Evidence for Repressional Role of an Inverted CCAAT Box in Cell Cycle-dependent Transcription of the Human DNA Topoisomerase IIα Gene*

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Expression of DNA topoisomerase IIα (topo IIα) is cell cycle-regulated at both the transcriptional and the post-transcriptional levels. In order to identify cis-acting elements responsible for transcriptional regulation during the cell cycle, we investigated NIH/3T3 cells stably transfected with luciferase reporter plasmids containing various lengths of the human topo IIα gene promoter. Serum-deprived cells expressed low levels of luciferase, and following serum-induced cell cycle entry luciferase levels were gradually elevated 2-fold. During S phase, a steep 3-fold increase in luciferase activity was seen, reaching its maximum approximately 22 h after serum addition. This pattern was observed with both a full-length (nucleotides (nt) −295 to +90) and a deletion (nt −90 to +90) promoter construct. In contrast, when testing a deletion construct (nt −51 to +90) lacking the first inverted CCAAT box (ICB1) the S phase-specific induction was absent. Mutation of ICB1 revealed that it had a repressive character, since luciferase levels rose rapidly to maximal levels immediately following serum addition. Furthermore, electrophoretic mobility shift assays demonstrated a marked decrease in ICB1 binding activity following serum addition. Together, this suggests a role of ICB1 in cell cycle-dependent repression of topo IIα transcription.

Type II DNA topoisomerases are essential nuclear enzymes that regulate DNA topology by creating a transient double strand break through which a second intact double helix is passed (reviewed in Refs. 1 and 2). They are also the key cellular targets for a number of clinically important anticancer agents such as etoposide and the anthracyclines, doxorubicin and daunorubicin (3).

There exist two isoforms of topoisomerase II (topo II)3 in higher eukaryotes, namely the α (170 kDa) and the β (180 kDa) isoform encoded by separate genes (4, 5). The α isoform is primarily required for chromosome (de)condensation and sister chromatid segregation during mitosis (6, 7), but roles for topo IIα in replication and transcription have also been proposed (1). In contrast, a precise biological function of topo IIβ has not yet been established, although recent evidence has emerged for a role during differentiation (reviewed in Ref. 8).

A major difference between the α and β isoform of topo II is their expression. The topo IIβ gene is constitutively expressed in proliferating as well as differentiated tissue (9), and its transcription rate is more or less constant throughout the cell cycle. In contrast, topo IIα activity is primarily associated with proliferating cells and progressively decreases as cells are induced to differentiate or deprived of serum (10). Levels of topo IIα enzyme also changes within a single cell cycle, with low levels during G0/G1 and accumulation during S and G2 to reach maximal levels during mitosis (11). This accumulation is obtained by enhancement of both transcriptional activity and mRNA stability during S phase (12, 13). This cell cycle-dependent pattern of expression is conserved among mammals, including mice and humans (14). However, no specific cis-acting DNA elements and/or trans-acting factors have been associated with this regulation.

Topo II activity is an important determinant for the cytotoxic effect of the topo II-targeting drugs. Thus, a direct correlation between topo II levels and drug sensitivity of cells is a common finding. Indeed, reduction in the amount of topo II enzyme is one mechanism by which cancer cells acquire drug resistance (reviewed in Ref. 15). For this reason, considerable effort has been made to determine the mechanisms regulating topo II expression. These investigations have revealed that topo IIα transcription is highly susceptible to environmental stimuli such as heat shock, growth arrest, and drug treatment. For instance, when Swiss 3T3 cells are confluence-arrested topo IIα mRNA is rapidly down-regulated in response to reduced binding of the transcription factor NF-Y to an ICB (16). Another ICB has been associated with both transcriptional activation and repression of the topo IIα promoter in response to heat shock and p53 expression, respectively (17, 18). During phorbol ester and sodium butyrate induced monocytic differentiation of promyeloid HL-60 cells the topo IIα promoter is trans-activated during the early stages, whereas it is down-regulated at later stages (19). Recently, the transcription factors c-MYB, B-MYB, NF-M, and Sp3 have been identified as trans-activators of the topo IIα gene promoter in various cellular backgrounds (20–22).

