Laminar flow arrests vascular endothelial cells at the G$_0$/G$_1$ phase with concurrent increase in p53 and p21$^{Waf1}$. We investigated the molecular mechanism by which laminar flow activates p53 and p21$^{Waf1}$ in endothelial cells. The application of a laminar flow (12 dyn/cm$^2$) increased the deacetylation at Lys-320 and Lys-373 of p53 and the acetylation at Lys-382 in human umbilical vein endothelial cells. Laminar flow increased the activity of histone deacetylase (HDAC) and the association of p53 with HDAC1. Treating human umbilical vein endothelial cells with trichostatin A (TSA), an HDAC inhibitor, abolished the flow-induced p53 deacetylation at Lys-320 and Lys-373. To investigate the role of the HDAC-deacetylated p53 in the flow activation of p21$^{Waf1}$, we found that TSA inhibited the activation at both the mRNA and protein levels. Deletion and mutation analyses of the p21$^{Waf1}$ promoter revealed that flow activated p21$^{Waf1}$ through p53 and TSA abrogated this p53-dependent activation. The expression plasmid encoding the p53 mutant, with Lys-320 and Lys-373 replaced by Arg, increased the activity of the co-transfected p21$^{Waf1}$ promoter, which demonstrates that HDAC-deacetylated p53 can transactivate the p21$^{Waf1}$ gene. The regulation of the p53-p21$^{Waf1}$ pathway by laminar flow was further supported by observations that flow caused an increase of p21$^{Waf1}$ level in the wild-type HCT116 (p53/+ cells) but not in the p53-null HCT116 cells.

By controlling cell cycle arrest and/or apoptosis, the p53 tumor suppressor plays a critical role in cell proliferation (see Refs. 1 and 2 for review). p53 exerts its functions by activating or repressing the transcription of target genes, including p21$^{Waf1}$, GADD45, Bax, and MDM2, whose gene products are required either to regulate cell cycle progression or to modulate the function of p53. Several distinct functional domains within p53 have been characterized: an N-terminal transactivation domain, tetramerization domain (amino acids 320–360), and a regulatory domain (amino acids 363–393). p53 activity is regulated by multiple post-translational modifications. The phosphorylation at Ser-6, Ser-9, Ser-15, Ser-20, Ser-33, Ser-37, Ser-46, Thr-18, and Thr-81 in the N-terminal leads to the stabilization of the p53 protein (see Ref. 3 for review). Phosphorylation at Ser-315 and Ser-392 and the sumoylation at Lys-386 are believed to enhance the binding of p53 to DNA and to elevate p53 transcriptional activity (4–8).

In response to genotoxic stresses such as UV irradiation, γ-irradiation, and DNA damage agents, p53 is also acetylated at multiple Lys residues (see Ref. 9 for review). The acetylation of p53 is mediated by two distinct classes of histone acetyltransferase. cAMP-responsive element-binding protein-binding protein (CBP)/p300 acetylates Lys-382 and, to a lesser extent, Lys-373 and Lys-381, whereas CBP/p300-associated factor (PCAF) acetylates Lys-320. The functional consequences of p53 acetylation are still not clearly defined. Both CBP/p300 and PCAF can increase the p53-mediated p21$^{Waf1}$ gene expression in vivo but seems to exert little effect on its binding to long DNA sequences or chromatin DNA (11). p53 is deacetylated by histone deacetylase 1 (HDAC1) or Sir2 (12–14). p53 deacetylation has been suggested to down-regulate the activation of genes such as Bax and p21$^{Waf1}$ (15–17).

Blood flow acts on the vascular endothelial cells (ECs), which play a crucial role in cardiovascular physiology and pathophysiology (see Ref. 18 for review). The shear forces result from local blood flow patterns, depending upon the vessel geometry. The regions under laminar flow (i.e. the straight parts of the arterial tree) have been found to be resistant to atherosclerosis, whereas disturbed flow regions at the bends and bifurcations are prone to lesion development (see Ref. 19 for review). The results of in vitro experiments using flow channels have demonstrated that laminar flow protects ECs from apoptosis induced by tumor necrosis factor-α, oxidized low density lipoprotein, and angiostatin II (20, 21). We and others have shown that laminar flow suppresses the transition from the G$_1$ to S phase and that this is associated with an increase in the expression of p21$^{Waf1}$ at mRNA and protein levels (22, 23). These changes are accompanied by decreases in the phosphorylation of retinoblastoma protein and in the activities of cdk2 and cdk4.

