

## Previews

# Creating Space for Synaptic Formation—A New Role for Microglia in Synaptic Plasticity

Yosif Zaki<sup>1</sup> and Denise J. Cai<sup>1,\*</sup><sup>1</sup>Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA\*Correspondence: [denise.cai@mssm.edu](mailto:denise.cai@mssm.edu)<https://doi.org/10.1016/j.cell.2020.06.042>

Memory formation is thought to occur in the brain through dynamic remodeling of the synaptic architecture between neurons. The cellular mechanisms underlying these dynamics remain unclear. In this issue, Nguyen et al. demonstrate a novel role for microglia in regulating synaptic formation by clearing extracellular matrix proteins that embed neurons.

The mammalian brain constantly constructs new memories and updates existing ones. This process involves complex dynamics in the biochemical environments of neurons, as well as in the synaptic architecture between them, both of which have been described extensively.

Dendritic spines on neurons dynamically form and eliminate synapses at specific sites, and this spine-specific remodeling has been a leading theory for the cellular basis of memory (Takeuchi et al., 2013). A precise balance of synapse formation and elimination is essential for proper learning and memory storage, and the ways in which the brain balances this process remains incompletely understood. An exciting recent study in this issue points to microglia, the brain's resident immune cells, as mediators of experience-dependent neuronal spine remodeling (Nguyen et al., 2020).

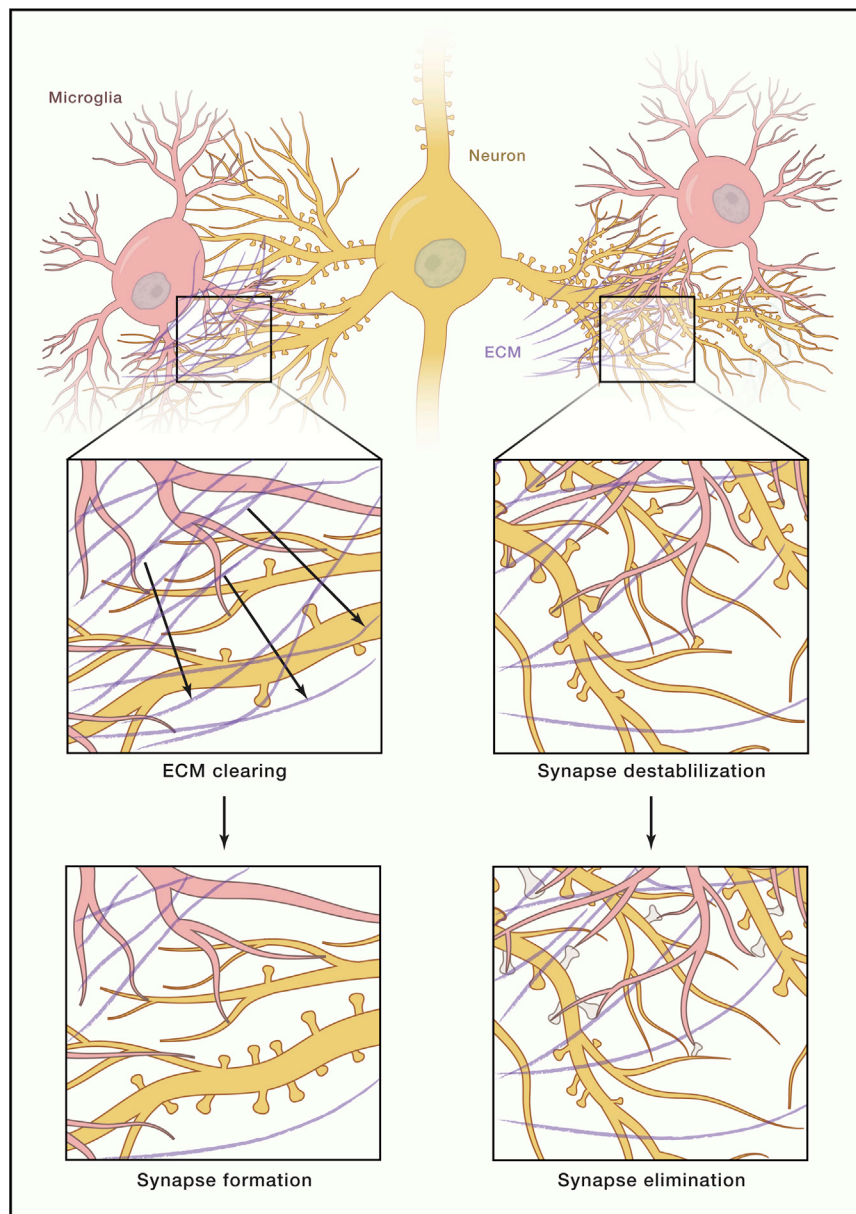
Neurons are embedded in a web of extracellular matrix proteins that provide structural support but limit their ability to undergo structural plasticity. In some brain regions, such as the cortex and hippocampus, networks of extracellular matrices form a reticulum termed a perineuronal net. Perineuronal nets provide structural support for neurons, but they can also influence buffering of ions in neurons and can protect them from oxidative stress (van 't Spijker and Kwok, 2017). These observations led to the speculation that perineuronal nets may play a role in the formation of long-term memories (Tsien, 2013). However, the mechanisms by which the extracellular neuronal environment is actively rearranged to support neuronal synaptic plasticity are not well

