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Cloning and characterization of the mouse JDP2 gene promoter reveal negative regulation by p53

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ABSTRACT

Jun dimerization protein 2 (JDP2) is a repressor of transcription factor AP-1. To investigate the transcriptional regulation of the JDP2 gene, we cloned the 5′-flanking region of the mouse JDP2 gene. Primer extension analysis revealed a new transcription start site (+1). Promoter analysis showed that the region from nt −343 to nt +177 contains basal transcriptional activity. Interestingly, the tumor suppressor p53 significantly repressed the transcriptional activity of the JDP2 promoter. Given that JDP2 inhibits expression of p53, our results suggest a negative feedback loop between JDP2 and p53, and a direct link between JDP2 and a key oncogenic pathway.

1. Introduction

The mammalian activating protein-1 (AP-1) proteins are homodimers or heterodimers composed of basic region-leucine zipper (bZIP) proteins that belong to the Jun (c-Jun, Jun B, and Jun D), Fos (c-Fos, Fos B, Fra-1, and Fra-2), and the closely related activating transcription factor (ATF2, LRF1/ATF3, and B-ATF) subfamilies [1]. Jun dimerization protein 2 (JDP2) was initially isolated based on its ability to interact with the c-Jun bZIP domain [1]. JDP2 can homodimerize or heterodimerize with other Jun family members and with ATF2, but not with c-Fos [1–4]. As a transcription factor, JDP2 binds both the TPA response element and cAMP response element to counteract an AP-1 activity [1,3]. Therefore, JDP2 functions as an AP-1 repressor to inhibit the AP-1 targeting gene expression.

JDP2 plays critical roles in many cellular processes including differentiation, apoptosis, antioxidant processes, senescence, cell cycle, and aging [5,6]. The role of JDP2 in tumor development is complex. Several studies have shown that JDP2 regulates of several key cancer-related genes including p53 [5,7–11]. JDP2 exerts its inhibitory role in ultraviolet-induced apoptosis by downregulating p53 [12]. The repression of p53 induction by JDP2 is mediated via an AP-1-like site in the p53 promoter, which differs from the consensus AP-1 site by a single base pair substitution. This motif, termed PF-1, also modulates p53 promoter activity in response to serum growth factors and can confer transcriptional repression on a heterologous promoter. Van der Weyden et al. recently reported that JDP2 transcriptionally downregulates the p53 promoter via an atypical AP-1 site and that JDP2 negatively regulates p53 transcription to promote mouse leukemogenesis in the context of p53 heterozygosity [10].

We have reported that JDP2 expression is downregulated in pancreatic carcinoma [13] and that JDP2 inhibits the epithelial-to-mesenchymal transition (EMT) in pancreatic cells [7,14], suggesting that JDP2 acts as a tumor suppressor. Heinrich et al. found that JDP2 inhibits Ras-induced transformation of NIH3T3 cells and represses formation of tumor xenografts of prostate cancer cells in mice [15]. However, virus insertional mutagenesis analysis has identified JDP2 as an oncogene in mouse lymphoma. JDP2-transgenic mice display potentiation of liver cancer [16–18]. In either case, it is important to determine how JDP2 expression is regulated.

In this study, we have cloned the genomic DNA which contained the mouse JDP2 promoter and characterized its JDP2 promoter region. We show that p53 represses the activity of a reporter gene whose transcription is driven by the 5′-regulatory region of the JDP2 gene, suggesting a negative feedback link between JDP2 and p53 tumor suppression.

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2. Materials and methods

2.1. Isolation of murine JDP2 genomic clones and sequence analysis

A 129/SvJ mouse liver-derived genomic library, constructed in a lambda FIX II vector (Stratagene, La Jolla, CA, USA), was screened with the full-length cDNA of murine JDP2 (accession number NM-030807) as a probe. The probe was labeled using a Random Primer DNA labeling kit (F. Hoffman-La Roche Ltd., Basel, Switzerland). Two positive clones (#12 and #17) were isolated from 10^6 plaques and confirmed by Southern hybridization. Southern blotting was performed as described previously [3]. Both clones were digested with *Not*I to release their inserts and then subcloned into the pBluescript II KS vector (Stratagene). Mapping and sequencing demonstrated that only the 5′-flanking region, noncoding exon 1, and most of intron 1 were included in both lambda phage clones.

