The SWI/SNF complex is required for the transcription of several genes and has been shown to alter nucleosome structure in an ATP-dependent manner. The tumor suppressor protein p53 displays growth and transformation suppression functions that are frequently lost in mutant p53 proteins detected in various cancers. Using genetic and biochemical approaches, we show that several subunits of the human SWI/SNF complex bind to the tumor suppressor protein p53 in vivo and in vitro. The transactivation function of p53 is stimulated by overexpression of hSNF5 and BRG-1 and dominant forms of hSNF5 and BRG-1 repress p53-dependent transcription. Chromatin immunoprecipitation assay shows that hSNF5 and BRG-1 are recruited to a p53-dependent promoter in vivo. Overexpression of dominant negative forms of either hSNF5 or BRG-1 inhibited p53-mediated cell growth suppression and apoptosis. Molecular connection between p53 and the SWI/SNF complex implicates that (i) the SWI/SNF complex is necessary for p53-driven transcriptional activation, and (ii) the SWI/SNF complex plays an important role in p53-mediated cell cycle control.

The p53 gene is frequently found to be mutated in human tumors (1). This suggests that p53 is important for the regulation of normal cell growth. Wild type p53 has been shown to activate transcription from specific DNA sequence elements both in vitro and in vivo (2, 3). Ectopic expression of p53 strongly activates, through consensus sequence p53-binding sites, a number of genes that have been implicated as functional targets in p53-induced cell growth suppression and apoptosis. These include GADD45 (4), p21 (5), cyclin G (6), IGF-BP3 (7), and Bax (8). In p53-regulated genes, where the protein product negatively regulates cell cycle progression, nucleosome disruption, and chromatin remodeling may be required as a part of the transcriptional control mechanism. Chromatin structure may be one of mediators that regulate p53 recognition of binding sites during the course of the cell cycle and therefore chromatin structure acts as a modulator of p53 driven gene expression. A series of genetic and biochemical studies in yeast showed that multisubunit complexes such as SWI/SNF are able to alter chromatin structure and 11 of the proteins in the SWI/SNF complex, SNF2/SWI2, SWI1, SNF5, SNF13, SWP73/SNF12, SWP61/Arp7, SWP59/Arp9, SWP29/TAF9, SNF11, and SNF6, might function by altering chromatin structure (reviewed in Refs. 9 and 10). SWI/SNF homologs have been identified in mammals and appear to have a conserved function (11, 12). The human SWI/SNF homologs of SWI2/SNF2 were referred as brahma (hbrm) and BRG-1 (13, 14). A human homolog of SNF5 (hSNF5) has also been cloned (15). Human SWI/SNF complex that contains hSNF5, hbrm, or BRG-1 protein as well as seven to 10 additional factors has been purified from various human cell lines (11, 13, 16, 17).

The possible implication of SWI/SNF complex in human cancer has been suggested by the evidence of the truncated mutation of hSNF5 in rhabdoid cancer (18), the predisposition to exencephaly and tumors by targeted disruption of BRG-1 of the mouse model (19), and the interaction between BRG-1 and tumor suppressor pRb (20). Given these previous findings and the hypothesis that chromatin structure affects p53 function, we speculate that SWI/SNF complex and p53 interacts physically and that this interaction contributes to p53-mediated transcriptional activation and cell growth suppression.

**Experimental Procedures**

**Plasmids and Antibodies—**pBJ5-BRG-1 and pBJ5-BRG-1(K798R) were gifts from Dr. G. Crabtree. pG13-Luc and p21 WAF1-Luc were kind gifts from Dr. B. Vogelstein and Dr. W. El-Deiry, respectively. pFR-Luc and pM were purchased from Stratagene and CLONTECH, respectively. pCDNA3-hSNF5 was described elsewhere (21). The pSRe1-Flag-hSNF5, pGEX-4T-1, and pCDNA3 version of hSNF5 and their derivatives were engineered by polymerase chain reaction (PCR) using the appropriate primers. pM-ε-Myc+ (1-262), pM-p53, pGEX-4T-1/p53, and pM-p53(1-83) were cloned using PCR with appropriate primers. The anti-hSNF5 antibody (sc-9751) and anti-p53 monoclonal antibody were purchased from Santa Cruz Biotechnology, Inc. and BD Transduction Laboratories, respectively. Anti-BRG-1 antibody was obtained from Dr. H. Kwon. Anti-BAP155 and anti-SRG3 antibodies were obtained from Dr. Rho H. Seong.

