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Mdm2's Dilemma: To Degrade or To Translate p53?

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In this issue of *Cancer Cell*, Gajjar et al. provide insight into how Mdm2 can both inhibit and enhance p53 activity. In the basal setting, Mdm2 binds p53 and promotes p53 degradation. Under stress conditions, ATM-dependent phosphorylation of Mdm2 results in its recruitment to p53 mRNA, thereby stimulating p53 translation.

The p53 tumor suppressor is a transcription factor that is induced in response to a variety of stress signals (Kruse and Gu, 2009). Under normal conditions, the p53 protein is kept at low levels in cells by ubiquitination-dependent proteosomal degradation mediated by its negative regulator, the E3 ubiquitin ligase Mdm2 (Figure 1A). Mdm2 is also a p53 transcriptional target and thus participates in a negative feedback loop with p53. Stress-mediated upregulation of Mdm2 has been considered a means by which p53 is able to regulate the duration and amplitude of its cellular effects.

In response to activation of specific oncogenic pathways, the ARF tumor suppressor is upregulated. ARF, in turn, interferes with Mdm2-dependent inhibition of p53 (Manfredi, 2010) (Figure 1B). In contrast, stimulation of the p53 pathway by genotoxic stress involves the DNA damage-activated kinase ATM, which has been shown to directly phosphorylate both p53 and Mdm2 (Kruse and Gu, 2009; Manfredi, 2010) (Figure 1C). The significance of ATM-dependent phosphorylation of Mdm2 was confirmed by the observation that phosphorylation of serine 395 on Mdm2 led to impaired p53 degradation (Maya et al., 2001). Biochemical studies have indicated that this is likely due to altered oligomerization, thereby attenuating the processivity of the E3 ligase activity of Mdm2 (Cheng et al., 2009). DNA damage has also been shown to induce the relocalization of Mdm2 to the nucleolus (Bernardi et al., 2004). It has been proposed that a nucleotide-binding motif within the Mdm2 E3 ligase RING domain facilitates nucleolar localization of Mdm2 (Poyurovsky et al., 2003). Candeias et al. (2008) then made the surprising observation that the p53 mRNA itself was able to interact directly with the RING domain of Mdm2. This interaction impaired the E3 ligase activity of Mdm2 and promoted p53 mRNA translation. It was unclear, however, under what biological settings such an interaction would have relevance.

In this issue of *Cancer Cell*, Gajjar et al. (2012) provide important insight by demonstrating that the DNA damage- and ATM-dependent phosphorylation of Mdm2 on serine 395 promotes the interaction of Mdm2 with p53 mRNA. This, in turn, is needed for p53 stabilization and apoptotic activity (Gajjar et al., 2012) (Figure 1D). By means of RNAi and overexpression experiments, these authors show that both ATM and Mdm2 are required to achieve full p53 apoptotic activity after DNA damage. Use of an Mdm2 isoform that does not bind to the p53 protein shows that a protein-protein interaction between Mdm2 and p53 is remarkably dispensable for this. It was further demonstrated that the interaction between p53 mRNA and the Mdm2 RING domain is necessary for p53-dependent apoptosis after genotoxic stress. Studies using a mutated p53 mRNA that no longer binds Mdm2 confirmed findings with a mutant Mdm2 protein that has a reduced affinity for the mRNA. These intriguing results support the notion that ATM-mediated phosphorylation of Mdm2 at serine 395 promotes allosteric changes in the RING domain, which in turn facilitate p53 mRNA binding. Finally, Gajjar et al. (2012) show that after DNA damage, the interaction between Mdm2 and p53 mRNA impairs Mdm2-dependent ubiquitination of p53. Thus, it is argued that the p53 mRNA-MDM2 interaction not only increases p53 translation but also inhibits p53 protein degradation as well.

In sum, this study demonstrates that Mdm2 can act as a positive regulator of p53 activity after genotoxic stress. It further provides an additional novel explanation for why Mdm2 is transcriptionally upregulated by p53 after DNA damage.

The finding that p53 mRNA relocalizes with Mdm2 in the nucleolus after DNA damage is especially interesting since the nucleolus is generally thought of as the site of ribosomal RNA transcription.

