The SET Protein Regulates G₂/M Transition by Modulating Cyclin B-Cyclin-dependent Kinase 1 Activity*

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The SET protein and the cell cycle inhibitor p21Cip1 interact in vivo and in vitro. We identified here the domain 181–277 of p21Cip1 as essential for the binding of SET. We also found that SET contains at least two domains of interaction with p21Cip1, one located in the fragment amino acids 81–180 and the other one in the fragment including amino acids 181–277. SET and p21Cip1 co-localize in the cell nucleus in a temporal manner. Overexpression of SET blocks the cell cycle at the G₂/M transition in COS and HCT116 cells. Moreover, SET inhibits cyclin B-CDK1 activity both in vivo and in vitro in both cell types. This effect is specific for these complexes since SET did not inhibit either cyclin A-CDK2 or cyclin E-CDK2 complexes. SET and p21Cip1 cooperate in the inhibition of cyclin B-CDK1 activity. The inhibitory effect of SET resides in its acidic C terminus, as demonstrated by the ability of this domain to inhibit cyclin B-CDK1 activity and by the lack of blocking G₂/M transition when a mutated form of SET lacking this C terminus domain was overexpressed in COS cells. These results indicate that SET might regulate G₂/M transition by modulating cyclin B-CDK1 activity.

SET was first identified as a gene that was fused to the CAN gene in a patient with acute undifferentiated leukemia, apparently as a result of a translocation (1). SET is a 39-kDa phosphoprotein widely expressed in human and mouse tissues and found predominantly in the cell nuclei, although it has been recently found associated to the endoplasmic reticulum (1–4). SET belongs to a family of proteins that also includes nucleosome assembly protein 1, testis-specific protein Y-encoded, the suppressor of presenilin 2 protein, the brain protein MB20, the some assembly protein 1, and DsRed expression vectors were gifts from Dr. H. P. Rahn (Munich). The open reading frame of SET cDNA was amplified by PCR using the following specific primers: sense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′, and antisense, 5′-gggggggaattctaatgtcggcgcaggcggcc-3′. The PCR product was purified, digested by EcoRI and HindIII sites, and cloned in-frame into pGEX-KG. cDNAs corresponding to different SET fragments (SET1, aa 1–80; SET2, aa 81–180; SET3, aa 181–277) were generated by PCR using the full-length SET cDNA as a template. The primers used to generate the different constructs were the following: SET1 sense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′, and antisense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′; SET2 sense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′, and antisense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′; SET3 sense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′, and antisense, 5′-gggggaatctaatgtcggcgcaggcggcc-3′. After amplification, SET1 cDNA was digested with EcoRI and HindIII, whereas SET2 and SET3 were digested with NdeI and HindIII. All fragments were cloned into pGEX-4T-2 vector. cDNA fragments of p21Cip1 (N terminus, aa 1–90; C terminus, aa 91–164) were obtained by PCR using specific primers and human p21Cip1 cDNA as a template. They were inserted into pGEX-4T-2 by BamHI–HindIII sites.

Green Fluorescent Protein (GFP) and DsRed Constructs—The GFP and DsRed expression vectors were gifts from Dr. H. P. Rahn (Munich). All SET constructs were cloned into BamHI–HindIII sites, and p21Cip1 was cloned into EcoRI–HindIII sites.

Protein Expression and Purification—Glutathione S-transferase

The abbreviations used are: CDK, cyclin-dependent kinase; GFP, green fluorescent protein; GST, glutathione S-transferase; aa, amino acids.

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(GST) fusion proteins were expressed in *Escherichia coli* and subsequently purified by absorption to glutathione–Sepharose beads as previously described (18). In several cases GST was separated from the GST fusion proteins by digestion with thrombin protease according to the manufacturer (Sigma).

