The MCM3 Acetylase MCM3AP Inhibits Initiation, but Not Elongation, of DNA Replication via Interaction with MCM3*

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Minichromosome maintenance (MCM) proteins are essential components of pre-replication complexes, which limit DNA replication to once per cell cycle. MCM3 acetylating protein, MCM3AP, binds and acetylates MCM3 and inhibits cell cycle progression. In the present study, we examined inhibition of the cell cycle by MCM3AP in a cell-free system. We show here that wild type MCM3AP, but not the acetylase-deficient mutant, inhibits initiation of DNA replication, but not elongation. Both wild type and acetylase-deficient mutant MCM3AP, however, can bind to chromatin through interaction with MCM3. These results indicate that MCM3 acetylase activity of MCM3AP is required to inhibit initiation of DNA replication and that association of MCM3AP to chromatin alone is not sufficient for the inhibition. We also show that interaction between MCM3 and MCM3AP is essential for nuclear localization and chromatin binding of MCM3AP. Furthermore, the chromatin binding of MCM3AP is temporally correlated with that of endogenous MCM3 when cells were released from mitosis. Hence, MCM3AP is a potent natural inhibitor of the initiation of DNA replication whose action is mediated by interaction with MCM3.

Assembly of pre-replication complexes (pre-RC) is a central mechanism used in eukaryotic cells to restrict DNA synthesis to once per cell division cycle. In budding yeast, the origin recognition complex (ORC) is bound to the origins of DNA replication throughout the cell cycle (1–3). After termination of mitosis, Cdc6 binds to ORC at replication origins and triggers the binding of a hexameric protein complex of MCM2–7. Recent studies indicate that another protein, Cdt1, is also required for the chromatin binding of the MCM protein complex (4). The proteins of the pre-RC, i.e. ORC, Cdc6, and the MCM protein complex, are conserved from yeast to mammalian cells, but metazoan systems have additional mechanisms to control the formation of pre-RCs. An example is geminin, which binds to Cdt1 and inhibits chromatin loading of the MCM protein complex (5, 6).

MCM3 acetylating protein, MCM3AP, was isolated from a human cDNA library by two-hybrid screening using human MCM3 as bait (7). MCM3AP can bind to and acetylate MCM3 (8). When MCM3AP is overexpressed, the proportion of cells in S phase decreases and the acetylase activity of MCM3AP is required to establish this inhibition of proliferation (8). An apparent splice variant of MCM3AP, GANP, has been isolated from mouse and human cDNA libraries (9, 10). GANP is a 210-kDa protein, and the entire sequence of MCM3AP is contained within the C-terminal of GANP (10). Like MCM3AP, GANP can bind to MCM3, and it does so through the C-terminal domain that is homologous to MCM3AP. However, acetylase activity of GANP has not been established. GANP is expressed during differentiation of a B cell line and its expression is concomitant with an increase of cell cycling time (9), consistent with the inhibitory effects of MCM3AP on cell cycle progression (8). Recently Kuwahara et al. (11) reported that the N-terminal fragment of GANP has primase activity, suggesting a possibility that GANP and MCM3AP have different functions. The functional relationship between MCM3AP and GANP remains to be clarified.

To determine how MCM3AP decreases the proportion of cells in S phase, we have now reconstituted in vitro the conditions under which MCM3AP can inhibit the cell cycle and asked which aspect of cell proliferation is inhibited. Using the in vitro system, we show that MCM3AP inhibits initiation of DNA replication, but not elongation. We also show here that binding to MCM3 is important for nuclear entry and chromatin binding of MCM3AP. Taken together, our results show that MCM3AP is a natural inhibitor of cell proliferation which targets the inhibition of DNA replication via interaction with MCM3.

