Nitric oxide (NO) is an important bioactive molecule involved in a variety of physiological and pathological processes. At the same time, NO is also an inducer of stress signaling, owing to its ability to damage proteins and DNA. NO was reported to be a potent activator of the p53 tumor suppressor protein. However, the mechanisms underlying p53 activation by NO remain to be elucidated. We report here that NO induces the accumulation of transcriptionally active p53 in a variety of cell types and that NO signaling to p53 does not require ataxia telangiectasia-mutated (ATM), poly(ADP-ribose) polymerase 1, or the ARF tumor suppressor protein. In mouse embryonic fibroblasts, NO elicits a down-regulation of Mdm2 protein levels that precedes the rise in p53. NO-induced down-regulation of Mdm2 protein but not its mRNA also occurs in several p53-deficient cell types and is thus p53-independent. The drop in endogenous Mdm2 levels following NO treatment is accompanied by a corresponding reduction in the rate of p53 ubiquitination. Thus, the down-regulation of Mdm2 by NO is likely to contribute to the activation of p53.

p53 is one of the best studied tumor suppressors. It is now appreciated that p53 is a pivotal integrator of stress signaling, and that many diverse types of stress can evoke a p53 response (1, 2). p53 is typically a very short-lived protein under normal conditions because of its fast proteasomal degradation. A key feature of the p53 response is p53 stabilization, leading to a rapid increase in p53 steady-state levels. Abundant evidence indicates that p53 stabilization largely relies on post-translational events that uncouple p53 from its proteasomal degradation (3, 4). A major E3 ubiquitin ligase for p53, whose activity serves as a rate-limiting factor for p53 degradation, is Mdm2 (5–7). Interestingly, the expression of the mdm2 gene is regulated by p53 itself (8, 9). This p53-Mdm2 autoregulatory feedback loop has been a focus of research in recent years, leading to the realization that many stress signals impinge on this loop to modulate the physical and functional interplay between p53 and Mdm2.

Different types of stress engage different mechanisms to uncouple the p53-Mdm2 feedback loop (10). In the case of ionizing radiation, the ATM kinase is essential for the rapid accumulation of p53. Ionizing radiation gives rise to at least three ATM-dependent events that impact on the p53-Mdm2 feedback loop, i.e. the phosphorylation of p53 on Ser-15 and Mdm2 on Ser-395 by ATM itself (11–13), and on Ser-20 of p53 by ATM-activated CHK2, a human checkpoint kinase (14, 15). In the case of aberrant oncogene expression, oncoproteins such as c-Myc, Ras, and β-catenin induce the expression of ARF, which binds to Mdm2 and inhibits its E3 ubiquitin ligase activity (16–19). Moreover, the binding of ARF to Mdm2 can sequester Mdm2 in the nucleolus (20, 21). Both of these mechanisms are proposed to reduce p53 ubiquitination and thereby increase its stability.

Nitric oxide (NO) is an important bioactive molecule involved in a variety of physiological and pathological processes. This membrane permeable and extremely short-lived (biological half-life: 1–10 s) molecule has been shown to be a regulator of cell killing by macrophages, a mediator of vasodilation and a neurotransmitter. Virtually every type of mammalian cell is under the influence of NO (22), because it is widely and actively synthesized. NO can be formed either by specific nitric-oxide synthases, which metabolize arginine to citrulline with the formation of NO or by nonenzymatic mechanisms involving the reduction of nitrite to NO under acidic and highly reduced conditions (reviewed in Ref. 23). NO can be stored in the form of S-nitrosothiols. In fact, S-nitrosothiols formed upon the reaction of NO with redox-activated thiols represent an active storage pool for NO (reviewed in Ref. 24).

The ability of NO to induce p53 accumulation has been observed in several studies. p53 accumulation was shown to occur upon treatment with exogenous NO donors in primary normal human fibroblasts, the murine monocye/macroage cell line RAW 264.7, the human promyelocytic leukemia cell line U937, and the human glioblastoma cell line A172 (25–27). However, the molecular mechanisms underlying the induction of p53 by NO have not been elucidated. We now report that NO signaling to p53 is independent of ATM, poly(ADP-ribose) polymerase 1 (PARP-1), or ARF. Of note, the induction of p53 by NO is preceded by a decrease in Mdm2 protein levels. This down-regulation of Mdm2 may be one of the events that contribute to p53 activation by NO.

