

Subject Review

MDM2, An Introduction

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Abstract

The murine double minute 2 (*mdm2*) gene encodes a negative regulator of the p53 tumor suppressor. Amplification of *mdm2* or increased expression by unknown mechanisms occurs in many tumors. Thus, increased levels of MDM2 would inactivate the apoptotic and cell cycle arrest functions of p53, as do deletion or mutation of p53, common events in the genesis of many kinds of tumors. MDM2 functions as an E3 ubiquitin ligase to degrade p53. MDM2 also binds another tumor suppressor, ARF. This interaction sequesters MDM2 in the nucleolus away from p53, thus activating p53. Many additional MDM2 interacting proteins have been identified. Functions of MDM2 independent of p53 have also been identified. This article is an introduction to MDM2, its structure and biological functions, as well as its relationship to its binding partners.

Identification of MDM2 and Biological Function

The murine double minute 2 (*mdm2*)¹ gene was originally identified as one of three genes (*mdm1*, 2, and 3) which were overexpressed greater than 50-fold by amplification in a spontaneously transformed mouse BALB/c cell line (3T3-DM). The *mdm* genes were located on small, acentromeric extrachromosomal nuclear bodies, called double minutes, which were retained in cells only if they provided a growth advantage. The gene product of the *mdm2* gene was later shown to be the one responsible for transformation of cells when overexpressed (1, 2).

Soon after the identification of the *mdm2* gene, the reason for its transformation potential was discovered. MDM2 was shown to bind the tumor suppressor p53 and inhibit p53-mediated transactivation (3). At the same time, *MDM2* gene amplification was observed in over one third of human sarcomas that retained wild-type p53 (4). These exciting studies led to the hypothesis that overexpression of MDM2 was another mechanism by which the cell could inactivate p53 in the process of transformation. Whereas this hypothesis is clearly valid, transformation is more

complex. Some tumors contain both high levels of MDM2 and mutations in the *p53* gene. The reasons for disrupting two components of the same pathway are unclear but suggest that MDM2 may have other growth-promoting functions.

Biochemically, MDM2 functions as an E3 ubiquitin ligase responsible for the ubiquitination and degradation of p53 (5–7). Ubiquitination of proteins occurs through a complex series of steps that involve E1, E2, and E3 proteins (8, 9). The E1 enzyme binds ubiquitin, a 76-amino acid protein, activating ubiquitin for further processing. The E2 conjugating enzyme accepts the activated ubiquitin from E1 and transfers it to the E3 enzyme, a ligase that covalently bonds the ubiquitin to the substrate. MDM2 functions as the E3 ligase to ubiquitinate p53 at several lysine residues (10, 11). It also has the ability to ubiquitinate itself (12, 13). The RING motif is common in E3 ligases and is responsible for the E3 ligase activity of MDM2 (see Fig. 1).

Until recently, MDM2 was believed to polyubiquitinate p53 for protein degradation similar to ubiquitination of itself. However, recent data indicate (14) that MDM2 mediates monomeric p53 ubiquitination on multiple lysine residues instead of polymeric ubiquitination. Monoubiquitination is involved in receptor endocytosis, virus budding, transcription, DNA repair, and caspase recruitment in apoptosis, while polyubiquitination generally causes protein degradation (8, 9). Because a chain of at least four ubiquitin molecules is believed to be necessary for efficient proteosomal degradation (15), other proteins must aid in polyubiquitination of p53. At least one report indicates that p300/CBP cooperates with MDM2 in polyubiquitination and degradation of p53.

In vivo experiments have convincingly demonstrated the importance of the MDM2/p53 interaction (16–18a). Mice lacking *mdm2* are early embryonic lethal and die before implantation. This phenotype is completely rescued by concomitant deletion of *p53*, suggesting that the embryo lethality was due to active p53. In generating a conditional allele of *mdm2* to examine the effects of loss of *mdm2* in the adult, Mendrysa *et al.* (18) generated mice with a hypomorphic allele that expresses approximately 30% of the total Mdm2 levels. These mice have decreased body weight and defects in hematopoiesis and are more radiosensitive than normal mice. These phenotypes are p53 dependent, emphasizing the importance of regulating MDM2 levels in many cell types. Thus, Mdm2 serves as a critical titrator of p53

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¹The abbreviations used are *MDM2*, human gene and oncogene; MDM2, human protein and isoform; *mdm2*, mouse gene; Mdm2, mouse protein.

