Subject Review

p53-Independent Functions of MDM2

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Abstract

The tumor suppressor p53 is inactivated by overexpression of MDM2 in about 10% of human tumors. However, p53 is inactivated by other mechanisms in the majority of tumors, raising the possibility that MDM2 may be irrelevant to transformation in most cases. However, MDM2 has been reported to have p53-independent functions, in cell cycle control, differentiation, cell fate determination, DNA repair, basal transcription, and other processes. Furthermore, MDM2 appears to contribute to the transformed phenotype in the absence of wild-type p53. Nevertheless, the number of studies is still limited, and the evidence in some cases does not unequivocally show that the functions are p53 independent. We will discuss the circuits of regulation involving MDM2 that do not directly concern p53. Hopefully, future work will consolidate our understanding of the p53-independent pathological functions of MDM2 and will lead to useful therapeutic interventions that target the majority of tumors.

Introduction

Although MDM2 has been extensively characterized as a regulator of p53, there is considerable evidence that MDM2 has p53-independent functions. We will describe the evidence from in vivo studies, including human tumors, transgenic mice, and cells in culture. We will portray the interactions of MDM2 with various factors (Fig. 1) that have effects on functions relevant to transformation, including cell cycle control, differentiation, DNA synthesis, RNA biosynthesis, transcription, and cell surface receptor turnover (Fig. 2). We will also consider the regulators of MDM2 that affect its functions, as far as they provide insights into the p53-independent functions of MDM2. Finally, we will discuss the hopes for tumor therapy. Certain aspects of the p53-independent functions of MDM2 are covered in other reviews in this series and will not be discussed in detail here.

In Vivo Evidence

Human Tumors

Human tumors containing both mutant p53 and MDM2 amplification are rare, but both modifications can occur within the same tumor and result in a poorer prognosis (1). The 12% of patients with bladder cancer that exhibit high levels of MDM2 and p53 mutation have a poorer prognosis than patients with either MDM2 amplification or p53 mutation (2). That there are two non-redundant mechanisms to inactivate p53 provides support for a p53-independent function of MDM2.

Alternative Splicing of MDM2

Alternative splicing of pre-mRNAs can give rise to proteins with different functions. Interestingly, more than 40 different splice variants of MDM2 transcripts have been identified both in tumors and normal tissues, and the majority of these variants do not contain sequences encoding the p53 binding site, suggesting that they have p53-independent functions (for additional information, see Ref. 3 and the other reviews in this issue). Some of these splice variants may arise from the loss of splicing fidelity during tumorigenesis, and may not have an important function (4). The functions of the MDM2 splice variants lacking the p53 interaction domain need to be individually evaluated in appropriate model systems.

Animal Models

Several studies have addressed the effect in vivo in mouse models of overexpression of MDM2 in the absence of p53 (see Table 1). Targeted expression to the mammary gland in mice inhibits mammary gland development and uncouples S phase from mitosis in a p53- and E2F1-independent manner (5, 6). Overexpression driven by the entire mdm2 gene predisposes to spontaneous tumor formation and reveals a p53-independent role for MDM2 in tumorigenesis. Only one line with the mdm2 gene as the transgenic was studied. It displays increased tumorigenesis, with a high incidence of sarcomas that is retained in a p53−/− background (7). Overexpression in the differentiating compartment of the epidermis inhibits differentiation in a p53-independent manner, but does not predispose to tumor formation (8). Similar results were obtained in transgenic mice in which the involucrin promoter drives Mdm2 expression to the spinous layer of the epidermis.2 In the CMV and involucrin-mdm2 mice, the mdm2 transgene appears to be expressed in cells in which p53 is not functional (see Fig. 3.