Glutathione S-transferase (GST) Pull-down Assays—Radiolabeled in vitro translated proteins were incubated with GST fusion protein in T buffer (50 μl Tris-HCl (pH 7.5), 200 μl NaCl, 5 μl EDTA, 2.5 μl dithiothreitol, 0.7 mg/ml bovine serum albumin, 0.5% Nonidet P-40). After glutathione-Sepharose beads were added, this mixture was incubated on a rotating machine (Nutator, Becton-Dickinson) for 1 h at room temperature. The beads were washed four times with T buffer, then 5 × loading dye (60 μl Tris-HCl (pH 6.8), 25% glycerol, 2% SDS, 14.4 mm 2-mercaptoethanol, 0.5% bromphenol blue) was added, and the proteins were subjected to SDS-PAGE.

**Immunoprecipitation and Glycerol Gradient Sedimentation—**293T
FIG. 1. Stimulation and inhibition of p53-dependent transcription by the SWI/SNF complex and dominant negative mutants of components of the SWI/SNF complex, respectively. A, effect of hSNF5, BRG-1, DN-hSNF5, and ATPase mutant BRG-1 (K798R) on p53-dependent transcription. 293T cells (BRG-1 present) were transiently transfected with the p53-directed reporter plasmid pG13-Luc alone or in combination with the expression plasmids pCDNA3-HA-p53, pCDNA3-hSNF5, pCDNA3-DN-hSNF5, pBJ5-BRG-1, and pBJ5-BRG-1(K798R). Results of the luciferase assays are expressed as relative luciferase activity (fold change), as compared with the luciferase activity detected with pG13-Luc alone. B, effect of hSNF5, BRG-1, DN-hSNF5, and ATPase mutant BRG-1 (K798R) on p53-dependent transcription in C33A cells (BRG-1 deficient). C, effect of hSNF5 on p53-dependent transcription in U2OS cells. D, effect of hSNF5 on p53-dependent transcription in Saos-2 cells. E, the hSWI/SNF complex stimulates transcription of the p21WAF1-Luc reporter in C33A cells. All transfections in this study were performed using the calcium precipitation methods. A portion of the cellular extracts was analyzed for p53 expression by Western blot. F, dependence of the activation function of p53 on SWI/SNF components. The p53 activation domain (amino acids 1–83) was fused to the DBD of LexA and introduced into yeast strains that carried a LexA-driven LacZ reporter gene. Activation of LacZ expression was assessed by measuring β-galactosidase activity. Values are means from three separate experiments. wt, wild type yeast; Δsnf5, SNF5-deficient yeast strain; Δsnf2, SNF2-deficient yeast strain. A portion of the cellular extracts was analyzed for LexA-p53-(1–83) expression by Western blot using monoclonal antibody against p53. Mock indicates blank vector-transformed yeast extracts.
cell nuclear extracts were prepared as described (22). Glycerol gradient sedimentation was carried out according to Tanese (23). 293T nuclear extract (2 mg) was applied to a 10-ml 10–30% glycerol gradient. Samples were centrifuged in a Beckman SW41 rotor at 40,000 rpm for 16 h at 4 °C. Twenty 0.5-ml fractions were collected from the top (F1) to the bottom (F20) of each gradient. Proteins in odd-numbered fractions were precipitated with trichloroacetic acid and separated by SDS-PAGE. For immunoprecipitations, even-numbered fractions (F2–F6, and F12–F16) were used to immunoprecipitate proteins with anti-HA antibodies.

Cell Culture and Luciferase Assays—The human embryonic kidney cell line 293T, human osteoblastoma Saos-2, U2OS, and human cervical carcinoma C33A cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. Reporter assays were performed as previously described (24) using the manufacturer’s instructions. We included pcDNA3-β-gal expression vector in each transfection. We checked transfection efficiency using β-galactosidase assay and the Western blot.

