/PD-L1, is commonly utilized to mobilize the immune system against a variety of malignancies (9). Research examining the use of immunotherapy in neurodegenerative diseases, such as AD and POCD, seems promising but appears relatively under-developed as a field. A ground-breaking report in *Nature Medicine* in 2015 showed that the PD-1 pathway blockade evoked an interferon- γ -associated systemic immune response, induced CNS recruitment of myeloid cell, and restrained accumulation of cerebral A β , which contributed to improvement of cognitive performance in heterozygous 5XFAD transgenic mouse models of AD (10). A recent study has also demonstrated that immune checkpoint blockade targeting the PD-1/PD-L1 pathway resulted in increased immunomodulatory monocyte-derived macrophages within the brain parenchyma and combated cognitive impairment in mouse models of both AD and tauopathy (11). However, the available evidence is inconsistent. Gomez-Nicol et al. observed no apparent impact of PD-1 deficiency on murine prion disease (ME7 strain). On the contrary, they found a slight exacerbation of the cognitive performance of ME7 mice upon PD-1 deficiency (12). The conflicting findings may attribute to different animal models presenting neurodegenerative diseases. Another potential reason could be non-specific expression of PD-1 on immune cells in the aged mouse, which is widely expressed in dendritic cells, B-cells, activated T-cells (both CD4+ and CD8+), and natural killer cells (9). The CD22 blockade appears to be more promising

than PD-1/PD-L1 blockade, and may exhibit better efficiency and lesser side effects as a therapeutic strategy in neurodegenerative diseases. Although CD22 is typically expressed in B-cells, it is specifically upregulated in aged microglia (1). Pluvinage et al. observed that blocking CD22 specifically in the CNS via cerebral injection, rather than blocking CD22 systemically via intraperitoneal injection, contributed to cognitive improvement in aged mice that showed that peripheral B-cells did not mediate neuroprotective effect of anti-CD22 treatment (1). Moreover, pro-phagocytic effect of anti-CD22 treatment was mainly mediated by resident microglia and not the infiltrating peripheral macrophages (13). Furthermore, the upregulated CD22 expression in microglia depends on age. The study showed that aged microglia increased the number of CD22 surface molecules approximately three times more than young microglia, and CD22 blockade treatment had effects that were more significant in the CNS of the aged mouse than that of the younger mouse (1). Above all, aged microglia specifically expressing CD22 in CNS could be a potential and viable molecular target in neurodegenerative diseases, especially for AD and POCD. However, the effect of anti-CD22 treatment on age-related diseases needs to further studies involving different animal models.

AUTHOR CONTRIBUTIONS

PW drafted the manuscript. JL revised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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