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1 Title: Repair of DNA double-strand breaks in plant meiosis: role of eukaryotic RecA  
2 recombinases and their modulators

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### **Abstract:**

13 Homologous recombination (HR) during meiosis is crucial for the DNA double-strand breaks (DSBs) repair  
14 that promotes the balanced segregation of homologous chromosomes and enhances genetic variation. In  
15 most eukaryotes, two recombinases RAD51 and DMC1 form nucleoprotein filaments on single-stranded  
16 DNA generated at DSB sites and play a central role in the meiotic DSB repair and genome stability. These  
17 nucleoprotein filaments perform homology search and DNA strand exchange to initiate repair using  
18 homologous template-directed sequences located elsewhere in the genome. Multiple factors can regulate  
19 the assembly, stability, and disassembly of RAD51 and DMC1 nucleoprotein filaments. In this review, we  
20 summarize the current understanding of the meiotic functions of RAD51 and DMC1 and the role of their  
21 positive and negative modulators. We discuss the current models and regulators of homology searches  
22 and strand exchange conserved during plant meiosis. Manipulation of these repair factors during plant  
23 meiosis also holds a great potential to accelerate plant breeding for crop improvements and productivity.

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## 1 **1. Introduction: Mechanism of strand invasion in DNA double-strand break (DSB) repair**

2 Meiosis is a specialized cell division required to produce haploid gametes in sexually reproducing  
3 organisms. During meiosis, a single round of replication is followed by two rounds of chromosome  
4 segregation. Homologous chromosomes (homologs) of maternal and paternal origins separate at the first  
5 meiotic division whereas sister chromatids segregate at the second division. At first meiotic division, the  
6 formation of crossovers (COs) with reciprocal exchange of DNA strands is crucial to establish physical  
7 connections called chiasmata between homologs. COs play an important mechanical role in promoting the  
8 accurate segregation of homologs. Complete absence or mislocalization of COs leads to chromosomal  
9 missegregation at meiosis, producing sterile and/or aneuploid offspring (refs. in Sasaki et al., 2010; Hunter,  
10 2015). COs are also a potent driving force of evolution as they create new allelic combinations and enhance  
11 genetic variation in eukaryotes. Plant breeders rely on the rate and position of COs in the genome to  
12 generate novel and favorable haplotypes. Therefore, manipulating COs frequency and distribution in a  
13 controlled manner in plants has the potential to substantially accelerate crop improvement programs  
14 (reviewed in Blary and Jenczewski, 2019; Taagen et al., 2020).

15 Genetic and cytological analyses suggest that the molecular mechanism of meiotic recombination is largely  
16 conserved in plants, though some differences exist compared to other eukaryotic organisms (reviewed in  
17 Mercier et al., 2015; Wang and Copenhaver, 2018). At the onset of meiosis, programmed induction of DNA  
18 double-strand breaks (DSBs) initiates recombination and is catalyzed by SPO11 transesterase and its  
19 partner proteins (refs. in Wang and Copenhaver, 2018). The nucleolytic resection of 5' ends at DSB sites  
20 yields 3' single-stranded DNA (ssDNA) tails (Fig. 1.1 & Fig. 3). These ssDNA tails are used as a query  
21 sequence to find an intact homologous template located elsewhere in the genome. The homology search  
22 necessitates the invasion of the ssDNA tails on template DNA. After homology recognition and DNA strand  
23 exchange, the invading 3' end is paired with the complementary strand of the homologous template,  
24 leading to displacement loop (D-loop) formation with heteroduplex DNA. The 3' ssDNA end can invade  
25 either a homolog or a sister chromatid and in both cases form the nascent D-loop (Fig.1-2a,1-2b). **During**  
26 **meiosis, a bias exists in invading homologs with possibly polymorphic DNA sequences over sister**  
27 **chromatids (Schwacha and Kleckner, 1997).** DSB repair on sister chromatids with identical DNA sequences,  
28 which are primarily used in somatic cells, does not leave any genetic traces and yields no chiasmata in  
29 meiosis (Fig1-3c, 1-3d, 1-5e).

30 At this stage, D-loops can be processed by alternative repair pathways (reviewed in Hunter, 2015). The  
31 disassociation of nascent D-loop or extended D-loop with DNA synthesis primed on the invading 3' end

1 over a polymorphic site can enforce a noncrossover (NCO) outcome event via synthesis-dependent-strand  
2 annealing (SDSA) pathway (Fig. 1-3a, 1-4a & 1-5a) (refs. in Hunter, 2015; Mercier et al., 2015; Wang and  
3 Copenhaver, 2018). Alternatively, a subset of nascent D-loops can be stabilized as single-strand invasion  
4 intermediates (Fig.1-3b). Once the second end of a DSB is captured and annealed to the displaced strand  
5 of the D-loop, it allows the formation of double-Holliday junction (dHJ) intermediates (Fig.1-4b). The  
6 asymmetric resolution of dHJ yields the COs belonging to class I (Fig.1-5b). dHJ can also produce NCO  
7 through the process of dHJ dissolution (Fig1-4c & 1-5c). Meiotic DNA transactions appear to be dynamic  
8 that can result in a variety of canonical and non-canonical recombination intermediates (Marsolier-  
9 Kergoat et al., 2018). These intermediates can either be dismantled or resolved to produce class II COs  
10 (Fig. 1-2c, 1-5d). Many organisms harbor both classes of meiotic COs, class II in plants presents only a minor  
11 fraction of wild-type COs, **discussed in two excellent reviews** (Mercier et al., 2015; Wang and Copenhaver,  
12 2018).

13 Central to the meiotic DSB repair are two DNA strand-exchange proteins - Radiation sensitive 51 (RAD51)  
14 and Disrupted Meiotic cDNA 1 (DMC1) - which are the eukaryotic homologs of eubacterial RecA  
15 recombinase (Fig. 2) (Lin et al., 2006). RAD51 plays role in both somatic and meiotic repair, while DMC1  
16 functions exclusively during meiosis. Both RAD51 and DMC1 function in three stages of the strand invasion  
17 process – presynaptic, synaptic, and postsynaptic. Presynaptic filaments result from the **assembly** of  
18 RAD51 and DMC1 on the ssDNA scaffold (Fig. 3) ( **reviewed in Crickard and Greene, 2018; Mhaskar et al.,**  
19 **2021**). During the synaptic stage, RAD51 and DMC1 promote D-loop formation by pairing the invaded  
20 strand with the donor template within the filament (Fig. 1 & Fig. 4). The postsynaptic stage is marked by  
21 the removal of RAD51 and DMC1 from the D-loop that allows DNA synthesis primed on the invading 3' end  
22 (Fig. 1 & Fig. 5). The process of strand invasion is fundamentally dynamic and its dynamics are ensured by  
23 the action of many modulators that can regulate nucleoprotein filament formation, stabilization,  
24 disassembly, homology search, and strand exchange. In this review, we focused on the role of the two  
25 RAD51 and DMC1 recombinases and their modulators in meiotic DSB repair in plants. We summarize the  
26 current understanding of the strand invasion step obtained in different eukaryotic organisms by  
27 interdisciplinary approaches and highlight molecular mechanisms likely conserved in plants. We also  
28 describe how the study of DSB repair factors provides tools to accelerate plant breeding programs.

## 29 **2.0 RAD51 and DMC1 are two eukaryotic RecA recombinases with specialized functions in DSB repair**

1 The presence of RAD51 and DMC1 in most eukaryotes poses a question: why do cells need two  
2 recombinases to perform the repair of meiotic breaks? This question requires an understanding of the  
3 evolutionary origin of both recombinases and their functional specialization during evolution.

#### 4 *2.1 Conservation of RAD51 and DMC1 in eukaryotes for meiotic DSB repair*

5 The *recA/RAD51* superfamily of recombinases appears to expand through a series of gene duplications in  
6 all three domains of life. Based on phylogenetic analyses, the *recA/RAD51* superfamily can be divided into  
7 three groups - *recA*, *RAD $\alpha$* , and *RAD $\beta$*  (Lin et al., 2006; Chintapalli et al., 2013) (Fig. 2A). The *recA* group  
8 consists of prokaryotic-like recombinases including all the bacterial *recA* and eukaryotic *recA* proteins in  
9 plants, protists, and some fungi (Lin et al., 2006). The *RAD $\alpha$*  group comprises the main recombinases in  
10 eukaryotes (*RAD51* and *DMC1*) and Archaea (*RadA*). The *RAD $\beta$*  group contains functionally more divergent  
11 and rapidly evolving eukaryotic *RAD51* paralogs and the archaeal *RadB*. These paralogs are structurally  
12 related to the *RAD $\alpha$*  recombinases and act as accessory factors without possessing catalytic activity for  
13 homology searches and DNA-strand exchange (reviewed in Bonilla et al., 2020).

14 In the *RAD $\alpha$*  subfamily, *RAD51* and *DMC1* proteins form two separate monophyletic groups (Ramesh et  
15 al., 2005; Lin et al., 2006). This represents a two-recombinases paradigm for meiotic recombination in the  
16 vast majority of sexually reproducing eukaryotes including budding yeast, fission yeast, plants, and  
17 mammals. The *RAD51* and *DMC1* genes appear to diverge following an ancient gene duplication event  
18 likely in the very early eukaryotic lineage (Ramesh et al., 2005). Sequence comparison of *RAD51* and *DMC1*  
19 proteins have identified amino acids specific to *DMC1* or *RAD51* lineages, supporting their functional  
20 divergence (Steinfeld et al., 2019).

21 The evolution of *RAD51* and *DMC1* is also marked by the repeated and independent loss of *DMC1* (Ramesh  
22 et al., 2005) in a few eukaryotes such as *Drosophila melanogaster*, *Caenorhabditis elegans*, *Sordaria*  
23 *macrospora*, *Ustilago maydis*, and *Neurospora crassa*. Interestingly, a close inspection of the *RAD51* gene  
24 phylogeny revealed that a few organisms harbor a faster-evolving *RAD51* gene within the eukaryotic family  
25 (Lin et al., 2006; Steinfeld et al., 2019). In the *RAD51*-only group, *D. melanogaster* and *C. elegans* possess  
26 rapidly evolving *RAD51* genes (Lin et al., 2006). The loss of *DMC1* in these organisms may be related to  
27 functional divergence of meiotic recombination and chromosomal interaction processes (Dernburg et al.,  
28 1998; McKim and Hayashi-Hagihara, 1998; Villeneuve and Hillers, 2001). Remarkably, the *C. elegans* *RAD*-  
29 *51* has acquired *DMC1* lineage-specific amino acids, suggesting an adaptive evolution of *RAD51* for  
30 promoting recombination between homologs (Steinfeld et al., 2019). However, the modified  
31 recombination process can not alone explain the loss of *DMC1* in other eukaryotes (Steinfeld et al., 2019).

1 Among plants *RAD51* and *DMC1* genes further witnessed the expansion of copy numbers per genome,  
2 owing to whole-genome duplication events. For example, *Physcomitrium patens* have two *RAD51* genes,  
3 both are important for recombination (Schaefer et al., 2010), while there are 2 or more copies of *RAD51*  
4 and *DMC1* genes in rice and maize (Table1). This expansion of *RAD51* and *DMC1* gene copies through  
5 duplication events in plants could promote functional diversification of meiotic recombination in the  
6 longer run, a hypothesis that remains to be explored. Plant genomes, but not fungi and mammals, also  
7 have additional *recA* homologs to maintain genome stability in organelles (Lin et al., 2006; Odahara et al.,  
8 2015).

## 9 2.2 Conserved and diverged biochemical roles of *RAD51* and *DMC1*

10 *In vitro* studies combining biochemical, biophysics, and structural biology approaches have significantly  
11 contributed to our molecular understanding of how *RAD51* and *DMC1* recombinases work. Both  
12 recombinases assemble into right-handed helical presynaptic filaments by polymerizing on the ssDNA  
13 overhangs (Benson et al., 1994; Sung, 1994; Sehorn et al., 2004; Sheridan et al., 2008). Both recombinases  
14 can also assemble on the double-stranded DNA (dsDNA), albeit with a lower affinity, to form dead-end  
15 toxic intermediates that can not perform homology searches (Holzen et al., 2006; Shah et al., 2010; Qiu et  
16 al., 2013; Candelli et al., 2014). The formation of functionally active presynaptic filaments relies on two  
17 conserved properties of recombinases – binding to adenosine triphosphate (ATP) and DNA scaffold. ATP  
18 bound-*RAD51/DMC1* form is proficient for presynaptic filament formation, while ATP hydrolysis leads to  
19 nucleoprotein filament turnover. Preventing ATP hydrolysis renders more stable *RAD51* presynaptic  
20 filaments with enhanced recombinase activity, but not that of *DMC1*, showing mechanistic differences  
21 between *RAD51* and *DMC1* (Chang et al., 2015). Both recombinases polymerize on ssDNA through a high-  
22 affinity DNA binding site called site I (Fig. 2B). The site I orientate around the central axis of presynaptic  
23 filament (Xu et al., 2017) and contains two conserved motifs called loop1 and loop2, which play distinct  
24 catalytic roles in the DNA strand exchange reaction leading to heteroduplex DNA formation (Ito et al.,  
25 2020). A second conserved DNA binding site called site II lies distant from the axis of presynaptic filament  
26 and serves as an entry gate to deliver ssDNA to the catalytic site I (Fig. 2B) and to capture donor dsDNA  
27 (Ito et al., 2020).