EXPERIMENTAL PROCEDURES

Cell Culture, Drug Treatment, and Cell Fractionation—HeLa cells and 293T cells were cultured as monolayers in 10% fetal calf serum in Dulbecco’s minimum essential medium. For examination of GFP-MCM3AP localization and in vivo DNA replication, 293T cells were grown on coverslips in 24-well plates. To analyze chromatin binding of endogenous MCM3AP and MCM3, cells were synchronized in mitosis by treatment with 2.5 mM thymidine for 25 h and then released into culture medium containing 0.04 μg/ml nocodazole for 12 h. Mitotic cells were shaken off plates, washed, and plated again. At specific time points after release from mitosis, cells were harvested and washed once with PBS and twice with hypotonic buffer (10 mM Hepes-KOH, pH 7.3, 5 mM KCl, 1.5 mM MgCl2, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, and protease inhibitors). Cells were resuspended in hypotonic buffer supplemented with 0.5% Nonidet P-40 and incubated on ice for 15 min, followed by a 15-min centrifugation at 3000 rpm at 4 °C. The pellets were washed twice with hypotonic buffer and then resuspended in hypotonic buffer supplemented with 0.5% Nonidet P-40 and

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were incubated with 2.5 mM thymidine in growth medium. After incubation for 20 h, cells were harvested and cultured for 24 h in growth medium followed by another thymidine incubation for 24 h. Then cells were harvested after 3-h culture. The nuclei were isolated from late G1 phase cells or S phase cells as described (12).

Plasmids, Recombinant Protein Expression, and Immunostaining—Plasmids of wild type and acetylase-deficient MCM3AP/EGFP C2, MCM3/pGADT79, MCM3/pCDSN 3.1 His, and wild type MCM3AP/pGAD424 were described previously (7, 8). To generate a MCM3-binding-deficient mutant of MCM3AP we used a QuikChange™ site directed mutagenesis kit (Stratagene) and the DNA sequence of the protein-coding region was confirmed by sequencing. The full-length cDNA of MCM2 was harbored in pcDNA3.1/His (Invitrogen) to express His6-tagged MCM2 in mammalian cells. For transfection of 293T cells, cDNA of MCM2 was harbored in pcDNA3.1/His (Invitrogen) to express His6-tagged MCM2 in mammalian cells. For transfection of 293T cells, we used LipofectAMINE Plus reagent (Invitrogen). After transfection, cells were incubated for 21 h and then washed and fixed with 2% paraformaldehyde for 5 min, then blocked by antibody buffer (2% bovine serum albumin, 0.04% SDS, 0.02% Triton X-100) for 30 min at 37 °C. His6-tagged proteins were detected with anti-polyhistidine antibody (Sigma) and visualized with Texas Red-labeled secondary antibody. Microscopy images were obtained using a Bio-Rad confocal microscopy system.

DNA Replication Assay—For in vivo DNA replication assays, we employed bromodeoxyuridine (BrdUrd) labeling (8). Twenty hours after transfection, cells were labeled with 50 μM BrdUrd for 1.5 h, then fixed with 2% paraformaldehyde and denatured in 50 mM NaOH for 5 min. Incorporated BrdUrd was probed with anti-BrdUrd antibody (American Biosciences) and visualized with Texas Red-labeled secondary antibody. The GFP-positive and BrdUrd-positive cells were counted to estimate the proportion of DNA-replicating cells.

For in vitro DNA replication assays, mimosine-treated HeLa nuclei were prepared as described previously (12). The soluble protein fractions were prepared from asynchronous wild type or mutant MCM3AP-transfected 293T cells or from vector-transfected 293T cells (American Biosciences) and visualized with Texas Red-labeled secondary antibody. The soluble GFP-positive and BrdUrd-positive cells were counted to estimate the proportion of DNA-replicating cells.

