News Release

Title

Dual Microglia Effects on Blood Brain Barrier Permeability Induced by Systemic Inflammation

Summary

The research team led by Prof. Hiroaki WAKE (Department of Molecular Cell Biology and Anatomy) of Graduate School of Medicine, Nagoya University (Dean: Kenji Kadomatsu, M.D., Ph.D) found a novel function of microglia on the permeability of the Blood Brain Barrier.

Peripheral organ status and systemic circulation are increasingly recognized as factors that impact cognitive performance and neuronal disease. This can range from acute severe illness and fever causing malaise and poor cognition, from sepsis causing subsequent neurological disease and cognitive failure, through to chronic systemic inflammation associated with smoking, diabetes, chronic periodontitis and even aging, leading to an increased risk of dementia or neurodegenerative disorders.

Although it is known that microglia respond to injury and systemic disease in the brain, it is unclear if they modulate blood-brain barrier (BBB) integrity, which is critical for regulating neuro-inflammatory responses. Here using the *in vivo* two photon microscope, they visualized microglia and vessels in living mice, and demonstrate that microglia respond to inflammation by migrating towards and accumulating around cerebral vessels, where they initially maintain BBB integrity via expression of the tight-junction protein Claudin-5 before switching, during sustained inflammation, to phagocytically remove astrocytic end-feet resulting in impaired BBB function.

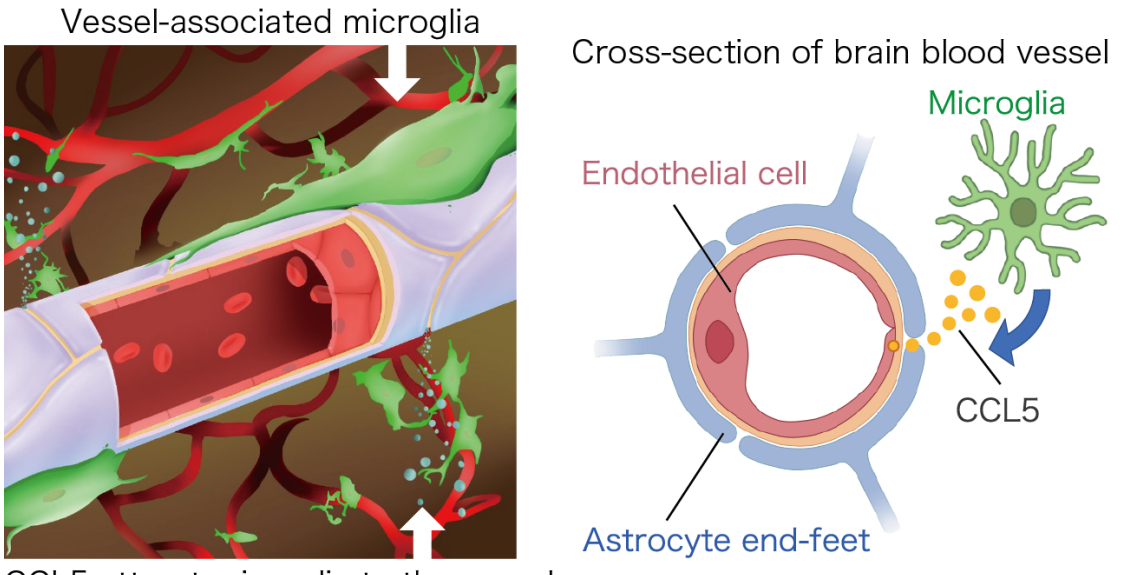
Research Background

BBB function is essential to maintain the homeostasis of the brain environment. It has been known that increased BBB permeability was observed in several neurological and psychiatric diseases. In addition, microglia as sole immune cell has been recently focused on their involvement in neurological and psychiatric diseases with their activation form. However little is known how microglia can have the function for BBB permeability. Here

in this study, the research team examined the role of microglial functions in regulation of BBB integrity, focusing on changes of microglia depends on inflammation progression. Using *in vivo* two-photon imaging, they showed that microglia migrated to the cerebral vessels in response to systemic inflammation which was associated with increased BBB permeability.

Research Results

The research team demonstrated that microglia respond to inflammation by migrating towards and accumulating around cerebral vessels. It was also found that the chemokine CCL5 produced by vascular endothelial cells attracts microglia to blood vessels during early systemic inflammation (Figure 1). Those accumulations promote CLDN5 expression in microglia to form tight junction with endothelial cells, and thus protect BBB integrity. Electron microscopy revealed that vessel-associated microglia directly contacted with the endothelial cells in the auto-immune disease model mouse. Prolonged inflammation results in microglia to be more activated phenotype, resulting in increased phagocytic function to actually phagocyte astrocytic end-feet that resulting in impaired BBB permeability. Furthermore, inhibition of microglia activation with minocycline reduced increase BBB permeability during late phase of inflammation. Our results implicate microglia as playing a dual role in BBB permeability during systemic infection and inflammation, with important implications for understanding how systemic diseases may adversely impact on neural circuits and brain functions (Figure 2).



CCL5 attract microglia to the vessel

Figure 1: Systemic inflammation triggers microglia migration to the cerebral vessels.
It was revealed that CCL5 is produced from endothelial cells during systemic inflammation, and that attract microglia to the vessels.

