TOP 10 RESEARCH ACHIEVEMENTS

Astrocytes phagocytose adult hippocampal synapses for circuit homeostasis

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In the adult hippocampus, synapses undergo constant formation and elimination. However, the exact function and regulatory process of synapse elimination in the adult brain are largely unknown. Here, we reveal a significant role of astrocytic phagocytosis in maintaining proper hippocampal synaptic connectivity and plasticity. By utilizing mCherry-eGFP phagocytosis reporters, we find that excitatory as well as inhibitory synapses are eliminated by glial phagocytosis in the adult hippocampal CA1 region. Surprisingly, our data show that astrocytes play a major role in neuronal activity-dependent elimination of excitatory synapses. Furthermore, knocking-out the phagocytic receptor Megf10 in adult astrocytes reduces their ability to eliminate excitatory synapses, and as a result, induces the accumulation of excessive but functionally impaired synapses. Finally, we show that Megf10 knock-out mice exhibit defective long-term synaptic plasticity with impaired hippocampal memory formation. Taken together, our data provide strong evidence that astrocytes eliminate unnecessary excitatory synaptic connections in the adult hippocampus through Megf10, and that this astrocytic function is critical for homeostasis of circuit connectivity important for cognitive functions.

1. Background

Adult synapses continuously undergo formation and elimination, and these synapse turnover events are well represented during experience-dependent plasticity and cognitive functions. However, how synapses in the adult brain get eliminated and whether synapse elimination plays a direct role in circuit homeostasis are not well known. Previously, we have found a phagocytic function of astrocytes in eliminating synapses during postnatal development (Chung et al., 2013, Nature). By phagocytosing synapses through the MEGF10 and MERTK phagocytic receptors, astrocytes actively contribute to activity-dependent synapse pruning and developmental circuit refinement. Moreover, contrary to the previous notion that microglia are the sole mediator of synapse elimination, astrocytes were shown to play a major role in eliminating synapses in developing brains. Based on this finding, we hypothesized that synapses in the adult brains is also refined by astrocytic phagocytosis, and that such elimination is critical for maintaining circuit homeostasis.

2. Contents

We first developed a novel sensor to detect synapse elimination by glial cells in the adult brains. We took advantage of an mCherry-eGFP reporter system that has been previously utilized to monitor autophagic acidification influx. Whereas both mCherry and eGFP maintain intact fluorescent intensities under neutral

pH conditions, only the mCherry but not eGFP signal is preserved in acidic environments, such as in the lysosome. By tagging an identical pH-indicator (i.e. mCherry-eGFP) to different synapse types, we show that our AAV-based synapse phagocytosis reporters accurately incorporate into excitatory and inhibitory synapses in vivo and produce mCherry-alone puncta when they are engulfed by glial cells (Fig 1).

Next, to specifically block synapse elimination by astrocytes, we generated astrocyte-specific Megf10 knock-out animals where Megf10 deletion was achieved by tamoxifen-induced Cre activation. Using these animals, we were able to selectively and locally downregulate astrocytic synapse phagocytosis in the hippocampus.

Using these novel tools, we show that, for the first time, it is astrocytes, but not microglia, that constantly eliminate excessive and unnecessary adult excitatory synaptic connections in response to neuronal activity. We further show that without this astrocytic function, precise re-patterning and homeostasis of hippocampal circuit connectivity cannot be maintained. As a result, the animal with defective astrocytic phagocytosis also showed impaired hippocampal learning and memory.

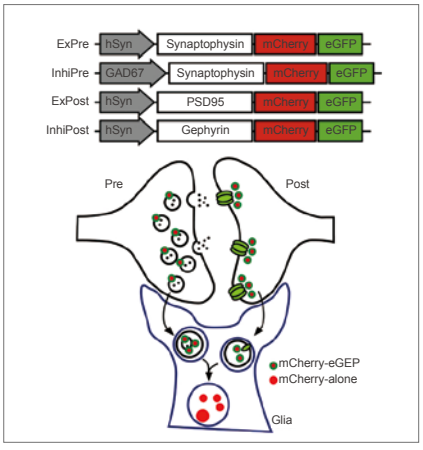

Figure 1.
A working model of mCherry-eGFP synapse phagocytosis reporter

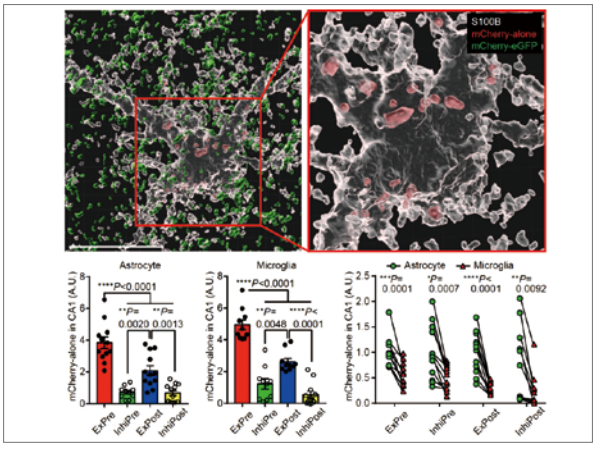

Figure 2.
3D reconstruction showing astrocyte (White, S100B) with reporter-tagged synapses (green, mCherry-eGFP) and engulfed synapses (red, mCherry-alone). Detailed quantification revealed astrocytes play a major role in eliminating excitatory synapses than microglia in the adult hippocampus.

3. Expected effects

Our paper challenges the general consensus in this field that microglia are the primary synapse phagocytes that control synapse number in the brains. By utilizing unbiased synapse phagocytic reporters, we show that at least in the adult hippocampal CA1 region, astrocytes are the major player in eliminating synapses, and this astrocytic function is essential for controlling synapse number and plasticity. Secondly, our study shed light on the functional role of synapse elimination during learning processes: not only making new ones, memory learning and storing information also require eliminating unnecessary connections. We provide evidence that astrocytes play a major role in this process.

We are just beginning to understand how astrocytic phagocytosis affects synapse maturation and homeostasis. In our preliminary data, each brain regions appears to have different rates of synapse elimination by astrocytes. Such differences can be originated from various internal or external factors. Elucidating how astrocytes integrate those factors and modulate each circuit would be our immediate next steps. Our long-term goal is understanding how astrocyte-mediated synapse turnover affects the initiation and progression of various neurological disorders.

Research outcomes

[Paper] Lee JH*, Kim JY*, Noh S, Lee H, Lee SY, Mun JY, Park HJ*, Chun WS*. Astrocytes phagocytose adult hippocampal synapses for circuit homeostasis, Nature (Article), 23 December 2020. (* Equally contributed).

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