28 Structural studies revealed that ssDNA within ATP-bound presynaptic filament is stretched ~1.5 fold  
29 relative to B-form DNA (Di Capua et al., 1982; Chen et al., 2008). This stretching could promote a fast and  
30 efficient homology search. Homology search proceeds through a sampling of consecutive 8-nucleotides  
31 that are stably captured by *RAD51* filaments (Danilowicz et al., 2015; Qi et al., 2015). However, biophysical

1 and structural studies show a difference in the mode of action between RAD51 and DMC1. DMC1 can  
2 stabilize the heteroduplex DNA with mismatches, likely by masking mismatches in the paired sequence of  
3 the invaded 3' end and donor template strand (Bugreev et al., 2011; Lee et al., 2015, 2017; Luo et al.,  
4 2021). Conversely, RAD51 is unable to stabilize imperfectly paired heteroduplex intermediates with  
5 mismatches (Lee et al., 2015, 2017). The difference between the ability of two eukaryotic recombinases is  
6 attributed to highly conserved lineage-specific amino acid residues within DMC1 and RAD51 in DNA  
7 binding sites (Steinfeld et al., 2019; Luo et al., 2021). These findings suggest that DMC1 functions like a  
8 “lower-fidelity” recombinase; the RAD51 acts as a “higher-fidelity” recombinase. Other differences  
9 between RAD51 and DMC1 are reviewed elsewhere (Masson and West, 2001; Brown and Bishop, 2015).  
10 Nonetheless, it is interesting to note that these recombinases can show differences in their recombinase  
11 activity in a species-specific manner. For example, plant RAD51 proteins showed higher DNA pairing  
12 activity compared to human RAD51 (Kobayashi et al., 2019).

### 13 *2.3 Cooperation of RAD51 and DMC1 in vivo functions for repairing meiotic breaks*

14 Pioneering genetic studies in budding yeast had identified *Rad51* and *Dmc1* genes and have since then  
15 significantly advanced our understanding of the functions and the relationship between these two proteins  
16 (Game and Mortimer, 1974; Game et al., 1980; Aboussekhra et al., 1992; Bishop et al., 1992; Shinohara et  
17 al., 1992). RAD51 and DMC1 proteins form nuclear foci on meiotic chromosomes (Bishop, 1994; Kurzbauer  
18 et al., 2012; Brown et al., 2015; Slotman et al., 2020). These RAD51 and DMC1 foci functionally correspond  
19 to meiotic presynaptic filaments involved in the strand invasion. The strand invasion of presynaptic  
20 filaments on homologs during meiosis enforces two important features unique to meiotic chromosome  
21 dynamics called pairing and synapsis (reviewed in Zickler and Kleckner, 2015). Pairing is defined as the  
22 spatial coalignment of homologous chromosomes. Chromosome synapsis is the physically tethering of  
23 homologs via the assembly of the synaptonemal complex (SC) between two homolog axes all along their  
24 entire length. The analysis of *dmc1* and *rad51* mutants in multiple organisms provided insights into their  
25 role in meiotic DSB repair (Bishop et al., 1992; Shinohara et al., 1992, 1997a; Bishop, 1994; Pittman et al.,  
26 1998; Couteau et al., 1999; Li et al., 2004; Dai et al., 2017). Meiotic DSB repair is not completed in *rad51*  
27 mutants suggesting DMC1 is not efficient to repair meiotic breaks in absence of RAD51 (Fig. 6d) (Shinohara  
28 et al., 1992; Li et al., 2004). In *dmc1* mutants, DSB repair is either blocked (such as in *S. cerevisiae* and mice)  
29 or biased toward repair on the sister chromatid as in Arabidopsis (Fig. 6c) (Couteau et al., 1999). In all  
30 cases, DMC1 deficiency is associated with abnormal homolog pairing and synapsis (Bishop et al., 1992;  
31 Pittman et al., 1998; Yoshida et al., 1998; Couteau et al., 1999). Both RAD51 and DMC1 are suggested to

1 cooperate to promote bias toward homologs, however, the strand-exchange activity of DMC1 is essential  
2 to perform interhomolog repair (Schwacha and Kleckner, 1997; Hong et al., 2013). Several arguments  
3 further suggest that RAD51 plays a supporting role. First, the absence of Dmc1 does not affect Rad51 foci  
4 formation during meiosis, however, Dmc1 foci are fewer and dull in absence of Rad51 suggesting that  
5 Rad51 promotes normal assembly of Dmc1 (Bishop et al., 1992; Shinohara et al., 1992, 1997a; Bishop,  
6 1994; Pittman et al., 1998; Couteau et al., 1999; Li et al., 2004; Kurzbauer et al., 2012). Second, in yeast  
7 and Arabidopsis the strand-exchange activity of RAD51 is dispensable for DMC1-mediated repair of meiotic  
8 breaks, arguing for a non-catalytic role of RAD51 (Cloud et al., 2012; Da Ines et al., 2013b). Third, in  
9 Arabidopsis and budding yeast, the presence of DMC1 somehow suppresses RAD51-mediated repair,  
10 which might be used as a backup pathway during meiosis (Hong et al., 2013; Lao et al., 2013; Uanschou et  
11 al., 2014). This downregulation of RAD51 activity could be important to prevent competition between  
12 RAD51 and DMC1 for repairing meiotic breaks (Tsubouchi and Roeder, 2006; Busygina et al., 2008, 2012;  
13 Liu et al., 2014; Callender et al., 2016).

#### 14 *2.4 Organization of in vivo RAD51 and DMC1 nucleoprotein filaments*

15 Since RAD51 and DMC1 both are essential for meiotic repair, the molecular organization of the two  
16 recombinases within the presynaptic filaments at meiotic DSBs is an important question. Two models  
17 (asymmetric and symmetric) of RAD51 and DMC1 organization during meiosis have emerged (Fig.3). The  
18 asymmetric model predicts that RAD51 and DMC1 form separate homotypic filaments at the opposite  
19 ends of a DSB. Consonant with this idea, the localization studies using epifluorescence microscopy showed  
20 that yeast and Arabidopsis Rad51 and Dmc1 foci colocalize in side-by-side partially offset cofoci, suggesting  
21 homofilaments formation at two ends of a DSB (Fig. 3)(Bishop, 1994; Shinohara et al., 2000; Kurzbauer et  
22 al., 2012). **Recently, high-resolution imaging of RAD51 and DMC1 in mouse spermatocytes pointed to a  
23 huge diversity in nanofoci configurations for both recombinases (Slotman et al., 2020). Altogether, these  
24 data raised the possibility of an asymmetric loading model.** This apparent differentiation of two ends of a  
25 DSB implied that DMC1-only filament is proficient to perform the strand exchange. However, both ends of  
26 a DSB can catalyze strand exchange as evidenced by different studies, arguing against the asymmetric  
27 loading of two recombinases (Oh et al., 2007; Martini et al., 2011; Marsolier-Kergoat et al., 2018).

28 The symmetric loading model describes the side-by-side colocalization of both RAD51 and DMC1 on the  
29 same ssDNA (Fig. 3) and is supported by the following studies. 1) Budding yeast Rad51 and Dmc1 *in vivo*  
30 are often detected as the paired cofoci at <400 nm distance by a super-resolution imaging study,  
31 suggesting two recombinases bound on the same end of a break (Brown et al., 2015). 2) High-resolution



1 *in vivo* maps of mouse RAD51 and DMC1 bound on the ssDNA along with their cytological localization  
2 during meiosis demonstrate a RAD51-DMC1-RAD51 configuration in which DMC1 near to break site and  
3 RAD51 away from the break site, strongly arguing for symmetric loading (Hinch et al., 2020). 3) Further,  
4 the nucleation rate of yeast Dmc1 is 33-fold lower compared to Rad51 and is stimulated by Rad51  
5 nucleation indicating that the Rad51 patch could function as a docking site for Dmc1 filament assembly  
6 (Lan et al., 2020). This study suggests that mechanistically Rad51 nucleation facilitates the assembly of  
7 Dmc1 homofilaments on the same DNA molecule.

### 8 **3.0 Positive modulators promote RAD51 and DMC1 functions**

9 Both RAD51 and DMC1 require *in vivo* many proteins which play a wide variety of roles in the nucleation,  
10 elongation, stabilization, and activation of presynaptic filaments and for DNA strand exchange reaction  
11 (Fig. 4). In this section, we describe positive modulators conserved in plants.

#### 12 **BRCA2**

13 *BREAST CANCER SUSCEPTIBILITY GENE 2 (BRCA2)* was originally identified in humans as being frequently  
14 mutated in breast cancer families (Wooster et al., 1995) and is essential for the maintenance of genomic  
15 stability (Venkitaraman, 2002). Biochemical and structural studies demonstrate that BRCA2 functions as a  
16 mediator protein – an activity that can stimulate the formation and activation of the presynaptic filaments  
17 (Pellegrini et al., 2002; Jensen et al., 2010; Liu et al., 2010; Thorslund et al., 2010; Martinez et al., 2016).  
18 Genetically, BRCA2 is required for RAD51 and DMC1 focus formation during HR repair (Yuan et al., 1999;  
19 Sharan et al., 2004; Seeliger et al., 2012). BRCA2 interacts directly with RAD51 and DMC1 (Thorslund et al.,  
20 2007) and can serve as cargo of both recombinases (Liu et al., 2010; Martinez et al., 2016). Thus, BRCA2  
21 facilitates RAD51 nucleation by bringing a sufficient number of protomers to the ssDNA that is coated with  
22 the high-affinity ssDNA binding protein, Replication protein A (RPA). BRCA2 together with its partner  
23 Deleted in split-hand/split-foot syndrome protein (DSS1) removes RPA and interacts with ssDNA, which in  
24 turn accelerates the presynaptic filament formation (Yang et al., 2002; Liu et al., 2010). Accordingly, the  
25 depletion of DSS1 in human cells disables HR repair (Kristensen et al., 2010). BRCA2 also prevents the  
26 binding of RAD51 to dsDNA (Carreira et al., 2009; Jensen et al., 2010), a binding that is inhibitory for the  
27 DNA strand exchange (reviewed in Reitz et al., 2021). Human BRCA2 protein diffuses in the cell within  
28 oligomeric complexes (Reuter et al., 2014; Paul et al., 2021). This intracellular BRCA2 oligomerization might  
29 regulate its localization (Lee et al., 2021). However, the structural mechanism of the oligomeric state of  
30 BRCA2 is currently unknown.

1 BRCA2 is evolutionarily conserved in most eukaryotes including vertebrates, flies, worms, plants, and smut  
2 fungi, but not in yeast. In the Plantae kingdom, euphyllophytes, lycophytes, and green algae all have  
3 retained BRCA2 homologs with exception of the Bryophyta clade (mosses). For example, BRCA2 homolog  
4 in *Physcomitrium patens* has not been detected so far. The analysis of BRCA2 conserved protein domain  
5 architecture presents interesting evolutionary features: 1) The protein size of BRCA2 is variable among  
6 different eukaryotic species – 3418 amino acids (aa) in humans; ~1200 aa in Arabidopsis and 383 aa in *C.*  
7 *elegans* (Lo et al., 2003). 2) the number of BRC repeats essential for interaction with RAD51/DMC1  
8 (Pellegrini et al., 2002; Rajendra and Venkitaraman, 2009), is highly variable within BRCA2 homologs – 8  
9 BRC repeats in human BRCA2; 4 in Arabidopsis; 1 in *Ustilago* (Lo et al., 2003). 3) A DNA binding domain  
10 (DBD) at the C-terminal of BRCA2 is well conserved in most eukaryotic homologs except in flies (Klovstad  
11 et al., 2008). The DBD supposedly provides the ssDNA-binding specificity of BRCA2. Studies on *Drosophila*  
12 BRCA2 homolog and in human cells with truncated BRCA2 suggested that DBD is dispensable to HR and  
13 cell survival (Klovstad et al., 2008; Siaud et al., 2011; Paul et al., 2021). Despite the central role of BRCA2  
14 in DSB repair, how BRCA2 diverged in terms of its domain architecture among eukaryotes has remained  
15 unclear so far.

