The TP53INP1 gene encodes two protein isoforms, TP53INP1α and TP53INP1β, located in the nucleus. Their synthesis is increased during cellular stress by p53-mediated activation of transcription. Overexpression of these isoforms induces apoptosis, suggesting an involvement of TP53INP1s in p53-mediated cell death. It was recently shown that p53-dependent apoptosis is promoted by homeodomain-interacting protein kinase-2 (HIPK2), which is known to bind p53 and induce its phosphorylation in promyelocytic leukemia protein nuclear bodies (PML-NBs). In this work we show that TP53INP1s localize with p53, PML-IV, and HIPK2 into the PML-NBs. In addition, we show that TP53INP1s interact physically with HIPK2 and p53. In agreement with these results we demonstrate that TP53INP1s, in association with HIPK2, regulate p53 transcriptional activity on p21, mdm2, pig3, and bax promoters. Furthermore, TP53INP1s overexpression induces G1 arrest and increases p53-mediated apoptosis. Although a TP53INP1α and HIPK2 additive effect was observed on apoptosis, G1 arrest was weaker when HIPK2 was transfected together with TP53INP1. These results indicate that TP53INP1s and HIPK2 could be partners in regulating p53 activity.

The stress-induced protein (SIP) gene, recently cloned by Tomasi et al. (1), is strongly activated in the diseased pancreas. The mouse SIP gene expands over ~20 kb and is organized in 5 exons. Exon 4 is alternatively spliced to generate two transcripts that encode proteins of 18 and 27 kDa (SIP18 and SIP27). SIP27 is identical to the TEAP protein, formerly described as a thymus-expressed protein (2). SIP18 and SIP27 are localized mainly in the nucleus, as shown in previous experiments using SIP-GFP fusion proteins (1). In vitro, expression of SIP mRNAs is strongly induced in fibroblasts submitted to various stress agents such as UV, base damage, ethanol, heat shock, and oxidative stress. It is noteworthy that mRNAs encoding SIP18 and SIP27 are concomitantly activated in response to these stresses. We also showed that SIP gene expression is p53-dependent (3). Finally, we found that overexpression of SIP18 or SIP27 induces apoptosis, indicating that SIP gene expression is a key element in p53-mediated cell death that occurs as a consequence of cellular stress.

Independently, Okamura et al. (4) cloned a new human gene named p53DINP1. This gene encodes a p53-inducible nuclear protein that promotes apoptosis when overexpressed in MCF7 cells. Sequence analysis revealed that SIP, p53DINP1, and TEAP are in fact alternative names for the same gene that was approved as TP53INP1 (tumor protein 53-induced nuclear protein 1) by the HUGO Gene Nomenclature Committee, with TP53INP1α and TP53INP1β proteins corresponding to SIP18 and SIP27, respectively.

Okamura et al. (4) demonstrated, using a very elegant approach, that TP53INP1s bind to a kinase that phosphorylates p53 at Ser-46, such a phosphorylation being apparently crucial for UV-induced apoptosis (5, 6). Unfortunately, that critical kinase was not identified in Okamura’s work. More recently, two papers showed that in subnuclear structures called promyelocytic leukemia protein nuclear bodies (PML-NBs), the homeodomain-interacting protein kinase-2 (HIPK2) binds to p53 and phosphorylates its Ser-46 to promote p53-dependent apoptosis (7, 8). Taken together, these data suggest that HIPK2 could be the kinase that binds to TP53INP1s. The aim of the present work was to investigate a possible relationship between TP53INP1s, HIPK2, and p53.
Cy-5 were from Jackson Immunoresearch; anti-V5 (46–0705) was from Invitrogen; monoclonal antibody TP53INP1 (anti-E12) was generated in our laboratory.2

