Cell Cycle 14:21, 3373–3378; November 1, 2015; Published with license by Taylor & Francis Group, LLC

p53-mediated control of gene expression via mRNA translation during Endoplasmic Reticulum stress

Ignacio López[1], Anne-Sophie Tournillon[1], Karin Nylander[2], and Robin Fåhraeus[1,2,3,*]

[1]Équipe Labellisée Ligue Contre le Cancer; Université Paris 7; INSERM UMR 1162 "Génomique fonctionnelle des tumeurs solides"; Paris, France ; [2]Department of Medical Biosciences; Umeå University; Umeå, Sweden; [3]RECAMO; Masaryk Memorial Cancer Institute; Brno, Czech Republic

Keywords: ER stress, MDM2, mRNA translation, p53, p53/47

© Ignacio López, Anne-Sophie Tournillon, Karin Nylander, and Robin Fåhraeus

*Correspondence to: Robin Fåhraeus; Email: robin.fahraeus@inserm.fr

Submitted: 07/22/2015

Revised: 08/26/2015

Accepted: 08/29/2015

http://dx.doi.org/10.1080/15384101.2015.1090066

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The moral rights of the named author(s) have been asserted.

p53 is activated by different stress and damage pathways and regulates cell biological responses including cell cycle arrest, repair pathways, apoptosis and senescence. Following DNA damage, the levels of p53 increase and via binding to target gene promoters, p53 induces expression of multiple genes including *p21*^{CDKN1A} and *mdm2*. The effects of p53 on gene expression during the DNA damage response are well mimicked by overexpressing p53 under normal conditions. However, stress to the Endoplasmic Reticulum (ER) and the consequent Unfolded Protein Response (UPR) leads to the induction of the p53/47 isoform that lacks the first 40 aa of p53 and to an active suppression of p21^{CDKN1A} transcription and mRNA translation. We now show that during ER stress p53 also suppresses MDM2 protein levels via a similar mechanism. These observations not only raise questions about the physiological role of MDM2 during ER stress but it also reveals a new facet of p53 as a repressor toward 2 of its major target genes during the UPR. As suppression of p21^{CDKN1A} and MDM2 protein synthesis is mediated via their coding sequences, it raises the possibility that p53 controls mRNA translation via a common mechanism that might play an important role in how p53 regulates gene expression during the UPR, as compared to the transcription-dependent gene regulation taking place during the DNA damage response.

The tumor suppressor protein p53 becomes activated when different stresses are infringed to cells, such as DNA damage, nutrient deprivation, viral infection or oncogene activation.[1,2] Following the well-studied DNA damage response, p53 induces a multitude of downstream target genes. The induction of different sets of gene products trigger particular biological effects that match the insults and are aimed at either preventing abnormal growth of compromised cells by reversible arrest of the cell cycle in G1 or G2 to facilitate repair processes, or at inducing irreversible outcomes including apoptosis or senescence.[3-6] Due to its importance in cellular and organism maintenance, p53 is inactivated by mutations in over 50 % of human cancers while changes in downstream and upstream pathways are thought to be present in most cancer cells.

Two of the major and best-described p53-target genes following DNA-damage are *p21*^{CDKN1A} (*p21Cip1/Waf1*) and *mdm2*, whose p53-dependent mRNA induction is mirrored by an increase in protein levels. Induction of p21^{CDKN1A} constitutes an important branch of the p53-dependent cancer protection and is observed at early stages of DNA damage response via its capacity to suppress both G1 and S phase cyclin and cyclin-dependent kinase (CDKs) activity and to prolong the G1 phase in order to prevent cells from entering replication carrying damaged DNA.[3,7] p21^{CDKN1A}-deficient mice have an increase in tumor incidence later in life.[8]

The E3-ubiquitin ligase MDM2 binds the conserved BOX-I motif in the N-terminus of p53 and masks p53's transactivation domain and catalyzes the ubiquitination of p53.[9] The *mdm2* P2 promoter includes a p53 binding site offering a putative regulatory p53-MDM2 feed-back loop.[10] Although MDM2-dependent control of p53 activity is vital

during mice development to subdue p53 activity, recent studies indicate that the p53-MDM2 feed-back loop is important during the DNA damage response but is not required to suppress p53 activity during mice development.[11] This can be explained by the observations that following genotoxic stress, MDM2, helped by its homolog MDMX, becomes a positive regulator of p53 by stimulating the rate of p53 protein synthesis and increasing its half-life.[12-14]

