MUC2 is one of the major components of mucins that provide a protective barrier between epithelial surfaces and the gut lumen. We investigated possible alterations of MUC2 gene expression by p53 and p21\(^{sdi1/Waf1/Cip1}\) in a human colon cancer cell line, DLD-1, establishing subclones in which a tetracycline-regulatable promoter controls exogenous p53 and p21 expression. MUC2 mRNA more significantly increased in response to p53 than to p21. Unexpectedly, MUC2 expression was also induced in human osteosarcoma cells, U-2OS and Saos-2, by exogenous p53. We next performed a reporter assay to test the direct regulation of MUC2 gene expression by p53. Deletion and mutagenesis of the MUC2 promoter region showed that it contains two sites for transactivation by p53. Furthermore, an electrophoretic mobility shift assay indicated that p53 binds to those elements. We analyzed MUC2 expression in other cell types possessing a functional p53 after exposure to various forms of stress. In MCF7 breast cancer and A427 lung cancer cells, MUC2 expression was increased along with the endogenous p53 level by actinomycin D, UV, and x-ray, but not in RERF-LC-MS lung cancer cells carrying a mutated p53. These results suggest that p53 directly activates the MUC2 gene in many cell types.

The tumor suppressor p53 gene is frequently mutated in a wide variety of human malignant tumors. p53 protein is a transcription factor and regulates the expression of a number of growth control genes involved in cell cycle progression, DNA repair, apoptosis, and angiogenesis. p53 is also suggested to induce differentiation in human tumor cells. In such cases, p21\(^{sdi1/Waf1/Cip1}\), one of the downstream target genes of p53, might mediate regulation of a cell type-specific phenotype through functional control of cyclin-dependent kinase and retinoblastoma family proteins. p53 would directly regulate tissue-specific genes related to differentiation. Furthermore, it was suggested that p53 regulates production of the extracellular matrix, cytoskeleton, and secreted proteins, although the machinery for the regulation has not yet been identified. Activation of these kinds of genes might be closely related with cellular differentiation and cell type-specific. It is possible that part of the genes regulated by p53 are not always the same among cell types because of differences in components of the transcription machinery, since the degree of differentiation and/or genetic and epigenetic alterations could be different. Therefore, to advance our understanding of the functions of p53, results obtained using different cell types need to be accumulated.

Mucins are the major components of mucus, which coats the epithelia of the intestines, airways, and other mucous membrane-containing organs. They are thought to provide a protective, lubricating barrier against particles and infectious agents on mucosal surfaces. MUC2 is one of the major secreted mucins in human large and small intestine. Several studies on MUC2 expression of colorectal carcinomas have revealed that it is strongly expressed in the mucinous carcinomas but decreased in nonmucinous carcinomas compared with normal mucosa. Furthermore, in a colon cancer cell line, its expression was increased along with cellular differentiation. Regulation of MUC2 by p53 has not yet been demonstrated, although the p53 gene is frequently mutated during the development of CRCs as in other cancers.

To investigate the biological significance of inactivation of the p53- and RB-signaling pathways, we have established subsets of cell lines in which a tetracycline-regulatable promoter controls the induction of tumor suppressor genes, and we are analyzing phenotypic alterations of cancer cell lines by these genes. We applied our system to a colorectal carcinoma cell line and screened alterations in the expression of several genes related to differentiation of the colon mucosa, including the MUC2 gene. Here, we demonstrate transcription of the MUC2 gene is directly stimulated by p53 and that activation occurs not only in colonic epithelial cells but also in other cell types.

**EXPERIMENTAL PROCEDURES**

**Cell Lines and Their Treatment**—The human colon cancer cell line DLD-1 and human lung cancer cell line RERF-LC-MS were obtained from the Japanese Cancer Resource Bank Cell Bank Center. The human lung cancer cell line A427 and human breast cancer cell line MCF7 were purchased from the American Type Culture Collection. All cells were grown in Dulbecco’s modified Eagle’s medium (Nissui) supplemented with 10% fetal calf serum at 37 °C in a humidified 5% CO\(_2\) atmosphere. From DLD-1 cells, we established subclones in which a tetracycline-regulatable promoter controls the induction of p53 and p21 in the same manner as described previously. Up53-1 and Sp53-3 cells are human osteosarcoma-derived subclones in which a tetracycline-regulatable promoter controls the induction of p53. These transfectants were maintained in culture medium containing hygromycin B (0.3 mg/ml; Invitrogen) and G418 (0.5 mg/ml; Invitrogen) with 1 μg/ml of tetracycline.