pGST-TP53INP1α and pGST-TP53INP1β, pGST-HIPK2-(1–1189), pGST-HIPK2-(1–853), pGST-HIPK2-(253–955), pGST-p53-(13–390), pGST-p53-(295–390), and pGST-p53-(955–390) were constructed in the pGEX plasmid (Amersham Biosciences) (Fig. 1a). The control plasmid pCMV/βgal was from Promega. pHIPK2-FLAG (8), pHIPK2-SPP and pLSIP (7), pTP53INP1α-V5, pTP53INP1β-V5, pTP53INP1α-GFP, and pTP53INP1β-GFP (1) as well as pPML-IV and pPML-L (10) were described previously. pcDNA-Hu-p53wt plasmid was a kind gift from A. Sparks (University of Dundee, United Kingdom).

**In Vitro Pull-down and Co-immunoprecipitation Assays**—GST fusion proteins were produced in *Escherichia coli* BL21 and purified on glutathione-Sepharose resin (Amersham Biosciences). Proteins translated in vitro were synthesized with a TNT-coupled reticulocyte lysate system in the presence of [35S]methionine according to the manufacturer’s instructions (Promega). Labeled proteins were incubated with 10 μg of GST fusion protein at 4 °C for 2 h with in vitro interaction buffer (50 mM Hepes, 150 mM NaCl, 1 mM EDTA, 1 mM EGTA, 10% (v/v) glycerol, 1% Triton X-100, and a mix of protease inhibitors), washed four times with 500 μl of in vitro interaction buffer, and two times with 500 μl of PBS. Bound proteins were eluted with 1× SDS sample buffer, separated by

**FIG. 1.** TP53INP1s interact with HIPK2 and p53 *in vitro.* a, schematic representation of GST-tagged HIPK2 and p53 constructs. b, GST pull-down assays of GST-TP53INP1α and GST-TP53INP1β with radiolabeled HIPK2. c, GST pull-down assays performed as described in b but with radiolabeled p53. d, GST pull-down assays using radiolabeled TP53INP1α and TP53INP1β with the following GST fusion proteins: GST-HIPK2-(1–1189), GST-HIPK2-NH2-(1–853), GST-HIPK2-COOH-(253–955), pGST-p53-(13–390), and pGST-p53-(295–390), and pGST-p53-(955–390), and pGST-p53-(295–390).
denaturing SDS-PAGE, and analyzed by autoradiography.

For in vivo co-immunoprecipitation, U2OS cells were plated on 60-mm Petri dishes and transiently transfected. Thirty-six hours after transfection, total cellular extracts were prepared with lysis buffer (50 mM Tris HCl, pH 7.5, 5 mM EDTA, 300 mM NaCl, 150 mM KCl, 1 mM dithiothreitol, 1% Nonidet P40, and a mix of protease inhibitors). Equal amounts of proteins were immunoprecipitated for 2 h at 4 °C with 10 μl/sample of anti-V5 monoclonal antibody (Invitrogen) on protein Agarose beads (Roche Applied Science). Immunocomplexes were collected by centrifugation, washed five times with lysis buffer, separated by SDS-PAGE, and blotted onto nitrocellulose membranes (Amersham Biosciences). Filters were blocked in Tris-buffered saline-Tween 0.1% plus 3% dried skimmed milk and incubated with horseradish peroxidase-conjugated IgG. Antibodies were detected with an enhanced chemiluminescence reaction kit (Amersham Biosciences) in accordance with the manufacturer's instructions.

**Immunofluorescence**—Cells were grown on coverslips in 6-well plates and transfected with 2 μg of expression vector. Twenty-four hours later they were washed once with 1× PBS, fixed for 15 min at room temperature in PBS-3% paraformaldehyde, and then washed twice with PBS and blocked in PBS, 50 mM NH₄Cl for 10 min at room temperature. Cells were then incubated for 60 min with the primary antibodies at room temperature and washed four times (5 min each) in PBS before incubation for 60 min with the appropriate fluorochrome-conjugated secondary antibodies. Cells were mounted on glass slides and examined with a confocal laser microscope (TCS NT Leica apparatus, Heidelberg, Germany).

