Stem Cells, Cell Fusion & Genetic Reprogramming

Epigenetic Reprogramming in Mammals
- Biological significance of genomic imprinting mechanism-

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The necessity of parents seems to be obvious, stemming from the fact that most living organisms have the sexual distinction of being either male or female and that the functioning of their reproductive organs creates the next generation. However, from a genetic viewpoint, are parents really needed to create a living organism? Possibility of parthenogenesis has already been demonstrated in nature as well as in the laboratory in the case of many living things including higher vertebrates (fish, amphibians, reptiles and birds). Mendel’s laws of inheritance may support these facts because they are presuppose that the genetic effects of a paternal gene inherited from father are identical to those of mother or, to phrase this academically, “phenotypes are alike when genotypes are alike”.

Only exceptions are mammals, including our own species, Homo sapiens. An experiment in parthenogenesis using mice, which was carried out in 1984 led to the present understanding that mammals are incapable of parthenogenesis. A special technique in developmental engineering called pronucleus transplantation(similar to nuclear cloning technique) permits the creation of eggs that have only female or male genetic materials both of which stop development just after implantation and never develop to term. As the memory of the parent of origin, imprinted on the genome, was thought to cause the difference between the genome function of the genetic material derived from each parent, the new research field of “genomic imprinting” was born. From a genetic point of view, this is explainable by the existence of have two kinds of special gene groups which are expressed exclusively either from the paternal genome (paternally expressed genes; Peg) or from the maternal genome (maternally expressed genes; Meg) in mammals.

The existence of two genes, one from each of the father and mother, is a safety
device for controlling development in living organisms. What, then, was the purpose of mammals developing a monoallelic gene expression mechanism at the expense of forfeiting this safety factor? Many hypotheses have been proposed on the biological significance of genomic imprinting, such as “Conflict hypothesis”, “prohibition of parthenogenetic development”, “a novel placenta hypothesis” and so on. From recent study on the reprogramming process of genomic imprinting memories in both of male and female germ cell lines, we have proposed another idea as “the complementation hypothesis” which explains the necessity of differential functions between paternal and maternal genomes and the existence of monoallelic expression system in mammalian development.
Animal Cloning by Somatic Cell Reprogramming

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ABSTRACT
Since it was first reported in 1997, somatic cell cloning has been demonstrated in several other mammalian species, such as sheep, cows, cats, mice etc. On mice, cloning can be performed from embryonic stem (ES) cells, fetus-derived cells, and adult-derived cells, both male and female. However, cloning efficiency is very low, 1-2% being typical (i.e. one or two live offspring per one hundred initial embryos). Moreover, cloned animals consistently display a variety of developmental abnormalities, ranging from placental anomalies to obesity to premature mortality of unknown cause. It has been suggested that even apparently 'normal' cloned individuals exhibit epigenetic defects. Similar deficiencies have also been reported in cloned blastocysts, such as abnormal gene expression patterns and the retention of somatic cell-like features. These abnormalities have been attributed to insufficiencies in the reprogramming of the donor nuclei. This failure in reprogramming may be caused by flaws in nuclear transplantation technology. Whatever the case, little is known about how such reprogramming plays out in either normal or artificial fertilization despite the central biological importance of this process. At this point, the thorny question of whether cloned blastocysts are inherently different from their 'natural' counterparts, or whether such differences are artifactual and therefore might be resolved by improvements in technique, remains open. Interestingly, the results of cloning depend on a person's skill. For example, two researchers performing a nuclear transfer side-by-side using the same materials can produce irreconcilably differing data. Such abnormalities and immature techniques notwithstanding, success in generating cloned offspring has opened new avenues of investigation and provides a valuable tool that basic research scientists have employed to study complex processes such as genomic reprogramming,
imprinting, and embryonic development.

On the other hand, recent years have seen active research into the possible applications of human ES cells in regenerative medicine, in which ES cells are envisioned as a potential source for cells to be used in cell replacement therapies. However, as with any allogeneic material, ES cells derived from fertilized blastocysts and the progeny of such cells inevitably face the risk of immunorejection on transplantation. It has been proposed that ES cells derived from embryos cloned from the host patient’s own cells represent a potential solution to the problem of rejection, as any replacement cells would be genetically identical to the host’s own. Interestingly, the establishing rate of ntES cell lines from cloned blastocysts is much higher than the success rate for the cloning of mice. It is suggested that some ntES cell lines were established from incompletely reprogrammed blastocysts, because those blastocysts cannot develop to full term. In this symposium, I will talk about the similarity and difference between ntES and ES cells.