

COMMENTARY

Restricted CD4⁺ T cell receptor repertoire impairs cognitive function via alteration of Th2 cytokine levels

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ABSTRACT

Despite the effects of CD4⁺ T cell dysfunction on cognitive and behavioral impairment are well established, the effects of Th2 cytokines on the adult hippocampal neurogenesis and cognitive function in restricted CD4⁺ T cell receptor (TCR) repertoire model have not been fully elucidated. We found that mice with restricted CD4⁺ repertoire TCR showed decreased adult hippocampal neurogenesis using OT-II mice. Moreover, we demonstrated that OT-II mice showed increased Th2 cytokine levels in peripheral organs and IL-4 levels in brain. Taken together, altered Th2 cytokine levels may impact learning and memory via impaired adult neurogenesis in restricted CD4⁺ repertoire TCR mice.

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CD4⁺ T cells and their cytokines are well-known as the most important peripheral immune system. Especially, Th2 cytokines released from type-2 (Th2) CD4⁺ T cell response are more procognitive than the Th1 cytokines released from type-1 (Th1) CD4⁺ T cell response.^{1,2} With these cytokines, peripheral immune cells including CD4⁺ T cells are able to infiltrate into the central nervous system (CNS) across the rigid blood brain barrier (BBB) that isolates the peripheral immune system from CNS.³⁻⁶ Furthermore, the normal functions of peripheral immune cells are important for CNS function, notably learning and memory.^{2,6} Therefore, in experimental animal models with restricted T cell receptor (TCR) repertoire, impaired function of CD4⁺ T cells led to a significant cognitive dysfunction. Moreover, inhibition of CD4⁺ T cells depressed adult hippocampal neurogenesis and further, caused cognitive impairment.^{7,8}

Adult hippocampal neurogenesis has been recognized as a prerequisite for normal cognitive homeostasis, and neurogenesis in the dentate gyrus is critical for learning and memory.⁹ In addition, previous studies have reported that the cognitive function is highly related to the peripheral immune cells, and CD4⁺ T

cell, one of the major peripheral immune cells, may affect the cognitive function.^{1,6,10} Despite the underlying mechanism was not fully examined, it has been suggested that CD4⁺ T cell may play a crucial role in both neurogenesis and the declined memory observed in transgenic animal models with immunodeficiency or restricted CD4⁺ TCR repertoire.⁸ Moreover, accumulating evidences supported that Th2 cytokines released by CD4⁺ T cells are responsible for maintaining cognitive functions and adult hippocampal neurogenesis.^{6,7} Thus, in this study, we verified the effect of T cell dependent cytokines, especially Th2 cytokines, on cognition and its underlying mechanisms that need to be addressed clearly for the first time. In addition, we used an animal model with restricted CD4⁺ TCR repertoire to examine the physiological and behavioral changes under the effect.¹¹

Mostly, when the antigen presenting cells presents an antigen to T cells via major histocompatibility complex II on their surfaces, the immune system is triggered to start, and T cells get activated.¹² However, OT-II mice have restricted CD4⁺ TCR repertoire that needs ovalbumin for activation. That is, this nonself-antigen specific CD4⁺ TCR can only recognize

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ovalbumin as antigen and cannot be activated without it.¹³ Interestingly, the naïve CD4⁺ T cells in OT-II mice lacking prior exposure to ovalbumin showed considerably increased Th2 cytokine levels in the periphery and interleukin-4 (IL-4) level in the CNS. However, this can be accounted for by several supporting studies that OT-II mice showed 4-fold increased ratio in the CD4 to CD8 ratio,^{14,15} and Th2 cytokine response could be triggered by endogenous IL-4 from naïve CD4⁺ T cells.¹⁶⁻¹⁹ Furthermore, patients with higher ratio of CD4 to CD8 have increased IL-4 level in peripheral blood; the ratio of CD4 to CD8 is more significant factor for production of IL-4 cytokine than the absolute number of CD4⁺ T cells.²⁰

Based on our *in vivo* results and previous study suggesting the expression of IL-4 receptors (IL-4R α) in neurons,² it can be speculated that overexpression of IL-4 may reduce the proliferation of progenitor cells in hippocampal neurogenesis and impair cognitive functions. Moreover, we conducted *in vitro* CCK-8 analysis and confirmed the direct inhibiting effect of up-regulated IL-4 on proliferation of neural stem cells.

Using proliferating cell nuclear antigen (PCNA) immunoblotting, in part, we demonstrated that up-regulated IL-4 inhibits the adult hippocampal neurogenesis by alteration of S-phase in DNA replication. Though further *in vivo* studies on the effect of IL-4 on neurogenesis in dentate gyrus need to be confirmed, these examinations sufficiently support that IL-4 overexpression in OT-II mice reduces adult hippocampal neurogenesis and cognitive functions.

