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## Meiosis as an Evolutionary Adaptation for DNA Repair

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### 1. Introduction

The adaptive function of sex remains, today, one of the major unsolved problems in biology. Fundamental to achieving a resolution of this problem is gaining an understanding of the function of meiosis. The sexual cycle in eukaryotes has two key stages, meiosis and syngamy. In meiosis, typically a diploid cell gives rise to haploid cells. In syngamy (fertilization), typically two haploid gametes from different individuals fuse to generate a new diploid individual. A unique feature of meiosis, compared to mitosis, is recombination between non-sister homologous chromosomes. Usually these homologous chromosomes are derived from different individuals. In mitosis, recombination can occur, but it is ordinarily between sister homologs, the two products of a round of chromosome replication. Birdsall & Wills (2003) have reviewed the various hypotheses for the origin and maintenance of sex and meiotic recombination, including the hypothesis that sex is an adaptation for the repair of DNA damage and the masking of deleterious recessive alleles. Recently, we presented evidence that among microbial pathogens, sexual processes promote repair of DNA damage, especially when challenged by the oxidative defenses of their biologic hosts (Michod et al., 2008). Here, we present evidence that meiosis is primarily an evolutionary adaptation for DNA repair. Since our previous review of this topic (Bernstein et al., 1988), there has been a considerable increase in relevant information at the molecular level on the DNA repair functions of meiotic recombination, and this new information is emphasized in the present chapter.

### 2. Meiosis in protists and simple multicellular eukaryotes is induced in response to stressful conditions that likely cause DNA damage

Eukaryotes appeared in evolution more than 1.5 billion years ago (Javaux et al., 2001). Among extant eukaryotes, meiosis and sexual reproduction are ubiquitous and appear to have been present early in eukaryote evolution. Malik et al. (2008) found that 27 of 29 tested meiotic genes were present in *Trichomonas vaginalis*, and 21 of these 29 genes were also present in *Giardia intestinalis*, indicating that most meiotic genes were present in a common ancestor of these species. Since these lineages are highly divergent among eukaryotes, these authors concluded that each of these meiotic genes were likely present in the common ancestor of all eukaryotes. Dacks and Roger (1999) also proposed that sex has a single

evolutionary origin and was present in the last common ancestor of eukaryotes. Recently, this view received further support from a study of amoebae. Although amoebae generally have been assumed to be asexual, Lahr et al. (2011) showed that the majority of amoeboid lineages were likely anciently sexual, and that most asexual groups have probably arisen recently and independently.

Eukaryotes arose in evolution from prokaryotes, and eukaryotic meiosis may have arisen from bacterial transformation, a naturally occurring sexual process in prokaryotes. The fundamental similarities between transformation and meiosis have been explored (H. Bernstein & C. Bernstein, 2010). Bacterial transformation, like meiosis, involves alignment and recombination between non-sister homologous chromosomes (or parts of chromosomes) originating from different parents. Both during transformation and meiosis, homologs of the bacterial *recA* gene play a central role in the strand transfer reactions of recombination, indicating a mechanistic similarity. Also, bacterial transformation is induced by environmental stresses that are similar to those that induce meiosis in protists and simple multicellular eukaryotes, suggesting that there was continuity in the evolutionary transition from prokaryotic sex to eukaryotic sex. Evidence indicates that bacterial transformation is an adaptation for repairing DNA (Michod et al., 1988; Hoelzer & Michod, 1991; Michod & Wojciechowski, 1994; reviewed by Michod et al., 2008). Thus meiosis may have emerged from transformation as an adaptation for repairing DNA.

Among extant protists and simple multicellular eukaryotes sexual reproduction is ordinarily facultative. Meiosis and sex in these organisms is usually induced by stressful conditions. The paramecium tetrahymena can be induced to undergo conjugation leading to meiosis by washing, which causes rapid starvation (Elliott & Hayes, 1953). Depletion of the nitrogen source in the growth medium of the unicellular green alga *Chlamydomonas reinhardtii* leads to differentiation of vegetative cells into gametes (Sager & Granick 1954). These gametes can then mate, form zygotes and undergo meiosis. Upon nitrogen starvation or desiccation, the human fungal pathogen *Cryptococcus neoformans* undergoes mating or fruiting, both processes involving meiosis (Lin et al., 2005).

In addition to starvation, oxidative stress is another condition that induces meiosis and sex. The haploid fission yeast *Schizosaccharomyces pombe* is induced to undergo sexual development and mating when the supply of nutrients becomes limiting (Davey et al., 1998). Moreover, treatment of late-exponential-phase *S. pombe* vegetative cells with hydrogen peroxide, which causes oxidative stress, increases the frequency of mating and production of meiotic spores by 4- to 18-fold (C. Bernstein & Johns, 1989). The oomycete *Phytophthora cinnamomi* is induced to undergo sexual reproduction by exposure to the oxidizing agent hydrogen peroxide or mechanical damage to hyphae (Reeves & Jackson, 1974). In the simple multicellular green algae *Volvox carteri*, sex is induced by heat shock (Kirk & Kirk, 1986). This effect can be inhibited by antioxidants, indicating that the induction of sex by heat shock is mediated by oxidative stress (Nedelcu & Michod, 2003). Furthermore, induction of oxidative stress by an inhibitor of the mitochondrial electron transport chain also induced sex in *V. carteri* (Nedelcu et al., 2004). The budding yeast *Saccharomyces cerevisiae* reproduces as mitotically dividing diploid cells when nutrients are plentiful, but undergoes meiosis to form haploid spores when starved (Herskowitz, 1988). When *S. cerevisiae* are starved, oxidative stress is increased and DNA double-strand breaks (DSBs) and apurinic/apyrimidinic sites accumulate (Steinboeck et al., 2010). Perhaps, in *S. cerevisiae*, the induction of sex by starvation is mediated by oxidative stress, analogous to the way induction of sex by heat is mediated by oxidative stress in *V. carteri*.

These observations suggest that meiosis is an adaptation for dealing with stress, particularly oxidative stress. It is well established that oxidative stress induces a variety of DNA damages including DNA DSBs, single-strand breaks and modified bases (Slupphaug et al., 2003). Thus we hypothesize that, in facultative sexual protists and simple multicellular eukaryotes, sex, with the central feature of meiosis, is an adaptive response to DNA damage, particularly oxidative DNA damage.

### **3. DNA damages induced by exogenous agents cause increased meiotic recombination**

If recombination during meiosis is an adaptation for repairing DNA damages, then it would be expected that exposure to DNA damaging treatments would increase the frequency of recombination, as measured by crossovers between allelic markers. Stimulation of allelic recombination was reported in the fruitfly *Drosophila melanogaster* in response to exposure to the DNA damaging agents UV light (Prudhommeau & Proust, 1973), X-rays (Suzuki & Parry, 1964), and mitomycin C (Schewe et al., 1971). X-rays induce recombination in meiotic cells not only of *D. melanogaster* females, but also of males, which normally display no recombination during meiosis (Hannah-Alava, 1964).

Increased meiotic recombination in response to X-irradiation has also been reported in *Caenorhabditis elegans* (Kim & Rose, 1987), and in *S. cerevisiae* (Kelly et al., 1983).

