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Cyclin B1 transcription is enhanced by the p300 coactivator and regulated during the cell cycle by a CHR-dependent repression mechanism

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Abstract Cyclin B is a central regulator of transition from the G_2 phase of the cell cycle to mitosis. In mammalian cells two B-type cyclins have been characterised, cyclin B1 and B2. Both are expressed with a maximum in G_2 and their synthesis is mainly regulated on the transcriptional level. We show that a single cell cycle genes homology region, lacking a functional cell cycle-dependent element in tandem with it, contributes most of the cell cycle-dependent transcription from the *cyclin B1* promoter. The coactivator p300 binds to the *cyclin B1* promoter and synergises with the transcription factor NF-Y in activating transcription of *cyclin B1*.

Key words: Cell division cycle; Cancer; Cell cycle-dependent element/cell cycle genes homology region; Cell cycle-dependent transcription; Chromatin immunoprecipitation; Histone acetyltransferase

1. Introduction

Cyclins are central regulators of the cell division cycle. They have been found to associate with cyclin-dependent kinases and thereby modulate their kinase activity [1]. Cyclin B forms a complex with the cdc2 protein kinase (cyclin-dependent kinase 1, cdk1) yielding the maturation-promoting factor (MPF) [2,3]. The MPF complex is essential for the transition from G_2 to mitosis. It functions also in controlling this checkpoint and is conserved in all eukaryotes [4–6].

In mammals two cyclin B forms have been characterised, cyclin B1 and cyclin B2. The function of cyclin B1 cannot be replaced by other proteins since knockout mice for the *cyclin B1* gene die in utero. However, cyclin B2-null mice are viable. Therefore, it seems that cyclin B1 can compensate for loss of cyclin B2, but not vice versa. Although cyclin B2 (−/−) mice appear to be normal, they seem to be less fertile and tend to be slightly smaller [7]. Distinct roles for the different forms of cyclin B have been suggested by their subcellular distribution. While cyclin B1 co-localises with microtubules, cyclin B2 associates with the Golgi apparatus [8]. However, most properties, including timing of their expression, indicate similar functions for the two proteins.

Cyclin protein levels oscillate during the cell cycle. B-type cyclins appear in S phase and accumulate in G_2 and mitosis before disappearing at transition from metaphase to anaphase. Synthesis of cyclin B during the cell cycle is mainly regulated on the transcriptional level [9]. For the *cyclin B2* gene we found that the transcription factor NF-Y is the main activator employing three CCAAT-boxes in the *B2* promoter [10]. Cell cycle-regulated transcription from this promoter is regulated by a cell cycle-dependent element (CDE) and cell cycle genes homology region (CHR) tandem element [11]. We had shown earlier for the transcription of *cdc25C*, *cyclin A* and *cdc2* genes that CDE/CHR elements repress transcription in the early phases of the cell cycle. Relief from this repression later in S and G_2 leads to the expression of these genes [12]. Later during mitosis, degradation by ubiquitin-mediated proteolysis leads to the impressive drop in cyclin B protein levels [9,13,14].

In regard to the *cyclin B1* cell cycle expression, two reports describe opposing results both implicating an E-box in transcriptional regulation of this gene, binding either the upstream stimulatory factor USF or the inhibitor Max [15,16]. In these reports the E-box serves as an activating site in one report or as a repressing element in the other, which is possibly connected to the use of different cellular systems in the two studies. Both reports attribute only about a two-fold regulation between resting and G_2/M cells to this E-box during the cell cycle. Furthermore, the more recent of the two papers concludes that there have to be additional regulatory elements to account for full cell cycle-dependent regulation with the main contribution residing in other parts of the *cyclin B1* promoter [15,16]. Recently, two other studies present evidence that the *cyclin B1* promoter is also subject to activation by c-Myc: binding of c-Myc to the activating E-box could be shown by electrophoretic mobility shift assays and chromatin immunoprecipitation (ChIP) [17,18].

Here, we describe that *cyclin B1* employs a CHR for cell cycle-dependent transcription and that the coactivator and histone acetyltransferase protein p300 enhances activation of *cyclin B1* transcription.

