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ORIGINAL ARTICLE

Heterogeneous transposable elements as silencers, enhancers and targets of meiotic recombination

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Abstract

During meiosis, DNA double-strand breaks are initiated by the topoisomerase-like enzyme SPO11 and are repaired by inter-sister chromatid and inter-homologue DNA repair pathways. Genome-wide maps of initiating DNA double-strand breaks and inter-homologue repair events are now available for a number of mammalian, fungal and plant species. In mammals, PRDM9 specifies the location of meiotic recombination initiation via recognition of specific DNA sequence motifs by its C2H2 zinc finger array. In fungi and plants, meiotic recombination appears to be initiated less discriminately in accessible chromatin, including at gene promoters. Generally, meiotic crossover is suppressed in highly repetitive genomic regions that are made up of transposable elements (TEs), to prevent deleterious non-allelic homologous recombination events. However, recent and older studies have revealed intriguing relationships between meiotic recombination initiation and repair, and transposable elements. For instance, gene conversion events have been detected in maize centromeric retroelements, mouse *MULE-MuDR* DNA transposons undergo substantial meiotic recombination initiation, *Arabidopsis Helitron* TEs are among the hottest of recombination initiation hotspots, and human TE sequences can modify the crossover rate at adjacent PRDM9 motifs in *cis*. Here, we summarize the relationship between meiotic recombination and TEs, discuss recent insights from highly divergent eukaryotes and highlight outstanding questions in the field.

Keywords Transposable elements · Meiosis · Recombination · Crossover · DNA repair · Epigenetics

Meiotic recombination initiation and repair

Meiotic recombination is initiated during prophase I of meiosis via the programmed induction of DNA double-strand breaks (DSBs) by a protein complex containing the topoisomerase-like enzyme SPO11 (Keeney et al. 1997; Lam and Keeney 2015b). Meiotic DSBs are processed, resected and then bound by the single-stranded DNA (ssDNA)-binding protein RPA, RAD51, a protein that stabilizes strand exchange intermediates and DMC1, a meiosis-specific RAD51-like protein. Together, this protein-DNA complex carries out a search for homologous sequences on sister chromatids or homologous chromosomes (Brown and Bishop 2015). DNA repair proceeds via recombination with either sister chromatids (inter-sister events) or homologous chromosomes (inter-homologue events). Inter-homologue events can be resolved as either crossovers, reciprocal exchanges of genetic material, or gene conversion events, copying of short tracts of sequence from one homologue to the other. In most species, one to two crossovers form per pair of homologous chromosomes, with the exception of the model fission yeast species *S. pombe* which makes more than ten crossovers per chromosome pair (Mercier et al. 2015). From mice to *Arabidopsis*, it has been established that a great excess of meiotic DSBs are formed over the number of crossovers formed (Chelysheva et al. 2010; Kauppi et al. 2013). For example, in *Arabidopsis*, approximately 200 initiating DSBs occur per meiosis, with 7 to 11 of these finally resolved as a

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crossover (1.5–2 crossover per chromosome pair) (Chelysheva et al. 2010; Giraut et al. 2011; Salomé et al. 2012; Choi et al. 2013). The tenfold excess of meiotic DSB number over crossover number highlights that meiotic DSBs generally do not limit crossover formation. Current efforts aim to understand whether the context, for instance timing and genomic location, of a given DSB influences the likelihood that it will be finally repaired as a crossover.

In recent years, orthogonal approaches have been developed and applied to map meiotic DSB landscapes at the genomic scale. These approaches include covalently linked SPO11 ChIP-chip, ssDNA-chip, SPO11 ChIP-chip, RPA ChIP-chip, sequencing of oligonucleotides covalently associated with immunoprecipitated SPO11 (hereafter SPO11-oligo seq), DMC1 ChIP-seq, RAD51 ChIP-seq and DMC1 ChIP-seq SSDS (ssDNA sequencing) (Borde et al. 2004, 2009; Blitzblau et al. 2007; Buhler et al. 2007; Ludin et al. 2008; Pan et al. 2011; Smagulova et al. 2011; Khil et al. 2012). These approaches give overlapping, but not equivalent, biological read outs, and therefore, they should not necessarily lead to the same genome-wide profile. For instance, formaldehyde cross-linked SPO11 ChIP-chip should detect all DNA regions that SPO11 can physically interact with, whereas SPO11-oligo seq will lead to the specific and direct detection of DNA regions that have been cut by SPO11. RPA-, DMC1- and RAD51-based methods detect processed and resected ssDNA associated with the respective protein. In Table 1, we provide an outline of studies that have been performed in divergent eukaryotes to map meiotic recombination initiation sites.

Eukaryotic genomes are highly occupied by repetitive sequences including transposable elements (TEs). TEs are mobile genetic elements that have, or had, the capacity to transpose to new genomic locations. Generally, only a small percentage of TE sequences in eukaryotic genomes retain the capacity to transpose. Many TE-derived sequences are previously active TEs that have lost functionality due to the accrual of deleterious mutations, or have been 'domesticated' to provide novel cellular functions (Jangam et al. 2017). TEs are often present at high copy number in different genomic locations, or in long tandem arrays of the same element. Therefore, TEs are potential threats to genomic stability as recombination between TEs can lead to ectopic recombination between non-homologous regions or non-homologous chromosomes.

Genomic regions that are highly occupied with transposable elements and repeats tend to be crossover suppressed in many organisms including *Arabidopsis*, *Drosophila* and rodents (Copenhaver et al. 1999; Rizzon et al. 2002; Wright et al. 2003; Jensen-Seaman et al. 2004). However, *C. elegans* and wheat DNA transposons associate with higher crossover rate, suggesting different TE classes and types may contribute to non-uniform patterns of meiotic crossover rate (Duret et al. 2000; Daron et al. 2014). A recent review has dealt with the evolutionary relationship between TEs and meiotic recombination rate, and highlights potential roles for TE insertion bias and selection in shaping the relationship (Kent et al. 2017). In this review, we will consider how experimentally mapped meiotic DSB and repair landscapes have demonstrated substantial recombination initiation and repair within TEs and repeated sequences. It is well established that TE classes, and also types within them, have different properties in terms of transposition mechanism, associated chromatin and silencing requirements. We will highlight the diversity of TEs and how this may lead to them playing context-dependent roles as silencers and enhancers of meiotic recombination.

Transposable element classes, variation and silencing

TEs were discovered by Barbara McClintock who found that their presence at the locus of a known maize gene can alter the gene's activity, and hence called them 'controlling elements' (McClintock 1956). Since McClintock's seminal discoveries on *Dissociation* (*Ds*) and *Activator* (*Ac*) (McClintock 1950), significant progress has been made on understanding TE transposition mechanisms, TE diversity in eukaryotic genomes and TE silencing via epigenetic pathways (Slotkin and Martienssen 2007; Bennetzen and Wang 2014; Chuong et al. 2016; Underwood et al. 2017).

Broadly, TEs can be split into those elements that transpose via RNA and cDNA intermediates by a copy-and-paste mechanism (class I) and those that transpose via only a DNA intermediate (class II) (Slotkin and Martienssen 2007; Feschotte and Pritham 2007; Chuong et al. 2016). Class I elements, otherwise known as retrotransposons, retroelements or endogenous retroviruses, transpose via expression of an RNA intermediate which is converted by reverse transcriptase into cDNA, and then reintegrated into the genome by an integrase (Slotkin and Martienssen 2007). Class II elements, otherwise known as DNA transposons, mainly transpose by a cut-and-paste mechanism where they are extracted from the genome by a transposase and then reintegrated at another genomic location (Feschotte and Pritham 2007). Exceptions to this are *Helitron* and *Maverick* class II elements which likely transpose via distinct replicative, copy-and-paste mechanisms (Feschotte and Pritham 2007). Both class I and class II elements come in autonomous or non-autonomous forms. Autonomous elements encode for all of the proteins required for their transposition. Most TEs are non-autonomous, and therefore require enzymatic activity encoded by a cognate autonomous element in order for transposition to occur. For instance, McClintock's *Ds*, a non-autonomous DNA transposon, is dependent on *Ac*, a related autonomous DNA transposon, for transposition (McClintock 1950; Slotkin and Martienssen 2007).

