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REVIEW

Molecular mechanisms and regulation of recombination frequency and distribution in plants

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Abstract

Key message **Recent developments in understanding the distribution and distinctive features of recombination hotspots are reviewed and approaches are proposed to increase recombination frequency in coldspot regions.**

Abstract Recombination events during meiosis provide the foundation and premise for creating new varieties of crops. The frequency of recombination in different genomic regions differs across eukaryote species, with recombination generally occurring more frequently at the ends of chromosomes. In most crop species, recombination is rare in centromeric regions. If a desired gene variant is linked in repulsion with an undesired variant of a second gene in a region with a low recombination rate, obtaining a recombinant plant combining two favorable alleles will be challenging. Traditional crop breeding involves combining desirable genes from parental plants into offspring. Therefore, understanding the mechanisms of recombination and factors affecting the occurrence of meiotic recombination is important for crop breeding. Here, we review chromosome recombination types, recombination mechanisms, genes and proteins involved in the meiotic recombination process, recombination hotspots and their regulation systems and discuss how to increase recombination frequency in recombination coldspot regions.

Introduction

Meiosis is an essential part of sexual reproduction in most organisms. This process halves chromosome numbers by coupling a single round of DNA replication with two consecutive rounds of nuclear division (meiosis I and meiosis II) to produce haploid gametes (Hillers et al. 2017; Kleckner 1996). During meiosis I, replicated homologous chromosomes align and undergo recombination between non-sister chromatids before separating. Then, during meiosis II, sister chromatids segregate, ultimately producing four gametes (Kleckner 1996) with each gamete containing one set of chromosomes. When one gamete from one sex combines with a gamete of the opposite sex, the chromosome number of the subsequent generation returns to the parental level, maintaining a steady state (Hillers et al. 2017). This process leads to new combinations of alleles present in the progenies. As a result, chromosome recombination during meiosis is regarded as the foundation for genetic diversity and the evolution of species.

Recombination rates vary across different regions of chromosomes (Blair et al. 2018; Henderson 2012; Kauppi et al. 2004). In most crop species, recombination rates are positively correlated with the distance from the centromere and gene densities but negatively correlated with transposable elements (Barakate et al. 2014; Blair et al. 2018; Henderson 2012; Kauppi et al. 2004; Phillips et al. 2010; Shen et al. 2017). The genomic region that has a relatively higher recombination frequency is referred to as recombination hotspot, while the region with a lower recombinant frequency is called a coldspot. Traditional crop breeding relies heavily on incorporating beneficial gene alleles from parental chromosomes into their offspring. Consequently, low recombination frequency hampers the selection of lines that pyramid favorable close-linked traits within coldspots in crop breeding programs. Due to increased food demand and rapidly deteriorating climate change, it is an urgent requirement to create new varieties that would possess high yields and better quality

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while being climate resilient. However, previous studies indicated that many genes, such as around one-third in barley, are located in recombination coldspot regions (Higgins et al. 2014). This poses a challenge for crop breeders, as achieving their objectives leads to a significant increase in breeding costs and cycle times.

Although recombination mechanisms are not yet fully understood, substantial progress has been made in studying recombination models. This review provides an overview of gene recombination types and genetic mechanisms, the genes participating in the recombination process, the classification of recombination pathways, the distribution of recombination events and their regulatory systems in plants. Additionally, we explore the potential for enhancing recombination rates in coldspot regions.

Gene recombination and genetic mechanisms

Recombination types

In genetics, recombination refers to the process of rearranging genetic material from different chromosomes or regions to create new DNA combinations (Rice 2002; Stapley et al. 2017). It can occur naturally in both eukaryotes and prokaryotes and can also be induced in a laboratory (Baker et al. 1976; Camerini-Otero and Hsieh 1995; Covo et al. 2012; Gratia 2017; Paques and Haber 1999; Schnable et al. 1998). Recombination types are primarily classified into four groups: homologous recombination, non-homologous recombination, site-specific recombination and transposition (Fig. 1).