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2. Materials and methods

2.1. Cell culture, transfections and fluorescence-activated cell sorting (FACS) analyses

NIH3T3 cells (DSMZ, Braunschweig, Germany) for cell cycle analyses were cultured and transfected as previously described [19].

Human foreskin fibroblasts (HFF) were cultured in a humidified atmosphere with 10% CO_2 at 37°C with Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% foetal calf serum (FCS, Biochrom, Berlin, Germany). For cell cycle analysis, cells were cultured for 48 h in DMEM without FCS. After this time cells were harvested for 0 h time points. The fibroblasts were stimulated with 20% FCS in DMEM to re-enter the cell cycle and subsequently analysed at indicated time points. FACS analyses were performed as described previously [19].

SaOS-2 cells (DSMZ) were cultured and transfected as described earlier [19,20]. Transfections using the expression plasmids for wild-type p300 (kindly provided by Antonio Giordano) [21], NF-YA, NF-YB and NF-YC [22] were carried out using Fugene 6 (Roche, Mannheim, Germany), according to the manufacturer's suggestions, with 0.8 μg hB1-Luci, 0.016 μg pRL-null vector per assay (Promega, Mannheim, Germany) and increasing amounts of p300 and the three NF-Y subunit-expressing constructs. The total amount of transfected DNA was held constant by adding pcDNA3.1HisC (Invitrogen, Breda, The Netherlands) plasmid. Luciferase assays were done as reported earlier [19].

2.2. RNA extraction and reverse transcription (RT)-PCR analysis

Total RNA extraction from NIH3T3 and HFF cells was carried out with TRIzol Reagent (Invitrogen) as suggested by the manufacturer. Real-time RT-PCR mRNA quantification was done with the Light-Cycler system (Roche). Specific primers for human cyclin B1 5′-AAGAGCTTTAAACTTTGGTCTGGG-3′; 5′-CTTTGTAAGTCCTTGATTTACCATG-3′ (GenBank accession number M25753) and mouse cyclin B1 5′-CAGAGTTCTGAACTTCAGCCTG-3′; 5′-TTGTGAGGCCACAGTTCACCAT-3′ (GenBank accession number X64713) were used at 1 μM with 0.5 mM $MgCl_2$ on 50 ng total RNA template in the QuantiTect SYBR Green RT-PCR mix (Qiagen, Hilden, Germany). The reverse transcriptase reaction was performed at 50°C for 20 min. Each cycle of the subsequent PCR included 15 s denaturation at 94°C, 20 s of primer annealing (55°C) and 15 s of extension/synthesis (72°C). Product quantification was optimal at 78°C. Calculations were carried out as described [23].

2.3. Western blot analysis

Western blots were prepared essentially as previously described [23]. A 1:200 dilution of the mouse monoclonal anti-cyclin B1 antibody (GNS1, Santa Cruz Biotechnology, Santa Cruz, CA, USA) was employed and analysed with Super Signal West Chemiluminescent substrate (Pierce, Perbio Science, Bonn, Germany) according to the manufacturer's instructions. Signals were recorded with a Luminescent Image Analyzer LAS-100 (Fuji, Düsseldorf, Germany). The blot was stripped and reprobed with a 1:5000 dilution of the mouse monoclonal anti-β-actin antibody (clone AC-15, Sigma, Taufkirchen, Germany).

2.4. Cloning of the human cyclin B1 promoter and creation of plasmid constructs

The *cyclin B1*-promoter firefly luciferase reporter construct hB1-Luci was obtained by PCR amplification with the primers B1-for 5′-CGGGTACCGTGACTTCCAGCGCCAGGAGTCTCTATC-3′ and B1-rev 5′-CATGCCATGGCTTCCTCTTCACCAGGCAGCAGCTC-3′ followed by cloning at *Kpn*I/*Nco*I sites into the pGL3-Basic vector (Promega, Mannheim, Germany). Sequencing of the final construct yielded the published sequence [15] (GenBank accession number U22364).