A less attended cellular scenario regarding p53 activity constitutes the Endoplasmic Reticulum (ER) stress that is triggered by several conditions including accumulation of unfolded or misfolded proteins, nutrient deprivation, or high rate of synthesis or underglycosylation of proteins.[15] Induction of ER stress is also caused by compounds like tunicamycin and thapsigargin that affect protein glycosylation or target Ca^{2+} homeostasis, respectively. In tissues, physiological fluctuations of protein production and folding, poor perfusion and lack of nutrient supply and oxidative stress, or pathological scenarios linked with viral infection, cancer and aging are all linked with ER stress.[15] Cells respond to ER stress through the unfolded protein response (UPR) that triggers an adaptive 3-branched pathway. The UPR inhibits global cap-dependent protein synthesis via PERK, promotes induction of ER chaperons and favors the elimination of misfolded proteins via ATF6 and IRE-1.[15,16] We have previously shown that during ER stress, a selective PERK-dependent induction of the alternatively translated p53 isoform p53/47 leads to increased 14-3-3σ expression and the corresponding G2/M arrest.[17] The levels of protein synthesis at G2/M are estimated to be 30 % less and, thus, the prolongation of this face of the cell cycle offers a window to facilitate repair of the damaged ER organelle and restore the balance between newly synthesized and mature proteins.[18] More recent data show that in order to avoid COP-1-mediated degradation of 14-3-3σ, the expression of $p21^{CDKN1A}$ is suppressed by p53-dependent mechanisms.[19]

We now report that the MDM2 protein levels are inhibited in the p53-positive HCT116 and A549 and in the p53–null H1299 and Saos-2 cell lines following expression of ectopic p53 during the UPR induced by treatment with thapsigargin (THAP) (**Fig. 1A**). As the suppression of MDM2 requires p53, this cannot be explained simply by PERK-mediated phosphorylation of eIF2α and instead implicates p53 in the inhibition of MDM2 expression during the UPR. The expression of the ER-located chaperone BIP, which is a target of the UPR at the transcription level, was used to monitor proper induction of the UPR. Importantly, the *mdm2* mRNA expression pattern was induced by p53 irrespectively of the UPR status of the cells (**Fig. 1B**). Hence, similar to $p21^{CDKN1A}$, p53 also suppresses the expression of MDM2 during the UPR.

Expression of 31 nanograms (ng) of *p53wt* cDNA in H1299 resulted in the down-regulation of an exogenous HA-tagged MDM2 (HA-MDM2) protein expression, as revealed using anti-HA antibodies (**Fig. 1C, upper right**). On the other hand, the levels of the endogenous MDM2 still increased when p53 was overexpressed due to the strong induction of *mdm2* mRNA levels as determined using RT-qPCR (**Fig. 1C, upper and lower left**). However, plotting the ratio of *mdm2* mRNA levels *vs*. MDM2 protein levels at 31 ng of p53 transfection shows that the mRNA expression increased over 2-fold as compared to MDM2 protein levels (**Fig. 1C, lower right**).

The suppression of *$p21^{CDKN1A}$* mRNA translation by p53 is mediated via its coding sequence and, thus, not via the more commonly described mechanisms of mRNA translation initiation control that act via the untranslated regions (UTRs).[19] This appears to also be the case for MDM2 as the exogenous HA-tagged MDM2 is actively suppressed. In addition, treatment with the proteasome inhibitor MG132 failed to prevent p53-mediated suppression of HA-MDM2 expression in thapsigargin-treated cells (**Fig. 1C, upper right**), supporting the notion that p53 does not affect the turnover rate of MDM2 but instead targets its rate of synthesis. Hence, similar to $p21^{CDKN1A}$, p53 also suppresses the expression of MDM2 by a mechanism that involves the inhibition of *mdm2* mRNA translation.

