Homeodomain-interacting Protein Kinase-2 Stabilizes p27kip1 by Its Phosphorylation at Serine 10 and Contributes to Cell Motility*2

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HIPK2 is a serine/threonine kinase that acts as a coregulator of an increasing number of factors involved in cell survival and proliferation during development and in response to different types of stress. Here we report on a novel target of HIPK2, the cyclin-dependent kinase inhibitor p27kip1. HIPK2 phosphorylates p27kip1 in vitro and in vivo at serine 10, an event that accounts for 80% of the total p27kip1 phosphorylation and plays a crucial role in the stability of the protein. Indeed, HIPK2 depletion by transient or stable RNA interference in tumor cells of different origin was consistently associated with a reduction of p27kip1 phosphorylation at serine 10 and stability. An initial evaluation of the functional relevance of HIPK2-mediated regulation of p27kip1 revealed that p27kip1 contributes to cell motility, rather than to cell proliferation, in cells that do not express wild-type p53.

The on-line version of this article (available at http://www.jbc.org) contains supplemental Figs. S1–S3.
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Mediated regulation of p27\(^{\text{kip1}}\) underscored a link with the cell cycle-independent activities of p27\(^{\text{kip1}}\). In particular, in p53-null cells, HIPK2 depletion was associated with a reduced cell motility that was rescued by expression of a phosphomimetic p27S10D mutant, whereas the expression of a non-phosphorylatable p27S10A mutant reduced cell motility in parental, HIPK2-proficient cells.

**EXPERIMENTAL PROCEDURES**

**Cell Cultures and Transfections**—Cells were maintained in Dulbecco’s modified Eagle’s medium with 10% fetal calf serum (FCS) (Invitrogen), glutamine, and antibiotics (complete medium) and transfected as described previously (18). For halflife determination of proteins, exponentially growing cells were seeded at 60% confluence, grown overnight, and treated with 20 µg/ml cycloheximide. To accumulate similar levels of the endogenous p27\(^{\text{kip1}}\) protein, cells were first starved for 16 h in the absence of FCS and then induced to re-enter the cell cycle by addition of complete medium. Cell number was determined by plating 1 × 10\(^6\) cells in complete medium and counting the total cell number every day for 6 days. MG132 (Calbiochem) was used at 5 mM. The following phosphorothioate antisense oligodeoxynucleotides were used: p27-AS, 5’-TGCTGACCT-GAGTCCTGACAT-3’; and p27-MS, 5’-GGTCTGACCT-GTACTCATC-3’. Oligonucleotides were used at a concentration of 200 nM and delivered by the Oligofectamine (Invitrogen).

**Plasmids**—HA-tagged wild-type p27\(^{\text{kip1}}\) and pFLAG-HIPK2/K221R constructs were used in interferinig and control vectors by N. Luttergold (13, 18, 19). The HA-tagged kinase and site-specific mutants p27S10D and p27S10A was a generous gift from M. Pagano (New York University School of Medicine).

**Protein Extraction, Immunoprecipitation, and Blotting**—Total cell extracts and immunoprecipitation protocols were described previously (13). The following antibodies were used: anti-p27\(^{\text{kip1}}\) (BD Transduction Labs, Ser(P)\(^{10}\) p27\(^{\text{kip1}}\) and anti-Thr(P)\(^{187}\) p27\(^{\text{kip1}}\) (Cell Signaling), anti-Thr(P)\(^{157}\) p27\(^{\text{kip1}}\) and anti-Thr(P)\(^{187}\) p27\(^{\text{kip1}}\) (Biogenesis Systems), anti-HIPK2 (4), and anti-\(\gamma\)-tubulin (Sigma, Immunotech), which was used to normalize protein loading.

**RNA Extraction, Reverse Transcription, and PCR Analysis**—Total RNA isolation and quantitative reverse transcription-PCR (RT-PCR) were as described (20). Each reaction was performed in triplicate. We used the 2\(^{-\Delta\Delta C_{T}}\) method to calculate relative expression levels (21). The following primers were used to amplify the p27\(^{\text{kip1}}\) transcript: forward primer, 5’-TGCCTAGAGGCAACTGAGAT-3’; and reverse primer, 5’-ATGA-ZAGTAACTGGCAAGCTG-3’. Expression of the \(G6PD\) gene was used to normalize the amounts of RNAs used in the experiments. The following primers were used: forward, 5’-GATC-TACCAGATGACACCATGAGATT-3’; and reverse, 5’-AGATATGTC-GTGGCAATCTCAG-3’.

