【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project : Identification of factors endowing the genome with a high plasticity in the mouse and their applications to biomedical researches

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Research Area : Comprehensive fields, Laboratory animal science
Keyword : Genomic reprogramming, mouse, genomic plasticity, nuclear transfer, ES cell

【Purpose and Background of the Research】

The fact that cloned animals are born following somatic cell cloning and pluripotent cells can be established by inducing reprogramming factors unequivocally indicates that the epigenetic changes imposed on the genome during differentiation are reversible and can be reprogrammed to the initial stages. However, these reverse epigenetic changes are too artificial and therefore prone to many kinds of epigenetic errors and incomplete reprogramming.

While we undertook many series of nuclear transfer cloning experiments in mice, we found that the genome of a certain strain of mice (129 strain) can be precisely reprogrammed in terms of the quality of cloned embryos (e.g., their global gene expression patterns) and the birth rates of clones. The 129 is the strain by which the first embryonic stem cells were established about 30 years ago and have been implicated to have some genomic plasticity. As the recipient ooplasm are common in all nuclear transfer experiments, we thought that the secret of this high genomic plasticity should reside within its genome. In other word, some factor(s) inside the 129 genome endow itself a high plasticity.

The goal of the present project is to identify the genomic plasticity factors in the 129 genome by employing the so-called “forward genetics”. We define the candidate genomic regions, surmise the candidate genes from the list in the relevant regions, and estimate the factors from their known biological functions. Finally, we expect that we will be able to transfer the factor(s) to other mouse strains and other mammalian species to establish iPS cells having a high quality and to generate healthy cloned animals efficiently.

【Research Methods】

We employ the principle of forward genetics throughout the project. We analyze phenotypes and gene expression patterns in embryos or pups reconstructed from recombinant inbred strains or consomic strains between C57BL/6 and 129 strains. Then we can define one or a few genetic regions responsible for correct genomic reprogramming comparable to that in the 129 genome. By combining gene modification techniques in mice, we identify the responsible factor(s). If possible, they will be transplanted into other mammalian species, which then will provide high quality iPS cells and efficient nuclear transfer cloning technology.

【Expected Research Achievements and Scientific Significance】

Generation of safe iPS cell and healthy cloning animals has been a long-awaited technology not only in basic science but also for future industry and medical practice. The results and information obtained from this project will enable us to reprogram the genome from a broad range of organisms more safely and more efficiently. This will also facilitate development of new strategies for human regenerative medicine and pharmaceutical sciences.

【Publications Relevant to the Project】

Inoue K, Kohda T, Sugimoto M, Sado T, Ogonuki N, Matoba S, Shiura H, Ikeda R, Mochida K, Fujii T, Sawai K, Otte AP, Tian XC, Yang X, Ishino F, Abe K, Ogura A. Impeding Xist expression from the active X chromosome improves mouse somatic cell nuclear transfer. Science 330: 496-499, 2010.

Inoue K, Kohda T, Lee J, Ogonuki N, Mochida K, Noguchi Y, Tanemura K, Kaneko Ishino T, Ishino F, Ogura A. Faithful expression of imprinted genes in cloned mice. Science, 295: 297, 2002.

【Term of Project】 FY2011-2015

【Budget Allocation】 158,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.go.jp/r-world/research/lab/brc/engineering/index.html
http://www.brc.riken.go.jp/lab/kougaku/