Mismatch Repair Regulates Homologous Recombination, but Has Little Influence on Antigenic Variation, in *Trypanosoma brucei* *

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Antigenic variation is critical in the life of the African trypanosome, as it allows the parasite to survive in the face of host immunity and enhance its transmission to other hosts. Much of trypanosome antigenic variation uses homologous recombination of variant surface glycoprotein (VSG)-encoding genes into specialized transcription sites, but little is known about the processes that regulate it. Here we describe the effects on VSG switching when two central mismatch repair genes, *MSH2* and *MLH1*, are mutated. We show that disruption of the parasite mismatch repair system causes an increased frequency of homologous recombination, both between perfectly matched DNA molecules and between DNA molecules with divergent sequences. Mismatch repair therefore provides an important regulatory role in homologous recombination in this ancient eukaryote. Despite this, the mismatch repair system has no detectable role in regulating antigenic variation, meaning that VSG switching is either immune to mismatch selection or that mismatch repair acts in a subtle manner, undetectable by current assays.

African trypanosomes are protistan parasites that infect mammals and are considered to have diverged early in eukaryotic evolution (1), prior to the radiation of animals, plants, and fungi. In the mammal *Trypanosoma brucei* resides in the bloodstream and tissue fluids, where it is subject to immune attack. To evade immune killing, it undergoes antigenic variation, a strategy for changing surface coats found in a diverse range of microbes (2, 3). The surface coat of *T. brucei* is composed of variant surface glycoprotein (VSG) (4). VSG genes are expressed from telomeric transcription units, called expression sites (ES), of which −20 can be used while the parasite is present in the mammalian host. Only one ES is expressed at a given time from a specific sub-nuclear domain (5), but coordinated transcriptional switches (termed in situ switches) can activate a silent ES and inactivate the transcribed site (6–12). *T. brucei* also contains hundreds of silent VSG genes, both in multigene arrays in the megabase chromosomes and at the telomeres of minichromosomes. This silent reservoir is activated by recombination reactions that move the genes into the ES, normally by a gene conversion process (13–15). The available evidence suggests that recombinational VSG switching occurs by homologous recombination. No specific sequence has been shown to be essential in activating VSG gene conversion, but instead the reactions use variable amounts of flanking sequence homologies (2). In addition, disruption of a gene encoding a major enzyme of eukaryotic homologous recombination, RAD51, impairs VSG switching (16). Consistent with this genetic analysis, inactivation of KU70 or KU80, which catalyze a non-homologous end-joining pathway of DNA repair in other organisms (17, 18), does not affect VSG switching (19). Surprisingly, mutation of *MRE11* also does not affect VSG switching (20), despite this gene encoding an enzyme that has been proposed to have many roles in homologous and non-homologous recombination (21).

Mismatch repair (MMR) plays a critical role in maintaining genetic stability, in part by correcting base mismatches that can arise through replication errors or chemical damage (reviewed in Refs. 22–25). In most bacteria, a homodimer of MutS binds mismatched DNA and is then recognized by a homodimer of MutL, which is thought to recruit downstream factors that catalyze the repair reaction. Eukaryotic MMR is catalyzed by MutS and MutL homologues, but here the proteins act as heterodimers. In *Saccharomyces cerevisiae* there are two MutS-related heterodimers. One is composed of *MSH2* and *MSH6* and recognizes base-base mismatches and small insertion/deletion loops, whereas the second is composed of *MSH2* and *MSH3* and binds a larger range of insertion/deletion loops. Two MutL heterodimers, composed of *MLH1* and either *PMS1* or *MLH3*, have been well characterized in *S. cerevisiae*, and a third (*MLH1*–*MLH2*) has recently come to light (26, 27). Essentially the same MutS- and MutL-related proteins are found in most eukaryotes, although there is some variation in the numbers that different organisms contain (28–30). We have shown that *T. brucei* contains orthologues of five such proteins and that at least two of them function in MMR. *An MSH2*-related gene has also been characterized in *Trypanosoma cruzi* (31, 32).

Mismatches can also arise during the DNA strand exchange step of recombination between non-identical DNA substrates. These are recognized by the MMR machinery, which either triggers mismatch correction, resulting in gene conversion, or recombination abortion (reviewed in Refs. 33 and 34). MMR anti-recombination activity has been described in bacteria, yeast, and mammals (35–37) and plays roles in speciation (35, 38, 39) and in maintaining genome stability (40–42). The mechanism(s) by which the MMR machinery aborts homologous recombination is not yet clear, but destruction of DNA strand exchange heteroduplexes by MMR-catalyzed nicking

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1 The abbreviations used are: VSG, variant surface glycoprotein; ES, expression sites; MMR, mismatch repair; MEPS, minimal efficient processing segments.

