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Glial Wnt dialogue controls synapses

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Synaptic connectivity in the brain is not solely sculpted by neurons, but also by the dynamic and coordinated activity of glial cells. Microglia are known to engage in synaptic pruning during early brain development. They survey the neuropil and phagocytose synapses that have been tagged for removal. Such synaptic tagging is guided by several neuroimmunological mechanisms, including cytokine receptor interactions (CX3CL1/CX3XR1-ADAM10)[1], phosphatidylserine[2], CD47/SIRPα[3], and complement systems[4,5]. In the latter mechanism, proteins like C1q and C3 are expressed on the surface by weak or obsolete synapses, and microglia recognize such complement 'tagged' synapses with their complement receptors, such as CR3[4]. Astrocytes extend their process to form tripartite synaptic junctions, at which they fine-tune neurotransmission[6]. Like microglia, astrocytes also mediate synaptic pruning via direct and indirect mechanisms. On one hand, astrocytes directly recognize and remove inactive synapses via MEGF10/MERTK pathways[7]. On the other hand, they release signaling molecules, which induce neurons to express 'eat-me' signals such as C1q, a component of the classical complement cascade involved in microglia-mediated pruning, thereby indirectly promoting pruning[8]. However, how microglia and astrocytes coordinate pruning remain unknown. Also, how do microglia sense weak and unnecessary synapses when they are wrapped by astrocytes?

A new study by Faust et al. presents a sophisticated model of inter-glial coordination, where microglia instruct astrocytes to retract from synapses, thereby creating a permissive environment for microglia-dependent synaptic pruning[9]. This process is crucial for activity-dependent synaptic remodelling, and redefines our view of glial cells as tightly coupled partners in neural circuit refinement. The authors used a sensory deprivation model, in which unilateral removal of whiskers in mice during early postnatal periods led to the elimination of thalamocortical synapses in the layer IV of the contralateral barrel cortex. They observed that while microglial engulfment of synapses increased, astrocytes unexpectedly retracted their processes from synaptic sites without engaging in engulfment themselves. To decipher the molecular mechanism behind this astrocytic retraction, the authors employed Aldh1l1-EGFP-L10a reporter mice to perform Translating Ribosome Affinity Purification and RNA sequencing (TRAP-Seq) on astrocytes. This approach revealed a significant upregulation of the Wnt/β-Catenin signaling pathway in the neuronal activity deprived hemisphere. Substantiating this finding, astrocyte-specific genetic deletion of APC, a negative regulator of the Wnt pathway, enhanced β-catenin signaling in astrocytes, and successfully phenocopied their process retraction. Through a combination of microglial TRAP-Seq, ligand-receptor analysis, and microglia-specific knockout of Wntless (Wls), a gene essential for Wnt secretion, the authors identified microglia-derived Wnts (e.g., WNT4, WNT7A) are key activators of the canonical Wnt/β catenin pathway in astrocytes. Wnt release from microglia was dependent on neuronal fractalkine (CX3CL1) signals acting on microglial CX3CR1, which in turn secrete Wnt ligands and subsequently activate canonical Wnt/β-catenin signaling in astrocytes, causing retraction of astrocytic processes. Remarkably, Wnt receptor signaling is upregulated in astrocytes in various disease contexts (e.g., Alzheimer's disease, epilepsy), where synaptic loss is a hallmark[10–12]. Thus, their model of glia-glia crosstalk mediated by neuronal signals has the potential to extend beyond brain developmental stages to disease states, offering a unifying logic for synapse elimination in pathology. Together, this work compellingly demonstrates that microglia act not merely as executors of synapse removal, but as instructional regulators that orchestrate a spatiotemporal reorganization of the synaptic environment by integrating neuronal signals and modulating astrocytic morphology. This finding fundamentally reshapes the classic 'tripartite synapse' concept, shifting the paradigm from a primary focus on neuron-astrocyte bidirectional communication towards a more dynamic, microglia-orchestrated, tripartite regulatory mechanism.