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

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A and B). But when Mdm2 expression is driven by the K14 promoter to the basal layer, the mice are predisposed to the development of hyperplastic lesions that progress to papillomas and squamous cell carcinomas (9), showing that the oncogenic potential of MDM2 in vivo is revealed when it is targeted to cells in which p53 suppresses tumorigenesis.

p53 levels are low in normal epidermis (Fig. 3A). p53 is activated during the exit from the proliferative state, resulting in inhibition of cell division and stimulation of differentiation. A consequence of p53 activation could be the MDM2 expression that is observed in the basal and the suprabasal layers. As keratinocytes differentiate, they become insensitive to p53-induced apoptosis. UV light induces p53 in the proliferative compartment of the basal layer, resulting in protection from the tumorigenic effects of DNA damage as a result of p53-induced cell cycle arrest or apoptosis. In transgenic mice, p53 is inhibited by Mdm2 produced in the basal layer, leading to decreased differentiation and increased proliferation (see Fig. 3C). The UV response is impaired by Mdm2, thereby decreasing the protective effect of p53. The reduced tumor suppressor function of p53 results in increased papilloma formation after chemical carcinogenesis and spontaneous accumulation of genetic lesions resulting in the appearance of hyperplastic lesions and carcinomas.

MDM2 is important for epidermal differentiation. It is highly expressed in normal human and mouse skin (10). Mdm2 overexpression in the granular layer perturbs the differentiation program (8). MDM2 has been implicated in regulation of differentiation in other systems (11). It may affect differentiation through inhibition of p53 and interaction with other molecules. p53 has been implicated in cell differentiation and development (12). p63, a homologue of p53, is important for epidermal differentiation (13, 14). However, it appears unlikely that MDM2 affects p63 activity because the variant expressed in the epidermis lacks the MDM2 interaction domain (15). Mdm2 is expressed in both the basal and suprabasal layers, in
which keratinocytes enter the differentiation program, suggesting that Mdm2 is involved in the early steps of differentiation, in which the decision occurs as to whether the basal proliferating cell will enter the proliferation program. In support of this hypothesis, it has been shown that MDM2 levels increase when keratinocytes are induced to differentiate in vitro (16). p53 activity could influence MDM2 levels because MDM2 is one of its target genes. However, p53 may not be the major determinant of the basal level of MDM2, p53 levels are low in uninduced conditions in the epidermis (17). Furthermore, MDM2 expression is independent of p53 in keratinocytes (10) and epithelia during mouse development (18). Constitutive MDM2 expression is thought to set the sensitivity of cells to p53 induction (19–24). The consequences of p53 induction are differentiation dependent in the epidermis, resulting in either cell cycle arrest or apoptosis in different compartments (25, 26). The basal levels of MDM2 may help determine whether p53 induction results in cell cycle arrest or apoptosis in different keratinocyte populations. Mdm2 overexpression in different layers of the skin has similar effects on differentiation, proliferation, and apoptosis. However, the molecular mechanisms of these effects are not identical because p53 removal has an effect only when MDM2 is expressed in the basal layer. These observations are explicable in the light of the known properties of MDM2 and p53. The role of p53 changes in different states of keratinocyte differentiation. p53 induction results in apoptosis of proliferating keratinocytes, whereas p53 is not activated in late-stage suprabasal cells.

### Table 1. Mouse Models of Mdm2 Function

<table>
<thead>
<tr>
<th>Promoter</th>
<th>Organ targeted</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLG</td>
<td>Mammary epithelium</td>
<td>16% adenocarcinomas and adenocanthomas, p53-independent effect</td>
<td>(5)</td>
</tr>
<tr>
<td>MDM2</td>
<td>Several organs</td>
<td>100% lymphomas and sarcomas, p53-independent effect</td>
<td>(7)</td>
</tr>
<tr>
<td>HCMV</td>
<td>Granular layer of the skin</td>
<td>Defective differentiation in the skin, p53-independent effect</td>
<td>(8)</td>
</tr>
<tr>
<td>K14</td>
<td>Basal layer of the skin</td>
<td>33% pre-neoplastic lesions, p53-dependent effect</td>
<td>(9)</td>
</tr>
</tbody>
</table>

