



Synapse-specific plasticity relies on neuroimmune interactions

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Synaptic plasticity is a critical process for brain function, regulating the wiring of neuronal circuits during development as well as the maintenance and modification of these circuits throughout life. When this process is disrupted, it can lead to a wide variety of neurodevelopmental and neurodegenerative disorders, which disrupt sensory, motor, and cognitive function, leading to a decrease in quality of life. Although plasticity happens at the level of individual synapses which connect neurons into neural circuits that perform these important computations, the brain is made up of many different cell types, whose interactions with neurons can modify circuit function. In particular, recent studies have highlighted the role of immune signals in both brain function and dysfunction. Molecular signals that have traditionally been associated with immune reactivity have been found to be expressed in the brain and used in circuit remodeling, especially during development (1). In fact, inflammatory cytokines are elevated in the blood and cerebrospinal fluid of patients with autism spectrum disorder, suggesting that inflammation may contribute to altered neurodevelopment (2). As such, there has been a renewed interest in understanding how the immune system interacts with synaptic plasticity during the development and remodeling of circuits throughout the brain. In PNAS, Marin et al. (3) explore how a canonical immune signaling pathway interacts with microglia, the brain's immune cells, and plays a role in developmental wiring of the nervous system.

Microglia have been increasingly implicated as critical participants in the process of synaptic plasticity since the discoveries that these cells are highly motile under physiological conditions (4, 5) and that they monitor neuronal state (6). Microglia interact with neurons both directly, whereby microglia physically touch both presynaptic and postsynaptic neuronal elements, and through diffusible signals, leading to changes in synaptic structure and function (7). The disruption of these interactions can impair synaptic plasticity. Recent research has begun to identify the molecular pathways that neurons and microglia use to communicate and orchestrate synaptic and circuit-level changes. Many of these pathways overlap with traditional immune signaling pathways. For instance, signaling from neurons to microglia can occur through neuronal expression and/or release of fractalkine which is detected by the microglial receptor Cx3cr1 (8), or through adenosine 5'-triphosphate release from neurons which can be detected by microglia via the purinergic receptor P2Y12 (9). Both of these pathways are critical to microglial responses to injury and disease, but both are also used in an activity-dependent manner during development to remodel circuits. Even molecules associated with classical immune functions such as the complement pathway (including C1q and C3) (10), which is used for tagging and removing debris and foreign bodies, major histocompatibility complex I (MHCI) (11), which is used for antigen presentation to the immune system, and tumor necrosis

factor-alpha (TNF-alpha) (12), a classic proinflammatory cytokine, have important roles in modulating synaptic strength based on circuit activity. Even though many of these signaling molecules and their receptors are expressed throughout the brain and life span, it appears that their use is not ubiquitous but is context dependent, varying both regionally and temporally. For example, in the visual system, developmental organization of the lateral geniculate nucleus depends on C1q (10) and MHCI (13) but not P2Y12 (14), while activity-dependent restructuring of primary visual cortex in later development requires P2Y12 (9) and TNF-alpha (12) but not C1q (15). Microglia themselves are similarly regionally and temporally heterogeneous. Microglial density, morphology, and receptor expression profile vary across brain regions in the mature brain and follow a developmental time course (16). However, how this regional and developmental heterogeneity in microglial profiles contributes to the diversity in mechanisms they employ to aid in synaptic remodeling is unclear.

While it is clear that specific molecular mechanisms operate in a context-dependent manner, synaptic plasticity is also synapse specific, and how immune molecules are targeted to specific synapses undergoing different forms of activity-dependent plasticity at different time scales has remained an open question. As an example, ocular dominance plasticity (ODP), which has been used as a model for activity-dependent synaptic remodeling, depends on an elegant progression of changes at specific synapses that represent different circuits and which may use different synaptic mechanisms of plasticity (17). ODP occurs during a particular developmental time period, which, in the mouse, occurs a week after eye opening. During this time, imbalance in the visual activity driving the two eyes, such as loss of input from one eye, can result in a remodeling of the circuits that carry this information. Synapses which carry information from the closed eye become weaker, while synapses that carry information from the open eye strengthen (Fig. 1), a process which is carefully orchestrated at the synaptic level. Intracortical connections in layer 2/3 appear to remodel faster than feedforward connection from the lateral geniculate nucleus to layer 4 (18).

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Author contributions: R.L.L. and A.K.M. wrote the paper.

The authors declare no competing interest.

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See companion article, "The nonclassical MHC class I Qa-1 expressed in layer 6 neurons regulates activity-dependent plasticity via microglial CD94/NKG2 in the cortex," [10.1073/pnas.2203965119](https://doi.org/10.1073/pnas.2203965119).

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Published June 23, 2022.

