GLIA

Remodelling the matrix

> microglia from *Il33* cKO mice showed less engulfed aggrecan than controls

Microglia have been implicated in the remodelling of synaptic connections, but it is not understood how this occurs. Now, Nguyen et al. find that, in adult mice, microglia promote experience-dependent hippocampal synaptic plasticity and memory consolidation by remodelling the extracellular matrix (ECM), and that neuronally expressed interleukin-33 (IL-33) has a key role in this process.

Previously, the same group found that, in early postnatal development in the thalamus and spinal cord, microglial cell-mediated synapse engulfment was driven by astrocytic expression of IL-33. Through use of a nucleus-localized knockin reporter (mCherry) mouse line ($Il33^{mCherry/+}$), here they found that in the adult mouse hippocampus IL-33 was mainly expressed by neurons.

Exposure of 3-month-old $Il33^{mCherry/+}$ mice for 4 weeks to an enriched environment increased the proportion of CA1 neurons that expressed IL-33. By contrast, placing such mice in social isolation for 4 weeks reduced the proportion of IL-33-expressing cells in the dentate gyrus (DG). This suggests that experience regulates IL-33 expression in hippocampal neurons.

Single-nucleus RNA sequencing of nuclei from hippocampal neurons revealed a cluster of neurons in the DG that exhibited enriched expression of genes involved in synapse formation and ECM remodelling. This cluster overlapped with neurons shown to be enriched in *Il33* expression.

Among mature DG granule cells from $Il33^{mCherry/+}$ mice, those with high mCherry levels, indicative of high IL-33 expression, exhibited higher levels of spine density and spine head filopodia, a marker of spine plasticity, than those with lower mCherry levels. Neurons with higher mCherry levels were also more likely to show expression of FOS, a marker of neural activity, than other neurons when $Il33^{mCherry/+}$ mice were placed in a novel environment for an hour. These data suggest that IL-33 expression is a feature of neurons with a greater probability of undergoing synaptic remodelling.

Quantitative PCR and in situ hybridization showed that microglia were the main type of hippocampal cell that expressed IL-1 receptor like-1 (IL1RL1), the IL-33 receptor. Mice in which *Il33* was conditionally knocked out in neurons (*Il33* cKO mice) or *Il1rl1* was conditionally knocked out in microglia (*Il1rl1* i-cKO mice) showed reduced spine density in the DG and CA1. Expression of a modified form of IL-33 in DG neurons, which allowed constitutive release of the cytokine, was sufficient to increase spine number, but this effect was not observed in *Il1rl1* i-cKO mice. These data indicate that spine formation and plasticity is promoted by IL-33-mediated neuron–microglial cell interactions.

Environmental enrichment increases neurogenesis and the integration of newborn neurons into circuits. *Il33* cKO mice had fewer newborn neurons than controls after a 5-week exposure to an enriched environment, suggesting IL-33 is required for an experience-dependent rise in newborn neurons.

The authors next examined whether IL-33 has a role in hippocampus-dependent memory. *Il33* cKO mice showed good memory recall and context discrimination shortly after training in a contextual fear discrimination task, but they developed a deficit in context discrimination 2–4 weeks later. This suggests that IL-33-mediated neuron–microglial cell interactions are important for memory consolidation.

How does the IL-33 signal affect microglia? Other studies have showed that IL-33 promotes microglial phagocytosis. Here, transcriptional profiling revealed that IL-33-exposed hippocampal microglia were strongly activated and showed upregulation of microglial genes associated with ECM regulation.

Strikingly, high-resolution imaging and 3D reconstruction revealed immunostaining for aggrecan — an ECM protein — in some lysosomes in microglia. Moreover, microglia from *Il33* cKO mice showed less engulfed aggrecan than controls. In line with these findings, *Il33* cKO mice showed a higher density of aggrecan and brevican, another ECM protein, perisynaptically in the DG molecular layer than did control mice. Together, these data suggest that neuronal IL-33 promotes microglial phagocytosis, restricting the amount of ECM near synapses.

This study shows that, in the hippocampus of adult mice, neuronally expressed IL-33 promotes microglial cell-mediated ECM remodelling, in turn promoting synaptic plasticity and the consolidation of memories.

Darran Yates

Credit: pavalena/Getty

ORIGINAL ARTICLE Nguyen, P. T. et al. Microglial remodelling of the extracellular matrix promotes synapse plasticity. *Cell* https://doi.org/10.1016/j.cell.2020.05.050 (2020)