Yeast Strains, Yeast Transformation, and Galactosidase Assay—The following yeast strains were gifts from Dr. Fred Winston: FY22 (MATα his3Δ200 leu2Δ202 uro3Δ52), FY1360 (MATα his3Δ200 leu2Δ202 lys2Δ173R2 snf2Δ1 LEU2), and FY1658 (MATα his3Δ200 leu2Δ52 lys2Δ1288 snf5Δ32). Media was prepared according to standard methods. Yeast strain FY22 and its isogenic mutant strains Δsnf2 (FY1360) and Δsnf5 (FY1658) were transformed using the LiAc/polyethylene glycol method (25). Galactosidase activity was determined in triplicate from the pools of three independent transformed colonies.

Cell Growth Suppression and Apoptosis Assay—Cells (1 × 10^5 cells per well) were plated in each well of a 6-well tissue plate and transfected with pCDNA3 constructs by using calcium phosphate precipitation. G418 (500 μg/ml) was added to the culture medium 48 h after transfection. The cells were incubated for 14–21 days, fixed with 10% acetic acid, 10% methanol for 15 min, and stained with 0.4% crystal violet in 20% ethanol for 15 min to visualize colonies. Apoptosis assays were done using Saos-2 cells. We co-transfected Saos-2 cells with expression vectors encoding enhanced green fluorescence protein and control vectors using GenePorter2 (Gene Therapy Systems). After 48 h, cells were collected and analyzed by FACSscan flow cytometry.

Chromatin Immunoprecipitation (ChIP) Assay—ChIP assays were performed essentially as described in the Upstate Biotechnology protocol. Briefly, a 10-cm dish of 50% confluent 293T cells was transfected with 2 μg of pFR-Luc reporter plasmid and 4 μg of pm or pm-p53-(1–83) plasmid. For ChIP of the endogenous p21WAF1 promoter region and β-actin promoter region, we transfected 4 μg of pcDNA3-HA-p53 into Saos-2 or 293T cells.
RESULTS

Some Components of SWI/SNF Complex Augment p53-dependent Transcription—First, we used transient transfection experiments to determine whether the transcriptional activation function of p53 could be modulated by the entire SWI/SNF complex or by individual components of the complex. Co-transfection of 293T cells with a p53 expression plasmid and a luciferase reporter plasmid alone (Fig. 1A). The transcriptional activity of p53 was further stimulated when expressed as a ligand and tested for interaction with in vitro translated radiolabeled p53 or BRG-1. GST-hSNF5 or GST-p53 were used as ligands and tested for interaction with the in vitro translated products. After washing with binding buffer, bound protein was released and analyzed by SDS-PAGE.

To investigate whether the function of the transcriptional activation domain of p53 is affected by the SWI/SNF complex, we measured the transcriptional activation activity of intact p53 and truncated p53 (amino acids (aa) 1–83, which is the activation domain), fused to the Gal4 DNA-binding domain (DBD) and the LexA-DBD alone, respectively. Our data indicate that the observed reduction of transcriptional activation by p53(1–83) in the snf5– and snf2– yeast strains is specific.

To investigate whether the function of the transcriptional activation domain of p53 is affected by the SWI/SNF complex, we measured the transcriptional activation activity of intact p53 and truncated p53 (aa 1–83, which is the activation domain), fused to the Gal4 DBD (the corresponding
expression plasmids were designated as pM-p53 and pM-p53-(1–83), respectively. A Gal4-dependent promoter linked to the luciferase gene (pFR-luc) was weakly stimulated by hSNF5 in p53-transfected 293T cells and was inhibited by dominant negative (DN)-hSNF5. To show that the dominant negative form of hSNF5 specifically represses the p53 transactivation domain, we used the c-Myc activation domain as a negative control (26). Gal4-c-Myc-(1–262), which has the c-Myc transcriptional activation domain fused to the Gal4 DBD, was not affected by hSNF5 or DN-hSNF5 (Fig. 2A). pFR-Luc was more effectively stimulated by hSNF5 in pM-p53-(1–83)-transfected cells (Fig. 2B). Co-transfection of the BRG-1 expression plasmid also stimulated transcriptional activation by pM-p53-(1–83), while the dominant negative BRG-1 (K798R) slightly stimulated p53 transactivation function.

