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Review

Roles of the DNA mismatch repair and nucleotide excision repair proteins during meiosis

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Abstract. Numerous proteins are involved in the nucleotide excision repair (NER) and DNA mismatch repair (MMR) pathways. The function and specificity of these proteins during the mitotic cell cycle has been actively investigated, in large part due to the involvement of these systems in human diseases. In contrast, comparatively little is known about their functioning during meiosis. At least three repair pathways operate during meiosis in the yeast *Saccharomyces cerevisiae* to repair mismatches that occur as a consequence of heteroduplex formation in recombination. The first pathway is similar to the one acting during postreplicative mismatch repair in mitotically dividing cells, while two pathways are responsible for the repair of large loops during meiosis, using proteins from MMR and NER systems. Some MMR proteins also help prevent recombination between diverged sequences during meiosis, and act late in recombination to affect the resolution of crossovers. This review will discuss the current status of DNA mismatch repair and nucleotide excision repair proteins during meiosis, especially in the yeast *S. cerevisiae*.

Key words. Meiosis; recombination; DNA mismatch repair; nucleotide excision repair; yeast.

Introduction

Cells possess a number of systems designed specifically to detect and eliminate errors in DNA. Two systems that have received a large amount of attention are DNA mismatch repair (MMR) and nucleotide excision repair (NER). Mutations in genes involved in these repair pathways have been implicated in a number of diseases. For example, mutations in the DNA mismatch repair gene *hMSH2* are associated with the onset of hereditary nonpolyposis colon cancer [1]. Similarly, the human disease xeroderma pigmentosum (XP) results from alterations in any of a number of genes involved in nucleotide excision repair (reviewed in [2–5]).

DNA mismatch repair and nucleotide excision repair pathways that operate during the mitotic cell cycle have been well characterized in both prokaryotes and eukaryotes. The MMR system acts to remove base-base mismatches and small loops that occur as a consequence of strand slippage during replication [6–8]. The NER system acts to repair bulky lesions, such as thymine dimers generated by ultraviolet (UV) irradiation (reviewed in [9]).

While the functioning of many of the proteins involved in these systems has been elucidated in some detail in mitotically growing cells, their activity in meiosis is not as well understood. During meiotic recombination in the yeast *Saccharomyces cerevisiae*, mismatches arise as a consequence of heteroduplex formation. Base-base mismatches and small loops are recognized and repaired by a repair system analogous to the MMR system that functions during vegetative growth. In addition, a second repair pathway corrects large loop mismatches; this pathway involves both MMR and NER components in

a novel interaction. Genetic evidence indicates that there is at least one more pathway for large loop repair. Mismatch repair proteins are also involved in crossover resolution late in recombination and in preventing recombination between diverged sequences.

An overview of DNA mismatch repair

The genes involved in mitotic postreplicative MMR were first identified and characterized in *Escherichia coli* (reviewed in [7, 9]). A model for DNA mismatch repair is diagrammed in figure 1. A mismatch that occurs as a consequence of a DNA replication error is detected and bound by the MutS protein. Hemimethylated sites, resulting from lack of methylation of the newly synthesized DNA strands, are bound by the MutH protein. MutS then recruits MutL, and the DNA surrounding the mismatch is looped out until the complex encounters a MutH protein, which stimulates a nuclease function of MutH to nick the strand containing the mismatch. Specificity for the reaction is provided by the methylated sites bound by MutH, ensuring the removal of the newly synthesized strand containing the mistake. Exonucleolytic activity followed by DNA synthesis finishes the correction of the mismatch.

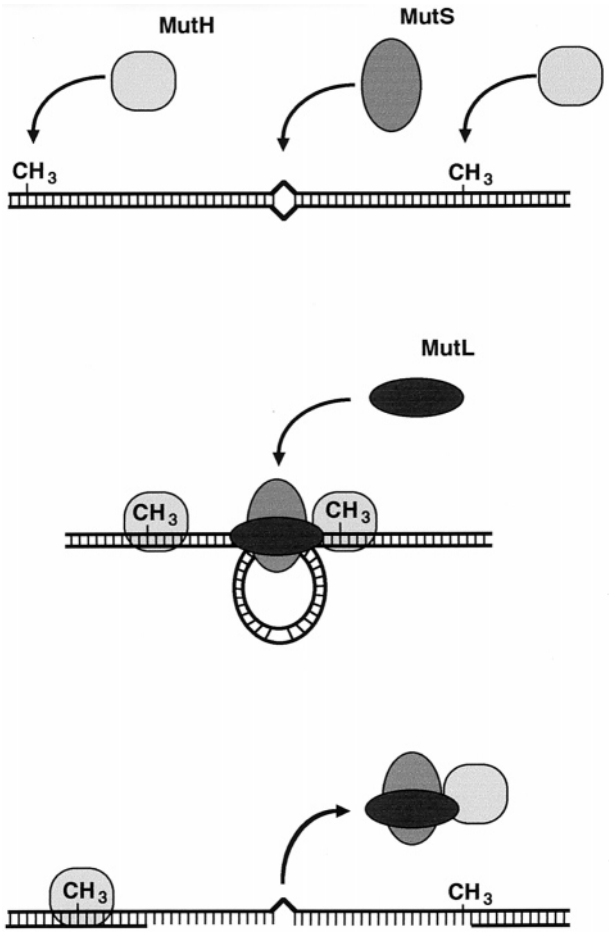

Figure 1. A model for the mitotic postreplicative DNA mismatch repair system in prokaryotes (reviewed in [7, 9]). A mismatch is bound by a *mutS* protein (grey oval), whereas hemimethylated sites are bound by *mutH* proteins (light grey boxes). A *mutL* protein (dark grey oval) is recruited to the mismatch-*mutS* complex, and the DNA surrounding the mismatch is looped out until a *mutH* protein is encountered, which nicks one strand of the DNA. The bases on the newly synthesized strand then are removed to allow correction of the mismatch.

