Cadmium Inhibits the Functions of Eukaryotic MutS Complexes*

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Exposure of yeast cells to low concentrations of cadmium results in elevated mutation rates due to loss of mismatch repair (MMR), and cadmium inhibits MMR activity in extracts of human cells (1). Here we show that cadmium inhibits both Msh2-Msh6- and Msh2-Msh3-dependent human MMR activity in vitro. This inhibition, which occurs at a step or steps preceding repair DNA synthesis, is observed for repair directed by either a 3′ or a 5′ nick. In an attempt to identify the protein target(s) of cadmium inhibition, we show that cadmium inhibition of MMR is not reversed by addition of zinc to the repair reaction, suggesting that the target is not a zinc metalloprotein. We then show that cadmium inhibits ATP hydrolysis by yeast Msh2-Msh6 but has no effect on ATPase hydrolysis by yeast Mlh1-Pms1. Steady state kinetic analysis with wild type Msh2-Msh6, and with heterodimers containing subunit-specific Glu to Ala replacements inferred to inactivate the ATPase activity of either Msh2 or Msh6, suggest that cadmium inhibits ATP hydrolysis by Msh6 but not Msh2. Cadmium also reduces DNA binding by Msh2-Msh6 and more so for mismatched than matched duplexes. These data indicate that eukaryotic Msh2-Msh3 and Msh2-Msh6 complexes are targets for inhibition of MMR by cadmium, a human lung carcinogen that is ubiquitous in the environment.

Experimental procedures

Cell-free Extracts, Mismatch Repair, and In Vitro Replication Assays—Procedures for extract and heteroduplex substrate preparation and for measuring repair activity were as described (22). The substrates used are in the legend to Fig. 1. SV40 origin-dependent DNA replication assays were performed as described (22). Where indicated, the reaction mixture was preincubated with 50 μM CdCl2 for 10 min at 0 °C prior to adding substrate.

Purification of Heterodimers—yMlh1-yPms1 was purified as described previously (24).

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The abbreviations used are: MMR, mismatch repair; IDL, insertion/deletion; RPA, replication protein A; RFC, replication factor C; PCNA, proliferating cell nuclear antigen.

δ are killed by cadmium, and proofreading defective diploid strains treated with cadmium survive and show synergistic mutagenesis with cadmium. These observations and the lack of or weak mutagenesis upon treatments with equivalent concentrations of other metals and agents causing DNA damage all suggest that cadmium-induced mutagenesis is not due to DNA damage per se but is rather due to inhibition of MMR of DNA replication errors. In further support of this hypothesis, cadmium inhibits the ability of extracts of human cells to repair a single-base insertion deletion mismatch in vitro (1), and cadmium treatment of cultured human cells suppresses MMR-mediated cell cycle arrest after exposure to the alkylating agent MNNG (5).

Possible protein targets for cadmium inhibition of MMR can be considered in light of extensive knowledge of eukaryotic MMR gained over the past ten years (reviewed in Refs. 6–15). Eukaryotic MMR is initiated when complexes of Msh2-Msh6 (MutSα) or Msh2-Msh3 (MutSβ) bind to a mismatch. MutSα is primarily responsible for repairing single base-base and insertion/deletion (IDL) mismatches, MutSβ is primarily responsible for repairing IDL mismatches containing multiple extra nucleotides in one strand, and the two complexes share responsibility for repairing IDL mismatches with one extra base. Eukaryotes also encode multiple MutL homologs that form different heterodimers. These heterodimers act as matchmakers to coordinate the various steps in MMR. MutLα (Mlh1-Pms1 in yeast) is involved in repairing a wide variety of mismatches, while MutLβ (Mlh1-Mlh2) and MutLγ (Mlh1-Mlh3) are thought to participate in repairing a subset of insertion-deletion mismatches. Several exonucleases are implicated in mismatch excision, especially including Exo1, and excision and DNA re-synthesis also require MutSα, MutLα, RPA, RFC, PCNA, and DNA polymerase δ (see Refs. 16 and 17 and references therein).