The suppression of HA-MDM2 by p53 occurred both under normal conditions and thapsigargin treatment indicating this capacity of p53 is ubiquitous. However, as with *$p21^{CDKN1A}$* mRNA and protein levels, an increasing amount of p53/47 prevented full-length p53 (p53FL)-mediated induction of *mdm2* mRNA levels and induced a decrease in MDM2 protein levels (**Fig. 1D**). The p53/47 isoform is initiated 40 codons downstream of the first AUG and lacks the first of p53's 2 transacting domains, including the conserved BOX-I motif that includes the MDM2 interaction site.[20] Hence, p53/47 has different activity and stability as compared to p53FL. It retains the DNA binding and oligomerisation domains and has the capacity to affect p53 related activities either as homo-tetramer, which binds the same promoter sequences as the p53FL isoform, or as hetero-oligomer with p53FL. *In vitro* and *in cellulo* data support the idea that p53/47 due to the lack of the N-terminus forms oligomers more easily as compared to p53FL so that relatively low levels of expression give a dominant cellular phenotype.[17] It is conceivable that the induction of p53/47 during the UPR prevents p53-mediated transcription of the *$p21^{CDKN1A}$* and *mdm2* mRNAs which then allows p53's translation suppressor activity of these 2 mRNAs to become prominent and physiologically important. The suppression of $p21^{CDKN1A}$ and MDM2 during the UPR can thus, be attributed to the induction of p53/47.

Animal models have indicated that p53/47 alters the activity of p53 and transgenic mice overexpressing p53/47 show a dramatic pre-mature aging phenotype and cells from such mice have altered stem cell pluripotency.[21,22] Furthermore, the presence of p53/47 in glioblastomas has indicated a role for this isoform in this type of cancer [23] and it will be important to test to which extent these different phenotypes reflects the suppression of gene expression in a similar fashion as with MDM2 and $p21^{CDKN1A}$.

Repression of gene expression by p53 via competing with activators for binding sites on gene promoters (*IGF-1R, POLD1*) or by interfering with transcriptional machinery (*cyclin B, Cox-2*) or by

recruiting chromatin remodelers (*Map4, surviving*), has been reported.[24] Also, p53 is able to repress translation of its own, *cdk4* and *fgf-2* mRNAs via binding to respective 5′UTR.[25] But it is surprising that the expression of 2 of the main p53 target genes during the DNA damage response are in fact actively suppressed by p53 during the UPR. We do not yet know the molecular mechanism of action of p53-mediated suppression of translation during the UPR, but in both cases it involves the coding sequences and not the UTRs. As different point mutations in p53 that suppress its DNA binding activity were shown to prevent suppression of *$p21^{CDKN1A}$* mRNA translation, it is possible that the effect of p53 on the

