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

Mechanisms underlying developmental establishment of adult neural stem cells and their stress responses

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Purpose and Background of the Research

●Outline of the Research

In the adult mammalian brain, neural stem cells (NSCs) reside in two areas, the hippocampus and the subventricular zone, and produce neurons throughout life. Adult neurogenesis has been shown to contribute to various cognitive functions such as learning and memory as well as mood control, and its defects have been associated with neurodevelopmental disorders and neurodegenerative diseases (Figure 1).

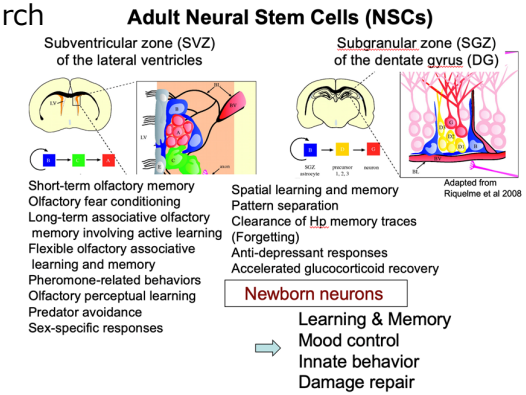

Figure 1. Adult neural stem cells and their proposed functions

So, it is important to elucidate how adult NSCs are established and maintained for a long period and how their fate is regulated in response to various environmental conditions such as stresses.

It has long been believed that adult NSCs are the remnants of embryonic NSCs involved in fetal brain development (Figure 2, top). However, we and other groups have identified embryonic origin of adult NSCs, which are set aside during development in a quiescent state (Furutachi et al. Nat Neurosci 2015; Harada et al. 2021; Yamaguchi et al. bioRxiv 2024) (Figure 2 bottom). In this study, we aim to elucidate how this embryonic origin of adult NSCs is formed during brain development and maintained through the postnatal stage and how this lineage is affected by embryonic and juvenile stress experiences.

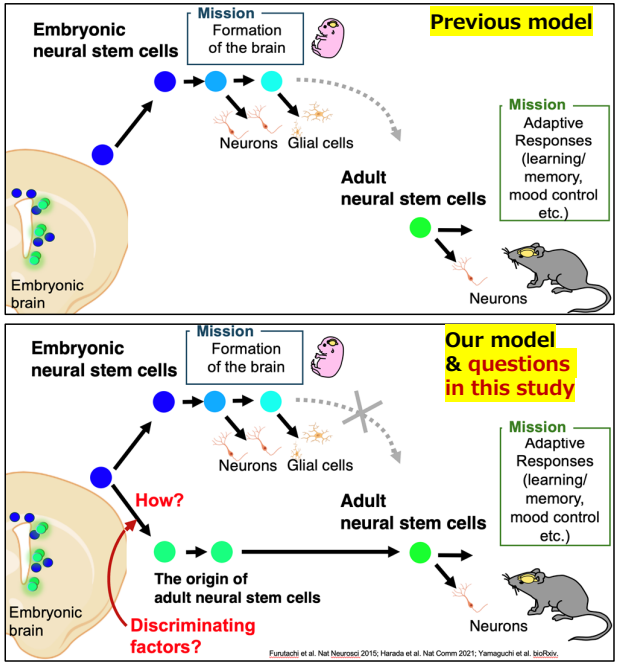

Figure 2. Discovery of the embryonic origin of adult neural stem cells

●Background of the study

We have previously shown that cell cycle arrest is responsible for the developmental acquisition of many properties of adult NSCs, including the long-term maintenance of stemness such as by activating the Notch-Hey1 and lysosomal pathways (Harada et al. Nat Comm 2021; Yuizumi et al. Stem Cells 2021, etc.). However, it is unclear how only some fast-dividing neuroepithelial cells are selected for this cell cycle arrest.

Expected Research Achievements

●How is the origin of adult NSCs formed and maintained?

In mice, cell cycle arrest is initiated in a small fraction of basal ganglia primordia around embryonic day 13. We will infer the trajectory of the adult NSC lineage from single cell transcriptomic analysis during this period and extract candidates of molecular signals that may be involved in the establishment of this lineage associated with the cell cycle arrest. The developmental relationship between adult NSCs and ependymal cells (which act as a niche for adult NSCs) will also be elucidated. In addition, we will investigate how the lineage of adult NSCs robustly maintains their ability to differentiate into neurons while maintaining their undifferentiated state as stem cells, and how they evade cellular damages (Figure 3).

● How do stress experiences affect the adult NSC lineage?

We have obtained preliminary results showing that the adult NSC lineage is affected by a variety of stress conditions. Therefore, we will examine in detail how each stress condition may affect the differentiation potential of the adult NSC lineage and the mechanisms by which these stress responses occur. We will also investigate how these stress responses may regulate brain functions.

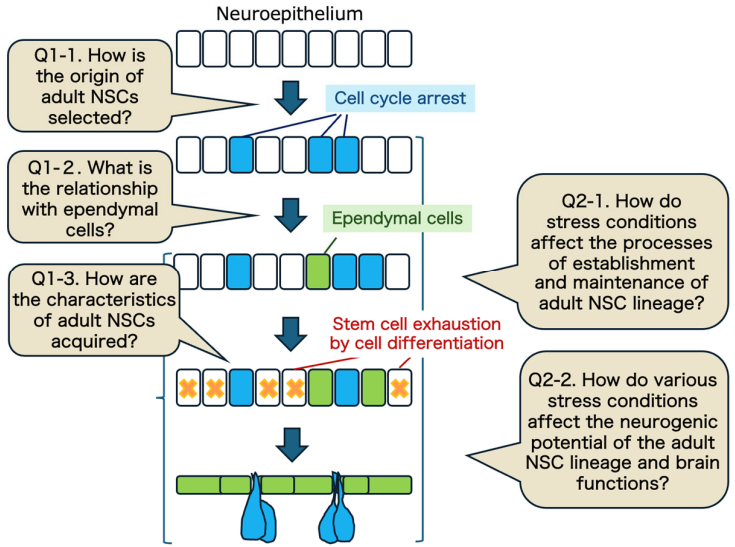

Figure 3. Research aims

Abnormalities in adult NSCs and neurogenesis have been reported to be associated with psychiatric and neurodegenerative disorders. This study is expected to provide basic knowledge about these diseases from a neurogenesis perspective, especially in relation to fetal and juvenile stress experiences, and to contribute to future therapeutic strategies.

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