In view of the importance of p53 and p21$^{Waf1}$ in cell cycle regulation and flow-induced changes in EC biology, we investigated the mechanisms by which laminar flow regulates p53 and p21$^{Waf1}$ in ECs. Our results revealed that Lys residues of p53 are differently regulated. Laminar flow leads to an in-
crease in acetylation at Lys-382 but a deacetylation at Lys-320 and Lys-373. This unique pattern of p53 deacetylation contributes, at least in part, to the activation of p21\(^{\text{Waf1}}\). These results provide new insights into the roles of p53 in regulating EC functions.

**EXPERIMENTAL PROCEDURES**

**Cell Culture and Stimulation by Laminar Flow or UV Irradiation—**Bovine aortic ECs (BAECs) were maintained in Dulbecco’s modified Eagle’s medium (Invitrogen) supplemented with 10% fetal bovine serum. Human umbilical vein ECs (HUVECs) were maintained in M199 medium (Invitrogen) supplemented with 25 mM HEPES, 2.5 mM glucose, 0.1 mg/ml heparin, 5 mM NaCl, 10% fetal bovine serum. The p53-null human colorectal cancer cell line HCT116/p53\(^{-/-}\) and its parental wild-type HCT116/p53\(^{+/+}\) were cultured in McCoy’s medium supplemented with 10% fetal bovine serum and 1% penicillin-streptomycin.

For laminar flow experiments, BAECs or HUVECs were cultured on collagen-coated glass slides (38 x 76 mm). The cells were exposed to a laminar flow generated by the pressure difference between the upper and lower reservoirs, with the effluent tissue culture medium circulated back to the upper reservoir through a peristaltic pump. The shear stress, determined by the flow rate and the channel dimensions, was 12 dyn/cm\(^2\), which is comparable with the physiological range in human major arteries and has been found to increase the amount of p53 (22). The pH was kept by gassing the flow system with a mixture of 95% air, 5% CO\(_2\), and the temperature was maintained at 37 °C. Static controls were cells cultured on slides not exposed to flow. For UV irradiation experiments, HUVECs were exposed to 100 J/m\(^2\) UV irradiation after 12 h of serum deprivation. The cells were harvested 1190), 2.26 kb (\(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\)), 2290 to \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\), \(\text{H11002}\)). p21/CE-Luc-33 contains only a p53 consensus element. \(\text{p21-CE-Luc-2290}\) was then inserted into the promoter region of the pGL2-basic vector to create plasmid p21-Luc-2290 that contains both the p53 and Renilla luciferase and 5' site of the Xho site of the plasmid was constructed by the use of PCR-based mutagenesis with pdNA1.1-p53 (24) as the template for Arg replacement of Lys-320, Lys-321, Lys-372, and Lys-373. The −2290 to +8 fragment of the p21\(^{\text{Waf1}}\) promoter sequence was amplified by PCR using a primer set of 5’-ctgtagcagctgagtagtctgg-3’ and 5’-ctgtagcagctgagtagtctgg-3’. The amplified fragment was then cloned into the pGL2-basic vector to create plasmid p21-Luc-2290 that contains both the p53 consensus element (−2255 to −2232) and Sp1/Sp3 sites (−50 to 150). p21-Luc-1190, p21-Luc-33, and p21/CE-Luc-33 were created from p21-Luc-2290 by deleting the respective fragments of 1.1 kb (−2290 to −1190), 2.26 kb (−2290 to −34) and 2.24 kb (−2233 to −34). p21-Luc-1190 contains only Sp1/Sp3 sites, whereas p21-Luc-33 contains a TATA box with neither p53 element nor Sp1/Sp3 sites. p21/CE-Luc-33 contains only a p53 consensus element. The various DNA plasmids were transfected into BAECs at 70% confluence using the LipofectAMINE method (Invitrogen). A total of 100 ng of plasmid was used for transfection efficiency. 12 h after transfection, the cells were passed onto glass slides and cultured for another 12 h before the flow experiments. The firefly luciferase and Renilla luciferase activity were detected by use of standard protocols.

