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Clone telomeres behave normally

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A team of researchers at Hannover Medical School, Germany, has found a telomerase-dependent telomere length-resetting event between the morula and blastocyst embryonic stages that they say keeps cloned embryo telomere length normal.

Because telomeres - the structures located at the end of chromosomes - lose a piece of their sequences with each cell division, short telomeres are usually correlated with age, said Heiner Niemann, professor and head of the Department of Biotechnology at the Institut für Tierzucht, Neustadt, Germany, who coauthored the study, published in the May 17 Proceedings of the National Academy of Sciences Early Edition, with Sonja Schaetzlein and colleagues.

Scientists had earlier looked at telomere lengths in cloned animals because there was some concern that such animals may exhibit premature aging. "There was quite an uproar with Dolly [the first sheep clone] in that when they measured telomere length, they were indeed obviously shortened compared to age-matched controls," Niemann said. However, later studies in cloned cattle and mice showed telomeres to be of normal length, he said.

The Hannover researchers compared lengths of telomeres in bovine donor nuclei and recipient cells. They then carried out nuclear transfer and analyzed telomere lengths at the morula and blastocyst stages in clones and *in vitro*-fertilized embryos. In the morula, cells are compact and mostly the same type, while the fluid-filled blastocyst comprises two different cell lines: the trophoblastic line, which later on forms the placenta, and the inner cell mass, from which the embryo proper is derived, Niemann said. "So [the morula-blastocyst transition] is a very critical stage."

The mean telomere length as determined by quantitative fluorescence in situ hybridization in different nuclei of adult fibroblasts was 10.84 ± 5.73 kb, 14.61 ± 4.58 kb in fetal fibroblasts, and 16.95 ± 2.51 kb in oocytes. Mean telomere lengths determined for individual blastocysts were 17.3 ± 2.66 kb in nuclei from fetal fibroblasts and 19.53 ± 4.6 kb in adult fibroblasts. *In vitro*-fertilized embryos had telomere lengths of 21.67 ± 3.92 kb. There was no significant difference between the different groups of blastocysts, whose telomeres were elongated compared with the morula stage, according to the paper.

The team also examined telomere length in telomerase knockout mice. "This system is really important because it is the only system that convincingly demonstrates that this [telomere] lengthening is due to telomerase," said Sandy Chang, a professor at the University of Texas at Houston.

Although they carried out nuclear transfer experiments with the knockout mice, the experiment ended before pups were born. "What if the telomerase knockout mice could be cloned? It would be very interesting," said Chang, who was not involved in the study. However, an earlier study of Dolly still contradicts the findings of the current paper, he said. "I don't know why there is such a discrepancy... could that be a species difference?"

The finding that telomeres elongate in embryogenesis and the timing of the morula-blastocyst transition "seem correct, in terms of that's the time when things become immortal," said Marilyn Monk, professor of molecular embryology at the Institute of Child Health in London.

"What might be more interesting is what happens between germ cells and the morula," Monk, who was not involved in the study, told us. "The data might suggest - although I don't know how significant it is - that there is a loss of telomere length in early development, in that oocytes and sperm appear to have longer length than the morula."

Monk said that the data might suggest that in the absence of telomerase in early development, a loss of telomere length could occur. "When telomerase starts to be expressed and accumulate in the embryos, then the telomeres lengthen again to the blastocyst and probably continue to lengthen into the germ line," she said.

"There's two things: the presence of telomerase and the particular stage of development. There does seem to be in evidence a resetting. I think it would have been interesting if they had done a time course during development," Monk said.

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