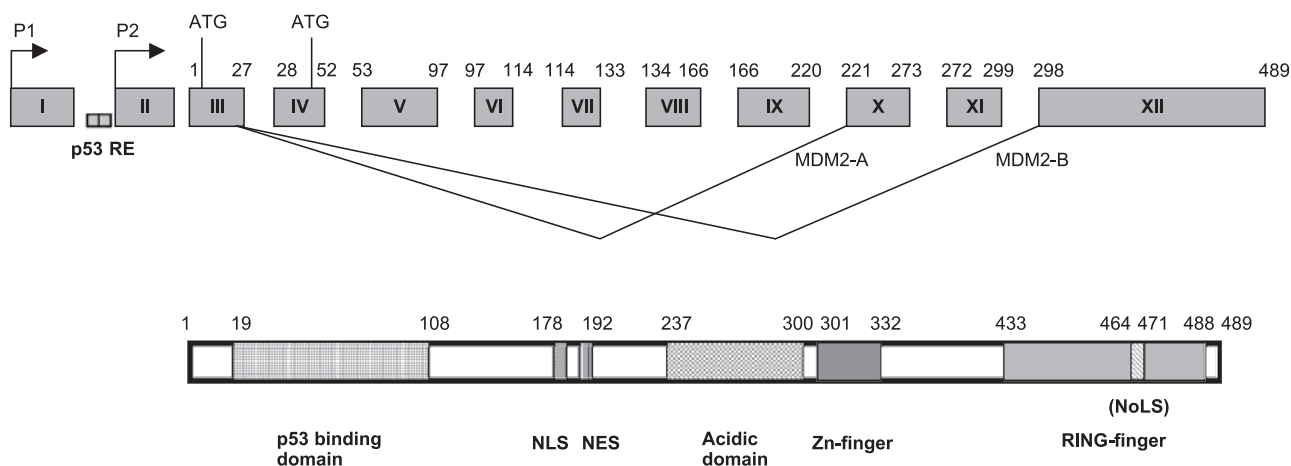


FIGURE 1. Structure of *mdm2* gene and protein. *mdm2* gene consists of 12 exons and two p53 responsive elements (*p53 RE*) in intron 1. Two promoters are shown by arrows. Full-length MDM2 p90 is translated from the first start codon ATG in exon 3 and the short form, p76, is translated from the second ATG in exon 4. Two major alternative splice variants in the human genes *MDM2-A* and *MDM2-B* are shown. Full-length Mdm2 and known motifs are also represented. *NLS*, nuclear localization signal; *NES*, nuclear export signal; *Zn-finger*, zinc-finger domain; *NoLS*, nucleolar localization signal; *RING-finger*, ring-finger domain. The numbers above the drawings denote amino acid numbers and roman numerals are exon numbers.

activity, and loss of Mdm2 results in an active p53 that has dire consequences to the cell and embryo.

Gene Structure and Protein Motifs

Both the *mdm2* gene and its human counterpart, *MDM2*, consist of 12 exons that can generate many different proteins. There are two different promoters, the second of which is responsive to p53. These promoters generate two proteins, the full-length p90 and a shorter protein p76 that initiates at an internal ATG (19–21 and see review by M. E. Perry [January 2004 issue, *MDM2*: Part II] for details). p76 is missing part of the p53-binding domain (Fig. 1) and it can act as a dominant negative inhibitor of p90 and activate p53. Alternative splicing of *MDM2* and the generation of short proteins also occurs in many human and mouse tumors. Numerous short MDM2 proteins which encode the carboxyl terminus of MDM2 have been identified (22 and see review by Bartel *et al.* in January 2004 issue, *MDM2*: Part II). In humans, *MDM2-A* and *MDM2-B* are the major splice variants that delete exons 4–9 and 4–11, respectively. Neither product contains the p53-binding motif. *MDM2-B*, also named *MDM2-ALT1*, interacts with full-length MDM2 and sequesters it in the cytoplasm (23). Multiple spliced variants were also present in murine tumors (24). Thus, these short MDM2 proteins may function as dominant negatives inhibiting the function of full-length MDM2 and thus amplifying the activity of p53. A vexing question, however, is why tumor cells would make these proteins in the first place. One possibility is that they represent a signal left over from when the cell was trying to maintain control. The presence of these proteins and subsequent activation of p53 would provide, however, an impetus for mutating p53 and may be the reason some cancers have both high levels of MDM2 and mutations in p53.