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and non-destructive reversal or rejection of the heteroduplexes has been suggested (33–35).

In T. brucei, transformed DNA appears to integrate into the genome almost exclusively by homologous recombination (43), suggesting that, as in yeast, homologous recombination is the major DNA double strand break repair pathway. Indirect evidence from such transformation experiments has suggested that MMR influences homologous recombination in both T. brucei (44) and the related parasite Leishmania (45). Given that T. brucei antigenic variation is heavily dependent on homologous recombination, mismatch repair might be envisaged to be an important regulatory component of the immune evasion process. Here we test the contribution that MMR makes to antigenic variation, and we quantify the constraint that MMR places upon homologous recombination in this parasite.

EXPERIMENTAL PROCEDURES

T. brucei Strains and Growth—T. brucei Lister 427 bloodstream cells were used and grown at 37 °C in HMI-9 medium (46). MS2H and MLH1 mutants for assaying VSG switching were made in strain 3174, a derivative of MITat1.2a (47). Determination of VSG switching frequency and pattern has been described previously (19, 19, 20). To assay the effect of base mismatches on recombination, MITat1.2a cells were transformed with the construct pTHT (43, 44); targeting of the HYG gene (see text) to the tubulin array was confirmed by Southern mapping with KpnI- or EcoRI-digested genomic DNA (data not shown). The constructs used to make MS2H and MLH1 mutants will be described elsewhere, as will the approaches to confirm the mutations.

Generation of HYG Targeting Constructs—Constructs to target HYG in the HTUB cell line were made by PCR on 2 ng of plasmid pTHT (43, 44) with primers HYGFor (5′-AAGGCGCGGACGACTGGAATCCTACGC-3′; Asc I site underlined) and HYGRev (5′-ATGGCGCGGCCTCCCGATCCGAGATGGG-3′; Asc I site underlined). Reactions were performed for 94 °C for 10 min, 30 cycles of 94 °C for 1 min, 65 °C for 1 min, 72 °C for 10 min; the 914-bp products were cloned into pCR2.1-TOPO (Invitrogen). Herculase polymerase (Stratagene) was used to make flanks homologous to HYG; sequencing revealed no base changes relative to HYG

The estimated VSG switching frequencies of the three MS2H+/− and MS2H−/− cell lines are shown in Fig. 1, compared with the wild type cells and the homozygotic mutant re-expressing MS2H. There is considerable variation in the VSG switching frequencies measured by this assay (16, 47), due almost certainly to fluctuations in the timing of individual VSG switching events during population growth, reflecting the randomness of this process in T. brucei. Nevertheless, statistical examination of the data revealed no significant difference in VSG switching frequency in any of the MS2H cell lines, indicating that MS2H mutation does not detectably influence the overall frequency.

VSG switching is a combination of in situ transcriptional switching events, which are not believed to involve recombination, and recombination events. Because it is possible that a high frequency of in situ switching might obscure an alteration in a relatively lower frequency of VSG recombinational switching resulting from MS2H deletion, we characterized the switching events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants. By using the antibiotic markers in the active ES, we can distinguish recombination events in a number of clonal switched variants.
general pattern was true in the MSH2 heterozygous cell lines. Inactivation of MMR would most likely be expected to increase recombination rates, but we found that neither recombinational VSG switching event became predominant or, alternatively, was reduced. MSH2 mutation does not appear to detectably alter the profile of VSG switching.

**Mutations of T. brucei MLH1 Does Not Affect VSG Switching**—Although MSH2 acts to suppress recombination, in *S. cerevisiae* it also functions, paradoxically, to promote homologous recombination in some circumstances. MSH2 and MSH3 cooperate with the nucleotide excision repair proteins RAD1 and RAD10 (49–52) to remove non-homologous 3' tails during the strand invasion step of homologous recombination and in another homology-dependent DNA repair pathway termed single strand annealing (reviewed in Ref. 53). No other yeast MMR proteins are involved in this tail removal (51), but all appear to contribute to the suppression of recombination between non-identical DNA substrates (54). We do not yet know the detailed molecular mechanisms of VSG switching, and therefore one potential explanation for the lack of altered VSG switching in the MSH2 mutants is that the enzyme both promotes the process, by processing 3' tails, and suppresses it by selecting against insufficiently matched recombining sequences. To address this, we examined the influence of MLH1 on VSG switching. Although MLH1 promotes meiotic recombination in at least some organisms (55, 56), it appears only to suppress mitotic recombination events, and *T. brucei* VSG switching occurs in dividing bloodstream stage cells that do not undergo meiosis.

