新学術領域研究「脳構築における発生時計と場の連携」共催

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Innate immune mechanisms of synapse remodeling

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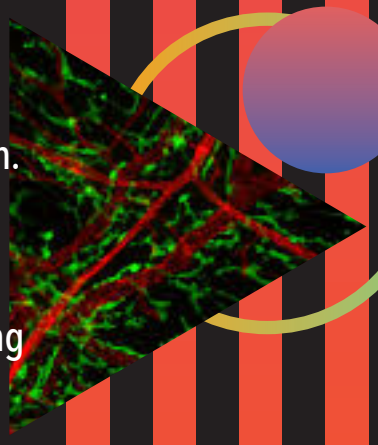
Neuronal synapse formation and remodeling is essential to central nervous system (CNS) development and adult learning. As such, alterations in synapse development and function is a central feature of neuropsychiatric diseases including autism, epilepsy, and schizophrenia. Innate immune signals regulate tissue remodeling in the periphery, but how this impacts CNS synapses is largely unknown. We found that the IL-1 family cytokine Interleukin-33 (IL-33) is physiologically required to promote synapse remodeling and maintain neural circuit function in the developing brain. We found that IL-33 is primarily expressed by developing astrocytes, the structural glia of the brain. Astrocyte-derived IL-33 signals primarily to microglia under physiologic conditions to promote microglial synapse engulfment. This astrocyte-microglial signaling pathway is required for normal circuit function in the thalamus, a brain region important for synchronizing neural activity. In ongoing work, we have identified a unique subpopulation of IL-33 expressing neurons in the adult hippocampus, a brain region essential for learning and new memory formation. Neuronal expression of IL-33 is experience dependent, and conditional deletion of IL-33 from neurons or its receptor in microglia leads to both structural and functional deficits in hippocampal neurons and impaired hippocampal-dependent behaviors. These data indicate physiologic and homeostatic roles for IL-33 signaling in brain development and learning, raising the question of how this delicate balance may be altered in the context of type 2 immune challenges such as brain injury.

参考文献： Vainchtein et al., Science 359, 1269–1273 (2018)



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