16 The role of plant BRCA2 is conserved in the maintenance of genomic stability. Unlike the lethality caused  
17 by disruption of the *BRCA2* gene in mammals that prevented genetic analysis, plant *brca2* mutants are  
18 viable and grow without developmental defects. Arabidopsis and rice *brca2* mutants however show  
19 hypersensitivity to genotoxic agents suggesting repairing DNA damage and genomic instability (Seeliger et  
20 al., 2012; Fu et al., 2020). Similar to their human homologs, both Arabidopsis and rice BRCA2 proteins  
21 interact with RAD51 and DMC1 (Siaud et al., 2004; Dray et al., 2006; Fu et al., 2020). During meiosis,  
22 Arabidopsis and rice mutants display a lack of RAD51 and DMC1 foci, incomplete synapsis, and  
23 chromosome fragmentation suggesting unrepaired breaks (Fig. 6d) (Seeliger et al., 2012; Fu et al., 2020).  
24 Further, DSS1, a partner of BRCA2, is also conserved in plants. Arabidopsis genome contains two DSS1  
25 homologs; both can interact with AtBRCA2 in the C-terminal DBD region (Dray et al 2006). However, the  
26 role of the Arabidopsis DSS1 in meiotic recombination remains to be determined.

## 27 **RAD52**

28 Radiation sensitive 52 (Rad52) is an evolutionarily conserved protein, though its functions vary in different  
29 eukaryotes. In budding yeast, Rad52 performs a variety of functions – 1) Rad52 has a mediator activity that  
30 promotes the loading of Rad51, but not of Dmc1, on RPA-coated ssDNA (Bishop, 1994; Lao et al., 2008); 2)  
31 Rad52 can anneal two complementary ssDNA strands in the single-strand annealing (SSA) DSB repair

1 pathway (Pâques and Haber, 1999); 3) Rad52 acts in the capture of second DSB end within the  
2 corresponding the D-loop to form dHJ (Fig. 1-4b) (Sugiyama et al., 2006; Lao et al., 2008; McIlwraith and  
3 West, 2008). Owing to diverse activities of Rad52, yeast *rad52* mutant displays strong phenotypes in all HR  
4 events involved in sensitivity to DNA damage agents, DSB repair, mating type-switching, gene targeting,  
5 and meiotic recombination (Symington, 2002). *Rad52*<sup>-/-</sup> mice surprisingly showed no significant DNA repair  
6 and recombination phenotypes (Rijkers et al., 1998), suggesting mammalian RAD52 is dispensable for HR,  
7 especially for its mediator roles. However, mammalian RAD52 becomes essential for cell viability when  
8 BRCA2 or several other HR proteins are absent (Lok et al., 2013). Mammalian RAD52 appears to play  
9 backup roles in HR and its strand-annealing-dependent function in recombination remains poorly  
10 understood.

11 Plants possess RAD52 homologs identified based on similarity to a well-conserved N-terminal domain of  
12 human RAD52 and *S. cerevisiae* Rad52 required for DNA binding and oligomerization - (Samach et al., 2011;  
13 Janicka et al., 2012). Plant RAD52 homologs appear to have lost the C-terminal domain conserved in  
14 human and budding yeast RAD52 that contains RPA and RAD51 interaction regions. Besides, phylogenetic  
15 analysis showed that the plant RAD52 homologs are closer to a group of mitochondrial genome  
16 maintenance proteins called Mgm101 in fungi (Chen et al., 1993; Mbantenkhu et al., 2011). The *S.*  
17 *cerevisiae* Mgm101 localizes to mitochondria and performs Rad52-like functions - ssDNA annealing and  
18 recombination of mitochondrial DNA (Meeusen et al., 1999; Mbantenkhu et al., 2011). One speculation is  
19 that fungi possess two types of related Rad52 proteins: one with DSB repair function in the nucleus and  
20 another that plays role in mitochondrial DNA integrity. It is unclear if plants possess only one type of RAD52  
21 protein for nuclear and mitochondrial functions. It is interesting to note that mammalian RAD52 homologs  
22 have no reported functions in mitochondria.

23 The roles of RAD52 in DSB repair and recombination are not well comprehended in plants. Two *Arabidopsis*  
24 RAD52 paralogs - RAD52-1/ ORGANELLAR DNA-BINDING PROTEIN 1 (ODB1) and RAD52-2/ ORGANELLAR  
25 DNA-BINDING PROTEIN 2 (ODB2) - are so far the best-studied plant RAD52 homologs. RAD52-1/ODB1  
26 localizes in the nucleus and mitochondria; RAD52-2/ODB2 is found in plastids (Samach et al., 2011; Janicka  
27 et al., 2012). Mitochondrial roles of RAD52-1/ODB1 include ssDNA binding, annealing, and maintenance  
28 of the mitochondrial genome (Janicka et al., 2012). The nuclear roles of RAD52-1/ODB and RAD52-2/ODB2  
29 are unclear. The *Arabidopsis rad52-1/odb1* and *rad52-2/odb2* are viable without any developmental  
30 defects. Sensitivity to Mitomycin C (MMC) of single or double mutants *rad52-1/odb1 rad52-2/odb2* is  
31 controversial, albeit these mutants can show lower somatic recombination upon MMC treatment, and a

1 slight reduction in fertility (Samach et al., 2011; Janicka et al., 2012). If the functional analysis performed  
2 in Arabidopsis can be extended to the plant kingdom, plant RAD52 proteins could have an Mgm101-like  
3 role in the organelles. Their nuclear role does not appear to play an essential role and it remains to be  
4 determined if plant RAD52 homologs could have a backup role in DSB repair like their mammalian  
5 counterparts.

## 6 **SDS**

7 SOLO DANCERS (SDS) might act as a plant-specific mediator protein as it is essential for the DMC1 focus  
8 formation. Hong Ma and colleagues identified the *Arabidopsis SOLO DANCERS (SDS)* gene in a genetic  
9 screen looking for sterile or reduced fertility mutants (Azumi et al., 2002). *Arabidopsis SDS* gene is  
10 expressed in male and female meiosis specifically (Huang et al., 2016) and is a unique cyclin-like protein  
11 with a **C-terminus** that shows high homology with other Arabidopsis cyclins (A-, B- and D-types) (Azumi et  
12 al., 2002; Wang, 2004; Zhang et al., 2013). The *Arabidopsis sds* mutant forms meiotic breaks but exhibits  
13 a lack of DMC1 foci, defects in homolog synapsis, and no meiotic CO formation, leading to only univalents  
14 at metaphase I (Fig. 6c) (Azumi et al., 2002; De Muyt et al., 2009). The absence of bivalents and  
15 chromosome fragmentation in *sds* mutant suggests that meiotic breaks are efficiently repaired in a RAD51-  
16 dependent manner using sister chromatid (De Muyt et al., 2009). Thus, SDS participates in imposing the  
17 DMC1 dependent interhomolog-bias repair of meiotic breaks in Arabidopsis. However, the role of SDS in  
18 regulating interhomolog repair may not be conserved in all plants. OsSDS rice homolog is essential for  
19 meiotic break formation, suggesting a functional divergence of the role of SDS in plants (Wu et al., 2015).  
20 Nonetheless, many questions regarding the mechanism of action of SDS remain unanswered: Is DMC1 the  
21 direct or indirect target of SDS activity? Which kinase does SDS interact with? How does OsSDS facilitate  
22 meiotic DSB formation? Are different roles of SDS conserved in other plant models?

## 23 **RAD51 paralogs**

24 RAD51 paralogs are RAD51-like proteins that presumably arose via the duplication and divergent evolution  
25 of a common ancestor (Lin et al., 2006). These paralogs have lost the ability to perform homology search  
26 and DNA strand exchange but they play critical *in vivo* functions in HR (**reviewed in** Sullivan and Bernstein,  
27 2018). *RAD51* paralogs are placed in the *RAD52* epistasis group of genes and display structural similarity  
28 to RAD51 with limited or no DNA sequence homology. All RAD51 paralogs can be divided into two sub-  
29 groups: canonical and non-canonical paralogs.

1 In *S. cerevisiae*, Rad55 and Rad57 are two RAD51 canonical paralogs, which form a dimeric complex needed  
2 for the Rad51 focus formation. The Rad55-Rad57 complex likely acts as a molecular chaperone to stabilize  
3 the Rad51 presynaptic filament and counteracts the anti-recombinase activity of the helicase Srs2  
4 (described below) (Liu et al., 2011; Roy et al., 2021). **The *rad55* and *rad57* mutants display mitotic Rad51**  
5 **foci in a temperature-dependent manner but lack RAD51 focus formation during meiosis, suggesting**  
6 **differential functions of the Rad55-Rad57 complex in somatic and meiotic cells (Lovett and Mortimer,**  
7 **1987; Gasior et al., 2001).** In mammals, there are five canonical RAD51 paralogs - RAD51B, RAD51C,  
8 RAD51D, XRCC2, and XRCC3 (Takata et al., 2001). The mammalian paralogs form two biochemically and  
9 functionally distinct complexes: BCDX2 (RAD51B-RAD51C-RAD51D-XRCC2) and CX3 (RAD51C-XRCC3)  
10 (Masson et al., 2001). RAD51C also participates in a complex with BRCA2, PALB2, and RAD51 (Park et al.,  
11 2014). Mouse knockouts of *Rad51b*, *Rad51c*, *Rad51d*, *Xrcc3*, or *Xrcc2* genes are embryonic lethal  
12 precluding the analysis of a meiotic phenotype (reviewed in Sullivan and Bernstein, 2018; Prakash et al.,  
13 2021). *In vitro* studies have shown that both the CX3 and the BCDX2 complexes facilitate the initiation and  
14 stabilize the RAD51 filament and thus stimulate the strand exchange activity. The CX3 complex may have  
15 functional similarity to the dimeric complex of paralogs in yeast Rad55-57. However, the precise molecular  
16 functions of these paralog complexes are not fully understood.

17 The canonical RAD51 paralogs have been identified in plant genomes including all five paralogs in the  
18 Arabidopsis genome - RAD51B, RAD51C, RAD51D, XRCC2, XRCC3 (Table 1). The five Arabidopsis RAD51  
19 paralogs form the CX3 and BCDX2 complexes, like their mammalian counterparts (Osakabe et al., 2002).  
20 The Arabidopsis and rice *rad51* paralog mutants are viable and do not show any vegetative growth defects  
21 but are hypersensitive to genotoxic drug treatment, suggesting their role in somatic DNA repair (Bleuyard  
22 et al., 2006; Wang et al., 2014). Moreover, RAD51B, RAD51D, and XRCC2 in Arabidopsis and rice act in both  
23 RAD51-dependent and RAD51-independent DNA repair pathways (Serra et al., 2013; Xu et al., 2018).  
24 Studies in different plant model species implicate RAD51 paralogs functions in meiotic recombination with  
25 strong or no visible effect on meiosis. The CX3 complex in Arabidopsis, maize, and rice is required for the  
26 efficient loading of RAD51 and DMC1 (Vignard et al., 2007; Zhang et al., 2015; Su et al., 2017; Jing et al.,  
27 2019). Disruption of *RAD51C* or *XRCC3* gene in Arabidopsis, rice, and maize displays similar phenotypes:  
28 sterility, meiotic DSB repair defects with strong chromosome fragmentation, impairment of RAD51 and  
29 DMC1 recruitment at DSBs (Fig. 6d) (Bleuyard and White, 2004; Bleuyard et al., 2006; Kou et al., 2012;  
30 Tang et al., 2014; Zhang et al., 2015; Su et al., 2017; Jing et al., 2019). Rice RAD51D may also act together  
31 with the CX3 complex as the disruption of the rice *RAD51D* gene results in DSB repair defects and lack of  
32 RAD51 and DMC1 focus formation (Byun and Kim, 2014; Zhang et al., 2020). Thus, the CX3 complex in

1 plants as well as potentially another complex including RAD51C and RAD51D in rice is involved in the  
2 stabilization of the RAD51/DMC1 nucleofilaments to promote strand exchange activity. Further, the  
3 absence of Arabidopsis XRCC2, and to a lesser extent RAD51B, increase meiotic crossover frequency  
4 slightly without any visible DSB repair defects (Da Ines et al., 2013a). RAD51B in *Physcomitrium patens* is  
5 essential for meiotic recombination repair as the absence of RAD51B leads accumulation of unrepaired  
6 meiotic breaks (Charlot et al., 2014). Altogether, these studies suggest diversification of canonical RAD51  
7 paralogs functions in meiotic breaks repair in plants.