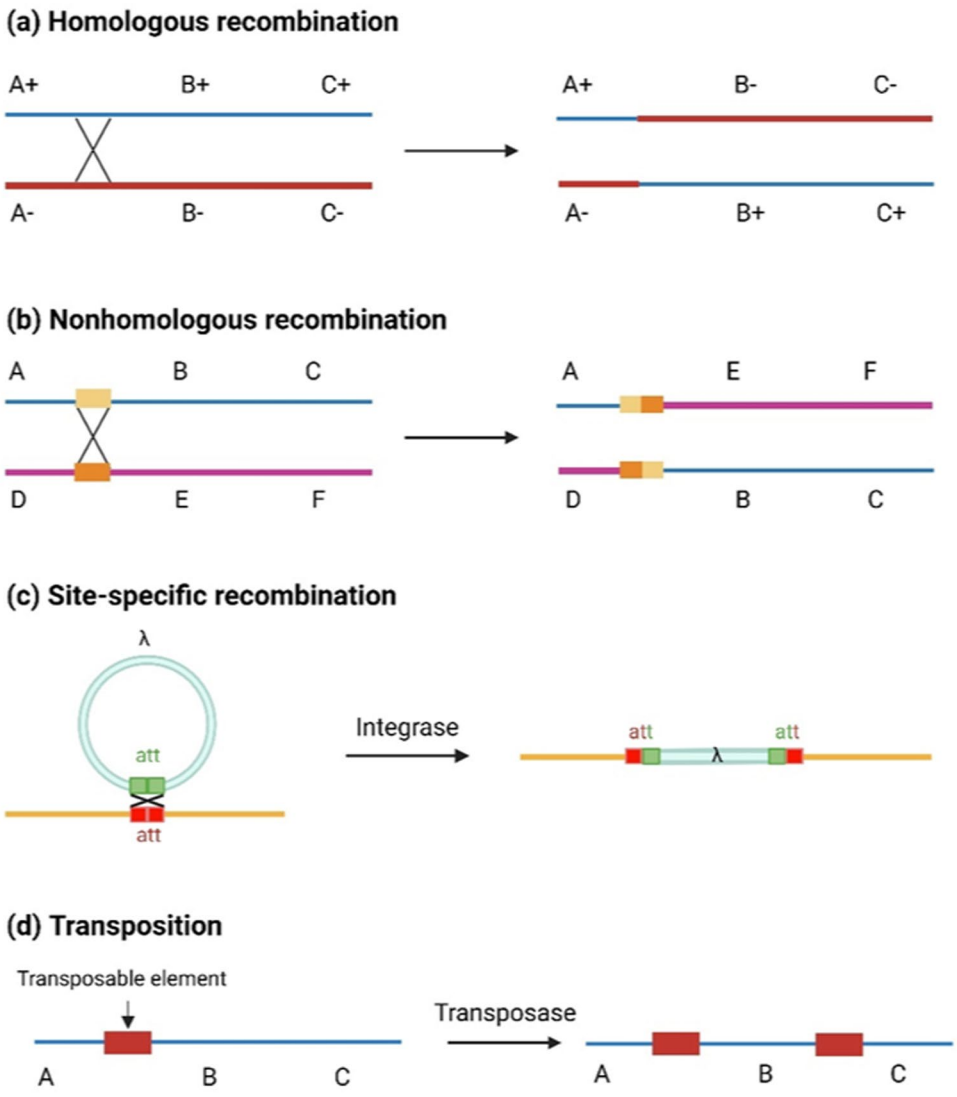

Fig. 1 Four recombination types. **a** The process of homologous recombination involves the DNA double-strand break and rejoining the strands. It results in an exchange of genetic information between the homologous chromosomes. **b** The yellow and orange blocks represent the segments at the sites of nonhomologous recombination. It does not require sequence homology between the DNA molecules and can introduce mutations at the site of the break. **c** Site-specific recombination catalyzed by site-specific recombinase enzymes, is usually observed between two different DNA molecules among bacteriophages, bacteria, and unicellular eukaryotes. **d** The red block represents the transposable element of DNA which could be integrated into the genome

Homologous recombination, known as general recombination, typically occurs during meiosis in eukaryotic cells (Camerini-Otero and Hsieh 1995). It involves the exchange of genetic information between the alleles of homologous chromosomes and generates genetic diversity in offspring. The occurrence of homologous recombination requires homologous segments that have large-scale significant similar sequences to line up in proximity. Non-homologous recombination process ligates the broken ends of DNA together directly with no requirement of a homologous sequence to serve as a template to repair DNA double-stranded breaks (DSBs) (Pannunzio et al. 2018). It is more prone to mistakes and can give rise to the deletion or insertion of genetic material at the break site and even chromosomal abnormalities. These outcomes can have significant consequences for gene function and regulation (Pannunzio et al. 2018). Site-specific recombination process is catalyzed by site-specific recombinases and reintegrates the DNA segments at specific sites (Grindley et al. 2006). The transposition process involves the movement of transposable elements within the genome. Replicative transpositions may result in the creation of a new copy (Fedoroff 2000). A homologous recombination during meiosis is the primary type of recombination employed in crop breeding programs. Therefore, our focus will be on this specific type of recombination.

Homologous recombination process

The genetic recombination process has a variety of forms and presents great complexities, varying among species. In the meiosis of eukaryotes, the widely accepted model of homologous recombination is primarily based on studies of DSB repair in *Saccharomyces cerevisiae* (Aylon and Kupiec 2004; Osman et al. 2011). This process is initiated by programmed DSB and involves rejoining of DNA sequences (Lake and Hawley 2016; Murakami and Keeney 2008). DSB repair could generate either crossover (CO) recombination or non-crossover (NCO) recombination through different pathways, including double Holliday junction (dHJ) model and synthesis-dependent strand annealing (SDSA) model. The CO recombination modifies two chromatids by exchanging large DNA fragments, while NCO only involves copying and replacing a short stretch of DNA without exchange (Fig. 2). Homologous chromosome pairing and recombination occur in the prophase phase of meiosis I (prophase I) (Azumi et al. 2002; Zickler and Kleckner 2015). The chromosomes start to condense and become thin filaments that could be visible under the light microscope during the Prophase I leptotene stage (Hartl and Ruvolo 2012). At the zygotene stage, homologous chromosomes align closely through the formation of a synaptonemal complex (SC), a unique proteinaceous structure (Fraune et al. 2012; Hartl and Ruvolo 2012; Heyting 1996; Hillers et al. 2017; Page and Hawley 2004). The SC is completely assembled during pachytene stage, and is considered to promote the initiation of recombination events (Fraune et al. 2012; Hartl and Ruvolo 2012; Hayashi et al. 2010; Hernandez-Hernandez et al. 2016; Hillers et al. 2017; Kouznetsova et al. 2011; Schramm et al. 2011). The CO takes place between two non-sister chromatids of the homologous chromosomes during the pachytene stage (Gilbert and Barresi 2016; Hartl and Ruvolo 2012). In the diplotene stage, homologous chromosomes start to separate from each other with the dissolution of SC and are only attached at chiasmata (Armstrong and Jones 2003; Hartl and Ruvolo 2012; Heyting 1996). Finally, the chromosomes become fully condensed during the diakinesis stage (Hartl and Ruvolo 2012; Taiz et al. 2015). Some studies suggest that homology along the chromosome arms is the main determinant of the recognition and pairing of homologous chromosomes, with centromeres playing a negligible role in this process during meiosis (Corredor et al. 2007; Lefrancois et al. 2016).