The DNA mismatch repair system in eukaryotes is more complex than in prokaryotes, as eukaryotes possess multiple homologues of the *mutS* and *mutL* proteins (table 1) (reviewed in [7, 10]). The mitotic MMR pathway has been extensively investigated in the budding yeast *Saccharomyces cerevisiae*, but homologues from other organisms are being identified and characterized as well. Many studies of DNA mismatch repair in yeast have taken advantage of the observation that mismatches occur at an elevated rate in tracts of simple sequence [11] (DNA in which from 1 to 14 nucleotides are tandemly reiterated), providing a defined substrate for the analysis of repair events. Yeast possesses seven homologues of the bacterial *mutS* protein (*MSH1* to *6* and *HSM3*), and four homologues of the *mutL* protein (*PMS1*, and *MLH1* to *3*). No homologues of the *mutH* protein have been identified. Yeast does not appear to methylate its DNA [12]; it has been suggested that the specificity during repair is provided by nicks remaining in the DNA following Okazaki fragment RNA primer removal after replication [7]. The nuclease activity provided by *mutH* in prokaryotes has not been identified in eukaryotes.

The genetic and physical interactions among the various *mutS* and *mutL* homologues in yeast in mitotically dividing cells have been characterized. Deletion of *MSH2*, *MLH1* or *PMS1* leads to severe defects in DNA mismatch correction. Double (*msh2 mlh1*, *msh2 pms1* or *mlh1 pms1*) and triple (*msh2 pms1 mlh1*) mutants have phenotypes similar to the single mutants. Mutation of *MSH3* or *MSH6* has less severe consequences, but *msh3 msh6* double mutants exhibit phenotypes equivalent to those of single mutants in the other genes [6, 13–15].

Msh2p has been shown to associate with DNA oligonucleotides containing a range of mismatches [16]. Msh2p can also complex with Msh6p to recognize small mismatches; this interaction involves a helix-turn-helix domain within Msh2p [17]. The *MLH1* and *PMS1* proteins are physically associated, and bind Msh2p when it is complexed with a DNA mismatch [18]. The *MLH1* and *PMS1* proteins interact at their carboxy termini [19].

Table 1. DNA mismatch repair genes.

Bacterial gene	*S. cerevisiae* gene	Human gene	Mitotic cell cycle function	Meiotic function
mutS	*MSH1*	?	mitochondrial stability	unknown
	MSH2	hMSH2	MMR: up to 14 base loops	base-base, small and large loop correction homeologous recombination
	MSH3	hMSH3	MMR: loops up to 14 bases	base-base and small loop correction
	MSH4	hMSH4	none	crossover resolution
	MSH5	?	none	crossover resolution
	MSH6	hMSH6	MMR: base-base mismatches	base-base and small loop correction
	HSM3	?	mutator	unknown
mutL	*PMS1*	hPMS2	MMR: up to 14 base loops	base-base and small loop correction homeologous recombination
	MLH1	hMLH1	MMR: up to 14 base loops	base-base and small loop correction crossover resolution
	MLH2	?	unknown	unknown
	MLH3	?	MMR: frameshifts (with *MLH1* in *MSH3* pathway)	unknown

These data led to a model for postreplicative MMR in yeast [8, 13, 14]. Work from a number of labs indicates that yeast possesses at least two tetrameric protein complexes that function to remove mismatches or small unpaired DNA loops arising from uncorrected mistakes during DNA replication. Both protein complexes contain two MutL homologues, Pms1p and Mlh1p (but see the discussion below of Mlh3p), and the MutS homologue Msh2p. One complex also contains the Msh3 protein, while the other contains the Msh6 protein. Complexes containing Msh6p effect the repair of base-base mismatches and single base loops, while Msh3p complexes repair loops up to a loop size of 14 bases [8].

The other *mutS* and *mutL* homologues are involved in other processes. The *HSM3* gene, which bears weak similarity to the other *mutS* homologues, may function in a repair pathway distinct from *PMS1* [20]; no meiotic phenotypes have been reported for *HSM3*. The *MSH1* gene product functions in the maintenance of mitochondrial DNA [21], while the *MSH4* and *MSH5* genes affect meiotic recombination (discussed below) but appear to have no role in MMR during the mitotic cell cycle [22, 23]. *MLH2* and *MLH3* were detected during the sequencing of the yeast genome (*Saccharomyces* Genome Database). Recently the Mlh3 protein was shown to interact with the Mlh1 protein. Genetic evidence indicates that the *Mlh1-Mlh3* protein complex may act in the *MSH3*-dependent MMR pathway. One possible model for the action of Mlh3p is that it replaces Pms1p in the Msh2p-Msh3p-Mlh1p-Pms1p tetramer during repair of a subset of frameshift mutations [24]. A role for the product of the *MLH2* gene has not yet been determined.

