Genetic and biochemical studies have indicated that mismatch repair proteins can interact with recombination intermediates. In this study, gel shift assays and electron microscopic analysis were used to show that the *Saccharomyces cerevisiae* MSH2/6 complex binds to Holliday junctions and has an affinity and specificity for them that is at least as high as it has as for mispaired bases. Under equilibrium binding conditions, the MSH2/6 complex had a $K_d$ of binding to Holliday junctions of 0.5 nM. The MSH2/6 complex enhanced the cleavage of Holliday junctions by T4 endonuclease VII and T7 endonuclease I. This is consistent with the view that the MSH2/6 complex can function in both mismatch repair and the resolution of recombination intermediates as predicted by genetic studies.

Virtually all recombination models propose the formation of heteroduplex joints during recombination in which a single strand from one parental DNA is paired with a complementary strand from another parental DNA (1, 2). When the two single strands differ in sequence, the resulting heteroduplex intermediate contains mispaired bases. These mispaired bases are generally processed by the MutHLS mismatch repair pathway in bacteria and the related pathway in eukaryotes that utilizes the MSH2, MSH3, MSH6, PMS1, and MLH1 gene products (3–5). Some specific mispaired bases like T-G, A-G, and A-C can also be repaired by the base-specific mismatch repair pathways, and some other mispaired bases like C-C and palindromic insertion mispairs sometimes escape repair at significant frequencies (3–6).

In addition to repairing mispaired bases, the MutHLS type of mismatch repair pathways are also known to play other roles in recombination. One example of this is that recombination between divergent, so-called homologous DNA sequences occurs at reduced frequency compared with recombination between homologous sequence (7). This regulation of recombination occurs as a consequence of the formation of mispaired bases in recombination intermediates and is also dependent on mismatch repair genes such as *mutS*, *mutL*, *MSH2*, *MSH3*, *MLH1*, *PMS1*, and probably other such genes. Such effects have been extensively documented in bacteria, yeast, and mammalian cells (7–18). Two models have been proposed that could explain these observations. One is that mismatch repair recognizes recombination intermediates that are formed from divergent DNAs and contain multiple mismatches and destroys them as a byproduct of repair (19, 20). Alternately, some combination of mismatch repair enzymes could recognize the formation of mispaired bases in recombination intermediates and block the formation of the mature recombination intermediate (21–23). Consistent with this latter model, *Escherichia coli* mismatch repair enzymes can block the RecA-mediated branch migration *in vitro* when the recombining DNAs contain sequence differences (24).

A second type of regulation of recombination has been observed during the study of gene conversion polarity gradients (6, 22, 23). Gene conversion polarity gradients are thought to be due to a gradient of heteroduplex DNA that is highest near the site where recombination initiates and decreases with increasing distance away from the initiation site. However, in mismatch repair-deficient mutants or when mutations that form mispairs that escape mismatch repair are located at the low end of the polarity gradient, the extent of apparent heteroduplex formation at the low end of the gradient is increased to the level seen at the high end of the gradient. Three models have been presented to explain this. One suggests that polarity gradients are due to restoration repair occurring specifically at the low end of the gradient (6). A second is that heteroduplex DNA formed at the low end of the gradient is specifically unwound when mispaired bases are present (22). The third is that, once mispaired bases are formed at the low end of the gradient, this causes the resolution of the Holliday junctions that are extending the heteroduplex regions. This would leave symmetrically located nicks in the recombinant DNA molecules, which could serve to initiate compensating mismatch repair that would eliminate the genetic consequences of heteroduplex DNA at the low end of the polarity gradient (22). Each of these models postulates the coordination of mismatch repair/recognition with the process of heteroduplex formation and recombination intermediate resolution.