**EXPERIMENTAL PROCEDURES**

**Cells and Tissue Culture**—Primary mouse embryonic fibroblasts (MEFs) were prepared from day 13.5 embryos and propagated at 37 °C in Dulbecco’s modified Eagle’s medium supplemented with nonessential amino acids, 60 μM β-mercaptoethanol, and 10% heat-inactivated fetal bovine serum (FBS, Sigma). MEFs were typically used after four passages in culture. AG03057 (ATM+/−, wtp53, mother) and AG03058 (ATM−/−, wtp53, daughter) cells were obtained from the National Institute of General Medical Sciences Human Genetic Mutant Cell
Repository (Coriell Institute, Camden, NJ). AG03057 and AG03058 and WI-38 cells (human fetal lung fibroblasts, wtp53) were maintained in minimum Eagle's medium supplemented with 20% non-heat-inactivated FBS. ARF knock-out MEFs were obtained from Dr. C. Sherr. p53-null mouse fibroblasts (line 35-8) were from Dr. G. Lozano. C3 cells (ATM null—human lymphocytes immortalized by Epstein-Barr Virus) were obtained from Dr. Y. Shiloh. PARP knock-out 3T3 cells and ARF-null and p53-null mouse fibroblasts as well as U2-OS cells (human osteosarcoma, wtp53) were maintained at 37 °C in Dulbecco's modified Eagle's medium supplemented with 10% heat-inactivated FBS. ML-1 (human leukemia cells, wtp53), H1299 cells (human lung adenocarcinoma, p53-null), and C9 cells were maintained at 37 °C in RPMI 1640 medium supplemented with 10% heat-inactivated FBS. HCT116 colorectal carcinoma cells in which the p53 gene has been eliminated by somatic knock-out (28) were provided by Dr. B. Vogelstein and maintained in McCoy's 5A medium supplemented with 10% FBS.

**Chemicals**—s-Nitroso-n-acetylpenicillamine (SNAP) (Sigma) and S-nitroso-glutathione (GSNO) (Alexis Biochemicals) were dissolved in PBS at a concentration of 50 mM and stored at −80 °C in small aliquots. C-PTIO (Biomol Research Laboratories, Inc.) was dissolved in PBS at −4 °C at 10 mM, stored at −80 °C, and used at a final concentration of 10 μM. MG132 (Calbiochem) was dissolved in Me2SO at a concentration of 50 mM and used at a final concentration of 25 μM. Cycloheximide (Sigma) was dissolved in PBS at −10 μg/ml and used at a final concentration of 10 μg/ml.

**Retroviral Infection**—High titer retroviral stocks were produced by transfecting retroviral constructs pBabe-puro or pBabe-PARP into 293T cells (2 × 10^6/10-cm dish) by the calcium phosphate coprecipitation method together with the ecotropic packaging vector pSV-ϕE-MLY, providing ecotropic packaging helper function. Virus-containing culture supernatants were collected 24–72 h post-transfection at 6-h intervals and pooled together. PARP knock-out 3T3 cells (2 × 10^6/10-cm dish) were infected with filtered supernatants. Fresh supernatants were added three times at 4-h intervals. 48 h post-infection, cells were trypsinized and replated for experiments.

**Transfection**—HCT116 cells were plated at 0.5 × 10^5/6-cm plate and transfected with the aid of the JetPEI reagent (PolyPlus Transfection) according to the manufacturer’s instructions. Transfection efficiencies were typically above 70%. GSNO treatment was performed 18 h after transfection.

**RNA Analysis**—Total RNA was extracted using the ULTRASPEC (Biotex Laboratories) reagent. Semi-quantitative reverse transcriptase (RT)-PCR was performed as described previously (29) using the following primer combinations: hp53, 5'-GTCAGCTGGTGTTATT-C'-3' and 5'-TCTCCGCCCAGTAGATTACCA-3'; hp21, 5'-CGCGACTGTGTGGACTGTGGTCATGAGCCC-3'; HD2, 5'-GACCTGAATACCAATGCTGCT-3' and 5'-GCACTCAAGATCGGATTCCA-3'; Mdm2, 5'-GTGCAAATACCAATGCTGCT-3' and 5'-GCACTCAAGATCGGATTCCA-3'; HDM2, 5'-CGACTATTCCCAACCATCG-3' and 5'-GCCGCATGCTTGTTATT-C'-3'.