The p53 interaction domain is encoded by the amino terminal 100 amino acids of MDM2. This domain binds the amino terminal transactivation domain of p53. Thus, even if

MDM2 cannot degrade p53, it interferes with the ability of p53 to interact with the transcription machinery. Other motifs include a nuclear localization signal and a nuclear export signal. These signals shuttle MDM2 back and forth between the cytoplasm and the nucleus and provide yet another means by which p53 activity is tightly regulated (25, 26). Amino acids 464–471 can function as a nucleolar localization signal (27), although the biological significance of this regulation is unclear. The central acidic domain of MDM2 is necessary for interaction with the ribosomal protein L5, and with p300/CBP (CREB-binding protein). Recently, this domain was found to contribute to p53 degradation because an MDM2 mutant lacking part of this domain ubiquitinated p53 well but failed to degrade p53 (28, 29). Downstream of the acidic domain is a zinc finger domain of unknown function followed by the RING domain, which has already been discussed.

A p53/MDM2 Regulatory Feedback Loop

p53 transcriptionally activates many target genes, one of which is the *mdm2* gene (21, 30). p53 binds the *mdm2* P2 promoter and transcriptionally up-regulates *mdm2* expression. Because Mdm2 inhibits p53 activity, this forms a negative feedback loop that tightly regulates p53 function. In turn, decreased p53 activity results in decreased Mdm2 to constitutive levels. MDM2 can also ubiquitinate itself and induce its own degradation (12, 13). This is yet another example of a different regulatory mechanism that titrates the levels of MDM2 and therefore p53 very precisely. So how does p53 escape the detrimental effects of binding MDM2? Upon DNA damage, p53 is posttranslationally modified to inhibit interactions with MDM2. Several kinases also phosphorylate MDM2 and modulate interactions with p53 (18a, 30a). This ability of p53 to regulate *mdm2* provides a feedback loop with an important role in regulating cell cycle progression and apoptosis (30b).

Other Proteins That Interact With MDM2

Several other proteins have been identified in various systems that also interact with MDM2 (31). Using yeast two hybrid screens or immunoprecipitation experiments, investigators identified many additional MDM2 interacting proteins. They are summarized in Tables 1 and 2. We divided these interacting proteins into two groups: those that function upstream of MDM2 (effectors) that specifically modify MDM2 and those that are downstream proteins (affectors) that are regulated by MDM2 such as p53. In most cases, the interaction has not been observed in multiple systems and these studies await further experiments to verify interactions at physiological levels.

Upstream Regulators of MDM2 (Effectors)

These proteins are mainly those that belong to the class of proteins that regulate MDM2 activity and include kinases, phosphatases, and proteins such as ARF that regulate the interaction of MDM2 with p53 (Table 1).

One of the first proteins discovered to interact with MDM2 is ARF (31a–33). ARF is an alternate reading frame protein expressed from the *INK4a* locus (34). The interaction of ARF with MDM2 blocks MDM2 shuttling between the nucleus and cytoplasm via the nucleolus (35–37). Nuclear export of p53 by MDM2 is required for efficient degradation (25, 35). Sequestration of MDM2 in the nucleolus thus results in activation of p53 (31–33, 36). Mutations in human ARF exon 2 disrupt its nucleolar localization and impair its ability to block nuclear export of MDM2 and p53 (38). This

deregulation results in increased nuclear MDM2 levels thus decreasing p53 and leading to transformation. This hypothesis is supported by experiments in mouse embryo fibroblasts. Most cells immortalize with time by losing p53, while cells lacking ARF immortalize without losing p53, suggesting that loss of ARF inactivates p53 (39). However, the mechanism of p53 stabilization by ARF via MDM2 inactivation is still controversial because some reports suggested that ARF can inhibit MDM2 ubiquitin ligase activity *in vitro* and can stabilize p53 without MDM2 relocation in the nucleolus (32, 40, 41).

Like ARF, the ribosomal protein L11 binds MDM2 and can sequester it in the nucleolus, resulting in stabilization of p53 levels (42). In transfection experiments, the addition of increasing amounts of L11 inhibits the degradation of p53 by MDM2. Functionally, the addition of L11 into U2OS cells caused an increase in G₁ arrest. Thus, both the levels of L11 and its localization within a cell affect p53 activity through interaction with MDM2. Similarly, hypoxia-inducible factor 1 α (HIF-1 α) also interacts with Mdm2 and enhances p53 function (43). This interaction (examined only in transfection experiments) prevents nuclear export of p53, but provides another example of a protein that may physically prevent MDM2 from binding p53.

