Clinical Interventions in Aging

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LETTER

PD-1 immune checkpoint blockade may be viable for the prevention and treatment of elderly patients with POCD [Letter]

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Dear Editor

Recently, we read with great interest the well-written review article published in the November 8, 2018 edition of the *Clinical Interventions in Aging* by Kotekar and colleagues titled "Postoperative cognitive dysfunction – current preventive strategies".[1] The article elegantly addressed the current preventive strategies for postoperative cognitive dysfunction (POCD). The authors concluded that the best preventive strategies for POCD may involve early recognition and management of potential perioperative risk factors, such as intraoperative anesthetic monitoring of the depth of anesthesia, Enhanced Recovery After Surgery and a multidisciplinary collaboration. Furthermore, the authors proposed that pharmacological interventions may be effective preventative and therapeutic strategies to attenuate POCD. We appreciate the efforts of the authors and would like to present our opinion on the review.

POCD is a highly prevalent condition with significant impact on the prognosis of elderly patients undergoing an operation, experiencing problems with memory, concentration, information processing, language comprehension, and social integration that can last for months or may even be permanent. Chronic neuroinflammation and accompanying accumulation of amyloid-β (Aβ) and phosphorylation of tau protein secondary to surgery and anesthesia are strongly implicated in the pathophysiology of POCD.[2] The exact cascade by which surgical stress and anesthesia induce neuroinflammation in association with POCD remains unknown. Boosting degenerative systemic immune response in elderly patients may be a potential pharmacological strategy in treating POCD. Although previous studies have highlighted the role of the systemic immune response in inducing neuroinflammation, these results still did not show a significant association between systemic immune response and neuroinflammation.[3,4] A famous study revealed that surgery-induced neuroinflammation was associated with infiltration of peripheral macrophages.[5] POCD is commonly observed in perioperative care in elderly patients; therefore, a limitation of this study is that they did not use aged mice as an experimental animal model of POCD.[2] Furthermore, elderly individuals more frequently present a degenerative systemic immune system and resident microglial priming in the aging brain, rather than the migration of peripheral macrophages, may have an important role in cognitive deficits after surgery.[6] Normal microglia respond to and degrade Aβ by phagocytosis; however, primed microglia become more proinflammatory and less phagocytic.[7] Current anti-

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inflammatory and immunosuppressive agents have demonstrated neuroprotection in POCD animal models, but there is no agreement on the efficiency of these treatments in clinical practice.[2] Given that most anti-inflammatory and immunosuppressive agents, such as ibuprofen,[8] can readily penetrate the blood-brain barrier damaged by surgical stress or anesthesia, current studies have not confirmed that these agents exert neuroprotective effects directly by targeting the systemic rather than the central immune response. Given the above, the systemic immune response induced by surgical stress and anesthesia may be the compensatory mechanism that maintains the stability of the immune-microenvironment in CNS. We, therefore, suggest that in POCD, degenerative systemic immunity should be boosted in elderly patients to drive an immune-dependent cascade needed for injured neuron repair.

Adaptive immune cell populations play an important role in restraining the accumulation of Aβ and neuroinflammation.[7] Baruch et al[9] found that disrupting immune tolerance by targeting regulatory T (Treg) cells induced the accumulation of monocyte-derived macrophages and Treg cells at sites of CNS pathology as well as Aβ clearance, contributing to a reversal of cognitive decline. While considering immune checkpoints to be regulatory pathways for maintaining the homeostasis of the systemic immune system, they further showed that immune checkpoint blockade directed against the programmed death-1 (PD-1) pathway, thereby evoking an IFN-γ-associated systemic immune response and inducing CNS recruitment of myeloid cell, caused clearance of cerebral Aβ, and improved cognitive performance.[10] In contrast to the continuous or bolus administration of anti-inflammatory and immunosuppressive agents in previous studies, immunotherapy conducted by PD-1 may maintain long-lasting beneficial effects. We, therefore, hypothesize that immunotherapy may be a potential therapeutic strategy for POCD, and PD-1 immune checkpoint blockade may be viable for the prevention and treatment of elderly patients with POCD in the future.

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Disclosure

The authors report no conflicts of interest in this communication.

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