Inactivation of MMR protein functions is well known to have numerous biological consequences, including genome instability, resistance to DNA damaging agents including chemotherapeutic drugs, altered class switch recombination and somatic hypermutation of immunoglobulin genes, emergence of pathogenic bacteria, infertility, and increased susceptibility to cancer (reviewed in Refs. 6, 7, 12, 13, 15, and 18–20). Because cadmium is ubiquitous in the environment and can accumulate in the body due to a long biological half-life (Ref. 21 and references therein), and because cadmium is a known carcinogen that inhibits MMR, we undertook the present study to identify the MMR protein target(s) and the mechanism of inhibition of MMR by cadmium. Here we present evidence that cadmium inhibits two functions of eukaryotic MutS complexes, ATP hydrolysis, and specific binding to mismatched DNA. These effects are sufficient to explain cadmium inhibition of MMR activity in vivo.

EXPERIMENTAL PROCEDURES

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medium containing 2% galactose and purified as previously described with the following modifications (25). The heterodimer was step eluted from a nickel resin column with 100 mM imidazole, 20 mM Tris, pH 8, 200 mM NaCl and 5 mM β-mercaptoethanol. After eluting from a 1-ml heparin column, the fractions were applied to a 1 ml HiTrap Q column. Eluted fractions were dialyzed against 20 mM Tris, pH 8, 200 mM NaCl, 1 mM EDTA, and 1 mM dithiothreitol and stored at −70 °C. ATPase Assays—ATPase activity was assayed at 30°C in 20 μl reaction mixtures containing 25 mM Tris, pH 7.5, 2.5 mM MgCl2, 200 mM NaCl, 1 mM EDTA, 0.1 mM dithiothreitol, 40 μg/ml bovine serum albumin. Concentrations of enzymes and ATP used were 300 nM yMsh2-yPms1 and 0.25–50 μM γ[32P]ATP, unless otherwise indicated. Where indicated, reaction mixtures were preincubated with 50 μM CdCl2 for 10 min on ice prior to adding ATP. Products were separated by thin layer chromatography using 0.4 M NH4HCO3 as solvent.

DNA Binding Assays—DNA equilibrium binding assays were performed as described (25, 26). G-T41 heteroduplex and A-T41 homoduplex were prepared from oligonucleotides: 5’-TCGTGTTTACAGCGTGTAATGAGAAGAAGCCCGGCGTTAC, 5’-GTTAGACCCAGGTTTTTTCTGGTTCCAGCGTTGAAGAACGA, and 5’-GGTAAACCGCCAGGGTTTTTTCTCATCAGCGTTGAAACAGA. Assays were performed using 0.5–100 nM yMsh2-yMsh6 protein and 1 mM DNA substrate. Where indicated, the reaction mixture was preincubated with 50 μM CdCl2 on ice for 10 min prior to adding substrate. Kd values were determined from gel shift data as described previously (27). RESULTS AND DISCUSSION

