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GENOMICS

Mapping meiotic breaks

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During meiosis, homologous chromosomes undergo a carefully regulated programme of double-strand break formation to promote pairing and recombination, generating haploid gametes and genetic diversity. Existing maps suffer from issues of resolution because resection spreads over more than a kilobase of DNA from the break site. Now, Lange *et al.* report a nucleotide-resolution map of break sites in mice.

The DNA breaks that initiate meiotic recombination are not randomly distributed in the genome but are grouped into 'hotspots', narrow zones between histones where the protein SPO11 uses a topoisomerase-like reaction to break the DNA backbone. Once the break has been generated, SPO11 is released covalently bound to short oligonucleotides, which the authors extracted from mouse testes and sequenced. By mapping the reads to the mouse reference genome, the team obtained a high-resolution map of break sites.

The resulting map challenges a 'hotspot-centric' view of meiosis, as 40% of mapped oligonucleotides originated outside of hotspots. Investigating the chromatin context around hotspots, a strong correlation was not observed with histone methylation, which suggests that chromatin modifications are an imperfect indicator of hotspot strength. At a chromosome scale, the authors found a negative correlation between size and SPO11 signal, with smaller chromosomes having a denser distribution of DNA breaks. Sex chromosomes had longer-lived double-strand breaks and a particularly high cleavage frequency in the pseudoautosomal region.

In preparation for recombination, the double-strand breaks are resected to expose a single-stranded region. The team combined SPO11–oligonucleotide and published single-stranded DNA sequencing data to determine amounts of resected DNA, observing substantial heterogeneity in resection lengths that spanned across multiple nucleosomes. Mapping the spatial relationship between breaks, resection and recombination, Lange *et al.* saw distinct patterns of resection and crossover centred around the double-strand break hotspots. Comparing these data to maps of resection in yeast, species-specific differences were identified, with mice having much shorter gene conversion tract lengths despite very similar resection lengths.

The team also mapped hotspots in mice deficient for ATM, which is a key component of the cellular response to double-strand breaks and inhibits further cleavage by SPO11. An increase in hotspots was seen as a result of ATM deficiency, as 'weaker' hotspots were now above the detection threshold. Moreover, ATM was found to shape chromosome-scale distribution of hotspots, as domains that were fairly poor in breaks experienced a disproportionately large increase in break frequency.

The maps generated by Lange *et al.* reveal that the control of recombination during meiosis is not limited to the generation of hotspots but has multiple levels of hierarchy and overlapping regulatory mechanisms. Hotspot distribution is influenced not only at a nucleotide level by local chromatin marks but also at a chromosome level by the double-strand break machinery, with distinct differences in hotspot distribution between autosomes and sex chromosomes. Using this high-resolution, nucleotide-scale map as a guide, further work can now elucidate how these different factors cooperate and compete to determine the recombination landscape of mammalian meiosis.

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ORIGINAL ARTICLE Lange, J. *et al.* The landscape of mouse meiotic double-strand break formation, processing, and repair. *Cell* http://dx.doi.org/10.1016/j.cell.2016.09.035 (2016)
FURTHER READING Baudat, F., Imai, Y. & de Massy, B. Meiotic recombination in mammals: localization and regulation. *Nat. Rev. Genet.* **14**, 794–806 (2013)