### **4. During mitosis and meiosis, DNA damages caused by diverse exogenous agents can be repaired by homologous recombination**

Molecular recombination (that is homologous physical exchange or informational exchange) during mitosis and meiosis functions as a DNA repair process designated homologous recombinational repair (HRR). Many of the gene products employed in mitotic HRR are also employed in recombination during meiosis. It is this consistent function of recombination across meiosis and mitosis in eukaryotes and transformation in prokaryotes that we seek to understand through the repair hypothesis. Mutants defective in HRR genes in *D. melanogaster* and yeast have reduced ability to repair DNA damages arising from a variety of exogenous sources. These mutants are also defective in recombination during meiosis. In general, loss of HRR capability causes increased sensitivity to killing by agents that harm cells primarily through induction of DNA damage. These agents are listed in Table 1. There have been no reports, that we know of, that HRR defective cells are sensitive to agents that harm cells by mechanisms other than primarily causing DNA damage.

In *D. melanogaster*, mutants defective in genes *mei-41*, *mei-9*, *hdm*, *spnA* and *brca2* have reduced spontaneous allelic recombination (crossing over) during meiosis and increased sensitivity to killing by exposure to numerous DNA damaging agents (Table 1). The Mei-41 protein is a structural and functional homolog of the human Atm (ataxia telangiectasia) protein (Hari et al., 1995), which plays a central role in HRR. The Mei-9 and Hdm proteins are components of a multiprotein complex that resolves meiotic recombination intermediates (Joyce et al., 2009). The SpnA protein is a homolog of yeast Rad51 (Staeva-Vieira et al., 2003), and Rad51 plays a central role in strand-exchange during HRR. The *D. melanogaster* Brca2 protein, a homolog of the human Brca2 protein that protects against breast cancer, regulates the activity of Rad51 protein in HRR. The Brca2 protein is required for HRR of DSBs during meiosis (Klovstad et al., 2008).

In *S. cerevisiae*, numerous mutant genes have been identified that confer sensitivity to radiation and/or genotoxic chemicals (Haynes & Kunz, 1981). Several of these mutant genes are also defective in meiotic recombination. For instance, the *rad52* gene is required for meiotic recombination (Game et al., 1980) as well as for mitotic recombination (Malone & Esposito, 1980). Mutants defective in the *rad52* gene are sensitive to killing by several DNA damaging agents (Table 1). Diploid cells of *S. cerevisiae* are able to repair DNA DSBs introduced by ionizing radiation, and this ability is lost in mutant strains defective in the *rad52* gene (Resnick & Martin, 1976). The Rad52 protein promotes the DNA strand exchange reaction of recombination during meiosis and mitosis (Mortensen et al., 2009).

Taken as a whole, these findings indicate that the products of genes *mei-41*, *mei-9*, *hdm*, *spnA*, and *brca2* in *D. melanogaster* and the *rad52* gene of yeast are required in meiosis for recombination and in somatic cells for HRR of potentially lethal DNA damages. Since the gene products that function in mitotic HRR are able to repair DNA damages from different sources, it can be reasonably assumed that these genes serve a similar DNA repair function during recombination in meiosis.

In the nematode *C. elegans* gonad, oocyte nuclei in the pachytene stage of meiosis, the stage in which HRR occurs, are hyper-resistant to X-ray irradiation compared to oocytes in the subsequent diakinesis stage of meiosis (Takanami et al., 2000). This hyper-resistance depends on expression of gene *ce-rdh-51*, a homolog of yeast *rad51* and *dmc1* that play a central role in meiotic HRR. Meiotic pachytene nuclei are also more resistant to heavy ion particle irradiation than the subsequent meiotic diplotene or diakinesis stages (Takanami et al., 2003). This resistance also depends on the *ce-rdh-51* gene, as well as on gene *ce-atl-1*. *ce-atl-1* is related to *atm* (ataxia -telangiectasia mutated), a gene necessary for repair of DSBs by HRR.

Coogan & Rosenblum (1988) measured repair of DSBs following  $\gamma$ -irradiation of rat spermatogenic cells during successive stages of germ cell formation. The stages were spermatogonia and preleptotene spermatocytes, pachytene spermatocytes and spermatid spermatocytes. The greatest repair capability was observed in pachytene, the stage of meiosis when HRR occurs. These findings indicate that HRR of  $\gamma$ -ray-induced DSBs occurs during meiosis. Several mammalian germ cell stages, including pachytene spermatocytes, produce levels of reactive oxygen species (ROS) sufficient to cause oxidative stress (Fisher & Aitkin, 1997). This observation suggests that HRR during meiosis may also remove DNA damages caused by natural endogenously produced ROS.

The results reviewed in this section indicate that, in both meiosis and mitosis, DNA damages caused by different exogenous agents are repaired by HRR, suggesting that DNA damages from natural endogenous sources (e.g. ROS) are similarly repaired. In general, DNA damage appears to be a fundamental problem for life. As noted by Haynes (1988), DNA is composed of rather ordinary molecular subunits, which are not endowed with any peculiar kind of quantum mechanical stability. He observed that its very "chemical vulgarity" makes DNA subject to all the "chemical horrors" that might befall any such molecule in a warm aqueous medium. The average amount of oxidative DNA damage occurring per cell per day is estimated to be about 10,000 in humans, and in rat, with a higher metabolic rate, about 100,000 (Ames et al., 1993). Most of these damages affect only one strand of the DNA, but a fraction, about 1-2%, are double-strand damages such as DSBs (Massie et al., 1972). These damages can be repaired accurately by HRR.

Organism	Mutant gene	Meiotic recombination	DNA damaging agent(s)	Sensitivity to killing by agent(s)	Reference
<i>D. melanogaster</i>	<i>mei-41</i>	Reduced	X-rays, UV, methyl methanesulfonate, nitrogen mustard, benzo(s)pyrene, 2-acetyl-aminofluorene	Increased	Baker et al., 1976; Boyd, 1978; Rasmuson, 1984
	<i>mei-9</i>	Reduced	X-rays, UV, methyl methanesulfonate, nitrogen mustard, benzo(s)pyrene, 2-acetyl-aminofluorene	Increased	Baker et al., 1976; Boyd, 1978; Rasmuson, 1984
	<i>hdm</i>	Reduced	methyl methanesulfonate	Increased	Joyce et al., 2009
	<i>spnA</i>	Reduced	X-rays	Increased	Staeva-Vieira et al., 2003
	<i>brca2</i>	HRR of DSBs is reduced	X-rays, methyl methanesulfonate	Increased	Klovstad et al., 2008
<i>S. cerevisiae</i>	<i>rad52</i>	Reduced	X-rays, methyl methanesulfonate, crosslinking agent 8-methoxypsoralen plus UV light	Increased	Haynes & Kunz, 1981; Henriques & Moustacchi, 1980; Game et al., 1980

Table 1. Mutants with reduced meiotic recombination and sensitive to killing by specific DNA damaging agents.

### 5. In humans and rodents, defects in HRR enzymes lead to infertility, as would be expected if removal of DNA damages is an essential function of meiosis

About 15% of all couples in the US are infertile, and an important cause of male infertility appears to be oxidative stress during gametogenesis (Makker et al., 2009). During spermatogenesis in the mouse, DNA repair capability declines after meiosis is complete, allowing accumulation of DNA damage (Marchetti & Wyrobek, 2008). Lewis & Aitken (2005) reviewed evidence that DNA damages in the germ line of men are associated with poor semen quality, low fertilization rates, impaired pre-implantation development, increased abortion, and elevated incidence of disease in the offspring including childhood cancer. They noted that the natural causes of this DNA damage are uncertain, but the major candidate is oxidative stress. On the hypothesis that meiosis is an adaptation for DNA repair, it is expected that loss of ability to repair DNA damages during meiosis would have adverse effects, including infertility. Although the finding of such adverse effects is expected on the hypothesis that meiosis is an adaptation for repairing naturally caused DNA

damages, this finding does not prove the hypothesis. Another possibility is that during meiosis damages are introduced in a programmed fashion, leading to HRR. Such HRR may be necessary for proper pairing and segregation of chromosomes, and this process may be required for fertility (see section 8 below).