2.2. Primer extension assays

A JDP2-specific antisense oligonucleotide (5′-CTGATGTGCCT GACGGGATC-3′) complementary to nucleotide (nt) 80–99 of the previously published cDNA sequence [3] was used as the primer. Full details are provided in the Supplementary data.

2.3. Plasmids

The reporter constructs were made using a promoterless *Firefly* luciferase reporter vector pGL3-basic (Promega, Madison, WI, USA). A 4.4 kb fragment obtained from phage clone #12 was subcloned into the *Bgl*II site of the pGL3-basic vector, generating the pGL3−4400/+177 vector. Six deletion constructs were produced by digestion of the pGL3−4400/+177 plasmid with the restriction enzymes *Xho*I (pGL3−3600/+177), *Sac*I (pGL3−1192/+177), and *Sma*I (pGL3−1192/+177Δ−921/−343 and pGL3−343/+177) followed by self-ligation. Two other deletion constructs (pGL3−896/+177 and pGL3−491/+177) were generated in two steps. pGL3−1192/+177 was originally digested with *Bam*HI and partially with *Not*I, and the resulting two fragments were ligated into the *Bam*HI–*Not*I site of the pBluescript II KS. Both of fragments were cut out again with *Sac*I and *Bam*HI, and were then ligated into the *Sac*I–*Bgl*II site of the pGL3-basic vector. pGL3−557/+177 was constructed using a PCR-based method. The primers mJDP2-PF4 (5′-TAGCTAGCTATATAGCCGGGGCTAATGC-3′) and J3R (5′-CTGA TGTGCCTGACGGGATC-3′) were used to amplify the desired fragment. The PCR products were then digested with *Nhe*I and *Bam*HI, and then ligated to the pGL3-basic vector that had been digested with *Nhe*I and *Bgl*II. All resulting constructs were confirmed by sequencing analysis. The expression vectors for the wild-type p53 (pCAG-wt-p53) and a mutant p53 (pCAG-MTp53 R273H) were constructed as described elsewhere [19].

2.4. Cells

F9 mouse teratocarcinoma cells were maintained in Dulbecco's modified Eagle's medium with 10% fetal bovine serum (FBS) (Life Technologies). H358 non-small-cell lung carcinoma cells with a p53-null mutation were cultured in RPMI 1640 medium with 10% FBS. HCT116 colon adenocarcinoma cells, which were wild type and homozygous for disruption of the p53 gene, were kindly provided by Dr. Bert Vogelstein (John Hopkins University, USA) and grown in McCoy's 5A modified medium supplemented with 10% FBS (Life Technologies).

2.5. Transfection and luciferase assays

The cells were transiently transfected in six-well plates at 50–80% confluence with Lipofectamine^{2000} reagent (Life Technologies) according to the manufacturer's protocol. Luciferase activities in cell lysates were measured using the Dual Luciferase Assay system (Promega). A *Renilla* luciferase expression plasmid, pRL-TK, was used as an internal control of transfection efficiency. The values of *Firefly* luciferase in each samples were normalized by that of *Renilla* luciferase in order to obtain the relative luciferase activity. The results were presented as fold inductions, which was calculated by dividing, the normalized relative luciferase activity in transfected cells compared with that of the control cells.

