第４１３回 発生研セミナー

Date: January 21st, 14:00～15:00

This seminar will be held using Zoom. Check your email and find the Zoom ID and passcode.

Meiotic recombination: breaking the genome for fertility and genome diversity

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Meiotic cells have developed a sophisticated molecular pathway allowing homologous chromosome to interact, pair and be connected. This pathway relies on homologous recombination events which are initiated by the programmed induction of DNA double strands breaks (DSBs). The absence of meiotic recombination leads to sterility. In mammals, about 300 DSBs are induced in each oocyte or spermatocyte at the onset of the first meiotic prophase. The control of DSB formation, in genomic localization, time and activity, is essential to ensure that all DBSs are repaired by homologous recombination. These molecular events are therefore at the same time a major challenge for genome stability and a driving force for generating genetic diversity at each generation, a unique feature of sexual reproduction.

Our lab has been aiming to understand the molecular mechanism and regulation of meiotic DSB formation, and specifically the control of the localization and the activity responsible for these events.

We discovered a few years ago that the distribution of meiotic recombination is determined by PRDM9 in humans and mice 1-3. PRDM9 is a sequence-specific DNA binding protein with a methyl-transferase activity, catalysing H3K4me3 and H3K36me3 4. We have determined the role of PRDM9 methyltransferase activity 5 and more recently identified HELLS, a chromatin remodeler as a partner of PRDM9 6,7. We have also identified the long-sought missing subunit for DNA break formation, TOPOVIBL, a partner of SPO11 carrying the catalytic activity, and also highlighting the evolutionary link with Type II DNA Topoisomerases 8,9. Our current view of how these molecular steps are coordinated to ensure the proper formation and repair of DSBs will be presented.

1 Baudat, F. *et al.* PRDM9 is a major determinant of meiotic recombination hotspots in humans and mice. *Science* **327**, 836-840 (2010).
2 Myers, S. *et al.* Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. *Science* **327**, 876-879 (2010).
3 Parvanov, E. D., Petkov, P. M. & Paigen, K. Prdm9 controls activation of mammalian recombination hotspots. *Science* **327**, 835 (2010).
4 Grey, C., Baudat, F. & de Massy, B. PRDM9, a driver of the genetic map. *PLoS Genet* **14**, e1007479 (2018).
5 Diagouraga, B. *et al.* PRDM9 Methyltransferase Activity Is Essential for Meiotic DNA Double-Strand Break Formation at Its Binding Sites. *Mol Cell* **69**, 853-865 e856 (2018).
6 Imai, Y. *et al.* PRDM9 activity depends on HELLS and promotes local 5-hydroxymethylcytosine enrichment. *eLife* **9** (2020).
7 Spruce, C. *et al.* HELLS and PRDM9 form a pioneer complex to open chromatin at meiotic recombination hot spots. *Genes Dev* **34**, 398-412 (2020).
8 Robert, T. *et al.* The TopoVIB-Like protein family is required for meiotic DNA double-strand break formation. *Science* **351**, 943-949 (2016).
9 Vrielynck, N. *et al.* A DNA topoisomerase VI-like complex initiates meiotic recombination. *Science* **351**, 939-943 (2016).

【連絡先】　染色体制御分野　石黒 啓一郎（内線６６０６）

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