**MLH1 mutants were created in *T. brucei* strain 3174, again...
Mismatch Repair Regulates Homologous Recombination in T. brucei—Although previous work has suggested indirectly that MMR influences recombination of transformed DNA constructs in T. brucei (44), the apparent lack of involvement in VSG switching made it important to test this genetically. To do this, we integrated a copy of the hygromycin phosphotransferase gene (HYG) into the tubulin array of the T. brucei genome (Fig. 3A), creating a unique sequence for recombination into the genome (see below). Two independent MSH2 mutants were created in the HYG transformant strain, each by two rounds of transformation with the constructs ΔMLH1::BSD and ΔMLH1::PUR. Southern analysis confirmed that HYG was retained in the +/− and −/− cells and that the MSH2 open reading frames had been deleted as expected; in addition, reverse transcriptase-PCR demonstrated that intact MSH2 transcript was no longer expressed in the −/− cells (data not shown).

To assess the impact of MMR on homologous recombination, we created a series of DNA constructs designed to integrate into the HYG marker following transformation of wild type, +/−, and −/− cells (Fig. 3, A and B). All the constructs contained a blomycin resistance cassette (BLE) to provide selection for recombination into the T. brucei genome. The resistance cassette was flanked upstream and downstream, respectively, by 445 and 449 bp of sequence derived from HYG, providing substrates for homologous recombination. The constructs in the series differed from each other in that the overall sequence identity between the HYG targeting flanks and the genomic HYG marker reduced progressively from 100 to 89% (Fig. 3B).

The consequences of increasing sequence divergence for homologous recombination was compared in MSH2wt and mutant cells by assaying the efficiency with which stable trans-formants arose following transformation of a fixed amount of each linear DNA construct. This is a valid measurement of homologous recombination efficiency because in RAD51wt T. brucei essentially all stable trans-formants integrate linear DNA by homologous recombination rather than by non-homologous reactions (43), and the formation of extrachromosomal replicons to yield antibiotic resistant T. brucei following the transformation of small, linear constructs has never been described (57). The results of this analysis are graphed in Fig. 4 and summarized in Table I.

In the wild type and MSH2+/− (MMR+) cells there was a 2.8-fold decrease in transformation efficiency with construct HYG01 (1% sequence divergence) compared with HYGwt (100% sequence identity), showing that even a small number of mismatches affect homologous recombination. This was true also in the MSH2−/− cells, where a smaller (1.8-fold), but still significant (p value <0.0001), decrease in transformation efficiency was observed. Evidently, with this amount of mis-
matches, the MMR system is not the sole determinant of homologous recombination efficiency in T. brucei. A steady decline in transformation efficiency was apparent in all cell lines as sequence divergence between the DNA constructs and genomic HYG increased, but this was more marked in the MMR+ cells than in the MSH2–/– cells. For example, MMR+ transformants were generated nearly 100-fold less frequently with HYGtwt, whereas only a 16-fold decrease was seen in the MSH2–/– cells.

The MSH2–/– cells showed a higher frequency of transformation than the MMR+ cells with all DNA constructs, demonstrating that MMR does indeed constrain homologous recombination in T. brucei, and this was significantly more marked if sequence mismatches were present (Fig. 4 and Table I). With HYGtwt (100% identity), transformants were generated 1.6-fold (p value <0.0001) more frequently in the MSH2–/– cells compared with MMR+ cells. With 1% sequence divergence (transformation with HYG01), this difference was raised somewhat to 2.4-fold. By using the constructs with 2–11% divergence (HYG02–HYG11), the MSH2–/– cells were transformed between 6.5- and 12-fold more efficiently than the MMR+ cells.

**DISCUSSION**

In this study we examined the influence of MMR on homologous recombination in the protistan parasite T. brucei by assaying the efficiency of DNA transformation. Increasing amounts of base mismatches had an increasingly detrimental effect on transformation efficiency. This was significantly alleviated in MSH2–/– mutants, arguing that recognition of the mismatches by the MMR machinery is responsible for some, but not all, of this homologous recombination inhibition. Our analysis was conducted in bloodstream stage T. brucei, but it seems highly likely that MMR also contributes to the requirement for greater than 92% sequence identity for construct targeting seen previously (44) in the procyclic stage. Similarly, it has been argued that a reduced recombination rate of constructs with 86% sequence identity in the related parasite Leishmania is also MMR-mediated (45). It should be noted, however, that our work demonstrates that DNA substrates with such high levels of sequence divergence are inefficiently recombined even in the absence of MMR, demonstrating that the kinetoplastid recombination machinery is itself sensitive to base mismatches (see below).