**Immunoprecipitation and Immunoblotting—**The cells were lysed in TNE buffer (20 mM Tris-HCl, pH 7.5, 150 mM NaCl, 1 mM EDTA, pH 8.0, and 0.2% Nonidet P-40) containing 25 μg/ml N-acetyl-Leu-Leu- norleucine-CHO (Calbiochem, San Diego, CA) and a protease inhibitor mixture (Le Roche, Palo Alto, CA). Two micrograms of rabbit anti-norleucine-CHO (Calbiochem, San Diego, CA) and a protease inhibitor (50 μg of the lysates were added to 200 μl of a reaction solution containing 10 mM Tris-HCl, 150 mM NaCl, 10% glycerol, and 2 x 10\(^{6}\) cpm [\(\text{H}\)]acetyl-histone peptide, with or without 50 mM sodium butyrate. The reaction mixture was incubated at room temperature on an orbital shaker for 12 h. A total of 50 μl of a quenching solution was added to stop the reaction, and the released \(\text{[H]}\)acetate was separated from the H4 peptide beads by centrifugation. The HDAC activity was then determined by radioisotope counting of the supernatant.

**RESULTS**

**Laminar Flow Deacetylates Lys-320 and Lys-373 of p53—**By using antibodies recognizing acetylated Lys-320, Lys-373, or Lys-382, we investigated the effect of laminar flow on the acetylation of p53. In HUVECs subjected to laminar flow (12 dyn/cm\(^2\)), there was decreased acetylation at Lys-320 and Lys-373 and sustained increase in acetylation at Lys-382 (Fig. 1A). In positive control experiments, UV irradiation (100 J/m\(^2\)) caused an increase in acetylation at Lys-320, Lys-373, and Lys-382 (Fig. 1B). Both laminar flow and UV irradiation increased the level of p53, as revealed by immunoblotting with anti-p53 DO1 mAb. Normalization of the amount of acetylated Lys to that of p53 confirmed that laminar flow deacetylated Lys-320 and Lys-373 but increased the acetylation of Lys-382. In contrast, UV irradiation increased the acetylation of all three Lys residues. Thus, laminar flow and UV irradiation impose different patterns of acetylation on p53.

**p53 Deacetylation in Response to Laminar Flow Is Mediated by HDAC—**Because p53 is a substrate of HDAC, we investigated the changes of HDAC activity in response to laminar flow and UV irradiation. As shown in Fig. 2A, laminar flow increased the HDAC activity in HUVECs as early as 2 h and was sustained for at least 8 h. In contrast, UV irradiation had little effect on HDAC activity. To test whether the flow-induced increase in HDAC activity was associated with p53, we studied the effect of laminar flow on the HDAC1-p53 association and on HDAC activity in anti-p53 immunoprecipitates. As shown in Fig. 2B, the application of laminar flow for 4 h increased the amount of HDAC1 co-immunoprecipitated with p53, which reveals an increased association of HDAC1 and p53. Further, the application of laminar flow for 4 h increased the level of p53, as revealed by immunoblotting with anti-p53 DO1 mAb. Both laminar flow and UV irradiation increased the acetylation of all three Lys residues. Thus, laminar flow and UV irradiation impose different patterns of acetylation on p53.
in ECs, gastric carcinoma cells, and NIH3T3 cells (25–27). However, the application of laminar flow to TSA-treated cells did not cause any further increase in the level of p21\(^{\text{Waf1}}\) mRNA. Immunoblotting revealed the same pattern of p21\(^{\text{Waf1}}\) regulation by laminar flow, TSA, and a combination in which TSA treatment was followed by flow (Fig. 4B). Fig. 4 indicates that TSA pretreatment abolished the flow-enhanced expression of p21\(^{\text{Waf1}}\) as a result of the inhibition of HDAC-deacetylated p53.