**Immunoblotting Analysis**—Cells were washed in ice-cold PBS and lysed in radiolmmune precipitation buffer. After three rounds of vigorous vortexing at 5-min intervals, the lysates were cleared by centrifugation at 4 °C for 10 min. Aliquots containing equal amounts of total protein were subjected to Western blot analysis with a mixture of the p53-specific antibodies DO-1 and PAb1801. Western blot analysis was performed as described previously (30) using the p53-specific antibody PAb421. WI-38 human diploid fibroblasts were exposed to 8 Grays of ionizing radiation (IR) from a γ-ray source or to the NO donor GSNO (1 mM final concentration). In the cultures analyzed in the bottom panel, the NO scavenger c-PTIO was added to the medium 1 h before treatment. Extracts were prepared and analyzed as in A. Ctr, nontreated control.

**RESULTS**

**NO Induces p53 Accumulation in a Variety of Cell Types**—To test the generality of the p53 response to NO, several different cell types were exposed to NO donors (either SNAP or GSNO), and p53 protein levels were monitored by Western blot analysis. A significant induction of endogenous p53 was seen in all wild type p53-containing cell types tested including the U2-OS human osteosarcoma cell line (Fig. 1A), the ML-1 human myeloid leukemia cell line (Fig. 1B), WI-38 human diploid fibroblasts (Fig. 1C), and MEFs (Fig. 3). The accumulation of p53 was time-dependent (Fig. 1A) and NO donor concentration-dependent (Fig. 1B) and was observed with both SNAP (Fig. 1A and B) and GSNO (Fig. 1C). Importantly, the addition of a NO scavenger, C-PTIO (10 μM), completely abolished the GSNO-induced increase in p53 but not the induction of p53 by ionizing radiation (Fig. 1C, lower panel), confirming that the effect of GSNO on p53 is indeed mediated specifically by NO. Hence, in agreement with earlier reports (25–27, 30), the pathways linking NO signaling to p53 are functional in many cell types including cancer-derived cells that retain wild type p53 expression.

The accumulation of p53 in response to NO was accompanied by induction of the p53 target genes p21/Waf1 (Fig. 2A) and hdm2 (Fig. 2B) observed at both protein and mRNA levels. Hence, as reported previously (31), the p53 protein induced by NO is transcriptionally active.

**NO Increases p53 Protein Stability**—The increase in p53 protein in response to NO might be because of either increased levels of p53 mRNA or translational and post-translational events. However, no changes in the concentration of p53 mRNA could be found when p53-specific RT-PCR analysis was performed with the samples used in Fig. 2 (data not shown). Hence, we asked whether the accumulation of p53 was attributed to increased protein stability. To that end, a cycloheximide chase experiment was performed with MEFs maintained either in the presence or absence of the NO donor GSNO. As shown in Fig. 3, exposure to GSNO elicited a significant prolongation of the half-life of p53. An analysis by quantitative densitometry revealed that whereas the half-life of p53 in untreated MEFs was ∼15 min, it increased to 140 min in GSNO-treated cells 15698

**Fig. 1. Time and dose-dependent induction of p53 by NO in different cell types.** A, U2-OS human osteosarcoma cells were exposed to the NO donor SNAP at a final concentration of 0.5 mM. Cell extracts were prepared after different times of treatment as indicated in hours (T(h)) above each lane. Aliquots containing equal amounts of total protein were subjected to Western blot analysis with a mixture of the p53-specific antibodies DO-1 and PAb1801. B, ML-1 human myeloid leukemia cells were exposed to the indicated amounts of SNAP. Extracts were prepared after 10 h of treatment and processed as in A but using the p53-specific antibody PAb421. C, WI-38 human diploid fibroblasts were exposed to 8 Grays of ionizing radiation (IR) from a γ-ray source or to the NO donor GSNO (1 mM final concentration). In the cultures analyzed in the bottom panel, the NO scavenger c-PTIO was added to the medium 1 h before treatment. Extracts were prepared and analyzed as in A. Ctr, nontreated control.
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Induction of p53 by NO Is Independent of ATM, PARP-1, or ARF. A, human diploid fibroblasts heterozygous or homozygous for ATM gene mutations (ATM+/− and ATM−/−, respectively) were treated with the NO donor GSNO (1 mM) for 10 h. Steady-state levels of p53 were determined by Western blot analysis using a mixture of the p53-specific monoclonal antibodies PAb421 and PAb248, the Mdm2-specific monoclonal antibody 2A10, or a polyclonal antibody directed against PARP-1. α-Tubulin served as a loading control. B, PARP-1 knock-out mouse 3T3 fibroblasts were infected either with a recombinant retrovirus encoding PARP-1 (v-PARP-1,+) or with control P8b-puro retrovirus (v-PARP-1,−) and incubated with or without 1 mM GSNO for 10 h. Cell extracts were subjected to Western blot analysis using a mixture of the p53-specific monoclonal antibodies PAb421 and PAb248, the Mdm2-specific monoclonal antibody 2A10, or a polyclonal antibody directed against PARP-1. α-Tubulin served as a loading control. C, embryonic fibroblasts derived either from control mice (MEFs) or from ARF-knock-out mice (ARF−−) were treated with 1 mM GSNO for 10 h. p53, Mdm2, and α-tubulin were analyzed as in B. The upper band in the apparent p53 doublet is probably a nonspecific background band.