Table 1 Genome-wide studies of meiotic recombination initiation based on ssDNA, immunoprecipitation of SPO11 or immunoprecipitation of ssDNA-binding proteins

Species	Approaches	Genotypes used	Reference
S. cerevisiae	Covalently linked protein-DNA chip	*rad50S*	(Gerton et al. 2000)
	ssDNA-chip	*dmc1*Δ	(Buhler et al. 2007)
		Wild type, *dmc1*Δ, *dmc1*Δ *zip1*Δ, *dmc1*Δ *ndj1*Δ	(Blitzblau et al. 2007)
		*dmc1*Δ, *dmc1*Δ *pch2*Δ, *dmc1*Δ *sir2*Δ, *pch2*Δ *rdn*ΔΔ *dmc1*Δ, *orc1-161 dmc1*Δ, *dmc1*Δ *pch2*Δ 2:12 trans.	(Vader et al. 2011)
	Covalently linked SPO11 ChIP-chip	*sae2*Δ	(Borde et al. 2004)
		rad50S	(Gerton et al. 2000) (Mieczkowski et al. 2006) (Buhler et al. 2007) (Blitzblau et al. 2007) (Robine et al. 2007)
		rad50S, *rad50S sir2*Δ	(Mieczkowski et al. 2007)
		Wild type, *rec8*Δ, *rad50S*, *rec8*Δ *rad50S*	(Kugou et al. 2009)
		Wild-type and two *rec114* mutants	(Carballo et al. 2013)
	RPA ChIP-chip	*dmc1*Δ, *dmc1*Δ *set1*Δ	(Borde et al. 2009)
	SPO11-oligo sequencing	Wild type	(Pan et al. 2011)
		3 *S. cerevisiae* strains and 3 related wild species	(Lam and Keeney 2015a)
S. pombe	Covalently linked SPO11/Rec12 ChIP-chip	Wild type and *rad50S*	(Cromie et al. 2007) (Hyppa et al. 2008)
	SPO11/Rec12 ChIP-chip	Wild type	(Ludin et al. 2008)
		Wild type, *H3K9A*, *set1*Δ	(Yamada et al. 2013)
	SPO11/Rec12-oligo sequencing	Wild type	(Fowler et al. 2014)
M. musculus	DMC1 ChIP-seq	Wild-type male, *Hop2* mutant male, *Spo11* mutant male	(Smagulova et al. 2011)
	RAD51 ChIP-seq	*Hop2* mutant male	(Smagulova et al. 2011)
	DMC1 ChIP SSDS	Wild-type isogenic and hybrid males, *Prdm9* mutant male	(Khil et al. 2012) (Brick et al. 2012)
		Spo11 (Gal) mutant, *Hop2* mutant, *Spo11 (Gal) Hop2* double mutant (all male)	(Smagulova et al. 2013)
		Mouse subspecies, hybrids and humanised *PRDM9* (all male)	(Davies et al. 2016) (Smagulova et al. 2016)
		Wild-type male and female, *Dnmt3l* mutant male	(Brick et al. 2018)
	SPO11-oligo sequencing	Wild-type male	(Lange et al. 2016) (Yamada et al. 2017)
H. sapiens	DMC1 ChIP SSDS	5 male samples (3 *PRDM9* genotypes)	(Pratto et al. 2014)
A. thaliana	SPO11-1-oligo sequencing	Wild-type and *met1* mutant (male-biased)	(Choi et al. 2018)
		kyp suvh5 suvh6 mutant (male-biased)	(Underwood et al. 2018)
Z. mays	RAD51 ChIP-seq	Wild-type male flowers	(He et al. 2017)

Large portions of the human (46% of 3.2 Gbp), mouse (37.5% of 2.7 Gbp), maize (85% of 2.2 Gbp) and *Arabidopsis* (21% of 125 Mbp) genomes are made up of TE sequences, whereas the *S. pombe* (0.35–0.8% of 12.5 Mbp) and *S. cerevisiae* (2.4–3.3% of 12 Mbp) genomes contain less TEs (Kim et al. 1998; Consortium IHGS 2001; Consortium MGS 2002; Wood et al. 2002; Buisine et al. 2008; Schnable et al. 2009; Chalopin et al. 2015). These values may be underestimates as many non-coding sequences likely represent degraded TE sequences (de Koning et al. 2011; Baud et al. 2019). The proportion of a genome that is composed of transposable elements is dependent on (i) the rates of TE transposition in the recent history of the species, and (ii) the rate of removal of transposable element sequences from the genome (Devos et al. 2002; Kapusta et al. 2017). Recent bursts of transposition can be identified by the presence of

many elements with few differentiating polymorphisms, while older elements have accrued random mutations can be more easily differentiated (Platt et al. 2016; Maumus and Quesneville 2016). Non-allelic homologous recombination (NAHR) between related TEs during meiosis and mitosis is a known cause for genomic rearrangement and structural change. Such events can lead to large duplications, deletions or even the transfer of genetic information from one chromosome to another (Mensah et al. 2014; Startek et al. 2015; Song et al. 2018). The latter is exemplified by the introduction onto the human Y chromosome of 105 kb from the human X chromosome, adjacent to the PAR1 region, due to non-allelic recombination between two *LTR6B* repeats (Mensah et al. 2014; Poriswanish et al. 2018).

Preventing TE transposition is necessary to avoid mutagenesis and genomic instability. An important step in the prevention of TE transposition is the prevention of TE expression by RNA polymerase II. Despite over a billion years of evolutionary divergence, the core machinery that silences TE expression in most fungi, plants and animals is based on RNA interference (RNAi) and small RNAs, DNA cytosine methylation and/or di-/tri-methylation of histone H3 Lysine 9 (H3K9me2/3) (Castel and Martienssen 2013). RNAi (piRNAs in animals and siRNAs in plants) can direct the methylation of TE sequences by de novo DNA methyltransferases and/or H3K9 methyltransferases, which leads to gene silencing (Castel and Martienssen 2013; Matzke and Mosher 2014). This transcriptional gene silencing (TGS) of TEs and repeats prevents the expression of TE RNAs, and thereby prevents transposition. As will be explored in this review, these pathways that prevent access of RNA polymerase II to TE promoters and repeats, by compacting DNA into heterochromatin, appear to also play important roles in preventing access of meiotic recombination initiation and repair proteins. Notably, in the popular meiotic model budding yeast (*S. cerevisiae)* RNAi, H3K9 methylation and DNA methylation have all been lost (Drinnenberg et al. 2009; Hickman et al. 2011; Roche et al. 2016). In *S. cerevisiae*, heterochromatin and TGS relies upon the action of SIR2, a conserved histone deacetylase, and a number of Saccharomyces specific factors (Hickman et al. 2011).

Particular classes and types of TEs are associated with different chromatin states, which may reflect their transposition mechanism. For instance, all class I TEs (retrotransposons) absolutely require expression in order to transpose; therefore, TGS plays a key role in preventing class I element transposition. TGS also plays an important role in the silencing of class II elements but not at the level of every individual element. For example, expression of fully cognate autonomous *Ping* class II TEs in rice can lead to hundreds of transposition events of related non-autonomous *mPing* TEs (Lu et al. 2017). Thus, TGS of just fully cognate TEs in a given class II family could be sufficient to prevent transposition of the whole family. These fundamental differences between class I and class II elements mean that class I elements are generally associated with higher levels of DNA methylation and less accessible chromatin. Potentially reflecting these differences, experimental detection of meiotic DSBs in a number of species suggests that different TE classes and types have different susceptibility to meiotic DSB formation. Here, we will explore these differences in a number of fungal, mammalian and plant species.