An overview of nucleotide excision repair

The NER pathway (fig. 2) is responsible for the removal of bulky, DNA helix-disrupting lesions such as those caused by UV irradiation, although it can also repair damage caused by a number of other agents (reviewed in [4, 5, 9, 25]) and some lesions that are not helix disrupting [26]. Most of the major components of NER have been identified in yeast and in higher eukaryotes. The reaction performed by the NER complex has been reconstituted in vitro [27]. In yeast NER has been best characterized in regions of the genome that are transcriptionally active, although a second, less well characterized, system exists that deals with lesions that occur at any location in the genome during any portion of the cell cycle.

DNA damage, such as a pyrimidine dimer resulting from exposure to UV radiation, is recognized and bound by Rad14p in yeast [28, 29]. The DNA in the vicinity of the lesion is unwound by a helicase (possibly the helicases encoded by either the *RAD3* [30] or *SSL2* [31] genes). The damaged strand is then excised by two endonucleases. In yeast DNA 5′ to the site of damage is cleaved by the Rad1p-Rad10p complex [32, 33], whereas DNA on the 3′ side is cleaved by Rad2p [34], liberating a short oligonucleotide containing the lesion. The single-stranded region then undergoes repair synthesis and ligation. This system functions most efficiently in regions of actively transcribed DNA, perhaps because a number of the gene products involved in NER are also components of the TFIIH transcription factor complex [35]. In yeast eight gene products make up this complex: the products of *TFB1*, *2*, and *3*, *SSL1* and *2*, *RAD3*, *KIN28*, and *CCL1*.

In addition to the transcription-coupled NER reaction described above, another nucleotide excision system ex-

ists to remove lesions that occur in transcriptionally silent regions of the genome. A number of yeast genes have been implicated in this type of repair, including *RAD4*, *RAD7*, *RAD16*, and *RAD23* [35, 36]. Mutations in this group of genes usually result in less severe phenotypes than mutations in other NER genes. Recently global genomic repair of lesions in humans was shown to be initiated by a complex of proteins containing XPC and HHR23B; this complex detected lesions prior to the action of the XPA protein [37]. Yeast has homologues of these genes (table 2), but their function has not been determined in *S. cerevisiae*.

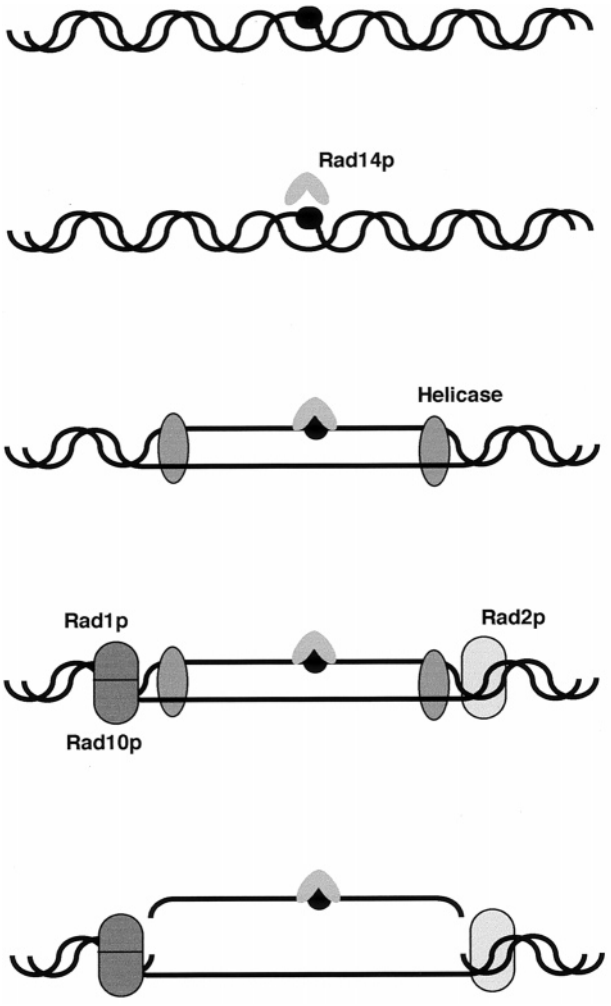

Figure 2. A model for nucleotide excision repair system in *Saccharomyces cerevisiae* (reviewed in [4, 5, 9, 25]) A bulky lesion in DNA is recognized and bound by the *RAD14* protein. A helicase activity (possibly the Rad3 or Ssl2 protein) unwinds the DNA locally. Two endonucleases (the Rad1p-Rad10p complex and the Rad2p enzyme) bind to the junction between single-stranded to double-stranded DNA and make a nick in the strand containing the lesion. Repair synthesis then fills in the single-stranded gap. While proteins are diagrammed individually here, they may be present as part of a multiprotein repair complex in vivo.

Three human diseases have been associated with mutations in NER genes: xeroderma pigmentosum, Cockayne's syndrome (CS), and trichothiodystrophy (TTD). Xeroderma pigmentosum is marked by an increased sensitivity to light, leading to an increase in skin carcinomas, and a number of neurological abnormalities (reviewed in [2, 3]). There are seven complementation groups for xeroderma pigmentosum, XPA to XPG, defined by the ability of fused fibroblasts to repair damage after UV irradiation. The genes mutated in these complementation groups have been identified (see table 2), and are homologues of yeast NER genes (reviewed in [4, 5, 25]). Cockayne's syndrome and trichothiodystrophy have overlapping symptoms with xeroderma pigmentosum, such as neurological degeneration, and some of the XP complementation groups overlap with the CS and TTD groups.