Inherited mutations in genes that specify proteins necessary for HRR cause infertility (Table 2) indicating that production of functional gametes depends on HRR. Genes *brca1*, *atm*, and *mlh1* are expressed in mitosis, but at a higher level in meiosis, and gene *dmc1* is expressed exclusively in meiosis (Table 2).

Gene	Species	Fold-increased expression in testes vs. somatic cells	Infertility in mutant females/males	References
<i>brca1</i>	Mouse	3×	male mice are infertile	Galetzka et al., 2007; Cressman et al., 1999
<i>atm</i>	human, mouse	4×	females and males in both humans and mice are infertile	Galetzka et al., 2007; Barlow et al., 1998
<i>mlh1</i>	Mouse	1.7×	female and male mice are infertile	Galetzka et al., 2007; Wei et al., 2002
<i>dmc1</i>	Mouse	specific for meiotic cells	female and male mice are infertile	Pittman et al., 1998

Table 2. Mutant genes defective in HRR that cause infertility in human and/or mouse

*Brc1* functions during both meiotic and mitotic recombination. The inheritance of a mutant *brca1* allele substantially increases a woman's lifetime risk for developing breast or ovarian cancer due to a deficiency in HRR of DNA DSBs in somatic cells. Male *brca1* defective mice are infertile due to meiotic failure during spermatogenesis (Table 2), indicating that HRR is necessary during meiosis.

The *Atm* protein acts during both meiotic and mitotic recombination in detection and signaling of DSBs, and is necessary for fertility of females and males in both humans and mice (Table 2). Gametogenesis is severely disrupted in *Atm*-deficient mice as early as the leptoneuma stage of prophase I, resulting in apoptotic degeneration (Barlow et al., 1998).

Mismatch repair protein *Mlh1* (homolog of *E. coli* MutL) is necessary for meiotic recombination (Wei et al., 2002). Mutation in the *mlh1* gene causes blockage at the pachytene stage of meiosis and female and male infertility (Table 2).

*Dmc1* is a meiosis specific gene. *Dmc1* protein (a homolog of *E. coli* RecA protein) functions during meiotic recombination to promote recognition of homologous DNA and to catalyze strand exchange. *Dmc1* deficient female and male mice are infertile due to arrest of gametes in meiotic prophase (Table 2).

The evidence reviewed in this section indicates that defective HRR of DNA damages during meiosis causes infertility.

## 6. Non-crossover (NCO) recombination during meiosis is likely an adaptation for DNA repair

Meiotic recombination appears to be a near universal feature of meiosis [although it may be absent in some situations, such as in *Drosophila* males (Chovnick et al., 1970)]. There are two

major classes of meiotic recombination. If, during recombination, the chromosome arms on opposite sides of a DSB exchange partners, the recombination event is referred to as a crossover (CO). If the original configuration of chromosome arms is maintained, the recombination event is referred to as a non-crossover (NCO) (see Figure 1). The relative occurrence of NCO or CO recombination events is relevant to evolutionary theories of meiosis which assume producing genetic variation is the function of meiosis. NCO events have little effect on linkage disequilibrium (the statistical association of genes at different loci) and so produce very little genetic variation in terms of new combinations of genes. However, CO and NCO events are equivalent from the point of view of HRR.

Data based on tetrad analysis from several species of fungi indicates that the majority (about 2/3) of recombination events during meiosis are NCOs [see Whitehouse (1982), Tables 19 and 38, for summaries of data from *S. cerevisiae*, *Podospora anserina*, *Sordaria fimicola* and *Sordaria brevicollis*]. More recent work also supports a bias towards NCOs during meiosis. In mouse meiosis there are  $\geq 10$ -fold more DSBs than CO recombinants (Moens et al., 2002), suggesting that most DSBs are repaired by NCO recombination. In *D. melanogaster* there is at least a 3:1 ratio of NCOs to COs (Mehrotra & McKim, 2006). These observations indicate that the majority of recombination events are NCOs. These NCOs involve informational exchange between two homologs but not physical exchange, and little genetic variation is created. Thus explanations for the adaptive function of meiosis that focus exclusively on crossing over are inadequate to explain the majority of recombination events.

Andersen & Sekelsky (2010) have argued that a common mechanism called “synthesis dependent strand annealing” (see section 7, below) is employed in both meiotic HRR of the NCO type and mitotic HRR (which is largely of the NCO type), and thus meiotic and mitotic NCOs probably have a similar function. Substantial evidence indicates that HRR during mitosis is an adaptation to repair DNA damages that originate from diverse endogenous and exogenous sources (e.g. endogenous ROS from oxidative metabolism and exogenous X-rays, UV, chemical carcinogens) (see examples in Table 1; also Lisby & Rothstein, 2009). Thus NCO recombination during meiosis, as in mitosis, likely functions to repair of DNA damages from diverse sources.

## 7. NCO recombination likely occurs by synthesis-dependent strand annealing

Molecular models of meiotic recombination have evolved over the years as relevant evidence accumulated. The model that has been most influential in recent decades has been the Double-Strand Break Repair model (Szostak et al. 1983). By this model, during each recombination event two Holliday Junctions (HJs) are formed and resolved (see Figure 1). Thus the Double-Strand Break Repair model can also be referred to as the Double Holliday Junction (DHJ) model. The DHJ model was considered to provide an explanation for both CO and NCO types of recombination events. However, Allers & Lichten (2001) showed that, although CO recombinants are likely formed by a pathway involving resolution of Holliday junctions, NCO recombinants arise by a different pathway that acts earlier in meiosis. Allers & Lichten (2001), McMahill et al. (2007) and Andersen & Sekelsky (2010) have presented evidence that NCO recombinants are generated during meiosis by an HRR repair process referred to as “Synthesis-Dependent Strand Annealing” or “SDSA” (see Figure 1). During SDSA the invading strand from a chromosome with a DSB is displaced from the D-loop structure of an intact chromosome and its newly synthesized sequence anneals to the other side of the break on the chromosome with the original DSB. This process can accurately



repair DNA DSBs by copying the information lost in the damaged homolog from the other intact homolog without the need for physical exchange of DNA. This process contributes little to genetic variation since the arms of the chromosomes flanking the recombination event remain in the parental position.

Youds et al. (2010) presented evidence that the RTEL-1 protein of *C. elegans* physically dissociates strand invasion events, thereby promoting NCO repair by SDSA (Figure 1). HRR events initiated by DSBs consequently divide into two subsets, a larger subset which undergoes SDSA forming NCO recombinants, and a smaller subset which undergo DHJ repair and form CO recombinants. Perhaps SDSA is the preferred mode of HRR for unprogrammed double-strand damages, and DHJ repair is used primarily for programmed DSBs to promote proper chromosome segregation.