Among many biological roles of IL-4 including immune system, the cytokine has both beneficial and harmful effects on our cognitive functions at the same time. The previous studies have demonstrated beneficial effects of IL-4.^{1,2,21} However, disadvantageous aspects of IL-4 have also been reported. Increased IL-4 levels induced degeneration of hippocampal CA1 region²² and inhibited the proliferation of retinal progenitor cells in the CNS.²³ Moreover, IL-4 overexpression was shown in many experimental models of autoimmune disorders such as encephalomyelitis, anemia, glomerulonephritis and arthritis, and vice versa.²⁴⁻²⁷ Correspondingly, allergic immune

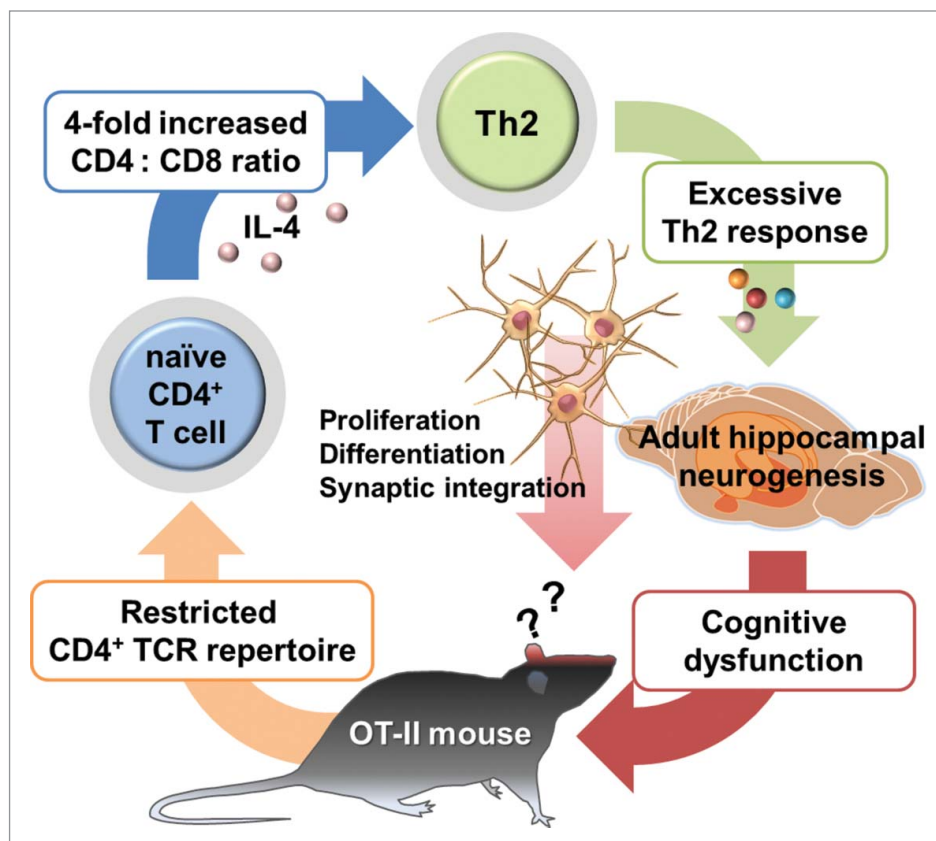


Figure 1. Proposed model of impaired cognitive function induced by alteration of Th2 cytokine levels. Mice with restricted CD4⁺ T cell receptor repertoire showed significant increased Th2 cytokine levels in peripheral and IL-4 in brain. Altered Th2 cytokine levels decrease the adult hippocampal neurogenesis as well as the cognitive function.

responses such as asthma are also associated with IL-4 level and further, affect cognitive function as risk factors.²⁸⁻³⁰ These studies demonstrate that the regulation of IL-4 expression is critical for managing the adaptive immune functions and CNS homeostasis. Furthermore, the level of IL-4 expression not only reduces adult hippocampal neurogenesis but down-regulates synaptic formation.

Taken together, the neurostructural mechanisms for impaired cognitive function in OT-II mice, an animal model with restricted CD4+ TCR repertoire, seemed to be down-regulated adult hippocampal neurogenesis and synaptic integration under investigation of markers for each; Ki-67, doublecortin, synaptophysin, respectively. These detrimental effects of increased Th2 cytokine levels were confirmed *in vitro* using CCK-8 analysis and immunoblotting analysis of PCNA. Our results are consistent with numerous studies and thus, regulating the levels of Th2 cytokine are important for maintaining neurogenesis and normal cognition (Fig. 1). However, still further studies are left on other possibilities for indirect effect of elevated Th2 cytokine level on adult hippocampal neurogenesis and cognitive behaviors. Moreover, as previous studies have reported that Th1 cytokine such as Interferon-gamma enhances the adult hippocampal neurogenesis,^{31,32} it could be valuable to clarify the roles of Th1 cytokines on cognitive functions and to examine the change of Th1/Th2 bias in animal model with restricted CD4+ TCR repertoire. These issues should be addressed soon to verify the main roles of CD4+ T cell related cytokines and the underlying mechanisms.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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