DNA mismatch generation during meiosis

In addition to mismatches that arise as a consequence of replication errors during the mitotic cell cycle, replication during S phase in meiosis can generate mismatches. These mismatches are indistinguishable from mismatches that occur during the mitotic cell cycle. Also, tracts of simple repetitive DNA show the same level of instability during vegetative replication and meiotic replication [6]. However, the process of recombination between homologous chromosomes during meiosis [38] can also generate mismatches as a result of sequence differences between the homologues. These mismatches are substrates for repair mechanisms. During meiosis in yeast, efficient correction of various types of mismatches is known to occur, based on studies involving crosses between haploid strains with defined alleles that generate base-base mismatches, small unpaired loops or large loops of DNA up to 10 kb in length [39].

Meiotic recombination initiates with a double-stranded DNA break by the product of the *SPO11* gene [40] (fig. 3). Following this scission event, long 3′ single-stranded regions are generated by resection of the 5′ DNA strand. At the *HIS4* locus, where the initiating DSB occurs in the intergenic region between *HIS4* and *BIK1* (fig. 3), this resection event goes towards either *HIS4* or *BIK1*, but rarely both simultaneously [41]. The single-stranded tail then invades its homologue, displacing one strand to be used as a substrate to repair the double-stranded break. The joint molecule formed by the strand invasion event is termed a heteroduplex. If the two strands comprising the heteroduplex contain sequences that differ, a mismatch will be created (reviewed in [38, 42]).

Table 2. Nucleotide excision repair genes.

S. cerevisiae gene	Mammalian group/gene	Mitotic cell cycle function	Meiotic function
RAD1	XPF/ERCC4	endonucleolytic cleavage	large loop repair
RAD2	XPG/ERCC5	endonucleolytic cleavage	none known/induced in meiosis
RAD3	XPD/ERCC2	essential helicase, ATPase	unknown
RAD4	XPC	multifunctional?	unknown
RAD7	?	nontranscribed DNA repair	unknown/induced in meiosis
RAD10	ERCC1	endonucleolytic cleavage	large loop repair
RAD14	XPA	damage recognition	none known
RAD16	?	nontranscribed DNA repair	unknown
RAD23	HHR23B	nontranscribed DNA repair	unknown/induced in meiosis
RAD25 (SSL2)	XPB/ERCC3	essential helicase	unknown

Mismatches within heteroduplex tracts can be substrates for repair. If the alleles that formed the heteroduplex have different phenotypes, then the manner in which the mismatch is dealt with can be monitored easily. As all four spore products of a single meiosis (a tetrad) can be recovered, events that deviate from Mendelian segregation (4 His + :4 His − segregation when heterozygous for a mutation at the *HIS4* locus, using the nomenclature of eight-spored fungi so that each of the eight DNA strands within the four spores is specifically identified) can be seen. Deviations from normal segregation known as gene conversions (either 6:2 or 2:6, with the wild-type allele listed first) represent a nonreciprocal exchange of information (a His + spore becomes a His − spore, for example) when a mismatch is corrected. If the mismatch goes uncorrected, following meiotic recombination one of the four spores will receive the chromosome containing the heteroduplexed region with the mismatch. The first round of replication following spore germination will generate two double-stranded DNA molecules that differ in sequence, with each being segregated to a different cell. The colony that forms from these cells will be sectored; one side of the colony will be His + while the other side will be His − . This type of event is known as a postmeiotic segregation (PMS) event, and scored as a 5:3 or 3:5 event (fig. 3).

The amount of recombination at an allele therefore is the percentage of tetrads exhibiting an aberrant segregation event, with gene conversion events representing repaired mismatches and PMS events representing lack of repair (fig. 3). Repair events that restore normal Mendelian segregation, known as restoration events, are not readily distinguishable from nonrecombinants and so cannot be counted, although restoration events have been shown to occur [43, 44].

Mismatches of any type or size can be generated by allowing recombination to create a heteroduplex between chromosomes with specific introduced sequence differences. For example, a diploid strain that is heterozygous for a T to A transition mutation will generate a T:T or an A:A mismatch (depending on which strands form the heteroduplex) if that region is incorporated into a heteroduplex during meiotic recombination.

The function of MutL homologues during meiosis

A screen for mutations that altered the apparent rate of recombination, as measured by the recovery of recombinant prototrophs following meiosis, identified a number of mutants, named *PMS* for post-meiotic segregation. The *pms1-1* mutation was extensively characterized; it has a mutator phenotype during the mitotic cell cycle and reduces the repair of mismatches during meiosis [45–48]. Mutations in *PMS1* did not significantly alter intergenic recombination between a number of linked loci [45]. Using heteroduplexes constructed in vitro and introduced into wild-type and *pms1* mutant backgrounds, Kramer et al. [47] showed that *PMS1* affected the repair of a large number of base-base mismatches and single-base loops, but had no effect on 38-base loops.

Identification of the *pms1* locus revealed that *PMS1* is a homologue of the bacterial *mutL* gene [49]. A null mutation in *PMS1* had a slightly more severe effect on postmeiotic segregation than the *pms1-1* mutation [49]. However, even with the deletion allele, some gene conversion events are detected. These tetrads could represent: (i) a *PMS1*-independent mismatch repair pathway, (ii) gene conversion via gap repair, rather than mismatch repair of a heteroduplex or (iii) the death of one cell immediately after the first cell division following spore germination, causing a PMS colony to appear to be a gene conversion colony. Finally, spore viability in a *pms1* mutant is significantly decreased [49, 50]. This decrease may be due to the accumulation of recessive lethal mutations in the diploid during mitotic growth, as limiting vegetative growth improved the percentage of spore viability. However, as the decrease was only partially alleviated [49], there might be a secondary func-

tion for *PMS1* during meiosis that leads to spore inviability when disrupted.