### Figure 3

**A.** Normal skin has low levels of p53 in the basal layer, which is activated when cells move into the differentiating compartment. MDM2, which is present in the suprabasal layer, inhibits p53 and regulates other unknown factors, thereby controlling differentiation. When normal epidermis is UV-irradiated, p53 levels increase in the basal layer and induce cell cycle arrest and apoptosis. **B.** In HCMV-MDM2 transgenic skin, overexpression of MDM2 inhibits differentiation of the granular layer independent of p53 but does not induce tumor formation. The p53 protective function after UV irradiation in the basal layer is unaltered. **C.** MDM2 overexpressed in the basal layer inhibits p53, increases proliferation in a p53-dependent manner, and favors tumor formation. When this skin is UV-irradiated, the protective functions of p53 are reduced.
MDM2, suggesting that inactivation of the MDM2-induced G1 phase transition of NIH 3T3 and normal human diploid cells contains a central zinc finger domain and a carboxyl-terminal domain of MDM2 required for MDM2-p53 interaction modulates normal muscle cell differentiation (30). The consequent increased cyclin-dependent kinase activity and phosphorylation of pRB results in increased E2F1/DP1 transactivation by a p53-dependent mechanism (38). MD2 induction of E2F1 transactivation was concluded to be seen if the other member of the pRB family, p130, is a tumor suppressor, and loss of these functions in tumors could unmask the positive effects of MDM2 on tumorogenesis.

The Cell Cycle

The Rb Family

pRB is a tumor suppressor that has functions similar to p53, in cell cycle inhibition and cell death. MDM2 modulates the activity of pRB, as well as p53 (32). MDM2 forms a complex with pRB in vivo, and perturbs pRB-mediated G1 arrest (32). Conversely, pRB impairs certain functions of MDM2 through the formation of a trimeric complex with p53. pRB thereby overcomes the ability of MDM2 to inhibit p53-mediated apoptosis (33). Mdm2 has been shown to confer a growth advantage to cells lacking p53 and pRB, and to overcome a G1 cell cycle arrest induced by p107, a member of the pRb family. The minimum transforming and p107-inhibiting region of Mdm2 corresponds to its p53-binding domain (28). It remains to be seen if the other member of the pRb family, p130, is a target for MDM2.

E2F1/DP1

MDM2 has been shown to interact with E2F1/DP1, a pRB-regulated transcription factor involved in S-phase progression. There is a striking similarity between a domain of E2F1 (amino acids 390–406) and the MDM2 binding domain of p53 (34). MDM2 stimulates E2F1/DP1-dependent activation of the E2F promoter, and DNA synthesis in cooperation with E2F1/DP1. MDM2 also increases degradation of the heterodimer, thereby inhibiting the pro-apoptotic effect of E2F1/DP1. Increased degradation may serve to reduce the amounts of E2F1/DP1 to levels appropriate for the G1-S phase transition (35). The growth-promoting and anti-apoptotic activities of MDM2 on E2F1 could be crucial for the p53-independent oncogenic activities. However, various studies suggest that the effects of MDM2 on E2F1 could be p53 dependent. MDM2 has been shown to inhibit E2F1-induced apoptosis, apparently by inhibiting E2F1 induction of p53 (36). In addition, E2F1 has been shown to be up-regulated in response to DNA damage in a p53-dependent manner (37). Microinjection of an antibody against a domain of MDM2 required for MDM2-p53 interaction or an antisense MDM2 oligonucleotide increases E2F-1 protein levels, suggesting that endogenous E2F1 may be sensitive to MDM2 protein because of its effects on p53. In another study, a set of cell lines with differing p53 and pRB was used to show that overexpression of MDM2 stimulates E2F1/DP1 transactivation by a p53-dependent mechanism (38). MDM2 induction of E2F1 transactivation was concluded to result from inhibition of p53-dependent transcription of p21. The consequent increased cyclin-dependent kinase activity and phosphorylation of pRB results in increased E2F1/DP1 transactivation (38). These different studies are not necessarily contradictory. Similar to the conclusions from studies in the epidermis previously mentioned, they may indicate that depending on the cellular background and the activity of p53, MDM2 can affect E2F1/DP1 transactivation by p53-dependent and -independent mechanisms.

MDMX

MDMX (MDM4) is structurally and functionally related to MDM2 (39). They are nearly identical in size, yet only share some common domains. They are similar within the p53-binding domain at their amino termini and both contain a central zinc finger domain and a carboxyl-terminal ring finger domain (40). Like MDM2, MDMX is an essential negative regulator of p53, because loss of
MDMX expression results in p53-dependent embryonic lethality in mice (41, 42). Although the current evidence suggests that the only role of MDMX in control cell proliferation and the cell cycle is through its regulation of p53, the possibility exists that MDMX may affect the p53-independent functions of MDM2. It may also have p53-independent functions that are not revealed in the mouse studies because of the early embryonic lethality of the inactivation.