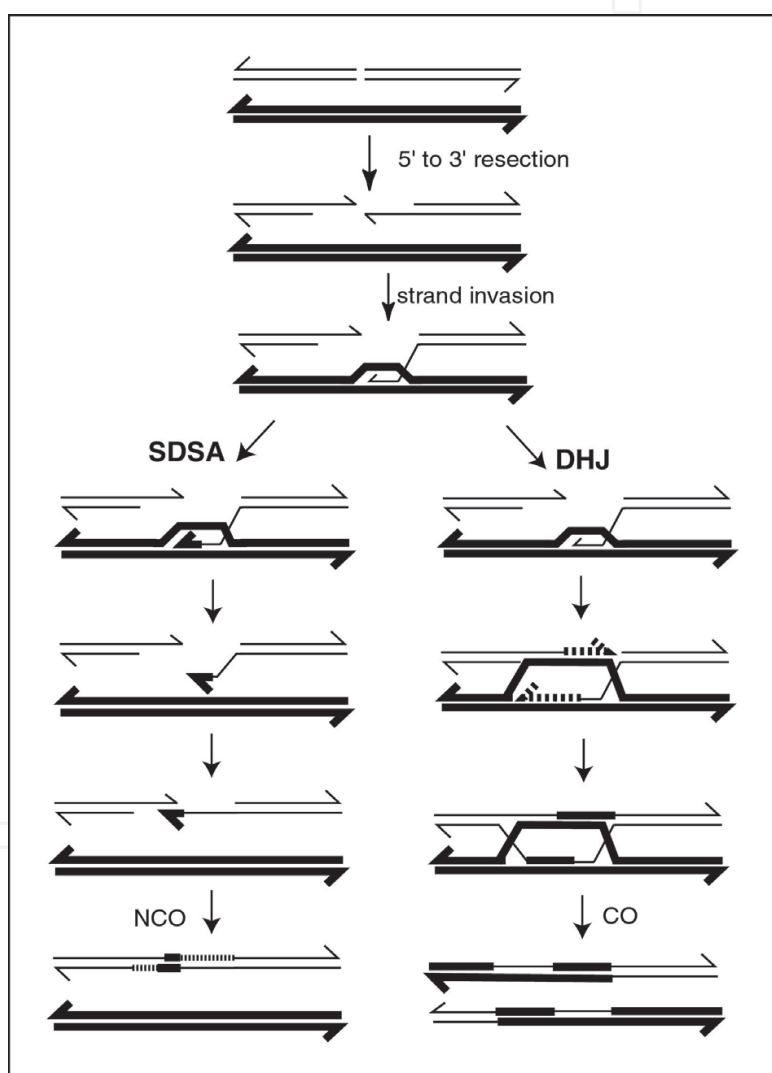


Fig. 1. Current models of meiotic recombination are initiated by a double-strand break or gap, followed by pairing with an homologous chromosome and strand invasion to initiate the recombinational repair process. Repair of the gap can lead to crossover (CO) or non-crossover (NCO) of the flanking regions. CO recombination is thought to occur by the Double Holliday Junction (DHJ) model, illustrated on the right, above. NCO recombinants are thought to occur primarily by the Synthesis Dependent Strand Annealing (SDSA) model, illustrated on the left, above. Most recombination events appear to be the SDSA type.

Although the SDSA model starts with a DSB, it would also be applicable to other types of double-strand damages such as interstrand-crosslinks, or a single-strand damage (e.g. an altered base) opposite a break in the other strand. In principle, both of these types of double-strand damages could be converted by nucleases to a DSB that would then be subject to SDSA.

### **8. The role of Spo11 in promoting accurate DNA repair can also facilitate proper chromosome segregation**

In the budding yeast *S. cerevisiae*, synapsis (pairing of homologous chromosomes) and synaptonemal complex formation depend on Spo11, a nuclease related to type II topoisomerases. Spo11 induces DSBs leading to HRR events of the CO type that form the physical association between homologs (chiasmata) needed for synaptonemal complex formation and proper disjunction of non-sister homologs at the first meiotic division. On the basis of these properties of Spo11, it is sometimes assumed that the primary function of meiotic recombination is to promote synapsis. However, as reviewed by Barzel & Kupiec (2008), this theme cannot be generalized, as synapsis occurs independently of Spo11 induced recombination in the nematode worm *C. elegans* and the fruitfly *D. melanogaster*. In *C. elegans*, synapsis between homologs occurs normally in a *spo-11* mutant (Dernburg et al., 1998). The *D. melanogaster* gene *mei-W68* encodes a *spo11* homolog (McKim & Hayashi-Hagihara, 1998). In *D. melanogaster* females, meiotic chromosome synapsis occurs in the absence of *mei-W68* mediated CO recombination (McKim et al., 1998). Electron microscopy of oocytes from females homozygous for *mei-W68* mutations that eliminated meiotic recombination revealed normal synaptonemal complex formation. In *D. melanogaster* females, meiotic recombination does not appear to be necessary for synapsis. Since the role of Spo11 is of substantial interest in current discussions of the adaptive significance of meiotic recombination, we offer a speculation on its possible role consistent with the DNA repair hypothesis. As shown in Figure 1, both the DHJ and SDSA models for HRR start with a DSB. During meiosis in *S. cerevisiae*, DSBs are formed by a process that usually depends on Spo11. In *S. pombe*, Spo11 homolog Rec12 generates meiotic recombinants and meiosis specific DSBs. In *C. elegans*, a Spo11 homolog seems to have a similar role. We propose that DNA damages of various types are converted to DSBs, a “common currency,” in order to initiate their recombinational repair (see also H. Bernstein et al., 1988). Spo11 appears to be employed in this process. Our reasoning is based on the precedents of the well-established pathways of nucleotide excision repair and base excision repair. In nucleotide excision repair, the initial steps of the pathway involve recognition of a wide variety of bulky damages followed by their removal to generate a single-strand gap, the “common currency” which is then repaired by a gap filling process. In base excision repair, a variety of altered bases are recognized by a corresponding variety of DNA glycosylases that generate an intermediate apurinic/apyrimidinic site, the “common currency” for further repair. On this reasoning, formation of DSBs by a Spo11-dependent process is part of an overall DNA repair sequence. In those species where the resolution of meiotic HRR by CO recombination is beneficial in promoting proper chromosome segregation at the first meiotic division, we think this benefit arose secondarily to the primary benefit of accurate DNA repair.

The function of recombination as a repair process may have arisen very early in the evolution of life [perhaps in the RNA world (H. Bernstein et al., 1984)], and the function of promoting synapsis during meiosis probably arose later in evolution in some eukaryotic lineages. If, in mammals, a major function of meiotic CO recombination, as distinct from NCO recombination, is to promote synapsis and proper chromosome segregation, then one might expect CO events to be localized to specific hot-spot sequences. Hot-spot determinants may also include specific proteins that bind to hot-spot sequences and facilitate CO recombination such as Prdm9 (Hochwagen and Marals, 2010). It is estimated that, in humans, the average number of endogenous DNA DSBs per somatic cell occurring at each cell generation is about 50 (Vilenchik & Knudson, 2003). This rate of DSB formation likely reflects unprogrammed damages, such as may be caused by ROS, and can be taken as an indication of the level of unprogrammed DSBs present in cells undergoing meiosis as well. In the human genome 25,000 hotspots for meiotic recombination have been identified (Myers et al., 2006). The average number of CO recombination events per hotspot is one CO event per 1,300 meioses. The large number of recombination hotspots is consistent with a wide distribution of sites vulnerable to unprogrammed DNA damage as well as specific sites where recombination would need to be induced to promote synapsis. A challenge for future research is the identification of the types of natural damages and programmed damages, and their frequencies, that are removed by CO recombinational repair during meiosis.