Meiotic double-strand break landscapes and transposable elements

Fungi

S. cerevisiae (budding yeast) and *S. pombe* (fission yeast) are classic meiotic models but their genomes contain relatively low numbers of repeats and transposable elements compared with mammalian and plant genomes. Nonetheless, the study of recombination initiation in these species has highlighted that meiotic DSBs are suppressed in repetitive sequences, and therefore, mechanisms to restrict DSB formation in TEs likely exist.

Meiotic DSBs within yeast repetitive elements

In *S. cerevisiae*, meiotic DSBs form throughout the genome but are concentrated at hotspots of recombination initiation and suppressed in high copy repeats (Gerton et al. 2000; Borde et al. 2004; Blitzblau et al. 2007; Buhler et al. 2007; Pan et al. 2011). SPO11-oligo seq was first developed in *S. cerevisiae* and involves the immunoprecipitation of SPO11 protein and its associated oligonucleotides (that represent meiotic DSB sites), followed by the purification and sequencing of the associated oligonucleotides to generate genome-wide meiotic DSB maps (Pan et al. 2011). In all organisms, SPO11-oligos are between 20 and 50 nucleotides in length; therefore, read mapping to repetitive regions is challenging as many reads map to multiple locations, and it is often not possible to discriminate between conserved regions of related TEs (Pan et al. 2011; Sasaki et al. 2013; Yamada et al. 2017; Choi et al. 2018). *S. cerevisiae* SPO11-oligo seq illustrated most meiotic DSBs are formed in non-repetitive intergenic regions that contain promoters and are depleted of nucleosomes (Pan et al. 2011). High copy repeats (retrotransposons, rDNA, telomeres and tRNA genes) are highly suppressed for meiotic DSBs, as they make up about 14% of the *S. cerevisiae* genome, yet only 1.14% of SPO11-oligos map to these regions (Pan et al. 2011). *S. cerevisiae* SPO11-oligo data mapped against a full-length yeast *Ty* long terminal repeat (LTR) retrotransposon showed enriched signal

in the 5′ LTR region which often contains a promoter (Pan et al. 2011).

Despite the suppression of meiotic DSBs within *S. cerevisiae* TEs, there is strong evidence that *S. cerevisiae* TEs can modify local rates of meiotic recombination initiation. Sasaki et al. analysed meiotic DSBs within and around all yeast *Ty* elements and found that regions flanking *Ty* elements were highly variable in SPO11-oligo frequency with many significantly hotter or colder than genome averages (Sasaki et al. 2013). A number of hotspots adjacent to *Ty* elements, and one within a *Ty* element, were confirmed by the physical detection of meiotic DSBs (Sasaki et al. 2013). Interestingly, the genetic deletion of two of these *Ty* elements led to reduced meiotic DSBs in adjacent 5′ regions, providing direct evidence that the TE promotes meiotic DSBs in adjacent regions (Sasaki et al. 2013) (Fig. 1a, b).

In *S. pombe*, repetitive regions are also suppressed for meiotic DSB formation by Rec12/SPO11 (Rec12 is the primary name for SPO11 in *S. pombe*) (Fowler et al. 2014). *S. pombe* Rec12-oligo seq revealed that there are relatively fewer recombination initiation hotspots compared with *S. cerevisiae*, and that these hotspots do not have as strong a preference for nucleosome-depleted regions (Fowler et al. 2014). High copy repeats accrued relatively fewer meiotic DSBs when compared with *S. cerevisiae* (Fowler et al. 2014). A detailed analysis of Rec12-oligo seq data specifically within TE sequences has yet to be performed. Interestingly, formaldehyde cross-linked Rec12 ChIP-chip indicated that Rec12 interacts with centromeric repeats (Ludin et al. 2008), but meiotic DSBs are not observed in centromeres by Rec12-oligo seq (Fowler et al. 2014).

Chromatin-based suppression of meiotic DSB formation in yeast

The heterochromatin system of *S. pombe* better reflects the silencing systems found in animals and plants than that of *S. cerevisiae*, because like animals and plants, it is based on RNAi and H3K9 methylation (Castel and Martienssen 2013). RNAi (*dcr1*Δ) and H3K9 methyltransferase (*clr4*Δ) mutants that have defects in centromeric silencing can also form meiotic DSBs within centromeric repeats unlike wild-type controls (Ellermeier et al. 2010). This suggests that RNAi directed H3K9me2 heterochromatin can directly supress meiotic recombination initiation in repeated sequences. H3K9 acetylation is an antagonistic mark to the silencing mark H3K9me2 (Alper et al. 2013), and mutation of H3K9 to an alanine residue slightly decreased SPO11 occupancy at *S. pombe* hotspots (Yamada et al. 2013). Consistently, a strong correlation was observed between formaldehyde cross-linked Rec12 ChIP-chip signal and H3K9 acetylation (Yamada et al. 2013).

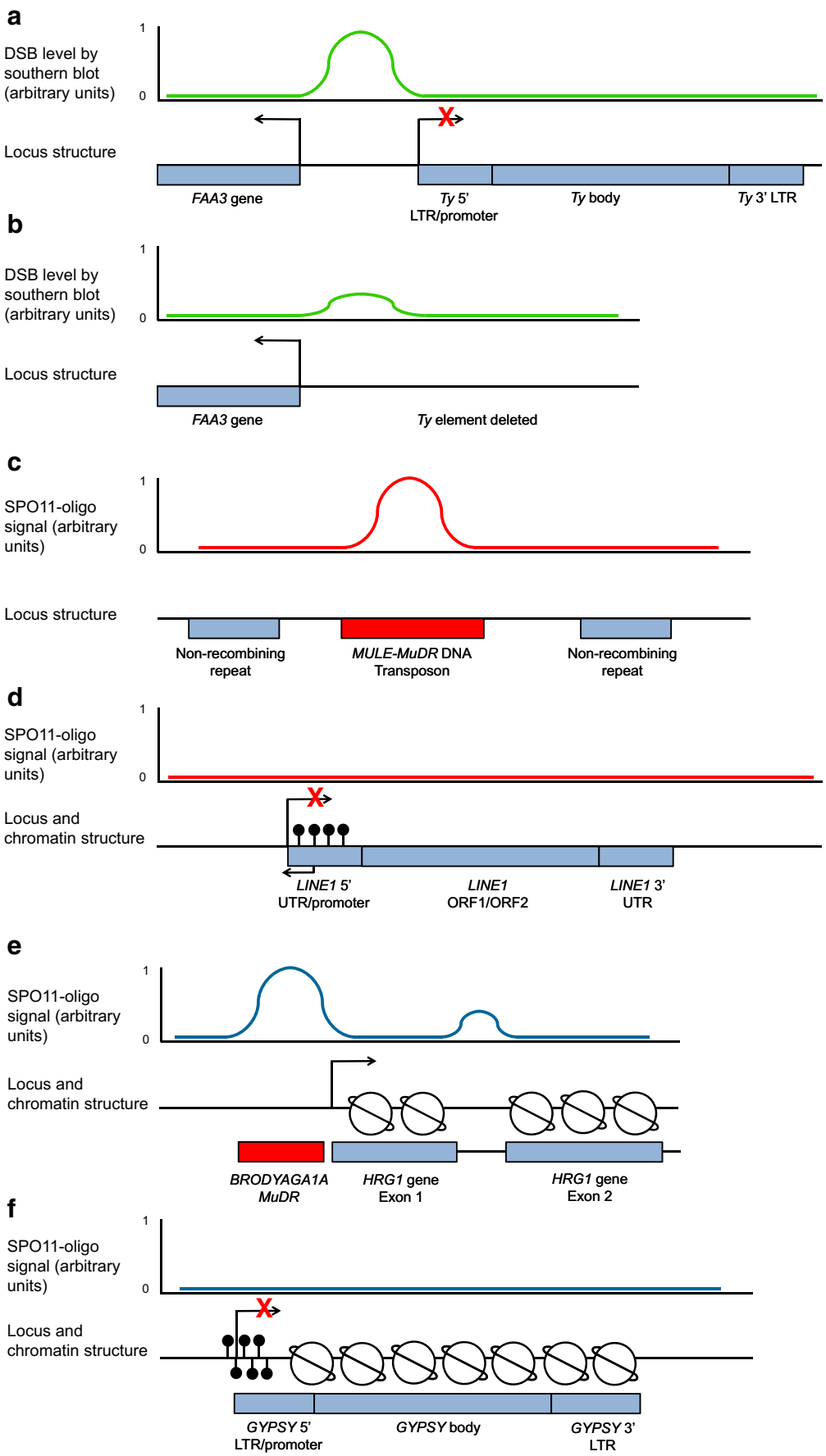
The mechanism of meiotic DSB suppression in *S. cerevisiae* TEs remains unknown. An interesting candidate may be the heterochromatin silencing pathway that is centred around SIR2 (see "Transposable element classes, variation and silencing" section). *S. cerevisiae* deacetylase *sir2* mutants, which lose silencing of telomeric repeats, mating type loci and genes embedded in rDNA (Hickman et al. 2011), exhibit increased mitotic and meiotic rDNA recombination (Gottlieb and Esposito 1989). In *sir2*, meiotic recombination initiation is increased in telomeres, rDNA and genes located close to rDNA, all direct targets of SIR2, and also a subset of other genes (Mieczkowski et al. 2007). An independent pathway involving PCH2 and ORC1 suppresses recombination initiation at the borders of rDNA heterochromatin and euchromatin (Vader et al. 2011). Application of SPO11-oligo sequencing in *sir2*, *pch2* and *orc1* mutant backgrounds could illuminate roles for these pathways in the suppression of meiotic DSB activity in *S. cerevisiae* *Ty* elements, and other repeats.

