MdmX Binding to ARF Affects Mdm2 Protein Stability and p53 Transactivation*

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Regulation of p53 involves a complex network of protein interactions. The primary regulator of p53 protein stability is the Mdm2 protein. ARF and MdmX are two proteins that have recently been shown to inhibit Mdm2-mediated degradation of p53 via distinct associations with Mdm2. We demonstrate here that ARF is capable of interacting with MdmX and in a manner similar to its association with Mdm2, sequestering MdmX within the nucleolus. The sequestration of MdmX by ARF results in an increase in p53 transactivation. In addition, the redistribution of MdmX by ARF requires that a nucleolar localization signal be present on MdmX. Although expression of either MdmX or ARF leads to Mdm2 stabilization, coexpression of both MdmX and ARF results in a decrease in Mdm2 protein levels. Similarly, increasing ARF protein levels in the presence of constant MdmX and Mdm2 leads to a dose-dependent decrease in Mdm2 levels. Under these conditions, ARF can synergistically reverse the ability of Mdm2 and MdmX to inhibit p53-dependent transactivation. Finally, the association and redistribution of MdmX by ARF has no effect on the protein stability of either ARF or MdmX. Taken together, these results demonstrate that the interaction between MdmX and ARF represents a novel pathway for regulating Mdm2 protein levels. Additionally, both MdmX and Mdm2, either individually or together, are capable of antagonizing the effects of the ARF tumor suppressor on p53 activity.

Cellular division is controlled predominantly by two distinct tumor suppressors, p53 and Rb. The p53 protein regulates cell cycle arrest and apoptosis because of its ability to transcriptionally activate specific target genes following various forms of genotoxic stress (1). The Rb protein controls entry into S-phase through its interaction with various members of the E2F family of transcription factors (2). Signaling between these two pathways involves an ever increasing number of proteins including p21WAF1, a target of p53-dependent transactivation and in-
Plasmids and Transfections—The p14ARF-GFP expression plasmid has been described previously (25). The p19ARF-Myc/His plasmid contains the murine ARF cDNA with a C-terminal Myc/His epitope tag. Mdm2-FLAG is in the pFLAG-CMV-2 vector (Sigma), which encodes a FLAG epitope tag onto the amino terminus of the Mdm2 protein. Human MdmX and MdmX-(1–446)-V5-His vector, which encodes a V5 epitope tag and a six-histidine tag onto the C terminus of the expressed protein. The human MdmX cDNA used as a template for amplification was kindly provided by Dr. Aart Jochensen. The PG15-luc plasmid was constructed by cloning 13 copies of a synthetic p53 DNA binding site upstream of a SV40 promoter-luciferase gene. MG15-luc contains 15 copies of a mutated p53 DNA binding site cloned upstream of the SV40 promoter-luciferase reporter gene. The pQE-β-gal plasmid was used to normalize transfection efficiency. In the p53 transactivation studies, ARF, mdm2, and MdmX expression plasmids were used. Transfections were performed using LipofectAMINE (Life Technologies, Inc.). In Fig. 3, a pHOOK plasmid (Invitrogen) was included with each transfection to allow immunoselection of transfected cells with Capture-Tec beads (Invitrogen). For Western analysis in Figs. 4 and 5, transfection efficiencies were normalized by the inclusion of a pG36-luciferase reporter plasmid (Promega) in each transfection.

Fluorescence Studies—Immunofluorescence analysis was performed 24 h after transfection. Transfected U2OS cells on chamber slides were fixed in 3% paraformaldehyde, permeabilized with 1% Triton X-100 in phosphate-buffered saline, and blocked for 2 h with 10% goat serum, 0.01% Tween 20 in phosphate-buffered saline. Primary antibody was added to a 1/10 dilution of blocking solution and incubated for 1 h. The cells were washed three times and incubated with the secondary antibody for 1 h. Nuclei were stained with 25 μg/ml Hoechst Dye (Sigma) for 2 min. B23 immunofluorescence was performed as described previously (25).

