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Synthetic chromosome evolves the yeast genome

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Genomic structural variations play a critical role in biological function and phenotypic diversity. Although small-scale variations, such as insertion, deletion, and point mutations, have been extensively investigated, studies on large-scale structural variations such as segmental duplication, inversion, and chromosome-scale variations remain limited. In the recent decade, with the development of synthetic biology, particularly the ability to synthesize whole chromosomes in yeast, scientists have been able to interpret the diverse phenotypic mechanisms underlying the complex genome architecture and function.

The design and synthesis of the entire genome of yeast, *Saccharomyces cerevisiae*, mark a significant achievement in synthetic biology (Dymond et al., 2011; Mitchell et al., 2017; Richardson et al., 2017; Shen et al., 2017; Wu et al., 2017; Xie et al., 2017; Zhang et al., 2017). In this progress, a method called SCRaMbLE (Synthetic Chromosome Rearrangement and Modification by LoxP-mediated Evolution) has helped in achieving complex genome reorganization and phenotypic evolution (Dymond et al., 2011; Shen et al., 2016; Blount et al., 2018; Jia et al., 2018; Hochrein et al., 2018; Liu et al., 2018; Luo et al., 2018; Shen et al., 2018; Wu et al., 2018). However, the correlation between evolved phenotype and genomic structural variation is studied less.

Yingjin Yuan from Key Laboratory of Systems Bioengineering in Tianjin University, China, and his group used the SCRaMbLE system on a synthetic ring chromosome V (ring_synV) to study the complex genomic rearrangement in yeast, thereby facilitating the evolution of the genome with improved properties (Figure 1A) (Wang et al., 2018). Wang et al. SCRaMbLEd a ring chromosome and generated aneuploid chromosomes I, III, VI, XII, XIII, and ring_synV in yeast (Figure 1A). In this process, the ring_synV tended to generate neochromosomes with complex structure variations when exposed to estradiol, a small molecule which induces Cre-mediated chromosome recombination. The change in topological organization of chromosomes should markedly decrease the steric hindrance between loxPsym sites, even those located far away in the linear distance. Wang and colleagues observed an increased number of novel junctions in the fifth cycle of SCRaMbLE (47 junctions) compared with the first cycle (29 junctions), indicating that the conditional inducible SCRaMbLE method can continuously achieve massive combination of genetic diversities, particularly for the ring_synV chromosome used in their study (Wang et al., 2018). Compared with traditional SCRaMbLE using a linear chromosome, ring chromosome-assisted SCRaMbLE enables increased complex chromosomal rearrangement events and improved phenotypic diversities.

More recently, Li et al. presented an innovative and valuable insight into genome architecture and function by comparing SCRaMbLE and rapid adaptive evolution methods in a partly synthetic yeast genome (Figure 1B) (Li et al., 2019). Using an anti-rapamycin readout system, Li et al. revealed that SCRaMbLE and rapid adaptive evolution methods prefer different types of variations on the chromosomal

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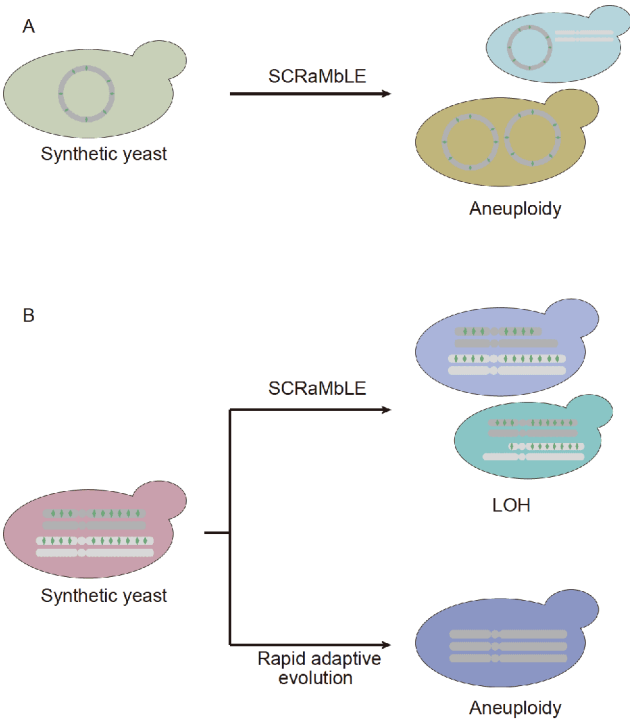

Figure 1 Schematic illustration of SCRaMbLE evolution and rapid adaptive evolution. (A) SCRaMbLEing the ring_synV chromosome in yeast induces aneuploidy. (B) In synthetic yeast, SCRaMbLE evolution prefers to induce loss of heterozygosity (LOH), whereas rapid adaptive evolution causes chromosomal duplication.

scale; SCRaMbLE method induces different levels of loss of heterozygosity (LOH; e.g., short-range LOH and long-range LOH and whole-chromosome LOH), whereas rapid adaptive evolution method is prone to cause chromosomal duplication, e.g., trisomy of chromosome VIII in this study (Figure 1B) (Li et al., 2019). For the first time, Li and colleagues revealed that SCRaMbLE can introduce the LOH event, which provided a novel research model in cancer research. Their study demonstrated that different paths of genomic variations could contribute to similar phenotypes in yeast, which would enhance our understanding of the genome architecture and function.

Although there has been great progress in synthetic yeast chromosomes and technologies in large-scale genome rearrangement for a broad range of applications (Dymond et al., 2011; Shen et al., 2016; Blount et al., 2018; Jia et al., 2018; Hochrein et al., 2018; Liu et al., 2018; Luo et al., 2018; Shen et al., 2018; Wang et al., 2018; Wu et al., 2018; Li et al., 2019), there is still a lack of knowledge regarding the mechanisms underlying genome architecture and function. We envision that whole-genome rearrangement in an entire synthetic yeast genome could be employed with an increase in the number of synthetic yeast chromosomes, which will finally answer the questions regarding the principles of genome organization, thereby promoting the generation of minimal genomes of eukaryotic organisms.

Compliance and ethics *The author(s) declare that they have no conflict of interest.*

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