8 The non-canonical RAD51 paralogs include the suppressor of *sgs1* hydroxyurea sensitivity (Shu) complex  
9 genes (Shor et al., 2005). Members of the Shu complex show structural similarity with RAD51 rather than  
10 a direct sequence homology (reviewed in Bonilla et al., 2020). Homologs of Shu complex proteins are  
11 identified in budding yeast (Shu1, Shu2, Psy3, and Csm1), fission yeast (Sws1/Shu2, Rdl1, Rlp1), in mice  
12 (SWS1/Shu2, SWSAP1/Shu1) and *C. elegans* (SWS1-1, RFS-1, RIP-1) (refs. in Martino and Bernstein, 2016).  
13 The consistent role of the Shu complex in different organisms is to promote, stabilize and protect  
14 presynaptic RAD51 filaments by mimicking the RAD51 structure. The yeast Shu complex, independently of  
15 Rad55/57 is needed to form RAD51 but not DMC1 foci in meiotic cells and for the interhomolog bias repair  
16 of meiotic breaks (Sasanuma et al., 2013). Similarly, the mouse Shu complex is essential for the formation  
17 of normal RAD51 and DMC1 foci numbers (Abreu et al., 2018; Matsuzaki et al., 2019). Contrary to canonical  
18 mammalian RAD51 paralogs, *Swsap1*<sup>-/-</sup> and *Sws1*<sup>-/-</sup> mice are viable (Abreu et al., 2018; Matsuzaki et al.,  
19 2019). Shu proteins from yeasts and mice can stabilize the Rad51 nucleofilaments and counteract the anti  
20 recombinase activity to protect presynaptic filaments (Bernstein et al., 2011; Liu et al., 2011; Lorenz et al.,  
21 2014; Matsuzaki et al., 2019). In addition, the *C. elegans* Shu protein (RFS-1) promotes the removal of the  
22 RAD-51 assembled on dsDNA (Ward et al., 2010). The *C. elegans* RFS-1 together with RIP1 is also proposed  
23 to remodel the presynaptic filaments to attain an open flexible conformation that stimulates DNA strand  
24 exchange reaction (Taylor et al., 2015). In plants, putative homologs of Shu proteins are identified in the  
25 Arabidopsis genome (Godin et al., 2015) but await their functional characterization.

## 26 **HOP2-MND1**

27 Homologous-pairing protein 2 (HOP2) and Meiotic nuclear division protein 1 (MND1) form an obligate  
28 heterodimeric complex that is essential for the repair of meiotic breaks (Leu et al., 1998; Rabitsch et al.,  
29 2001; Gerton and DeRisi, 2002; Tsubouchi and Roeder, 2002; Zierhut et al., 2004). Homologs of HOP2 and  
30 MND1 are widely conserved in eukaryotes including yeast, mammals, and plants, but they are absent in  
31 *D. melanogaster*, *C. elegans*, and *S. macrospora*, all of which also lack DMC1 (Ramesh et al., 2005). This

1 observation suggested a functional relationship between the HOP2-MND1 complex and DMC1 during  
2 meiotic DSB repair. Both *HOP2* and *MND1* genes show meiosis-specific expression and their disruption in  
3 the budding yeast and mice showed several similar meiotic defects: unrepaired breaks, partial synapsis  
4 between non-homologous chromosomes, accumulation of RAD51 and DMC1 foci (Leu et al., 1998;  
5 Petukhova et al., 2003). These studies suggested the essential role of HOP2 and MND1 in meiotic DSB  
6 repair after the assembly of presynaptic filaments. Slightly different meiotic phenotypes are also observed  
7 between mice *Hop2*<sup>-/-</sup> and *Mnd1*<sup>-/-</sup> mutants. The *Mnd1*<sup>-/-</sup> spermatocytes display a higher degree of DSB  
8 repair and chromosome synapsis when compared with *Hop2*<sup>-/-</sup> spermatocytes (Pezza et al., 2014). This  
9 raised the possibility that HOP2 may act alone as a recombinase in absence of MND1 (Pezza et al., 2014).  
10 **MND1 could inhibit in vitro the strand exchange activity of HOP2 upon heterodimeric complex formation**  
11 **(Pezza et al., 2006), though the biological role of such an inhibitory activity of MND1 remains controversial.**  
12 The mammalian HOP2-MND1 complex might also function in somatic cells as it promotes RAD51-  
13 dependent recombination between telomeres in specific cell lines (Cho et al., 2014). The mammalian  
14 HOP2-MND1 complex stimulates the DNA strand exchange activity of both RAD51 and DMC1  
15 nucleofilament in biochemical studies (Petukhova et al., 2005). However, the activity of the yeast Hop2-  
16 Mnd1 complex is a bit different as it stimulates specifically the strand-exchange activity of Dmc1 filaments  
17 (Chan et al., 2014). Structural studies illustrated that Hop2 and Mnd1 acquire an elongated V-shaped  
18 heterodimer complex, consisting of two juxtaposed wing-helix domains (WHD) connected to two  
19 elongated rod-shaped recombinase-binding domains (Kang et al., 2015). The Hop2-Mnd1 complex binds  
20 to dsDNA with a high affinity and specificity over ssDNA. Together these studies suggest that HOP2-MND1  
21 activity helps DMC1 alone or both DMC1 and RAD51 to capture dsDNA during meiosis.

22 In plants, the *Arabidopsis Athop2* and *Atmnd1* mutants show strong meiotic DSB repair phenotypes (Fig.  
23 6d); the role of AtHOP2 and AtMND1 is unclear in mitotic DNA repair (Domenichini et al., 2006;  
24 Kerzendorfer, 2006). Both *Athop2* and *Atmnd1* meiocytes display the normal number of RAD51 and DMC1  
25 foci and formation chromosome fragmentation at metaphase I due to unrepaired breaks that lead to male  
26 and female sterility (Kerzendorfer, 2006; Panoli et al., 2006; Vignard et al., 2007; Uanschou et al., 2014).  
27 However, the rice *Oshop2* mutant shows a less severe meiotic phenotype with rare chromosome  
28 fragmentation when compared to phenotypes in the *Arabidopsis Athop2* mutant (Shi et al., 2019) raising  
29 questions of mechanistic differences or if *Oshop2-1* is a null mutant. OsHOP2 may also play a role after the  
30 strand invasion step in the maturation of crossovers (Shi et al., 2019).

1 Arabidopsis AtHOP2 and AtMND1 proteins form a heterodimer complex and interact with DMC1 and  
2 RAD51 (Kerzendorfer et al., 2006; Vignard et al., 2007; Uanschou et al., 2014; Rampler et al., 2015).  
3 Conformational flexibility analysis of AtHOP2-AtMND1 revealed the coexistence of different forms that  
4 could participate in the helper function of the complex with the recombinases (Rampler et al., 2015).  
5 Interestingly, the optimal stimulation of DMC1 for meiotic inter-homolog repair is dependent on the  
6 quantity and stability of the AtHOP2-AtMND1 complex (Uanschou et al., 2014). Rice OsHOP2 and OsMND1  
7 stimulate the rice DMC1A and DMC1B activity for the D-loop formation, but similar stimulation of  
8 OsRAD51 activity is unclear (Uanschou et al., 2014). Both Arabidopsis and rice HOP2 and MND1 proteins  
9 decorate the meiotic chromosome during early prophase I; their localization is not affected in the absence  
10 of recombination, axis formation, or cohesion. Surprisingly given their obligate helper role in the DMC1  
11 function, HOP2 and MND1 do not colocalize with DMC1. One hypothesis is that the HOP2-MND1 complex  
12 opens the double helix of the donor DNA to facilitate the invasion step and interacts with DMC1 in a highly  
13 dynamic and transient manner (Crickard et al., 2019a).

#### 14 **4.0 Negative modulators dismantle RAD51/DMC1-mediated recombination intermediates**

15 Negative regulators can limit one or more steps of the strand invasion process at presynaptic, synaptic,  
16 and postsynaptic stages (Fig. 5). These modulators act as guardians of the genome to prevent the  
17 illegitimate outcome from HR, comprising of DNA helicases, ATPases, and translocases.

#### 18 **SRS2**

19 The Srs2 (Suppressor of Rad Six) is a well-characterized ATP-dependent helicase that promotes DSB repair  
20 by the SDSA pathway (Fig. 1-3a, 1-4a & 1-5a) (Aboussekhra et al., 1989; Rong et al., 1991; Robert et al.,  
21 2006; Saponaro et al., 2010). Genetic studies revealed an increase of COs and a proportional decrease in  
22 NCOs in yeast *srs2Δ* and a synthetic lethality of *srs2Δ* with a series of mutants involved in DNA repair  
23 (reviewed in Marini and Krejci, 2010; Niu and Klein, 2017). Removal of Rad51 activity can efficiently  
24 suppress these defects, revealing an epistatic interaction between Srs2 and Rad51 (Aboussekhra et al.,  
25 1992). The Srs2 also plays a role during yeast meiosis by preventing the aggregates of Rad51 foci toxic  
26 intermediate during late prophase I (Sasanuma et al., 2019). Interestingly, The loss of Srs2 activity does  
27 not affect Dmc1 behavior during meiosis. Biochemical studies provided direct evidence for the anti-  
28 recombinase functions by showing that Srs2 efficiently dismantles Rad51 presynaptic filaments but not  
29 Dmc1 filaments (Krejci et al., 2003; Veaute et al., 2003; Crickard et al., 2018, 2019b). This strippase activity  
30 of Srs2 is dependent on its translocase function and physical interaction with Rad51 protein. In mammals,  
31 there are no clear homologs of Srs2. Several helicases including RecQL5, hFBH1, and PARI are proposed to



1 play Srs2-like functions. Homologs of Srs2 are conserved in plants and most other eukaryotes (Knoll and  
2 Puchta, 2011). Similar to yeast Srs2 activity, Arabidopsis AtSRS2 is biochemically shown to possess a 3'–5'  
3 helicase and single-strand annealing activity and can process branched DNA structure (Blanck et al., 2009).  
4 However, no *in vivo* role of AtSRS2 has been reported to date. So far, the only characterized mutant in  
5 plants is *Physcomitrium patens srs2Δ*, which shows neither any hypersensitivity against DSB inducing drugs  
6 nor any effect on gene targeting efficiency (Charlot et al., 2014). Thus, *in vivo* function of SRS2 in plants  
7 remains elusive.

## 8 **The FIGL1 complex**

9 The FIGL1 complex consists of two proteins - FIDGETIN-like-1 (FIGL1) and FIDGETIN-like-1 interacting  
10 protein (FLIP) - identified as a novel regulator of the strand invasion process (Yuan and Chen, 2013; Girard  
11 et al., 2015; Fernandes et al., 2018; Kumar et al., 2019). Both FIGL1 and FLIP are evolutionarily conserved  
12 in most eukaryotes except fungi. Interestingly, FIGL1 orthologs are detected in many species without FLIP,  
13 while FLIP systematically co-occurs with FIGL1 (Fernandes et al., 2018). This suggests that the FIGL1  
14 functions may not be fully dependent on FLIP, which might play supporting roles. FIGL1 and FLIP interact  
15 to likely form a complex, the stoichiometry of which is yet unknown. FIGL1 is an unfoldase of the AAA-  
16 ATPases family implicated in the ATP-dependent disassembly of protein aggregates; FLIP harbors a  
17 conserved specific DUF4487 domain (domain of unknown functions). *Figl1<sup>-/-</sup>* and *Flip<sup>-/-</sup>* mice are embryonic  
18 lethal preventing analysis of their cellular functions (<https://www.mousephenotype.org>; MGI:1890648 &  
19 MGI:3590554). However, polymorphisms analysis in mice linked the *Figl1* gene with reduced testis weight  
20 and infertility, suggesting a plausible role of FIGL1 in mammalian meiosis (L'Hôte et al., 2011). Human  
21 FIGNL1 is required for efficient homologous recombination-mediated DNA repair and resistance to  
22 genotoxic drug treatment in somatic cells (Yuan and Chen, 2013). Human FIGNL1 also interacts with  
23 RAD51, and DMC1 (Fernandes et al., 2018) and can disrupt RAD51-ssDNA filaments in biochemical assays,  
24 indicating that FIGNL1 acts as an anti-recombinase (Matsuzaki et al., 2019). The function of mammalian  
25 FLIP is currently unknown.