Immunoprecipitation, Western Analysis, and p53 Reporter Assays—For immunoprecipitation and Western blot experiments, whole cell extracts were made 24 h following transfection by incubating cell pellets for 30 min in lysis buffer (50 mM Tris, pH 8.0, 150 mM NaCl, 1% Nonidet P-40) containing a protease inhibitor mixture (Sigma). Immunoprecipitation analysis was performed by adding 100 μg of pHOOK cell extracts with 1 μg of monoclonal V5 antibody in a total volume of 300 μl of phosphate-buffered saline containing 5 mM EDTA and 0.5% Triton X-100. Following overnight incubation, 25 μl of protein G-agarose was added and incubated an additional 1 h before washing three times for 30 min each time. Pellets were resuspended in 25 μl of 2× SDS loading buffer and resolved using 10% SDS-polyacrylamide gel electrophoresis followed by transfer of proteins to a polyvinylidene difluoride membrane (Millipore) using a Transblot system (Bio-Rad). Immunoblotting was performed as described previously (26) using primary antibody dilutions of 1:1,000–1:5,000 and secondary dilutions of 1:5,000–1:10,000. For p53 reporter assays, extracts were made 24 h after transfection. p53 transactivation was determined by quantifying luciferase activity in aliquots from whole cell extracts using a luciferase assay system (Promega). β-Galactosidase activity was determined by incubating protein extracts in 100 mM sodium phosphate, pH 7.4, 1 mM MgCl2, 50 mM β-mercaptoethanol, and 650 μg/ml O-nitrophenyl-β-D-galactopyranoside at 37 °C for 0.5–2 h. β-Galactosidase activity was calculated by converting the absorbance read at 420 nm into milliunits of β-galactosidase activity per microliter of extract. All luciferase and β-galactosidase assays were performed in duplicate. Error bars of relative p53 transactivation represent the average deviation for the relative luciferase units divided by the milliunits of β-galactosidase.

RESULTS

Coexpression of ARF Localizes MdmX to the Nucleolus and Activates p53 Transactivation—Previous studies have demonstrated that ARF is localized to the nucleolus (10, 15, 18, 25). The Mdm2 protein, although not found in nucleoli in the absence of ARF, can be mobilized to nucleoli following either coexpression of ARF or induced ARF expression (14, 15). Based on the homology between Mdm2 and MdmX, we first examined whether MdmX was found in nucleoli or could be colocalized with ARF. U2OS cells, which do not express ARF yet do possess wild-type p53 protein (10), were transiently transfected with an expression plasmid encoding a V5-epitope tagged human MdmX protein in the presence or absence of an expression plasmid encoding an ARF-GFP fusion protein. In the absence of ARF (or in the presence of GFP, data not shown), MdmX showed no nucleolar localization (Fig. 1A, panel l). However, upon coexpression of ARF, MdmX became localized to the nucleolus (Fig. 1A, panels j and k). When MdmX and ARF signals were overlaid they demonstrated clear colocalization (Fig. 1A, panels m and n). ARF localization to the nucleolus (Fig. 1A, panel e) was confirmed in transfected U2OS cells by demonstrating that ARF colocalized with the nucleolus protein B23 (Fig. 1A, panels p and q).

To determine the effect of ARF expression on MdmX regulation of p53 transactivation, U2OS cells were transfected with the p53-responsive promoter PG15-luc. As expected, transfection of the p53-responsive promoter (PG15-luc) into cells possessing wild-type p53 protein led to a 6-fold increase in p53 transactivation when compared with transfection of a p53 reporter plasmid containing mutant p53 DNA binding sites (MG15-luc; Fig. 1B). Coexpression of a human MdmX expression vector led to a modest 20% decrease in the activity of the p53 responsive promoter (Fig. 1B). With increasing levels of MdmX expression vector, p53 transactivation levels did not continue to de-
pools of free p53 protein (Fig. 1), thereby stabilizing and maximizing the nuclear effect. The elevated ARF protein levels most likely mean that the ARF-GFP expression vectors led to a dose-dependent increase in p53 transactivation, suggesting cellular extracts (top panels), GFP (middle panels), and MdmX (bottom panels). Although coexpression of full-length MdmX with ARF resulted in the mobilization of MdmX to the nucleolus (panel g), deletion of the NrLS of MdmX abrogated the ability of ARF to sequester MdmX to the nucleolus (Fig. 2). The C terminus of MdmX is required for colocalization with ARF. A, amino acid alignment of human Mdm2, human MdmX, Mdm2, and MdmX demonstrating the conservation of a nucleolar localization sequence, (R/K)(R/K)(R/K)X(R/K). B, cellular localization of MdmX and ARF-GFP proteins in transfected U2OS cells. Cells were examined for nuclear DNA (top panels), GFP (middle panels), and MdmX (bottom panels). Although coexpression of full-length MdmX with ARF resulted in the mobilization of MdmX to the nucleolus (panel g), deletion of the NrLS of MdmX abrogated the ability of ARF to sequester MdmX to the nucleolus (panel h).

