グローバル COE 特別セミナー

分子細胞生物学研究所セミナー

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演題 **The Evolution of Replication Origins and Genome Architecture.**

日時 11 月 1 日（ 月） 14:00~15:00

場所 東京大学分子細胞生物学研究所　セイホクギャラリー

Replication is central to the role of DNA as the genetic material, yet the act of replication puts the genome in peril. Over long time periods, the consequent damage could lead to genome rearrangements that provide a selective advantage and lead to speciation events. We have explored the possible role that replication origins—the sites in chromosomes where replication begins—have in the generation of amplification and translocation events in the yeast Saccharomyces cerevisiae, and in turn have analyzed the evolution of replication origins in near (Saccharomyces bayanus) and distant (Kluyveromyces waltii) relatives of S. cerevisiae.

Comparison of the genome of S. cerevisiae with that of the pre-whole-genome duplication yeast, K. waltii, reveals that greater than 90% of the genes have been conserved in >700 syntenic blocks. The endpoints in synteny mark the sites of genomic rearrangements that have occurred in one or the other of the two species since their divergence ~150 MYA. One of the striking features shared by these rearrangement breakpoints is that they map near known early origins of replication in the S. cerevisiae genome. Laboratory-induced rearrangements also occur in regions of the S. cerevisiae genome where origins are found. To explore possible mechanisms for how origins of replication could be involved in generating genome rearrangements we have analyzed a particular amplification event that occurs during prolonged growth in low sulfur medium. Under these conditions, the SUL1 gene (high affinity sulfur transporter) and the adjacent origin of replication, ARS228, amplify in a head-to-head/tail-to-tail configuration. We have devised a new model for how an error in replication from this origin of replication can generate the SUL1 amplicon and similar amplicons found in human tumors and congenital abnormalities.

To analyze the evolution of origins of replication we have undertaken an analysis of ARS elements in both S. bayanus and K. waltii and have characterized the genome-wide dynamics of replication in these two species. The ARS consensus sequences are identical and the locations of origins are highly conserved in S. bayanus and S. cerevisiae. However, we have identified species-specific origins, as well as some origins that have changed the time in which they fire in the S phase. The comparisons between S. cerevisiae and K. waltii show that even though the ARS consensus sequence has barely changed over 150 M years, the locations of origins in K. waltii and S. cerevisiae have diverged greatly and only the most basic features of replication timing (early centromeres and late telomeres) and origin spacing (an origin every ~35 kb) have been conserved. These findings pose a conundrum: How are the consensus sequences and spacing of origins maintained while their exact locations are not?

1. Alvino GM, Collingwood D, Murphy JM, Delrow J, Brewer BJ, Raghuraman MK. Replication in hydroxyurea: it's a matter of time. Mol Cell Biol. 2007 Sep;27(18):6396-406.

2. Feng W, Collingwood D, Boeck ME, Fox LA, Alvino GM, Fangman WL, Raghuraman MK, Brewer BJ. Genomic mapping of single-stranded DNA in hydroxyurea-challenged yeasts identifies origins of replication. Nat Cell Biol. 2006 Feb;8(2):148-55.

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