BRG-1 and hSNF5 interact with p53 in Vivo and In Vitro—We next sought to determine whether physical interaction between p53 and hSNF5 is the molecular basis of the SWI/SNF requirement for p53-dependent transcription. Expression vectors for hemagglutinin (HA)-tagged p53 and FLAG-tagged hSNF5 were co-transfected into 293T cells, and the cell lysates were immunoprecipitated with the HA antibody. Western blots showed that HA-p53 interacted specifically with FLAG-hSNF5 (Fig. 3A, left panel). We also carried out co-immunoprecipitation assays between HA-p53 and BRG-1.

BRG-1 was co-expressed with HA-tagged p53 or mock plasmid in 293T cells, and the association of BRG-1 with HA-p53 was examined by immunoprecipitation. Immunoblotting demonstrated that HA-p53 binds specifically to BRG-1 (Fig. 3A, right panel). The interactions among p53, hSNF5, and BRG-1 were further confirmed by co-immunoprecipitation in C33A cells (Fig. 3B) and U2OS cells (Fig. 3C), which have endogenous p53 protein. From these results, we conclude that endogenous p53 interacts with endogenous hSNF5 and BRG-1 in vivo. To decipher whether hSNF5 binds directly with p53, we carried out in vitro binding assays using in vitro translated p53 and GST-hSNF5. In vitro translated p53 was retained on the GST-Sepharose column by the GST-hSNF5 fusion protein, compared with a GST control (Fig. 3D). We also carried out in vitro binding assay using in vitro translated BRG-1 and GST-p53. In vitro translated BRG-1 was retarded on the GST-p53, indicating that p53 binds to BRG-1 in vitro. We also performed a GST pull-down assay using GST-DN-hSNF5 and in vitro translated p53 (data not shown). p53 interacted with DN-hSNF5, indicating that DN-hSNF5 represses p53-dependent transcription via both deregulation of SWI/SNF and direct binding to p53. This also explains why DN-hSNF5 efficiently repressed p53-dependent transcription in C33A cells.

The SWI/SNF Complex and p53 Form a Complex in Vivo—The SWI/SNF complex functions as a large multiprotein complex (~2 MDa) that regulates gene expression through the alteration of chromatin architecture (11, 12, 17). Our observed interactions between p53 and some components of the SWI/SNF complex suggested that these proteins might function together to alter chromatin structure. To determine whether p53 is associated with the high molecular weight SWI/SNF complex, we fractionated human cell (293T) nuclear lysates with anti-BRG-1 antibody and anti-hSNF5 antibody. Proteins of interest are indicated with arrows. B, combined glycerol gradient fractions were immunoprecipitated with anti-p53, subjected to electrophoresis, and shown with an arrow. B, combined glycerol gradient fractions were immunoprecipitated with anti-p53, subjected to electrophoresis, and blotted with anti-BRG-1 antibody and anti-hSNF5 antibody. Proteins of interest are indicated with arrows.
through a glycerol gradient and used immunoblot analysis of the fractions to determine where the proteins of interest were eluted (Fig. 4A). p53, BRG-1, BAF155, and hSNF5 are co-sedimented in the same fractions near the bottom of the gradient, suggesting that they are all part of a large protein complex. To show that the co-fractionated SWI/SNF complex and p53 interact physically, we performed immunoprecipitation assays. When the glycerol gradient fractions were immunoprecipitated with anti-p53 antibody, BRG-1, hSNF5, and p53 are co-precipitated from the same fractions of the gradient in which they co-sediment (Fig. 4B). These results indicate that the SWI/SNF complex and p53 form a complex in vivo. Heterogeneity of SWI/SNF complexes suggests that many forms of SWI/SNF exist in mammalian cells (11, 12, 17). Our data do not exclude the possibility that p53 forms another unknown portion of SWI/SNF complex or p53 forms multiple complexes with all distinct SWI/SNF complexes existing in cells. Which SWI/SNF complexes are involved in gene expressions by p53 remains to be investigated.

