Heredity (2011) 106, 710–711

www.nature.com/hdy

NEWS AND COMMENTARY

Positioning of recombination in yeast and mammals

Is the control of recombination conserved among diverse eukaryotes?

L Goodstadt and CP Ponting

Heredity (2011) **106,** 710–711; doi:10.1038/hdy.2010.88; published online 7 July 2010

Late in 2009, several research groups independently alighted on a histone 3 lysine 4 (H3K4) trimethylase, PRDM9, as the first known determinant of meiotic recombination hotspots in metazoa (Cheung *et al*., 2010, and references therein). Earlier, hotspot activity in budding yeast was found to be regulated by its only H3K4 trimethylase, encoded by the *Set1* gene (Sollier *et al*., 2004). This apparent conservation of mechanism across diverse eukaryotes led Wahls and Davidson (2010), in a recent opinion article, to propose a 'unifying model' of recombination. They suggest that the positioning of recombination in eukaryotic species as different as fungi and humans is determined by the transcription factor recognition of specific DNA sites followed by histone modification and chromatin remodelling (Figure 1).

In mammals and in yeast, meiotic recombination is essential for the regular segregation of homologous chromosomes during meiotic cell divisions (Coop and Przeworski, 2007). For example, if meiotic recombination is reduced or positioned suboptimally, this may result in congenital trisomatic birth defects. Recombination is nonrandomly concentrated at 'hotspots' that together occupy only a small fraction of the genome. This has profound implications for gene and genome evolution. For example, meiotic recombination is correlated with increases in mutation rate and in GC content, and it disrupts the co-inheritance of physically linked alleles, thereby generating diversity and promoting efficient response to natural selection.

In mammalian meiosis, double-stranded breaks (DSBs), which precede recombination, cluster at these hotspots. The zinc-finger domains of human PRDM9 bind preferentially to a minority (~40%) of such hotspots through a degenerate 13-bp consensus motif (Myers *et al*., 2008). Hotspots are also evident in yeast, with one or more of five classes of degenerate DNA sequence motifs being present in 60% of randomly generated DSB hotspots for *Schizosaccharomyces pombe* (Steiner *et al*., 2009). Across the eukaryotic lineage, meiotic DNA cleavage activity is catalysed by orthologous Spo11 enzymes, thereby placing a conserved enzymatic activity at the heart of this fundamental cellular process.

Are molecular processes controlling recombination, other than Spo11-mediated DNA cleavage, also broadly conserved over eukaryotic evolution? Wahls and Davidson (2010) present evidence that this is, indeed, the case. They point to associations between histone H3K4 trimethylation and recombination at hotspots that are seen in both mouse and yeast (Borde *et al*., 2009; Buard *et al*., 2009). Furthermore, most yeast hotspots might be bound by zinc-finger or other transcription factors, as they are in mammals (by PRDM9). Could the participation of histone H3K4 trimethylases and transcription factors in recombination for organisms as different as yeasts and mammals be mere coincidence? Not at all, argue Wahls and Davidson. They instead propose that these molecules contribute to a phyletically conserved process, which requires first the binding of transcription factors to hotspot motifs, which then induces histone modifications, and is followed by the recruitment of the recombination molecular machinery to the hotspot (Figure 1).

Their model is attractive both in its simplicity and its relevance to a broad swathe of cellular life. It is also consistent with the conservation of many other fundamental cellular processes across single- and multicellular eukaryotic life. Nevertheless, they acknowledge that problems remain, two of which we discuss here.

First, although histone modification has been associated with recombination, it is yet unclear which particular histone marks (for example, acetylation, ubiquitylation, dimethylation or trimethylation) facilitate Spo11 recruitment and DSB formation, and whether these histone signals for hotspots are conserved across Eukarya. For example, the apparent pre-eminent role of methylation in determining budding yeast recombination hotspots has yet to be supported in fission yeast. Even in *Saccharomyces cerevisiae*, H3K4me3 cannot be a sufficient code for DSB hotspot initiation because this histone mark also reflects an active transcriptional state of genes (Berger, 2007). Moreover, DSBs still occur in the absence of H3K4me3 (Borde *et al*., 2009).