Promoter mutants were created by PCR-based targeted mutagenesis on the basis of hB1-Luci employing the primers CDEmut-for 5′-AGGCCAATAAGGAGGGAGCATTACGGG-3′, CDEmut-rev 5′-TCAGATTTAAACCCCGTAATGCTC-3′, CHRmut-for 5′-GAGGGAGCAGTGCGGGGTGCATATCTG-3′, CHRmut-rev 5′-AGCCAGCCTAGCCTCAGATATGCACCC-3′.

2.5. ChIP assays

ChIPs were carried out guided by a published procedure [24]. NIH3T3 cells were crosslinked with 1% formaldehyde for 18 h after serum restimulation. p300 protein crosslinks were precipitated using 1 μg of rabbit polyclonal anti-p300 antibody (C-20, Santa Cruz Biotechnology). As negative control served a mixture of 0.5 μg mouse monoclonal anti-cyclin B1 antibody (GNS1, Santa Cruz Biotechnology) and 0.5 μg goat polyclonal anti-cyclin B2 antibody (N-20, Santa Cruz Biotechnology). Samples were analysed using Taq DNA Polymerase (Qiagen) according to the manufacturer's suggestions with the following primers: mouse cyclin B1 5′-GACTTGTGCGCAGGCATAGAGC-3′ and 5′-GACACCCTAACCTCTGGCTATC-3′ (GenBank accession number AC112701); mouse α-globin 5′-GGGCAACTGATAAGGATT-3′ and 5′-AGCACCATGGCCACCAATCT-3′ (GenBank accession number X05379). PCR products were run on a 3% agarose gel and stained with SYBR Green (Biozym, Hess. Oldendorf, Germany).

3. Results and discussion

3.1. Cell cycle-dependent expression of cyclin B1

The central characteristic of cyclins is their periodical appearance during the cell division cycle. We tested expression of cyclin B1 during cell division in mouse NIH3T3 cells and HFF on the mRNA and protein level (Fig. 1). Through serum deprivation cells were led into the G_0 phase which is given as the 0 h time point. Addition of serum to the medium stimulated the cells to proceed through the cell cycle. At various time points samples were analysed for mRNA, protein and DNA content per cell. Cyclin B1 mRNA appears when most cells are in G_2/M. Hardly any expression is seen in G_0 cells and when cells go through G_1 and S phases (Fig. 1A,B). When a substantial portion of the NIH3T3 cells enter G_2 after about 18 h of restimulation, the cyclin B1 mRNA concentration strongly increases and accumulates until the time when cells become more asynchronous at about 24 h. In human fibroblasts expression of cyclin B1 mRNA is similar. However, the human cells reach the point at which most cells are in G_2 about 6 h later than the mouse cells (Fig. 1C and data not shown). Cyclin B1 protein is expressed with the same kinetics lagging about 2 h behind the mRNA expression (Fig. 1D). Taken together, these observations show that cyclin B1 is expressed in G_2/M and that the appearance of cyclin B1 protein follows the rise of cyclin B2 mRNA indicating that the regulation of transcription determines the timing of cyclin B1 protein synthesis. These results are similar to the findings seen for the expression of cyclin B2 [11]. Our results are consistent with previous observations where cyclin B1 expression was examined in cells after thymidine or nocodazole block [7,25]. Expression timing detected here is also in agreement with a cyclin B1 function at G_2/M transition.

3.2. Nucleotide sequence conservation of regulatory sites in cyclin B promoters

A comparison of human and mouse *cyclin B1* and *cyclin B2* upstream regulatory regions pinpoints conserved sites (Fig. 2). Although the overall nucleotide identity is low, we find distinct regions of similarity. Most strikingly, the two CCAAT-boxes, which bind to NF-Y trimeric transcription factors, are not only perfectly identical in their nucleotide sequence in all four promoters but also their distances are conserved. In *cyclin B1* the distance of 32 bp and in the *cyclin B2* promoter of 33 bp are constant in both human and mouse promoters (Fig. 2). The functional importance of these NF-Y binding sites as the dominant activating elements has been documented for the mouse *cyclin B2* and human *cyclin B1* promoters [10,26].