understood. A cell type that could actively respond to diffusible molecules and directly dismantle the extracellular matrix would be in an ideal position to drive synaptic plasticity through destabilization of the extracellular environment.

Such a cell type may well be microglia. Often referred to as the resident macrophages of the brain, microglia migrate from the fetal yolk sac to the brain in early embryonic development, where they phagocytose cellular debris and respond to immune challenges. Because these functions closely resemble the functions of peripheral macrophages, microglia were proposed to function primarily as supportive immune cells in the brain (Sierra et al., 2019). More recently, it has become clear that microglia also participate in critical homeostatic brain functions previously ascribed to just neurons, including synapse elimination (Figure 1, right column). Microglia are attracted to nearby synapses first during postnatal development where they aid in synaptic pruning. In adulthood, they continue to be attracted to neuronal synapses and participate in synapse elimination; however, this glia-neuron communication system remains incompletely understood (Wilton et al., 2019). In a 2010 study, it was observed that microglia hovered near neurons in the visual cortex during normal visual experience but that light deprivation prompted microglia to change morphology, extend their processes, and phagocytose nearby synapse-associated molecules (Tremblay et al., 2010). These observations led the study's investigators to speculate three possible ways that microglia might have

been interacting with the extra-neuronal space: (1) microglia were eliminating existing synapses, (2) they were modifying existing synapses, or (3) they were remodeling the extracellular matrix to enable more effective synaptic remodeling (Tremblay and Majewska, 2011). Since then, the first two mechanisms have been described in the context of development, adulthood, and neurological disease (Wang et al., 2020; Wilton et al., 2019), and in these cases, microglia have promoted synaptic turnover. Whether microglia could influence synaptic formation, however, has remained unclear.

In this issue of *Cell*, Nguyen et al. describe a mechanism by which microglia promote synapse formation in response to experience (Nguyen et al., 2020). Microglia are attracted to hippocampal dendrites by the neuron-secreted cytokine, interleukin-33 (IL-33), and then respond by ingesting the extracellular matrix proteins aggrecan and brevican, which then creates space for synapse formation. Knocking out either *Il33* or its receptor *Il1r1* led to decreased dendritic spine head filopodia in hippocampus, decreased intrinsic excitability of the hippocampal neurons, and worsened discrimination in a fear discrimination behavioral assay. Increased IL-33 signaling rescued age-related decreases in spine head filopodia and rescued behavioral enrichment-induced expression of cFos—a marker for neuronal activity. These results suggest that microglia not only promote synapse elimination but can also influence synapse formation in the adult brain, which is



**Figure 1. Microglia Are Capable of Promoting Both Formation and Elimination of Synapses**

A neuron (yellow) is displayed with dendrites that have few spines (left) versus many spines (right). Microglia (pink) hover near dendrites on both sides of the neuron and exert opposing effects on either side. Left column depicts microglial effects on synapse formation, a novel mechanism described in this issue by [Nguyen et al. \(2020\)](#): this dendrite is embedded in an extracellular matrix (purple) which, when cleared by microglia, promote an increase in synapse formation (top box is before clearing, bottom box is after). Right column depicts microglial effects on synapse elimination, a mechanism previously described by [Wilton et al., 2019](#): this dendrite has many dendritic spines, which are directly phagocytosed by microglia (top box is before clearing, bottom box is after).

critical for learning and memory. This bidirectional influence on synapse maintenance lends to a push-pull mechanism of synaptic plasticity that microglia uniquely appear capable of directing ([Figure 1](#)).