**Trans-activation Assays**—Cells were transiently transfected with reporter vectors in which the luciferase gene was driven by the p53-dependent intronic promoter of the murine mdm2 gene (11), the human bax promoter (12), the pig3 promoter (13), or the p21WAF1 promoter (kindly provided by M. Oren and B. Vogelstein). Transcriptional activity was evaluated after co-transfection with the indicated expression constructs. Twenty-four hours after transfection, cellular extracts were analyzed for luciferase activity and results were normalized to β-galactosidase activity. All co-transfections were balanced with pcDNA4 empty vector.

**Western Blot Analysis**—For Western blot analysis of p21 expression, 100 μg of total cellular extracts were separated by SDS-PAGE, blotted onto polyvinylidene difluoride membrane (Amersham Biosciences), and subsequently incubated with anti-p21WAF1 monoclonal antibody and anti-β-tubulin for loading control. Filters were washed in Tris-buffered saline-Tween and then incubated with horseradish peroxidase-conjugated IgG. Antibodies were detected with an enhanced chemiluminescence reaction kit (Amersham Biosciences) in accordance with the manufacturer's instructions.

**Cell Cycle Analysis**—Cells were transiently transfected with the indicated expression constructs. The following day, they were fixed in methanol-acetone (4:1 v/v) for 30 min. Cells were stained with 18 μg/ml propidium iodide (Sigma) for 15 min at room temperature in the presence of 20 μg/ml RNase A (United States Biochemical Corp., Cleveland, OH). GFP-positive cells were sorted in the FL1 channel of a FACS Calibur (BD Biosciences) equipped with CELLQUEST software. Their cellular content was measured with a logarithmic amplification in the FL3 channel.

**Colony Formation Assay**—RKO cells (10⁵) were plated into 10-cm Petri dishes and transfected 24 h later with the indicated expression vectors using FuGENE-6 reagent as described above. The transfected cells were selected in puromycin and G418 (0.5 mg/ml) for 10 days and stained with crystal violet to assess the number of colonies. That experiment was repeated three times.

**Cell Death Assays**—Cell death was evaluated in HEK 293 cells transfected with pCMV/GFP, pTP53INP1α-GFP, or pTP53INP1β-GFP alone or in combination with pHIPK2-FLAG. Cells were plated on glass
coverslips for 16 h prior to transfection. 36 h after transfection, cells expressing GFP or TP53INPs-GFP fusion proteins were scored for morphological features of apoptosis by phase contrast and fluorescence microscopy; the number of green cells presenting this morphology on six different optic fields were recorded. This experiment was done in triplicate.

RESULTS AND DISCUSSION

TP53INP1s Bind HIPK2 and p53—The first experiment was designed to examine whether TP53INP1s bind to HIPK2. To this end, in vitro pull-down experiments were carried out to demonstrate a direct interaction between GST-TP53INP1α and GST-TP53INP1β with HIPK2. As shown in Fig. 1b, both GST-TP53INP1α and GST-TP53INP1β bind to the 35S-labeled HIPK2, whereas HIPK2 does not bind to the control GST protein. Surprisingly, we also found that GST-TP53INP1α and GST-TP53INP1β bind to 35S-labeled p53 (Fig. 1c). These direct in vitro interactions were confirmed by reciprocal binding experiments using GST-HIPK2 and GST-p53 together with 35S-labeled TP53INP1α and TP53INP1β (Fig. 1d). To further establish that TP53INP1α and TP53INP1β also interact with HIPK2 and p53 in vivo, we co-transfected HEK 293 cells with TP53INP1α-V5 constructs with either HIPK2-FLAG or p53 constructs. As shown in Fig. 2, TP53INP1αβ bind to p53 and HIPK2. To confirm endogenous interactions, γ-irradiation was used to induce a stress in RasV12/E1A-transformed MEFs, which are known to trigger TP53INP1 expression (4, 9). Twen-