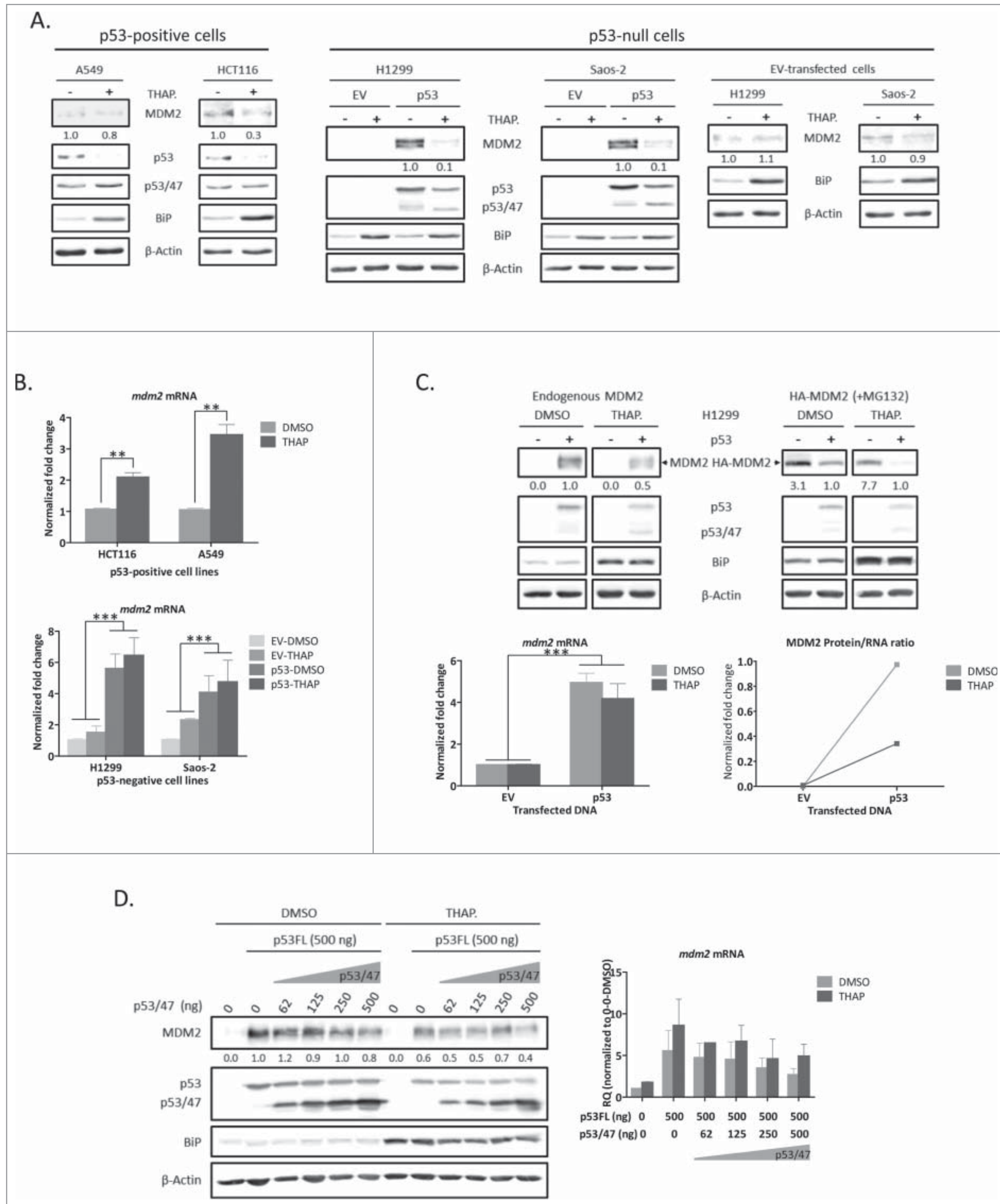

Figure 1. For figure legend, see next page.

p21^{CDKN1A} mRNA is indirect via a hitherto unknown p53 gene target.[19] It is also possible that it is direct and that p53 binds a class of mRNAs via the DNA-binding domain and, hence, mutations in p53 that affect DNA binding also affect RNA binding. A direct interaction with mRNAs has been proposed for *p53, cdk4* and *fgf-2* and similar observations have been done regarding the *mdmx* mRNA (unpublished data). Hence, the possibility of 2 different pathways to control mRNA translation by p53 cannot be excluded.

Nevertheless, it is clear that p53 has an mRNA translation suppressor activity and this raises some important questions: **i**) which RNAs are targeted by p53 and what mediates the specificity to some mRNAs and not others? **ii**) is the effect of p53 direct or indirect? **iii**) what are the underlying molecular mechanisms? **iv**) and, finally, what are the physiological implications? We have started to address some of these questions and a deletion series of the *p21^{CDKN1A}* mRNA indicated that 2 separate sequences are required for translation control, which makes interference by ncRNAs less likely mediators and instead points toward a structured region in the RNA as being critical.[19] This can form a platform to which RNA structure-sensitive protein/s can bind and this would help to explain why there is no apparent sequence homology between the *mdm2* and *p21^{CDKN1A}* mRNAs, or the other mRNAs implicated as targets for p53 trans-suppression activity. If so, this makes predictions of which RNAs that are p53 targets more difficult. In terms of how p53 mediates translation suppression it is important to keep in mind that more than one mechanism might be in place and it is safer to investigate each mRNA suppressed by p53 separately before any general conclusions are drawn. Protein-RNA binding assays together with *in vitro* translation should help to address if p53 affect translation directly or via downstream targets. However, *in vitro* translation systems are not the same as cell-based assays and if folding of RNA structures plays a role, then this might have significant consequences using *in vitro* transcribed mRNAs. Another important aspect is to differentiate p53 activities toward DNAs and RNAs in order to generate tools required to investigate the cell biological role of mRNA translation control. This could be achieved either by identifying differences in the RNA binding vs DNA binding capacity or by separating the trans-activation from the trans-suppression. The specificity of trans-suppression will depend on different cellular factors linking p53, or its downstream target factor, with the translation machinery and a major step forward will be to identify the target/s in the RNA translation process. Hence, the characterization of mRNAs affected by p53, as well as identification of the targets within the translation machinery, will play equal important roles in elucidating the underlying molecular and physiological role of p53 trans-suppressor activity.