Mammals

Mammalian meiotic DSB hotspot locations are specified by PR-domain containing protein 9 (PRDM9), which appears to direct SPO11 activity to discrete genomic regions (Baudat et al. 2010; Myers et al. 2010). PRDM9 contains an N-terminal KRAB domain, a PR/SET domain that can methylate histone H3 on Lysine 4 and Lysine 36, and a C-terminal tandem array of zinc fingers, which has DNA-binding capacity (Grey et al. 2018). In humans, the zinc finger array recognizes specific DNA sequence motifs between 13 and 30 nucleotides in length (Altemose et al. 2017). In mice and humans, meiotic DSB hotspots overlap with PRDM9 motifs, based on DMC1 ChIP-seq, RAD51 ChIP-seq, DMC1 ChIP SSDS and SPO11-oligo seq (Smagulova et al. 2011; Brick et al. 2012; Pratto et al. 2014; Lange et al. 2016; Altemose et al. 2017). PRDM9-mediated meiotic DSB hotspots are in intergenic regions, away from genes (Smagulova et al. 2011; Brick et al. 2012; Pratto et al. 2014). In *Prdm9* male mouse mutants, meiotic recombination initiation reverts to gene promoters, as occurs in wild-type fungi and plants (Brick et al. 2012; Choi and Henderson 2015).

Different mouse TE classes have different capacities for meiotic DSB formation

In mammalian genomes, TEs are much more diverse and numerous compared with the two model yeasts, yet like yeast TEs and repeats they are generally highly suppressed for meiotic DSB formation (Smagulova et al. 2011; Brick et al. 2012; Lange et al. 2016; Yamada et al. 2017). In order to make high-confidence conclusions from SPO11-oligo mapping in mouse TEs, Yamada et al. used 4 read mapping approaches, in



◀ **Fig. 1** Schematic of meiotic recombination initiation in and around transposable elements in *S. cerevisiae* (**a** and **b**), mice (**c** and **d**) and *Arabidopsis* (**e** and **f**). **a** Meiotic DSB level in the *S. cerevisiae FAA3* gene and *TyEST3-FAA3* class I retrotransposon, based on data from Sasaki et al. 2013. Note the strong meiotic DSB hotspot in the *FAA3* promoter, 5′ of the Ty element. **b** Meiotic DSB level at the same locus as in (**a**) but in a strain where the complete *TyEST3-FAA3* element has been deleted. The recombination hotspot in the *FAA3* promoter has threefold reduced meiotic DSB level in the absence of the *Ty* element, suggesting the *Ty* element contributes to hotspot activity. Adjacent meiotic DSB hotspots, and an unlinked hotspot, did not change significantly in the deletion line (not shown in figure). Based on Sasaki et al. 2013. **c** Meiotic DSB level in a mouse MuDR DNA transposon. *MULE-MuDR* elements accrue a substantial amount of meiotic DSBs during mouse male meiosis based on SPO11-oligo sequencing (Yamada et al. 2017). **d** Meiotic DSB level in a mouse *LINE1* retrotransposon. *LINE1* elements are highly suppressed for recombination initiation in mice (Yamada et al. 2017). In the *Dnmt3l* DNA methylation deficient mutant, meiotic recombination initiation can occur in *LINE1* promoters during male meiosis (Zamudio et al. 2015). *Dnmt3l* mutants also express *LINE1* elements and experience meiotic catastrophe (Zamudio et al. 2015). **e** Meiotic DSB level in and around the Arabidopsis gene *HOT R GENE 1 (HRG1)*. The *HRG1* promoter contains a MuDR DNA transposon, which is nucleosome depleted and accrues meiotic DSBs (Choi et al. 2018). The MuDR element appears to enhance crossover within *HRG1*, which was originally genetically mapped as a meiotic crossover hotspot (Choi et al. 2016). **f** Meiotic DSB level in an *Arabidopsis GYPSY* retrotransposon. *GYPSY* retrotransposons are present in tandem arrays within, and adjacent to, *Arabidopsis* centromeres. *GYPSY* elements are highly methylated, and silent for transcription and recombination initiation in wild-type *Arabidopsis* (Choi et al. 2018). Loss of CG methylation, or non-CG methylation and H3K9 methylation, leads to increased meiotic DSBs within *GYPSY* elements (Choi et al. 2018; Underwood et al. 2018)

parallel, with varying levels of read mapping stringency. All four methods showed that the frequency of SPO11-oligos in repeats is less than would be expected given the fraction of the mouse genome made up of repeats (Yamada et al. 2017).

Despite the overall suppression of TEs for meiotic DSBs in mice, significant heterogeneity in meiotic DSB formation was exhibited between different TE classes and types (Yamada et al. 2017). DSB levels in TEs were interrogated in order to see whether DSBs in different TEs classes were formed in proportion to the amount of the genome composed of the given TE class (Yamada et al. 2017). Through this approach, the *MULE-MuDR* DNA transposons have two orders of magnitude more meiotic DSBs than expected (Fig. 1c), and *Tc-Mar Mariner*, *hAT-Charlie* and *PiggyBac* DNA transposons also accrue more meiotic DSBs than expected (Yamada et al. 2017). At the other extreme, *Dong-R4* non-LTR retrotransposons are three orders of magnitude more suppressed for meiotic DSBs than was expected, and *L1* and *IAP* retrotransposons also accrued less meiotic DSBs than expected (Yamada et al. 2017) (Fig. 1d). DMC1-ChIP-seq in mice has also shown that *L1* elements are underrepresented at recombination initiation hotspots, while a number of LINE, SINE, LTR and DNA transposon classes are overrepresented (Smagulova et al. 2011). This variation in meiotic DSB frequency in different TE types and classes highlights the importance of splitting up TEs into classes, and not treating all repeats as a single group. In the future, it would be insightful for direct comparisons to be made between SPO11-oligo seq, DMC1 ChIP-seq and DMC1 SSDS data in transposable elements.