The extent to which T. brucei homologous recombination, acting on both identical and non-identical substrates, is enhanced by mutation of the MMR system is comparable with that seen in yeast and mammals. In S. cerevisiae, mutation of msh2 and msh3, although not all MMR genes, leads to a small increase in recombination between perfectly matched substrates (48, 54), and the level of the increase we found in T. brucei for an MSH2–/– mutation (1.6-fold) appears comparable. The molecular basis for this increase remains unclear (48). In bacteria and yeast, increasing amounts of base mismatches cause an exponential decrease in recombination rates in MMR-proficient cells (48, 58, 59), and we find the same effect in T. brucei. In Escherichia sp. and Salmonella sp., this effect is mainly attributable to MMR over a wide range of sequence divergence, because base mismatches only weakly affect RecA-catalyzed recombination (60, 61) and only slightly reduce recombination rates in mutS mutants (62). In Bacillus subtilis, in contrast, MMR appears to play only a small role (63), with the recombination machinery largely responsible for substrate selection (although this might be a consequence of transformation occurring under starvations conditions (33)). Streptococcus pneumoniae seems to fall somewhere between these extremes (64, 65). In S. cerevisiae, MMR is the sole determinant of decreased recombination up to around 10% sequence divergence, and thereafter the recombination machinery itself becomes sensitive to base mismatches (48). Over a narrower range of sequence divergence (up to 1.5%), MMR appears to play a similarly primordial role in regulating mammalian recombination (66). Our results suggest that T. brucei homologous recombination is somewhat different from the other eukaryotes examined thus far. Although the T. brucei MSH2–/– mutants recombined more frequently than MMR+ cells at all levels of sequence divergence (1–11%), indicating the importance of this system in regulating homologous recombination, both cell types also showed a cumulative reduction in recombination efficiency with increasing mismatches and a significant drop at just 1% divergence. This indicates that the MMR machinery alone does not determine the success or failure of recombination on mismatched substrates, but most likely the homologous recombination machinery itself is sensitive to mispaired bases during strand exchange. Although this distinction from yeast might be accounted for by the different assays used (indeed, some experimental systems in S. cerevisiae have failed to detect a role for MMR in regulating recombination (67, 68)), it may also indicate that eukaryotes, like bacteria, vary in the balance they strike between substrate selection by the recombination ma-

**Table I**

**Summary of recombination frequencies**

The mean transformation frequencies (×10⁻⁶) of the two MSH2–/– mutants (MMR−) were averaged and shown at each level of sequence divergence, as was the data for wild type cells and both MSH2+/− cells (MMR+). For both data sets, values highlighted in gray show the fold reduction relative to substrates with 100% sequence identity. MMR−/− MMR+ provides a measure of the fold increase in transformation frequency of the MSH2–/– cells relative to MMR+ cells.

| Identity (%) | MMR+ | MMR− | MMR− / MMR+ |
|-------------|------|------|-------------|
| 100         | 9.34 | 14.7 | 1.57        |
| 99          | 3.39 | 2.76 | 2.43        |
| 98          | 0.93 | 10.0 | 6.04        |
| 97          | 0.47 | 19.9 | 41.6        |
| 95          | 0.26 | 33.4 | 20.8        |
| 93          | 0.17 | 54.9 | 32.1        |
| 89          | 0.10 | 93.4 | 4.07        |

**Fig. 5.** Regression analysis of the relationship between transformation frequency and sequence divergence. In transformation frequency was plotted for the combined data in Table I relative to % divergence: MSH2–/– represents the data from the two homozygous mutants, whereas MMR+ shows the combined wild type and MSH2+/− data. To the side of each line of best fit the coefficient of determination (R²) and slope (in parentheses) are indicated.
chinery and mismatched substrate rejection by the MMR machinery.

Minimal efficient processing sequences (MEPS), the shortest length of perfect sequence homology required for efficient recombination, is a concept first suggested by Shen and Huang (69) in examining the relationship between substrate size and recombination rate in bacteria. It has subsequently been extended to substrates of fixed length with increasing mismatches in both bacteria and yeast (48, 62). MEPS can be predicted from substrates of fixed length with increasing mismatch and mismatched substrate rejection by the MMR machinery and DNA substrates nor deletion of MSH2 should affect transformation efficiency, it is a valid means to determine MEPS length in *T. brucei*. Performing this analysis (Fig. 5), we find a log-linear relationship across the range of sequence divergence for both the MMR+ and MSH2−/− cells. We calculate that in MMR+ *T. brucei* the MEPS is 142 bp (44–210 at 95% confidence interval), whereas MSH2−/− cells display an altered regression slope and a reduced MEPS of 103 bp (62–135 bp at 95% confidence interval). This illustrates that the MMR system influences the rate of recombination, as expected. It also shows that the underlying recombination system requires somewhat longer basal substrate homology than described in *S. cerevisiae* and bacteria (48, 62). Our MEPS estimate is somewhat shorter than that made, by very different means, by Papadopoulou and Dumas (45) in *Leishmania*. Transformation experiments have shown that *T. brucei* can recombine shorter substrates than the MEPS length determined here, and this can be quite efficient (70, 71), but our previous work has suggested that these reactions may be catalyzed by a distinct recombination pathway (see below) from the RAD51-dependent reactions in this present study. Why *T. brucei* RAD51-dependent recombination requires relatively long substrates awaits analysis.