As a perspective, it is worth considering the possibility that different aspects of p53 are prominent during different cellular conditions and the fact that p53 has opposite effects on p21^{CDKN1A} and MDM2 expression during the DNA damage vs the UPR justifies this notion. The DNA damage response and over expression of p53 gives to a large extend a similar cell phenotype in *in cellulo* conditions via the induction of mRNA levels but this is not the case for ER stress. Why is this? The suppression of protein synthesis by inactivation of eIF2α during the UPR relates to the need of the cell to slow down synthesis

Figure 1 (See previous page). p53 down-regulates MDM2 expression under Endoplasmic Reticulum stress. (**A**) Western blots of cell lysates extracted from p53-positive A549 and HCT116 (left) and Empty Vector (EV)- (right) or p53-transfected (center) p53-null H1299 and Saos-2 cell lines show that MDM2 expression is down-regulated on a p53 and ER stress dependent manner. Expression of MDM2 was estimated from densitometry analysis performed with Bio-PROFIL Bio 1-D software (Vilbert Lourmat) on chemiluminescence images acquired using CHEMI-SMART 5000 documentation system and Chemi-Capt software (Vilbert Lourmat). Values of MDM2 were normalized against their correspondent actin value and then against DMSO-treated cells in the case of A549 and HCT116 and EV- or p53-transfected and DMSO-treated cells in the case of H1299 and Saos-2. 500 ng of DNA were used in transfection. (**B**) Samples from A were analyzed in parallel for the effect of p53 expression on endogenous *mdm2* mRNA levels using relative RT-qPCR for p53-positive (top) and EV- of p53-transfected p53-negative (below) cell lines. Values were normalized against actin and are presented as fold change relative to DMSO-treated cells in the case of HCT116 and A549 and relative to EV-transfected and DMSO-treated cells for H1299 and Saos-2, set to 1 (mean ± s.d., n = 3 performed in duplicates). (**C**) Western blots show expression of endogenous MDM2 (upper left) or exogenous HA-tagged MDM2 carrying only the coding sequence (HA-MDM2) (upper right) in the presence or absence of a small amount (31 ng) of transfected p53 in H1299 cells. In the case of exogenous HA-MDM2, cells were also treated with proteasome inhibitor MG132 (25 μM, 2 h) to minimize effects related to protein stability. Values of MDM2 and HA-MDM2 protein expression were obtained as in A and normalized against their correspondent actin value and then against p53-transfected and DMSO-treated cells in the case of MDM2 and against p53-transfected and DMSO or THAP-treated cells for HA-MDM2. Relative RT-qPCR on endogenous *mdm2* was carried out in parallel (lower left). Values were normalized against actin and are presented as fold change relative to EV-transfected and DMSO-treated cells, set to 1 (mean ± s.d., n=3 performed in duplicates). Ratio of protein/RNA for endogenous MDM2 expression were calculated and presented as fold change compared to p53-transfected and DMSO-treated cells (lower right). (**D**) Endogenous MDM2 expression was analyzed in H1299 cells co-transfected with increasing amounts of p53/47 (0-500 ng) and a fixed amount of p53FL (500 ng). Cell lysates and mRNA levels were analyzed in parallel by western blot (left) and relative RT-qPCR (right), respectively. Values of MDM2 protein expression were normalized against actin. The value 1.0 was set for 500 ng of p53FL-transfected and DMSO-treated cells in western blot quantification. Values of RT-qPCR were normalized against actin and presented as fold change relative to EV-transfected and DMSO-treated cells (mean ± s.d., n = 3 performed in duplicates). For all experiments, 2×10^5 cells were seeded 24 h before transfection in 6-well plates. Thapsigargin (THAP., 100 μM) or DMSO treatments were done for 16 h. MDM2 was detected using 4B2 monoclonal antibody, HA-MDM2 was detected with an anti HA monoclonal antibody and both endogenous and exogenous p53 isoforms were detected using ACMDD serum (rabbit polyclonal antibody raised against peptide MDDLMLSPDDIEQC recognizing the N-terminus of p53/47).[30] BiP expression was used as a positive control for ER stress induction and β-Actin as loading control. Blots represent n ≥ 2. For all RT-qPCR, primers used to amplify MDM2 are: Forward 5′ ATCTACAGGGACGCCATC 3′ and Reverse 5′ CTGATCCAACCAATCACCTGAA 3′. In B top, Student's t-test compared data to the reference point as indicated. In B bottom and C down left, 2-way ANOVA compared data of the effect of treatment and transfection of p53 on *mdm2* mRNA expression as indicated (for all, $^{**}P < 0.01$; $^{***}P < 0.001$).