Several kinases have been shown to phosphorylate MDM2. These are reviewed by Meek and Knippschild (30a). The ATM kinase phosphorylates MDM2 on serine 395 and impairs the degradation and nuclear export of p53 by MDM2 (44–46). Phosphatidylinositol 3-OH-kinase (PI3-kinase) and its downstream target, Akt/PKB serine-threonine kinase, following

Table 1. Effectors That Interact With MDM2

Proteins	Effect on MDM2			MDM2 Localization	p53 Dependency	Physiological Interaction Measured	References
	Self Ub	p53 Ub	p53 Stability or Activity				
ARF	down	down	up	Nucleolar relocation of MDM2 by ARF may not be essential for p53 stabilization.	ARF binds MDM2 independent of p53.	No	(31–41)
L11	N.E.	N.E.	up	L11 causes nucleolar relocation of MDM2.	N.E., but L11 and p53 bind to different regions on MDM2.	Yes	(42)
MDM4	Up but polyubiquitination was inhibited	varies	Stable but activity down	MDM4 inhibits MDM2-mediated degradation and nuclear export of p53.	p53-independent interaction	Yes	(110–116)
P300/CBP	N.E., but p300 stabilizes Mdm2	up	down	p300 recruits Mdm2 to nuclear body-like structure.	p300 binds p53 and/or Mdm2 independently.	Yes	(57–61)
PI3K/akt	N.E.	up	down	PI3K/akt promotes MDM2 from cytoplasm to nucleus.	p53-independent interaction	Yes	(47–50)
Tsg101	down	N.E.	down	N.E.	p53-independent interaction	No	(62, 63)
Ubc9/Sumo1	down	up	down	N.E.	p53-independent interaction	No	(64–66)
Cyclin G/PP2A	N.E.	N.E.	down	N.E.	p53-independent interaction	No	(54–56)
HIF-1 α	N.E.	down	up	HIF-1 α protects nuclear export of p53 by Mdm2.	HIF-1 α binds p53 independently but enhances <i>in vivo</i> association of p53 and HIF-1 α .	No	(43)
ATM	N.E.	N.E.	up	ATM impairs nuclear export of p53 by MDM2.	MDM2 phosphorylation is p53 independent.	Yes	(44–46)
CK2	N.E.	N.E.	Slightly down	N.E.	N.E.	No	(67, 68)
c-abl	N.E.	down	up	N.E.	N.E.	No	(51–53)

Ub: ubiquitination. N.E.: not examined.

Table 2. Affectors That Interact With MDM2

Proteins	Consequence of Interaction	p53 Dependency	Physiological Interaction Measured	References
p53	MDM2 ubiquitinates p53 and induces degradation.		Yes	(3, 4, 87, 88)
p73	MDM2 inhibits p73 activity without degradation.	No	No	(89–92)
P63	MDM2 stabilizes p63 and increases the transcriptional activity.	No	No	(93)
RB	MDM2 inhibits the ability of RB to inhibit E2F1 function.	No	Yes	(69, 70)
MTBP	Mdm2 cancels MTBP-induced G ₁ arrest p53 independently.	No	No	(94)
PML	MDM2 promotes PML nuclear exclusion and inhibits PML-dependent transactivation.	No	No	(95)
E2F/DP1	Mdm2 stimulates E2F/DP1 transcriptional activity and DNA synthesis, while Mdm2 can antagonize the apoptotic property of E2F.	No	Yes (DP1)	(73, 74)
Sp1	Mdm2 inhibits Sp1 DNA binding but RB restores it.	No	Yes	(71, 72)
Numb	Mdm2 alters subcellular localization of Numb and accelerates the degradation.	N.E.	No	(79, 80)
AR	Akt/MDM2 targets AR ubiquitination and degradation.	N.E.	Yes	(78)
P300/CBP	Mdm2 blocks the interaction of p53 and the co-activator p300/CBP.	No	Yes	(75–77)
PCAF	MDM2 inhibits PCAF-mediated p53 acetylation and activation.	N.E.	No	(85)
HDAC	MDM2-HDAC1-mediated deacetylation of p53 is required for its degradation.	No	Yes	(86)
L5/RNA	MDM2 may have functions in ribosomal biogenesis or translational regulation.	Complex with p53	Yes	(81–83)
DNA pol. ϵ	MDM2 stimulates the activity of DNA polymerase ϵ .	No	No	(99, 100)
TAFII250	MDM2 activates cyclin A promoter through complex with TAFII250.	N.E.	No	(97, 98)
TBP/TFIIIE small subunit	The interaction may inhibit basal transcriptional machinery.	N.E.	No	(96)

mitogen-induced activation also appear to bind and phosphorylate MDM2 on serines 166 and 186 (47–49). Phosphorylation on these sites is necessary for translocation of MDM2 from the cytoplasm into the nucleus. Expression of constitutively active Akt promotes nuclear entry of MDM2, diminishes cellular levels of p53, and decreases p53 transcriptional activity (50).