Cadmium Inhibition of in Vitro Human Mismatch Repair—We previously showed that low concentrations of cadmium inhibit MMR activity in vitro by extracts of human cells using a substrate containing a 1-base IDL mismatch and a nick to direct strand-specific repair that is located 5’ to the mismatch (see Ref. 1 and left most entry in Fig. 1A). To determine whether cadmium inhibits both MutSα-dependent and MutSβ-dependent MMR, and to determine whether cadmium inhibits MMR involving excision initiated at both 3’ or 5’ nicks, we began this study by examining the ability of cadmium to inhibit MMR using four additional substrates. The MutSα-dependent repair of a G-C mismatch with a nick either 3’ or 5’ to the mismatch was inhibited by 50 μM CdCl2 (Fig. 1A). Additionally, the repair of a 2-base IDL mismatch that was previously shown to depend on MutSβ (28) was also inhibited by 50 μM CdCl2. These results in human cell extracts are consistent with genetic evidence in yeast (1) indicating that cadmium inhibits both MSH2-MSH3- and MSH2-MSH6-dependent repair of base substitution and IDL mismatches. They further show that cadmium inhibition occurs when the nick that serves as the strand discrimination signal is located either 3’ or 5’ to the mismatch. Effect of Other Divalent Metals on MMR Activity—Two proteins involved in MMR, the large subunit of RPA (29) and DNA polymerase δ (30), are known to contain zinc fingers. Like zinc, cadmium has a high affinity for sulfhydryl groups in proteins and can compete with zinc for binding to zinc metalloproteins. We therefore tested whether zinc can prevent cadmium inhibition of MMR activity. In the absence of zinc, 15 μM CdCl2 moderately inhibited MMR (Fig. 1B). Addition of an equal amount of ZnSO4 did not reverse this inhibition (Fig. 1B). This is interesting because zinc is reported to protect against cadmium-induced carcinogenesis (see Ref. 31 and references therein). Thus, the protection awarded by zinc in vitro may occur through another mechanism. Rather than protection, here we observe that zinc alone inhibited MMR activity (Fig. 1, B and C), and the inhibitory effects of cadmium and zinc were additive (Fig. 1B). These data suggest that cadmium is not inhibiting mismatch repair by replacing zinc in a zinc metalloprotein. Instead, they are consistent with the possibility that both metals may inactivate a common MMR protein target. Note that zinc inhibition of MMR is not observed in yeast (1), suggesting that other factor(s) affect the accessibility of metal ions to MutSα in vivo. In contrast to inhibition of MMR activity by cadmium and zinc, neither CoCl2, MnCl2, or NiSO4 inhibited MMR activity (Fig. 2C and Ref. 1). Effects of Cadmium on DNA Replication—Our initial study (1) demonstrated that MMR was inhibited in vivo by concentrations of cadmium that had little effect on yeast cell growth. This implies that cadmium does not strongly inhibit DNA replication. To test this in the human system, we examined the ability of CdCl2 to inhibit SV40 origin-dependent DNA replication catalyzed by the same extracts that were used to measure MMR activity. Addition of 50 μM CdCl2, which strongly inhibits MMR activity (Fig. 1A and Ref. 1), had a negligible effect on replication activity or on the distribution of replication products (Fig. 1D). The fact that cadmium does not inhibit yeast cell growth and has little effect on SV40 origin-dependent DNA replication in human cell extracts suggests that those proteins common to replication and MMR, i.e. RPA, RFC, PCNA, and DNA polymerase δ, are unlikely targets for cadmium inhibition of MMR activity. In addition, the assay used to detect MMR activity in our initial study (1) and in Fig. 1A does not require repair DNA synthesis (32). Therefore, cadmium is most likely inhibiting human MMR activity in vitro at a step or steps prior to DNA polymerase-β-mediated elongation.
Cadmium Inhibition of Msh2-Msh6 ATPase

Effect of 50 μM CdCl₂ on yMlh1-Pms1 and yMsh2-yMsh6 ATPase activity

| Protein                      | Km  | Kcat | Kcat/Km |
|------------------------------|-----|------|---------|
| yMlh1-Pms1                  | 19.3| 0.19 | .001    |
| yMlh1-Pms1 + 50 μM cadmium  | 15.2| 0.14 | .001    |
| yMsh2-Msh6                  | 9.6 | 5.0  | 0.52    |
| yMsh2-Msh6 + 50 μM cadmium  | 28.2| 2.3  | 0.08    |
| yMsh2E768A-Msh6             | 0.6 | 0.6  | 1.0     |
| yMsh2E768A, Msh6 + 50 μM cadmium | 4.2 | 0.2 | 0.05 |
| yMsh2-Msh6E1068A            | 3.9 | 0.2  | 0.05    |
| yMsh2-Msh6E1068A + 50 μM cadmium | 4.5 | 0.2 | 0.04 |

