Medical & healthcare, Drug development

Molecular mechanisms of gross chromosomal rearrangements

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Abstract

The centromere is a chromosomal region that plays an important role in chromosome segregation. However, it is also a chromosomal fragile region where DNA repeat sequences are present and chromosomal aberrations are likely to occur. Gross chromosomal rearrangements (GCRs) cause cell death and cancer. However, it is unclear how GCRs occur. We have been identifying factors involved in GCRs in fission yeast. We found that the Rad52 protein induces centromere repeat-mediated GCRs by promoting the single-stranded DNA annealing (SSA) reaction. We also found that ubiquitination of the DNA-binding ring-form protein PCNA and the arginine methyltransferase Skb1/PRMT5 play roles in GCRs.

Background & Results

From yeast to humans, Rad51-dependent homologous recombination (HR) is important for maintaining chromosome integrity. However, the molecular mechanisms underlying GCRs are not well understood. Using fission yeast, we have developed the system to quantify spontaneous GCR rates and to determine the structure of aberrant chromosomes formed. Using this system, we have shown that the single-stranded DNA annealing (SSA) reaction mediated by the Rad52 protein forms GCR products through centromere repeat sequences. We also found that Mus81 endonuclease, which preferentially promotes crossover recombination, causes GCRs. These results suggest that Rad52 forms recombination intermediates between centromere repeats, and Mus81 cleaves these intermediates, resulting in GCRs. We have shown that the ubiquitination of the 107th lysine (K107) of PCNA ring-like protein complexes by the Rad8/HLTF ubiquitin ligase causes Rad52-dependent GCRs. Genetic screening identified Skb1/PRMT5 and Srr1/SRRD as the factors that cause GCRs. Interestingly, all the above GCR factors we identified in fission yeast are highly conserved throughout eukaryotes, including humans. This suggests that GCRs have not only negative aspects, such as cell death and genetic diseases, but also positive aspects, such as environmental adaptation and evolution. We aim to elucidate the GCR mechanism by clarifying the function of the factors involved in GCRs.

Significance of the research and Future perspective

Although the centromere region plays an important role in maintaining chromosome stability, its DNA sequence is not highly conserved and varies widely among species (centromere paradox). This study has greatly advanced our understanding of the molecular mechanism that causes the centromere paradox, which has long been a mystery. Further study will facilitate the development of drugs for the diagnosis and treatment of genetic diseases, such as cancer, caused by GCRs.

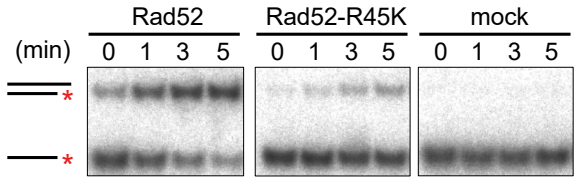

Figure 1. Rad52-dependent single-strand annealing

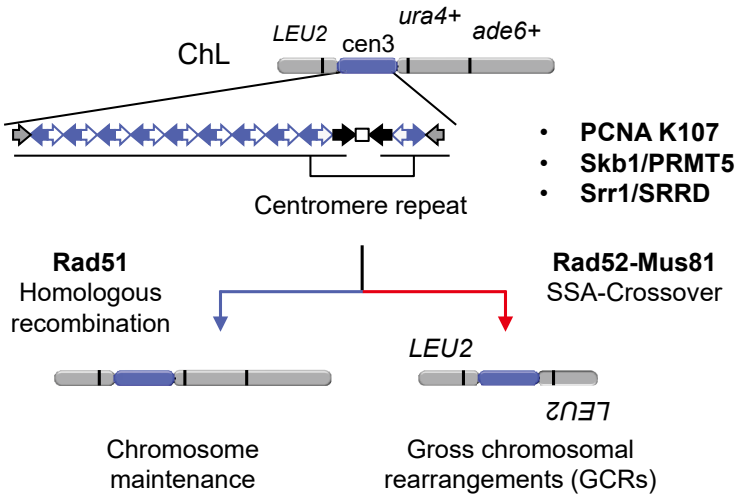

Figure 2. Gross chromosomal rearrangements at centromeres

Patent

Treatise
Mongia, Piyusha; Nakagawa, Takuro et al. Fission yeast Srr1 and Skb1 promote isochromosome formation at the centromere. Communications Biology. 2023, 6(1), 551. doi: 10.1038/s42003-023-04925-9
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URL https://www.bio.sci.osaka-u.ac.jp/~takuro/science/markdown/

Keyword gross chromosomal rearrangements, centromere, DNA repeat sequence, cancer, Rad52