Actinomycin D, solubilized in H\(_2\)O, was added to the culture medium at a final concentration of 5 μM. Prior to UV irradiation, the culture medium was removed, and the cell layer was then irradiated at 12 μW/cm\(^2\) with a Stratalinker (Stratagene) and further cultured in the original conditioned medium. X-ray irradiation was performed in the

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The abbreviations used are: CRC, colorectal carcinoma; Tc, tetracycline; RT-PCR, reverse transcription-PCR; mAb, monoclonal antibody; EMSA, electrophoretic mobility shift assay.
culture medium with 60 grays from an MBR-1505R2 x-ray source (Hitachi Medical Corp.) at a dose rate of 3 grays/min with settings at 5 mA and 150 kV.

**Western Blotting**—Cells were lysed with lysis buffer as described elsewhere (19). First, 50 μg of cellular protein was separated by 8% SDS-PAGE and electroblotted to a Hybond-ECL nitrocellulose membrane (Amersham Biosciences). Equal loading of protein was confirmed by staining the membrane after detection. After blocking, the membranes were incubated with anti-p53 monoclonal antibody (mAb) PAb1801 (Oncogene Science). The blots were then probed using an ECL Western blotting detection system (Amersham Biosciences).

**RT-PCR Analysis**—Total RNA was isolated from the cells using a RNeasyTM Total RNA Kit (Qiagen) with DNase I. RT-PCR was performed in 20 μl of a reaction mixture consisting of 45 mM forward and reverse primers, 1 × EZ buffer, 300 μM each dNTP, 2 units of rTth DNA polymerase (PerkinElmer Life Sciences), and 0.1 μg of template total RNA. The primers for the amplification of MUC2 were 5'-GAC CTC CAG CAC CAT CCT GCT GTG AGT GGT AGA AAT C-3' and 5'-GCC AGC AAC AAT TGA CAC GAT CTG ACT T-3'. The primers for p21 were 5'-GTG AGC ACT CCT GGG ACT TGG ACT T-3' and 5'-GGC GTT TGG AGT GGT AGA AAT C-3'. The primers for β-actin were described previously (21). RT-PCR products were electrophoresed in a 2.5% agarose gel and visualized by ethidium bromide staining. The integrity of RT-PCR was confirmed by sequencing a part of the RT-PCR products.

**Cloning and Analysis of the Human MUC2 Promoter**—For the reporter analysis of the MUC2 promoter, DNA fragments containing MUC2 genomic sequences were amplified from normal human genomic DNA using the PCR and primers based on the DNA sequence of human genomic MUC2 (GenBankTM accession number U67167). The amplified DNA fragment was subcloned into the luciferase reporter vector pGL3-Basic (Promega). Deletion mutants were generated by PCR (22). The p53 expression vector was constructed by ligating p53 cDNA from pTKp53neo (19) into the pCMV3.1+ vector (Invitrogen). Cells were transfected using Effectene™ transfection reagent (Qiagen) in the presence of trace amounts of phosphorlase-TK. Luciferase assays were performed using the Dual Luciferase Assay System (Promega), and all activity was normalized to Renilla luciferase activity.

**Electrophoretic Mobility Shift Assay**—Complementary single-stranded oligonucleotides were labeled with γ[32P]ATP and annealed to produce the following double-strand oligonucleotides: M1 5'-CTG CTC CAG CAC CAT CCT GCT GGG ACT TGG ACT T-3' and M2 (5'-TCC GTA ACA TGT CCC CCT GCG GGT CCA TCT GTC CCA-3'). Three micrograms of nuclear extract and 0.18 pmol of labeled double-stranded oligonucleotide were incubated in a total volume of 20 μl of DNA binding buffer containing 10 mM Tris-HCl (pH 7.5), 10% glycerol, 0.05% Nonidet P-40, 1 mM EDTA, 0.5 mM diithiothreitol, 50 mM KCl, 5 mM MgCl2, and 50 μg/ml poly(dI-dC)/poly(dI-dC) for 20 min at room temperature. For competition experiments, a 15- or 60-fold excess of the unlabeled double-stranded oligonucleotides was added to the binding reaction before the labeled oligonucleotide. These competitors were M1 oligonucleotide, M2 oligonucleotide, a p53 consensus oligonucleotide from the human GADD45 promoter 5'-GTA CAC AAG TGC GGG GCC CCT CGT-3', and its mutant oligonucleotide 5'-GTT TGG GGG GCC GGT CCT TGC CTC GCT GGC GAT C-3' (22). For a supershift assay, 0.25 μg of the monoclonal antibodies PAb1801 and PAb421 (Oncogene Science) and normal mouse IgG (Santa Cruz Biotechnology) were added to the reaction mixture at 20 min after starting the incubation, and the mixture was incubated for a further 20 min. Samples were loaded on a native 4% acrylamide gel in 0.5 X TBE and electrophoresed at 4 °C and 150 V for 90 min. The gel was dried and visualized using the Molecular Analyst phosphorimaging system (Bio-Rad).