Genes involved in DSB formation

DSB could be caused by exogenous or endogenous factors in a variety of circumstances. Genes that function in DSB formation are exceptionally diverse, which makes the study of the mechanism extremely complex (Table 1). During meiosis, the conserved SPO11 protein is one of the primary participants involved directly in the DSB process (Keeney and Neale 2006; Lam and Keeney 2015). It shares homology with the subunit A of archaeal topoisomerase VI (TopVIA), a type II DNA topoisomerase (Bergerat et al. 1997; Gadelle et al. 2003; Keeney 2008). Two hybrid active sites of the Spo11 contain tyrosine which reacts with the phosphodiester linkage of DNA to cleave DNA strands (Diaz et al. 2002; Nichols et al. 1999; Shingu et al. 2010). In addition, the homolog of archaeal topoisomerase VI subunit B (TopVIB), known as the meiotic topoisomerase VI B subunit (MTOPVIB), forms a complex with SPO11 and is also required for DSB formation in the meiotic recombination process (An et al. 2011; Fu et al. 2016; Robert et al. 2016; Tang et al. 2017; Vrielynck et al. 2016; Xue et al. 2016). Studies in *S. cerevisiae* indicate that SPO11 alone is insufficient to generate DSB. There are at least nine other proteins that promote DSB formation, namely Ski8, Mei4, Mer2, Mre11, Rad50, Rec102, Rec104, Rec114, and Xrs2 (Cole et al. 2010; Lam and Keeney 2015; Neale et al. 2005). They can form several different interacting subcomplexes, Spo11-Ski8, Rec102-Rec104, Rec114-Mei4-Mer2 and Mre11-Rad50-Xrs2 (MRX) (Lam and Keeney 2015; Li et al. 2006; Maleki et al. 2007). It is worth noting that the MRX complex is not only recruited during DSB formation but also plays a role in the subsequent DSB repair processes (Borde et al. 2004; Williams et al. 2007).