RESULTS

MCM3AP Inhibits Initiation of DNA Replication in vitro, but Not Elongation—To clarify the mechanism of MCM3AP-induced cell cycle inhibition, we analyzed DNA replication in vitro using nuclei prepared from HeLa cells arrested in late G1 phase with mimosine (13). Consistent with the report by Krude et al. (12), in vitro initiation of DNA replication was observed in nuclei from mimosine-treated cells, incubated with a soluble protein fraction, whereas elongation of existing forks was abolished with the fraction. The soluble protein fractions were also prepared from transfected 293T cells, and their abilities to support DNA replication were assessed. When mimosine-arrested nuclei were incubated in protein extracts prepared from vector-transfected cells, DNA was replicated in more than 30% of nuclei, as opposed to less than 10% of nuclei replicating in the absence of the soluble protein fraction. When the soluble protein fraction containing wild type GFP-MCM3AP was used for in vitro DNA replication, no significant increase of replicating nuclei above the background was observed (Fig. 1A). However, the protein fractions containing the acetylase-deficient mutant of MCM3AP, in which His471, Gly472, and Gly474 were replaced by alanines, failed to initiate DNA replication in the cell free system (Fig. 1A). In our previous transfection experiments (8), this mutant failed to lower the proportion of whole cells in the S phase. This extends the results of whole cell transfection experiments (8), which showed a decreased proportion of cells in S phase after transfection with MCM3AP, but it does not show whether the effect is on the regulatory step of initiation of DNA replication or only elongation. To assess the effect of MCM3AP on elongation of DNA synthesis, we used S phase nuclei instead of late G1 phase nuclei. Unlike initiation, elongation of DNA replication in S phase nuclei occurs in the absence of the soluble protein fraction as long as nucleoside triphosphates and deoxynucleoside triphosphates are present (‘‘without soluble fraction’’ in Fig. 1B and Ref. 12). In contrast to mimosine-arrested nuclei, wild type MCM3AP-GFP did not have any new DNA replication in S phase nuclei (Fig. 1B), indicating that it can only block the initiation step in DNA replication. The expression levels of MCM3APs were examined by Western blotting as indicated in Fig. 1C. When soluble protein fractions were analyzed from similar numbers of transfected cells, the same amount of MCM3 was found in each fraction, and similar amounts of wild type or mutant GFP-MCM3APs were expressed in the transfectants. These results...
Acetylase-deficient and wild type GFP-MCM3AP bind to chromatin in vitro. A, mimosine-treated HeLa nuclei were incubated with soluble protein fractions prepared from cells that were transfected by either wild type or acetylase-deficient GFP-MCM3AP or by vector (GFP) in the same conditions as the in vitro DNA replication assay except without added digoxigenin labeled dUTP. After nuclei were attached to coverslips, they were stained by propidium iodide. B, after incubation with soluble protein fractions, nuclei were washed out with buffer containing 50 mM Tris-HCl, 100 mM NaCl, and 2 mM MgCl₂, and then the nuclei were incubated with or without 50 units/ml of DNase I in the same buffer at 37 °C. After 30 min, the nuclei were attached to coverslips and observed by confocal microscopy. C, nuclei were sequentially incubated with the soluble protein fraction prepared from cells that were transfected with wild type MCM3AP followed by DNase I as in B. The reaction mixtures were centrifuged, and the supernatants were analyzed by SDS-PAGE and blotted to PVDF membrane. The membrane was incubated with anti-MCM3 antibody or anti-MCM3AP antibody. Antibodies bound to the membrane were detected by HRP-labeled secondary antibody and visualized by ECL (Amersham Biosciences). D, chromatin-bound protein fractions containing 40 μg of proteins were analyzed by SDS-PAGE and blotted to PVDF membrane. The membrane was incubated with anti-MCM3 antibody or anti-MCM3AP antibody. Antibodies bound to the membrane were detected by HRP-labeled secondary antibody and visualized by ECL.