PML
The tumor suppressor protein PML and MDM2 have opposing effects on p53. PML stimulates p53 activity by recruiting it to nuclear foci termed PML-nuclear bodies (PML-NBs). An in vivo interaction between MDM2 and PML has been reported recently that is independent of p53 (43). Two regions of MDM2 interact with PML: the central region with the COOH-terminal half of PML (300–633) and the RING finger with the RING finger of PML (1–200). Interestingly, sumoylation of PML inhibits the interaction. MDM2 inhibits PML by exclusion from the nucleus, similar to one of the mechanisms by which MDM2 inhibits p53. MDM2 inhibits the ability of PML to stimulate the transcriptional activity of a GAL4-CBP fusion protein. The importance of MDM2 regulation of the activity and localization of PML in the tumor suppressor function of PML remains to be established.

MTBP
A novel MDM2 binding protein (MTBP) has been identified using two-hybrid screens (44). The central region of MDM2 (amino acids 167–304) binds to the carboxyl-terminal 380 amino acids of MTBP. MTBP induces G1 arrest in a p53-independent manner, and this arrest can in turn be inhibited by MDM2. Further studies are required to establish the significance of the interactions of MDM2 and MTBP regulation of the cell cycle.

TGF-β1
Resistance to transforming growth factor β (TGF-β) inhibition of cell proliferation is linked to tumorigenesis. MDM2 was isolated in a screen for factors that rescue TGF-β sensitivity of mink lung epithelial cells. Rescue results from the effects of MDM2 on pRb/E2F and does not involve p53 (45). Increased MDM2 expression correlates with TGF-β resistance in human breast tumor cells. These observations raise the possibility that MDM2 may confer TGF-β resistance through its effects on pRb, at least in certain cell types (46). Further studies are needed to consolidate and extend these observations.

Differentiation
Numb
The Numb protein was isolated in a screen for factors that interact with MDM2 (47). Drosophila Numb antagonizes Notch signaling and is involved in neural cell differentiation and cell fate determination. The NH2-terminal region of MDM2 binds to Numb, the same region that interacts with p53. MDM2 alters the subcellular localization of Numb and promotes its degradation. Recent evidence strongly suggests that MDM2 functions as a ubiquitin ligase toward hNumb and that it induces its ubiquitination and degradation in cells (48). The possibility that the interaction between Numb and MDM2 contributes to the oncogenic properties of MDM2 through effects on differentiation requires further investigation.

DNA Synthesis
DNA Polymerase ε
The physical interaction between human DNA polymerase ε and human MDM2 has been established by a yeast two-hybrid screen, an in vitro binding assay, and in vivo co-immunoprecipitation (49). MDM2 expressed in and purified from either Escherichia coli or insect cells stimulates the activity of DNA polymerase ε in vitro. Moreover, the COOH-terminal domain of DNA polymerase ε, to which MDM2 binds, and the NH2-terminal 166 amino acids of MDM2, to which DNA polymerase ε binds, are both essential for the stimulation (50). The proposed roles of DNA polymerase ε include DNA repair, recombination, replication, damage sensing, and chromatin remodeling. In response to DNA damage, MDM2 may mediate a reconfiguration process that allows DNA polymerase ε to associate with repair/recombination proteins.

Ribosome Biosynthesis
Ribosomal Protein L5 and 5S RNA
A possible function for MDM2 in ribosome biosynthesis or in translational regulation is suggested by the specific interaction of the central domain of MDM2 domain with L5 (a component of the large ribosomal subunit) and the COOH-terminal domain with 5S rRNA (51–53). MDM2 has a nucleolar localization signal and is found in the nucleolus (54), the site of ribosome biosynthesis and assembly. These observations raise the interesting speculation that MDM2 has a role in ribosome assembly, transport, or RNA synthesis.