**Cell Cultures and Transfections**—The colon carcinoma HCT116 cell line and the monkey COS-7 cell line were cultured in Dulbecco’s modified Eagle’s medium (Biological Industries) containing 10% heat-inactivated fetal calf serum. Both cell types were maintained at 37 °C in a humidified atmosphere containing 5% CO2. Transfections of COS and HCT116 cells were performed with Effectene (Qiagen) as directed by the manufacturer. Cells were incubated overnight at 37 °C, and fresh medium was added after 12–18 h. Then cells were harvested at different times after transfection. To measure the effect of GFP-SET expression on CDK1 activity, transfected cultures were subjected to cell sorting to separate GFP- or GFP-SET-expressing cells. Cell sorting gave a 90% purity. Then separated cells were subjected to immunoprecipitation and kinase assay as described below.

**Antibodies**—Antibodies against cyclin A were from Santa Cruz (H-32). All the other antibodies, including anti-cyclin B1 (105–158), anti-cyclin E (06–459), anti-phospho histone H1 (06–597), and anti-phospho histone H3 (06–570), were from Upstate Biotechnology.

**Immunofluorescence**—Transfected cells were seeded in culture dishes containing glass coverslips and allowed to grow for at least 24 h. Cells were fixed with ethanol:acetic acid (95:5) and incubated with primary antibodies for 1 h at 37 °C. After washing three times (5 min each) in phosphate-buffered saline, cells were incubated with secondary antibodies conjugated with cyanine 3 (Jackson) for 45 min at 37 °C. After washing, coverslips were mounted on slides with Mowiol (Calbiochem). Immunofluorescence was recorded using a confocal laser fluorescence microscope.

To analyze the intracellular localization of DsRed-SET and GFP-p21Cip1, cells transfected with these plasmids were fixed with 4% paraformaldehyde for 10 min at room temperature. After washing, coverslips were mounted on slides with Mowiol, and immunofluorescence was recorded using a confocal laser fluorescence microscope.

**Immunoprecipitation and CDK1 Kinase Assays**—Cells were lysed in buffer A (50 mM Tris-HCl, pH 7.4, 250 mM NaCl, 5 mM EDTA, 50 mM NaF, 0.1% Triton X-100, 0.5 μg/μl aprotinin, 10 μg/ml leupeptin, 1 mM phenylmethylsulfonyl fluoride, and 0.1 mM Na3VO4) for 30 min on ice. Lysates (0.1–0.5 mg of protein) were incubated with 2 μg of anti-cyclin B1 antibodies overnight at 4 °C. Then, protein G-agarose beads (Sigma) were added, and samples were incubated for 1 h at 4 °C. After 3 washes in buffer A and 2 in kinase buffer (50 mM Tris-HCl, pH 7.8, 20 mM MgCl2, 0.1% Triton X-100), immunoprecipitates were resuspended in a final volume of 20 μl of kinase buffer containing 4 μg of histone H1 (Roche Molecular Biochemicals) and 2 mM dithiothreitol. Then they were incubated with different amounts of recombinant SET protein and GST-p21Cip1 for 10 min. A kinase reaction was initiated by the addition of 30 μl of ATP containing 10 μCi of [γ-32P]ATP (Amersham Biosciences). After incubation for 30 min at 30 °C, reactions were stopped by the addition of Laemmli sample buffer. Histone H1 was separated on 12% SDS-polyacrylamide gels, which were then stained with Coomassie Blue and Laemmli sample buffer. Histone H1 was separated on 12% SDS-polyacrylamide gels, which were then stained with Coomassie Blue and dried. Densitometry was detected by autoradiography.

**Pull-downs with Purified Proteins**—Pull-down experiments were performed as previously described (19). SET protein, the different fragments of SET, and the different peptides and fragments of p21Cip1 were coupled to BrCN-activated Sepharose 4B, as indicated by the manufacturer. Then, samples (1–4 μg of protein) were incubated with 2 μg of immobilized protein or peptide in the binding buffer (50 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1 mM dithiothreitol, 1% Triton X-100) for 2 h at room temperature. The beads were then extensively washed with binding buffer. The unbound fraction was the supernatant of the first wash.