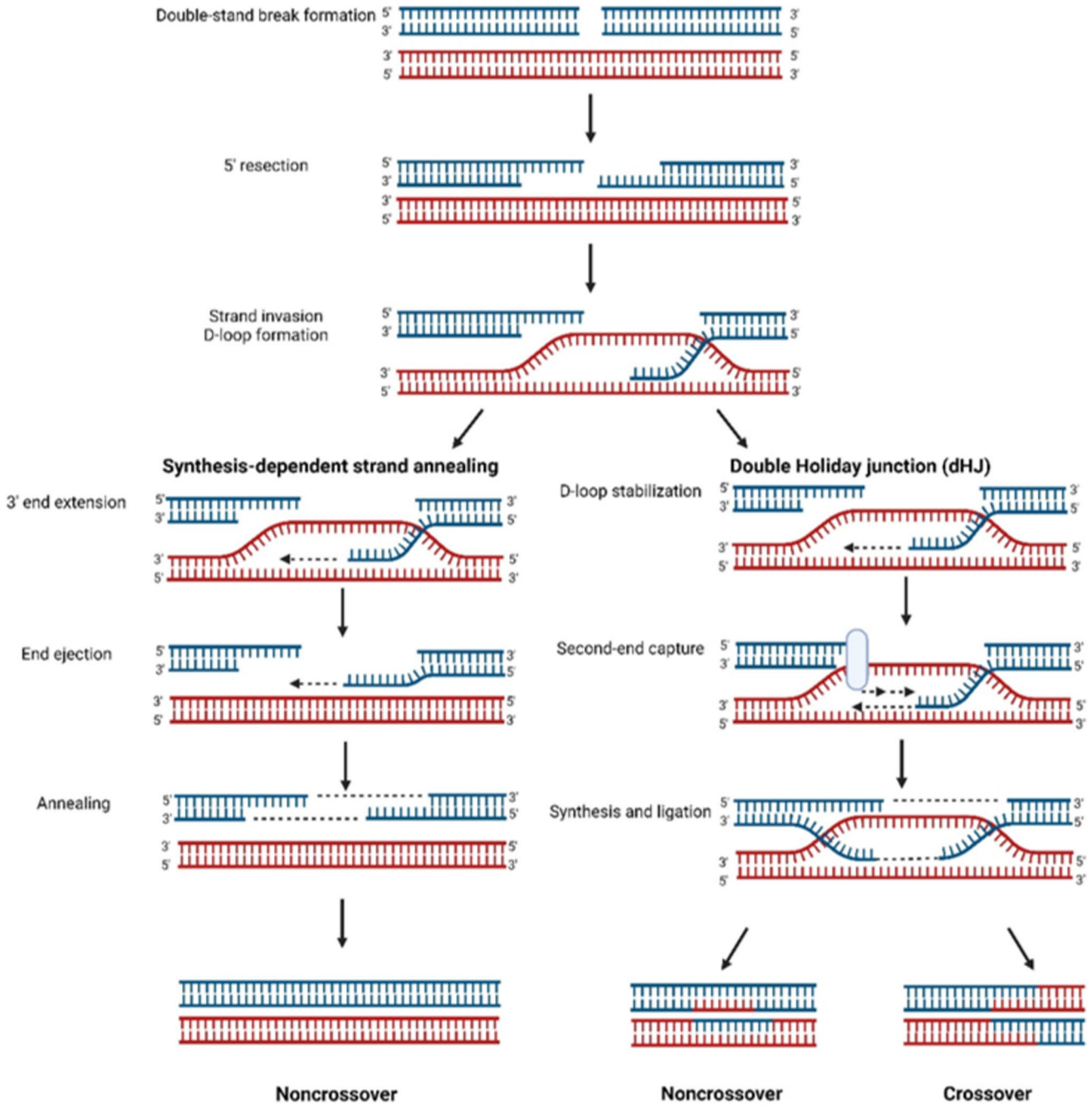

Fig. 2 CO and NCO produced from the homologous recombination. The homologous recombination begins with the DNA double-strand breaks of one of the homologous DNA duplexes, shown as blue strands. The 5′ end of the DSB is resected by specific nucleases to generate 3′ single-stranded DNA. One of the 3′ ends invades another homologous DNA duplexes which are shown as red strands, forming a displacement loop (D-loop) structure. DNA polymerase extends the invading 3′ end strand to generate the new DNA. For SDSA, the newly synthesized strand is displaced from the D-loop and then anneals, and typically produces NCO products. The formation of dHJ is derived from capturing the second end of the break after DNA synthesis extends the invading strand. It is resolved by cutting the non-crossed strands and producing NCO or by cutting the crossed strands and creating COs

There are functional divergences and significant sequence evolutionary divergences among some DSB proteins across different species. For example, AtMRE11 and AtRAD50 only participate in the DNA repair process rather than generating DSB**,** and Ski8 is involved in DSB formation in *S. cerevisiae* but not in *Arabidopsis* (Jolivet et al. 2006; Osman et al. 2011). In rice, OsSPO11-1 and OsSPO11-4 participate in DSB formation, while

Table 1 List of genes involved in DSB and repair

Function	Protein	Species	Reference
DSB formation	SPO11-1	*Arabidopsis*	Grelon et al. (2001); Hartung et al. (2007)
		Rice	Yu et al. (2010)
	SPO11-2	*Arabidopsis*	Hartung et al. (2007); Stacey et al. (2006)
	SPO11-4	Rice	An et al. (2011)
	MTOPVIB	*Arabidopsis*	Vrielynck et al. (2016)
		Rice	Xue et al. (2016)
	PRD1	*Arabidopsis*	De Muyt et al. (2007)
	PRD2	*Arabidopsis*	De Muyt et al. (2009)
	PRD3	*Arabidopsis*	De Muyt et al. (2009)
	PAIR1	Rice	Nonomura et al. (2004)
	DFO	*Arabidopsis*	Zhang et al. (2012)
	CRC1	Rice	Miao et al. (2013)
	PHS1	*Arabidopsis*	Ronceret et al. (2009)
		Maize	Pawlowski et al. (2004)
DSB repair	MRE11	*Arabidopsis*	Puizina et al. (2004)
		Rice	Ji et al. (2013)
	RAD50	*Arabidopsis*	Bleuyard et al. (2004)
	NBS1	*Arabidopsis*	Waterworth et al. (2007)
	COM1	*Arabidopsis*	Uanschou et al. (2007)
		Rice	Ji et al. (2012)
	RAD51	*Arabidopsis*	Da Ines et al. (2012); Su et al. (2017)
		Rice	Byun and Kim (2014); Kou et al. (2012); Tang et al. (2014)
		Maize	Li et al. (2007)
	DMC1	*Arabidopsis*	Couteau et al. (1999); Da Ines et al. (2012)
		Rice	Deng and Wang (2007)
	RPA	*Arabidopsis*	Aklilu et al. (2014)
		Rice	Chang et al. (2009b); Li et al. (2013); Shultz et al. (2007)
	BRCA2	*Arabidopsis*	Siaud et al. (2004)
	MND1	*Arabidopsis*	Panoli et al. (2006); Vignard et al. (2007)
	HOP2	*Arabidopsis*	Uanschou et al. (2013)
	XRCC2	*Arabidopsis*	Wang et al. (2014)
	XRCC3	*Arabidopsis*	Bleuyard and White (2004); Su et al. (2017)
	RFC1	*Arabidopsis*	Liu et al. (2013)
	SDS	*Arabidopsis*	Azumi et al. (2002)
		Rice	Chang et al. (2009a)

Table 1 (continued)

Function	Protein	Species	Reference
CO and NCO formation	MER3/RCK	*Arabidopsis*	Chen et al. (2005); Mercier et al. (2005)
		Rice	Chang et al. (2009a)
	MUS81	*Arabidopsis*	Hartung et al. (2006); Higgins et al. (2008a)
	MSH4	*Arabidopsis*	Higgins et al. (2004)
	MSH5	*Arabidopsis*	Higgins et al. (2008b)
		Rice	Luo et al. (2013)
	ZIP4	*Arabidopsis*	Kuromori et al. (2008)
		Rice	Shen et al. (2012)
	PSS1	*Arabidopsis*	Duroc et al. (2014)
		Rice	Zhou et al. (2011)
	Ph1	Wheat	Griffiths et al. (2006)
	HEI10	*Arabidopsis*	Chelysheva et al. (2012)
		Rice	Wang et al. (2012)
	MLH1	*Arabidopsis*	Dion et al. (2007)
	MLH3	*Arabidopsis*	Jackson et al. (2006)
	ZYP1	*Arabidopsis*	Higgins et al. (2005)
		Barley	Barakate et al. (2014)
	FANCM	*Arabidopsis*	Crismani et al. (2012); Knoll et al. (2012)
		Brassica	Blary et al. (2020)
	RTEL1	Barley	Barakate et al. (2021)
	RECQ4	*Arabidopsis*	Seguela-Arnaud et al. (2015)
		Tomato	De Maagd et al. (2020)
	Top3 α	*Arabidopsis*	Seguela-Arnaud et al. (2017); Seguela-Arnaud et al. (2015)
	FIGL1	*Arabidopsis*	Fernandes et al. (2018a)