26 The *Arabidopsis AtFIGL1* and *AtFLIP* genes were discovered in a forward genetic screen designed to identify  
27 anti-crossover factors that limit meiotic CO frequency (Girard et al., 2015). *Atfigl1* and *atflip* mutants  
28 displayed hyper-recombination phenotype with elevated meiotic CO frequency and increased RAD51 and  
29 DMC1 foci number during meiosis. Both *atfigl1* and *atflip* mutants are fertile with a very mild defect in  
30 bivalents formation at metaphase I (Fig. 6b). However, *figl1* and *flip* mutants in rice, pea, and tomato show  
31 sterility phenotype linked to severe chromosome fragmentation at metaphase I, strongly arguing for the

1 critical role of the FIGL1 complex in meiotic DSB repair (Hu et al., 2017; Zhang et al., 2017; Mieulet et al.,  
2 2018). Besides, the FIGL1 complex antagonizes the function of two positive mediators, SDS and BRCA2, in  
3 regulating RAD51 and/or DMC1 focus formation and SC assembly during meiosis (Girard et al., 2015;  
4 Fernandes et al., 2018; Kumar et al., 2019). This antagonism also operates between positive and negative  
5 regulators in somatic cells for HR repair (Kumar et al., 2019; Matsuzaki et al., 2019). Altogether, the FIGL1  
6 complex presents a conserved and likely non-translocase negative regulator of strand invasion, and the  
7 underlying molecular mechanism of which is currently unclear.

## 8 **FANCM**

9 Fanconi anemia group M protein (FANCM) belongs to a family of DNA helicase/translocase with its  
10 orthologs conserved in archaea, yeasts, mammals, and plants (refs. in Xue et al., 2015; Dorn and Puchta,  
11 2019). Genetic studies identified FANCM homologs as a key regulator in suppressing CO formation and  
12 promoting the SDSA pathway during DSB repair in both somatic and/or meiotic cells (Sun et al., 2008;  
13 Prakash et al., 2009; Lorenz et al., 2012). Biochemically, human FANCM and yeast orthologs (budding  
14 yeast, Mph1 and fission yeast, Fml1) share a variety of activities including the dismantling of D-loops in an  
15 ATP hydrolysis-dependent manner (Sung and Klein, 2006; Gari et al., 2008; Prakash et al., 2009). Of note,  
16 Mph1 is capable of disrupting the Rad51-bound D-loop. These biochemical observations support a direct  
17 role of FANCM helicases in channeling D-loops into the SDSA pathway by suppressing CO formation during  
18 HR. Recently, Mph1 is also shown to dissociate precocious D-loops between sister chromatids at meiosis  
19 to ensure recombination between homologous chromosomes (Sandhu et al., 2020).

20 The *Arabidopsis AtFANCM* gene is identified as an anti-crossover factor that suppresses meiotic CO  
21 formation (Crismani et al., 2012; Knoll et al., 2012). The genetic ablation of *FANCM* in *Arabidopsis* resulted  
22 in a 3-fold increase in CO frequency during meiosis (Crismani et al., 2012). *AtFANCM* specifically suppresses  
23 meiotic COs arising from the MUS81-dependent pathway and acts along with its two cofactors, *AtMHF1* &  
24 *AtMHF2* to limit meiotic CO (Girard et al., 2014). Surprisingly, loss of *AtFANCM* activity in a hybrid  
25 background did not lead to an increase in meiotic CO frequency, suggesting that level of heterozygosity or  
26 sequence polymorphism could impair the anti-crossover effect of *FANCM* (Girard et al., 2015; Ziolkowski  
27 et al., 2015). However, the hybrid background effect on the *AtFANCM* activity was alleviated by the loss of  
28 *AtFIGL1* function in double mutants, displaying a multiplicative increase in meiotic COs in the inbred and  
29 hybrid background suggesting they act sequentially (Girard et al., 2015). The role of *FANCM* in limiting  
30 meiotic CO appears to be conserved across plant species as *fancm* mutants in *Brassica napus*, rice, tomato,  
31 and pea crop species show a significant increase in meiotic COs frequency (Blary et al., 2018; Mieulet et

1 al., 2018). Interestingly, the *fancm* mutants in *Lactuca sativa* (Lettuce) display reduced fertility and  
2 univalents at metaphase I, despite having a normal level of class I HEI10 foci, suggesting a divergent role  
3 for FANCM (Li et al., 2021).

#### 4 **RTEL1**

5 RTEL1 (Regulator of Telomere Length 1) was first identified for its role in the maintenance of telomere  
6 length in mice (Ding et al., 2004). RTEL1 is an iron-sulfur cluster containing DNA helicase and a member  
7 within the DEAH subfamily of the superfamily 2 helicases (reviewed in Uringa et al., 2011). RTEL1 is  
8 conserved in most eukaryotes with an exception in budding yeast. The genetic and biochemical properties  
9 of RTEL1 strongly support for anti-recombinase roles of RTEL1 that are crucial for DNA repair beyond its  
10 role in telomere maintenance. The purified human RTEL1 can disrupt D-loop in the presence of calcium  
11 with no detectable disruption activity toward RAD51 nucleofilaments (Barber et al., 2008). In *C. elegans*,  
12 combining *rtel-1* mutation with other HR mutants can cause synthetic lethality phenotype with an  
13 accumulation of RAD-51 foci, suggesting an essential role of RTEL-1 in regulating HR (Wicky et al., 2004;  
14 Barber et al., 2008; Ward et al., 2010). The *C. elegans* RTEL-1 also promotes NCO formation during meiosis  
15 and is needed to enforce the normal distribution and frequency of meiotic COs (Youds et al., 2010).

16 In plants, the Arabidopsis AtRTEL1 homolog has been identified and characterized for its in vivo functions  
17 (Knoll et al., 2012; Recker et al., 2014). AtRTEL1 is essential for telomere elongation and counteracts HR in  
18 somatic cells (Recker et al., 2014). Interestingly, the *Arabidopsis rtel1* mutant when combined with *recq4a*  
19 mutation showed a synthetic lethality phenotype that leads to drastic developmental growth defects  
20 (Recker et al., 2014). During meiosis, downregulation of RTEL1 in barley causes a significant increase of  
21 COs at distal chromosomal regions without a change in total CO numbers (Barakate et al., 2021). However,  
22 it remains elusive how RTEL1 might regulate meiotic COs distribution in plants.

#### 23 **The RECQ4-TOP3-RMI (RTR) complex**

24 The RECQ4-TOP3-RMI complex is well conserved in eukaryotes and is known by different names: the RTR  
25 complex in plants, BTR in mammals, and STR in *S. cerevisiae*. The RTR/BTR/STR complex is a major regulator  
26 that processes early and late recombination intermediates during HR. The function of this complex relies  
27 on a DNA helicase, a topoisomerase (Topoisomerase3 $\alpha$ ; TOP3 $\alpha$ ), and non-catalytic structural protein,  
28 (RecQ-mediated instability 1; RMI1). All three components of this complex can act together and also in an  
29 independent manner. The DNA helicase activity is contributed by the RecQ helicases family: Bloom's  
30 Syndrome Helicase (BLM) in humans, Slow growth suppressor 1 (Sgs1) in *S. cerevisiae*, and RECQ4 in plants.

1 Biochemically, BLM/Sgs1 homologs display DNA structure-specific helicase activity (Karow et al., 1997;  
2 Bennett et al., 1998; Schröpfer et al., 2014), and can dismantle Rad51-ssDNA filament as well as D-loop,  
3 **implicating** them in regulating strand invasion to promote NCO formation (Wu et al., 2001; Bachrati et al.,  
4 2006; Bugreev et al., 2009; Fasching et al., 2015; Crickard et al., 2019b). The BTR/STR complex is also  
5 referred to as “dissolvosome” that dissolves dHJ through the branch migration activity of BLM and the  
6 decatenation activity of TOP3 $\alpha$  (Bizard and Hickson, 2014) (Fig 1.4c). In concordance with these activities,  
7 the genetic ablation of the human *BLM* or the yeast *Sgs1* gene in somatic cells exhibits severe cytogenetic  
8 abnormalities attributed to an elevated level of mitotic CO frequency (Ira et al., 2003; Payne and Hickson,  
9 2009), suggesting that BLM and Sgs1 suppress CO formation. BLM and Sgs1 also have meiotic functions.  
10 Knockout down of the mice *Blm* during meiosis results in improper pairing and synapsis as well as an  
11 increase in chiasmata (Holloway et al., 2010). In yeast, *sgs1* mutant has normal meiotic CO formation but  
12 surprisingly the timing of NCO formation is delayed as compared with the wild-type (De Muyt et al., 2012).  
13 However, the absence of Sgs1 results in the formation of aberrant multichromatid recombination  
14 intermediates, suggesting Sgs1 is critical for preventing illegitimate meiotic recombination (Oh et al., 2007,  
15 2008). Independent of the Sgs1, the TOP3 $\alpha$  and RMI1 subcomplex from humans and yeast can also  
16 promote the dissolution of the D-loop intermediates (Fasching et al., 2015). Aberrant multichromatid  
17 intermediates accumulate due to the inactivation of Top3 $\alpha$  or Rmi1 in meiosis as seen in the absence of  
18 Sgs1, albeit with severe fertility defects in *top3 $\Delta$*  and *rmi1 $\Delta$*  (Kaur et al., 2015; Tang et al., 2015).

19 In plants, RECQ4 helicase shows similar properties to Sgs1 and is best studied in Arabidopsis, which harbors  
20 two RecQ4 homologs, RECQ4A, and RECQ4B (Hartung et al., 2000, 2007). Both AtRECQ4A and AtRECQ4B  
21 play redundant roles in meiotic DNA repair and only simultaneous loss of both AtRECQ4s in the double  
22 mutant resulted in up to a 6-fold increase in meiotic CO frequencies (Séguéla-Arnaud et al., 2015;  
23 Fernandes et al., 2018). Like FANCM, AtRECQ4s suppress COs dependent on MUS81 activity. Further, *recq4*  
24 mutants are shown to increase ~3-fold meiotic COs in rice, pea, and tomato (*Solanum lycopersicum*)  
25 (Mieulet et al., 2018). Certain point mutations in the Arabidopsis *AtTOP3 $\alpha$*  and *AtRMI1* also lead to an  
26 elevated level of meiotic CO frequency indicating that TOP3 $\alpha$ -RMI1 possesses anti-crossover activity  
27 (Séguéla-Arnaud et al., 2015). **The role of TOP3 $\alpha$ -RMI1 has been studied in tomato and points to the**  
28 **differentiation of function of this complex between plant species (Whitbread et al., 2021).**

### 29 ***RAD54 and RDH54***

30 The budding yeast Rad54 and its paralog Rdh54 are two motor proteins of the SWI2/SNF2 helicase family  
31 (**reviewed in Ceballos and Heyer, 2011; Crickard, 2021**). **Both helicases perform pro-recombinogenic**

1 functions during the DSB repair by stabilizing presynaptic filament, mediating strand exchange, and  
2 displacing recombinases from the dsDNA in the D-loop. Genetic and biochemical studies have  
3 corroborated partially redundant and distinct roles of Rad54 and Rdh54. These studies have demonstrated  
4 that Rdh54 preferentially functions with Dmc1 to promote repair between homologs whereas Rad54  
5 stimulates Rad51-mediated repair between sister chromatids (Klein, 1997; Shinohara et al., 1997b, 2000;  
6 Arbel et al., 1999; Bishop et al., 1999; Nimonkar et al., 2012; Crickard et al., 2020). Overall, biochemical  
7 properties of Rad54 and Rdh54 are strikingly similar in terms of ATPase activity, translocation along dsDNA,  
8 remodeling of chromatin by sliding nucleosome, stimulation of D-loop reaction by RAD51 and DMC1, and  
9 removal of RAD51 bound to dsDNA (Solinger et al., 2002; Holzen et al., 2006; Bianco et al., 2007; Nimonkar  
10 et al., 2007, 2012; Santa Maria et al., 2013; Tavares et al., 2019). Recently, direct roles of Rad54 in  
11 homology search have been discovered. Rad54 promotes the binding of RAD51-nucleofilaments to dsDNA  
12 and facilitates homology search in an ATP-dependent translocation along the dsDNA (Crickard et al., 2020).  
13 Whether Rdh54 plays similar roles remains to be identified. Besides the pre-recombinogenic roles, both  
14 translocases are crucial in preventing RAD51 and DMC1 focus formation resulting from the off-pathway  
15 dsDNA binding activity in cells (Holzen et al., 2006; Shah et al., 2010). This erroneous RAD51 binding on  
16 dsDNA causes growth arrest and chromosome loss in the absence of translocase activity (Shah et al., 2010).