3. Results

3.1. Isolation and sequence analysis of 5′-upstream region of murine JDP2 in genomic clones

To analyze the transcriptional regulation of JDP2, we cloned 5′-upstream of the JDP2 gene by screening the recombinant lambda phages from a mouse strain 129/SvJ genomic library using JDP2 cDNA as a probe. Two positive clones (Clones #12 and #17) were isolated by the screening, and both clones contained the JDP2 sequence as confirmed by Southern blot analysis (Fig. 1A). Further sequence analysis indicated that the insert of clone #17 (∼12 kb in length) overlapped completely with that of clone #12 (∼15 kb in length) (Fig. 1B). We used clone #12 to characterize further the genomic structure of the JDP2 gene. We obtained an 11 kb genomic sequence from clone #12 by sequencing. A comparison of the obtained 11 kb sequence with the nucleotide sequence of JDP2 cDNA showed that only the first 115 bp sequence, immediately upstream of the start codon of JDP2 cDNA, was included in this genomic sequence (Fig. 1B). Next, we performed a BLAST search with the full-length sequence of clone #12 in the mouse genome database. Our search results revealed that the genomic sequence we cloned contained the 5′-upstream region, noncoding exon 1, and most of intron 1 of the JDP2 gene (Fig. 1B).

3.2. Mapping of the transcription initiation site by primer extension

The transcription initiation site(s) of the murine JDP2 gene were defined by primer extension analysis performed with an end-labeled synthetic oligonucleotide complementary to bases 80–99 of the 5′-untranslated region (UTR) present in the JDP2 cDNA. In the presence of total RNA isolated from F9 cells, several extended products were observed. None of these bands was detectable in the control lane containing the yeast tRNA (data not shown). The major fragment corresponded to a major transcription initiation site located 95 bp upstream of the first nucleotide of previously published JDP cDNA [3]. This was defined as nucleotide +1 of JDP2 mRNA. The exact position of the new transcription start site with respect to the sequence of the JDP2 5′-UTR region is indicated in Fig. 2B.

We were unable to find the typical putative promoter elements that include a TATA box, CCAAT box, or GC-box within the upstream region of the major transcription initiation site. However, computer analysis revealed that this region contained a high GC content and multiple putative regulatory elements (Fig. 2B). Some TATA-less core promoters contain an initiator (Inr) and downstream promoter element (DPE) [20,21]. The general sequences of the Inr and DPE are YYANWYY (C/T C/T A N A/T C/T C/T) and RGWYV(T) (A/G G A/T C/T A/C/G (T)), respectively. Fig. 2B shows an Inr around the +1 site and a DPE sequence downstream from the transcription start site. These data suggest that the +1 site corresponding to position 85,599,923 on mouse chromosome 12 is very likely a novel transcription start site of the JDP2 gene with a core promoter structure around it.