Roles for DNA methylation in meiotic DSB control in mouse TEs

In order to comprehend differential meiotic DSB formation between different TE types, it is important to consider DNA methylation, chromatin modifications and chromatin. This is highlighted by the large defects observed in male meiosis in mice with defective DNA methylation due to the mutation of *DNMT3L*, a gene that encodes an important co-factor for the major mouse de novo DNA methyltransferase DNMT3A (Bourc'his and Bestor 2004; Zamudio et al. 2015). Mouse *L1* and *IAP* retrotransposons are highly methylated as part of TGS via a pathway that involves MIWI2, an Argonaute protein that binds piRNAs for the targeting of DNA methylation to TEs, and DNMT3L (Zamudio et al. 2015). *Miwi2* and *Dnmt3l* single mutants both express *L1* and *IAP* retrotransposons in mice spermatogonia, with the greatest expression observed at the onset of male meiosis (Zamudio et al. 2015). Pertinently, not all *L1* subtypes showed this trend, in this case highlighting heterogeneity within a single TE type (Zamudio et al. 2015). Zamudio et al. went on to show that *L1* and *IAP* retrotransposons lose meiotic DSB suppression in the DNA methylation defective *Dnmt3l* background, based on SPO11 dot blot and DMC1 ChIP–qPCR experiments (Zamudio et al. 2015) (Fig. 1d).

An extension to these results is the recent genome-wide profiling of recombination initiation by DMC1 ChIP-seq SSDS in *Dnmt3l* male mice, and wild-type female mice (Brick et al. 2018). At the onset of meiotic DSB formation, DNA methylation reprogramming has occurred in female mice, whereas in males, this is not the case (Seisenberger et al. 2012). Despite equivalent *PRDM9* alleles, Brick et al. found differential usage of recombination initiation hotspots between wild-type male and female mice, and that differential DNA methylation between males and females may underlie this alternative hotspot usage (Brick et al. 2018). Brick et al. compared male meiotic DNA methylation profiles of male-biased hotspots with female-biased hotspots. In male meiosis, male-biased hotspots have lower DNA methylation than female-biased hotspots, whereas both sets of hotspots have low methylation in females due to DNA methylation reprogramming.

In order to test for a causal role for DNA methylation in the silencing of female-biased hotspots in male meiosis, Brick et al. checked for DSB formation at female-biased hotspots in the *Dnmt3l* mutant male map. Interestingly in *Dnmt3l* male mutants, meiotic DSBs increase in female-biased hotspots and

reduce in male-biased hotspots (Brick et al. 2018). This suggests that DNA methylation may partially explain differences in recombination initiation between male and female meiosis, and is consistent with previous results that PRDM9 binding may be sensitive to DNA methylation status (Tiemann-Boege et al. 2017; Brick et al. 2018). Given the previous findings on increased recombination initiation in TEs in *Dnmt3l* male mutants (Zamudio et al. 2015), it would be interesting to explore whether female-biased hotspots that increase in male meiosis in the *Dnmt3l* background have any relations with TEs or repetitive sequences.

Plants

Meiotic DSB maps in Arabidopsis and maize and their overlap with TE sequences

In *Arabidopsis*, SPO11-1 and SPO11-2 are non-redundantly required for the formation of meiotic DSBs via their catalytic tyrosine residues (Grelon et al. 2001; Stacey et al. 2006; Hartung et al. 2007; Wang and Copenhaver 2018). Using the same approach as originally applied in *S. cerevisiae*, *Arabidopsis* SPO11-1 oligos were mapped in wild-type *Arabidopsis* (Pan et al. 2011; Choi et al. 2018; Underwood et al. 2018). Approximately 92–93% of SPO11-1-oligo reads align uniquely to the genome and the other 8% map to repetitive sequences including TEs and centromeric repeats (Choi et al. 2018). Since TEs and repeats occupy approximately 21% of the *Arabidopsis* genome (Buisine et al. 2008), these regions are suppressed for meiotic DSBs (8% of SPO11-1 oligos vs 21% genome) but not as much as repeated sequences in *S. cerevisiae* (1.14% of SPO11-oligos vs 14% genome) (Pan et al. 2011; Choi et al. 2018). At the chromosome scale, SPO11-1-oligonucleotides are highly enriched in the gene-dense euchromatic chromosome arms and are reduced towards the centromeres, where TE density, DNA methylation and nucleosome occupancy increases (Choi et al. 2018; Underwood et al. 2018). The strong anti-correlation between SPO11-1-oligonucleotides and nucleosome occupancy/DNA methylation indicates that chromatin accessibility is a major determinant in meiotic DSB formation in *Arabidopsis*, similar to *S. cerevisiae* (Pan et al. 2011; Choi et al. 2018).

In diverse TE families and repetitive regions in *Arabidopsis*, the quantitative relationship between DSB formation and DNA accessibility is evident. SPO11 activity in repetitive regions appears to follow similar rules as in gene-rich regions, where the level and distribution of SPO11-1-oligos depends on AT-richness, nucleosome occupancy and epigenetic modifications (Underwood et al. 2017, 2018; Choi et al. 2018). Generally, class I retrotransposons such as *Copia* and *Gypsy* elements are DSB coldspots with very few SPO11-1-oligos due to the high levels of DNA methylation, H3K9me2 and nucleosome occupancy (Fig. 1f). These DSB cold transposons are enriched in centromeres (Underwood et al. 2017; Choi et al. 2018). Interestingly, SPO11-1-oligo seq revealed that specific families of DNA transposons, including *Helitrons*, *Tc1/Pogo/Mariner* and *MuDR* are substantial DSB hotspots (Fig. 1e), while other class II TEs (e.g. *En/Spm*) are DSB coldspots. Thus, *MuDR* and *Tc1/Pogo/Mariner* elements have been identified as meiotic DSB hotspots in mice and *Arabidopsis*, suggesting that these elements may have specific characteristics that make them susceptible to meiotic DSB formation (Yamada et al. 2017; Choi et al. 2018).

In *Arabidopsis*, DSB hotspot DNA transposons are frequently located between DSB coldspot transposons (i.e. alternating) in pericentromeres, and also in regions of lower TE density including chromosome arms. They share genetic and epigenetic features with genic DSB hotspots, displaying high AT sequence richness, low levels of nucleosome occupancy, DNA methylation and H3K9me2. Most DSB hotspot DNA elements are non-autonomous short fragmented elements, indicating that they might have accrued deletions and mutations during DSB repair. The SPO11-1-oligos of DSB hotspot transposons are produced inside the DNA elements, with high peaks around TE start and end sites. DSB hotspot DNA elements are significantly associated with gene families such as *DEFENSIN* and *R* genes involved in plant immunity, indicating a potential contribution to adaptation via enhancing meiotic recombination (Choi et al. 2018). A prime example is *HOT R GENE 1*, which has nucleosome-depleted *MuDR* elements in its promoter and terminator (Choi et al. 2016, 2018) (Fig. 1e). These *MuDR* elements appear to enhance meiotic recombination initiation in adjacent regions while crossovers are observed within the gene (Choi et al. 2016, 2018) (Fig. 1e).