OsSPO11-2 and OsSPO11-3 are not involved in DSB formation (An et al. 2011; Yu et al. 2010). *Arabidopsis* is widely accepted as a model system in plant scientific research, containing three SPO11 homologs, AtSPO11-1, AtSPO11-2, and AtSPO11-3 (Hartung and Puchta 2000; Stacey et al. 2006). However, only AtSPO11-1 and AtSPO11-2 are essential for DSB formation, likely acting as heterodimers in meiotic recombination (Grelon et al. 2001; Hartung et al. 2007; Stacey et al. 2006). Numerous proteins, such as AtPRD1, AtPRD2, AtPRD3 and AtDFO, participate in DSB formation in *Arabidopsis* (Muyt et al. 2009, 2007; Zhang et al. 2012). The protein AtPRD1 shows interactions with AtSPO11-1, AtSPO11-2, MTOPVIB, AtPRD3 and AtDFO, although there is currently no evidence of its interaction with AtPRD2 (Muyt et al. 2007; Tang et al. 2017).

DSB end processing and a single strand DNA invasion

After DSB, SPO11 remains covalently linked to the 5′ terminal of each broken DNA strand (Keeney et al. 1997; Lam and Keeney 2015; Neale et al. 2005). The MRX complex (composed of MRE11, RAD50, Xrs2) works with Com1/Sae2 (Table 1) to resect the 5′ end on each side of the DSB and remove SPO11 (Aylon and Kupiec 2004; Cannavo and Cejka 2014). Further resections of the 5′ termini are conducted by exonuclease 1 (EXO1), resulting in the generation of 3′ ssDNA tails (Garcia et al. 2011). With the assistance of recombinases, these ssDNA tails invade the homologous duplex DNA to form a recombination intermediate known as D-loop (Hunter 2015; Hunter and Kleckner 2001; Lichten 2001; Martinez-Perez and Colaiacovo 2009; Wang and Copenhaver 2018). A replication protein A (RPA) binds

the 3′ terminus to prevent degradation and remove secondary structures, facilitating the recruitment of recombinases (Soustelle et al. 2002; Wold 1997). RPA is a heterotrimeric complex that consists of three subunits: RPA1, RPA2 and RPA3 (Ribeiro et al. 2016) (Table 1). RPA also act on DNA annealing which is promoted by Rad52 protein during second-end capture (Nimonkar et al. 2009; Sugiyama et al. 2006; Wang and Haber 2004). Once the 3′ ssDNA tails are protected, recombinase A (RecA)-like related recombinases are loaded to form presynaptic nucleoprotein filaments. These filaments facilitate the invasion of free 3′ end ssDNA into the duplex DNA of the paired homologous chromosome, forming the D-Loop in yeast (Brown and Bishop 2015; Shinohara et al. 1992). Two homologs of the bacterial RecA, Rad51 and Dmc1, have been discovered in most eukaryotic organisms (Table 1) (Bishop et al. 1992; Brown and Bishop 2015; Shinohara et al. 1992). Both recombinases play crucial roles in efficient meiotic recombination. Rad51 not only directly facilitates recombination during mitosis but also participates in meiotic recombination, whereas Dmc1 is merely required for meiotic recombination (Bishop 2012; Bishop et al. 1992; Shinohara et al. 1992).

DSB repair

The current meiotic DSB repair model is broadly divided into two categories: the dHJ model and the SDSA model. Both of these models have been observed in yeast system (Mitchel et al. 2010). In the dHJ model, the invading 3′ end function as a primer to initiate the DNA synthesis using invaded DNA as the template (Szostak et al. 1983). Consequently, the newly synthesized DNA contains a specified sequence which is the same as the invaded DNA. The strand invasion and second end capture lead to the formation of dHJ, which are resolved to form CO or NCO products (Szostak et al. 1983; Wyatt and West 2014). The characteristic of the SDSA model is strand displacement, where the invading strand can anneal with the other 3′ single-stranded end (Szostak et al. 1983). In the SDSA model, only one DNA terminal participates in the invasion process, while another one utilizes newly synthesized DNA as a template for synthesis. This process results in the formation of NCO products (Szostak et al. 1983).

In general, the majority of CO products are formed through the dHJ intermediate, while most NCO is primarily produced via the SDSA (Allers and Lichten 2001; McMahill et al. 2007). These intermediates can either undergo a repair, resulting in gene conversions, or they can segregate during the next round of replication. In addition, the dissolution of dHJs could also give rise to some NCO products (Wyatt and West 2014). Usually, only a small proportion of meiotic DSBs are repaired into COs in plants. Meiotic DSBs are generated in excess with more than 90% of plant DSBs being repaired using the sister chromatid as a template or being resolved as NCO (Mercier et al. 2015).

DSB and CO events are associated with chromosome number and size

The identification of recombination distribution provides valuable insights into genome evolution and plant breeding. Distribution patterns of DSB and CO, along with their hotspots, have been reported in various species (Table 2).