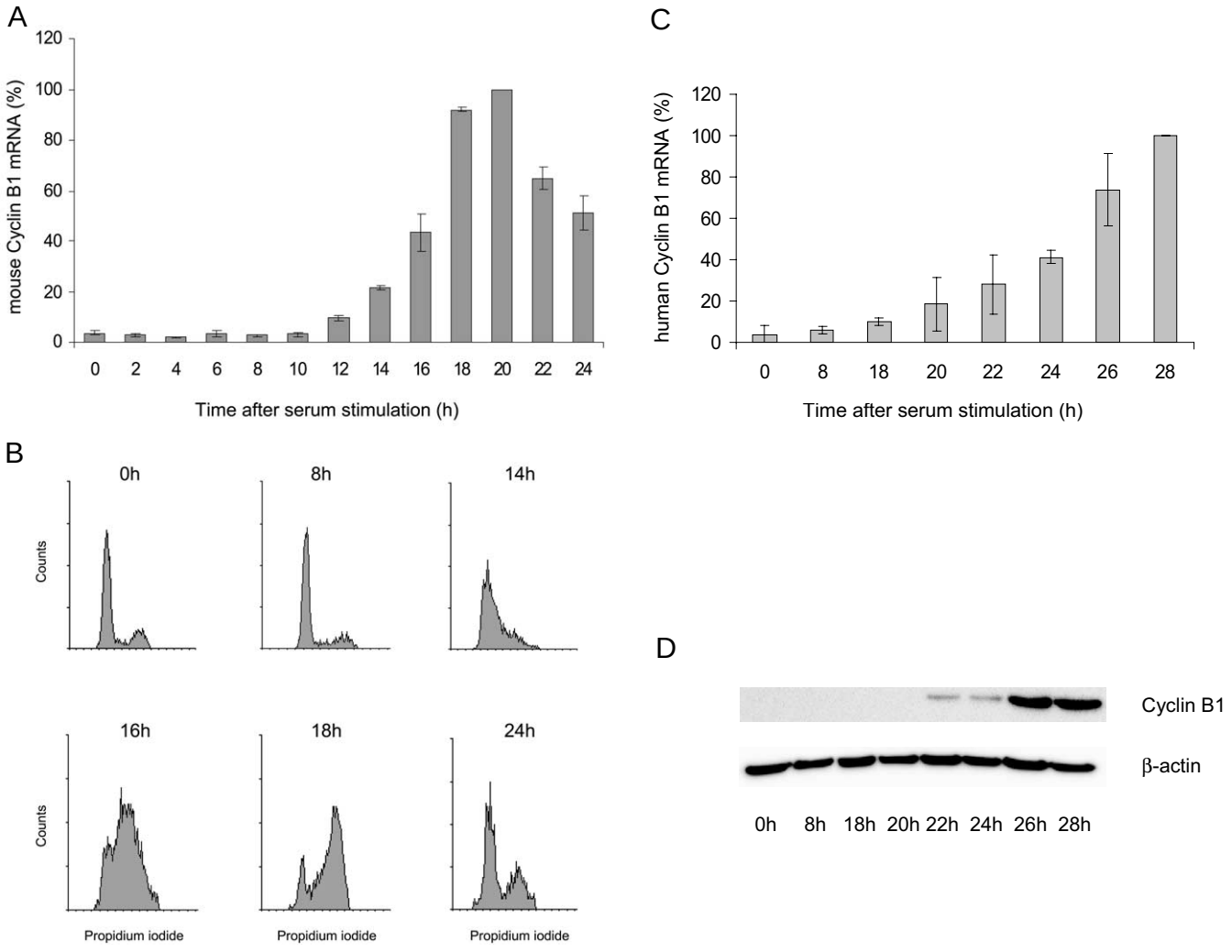

Fig. 1. Cell cycle-dependent expression of chromosomally derived cyclin B1. NIH3T3 mouse fibroblasts and HFF were serum-starved and re-stimulated by addition of serum to the medium. After 48 h of starvation, the 0 h time point represents cells mostly resting in G_0. The following time points give results after serum restimulation. A: Cyclin B1 mRNA expression from NIH3T3 cells as measured by RT-PCR standardised relative to total RNA; averages of two experiments are given. B: FACS analyses of NIH3T3 cell populations at selected time points before and after serum addition. Cells were stained with propidium iodide and measured for DNA staining per cell. C: Expression of cyclin B1 mRNA in HFF cells with total RNA as standard quantified by RT-PCR. Averages of two experiments are given. D: Cyclin B1 protein expression detected by immunoblotting. β-Actin served as a loading control.