The Requirement of a Nucleolar Localization Signal in MdmX—Based on the requirement for a conserved stretch of basic amino acids, or NrLS, in the RING domain of Mdm2 (19, 21), we examined whether MdmX contains a similar NrLS. Fig. 2A compares the NrLS of Mdm2 with the putative NrLS of both human and murine MdmX. Both human and murine MdmX sequences have a conserved (R/K)(R/K)(R/K) motif previously shown to be required for the nucleolar localization of the ARF-Mdm2 complex (19, 21). To examine the importance of the putative NrLS in MdmX, a deletion mutant of MdmX lacking the RING finger domain, which contains the NrLS, was constructed, and its ability to colocalize with ARF was tested. The deletion matched a similar deletion made in Mdm2, which demonstrated the requirement for a NrLS in the Mdm2 RING finger for proper Mdm2-ARF nucleoli localization (19, 21). As seen with Mdm2, MdmX-(1–446), which lacked the MdmX RING domain, was unable to colocalize to the nucleolus with ARF (Fig. 2B, panel h). Surprisingly, ARF was not completely prohibited from entering the nucleolus when coexpressed with MdmX-(1–446) (Fig. 2B, panel e), contrasting the results reported with NrLS-deficient Mdm2 proteins (19, 21). In any event, expression of MdmX-(1–446) did lead to a greater accumulation of ARF in the nucleoplasm when compared with coexpression with full-length MdmX (Fig. 2B, compare panels d and e).

The inability of MdmX-(1–446) to maintain ARF within the nucleoplasm may simply represent differences in ARF binding to MdmX and MdmX-(1–446). To test this possibility, H1299 cells were transfected as described in Fig. 2B, MdmX protein was immunoprecipitated, and the interaction with ARF was confirmed by Western analysis. Based on immunoprecipitation results (Fig. 3A), both full-length MdmX and MdmX-(1–446) were capable of interacting with ARF. Comparing the immunoprecipitations to a parallel immunoblot (Fig. 3A, lower panel), there appears to be a slight but reproducible decrease in the amount of ARF bound to MdmX-(1–446) relative to full-length MdmX. Perhaps the interaction between ARF and MdmX is not as stable in the nucleoplasm as it is in the nucleolus. The nucleolar localization of ARF in transfected H1299 cells (Fig. 3B) confirmed that ARF localization was comparable with that seen in U2OS cells. We also examined a more truncated version of MdmX, amino acids 1–363, which also binds to ARF but is unable to colocalize to the nucleolus. ARF was not completely prohibited from entering the nucleolus when coexpressed with MdmX-(1–363), which lacked the MdmX RING domain (Fig. 3B, panel h).

Fig. 3. Direct interaction of ARF and MdmX. A, H1299 cells were transfected with ARF (1.5 μg) and a V5-tagged human MdmX or MdmX-(1–446) (4.0 μg) as indicated. A pHook plasmid was also included (1.5 μg), and the transfected population was selected using Capture Tec beads. Western blot analysis of MdmX immunoprecipitated cellular extracts (top panel). Both full-length MdmX and MdmX-(1–446) are able to interact with ARF. The bottom panels are Western blots containing 10% of each whole cell extract probed for GFP-tagged ARF or MdmX. B, H1299 transfected with ARF and examined by immunofluorescence for ARF and B23 localization. Like U2OS cells (Fig. 1), ARF colocalizes with B23 in the nucleolus of H1299 cells.
Regulating Mdm2 Stability and p53 Transactivation—Because ARF and MdmX have both been reported to individually stabilize the Mdm2 protein (10, 23, 24), we next examined how MdmX affects the stability of Mdm2 either alone or in the presence of increasing levels of ARF protein. Although studies examining mdm2x gene expression have failed to uncover any significant modulation (27, 28), one group has reported substantially higher levels of mdm2x mRNA in the thymus of both human and mouse (29) suggesting that elevated Mdm2 mRNA may occur in specific tissues. In agreement with previously reported data, MdmX was able to stabilize the Mdm2 protein (Fig. 4A, lane 3). In contrast, coexpression of MdmX and ARF together had a dose-dependent antagonistic effect on the ability of both proteins to stabilize Mdm2 protein (Fig. 4A, lanes 4–6). Interestingly, there was also a slight, but reproducible, decrease in MdmX protein levels as ARF protein levels increased and Mdm2 protein levels decreased (Fig. 4A, lanes 3–6). It is possible that the decrease in MdmX protein levels results from a decrease in MdmX:Mdm2 complex formation. This would be in agreement with one recent study in which Mdm2 mutants lacking the RING finger domain showed decreased protein stability relative to full-length Mdm2 (30).