**Fluorescent Immunoassay**—Cells were seeded onto sterile glass coverslips in six-well plates 36–48 h before fixation and cultured in the presence or absence of 5 μM actinomycin D for 24 h. The cells were washed with Tris-buffered saline, fixed in 4% paraformaldehyde for 20 min, and permeabilized with 100% methanol for 1 min. The coverslips were washed with phosphate-buffered saline, blocked with 8% bovine serum albumin in Tris-buffered saline for 20 min, washed with phosphate-buffered saline, and then incubated with the anti-MUC2 antibody (cp58; BD Pharmingen) for 2 h. After washing with Tris-buffered saline three times, the coverslips were incubated with secondary antibody (fluorescein isothiocyanate-conjugated goat anti mouse Ig; Dako) for 1 h. After another wash in Tris-buffered saline, the coverslips were mounted and examined under a fluorescent microscope (Olympus).

**RESULTS**

**MUC2 mRNA Levels Are Elevated in Response to p53 Induction**—To investigate possible alterations in gene expression related to differentiation of the colonic mucosa by p53 and p2118,19/Waf1/Cip1, we established subclones, in which a tetracycline-regulatable promoter controls the induction of p53 and p21, from a human colon cancer cell line, DLD-1, carrying mutated p53 genes (24) (Fig. 1A). In Dp53-1 and Dp53-7 cells, exogenous p53 protein was significantly induced by the removal of Tc, the amount produced differing between them, and a slight leakage of expression of the introduced gene was observed. In Dp21-1 cells, the introduced p21 gene was expressed by the withdrawal of Tc, whereas the amount produced differing between them, and a slight leakage of expression of the introduced gene was observed. In Dp21-1 cells, the introduced p21 gene was expressed by the withdrawal of Tc, whereas the amount produced differing between them, and a slight leakage of expression of the introduced gene was observed. In Dp21-1 cells, the introduced p21 gene was expressed by the withdrawal of Tc, whereas the amount produced differing between them, and a slight leakage of expression of the introduced gene was observed.
Protein lysates were prepared from cells cultured with or without 1 μg/ml of Tc at the indicated time points. The blots were probed with anti-p53 mAb. A representative RT-PCR analysis of MUC2 and p21 mRNA expression was related to the presence of p53 in both complexes.

p53 Transactivates the MUC2 Promoter at Two Sites—Since the increase in MUC2 mRNA expression was related to the induction of p53 protein, we searched for candidate elements in the MUC2 gene that may interact with p53. This gene was found to possess two sites with convincing homology to the published p53 consensus sequence (25) in its 5′ promoter region. One sequence, designated M1, is located 1100 bp and the other sequence, M2, 650 bp upstream of the first exon (Fig. 3A). Both putative p53-binding sites in the MUC2 gene matched the consensus sequence in 18 of 20 bp. Furthermore, one more 10-bp motif, that matched the consensus sequence in 7 of 10 bp, was next to the upstream site at a distance of 1 bp in M1.

To investigate the functional significance of these sites, we cloned the 5′ promoter region of the MUC2 gene, comprising two putative p53-binding sites, into pGL3-Basic (WT−1411/+27 construct in Fig. 3B) and compared its response to p53 with that of reporter vectors harboring deletions of these sites (Fig. 3B). The WT−1411/+27 construct showed a 2.7-fold increase of activity due to p53 expression. In contrast, the WT−636/+27 construct, which lacked the sequence from −637 to −1411 of the WT−1411/+27 construct, displayed no remarkable increase in response to p53 (1.1-fold). The Δ−1146/−1097 construct, which had only the proximal p53-binding site (M2), showed little increase of activity (1.2-fold). The Δ−676/−642 construct, which had only the distal site (M1), displayed a 2.0-fold increase. Finally, a slight decrease of activity was observed in the Δ−1146/−1097 Δ−676/−642 construct (0.8-fold), which lacked both M1 and M2 due to a small deletion around each site.

