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NEURAL DEVELOPMENT

Instigating engulfment

> conditional knockout of *Il33* in astrocytes in the developing spinal cord led to a rise in the number of excitatory and inhibitory inputs to α-motor neurons

Astrocytes and microglia are implicated in the formation and remodelling of synapses, although the underlying mechanisms remain to be fully elucidated. A new study shows that, in the spinal cord and thalamus of mice, astrocyte-generated interleukin-33 (IL-33) regulates neural circuit development by instructing microglia to engulf synapses.

Vainchtein, Chin and colleagues found that *Il33* mRNA was upregulated in forebrain astrocytes in mice at postnatal day 9. Moreover, through the use of an *Il33* promoter reporter and immunohistochemistry, they showed that IL-33 was upregulated in a subpopulation of spinal cord and thalamus astrocytes in grey matter — with few other cell types showing IL-33 expression — during postnatal development.

IL-33 levels rose in the visual nucleus of the thalamus at the time mouse pups opened their eyes, and this upregulation was precluded by removing, at birth, the visual afferent sensory synapses, preventing synapse maturation. Furthermore, in thalamic and spinal cord astrocytes, developmental IL-33 expression was associated with expression of proteins involved in synapse-related functions of astrocytes. Together, these data suggest that IL-33 has a role in synapse development.

In the absence of IL-33, the authors detected increases in the spontaneous and evoked oscillatory activity in an intrathalamic circuit. They hypothesized that this hyperactivity resulted, at least partly, from an overabundance of glutamatergic synapses. Supporting this assertion, miniature excitatory postsynaptic currents in neurons in the ventrobasal thalamus — which formed part of the circuit — from IL-33-deficient mice were more frequent but showed no changes in kinetics or amplitude. In addition, conditional knockout of *Il33* in astrocytes in the developing spinal cord led to a rise in the number of excitatory and inhibitory inputs to α-motor neurons, the primary output neurons of sensorimotor spinal cord circuits.

These findings indicate that IL-33 has a role in determining the correct synapse number, but what is the underlying mechanism? Quantitative PCR revealed that the IL-33 co-receptor was expressed only in microglia, suggesting that the cytokine signals to these cells. Interestingly, local administration of IL-33 increased the levels of postsynaptic density protein 95 — a key component of the postsynaptic scaffold — in microglia in the spinal cord and the thalamus. Moreover, injection of IL-33 into the spinal cord during development halved the number of excitatory synapses. Thus, IL-33 seems to promote the proposed microglial engulfment of synapses and restrict synapse numbers.

Together, these findings indicate that astrocyte-derived IL-33 has a key role in the development of thalamic and spinal cord neural circuits by promoting microglial cell-mediated removal of synapses.

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ORIGINAL ARTICLE Vainchtein, I. D. et al. Astrocyte-derived interleukin-33 promotes microglial synapse engulfment and neural circuit development. *Science* https://doi.org/10.1126/science.aal3589 (2018)