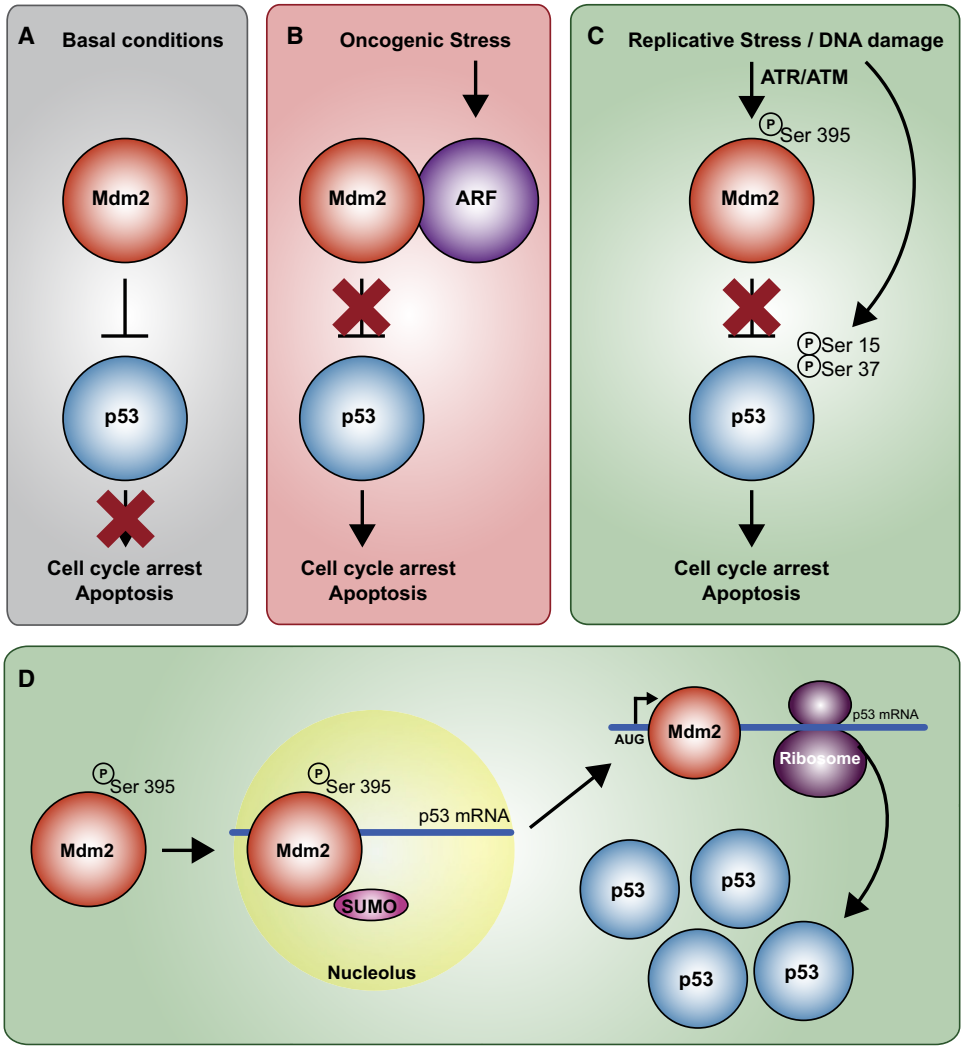

Figure 1. Mdm2 Acts as a Positive or Negative Regulator of p53 Activity in Response to Different Stresses

(A) Under basal conditions, Mdm2 inhibits p53 function by ubiquitination of p53 through its E3 ubiquitin ligase activity, leading to proteosomal-dependent degradation of p53, and by direct interference with the ability of p53 to act as a transcription factor.

(B) Oncogenic signaling has been shown to upregulate ARF at the transcriptional level. ARF binds to Mdm2 and inhibits its E3 ubiquitin ligase activity, thereby increasing p53 protein levels by alleviating proteosomal-dependent degradation of p53. In this case, Mdm2 behaves as an oncogene. In certain cancers, Mdm2 is indeed overexpressed.

(C) Other signals such as replicative stress or DNA damage activate the ATM or ATR kinases. ATM, in particular, has been shown to phosphorylate both p53 and Mdm2 and stabilize p53. The phosphorylation of p53 on serine 15 and serine 37 inhibits its interaction with Mdm2, and the phosphorylation of Mdm2 on serine 395 impairs Mdm2-mediated p53 degradation.

(D) Gajjar et al. (2012) demonstrate that phosphorylation of Mdm2 on serine 395 induces the binding of p53 mRNA to the RING domain of Mdm2, the sumoylation of Mdm2, and the relocalization of Mdm2 to the nucleolus. This p53 mRNA-Mdm2 interaction enhances p53 translation and inhibits Mdm2 E3 ubiquitin ligase activity toward p53 protein (Gajjar et al., 2012). Overall, phosphorylated Mdm2 on serine 395 is a positive regulator of p53. In this case, Mdm2 acts as a tumor suppressor.