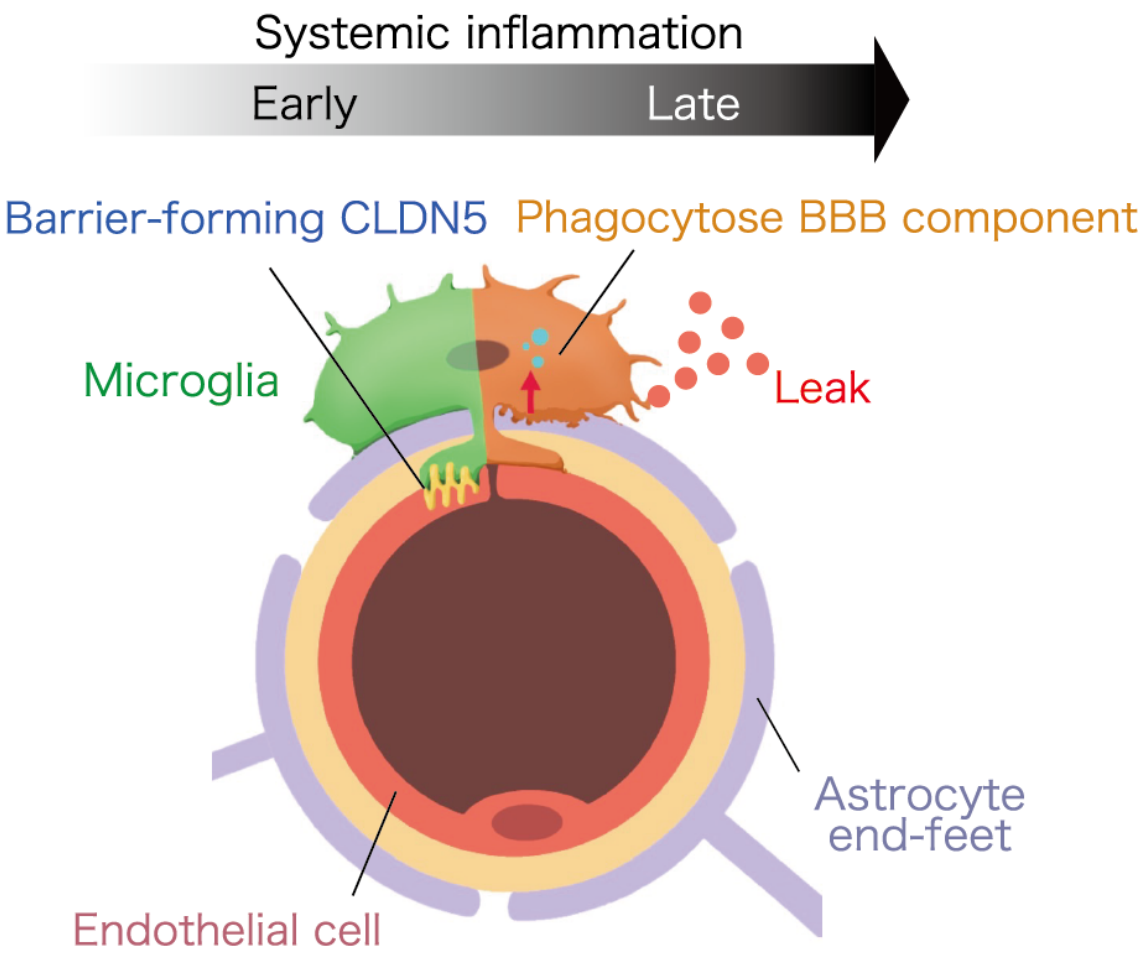


Figure 2: Functions of microglia involved in changes of blood-brain barrier due to systemic inflammation.
CLDN5 positive microglia maintain BBB integrity during early phase of inflammation. Microglia phagocytosis astrocytic end-feet impaired BBB function in late phase.

Research summary and future perspective
Microglia accumulate in blood vessels in response to CCL5 signals in early phase of systemic inflammation. Microglia are involved in both the protection and impairment of the BBB, depending on inflammation progression. Inhibition of microglia activation

suppressed the BBB dysfunction. This result should help to contribute to the development of new preventive and therapeutic methods in diseases of the central nervous system caused by systemic inflammation.

Publication

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Koichiro Haruwaka[1,2,3], Ako Ikegami[1], Yoshihisa Tachibana[1], Nobuhiko Ohno[4,5], Hiroyuki Konishi[6], Akari Hashimoto[1], Mami Matsumoto[7,8], Daisuke Kato[1,9], Riho Ono[1], Hiroshi Kiyama[6], Andrew J Moorhouse[10], Junichi Nabekura[2,3] and Hiroaki Wake[1,9,11,12*]

1. Division of System Neuroscience, Kobe University Graduate School of Medicine, Kobe, Japan
2. Division of Homeostatic Development, National Institute for Physiological Sciences, National Institutes of Natural Sciences, Okazaki, Japan
3. Department of Physiological Sciences, The Graduate School for Advanced Study, Hayama, Japan
4. Department of Anatomy, Division of Histology and Cell Biology, Jichi Medical University, Tochigi, Japan
5. Division of Ultrastructural Research, National Institute for Physiological Sciences, Okazaki, Japan
6. Department of Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine, Nagoya, Japan
7. Section of Electron Microscopy, Supportive Center for Brain Research, National Institute for Physiological Sciences, Okazaki, Japan
8. Department of Developmental and Regenerative Biology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan
9. Department of Anatomy and Molecular Cell Biology, Nagoya University Graduate School of Medicine, Nagoya, Japan
10. School of Medical Sciences, The University of New South Wales, Sydney, Australia
11. Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Saitama, Japan
12. Precursory Research for Embryonic Science and Technology, Japan Science and Technology Agency, Saitama, Japan.

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