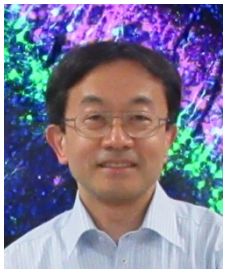
【Grant-in-Aid for Scientific Research (S)】

Broad Section G



Title of Project： Mechanisms of corticogenesis in the developing brain

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Research Project Number: 20H05688 Researcher Number：90280734
Keyword：cortex, development and differentiation, morphogenesis, neuron, glia

【Purpose and Background of the Research】

Mammalian brains have an important structure called the cortex on the surface of the brain, which is composed of innumerable neurons arranged in a layered structure.

In this study, we propose to clarify the mechanism by which the three-dimensional basic structure of the cortex is constructed during development through interactions among the cells that compose it. First, we intend to clarify the mechanisms by which the cerebral cortical neurons migrate from their site of birth, appropriately differentiate into specific subtypes of neurons, and then are arranged in orderly layers near the brain surface. In addition, we shall attempt to clarify where and how astrocytes, which are more abundant than neurons in the brain, are produced, differentiated, and widely distributed in the cortex. Furthermore, we shall attempt to understand how the three-dimensional global morphological changes of the entire tissue are controlled by cell-cell interactions and the like.

【Research Methods】

Neurons in the cerebral cortex form a layered structure just beneath the surface of the brain in a so-called “inside-out.” Reelin, a molecule that controls the cell migration and positioning in this manner, is secreted by the Cajal-Retzius cells in the marginal zone on the surface of the brain. We previously determined that reelin alone regulates the arrangement of the cortical neurons in this “inside-out” manner, through experiments in which reelin was expressed ectopically. In this study, we shall attempt to identify the underlying molecular mechanisms. We also determined that the final differentiation fate of each neuron can be modified by extracellular factors, and shall attempt to identify the underlying mechanisms. Since we recently discovered that astrocytes show a completely different migration pattern from that of the cortical neurons, we will also explore the mechanisms underlying the regulation of the dynamics and differentiation of astrocytes. Reelin was also found to play an important role in the formation of the brain gyri/sulci, so that we propose to investigate the changes that reelin causes in its target cells and clarify the mechanisms that control the morphological changes of the entire tissue.

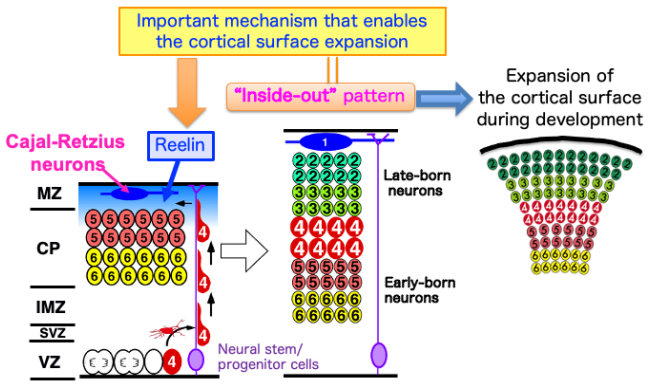

Figure 1 Development of cerebral cortex

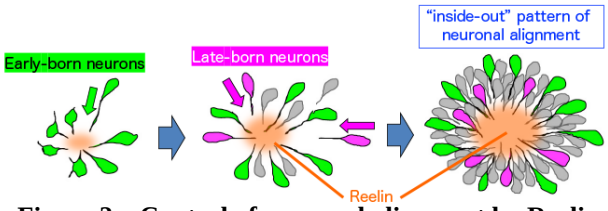

Figure 2 Control of neuronal alignment by Reelin

【Expected Research Achievements and Scientific Significance】

In recent years, attention has been focused on the possibility of minute abnormalities of the cortex that occur during development contributing to various neuropsychiatric disorders. In particular, abnormality of reelin regulation has been implicated in the development of schizophrenia, etc., and the results of this study might contribute to elucidation of the pathophysiology of these diseases.

【Publications Relevant to the Project】

- Matsunaga, Y., Noda, M., Murakawa, H., Hayashi, K., Nagasaka, A., Inoue, S., Miyata, T., Miura, T., Kubo, K., and Nakajima, K. "Reelin transiently promotes N-cadherin-dependent neuronal adhesion during mouse cortical development.", ***Proc. Natl. Acad. Sci. U.S.A.***, 114 (8), 2048-2053 (2017).
- Oishi, K., Aramaki, M., and Nakajima, K. “Mutually repressive interaction between Brn1/2 and Rorb contributes to establishment of neocortical layer 2/3 and layer 4.”, ***Proc. Natl. Acad. Sci. U.S.A.***, 113 (12), 3371-3376 (2016).

【Term of Project】 FY2020- 2024

【Budget Allocation】 151,300 Thousand Yen

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