

News Release

Title

Astrocyte is the secondary phagocyte in the brain

Key Points

- A new mechanism, which backs up microglial phagocytic activity in the brain, was found.
- Astrocytes are capable of compensating for phagocytic activity of impaired microglia.
- The regulation of phagocytic property of astrocytes may lead to new therapies that accelerate debris clearance in the aged and injured brain.

Summary

Assist. Prof. Hiroyuki Konishi and Prof. Hiroshi Kiyama (Department of Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine) found a new mechanism that accelerates clearance of cellular debris in the brain.

The frequency of spontaneous cell death increases with aging in the brain. A large number of cells die in the event of brain injury such as ischemia. Because accumulation of cellular debris causes detrimental effects on surrounding cells, rapid removal of dying or dead cells is crucial for the maintenance of brain environment. Microglia, a type of glial cells in the brain, are well-known as professional phagocytes of cellular debris. The present study revealed that astrocytes, another type of glial cells, served as the secondary phagocytes that back up microglia. Microglia were the primary phagocytes, and astrocytes did not perform phagocytosis in a healthy brain, although they possessed phagocytic machinery. Upon impairment of microglial phagocytosis, however, astrocytes elicited their phagocytic activity to compensate for microglial dysfunction. Further investigation of the compensatory function of astrocytes may lead to new therapies that accelerate debris clearance from the aged or injured brain.

Research Background

Cell death occurs with some frequency even in a healthy brain. Because accumulation of cellular debris causes detrimental effects on surrounding cells, such as excessive inflammation, rapid removal of dying or dead cells is crucial for the maintenance of brain environment. Microglia are well-known as professional phagocytes of cellular debris in the brain. While the frequency of spontaneous cell death is increased with aging, microglial phagocytic capacity is reduced. In the event of neural injury such as ischemia and spinal cord injury, a large amount of cellular debris can overwhelm microglial capacity. In this context, alternative clearance systems may support microglial phagocytosis in the brain.

Research Results

To address a possible existence of alternative clearance system, a microglia ablation model, in which microglial debris can be tracked in the absence of microglial phagocytosis, can provide insights. In an ablation model highly specific for microglia, microglial debris were completely cleared even in the absence of functional microglia (Figure 1), suggesting that microglia-independent clearance system was actuated. We found that astrocytes became activated with upregulation of glial fibrillary acidic protein (GFAP) and extended their processes to phagocytose microglial debris (Figure 2). Gene knockdown experiment revealed that Axl and Mertk expressed on astrocytic plasma membrane cooperatively worked as the main phagocytic receptors for microglial debris (Figure 3). Both Axl and Mertk were expressed in astrocytes even in a healthy brain, suggesting that astrocytes possess phagocytic machinery in the steady state.

These results suggested that astrocytic phagocytosis compensated for microglial dysfunction; however, this phenomenon was demonstrated in an artificial condition, in which most microglia were ablated in a short period of time. We therefore tested the phenomenon in a more natural condition (Figure 4). In a healthy brain, there are a small number of cellular debris, all of which were phagocytosed by microglia in wild-type mice. In IRF8 knockout mice, however, microglial phagocytic activity was impaired, and almost a half of cellular debris were phagocytosed by astrocytes, not by microglia. These results indicate that astrocytic phagocytosis is elicited by and compensates for microglial dysfunction (Figure 5).

Figure 1: Clearance of microglial debris after microglial ablation

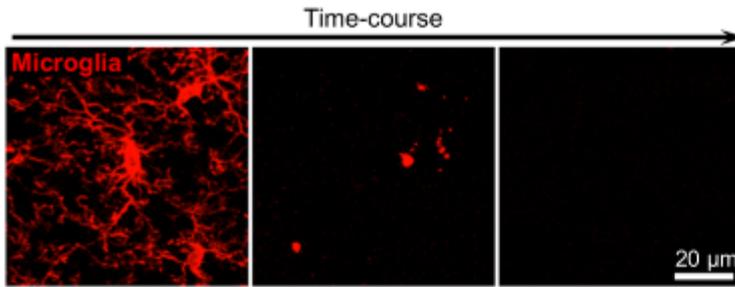


Figure 2: Phagocytosis of microglial debris by astrocytes

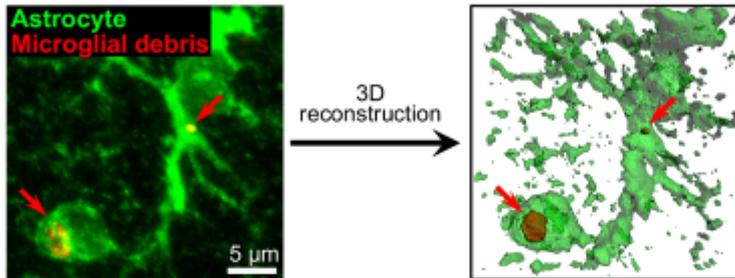


Figure 3: Axl and Merck cooperatively act as phagocytic receptors of astrocytes

Amount of microglial debris phagocytosed by astrocytes

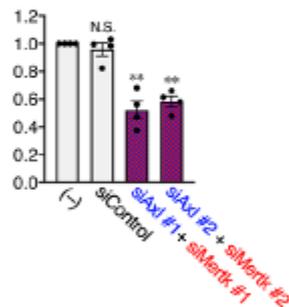


Figure 4: Phagocytosis of spontaneous apoptotic cells by astrocytes in IRF8^{-/-} mice

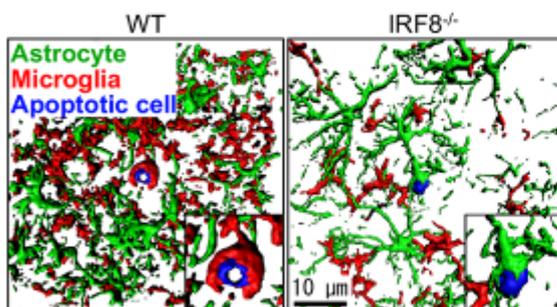
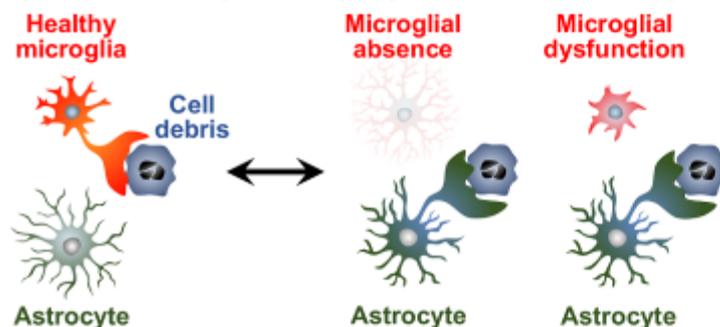


Figure 5: Astrocytic phagocytosis is actuated by microglial dysfunction



Research Summary and Future Perspective

The present study demonstrated that astrocytes possess phagocytic machinery, which can be actuated in the event of microglial dysfunction. Further studies are necessary to reveal mechanisms underlying induction of the phagocytic action of astrocytes. Investigation of phagocytic properties of astrocytes may lead to new therapies that accelerate debris clearance in the aged and injured brain.

Publication

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