However, several studies support the idea that it might also be involved in the processing or nuclear export of specific messenger RNAs (Pederson, 2011). Nevertheless, little is known about the relationship between mRNA and the nucleolus. The present study rekindles the idea that the nucleolus and mRNA processing are functionally connected.

While these nucleolar events are intriguing, the key outcome is an enhancement of p53 protein synthesis, a process that occurs in the cytoplasm. With this in mind, a molecular explanation is still needed for how p53 mRNA is then relocated from the nucleolus to the cytoplasm. In their previous study, Candeias et al. (2008) showed that Mdm2 is associated with polysomes in the cytoplasm, raising the intriguing possibility that Mdm2 is actually exported to the cytoplasm along with p53 mRNA and that Mdm2 may enhance p53 translation once there. Mdm2 is known to interact with several ribosomal proteins (Zhang and Lu, 2009). These interactions may indeed be at play in this process. The molecular mechanism by which the transient Mdm2-dependent nucleolar targeting of p53 mRNA enhances its translation also remains to be explored.

In summary, the significance of the study lies not only in its elucidation of a new role for p53-mediated induction of

Mdm2 after DNA damage, it begins to provide a molecular explanation for how Mdm2 may act either as an oncogene or a tumor suppressor, depending upon the particular context (Manfredi, 2010). This latter notion has important implications for the prognosis and treatment of tumors with aberrant Mdm2 expression.

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Polycomb Regulates NF-κB Signaling in Cancer through miRNA

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The mechanisms leading to the constitutive activation of NF-κB in cancers and the pathways upstream and downstream of this activation are not fully understood. In this issue of *Cancer Cell*, Yamagishi et al. demonstrate that Polycomb-mediated silencing of miR-31 is implicated in the aberrant activation of NF-κB signaling in tumors.

Differential gene expression distinguishes one cell type from another and enables cells to build specialized tissues. Once a cell fate decision is made, the cell must be able to silence the transcriptional programs that could potentially lead to other lineages, because the DNA content of all cells is the same. Epigenetic factors play a crucial role in this type of gene expression regulation. The Polycomb group of proteins plays a pivotal role in silencing and in the long-term repression of genes implicated in cell fate decisions (Richly et al., 2010). Polycomb proteins belong either to Polycomb repressive complex 1 (PRC1) or PRC2. The PRC2 component EZH2 methylates lysine 27 of histone H3, which attracts the PRC1 complex; the presence of both PRC1 and PRC2 at promoter regions leads to transcriptional silencing (Richly et al., 2011).

It is now clear that, in addition to epigenetic complexes, microRNAs (miRNAs) also contribute greatly to posttranscriptional gene regulation. miRNAs are endogenous, short (~23 nt) RNAs that suppress gene expression via sequence-specific interactions with the 3′ untranslated regions of related mRNA targets. miRNAs affect gene silencing via both translational inhibition and mRNA degradation. Several miRNAs have been reported to have a direct role in oncogenesis, and indeed, abnormal miRNA expression is a common feature of diverse types of cancers, suggesting potential diagnostic or prognostic biomarker uses.

The NF-κB transcription factor family regulates the expression of diverse genes involved in development, cell growth, immune responses, apoptosis, and neoplastic transformation. Activation of NF-κB is a tightly regulated event. In non-malignant cells, NF-κB is activated only after appropriate stimulation, after which it transiently upregulates the transcription of its target genes. In tumor cells, different types of molecular alterations may result in an impaired regulation of NF-κB activation and deregulated expression of target genes due to constitutively active NF-κB. Recent studies have also demonstrated that miRNAs modulate NF-κB signaling in both normal and pathological scenarios (Lu et al., 2011; Ma et al., 2011).

Adult T cell leukemia/lymphoma (ATL) is an aggressive neoplasm of mature $CD4^+$ T lymphocytes caused by the human T cell leukemia/lymphoma virus type 1 (HTLV-1) infection. Aberrant activation of NF-κB stimulates cell growth and anti-apoptotic responses in ATL cells and thus directly participates in ATL pathogenesis. Recently, correlations between the epigenetic machinery, NF-κB activation, and ATL pathology have been suggested (Sasaki et al., 2011). However, mechanistic insights are lacking. Tax, an