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Advancement in controlling meiotic recombination for plant breeding

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***Abstract*---**Meiotic recombination (Crossover) that takes place during gamete formation in all the sexually reproducing organisms creates genetic diversity which is very important for crop improvement and the evolution of new varieties when natural and artificial selection act upon this. Research spotlight from the year focused on the potential of tinkering with the mechanism of meiotic recombination to generate genetic diversity for crop improvement and plant breeding purposes. Several approaches are applied to increase CO frequency, alter CO distribution and induce COs between non-homologous chromosomal regions and how to practically apply these in breeding programs. In this review, we describe how altering meiotic recombination frequency could be beneficial for plant breeding and their practical applications for crop improvement.

***Keywords*---**meiotic recombination (MR), crossover (CO), double standard breaks (DSBs), genetic diversity.

Introduction

Meiotic recombination (MR) is a fundamental aspect of all sexually reproducing organisms and plays an important role in mixing the maternal and paternal genomes. The parental chromosomal content is reduced by half (N) in the gametes because a single round of DNA replication is followed by two successive nuclear divisions in meiosis I (1,2). The reciprocal exchange of genetic material between homologous chromosomes is important to create genetic diversity and an essential process for proper segregation of chromosomes during gamete formation in all organisms (3,4).

Most of the understanding of MR comes from the cytogenetic, genetics and molecular analysis carried out in budding yeast. The process of MR initiates with

the formation of double-stranded DNA breaks (DSBs) created by a conserved protein SPO11, which shares homology with topoisomerase VI from archaeon *Sulpholobus shibatae* (5,6). Following break formation, resection of 5` carried out by a protein complex of MRE 11 and RAD50 generates a 3` single-stranded DNA (ssDNA) of hundreds to thousands nucleotide in length (7). This 3` single-stranded overhang bounded by RAD51 and DMC1 recombines to form a nucleoprotein filament and this complex invades the other intact homologous chromosome or sister chromatid for homology search and generates a recombination intermediate (7). These recombination intermediates further proceed via two different repair pathways to resolve as CO and non-CO (NCO) products. Most of the COs take place through the resolution of dHJ by the activity of structure-specific endonucleases (8). To facilitate the proper segregation of chromosomes during meiosis, at least one CO is mandatory which is referred to as CO assurance (9,10). COs are distributed non-randomly along the chromosomes and multiple COs on the same chromosome are spaced apart through the phenomenon of interference, where the occurrence of a CO at one place affect the occurrence of a second CO nearby (9). Two types of COs are reported in most organisms, known as type I and type II COs. Type I CO is interference sensitive and it depends on the functional activity of ZMM group of proteins (also known as the synapsis initiation complex) and accounts for 70-85% of COs formation. Type II CO is interference insensitive and it depends on the function of MMS and UV sensitive 81 (MUS81) protein for CO formation (2,11).