C-abl is required for accumulation of p53 in response to DNA damage (51). In transfection experiments, c-abl neutralizes the inhibitory effect of MDM2 on p53 via phosphorylation of MDM2 on tyrosine 394. An MDM2 mutant that alters tyrosine 394 to phenylalanine increased the ability of MDM2 to degrade p53 (51–53).

Other kinases have been shown to phosphorylate MDM2 although all of these experiments have been performed *in vitro* or in transfection experiments and need to be validated by examining endogenous levels.

Phosphatases also appear to play a role in regulating MDM2. Cyclin G is a regulatory component of the active PP2A holoenzyme, which binds and activates MDM2 through dephosphorylation (53–55). In fact, cells null for *cyclin G* show increased phosphorylation of Mdm2 (54).

p300/CBP is another protein that interacts with Mdm2, cooperating to degrade p53 (57, 58). Phosphorylation of MDM2 by Akt enhances its nuclear localization and its interaction with p300/CBP, inhibits interaction with ARF, and increases p53 degradation (47–49). MDM2 mutants lacking part of the acidic domain that overlaps the p300/CBP-binding domain failed to degrade p53 but accumulated monoubiquitinated p53 (29). *In vitro*, p300/CBP was required for polyubiquitination of p53 (59). This is an unusual role for p300/CBP because it was originally identified as a transcriptional coactivator with acetylase activity (60). However, this acetylase activity is not required for stabilization of Mdm2 (61).

Downstream Proteins Regulated by MDM2 (Affectors)

Thus far we have concentrated on the effect of MDM2 on p53 because this interaction has been verified in numerous

studies. But many other proteins that interact with MDM2 also appear to be regulated by MDM2. A complete list of these proteins is provided in Table 2. A short description of each of their functions is also provided. We will discuss in detail only those for which *in vivo* interactions of endogenous proteins have been examined.

Using immunoprecipitation experiments with U937 cell lysates (leukemia cells), MDM2 was identified as an RB-binding protein. RB is a potent tumor suppressor that is mutated in different kinds of cancers. MDM2 inhibits the ability of RB to inhibit E2F1 function, thus inhibiting arrest of the cell cycle in G₁ (69, 70). However, there is no evidence that MDM2 ubiquitinates or degrades RB.

Mdm2 also interacts with the transcriptional activator Sp1 *in vivo* (71, 72). Mdm2 binding to Sp1 does not allow Sp1 interactions with its specific DNA binding sequence thus blocking transcription. The Sp1/Mdm2 interaction is competed by the addition of RB, reactivating Sp1 transcriptional control. Because Sp1 is a general transcription factor, the significance of this interaction remains unknown. Again there is no evidence that Mdm2 degrades Sp1.

The E2F1 transcription factor functions as a heterodimer with DP1 to activate genes required for S phase. Martin *et al.* (73) showed that Mdm2 contacts E2F1 and DP1 in immunoprecipitation experiments in NIH3T3 cells. The Mdm2/E2F1/DP1 complex stimulates transcription. Additional reports indicate that Mdm2 stimulates the growth-promoting activity of E2F1 similar to the first set of experiments. Additionally, MDM2 blocks the apoptotic activity of E2F1 (74). These experiments indicate that MDM2 promotes cell proliferation by regulating other important components of the cell cycle in addition to regulating p53.

The transcriptional coactivator p300/CBP not only interacts with MDM2 as mentioned, but it also interacts with and acetylates p53 to enhance p53 activity (75). Because MDM2 and p53 bind p300/CBP independently, MDM2 inhibits the interaction of p53 with p300/CBP, resulting in reduced activity of p53 (76). Additionally, Kobet *et al.* (77) showed that MDM2

inhibits p300/CBP-dependent p53 acetylation. As discussed, p300/CBP regulates MDM2 stability and cooperates with MDM2 to degrade p53 (57–59, 61). Thus, because p300/CBP not only regulates the function of MDM2, but its activity is also regulated by MDM2, it must be placed in both categories as an effector and affecter with regard to MDM2.