Acetylase Activity Is Not Required for Chromatin Binding—Fig. 2A shows that both wild type and acetylase-deficient GFP-MCM3AP bind to nuclei under the same conditions as those used for the in vitro DNA replication assay in Fig. 1 (except without added digoxigenin dUTP). Nuclear membranes were not required for binding of MCM3AP to nuclei, as it was still observed in the presence of detergent (Fig. 2A). GFP-MCM3AP could be released from nuclei by DNase I treatment (Fig. 2B), indicating that it was bound to chromatin. To clarify the manner of MCM3AP binding on chromatin, soluble proteins were washed out after the in vitro binding of GFP-MCM3AP. GFP-MCM3AP was then released from the chromatin with DNase I and immunoprecipitated with anti-GFP antibody. As shown in Fig. 2C, MCM3 was co-precipitated with GFP-MCM3AP, demonstrating that MCM3AP can bind to chromatin-bound MCM3. These results suggest that MCM3AP can associate with chromatin through MCM3. To assess whether the chromatin binding of MCM3AP is correlated with that of MCM3 in vivo, we examined the behavior of endogenous proteins on chromatin during and after release from mitosis. Consistent with the results described above, binding of endogenous MCM3 and MCM3AP to chromatin occurred over the same time course. As expected from reports in the literature (2, 3, 14, 15), the amount of chromatin-bound MCM3 is increased after release from mitosis and reaches its peak at 7 h after release, decreasing thereafter (Fig. 2D). The chromatin-bound MCM3AP also increased after release from mitosis in parallel to the increase of chromatin-bound MCM3, (Fig. 2D). These results suggest that interaction with MCM3 correlates with chromatin binding of MCM3AP in vivo as well as in vitro. The acetylase activity of MCM3AP is not required for chromatin binding as the acetylase-deficient mutant binds to chromatin equally well.

Both Chromatin Binding and Nuclear Localization of MCM3AP Are MCM3-dependent—Next, we examined the cell-cycle localization of GFP-MCM3AP when overexpressed in the conditions that inhibit cell cycle progression (8). The localizations of overexpressed wild type and the acetylase-deficient mutant of MCM3AP were mainly cytoplasmic (Fig. 3A). However, when cells were treated with leptomycin B, an inhibitor of CRM1-dependent nuclear export, both the wild type and the acetylase-deficient mutant of MCM3AP were localized in the nucleus (Fig. 3A). These results indicate that overexpressed exogenous MCM3AP can be actively exported from the nucleus, while the smaller amounts of endogenous MCM3AP remain

*Fig. 2. Acetylase-deficient* and wild *type GFP-MCM3AP bind to chromatin in vitro*. A, mimosine-treated HeLa nuclei were incubated with soluble protein fractions prepared from cells that were transfected by either wild type or acetylase-deficient GFP-MCM3AP or by vector (GFP) in the same conditions as the in vitro DNA replication assay except without added digoxigenin labeled dUTP. After nuclei were attached to coverslips, they were stained by propidium iodide. B, after incubation with soluble protein fractions, nuclei were washed with buffer containing 50 mM Tris-HCl, 100 mM NaCl, and 2 mM MgCl₂, and then the nuclei were incubated with or without 50 units/ml of DNase I in the same buffer at 37 °C. After 30 min, the nuclei were attached to coverslips and observed by confocal microscopy. C, nuclei were sequentially incubated with the soluble protein fraction prepared from cells that were transfected with wild type MCM3AP followed by DNase I as in B. The reaction mixtures were centrifuged, and the supernatants were analyzed by SDS-PAGE and blotted to PVDF membrane. The membrane was incubated with anti-MCM3 antibody or anti-MCM3AP antibody. Antibodies bound to the membrane were detected by HRP-labeled secondary antibody and visualized by ECL (Amersham Biosciences). D, chromatin-bound protein fractions containing 40 μg of proteins were analyzed by SDS-PAGE and blotted to PVDF membrane. The membrane was incubated with anti-MCM3 antibody or anti-MCM3AP antibody. Antibodies bound to the membrane were detected by HRP-labeled secondary antibody and visualized by ECL.