The *MLH1* gene was identified by a polymerase chain reaction (PCR) strategy using sequences from prokaryotic *mutL* genes and yeast *PMS1* [51]. Deletion of the *MLH1* gene product had an effect on recombination and spore viability that was equivalent to or exceeded the effects of the *pms1* mutation. The frequency of aberrant segregation was increased at a number of loci, as was the percentage of postmeiotic segregation for point mutations and four-base insertions. A *pms1 mlh1* double mutant had phenotypes equivalent to those exhibited by the single mutants, indicating that both gene products probably act in the same pathway for meiotic repair of small mismatches and loops [51], a result consistent with their role in mitotic postreplicative DNA mismatch repair [6]. Unlike *PMS1*, deletion of *MLH1* also decreased the amount of crossing over normally observed between a number of genetically linked loci [50]. The *mlh1* effect on intergenic recombination showed variability depending on the locus examined. This result is reminiscent of the phenotypes of mutations in *MSH4* and *MSH5* (discussed below).

Novel meiotic phenotypes have been associated with deletion of *mutL* homologues in the mouse (reviewed in [52]). Inactivation of the mouse gene *PMS2* (a *mutL* homologue most closely related to yeast *PMS1*) leads to an increase in carcinomas and microsatellite instability, but also results in male infertility due to abnormal spermatozoa formation [53]. Axial elements in the synaptonemal complex that arises during meiotic recombination failed to fully form, leading to chromosomes that did not synapse. Both male and female *MLH1*-deficient mice were infertile, and exhibited an increased level of unassociated homologous chromosomes during later stages of meiosis [53, 54]. The *MLH1* protein binds in discrete foci along synapsed chromosomes [55], leading to the suggestion that *MLH1* in mice is involved in meiotic crossing over. Double-labelling experiments [56] show a colocalization of the *MLH1* protein and replication protein A (RPA, a single-stranded DNA-binding protein) at late recombination nodules. The effects on fertility are not general to mutations in MMR genes, as mutation of the mouse homologues of *MSH2* [57] and *MSH6* [58] did not result in sterility.

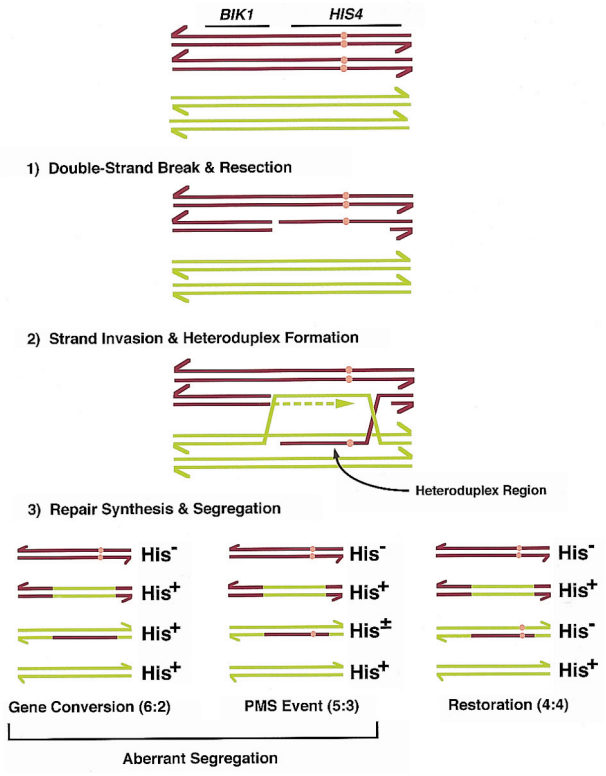

Figure 3. A diagram for recombination during meiosis in *Saccharomyces cerevisiae*. The *HIS4-BIK1* interval on chromosome III is shown, with the extent of each gene indicated by the thin horizontal line at the top. Each DNA strand is shown following meiotic DNA replication, with the 5′ end indicated by the arrow. A heterozygous *HIS4* diploid is depicted; the red chromosomes are *his4* due to a mutation (pink circle), whereas the green chromosomes are *HIS4*. Recombination is initiated by a blunt double-strand break between *HIS4* and *BIK1* [112], followed by resection of one strand toward either *HIS4* or *BIK1* [41] (step 1). This single-stranded tail invades the *HIS4* locus on the homologue, creating a heteroduplex and displacing a strand to serve as a template for repair synthesis (dashed line). Sequence differences between the two homologues, such as the mutation in the *his4* homologue, will create mismatches when present in heteroduplex DNA (step 2). Recombination and chromosome segregation are then completed, with each spore receiving one haploid chromosome (step 3) with the His phenotype indicated next to it. A repair event that removes the mutation will generate a 6:2 (wild type:mutant) gene conversion event, while a repair event that duplicates the mutation will restore normal 4:4 Mendelian segregation (using the nomenclature of eight-spored fungi). Failure to repair will result in a 5:3 PMS event. Shown here is an event in which a mutant strand initiates recombination; if the wild-type chromosome is broken, the sequence of events is identical, but the types of aberrant segregation events observed are inverted (2:6 gene conversion rather than 6:2 and 3:5 PMS rather than 5:3).

