News Release

Title

The new function of pericytes in the developing brain

–Pericytes facilitate microglial homeostasis and contribute to brain development–

Summary

In this study, Assistant Professor Yuki Hattori and Professor Takaki Miyata in Nagoya University Graduate School of Medicine (dean: Kenji Kadomatsu, M.D., Ph. D.) demonstrated that pericytes, the mural cells surrounding vascular endothelial cells, contribute to microglial homeostasis in the developing brain.

Microglia are the resident immune cells in the central nervous system. These cells provide various functions, such as promoting the differentiation of neural progenitors and supporting vascular formation. On the other hand, pericytes have been reported to play roles in the regulation of vascular circulation and the maintenance for blood brain barrier integrity.

The research group newly found that pericytes support microglial survival and proliferation in the developing cerebral walls. In the developing brain, pericytes partly cover the capillary surface area. Of note, microglia are preferentially associated with the vascular region covered with pericytes. They showed that microglial density was markedly decreased in the pericyte-depleted mouse brains. In addition, pericyte depletion resulted in a failure of microglia to promote the differentiation of neural progenitors. Moreover, in vitro coculture of isolated microglia and pericytes from the embryonic brain indicated that pericytes promote microglial proliferation via the production of soluble factors.

This study suggests that pericytes function not only in the vascular stability but also in microglial homeostasis in the developing brain. It is important to know the correlation and interaction between the various cell types that constitute the brain for the better understanding of brain development. These findings will expand our knowledge and help elucidate the mechanism of brain development both in healthy and disease conditions.

This study was performed with the cooperation of Professor Akiyoshi Uemura in Nagoya City University Graduate School of Medical Sciences.

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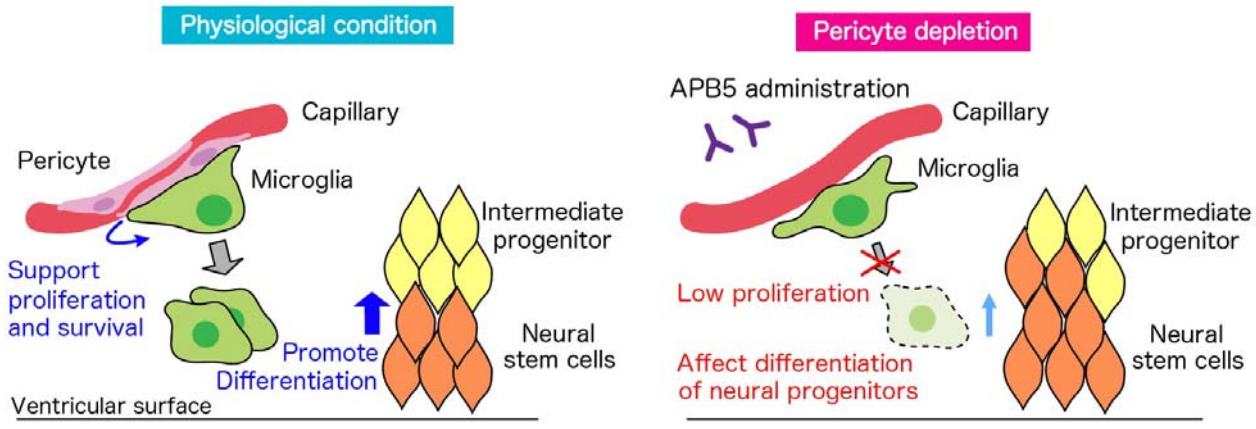