**RESULTS**

**Identification of the p21Cip1 Domains That Interact with SET**—We previously reported that SET binds to a peptide of p21Cip1 containing aa 145–164 (14). However, the binding analysis performed in this previous study did not cover all the p21Cip1 sequence. To define more precisely the SET-binding domains of p21Cip1, this protein was fractionated in two parts we named NT domain (aa 1–90) and CT domain (aa 91–164). Then, the binding of SET to these fragments was analyzed by pull-down experiments. Results showed that SET only bound to the CT domain of p21Cip1 (data not shown).

We subsequently analyzed the binding of SET to four synthetic peptides from this CT domain of p21Cip1, 1 (aa 84–98), 2 (aa 99–121), 3 (aa 122–139), and 4 (aa 140–164). Peptides were coupled to Sepharose 4B and pull down experiments were performed. Results showed that SET only significantly bound to peptide 4 (Fig. 1A). These results together with those previously reported (14) indicate that the p21Cip1 region, including aa 140–164, contains the SET binding domain of p21Cip1. To analyze in detail the putative SET-binding sites in this p21Cip1 region, we studied the binding of SET to 4 overlapping peptides from this domain named 4A (aa 140–150), 4B (aa 145–155), 4C (aa 150–160), and 4D (aa 155–164). Pull-down experiments showed that SET bound to peptides 4A, 4C, and 4D but not to 4B (Fig. 1B), indicating that p21Cip1 binds to SET by two separated domains (aa 140–144 and aa 156–160). To further confirm the relevance of the region including aa 155–160 in the binding to SET, we generated mutated p21Cip1 fragments by changing aa 157 (Leu) and aa 159 (Phe) to Asp. Specifically, we generated the mutated peptides 4C-DID (aa 150–160 with the mutations), 4-DID (aa 140–164 with the mutations), and also the fragment CT-DID (aa 84–164 with the mutations). The binding analysis clearly indicated that all these fragments containing the mutation did not associate with SET (Fig. 2).
Thus, the $^{157}\text{LIF}^{159}$ domain of the C terminus of $p21_{\text{Cip1}}$ is essential for the SET-$p21_{\text{Cip1}}$ interaction.

Identification of the SET Domains That Interact with $p21_{\text{Cip1}}$—To identify the SET domains that interact with $p21_{\text{Cip1}}$, we generated three SET fragments, SET1 (aa 1–80), SET2 (aa 81–180), and SET3 (aa 181–277) (Fig. 3A). Then the binding of these three fragments of SET to $p21_{\text{Cip1}}$ peptides 1–4 coupled to Sepharose 4B was analyzed by pull-down experiments. Results showed that SET2 and SET3 but not SET1 associated with $p21_{\text{Cip1}}$ peptide 4 (Fig. 3B). Neither SET2 nor SET3 bound to the mutated peptide 4-DID (Fig. 3B). Then, the binding of SET fragments to $p21_{\text{Cip1}}$ peptides 4A (aa 140–150), 4B (aa 145–155), 4C (aa 150–160), and 4D (aa 155–164) was studied. Results indicated that fragments SET2 and SET3 bound to peptides 4C and 4D, although SET3 in addition bound also to peptide 4A (Fig. 3C). These results revealed that $p21_{\text{Cip1}}$ putative binding sites are present in SET2 and SET3 fragments. The binding site from SET2 only binds to aa 156–160 of $p21_{\text{Cip1}}$, whereas the binding site(s) in SET3 might associate with aa 140–144 and/or aa 156–160 of $p21_{\text{Cip1}}$.

Nuclear Co-localization of SET and $p21_{\text{Cip1}}$—COS cells were transfected with DsRed-SET and GFP-$p21_{\text{Cip1}}$ as described under “Experimental Procedures,” and the intracellular distribution of both proteins was analyzed by confocal microscopy. A, a diffused pattern of both proteins, showing that a clear co-localization in perinucleolar areas was observed in a significant number of cells. B, in other cells a punctuated pattern of SET and a diffused pattern of $p21_{\text{Cip1}}$ without co-localization was observed. C, other cells showed a punctuated pattern of both proteins without co-localization. D, immunofluorescence experiments using anti-SET and anti-$p21_{\text{Cip1}}$ antibodies.