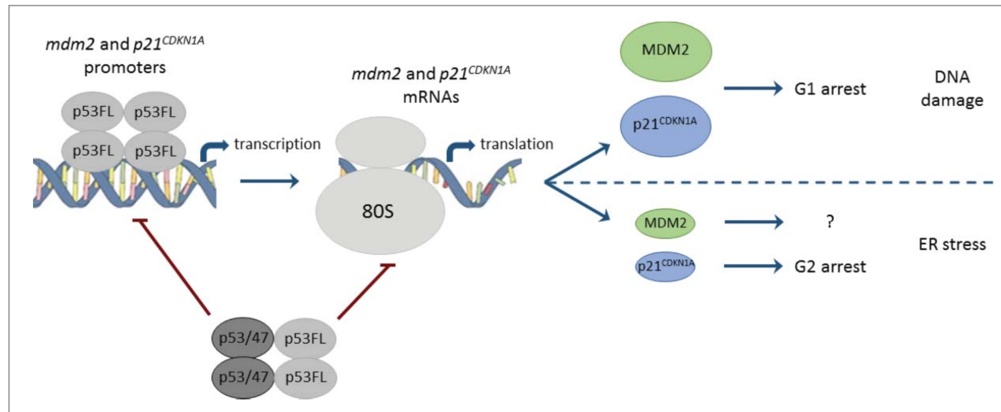

Figure 2. Model depicting how p53 and p53/47 control p21^{CDKN1A} and MDM2 expression differentially during DNA damage and ER stress context. In the DNA damage pathway, p53 full length (p53FL) acts at the transcription level to induce both *p21^{CDKN1A}* and *mdm2* mRNAs. The induction of p21^{CDKN1A} leads to G1 cell cycle arrest. During DNA damage, MDM2 acts as a positive regulator of p53 activity. The suppression of p21^{CDKN1A} and MDM2 during the UPR is attributed to the induction of p53/47, which prevents p53FL-mediated induction of *p21^{CDKN1A}* and *mdm2* mRNA levels. This allows p53 isomer-dependent suppression of *p21^{CDKN1A}* and *mdm2* mRNA translation to become dominant and results in lower p21^{CDKN1A} and MDM2 protein levels. Suppression of p21^{CDKN1A} levels is required to arrest in G2 during the UPR but the physiological role of MDM2 suppression remains to be elucidated.

of proteins in order to facilitate ER repair. However, some proteins required for the ER repair are induced at the level of protein synthesis and it raises the question if translation control during the UPR is a more favorable mechanism whereby protein expression can be controlled. Hence, during the UPR it might be less efficient for p53 to rely on transcription control to regulate gene expression and instead, or additionally, it targets mRNA translation.

Another aspect of these data is the questions of why MDM2 expression is suppressed during the UPR. In the case of p21^{CDKN1A} it was shown that it regulates the stability of 14-3-3σ and unless p21^{CDKN1A} levels are suppressed the cells fail to arrest in G2/M (**Fig. 2**).[17,19] But for MDM2 we still do not know. MDM2 is predominantly known for its role as a regulator of p53 but we have no evidence that MDM2's capacity to regulate p53 stability is different during the UPR as compared to normal conditions. A possible scenario would include MDM2's capacity to interact with ribosomal factors. It is well described that MDM2 interacts with ribosomal factors L5, L11, L23, S7 and the 5S complex.[26,27] The former interactions have been attributed to the control of MDM2 E3 ligase activity toward p53 and the binding to the L5/L11 complex stabilizes p53.[27] However, the role of MDM2 in stimulating p53 synthesis during the DNA damage response opens for the possibility that these interactions might also have the reverse functions and MDM2 might play a role in regulating ribosomal biogenesis. It is possible that such regulation might be acting during the UPR within the global control of protein synthesis and furthermore, it has been described that the MDM2-binding protein Arf which interacts within the same domain as ribosomal factors, inhibits the processing of rRNA.[28] Furthermore, p53 suppresses RNApol III activity via TFIIIB, suggesting that ribosomal biogenesis is interlinked with the p53 pathway and a target for p53 tumor suppressor activity.[29]

This article illustrates that p53 can have opposite functions toward the same gene depending on cellular conditions. A similar observation has been done on MDM2 that targets p53 for degradation during normal conditions but stimulates p53 synthesis following DNA damage.[12] In this case the switch is also mediated by an mRNA, implicating a broader role of mRNA as regulatory switches in the p53 pathway.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Antibodies against p53, MDM2 and HA-Tag were kindly provided by Dr. Borek Vojtesek.

Funding

This work was supported by la Ligue Contre le Cancer, the Inserm and the project MEYS-NPS I-L01413. I. L. is funded by AXA Research Fund.