Key Points

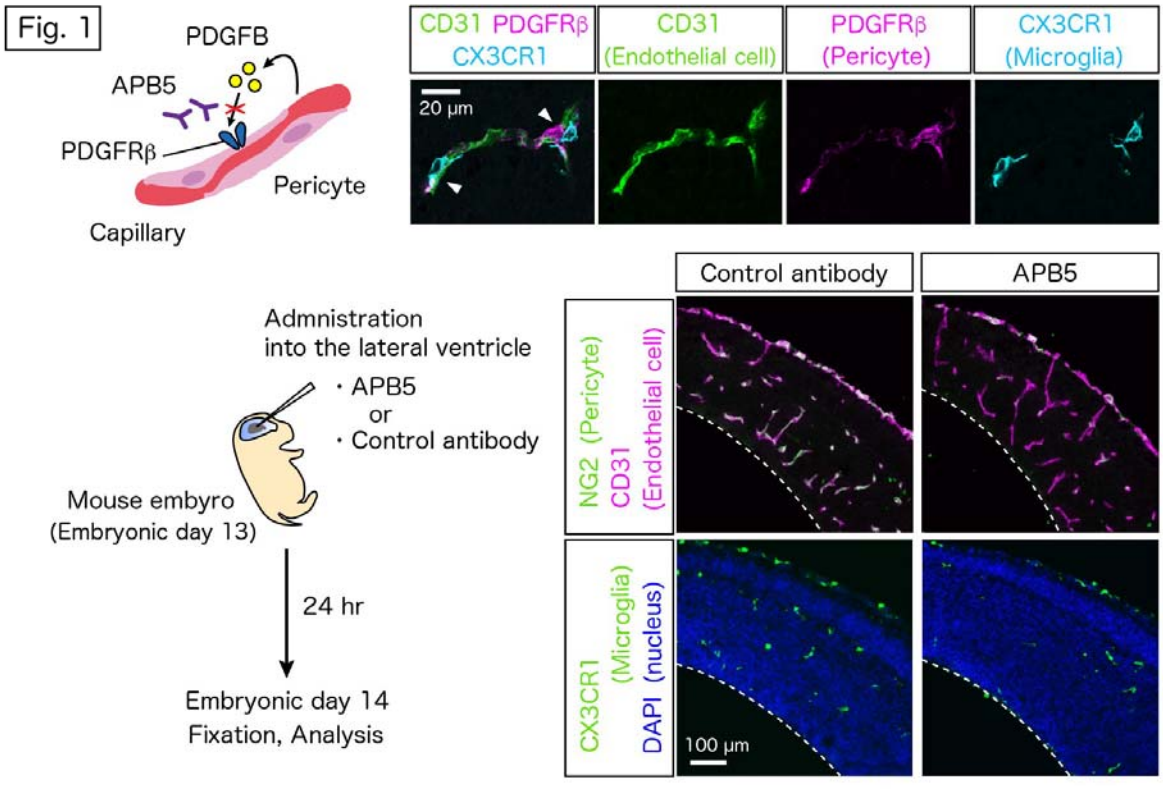
- ○ The research group succeeded in specifically removing pericytes by the injection of function-inhibiting antibody against pericytes into the ventricle of mouse embryos.
- ○ Pericyte removal caused a decrease of microglia in the cerebral wall and affected the differentiation of neural progenitors.
- ○ This study suggests that pericytes function not only in the maintenance of cerebral microcirculation and blood brain barrier integrity but also in microglial homeostasis in the developing cerebral walls.

1. Research Background

Our brains are composed of not only neural lineage cells but the immune cells microglia, and these cells cooperatively work for brain proper function. Microglia are born at yolk sac in the early embryonic stage, and then colonize the brain with increasing their cell number. There is increasing evidence of microglial function in the developing brain, i.e., they promote the differentiation of neural progenitors, regulate the positioning and maturation of neurons, and also contribute to vascular formation. On the other hand, pericyte, the mural cells surrounding vascular capillaries, support the maintenance and stability of vascular formation. The research group found that microglia are selectively associated with the vascular region which is covered with pericytes and investigated the interaction between pericytes and microglia.

