Astrocytic IL-33 Signals Microglia to Engulf Synapses

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A growing body of research suggests that glial cells regulate synapse formation, maintenance, and pruning. In the February 1 Science, researchers led by Anna and Ari Molofsky at the University of California, San Francisco, identify a new signal that mediates elimination of synapses. Interleukin-33, released by astrocytes in the developing brain, stimulates microglia to gobble up synapses, they report. Mice lacking the cytokine retained too many synapses and had overactive circuits. Injecting exogenous IL-33, on the other hand, whetted the microglia's appetite and depleted synapses. "We increasingly appreciate that immune molecules, typically associated with fighting infection, also play beneficial roles in healthy tissues," Anna Molofsky told Alzforum. It is not yet known if IL-33 plays any role in synapse loss during disease.

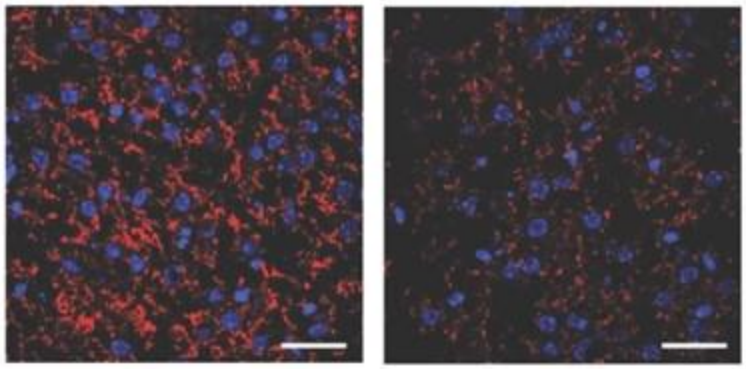
- Astrocytes in developing brain release IL-33, which stimulates microglia to eat synapses.
- Mice lacking IL-33 have excess synapses and hyperexcitable circuits.
- In AD mouse models, however, IL-33 lowers amyloid and improves memory.

It is known that microglia and astrocytes prune synapses in the developing brain in response to signals from immune proteins of the complement system (Dec 2013 conference news; Dec 2014 news; Mar 2015 conference news). Because IL-33 mediates repair and remodeling in many tissues, in addition to its role in immune cell maturation and chemotaxis, Molofsky and colleagues wondered if it might contribute to synaptic remodeling as well (Gadani et al., 2015; Pomeshchik et al., 2015; Molofsky et al., 2015).

Joint first authors Ilia Vainchtein and Gregory Chin found that one-month-old IL-33 knockout mice had more electrical activity in their thalamuses than did controls, suggesting overly abundant synapses. Indeed, motor neurons in the spinal cord sported about 50 percent more synapses than did those in controls. Knockouts also had weak sensorimotor reflexes, which are mediated by motor neurons.

How might loss of the cytokine contribute to excess synapses? Neither the cytokine nor its receptor were expressed in neurons of wild-type mice, the authors found. Instead, IL-33 was made only in gray-matter astrocytes, while its receptor, IL1RL1, turned up only on microglia.

Therefore, the authors looked for changes in gene expression in these cell types in the IL-33 knockouts. They found almost 500 genes with altered expression in microglia, but no changes in astrocytes.



Scene of Destruction.

Injecting IL-33 into the thalamus (right) leads to a massive loss of the synaptic marker synapsin-1 (red) compared to control thalamus (left). [Courtesy of Science/AAAS.]

Turning to microglial activity, the authors detected differences in phagocytosis. Microglia in one-month-old IL-33 knockouts contained only half as many postsynaptic markers as microglia from controls. In contrast, injecting IL-33 into the brain or spinal cord caused microglia to gobble up 50 percent more synapses (see image above). This was determined by both an increase in postsynaptic markers inside microglia and a loss of co-localized pre- and postsynaptic markers on neurons. Mice lacking the IL-33 receptor were protected from this loss. In addition, purified microglia in cultures treated with IL-33 swallowed about twice as many synaptosomes in a day as did control cultures.

The findings indicate that microglia devour synapses, but whether they prune connections from healthy cells or engulf debris from dying neurons remains a mystery, Anna Molofsky noted. She plans to explore the underlying mechanism, as well as how IL-33 interacts with other players in synapse elimination, such as complement. Perhaps IL-33 primes microglia to eat, while complement tags specific synapses for destruction, she suggested.