Overexpression of SET Blocks Cell Cycle at $G_2/M$—To analyze the possible role of SET in cell cycle regulation we studied the effect of SET overexpression on cell cycle progression. By...
using laser-scanning confocal analysis, we determined the amount of DNA in COS and HCT116 cells transfected with GFP-SET or GFP. As shown in Fig. 5, SET overexpression induced a clear increase in the number of cells at G2/M and a decrease in the number of cells in G1 in both cell types. These results suggest that overexpression of SET blocks cell cycle at G2/M. To further confirm this possibility, experiments analyzing the effect of SET overexpression on histone H3 phosphorylation (this phosphorylation only occurs in mitotic cells) were performed on COS and HCT116 cells. Results revealed that in both cell types transfected with SET, no phosphorylated histone H3 was observed (Fig. 6, A and B). In contrast, cells transfected only with GFP showed this phosphorylation (Fig. 6, A and B). Overexpression of SET did not block the cell cycle at S phase since transfected cells showed bromodeoxyuridine incorporation (data not shown). These results support the hypothesis that SET might be involved in the regulation of G2/M transition.

Role of SET on Cyclin B-CDK1 Activity—Evidence presented here showing that overexpression of SET blocked cell cycle progression at G2/M and the fact that SET binds to cyclin B (17) suggests that SET alone or together with p21Cip1 might be involved in the regulation of cyclin B-CDK1 activity. Thus, we first studied the effect of SET overexpression on histone H1 phosphorylation (histone H1 phosphorylation depends on cyclin B-CDK1 activity). These experiments were performed on COS and HCT116 cells transfected with GFP-SET or GFP as a control. Results revealed that cells overexpressing SET did not show H1 phosphorylation, whereas those transfected only with GFP did (Fig. 6, C and D). We subsequently studied the effect of SET overexpression on cyclin B-CDK1 activity. At 48 h after transfection with GFP-SET or GFP alone, COS and HCT116 cells were subjected to immunoprecipitation using anti-cyclin B antibodies. Then immunoprecipitates were analyzed for CDK1 activity. Results indicated that after SET transfection cyclin B-CDK1 activity was clearly inhibited in both cell types (Fig. 7A). To analyze whether SET might directly regulate cyclin B-CDK1 activity, HCT116 cell extracts were immunoprecipitated with specific anti-cyclin B antibodies. Then CDK1 activity was determined in the immunoprecipitates in the presence or absence of exogenous SET. As shown in Fig. 7B, CDK1 activity was inhibited by the addition of 1–2 μM purified SET. Inhibition was dose-dependent, and the effect was similar to that observed by recombinant GST-p21Cip1 (Fig. 7B). Interestingly, this effect was specific for cyclin B-CDK1 because cyclin A-CDK2 and cyclin E-CDK2 activities were not affected by the addition of purified SET (Fig. 8A). SET and p21Cip1 generate an additive inhibitory effect. The addition of 0.5 μM SET and 0.5 μM p21Cip1 inhibited cyclin B-CDK1 activity, whereas at these doses SET and p21Cip1 added alone only produced a limited inhibition (Fig. 8B). To determine which domain of SET was involved in the inhibition of cyclin B-CDK1 activity, we studied the effect of SET fragments (SET1, SET2, and SET3) on this activity. Results indicate that SET3 fragment contains the cyclin B-CDK1 inhibitory domain (Fig. 8C). To further confirm this possibility, we analyzed the binding of cyclin B to a mu-

![Fig. 5. Effect of SET overexpression on cell cycle.](http://www.jbc.org/)

