Title of Project : Interplay of developmental clock and extracellular environment in brain formation

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Research Project Number : 16H06479 Researcher Number : 80224369

【Purpose of the Research Project】

During development, many events such as cell proliferation and differentiation occur at predictable times. If stem cells grow for too long or too short periods, the organ size will be abnormal. If differentiated cells are born at wrong times, they cannot interact with their neighbors properly. Either case results in abnormal tissue formation.

During cortical development, neural stem cells proliferate while changing their competency over time according to the programmed schedule. They give rise to deep-layer (layers 5 and 6) neurons first and then superficial-layer (layers 2, 3, and 4) neurons (Fig. 1). After neurogenesis, neural stem cells produce glial cells (Fig. 1). Eventually, the complex structures such as layers, columns, and areas are formed. Because neural stem cells are able to change their competency autonomously, it has been suggested that an internal biological clock may control the developmental processes in these cells. On the other hand, extracellular environments, which also change over time, feedback to the clock in neural stem cells. Thus, the interplay of developmental clock in neural stem cells and extracellular environment is very important for neocortical development. In this project, we aim to elucidate the regulatory mechanism of developmental time not only for brain formation but also for other organogenesis.

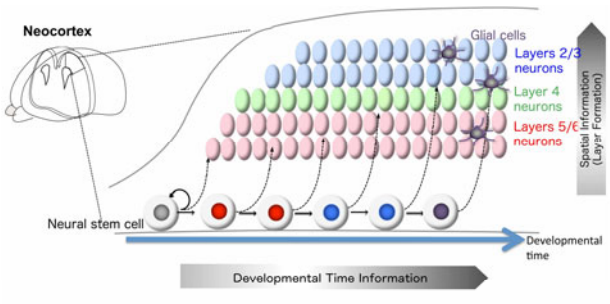

Figure 1: Neocortical development. Developmental time information programmed in stem cells is transformed into spatial information, which feedbacks to stem cells.

【Content of the Research Project】

In this project, the following three groups of researchers will collaborate with each other to elucidate the developmental timing mechanism.

Group A01 aims to understand the cellular timing mechanism, such as domino and clock factors. Group A02 aims to elucidate the interplay between cells (cellular clock) and extracellular environment. Group A03 will work together with A01 and A02 for 3D ES cell cultures, mathematical modeling, and new probe synthesis.

【Expected Research Achievements and Scientific Significance】

Spatiotemporal expression of key factors and signaling molecules will be quantified during the developmental time course, and by using such quantified data, mathematical modeling will be made. Through such analyses, our understanding of developmental timing mechanisms (domino, clock, or mixed) will be promoted, which may create a new research field, developmental chronobiology.

It is well known that the developmental time scale is different from species to species. For example, human development takes much longer than mouse development. Interestingly, this difference is reproduced in 3D ES cell cultures. Differentiation processes from human ES cells take much longer than those of mouse ES cells, suggesting that species difference in developmental time is encoded within cells. Currently, the mechanisms for such species difference are not known, but this project will promote our understanding of these mechanisms and may help shorten the time required for human ES cell-derived tissue regeneration.

【Key Words】

Developmental clock: the mechanism to induce and stop each event at predictable times during development
Stem cell: undifferentiated cell that has potential to give rise to multiple mature cell types

【Term of Project】 FY2016-2020

【Budget Allocation】 1,181,800 Thousand Yen

【Homepage Address and Other Contact Information】

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