Transcription
TBP and TAFq250
MDM2 interacts in vivo and in vitro with the general transcription factor TFIIID but not with TFIIIB, another general factor (55–58). Different domains of MDM2 contact two subunits of the complex, the acidic domain contacts TBP and the Ring finger contacts TAFq250 (59; Fig. 1). MDM2 activates the promoter of cyclin A, a gene that is important for S-phase entry (59). Expression of MDM2 activates the cyclin A gene promoter but not c-fos, suggesting that the effects of MDM2 are specific. Overexpression of MDM2 inhibits the cyclin A promoter, possibly by titration of general transcription factors. The mechanisms of repression of the cyclin A and fos promoters appear to be different. Cyclin A repression is lost by deleting the COOH terminus, whereas that of c-fos is lost by removal of the acidic domain. These observations link the activity of MDM2 with cyclin A, a regulator of the cell cycle. Further studies are required to determine whether MDM2 acts directly, through for example effects on E2F/pRb family members that regulate this promoter, or whether the effects are less direct, through effects on the cell cycle.
MDM2 can also directly interact with the transcriptional coactivator p300 (60, 61). The consequences of the interaction are complex, and appear to involve effects of p300 on p53 and MDM2 protein turnover and MDM2 synthesis. p300 is required for MDM2 gene induction by p53, and inhibition of p300 results in stabilization of p53 and apoptosis (61). Interestingly, inhibition of TAFII250 similarly inhibits MDM2 induction by p53 and causes apoptosis, suggesting that the p53-MDM2 loop is a sensor of transcriptional defects (62). p300 overexpression increases MDM2 protein levels without effects on MDM2 mRNA. p300 associates with MDM2 in nuclear body-like structures where MDM2 might be protected from proteasomal degradation (63). The functional consequences of the p300-MDM2 interaction on the p53-independent functions of MDM2 remain to be further elucidated.

**NF-κB/p65**

MDM2 has been shown to induce the expression of the p65 subunit of NF-κB through effects on the p65 promoter (64). NF-κB has various roles, including inhibition of apoptosis in response to chemotherapy in certain neoplastic cells. MDM2 overexpression in leukemic bone marrow cells of patients with BCP-ALL or in an ALL cell line (EU-4) has been associated with elevated expression of p65 and in vitro resistance to doxorubicin. MDM2 expression in the absence of p53 increases p65 promoter activity, apparently by direct binding of MDM2 to the Sp1 site. Further studies are required to establish whether the induction of p65 by MDM2 is an important p53-independent role of MDM2 in tumorigenesis.

**β2-Adrenergic Receptor and β-Arrestin**

β-Arrestin regulates the internalization of G protein-coupled receptors (GPCRs) away from the cell membrane. Internalized receptors are either recycled back to the surface after dephosphorylation, or are degraded. MDM2 has been shown to be a key factor in the sequestration of the cell surface β2-adrenergic receptor (β-AR) through interactions with β-arrestin (65). Agonist stimulation of β-AR leads to rapid ubiquitination of both the receptor and the receptor regulatory protein, β-arrestin. Abrogation of β-arrestin ubiquitination, either by expression in MDM2-null cells or by dominant-negative forms of MDM2 lacking E3 ligase activity, inhibits receptor internalization with marginal effects on receptor degradation. However, a β-AR mutant lacking lysine residues, which was not ubiquitinated, was internalized normally but was degraded ineffectively. These findings show that β-arrestin is a substrate for MDM2 ubiquitination, and that MDM2 is involved in β-AR trafficking. MDM2 may connect extracellular signals mediated through GPCRs to p53 or to other cellular effectors (66).

**Regulators of MDM2**

A variety of factors other than p53 regulate MDM2 activity, and they may have effects on the p53-independent functions of MDM2.

**The ARF (p19ARF/p14ARF)-MDM2-p53 Pathway**

ARF is a central player in tumor surveillance due to its ability to protect p53 from MDM2-mediated degradation (67–70). Human ARF sequesters MDM2 in the nucleolus and blocks nuclear export of MDM2 and p53 (71, 72). However, ARF can also affect the p53-independent functions of MDM2. In transgenic mice, MDM2 expression directed to the mammary epithelium disrupts the cell cycle, resulting in multiple rounds of DNA synthesis without proper cell division and poor mammary gland development. These effects are p53 and E2F1 independent, because MDM2 transgenic mice that are null for ARF have enhanced defects, as if more MDM2 is free to exert the phenotype (73).