The Induction of p21\(^{\text{Waf1}}\) by Laminar Flow Is p53-dependent—Because TSA could induce p21\(^{\text{Waf1}}\) under static conditions but inhibited the flow-induced p21\(^{\text{Waf1}}\) we manipulated the sites in the p21\(^{\text{Waf1}}\) promoter constructs that respond to p53 and TSA to reinforce the observation that distinct mechanisms are involved in the induction of p21\(^{\text{Waf1}}\) by laminar flow and by TSA. Compared with Me\(_2\)SO treatment, both laminar flow and TSA induced the luciferase activity of p21-Luc-2290, in which the luciferase reporter is driven by the 2.3-kb promoter region.

To test further the molecular mechanism by which the HDAC1-p53 pathway regulates the transcription of p21\(^{\text{Waf1}}\), the expression plasmid p53K320R/K373R was created to encode a p53 mutant in which Lys-320/321 and Lys-373/374 were replaced by Arg. Such a replacement would mimic the deacetylation of these two residues by laminar flow. As shown in Fig. 5B, cells co-transfected with the wild-type p53 expression plasmid showed increased luciferase activity of p21-Luc-2290 by 30 ± 2-fold compared with cells co-transfected with pCDNA3. Co-transfection of p53K320R/K373R further increased the induction of the p21\(^{\text{Waf1}}\) promoter (42 ± 5-fold), which indicates the effect of p33 deacetylation on the activation of p21\(^{\text{Waf1}}\). Together, Figs. 4 and 5 demonstrate that the laminar flow induction of p21\(^{\text{Waf1}}\) in ECs depends on the HDAC deacetylation of p53 at Lys-320 and Lys-373.

DISCUSSION

Laminar flow increases p53 and p21\(^{\text{Waf1}}\) in ECs, which is associated with the arrest of cells in the G\(_1\) to S phase transition (22, 23). In the current study, we show that laminar flow-induced HDAC can cause the specific deacetylation at Lys-320 and Lys-373 of p53. Further support for our findings was obtained from the application of laminar flow to ECs transfected with an expression plasmid which encodes p33 K320R/K373R. This plasmid increased p21\(^{\text{Waf1}}\) expression by 30 ± 2-fold compared with cells co-transfected with pCDNA3. Co-transfection of p53K320R/K373R further increased the induction of the p21\(^{\text{Waf1}}\) promoter (42 ± 5-fold), which indicates the effect of p33 deacetylation on the activation of p21\(^{\text{Waf1}}\). Together, Figs. 4 and 5 demonstrate that the laminar flow induction of p21\(^{\text{Waf1}}\) in ECs depends on the HDAC deacetylation of p53 at Lys-320 and Lys-373.

By using HCT116p53\(^{+/+}\) cells and its isogenic p53-null cells, we explored further whether p53 is necessary for the laminar flow induction of p21\(^{\text{Waf1}}\). The application of laminar flow augmented p21\(^{\text{Waf1}}\) in HCT116p53\(^{+/+}\) cells but not in HCT116p53\(^{−/−}\) cells (Fig. 6). In separate experiments, p21\(^{\text{Waf1}}\) was induced by TSA in both cell types. These results indicate that p53 is necessary for the activation of p21\(^{\text{Waf1}}\) by laminar flow but not by TSA.