A different type of effect of mismatch repair-related proteins on recombination was observed through the discovery of *Saccharomyces cerevisiae* MSH4 and MSH5 (25, 26). These proteins are apparently not required for mismatch repair but are required for meiotic crossing over, as mutations in *MSH4* and *MSH5* reduce the frequency of crossing over and cause defects in chromosome segregation during meiosis. Humans and mice
also contain MSH4 and MSH5, and mice containing mutations in MSH5 have meiotic defects suggesting that the human and mouse proteins act in the same processes as the S. cerevisiae proteins (27, 28). In both humans and S. cerevisiae, MSH4 and MSH5 form a heterodimer consistent with the results that mutations in each of the two S. cerevisiae genes cause similar defect in meiotic crossing over (28, 29). Recent studies have suggested that MLH1 plays a role in meiotic crossing over similar to that proposed for MSH4 and MSH5 (30). One possible explanation for these observations is that MSH4, MSH5, and possibly MLH1 interact with recombination intermediates and regulate their resolution.

Although it is clear that mismatch repair and mismatch repair-related proteins play important roles in regulating recombination, particularly in eukaryotes, there is little information about the mechanism of these processes. In the first two cases discussed above, there must be some interaction between the processes that recognize and repair mispaired bases and the processes/intermediates that form heteroduplex DNA. In the latter case, MutS-related proteins play a role in how recombination intermediates are resolved, suggesting they may actually recognize recombination intermediates. In previous studies, we demonstrated that MSH2 can recognize Holliday junctions in DNA, suggesting it may play a role in the processing of Holliday junctions (31). It is known that MSH2 functions in a complex with either MSH3 or MSH6 and that the MSH2/3 and MSH2/6 complexes have different mispair recognition properties compared with MSH2 alone (for reviews see Refs. 3, 5, 32, and 33). To further analyze the role of MSH2 in Holliday junction processing, we have investigated the ability of MSH2-MSH6 complex to recognize Holliday junctions and modify their processing by Holliday junction resolution enzymes.

**MATERIALS AND METHODS**

**Purification of S. cerevisiae MSH2/6—** S. cerevisiae MSH2/MSH6 was purified using a method similar to that described by Alani (34). MSH2 and MSH6 were coexpressed in the presence of galactose from strain RKY2418 containing pRDK354 encoding MSH2 and pDRK568 encoding MSH6. Cell extracts were made from galactose-induced cells by grinding under liquid nitrogen, and the MSH2-MSH6 was purified by sequential chromatography on PBE94, single-strand DNA pullulanose, and Q-Sepharose using chromatography conditions that were essentially the same as those described by Alani (34). Details of the purification will be described elsewhere. Analysis of the protein preparation by SDS-PAGE is presented in Fig. 1A. Densitometric analysis demonstrated that the purity of MSH2/6 in the final fraction was determined to be greater than 95% and the molar ratio of MSH2 to MSH6 was 1:1. Gel filtration analysis using a Pharmacia SMART column supported by 400-mesh copper grids. The grids were stained with sequential washes of water and a graded ethanol series, air-dried, and rotary shadowcast at 10⁻⁷ torr with tungsten. Samples were examined in a Philips CM12 instrument. Images were taken on sheet film, scanned with a Nikon LS4500 AF film scanner, and the contrast adjusted with Adobe Photoshop.

**Formation of MSH2/6·Holliday Junction Complexes for Electron Microscopy—** Complexes of MSH2/6 with Holliday junction DNA were formed by incubating the DNA (5 μg/ml) with MSH2/6 in a 20-μl volume at a molar ratio of 40 MSH2/6 heterodimers per Holliday junction DNA for 15 min at room temperature in a buffer containing 40 mM NaCl, 20 mM HEPES, pH 7.6, 0.1 mM EDTA, 0.1 mM DTT, and 40 μg/ml bovine serum albumin. The DNA-protein complexes were then prepared for EM by fixation with 0.6% glutaraldehyde for 10 min at room temperature, followed by filtration through 2-ml columns of BioGel A5m (Bio-Rad). The purified DNA samples were mixed with a buffer containing 2 mM spermidine, 0.15 M NaCl, and applied for 30 s to thin carbon foils on drops of 400-mesh coverslips. The grids were washed with sequential washes of water and a graded ethanol series, air-dried, and rotary shadowcast at 10⁻⁷ torr with tungsten. Samples were examined in a Philips CM12 instrument. Images were taken on sheet film, scanned with a Nikon LS4500 AF film scanner, and the contrast adjusted with Adobe Photoshop.