The function of MutS homologues during meiosis

Upon the realization that the *PMS1* gene was a homologue of the prokaryotic *mutL* gene, the search for other homologues began. As in the cloning of *MLH1*, degenerate primers were used to screen yeast genomic DNA for *mutS* homologues. Two genes were identified and characterized initially [59], only one of which appears to possess a meiotic function. The *MSH2* gene (MutS homologue) is involved in both MMR and meiotic recombination [21]. Deletion of the *MSH2* gene was shown to have a drastic effect on repair during meiotic

recombination, equivalent to that of the *pms1* mutation [21, 60]. Alleles that normally generated predominantly gene conversion events during recombination exhibited a high level of PMS. The overall level of aberrant segregation of heterozygous alleles increased in an *msh2* mutant strain. This apparent increase in recombination frequency results when restoration tetrads (which normally are not detectable as recombination events in strains with a wild-type mismatch repair system) become PMS tetrads because of loss of the repair activity that corrects the mismatch, leading to an observable increase in recombination. Finally, spore viability was decreased by about two-thirds. This result is similar to the spore inviability seen in *pms1* and *mlh1* mutants [50].

Some gene conversion tetrads are still detected in *msh2* strains [21, 60], as in other mismatch repair mutant strains (discussed above). It is not known what activity is responsible for this background level of gene conversion. However, a biochemical activity from mitotic yeast cells that binds loops in an Msh2p-independent manner has been reported [61].

In addition to its effects on repair of small mismatches that occur as a consequence of heteroduplex formation during meiotic recombination, the *MSH2* gene has also been implicated in the creation of polarity gradients for recombination [60]. In yeast, recombination often is highest at one end of a gene (reviewed in [62]). This decline in recombination across the gene is known as a polarity gradient. In yeast the high end of the gradient can be at the 5′ (i.e. *HIS4* [63] and *ARG4* [64]) or 3′ (i.e. *HIS2* [65, 66]) end of the gene, but it is located adjacent to a recombination-initiating double-strand break. One model to explain polarity gradients is that mismatches within heteroduplex DNA interact with the DNA mismatch repair machinery to block or reverse heteroduplex migration. This 'heteroduplex rejection' model was based partly on the observation that a mutation in *MSH2* reduced the polarity gradient at *HIS4* and *ARG4* [60]. Further data from experiments on the polarity gradient at *HIS4* argue that the polarity gradient at that locus is due primarily to a switch from conversion-type to restoration-type repair along the polarity gradient—the 'restoration/conversion' model [44, 67]. However, as pointed out by Nicolas and Petes [62], polarity gradients at other loci may be the result of complex interactions of a number of factors, including elements of the restoration/conversion model, DNA mismatch repair factors (as suggested by the heteroduplex rejection model) and variations in the length of the single-stranded DNA tract formed during resection after double-strand break formation.

Deletion of the *MSH3* gene has a lesser effect on meiotic recombination [68] than an *msh2* mutation. When recombination at four alleles was analyzed, one allele showed a significant increase in the level of PMS when *MSH3* was deleted. Another study [50] also showed an increase in PMS frequency in an *msh3* strain, but only about a third of the increase seen in *msh2* and *pms1* mutant strains. Spore viability was reduced in this strain background. As with other *mutS* and *mutL* homologues, the severity of the *msh3* mutation during meiosis is comparable to its mitotic MMR phenotype.

A meiosis-specific *mutS* homologue, *MSH4*, appears to play a role late in recombination during the resolution of reciprocal crossovers, rather than earlier in meiosis during mismatch detection and correction. The *MSH4* gene [22] was identified in a screen for genes that were expressed during meiosis; it is not expressed during vegetative growth. No mitotic phenotypes of an *msh4* deletion were identified. Analysis of meiotic recombination indicated that the level of PMS and gene conversion were unaltered in an *msh4* strain for alleles that were significantly affected by an *msh2* deletion. Spore viability following meiosis was greatly reduced, however, and the pattern of spores recovered per tetrad indicated a problem in chromosome separation during meiosis I division. The amount of reciprocal recombination (crossovers) was reduced in a number of intervals examined. A similar alteration in crossover frequency was seen with an *MLH1* mutation [50], and the two genes may act in the same pathway. The *MSH4* protein localizes to meiotic nuclei in a punctate pattern, with approximately 60 foci of staining distributed along the chromosomes. This number correlates with estimated numbers of crossover recombination events per genome; Msh4p and Mlh1p may be components of the machinery that regulates or resolves crossovers during meiotic recombination. Recently a human *mutS* homologue was identified that had its greatest similarity to yeast *MSH4* and showed testis- and ovary-specific expression [69], indicating that it might be the human *MSH4* gene.

A screen for mutants that are defective in interhomologue recombination during meiosis revealed the presence of a second meiosis-specific *mutS* homologue, *MSH5* [23]. Deletion of *MSH5* resulted in phenotypes very similar to those seen in *msh4* mutants: decreased spore viability indicative of meiosis I nondisjunction, decreased crossing over but no effect on gene conversion or PMS frequency and no alteration in mutation frequency during vegetative growth. Analysis of an *msh4 msh5* double mutant indicated that the two genes probably function in the same pathway for reciprocal recombination. This result was confirmed by coimmunoprecipitation and two-hybrid interaction experiments, which demonstrated that Msh4p and Msh5p form a complex [70]. This interaction does not require adenosine triphosphate (ATP) binding; mutations in this domain in *MSH5* did not affect the proteins's

two-hybrid interaction with Msh4p. Two-hybrid experiments also demonstrated that Msh5p did not interact with either Msh2p or Msh6p, indicating that the meiotic crossover and DNA mismatch repair MutS complexes are distinct.