2. Research Results

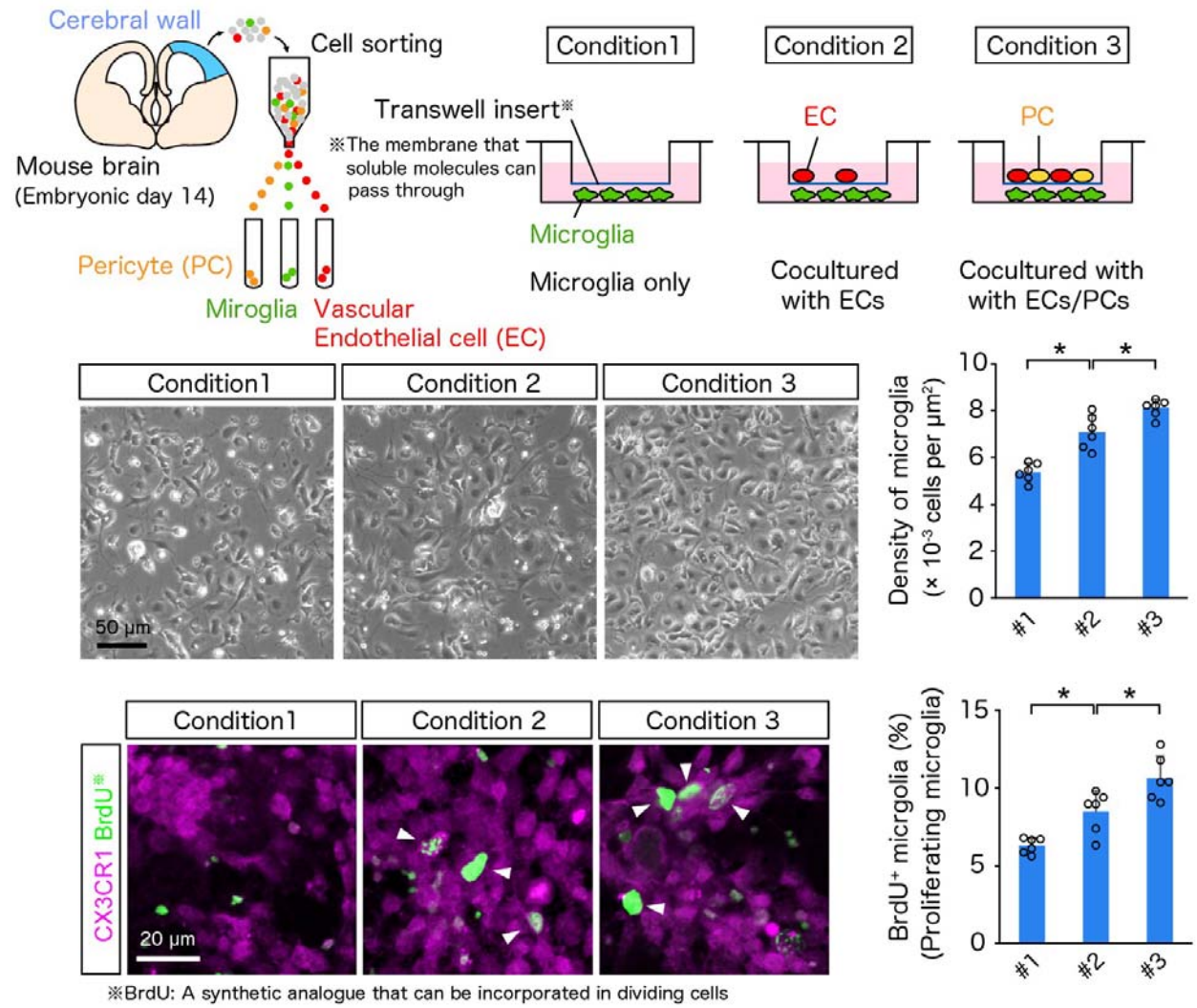
In the developing cerebral wall, about half of microglia are in contact with blood vessels. About 80% of the surface area of vascular endothelial cells is covered with pericytes. The research group found that microglia do not directly contact with blood vessels, but selectively associate with the area which is covered with pericytes (Fig. 1).