DSB varies considerably across different species. About 200 DSB events in *Arabidopsis* (Sanchez-Moran et al. 2007) and ~ 500 DSBs in maize (Pawlowski et al. 2003) have been detected. More DSB events (2100) have been identified in bread wheat as wheat has a larger genome size and a greater number of chromosomes (Gardiner et al. 2019). This suggests a correlation between the number of chromosomes and the genome size with the frequency of DSB events.

Only a small amount of DSBs are repaired into CO, for example, about 4% in maize (Sidhu et al. 2015). In *Arabidopsis* ($2n = 10$), the number of COs ranged from 7 to 13 across different studies, with six NCOs reported. In

Table 2 Recombination profile in different species

Species	DSB	NCO	CO	Chr. pairs	Genome size	Reference
Arabidopsis	–	–	8–13	5	0.135 Gb	Lian et al. (2022)
Arabidopsis	~200	–	7–11	5	0.135 Gb	Sanchez-Moran et al. (2002)
Arabidopsis	–	6	9	5	0.135 Gb	Lu et al. (2012)
Maize	–	–	16–19	10	2.4 Gb	Sidhu et al. (2015)
Maize	~500	–	20	10	2.4 Gb	Anderson et al. (2003); Pawlowski et al. (2003)
Maize	218–608	–	11.2–19.4	10	2.4 Gb	Sidhu et al. (2015)
wheat	~2100	–	55	21	17 Gb	Gardiner et al. (2019)
Barley	–	–	19–24	7	5.1 Gb	Phillips et al. (2015)
Soybean	–	25	49–59	20	1.1 Gb	Ma et al. (2023)
Cucumber	–	–	12.9–13.8	7	0.367 Gb	Wang et al. (2023)

soybean ($2n = 40$), the average number of COs per recombinant line is 49–59, while NCOs are about 25, about half of the CO events. In cucumber ($2n = 14$), a dicot species, the average number of COs per individual ranges from 12.9 to 13.8, approximately one for each chromosome. In maize ($2n = 20$), a monocot species, approximately 500 DSBs were identified per cell, while only 20 COs were formed. In bread wheat, 55 COs were identified, while in barley ($2n = 14$), 19–24 COs were estimated across 45 genetic mapping populations (Table 2). The total number of COs is associated with the number of chromosomes. Soybean and bread wheat contain similar pairs of chromosome numbers, 20 and 21, respectively, and their COs are both around 55 (Table 2). For the species with a smaller number of chromosomes (5—10 pairs), e.g. *Arabidopsis*, cucumber, maize and barley, their corresponding COs are less than 25, confirming that the number of COs is positively correlated with the number of chromosomes. Besides, chromosome size also shows influence on CO events. For example, both cucumber and barley have seven pairs of chromosomes, but the genome size in barley is 13.5 times greater than that of cucumber. The considerably longer chromosomes in barley compared to cucumber lead to nearly twice as many.

In plants, typically one to two COs are distributed across most individual chromosomes (Jones and Franklin 2006; Sidhu et al. 2015), with the majority of DSBs being repaired as NCOs through DNA synthesis, utilizing the homologous chromosome as a template or the sister chromatid (Allers and Lichten 2001). Nevertheless, regardless of the mechanisms, as indicated by the studies listed in Table 2, the majority of genetic variation generated by meiotic recombination in plants originates from COs.

The factors determining whether COs or NCOs form from DSB are poorly understood. Studies conducted in mouse, *C. elegans,* and budding yeast have indicated that CO numbers are not impacted by DSB numbers, even when the number of DSB varies significantly (Cole et al. 2012; Martini et al. 2006; Rosu et al. 2011; Yokoo et al. 2012). In contrast, a strong correlation between the number of meiotic DSBs and COs has been found in maize (Sidhu et al. 2015) with 25.8% of bivalents having single chiasma, 72.6% forming two chiasmata and only 1.7% displaying three chiasma (Sidhu et al. 2015).

Furthermore, variations in recombination frequency exist between genders within the same species (Lenormand and Dutheil 2005; Martinez-Perez and Colaiacovo 2009). For example, in *Arabidopsis,* the recombination rate is higher males than in females, particularly in the sub-telomeric region (Giraut et al. 2011). A similar difference has been found in barley, with male gametes showing more COs than female gametes (Phillips et al. 2015).

CO hotspot distribution across chromosomes

A prerequisite for the formation of recombination is the occurrence of DSB. In the search of DSB hotspots, researchers have found a close relationship between the number of hotspots and chromosome length, with the average hotspot length being 1 ~ 2 kb (He et al. 2017; Paul et al. 2016). In maize, there is a low frequency of CO hotspots occur in the centromeric and pericentromeric chromosome regions, while these regions exhibit a high frequency of the DSB hotspots (He et al. 2017). In *S. cerevisiae*, hypomorphic mutants of *spo11* show a decrease in DSB number but not CO numbers (Martini et al. 2006). As the repair of DSB can proceed via either the CO pathway or the NCO pathway, an increase in CO may occur at the cost of NCOs, maintaining homeostasis (Martini et al. 2006). Consequently, there isn't an absolute correlation between the *spo11* alleles and COs. Therefore, it is impossible to solely identify the recombination spots based on DSB spots.

Meiotic recombination events are unevenly distributed and are restricted to certain regions, particularly at the distal ends of chromosome arms (He et al. 2017; Lukaszewski 1992; Paigen and Petkov 2010; Petes 2001). The preferential distribution of CO hotspots is in gene-rich regions where the chromatin is easily accessible by DSB complex. Furthermore, structure variations, such as large inversions, have been reported to influence the recombination rate in barley. For example, no recombination event can be identified within a large 141 Mb inversion region on chromosome 7H from the DH population of RGT Planet and Hindmarsh (Jayakodi et al. 2020).