**RESULTS**

**MSH2/6 Binds to Holliday Junctions—** In previous experiments, MSH2 was observed to bind to oligonucleotide duplexes containing Holliday junctions (31) in addition to its ability to recognize mispaired base present in oligonucleotide duplexes (36, 37). In contrast, the available evidence suggests that isolated MSH6 only interacts with DNA nonspecifically (34, 38, 39). Because MSH2 is known to function in a complex with MSH6 (3, 5, 34, 40, 41), we tested whether MSH2/6 heterodimers would also bind to Holliday junctions. In the present experiments, gel mobility shift experiments were used to assess the binding of MSH2/6 to the same series of eight Holliday junction substrates (J0-J12) previously used to study binding of MSH2 (31). In addition, binding of MSH2/6 to a control oligonucleotide homoduplex (G:G) and an oligonucleotide heteroduplex (G:T) was assessed. The MSH2/6 preparation (Fig. 1A) used in these experiments was greater than 95% pure, had a molar ratio of MSH2 to MSH6 of 1:1, and did not contain any free MSH2 or free MSH6. In experiments where increasing amounts of MSH2/6 were incubated with a fixed amount of different DNA substrates, increasing amounts of MSH2/6 complexed with either the J12 Holliday junction or G:T- or G:C-containing duplexes were observed (Fig. 1B). In this case, the relative affinity of MSH2/6 for the different DNA substrates appeared to be J12 > G:T > G:C. Similarly, in experiments with a fixed amount of MSH2/6 and increasing amounts of either G:C- or G:T-containing duplex substrates, MSH2/6 bound to greater amounts of J12 at lower substrate concentration than to a G:T-containing duplex. The binding of MSH2/6 to J12 and
G:T-containing duplex was found to be saturating at 1.1 and 0.9 pmol of MSH2/6 per pmol of substrate, assuming that the active species is a MSH2/6 heterodimer.

In previous experiments with MSH2, equilibrium binding conditions were not achieved (31). To determine if equilibrium binding was observed with MSH2/6, two different experiments were performed with J12 Holliday junction, and the G:T- and G:C-containing duplexes. In one experiment, each labeled substrate was mixed with different amounts of unlabeled competitor (molar ratios of 2.5:1 to 50:1 were tested) and incubation with MSH2/6 at a 5:1 ratio of MSH2/6 per labeled substrate was performed for 60 min prior to measuring the relative amount of labeled substrate present in complex. In a second experiment, MSH2/6 was incubated with labeled J12, G:T, or G:C substrate for 60 min to preform complexes. Then the same ratios of unlabeled competitors were added and incubation continued. The results showed equal amounts of competition independent of whether competitors were added before or after the MSH2/6 complexes were formed with labeled substrate (not shown). This demonstrated that, under the binding conditions used in the present experiments, equilibrium binding is achieved. This allows the data of Fig. 1C to be analyzed by Scatchard analysis yielding \( K_d \) values of 0.5 and 0.7 nM for MSH2/6 binding to the J12 and G:T substrates, respectively.