17 Homologs of Rad54 and Rdh54 are conserved in other eukaryotes. Fissions yeast and vertebrates have two  
18 paralogs; only one *RAD54* gene is identified in *Drosophila* and *C. elegans*. RAD54 in flies and worms is  
19 essential for meiotic DSB repair and normal fertility (Kooistra et al., 1997) (Mets and Meyer, 2009). On the  
20 contrary, the *Rad54<sup>-/-</sup>*, *Rad54B<sup>-/-</sup>* and *Rad54<sup>-/-</sup> Rad54B<sup>-/-</sup>* double knockout mice are viable and fertile (Essers  
21 et al., 1997; Joanna et al., 2006; Messiaen et al., 2013), suggesting the role of RAD54 may not be fully  
22 conserved in all species. However, human RAD54 translocases have a conserved role in suppressing the  
23 off-pathway RAD51 focus formation in tumor cells (Mason et al., 2015).

24 A clear homolog of RAD54 is identified in plants, while the existence of Rdh54 homologs is difficult to  
25 assess in plant genomes (Table 1). The Arabidopsis AtRAD54 is the best-characterized RAD54 homolog in  
26 plants. AtRAD54 forms foci in living cells upon gamma irradiation (Hirakawa and Matsunaga, 2019).  
27 *Atrad54* mutant display sensitivity to DNA damaging agents and reduced frequency of HR in somatic cells  
28 (Shaked et al., 2005; Osakabe et al., 2006). AtRAD54 interacts with AtRAD51 suggesting that RAD54 may  
29 have a similar role in Arabidopsis somatic cells than in *S. cerevisiae*. Despite the role in RAD51-mediated  
30 DSB repair in somatic cells, AtRAD54 appeared to play a non-essential role during meiotic DSB repair as  
31 *Atrad54* mutants are fertile. However, recent work has reported that the lack of AtRAD54 has no

1 detectable effect on meiosis progression or CO formation and interference but AtRAD54 becomes  
2 essential for the RAD51-mediated repair of meiotic breaks in absence of DMC1 (Hernandez Sanchez-  
3 Rebato et al., 2021). This study argues for the existence of a DMC1-specific RAD54-like plant homolog,  
4 which has remained unidentified so far.

## 5 **5.0 Other regulators**

### 6 **MCM8**

7 Mini-chromosome maintenance (MCM) 8 is a member of the MCM protein family that forms replicative  
8 helicase required for DNA replication. MCM8 is emerging as an important mediator of HR repair and  
9 genome integrity. MCM8 is evolutionarily conserved in most eukaryotes with exception of yeasts and *C.*  
10 *elegans* (Liu et al., 2009). MCM8 was first identified in the *Drosophila melanogaster* as a *recombination*  
11 *defective* (REC) gene. MCM8 deficiency in flies displayed infertility due to a higher level of nondisjunction  
12 attributed to a 95% reduction in meiotic CO formation and increased gene conversion events that have  
13 shorter track lengths than in wild-type flies (Grell, 1984; Blanton et al., 2005). *Drosophila* MCM8 together  
14 with MEI-217 and MEI-218 promote class I CO formation and inhibits class II CO by antagonizing the anti-  
15 CO activity of fly BLM helicase (Kohl et al., 2012; Hartmann et al., 2019). It was proposed that *drosophila*  
16 MCM8 functions at the strand invasion and DNA synthesis step to give rise to CO formation. Consistent  
17 with such roles in meiotic DSB repair, *Mcm8*<sup>-/-</sup> mice are sterile due to gametogenesis arrested in prophase  
18 I with unrepaired breaks judged from an accumulation of DMC1 foci (Lutzmann et al., 2012).

19 MCM8 homologs in plants are also identified. The *Arabidopsis* AtMCM8 plays a role in meiotic DSB repair  
20 as *Arabidopsis Atmcm8* mutant exhibits a limited level of chromosome fragmentation at meiosis (Crismani  
21 et al., 2013). No detectable effect on CO formation was observed in absence of AtMCM8. The DSB repair  
22 defect in the *Atmcm8* mutant is greatly amplified in the absence of DMC1 activity or when DMC1 kinetics  
23 is changed (Crismani et al., 2013). This led to a hypothesis that *Arabidopsis* MCM8 is required for RAD51-  
24 mediated meiotic DSB repair. The precise roles and biochemical properties of MCM8 helicase have been  
25 elusive to date.

### 26 **MSH2**

27 Mismatch repair protein 2 (MSH2) is a principal component of the MutS heterodimers, which are involved  
28 in post-replicative mismatched base correction and rejection of heteroduplex DNA during HR (**Reviewed**  
29 **in** Kunkel and Erie, 2005; Pećina-Šlaus et al., 2020). Msh2 creates two distinct heterodimers - MSH2-MSH6  
30 and MSH2-MSH3 - conserved in eukaryotes. Msh2 exhibits anti-recombinogenic roles during HR. In

1 budding yeast, Msh2 promotes heteroduplex rejection by recruiting DNA helicases, which can dismantle  
2 mismatched D-loops (Myung et al., 2001; Spies and Fishel, 2015; Chakraborty and Alani, 2016; Tham et al.,  
3 2016) suggesting that the MMR machinery can limit HR between sequences with greater divergence. The  
4 loss of the Msh2 activity also impacts both CO and NCO formation during meiosis. Genome-wide analyses  
5 revealed a 20% to 40% increase in the meiotic CO frequency when Msh2 is inactivated in *S. cerevisiae*  
6 hybrids exhibiting around 0.6% sequence divergence (Martini et al., 2011; Cooper et al., 2021). The  
7 comparison of the meiotic CO landscape suggested that Msh2 suppresses class I CO formation in regions  
8 with greater sequence divergence (Cooper et al., 2021). The yeast *msh2* mutant also shows a 3-fold  
9 increase in NCO and shorter conversion tracts relative to wild type (Martini et al., 2011). These results led  
10 to a hypothesis that Msh2 binding could stabilize some mismatch containing recombination intermediates  
11 that are repaired as NCOs with long tracts or COs. In mammals, the *msh2*<sup>-/-</sup> mice show surprisingly no  
12 substantial change in meiotic CO and NCO frequency at two hotspots with (0.6% and 1.8%) different levels  
13 of sequence divergence (Peterson et al., 2020). However, the molecular analysis indicated that MSH2 plays  
14 important role in mismatch corrections during mammalian meiosis. It suggests that MMR may not function  
15 similarly in meiotic cells in different organisms.

16 In plants, MSH2 forms a heterodimer with a plant-specific member MSH7, in addition to MSH3 and MSH6  
17 (Lario et al., 2015). The MMR machinery in plants effectively suppresses HR in somatic cells between  
18 homologous and homeologous sequences contributed by different subgenomes in polyploid species  
19 (Emmanuel et al., 2006; Li et al., 2006; Trouiller et al., 2006). During meiotic HR, the *Arabidopsis Atmsh2*  
20 mutant shows a 40% increase in CO frequency compared with wild type in one interval located at  
21 chromosome 5 (Emmanuel et al., 2006). However, a recent genome-wide analysis revealed no significant  
22 change in the meiotic crossover numbers in the *Arabidopsis Atmsh2* mutants, albeit the local CO  
23 association with elevated polymorphism density was reduced (Blackwell et al., 2020). At the chromosome  
24 level, the CO landscape is altered in absence of AtMSH2. In the *Atmsh2* in different hybrid backgrounds,  
25 CO formation remodels from the diverse pericentromeric regions towards the less-polymorphic sub-  
26 telomeric regions (Blackwell et al., 2020). At megascale, the juxtaposition of the heterozygous and  
27 homozygous regions favors an increase in CO formation in the heterozygous region in wild-type, but not  
28 in *Atmsh2*, showing CO increase in the heterozygous region is MSH2 dependent (Blackwell et al., 2020).  
29 Altogether, this study establishes a pro-crossover role of AtMSH2 in regions of higher sequence diversity.  
30 MSH7 is also implicated in suppressing meiotic recombination between homologous and homeologous  
31 sequences (Lario et al., 2015; Serra et al., 2021). A recent study mapped the *MSH7* gene as a causative  
32 sequence at the *ph2* locus identified in hexaploid wheat species with three subgenomes (Serra et al., 2021).

1 The *ph2* locus promotes meiotic CO formation between homeologous sequences of different subgenomic  
2 origins, generally prevented in wild type. The wheat *msh7* mutant recapitulates the *ph2* phenotype with a  
3 5.5-fold increase in homoeologous recombination at the expense of homologous recombination (Serra et  
4 al., 2021). Thus, MSH7 could assure meiotic stability in newly formed allopolyploids by limiting  
5 recombination between ecotopic or distantly related sequences. In conclusion, the anti-recombinogenic  
6 roles of MMR in somatic cells appear to be conserved in eukaryotes whereas meiotic MMR functions may  
7 differ in different tested organisms. The reasons for these differences are unknown and require further  
8 investigation to understand the relationship between sequence divergence and meiotic recombination.

## 9 **6.0 The potential applications of DSB repair proteins in plant breeding**

10 Plant breeding aims at generating new elite varieties to achieve food security challenges with the world's  
11 growing population and changing climatic conditions. The studies of plant DSB repair proteins provide  
12 means to manipulate genetic variations in plants and hold the potential to drive crop improvements and  
13 productivity. In this section, we describe DSB repair factors exploited for developing new tools for plant  
14 breeding.

15 1) **Reducing meiotic recombination for plant breeding** - DMC1 is a candidate for reverse breeding and  
16 heat tolerance

17 Reverse breeding is based on reducing recombination in the selected hybrid background (Dirks et al.,  
18 2009). Hybrid varieties with the hybrid vigor outperform their inbred parents and are of huge commercial  
19 interest in agriculture. The inactivation of *DMC1* in plants eliminates meiotic crossovers between parental  
20 chromosomes and produces a low amount of viable gametes. In the first step, the gametes obtained from  
21 such plants contain a combination of non-recombinant chromatids and are used for producing double  
22 haploids plants to generate homozygous parental lines. In the second step, homozygous parental lines  
23 were mated to create new or same heterozygous hybrid plant varieties. Thus, Reverse breeding can create  
24 new or reconstitute the original hybrid plants in two main steps (Wijnker et al., 2012). Reverse breeding  
25 allows faster and more efficient production of homozygous parental lines, which can be propagated  
26 indefinitely by breeders.

27 Interestingly, wheat DMC1 is recently identified as a candidate gene that can stabilize meiosis at low  
28 temperatures. The absence of the wheat *DMC1* copy on chromosome 5D exhibited a high level of meiotic  
29 chromosomes without synapsis and univalents at metaphase I at low temperatures (Draeger et al., 2020).



1 This suggests that the *DMC1* gene can serve as an allelic marker for breeders to identify and select cold-  
2 temperature-tolerant wheat varieties.

### 3 2) Increasing meiotic recombination for plant breeding – the inactivation of anti-CO factors

4 Plant breeders traditionally rely on meiotic crossovers to generate novel and favorable haplotypes. Low  
5 frequency and uneven distribution of COs along chromosomes limit genetic variation and have a direct  
6 impact on the speed and efficiency of a breeding program. Therefore, manipulation of COs in a controlled  
7 manner is argued to untapped the genetic diversity which is otherwise inaccessible to breeders. Recent  
8 advances in the field have provided different approaches to manipulate meiotic COs and have been  
9 reviewed elsewhere (Blary and Jenczewski, 2019; Fayos et al., 2019; Taagen et al., 2020). Two anti-CO  
10 factors (FANCM and RECQ4) that negatively regulate strand invasion, and are described in the previous  
11 section, have been proven to be potential candidates for model-to-crop translation to increase CO  
12 frequency. Mutation in the *FANCM* gene can increase several folds in inbred *Arabidopsis* ecotype as well  
13 as crop species such as brassica, rice, and pea. Loss of FANCM is affected by the level of sequence  
14 polymorphism as the *arabidopsis fancm* mutant plants in the hybrid background do not show any increase  
15 in meiotic CO. Unlike FANCM, RECQ4 is not affected by the level of sequence polymorphism and *recq4*  
16 mutant in different species demonstrated the highest increase in CO rates. However, the loss of RECQ4 in  
17 pea seems to affect fertility. Altogether, both helicases provide a toolkit that could be customized to  
18 different crops for plant breeding programs.