hSNF5 and BRG-1 Are Recruited into p53-responsive Promoter—On the basis of the above genetic and biochemical data, we postulated that hSNF5 and BRG-1 activate p53-dependent transcription by recruiting the SWI/SNF complex to p53-specific promoters in vivo. Heterogeneity of SWI/SNF complexes suggests that many forms of SWI/SNF exist in mammalian cells (11, 12, 17). Our data do not exclude the possibility that p53 forms another unknown portion of SWI/SNF complex or p53 forms multiple complexes with all distinct SWI/SNF complexes existing in cells. Which SWI/SNF complexes are involved in gene expressions by p53 remains to be investigated.

**Fig. 6.** Effect of dominant negative hSNF5 and BRG-1 on p53-mediated apoptosis. A, Saos-2 cells were co-transfected with pCDNA3, pCDNA3-p53 (p53), pCDNA3-hSNF5 (hSNF5), pBJ5-BRG-1 (BRG-1), pCDNA3-DN-hSNF5 (DN-hSNF5), and pBJ5-BRG-1-K798R (BRG1[K798R]), as indicated. Propidium iodide-stained cells were analyzed by FACs. B, data shown are the percentage of hypoploid apoptotic cells in the FACs analysis. The total amounts of DNA were adjusted to 10 μg/assay by adding pCDNA3. The same results were obtained in U2OS cells (data not shown).

**Fig. 7.** Effect of hSNF5 and dominant negative hSNF5 on p53-mediated growth suppression. A, colony formation analysis. Saos-2 cells grown in 60-mm dishes were transfected with pCDNA3, pCDNA3-p53, pCDNA3-hSNF5, pCDNA3-DN-hSNF5, pCDNA3-p53 + pCDNA3-hSNF5, pCDNA3-p53 + pCDNA3-DN-hSNF5 (5 μg each). The total amounts of DNA were adjusted to 10 μg/assay by adding pCDNA3. The same results were obtained in U2OS cells (data not shown). B and C, colony formation assays were summarized. Each value represents the mean of triplicates. The colony formation number of pCDNA3-transfected cells was representative to 100% of relative plating efficiency.
and the presence of the endogenous SWI/SNF complex and HA-p53 on the p21^{WAF1} promoter region was detected using the ChIP assay (Fig. 5B). As a positive control, anti-HA precipitates showed a dramatic increase in PCR band density. The immunoprecipitates from cells transfected with the control plasmid did not contain hSNF5 or BRG-1 (Fig. 5B, left panel). In contrast, immunoprecipitates acquired with antibodies to BRG-1 and hSNF5 clearly showed PCR bands in the cells transfected with the p53 expression plasmid (Fig. 5B, right panel). We also obtained similar results in 293T cells (data not shown). We also used endogenous β-actin promoter as a negative control. As shown in Fig. 5B, SWI/SNF was not recruited into β-actin promoter region. Therefore, the ChIP assay suggests that (i) hSNF5 is recruited into a promoter region via the NH_{2}-terminal domain of p53 and (ii) p53 appears to recruit the SWI/SNF complex to the promoter region via protein-protein interactions with hSNF5 or BRG-1 in vivo.