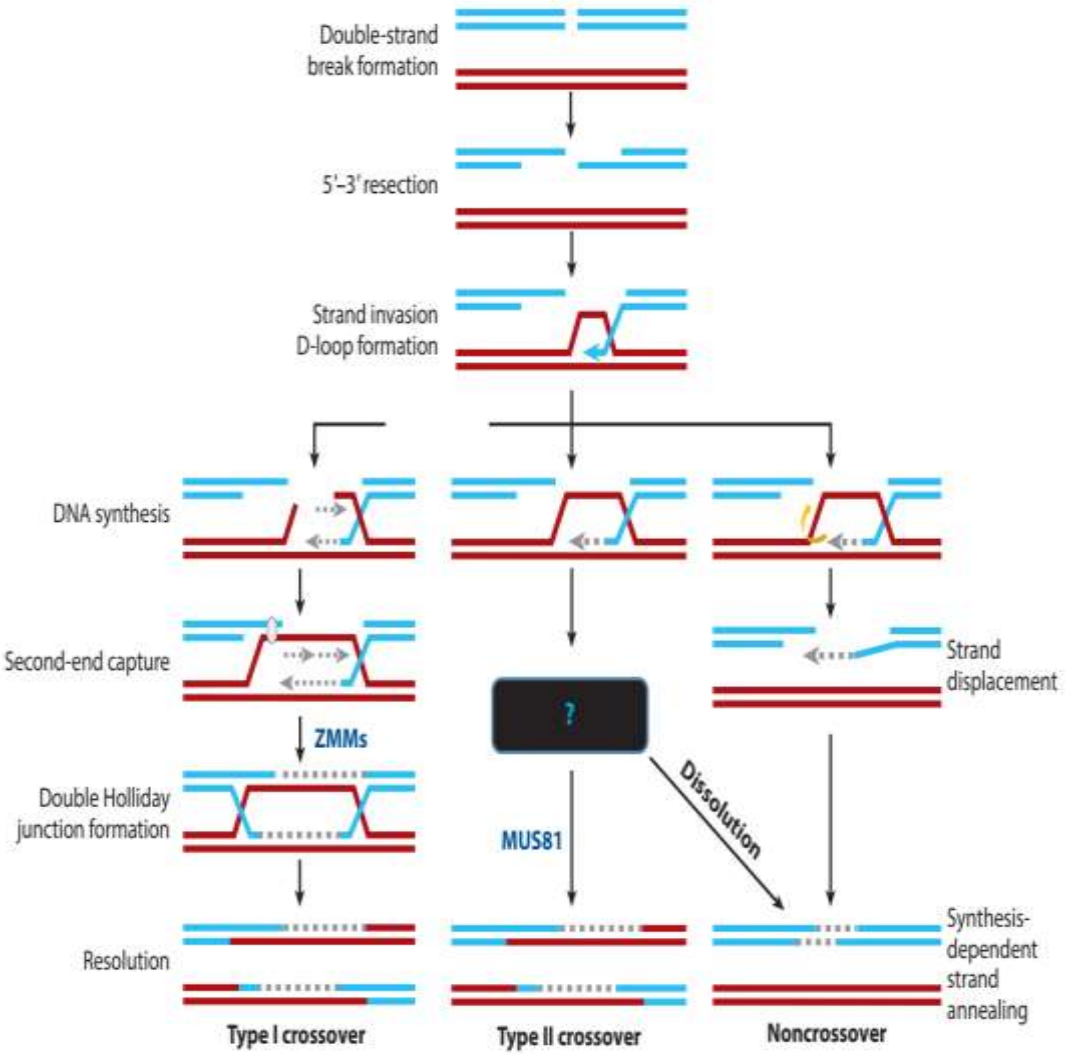

Figure 1: Model for MR

MR initiates with the formation of double-strand breaks (DSBs) by topoisomerase like endonuclease. DSB ends are resected to yield 3' single-strand tails, which invade the other intact double-stranded homologous chromosome to form a D loop. The DSBs repair via two different pathways, example, synthesis-dependent strand annealing (SDSA) and DNA double-stranded break repair (DSBR). DNA synthesis (*dashed lines*), second-end capture, and ligation lead to the formation of double Holliday junctions, resolution of these dHJs through ZMM pathway results in interference sensitive (type I) CO formation. A portion of these dHJs resolved via MUS81 dependent pathway results in Interference-insensitive (Type II) COs. Recombination intermediates that do not participate in second-end capture can instead be processed by the synthesis-dependent strand annealing pathway (SDSA), which produces NCOs (12).

Cytogenetic studies in budding yeast have revealed that meiotic NCOs are produced via the synthesis-dependent strand annealing (SDSA) pathway (13) and to a small extent produced by the dissolution or resolution of dHJs. The total number of DSBs generated are significantly higher in comparison to the number of COs formed (14), suggesting that only a small fraction of the recombination intermediates mature as COs. MR generates genetic diversity by reciprocal exchange of chromosomal segments between the homologous chromosomes and brings novel allelic combinations together in a species, upon which natural selection can be applied for crop improvement (15). In most organisms, including plants, MR is an essential process which also plays an important role in the proper segregation of homologous chromosomes during gamete formation (16). At least a single CO is mandatory per homolog pair, known as an obligate CO for proper chromosome segregation, during gamete formation. Failure to form CO or any defect in the process results in the missegregation of chromosomes, which is associated with reduced fertility and aneuploidy (17).

Methods to Control Crossover formation in Plants

Patterning of Meiotic crossover formation

The occurrence of crossovers throughout the genome takes place in a non-random fashion in most organisms. Nearly 80% of the crossover is concentrated in the one-fourth region of the genome (18). Certain regions in the genome are very sensitive to higher crossover rates while the other regions that are very poor for crossover formation are known as hot spots and cold spots respectively. In Plants, the crossover is generated very close to the specific regions of a gene known as promoter and terminator where DNA is accessible (12). In Arabidopsis, most of the crossover hotspots are very closely associated with the DSB hotspots (18). Studies identified several specific features and genomic regions associated with the formation of DSB/CO hotspots including nucleosome free and hypomethylated regions throughout the genome in both Arabidopsis and maize (18,19). At a broader scale, most of the crossover concentrated in distal euchromatic regions and the centrally located regions such as centromeres are usually poor in COs in plants (11,20).

