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

Biological Sciences (Biological Sciences)

Title of Project : Elucidation of Mechanisms Regulating Neural Stem/Progenitor Cell Fate

Yukiko Gotoh
(The University of Tokyo, Graduate School of Pharmaceutical Sciences, Professor)

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Research Area : Biological Sciences, Neuroscience
Keyword : Neural stem cell, Neocortex, Development, Chromatin

【Purpose and Background of the Research】

One of the fundamental questions in understanding tissue development is how multipotent progenitors/tissue stem cells give rise to various cell types in a defined order to achieve appropriate tissue organization. Neocortical neural stem/progenitor cells (NPCs) attract much attention since these cells give rise to neuronal and glial cell types in a developmental-stage dependent manner with striking precision and can be used as a model system to address this developmental issue. We have previously shown that polycomb group (PcG) complex and high mobility group A (HMGA) proteins play pivotal roles in driving fate switches of NPCs during neocortical development (Hirabayashi et al. Neuron 2009; Kishi et al. Nat. Neurosci. 2012; Morimoto-Suzki et al. Development 2014). Therefore, in this study, we aim to investigate how these proteins are regulated and how they control the fate of NPCs in a developmental stage-dependent manner.

In contrast to embryonic NPCs that quickly and sequentially produce a variety of neural cell types in a limited time, adult NSCs have a very different mission. Namely, they have to produce the same sets of neural cell types for a very long time (a lifetime) with little changes in their differentiation potentials. Recently, we have identified an embryonic origin of adult NSCs residing in the subependymal zone (Furutachi et al. Nat. Neurosci. 2015). We therefore aim to investigate the molecular basis of differences between this embryonic "origin" of adult NSCs and other embryonic NPCs, particularly focusing on their differentiation potentials.

【Research Methods】

We will examine what mechanisms might regulate the target specificity of PcG in a developmental time-dependent manner by focusing on the neurog1 and fezf2 loci. We will examine cis and trans elements necessary for PcG targeting to these loci.

Our previous work (Kishi et al., Nat. Neurosci. 2012) revealed that HMGA proteins mediate the open chromatin state in early-stage NSCs, conferring the neurogenic potential on them. We will thus investigate the genome-wide regulation of the chromatin state in NPCs.

We will isolate the embryonic origin of adult NSCs and compare their features with other embryonic NPCs.

【Expected Research Achievements and Scientific Significance】

We hope that our work will shed light on general mechanism of stem cell fate control.

【Publications Relevant to the Project】

Furutachi,S., Miya,H., Watanabe,T., Kawai,H., Yamasaki,N., Harada,Y., Imayoshi,I., Nelson,M., K.I. Nakayama, Hirabayashi,Y. and Gotoh,Y.: Slowly dividing neural progenitors are an embryonic origin of adult neural stem cells. **Nat Neurosci.**18(5):657-65,2015

Kishi, Y., Fujii, Y., Hirabayashi, Y. and Gotoh, Y.: HMGA proteins regulate global chromatin state and the neurogenic potential in neocortical precursor cells.**Nat.Neurosci.** 15, 1127-1133, 2012.

Hirabayashi, Y., Suzki, N., Tsuboi, M., Endo, T.A., Toyoda, T., Shinga, J., Koseki, H., Vidal, M. and Gotoh,Y.:Polycomb limits the neurogenic competence of neural precursor cells to promote astrogenic fate transition.**Neuron**63,600-613,2009

【Term of Project】

FY2015-2019

【Budget Allocation】

143,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~molbio/