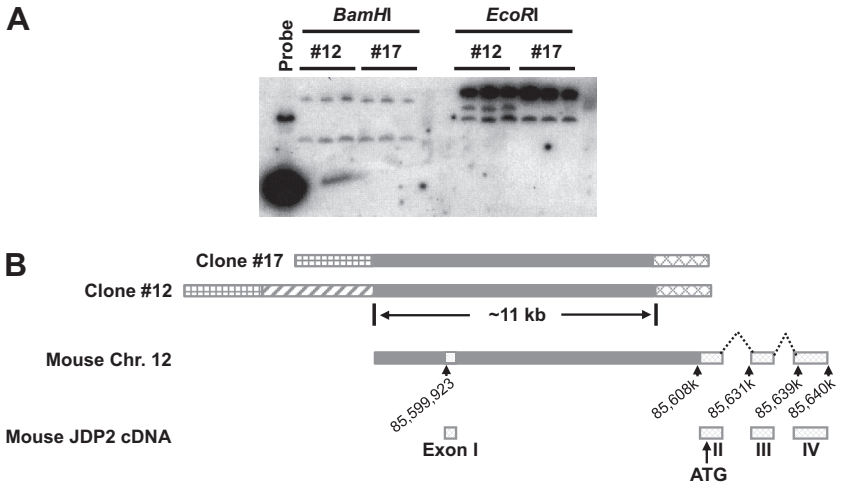

Fig. 1. Isolation of murine JDP2 genomic clones. (A) A 129/SvJ mouse liver-derived genomic library was screened with the full-length cDNA of murine JDP2 as a probe. Two positive clones (#12 and #17) were isolated and confirmed by Southern blotting. (B) The inserts from both clones were released by digestion, subcloned into the pBluescript II KS vector, and sequenced. Mapping and sequencing demonstrated that the 5′-flanking region (crossed box), noncoding exon 1, and most of intron 1 of the JDP2 gene were included in the 11-kb insert (hatched box). The genomic locations of each exon in mouse chromosome 12 are presented (Exon I, II, III and IV). Exons (light gray boxes) and the 1st intron (gray box) were indicated. The location of the newly identified transcription initiation site (85,599,923) is shown.

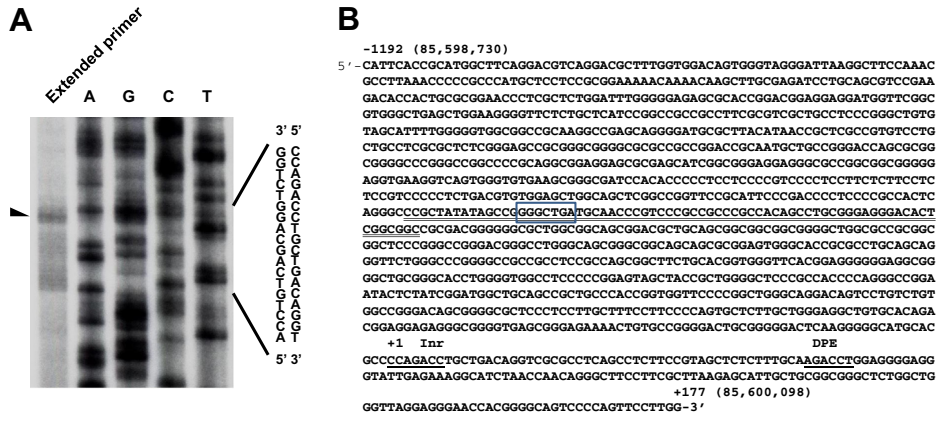

Fig. 2. Identification of the new transcription initiation site. (A) Primer extension assays were performed using total RNA isolated from F9 cells and an end-labeled JDP2-specific antisense oligonucleotide. The extension products were separated on a polyacrylamide gel, dried and subjected to autoradiography. A genomic sequencing ladder was created with the same primer to identify the genomic location of transcription initiation site (arrow). (B) The nucleotide sequence of the 5′-upstream region of the mouse JDP2 gene. The numbers represent the nucleotide position relative to the newly identified transcription initiation site (+1). The initiator sequence (Inr) and downstream promoter element (DPE), the sequences frequently seen within TATA-less core promoters, are underlined. The p53-responsive region is double underlined. The putative p53-binding site is boxed.

3.3. Identification of the JDP2 gene promoter region

To identify the promoter region, we subcloned the JDP2 5′-upstream promoter sequence (−4.4 kb to +177 bp) and a series of deleted sequences into the upstream of a firefly luciferase reporter gene in a pGL3-basic vector (Fig. 3). All the constructs were transiently transfected into F9 cells, and a dual luciferase assay was performed 24 h after transfection. Transfection of the −4400/+177 and −3800/+177 constructs resulted in a 7.5- and 11-fold increases in luciferase activity, respectively, compared with the promoter-less pGL3-basic construct, whereas the −1192/+177 construct increased luciferase expression by about 15-fold (Fig. 3A). These finding suggest that the promoter region lies between −1192 and +177 and that the region between −4400 and −1192 may contain negative regulatory element(s). Moreover, the luciferase activities of pGL3−896/+177 and pGL3−557/+177 were 29- and 15-fold, respectively, compared with the empty vector pGL3-basic. These results indicate the presence of negative and positive regulatory elements in the −896/−557 sequence and the −1192/−896 sequence, respectively. Further deletions to −491 and −343 decreased the luciferase activity. However, a 3.5-fold increase in luciferase activity was observed when the deletion was extended to −343. Thus, the basal promoter activity resides in the −343 to +177 region, which lacks the TATA sequence but contains the Inr and DPE core promoter structure.