MUC2 Promoter Contains Two p53 Binding Elements—To investigate whether p53 could in fact bind to those p53-responsive elements identified in the MUC2 promoter, we performed an EMSA using nuclear extract from Dp53-1 or Sp53-3 cells that were cultured without or with tetracycline for 24 h. As shown in Fig. 4A, two oligonucleotides, M1 and M2, were bound more by the nuclear extracts from p53-induced cells than from uninduced cells. These bindings were competed by an excess of unlabeled M1 or M2, as well as an excess of p53-binding oligonucleotides from the GADD45 gene, but not by the mutated GADD45 sequence (Fig. 4B). The anti-p53 mAb PAb1801 caused a supershift of M1 and M2 complexes efficiently (Fig. 4C, a and c). On the other hand, another anti-p53 mAb PAb421 efficiently supershifted M1 oligonucleotide and enhanced the binding (Fig. 4C, upper panel, b), whereas it appeared to inhibit the binding to M2 oligonucleotide and supershifted what little DNA-binding complex was detected only slightly (Fig. 4C, lower panel, d). These supershift experiments demonstrated the presence of p53 in both complexes.

MUC2 mRNA and Protein Levels Are Elevated in Response to p53 Activation by Cell Stress—We next determined whether MUC2 expression was induced by the activation of endogenous p53 through cellular stress such as actinomycin D treatment, UVC, and x-ray irradiation (26, 27). In MCF7, in which the p53 gene is a wild type (28), endogenous p53 protein increased in response to these stresses to different degrees (Fig. 5A). The MUC2 and p21 transcripts were increased along with p53 alteration, although relative amounts of MUC2 mRNA were not always correlated with those of p21 (Fig. 5B). In A427, another cell line carrying the wild-type p53 gene (29), endoge-
nous p53 was also increased by stress, and the MUC2 transcripts were expressed except in the case of x-ray irradiation. p21 transcripts increased in proportion to p53 protein. On the other hand, in RERF-LC-MS, carrying a mutated p53 gene (30), although p53 protein was detected and its amount changed little, MUC2 mRNA was not detected and not increased by the stresses. Induction of MUC2 expression along with an increase in p53 protein caused by actinomycin D was also observed in other cell lines, U-2OS osteosarcoma and HepG2 hepatoma carrying wild-type p53 (31, 32), but not in Saos-2 osteosarcoma cells lacking the suppressor gene (31) (data not shown). In MCF7 and A427 cells, an increase in endogenous p53 was observed from 3 h after the addition of actinomycin D, with the alteration being more evident in MCF7 than in A427 (Fig. 5C). The enhanced MUC2 and p21 expression was well correlated with p53, although the expression of MUC2 was delayed in comparison with that of p21 (Fig. 5D). Induction of MUC2 and p21 expression was not observed in RERF-LC-MS up to 12 h after actinomycin D treatment.

To demonstrate the up-regulation of MUC2 protein expression in MCF7 cells caused by an increase in p53 protein following exposure to stress, we performed immunofluorescence analysis, since it is hard to detect MUC2 protein of more than 550 kDa (11, 12) by conventional Western blot analysis. A representative result is shown in Fig. 6. The fluorescence was observed in some cells at 24 h after actinomycin D treatment (Fig. 6a) but not in the nontreated MCF7 cells (Fig. 6c). In positive cells, fine granules were detected in the cytoplasm, particularly in the perinuclear region (Fig. 6e). A similar positive result was obtained in A427 cells after actinomycin D treatment but not in RERF-LC-MS cells (data not shown).

To further confirm the increase of MUC2 protein, we carried out Western blot analysis by using an agarose gel instead of the polyacrylamide gel. In MCF7 and A427 cells, a smeary band was observed in the samples treated with actinomycin D, UVC, and x-ray but not in the control (Fig. 7A). In RERF-LC-MS cells, it was never detected (data not shown). The intensity of the smeary band was extremely increased by UVC treatment in MCF7 and was not so much increased by actinomycin D treatment in MCF7 and A427 cells. Finally, the smeary band was also detected in Dp53-1 cells at 12 h after induction of wild-type p53 but not in the absence of wild-type p53 (Fig. 7B).

**DISCUSSION**

In this study, we demonstrated that MUC2 expression was increased along with the induction of exogenous wild-type p53 in some carcinoma cell lines. There are two putative p53-binding sites in the promoter region of the MUC2 gene. Our results showed that each of them contributed to stimulation of the promoter activity of the MUC2 gene. EMSA has revealed that p53 binds to those p53-responsive elements. Interestingly, in EMSA using mAbs, the binding of p53 to the distal element was enhanced by PAb421, whereas that to the proximal element was reduced. Although the difference would be partly due to the length and/or number of 10-bp motifs, our result was similar to the case for the p21 gene (33). However, the increase in MUC2 expression did not always parallel that of p21 in the cell lines examined. To date, many genes have been reported to be regulated by p53, and the time course of mRNA expression differs among them (9, 34). This would be due to differences in the stability of the mRNA and in the context of the p53-binding sequence in the regulatory region. Moreover, indirect effects of p53 might play an important role. Recently, it was suggested that modification of the p53 protein such as phosphorylation and/or acetylation determines its transcriptional properties in-
the same in each field (a, b, and e) or absence (c and d) of 5 nM of actinomycin D, cells were fixed and immunofluorescently stained for MUC2 protein. Cells were photographed using fluorescence (a and c) or bright field microscopies (b and d) of the same field (a and c). Photographs in a–d were taken at ×200. The photograph in e was taken using a fluorescence microscope with original magnification of ×400.