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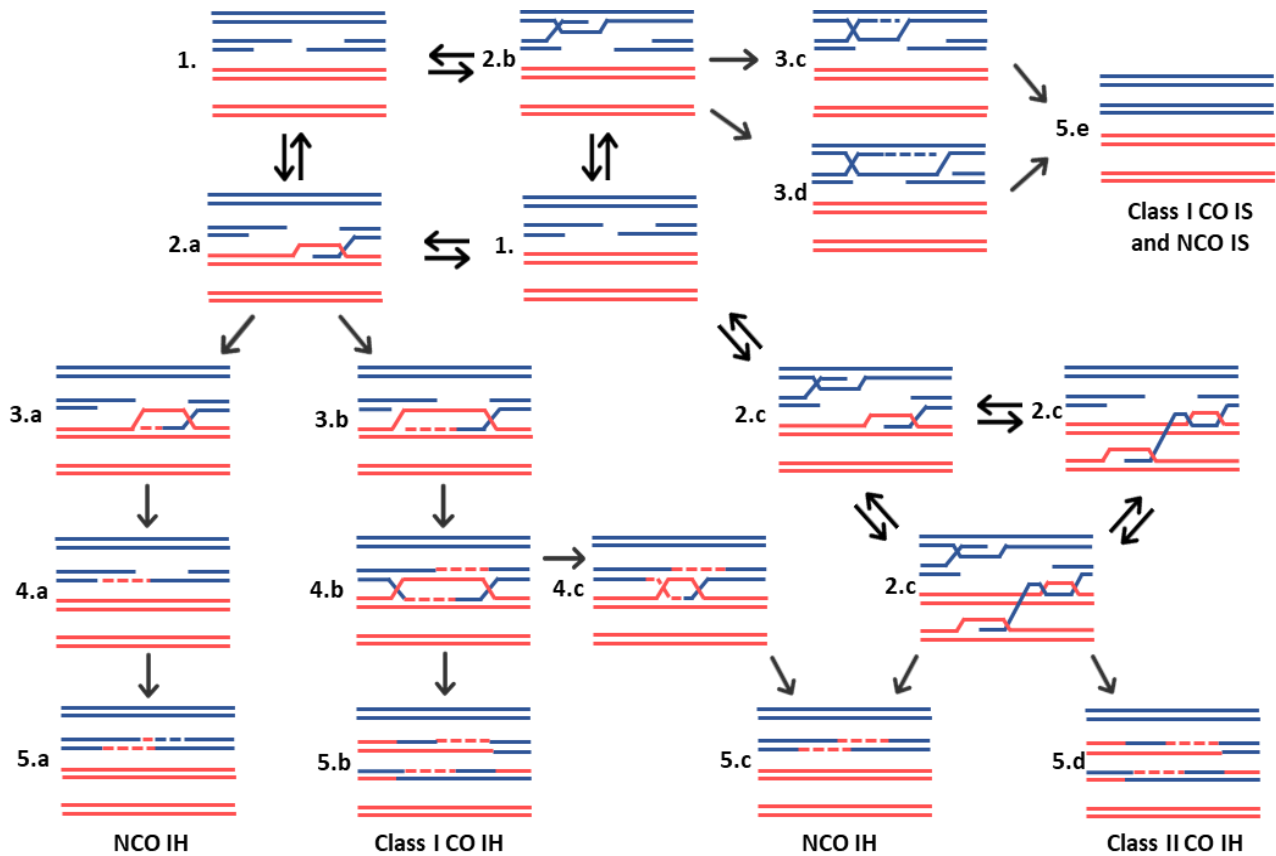
#### 25 **Conflict of Interest:**

26 None declared.

#### 27 **Author's contribution:**

28 RK and CM conceived the review topic and structure. CE, CM, and RK wrote the review. CE prepared Figure  
29 1 and Table 1. Figures 2, 3, 4, 5, and 6 were prepared by RK. CM and RK edited the review. All authors  
30 approved the final version.

1 **Figures:**

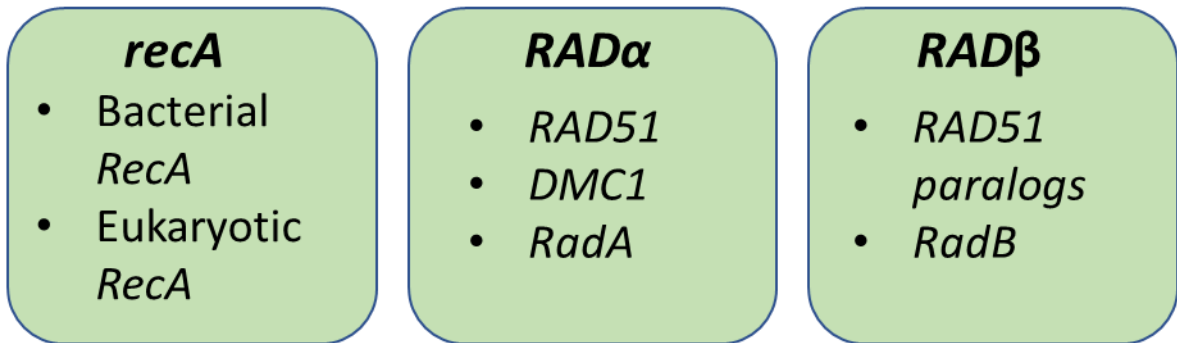


2 **Figure 1: Model of meiotic DSB repair.** Meiotic breaks are repaired using one of two templates -  
 3 homologous chromatid or sister chromatid. Blue and red colors represent homologous chromatids with  
 4 four lines in the same color denoting two DNA strands of each sister chromatid. After DSB formation, the  
 5 resection of 5' ends generates 3' single-strand DNA (ssDNA) tails at DSB sites (1). Invasion of the 3' tails on  
 6 a homolog or sister chromatid followed by a DNA strand exchange can produce interhomolog (IH) or  
 7 intersister (IS) nascent D-loop intermediates, respectively (2a & 2b). Multi-invasion of the 3' tails on a  
 8 homolog and/or sister chromatid can give rise to aberrant recombination intermediates (non-exhaustive  
 9 representation, 2c). The nascent D-loop structures are not very stable but can be extended with DNA  
 10 synthesis primed on the invading 3' end. The disassociation of these D-loops leads to a noncrossover (NCO)  
 11 outcome between IH or IS via synthesis-dependent-strand annealing (SDSA) pathway (3a, 4a & 5a, 3c &  
 12 5e). Alternatively, two types of COs – class I and class II - are formed through the stabilization of IH D-loop  
 13 intermediates. The capture of the second 3' end within the stabilized D-loops (3b & 3d) followed by further  
 14 DNA synthesis and ligation of nicks allow the formation of double Holliday junction (dHJ) intermediates  
 15 (4b). The processing of dHJ can generate CO or NCO repair products. A specific resolution of dHJs leads to  
 16 the formation of class I COs (5b), while the dissolution of dHJ can generate NCO (4c & 5c). IH NCOs and

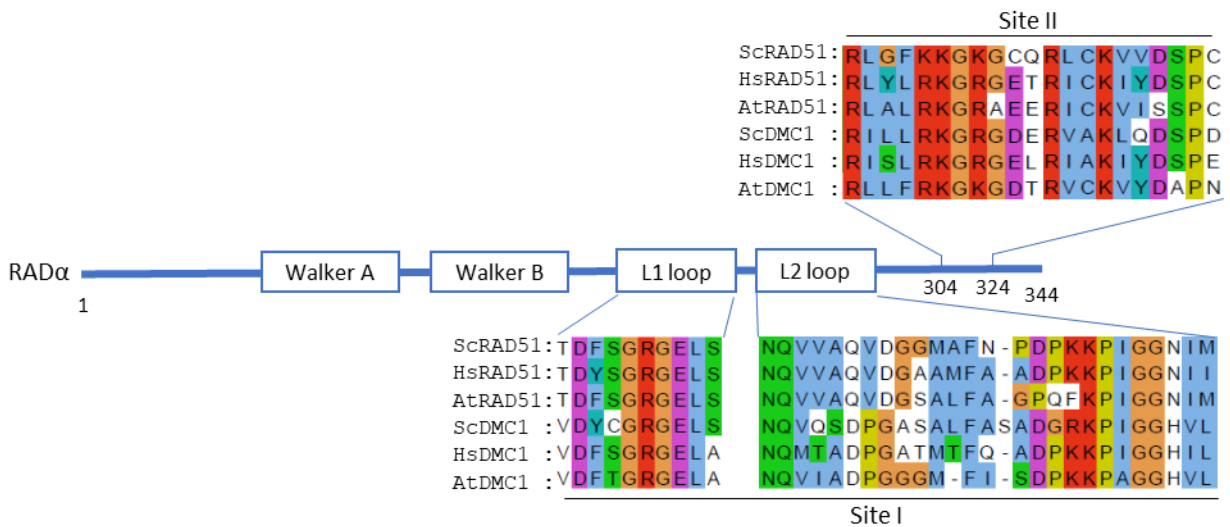
- 1 Class II CO can be generated through the resolution of aberrant/complex recombination intermediates
- 2 **(5d)**. Repair events using sister chromatids are not genetically traceable, but similar biochemical steps are
- 3 involved to generate IS CO and NCO **(5e)**. DSB, double-strand breaks; CO, crossover; NCO, noncrossover;
- 4 IH, interhomolog; IS, intersister
- 5

A

The *recA/RAD51* superfamily



B

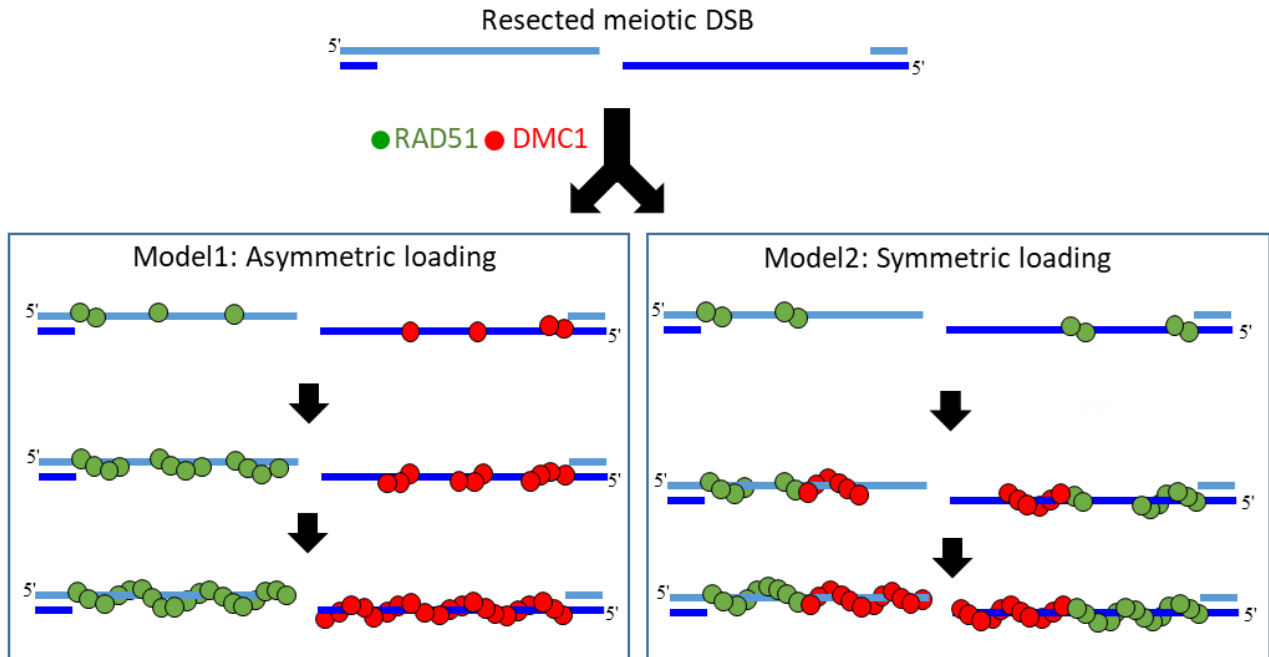


1 **Figure 2. The *recA/RAD51* gene family and the conserved domain architecture of *RADα* members.**

2 A) The *recA/RAD51* gene family is divided into three groups comprising eubacterial, archaeal, and  
 3 eukaryotic genes.