Dominant Forms of BRG-1 and hSNF5 De-regulate p53-mediated Cell Growth Arrest and Apoptosis—Ectopic expression of p53 in p53-deficient cells results in the suppression of cell growth, as assayed by a reduction in colony formation (28). Induction of p53 in response to DNA damage and subsequent expression of p21^{WAF1} might contribute to the inhibition of normal function of G_{1}-specific cyclin-dependent kinases, resulting in cell cycle arrest (5, 29, 30). Our results suggest that the hSWI/SNF complex is necessary for p53-dependent transcription, and we showed that dominant negative mutant versions of hSNF5 and BRG-1 reduced transcription from the p21^{WAF1} promoter, which is dependent upon p53 (Fig. 1C). To determine whether p53-induced apoptosis could be affected by dominant negative BRG-1 and hSNF5, Saos-2 cells were transiently transfected with plasmids encoding p53 and/or various other proteins. Forty-eight hours after transfection, we assessed the hypoploid (<2n) apoptotic cell fraction. As expected, cells expressing p53 plus the dominant negative forms of hSNF5 and BRG-1 showed a decreased level of p53-induced apoptosis, compared with cells transfected with the p53 vector alone (Fig. 6, A and B). Next, expression of p53 protein in p53-deficient cells results in suppression of cell growth as assayed by a reduction in colony formation (28). The above results indicated that the hSWI/SNF complex was required for p53-dependent transcription and dominant negative mutant hSNF5 or BRG-1 (K798R) reduced the p21^{WAF1} promoter which is dependent upon p53 (Fig. 1C). To decipher whether SWI/SNF complex is required for p53-mediated cell growth suppression, cells were co-transfected with p53 and dominant negative hSNF5 or wild type hSNF5 using liposome-mediated transfection methods. Cells transfected with p53 and dominant negative hSNF5 or wild type hSNF5 using liposome-mediated transfection methods showed that the SWI/SNF complex is required for p53-mediated cell growth suppression in mammalian cells.

DISCUSSION

In this study, we showed that p53 interacts with BRG-1 and hSNF5 and that the activation domain-mediated targeting of the components of the SWI/SNF complex to promoters activates p53-dependent transcription in vivo. Activation domain from Gal4, Gen4, Swi5, GR, and HSF1 interacts with the SWI/SNF complex, suggesting that the activation domain-mediated targeting of the complex to the nucleosome is an important step in SWI/SNF transcription activation (27, 31–34). Our study is consistent with these findings. However, several groups reported that different domains from the activation domain of activators recruits the SWI/SNF complex. For example, zinc finger DNA-binding domain of EKLF interacts with the SWI/SNF in vitro (35). In addition, the acidic transactivation domain of VP16 interacts with hSWI/SNF very weakly (35, 36). Although there is a discrepancy in binding activity between the in vivo and in vitro transcription system, it is important for transcriptional activation in nucleosome context to target the SWI/SNF complex to the promoter by protein-protein interaction between specific activators and chromatin remodelers.

To date, there are several evidences of which chromatin remodeling complex contributes to human cancer development (18–20, 37, 38). The absence of a properly formed SWI/SNF complex can contribute to tumorigenicity either by the lack of proper expression of tumor suppressors or by the disruption of the required interaction with tumor suppressors such as Rb and p53. In addition, the SWI/SNF complex can contribute to cancer formation by interacting with several oncoproteins produced by chromosomal translocation, such as human synovial sarcoma-associated chimeric protein SYT-SSX (39). SYT-SSX1 required chromatin remodeling factor hBRM/hSNF2 for establishing anchorage-independent cell growth. What role does BRG-1 complex play in p53-mediated cell death? We think p53 utilizes SWI/SNF complex not only for the transactivation of genes for cell growth arrest but also for transrepression of genes critical for cell survival. p53 binds to mammalian Sin3 (mSin3A) complex, a histone deacetylase complex, and deregulation of histone deacetylase activity by trichostatin A inhibits p53-induced apoptosis (40). The hBrm complex and one of the BRG-1 complexes also contain components of the mSin3 complex (41). These data suggest that the SWI/SNF complex interacts functionally with p53 and that the candidate roles of BRG-1 complex as a tumor suppressor are originated from the molecular connection with tumor suppressor p53 and/or pRb. Our data indicate, therefore, that the SWI/SNF complex functionally interacts with p53 and is necessary for p53-mediated transactivation function. hBrm, a mammalian homolog of Dro sophila brm, is involved in growth control (43, 44). Because p53 has an important role in cell proliferation, differentiation, and apoptosis, it may be one of the targets for the SWI/SNF complex in mediating its cellular functions. Thus, like other tumor suppressors, SWI/SNF may contribute to a wide range of human cancers including smooth muscle cancer (44) through binding to p53. As chromatin-associated factors and cellular transformation are related, protein-protein interaction between p53 and the SWI/SNF complex may be significant for understanding the deregulation mechanism of p53 in the tumor cell or tumor virus-infected cells.

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