

## Microglia: The new players in regulating the brain development.

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Microglia are the immune cells in the central nervous system and control the brain homeostasis [1]. When microglia find either infected or dead cells in brain, they are activated and ingest debris to maintain the normal brain condition. Although microglia modulate brain environment via macrophage-like aspects, they also play important roles in the developing brain. In the past few years, several researchers found a novel property of microglia that underlie the development of brain. These findings possibly shed light on the novel mechanisms by which the higher brain functions are mediated by microglia.

A few years ago, it was reported that microglia arise from embryonic yolk sac and infiltrate into brain during early developmental stage, followed by differentiation of matured microglia [2]. It was also reported that microglia are differentiated from monocyte-derived macrophage, which invade the injured brain [3]. After maturation, microglia govern the immune system in brain. Perturbed brain homeostasis by runaway microglia leads to neurotoxicity associated with neurodegenerative disorders such as Alzheimer diseases and Parkinson's diseases [4]. Therefore, precise control of microglia is critically important for modulating the brain circumstances. In addition, recent finding has demonstrated that microglia are not only responsible for the regulation of injured brain, but also associate with the normal brain development [5].

It has been shown that microglia are active and survey the synaptic region even in a resting state. *In vivo* imaging analysis revealed that microglia labeled by Iba1-EGFP elongate their processes to check the synaptic sites in intact brain [6], suggesting that one of the microglial functions is to survey the brain environment in uninjured circumstances. This observation raised the question of why microglia are dynamic even in normal conditions. Recently, several researches have provided potential clues to answer this question. A large number of synapses in neonatal brain are eliminated after connecting excess synapses when synapses are not activated by external stimulation. For instance, complement receptor 3 (CR3) on microglia recognizes complement component C3,

which are localized in synapse-enriched sites, contributing to engulfment of the silent synapses [7]. In addition, another complement, C1q also plays an important role in the regulation of microglial engulfment in retinal ganglion site [8]. Notably, C1q expression is regulated by transforming growth factor (TGF)- $\beta$  signaling [9], leading to an activation of microglia. These observations suggested that extracellular proteins, such as growth factors and cytokines, are crucial for controlling the synapse pruning via microglial functions.

There is no doubt that an establishment of neuronal circuit mediated by microglia is essential for brain development. Perturbed microglial functions are known to be associated with developmental disorders, such as autism [10]. Indeed, the number of activated microglia is increased in an autistic spectrum disorder cases [11]. Moreover, microglial distributions are preferentially changed in prefrontal cortex in autistic post-mortem brain [12]. These observations may provide a relationship between abnormal microglial activity and developmental disorders. However, little is known about the mechanisms that link microglial properties to developmental disorder despite its importance. Under developmental stages, an uptake of nutrients from dietary components is crucial for the formation of tissues, including brain. It is easy to assume that lack of nutrients impairs an acquirement of higher brain functions. Intriguingly, recent study has suggested that uptake of breast milk containing tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which is a typical cytokine that activates microglia, is implicated in hippocampal development [13]. Moreover, gut microbiota is involved in regulating the microglial maturation and functions via production of short-chain fatty acids [14]. These observations imply that dietary components and gut bacteria may be significant factors that control microglial activation under developmental stages. Thus, elucidation of this mechanism would be challenging future work.

Consequently, microglia are thought to be key players that control brain development through regulating both synaptic pruning and neural circuit. Given that microglia are essential for the normal brain functions, precise control

of their activation may be useful pharmacological target against not only neurodegenerative disorders but also developmental disorders.

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