Deletion of *MSH6* increases the PMS frequency of a two-base duplication but only to about 10% of the level seen with an *msh2* or *pms1* mutation in the same strain background [50]. The total level of aberrant segregation also decreased, although only a small number of tetrads were examined. Spore viability was not affected by removal of *MSH6*. The effects of an *msh6* mutation during meiotic mismatch repair are similar to its effects on mitotic mismatch repair.

A phylogenetic comparison of the protein sequences of the various *mutS* homologues from numerous organisms was used to generate a possible evolutionary relationship tree for the *mutS* family [71]. Based on this analysis, two main families, *mutS-I* and *mutS-II*, were described, with *mutS-I* members responsible for MMR and *mutS-II* members for chromosome crossover and segregation. In *S. cerevisiae*, *MSH1*, *MSH2*, *MSH3* and *MSH6* fall in the mutS-I group, whereas *MSH4* and *MSH5* are in the mutS-II group.

The term homeologous recombination is used to describe recombination between similar but diverged sequences, such as dispersed copies of a duplicated gene. Homeologous recombination occurs at a rate orders of magnitude less frequently than homologous recombination. However, mutation of *mutS* and *mutL* raised the frequency of homeologous recombination between *E. coli* and *Salmonella typhimurium* [72]. Homeologous recombination is seen in *Saccharomyces cerevisiae* during mitosis [73–76] and meiosis [77], and the DNA mismatch repair system is involved in this type of recombination. A mutation in *PMS1* alleviates the decrease in meiotic recombination caused by the presence of multiple sequence differences in an interval, for example [78]. In crosses between the diverged species *S. cerevisiae* and *S. paradoxus*, spore viability, meiotic recombination and chromosome disjunction were improved by up to an order of magnitude by introduction of mutations in *MSH2* and *PMS1* [79]. In diploid *S. cerevisiae* strains in which one copy of chromosome III is derived from *S. paradoxus*, deletion of *MSH2* and *PMS1* increased intergenic recombination between a number of loci on chromosome III [80]. Intriguingly, an *msh2 pms1* double mutant was more effective in increasing recombination than either mutant individually, raising the possibility that *MSH2* and *PMS1* have separable and distinct roles in homeologous recombination. Homeologous recombination does not require the meiosis-specific *MSH4* gene [22].

The function of nucleotide excision repair proteins during meiosis

Until recently the various genes involved in nucleotide excision repair in yeast were thought not to play a role in meiotic recombination. Initial studies of mutants in a number of NER genes including *RAD1* showed no alteration in the frequency of PMS for heterozygous mutations during meiosis [81, 82]. Exposing *rad1* diploids to ultraviolet radiation did reduce the amount of crossing over during meiosis, however [83]. A study utilizing diploids that were heterozygous for a 26-bp insertion in the *HIS4* gene showed that deletion of the *RAD1* gene significantly increased the PMS of the allele [84]. The frequency of PMS increased only slightly for base-base mismatches and 4-base loops. Deletion of *RAD10* has an identical effect on the PMS frequency of the 26-base loop (D. Kirkpatrick and T. Petes, unpublished observation), indicating that the *RAD1-RAD10* complex is probably required for loop repair during meiosis in yeast, but not for repair of small loops or mismatches.

Analysis of the relative frequency of the various types of recombinants recovered in *RAD1* and *rad1* strains indicated that loss of Rad1p activity resulted in a decrease in the number of repair events in which the 26-base loop was filled in, but no alteration in those repair events in which the loop was removed. This finding is consistent with the idea that Rad1p is acting to cleave the DNA strand in the heteroduplex that is opposite the 26-base loop, rather than removing the loop itself.

This report was the first demonstration of a role for the *RAD1/10* endonuclease during meiotic recombination in *S. cerevisiae*. A *Drosophila melanogaster* mutant, *mei-9*, exhibits an elevated level of PMS [85]. The *mei-9* gene is the fruitfly homologue of the *RAD1* gene, demonstrating that NER proteins may function during meiosis in other organisms [86, 87].

In yeast Rad1p functions during certain types of recombination in the mitotic cell cycle. Mutations in *RAD1* and *RAD10* affect recombination between duplicated sequences [88–90], in a pathway that is independent of *RAD52*. However, unlike its role in meiotic loop repair, in mitotic recombination events the Rad1p-Rad10p complex is believed to be involved in removing a region of single-stranded DNA [91, 92]. A detailed discussion of the *RAD1-RAD10* contribution to certain types of mitotic recombination is beyond the scope of this review.