We have investigated human topo IIα gene regulation during the cell cycle. Using NIH/3T3 cells stably transfected with luciferase reporter plasmids containing various promoter segments we show that induction of topo IIα promoter activity was sensitive to treatment with aphidicolin and roscovitine. Furthermore, S phase-specific induction can be partially reversed by treatment with the same drugs. In addition, we demonstrate that an ICB within the minimal promoter is required for G0/
G1-specific repression of topo IIα transcription and that this ICB is differentially occupied during the cell cycle in a manner inversely related to promoter activity. Therefore, we propose that topo IIα transcription is cell cycle-regulated by a repressive mechanism.

**MATERIALS AND METHODS**

**Plasmids**—Human topo IIα gene promoter constructs (−562-TOP2LUC, −384-TOP2LUC, −295-TOP2LUC, −295(mSP1)TOP2LUC, −148-TOP2LUC, −90T-OP2LUC, −51TOP2LUC, and 51TOP2LUC) were stably transfected by cotransfecting the pTK-Hyg vector (CLONTECH) 10:1 (w/w) by the calcium phosphate method (23). Stable transfectants were selected for 4 weeks with 200 μg/ml hygromycin B (Calbiochem). Subsequently, cells were maintained in DMEM containing 200 μg/ml hygromycin B. As we only investigated the relative changes of a given promoter construct, the entire population of resistant cells rather than individual clones was pooled, thus eliminating effects due to copy number and site of integration. Synchronization of stably transfected NIH/3T3 cells by serum starvation was performed by incubating cells for 72 h in DMEM containing 0.5% fetal calf serum.

**Thymidine Incorporation and Luciferase Assay of NIH/3T3 Cells**—Preparation of nuclear extracts—NIH/3T3 stable topoisomerase IIα promoter transfectants were seeded in six-well clusters (approximately 2 × 10⁶ cells/well) and serum-starved to obtain synchronized populations. Cells were released into growth medium just prior to harvest, cells were incubated in prewarmed and CO₂-equilibrated complete medium containing 5 μg/ml [methyl-³²H]thymidine (47.0 Ci/mmol; Amersham Pharmacia Biotech). The following oligonucleotides (together with complementary ones) were used for EMSAs (5′ to 3′): GAGTCAGGGATTGGCTGGTCTGCTCTGGCGGC (mMBS); GAGCTCCCTAGTCAAGCCCGGTC (mMBS); GGCTCTTCTTCCTA (mSP1); GTCAGGCATGGTGTGCC (mICBI) with the changed nucleotides in bold. Mutations were verified by sequencing of 1–2 μg of plasmid (not shown). All primers were purchased from Life Technologies, Inc.

**Cell Culture**—The mouse fibroblast cell line NIH3T3 (gift from C. Caradelli) was maintained in Dulbecco’s modified Eagle’s medium, supplemented with 10% fetal calf serum, 100 units/ml penicillin G, and 100 μg/ml streptomycin sulfate (Life Technologies, Inc.), in an incubator at 37 °C in a humidified atmosphere containing 5% CO₂. NIH/3T3 cells were stably transfected by cotransfecting the −562-TOP2LUC, −384-TOP2LUC, −295-TOP2LUC, −295(mSP1)TOP2LUC, −295(mMYB)TOP2LUC, and −295(mICBI)TOP2LUC constructs together with the pTK-Hyg vector (CLONTECH) 10:1 (w/w) by the calcium phosphate method (23). Stable transfectants were selected for 4 weeks with 200 μg/ml hygromycin B (Calbiochem). Subsequently, cells were maintained in DMEM containing 200 μg/ml hygromycin B. As we only investigated the relative changes of a given promoter construct, the entire population of resistant cells rather than individual clones was pooled, thus eliminating effects due to copy number and site of integration. Synchronization of stably transfected NIH/3T3 cells by serum starvation was performed by incubating cells for 72 h in DMEM containing 0.5% fetal calf serum.