ATM activity is dispensable for the activation of p53 by NO. This conclusion was also confirmed by monitoring the reactivity of Mdm2 with the monoclonal antibody 2A10. Phosphorylation of Mdm2 by ATM leads to a substantial drop in 2A10 reactivity (13, 36). However, exposure of cells to NO did not cause any measurable change in the reactivity of Mdm2 with 2A10 (data not shown), arguing that NO does not trigger ATM activation.

An attractive candidate for mediating the activation of p53 by NO is the enzyme PARP-1. NO is a potent activator of PARP-1 through its ability to cause single strand DNA breaks (37, 38). Furthermore, PARP-1 can engage in direct protein-protein interactions with p53 (39). Therefore, we compared the induction of p53 by NO in 3T3 fibroblasts from PARP-1 knockout mice (40) and in derivatives of these 3T3 fibroblasts in which PARP-1 expression had been reconstituted by infection with a PARP-1 retrovirus. As shown in Fig. 4B, there was no measurable difference between these two cell types with regard to either p53 protein accumulation or induction of Mdm2, a product of a p53 target gene. Thus, PARP-1 appears dispensable for the activation of p53 by NO.

Some signaling pathways, in particular oncogenic stress, lead to p53 stabilization by triggering the synthesis of the ARF tumor suppressor protein (17). The binding of ARF to Mdm2 inactivates the latter and renders p53 more stable. Therefore, it was of interest to find out whether ARF played a role in the signaling from NO to p53. To that end, the effect of NO on p53 was studied in MEFs from ARF-null mice and in their wild type counterparts. As seen in Fig. 4C, the ablation of ARF expression did not compromise the ability of NO to promote an increase in the steady-state levels of p53 and Mdm2, implying that ARF is not required for the activation of p53 by NO.

**NO Down-regulates Mdm2 Protein Levels**—Because the degradation of p53 is largely dependent on the activity of Mdm2, we performed a more detailed time course analysis of p53 and Mdm2 in wild type MEFs exposed to NO donors. Unexpectedly,
were treated with 1 mM GSNO for 1, 2, or 4 h. At each time point, protein extracts were subjected to Western blot analysis using separately the Mdm2-specific monoclonal antibody 2A9. β-Catenin was used as a loading control. C, spontaneously immortalized fibroblasts derived from p53 knock-out mice (cell line 35-8) were treated with 1 mM GSNO for 1, 2, or 4 h. At each time point, protein extracts and total RNA were prepared from parallel cultures. Protein extracts were subjected to Western blot analysis using separately the Mdm2-specific monoclonal antibodies 2A10 and 4B2. RNA samples were subjected to semi-quantitative RT-PCR using primers specific for either Mdm2 or GAPDH as a control.

Although extended exposure to NO augmented the levels of Mdm2 owing to the activation of the mdm2 gene by p53 (see Fig. 4C), an opposite picture was revealed at early phases of the NO response. As seen in Fig. 5A, exposure of MEFs to GSNO led to a rapid drop in Mdm2 protein, clearly preceding the rise in p53. As expected, Mdm2 levels increased again and became further augmented at later time points, subsequent to the induction of p53 as also seen in Fig. 2B.