This study raises novel questions about how microglia and neurons interact to regulate synaptic plasticity in the adult brain. For example, while microglial breakdown of the extracellular matrix has now been shown to promote

synapse formation, it is unknown whether this same process can influence synapse destabilization and elimination, and, in turn, promote forgetting. Because perineuronal nets provide structural support for neurons, their breakdown could influence synapse breakdown as well. Additionally, the ability of microglia to fine tune synapses on specific neurons could underlie how novel experiences are integrated with existing memories. [Nguyen et al. \(2020\)](#) demonstrate that IL-33 is secreted in an experience-dependent fashion, so microglia could strengthen synapses activated by multiple separate experiences, linking their likelihood of being activated together. Last, it will be of great interest to know how neuron-glia interactions go awry in cases of aging and neurodegeneration. The authors show that IL-33 levels decrease in aging and that artificially increasing its release can increase cFos levels back to levels seen in young adults; this finding suggests that age-related (and perhaps neurodegeneration-related) deficits in neuronal excitability may be treatable with interventions that target microglia or specifically target IL-33 signaling. Understanding the cellular mechanisms that govern neuronal plasticity continues to be one of the frontiers of contemporary neuroscience. Nguyen et al. provide compelling evidence that microglia have a critical role in synapse formation through their regulation of extracellular matrix. Taken together with the prior literature, this suggests that microglia are capable of bidirectionally modulating synaptic plasticity through spine formation and elimination. This work lays the foundation for further exploration of microglia as drivers of synaptic plasticity.

#### ACKNOWLEDGMENTS

We would like to thank Sima Rabinowitz for editorial assistance and Philip Hwang, Christopher Guevara, and Mackenzie Lemieux for feedback on a prior version of the manuscript. This was supported by the 1 DP2 MH122399-01 from NIH Director's New Innovator Award, 1R01MH120162 - 01A1 from NIMH, One Mind Rising Star Award, McKnight Memory and Cognitive Disorders Award, Klingenstein-Simons Fellowship, Brain Research Foundation Award, NARSAD Young Investigator Award, and the Mount Sinai Distinguished Scholar Award to D.J.C.

REFERENCES

- Nguyen, P.T., Dorman, L.C., Pan, S., Vainchtein, I.D., Han, R.T., Nakao-Inoue, H., Taloma, S.E., Barron, J.J., Molofsky, A.B., Kheirbek, M.A., and Molofsky, A.V. (2020). Microglial remodeling of the extracellular matrix promotes synapse plasticity. *Cell* 182, this issue, 388–403.
- Sierra, A., Paolicelli, R.C., and Kettenmann, H. (2019). Cien Años de Microglía: Milestones in a Century of Microglial Research. *Trends Neurosci.* 42, 778–792.
- Takeuchi, T., Duszakiewicz, A.J., and Morris, R.G. (2013). The synaptic plasticity and memory hypothesis: encoding, storage and persistence. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 369, 20130288.
- Tremblay, M.E., and Majewska, A.K. (2011). A role for microglia in synaptic plasticity? *Commun. Integr. Biol.* 4, 220–222.
- Tremblay, M.E., Lowery, R.L., and Majewska, A.K. (2010). Microglial interactions with synapses are modulated by visual experience. *PLoS Biol.* 8, e1000527.
- Tsien, R.Y. (2013). Very long-term memories may be stored in the pattern of holes in the perineuronal net. *Proc. Natl. Acad. Sci. USA* 110, 12456–12461.
- van 't Spijker, H.M., and Kwok, J.C.F. (2017). A Sweet Talk: The Molecular Systems of Perineuronal Nets in Controlling Neuronal Communication. *Front. Integr. Neurosci.* 11, 33.
- Wang, C., Yue, H., Hu, Z., Shen, Y., Ma, J., Li, J., Wang, X.D., Wang, L., Sun, B., Shi, P., et al. (2020). Microglia mediate forgetting via complement-dependent synaptic elimination. *Science* 367, 688–694.
- Wilton, D.K., Dissing-Olesen, L., and Stevens, B. (2019). Neuron-Glia Signaling in Synapse Elimination. *Annu. Rev. Neurosci.* 42, 107–127.