References

1. Efeyan A, Serrano M. p53: guardian of the genome and policeman of the oncogenes. Cell Cycle 2007; 6:1006-10; PMID:17457049; http://dx.doi.org/10.4161/cc.6.9.4211
2. Vousden KH, Lane DP. p53 in health and disease. Nat Rev Mol Cell Biol 2007; 8:275-83; PMID:17380161; http://dx.doi.org/10.1038/nrm2147
3. El-Deiry WS, Harper JW, O'Connor PM, Velculescu VE, Canman CE, Jackman J, Pietenpol JA, Burrell M, Hill DE, Wang Y, et al. WAF1/CIP1 Is Induced in p53-mediated G1 Arrest and Apoptosis. Cancer Res 1994; 54:1169-74; PMID:8118801
4. Kastan MB, Zhan Q, el-Deiry WS, Carrier F, Jacks T, Walsh WV, Plunkett BS, Vogelstein B, Fornace AJ, Jr. A mammalian cell cycle checkpoint pathway utilizing p53 and GADD45 is defective in ataxia-telangiectasia. Cell 1992; 71:587-97; PMID:1423616; http://dx.doi.org/10.1016/0092-8674(92)90593-2
5. Miyashita T, Reed JC. Tumor suppressor p53 is a direct transcriptional activator of the human bax gene. Cell 1995; 80:293-9; PMID:7834749; http://dx.doi.org/10.1016/0092-8674(95)90513-8
6. Lanigan F, Geraghty JG, Bracken AP. Transcriptional regulation of cellular senescence. Oncogene 2011; 30:2901-11; PMID:21383691; http://dx.doi.org/10.1038/onc.2011.34
7. Efeyan A, Collado M, Velasco-Miguel S, Serrano M. Genetic dissection of the role of p21Cip1/Waf1 in p53-

mediated tumour suppression. Oncogene 2007; 26:1645-9; PMID:16964282; http://dx.doi.org/10.1038/sj.onc.1209972