**RESULTS**

**Promoter Activity in Stable Cell Lines Exhibits Wild Type Behavior**—The topo IIα transcription pattern is characterized by an increase during S phase of the cell cycle. To examine this pattern in detail, cell lines stably transfected with a range of different promoter constructs were prepared. The feasibility of this system required that a stably transfected full-length promoter construct would mimic the previously described expression pattern of topo IIα mRNA (12). NIH/3T3 cells stably transfected with the −562TOP2LUC construct were synchronized by serum starvation, and luciferase activity and incorporation of radioactively labeled thymidine was measured every 2 h for a period of 22 h following serum addition. Low levels of luciferase activity and thymidine incorporation were observed in serum-starved cells (Fig. 1A). Upon serum addition, when the cells treated with Me₆SO re-entered the cell cycle, an immediate elevation of luciferase activity was detected reaching a plateau after approximately 4–6 h (Fig. 1A). Subsequently, as cells entered S phase, seen as a steep increase in thymidine incorporation (12–14 h after serum addition), a concomitant increase in luciferase activity was seen that continued throughout the entire time course (Fig. 1A). Together, this fitted the expected expression pattern of topo IIα mRNA and, as an identical pattern, was obtained in untreated cells (data not shown; Fig. 3A); this approach was accordingly regarded as feasible.

**S Phase Entry Is Necessary for Induction of Topo IIα Gene Transcription**—It has been demonstrated that the accumulation of topo IIα mRNA during late S phase can occur independently of DNA synthesis and S phase entry (12). Specifically, treatment of synchronized HeLa cells with the DNA polymerase-inhibitor aphidicolin only slightly delayed topo IIα mRNA accumulation. In order to investigate if the transcriptional induction of the topo IIα gene promoter also was insensitive to DNA synthesis inhibition, cells synchronized by serum starvation were treated with 3 μM aphidicolin or 25 μM roscovitine from 1 h after serum addition and throughout the 22-h time course. When treated only with solvent (Me₆SO) a normal expression pattern was observed (Fig. 1A). In contrast, treatment with aphidicolin or roscovitine abolished DNA synthesis and hence entry into S phase (Fig. 1, B and C). Accordingly, no S phase-specific induction of luciferase expression was seen (Fig. 1, B and C). However, an induction to almost wild type levels (Fig. 1D, black bars) could be re-established in aphidicolin- and roscovitine-treated cells when the drug was removed 16 h after serum addition and the cells incubated for another 8 h.
8 h in the absence of drug (Fig. 1D, middle panel), indicating that the induction indeed was S phase-specific.

Interestingly, an approximately 2.5-fold increase in luciferase activity occurred in aphidicolin-treated cells 4–6 h following serum addition (Fig. 1B). In roscovitine-treated cells, an approximately 2-fold increase in luciferase was also observed, although with different kinetics (Fig. 1C). This immediate elevation of luciferase expression was also found in MeSO4-treated cells (Fig. 1A), implying either the presence of a specific serum-responsive cis-acting element in the promoter or a "global" effect of serum addition.

**Induction of the Topo IIα Promoter Is Dependent on Active S Phase Progression**—In order to investigate if S phase entry per se was sufficient to mediate the observed S phase-specific induction of luciferase activity, or if ongoing DNA synthesis was required, cells were treated with aphidicolin or roscovitine 14 h after serum addition when DNA synthesis had started (see Fig. 1A). In addition, cells were treated with actinomycin D or cycloheximide to inhibit RNA or protein synthesis, respectively. As expected, treatment with solvent (MeSO4) had no effect on luciferase activity, whereas drug treatment more or less abolished the S phase-specific induction. In the case of actinomycin D, luciferase levels remained almost constant (Fig. 2), presumably due to contributions from already transcribed luciferase mRNAs and active luciferase protein. As seen, treatment with cycloheximide caused a steady decrease in luciferase activity (Fig. 2), reflecting the luciferase protein half-life of approximately 3 h (24). Although greatly impairing the S phase-specific induction, treatment with roscovitine or aphidicolin did not completely abrogate transcription of luciferase mRNA, as reflected by the higher levels of luciferase activity compared with the actinomycin D-treated cells (Fig. 2).