Unlike *Arabidopsis*, the maize genome-wide DSB map by RAD51 ChIP-seq showed that the majority of meiotic DSBs occur in repetitive DNA such as *Gypsy* retrotransposons which occupy large parts of chromosomes, including pericentromeres and centromeres (He et al. 2017). Only 26% of DSB hotspots are located near genes (He et al. 2017). Although the pattern of meiotic DSBs in maize exhibits a trend of enrichment in nucleosome-depleted regions in gene and repetitive sequences, the formation of DSBs in maize appears to be the most promiscuous among the tested organisms so far. Since crossovers are still limited to genic regions in maize (Li et al. 2015; Kianian et al. 2018), it is likely that maize will be a good model organism for the future study of how DSBs disfavour crossover formation in transposons, and favour crossover formation around genes. The DSB maps in *Arabidopsis* and maize indicate both conserved and species-specific patterns of meiotic recombination initiation, likely due to different genome and epigenome characteristics. Mapping meiotic DSB sites in diverse plant genomes will further reveal the contribution of TEs to plant recombination initiation landscapes.

Epigenetic control of meiotic DSB formation within Arabidopsis TEs

The formation of meiotic DSBs in *Arabidopsis* TEs close to centromeres was recently shown to be suppressed by epigenetic modifications, including DNA methylation and H3K9me2 (Underwood et al. 2017, 2018; Choi et al. 2018). SPO11-1-oligo sequencing in *met1* and *suvh4 suvh5 suvh6* mutants, defective in maintenance of CG DNA methylation and H3K9me2/non-CG methylation respectively, revealed that meiotic DSBs are increased significantly around centromeric repeats (*CEN180*), retrotransposons and normally cold DNA element families such as *En/Spm*. Intriguingly, the increased DSBs at repetitive DNA in the epigenetic mutants strongly overlap with regions of reduced nucleosome occupancy, indicating that epigenetic factors may restrict meiotic recombination initiation, as well as transcription, by limiting DNA accessibility. Since other histone variants (e.g. H2A.W) and chromatin modifications (e.g. H3K27me1) contribute to heterochromatin formation in plants (Jacob et al. 2010, 2014; Yelagandula et al. 2014), it will be interesting to elucidate how these factors affect meiotic DSB landscapes at high-resolution via SPO11-1-oligo sequencing. SPO11-1-oligo sequencing may also be applied to understand sex-specific DSB patterns in plants, which is especially interesting given the known differences in DNA methylation reprogramming between male and female reproductive lineages in plants (Hsieh et al. 2009; Calarco et al. 2012).

Meiotic double-strand break repair (crossover and gene conversion) and transposable elements

In this section, we address the repair of meiotic DSBs that have occurred within TEs. It appears that heterochromatin (including H3K9 methylation and DNA methylation) may play an important role in favouring non-crossover based repair in diverse species. We also describe the role that TEs may play in modifying the choice between crossover or non-crossover at adjacent hotpots, by recruiting repressors and heterochromatic states.

Fungi

Despite the evident suppression of meiotic DSB formation in *S. cerevisiae* TEs and high copy repeats, on average two to three DSBs occur in high copy repeats per meiosis, suggesting pathways that actively prevent non-allelic crossover likely exist (Pan et al. 2011). In light of genomic data that shows most *S. cerevisiae* meiotic DNA repair events occur in genic regions (Mancera et al. 2008), the discovery of meiotic DSBs within and adjacent to yeast *Ty* elements (see "Meiotic double-strand break landscapes and transposable elements" section) (Pan et al. 2011; Sasaki et al. 2013) may seem surprising. However, meiotic DNA repair events were found in *Ty* elements in the 1980s (Roeder 1983; Kupiec and Petes 1988a, 1988b), suggesting meiotic DSBs in such elements must occur. Unequal crossing over between two different *Ty* TEs, linked by approximately 21 kb and in the same orientation on Chromosome III, was found to occur at the relatively high frequency of 1% in diploid meiotic yeast cells (Roeder 1983). As these elements were in the same orientation and they were highly linked, this configuration may be highly prone to NAHR. There is also evidence for gene conversion between non-allelic *Ty* elements, including events between non-homologous chromosomes (Kupiec and Petes 1988b). More recently, NAHR between *Ty* elements has been demonstrated to play a role in genome structural change during *Saccharomyces* domestication and evolution (Yue et al. 2017), albeit these events could be of mitotic or meiotic origin. In the future, it will be interesting to understand the role of heterochromatin pathways in suppressing crossover between yeast *Ty* elements, and more generally harnessing the power of yeast forward genetics to identify NAHR suppressive pathways.

The mechanism of meiotic crossover suppression in *S. pombe* centromeric repeats has important implications in animals and plants, given the similar nature of heterochromatin formation between these systems (Nambiar and Smith 2016). RNAi (*dcr1*Δ) and H3K9 methyltransferase (*clr4*Δ) mutants have not only increased meiotic DSB formation in centromeric repeats (see "Meiotic double-strand break landscapes and transposable elements" section) but also increased crossovers (Ellermeier et al. 2010). Indeed in *S. pombe*, it appears that all six heterochromatin mutants that have increased meiotic DSBs in centromeric repeats also have increased crossover in the same region (Ellermeier et al. 2010). Recent work has shown the important role of pericentromeric cohesion complexes in establishing meiotic DSB repression, and thereby also crossover suppression (Nambiar and Smith 2018). Understanding whether euchromatic and heterochromatic cohesin complexes also have different roles in recombination in animals and plants will be of future interest.

Given the role of DNA methylation in controlling meiotic DSBs in many species (see "Meiotic double-strand break landscapes and transposable elements" section) including mice and *Arabidopsis*, it is important to consider a classic study in the fungus *Ascobolus immerses*. In *Ascobolus*, it was possible to dissect the roles of DNA methylation during meiotic recombination at the pre- and post-recombination initiation stages (Maloisel and Rossignol 1998). Using the methylation-induced premeiotically (MIP) system, a known meiotic crossover hotspot was methylated. Clones that were methylated on both homologoues exhibited several hundred

fold reduced crossover, while clones that were methylated on only a single homologue still had fiftyfold reduced crossover (Maloisel and Rossignol 1998). In the clones with just a single methylated homologue, meiotic DSB formation should occur normally on the non-methylated homologue suggesting that DNA methylation may also suppress meiotic crossover at a stage of meiotic crossover (i.e. after the initiation of recombination). In the future, it will be interesting to understand how DNA methylation inhibits later stages of crossover formation at TE and non-TE sequences, including the identification of methylation sensitive meiotic stages and factors.

Mammals

TE sequences as targets of meiotic crossover

The study of fine-mapped meiotic crossover events in the human genome has implicated a role for TEs in shaping crossover distributions in mammalian genomes. Human and mouse crossover hotspots are typically between 1 and 2 kb in length, they occur outside genes, and have a distribution of approximately one hotspot every 100 kb (Jeffreys et al. 2001; Myers et al. 2005; Paigen et al. 2008). The initial genome-wide identification of human crossover hotspots found that a particular repeat class, *THE1A/B* retrotransposons, were significantly overrepresented in crossover hotspots compared with randomly matched coldspot regions (Myers et al. 2005). Remarkably, *THE1A/B* retrotransposons that overlapped with crossover hotspots were five to sixfold more likely to contain the specific sequence motif CCTCCCT than *THE1A/B* retrotransposons that did not overlap crossover hotspots (Myers et al. 2005). The CCTCCCT motif is also present at crossover hotspots outside of *THE1A/B* retrotransposons, but CCTCCCT motifs present within a *THE1A/B* repeat are twenty to thirtyfold more likely to lead to a crossover hotspot indicating a strong modifying effect of local context (Myers et al. 2005). In the same study, it was shown that *L1* retrotransposons are highly underrepresented in crossover hotspots, which mirrors more recent work in mice that has shown *L1* elements are highly suppressed for meiotic DSB formation (see "Meiotic double-strand break landscapes and transposable elements" section) (Myers et al. 2005; Smagulova et al. 2011; Zamudio et al. 2015; Yamada et al. 2017).