8. Adnane J, Jackson RJ, Nicosia SV, Cantor AB, Pledger WJ, Sebti SM. Loss of p21WAF1/CIP1 accelerates Ras oncogenesis in a transgenic/knockout mammary cancer model. Oncogene 2000; 19:5338-47; PMID:11103935; http://dx.doi.org/10.1038/sj.onc.1203956
9. Barak Y, Juven T, Haffner R, Oren M. mdm2 expression is induced by wild type p53 activity. EMBO J 1993; 12:461-8; PMID:8440237
10. Barak Y, Gottlieb E, Juven-Gershon T, Oren M. Regulation of mdm2 expression by p53: alternative promoters produce transcripts with nonidentical translation potential. Gen Dev 1994; 8:1739-49; PMID:7958853; http://dx.doi.org/10.1101/gad.8.15.1739
11. Pant V, Xiong S, Jackson JG, Post SM, Abbas HA, Quintas-Cardama A, Hamir AN, Lozano G. The p53-Mdm2 feedback loop protects against DNA damage by inhibiting p53 activity but is dispensable for p53 stability, development, and longevity. Gen Dev 2013; 27:1857-67; PMID:23973961; http://dx.doi.org/10.1101/gad.227249.113
12. Candeias MM, Malbert-Colas L, Powell DJ, Daskalogianni C, Maslon MM, Naski N, Bourougaa K, Calvo F, Fahraeus R. P53 mRNA controls p53 activity by managing Mdm2 functions. Nat Cell Biol 2008; 10:1098-105; PMID:19160491; http://dx.doi.org/10.1038/ncb1770
13. Naski N, Gajjar M, Bourougaa K, Malbert-Colas L, Fahraeus R, Candeias MM. The p53 mRNA-Mdm2 interaction. Cell Cycle 2009; 8:31-4; PMID:19106616; http://dx.doi.org/10.4161/cc.8.1.7326
14. Malbert-Colas L, Ponnuswamy A, Olivares-Illana V, Tournillon AS, Naski N, Fahraeus R. HDMX folds the nascent p53 mRNA following activation by the ATM kinase. Mol Cell 2014; 54:500-11; PMID:24813712; http://dx.doi.org/10.1016/j.molcel.2014.02.035
15. Zhao L, Ackerman SL. Endoplasmic reticulum stress in health and disease. Curr Opin Cell Biol 2006; 18:444-52; PMID:16781856; http://dx.doi.org/10.1016/j.ceb.2006.06.005
16. Lisbona F, Hetz C. Turning off the unfolded protein response: an interplay between the apoptosis machinery and ER stress signaling. Cell Cycle 2009; 8:1643-4; PMID:19411860; http://dx.doi.org/10.4161/cc.8.11.8637
17. Bourougaa K, Naski N, Boularan C, Mlynarczyk C, Candeias MM, Marullo S, Fahraeus R. Endoplasmic reticulum stress induces G2 cell-cycle arrest via mRNA translation of the p53 isoform p53/47. Mol Cell 2010; 38:78-88; PMID:20385091; http://dx.doi.org/10.1016/j.molcel.2010.01.041
18. Pyronnet S, Dostie J, Sonenberg N. Suppression of cap-dependent translation in mitosis. Gen Dev 2001; 15:2083-93; PMID:11511540; http://dx.doi.org/10.1101/gad.889201
19. Mlynarczyk C, Fahraeus R. Endoplasmic reticulum stress sensitizes cells to DNA damage-induced apoptosis through p53-dependent suppression of p21(CDKN1A). Nat Commun 2014; 5:5067; PMID:25295585; http://dx.doi.org/10.1038/ncomms6067
20. Candeias MM, Powell DJ, Roubalova E, Apcher S, Bourougaa K, Vojtesek B, Bruzzoni-Giovanelli H, Fahraeus R. Expression of p53 and p53/47 are controlled by alternative mechanisms of messenger RNA translation initiation. Oncogene 2006; 25:6936-47; PMID:16983332; http://dx.doi.org/10.1038/sj.onc.1209996
21. Maier B, Gluba W, Bernier B, Turner T, Mohammad K, Guise T, Sutherland A, Thorner M, Scrable H. Modulation of mammalian life span by the short isoform of p53. Gen Dev 2004; 18:306-19; PMID:14871929; http://dx.doi.org/10.1101/gad.1162404
22. Ungewitter E, Scrable H. Delta40p53 controls the switch from pluripotency to differentiation by regulating IGF signaling in ESCs. Gen Dev 2010; 24:2408-19; PMID:21041409; http://dx.doi.org/10.1101/gad.1987810
23. Takahashi R, Giannini C, Sarkaria JN, Schroeder M, Rogers J, Mastroeni D, Scrable H. p53 isoform profiling in glioblastoma and injured brain. Oncogene 2013; 32:3165-74; PMID:22824800; http://dx.doi.org/10.1038/onc.2012.322
24. Ho J, Benchimol S. Transcriptional repression mediated by the p53 tumour suppressor. Cell Death Differ 2003; 10:404-8; PMID:12719716; http://dx.doi.org/10.1038/sj.cdd.4401191
25. Riley KJ, Maher LJ, 3rd. p53 RNA interactions: new clues in an old mystery. RNA 2007; 13:1825-33; PMID:17804642; http://dx.doi.org/10.1261/rna.673407
26. Chen D, Zhang Z, Li M, Wang W, Li Y, Rayburn ER, Hill DL, Wang H, Zhang R. Ribosomal protein S7 as a novel modulator of p53-MDM2 interaction: binding to MDM2, stabilization of p53 protein, and activation of p53 function. Oncogene 2007; 26:5029-37; PMID:17310983; http://dx.doi.org/10.1038/sj.onc.1210327
27. Horn HF, Vousden KH. Cooperation between the ribosomal proteins L5 and L11 in the p53 pathway. Oncogene 2008; 27:5774-84; PMID:18560357; http://dx.doi.org/10.1038/onc.2008.189
28. Itahana K, Bhat KP, Jin A, Itahana Y, Hawke D, Kobayashi R, Zhang Y. Tumor suppressor ARF degrades B23, a nucleolar protein involved in ribosome biogenesis and cell proliferation. Mol Cell 2003; 12:1151-64; PMID:14636574; http://dx.doi.org/10.1016/S1097-2765(03)00431-3
29. Crighton D, Woiwode A, Zhang C, Mandavia N, Morton JP, Warnock LJ, Milner J, White RJ, Johnson DL. p53 represses RNA polymerase III transcription by targeting TBP and inhibiting promoter occupancy by TFIIIB. The EMBO J 2003; 22:2810-20; PMID:12773395; http://dx.doi.org/10.1093/emboj/cdg265
30. Powell DJ, Hrstka R, Candeias M, Bourougaa K, Vojtesek B, Fahraeus R. Stress-dependent changes in the properties of p53 complexes by the alternative translation product p53/47. Cell Cycle 2008; 7:950-9; PMID:18414054; http://dx.doi.org/10.4161/cc.7.7.5626