To investigate the relationship between pericytes and microglia, the research group established the method to remove pericytes in the brain. They administered a neutralizing antibody against pericyte-derived growth factor receptor beta (PDGFRb) to the lateral ventricle of mouse embryos. This antibody (clone name: APB5) inhibits the signal activation by platelet-derived growth factor beta (PDGFB), which is necessary for pericyte proliferation. The administration of APB5 successively depleted pericytes by inducing them to undergo apoptosis. They found that the density of microglia was significantly decreased in pericyte-depleted brains compared to control groups.

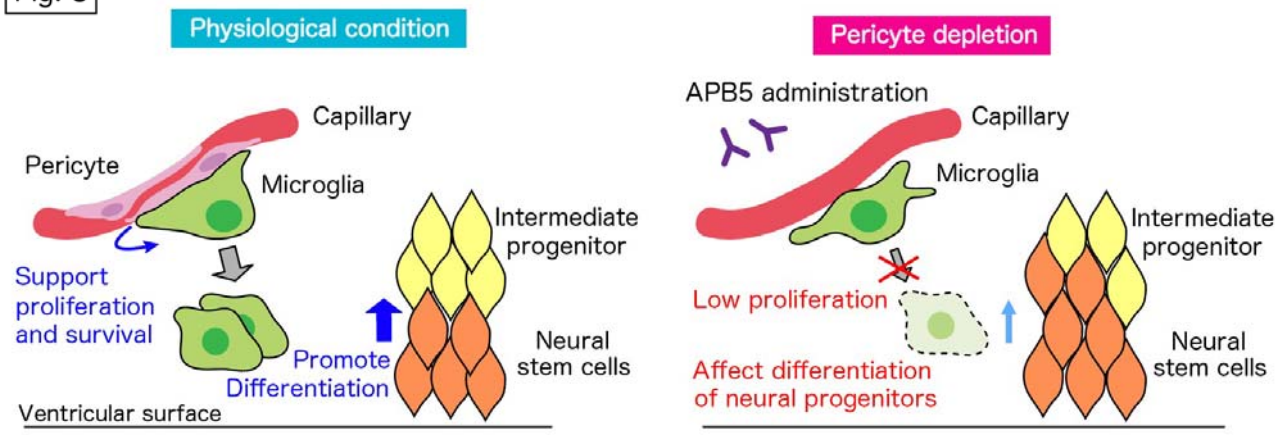
To test whether pericytes directly contribute to microglial proliferation, the research group performed triple co-culture experiment of pericytes, microglia, and vascular endothelial cells, which are isolated from brain tissue. When cultured with only vascular endothelial cells, microglial proliferation was increased compared to microglia only culture, but it was augmented by the addition of pericytes together with endothelial cells. These results indicate that pericytes directly support the survival and proliferation of microglia (Fig. 2).

Fig. 2



Previous studies showed that microglia promote the differentiation of neural stem cells into intermediate progenitors. They compared the number of these cell types between in pericyte-depleted brains and control groups, and found that the number of intermediate progenitors was significantly decreased in pericyte-depleted brains. In contrast, the number of neural stem cells was increased, instead. These results indicate that a decrease in microglia due to pericyte removal caused an increase in immature neural stem cells because microglia could not fully function of promoting the differentiation of neural progenitors (Fig. 3).

Fig. 3



3. Future Perspective

Previous studies reported that pericyte play roles in stabilization of vascular structure, maintenance of blood-brain barrier, and regulation of microvascular circulation. Here, the research group newly demonstrated that pericytes also contribute to microglial homeostasis by supporting the proliferation of these cells. This research is expected to contribute to the better understanding of the molecular mechanism of brain development under not only physiological conditions but also pathological state. In recent years, it has been suggested that maternal immune activation (infectious diseases, undernutrition, preeclampsia, etc.) change the environment in the fetal brain and lead to the development of mental illness. Thus, it is important to investigate the function of not only neural cells but also various cell types such as microglia, pericytes, and vascular endothelial cells, and the significance of the interaction between these cell types. This study may provide valuable insights into brain development research.

4. Acknowledgements

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5. Publication

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Title: Embryonic pericytes promote microglial homeostasis and their effects on neural progenitors in the developing cerebral cortex

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