To further analyze the specificity of MSH2/6 for Holliday junctions, a series of competition experiments were performed in which labeled G:T-containing substrate was mixed with different amounts of unlabeled G:T-, J12, or G:C-containing competitors and the amount of complex formed between MSH2/6 and labeled G:T-containing substrates was measured. Analysis of the results showed that J12 was a slightly better competitor than G:T, which was a significantly better competitor than G:C (Fig. 2A). When these data were analyzed by the method of Chi and Kolodner (42), MSH2/6 was found to have a 9.4- and 5.6-fold greater affinity for J12 and G:T, respectively, compared with G:C. In a second series, a 10-fold excess of eight different Holliday junctions, as well as G:T- and G:C-containing duplexes, were tested for their ability to compete for binding of MSH2/6 to labeled G:T-containing substrate (Fig. 2B). The results showed that under these conditions, theoretical competition was observed for the G:T competitor. The G:T competitor was about a 7-fold better competitor than G:C, and all of the Holliday junctions tested were significantly better competitors than the G:T competitor, with some being up to 3-fold better competitors than the G:T competitor. These data demonstrate that MSH2/6 binds specifically to both G:T- and Holliday junction-containing substrates compared with G:C-containing substrate and that MSH2/6 likely recognizes Holliday junctions with greater affinity than the G:T-containing substrate tested here. In a study to be published elsewhere, we have analyzed the ability of MSH2/6 to recognize 65 different mispaired base-containing DNAs including all possible base-
base mispairs and numerous insertion/deletion mispairs ranging from +1 base to +16 bases. In no case did the affinity of MSH2/6 for another mispaired base exceed the affinity seen here for the G:T-containing substrate. Thus MSH2/6 appears to generally have a higher affinity for the Holliday junctions studied here than for mispaired bases.

**Visualization of MSH2/6 Bound to Holliday Junctions**—The preceding experiments demonstrate that MSH2/6 binds strongly to DNA molecules containing a Holliday junction, but do not address the question whether it binds directly to the junction as contrasted to binding along an arm or as an extreme case, binding to the ends of the four arms and then coalescing to form a more stable complex. To address this, EM was used to examine complexes of MSH2/6 with a synthetic Holliday junction DNA (31, 35) containing four arms of ~565 base pairs extending from the J12 junction of Picklesley et al. (43) as described previously (31, 35). This DNA, termed Hol565, was incubated with MSH2/6 at a ratio of 40 heterodimers per junction DNA for 15 min and the samples then fixed with glutaraldehyde followed by preparation for EM (44). Examination of fields of molecules revealed Holliday junction DNAs with four extended arms and, in many cases, with proteins bound (Fig. 3). In one experiment, 79% of the DNA molecules scored (n = 89) showed MSH2/6 bound while 21% of the molecules were protein-free. Of the Holliday junction molecules containing MSH2/6, 82% showed a large protein complex centered over the junction while 18% had protein balls located along one or more arms or at a DNA terminus. In general, the four DNA arms exiting the MSH2/6 complex were well separated from each other, often taking nearly 90° trajectories. When the incubation buffer contained 5 mM MgCl₂, conditions used below for the endonuclease cleavage experiments, all four DNA arms were most often folded back on themselves, generating a thick DNA filament having the length of one DNA arm and with a protein complex at one end (not shown). Reduction of the molar ratio of MSH2/6 to Holliday junction DNA to 5:1 resulted in a lower amount (25%) of the Holliday junction DNA-containing bound protein. From these results we conclude that the protein is mostly localizing to the junction as contrasted to elsewhere on the DNA and binds with very high specificity as shown above.

Previous EM studies demonstrated that MSH2 can also bind
to Holliday junctions (31). Using the same substrates and binding conditions, 25% of the Holliday junctions had MSH2 bound at a single site and 75% were protein-free. Of the DNAs with MSH2 bound, 61% had MSH2 bound at the junction, 21% had MSH2 bound at an end and 18% had MSH2 bound at a single internal site on an arm. As described above, MSH2/6 complex bound to over three times more DNA molecules and with a greater proportion of binding at the junction. These results suggest that MSH2/6 has a greater affinity and specificity for Holliday junctions compared with MSH2 alone.