### **9. During meiosis, CO recombination can repair DNA damages independently of Spo11**

In a *spo11* mutant of *S. cerevisiae*, the meiotic defects in recombination and synapsis are alleviated by X-irradiation, indicating that X-ray induced DNA damages can initiate CO recombination leading to synapsis independently of Spo11 (Thorne & Byers, 1993). Also, in *C. elegans*, Spo11 is required for meiotic recombination, but radiation induced-breaks alleviate this dependence (Dernberg et al., 1998). These findings indicate that unprogrammed DNA damages induced by X-rays can be repaired by HRR during meiosis independently of Spo11. In both *S. pombe* and *C. elegans*, mutants deficient for Spo11 undergo meiotic CO recombination when single base lesions of the type dU:dG are produced in their DNA (Pauklin et al., 2009). This recombination does not involve production of large numbers of DSBs, but does require uracil DNA-glycosylase, an enzyme that removes uracil from the DNA backbone and initiates base excision repair. These authors proposed that base excision repair of a uracil base, an abasic site, or a single-strand nick are sufficient to initiate meiotic CO recombination in *S. pombe* and *C. elegans*.

In a Rec12 (Spo11 homolog) mutant strain of *S. pombe*, meiotic recombination can be restored to near normal levels by a deletion in *rad2* that encodes an endonuclease involved in Okazaki fragment processing (Farah et al., 2005). Both CO and NCO recombination were increased, but DSBs were undetectable. On the basis of the biochemical properties of Rad 2, these authors proposed that meiotic recombination can be initiated by non-DSB lesions, such as nicks and gaps, which accumulate during premeiotic DNA replication when Okasaki fragment processing is deficient.

In general the findings reviewed in this section indicate that DNA damages arising from a variety of sources can be repaired by meiotic HRR of the CO type, and that this repair may occur independently of Spo11.

## 10. DNA repair likely provides the strong short-term advantage that maintains meiosis, while genetic variation may provide a long-term advantage

Evolutionary explanations for sex have often assumed that the adaptive advantage of meiosis arises from the genetic variation produced. A variety of models and reviews have been presented in this active area of research (e.g. Barton & Charlesworth, 1998; Otto & Gerstein, 2006; Agrawal, 2006). However, Otto & Gerstein (2006) have also pointed out that in a fairly stable environment, individuals surviving to reproductive age have genomes that function well in their current environment. They raise the question of why such individuals should risk shuffling their genes with those of another individual, as happens during meiotic recombination. This consideration, and others, have led many investigators to question whether production of genetic diversity is the principal adaptive advantage of sex. Heng (2007) and Gorelick & Heng (2010) reviewed evidence that sex actually decreases most genetic variation. Their view is that sex acts like a coarse filter, weeding out major changes, such as chromosomal rearrangements, but allowing minor variation, such as changes at the nucleotide or gene level (that are often neutral), to flow through the sexual sieve. Thus, they consider that sex acts as a constraint on genomic variation, thereby limiting adaptive evolution.

We consider that the major adaptive advantage of meiosis is enhanced recombinational repair. In contrast to the variation hypothesis, DNA repair provides an appropriate explanation for the adaptive advantage of sex (and meiosis) in the short-term, since its benefits are large enough (removal of DNA damages that would be deleterious/lethal to gametes or progeny) to plausibly balance the large costs of sex. The large costs of sex include the “cost of males” (Maynard Smith, 1978; Williams, 1975), “recombinational load” that arises from the randomization of genetic information during sex and loss of coadapted gene complexes (Shields, 1982), the cost of mating (Bernstein et al., 1985b), and cost of sexually transmitted disease (Michod et al., 2008).

The hypothesis that meiosis is an adaptation for DNA repair can be consistently applied to all organisms that have sex, including the facultative sexual organisms discussed above, as well as species that undergo meiosis but experience little or no outcrossing, as described below. If, in the long-term, the genetic variation produced by sex increases the rate of adaptation, as proposed by a number of authors (Goddard et al., 2005; Colegrave et al., 2002; Kaltz & Bell, 2002; Cooper et al., 2005; de Visser & Elena, 2007; Peters & Otto, 2003), this would be an added benefit. However, in the short-term, we consider it unlikely that the benefit of variation is large enough to maintain sex.

In nature, many organisms that undergo meiosis outcross only rarely or not at all. In these cases, meiosis generates little or no genetic variation. In the budding yeast *S. cerevisiae*, outcrossing sex, in contrast to inbreeding sex, appears to be very infrequent in nature. Ruderfer et al. (2006) estimated that the ancestors of three *S. cerevisiae* strains outcrossed in nature only about once every 50,000 generations. On the other hand, mating between closely related yeast cells is likely to have been much more common in nature. Mating can occur when haploid cells of opposite mating types, MAT $\alpha$  and MAT $a$ , come into contact. As pointed out by Zeyl & Otto (2007), mating between closely related cells is common for two reasons; (1) the close physical proximity of cells of opposite mating type from the same ascus (the sac that contains the products from a single meiosis), and (2) homothallism, the ability of haploid cells of one mating type to produce daughter cells of the opposite mating type. Thus, in nature, the meiotic events that produce little or no recombinational variation

are much more frequent than meiotic events that do produce recombinational variation. This disparity is consistent with the idea that the primary adaptive function of meiosis in *S. cerevisiae* is HRR of DNA damages, since this benefit is realized in meiosis resulting from either inbreeding or outcrossing. If the primary adaptive function of meiosis were to generate genetic variation, it is difficult to understand how the complex process of meiosis could be selectively maintained in *S. cerevisiae* during the many generations in which there is no outcrossing.

Various levels of inbreeding due to consanguineous mating are known in many species. One extreme, but well studied, example among vertebrate species is the Mangrove Killifish, *Kryptolebias marmoratus*, which inhabits brackish water mangrove habitats from Brazil to Florida. These fish produce sperm and eggs by meiosis and reproduce routinely by self-fertilization. Each hermaphroditic individual normally fertilizes itself when a sperm and egg that it has produced by an internal organ unite inside the fish's body (Sakakura et al., 2006; for review see Avise, 2008). In this highly inbred hermaphroditic species meiotic recombination does not produce significant allelic variation, suggesting that meiosis is retained for some other adaptive benefit.

In higher plants, outcrossing sexual reproduction is the most common mode of reproduction, but about 15% of plants undergo meiosis and are principally self-fertilizing (C. Bernstein & H. Bernstein, 1991). We infer from these examples that the generation of genetic variation is not likely to be the adaptive benefit maintaining meiosis in these organisms. However, meiosis may be maintained by the adaptive benefit of HRR of DNA damage, since this benefit does not depend on outcrossing, nor that the participating chromosomes carry different alleles.

The meiotic function of repairing DNA damages primarily acts to preserve the existing genome. The generation of new genomic variants, a consequence of recombinational repair processes, appears to be a secondary effect that may provide a benefit in the long-term.

As discussed above, most HRR events during meiosis are of the NCO type, which generate minimal genetic variation compared to the CO type. This is consistent with the DNA repair hypothesis, since both the CO and NCO types of recombination can repair DNA. On the assumption that the generation of variation is the primary benefit of meiosis, the majority of HRR events, those of the NCO type, provide no significant benefit and hence are wasteful.