In most of the plant species, it is reported that the formation of the crossover is highly suppressed at and near the centromeric regions which are highly methylated and hetero-chromatic (21). The molecular mechanism lying behind this suppression is still poorly understood and a recent study in Arabidopsis observed that certain epigenetic marks such as H3K9me2 and DNA methylation are responsible for crossover suppression at centromeric and pericentromeric regions (21). Although, methylation intensity has a significant role in the determination of crossover rates in centromeric regions. there is no change in the total number of crossover formations in hypo-methylated mutants. For example, loss of CG DNA methylation in Arabidopsis leads to an increase in centromere-proximal, while pericentromeric COs are redistributed toward euchromatic distal regions (22). Besides these primary and secondary chromosomal structures, the other important factor playing an important role in shaping the crossover landscape is the comparison of crossover patterning between males and females. The number and distribution of crossover along the chromosome depend on the

parental sex in most, but not in all the species which is known as heterochiasmy (23,24).

The crossover between non-homologous Chromosomes

Meiotic crossover is one among the various DNA repair methods which occur when there is any type of mismatch or damage happened in the genome. It is a sequence homology-based repair method where the DNA damages are repaired between homologous chromosomes or chromatids. It is reported that the frequency of crossover decreased with the increased sequence divergence between chromosomes (25). This suppression of crossover frequency due to sequence divergence is primarily due to the presence of mismatch base pairs within the recombination intermediates and their destabilization induced mismatch repair system. Besides this general observation that the crossover moves away from the non-homologous sequence was recently challenged by a study conducted by Ziolkowski et al. (2015) in Arabidopsis and they observed a significant increase in crossover frequency in megabase region heterozygous region juxtaposed to the homozygous region. These increased crossover rates in heterozygous regions are compensated by a decrease in juxtaposed homozygous regions. A recent study in Arabidopsis reported that all the recombination intermediates do not have similar sensitivity to divergence sequence and extra-CO in *figl1* and *recq4* is unaffected by polymorphisms in a hybrid context, but in the case *of fancm* mutants, these additional COs are only observed in pure inbred lines, not in the hybrids.

Reshuffle of Genetic Information

Meiotic recombination is a crucial phenomenon for plant breeding purposes which facilitates plant fertility and generates genetic diversity. In addition to genetic diversity which is resulting due to the mixing of maternal and paternal genomes through recombination, it will also bring new allelic combinations upon which natural selection can be applied and resulted in the evolution of new species and crop improvement. It is reported that the mean number of crossover per homologous chromosome is rarely exceeded three per bivalent. This limitation of crossover numbers has direct and indirect consequences on genetic diversity because of the inherent mutagenic nature of CO formation (26)) and its influence on the selection (27).

Beneficial allele combinations are maintained but harmful deleterious mutations are difficult to remove from crossover poor regions

The important facilities offered by meiotic recombination to generate genetic diversity are limited by another factor is an uneven distribution of meiotic crossovers throughout the genome. Although the regions with poor crossover tendency are enriched with repeated DNA sequences, this does not mean that these regions are completely devoid of gene occupancy (19). For example, in barley and maize, nearly 20% and in wheat chromosome 3B nearly 80% of total gene content is present in crossover poor regions (20,28). Few genes among these are quite an interest for plant breeders for breeding purposes. Due to the lower efficiency of crossovers in these regions blocks of strong linkage disequilibrium spanning large intervals are created resulting in the reduction of the chance of a

gene undergoing recombination. This process is not only reducing the occurrence of genetic diversity in these low recombining regions but also has a significant impact on removing deleterious mutation that accumulates in these regions (29).

Methods to Enhance (Increase) Crossover Formation in Plants

MR brings the new allelic combination together from the pre-existing allelic variation and is a crucial process for the improvement of plant breeding. Our understanding of MR and its role in generating genetic diversity has advanced considerably over the last 10-15 years (3,4). The discovery of DNA sequencing technology plays an important role in the understanding of high-resolution genetic and epigenetic information in plant genomes. The genome-wide genetic and epigenetic information further leads to accelerating plant breeding programs via high-throughput genotyping, linkage and association mapping (3,4). In addition, the understanding of mechanisms that control genetic and epigenetic processes during MR helped in the improvements of breeding programs and the creation of genetic diversity can be applied for crop improvement (11). Here we have described some of the recent advancements to manipulate MR frequency and their distribution with the perspective to improve plant breeding.