The androgen receptor (AR) is a transcription factor that is translocated to the nucleus on binding to its ligand, androgen. Many tumors are androgen independent. AR was shown to bind a region encompassing the RING domain of MDM2. This interaction was clearly present endogenously in LNCaP cells. In co-transfection experiments, AR is also ubiquitinated and degraded by MDM2. MDM2 RING finger mutants cannot degrade AR. Akt phosphorylates AR and MDM2 and increases the efficiency of degradation of AR by MDM2 (78). Thus, AR may be another target of the E3 ligase MDM2. One other protein, Numb, has been identified as an Mdm2 interacting protein that is also degraded by Mdm2 (79, 80). Numb is important in specifying cell fate during development. The implications of this interaction await further experiments.

The ribosomal L5 protein is associated with MDM2 and MDM2-p53 complexes, suggesting a role for MDM2 in ribosomal biogenesis, ribosomal transport to the nucleus, or regulation of translation (81–83). MDM2 binds the L5/5S ribosomal ribonucleoprotein particle and can also bind to specific RNA sequences or secondary structures, suggesting a role for MDM2 in translational regulation in a cell (82). These experiments were all performed in the presence of p53 so it is unclear if p53 is required as part of the MDM2/L5 complex. One additional role for MDM2 in translation has been identified. MDM2 interacts with the amino terminus of p53 during translation, enhancing the generation of a p53 protein of M_r 47,000 that is immune to degradation (84). The alteration in ratio between the two p53 proteins alters target specificity.

Unfortunately, many different assays are used to measure MDM2 function in different experiments, and it is possible that some of these interacting proteins regulate only certain functions of MDM2. Because MDM2 can ubiquitinate both itself and p53, with opposing functions on proliferation, these are obviously important roles of MDM2 that should be distinguished. Additionally, the ability to sequester MDM2 in an inappropriate cellular compartment also affects MDM2 function. These analyses have also been performed in many different kinds of cells and the potential of *Mdm2* to generate multiple proteins may also complicate the results. These variables must be examined in more detail.

MDM4

An overview of MDM2 would not be complete without mentioning the MDM2-related protein, MDM4. *Mdm4*, also known as *MdmX*, was identified and shown to inhibit p53 activity, although not as well as MDM2 (101). The most convincing experiments that MDM4 was also a critical regulator of p53 were experiments performed in the mouse. Mice lacking *mdm4* are early embryo lethals that die due to lack of proliferation (102–104). The *mdm4* null phenotype is

completely rescued by deletion of the *p53* gene. Thus, the embryonic death is due to induction of the p53 pathway. These data suggest that *Mdm4* may be another critical regulator of p53 and that human tumors might also exhibit increased levels of MDM4. Increased MDM4 levels have already been observed in human tumor cell lines and in some glioblastomas (105, 106).

The question remains as to why p53 needs two inhibitors (probably more because recent data have identified additional p53 inhibitors; 107–109). Some studies have shown that MDM4 interacts with and stabilizes MDM2 through their RING domains (110–113). This suggests cooperation between the two proteins in inhibiting p53 function. In some papers, however, this interaction of MDM4 and MDM2 seems to stabilize p53 protein which is opposite of what is expected (111–115). The controversy was explained by careful measurement of the ratio of MDM2 to MDM4. When the MDM4 levels are less than 2:1 with MDM2, p53 stability is decreased (116). On the other hand, increased MDM4 levels causes increased stability although the activity of p53 is decreased (114). Most studies have not been able to ascribe E3 ligase function to MDM4, suggesting that it may simply bind p53 and prevent interaction of p53 with MDM2. The presence of MDM4 appears to inhibit p53 by masking the transcriptional activation domain. It also prevents MDM2 degradation and translocation of p53 by MDM2 (114). Thus, these two closely related inhibitors may in fact have different roles in inhibiting p53.

In summary, the MDM2 protein plays a critical role in regulating cell proliferation and apoptosis. A further understanding of the regulators of MDM2 and the relationship between MDM2 and its binding partners, especially those that affect the cell cycle, is needed. A more detailed analysis of the MDM2-p53 pathway and p53-independent functions of MDM2 will provide more insight into the mechanisms of cellular homeostasis as well as tumorigenesis. The ability to perturb MDM2 function in tumors may aid in combating cancer especially when p53 is wild type.

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