Even though, during meiosis, the frequency of CO recombination is ordinarily substantially less than the frequency of NCO recombination, during mitosis the frequency of CO compared to NCO recombination is even lower (e.g. Virgin et al., 2001; Prado et al., 2003). The higher frequency of CO recombinants during meiosis compared to mitosis may reflect the role of CO recombinants in promoting synapsis during meiosis (see section 8, above), a process distinct to meiosis.

## **11. During meiosis, HRR may remove a class of damages that cannot be accurately repaired during mitosis**

HRR during meiosis offers unique advantages compared to HRR during mitosis, based on the opportunity for non-sister homologs to pair and recombine during meiosis, which does not happen during mitosis. In mitosis, HRR involves interaction between the sister-chromosomes formed upon DNA replication. Thus, in mitosis, HRR is limited to the phases of the cell cycle during DNA replication (S phase) and after DNA replication (G2/M). Prior to DNA replication (G1 phase) in mitosis, double-strand DNA damages, such as DSBs, are

repaired by an inaccurate process, non-homologous end-joining (NHEJ), which generates mutation. Double strand damages arising after DNA replication, may be repaired during mitosis by HRR between sisters (Tichy et al., 2010). However, meiotic recombination can cope in a non-mutagenic way with double strand damages which arise at any point in the cell cycle.

Meiotic G1 phase cells appear to be more resistant to the lethal effects of X-irradiation than mitotic G1 phase cells (Kelly et al., 1983). This finding suggests that repair of DSBs is more efficient during meiotic than mitotic G1 phase, as DSBs are a common consequence of X-irradiation. We speculate that during meiosis, in contrast to mitosis, double-strand damages occurring prior to DNA replication may be accurately repaired by HRR because pairing occurs between non-sister chromosomes. If this is so, meiotic cells have the advantage, compared to mitotic cells, of being able to accurately and efficiently repair double-strand damages that occur both before and after replication. As a result, germ cells would tend to be protected against the mutagenic effect of inaccurate NHEJ that typically occurs prior to replication in mitotic cells.

Mao et al. (2008) presented evidence that one type of somatic cell, human fibroblasts, utilizes error-prone NHEJ as the major DSB repair pathway at all cell cycle stages. In these cells, HRR is nearly absent prior to replication (G1 phase) and is used, when it occurs, primarily in the S phase. Even after the S phase when two sister-chromosomes are present (the G2/M phase), NHEJ is elevated and HRR is in decline.

The situation is somewhat different in mammalian embryonic stem (ES) cells compared to differentiated somatic cells (Tichy et al., 2010). ES cells give rise to all of the cell types of an organism. Because mutations at this early embryonic stage are passed on to all clonal descendents, they can be seriously detrimental to the organism as a whole. Therefore robust mechanisms are needed in ES cells for reducing DNA damages (or eliminating damaged cells) in order to reduce mutations. Mouse ES cells were found to predominantly use high fidelity HRR to repair DSBs, compared to somatic cells that predominantly used NHEJ (Tichy et al., 2010). Furthermore mouse ES cells lack a G1 checkpoint and do not undergo cell-cycle arrest upon receiving DNA damage prior to DNA replication. Rather, they undergo p53-independent apoptosis in response to DNA damage (Aladjem et al., 1998). Consistent with these findings, mouse ES stem cells have a mutation frequency about 100-fold lower than that of isogenic mouse somatic cells (Cervantes et al., 2002), but, as discussed next, at a likely cost resulting from somatic selection against cells with unreparable DSBs which arise before DNA replication.

These results imply that a low mutation rate is achievable in mitotic cells by using apoptosis to remove cells with DNA damages that are present prior to replication, and using HRR, rather than NHEJ, to remove double-strand damages present subsequent to DNA replication. The non-sister chromosomes present in every diploid somatic cell during mitosis, in principal, might pair and undergo accurate HRR (as in meiosis), but this does not ordinarily occur, presumably because, in somatic cells, the benefit is outweighed by costs [e.g. loss of heterozygosity and expression of deleterious recessive alleles including those leading to cancer]. Meiosis is therefore unique, in that DNA damages occurring both prior to and after DNA replication can be subject to high fidelity HRR between non-sister homologs. This would avoid the high costs of both deleterious mutation and loss of potential gametes due to apoptosis.

In humans at each cell division, 30,000-50,000 DNA replication origins are activated (Mechali et al., 2010). Thus the chromosome is ordinarily replicated in segments. We

postulate that any segment containing a DSB will fail to complete its replication until the DSB is repaired. This limited and temporary blockage of replication may result directly from the break itself, or occur as a response to regulatory events set off by proteins that specifically bind to the broken ends. In any case, HRR can be carried out during the subsequent prophase I stage of meiosis, when the segment containing a DSB pairs with a non-sister homologue. This repair would then allow chromosome replication to be completed.

## **12. DNA damage during the mitotic divisions of the germ line in multicellular organisms**

In multicellular eukaryotes there are typically many mitoses during germ line development, and only a single final meiosis leading to gamete formation. During the mitotic cell divisions in the germ line, DSBs and other double-strand damages occurring after DNA replication are likely repaired by HRR or eliminated from the cell lineage by death and/or apoptosis of the damaged cell. We have argued above (section 11) that because of the lack of pairing of non-sister homologs during mitosis, HRR is unable to accurately repair double-strand damages occurring before replication. Thus when double-strand damages occur prior to replication during the mitotic divisions in the germ line the consequence will be either increased mutation or increased apoptosis. By analogy with the strategy used by somatic stem cells (section 11, above), we think that the preferred strategy during these mitotic divisions is likely to be apoptosis, since this avoids mutations in the germ line that could be passed on to progeny. However, double-strand damages occurring prior to replication during meiosis need not lead to apoptosis (which would likely decrease fecundity), since these can be accurately repaired by HRR between non-sister chromosomes. The consequence will be enhanced gamete viability and fecundity, that is, enhanced fitness. In the mitotic divisions of the germ-line prior to meiosis, loss of cells due to DNA damage-induced apoptosis need not be very costly to organism fitness, since such losses could be made up by extra cell divisions of undamaged cells. However, the loss of sperm or egg cells due to unrepaired DNA damage would likely have substantial costs to fitness due to loss of fertility and progeny, as discussed above in section 5.

## **13. Why is meiosis frequently associated with outcrossing?**

While the focus of this article is on the adaptive benefit of meiosis itself, we briefly consider why meiosis is frequently associated with outcrossing, where the chromosomes involved in recombination come from different unrelated parents in a prior generation. Previously, we discussed examples of meiosis occurring in association with inbreeding and self-fertilization. Meiosis with inbreeding will be favored when the costs of mating are high (e.g. the cost of finding a mate at low population density). These examples of inbred meiosis were presented to illustrate our argument that meiosis provides an adaptive advantage (accurate DNA repair) independent of whether significant recombinational variation is also produced. However, meiosis is often associated with outcrossing, and we now consider why.

