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Uncovering new details of the brain's first line of defense

Researchers report in unprecedented detail how some of the brain's immune cells develop, and how to distinguish them from other cells

Fukuoka, Japan—Thanks to over a century of modern neuroscience, we have made significant strides in our understanding of the brain. Nonetheless, we have only just begun to scratch the surface of how this amazingly complex organ works.

Digging deeper into this perplexing puzzle, researchers from Kyushu University's Faculty of Pharmaceutical Sciences have now analyzed in unprecedented detail the development and genetic profile of a set of cells that construct the brain's immune system.

Their new insights, published in the journal *Nature*, could pave the way for better understanding the origins and mechanisms behind leading brain-related pathologies such as Alzheimer's disease and multiple sclerosis.

"Many people are familiar with how neurons connect together to send signals across the brain, but there are also blood vessels that supply the brain with oxygen, and glial cells that act as the brain's support network and immune system," explains Takahiro Masuda, who led the study. "In fact, even the most generous estimates suggest only about half of the cells in our brains are neurons, so studying the other cells is just as vital for uncovering how the brain works."

With this in mind, the research team has been focusing on a series of cells called 'central nervous system associated macrophages' a type of immune cells that protect the brain from infection. These macrophages are thought to be involved in almost all known neurodegenerative diseases due to their critical role as the immune cells of the brain.

Over the years, research has shown that many different kinds of these cells exist. For this study, the team was particularly interested in the macrophages surrounding blood vessels and those located in the meninges—the layers that surround the brain—known as 'perivascular macrophages' and 'meningeal macrophages,' respectively.

"Until now, these cells were not distinguished from other immune cells, and how and where these critical cells develop was significantly understudied," continues Masuda. "So, we investigated fundamental characteristics of these cells, such as how to distinguish them from other cells in the brain, their exact locations, how they develop, what kind of genes they express, and how they interact with other cells."

These macrophages, along with the brain's other immune cells called microglia, originate from outside the embryo in an area known as the 'yolk sac.' As the organism develops, cells

migrate from the yolk sac into the brain. Using a technique called 'fate-mapping,' the team precisely traced where these cells ended up and discerned what leads them to become perivascular macrophages and meningeal macrophages.

"We found that meningeal macrophages develop in the same way as other microglia and are formed during gestation. Perivascular macrophages, on the other hand, actually begin to form after birth, and originate from the meningeal macrophages. This was very unexpected," states Masuda.

Through their research, the team was also able to identify the specific genes that lead to the generation of meningeal and perivascular macrophages.

"Identification of these genes will finally allow us to distinguish meningeal and perivascular macrophages from other microglia," explains Masuda. "Now that we can study them individually, we can get a clearer picture of their functions."

These findings are expected to open new avenues of understanding on the role of these cells in the brain.

"Now that we know they are distinct, the next step is to figure out their functions. As their mechanisms are revealed, we hope to understand their role in pathologies like Alzheimer's, autism spectrum disorder, and multiple sclerosis," concludes Masuda.

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For more information about this research see "Specification of CNS macrophage subsets occurs postnatally in defined niches," Takahiro Masuda, Lukas Amann, Gianni Monaco, Roman Sankowski, and Marco Prinz, *et al.*, *Nature* (2022). https://doi.org/10.1038/s41586-022-04596-2

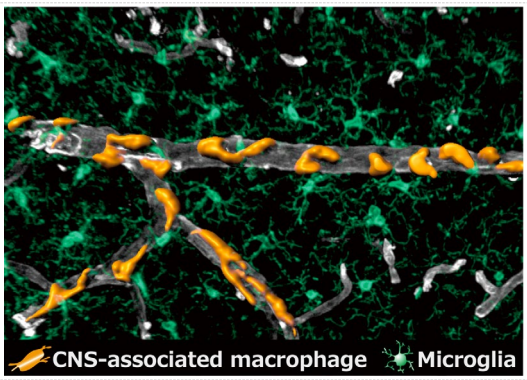

Fig. 1. Image of central-nervous-system-associated macrophages in the brain. Perivascular macrophages (in orange) surrounding a vein in the brain (in grey). Microglia (in green) occupy the surrounding space as the other cells of the brain's immune system. (Kyushu University/Takahiro Masuda)

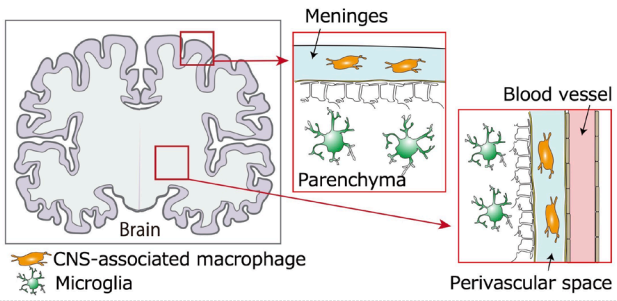

Fig. 2. Location and distribution of central-nervous-system-associated macrophages. This diagram shows how macrophages associated with the central nervous system (CNS) are distributed in the brain. Meningeal macrophages are localized in the meninges. Perivascular macrophages surround the arteries of the brain in the perivascular space.

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For more information about this research, see "A high-valent Fe(IV)-peroxo core derived from O2," Takahiro Kishima, Takahiro Matsumoto, Hidetaka Nakai, Shinya Hayami, Takehiro Ohta, and Seiji Ogo, *Angewandte Chemie International Edition* (2015), https://doi.org/10. 21507022

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Fig. 1.

Fig. 2.

・ 参考図の解説を明記する

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