Fig. 3. TP53INP1s co-localize with HIPK2 and p53 into PML-NBs. a, immunofluorescence staining of U2OS cells overexpressing TP53INP1α-GFP, HIPK2-FLAG, and PML-IV. GFP (intrinsic green fluorescence) and PML-IV staining by TRITC-conjugated antibodies and HIPK2-FLAG staining by Cy-5-conjugated antibodies are shown. b, immunofluorescence staining of U2OS cells overexpressing TP53INP1s-GFP, p53, and PML-IV. Cells were treated as described in a. c, immunofluorescence staining of MEFs overexpressing TP53INP1s-GFP. Endogenous PML and transfected PML-IV were stained by TRITC-conjugated antibodies.
hipk2 are both associated with endogenous tp53inp1 and p53. as shown in fig. 1

three independent transfections.

ty-four hours after irradiation, cells were collected and homogenized, and total cellular extracts were immunoprecipitated with tp53inp1α/β antibodies. as shown in fig. 2b, p53 and hipk2 are both associated with endogenous tp53inp1α/β. taken together, these results clearly demonstrate that overexpressed and endogenous tp53inp1α/β proteins interact with hipk2 and p53 in vitro and in vivo.

we next performed gat-pull down experiments to identify the regions through which tp53inp1α and β bind to hipk2 and p53. as shown in fig. 1d, tp53inp1α and tp53inp1β bind to gat-hipk2 and to the gat-p53 in the c-terminal region of both proteins. it is known that the region comprising amino acids 553 to 955 of hipk2 binds to the c-terminal region of p53 (amino acids 295–390) (7, 8). therefore, a competition between tp53inp1s and hipk2 for p53 binding is conceivable. interestingly, the c-terminal region of p53 has already been characterized as a regulatory region (14) to which several regulatory proteins can bind (15). the complex interaction between tp53inp1s, hipk2 and p53 we demonstrated in the present study suggest that it could be involved in a regulatory mechanism.

TP53INP1s Co-localize with HIPK2 and p53 into the PML-NBs—The subcellular distributions of TP53INP1α, TP53INP1β, HIPK2, and p53 were next studied. It was recently demonstrated that PML-IV, a PML splice variant, can relocalize p53 into PML-specific sub-nuclear structures named PML nuclear bodies (10). This relocalization promotes several p53 post-translational modifications, which enhance its trans-activation activity (16). PML-NBs are cell cycle-regulated nuclear structures that appear as punctate foci in interphase nuclei (17). Promyelocytic leukemia protein, the most prominent component of these structures, plays a fundamental role in directing complex protein-protein interactions (18). The possible role of PML-NBs in cell growth control is suggested by studies in PML knock-out mice that indicate their tumor suppressor and pro-apoptotic functions (19, 20). Other evidence implicates PML-NBs in the control of gene expression (21) and as a potent growth suppressor by inducing G1 cell cycle arrest (22). HIPK2 is also localized into the PML-NBs with PML-IV (7, 8). We show here that both TP53INP1α and TP53INP1β are also recruited by PML-IV into the PML-NBs and therefore co-localize with HIPK2 and p53 (fig. 3, a and b). Contrary to PML-IV, PML-L, another splice variant of PML, is unable to recruit HIPK2 and p53 into the PML-NBs (7, 10). We demonstrated that PML-L was also unable to recruit TP53INP1α and TP53INP1β (data not shown). Recruitment by PML-IV of TP53INP1α or HIPK2 within the PML-NBs seems to be independent of p53 because it occurs in p53−/− MEFs (data not shown). finally, control experiments using MEF (showing endogenous nuclear bodies) revealed a faint colocalization signal for nuclear bodies and TP53INP1s. As expected, overexpression of PML-IV in MEF also induces a strong TP53INP1s recruitment into the PML-NBs (fig. 3c). Taken together, these results demonstrate that PML-IV isoform recruit p53, HIPK2, and both TP53INP1α and TP53INP1β into PML-NBs. The interactions between these proteins may be facilitated or promoted by such a co-localization, which may also help positioning the resulting complex near its site of action.