**Preparation of Recombinant p27\(^{\text{kip1}}\) Protein and In Vitro Kinase Assay**—The cDNAs encoding human p27\(^{\text{kip1}}\) and its S10A mutant derivative were prepared and purified as described (22). HIPK2-containing complexes were obtained by immunoprecipitation as described (23). Active recombinant HIPK2 was from Millipore.

**Flow Cytometry**—The cell cycle profiles of H1299-CV and H1299i cells were analyzed by DNA content evaluation. Cells were collected, fixed in 70% ethanol, and stored at 4 °C for a few days. Then cells were washed with PBS without Ca\(^{2+}\) and Mg\(^{2+}\), stained with 50 µg/ml propidium iodide containing RNase (20 µg/ml), and analyzed with a FACSCalibur cytosfluorometer. Cell debris and fixation artifacts were gated out, and G1, S, and G2/M populations were quantified using CellQuest software (BD Biosciences). A similar number of events were analyzed in each experiment.

**Transient and Stable RNA Interference**—HIPK2 transient interference was obtained by HIPK2-specific (HIPK2i) stealth RNAi sequences (a mixture of different sequences used alone or in combination with similar readout) and by universal negative control stealth RNAi Negative Medium GC Duplexes (Invitrogen). Cells were induced using RNAiMAX reagent (Invitrogen). HIPK2 interference of H1299 and RKO cells by shRNA have been described previously (13).

**Motility Assay**—Cells were seeded at 80% confluence in 60 mm dishes for 24 h. A linear scratch was made across the diameter of the dish using a 1:1 mixture of 0.1% FCS-containing medium and 0.1% FCS, incubated for the indicated times, and rinsed with PBS. The dish was incubated at 37 °C for 30 min, and then rinsed with PBS. A Nikon Eclipse Ti microscope (Zeiss) at a magnification of 200× was used to monitor cell motility. Phases (Transwell) were visualized by microscopy (Zeiss) at a magnification of 40×. The cells remaining on the upper surface were wiped off with a cotton tip. The cells that migrated to the underside of the filter were fixed, stained with crystal violet (Sigma), and counted by bright field microscopy at 40× magnification in five random fields.

**Statistical Analysis**—For the comparison between two groups of experiments, the Student’s t test was used. Statistical significant difference was considered when \(p<0.05\). Experiments were done in three or five independent experiments, and the data are presented as mean ± S.D.

**RESULTS**

**HIPK2 Depletion Consistently Correlates with Reduction of p27\(^{\text{kip1}}\) Expression**—To investigate the role played by HIPK2 in oncogenesis, we performed a series of Western blots (WBs) with a panel of apoptosis-, cell cycle-, and DNA HIPK2 damage-related factors on TCEs from HIPK2-proficient cells and cells with HIPK2 knocked out. In particular, HCT116, U2OS, and Saos-2 cells were specifically depleted of HIPK2 by transient transfection of three different siRNAs used singly or as a mixture; HIPK2-depleted H1299 and RKO cells were obtained by stable transfection of a vector encoding an HIPK2-specific shRNA and have been described previously (H1299 and RKOi, respectively; Refs. 13 and 24). Interestingly, we observed a sig-
significant and reproducible down-regulation of the CDK inhibitor p27kip1 in each of the cell lines exhibiting HIPK2 interference. As shown in Fig. 1A, a consistent reduction of p27kip1 protein expression (although with different intensities among the cell lines) was detected in cells with knockdown of HIPK2 compared with controls that was independent of the type of HIPK2-specific interference. Because these cell lines are either wild-type p53-proficient (HCT116, U20S, and RKO) or p53-null (H1299 and Saos-2), the observed p27kip1 down-regulation is clearly independent of the TP53 gene status. These data underscore a strong correlation between HIPK2 depletion and p27kip1 repression, suggesting a role for HIPK2 in the regulation of p27kip1 expression.

HIPK2 Regulates p27kip1 Protein Stability—To investigate whether HIPK2 regulates p27kip1 expression, we first evaluated p27kip1 gene transcription by quantitative RT-PCR on mRNAs extracted from HIPK2 stably depleted cells and control vector stably transfected H1299 cells (H1299i and H1299-CV, respect-
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—It has been shown that p27kip1 protein stability and thereby the protein level are finely regulated by its phosphorylation status. Therefore, we investigated whether HIPK2 is able to phosphorylate p27kip1 by performing an immunocomplex kinase assay. FLAG-HIPK2 was transiently transfected and TCEs were immunoprecipitated. The immunocomplexes were then incubated with recombinant p27kip1 and p27-Ser10 phosphorylation levels was detected in the HIPK2-depleted cells compared with controls (Fig. 1C), indicating that the p27kip1 protein is less stable in HIPK2-depleted cells. Comparable results were obtained from similar experiments in the wild-type p53-carrying HIPK2-proficient RKO-CV or stably depleted RKOi cells (supplemental Fig. S1). Taken together, these results suggest that HIPK2 might have a role in the stability of the p27kip1 protein that is independent of p53 expression.