**Binding of MSH2/6 to Holliday Junctions Enhances Their Cleavage by Two Junction-specific Endonucleases**—In order to further characterize the binding of MSH2/6 to Holliday junctions, we tested whether the binding of MSH2/6 would occlude the Holliday junction from access by the Holliday junction resolution enzymes T4 endo VII and T7 endo I. Complexes of MSH2/6 were formed with a 32P-labeled Holliday junction DNA containing 75-bp arms (Hol75 DNA (35)). The DNA was incubated with either no MSH2/6 or 40 heterodimers per junction DNA. T4 endo VII (1, 2, 5, or 10 ng) or T7 endo I (1, 2, 3, 5, or 12 ng) were added to each sample, and incubation continued under conditions where the enzymes were competent for cleavage. The DNA was deproteinized, electrophoresed on an acrylamide gel, and imaged by autoradiography. As shown in Fig. 4 (A and B) and quantified by phosphoimager analysis (Fig. 4C), the binding of MSH2/6 to the Hol75 DNA significantly facilitated its cleavage by both enzymes as contrasted to parallel incubations lacking MSH2/6. Under the salt conditions required for enzyme cleavage, approximately half of the Holliday junctions would have been complexed by MSH2/6. The effect of MSH2/6 was particularly evident when only 1 ng of T4 endo VII was present in the reaction; under these conditions, at least a 2-fold enhancement of cleavage was observed in the presence of MSH2/6. A prior study of the binding of p53 to Holliday junctions (35) similarly revealed that, although the junctions were hidden by a large mass of protein (as seen by EM), they were nonetheless more sensitive to cleavage by two well-characterized junction-resolving enzymes, T4 endo VII and T7 endo I.

To follow the kinetics of junction cleavage, the Hol75 DNA was preincubated with either no MSH2/6 or 40 heterodimers per DNA, followed by the addition of 100 ng of T4 endo VII or T7 endo I for 15 min. Aliquots were removed over this period and the cleavage patterns analyzed by acrylamide gel electrophoresis. The results (Fig. 5) revealed that, for both enzymes, the rate of cleavage of the Holliday junctions was markedly greater when the Holliday junctions were first complexed by MSH2/6. The greatest difference was noted with T7 endo I (Fig. 5, B and C), where a roughly 3-fold difference in the rate of cleavage was observed. These data suggest that MSH2/6 binds to Holliday junctions and alters their structure in some way so as to either make them more assessable to the Holliday junction resolution enzymes tested or increase the activity of these enzymes on the substrate DNA.

**DISCUSSION**

Genetic studies demonstrating that mismatch repair proteins might play a role in the resolution of recombination intermediates previously led us to perform experiments demonstrating that MSH2 protein could specifically recognize Holliday junction recombination intermediates (22, 23, 31, 45). Because MSH2 is known to function as part of a complex with other MutS-related proteins, we have now extended our previous studies to the analysis of the interaction between the MSH2/6 complex and Holliday junctions. The results of these studies indicate that the MSH2/6 complex can interact with DNA molecules containing Holliday junctions due to a specific interaction with the Holliday junction. Several observations support this view. First, a high proportion of the Holliday junctions would have been complexed by MSH2/6. The effect of MSH2/6 was particularly evident when only 1 ng of T4 endo VII was present in the reaction; under these conditions, at least a 2-fold enhancement of cleavage was observed in the presence of MSH2/6. A prior study of the binding of p53 to Holliday junctions (35) similarly revealed that, although the junctions were hidden by a large mass of protein (as seen by EM), they were nonetheless more sensitive to cleavage by two well-characterized junction-resolving enzymes, T4 endo VII and T7 endo I. To follow the kinetics of junction cleavage, the Hol75 DNA was preincubated with either no MSH2/6 or 40 heterodimers per DNA, followed by the addition of 100 ng of T4 endo VII or T7 endo I for 15 min. Aliquots were removed over this period and the cleavage patterns analyzed by acrylamide gel electrophoresis. The results (Fig. 5) revealed that, for both enzymes, the rate of cleavage of the Holliday junctions was markedly greater when the Holliday junctions were first complexed by MSH2/6. The greatest difference was noted with T7 endo I (Fig. 5, B and C), where a roughly 3-fold difference in the rate of cleavage was observed. These data suggest that MSH2/6 binds to Holliday junctions and alters their structure in some way so as to either make them more assessable to the Holliday junction resolution enzymes tested or increase the activity of these enzymes on the substrate DNA.
junction-containing DNAs can be bound by MSH2/6. Binding saturation occurs at a molar ratio of approximately 1 MSH2/6 complex per Holliday junction. This value is similar to that obtained with a G:T mispair-containing substrate, a mispair known to be efficiently recognized by MSH2/6 in vitro and in vivo. Second, competition experiments and equilibrium binding experiments have shown that MSH2/6 complex has a higher affinity for Holliday junctions than for either control duplex DNAs or DNAs containing well recognized mispairs like G:T.