Second, the currently identified DNA-binding proteins that determine DSB positioning show no signs of being conserved between fission and budding yeasts, or between these yeasts and metazoans. The extremely rapid evolution of Prdm9's DNA-binding determinants is strikingly different to the situation in yeast. Moreover, although there is little evidence for turnover either among yeast hotspots or the consensus sequences that define them (Tsai *et al*., 2010), primate recombination hotspots are extremely short lived, with the Prdm9 zinc-fingers that bind them changing at a correspondingly rapid pace (Oliver *et al*., 2009; Myers *et al*., 2010).

The rapidity by which mammalian hotspots are turned over might resolve the 'recombination hotspot paradox' (Boulton *et al*., 1997) and may explain the extreme positive selection driving *Prdm9* sequence change. As DSBs are repaired using the homologous chromosome as a template, 'hot' alleles with high recombination-initiation activity are constantly being replaced by 'cold' low-activity homologues. Once hotspots become substantially depleted, new Prdm9 alleles with altered DNA-binding specificity will be favoured, redirecting recombination to newly 'hot' sites, and thus ensuring a necessary number of crossover events to support disjunction. These rapid changes, however, come with an evolutionary cost, as combinations of incompatible *Prdm9* alleles apparently result in male infertility (Vyskocilova *et al*., 2009). This, presumably, is the basis for why *Prdm9* is a species-incompatibility gene (Mihola *et al*., 2009).

By contrast to this situation in mammals, recombination hotspots appear to be highly conserved between *Saccharomyces paradoxus* and *S. cerevisiae* (Tsai *et al*., 2010), species that are considerably more divergent than are chimpanzees and humans that do not share hotspots. The low frequency of sex and

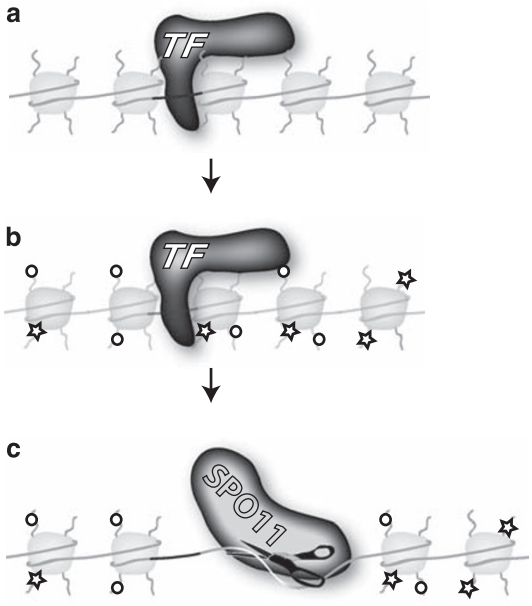

Figure 1 A simplified representation of Wahls and Davidson's pan-eukaryotic model for recombination positioning. (**a**) Consensus DNA recognition sites (dark segment) within recombination hotspots are recognized by a transcription factor (TF), such as Prdm9 in mammals or Atf1-Pcr1 in yeast. Identifiable sequence motifs near hotspots fall into many classes, each presumably recognized by a separate TF. (**b**) In yeast, TFs recruit histone modification enzymes that add, or subtract, methyl, acetyl or ubiquitin marks (circles or stars), for example, to adjacent nucleosomes. In mammals, the hotspot-recognizing Prdm9 is itself a H3K4 trimethylase. (**c**) These histone modifications then recruit further elements of the recombination machinery, including Spo11, presumably to more open chromatin. This catalyses DSBs in the vicinity of the hotspot.

outcrossing (estimated as 1 in 10 000 generations in *S. paradoxus*), and hence meiotic recombination, in some wild-type yeasts (Tsai *et al*., 2008) may explain why a similarly rapid attrition of yeast recombination sites is not seen. There is accordingly little selective pressure for sequence change among yeast transcription factors governing the positioning of DSBs. This suggests that when seeking additional regulators of recombination hotspots in animals, we should be considering rapidly changing DNA-binding proteins rather than sequence-conserved yeast orthologues.

Several meiotic proteins, and their functions, appear to be conserved across the eukaryotes. This has allowed the use of tractable model organisms, including yeast, to reveal mechanisms whose disruptions underlie rare developmental abnormalities in humans. However, it is also becoming clear that other meiotic proteins show little sequence conservation and do not have corresponding orthologues across diverse taxa. Even *Prdm9*, which appears to have such a central role in mice and humans, has either lost its DNA-binding specificity or protein-coding function multiple times in different animal lineages (Oliver *et al*., 2009). It is not difficult to think of reasons why meiotic pathways might have co-opted different genes and mechanisms in different lineages: for those species in which crossovers are essential for chromosomal segregation, the positioning of hotspots could vary with the great differences among eukaryotic genome architectures. To what extent can an overarching model explain the positioning of recombination across eukaryotic species? On balance, it appears to us that the numerous differences outweigh the few similarities: the control of recombination position appears not to be substantially conserved across diverse Eukarya.