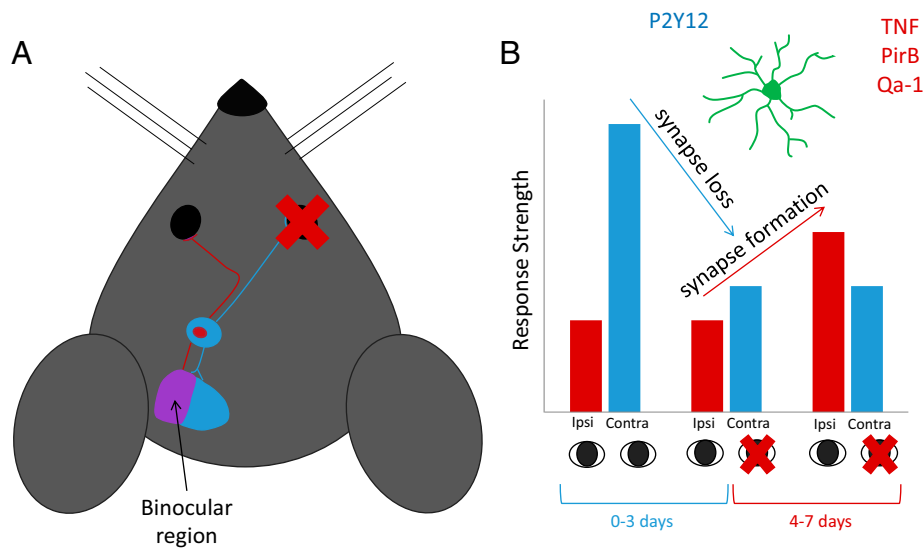


Fig. 1. Immune signaling and ODP. (A) In mouse primary visual cortex, neurons receive input from both eyes but respond preferentially to input from the contralateral eye (contra). (B) If input from the contralateral eye is lost, neurons compensate for the loss of input with an initial period of removal of synapses representing the closed eye followed by a period of formation of synapses representing the remaining, ipsilateral eye (ipsi). This process involves communication between neurons and microglia via multiple immune signaling molecules which contribute to different phases of synaptic remodeling (synapse loss: P2Y12; synapse gain: tumor necrosis factor [TNF] and MHCII signaling molecules, PirB and Qa-1).

Similarly, closed eye synapses undergo depression soon after eye closing, while synapses that serve the open eye strengthen later, possibly through a homeostatic mechanism (19, 20). The Shatz laboratory has previously used this model system to provide one of the early insights into how immune signals are used in nontraditional ways to support synaptic remodeling, identifying an MHCII receptor as a “brake” on ODP (11). Now, in PNAS, Marin et al. (3) further this work by not only identifying an MHCII-based signaling pathway mediating developmental plasticity but also identifying a specific set of neurons and projections that employ this mechanism to enact synapse-specific activity-dependent changes to the visual system.

Using RNAscope and transgenic mouse lines, Marin et al. (3) find that the nonclassical MHCII molecule Qa-1 is expressed in layer 6 corticothalamic neurons as well as their synapses locally in the thalamus. The authors go on to show that Qa-1 expression is activity dependent and developmentally regulated by visual experience during the visual critical period, and loss of Qa-1 results in overexpansion of the remaining active neurons following loss of visual input from one eye. This supports their previous findings where a different MHCII interaction restricted ODP, suggesting that MHCII signaling may be used broadly to inhibit plasticity at specific synapses, although this would require additional study. Finally, Marin et al. demonstrate that MHCII function in ODP requires an interaction with microglia, as these cells express a binding partner for Qa-1 and disrupting this binding prevents the microglial morphological response to loss of visual input. This provides a link between the previous literature on MHCII signaling in plasticity and the studies that show microglial roles in synapse remodeling. The authors propose that this molecule

acts at the synapse and interacts with microglia to mediate activity-dependent neuronal plasticity, specifically restricting the expansion of open-eye territory during ODP, raising the intriguing possibility that specific MHCII interactions could inhibit plasticity within specific connections that represent certain types of information within the circuit.

These exciting findings elucidate an additional component of the complex process regulating developmental wiring of the brain and provide insight into how plasticity may be implemented by an interplay of different cell types at the level of specific inputs and outputs. While Qa-1 appears to act as a stop signal in synapses formed by corticothalamic layer 6 neurons, it will be important to determine how the neuron–microglia interaction through Qa-1 signaling mediates synaptic rearrangement. This could be through direct binding which could shield the synapse from other signals or interfere with synaptic receptor rearrangement, through remodeling of the extracellular milieu which can be inhibitory for plasticity, or by blocking synapse engulfment by microglia or astrocytes. Additionally, given the heterogeneity of mechanisms of plasticity, further research could define whether this mechanism is also used by other cells in other regions and at other developmental time points or in different forms of plasticity, including Hebbian and homeostatic forms. Lastly, given that many immune signaling pathways are used by neurons and microglia for both physiological and pathological responses, it will be interesting to determine how Qa-1 functions during disease or injury. While lots of questions remain unanswered, the work presented by Marin et al. (3) represents a step forward in defining the mechanisms by which neuroimmune signals regulate synapse-specific remodeling.

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