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Cyclin B1 human  CTGCAGCTGC CCGAGAGCGC AGGCGCAGAG GCAGACCACG TGAGAGCCTG GCCAGGCCTT  -295
Cyclin B1 mouse  CAGCAATGCG ACTTGTGCGC AGGCATAGAG CCTGACCTCG CGAGGGGTGG GCGGTGCTGC  -282
                                                    E-box

Cyclin B1 human  CCGGCCTAGC CTCACTGTGG CCCCGCCCCT CTCGAACGCC T.........  ....TCGCGC  -248
Cyclin B1 mouse  CAGCGGCAGC CTCGCTCTGG CCCCGCCCCC GCCCCACCCC CGCCGAACTT GGGATCGCGG  -222

Cyclin B1 human  GATCGCCCTG GAAACGCATT CTCTGCGACC GGCAGCCGCC AATGGGAAG. GGAGTGAGTG  -189
Cyclin B1 mouse  GATCGCCCAG GAAACGCATT CTACGGGAAC CCGCGGCGCC AATGGGAAG. AGAGCGAGTG  -163
Cyclin B2 human  TTCAGCCAAT GAGAGTGCGA GAGTGCATCT TGTGTTGGCC AATGAGAACA GCGACCCGTG  -189
Cyclin B2 mouse  GCCAGCCAAT CAACGTGCAG AAAGGCCTTC CAGTCTAGCC AATGGGTTGC GCGGCCCCTG  -145
                       NF-Y1                                 NF-Y2

Cyclin B1 human  CCACGAACAG GCCAATAAGG AGGGAGCAGT GCGGGGTTTA AATC.TGAGG CTAGGCTGGC  -130
Cyclin B1 mouse  CCACGAACTG GCCAATGAGG AGCGAGCGGC CCGGGGTTTA AACCTAAGCC C..GGCAGAC  -105
Cyclin B2 human  CGCAGGGCCG CCCAATGGGG CGCAAGCGAC GCGGTATTTG AATCCTGGAA CAAGGCTACA  -129
Cyclin B2 mouse  CGTGCGTCTA GCCAATAGTG CGTCAGCGGC GCGGTATTTG AATCGCGGAC CG.GGCGGTG  - 86
                          NF-Y3              CDE          CHR
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Fig. 2. Comparison of nucleotide sequences from *cyclin B* promoters. Conserved elements are indicated in bold. CDE, CHR and CCAAT-boxes identified earlier in the *cyclin B2* promoter [10,11] together with the related sites in the *cyclin B1* promoters are boxed. Numbering is relative to the translational start codons.

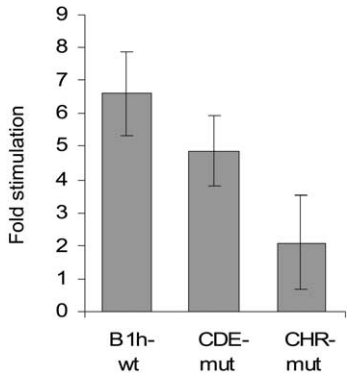

Fig. 3. Expression from a *cyclin B1*-promoter luciferase reporter comparing activity in G_2/M versus resting cells. Mutation of the CHR leads to a loss of cell cycle regulation. Luciferase reporter plasmids carrying the human *cyclin B1* upstream region together with a *Renilla* luciferase-expressing control plasmid were transfected into NIH3T3 fibroblasts. Cells were synchronised by serum starvation for 66 h and restimulated. Ratios of luciferase activities from cell lysates 24 h after restimulation to activities in resting cells are given. Averages with standard deviations from six experiments are shown. *Renilla* luciferase was employed to standardise *cyclin B1* firefly luciferase reporter expression.