Some studies show that recombination hotspot tends to present near gene promoters (Choi et al. 2013; Mancera et al. 2008; Pan et al. 2011; Petes 2001; Wu and Lichten 1994). Research on the hexaploid wheat genome has shown that recombination hotspots typically occur near the coding regions of the chromosomes (Darrier et al. 2017) with about 95% of the recombination being distributed in 18 major and 30 minor gene-rich regions (Erayman et al. 2004). Similarly, studies in maize have suggested that approximately 90% hotspots are distributed in gene-rich regions (Fu et al. 2001; Gore et al. 2009; Kianian et al. 2018; Li et al. 2015; Rodgers-Melnick et al. 2015; Sidhu et al. 2015). A recent comprehensive study in cucumber revealed that over 93% of the COs are either in genes or their 10 kb regions. Among these, about 45% of COs occurred in distal intergenic regions, 25% in the promoter regions (2 kb upstream), 13% in introns, 10% in coding sequences, and 7% in untranslated regions (Wang et al. 2023).

McConaughy et al. (2023) identified 451 CO hotspots from two soybean mapping populations. These hotspots

are distributed across the entire soybean genome with around 27% of them located in the pericentromeric regions. In barley, recombination is severely suppressed in some regions (Kunzel et al. 2000). Repetitive sequences are associated with distinct chromatin modifications, and their expansion suppresses the recombination rate (Henderson 2012). Hotspots account for less than 5% of the genome region. Distal CO occurrence is 25 times greater than interstitial chiasmata (Higgins et al. 2012).

Hotspots DNA motifs

Recombination events are correlated with the presence of specific DNA sequences (Zelkowski et al. 2019). DNA and chromatin features are associated with DSB hotspots. The popular motifs with the hotspots include CCN repeat motif, poly-A motif, and min-inverted-repeat transposable elements.

In *Arabidopsis*, DSB hotspots are correlated to CO hotspots. Three DNA motifs (A-rich, CCN and CTT) have been found to be enriched in CO regions (Shilo et al. 2015). In maize, an associated 20-bp-long, GC-rich sequence motif is similar to the CCN motif identified in *Arabidopsis* (Shilo et al. 2015). The recombination hotspot in maize is located in the bronze and *Stc1* locus (Fu et al. 2001; He and Dooner 2009) and the recombination event is significantly enriched in GC-rich regions, which is similar to the CCN motif identified in *Arabidopsis* and yeast (Gerton et al. 2000; Liu et al. 2009; Sidhu et al. 2015). In cucumber, numerous hotpot motifs are identified for DSB, including the TATA repeat (Wang et al. 2023).

The regulation of recombination

The precise control of the frequency and distribution of meiotic recombination events remains challenging. Previous studies indicated that homologous chromosome pairing typically results in generated at least one CO event per chromosome (Bishop and Zickler 2004; Hillers 2004; Kleckner et al. 2004; Martini et al. 2006; Shinohara et al. 2008). However, a recent report showed that the absence of COs in some chromosomes in a few F_2 lines in cucumber (Wang et al. 2023). Meiotic recombination distribution is uneven along chromosomes, and its regulation can be classified into chromosome-level regulation, genome-level regulation and other mechanisms (Kauppi et al. 2004; Lichten and Goldman 1995; Petes 2001; Sidhu et al. 2015).

Chromosome level regulation

The frequency of COs increases from centromeres to telomeres, with notably low frequency observed in the telomeric region (Chen et al. 2008; Higgins et al. 2012; Liu et al. 2009; Saintenac et al. 2009, 2011; Salome et al. 2012; Sidhu et al. 2015). In most organisms, each chromosome pair usually every undergoes one or two COs (Martini et al. 2006). When more than two COs present on the homologous recombination, one CO tends to suppress the occurrence of others in nearby regions, a phenomenon known as CO interference (Hillers 2004; Jones 1984; Kleckner et al. 2004; Muller 1916). This phenomenon also appears during the DSB period. For example, the occurrence of a DSB on one chromosome of *S. cerevisiae* suppresses the frequency of DSB generation on its homolog at the same and nearby positions (Fukuda et al. 2008; Xu and Kleckner 1995).

In cucumber, however, Wang et al. (2023) observed the absence of COs on chromosomes 3,4 and 5 in the individual line Y-154, no CO on chromosome 3 and 4 in the line X-69, no CO on chromosome 7 in line Y-231, and no CO on 1,5,6 in Y-284 (Wang et al. 2023), suggesting that this regulation system may not work in cucumber.

Genome level regulation

Recombination events tend to cluster in short specific genome regions of the genome (Marand et al. 2017). Studies in the mammalian species revealed the correlation between hotspot location and certain sequence motifs (Buard and de Massy 2007; Myers et al. 2005; Parvanov et al. 2010; Shifman et al. 2006; Smagulova et al. 2011). In humans and mice, the meiotic recombination hotspots are closely linked to the specific recognition DNA sequence of PRDM9 zinc finger protein (Borde and de Massy 2013; De Massy 2013). However, PRDM subfamilies are absent in plants (Zhang and Ma 2012). In plants, meiotic recombination hotspots tend to occur in regions close to gene promoters and terminators associated with active chromatin modifications (Choi et al. 2013; Drouaud et al. 2013; Fu et al. 2002; He et al. 2017; Wang and Copenhaver 2018). Previous studies in *Arabidopsis* indicated a consistency between recombination hotspots and DSB hotspot regions (Choi et al. 2013; Horton et al. 2012). However, recombination events in maize are only associated with the DSBs close to the genes (He and Dooner 2009; Yao et al. 2002).