The CCTCCCT 7-mer motif was later shown to be part of a larger CCNCCNTNNCCNC 13-mer motif that underlies at least 40% of human crossover hotspots (Myers et al. 2008). *L2* and *Alu* retrotransposons that contain this consensus 13-mer motif are also human crossover hotspots, while related repeats that have substitutions in the 13-mer are not hotspots (Myers et al. 2008). The strong genetic component of crossover hotspot location is due to the hotspot defining protein PRDM9 which was independently identified via the human consensus 13-mer motif and conventional genetic mapping in mice (see "Meiotic double-strand break landscapes and transposable elements" section) (Baudat et al. 2010; Myers et al. 2010; Grey et al. 2018).

The *PRDM9* gene is rapidly evolving in mammals, as are crossover hotspot locations which are not conserved between humans and chimpanzees (Winckler et al. 2005; Ptak et al. 2005; Myers et al. 2010). Consistently, the chimpanzee PRDM9 protein is predicted to recognize a different DNA sequence motif (Myers et al. 2010). Multiple lines of evidence suggest the 13-mer consensus motif of human PRDM9 arose after the divergence from chimpanzees (Myers et al. 2010). The motif is depleted in the human genome compared with the chimpanzee genome, especially in the context of *THE1* repeats, consistent with GC biased gene conversion events in human leading to motif degradation (Myers et al. 2010; Odenthal-Hesse et al. 2014; Arbeithuber et al. 2015).

An independent line of evidence from gorillas also suggests that PRDM9 targets sequence motifs within repeat sequences for meiotic recombination, and that the repeats subsequently accrue substitutions due to GC biased gene conversion during DNA repair (Wacholder and Pollock 2017). Like in humans, a suspected PRDM9 motif was reported to be degraded in gorillas (Wacholder and Pollock 2017). A genome-wide scan for interlocus gene conversion and deletion events in *Alu* retrotransposons across the great apes found a large excess of these events in the gorilla lineage (Wacholder and Pollock 2017). These events were associated with a 15-bp motif in gorillas but not in other great ape species, and the same motif is depleted in gorilla *Alu* elements compared to other great apes (Wacholder and Pollock 2017). Motif degradation can be partially explained by interlocus conversion events, but again appears to be mainly because of GC biased gene conversion (Wacholder and Pollock 2017). It has not escaped our notice that the GC biased gene conversion or crossover (Odenthal-Hesse et al. 2014; Arbeithuber et al. 2015) in TEs could play a role in the mutation of functional elements within TEs, including ORFs. This could represent a convenient route for the mutation, degradation and potentially the domestication of TEs. Further, GC biased gene conversion will lead to the accumulation of cytosine residues, a prerequisite for DNA cytosine methylation based silencing.

Orthogonal evidence for TEs being PRDM9 targets came from searching for potentially extinct PRDM9 target motifs that are depleted in the human genome (Wacholder and Pollock 2017). Nineteen consensus motifs were found to be depleted in the human genome, whose adjacent regions exhibit hallmarks of GC biased gene conversion specifically in the human lineage (Wacholder and Pollock 2017). Five of the nineteen depleted motifs are frequently found within TEs

(including *hAT-Charlie*, *ERVL-MaLR* and *Alu* elements). Notably, the motifs found in *hAT-Charlie* and *ERVL-MaLR* repeats are between 2 and 3.8 times more likely to become depleted when located inside a repeat compared with a random genomic location (Wacholder and Pollock 2017). This could reflect either a preference for GC biased gene conversion within repeats rather than less mutagenic alternatives, or a general higher recombination rate in repeat located motifs.

TE sequences as local modifiers of meiotic crossover

In a recent study, Altemose et al. have addressed how PRDM9 motif context can affect ultimate crossover likelihood (Altemose et al. 2017). ChIP-seq of tagged PRDM9 was performed in order to map-binding sites in human HEK293T cells (Altemose et al. 2017). One hundred seventy thousand PRDM9 peaks were identified, and PRDM9 binding to multiple motifs and at promoters was detected (Altemose et al. 2017). The number of potential PRDM9-binding sites far outweighs the number of recombination hotspots (18,000) that were found in human DMC1 ChIP-seq SSDS (Pratto et al. 2014).

Altemose et al. hypothesised that sequence motifs other than PRDM9-binding motifs may influence recombination rate at the local level *in cis*, but they may be difficult to detect if they only act at a subset of total hotspots (Altemose et al. 2017). Therefore, PRDM9-binding sites located within 20,000 *THE1B* retrotransposon elements present in the human genome were analysed. Seventeen motifs were found to influence PRDM9 binding within *THE1B* elements. All motifs were located within predicted PRDM9-binding regions, i.e. PRDM9-binding per se is not influenced by motifs outside of this region. Altemose et al. independently tested for motifs that modify the likelihood of a PRDM9-binding site within a *THE1B* element to become a recombination hotspot (based on LD crossover signal). From this analysis, four motifs were found that map well outside the PRDM9-binding region and were described as 'non-PRDM9 recombination influencing motifs'. The strongest motif is ATCCATG. The presence of this 'non-PRDM9 recombination influencing motif' adjacent to the consensus PRDM9 motif leads to a 2.5-fold reduction in crossover at the hotspot defined by the consensus motif. Altemose et al. went on to independently search for motifs that underscore chromatin states from NIH Roadmap Epigenomics Consortium data. Strikingly, ATCCATG came out as the strongest single predictor for the 'heterochromatin state', marked by enriched H3K9me3 (Altemose et al. 2017)

Human KRAB zinc finger proteins (KZFP) bind a huge repertoire of TEs, have been implicated in TE domestication and can direct the silencing mark H3K9me3 in mammals by recognizing specific sequence motifs and recruiting TRIM28 (a universal corepressor) and SETDB1 (an H3K9 methyltransferase) (Imbeault et al. 2017; Ecco et al. 2017). KZFP genes are abundant in mammalian genomes, and recently, 222 of the 350 human KZFP-binding locations were mapped by ChIP-seq (Imbeault et al. 2017; Ecco et al. 2017). Remarkably, three KZFPs (ZNF100, ZNF430 and ZNF766) and TRIM28 bind to sites that overlap 'non-PRDM9 recombination influencing motifs' in *THE1B* repeats (Altemose et al. 2017). The capacity of KZFPs to recruit H3K9me3 and 'heterochromatin' to regions adjacent to PRDM9-binding motifs mean they could act as anti-crossover factors.

It is plausible that PRDM9 might be an anti-TE factor because it targets some TEs for potentially mutagenic recombination, while the combined action of KZFPs, TRIM28 and H3K9me3 appears to suppress crossover, and thereby favour gene conversion and/or sister chromatid based repair of TE DSBs (Imbeault et al. 2017; Yamada et al. 2017; Altemose et al. 2017). In the future, it will be important to discover whether 'non-PRDM9 recombination influencing motifs' can also be found in other mammals including mice, which could serve as a system to genetically interrogate the roles of these motifs and KZFPs in the modification of crossover rate.