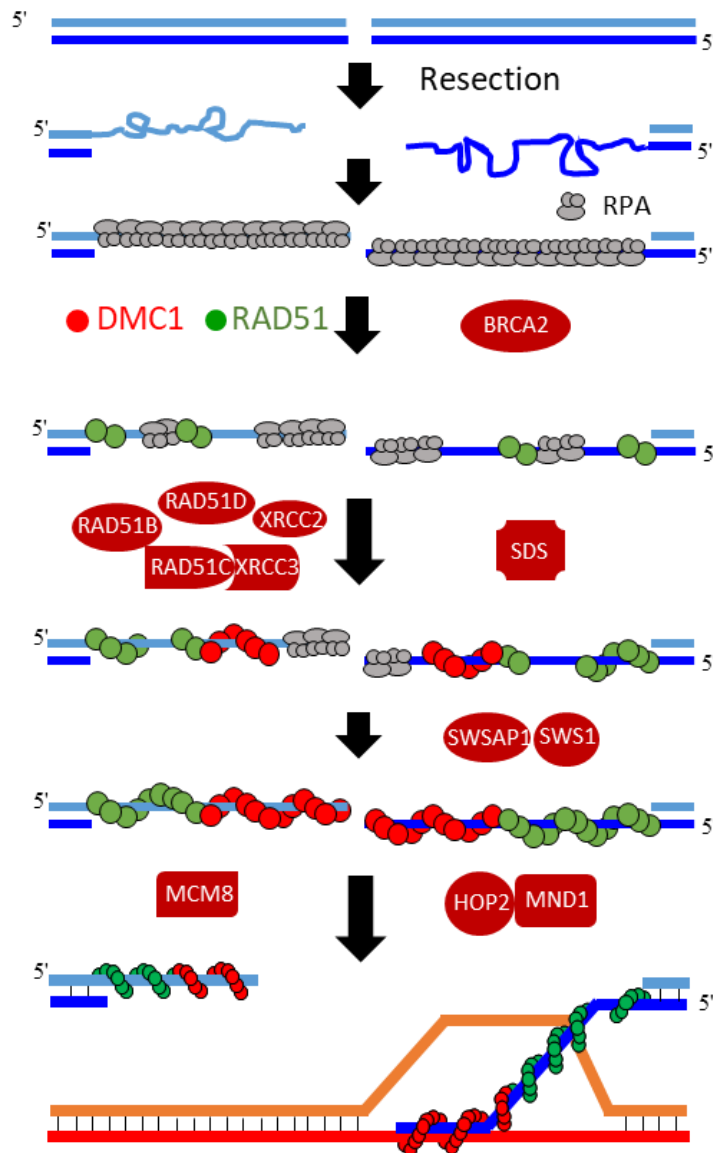
4 B) Organization of the conserved protein domains in eukaryotic *RADα* genes. Two DNA binding sites – site  
 5 I (Loop1 & Loop2) and site II - are located towards the C-terminal. Sequence conservation of both DNA  
 6 binding sites in *RAD51* and *DMC1* is shown from *Arabidopsis thaliana* (At), *Homo sapiens* (Hs),  
 7 *Saccharomyces cerevisiae* (Sc).

8



1  
 2 **Figure 3. The current models of meiotic presynaptic filament organization.**  
 3 After the processing of meiotic DSBs, both RAD51 and DMC1 polymerize on the ssDNA. Two models of  
 4 RAD51 and DMC1 organization at meiotic break sites are presented. Asymmetric model predicts the  
 5 assembly of RAD51 and DMC1 filaments at the two opposite ends of the same DSB. In the symmetric  
 6 model, both RAD51 and DMC1 are assembled at two ends of a DSB resulting in co-paired focus formation  
 7 of two recombinases.

8



1

2 **Figure 4. The positive modulators of the strand invasion step during HR in plants.**

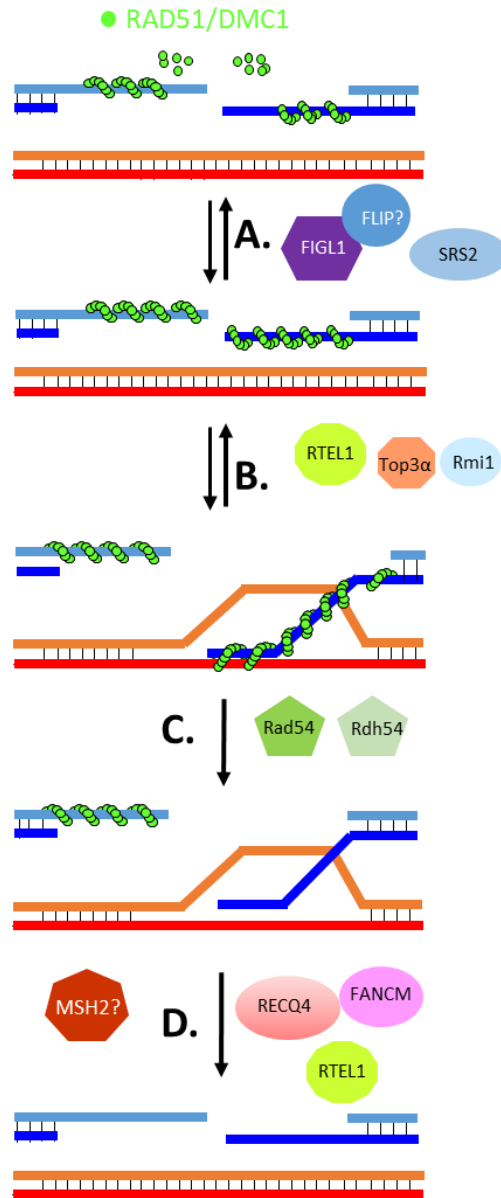
3 Positive modulators from plants are shown in magenta color. The mediator protein facilitates the

4 polymerization of RAD51 and DMC1 on RPA-coated ssDNA. Additional modulators stabilize and protect

5 the nucleofilament of the two recombinases on ssDNA. Modulators are also needed to activate the

6 nucleofilament for homology searches and strand exchanges.

7



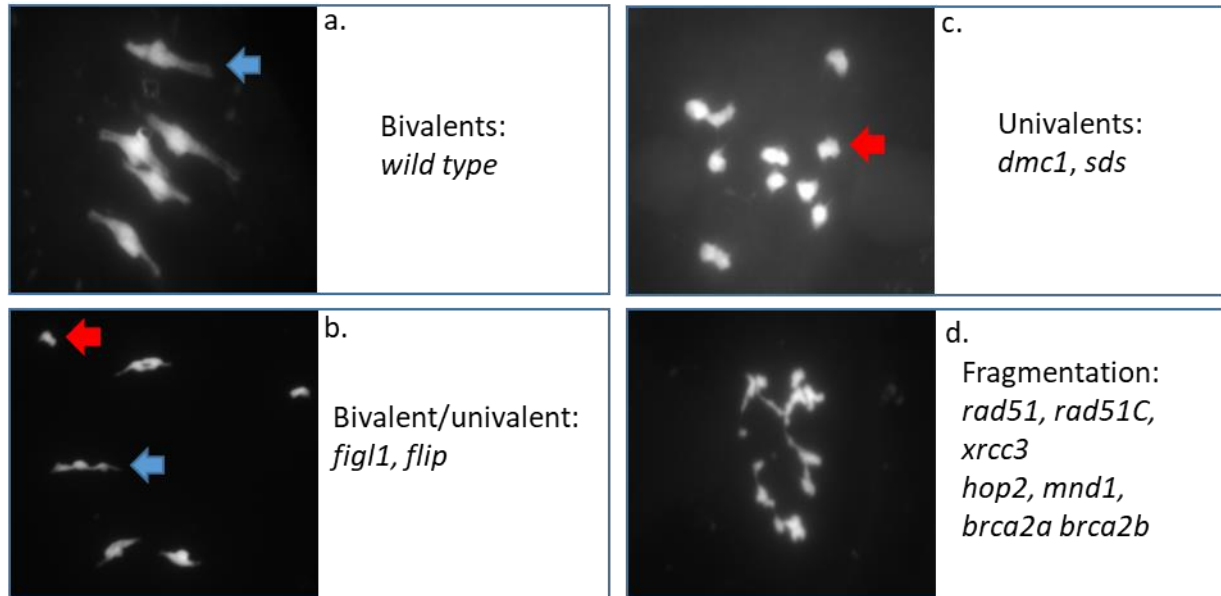
1  
 2 **Figure 5. Negative modulators that dismantle nucleoprotein filaments and D-loop formation during the**  
 3 **meiotic DSB repair.**

4 Various modulators can regulate the homology search and strand invasion process at different steps.

- 5 A. SRS2 helicase and FIGL1 both can disassemble RAD51 nucleoprotein filaments to limit the strand  
 6 invasion process at an early stage. FIGL1 interacts with FLIP to form a complex, and its underlying  
 7 mechanisms to dismantle presynaptic filaments are yet unknown.

- 1 B. After strand invasion, D-loop intermediates bound by Rad51 can be dissolved by the Top3-Rmi1  
2 complex in topoisomerase mediated mechanism. RTEL1 can also dismantle D-loop intermediates  
3 bound by the recombinase.
- 4 C. The pro-recombination Rad54 translocase and its paralog Rdh54 promote homology search and  
5 strand invasion by binding to nucleoprotein filaments. Translocase activity of Rad54 helps to  
6 displace Rad51 from the heteroduplex in D-loop intermediates, leaving 3' end accessible for  
7 initiation of DNA synthesis.
- 8 D. RECQ4, FANCM, and RTEL1 helicase can unwind D-loop intermediates at postsynaptic stages to  
9 promote repair by the SDSA pathway. Mismatch repair machinery protein MSH2 might also act on  
10 the postsynaptic invasion step to correct mismatches in heteroduplex and to suppress CO  
11 formation.
- 12





1

2 **Figure 6. Phenotypes of defects in meiotic DSB repair at metaphase-I in Arabidopsis.**

3 a. Five bivalents held together by CO at metaphase I in Arabidopsis *wild type* meiosis indicate the  
4 completion of meiotic DSB repair with obligate CO formation between homologs.

5 b. Loss of obligate CO formation or a mild reduction in CO formation is represented by four bivalents  
6 and a pair of univalent. *figl1* and *flip* mutant plants display a low frequency of metaphase cells  
7 with bivalents and univalent.

8 c. The presence of 10 univalents at metaphase I result from either a complete lack of meiotic breaks  
9 or repair of meiotic DSB using sister chromatids as observed in Arabidopsis *dmc1* and *sds* mutants.

10 d. Fragmentation of meiotic chromosomes is observed due to incomplete or lack of meiotic break  
11 repair. Mutations in a number of positive modulator genes show strong fragmentation suggesting  
12 that these factors are indispensable for the meiotic break repair.

13 Arrows in blue and red colors indicate bivalent and univalent, respectively.

14

Organism Gene	Arabidopsis	Maize	Rice	Wheat	Tomato	Physcomitrium	Barley
<i>RAD51</i>	•	•••••	••	•••	••	••	•
<i>DMC1</i>	•	•••••	••	••	•	•	•
<i>RAD51B</i>	•	•	•	•••	•	•	•
<i>RAD51C</i>	•	•	•	•••	••	•	•
<i>RAD51D</i>	•	•	•	•••	•	•	•
<i>XRCC2</i>	•	•	•	•••	•	•	•
<i>XRCC3</i>	•	•	•	••••	•	<del> </del>	•
<i>HOP2</i>	•	••	•	•••	•	•	•
<i>MND1</i>	•	•	•	•••	•	•	•
<i>RAD52</i>	••	••••••••	••	••••••••	•••	••	••••••••
<i>RAD54</i>	•	•	•	•••	•	••	••••
<i>BRCA2</i>	••	•	••	•••••	••	<del> </del>	••
<i>Srs2</i>	•	<del> </del>	<del> </del>	<del> </del>	<del> </del>	<del> </del>	<del> </del>
<i>FIGL1</i>	•	•	•	•••	•	•	•
<i>FLIP</i>	•	•	•	••	•	•	•
<i>FANCM</i>	•	•	•	•••	•	•	<del> </del>
<i>BLM/Sgs1</i>	••	•	•	•••	•	•	•
<i>RTEL1</i>	•	•	•		•	•	
<i>DSS1</i>	••	••	•	•	•	•	•

1  
2 Table 1: List of the different known regulators of DMC1 and RAD51 in Arabidopsis and their homologs in  
3 different crops and *Physcomitrium*. Each black dot denotes one copy of the homolog and the crossed-out

1 boxes indicate that homologs of these genes are not identifiable in “the PANTHER” database  
2 (<http://pantherdb.org>).

3

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