**The TSG101/MDM2 Regulatory Loop**

TSG101 is a tumor suppressor, the loss in fibroblasts of which, results in cellular transformation and the ability to form metastatic tumors in nude mice. tsg101−/− embryos fail to develop beyond day 6.5 of embryogenesis (E6.5). Mutant embryos have decreased cellular proliferation, and increased p53 protein accumulation by a posttranscriptional mechanism. Elimination of p53 in null animals prolongs survival, showing that there is a functional connection between TSG101 and the p53 pathway in vivo (74). TSG101 participates with MDM2 in an autoregulatory loop that modulates the levels of both proteins and p53, by affecting protein decay (75). TSG101 inhibits MDM2 ubiquitination, and the stabilized MDM2 negatively regulates p53 and accelerates decay of TSG101. The effects of TSG101 on MDM2 may also influence the p53-independent functions of MDM2 (75).

**p53-Independent Activation of MDM2 Expression**

MDM2 gene expression is regulated by mechanisms that are independent of p53. MDM2 expression during development is tissue-specific and is independent of p53 in different organs (18). High levels of MDM2 expression are observed in human tumor cell lines with little or no functional p53 (76). MDM2 expression increases following FGF-2 treatment of cells (77), and in cells harboring a chimeric M-CSF/platelet-derived growth factor (PDGF) receptor (77, 78). The MDM2 promoter has been shown to be a target of the Ras/mitogen-activated protein (MAP) kinase pathway, and hence activation of Ras during normal cell signaling or through mutation in neoplastic transformation can increase MDM2 functions (76). MDM2 promoter regulation in T47D breast cancer cells has been shown to be independent of p53 and Ras/MAP kinase signaling, but dependent on the composite AP1-ETS motif and a nonconserved upstream (nmGGGGG; 5) repeat sequence. MDM2 promoter activity is increased by the ETS2 expression through the AP1-ETS element (79). Further studies are required to determine how altered MDM2 expression through these different pathways affects the p53-dependent and -independent functions of MDM2.

**AKT/PKB**

PKB phosphorylates MDM2 on several residues, resulting in translocation of MDM2 to the nucleus, where it can regulate...
p53 (80–82). PKB also forms a complex with MDM2 and the androgen receptor (AR), which controls prostate cell growth and apoptosis. Complex formation results in AR phosphorylation, ubiquitination, and proteasome-mediated AR degradation. PKB-induced AR ubiquitination and degradation is inhibited in MDM2-null cells, as expected from MDM2 being involved. The E3 ligase activity of MDM2 and phosphorylation of MDM2 by PKB are required for AR ubiquitination and degradation. Interestingly, p53 recruits MDM2 to another nuclear receptor, the glucocorticoid receptor (GR), resulting in triple complex formation and ubiquitination-dependent degradation of GR (83). Thus, MDM2 can be an E3 ligase for factors other than p53, and either p53 or another factor can recruit MDM2 to its target.

The Hopes for Therapy

The potential value of MDM2 as a drug target for cancer therapy has been studied with breast cancer cell lines (84). MDM2 expression was inhibited with a specific antisense oligonucleotide. In MCF-7 cells that express wild-type p53, inhibition of MDM2 expression resulted in elevated p53 and p21 levels. In MDA-MB-468 cells, which express mutant p53, inhibition of MDM2 expression increased p21 levels but had no effect on p53 levels. I.p. administration of antisense MDM2 inhibited tumor growth in nude mice bearing MCF-7 or MDA-MB-468 xenografts. In both types of tumor, several chemotherapeutic agents enhanced the effects of MDM2 down-regulation. These results suggest that MDM2 has a role in tumor growth through both p53-dependent and p53-independent mechanisms.

In conclusion, MDM2 protein has been shown to interact with a large number of cellular proteins besides p53. Although the exact function and significance of these interactions are not fully understood, the p53-independent functions of MDM2 may have a role in cancer etiology and progression, indicating that the MDM2 oncogene is a potential molecular target for cancer therapy. The study of cellular functions that are involved in the oncogenic properties of MDM2 is an important topic for future research that should help in the development of new therapeutics against cancer.

References


p53-Independent Functions of MDM2

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