Laboratory of Genome-Chromosome Functions

Institute for Protein Research

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Homologous recombination, an exchange reaction of DNA strands, plays an important role in stabilizing genome and producing diversity. It plays an essential role in the repair of DNA damage during somatic cells and in chromosome segregation during meiosis. Genome instability caused by a defect in the recombination leads to cancer, and infertility, miscarriage, and aneuploidy such as Down's syndrome. To elucidate the molecular mechanisms and regulation of genome stability by mitotic and meiotic recombination and associated genomic pathologies, we are studying the functions of genes and proteins involved in these processes using yeast, mouse, and cultured human cells, using molecular biological, genetic, cell biological tools, combined with biochemical, structural and genomic techniques.

Analysis of proteins involved in homologous recombination in eukaryotes

During cell division, homologous recombination plays an important role in repairing DNA damage. Recombination begins with a DNA double-strand break (DSB) and uses the single-stranded DNA (ssDNA) resulting from the processing of the DSB ends to find homologous double-stranded DNA. This reaction is mediated by a right-handed helix structure created on ssDNA by RecA in prokaryotes and its homolog Rad51 in eukaryotes (Fig. 1), but the detailed molecular mechanism on how Rad51 catalyzes homology search are still unknown. In eukaryotes, the formation of Rad51 filaments is tightly regulated by a variety of factors such as, Brca2 responsible for familial breast cancer,. We recently identified a new protein complex called the Csm2-Psy3 complex and determined its structure for Rad51 filament formation (Fig. 1). Our goal is to elucidate Rad51 filament formation and its function at the molecular level. At the same time, we are also analyzing the meiosis-specific RecA homologue Dmc1 and its regulators. Meiotic recombination prefers DNA in homologous chromosomes rather than sister chromatids. This partner choice in the recombination is mediated by Dmc1 and meiotic chromosomes structures. We are also studying the mechanism of partner choice in meiotic recombination.

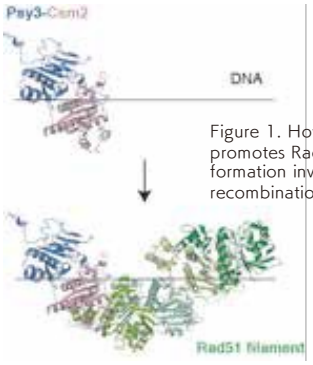

Figure 1. How Csm2-Psy3 promotes Rad51 filament formation involved in recombination.

Molecular mechanisms of regulation of meiotic recombination by chromosome structure and motion.

In meiosis, which is necessary for gamete formation, DNA replication is followed by two successive nuclear divisions. Homologous chromosomes are segregated in the first meiotic division. To facilitate the segregation of the chromosomes, homologous recombination creates physical linkage between homologous chromosomes. Homologous recombination in meiosis involves the formation of crossover recombination, reciprocal exchange of paternal and maternal DNAs, which is regulated in number and distribution on chromosome tightly. Dynamic chromosome morphogenesis and chromosome rearrangement inside of nuclei also occur during meiosis in conjunction with recombination. In particular, synaptonemal complexes that pair homologous chromosomes (Figure 2) and bouquet formation (Figure 3), in which telomeres are clustered at a single location on the nuclear membrane, are well known. Understanding the link between meiotic recombination and chromosome structure generates novel concepts about the molecular mechanisms of DNA biochemical reactions that occur on chromosomes.

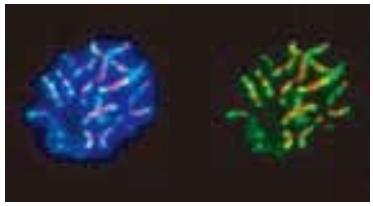

Figure 2. Synaptonema complex. Proteins of the synaptonema complex are distributed linearly (green, red) and DNA (blue), and homologous chromosomes pair on this structure

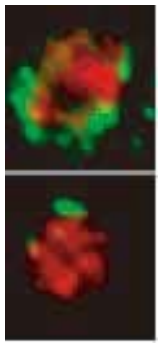

Figure 3. Telomere clustering (bouquet formation) during 3.meiosis. In bouquet formation, telomeres (green) cluster from the periphery of the nucleus (top) to a single location (bottom).
Red indicates localization of proteins involved in recombination

Analysis of the mechanism of homologous recombination in human cells and mouse

Recently, attention has been focused on cellular tumorigenesis and recombination defects linked with genome instability. To elucidate the molecular mechanisms of recombination in higher eukaryotes, we have established a system to analyze homologous recombination in human cells and mice. In particular, we are analyzing the molecular mechanisms of recombination in human cells and the chromosomal aberrations caused by the disruption of recombination through analysis of factors involved in homologous recombination in human cells and creation and analysis of knockout mice (Fig. 4) .

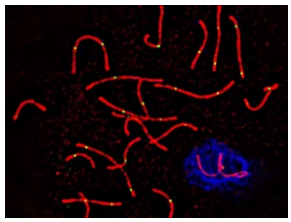

Figure 4. Chromosome structure (red) and recombination nodule (green) during meiosis I

Be ambitious and enthusiastic, and aim to do research with good integrity that will be well-recognized around the world.

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