Conflict of interest

The authors declare no conflict of interest.

L Goodstadt and CP Ponting are at the MRC Functional Genomics Unit, Department of Physiology, Anatomy and Genetics, University of Oxford, South Parks Road, Oxford OX1 3QX, UK.

e-mail: chris.ponting@dpag.ox.ac.uk

Berger SL (2007). The complex language of chromatin regulation during transcription. *Nature* **447**: 407–412.

Borde V, Robine N, Lin W, Bonfils S, Geli V, Nicolas A (2009). Histone H3 lysine 4 trimethylation marks meiotic recombination initiation sites. *EMBO J* **28**: 99–111.

Boulton A, Myers RS, Redfield RJ (1997). The hotspot conversion paradox and the evolution of meiotic recombination. *Proc Natl Acad Sci USA* **94**: 8058–8063.

Buard J, Barthes P, Grey C, de Massy B (2009). Distinct histone modifications define initiation and repair of meiotic recombination in the mouse. *EMBO J* **28**: 2616–2624.

Cheung VG, Sherman SL, Feingold E (2010). Genetics. Genetic control of hotspots. *Science* **327**: 791–792.

Coop G, Przeworski M (2007). An evolutionary view of human recombination. *Nat Rev Genet* **8**: 23–34.

Mihola O, Trachtulec Z, Vlcek C, Schimenti JC, Forejt J (2009). A mouse speciation gene encodes a meiotic histone H3 methyltransferase. *Science* **323**: 373–375.

Myers S, Bowden R, Tumian A, Bontrop RE, Freeman C, MacFie TS *et al.* (2010). Drive against hotspot motifs in primates implicates the PRDM9 gene in meiotic recombination. *Science* **327**: 876–879.

Myers S, Freeman C, Auton A, Donnelly P, McVean G (2008). A common sequence motif associated with recombination hot spots and genome instability in humans. *Nat Genet* **40**: 1124–1129.

Oliver PL, Goodstadt L, Bayes JJ, Birtle Z, Roach KC, Phadnis N *et al.* (2009). Accelerated evolution of the Prdm9 speciation gene across diverse metazoan taxa. *PLoS Genet* **5**: e1000753.

Sollier J, Lin W, Soustelle C, Suhre K, Nicolas A, Geli V *et al.* (2004). Set1 is required for meiotic S-phase onset, double-strand break formation and middle gene expression. *EMBO J* **23**: 1957–1967.

Steiner WW, Steiner EM, Girvin AR, Plewik LE (2009). Novel nucleotide sequence motifs that produce hotspots of meiotic recombination in *Schizosaccharomyces pombe*. *Genetics* **182**: 459–469.

Tsai IJ, Bensasson D, Burt A, Koufopanou V (2008). Population genomics of the wild yeast *Saccharomyces paradoxus*: quantifying the life cycle. *Proc Natl Acad Sci USA* **105**: 4957–4962.

Tsai IJ, Burt A, Koufopanou V (2010). Conservation of recombination hotspots in yeast. *Proc Natl Acad Sci USA* **107**: 7847–7852.

Vyskocilova M, Prazanova G, Pialek J (2009). Polymorphism in hybrid male sterility in wild-derived *Mus musculus musculus* strains on proximal chromosome 17. *Mamm Genome* **20**: 83–91.

Wahls WP, Davidson MK (2010). Discrete DNA sites regulate global distribution of meiotic recombination. *Trends Genet* **26**: 202–208.

Editor's suggested reading

Kuhn GCS, Teo CH, Schwarzacher T, Heslop-Harrison JS (2009). Evolutionary dynamics and sites of illegitimate recombination revealed in the interspersion and sequence junctions of two nonhomologous satellite DNAs in cactophilic *Drosophila* species. *Heredity* **102**: 453–464.

Kochakpour N, Moens PB (2008). Sex-specific crossover patterns in Zebrafish (*Danio rerio*). *Heredity* **100**: 489–495.