TP53INP1s and HIPK2 Modify p53 Trans-Activation Activity—Under normal conditions, p53 is a short-lived protein, tightly regulated and maintained at a low and sometimes undetectable level (23). After stress, p53 is activated mostly at the post-translational level by a complex series of modifications including phosphorylation and acetylation of specific residues, protein-protein interactions, and subcellular relocalization (24, 25). p53 activation leads to the transcription of several genes of which the products can trigger a variety of important biological processes such as cell cycle arrest, apoptosis, DNA repair, replicative senescence, or differentiation (26). To control accurately such a variety of mechanisms, the p53 effects on transcription must be highly dependent on the promoter context, type of stimulus, and cellular environment (27). We suggest that TP53INP1s are involved in such a regulation. To further characterize their functional relevance to HIPK2 and p53 with respect to p53-dependent transcription, we used p53−/− MEFs as a model to exclude endogenous p53 synthesis. Their transfection together with a p53-expressing vector and a plasmid containing the luciferase reporter gene controlled by multimers of the intact p53-binding site (p53-TA-Luc) allowed the monitoring of p53 transcription, we used p53−/− MEFs as a model to exclude endogenous p53 synthesis. Their transfection together with a p53-expressing vector and a plasmid containing the luciferase reporter gene controlled by multimers of the intact p53-binding site (p53-TA-Luc) allowed the monitoring of p53 transcriptional activity. Then p53−/− MEFs were transfected with vectors expressing TP53INP1α-V5 or TP53INP1β-V5 either alone or in combination with HIPK2-FLAG. Fig. 4 shows that HIPK2 increased p53 transcriptional activity as demonstrated previously (8). TP53INP1α or TP53INP1β expressions also increased p53 trans-activation activity more than 2-fold. A dose-dependent effect was observed (data not shown). Surprisingly, TP53INP1 co-expression with HIPK2 resulted in a reduction of p53 activity indicating a functional interaction. Similar results were obtained using HeLa and SW480 cells (data not shown). We concluded that TP53INP1s regulate p53 transcriptional activity and that HIPK2 might participate in this regulation. To further support this hypothesis, we conducted similar experiments using the luciferase reporter gene under the control of several p53-responding promoters (p21, mdm2, bax, and pig3) instead of the p53-binding site (fig. 5). p53 activation of p21, mdm2, and bax promoters was increased to various extents by TP53INP1α and TP53INP1β, contrary to the pig3 promoter, which was not activated. The most noticeable was the p21 promoter, in which p53-dependent expression was increased more than 5-fold by TP53INP1α and more than 4-fold by TP53INP1β.
HIPK2 alone did not influence p53 transcriptional activity on p21 and mdm2 promoters, abolished the TP53INP1 stimulation of p21 promoter, and enhanced that of mdm2 promoter. p53-mediated activation of the bax promoter was increased by TP53INP1s and HIPK2 without further influence on their co-expression. Finally, TP53INP1 expression, which did not alter the p53 activity on the pig3 promoter, prevented its activation by HIPK2. Similar results were obtained using other cell lines such as HeLa, SW480, and HEK 293 (data not shown). As a control, we monitored by Western blotting the expression of p21 protein in MEF p53−/−/− MEFs was transfected with combinations of pTP53INP1α-V5, pTP53INP1β-V5, pcDNA-Hu-p53wt, and pHIPK2-Flag. Results were normalized to β-galactosidase activity. Reporter gene activation induced by pcDNA-Hu-p53wt was arbitrarily set at 100%. Results are expressed as mean values ± S.D. for at least three independent transfections.

