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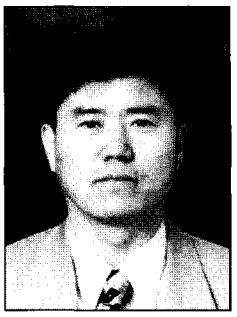
Yong-Mahn Han

Korea Advanced Institute of Science and Technology



1997 - Present	Principal Research Scientist, KRIBB
1996 - 2003	Affiliated Professor, Department of Animal Science, Chungnam National University
1997 - 1998	Postdoctoral Fellow, Univ. of Missouri-Columbia, Dr. Randall S. Prather
1993	Ph.D., Department of Bioscience (Molecular Biology), Korea Advanced Institute of Science and Technology (KAIST)
1992 - 1997	Senior Scientist, KRIBB
1986 - 1992	Researcher, Korea Research Institute of Bioscience and Biotechnology (KRIBB)
1986	MS, Department of Animal Science (Reproductive Physiology), KonKuk University, Korea
1984 - 1986	Teaching Assistant, Department of Animal Science, KonKuk University
1984	BS, Department of Animal Science, KonKuk University, Korea

Epigenetic Reprogramming in Cloned Embryos

Yong-Mahn Han, Ph.D.

Center for Development and Differentiation, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon, Korea

To obtain developmental competence of cloned embryos to term, the differentiated cell nucleus should be subject to epigenetic reprogramming processes including chromatin remodeling and DNA methylation during preimplantation development. In the somatic cell nuclear transfer, many clinical anomalies such as high abortion rates, increased body weight, and early death after birth have been reported. These developmental failures could be due to aberrant reprogramming in the reciprocal interactions between donor nuclei and enucleated oocyte cytoplasm (1). In this context, it has been demonstrated that reprogramming of DNA methylation (2, 3), expression of imprinted and non-imprinted genes (4, 5), X-chromosome inactivation (6), and telomerase activity (7) are incomplete in cloned embryos during early development as compared with normal embryos. Especially, abnormal epigenetic reprogramming may lead to faulty or differential gene expression, thereby resulting in developmental defects of cloned embryos.

Dynamic epigenetic modifications of the genome occur during early embryonic development in mammals. An intrinsic difference in the early embryonic development between fertilization and somatic cell cloning may arise from distinct chromatin architectures between spermatozoa and somatic cells. In fact, activation and remodeling in a reconstructed oocyte with a somatic cell nucleus might obviously differ from the normal fertilization process. Maternal and paternal genomes should reprogram to reach a totipotent state for normal development. During fertilization, the sperm genome remodels in the oocyte cytoplasm after replacement of its protamines with oocyte histones. In the somatic cell nuclear transfer, however, remodeling of somatic chromatins may be entirely discriminated because of a paucity of sperm factors and incomplete microenvironment within the enucleated oocyte cytoplasm. Differences of chromatin remodeling may be also due to diverse histone variants between germ and somatic cells (8, 9). A variant subtype of histone linker H1, H1foo, is rapidly replaced with somatic H1 linker histone after fertilization or somatic cell nuclear transfer (10, 11). However, how the maternal and paternal genomes reprogram to set chromatin structure is still poorly understood.

In early embryonic development, activation of embryonic genome is a critical event for onset of transcription. In the bovine, initial genomic activation occurs from 8- to 16-cell embryos. Histone hyperacetylation results in increased expression of transgenes in early stages of mouse embryos (12), indicating that histone acetylation may be involved in the embryonic gene expression. Several genes that are required for development are abnormally expressed in cloned bovine embryos (13), although

it is unclear whether abnormal gene expression is directly correlated to the epigenetic reprogramming in cloned embryos.

In this study, the acetylation status of histone H4 at lysine 5 (AcH4K5) was examined to monitor epigenetic reprogramming of somatic chromatins in cloned embryos. As results, we found the anomaly of cloned embryos in the dynamic modulation of histone H4 acetylation. Histone acetylation status of somatic cell chromatins seldom reprogrammed in the enucleated oocyte cytoplast and its levels were arbitrarily fluctuated in early cloned embryos. Along with histone acetylation, two imprinted genes were aberrantly expressed in cloned bovine embryos as compared with normal embryos. From our findings, it assumes that epigenetic state of the somatic chromatin is reset in the oocyte cytoplast itself. This behavior of the somatic chromatin may give rise to an aberrant reprogramming during early development, thereby leading to abnormal expression of embryonic genes in cloned embryos. In addition, we suggest that epigenetic reprogramming of cloned embryos may be dependent on the status of donor cell chromatin. Understanding the epigenetic reprogramming of differentiated cell nuclei during early development will contribute to elucidating the mechanisms related to various cellular functions such as differentiation, apoptosis and aging.

References

1. Kang YK, Lee KK & Han YM. (2003) Curr Opin Cell Biol 15, 290-5.
2. Bourc'his D, Le Bourhis D, Patin D, Niveleau A, Comizzoli P, Renard JP & Viegas-Pequignot E. (2001) Curr Biol 11, 1542-6.
3. Kang YK, Koo DB, Park JS, Choi YH, Chung AS, Lee KK & Han YM. (2001) Nat Genet 28, 173-7.
4. Humpherys D, Eggan K, Akutsu H, Friedman A, Hochedlinger K, Yanagimachi R, Lander ES, Golub TR. & Jaenisch, R. (2002) Proc Natl Acad Sci USA 99, 12889-94.
5. Boiani M, Eckardt S, Scholer HR & McLaughlin KJ. (2002) Genes Dev 16, 1209-19.
6. Xue F, Tian XC, Du F, Kubota C, Taneja M, Dinnyes A, Dai Y, Levine H, Pereira LV & Yang X. (2002) Nat Genet 31, 216-20.
7. Shiels PG, Kind AJ, Campbell KH, Waddington D, Wilmut I, Colman A & Schnieke AE. (1999) Nature 399, 316-7.
8. Sarma K & Reinberg D. (2005) Nat Rev Mol Cell Biol 6, 139-49.
9. Kimmins S & Sassone-Corsi P. (2005) Nature 434, 583-9.
10. Teranishi T, Tanaka M, Kimoto S, Ono Y, Miyakoshi K, Kono T & Yoshimura Y. (2004) Dev Biol 266, 76-86.
11. Gao S, Chung YG, Parseghian MH, King GJ, Adashi EY & Latham KE. (2004) Dev Biol 266, 62-75.
12. Thompson EM, Legouy E, Christians E & Renard JP. (1995) Development 121, 3425-37.
13. Pfister-Genskow M, Myers C, Childs LA, Lacson JC, Patterson T, Betthauser JM, Goueleke PJ, Koppang RW, Lange G, Fisher P, Watt SR, Forsberg EJ, Zheng Y, Leno GH, Schultz RM, Liu B, Chetia C, Yang X, Hoeschele I & Eilertsen KJ. (2005) Biol Reprod 72, 546-55.