*Fig. 3. MCM3, but not MCM2, causes MCM3AP to accumulate in the nucleus*. A, wild type MCM3AP or the acetylase-deficient mutant were expressed in 293T cells as GFP-tagged proteins. Twenty hours after transfection, cells were incubated with or without 10 nM leptomycin B in growth medium for 1.5 h. Cells were fixed by 4% paraformaldehyde and observed by confocal microscopy. B, 293T cells were transfected by the combinations of the plasmids indicated. After cells were fixed, His₆-tagged proteins were detected by anti-polyhistidine antibody, visualized by a Texas Red-labeled secondary antibody, and compared with GFP fluorescence from GFP-MCM3AP.
was assessed in vivo. A Leptomycin B as described in the legend to Fig. 3.

A binding-deficient mutant was expressed in 293T cells with or without GFP fluorescence from the GFP-MCM3AP mutant. Visualized by a Texas Red-labeled secondary antibody, and compared deficient mutant MCM3AP and His6-tagged MCM3. After cells were transfected by the combinations of GFP-tagged MCM3-binding

A mutation in MCM3AP that abolishes MCM3 binding prevents nuclear accumulation. A, MCM3AP was mutated as indicated. The ability of mutant and wild type MCM3AP to bind to MCM3 was assessed by yeast 2-hybrid assay. Two-hybrid assay was performed as described (7). The blue color indicates interaction. B, nuclei isolated from mimosine-treated HeLa cells were incubated with the soluble protein fraction prepared from cells that were transfected by either wild type or MCM3-binding-deficient MCM3AP as in Fig 2A. C, 293T cells were transfected by the combinations of GFP-tagged MCM3-binding-deficient mutant MCM3AP and His6-tagged MCM3. After cells were fixed, His6-tagged MCM3 was detected by anti-polyhistidine antibody, visualized by a Texas Red-labeled secondary antibody, and compared with GFP fluorescence from the GFP-MCM3AP mutant. D, the MCM3-binding-deficient mutant was expressed in 293T cells with or without Leptomycin B as described in the legend to Fig. 3A. E, DNA replication was assessed in vivo and in vitro, in the presence of wild type or mutant MCM3AP. For in vivo assay, GFP-tagged wild type or mutant MCM3AP, or GFP alone, was expressed in 293T cells. The proportion of GFP-positive cells that were also BrdUrd-positive is indicated. For in vitro assay, soluble protein fractions were prepared from cells that were transfected by wild type or mutant MCM3AP or vector alone. Dioxigenin-positive nuclei were scored as a percentage of the total number of nuclei, as in Fig. 1A.

localized in nuclei (8). As MCM3AP can bind to MCM3, which is a constitutively nuclear protein, the effect of MCM3 on the localization of MCM3AP was examined. Fig. 3B shows that overexpression of MCM3 causes overexpressed MCM3AP to accumulate in the nucleus, instead of in the cytoplasm. Coexpression of GFP-MCM3AP with MCM2, another MCM protein that appears to contain an NLS, did not have any effects on GFP-MCM3AP localization (Fig. 3B). Thus, MCM3AP is a protein that can shuttle between the nucleus and cytoplasm and can accumulate in the nucleus in an MCM3-dependent manner.

Two different effects of MCM3 binding could explain the results in Fig. 3. One is that MCM3 binding is required for nuclear import of MCM3AP; the other is that nuclear import of MCM3AP is independent of MCM3, while nuclear binding and retention of MCM3AP depends on MCM3. To distinguish between these two alternatives, we used a mutant MCM3AP that could not bind to MCM3. Leu237, Val240, Val241, and Leu242 were substituted with alanines (Fig. 4A). Although we were initially seeking a different phenotype, we found that this mutant MCM3AP could not interact with MCM3 in yeast, whereas wild type MCM3AP could (Fig. 4A). Consistent with the results shown in Fig. 4A, the MCM3-binding-deficient mutant also failed to bind to chromatin under conditions where wild type MCM3AP bound (Fig. 4B), and co-expression of MCM3 had no effect on the cytoplasmic localization of the mutant (Fig. 4C) unlike its effect on wild type MCM3AP (Fig. 3B). These results indicate that the binding-deficient mutant MCM3AP cannot associate with MCM3 in either mammalian cells or yeast.