Altogether, these data indicate that p53 transcriptional activity on p53-responsive promoters is regulated by HIPK2 and TP53INP1s. The direction and intensity of the changes can be different depending on the promoter used but not on the cell line studied. Intracellular levels of TP53INP1s and HIPK2 strongly influence p53 activity. Differences in p53 activities on different promoters might be attributed in part to different levels of TP53INP1s and HIPK2.

**TP53INP1s Regulate p53**

**TP53INP1s and HIPK2 Are Involved in p53-mediated Regulation of Cell Cycle and Apoptosis**—Our results show that TP53INP1s and HIPK2 can regulate the p53 activity on genes involved in cell cycle regulation (mdm2 and p21) and apoptosis (pig3 and bax). We therefore analyzed by flow cytometry the consequences of their overexpression in HEK 293
cells on the cell cycle and apoptosis (Fig. 7a). As a control, cells were transfected with pCMV/GFP empty expression plasmid. After 24 h, transfection with either pTP53INP1α-GFP or pTP53INP1β-GFP resulted in a significant increase in the percentage of cells in G1 phase (71.1 and 69.5%, respectively, versus 55.5% in control cells) indicating a G1 cell cycle arrest. In agreement with previous results (1, 4), we also found a small but significant increase in the percentage of cells in sub-G1 phase (from 5.9 to 8.3 and 8.4%) associated with increased apoptosis. p21, in which p53-mediated activation is enhanced by TP53INP1s (see Fig. 5), could be one of the molecules involved in the increase in G1 phase arrest (28). Overexpression of HIPK2 also enhances sub-G1 phase arrest (from 5.9 to 8.8%) as reported previously (7, 8). In contrast with TP53INP1s, HIPK2 produced a moderate and reproducible increase in the percentage of cells in G2/M phase (from 28.4 to 31.6%) as well as a decreased percentage of cells in G1 phase (from 55.5 to 46.8%). An increased percentage in G2/M was reported previously, but that result was not discussed by the authors (7, 29, 30). Finally, when one of the TP53INP1s was overexpressed alone, the percentage of cells in G1 phase was higher than when HIPK2 was co-expressed. With TP53INP1α, the proportion of cells in G2/M phase was increased concomitantly, suggesting a competition between the two proteins in the regulation of p53 activity. By contrast, the effects of TP53INP1s and HIPK2 on apoptosis were additive. Similar results in the cell cycle and apoptosis were found in mouse embryo fibroblasts (data not shown), suggesting that the partnership of TP53INP1s with HIPK2 is not cell type-specific.

We next used RKO cells, which allow expression of either TP53INP1α-GFP or TP53INP1β-GFP alone or in combination with HIPK2-FLAG. Their activity was monitored by colony formation assay. As a control, RKO cells were transfected with pLxSP and pCMV/GFP empty vectors. As shown in Fig. 7b, cells transfected with the empty vector formed abundant colonies. On the contrary, the number of colonies formed by cells overexpressing either pTP53INP1α or pTP53INP1β was drastically reduced. A smaller number of colonies was further seen upon transfection of either pTP53INP1α or pTP53INP1β plasmid in combination with pHIPK2.

HEK 293 cells were also transfected with either pTP53INP1α-GFP or pTP53INP1β-GFP (alone or in combination with pHIPK2-FLAG) or with the pCMV/GFP expression plasmid as a control. Forty-eight hours after transfection, cells were analyzed by phase contrast and fluorescence microscopy for typical morphological features of apoptosis including significant membrane blebbing, vacuolization, and nuclear condensation. As shown in Fig. 7c, the number of GFP-positive cells showing morphological features of apoptosis was greater in cells transfected with either pTP53INP1α or pTP53INP1β plasmid in combination with pHIPK2.
cell status was confirmed by terminal deoxynucleotidyltransferase-mediated dUTP nick end-labeling (TUNEL; data not shown). Altogether, these data suggest that TP53INP1s and HIPK2 influence p53 activity and play a role in cell cycle regulation and apoptosis.

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