It appears that activation by NF-Y through conserved CCAAT-boxes is a general feature of *cyclin B* promoters.

The elements responsible for cell cycle-dependent transcription cannot be delineated so easily. In the case of genes expressed in G_2/M, like *cyclin B2*, a mechanism which includes CDE/CHR elements has been depicted [11,12]. For *cyclin B1* two reports had implicated an E-box in cell cycle regulation of this gene [15,16]. We compared the upstream regions of human to mouse *cyclin B1* genes and found that the E-box region from the human promoter is not conserved in the mouse (Fig. 2). Two essential nucleotides of the 5′-CANNTG-3′ E-box consensus are changed in the respective mouse sequence. Given the sequence-specific requirements of HLH proteins acting on E-boxes, taken together with results on E-box regulation of *cyclin B1* summarised in the introduction, we are tempted to conclude that this element is unlikely to be the only responsible for cell cycle-dependent transcriptional regulation in the *cyclin B1* promoter.

In search for other cell cycle elements the alignment in Fig. 2 yielded some similarity in the CDE/CHR tandem element previously found to regulate cell cycle-dependent transcription in the mouse *cyclin B2* promoter [11]. This region in the *cyclin B1* promoter had been analysed once, but only found irrelevant for the activation by a forkhead transcription factor and not tested for cell cycle relevance [27]. In the CDE region we hardly find any nucleotides which are conserved in all four genes (Fig. 2). However, the CHR is, with the exception of one nucleotide, identical in all four promoters.

3.3. *A new CHR-like site regulates cell cycle-dependent repression of* cyclin B1 *transcription*

In order to elucidate a potential function of these homologous sites for transcriptional regulation of *cyclin B1* expression we tested wild-type and mutant reporter constructs. To this end, we cloned the human *cyclin B1* promoter from the translational start codon up to 1133 bp of the upstream region into the firefly luciferase-expressing reporter plasmid hB1-Luci. A similar construct had previously been shown to confer cell cycle-dependent transcription [28] consistent with the timing seen for expression from the chromosomal gene (Fig. 1). Therefore, such a construct can be employed to assay for cell cycle regulation.

We compared this wild-type construct with mutants in the putative CDE and CHR sites in transfected cells which were serum-starved and restimulated. As a measure for cell cycle regulation of promoter constructs, ratios of luciferase activities from G_2/M to values from G_0 cells were calculated (Fig. 3). In this assay the wild-type *cyclin B1* construct displays a cell cycle stimulation of more than six-fold. The mutation in the putative CDE changes regulation only marginally, which had been observed earlier [28]. However, alteration of the so far untried CHR-like site left only a small remaining regulation of about two-fold (Fig. 3). This loss of regulation is due to an increase of activity in resting cells rather than a further stimulation of transcription in cells in later cell cycle phases (data not shown). The implied loss of repression is a general feature of CHR-dependent regulation and has been observed with all CHRs identified so far. This regulation seen in the *cyclin B1* promoter is resembling that seen in the *cyclin B2* promoter [11,12].