A disadvantage of inbreeding, especially of self-fertilization, is expression of deleterious recessive mutations, resulting in inbreeding depression. Analysis of the effects of masking deleterious recessive mutations (genetic complementation) using heuristic modes and arguments indicated that complementation provides benefits sufficient to maintain

outcrossing (H. Bernstein et al., 1985a, 1987; Michod, 1995). However, more explicit population genetic models have raised some issues that are in need of further clarification. In population genetics terms, the basic effect of outcrossing is to bring populations to Hardy-Weinberg (HW) equilibrium. Thus, outcrossing can be beneficial if there is another force that pushes the population away from HW equilibrium (generating either an excess or a deficit of heterozygotes) and if it's advantageous to go closer to HW equilibrium. One possible force that generates departure from HW equilibrium is dominance: for example if deleterious alleles tend to be recessive, after selection there will be an excess of heterozygotes (and a deficit of homozygotes). However in this case outcrossing is costly in the short term (because it tends to expose deleterious alleles), but beneficial in the long term (because purging them becomes more efficient). Otto (2003) showed that under this scenario high rates of outcrossing are favored only if deleterious alleles are weakly recessive (dominance close to 0.5). Another potential force pushing away from HW equilibrium considered by Roze and Michod (2010) is gene conversion which creates homozygosity. Gene conversion could result from mitotic HRR between sister chromosomes as discussed above. In this case (and if deleterious alleles tend to be partially recessive) outcrossing is beneficial in the short term (because it masks deleterious alleles) but disadvantageous in the long term (because purging is less efficient). The magnitude of this force may be estimated from rates of loss of heterozygosity during development [discussed in Roze and Michod (2010)]. The few estimates which exist indicate that the loss of heterozygosity is low, and thus this selective force for outcrossing may be weak. Clearly, we need more estimates of this critical parameter to know how large this force for outcrossing may be.

Another consequence of outcrossing is the generation of new genetic variants which may provide an additional long-term advantage.

#### **14. The special case of asexual bdelloid rotifers**

Bdelloid rotifers are common invertebrate animals. They are apparently obligate asexuals that reproduce by parthenogenesis. These organisms are extraordinarily resistant to ionizing radiation (Gladyshev and Meselson, 2008). This resistance appears to be a consequence of an evolutionary adaptation to survive desiccation in ephemerally aquatic habitats. Such desiccation causes extensive DNA breakage, which they are able to repair. Bdelloid primary oocytes are in the G1 phase of the cell cycle and thus lack sister chromatids. Welch et al. (2008) proposed a mechanism of repair involving interaction of non-sister co-linear chromosome pairs, which are maintained as templates for repair of DNA DSBs caused by the frequent desiccation and rehydration. Thus although these organisms apparently lack sex and meiosis, an essential feature of meiosis, HRR between non-sister homologs appears to be retained.

#### **15. Conservation among eukaryotes of RecA-like proteins as key components of the HRR machinery acting during meiosis**

Sex appears to be universally based on RecA-like proteins. RecA-like proteins play a key role in HRR, and the HRR machinery and its mechanism of action appear to be highly conserved among eukaryotes. The *rad51* and *dmc1* genes in the eukaryotic yeasts *S. cerevisiae* and *S. pombe* are orthologs of the bacterial *recA* gene. The *dmc1* gene is found in



many different eukaryote species, and has been reported, for instance, in the protists *Giardia*, *Trypanosoma*, *Leishmania*, *Entamoeba* and *Plasmodium* (Ramesh et al., 2005). Rad51 and Dmc1 proteins are recombinases that interact with single-stranded DNA to form filamentous intermediates called presynaptic filaments, and these filaments initiate HRR (Sauvageau et al., 2005; San Filippo et al., 2008). Dmc1 recombinase functions only during meiosis, whereas Rad51 recombinase acts in both somatic HRR and in meiosis. When it functions in meiosis, Rad51 mainly uses a sister chromosome for HRR. In contrast, Dmc1 mainly uses the non-sister homologous chromosome. The yeast Rad51 recombinase catalyzes ATP-dependent homologous DNA pairing and strand exchange, as does the bacterial RecA recombinase (Sung, 1994). The tertiary structure of the Dmc1 recombinase has an overall similarity to the bacterial RecA recombinase (Story et al., 1993). These observations suggest that the bacterial RecA that functions in the bacterial sexual process of transformation, and the yeast Rad51 and Dmc1 recombinases that act in meiosis have similar functions, consistent with the idea that meiotic recombination evolved from simpler sexual processes in bacteria.

We next consider evidence that RecA orthologs play a key role in meiosis, not only in protists, but also in multicellular eukaryotes. RecA orthologs act in meiosis in a range of animals (e.g. nematodes, chickens, humans and mice) and plants (e.g. *Arabidopsis*, rice and lilies). The *rad51* gene is expressed at a high level in mouse testis and ovary, suggesting that Rad51 protein is involved in meiotic recombination (Shinohara et al., 1993). In mice, mutations in the *dmc1* gene cause sterility, failure to undergo intimate pairing of homologous chromosomes and an inability to complete meiosis (Pittman et al., 1998; Yoshida et al., 1998; see also Table 2). In the nematode *C. elegans*, resistance to DNA damage caused by X-irradiation in the meiotic pachytene nuclei depends on a RecA-like gene (Takanami et al., 2000). RecA gene orthologs are also expressed in chicken testis and ovary and in human testis. In humans, Dmc1, the meiosis-specific recombinase, forms nucleoprotein complexes on single-stranded DNA that promote a search for homology and carry out strand exchange, the two necessary steps of genetic recombination (Sehorn et al., 2004; Bugreev et al., 2005).

In lily plants, genes *lim15* and *rad51* are orthologs, respectively, of the *dmc1* and *rad51* genes of yeast. The lily proteins Lim15 and Rad51 colocalize on chromosomes in various stages of meiotic prophase I, and form discrete foci (Terasawa et al., 1995). The proteins of these foci are considered to participate in the search for, and pairing of, homologous sequences of DNA. In another plant, *Arabidopsis thaliana*, meiotic recombination requires Dmc1 (Couteau et al., 1999) and Rad51 (Li et al., 2004). In the rice plant, an ortholog of *dmc1* is necessary for meiosis and has a key function in the pairing of homologous chromosomes (Deng and Wang, 2007).

In general, both animals and plants have RecA-like proteins that appear to have a central function in meiotic HRR. Furthermore, bacterial RecA and its animal and plant orthologs have very similar roles in the HRR events during the sexual processes of bacterial transformation and eukaryotic meiosis. In all cases, the RecA protein or RecA-like protein assembles on single-stranded DNA to form a pre-synaptic filament. This filament then attaches to a duplex DNA molecule and searches for homology in its target. When the presynaptic molecule locates an homologous sequence in the duplex molecule, it is able to form a DNA joint [Figure 2]. These joints are then processed further to complete the HRR event.