The ability of NO to modulate the levels of Mdm2 was further explored in p53-null cells where the analysis is made simpler by the absence of a later Mdm2 induction attributed to p53 activation. Indeed, incubation of p53-deficient H1299 human lung adenocarcinoma cells with GSNO resulted in a substantial and extended drop in Hdm2 (Fig. 5B). Consistent with the absence of p53, a second wave of Hdm2 induction did not occur in these cells. A pronounced decrease in Mdm2 quantified with the aid of two different monoclonal antibodies was also evident in GSNO-treated p53-null MEFs (Fig. 5C, left-hand panel). This decrease was not the result of down-modulation of mdm2 mRNA, because semi-quantitative RT-PCR analysis did not reveal any significant change in the concentration of the corresponding transcripts (Fig. 5C, right-hand panel). Together, these observations support the notion that the induction of p53 by NO, at least in the early phase of the response, is achieved through down-regulation of Mdm2 protein levels.

**NO Attenuates p53 Ubiquitination by Endogenous Mdm2**—Mdm2 promotes p53 degradation by driving p53 ubiquitination. Therefore, it appeared plausible that the stabilization of p53 by NO is attributed to reduced p53 ubiquitination as a result of the drop in total Mdm2 levels. This observation was investigated in p53-deficient human colorectal carcinoma HCT116 cells (28). First, to confirm that the effect of NO could also be exerted on exogenous p53, these cells were transfected with a very small amount of p53 expression plasmid. As seen in Fig. 6A, NO indeed augmented the accumulation of the transfected p53 protein along with a reduction in the levels of endogenous Hdm2 protein. However, the total amounts of p53 produced in these transfected cultures were too low to allow further analysis of p53 ubiquitination. Therefore, a similar experiment was performed using higher inputs of p53 expression plasmid DNA. An analysis of relatively small aliquots of the resultant cell extracts revealed again the expected drop in Hdm2 (Fig. 6B, right-hand panel). However, this time there was no significant increase in p53, presumably because the transected p53 was in large excess over endogenous Hdm2. These conditions simplified the quantitative analysis of p53 ubiquitination, because no adjustment had to be made for differences in total p53 protein. Importantly, when larger amounts of the same extracts were subjected to analysis with p53-specific antibodies, a significant reduction was observed in the intensity of the bands corresponding to ubiquitinated forms of p53 (Fig. 6B, left-hand panel). A similar picture was seen when HCT116 cells were cotransfected with expression plasmids for p53 and hemagglutinin-ubiquitin followed by analysis of p53-ubiquitin conjugates (data not shown). Hence, the NO-induced drop in total Mdm2 protein is accompanied by a corresponding drop in p53 ubiquitination, which presumably underlies the subsequent stabilization of p53.
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DISCUSSION

The mechanisms underlying the stress-induced stabilization and activation of p53 are being extensively studied (3, 4, 10, 41, 42). Although the ability of NO to up-regulate p53 is well documented, the detailed molecular analysis of the underlying mechanisms is complicated by the fact that NO is a very pleiotropic agent, which can cause several different types of protein modifications, lipid oxidation, and DNA strand breaks. NO causes DNA damage through its derivatives dinitrogen trioxide (N2O3 = NO + NO2) and peroxynitrite (ONOO·). The resultant types of DNA damage include cross-linking, formation of abasic sites, and single strand breaks (reviewed in Ref. 32). The utilization of cells bearing deficiencies in several DNA damage-induced pathways enabled us to rule out some of those pathways as key mediators of the activation of p53 by NO. Thus, ATM was found to be dispensable for such activation, arguing against a major role of double-stranded DNA breaks. A more probable candidate was PARP-1, because this enzyme can be strongly activated by NO and because it has been implicated by several studies in the DNA damage-induced p53 response (43–46). Furthermore, PARP-1 coimmunoprecipitates with p53 and PARP-2 protein (49) as well as other DNA damage-induced signaling events may play a role in p53 activation by NO. Similarly, our findings also appear to exclude ARF as a major contributor to NO-induced p53 accumulation. This sets NO clearly apart from oncogenic stress, which utilizes ARF as a major contributor to NO-induced p53 accumulation.

In conclusion, our findings further underscore the multiplicity of molecular mechanisms employed by different stress signals to activate p53 as well as the central role of Mdm2 in these signaling pathways.

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