## Therapeutic TVs for Crossing Barriers in the Brain

Zhen Zhao<sup>1,\*</sup> and Berislav V. Zlokovic<sup>1,\*</sup>

<sup>1</sup>Department of Physiology and Neuroscience, Zilkha Neurogenetic Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

\*Correspondence: [zzhao@usc.edu](mailto:zzhao@usc.edu) (Z.Z.), [zlokovic@usc.edu](mailto:zlokovic@usc.edu) (B.V.Z.)  
<https://doi.org/10.1016/j.cell.2020.06.041>

**Brain disorders are at the leading edge of global disease burden worldwide. Effective therapies are lagging behind because most drugs cannot reach their targets in the brain because of the blood-brain barrier (BBB). The new development of a BBB transport vehicle may bring us a step closer to solve this problem.**

If curing brain diseases is equivalent to the Mars mission in biomedicine, then delivering drugs across the blood-brain barrier (BBB) is unquestionably the Moonshot. Since the discovery of the BBB by German physician Paul Ehrlich in the late 1800s, generations of scientists and engineers tried to understand how to breach the BBB for successful delivery of drugs to the central nervous system (CNS), but none have fully succeeded. Recently, biotechnology and pharmaceutical companies have joined the race proposing cutting-edge antibody-based technologies. Two new reports from Denali Therapeutics definitely showcased their success in creating a promising platform (Kariolis et al., 2020; Ullman et al., 2020), which perhaps could be our Falcon 9 for the next step.

The BBB is the gate keeper of the CNS, uniquely separating brain internal milieu from the circulating blood. The BBB limits toxic substances, pathogens, and >99% of drugs from entering the brain, yet at the same time selectively controls trans-

port of ions, nutrients, and essential signaling molecules through its highly specialized transport systems (Sweeney et al., 2019). The receptor-mediated transcytosis (RMT) is one of the secret passages within the BBB. RMT is a series of tightly regulated cellular events in the endothelium, starting with clathrin-mediated receptor endocytosis and followed by intracellular trafficking of the endosomes containing the “cargo” and sorting of the vesicles toward directed exocytosis, rather than lysosomal-mediated degradation, a process guided by small Rab GTPases (Zhao et al., 2015). Many growth factors and signaling peptides, such as leptin, insulin, insulin-like growth factor, lipoproteins, and transferrin, are delivered to the brain across the BBB via RMT. Therefore, targeting the RMT systems offers a tremendous opportunity for CNS drug delivery (Sweeney et al., 2019).

Transferrin receptor (TfR) was the first extensively utilized as an RMT system for transport of antibodies and antibody-conjugates across the BBB (Friden

et al., 1991) (see Figure 1). A monoclonal antibody OX-26 was the first experimental vessel, which transported methotrexate conjugates across the murine BBB to reach the brain parenchyma side. Following this report, other BBB associated receptors, such as insulin receptors, have been actively tested for their potential for CNS drug delivery (Zuchero et al., 2016). Because RMT efficiency is highly dependent on the abundance and spatial distribution of the receptors, TfR, as one of the top transmembrane proteins enriched at the BBB (Zuchero et al., 2016), has become the principal target for antibody designing and optimization.

The second generation of therapeutic antibodies that recognize TfR for transverse BBB delivery were based on antibody engineering. One approach used protein fusion, where the high-affinity TfR monoclonal antibody (e.g., 8D3) was fused to an anti-amyloid single chain Fv (ScFv) antibody (Zhou et al., 2011) or to a recombinant protein for replacement therapy (Ullman et al., 2020). Genentech