Fig. 6. Expression of MUC2 protein in MCF7 cells by actinomycin D. After 24 h of incubation in the presence (a, b, and e) or absence (c and d) of 5 nM of actinomycin D, cells were fixed and immunofluorescently stained for MUC2 protein. Cells were photographed using fluorescence (a and c) or bright field microscopies (b and d) of the same field (a and c). Photographs in a–d were taken at ×200. The photograph in e was taken using a fluorescence microscope with original magnification of ×400.

Fig. 7. Increase of MUC2 protein in MCF7 and A427 cells in response to cellular stress and in Dp53-1 cells by induction of wild-type p53. A, a representative Western blot showing an increase in MUC2 protein in MCF7 and A427 cells due to cellular stress. Protein samples were the same as described in the legend to Fig. 5A. B, a representative Western blot showing an induction of MUC2 protein in Dp53-1 cells. Cells were harvested at 12 h after culture with or without 1 μg/ml Tc, and their protein samples were the same as described in Fig. 1C. The cell lysates were separated by 3.5% agarose gel containing 0.1% SDS and 0.375 M Tris-HCl (pH 8.8) and transferred to nitrocellulose membrane. The membranes were incubated with the anti-MUC2 antibody including the selection of target genes (2–4). It would be interesting to study the above issues to explain the differences in the regulation of MUC2 and p21 by p53 as well as the responses by cell lines.

In addition to exogenous p53, MUC2 expression was induced along with the increase in endogenous wild-type p53 after cellular stress. In the immunofluorescence analysis, the staining pattern and the percentage of MUC2-positive cells were consistent with those for colonic goblet cells (13, 14, 16, 35). This result supports our findings at the protein level. Overall, an increase in MUC2 expression accompanied by induction of wild-type p53 protein was observed in colon, lung, breast cancer, osteosarcoma, and hepatoma cell lines. Although it would not be entirely ruled out that MUC2 was induced by indirect effects of p53 or by some other process rather than by the effects of p53 in the case of cellular stress, our results indicate that the MUC2 gene is one of the p53-inducible genes. The MUC2 gene was reported to be regulated by DNA methylation of the promoter region and the Sp family of transcription factors (15, 36, 37). However, little is known about its regulation by cellular stress. In light of the protective function of mucin, it is possible that cellular stress promotes the construction of a protective barrier around damaged cells by the production of MUC2 via p53. The physical barrier constructed by MUC2 would be readily permeable to ions and low molecular weight solutes but obstructive to larger molecules such as damaging proteases. Therefore, the barrier would not be effective against cellular stress but would protect the surroundings from damaged cells.

Several clinical studies have been performed on MUC2 expression. In CRCs, it was reported that there was an inverse association between the immunoreactivity of MUC2 and alteration of p53 (16). Furthermore, in contrast to nonmucinous CRCs, in mucinous carcinomas, MUC2 was expressed at relatively high levels, but alterations of p53 were not so frequently detected (38). These correlations between MUC2 and p53 in CRCs would be partly due to the regulation of the MUC2 gene by p53. On the other hand, it was shown that detection of MUC2 expression was a favorable prognostic indicator in gastric carcinomas, intrahepatic bile duct tumors, and pancreas tumors (39–42). Although MUC2 was suggested to be involved in the suppression of tumor formation in mice (43), in those cases, tumors with MUC2 expression might retain wild-type p53.

In conclusion, our results showed that MUC2 expression is transcriptionally regulated by p53 protein in several cell lines. MUC2 protein contains more than 5100 amino acid residues and has a complex structure with high glycosylation (12, 44, 45). Therefore, it is difficult to study by conventional techniques. The biological function of MUC2 protein remains to be clarified. It would be interesting to determine whether MUC2 contributes to the survival of damaged cells and/or surrounding cells and to clarify the mechanisms of another biological function that was recently suggested by Velcich et al. (46). Further investigation is necessary to reveal the biological significance of the stimulation of the MUC2 gene by p53.

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Regulation of MUC2 by p53

48275