**Sequences between bp −90 and −51 Are Required for Proper S Phase Induction**—The expression pattern mediated by the full-length promoter is, as mentioned, characterized by a steep increase in transcriptional activity coinciding with the onset of S phase (see Fig. 1A). This results in an approximately 7-fold induction relative to promoter activity in serum-starved cells, while the induction is only about 3-fold compared with the activity levels reached at the immediate plateau at 6–12 h (Figs. 1A and 3A). All deletion constructs tested displayed similar thymidine incorporation patterns, although with some variations in incorporated counts (Fig. 3; data not shown). When deleting sequences between bp −562 and −90, no significant changes were observed in the ability of the constructs to mediate the S phase-specific induction of luciferase activity (Fig. 3, A–C), and induction levels ranged from 4- to 7-fold when comparing maximal observed luciferase activities with those in serum-starved cells (Table I). Interestingly, when comparing the induction from the immediate plateau levels to maximal levels, the increase only ranged between approximately 2.5- and 3-fold (Table I). Thus, although important for basal pro-
transcriptional induction in a heterologous context. In contrast, this promoter activity per se, the sequences between bp −562 and −90 are dispensable with regard to mediating S phase-specific transcriptional induction in a heterologous context. In contrast, this induction was greatly impaired when deleting sequences between bp −90 and −51 (Fig. 3D). Although capable of an approximately 3-fold total induction, the S phase-specific induction was almost absent (Fig. 4D). Most notable was the sharp and rapid increase in luciferase activity immediately after serum addition, reaching a plateau after approximately 6 h (Fig. 4D). From this plateau the levels did not increase significantly as the cells progressed into S phase (Fig. 4D; Table I). Together this suggests an important repressive role of ICB1 in the S phase-specific induction of the topo IIα gene.

ICB1 Binding Activity Decreases in Response to Cell Cycle Re-entry—Since the abovementioned data indicated that ICB1 might have a role in regulating S phase-specific induction of human topo IIα promoter activity, we decided to investigate if a cell cycle-dependent ICB1 binding activity was present in NIH/3T3 cells. In order to do so, nuclear extracts were prepared from synchronized cells at different time points following serum addition and tested for ICB1 binding activity in EMSAs. When examining exponentially growing NIH/3T3 cells with a oligonucleotide probe harboring ICB1, they contained a probe binding activity (Fig. 5A). Serum-starved cells (t = 0 h; Fig. 5A, lane 3) contained large amounts of probe binding activity compared with exponentially growing cells (Fig. 5A, lane 2). As cells were stimulated to cell cycle re-entry by serum starvation, the levels of binding activity rapidly decreased, reaching a plateau value in asynchronous cells (Fig. 5A, lane 1). Immobilization of ICB1 was not increased by re-entry. This suggests an important role of ICB1 in S phase-specific induction of the topo IIα gene.
addition (t = 0 h), probe binding activity decreased as cells progressed through the cell cycle (Fig. 5A, lanes 4–9). Most notable are the very reduced levels of probe binding activity in nuclear extracts from cells 12–20 h post-stimulation (Fig. 5, lanes 6–8), when cells were in S phase (Fig. 1A). Twenty-four hours after serum addition, a slight increase in binding activity was observed (Fig. 5A, lane 9), presumably coinciding with entry into mitosis.

To demonstrate that the probe binding activity was dependent on ICB1, a series of EMSA experiments with various competitors were conducted. Nuclear extracts from exponentially growing cells were incubated with labeled ICB1 probe alone or in combination with 100-fold excess of unlabeled ICB1 or mICB1 probe. Coincubation with a probe containing a mutation in ICB1 (mICB1) did not reduce the amount of probe-protein complex (Fig. 5B, lane 4), whereas the ICB1 probe was an efficient competitor when added in 100-fold excess (Fig. 5B, lane 3).