The Induction of p21\(^{\text{Waf1}}\) by Laminar Flow Is p53-dependent—Because TSA could induce p21\(^{\text{Waf1}}\) under static conditions but inhibited the flow-induced p21\(^{\text{Waf1}}\) we manipulated the sites in the p21\(^{\text{Waf1}}\) promoter constructs that respond to p53 and TSA to reinforce the observation that distinct mechanisms are involved in the induction of p21\(^{\text{Waf1}}\) by laminar flow and by TSA. Compared with Me\(_2\)SO treatment, both laminar flow and TSA induced the luciferase activity of p21-Luc-2290, in which the luciferase reporter is driven by the 2.3-kb promoter region of the p21\(^{\text{Waf1}}\) gene, by 4.5 ± 0.8 and 5.5 ± 0.5-fold, respectively. However, the promoter activity induced by TSA was not further increased by laminar flow (Fig. 5A). Deletion of the N-terminal 1.1 kb that contains the p53-binding site abolished the flow-induced but not the TSA-induced luciferase activity. Further deletion of the Sp1/Sp3 site, which resulted in the −33 to +1 fragment containing only the TATA box of the p21\(^{\text{Waf1}}\) promoter, diminished the response to both flow and TSA. Insertion of the sequence aggaacatgtcccaacatgttgag (e.g. the p53 target site) immediately upstream of the −33 to +1 fragment restored the induction of luciferase activity by flow but not by TSA. More importantly, TSA treatment abolished this p53-dependent induction by laminar flow.

To test further the molecular mechanism by which the HDAC1-p53 pathway regulates the transcription of p21\(^{\text{Waf1}}\), the expression plasmid p53K320R/K373R was created to encode a p53 mutant in which Lys-320/321 and Lys-373/374 were replaced by Arg. Such a replacement would mimic the deacetylation of these two residues by laminar flow. As shown in Fig. 5B, cells co-transfected with the wild-type p53 expression plasmid showed increased luciferase activity of p21-Luc-2290 by 30 ± 2-fold compared with cells co-transfected with pCDNA3. Co-transfection of p53K320R/K373R further increased the induction of the p21\(^{\text{Waf1}}\) promoter (42 ± 5-fold), which indicates the effect of p33 deacetylation on the activation of p21\(^{\text{Waf1}}\). Together, Figs. 4 and 5 demonstrate that the laminar flow induction of p21\(^{\text{Waf1}}\) in ECs depends on the HDAC deacetylation of p53 at Lys-320 and Lys-373.

By using HCT116p53\(^{+/+}\) cells and its isogenic p53-null cells, we explored further whether p53 is necessary for the laminar flow induction of p21\(^{\text{Waf1}}\). The application of laminar flow augmented p21\(^{\text{Waf1}}\) in HCT116p53\(^{+/+}\) cells but not in HCT116p53\(^{−/−}\) cells (Fig. 6). In separate experiments, p21\(^{\text{Waf1}}\) was induced by TSA in both cell types. These results indicate that p53 is necessary for the activation of p21\(^{\text{Waf1}}\) by laminar flow but not by TSA.
Interestingly, laminar flow increases Lys-382 acetylation but deacetylates Lys-320 and Lys-373 through the flow-activated HDAC. This pattern of changes in p53 acetylation is different from that induced by UV irradiation, which acetylates p53 at all three sites in ECs (Fig. 1). CBP/p300 acetylates Lys-382 and to a lesser extent Lys-373, whereas PCAF acetylates Lys-381.

Laminar flow may also activate HDAC2 and HDAC3. Several previous studies suggested a positive correlation between p53 acetylation and p21\(^\text{Waf1}\) expression. Genotoxic stresses or TSA increase both p53 acetylation and p21\(^\text{Waf1}\) activation (9). The overexpression of HDAC1 or PID decreases the p53 transactivation of p21\(^\text{Waf1}\) (13, 15, 16). How p53 acetylation affects p21\(^\text{Waf1}\) transcription is still unclear. A p53 mutant with Lys-320, Lys-373, or Lys-382 substituted by Ala, which is a manipulation that mimics sustained acetylation, has little effect on the level of p21\(^\text{Waf1}\), although such mutations increase the DNA binding activity of the mutated p53 in vitro (31). Our data demonstrate for the first time that p53 acetylation at Lys-320 and Lys-373 can activate p21\(^\text{Waf1}\) (Fig. 5B). When TSA was included in flow experiments, the p53 acetylation by HDAC was abrogated.