HIPK2 Phosphorylates p27kip1 at Serine 10—It has been shown that p27kip1 protein stability and thereby the protein level are finely regulated by its phosphorylation status. Therefore, we investigated whether HIPK2 is able to phosphorylate p27kip1 by performing an immunocomplex kinase assay. FLAG-HIPK2 was transiently transfected, and TCEs were immunoprecipitated. The immunocomplexes were then incubated with recombinant p27kip1 and p27-Ser10 phosphorylation levels. HIPK2 was able to phosphorylate p27kip1. Therefore, we confirmed the capability of HIPK2 to phosphorylate p27kip1 on sites Serine 10. As shown in Fig. 2B, HIPK2 did not phosphorylate these other sites.

To test whether HIPK2 is able to directly phosphorylate p27-Ser10, in vitro kinase assays were performed by incubating purified HIPK2 and p27kip1 recombinant proteins. As shown in Fig. 2D, HIPK2 phosphorylated p27kip1 directly, whereas it was not able to phosphorylate the p27S10A mutant. Next, we investigated the capability of HIPK2 to phosphorylate p27kip1 on sites other than serine 10. In vitro kinase assays were performed and followed by WB analysis using specific antibodies directed against the phosphorylated sites Thr157, Thr187, and Thr198 of p27kip1. As shown in Fig. 2D (lower panels), HIPK2 did not phosphorylate these other sites.

To confirm the ability of HIPK2 to phosphorylate p27-Ser10, we evaluated the phosphorylation at serine 10 in cells following knockdown of HIPK2 (H1299i). As shown by immunoprecipitations followed by WB analysis, p27-Ser10 phosphorylation was reduced in these cells compared with the control (H1299-CV) (Fig. 3A). Because the lower phosphorylation level at p27-Ser10 was associated with a lower amount of p27kip1 protein (Fig. 3B), the degradation of p27kip1 was blocked by treatment with the proteasome inhibitor MG132. This treatment rendered the same amount of p27kip1 protein in H1299-CV and H1299i cells comparable. As shown in Fig. 3C, the phosphorylation level of p27-Ser10 was reduced in the HIPK2-proficient cells compared with the HIPK2-depleted cell line, supporting the idea that the phosphorylation extent at p27kip1 Ser10 affects the stability of this residue.

—p27kip1 repression induced by HIPK2 depletion does not affect cell proliferation—p27kip1 was originally discovered as a CDK inhibitor that plays a crucial role in cell cycle arrest (22). However, p27kip1 also has cell cycle-independent functions (31). To begin evaluating the functional relevance of HIPK2-mediated regulation of p27kip1, we first assessed whether p27kip1 contributes to the cell cycle modifications induced by HIPK2 depletion in our cells. To this end, the proliferation rate of H1299-CV and H1299i cells was measured in the presence of specific antisense oligonucleotides (p27-AS) that selectively block the synthesis of p27kip1. As a control, the same dose of a sequence-scrambled oligonucleotide with similar base composition but random sequence was used (see “Experimental Procedures”). The efficacy of the antisense oligonucleotide was
assessed by WB for 6 days after transfection (Fig. 5A). As already reported for other cell types (10, 11), HIPK2 depletion reduced the proliferation rate of H1299 cells as shown by the reduced cell number of H1299i compared with H1299-CV control cells and by the mild increase of the G1 phase of the cell cycle (supplemental Fig. S2). As expected after depletion of a proapoptotic factor, the reduced cell number was not due to increased cell death (supplemental Fig. S2). Nevertheless, inhibition of p27kip1 expression did not modify the proliferation rate of both HIPK2-proficient and -depleted cells (Fig. 5B), suggesting that the HIPK2/p27kip1 interaction is not involved in cell cycle regulation.

p27kip1 Repression Induced by HIPK2 Depletion Reduces Cell Motility in p53-null Cells—Among p27kip1 cell cycle-independent functions is a role in cell motility, although this role still remains controversial because both inhibitory and stimulating effects on migration have been reported (32). Recently, HIPK2 depletion was shown to promote anchorage-independent growth and invasion in wild-type p53-positive tumor cells through induction of β4 integrin transcription (15). Thus, we asked whether HIPK2/p27kip1 interaction might be involved in cell motility. To this end, scratch wound healing assays were performed with HIPK2-proficient RKO, H1299, and Saos-2 control cells and their relative HIPK2-depleted counterparts.