Enhancing CO Rates by disrupting Anti-CO genes

Plant breeding programs depend on meiotic COs that allow the generation of desired traits into elite species and remove undesired traits in the crop plant genome. Further, some regions are virtually lacking COs, such as the regions flanking centromeres (30). This devoid of COs in heterochromatic regions limits the genetic diversity that can be created in breeding programs and in addition, limits the power of genetic mapping in pre-breeding research. Increasing recombination frequency in both euchromatin and heterochromatin is a necessity for a successful plant breeding program (31). In *Arabidopsis thaliana*, three pathways have been identified using forward screen approaches that limit recombination and these pathways depend on the anti-CO activity of the following proteins, (i) FANCM helicase and its cofactors (32) (ii) the BLM/Sgs1 helicase homologues RECQ4A and RECQ4B and the associated proteins TOP3α and RMI1 (33,34) (iii) the FIGL1 AAA-ATPase (35).

The single mutant of all three genes showed a significant increase in MR rates compared to wild type in both homozygous and heterozygous backgrounds. Mutation in anti-CO fancm leads to a 3 fold increase in CO frequency in the homozygous background and there were no obvious somatic phenotypic changes in plants. In the heterozygous background, fancm mutation did not show any change in CO frequency, which indicates that this mutant recombination intermediate in the heteroduplex state is sensitive to strong CO suppression (35–37). RECQ4A/B is two redundant orthologs of BLM/Sgs1 helicase of humans and yeast respectively, and form a strong complex with TOP3α and RMI1 that exhibit the strongest anti-CO activity (33,34). Compared to FANCM mutants, a double mutant of both recq4a recq4b showed a 5-6 fold increase in CO frequency in both homozygous and heterozygous backgrounds. Finally, FIGL1 and its associated factors restrict the invasion of single-stranded DNA to another homologous chromosome, thus the CO frequency restricts by controlling the activity of DMC1

and RAD51 recombinase (35,38). The above results indicate that the anti-CO genes controlled the CO formation by three different pathways and by disrupting these genes we can generate a significant enhancement in recombination frequency.

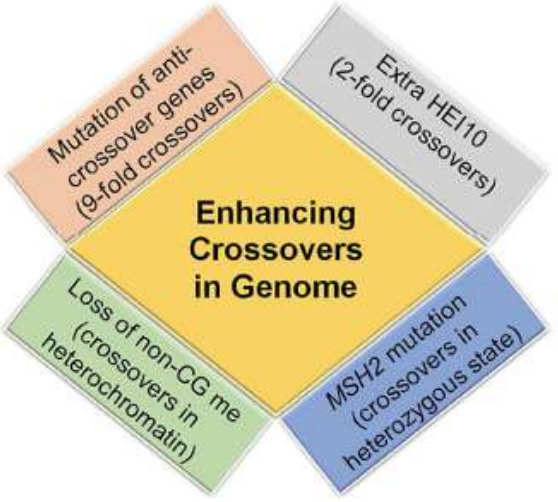

Figure 2. Different Ways to Control CO frequency and location in plant genomes (39)

A dose-dependent increase in crossover frequency by adding an extra copy of pro-crossover gene

In addition to genetic disruption of anti-CO genes to enhance CO rates, the genetic variation in certain pro-CO genes such as RNF212, PRDM9 and HEI10, also regulates the distribution and frequency of CO formation throughout the genome (40). HEI10, a RING finger-containing protein that is well conserved among species and shows structural and functional similarity with the yeast Zip3 ZMM and is required for class I CO (CO) formation in *Arabidopsis thaliana (41)*. QTL mapping between Col-0 and Ler-0 accession identified two variants of HEI10 gene in *Arabidopsis thaliana*, which encodes for conserved E3 ubiquitin ligase required for CO formation via ZMM pathway (40). Recent studies in *Arabidopsis* revealed the role of HEI10 in a dose-dependent manner to increase CO frequency (40,42). In hybrid plants, an introduction of a single extra copy of the HEI10 variants results in a 2-fold increase in CO numbers and a 4- fold increase in the total number of CO occurs when the addition of HEI10 combined with recq4a/b mutation (42).