Accordingly, the induction of p21\(^\text{Waf1}\) was attenuated (Figs. 3 and 5A). These results suggest that the deacetylation of p53 at these two Lys residues is necessary for the induction of p21\(^\text{Waf1}\) by flow. Although deacetylation (Lys-320 and Lys-373) and acetylation (Lys-382) are concurrent in response to laminar flow, p53 can also undergo phosphorylation at Ser-15 and Ser-20 (data not shown). It is likely that a synergistic effect
resulting from the intricate coordination of acetylation, deacetylation, and phosphorylation mediates the activation of p21<sub>Waf1</sub>. Such a synergy is reminiscent of the modulation of p53 acetylation at Lys-382 by phosphorylation at Ser-33 and Ser-37 in response to DNA damage (32).

Both p53-dependent and -independent pathways have been reported to regulate the transcription of p21<sub>Waf1</sub>. In addition to the p53 consensus element, several Sp1 and Sp3 binding sites exist in the promoter region of the p21<sub>Waf1</sub> gene. By inhibiting HDAC to increase p53 acetylation, TSA activates the expression of p21<sub>Waf1</sub> through Sp1/Sp3 in a p53-independent manner (26, 27, 33). Laminar flow activates only the p21<sub>Waf1</sub> gene through distinct mechanisms. This notion is further supported by the induction of p21<sub>Waf1</sub> by laminar flow in HCT116p53<sup>−/−</sup> cells but not their p53-null counterparts (Fig. 6). p53-dependent p21<sub>Waf1</sub> expression has been observed in the HCT116 cell system in response to c-Jun NH<sub>2</sub>-terminal kinase perturbation or doxorubicin, a DNA-damaging drug (34, 35). The lack of p21<sub>Waf1</sub> in HCT116/p21<sup>−/−</sup> cells has been linked to the increased sensitivity of these cells to apoptosis induced by anti-cancer drugs (36, 37), yet the G<sub>1</sub> arrest was completely abrogated in response to DNA damage (38). Thus, the p53-dependent p21<sub>Waf1</sub> expression may have dual functions depending upon the types of cells and the stimuli they receive; although the p53-dependent p21<sub>Waf1</sub> expression arrests cells in G<sub>1</sub>/G<sub>0</sub>, it would also protect the cells from apoptosis.

The ECs at the straight part of the arterial tree are quiescent, whereas ECs at branch points have an accelerated mitotic rate (39). Undisturbed versus disturbed flows associated with vascular geometry have been suggested to play an important role in regulating EC cycle progression. The physiological implication of the current study is that laminar flow, by preventing EC mitosis, can minimize the lipoprotein permeability through the EC junction at the straight part of the vessel. A recent study by Rössig et al. (25) demonstrates that inhibition of HDAC activity is associated with an attenuated expression of endothelial nitric oxide synthase in ECs, as well as impaired vasorelaxation. Thus, the laminar flow-increased HDAC activity may also contribute to an optimal level of eNOS expression.
Flow Regulation of HDAC-p53-p21Waf1

Protein levels were detected by immunoblotting. The wild-type p53 (data not shown). Through the HDAC1-p53-gene sequence of the p21WAF1/CIP1/Waf1 gene, we found that the UV-induced apoptosis in ECs transfected with p53-null gastric carcinoma cells (26, 40). In line with this concept, we observed up-regulation by the deacetylated p53 is seen in HCT116p53+/H11546- cells and their p53-null counterparts were subjected to laminar flow for the times indicated. A total of 50 µg of the cell lysates was immunoblotted with anti-p21Waf1 antibody. Waf1 and α-tubulin antibody.

Physiological levels of laminar flow not only arrest the EC cell cycle and increase vessel relaxation but also prevent apoptosis. This possibility is supported by the finding that TSA inhibition of HDAC induces the apoptosis of several cell types such as Huh-7 hepatoma cells and MKN-7 gastric carcinoma cells (26, 40). In line with this concept, we found that the UV-induced apoptosis in ECs transfected with p53K320R/K373R was 50% lower than in cells transfected with the wild-type p53 (data not shown). Through the HDAC1-p53-p21Waf1 pathway, laminar flow-generated mechanotransduction and signaling can arrest ECs at the G0/G1 phase of the cell cycle while preventing apoptosis, which would be beneficial to vascular homeostasis.

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The Role of p53 Deacetylation in p21\(^{Waf1}\) Regulation by Laminar Flow
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