**DISCUSSION**

Cell cycle-dependent regulation of human DNA topo IIα gene expression is controlled both at the transcriptional and post-transcriptional levels. To investigate the transcriptional changes in topo IIα expression during the cell cycle, a panel of NIH/3T3 cell lines stably transfected with luciferase reporter plasmids containing various lengths of the human topo IIα promoter was constructed. The entire population of resistant cells, rather than individual clones, was pooled in order to eliminate unwanted effects due to copy number and site of integration. Initial experiments indicated that this was a feasible approach, as the luciferase activity pattern in synchronized cells mimicked previously observed topo IIα expression patterns (12, 14). Furthermore, the 2–3-fold S phase-specific induction levels observed were comparable with previously reported levels (12–14). Interestingly, transcriptional activation could be blocked in a reversible manner by treatment with the DNA synthesis inhibitor aphidicolin or the CDK inhibitor roscovitine. In contrast, aphidicolin does not interfere with the timing of changes in topo IIα mRNA stability in HeLa cells (12). A similar discrepancy is also observed when cells are heat shocked: topo IIα mRNA stability decreases upon heat shock, whereas the topo IIα promoter
is activated (12, 17). Supposedly, these differences reflect different regulatory mechanisms responsible for controlling topo IIα gene expression at the transcriptional and post-transcriptional levels, respectively.

Experiments with synchronized NIH/3T3 stable transfectants indicated that an ICB situated between bp −90 and −51 in the topo IIα promoter (ICB1) played an important role in the S phase-specific induction of the promoter. Specifically, loss of ICB1 function resulted in abrogation of the S phase-specific induction by prematurely inducing the promoter during the G1 phase of the cell cycle. In addition, EMSA experiments demonstrated a cell cycle-dependent ICB1 binding activity in NIH/3T3 nuclear extracts. Binding to ICB1 was most pronounced in serum-starved cells, and as cells entered S phase, ICB1 binding was markedly decreased. Together, these data suggest a role for ICB1 in transcriptional repression of the topo IIα gene.

The presence of an ICB1 binding activity has been described in several studies (17, 25); however, none of these have addressed its occupation as a function of growth state. Nevertheless, ICB1 has been proposed to mediate repression of topo IIα transcription. In vivo footprint analysis of the human topo IIα promoter revealed that promoter activation by heat shock was accompanied by reduced protein binding to ICB1 (17). Interestingly, ICB1 has previously been associated with p53-mediated repression of the topo IIα promoter (18). The CDK inhibitor p21Waf1/Cip1 is transcriptionally activated by p53 in response to DNA damage, which among other things leads to inhibition of DNA synthesis (reviewed in Ref. 26). Our data suggest that transcriptional activation of the topo IIα gene can be suppressed by inhibition of ongoing DNA synthesis and CDK activity. Thus, p53-mediated repression of the topo IIα promoter may be an indirect effect of DNA synthesis and CDK inhibition as a consequence of p21Waf1/Cip1 activation. This is supported by the fact that the topo IIα promoter does not contain a bona fide p53 binding site.

ICBs are predominantly bound by the transcriptional activator NF-Y (27, 28). However, evidence has accumulated for a more complex role for ICBS, other than mediation of transcriptional activation (reviewed in Ref. 29). For instance, there is now evidence for a more complex role for ICBs, other than mediation of transcriptional activation (reviewed in Ref. 29). For instance, binding to ICB1 was most pronounced in serum-starved cells, and as cells entered S phase, ICB1 binding was markedly decreased. Together, these data suggest a role for ICB1 in transcriptional repression of the topo IIα gene.

In summary, we have shown that the transcriptional induction of the topo IIα gene requires S phase entry, ongoing DNA synthesis, and CDK2 and/or CDK2 activity. Furthermore, we have demonstrated that ICB1 plays an important repressive role in the transcriptional regulation of topo IIα. The challenge now is to identify an ICB1-binding protein complex and delineate the biochemical changes responsible for its differential occupation of ICB1.

Acknowledgments—We are indebted to Dr. David Kroll for his generous gift of gene promoter constructs and to Dr. C Caradelli for supplying NIH/3T3 cells. The technical assistance of Shanne Christianson is highly appreciated.

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