## Transformation in Bacteria      Meiosis in a Eukaryote

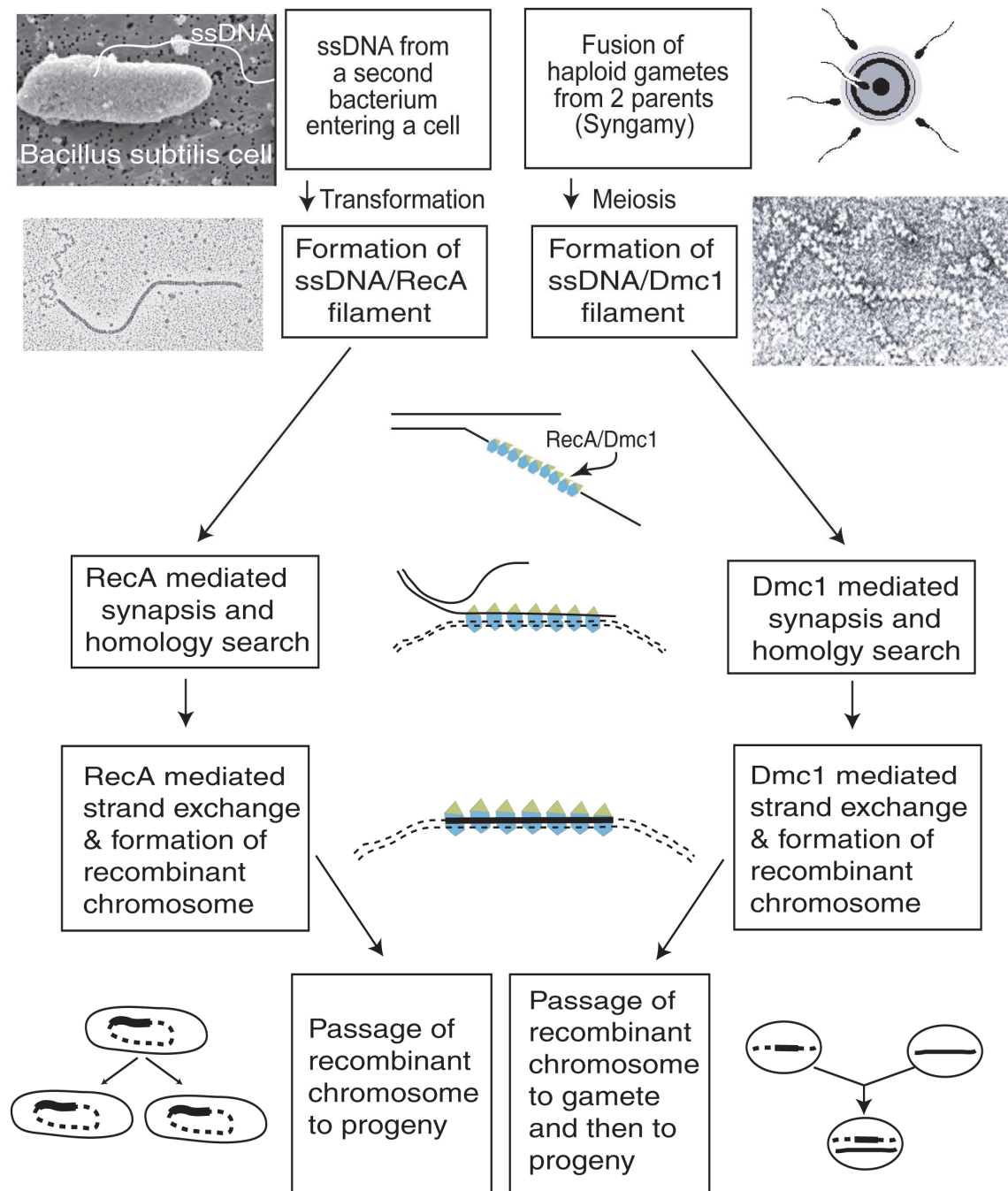


Fig. 2. Conservation of the key components of the HRR machinery during the sexual process of transformation in bacteria and during meiosis in eukaryotes. The bacterial RecA protein or the eukaryotic RecA-like protein, Dmc1, assembles on single-stranded DNA to form a pre-synaptic filament. This filament then attaches to a duplex DNA molecule and searches for homology in its target. When the pre-synaptic molecule locates an homologous sequence in the duplex molecule, it is able to form a DNA joint. These joints are then processed further to complete the HRR event.

## 16. Summary

Currently there is no general agreement among biologists on the adaptive function of sex. Meiosis, a key stage of the sexual cycle, involves close pairing and physical recombination and information exchange between homologous chromosomes ordinarily derived from two different parents. Fundamental to solving the problem of why sex exists is achieving an understanding of the function of meiosis.

A primitive form of meiosis was likely present early in the evolution of eukaryotes, perhaps in the single-celled ancestor of all eukaryotes that arose from ancestral bacteria over 1.5 billion years ago. Meiosis may be derived from bacterial transformation, a prokaryotic sexual process that promotes homologous recombinational repair of DNA as shown in Figure 2. Among extant single-cell eukaryotes, meiosis and facultative sex are ubiquitous. Entry into the sexual cycle ordinarily occurs in response to stressful conditions, such as oxidative stress, that tend to be associated with DNA damage. Thus meiosis may be an adaptation for dealing with such stresses and the resulting DNA damages. Consistent with this idea, exposure of eukaryotes to various DNA damaging agents increases meiotic recombination. Both in mitosis and meiosis, DNA damages caused by different exogenous agents are repaired by HRR, suggesting that DNA damages from natural sources (e.g. ROS) are also repaired by HRR. The consistent function of recombination in DNA repair across meiosis and mitosis in eukaryotes, and transformation in prokaryotes, is what we seek to understand through the repair hypothesis.

Defective HRR during meiosis causes infertility in humans and rodents, suggesting that removal of DNA damages is an essential function of meiosis. The majority of HRR events during both mitosis and meiosis are of the NCO type. NCO recombination is able to repair DNA damages from diverse sources. Furthermore NCO recombination likely occurs by synthesis-dependent strand annealing, a mechanism that involves a small exchange of information between two chromosomes but not physical exchange of DNA. Explanations of the adaptive function of meiosis that focus exclusively on crossing over, the minority of recombination events, are inadequate to explain the majority, the NCO type.

The Spo11 protein, a nuclease, produces DSBs that can initiate recombination and promote proper chromosome segregation. We speculate that Spo11 is part of a process that converts a variety of types of DNA damages to a “common currency,” the DSB, which is then subject to HRR. During meiosis, DNA damages arising from a variety of sources can be repaired by HRR of the CO type, and this repair may occur independently of Spo11.

Genetic variation produced by meiotic recombination may provide a long-term benefit at the population level by reducing linkage disequilibrium and providing gene combinations on which selection can more effectively act, but the short-term adaptive benefit that maintains the machinery of meiosis is likely DNA repair. In contrast to mitosis, meiosis may allow greater accuracy in the repair of DNA damages, since double-strand damages occurring prior to DNA replication can, in principle, be accurately removed by HRR between non-sister homologous chromosomes, a process that is largely unavailable during mitosis.

Among different species, meiosis is frequently associated with outcrossing. This probably reflects the benefit of masking deleterious recessive alleles. However, numerous species that undergo meiosis are largely inbreeding or self-fertilizing. This implies that meiosis provides a benefit (accurate DNA repair) independently of the benefit of outcrossing and masking deleterious recessive alleles.

Animals and plants have RecA-like proteins that have key functions in meiotic recombination involving homology recognition and strand exchange. The function of these eukaryotic proteins is similar to the bacterial RecA protein that acts during the bacterial sexual process of transformation, further suggesting that eukaryotic meiosis may have evolved from simpler sexual processes in bacteria.

## 17. Conclusion

DNA damages appear to be a ubiquitous and serious problem for all of life. We consider that the heightened ability of meiosis to repair such damages in the DNA to be passed on to the next generation is a capability sufficient to explain its widespread occurrence.

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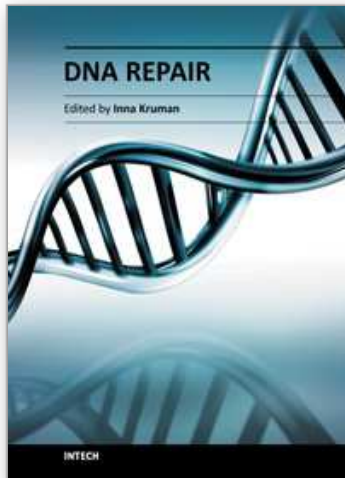
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