Fig. 4D shows that even when export was blocked with leptomycin B, the mutant MCM3AP that fails to bind to MCM3 still failed to accumulate in the nucleus. These results indicate that MCM3 binding is required for both nuclear import and chromatin binding of MCM3AP.

The MCM3-binding-deficient mutant was examined in DNA replication assays in vivo and in vitro. Overexpression of the MCM3-binding mutant of MCM3AP did not show any significant effects on incorporation of BrdUrd, whereas overexpression of wild type MCM3AP inhibits it (Fig. 4E, left). In vitro DNA replication assays were performed with mimosine-arrested G1 nuclei and soluble protein fractions containing either the MCM3-binding-deficient mutant of MCM3AP or wild type MCM3AP. The soluble protein fraction from cells expressing the MCM3-binding-deficient mutant MCM3AP supports in vitro DNA replication as efficiently as the soluble protein fraction obtained from vector transfected cells, whereas the soluble protein fraction containing wild type MCM3AP does not (Fig. 4E, right). These results indicate that neither the MCM3-binding mutant of MCM3AP nor the acetylase-deficient mutant of MCM3AP inhibit DNA replication in the way that wild type MCM3AP inhibits.

**DISCUSSION**

We have shown previously (8) that MCM3AP is an acetylase that specifically acetylates MCM3 and that exogenous expression of MCM3AP decreases the number of cells in S phase. We have also shown that a mutation that blocks acetyltransferase function abolishes the effects on the cell cycle (8). Here we show that the decreased proportion of cells in the S phase is directly due to inhibition of the initiation of DNA replication and not just due to arrest at another point in the cycle. Thus, cytosolic extract from cells expressing wild type MCM3AP inhibits DNA replication of late G1 nuclei in vitro, whereas the mutant that lacks acetylase activity does not inhibit DNA replication. The inhibition is specific for initiation, but not elongation of DNA replication. Thus, the ability of S phase nuclei to continue elongation of DNA synthesis is not inhibited by extracts containing MCM3AP, whereas initiation in late G1 nuclei is inhibited.

In addition to demonstrating an effect on the initiation of DNA replication by MCM3AP, the present study also demonstrates that the accumulation of MCM3AP in the nucleus is dependent upon interaction with MCM3. We showed that MCM3 is required for two phases of accumulation on chroma-
tin. First, interaction is required for entry into the nucleus, and second, interaction with MCM3 is required for MCM3AP to bind to chromatin. MCM3 is a constitutive nuclear protein even when the protein is overexpressed, and it is known to contain a nuclear localization signal (7, 16). There is a precedent for MCM3 determining the nuclear localization of another protein that is bound to it. When mouse MCM5 is overexpressed, its localization is mainly cytoplasmic, but co-expression of exogenous MCM3 redirects the overexpressed MCM5 to the nucleus (17), in a similar manner to that shown for MCM3AP in the present paper. It is important to note that although overexpressed MCM3AP requires overexpressed MCM3 to localize it to the nucleus, the much smaller amounts of endogenous MCM3AP are likely to be constitutively localized to the nucleus by interaction with endogenous MCM3 in normal cells.

MCM proteins are known to be essential for initiation of DNA replication throughout eukaryotes (see Ref. 18 for review), so they are attractive potential targets for a regulatory enzyme that can inhibit DNA replication. Our data show that the intrinsic acetylase activity of MCM3AP is essential for the inhibition of DNA synthesis by MCM3AP and we have shown that the intrinsic acetylase activity of MCM3AP is likely to be constitutively localized to the nucleus by interaction with endogenous MCM3 in normal cells.

In conclusion, we have established that MCM3AP directly inhibits initiation of DNA replication via binding to MCM3.

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