In previous experiments, MSH2 was observed to bind to oligonucleotide duplexes containing Holliday junctions (31) in addition to its ability to recognize mispaired bases. MSH6 in oligonucleotide duplexes (36, 37). In contrast, MSH2/6 appears to be in equilibrium with Holliday junctions, an unstable complex and a stable complex. In contrast, MSH2/6 appears to be in equilibrium with Holliday junctions in solution and only one type of complex is formed. Finally, EM experiments demonstrate that, compared with MSH2, MSH2/6 shows a greater specificity for binding at the junction compared with interaction at other locations on the Holliday junction-containing substrate. These observations indicate that not only does the presence of the MSH6 subunit change the character of the interaction between MSH2 and Holliday junctions, it also increases the specificity and affinity for interaction with Holliday junctions. These data support the idea that MSH6 modifies the intrinsic ability of MSH2 to recognize Holliday junctions and further support the idea that the MutS family of proteins interact with structures like Holliday junctions in vivo.

A number of genetic studies have demonstrated that mismatch repair proteins interact with recombination intermediates and alter their resolution and/or processing in response to the extent of mispairing between the recombining DNAs. One idea that has been suggested is that proteins like MSH2 or, as shown here, MSH2/6 can coordinate the resolution of recombination intermediates in response to mispairing by virtue of their ability to recognize both mispaired bases and structures like Holliday junctions (22, 31). The observation that the binding of MSH2/6 to Holliday junctions enhanced the cleavage of these structures suggests that the interaction between MSH2/6 and Holliday junctions alters the structure of the Holliday junction in some way that enhances their accessibility to the T4 and T7 endonucleases. It was not possible to test the effect of
MSH2/6 on the appropriate eukaryotic Holliday junction resolution enzymes because the identity of these proteins has not yet been clarified and they are not available in pure form. However, the observation that MSH2/6 enhances the cleavage of Holliday junctions suggests that MSH2/6 and possibly other MutS-related proteins may be components of the Holliday junction resolution machinery. This suggests that MSH2/6 could be a useful reagent for use in the identification of other proteins that function in Holliday junction resolution.

Genetic and biochemical studies have documented three different heterodimeric complexes of MutS-related proteins that function in the nucleus in genetic recombination and in some cases mismatch repair. These are MSH2/6, MSH2/3, and MSH4/5, the latter of which appears to only be required for efficient meiotic crossing over (3, 5, 29, 40, 41). MSH2 appears to have an intrinsic ability to recognize mispaired bases and other structures in DNA and the MSH3 and MSH6 subunits appear to alter the ability of MSH2 to interact with these structures as well as possibly interact with other proteins (3). It is not known what structures MSH4, MSH5, or the MSH4/5 complex recognize in DNA. However, by analogy to the properties of MSH2, MSH3, and MSH6 and taking into account the genetics of MSH4 and MSH5, it seems likely that MSH4/5 also recognizes some DNA structure involved in recombination. Such recognition could occur in conjunction with other MSH proteins and other mismatch repair proteins like MLH1 (30). It seems likely that it is different DNA structure recognition properties of these complexes and different abilities to interact with other proteins and recombination/repair pathways that accounts for the different roles these proteins appear to play in recombination.

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