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

Broad Section I

Title of Project： **Neurogenesis and its pathogenesis in the neonatal brain: an integrated understanding using advanced analytical techniques**

SAWAMOTO Kazunobu

(Nagoya City University, Graduate School of Medical Sciences, Professor)

Research Project Number: 20H05700 Researcher Number：90282350

Keyword：neonatal brain, neurogenesis, neural development, brain diseases, preterm birth

【Purpose and Background of the Research】

The number of patients with cerebrovascular diseases and dementia is increasing among the elderly, due to the rapid aging of the population and the declining birth rate in Japan. On the other hand, the development of perinatal care has enabled premature and preterm infants to survive, but the proportion of newborns with brain dysfunction is increasing.

New neurons, continuously generated in the human neonatal brain from neural stem cells, are thought to be involved in normal brain development and disease pathogenesis. To translate this phenomenon into therapies, we need to elucidate the mechanism of brain cell production, or "neurogenesis".

We have been studying the migration of new neurons produced from stem cells in the ventricular-subventricular zone (V-SVZ) of the postnatal brain. We have discovered various mechanisms by which neonatal neurons interact with their surrounding cells. In this study, we aim to investigate the mechanisms and pathogenesis of neurogenesis in the neonatal brain in an integrated and comprehensive manner, and to gain a more complete understanding of the mechanisms.

【Research Methods】

In this study, we will use several recently-established analytical-techniques to elucidate the interaction between migrating and maturing brain cells and surrounding cells, during the neonatal period. Three-dimensional electron microscopy (SBF-SEM) techniques will be used to reveal the fine morphology of stem cells and their surrounding cells. To elucidate the molecular mechanisms responsible for cell-cell interactions by multi-omics analysis including 3D electron microscopy, metabolomic analyses, proteome, and single-cell RNA-seq.

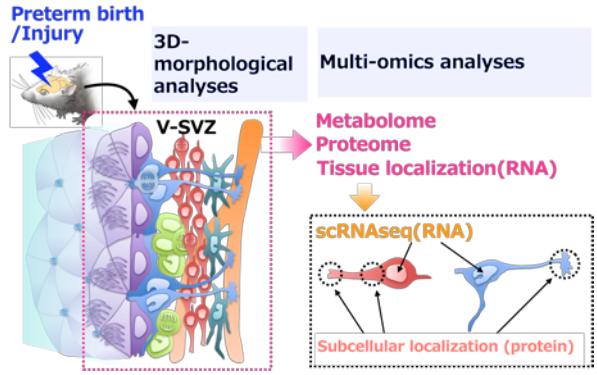

Figure 1 Methods used in this study

Shinji Saito (Nagoya City University) will evaluate the preterm birth model and provide clinical medical advice as a pediatrician, Kotaro Kimura (Nagoya City University) will analyze cell migration patterns and electron microscopy images using AI technology, and Katsura Zaitsu (Nagoya University) will conduct metabolomic analysis using PESI-MS/MS.

【Expected Research Achievements and Scientific Significance】

This study will enable us to capture the cellular architecture of the V-SVZ and morphological changes in each cell during development, as well as to comprehensively understand the mechanisms and significance of these changes at the level of genes, proteins and metabolites. The results of this research may extend beyond the scope of neuroscience to other medical and biological fields. In addition, the research may lead to the elucidation of the causes of developmental disorders and to the development of preventive and therapeutic methods, as well as providing clues to understanding the low regenerative capacity of the adult brain and contributing to the development of new treatments for intractable neurological diseases.

【Publications Relevant to the Project】

- Jinnou H, Sawada M, Kawase K, …, Ajioka I, Saitoh S, Sawamoto K. Radial glial fibers promote neuronal migration and functional recovery after neonatal brain injury. ***Cell Stem Cell*** 22: 128-137 (2018)
- Kaneko N, Herranz-Pérez V, Otsuka T, …, Kawaguchi Y, García-Verdugo JM, Sawamoto K. New neurons use Slit-Robo signaling to migrate through the glial meshwork and approach a lesion for functional regeneration. ***Sci Adv*** 4: eaav0618 (2018)
- Sawada M, Ohno N, Kawaguchi M, …, Nakagawa H, Uemura A, Sawamoto K. PlexinD1 signaling controls morphological changes and migration termination in newborn neurons. ***EMBO J*** 37: e97404 (2018)

【Term of Project】 FY2020-2024

【Budget Allocation】 119,900 Thousand Yen

【Homepage Address and Other Contact Information】

http://k-sawamoto.com/

sawamoto@med.nagoya-cu.ac.jp