FIGURE 2. HIPK2 phosphorylates p27kip1 at serine 10. A, FLAG-HIPK2 was overexpressed in HEK293 cells, TCEs were immunoprecipitated with anti-FLAG Ab, and kinase assays were performed on recombinant p27kip1 protein in the presence of [γ-32P]ATP. Kinase reaction products were resolved by SDS-PAGE and analyzed by autoradiography (upper panel). WB of immunocomplexes was performed with the indicated Abs (lower panels). B, TCEs from HEK293 cells transfected with FLAG-HIPK2 or its KD mutant, FLAG-HIPK2/K221R, were immunoprecipitated (IP) with anti-FLAG Ab. The immunocomplexes were incubated with calf intestinal phosphatase (CIP), resolved by SDS-PAGE, and analyzed by WB for the expression levels of HIPK2, its KD mutant, p27kip1, p27kip1 phospho-Ser10, and p27kip1 phospho-Thr157. The samples were analyzed by WB using the indicated Abs. Lower panel, in vitro kinase assays were performed incubating active recombinant HIPK2 with recombinant p27kip1 or p27kip1A recombinant proteins. The samples were analyzed by WB using specific Abs for the p27kip1 phosphorylated forms at threonine 157, threonine 187, and threonine 198. For A, B, C, and D, one representative of three independent experiments is shown.
Cell monolayers were scratched with a sterile pipette tip and incubated under standard conditions. In agreement with the previously observed increased invasion ability promoted by HIPK2 depletion (15), an accelerated closure of the wound was observed in the wild-type p53-expressing RKO cells (Fig. 6A). In contrast, in the two p53-null cell populations (i.e. H1299 and Saos-2), we found that control cells were evenly distributed at the wound area, whereas the HIPK2-depleted cells exhibited delayed closure of the wound (Fig. 6, B and C). Because we have already shown that the proinvasion activity of HIPK2 depletion in wild-type p53 cells depends upon p53-mediated transcription of p27kip1 (15), we focused our attention on the reduced cell motility observed in the p53-null cells. We investigated this process in H1299 and Saos-2 cells by Transwell chamber assays. HIPK2-proficient and -depleted H1299 cells were transfected with vectors encoding the wild-type p27 or its derivatives p27S10A and p27S10D whose expression was assessed by WB (Fig. 7A). Consistent with the scratch wound healing assays, 48 h after plating, a significant reduction of cell migration (about 85%) was observed in HIPK2-depleted cells compared with controls (Fig. 7B and supplemental Fig. S3). Next, we tested whether this reduction in cell migration is functionally linked to the HIPK2-mediated phosphorylation of p27-Ser10. As shown in Fig. 7B, restoring wild-type p27kip1 protein expression in HIPK2-depleted cells partially rescued cell motility.

DISCUSSION

HIPK2 is an emerging regulator of cell survival and proliferation in development and in response to cell damage (3, 4). These functions are mediated by the physical interaction of HIPK2 with a still increasing number of targets. HIPK2 was shown to phosphorylate several of these targets in vitro and in vivo, and its kinase activity is frequently, although not always, required for the subsequent biological functions (3, 4). Here we have identified a new target of HIPK2, the CDK inhibitor p27kip1, which is phosphorylated by HIPK2 at serine 10 and stabilized. By comparing the expression of a series of apoptosis-, cell cycle-, and DNA damage-related factors in cells expressing HIPK2 or in which HIPK2 was knocked down, we found a significant and reproducible down-regulation of p27kip1 in all of the latter.

