【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project：Molecular mechanisms that determine kinetochore orientation acting at the heart of genome transition

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Research Area：Biology

Keyword：Genetics, Genome

【Purpose and Background of the Research】

During the mitotic cell cycle, chromosomes are replicated and segregated equally to daughter cells (Fig. 1). Chromosome mis-segregation in mitosis results in apoptosis, or otherwise may contribute to tumorigensis. To generate progeny, the number of chromosomes is once reduced by half to produce haploid gametes, a process called meiosis. Meiotic chromosome segregation is also important clinically, as failures in this process cause miscarriage and birth defects such as Down syndrome in humans. Thus, it is very important for biology and medical science to understand the regulatory mechanisms of chromosome segregation.

We have shown that the meiosis-specific kinetochore protein Moa1 and cohesin Rec8 play an essential role in establishing the mono-orientation of kinetochores, presumably by establishing cohesion at the core centromere. Here we will analyze the molecular details of this mechanism. By analyzing a novel germ line-specific kinetochore protein in mice, we will also study the conservation of the concept developed in fission yeast. Moreover, we will study the regulation of shugoshin, a protein required for the centromeric protection of cohesion and with another unknown function required for bi-polar attachment of the kinetochore to microtubules. Thus, we aim to reveal the fundamental principle that determines chromosome orientation.

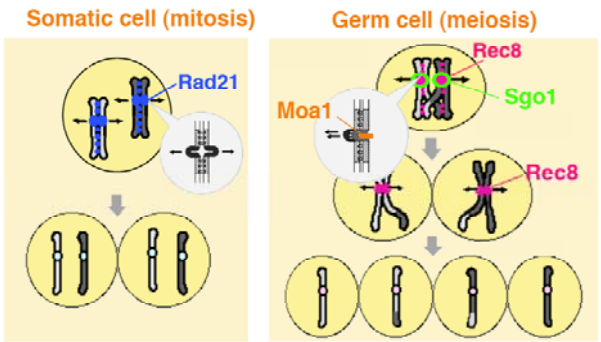

Fig 1. The difference between mitotic and meiotic chromosome segregation, and factors that regulate them.

【Research Methods】

By using molecular genetics in fission yeast, we will reveal the molecular function of Moa1, a protein required for mono-orientation of kinetochores. Moreover, we will identify a novel gene, the product of which is localized at kinetochores only in mice germ cells. Knockout of such factors will reveal its function during meiosis. Throughout these analyses, we will compare the conservation of the system between fission yeast and mice. Moreover, we will reveal the molecular mechanism by which shugoshin localizes to centromeres.

Aurora B kinase plays a central role in regulating kinetochore michrotubule attachment. We will reveal the molecular mechanism by which shugoshin recruits Aurora B to centromeres and its conservation in mice.

【Expected Research Achievements and Scientific Significance】

Our study may reveal the universal mechanism by which the orientation of kinetochores in eukaryotes is determined, including in humans. Thus, our study will have an enormous impact, not only from the viewpoint of basic biology, but also from a medical point of view.

【Publications Relevant to the Project】

・ Yamagishi, Y., Sakuno T., Shimura, M. and Watanabe, Y. Heterochromatin links to centromeric protection by recruiting shugoshin *Nature* 455, 251-255 (2008).
・ Yokobayashi, S. and Watanabe, Y. The kinetochore protein Moa1 enables cohesion-mediated monopolar attachment at meiosis I. *Cell* 123, 803-817 (2005).

【Term of Project】 FY2009-2013

【Budget Allocation】 362,400 Thousand Yen

【Homepage Address and Other Contact Information】

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