【Biological Sciences（Agricultural sciences）】

Mechanisms for methylation imprinting establishment after fertilization

Keiji Tanimoto
(University of Tsukuba, Graduate School of Life and Environmental Sciences, Associate Professor)

【Outline of survey】

Mammals inherit one genome from each parent and most genes are expressed from both alleles. Normal embryonic development requires both a male and female genome, because some genes remember their parental origin and are transcribed quite specifically from only one of the two parental alleles (genomic imprinting). In the Igf2/H19 locus, the Igf2 gene is transcribed when paternally inherited, while the H19 gene is maternally transcribed. Imprinted genes are often associated with differentially methylated regions (DMRs) that control monoallelic gene expression. It is generally accepted that DMRs establish their allelic methylation during gametogenesis. Since some DMRs are methylated during oogenesis and others during spermatogenesis, it is suggested that DMRs contain genetic “marks” that allow (or prevent) methylation acquisition at nearby CpG dinucleotides in only one of the gametes. In this study, I propose to search for the DNA sequence that is required and sufficient for establishment of methylation imprinting, through which further understanding of the molecular mechanism of genomic imprinting is anticipated.

【Expected results】

By examining YAC (yeast artificial chromosome) transgenic mice, I have shown that genomic imprinting could be recapitulated at a heterologous genomic locus by simply grafting the H19 DMR into an irrelevant (human beta-globin) genetic locus. Surprisingly, methylation imprinting was established after fertilization in these transgenic mice, which was different from what is observed at the endogenous Igf2/H19 locus. By determining the minimal cis DNA sequences within the H19 DMR that establish the parent of origin-dependent methylation pattern during the post-fertilization period in this experimental system, we expect to define the molecular entity that must be inherited.

【References by the principal investigator】

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【Budget allocation】 80,000,000 yen (direct cost)

【Homepage address】 http://akif2.tara.tsukuba.ac.jp/