![Fig. 6. Effect of SET overexpression on phosphorylation of histones H3 and H1.](http://www.jbc.org/)
Fig. 7. Role of SET on cyclin B-CDK1 activity. A, COS and HCT116 cells were transfected with SET-GFP or GFP alone. At 48 h after transfection, cells were separated using a cell sorter. Cell extracts (0.1 mg) were subjected to immunoprecipitation using anti-cyclin B antibodies. Immunoprecipitates (IP) were then analyzed for CDK1 activity as indicated under "Experimental Procedures." B, HCT116 cell extracts were immunoprecipitated with specific anti-cyclin B antibodies. Then CDK1 activity was determined in the immunoprecipitates in the absence (C+) or in the presence of different concentrations of exogenous SET, GST-SET, or GST-p21Cip1.

Fig. 8. SET specifically inhibits cyclin B-CDK1 activity, and its effect is additive to that of p21Cip1. A, HCT116 cell extracts were immunoprecipitated with specific antibodies against cyclins B, A, or E. Then CDK activities associated with these cyclins were determined in the immunoprecipitates (IP) in the absence (C+) or in the presence of different concentrations of exogenous SET. B, cyclin B-CDK1 activity was determined in immunoprecipitates from HCT116 cell extracts in the absence (C+) or in the presence of 0.5 μM SET or p21Cip1 alone or in combination. C, cyclin B-CDK1 activity was determined in immunoprecipitates from HCT116 cell extracts in the absence (C+) or in the presence of 2 μM concentrations of the different SET fragments (SET1, SET2, and SET3).

Fig. 9. Overexpression of a mutant form of SET, lacking aa 181–277, did not block cell cycle progression. A, Molt-4 extracts were loaded in affinity columns of SET or SET lacking aa 181–277 (SET1 + 2), and the binding of cyclin B1 was analyzed by Western blot. B, intracellular localization of GFP, GFP-SET1 + 2, or GFP-SET in transfected COS cells. C, by using laser-scanning confocal analysis, the amount of cellular DNA in COS cells transfected with GFP (black bars), GFP-SET (gray bars), and GFP-SET1 + 2 (empty bars) was determined. Results are represented as the mean values of the percentage of cells in the different phases of the cell cycle ± S.D. of three independent experiments carried out in duplicate. Statistically significant differences were evaluated by Student’s t test. (*p < 0.01).

DISCUSSION

SET is a cyclin B-interacting protein that recently has been shown to associate with the CDK inhibitor p21Cip1 (14, 17). We report here that SET inhibits cyclin B-CDK1 activity both in vivo and in vitro and that this inhibitory capacity is additive to that of p21Cip1. Thus, SET might be involved in the regulation of G2/M transition.

Our results revealed that SET binds to two specific domains of p21Cip1 located at the C terminus (aa 140–144 and aa 156–164). The later domain is essential for the binding of SET to p21Cip1 since specific mutations in this region block the association between both proteins. Thus, domain 140–144 might help the binding, but it is not enough for maintaining a stable association with SET when domain 156–164 is mutated. The C terminus of p21Cip1, which includes the 156–164 domain, also binds a number of proteins including proliferating cell nuclear antigen, the E7 oncoprotein of the human papilloma virus, Gadd45, c-Myc, and calmodulin among others (19–23). This fact suggests an important role for this p21Cip1 region in the control of cellular functions. Studies to analyze the ability of SET to compete with these other p21Cip1-binding proteins for the association with p21Cip1 are still lacking. Thus, the possible involvement of SET on the modulation of the binding of p21Cip1 to these important cell cycle regulators is still unknown.
SET binds to p21Cip1 also by two domains, one located at the central region of SET, whereas the other one is placed at the C-terminal region. These results suggest that SET might associate with two p21Cip1 molecules at the same time or, alternatively, that the two SET-binding sites of p21Cip1 (aa 140–145 and 156–164) might bind to two different domains of SET. Experimental work to answer this question is under way in our laboratory.