Other regulation factors

Recombination events can be influenced by extrinsic conditions, such as biotic stress, extreme temperature, chemical substances, nutrients, and UV radiation (Boyko et al. 2007;

Higgins et al. 2012; Lucht et al. 2002; Mickelbart et al. 2015; Molinier et al. 2006; Phillips et al. 2015). The formation of COs relies on the ZMM protein or the endonuclease Mus81 (Berchowitz et al. 2007; Bishop and Zickler 2004; Borner et al. 2004; Santos et al. 2003; Mercier et al. 2005; Shinohara et al. 2008). Posttranslational modification could influence the activity and stability of proteins related to meiotic recombination, thereby regulating recombination events (Wang and Copenhaver 2018). DNA methylation has also implicated in regulating the formation of meiotic recombination (Buard and de Massy 2007).

The effect of temperature on miotic recombination has been reported in several species. In *Allium ursinum*, exposure to 35 °C for 30 h resulted in a detrimental effect on chromosome synapsis (Loidl 1989), whereas in barley, synapsis failed to occur at 35 °C (Higgins et al. 2012). In addition, the distribution and frequency of Chiasmata were altered when exposed to temperatures of 30 °C and 22 °C. At 30 °C, there was an increase in interstitial/proximal chiasmata, but the average number of chiasmata and COs per cell were significantly decreased (Higgins et al. 2012).

Phillips et al. (2015) found that the recombination rate during male meiosis consistently suppressed that of females. Moreover, in barley, as the temperature increased from 15 °C to 25 °C and 30 °C, the recombination rate increased during male meiosis but decreased during female meiosis. Similarly, in *Arabidopsis*, Giraut et al. (2011) demonstrated higher CO frequencies during male meiosis.

How to increase CO frequency

CRISPR-Cas9

The main limitation of targeted homologous recombination is DSB formation. The homologous recombination frequency can be enhanced dramatically when the DSB occurs at the target locus (Hayut et al. 2017; Puchta and Fauser 2013). Therefore, it is essential to find effective methods for inducing greater DSB formation. Sequence-specific nucleases (SSNs) are recognized for their capability to generate DSB at a specific site (Belhaj et al. 2015). The development of sequence-specific nuclease, including zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs), has already proven successful in targeted gene editing in plants (Mao et al. 2019; Podevin et al. 2013; Voytas and Gao 2014; Wang et al. 2019). However, challenges associated with the design and construction of large modular proteins have hindered their widespread adoption (Doudna and Charpentier 2014). In addition, ZFNs have shown a high fault rate during DNA sequence recognition and cleavage (Voytas 2013). In contrast, the CRISPR-Cas method has emerged as a versatile solution. In recent years, the CRISPR-Cas system, a relatively easy and powerful gene-editing tool, has achieved rapid development. Most studies have used CRISPR-Cas9 technology to edit genes in homozygous tissues, potentially increasing the occurrence of DSB. Recently, the CRISPR-Cas9 system has been used in targeted recombination in tomatoes (Hayut et al. 2017). In this study, the F_1 hybrid seed was used for targeted DNA editing, resulting in homologous CO events. Applying the allele specific recombination analysis suggests that the homologous recombination rate can be increased by generating DSB (Hayut et al. 2017).

Mutation

Mutating genes involved in COs is a powerful tool to increase CO frequency. *FANCM* and *RECQ4* are key players in the CO pathway, and the impact of mutations in these genes on CO rate has been extensively studied in *Arabidopsis* (Crismani et al. 2012; Seguela-Arnaud et al. 2015). For instance, *fancm* (Crismani et al. 2012) and *recq4a/b* (Seguela-Arnaud et al. 2015) mutants exhibit a nearly 3–5.9 folds increase in recombination rate (Fernandes et al. 2018b).

The AAA-ATPase FIDGETIN-like 1 (FIGL1) negatively regulates CO formation at the early stages (Girard et al. 2015). The *figl1* mutation enhances the CO rate by 1.5 times (Girard et al. 2015) and when combined with a*recq4a/b* double mutation, the CO rate is significantly increased (7.8-fold) (Fernandes et al. 2018b). Remarkably, this mutant exhibits 60.7 COs per meiosis, compared to only 7.8 COs in the wild type (Fernandes et al. 2018b).

Other approaches

Higher temperatures increase recombination rates in male meiosis in barley (Phillips et al. 2015) with CO events increasing by 40% when the temperature rose from 15 °C to 30 °C (Phillips et al. 2015). This approach can be tried in other crops to increase the recombination rate. Furthermore, DNA methylation occurs across the plant genome, regulating gene expression (Jeddeloh et al. 1998) and silencing transposable element activity (Slotkin and Martienssen 2007). Changing DNA methylation patterns has been shown to alter CO distribution in mutant plants. For instance, loss of CG methylation in *Arabidopsis* leads to changes in CO distribution (Melamed-Bessudo and Levy 2012; Mirouze et al. 2012). These studies suggest that modifying methylation patterns can remodel CO distribution in plants.

Conclusion

While there are slight variations in CO distribution patterns, most recombination events occur toward the ends of chromosomes. In plant breeding programs, changing temperatures,

creating mutations, reducing methylation patterns, and targeting CRISPR-Cas9 system can be used to regulate the recombination frequency within coldspots. With the development of whole genome sequencing, the identification of recombination spots becomes more precise. High-density genetic maps and resequencing data can be used to identify the precise location of the CO events and their associated motifs. A better understanding of CO and targeting hotspots will facilitate CO regulation in crop breeding programs.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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