Epigenetic Activation of CO in Heterochromatic Regions of Genome

In *Arabidopsis*, the creation of mutation in anti-CO genes and adding an extra copy of pro-CO genes results in the formation of more COs in the gene enriched euchromatic region, but the frequency of CO remains suppressed in gene sparse

heterochromatic, pericentromeric and centromere regions (42). Both the centromere and pericentromeric regions are highly occupied with heterochromatic marks such as cytosine methylation, H3K9me2 and transposons (43). Heterochromatic regions are highly methylated, and it was expected that the removal of cytosine methylation from the heterochromatic region should increase the CO formation in this region. Unfortunately, the studies in *Arabidopsis*, where the loss of DNA CG methylation by mutation of MET1 or DDM1 led to a decrease in CO numbers around the centromeres and an increase in the sub-telomeric region, indicates the reshaping of CO distribution along the chromosomes without changing the total number of COs (22,44,45). In *Arabidopsis*, non-CG methylation of CHG and CHH context maintained by the activity of CHROMOMETHYLASE (CMT3 and CMT2) and de novo DNA methyltransferases DOMAINS REARRANGED METHYLTRANSFERASE (DRM1 AND DRM2), (46). Mutants showing loss of non-CG or H3K9me2 methylation exhibit enhanced CO frequency around the pericentromeric but not in the centromeric region, although the centromeric regions experience an increased number of DSBs (47). Therefore, this epigenetic alteration in non-CG or H3K9me2 methylation can be applied in crop breeding programs to create new allelic combinations and diversity in large pericentromeric regions.

Manipulation of CO by CRISPR and RNAi Approach

The dependence of a crop breeding program on the frequency and distribution of CO can delay breeding time and restrict both different allelic combinations and genetic mapping of desirable traits throughout the genome. To overcome these problems, recent studies developed certain genome editing systems such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), to accelerate crop breeding programs and unlock genetic diversity. CRISPR is used as a precise genome editing tool to manipulate higher eukaryotic genomes and control MR (48). CRISPR technology represents DNA-free gene editing tools that can be applied directly to the genomes of elite crop cultivars to create genetic variation, which controls certain desirable traits, such as productivity and herbicide resistance (48). Besides, accelerating a crop breeding program by increasing genome-wide CO frequency in both heterochromatin and euchromatin regions can be achieved by the mutation or knock-down of the genes encoding anti-CO factors using CRISPR or RNAi systems.

Alter Crossover Patterning by use of Polyploidy

Polyploidization or the duplication of a whole chromosome set is very common in plants compared to animals and it is an important force in the evolution of new species (49,50). Polyploidization is involved in speciation and biodiversification, providing new genetic combinations in natural populations to favour evolution and increasing organism complexity. Autopolyploidy originates from intraspecific whole genome duplication while allopolyploidy is generated by interspecific hybridization. The frequency of CO varies with the ploidy level (11,51). Both allopolyploid and autopolyploid in *Arabidopsis* and *Gossypium* showed a significant higher CO frequency in tetraploids compared to diploid plants (52). Interestingly, a study in *Brassica* observed that the unpaired chromosome in polyploidy conditions can promote the CO formation and they observed the

highest number of univalent and CO in allotriploid; intermediate in allotetraploids and lowest in the diploid plants. The above results indicate that both the number of chromosome sets and their pairing dynamics influence the CO formation independently (53). A study of CO interference in allotriploids suggested that the increased number of COs occurs through the class I pathway by weakening the interference between adjacent COs rather than an increase in class II COs (53).

Alter Crossover Rates by Manipulating Environmental Factors

Methods to increase COs in recombination poor regions such as peri-centromeric and centromeric would increase genetic diversity and brings desirable trait together that will be beneficial for plant breeding programs. Various abiotic and biotic treatments have been applied to alter CO frequency in crop plants. The important abiotic factors include temperature stress (both heat and cold stress), UV radiation, chemical agents, drought and salinity (54). Among these, the effect of temperature stress on MR has been studied extensively in several organisms and observed a significant change in crossover frequency with altered temperature (55). Chemicals known as DNA damaging agents such as UV radiation and cisplatin have been successfully used to induce MR in mutant plants that lack DSBs formation (56) and in some wild type plants. Among biotic stress, attack by a certain pathogen such as oomycetes, viruses, bacteria and nematodes, induces stress response which is known to alter MR in some organisms. A significant increase in CO frequency was observed when *Drosophila* was infected with the pathogen *Wolbacbia pipientis*. Similar results were obtained when plants such as *Arabidopsis*, tomato, barley and rice were treated with different pathogens (57–61).

Conclusion

Development of new crop varieties and accelerated plant breeding programmes, the application of cytogenetic, genetic and phenotypic techniques play an important role in the current agriculture practice. Technologies aimed at controlling CO formation have the potential to harness the portion of genetic diversity that remains inaccessible to breeders. Although all the above-mentioned strategies contribute a lot to genetic gains but their practical application are very limited and an important factor is the challenge of translating the knowledge gained from model species to crop plants. The innovation of new genome editing techniques such as CRISPR will defiantly speed up the plant breeding program by the introgression of new allelic combinations and traits for the development of new varieties.

Conflict of Interest

We wish to confirm that there are no known conflicts of interest associated with this publication.

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