As expected, overexpression of MdmX(1–446) protein was not able to stabilize Mdm2 protein when expressed in U2OS cells (Fig. 4B, lane 5), nor was it able to antagonize the ability of ARF protein to stabilize Mdm2 protein (Fig. 4B, lane 4). The inability of MdmX(1–446) to reverse the ARF-induced stability of Mdm2 implies that the association of MdmX and ARF may not be sufficient to reverse the ARF stability of Mdm2 and that nuclear localization of ARF and MdmX is required to destabilize Mdm2.

The results shown in Fig. 4A demonstrated that the stability of both MdmX and Mdm2 decreased as ARF protein levels increased. To determine whether the decrease in MdmX stability was dependent upon Mdm2 or ARF, MdmX was expressed in U2OS cells with increasing ARF in the absence of Mdm2. Under these transfection conditions, increasing ARF protein levels did not affect MdmX protein levels (Fig. 5A), consistent with the stability of MdmX in Fig. 4A being more dependent on the presence of elevated Mdm2 than ARF levels. Finally, there was no alteration in ARF levels as in transfections containing increasing levels of MdmX expression vector (Fig. 5B). Taken together, the results shown in Fig. 5 suggest that the association between MdmX and ARF has no dramatic effect on the stability of either protein.

Finally, to examine the effects of coexpressing Mdm2, MdmX, and ARF on endogenous p53 transactivation, U2OS cells were transfected with the indicated plasmids and the p53-responsive promoter, PG13-luc (Fig. 6). As expected, transfection of Mdm2 and MdmX expression vectors together, led to a >90% decrease in p53 transactivation (Fig. 6A). The inhibition of p53 transactivation by transfection with Mdm2 and MdmX expression vectors was reversed, in a dose-dependent manner, by coexpression with ARF expression vectors (Fig. 6A). The increase in p53 transactivation seen in transfections of increasing ARF in the presence of constant Mdm2 and MdmX most likely results from with ARF nuclear sequestration of Mdm2 (14, 15) and MdmX (Fig. 1) or the decreased protein stability of Mdm2 and MdmX (Fig. 4A). Finally, consistent with the antagonist effects of ARF and MdmX functioning through nuclear sequestration, a 5-fold increase in p53 transactivation detected when ARF was overexpressed in U2OS cells was inhibited in a dose-dependent manner with transfection of increasing levels of MdmX expression plasmid (Fig. 6B). Taken together with the results in Fig. 1B, these data demonstrate that MdmX regulation of p53 transactivation is not limited to its direct association with p53 (29) or with Mdm2 (22) but can also be elicited through MdmX association with ARF.

**DISCUSSION**

Both ARF and MdmX are capable of regulating p53 protein levels through binding to and inhibiting Mdm2 function. How-
ever, MdmX also binds directly to p53, resulting in the nucleoplasmic sequestration of p53 protein and inhibition of p53 transactivation (22). We demonstrate in this report that in addition to mobilizing Mdm2 to the nucleolus, ARF can also interact with and direct the nucleolar localization of MdmX (Fig. 1A). Redistribution of MdmX requires the C-terminal RING domain of MdmX that contains a conserved stretch of basic amino acids recently identified as an NrLS in Mdm2 (Fig. 2). Mobilization of MdmX from the nucleoplasm to the nucleoli segregates MdmX from p53, resulting in a decrease in the ability of MdmX to interact with and inhibit p53 transactivation (Fig. 1B). Furthermore, we show that coexpression of MdmX with ARF and Mdm2 results in a decrease in Mdm2 stability, indicating that interaction of MdmX and ARF prohibits the stabilizing interaction between Mdm2 and ARF and likely blocks MdmX interactions with Mdm2. Interestingly, although the coexpression of MdmX, Mdm2, and ARF results in decreased Mdm2 protein levels relative to Mdm2 alone, it also resulted in a lower level of p53 transactivation relative to ARF alone (Fig. 6A). These data are consistent with a model in which the nucleolar sequestration of MdmX through MdmX-ARF complexes releases Mdm2, leading to its eventual degradation (Fig. 7).