Another unanswered question is whether IL-33 contributes to neurodegenerative synapse loss, a process triggered by complement (Nov 2015 conference news; May 2016 news). If it does, then having less IL-33 might be beneficial.

However, previous studies in AD mouse models report the opposite. Nancy Ip at the Hong Kong University of Science and Technology, China, found that administering IL-33 to APP/PS1 mice improved memory and synaptic plasticity while lowering soluble Aβ and plaque load (Fu et al., 2016). Conversely, mice lacking this cytokine accumulate DNA damage, develop tauopathy, and lose neurons as they age (Carlock et al., 2017).

In people, too, Jean-Charles Lambert at Institut Pasteur de Lille, INSERM, France, reported that lower IL-33 expression associated with AD, while a protective haplotype that boosts IL-33 expression reduced cerebral amyloid angiopathy (Chapuis et al., 2009).

“As usual in science, the new data complicated the story a bit,” Lambert said. He noted that Molofsky and colleagues examined developing brains, and the effects might be different in aged brains. “It would be informative to see how IL-33 affects pruning as a function of Aβ exposure,”

he suggested. Ip believes both her and Molofsky's findings can be explained by IL-33 stimulating microglial phagocytosis of debris. "It is interesting to speculate that IL-33 clears unwanted materials through the activation of microglia during neural development and in the disease state," she wrote to Alzforum.—Madolyn Bowman Rogers

COMMENTS

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The study by Vainchtein et al. emphasizes the roles of glial cells in synapse refinement during neuronal circuit development. While the involvement of microglia in synaptic engulfment in postnatal development and neurological diseases is well established, how the actions of the microglia are triggered during the process remains unclear. This study shows that Interleukin-33 (IL-33), a cellular alarmin that is important for tissue homeostasis, is released from the synapse-associated astrocytes and mediates synapse refinement in the spinal cord and the thalamus by facilitating the microglial engulfment of synapses. These findings provide us with some clues on the possible coordinated interplay of astrocytes, microglia, and neurons during the refinement of the synaptic connectivity.

Synaptic loss is highly associated with memory decline in AD and is an early hallmark of the disease. Interestingly, our previous findings showed that IL-33 injection restored the synaptic plasticity deficit and reduced AD-like pathology in AD-transgenic mouse models through the modulation of microglial phenotypes (Fu et al., 2016). In our study, we demonstrated that IL-33 skewed the microglia toward an alternative activation state with an enhanced Aβ phagocytic ability in AD. Thus, it is interesting to speculate that IL-33 clears the unwanted materials through the activation of microglia during neural development and in the disease state. Together with the recent identification of a new microglial subtype known as disease-associated microglia (DAM) in AD transgenic mouse model, and the discovery of the change in proportion of different microglial subtypes during the progression of AD (Keren-Shaul et al., 2017), it is expected that the roles of microglia in AD are quite complicated.

Current understanding of the roles of microglia in AD is diverse and controversial. They are involved in the engulfment of synapses, phagocytic uptake of Aβ, as well as the regulation of the inflammatory status. To have a better understanding of the crosstalk between glial cells and neurons in AD, it is critical to identify the regulation of different subtypes of microglia and evaluate their functions during the progression of AD and after IL-33 treatment. While microglia and innate immune-associated pathways are suggested to mediate the early synaptic loss in this disease (Hong et al., 2016), it will be of great interest to examine the exact roles of IL-33/ST2 in the regulation of synapse dysfunctions in AD, and investigate the involvement of different glial cell types and their coordination during the process.

It will also be of interest to study the cellular mechanisms that underlie the action of IL-33 in synaptic refinement. This study reports that there is a decrease of gene candidates, including different chemokine members such as Cxcl1, Cxcl10, and Cxcl2, in the microglia of IL-$33^{-/-}$ mice. Indeed, reduction of chemokines is also observed at the injury sites in IL-$33^{-/-}$ mice after spinal cord injury, which is associated with reduced recruitment of monocytes and impaired recovery (Gadani et al., 2015). Thus, it is worth examining whether the action of IL-33 on the microglial-mediated functioning during development and at the injury state is via the regulation of chemokines in the microglia.

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We fully agree with Dr. Ip's insightful comments.

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