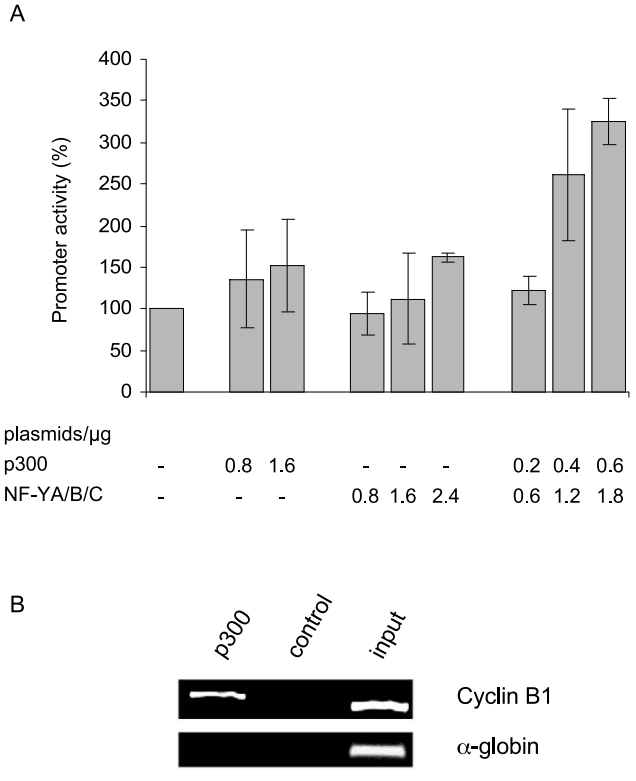

Fig. 4. p300 activates transcription from the *cyclin B1* gene and binds to its promoter. A: Increasing amounts of plasmids expressing the three subunits of NF-Y (A, B and C) and p300 were cotransfected with the *cyclin B1* promoter reporter and a *Renilla* luciferase control plasmid in SaOS-2 cells. The total amount of DNA was held constant in all transfections by adding an irrelevant plasmid. Firefly luciferase was measured and standardised to *Renilla* luciferase activity. Expression from the *cyclin B1* promoter without cotransfection was set at 100%. Assays from three independent experiments with standard deviations are shown. B: ChIP experiments with antibody directed against p300 on the *cyclin B1* promoter. The antibodies used in the control lane were directed against non-DNA binding protein. The *α-globin* gene served as negative control promoter.

Thus, a marked difference between *cyclin B1* and *B2* regulation lies in the function of the CDEs. The region upstream of the CHR described here for the *cyclin B1* promoter plays hardly any role in cell cycle-dependent transcription. Cell cycle regulation resides mostly in a novel CHR (Figs. 2 and 3). A variable contribution of the CDE in CDE/CHR tandem elements has been observed since the first description of this regulatory mechanism. In our original paper, cell cycle regulation of *cyclin A*, *cdc2* and human *cdc25C* promoters was based equally on intact CDE and CHR sites [12]. In the mouse *cyclin B2* promoter contribution of the CHR was more pronounced than that of the CDE [11]. Recently, we discovered a CHR in the mouse *cdc25C* promoter which does not require a CDE in conjunction with the CHR [19]. Taken together, we demonstrate that a novel CHR with the sequence 5′-TTTAAA-3′, which is different from the previously established consensus of 5′-TTTGAA-3′, has a central role in cell cycle-dependent transcription of the *cyclin B1* promoter.

3.4. *The coactivator p300 stimulates* cyclin B1 *transcription and binds to its promoter*

The members of the p300/CBP protein family, which display histone acetyltransferase activity, had been shown to be coactivators in many growth-related systems [29]. Since cyclin B1 is important for growth control, we wondered if these coactivators can function in transcriptional activation of the *cyclin B1* gene. We cotransfected the wild-type *cyclin B1* reporter with increasing amounts of a plasmid expressing p300 (Fig. 4A). A modest increase in reporter activity is observed. In parallel, assays were carried out in which the three subunits making up the NF-Y transcription factor were tested. Increasing expression of NF-Y leads to a similar increase of transcription from the *cyclin B1* promoter. The third part of the experiment combines the lower plasmid amount transfections of p300 and NF-Y in one series of cotransfections. At the highest plasmid quantity, which is still smaller than what could be used for p300 and NF-Y individually, stimulation over the control without cotransfection is more than threefold. Considering the limitation in the total amount of DNA, which could be cotransfected when combinations of NF-Y- and p300-expressing plasmids were used, it appears that NF-Y and p300 synergise in the activation of the *cyclin B1* promoter (Fig. 4A).

To test for in vivo protein binding of p300 to the promoter we performed ChIP assays. Employing the DNA fragment carrying the conserved CCAAT-boxes in ChIPs yielded a signal for p300 on the *cyclin B1* promoter (Fig. 4B).

In summary, our experiments indicate a single CHR site to contribute most to the cell cycle-dependent transcription of the *cyclin B1* promoter. Furthermore, the coactivator p300 binds to the promoter and synergises with NF-Y in the activation of *cyclin B1* transcription.

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