Relationships between the expansion and contraction of KZFP family genes, and the presence of the *PRDM9* gene could also be important to understand the control of recombination and genome structure in vertebrate genomes. Notably, bird genomes possess relatively few KZFP genes (all genomes studied to date have less than fifty; most less than ten), have lost *PRDM9* genes, and have relatively compact genomes with lower TE content compared to other vertebrates (Singhal et al. 2015; Kapusta et al. 2017; Imbeault et al. 2017). All mammalian genomes studied to date have at least two hundred KZFP genes, apart from platypus which encodes only 43 KZFP genes, and also lacks a functional *PRDM9* gene (Imbeault et al. 2017; Baker et al. 2017). Other mammals are known to have lost *PRDM9*, including dogs, and yet retain high numbers of KZFP genes (Baker et al. 2017). Given that platypus is one of only five extant monotreme species, and is considered a living fossil; this mammalian lineage may have lost a functional *PRDM9* gene at a relatively older evolutionary time point compared to other mammals. The study of further extant monotreme species' genomes may be able to provide insight into whether *PRDM9* and KZFP genes are antagonistic factors.

Plants

Genome-wide maps of crossover sites have been generated in diverse plant genomes, including *Arabidopsis*, *Mimulus*, tomato, potato, rice, wheat and maize (Giraut et al. 2011; Wijnker et al. 2013; Choi et al. 2013; Hellsten et al. 2013; Choulet et al. 2014; Li et al. 2015; Si et al. 2015; Shilo et al. 2015; Demirci et al. 2017; de Haas et al. 2017; Darrier et al.

2017; Marand et al. 2017; Kianian et al. 2018). At the chromosome scale, crossovers in plants are predominantly formed in gene-rich chromosome arms and often biased to subtelomeric regions, correlating with gene density. In contrast, crossovers are strongly suppressed across pericentromeres and centromeres, and thereby exhibit a strong anti-correlation with DNA methylation level, and TE density. The introduction of DNA methylation on a euchromatic crossover hotspot is sufficient to silence crossover recombination (Yelina et al. 2015). At fine scales, it has been shown that crossovers are highly enriched around genes, with higher peaks at gene transcription start and termination sites in *Arabidopsis*, *Mimulus*, potato and maize (Choi et al. 2013; Hellsten et al. 2013; Li et al. 2015; Shilo et al. 2015; Marand et al. 2017; Kianian et al. 2018). The two higher peaks of crossovers at gene transcription start and termination sites overlap mostly with SPO11-1-oligo landscapes around genes in *Arabidopsis* (Choi et al. 2013, 2018; Shilo et al. 2015). Similar to *Arabidopsis*, maize, potato and wheat also show higher enrichment of crossovers around gene transcription start and termination sites, indicating that chromatin structure may be a key determinant in crossover location around genes (Darrier et al. 2017; Marand et al. 2017; Kianian et al. 2018).

Consistently, crossovers in genic regions exhibit a positive relationship with low nucleosome occupancy, high AT-richness (A/T polymers) and specific DNA motifs (CTT, CCN) (Wijnker et al. 2013; Choi et al. 2013, 2018; Shilo et al. 2015). Although it is still challenging to generate fine-scale maps of crossovers in transposons and repetitive DNA due to the limited number of crossovers, the likelihood of crossover formation in transposons appears to depend on the family of transposons and plant species. In *Arabidopsis*, the crossover pattern correlates with densities of euchromatic DNA elements (*Tc1/Pogo/Mariner* and *Helitrons*) at broad scales, while crossovers anti-correlate with heterochromatic DNA elements (*En/Spm*), and retrotransposons such as *Gypsy* and *Copia* (Horton et al. 2012; Choi et al. 2018; Underwood et al. 2018). In potato, crossovers are significantly enriched around the *Stowaway* family of miniature inverted-repeat DNA transposons (MITEs) (Marand et al. 2017). Similarly, an insertion of a *MuDR* DNA transposon was able to promote crossover rate across the maize *a1* allele, potentially by increasing meiotic DSBs, and insertion frequencies of *Mu* transposons correlate with crossover rates in maize (Yandeau-Nelson et al. 2005; Liu et al. 2009). Thus, DSB hotspot DNA transposons may promote crossovers when they insert near to genes in plant genomes.

Plant centromeres are almost fully suppressed for meiotic crossover (Copenhaver et al. 1999; Choulet et al. 2014; Shilo et al. 2015; Marand et al. 2017; Choi et al. 2018). However, in maize, gene conversion events were detected in centromeric retroelements and have occurred over generations, indicating that meiotic DSBs in repetitive regions are preferentially repaired via non-crossover pathways (Shi et al. 2010). Interestingly, *Arabidopsis* non-CG methylation mutants including *cmt3* exhibit increased crossovers across the pericentromeres and centromeres, while loss of CG methylation leads to reduced centromeric crossover and increased euchromatic crossover (Yelina et al. 2012, 2015; Mirouze et al. 2012; Melamed-Bessudo and Levy 2012; Colomé-Tatché et al. 2012; Underwood et al. 2018). It is notable that increased crossovers in the *cmt3* non-CG DNA methylation mutant in Col/Ler intraspecific hybrids mostly mapped to pericentromeres but not centromeres, where DSBs are elevated in the related *suvh4 suvh5 suvh6* mutant which has reduced non-CG methylation and H3K9me2 (see "Meiotic double-strand break landscapes and transposable elements) (Underwood et al. 2018). It appears that non-CG methylation/H3K9me2 and CG methylation have distinct inhibitory effects on transcription, DSB formation, repair and crossover formation in TEs.

It will be interesting to address how crossovers are influenced in plant genomes by other layers of plant heterochromatin such as H2A.W, H1 and H3K27me1, (Zemach et al. 2013; Jacob et al. 2014; Yelagandula et al. 2014). For example, *Arabidopsis* has three H2A.W variants (H2A.W6, H2A.W7, H2A.W12) and they contribute redundantly to heterochromatin formation (Yelagandula et al. 2014). However, it remains unknown how each or combinations of them can affect meiotic crossovers in heterochromatic regions. It is known that only H2A.W7 is phosphorylated by ATM and cooperatively involved in DNA repair with H2A.X variants (Lorković et al. 2017). H3K27me1 is required to silence a subset of transposons and inhibits DNA over-replication in heterochromatin (Jacob et al. 2010, 2014). Given that DNA replication timing is also tightly linked to meiotic recombination, it is possible that loss of H3K27me1 may increase crossovers across the pericentromeres and centromeres.

Summary and outlook

The unprecedented resolution of meiotic DSB and DNA repair landscapes by novel sequencing approaches has provided great insight into the roles of TEs as silencers and enhancers of meiotic recombination. Diverse transposable elements in mammals, fungi and plants are targets of meiotic recombination initiation. Gathering further quantitative data will be important to fully address how often TEs are cut by SPO11. A causal role for DNA methylation in differential meiotic DSB formation between male and female mice has recently been described. Whether TEs underlie this difference and whether it also occurs in other animal or plant species remains to be seen. In the future, it will be interesting to explore the genomic landscapes of meiotic DSBs in more species, including classic meiosis models like *Drosophila* and *C. elegans*, and also novel species.

There is strong evidence in maize and humans for gene conversion mediated repair of meiotic DSBs in TEs, but a full understanding of how DSBs in TEs are repaired is still lacking. It is probable that sister chromatid-based DNA repair could play an important role in this process, but this repair pathway is genetically undetectable. It will also be important to address how the decision of repair pathway affects the integrity of the TE itself and the genome as a whole. Indeed, meiotic DSB events in TEs may even often lead to non-viable gametes that are not recovered in the next generation.

A current technical hurdle is the detection of enough recombinant outcomes at recombination initiation hotspots in TEs to make firm conclusions on how these DSBs are repaired. The sequencing of more repair outcomes either by targeted sequencing approaches, or simply deeper sequencing will shed more light on inter-homologue repair at recombination initiation hotspots in TEs. In the future, reference quality genomes will be produced in a facile manner in diverse organisms with heterogeneous TE contents and genome structures. Such resources will open up avenues for the study of recombination initiation in TEs in different contexts, allowing us to more fully understand genome 'controlling elements' and their roles in meiotic recombination, reproduction and heredity.

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