A number of other components of the NER pathway are not required for loop repair [84]. The *RAD14* gene product is believed to bind to lesions to initiate repair [28, 29], but deletion of the gene has no effect on the repair of the 26-base meiotic loop. Deletion of the

RAD2 gene, which encodes the other endonuclease required during NER [34] (see fig. 2), does not increase the level of PMS, although the total level of recombination is lowered. The yeast genome has four other genes that are related to the *RAD2* gene: *RAD27*, *DIN7*, *EXO1* and *YEN1*. Interestingly, transcription of both *RAD2* [93] and *DIN7* [94] are induced during meiosis, although no role for either gene during meiosis has been discovered. *RAD27* has been shown to be involved in processing of Okazaki fragments during replication, and mutations in *RAD27* affect the stability of micro- and minisatellite DNA during mitotic growth in yeast [95–99]. *EXO1* encodes a 5′–3′ exonuclease that interacts with Msh2p in a two-hybrid screen [100]. Deletion of *EXO1* is lethal in combination with *RAD27* deletions, shows a mutator phenotype during vegetative growth [100] and is involved in direct repeat recombination during mitosis [101]. Possible roles for *EXO1* in meiotic recombination have not been fully examined yet. However, mutations in the *Schizosaccharomyces pombe EXO1* gene exhibit a mutator phenotype consistent with a role in mismatch repair, and is induced in meiosis [102, 103], as is the *Saccharomyces cerevisiae EXO1* gene [104]. It is possible that one or more of these genes, individually or together, might play a role in loop repair during meiotic recombination. Other NER genes (*RAD7*, *RAD18* and *RAD23*) also show a meiotic transcription induction and should be examined for meiotic repair activity [105–107].

The *RAD1*-dependent repair of large loops during meiotic recombination also involves a component of the MMR pathway [84]. Deletion of the mismatch repair gene *MSH2* affects the frequency of PMS of the 26-base loop to the same extent as the *RAD1* deletion. In fact, the *rad1 msh2* double mutant has the same level of repair as the single mutants, indicating that the two gene products probably function in the same pathway for the repair of 26-base loops during meiosis. This result is surprising, as repair complexes containing Msh2p have an upper limit of 14 bases during the mitotic cell cycle [8].

One model to explain the above data is that Msh2p recognizes the loop structure and recruits the Rad1-Rad10 protein complex to cleave the strand opposite the loop. However, approximately 50% of the loop mismatches that occur in heteroduplex DNA at the *HIS4* locus are still repaired in the *rad1 msh2* mutant, indicating that there is at least one more system capable of repairing large loop mismatches during meiosis. Perhaps other components of the DNA mismatch repair system might act in large loop correction. The contribution, if any, of other MutS and MutL homologues in large loop repair has not yet been determined. However, previous experiments using a 38-base deletion in the *ADE8* gene showed that the PMS frequency of that allele was not affected by a mutation in *PMS1* [45, 47]. These results point to an interesting association of components from two different repair pathways. A few other examples of an intersection between NER and MMR have been reported. Certain types of mitotic recombination events that require the *RAD1* protein also require some DNA mismatch repair proteins. When a double-strand break is generated during the mitotic cell cycle, repair can occur through single-strand annealing between direct repeats; *RAD1* is required to help remove nonhomologous DNA sequences [91]. *MSH2* and *MSH3* are also required, acting when the annealing repeats contain some sequence differences [108, 109]. Another example occurs in *E. coli*, where *mutS* and *mutL* mutants specifically affect transcription-coupled NER at the lac operon following UV irradiation [110].

The effects on meiotic recombination and mismatch correction of mutations in many of the genes involved in NER have yet to be determined. While initial analysis of a number of them indicated no meiotic functions [81], many need to be tested with a full range of substrates.

Summary

Pathways exist in eukaryotic cells to repair numerous types of DNA lesions. Two of these mechanisms, the mismatch repair system and the nucleotide excision repair system, perform a number of functions during meiosis. Some of these activities were predictable from the well-characterized mitotic cell cycle functions of the repair pathways. Other interactions, such as the joint requirement for NER and MMR proteins (Rad1p/Rad10p and Msh2p) in large loop correction during meiotic recombination [84] or the requirement for some of the *mutS* and *mutL* homologues in intergenic recombination in yeast and mammals (reviewed in [52]), were not as readily apparent.

Currently there seem to be at least three repair pathways operating after mismatches are generated during heteroduplex DNA formation in meiotic recombination. The first pathway, similar to the postreplicative DNA mismatch repair pathway that operates during vegetative growth, appears to be specific for base-base mismatches and small loops. It utilizes two *mutL* homologues (*MLH1* and *PMS1*) and three *mutS* homologues (*MSH2*, *MSH3* and *MSH6*). A second pathway, specific for large loops, requires *RAD1*, *RAD10* and *MSH2*. Genetic evidence indicates that there is likely to be another large loop repair pathway that is *RAD1*- and *MSH2*-independent. In addition, two *mutS* homologues, *MSH4* and *MSH5*, and the *mutL* homologue *MLH1* have a later role in recombination during the resolution of crossovers. The products of some of these

genes also function to prevent recombination between diverged sequences.

Much work remains to be done to characterize the substrate specificities and interactions of the proteins currently known to be involved in mismatch correction during meiosis, and to identify other proteins that play roles in these processes. For example, what is responsible for the gene conversion events detected in *msh2*, *pms1* or *mlh1* mutants when alleles that generate base-base or small mismatches are examined? At what loop size does the *RAD1*-dependent pathway begin to function? How are *MSH4*, *MSH5* and *MLH1* functioning in the control of crossovers late in recombination? Finally, it is quite possible that DNA repair systems other than those discussed here also function during meiotic recombination. An interaction during methylation damage repair between the nucleotide excision repair system and the base excision repair system has recently been demonstrated in *S. cerevisiae*, for example [111].

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