Evidence That Cadmium Inhibits ATP Hydrolysis by Msh6 but Not Msh2—MutSo belongs to the ABC transporter family of ATPase proteins, and it has two composite ATPase active sites, each comprised of five conserved motifs contributed by one subunit and a sixth motif contributed in trans by the other subunit. Among these motifs, the Walker B motif of Msh2 and Msh6 contains a conserved glutamate residue that is essential for ATP hydrolysis (25). To determine whether cadmium inhibits ATP hydrolysis by Msh2, Msh6, or both, we performed steady state kinetic analysis of ATP hydrolysis by purified mutant heterodimers containing an inactivating glutamate to alanine substitution in the Walker B motif of either Msh2 (E768A) or yMsh6 (E1062A). Cadmium reduced the efficiency of ATP hydrolysis by the Msh2E768A-Msh6 heterodimer by 20-fold but had no effect on the efficiency of ATP hydrolysis by the Msh2-Msh6E1062A hetetodimer (Table I and Fig. 2C). These results indicate that cadmium inhibits the ATPase activity of yeast MutSo but not MutLo.

Inhibition of yMsh2-Msh6 Mismatch Recognition by Cadmium—The structure of bacterial MutS proteins (33–37) and the relationship of CdCl₂ concentration and inhibition of yMsh2-yMsh6 ATPase concentration was 30 nM. Reactions lacking nickel agarose beads (data not shown). Because cadmium does not inhibit the ATPase activity of MutS mutants heterodimers containing an inactivating glutamate to alanine substitution in the Walker B motif of either Msh2 (E768A) or yMsh6 (E1062A). Cadmium reduced the efficiency of ATP hydrolysis by the Msh2E768A-Msh6 heterodimer by 20-fold but had no effect on the efficiency of ATP hydrolysis by the Msh2-Msh6E1062A heterodimer (Table I and Fig. 2C). These results indicate that cadmium inhibits ATP hydrolysis by yMsh6, but it does not inhibit ATP hydrolysis by yMsh2. This could be due to selective interaction of cadmium with MutSo protein. Alternatively, because residues from Msh2 contribute to the composite ATPase active site in Msh6, ATP hydrolysis by Msh6 could be inhibited by cadmium interactions with Msh2. Experiments are under way to identify the target residues within Msh2 and/or Msh6 that are responsible for cadmium inhibition.

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pair duplex DNAs that were either completely matched or contained a single G-T mismatch. The results show that in the absence of cadmium, and as expected based on earlier studies (38), yeast MutSα binds to mismatched DNA with 34-fold higher affinity than it binds to matched DNA (Table II). However, in the presence of 50 μM CdCl₂, MutSα binding affinity for mismatched DNA was reduced by 18-fold, to the Kd value only slightly higher than that for binding to matched DNA (Table II). Cadmium also reduced binding to matched DNA, but the Kd only increased by 1.6-fold, from 34 to 55 nM (Table II). These results demonstrate that cadmium reduces the DNA binding affinity of MutSα as well as its ability to discriminate between matched and mismatched DNA.

Summary and Implications—The results presented here are consistent with cadmium inhibition of MutSα and MutSβ-dependent MMR activity through interactions that inhibit ATP hydrolysis and reduce DNA binding affinity and mismatch recognition specificity by MutSα and, by extrapolation, perhaps MutSβ. Alone or in combination, these biochemical effects are sufficient to explain the inhibition of human MMR activity observed in vitro and of yeast MMR in cells (1) and the altered response of human cells to alkylination damage (5). However, the results presented here do not completely exclude that cadmium might also interfere with other proteins or steps in MMR.

The interactions of cadmium with Msh2 and/or Msh6 that are responsible for inhibition are unknown. Cadmium could perhaps inhibit ATP hydrolysis by competing with magnesium binding at the ATPase active site that is required for hydrolysis. Although this possibility cannot yet be excluded, it seems unlikely for three reasons. First, cadmium cannot replace magnesium at the ATPase active site that is required for hydrolysis and reduce DNA binding affinity and mismatch recognition specificity by MutSα (data not shown), and the effects we report are observed using cadmium (38), yeast MutSα and MutSβ (1999) Curr. Opin. Genet. Dev. 9, 89–96

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