A previous report demonstrated by immunoprecipitation experiments that SET and p21Cip1 might be associated in vitro (14). Here we demonstrate the in vitro co-localization of both proteins by ectopically expressing p21Cip1. Overexpression of SET in two different cellular types, COS and HCT116, induced the inhibition of cell cycle progression at G1/M transition. This block is associated with the inhibition of cyclin B-CDK1 activity, indicating that SET might be involved in the control of mitosis entry by regulating the activity of cyclin B-CDK1 complexes. Results from in vitro experiments revealing that SET inhibits cyclin B-CDK1 activity at concentrations similar to those of p21Cip1 strongly support this hypothesis. Interestingly, the inhibitory effect of SET and p21Cip1 are additive, suggesting that they might cooperate in regulating cyclin B-CDK1 activity under specific circumstances, as for instance after DNA damage. This cooperation in the inhibition of cyclin B-CDK1 might be similar to that occurring between Gadd45 and p21Cip1 (14) after DNA damage (25, 26). The specific domain of SET involved in cyclin B-CDK1 inhibition is located at the C-terminal region (SET3) that contains a long very acidic domain (aa 225–277). Recently, it has been shown that Gadd45 binds to CDK1 and inhibits the activity of cyclin B-CDK1 complexes (27, 28). Interestingly, the Gadd45 domain responsible for the inhibition is an acidic patch including the sequence DEDDDR (28). Moreover, Ran, a small nuclear GTPase implicated in both cell cycle progression and nuclear export (29, 30), also contains an acidic motif with similar amino acid composition in its C-terminal domain (DEDDDL) (31). It has been shown that overexpression of Ran induces G2/M arrest, whereas deletion of the DEDDDL motif abolishes this activity (29). Interestingly, the C-terminal region of SET contains an acidic sequence 260DEDDE268 that is very similar to those of Gadd45 and Ran, involved in the regulation of cyclin B-CDK1 activity and G2/M transition. All these results suggest that this sequence included in the C terminus of SET is the one involved in the inhibition of cyclin B-CDK1 activity and, consequently, in G2/M block. However, this still remains to be proved.

Results reported here together with recent reports indicate that SET has a relevant role in the regulation of CDK activities. A previous report revealed that SET blocks the inhibitory effect of p21Cip1 on cyclin E-CDK2, thus allowing a cyclin E-CDK2 activity in the presence of p21Cip1 (14). In this case, SET plays a role as an “activator” of these complexes in G1. Recently, it has been shown that SET binds to p35Nckα and p35Nckα (15). Both proteins are activators of the neuronal CDK5 (16). SET and p35Nckα co-localize in the nucleus of cultured cortical neurons, and in vitro experiments indicated that SET enhanced the activity of p35Nckα-CDK5. Interestingly, the acidic tail of SET is required for the stimulatory effect on p35Nckα-CDK5 (15). Results reported here indicate that in addition to the positive regulation of CDK2 and CDK5 activities, SET might also play a role as a negative regulator of CDK1. This information reveals that SET plays a dual role in the cell cycle as a positive regulator of G1/S and as a negative regulator of mitosis entry. A possibility that has to be investigated is that SET might be involved in blocking cyclin B-CDK1 during S phase and G2, avoiding a premature activation of these complexes before cells would be ready to enter mitosis.

SET is also a potent inhibitor of protein phosphatase 2A, which is involved in different cellular functions, including cell proliferation (10). This fact suggest a concerted regulation by SET of phosphorylation/dephosphorylation of nuclear proteins during cell proliferation but also during other cellular processes requiring the activity of CDKs.

Results of this study are the first to demonstrate that SET is a negative regulator of cyclin B-CDK1 in vivo and in vitro and as a consequence of mitosis entry. The fact that SET is also involved in the regulation of chromatin structure by modulating histone acetylation (11) places this protein in a key position in the regulation of cell cycle. On the one hand, SET might be involved in the control the phosphorylation status of nuclear proteins by regulating CDK and protein phosphatase 2A activities. On the other hand, SET might control transcriptional activity of chromatin by regulating histone acetylation and chromatin condensation. The protein p21Cip1 might participate in these processes, although its role still remains unclear.

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