This work revealed no strong evidence for an influence of MMR on *T. brucei* antigenic variation, a substantial component of which is driven by homologous recombination. This could be explained by a number of hypotheses. The first, and perhaps simplest, explanation is that most recombinational VSG switching reactions act on perfectly matched sequences. The assay we use to measure VSG switching frequencies is not capable of detecting the very small increase in recombination frequency (1.6-fold) we find on 100% identical substrates, whereas the large increases in recombination frequency (mean 9-fold) seen on substrates with 2–11% mismatches would be clear, as evidenced by the fact that RAD51−/− mutants in the same 3174 strain show a readily detectable mean 7.9-fold reduction in VSG switching frequency compared with wild type cells (*p* value 0.001; (16) and data not shown). This explanation might be surprising, however, because most VSG genes are activated by recombination reactions involving highly degenerate 70-bp repeat flanking sequences, making a perfect match rare (72). Moreover, imposing a perfect match would have important ramifications for how the VSG repertoire is used during antigenic variation (see below). In the *T. brucei* system we have used most switches appear, in fact, to delete both antibiotic genes and therefore do not recombine on the 70-bp repeats but on an upstream, presumably expression site-associated, gene sequence that may provide greater degrees of homology (47). Nevertheless, gene conversion events that remove just the VSG221 and G418 resistance marker, and must recombine using the 70-bp repeats, are readily detectable, and we find no evidence that these become more frequent after MSH2 inactivation. A second explanation for our data could be that VSG switching reactions are “immune” from surveillance by the MMR machinery, setting them apart from general recombination reactions. One way this might be achieved is by exploiting a novel pathway of homologous recombination. We know that *T. brucei* poses at least two pathways of homologous recombination: the predominant pathway is RAD51-dependent, and another is RAD51-independent and appears to act on short substrates (43). Although the use of short regions of homology as substrates might circumvent MMR action on any mismatches, the lack of RAD51 involvement in this pathway is incompatible with the important role of this enzyme in VSG switching (16). The actively transcribed bloodstream expression site found is in a specific subnuclear domain called the expression site body (5). We have much to learn about the expression site body, but it is possible that the telomeric VSG gene is contained in this structure, and it is also the environment in which VSG switching by recombination takes place. In theory, at least, the organization of the expression site body might exclude the MMR machinery from scanning VSG recombination reactions. Blundell et al. (44) have suggested a third explanation: perhaps *T. brucei* can suppress the MMR system to allow VSG switching to proceed. There is no evidence to support such a contention, but transient down-regulation of MMR has been suggested previously (63, 73) to occur in a number of bacterial species.

The *T. brucei* strain used in these experiments undergoes antigenic variation at rates of around 0.1–1.0 × 10−6 events/cell/generation. This is significantly lower than the rates described in other strains, referred to as pleomorphic, which switch around 10−5–10−2 events/cell/generation (reviewed in Ref. 2). A higher switch rate appears to result from a greater use of recombinational events (15), but the underlying cause(s) remains unknown. From this work, we can exclude that impairment or down-regulation of MMR in pleomorphic *T. brucei* cells *T. brucei* unconstrains recombination and gives rise to a high VSG switching rate. Therefore, this is not comparable with the −1000-fold increase in recombination rates found as a result of MutS or MutL inactivation in at least some bacteria (35, 74, 75), or the important role that mismatch repair plays in regulating phase variation in *Neisseria meningitidis* (76). Nevertheless, MMR clearly influences substrate selection in *T. brucei* homologous recombination, and it would therefore be interesting to determine whether it contributes to VSG switching in a subtle way by influencing the VSG genes that are selected for activation during a long term infection. It is known that VSG activation displays a hierarchy, which likely extends the time of the parasite infection (2, 77), and MMR-dependent selection of VSGs and flanks with sufficient sequence homology could be one component of this.

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