The sophisticated microglia-astrocyte dialogue uncovered by Faust and colleagues serves as a broader paradigm shift, where glia-glia interactions must be considered as a fundamental component of sculpting neural circuit architecture. This principle could be easily extended beyond synaptogenesis to processes as diverse as myelination, where a growing body of evidence indicates that not only neuron-glia interactions, but also glia-glia interactions, play essential roles in modulating neuronal and brain function throughout development and in disease contexts. For instance, in the developing corpus callosum, microglia phagocytose oligodendrocyte precursor cells (OPCs), thereby influencing myelination[13]. In other settings, microglia-derived neuropilin-1 promotes OPC proliferation, further shaping myelin dynamics[14]. In demyelinating disorders such as multiple sclerosis, astrocytes support the survival of regenerating oligodendrocytes through downregulation of the Nrf2 pathway, and enhanced astrocytic cholesterol biosynthesis[15]. In this context, the work by Faust et al. reveals a more refined form of glia-glia cooperation—one that directly shapes the synaptic landscape. As OPCs engulf synapses during development, it is intriguing to understand how the three cell types, microglia, astrocyte, and OPCs coordinate their activity in synapse refinement. Together, systematically investigating multicellular interactions among glial cells is essential to fully understand the fundamental mechanisms governing brain function in health and disease.

While this work is elegant and provocative, it also raises several challenges and questions. The model is based on whisker deprivation in early postnatal mice and thalamocortical synapses in the barrel cortex. It remains to be seen whether such microglia-astrocyte Wnt signaling is a general mechanism across brain regions, ages, or in learning-induced synapse remodeling. Testing the universality of this concept will require investigations across diverse sensory deprivation paradigms such as learning-induced plasticity models (e.g., motor learning, fear conditioning), and region-specific genetic manipulations (e.g., using Cre drivers for distinct cortical or subcortical areas or tamoxifen-dependent conditional manipulation at different stage of development) for systematic validation. In addition, it remains to be further addressed how Wnt receptor

activation in astrocytes translates into process retractions. One plausible route is through cytoskeletal reorganization via actin dynamics, a canonical function of Wnt/β-catenin signaling. Nevertheless, a key objective is to determine whether astroglial retraction simply enables microglial access or also actively initiates programs of synaptic pruning in both these cells. This can be tested by developing methods for selectively inhibiting retraction of astroglial processes (e.g., astrocyte-specific blockade of Wnt effectors). If microglial engulfment is subsequently blocked, it would indicate that retraction is a critical permissive step. Precisely teasing apart these contributions will be a challenge for future studies.

In a nutshell, the work by Faust et al. elegantly demonstrates a highly orchestrated interglial communication—microglia instruct astrocytes to relinquish their perisynaptic hold, thereby permitting microglial access and synaptic pruning. This fine coordination exemplifies how glial cells do not act in isolation but as a synchronized ensemble supporting neuronal circuit refinement. Going forward, it will be important to test the generality of such glia-glia mechanism across brain regions, developmental stages, and various forms of short- and long-term plasticity. As a long-term goal, uncovering precise molecular players, glial cell effectors, and the regulators of glia-glia interactions in disease contexts will be equally critical. In-depth understanding of microglia-astrocyte communications might have a significant implication for treating neurological diseases characterized by excessive synapse loss, such as Alzheimer's disease, potentially by identifying novel therapeutic targets to modulate glia-glia signaling pathways. But perhaps more deeply, this work suggests that the next frontier in neuroscience is not only mapping neuronal connectivity, but mapping glial connectivity and signaling. Understanding how glial cells talk to each other, and to neurons, may unlock new dimensions in our understanding of brain functions and how they go off track during dysfunctions.

Ethical statements

Not applicable.

Author contributions

The authors confirm their contributions to the paper as follows: study conception: Bai X; manuscript writing and revision: Zhao J, Agarwal A, Bai X. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Not applicable.

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Conflict of interest

The authors declare that they have no conflict of interest.

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