Originally identified as an inhibitor of cyclin-CDK complexes, p27kip1 exerts several cell cycle-independent roles,
including regulation of the actin cytoskeleton, cell migration, and cell differentiation (32, 33). The complexity of these physiological functions is paired with as much complexity in tumorigenesis. Indeed, both oncosuppressive and oncogenic activities of p27kip1 are known, although a detailed mechanistic explanation of this duality is still under study (34, 35). Many different signaling pathways regulate p27kip1 levels, function, and subcellular localization through transcriptional, translational, and post-translational modifications (36). Our in vitro and in vivo biochemical characterization showed that HIPK2 phosphorylates p27kip1 at serine 10 and contributes to its stability. Among several sites, phosphorylation at serine 10 represents the major phosphorylation site of p27kip1, accounting for about 80% of the phosphorylation level, and different kinases can execute this specific modification. The Myrk/Dyrk1B kinase was shown to phosphorylate p27-Ser10, and stabilize p27kip1 during the G0 phase of the cell cycle by maintaining it within the nucleus where it can bind to CDK2 and induce cell cycle arrest (29). In contrast, the Kis kinase phosphorylates p27-Ser10 during the G1 phase by enabling p27kip1 to bind CRM1, a carrier protein for nuclear export, and to be transported into the cytoplasm for degradation (28, 37–39). We did not find any correlation between the HIPK2-mediated phosphorylation of p27kip1 and cell proliferation but rather a link with cell motility, suggesting that HIPK2 phosphorylates p27-Ser10 in cell cycle-unrelated conditions.

Although HIPK2-mediated phosphorylation of p27-Ser10 was linked to p27kip1 stability in all the cells we analyzed and was independent of the TP53 gene status, we observed opposite biological outcomes in wild-type p53-positive and p53-null cells. Interestingly, p27kip1 was shown to regulate cell migration by stimulating or blocking cell movements. Primary fibroblasts from p27-null mice failed to migrate (33) and have increased numbers of actin stress fibers that control the formation of
lamellipodia (32). Furthermore, p27kip1 was shown to promote cell migration through binding of RhoA and inhibition of its activation, thereby promoting tumor invasiveness (32, 33). The data we obtained by HIPK2 depletion in p53-null cells are in agreement with these observations: in these cells, we observed an extensive network of stress fibers compared with the HIPK2-proficient counterparts (data not shown). In contrast, the data we obtained in wild-type p53-positive cells are consistent with the oncosuppressive functions of p27 because the reduction of p27-Ser10 phosphorylation and subsequently of p27 expression was associated with increased migration and tumor invasion. This duality of p27kip1 function in tumorigenesis is thought to be linked to the subcellular distribution of the protein with the nuclear localization having a tumor suppressing function and the cytoplasmic localization having an oncogenic

**FIGURE 6.** HIPK2 depletion reduces cell motility.

A–C, migration of HIPK2-proficient or -depleted RKO (A), H1299 (B), and Saos-2 (C) cells following 24-h wounding of a confluent cell monolayer. Representative images were captured with a 40× objective.

**FIGURE 7.** p27kip1 repression induced by HIPK2 depletion reduces cell motility in p53-null cells.

H1299-CV and H1299i cells were transfected with the control pcDNA3.1 vector or with vectors encoding wild-type p27-HA, p27S10A-HA, or p27S10D-HA. A, TCEs from transfected cells were analyzed by WB for the indicated proteins. B, cells from the same transfection analyzed in A were seeded on 5-mm pore size Transwell filters and allowed to migrate toward 10% FCS. After 48 h, cells on the underside of the filters were fixed, stained, and analyzed as indicated under “Experimental Procedures.” Upper panel, one representative experiment of five independent ones is shown. Cell motility was visualized at 40× magnification. Lower panel, migrated cells were quantified and expressed as mean ± S.D. (lines) of five independent experiments, assuming the value of control vector-transfected H1299 cells was equal to 1. Statistical significance was assessed for the differences between H1299-CV cells transfected with control or p27S10A-HA vectors (*) and between H1299i cells transfected or not with p27-HA (**) and p27S10D-HA (***) (p < 0.05).
function (35). We studied the subcellular localization of p27kip1 in cells depleted or not for HIPK2 but did not find significant correlations with their different migration activities (data not shown), indicating that other factors might be involved in the phenotypes we observed. We have previously shown that in wild-type p53-expressing cells, but not in p53-null cells or cells expressing mutant p53 (15), HIPK2 depletion activates wild-type p53-expressing cells, but not in p53-null cells or cells phenotypes we observed. We have previously shown that in gene status might influence the duality of its prosurvival and invasion activities. Here we show that HIPK2 depletion is associated with p27kip1 repression in both wild-type p53-positive and p53-null cells. However, the latter have reduced, rather than increased, migration activity, suggesting that other factors might be involved in the correlations with their different migration activities (data not shown), indicating that other factors might be involved in the p27kip1 migratory response. Further extensive evaluation is required to support this hypothesis. Interestingly, p27kip1 deficiency was recently shown to be associated with migration defects in vivo in mouse gliomas in which the TP53 gene is frequently mutated (30). Overall, our study identifies p27kip1 as a new target of HIPK2 and suggests a new role played by their interaction in cell motility.

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