Because the ability of MdmX to stabilize Mdm2 (Fig. 7A) is lost upon coexpression of ARF, we predict that the existence of an equilibrium between MdmX-Mdm2, Mdm2-ARF, and MdmX-ARF complexes may ultimately balance the levels of both Mdm2 and p53 (Fig. 7, B and C). Clearly a key factor in this effect is the ratio of MdmX and Mdm2 protein. It is worth noting that the MdmX protein has a much greater half-life than Mdm2; therefore, it is likely that in these present studies when cotransfecting equal molar amounts of mdm2 and mdmX plasmids, the MdmX protein concentration is significantly higher than that for Mdm2 protein. Studies comparing the various binding affinities between the Mdm2, MdmX, and ARF heterodimeric complexes are currently ongoing. At the cellular level we speculate that in tissues such as the thymus, brain, and testis, where higher levels of mdmX transcripts have been reported relative to other tissues (28, 29), that ARF-MdmX interactions (Fig. 7C) may play a role consistent with those observed in these overexpression studies.

Taken together, the observations detailed here support a model whereby MdmX is responsible for maintaining the nucleoplasmic localization of p53 protein and inhibition of p53 transactivation (22). We demonstrate in this report that in addition to mobilizing Mdm2 to the nucleolus, ARF can also interact with and direct the nucleolar localization of MdmX (Fig. 1A). Redistribution of MdmX requires the C-terminal RING domain of MdmX that contains a conserved stretch of basic amino acids recently identified as an NrLS in Mdm2 (Fig. 2). Mobilization of MdmX from the nucleoplasm to the nucleoli segregates MdmX from p53, resulting in a decrease in the ability of MdmX to interact with and inhibit p53 transactivation (Fig. 1B). Furthermore, we show that coexpression of MdmX with ARF and Mdm2 results in a decrease in Mdm2 stability, indicating that interaction of MdmX and ARF prohibits the stabilizing interaction between Mdm2 and ARF and likely blocks MdmX interactions with Mdm2. Interestingly, although the coexpression of MdmX, Mdm2, and ARF results in

![Fig. 7. Model of MdmX, Mdm2, and ARF nuclear interactions.](image-url) Based on results from these studies and previous reports (22–24), the effects of ARF on Mdm2 and MdmX nuclear localization and effects on p53 stability are described. Additionally, the observations concerning Mdm2 and MdmX with respect to p53 stability and transactivation (TA) are detailed.

**FIG. 6.** p53 transactivation represents a balance of MdmX/Mdm2 and ARF. p53 transactivation levels in U2OS cells transfected with mdm2, mdmX, and ARF expression vectors. p53 transactivation was monitored by transfecting the PG13-luc (PG) luciferase reporter plasmid. A, cotransfection of mdmX and mdm2 expressed results in a decrease in p53-dependent transactivation. The addition of ARF expression vector increases p53 transactivation in the presence of constant MdmX and Mdm2. B, increasing amounts of mdmX expression vector results in a dose-dependent reversal of the increase in p53 transactivation induced by ARF. MG13-luc reporter activity was not affected by overexpression of ARF (data not shown). Relative p53 transactivation represents the p53 induction of luciferase activity normalized to the transfection efficiency (β-galactosidase assays).

[Figure 6](image-url)

[Figure 7](image-url)
We are presently exploring the possibility that ARF-MdmX interactions in these tumors produce this malignant phenotype.

Although our original model outlined MdmX as an inhibitor of Mdm2-mediated degradation (22), the data presented here argue that MdmX together with ARF may act antagonistically to allow more rapid Mdm2 turnover (Fig. 7). Most likely, both mechanisms are utilized to maintain steady state levels of Mdm2 and p53 in normal cells. It is also possible that the interaction between MdmX and ARF affects pathways other than those relating to p53 and Mdm2. In fact, exogenously expressed ARF can induce a cell cycle arrest in triple knock-out cells lacking p53, mdm2, and ARF (33). Interestingly, the expressed ARF can induce a cell cycle arrest in triple knock-out than those relating to p53 and Mdm2. In fact, exogenously expressed ARF can induce a cell cycle arrest in triple knock-out cells lacking p53, mdm2, and ARF (33). Interestingly, the expressed ARF can induce a cell cycle arrest in triple knock-out cells lacking p53, mdm2, and ARF (33).

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