Yao et al. recently reported that the sequence −261 to +54 of the JDP2 gene, which corresponds to −767 to −452 in our study, is required for the basal promoter activity of the JDP2 gene [22]. This region contains another transcription start site located 507 bp upstream from +1, as shown in Fig. 2B. In agreement with this report, deletion of the sequence between −921 and −343 in the pGL3−1192/+177 construct markedly reduced the luciferase expression (Fig. 3C). Moreover, the 3′-deleted construct pGL3−557/−302 showed full promoter activity (Fig. 3C), indicating that the region between −557 and −452 contains a promoter, that is independent of the promoter located between −343 and +177. Importantly, the pGL3−1192/+177−921/−343 construct retained luciferase expression, which was about 2.5-fold higher compared

with the control expression, supporting that idea that a basal promoter region lies between −343 and +177.

3.4. Transcriptional repression of the JDP2 promoter by p53

To identify transcription factors that might regulate JDP2 transcription, we searched putative transcription factor-binding sites within the sequence −1192 to +177 using PROMO software. Interestingly, multiple potential p53-binding sites were observed in 5′-upstream promoter region. To determine whether p53 plays a role in JDP2 gene regulation, we assessed H358 non-small-cell lung carcinoma cells with a p53-null mutation and HCT116 colon adenocarcinoma cells homozygous for disruptions of the p53 gene. Both cell lines were transiently transfected with the full-length JDP2 promoter construct (pGL3−1192/+177) and a wt-p53 cDNA expression vector. As shown in Fig. 4A. wt-p53 reduced the activity of the JDP2 promoter by 6–7-fold in H358 cells. A similar level of repression by p53 was observed in the HCT116 p53-null cells (Fig. 4A, right panel). In the same experiments, a mutant p53, p53R273H, also inhibited the JDP2 promoter activity to some extent, although the level of repression was weaker than that by wt-p53 in both cell lines. In addition, with increasing amounts of the wt-p53 expression vector, a dose-dependent decrease in JDP2 promoter activity was observed in both cell lines (Fig. 4B). Thus, we conclude that p53 represses the activity of the JDP2 promoter.

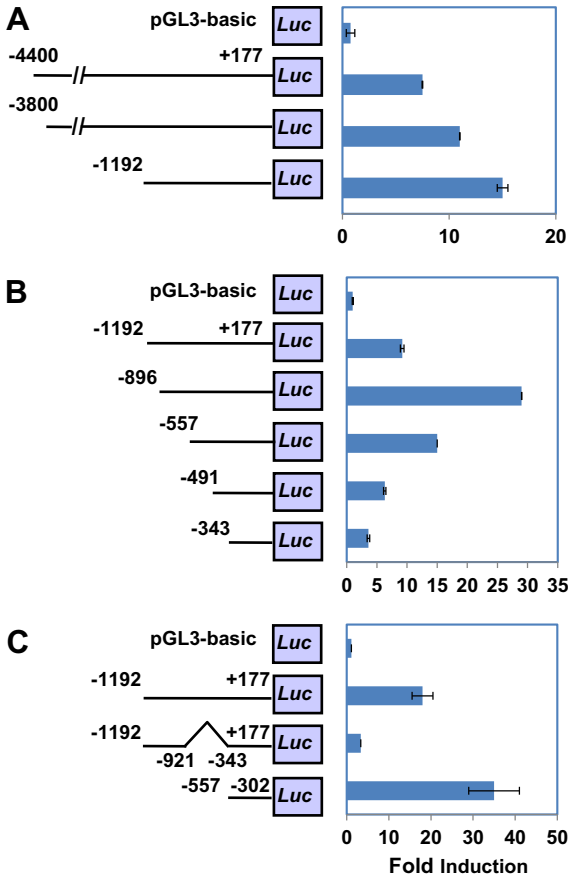

Fig. 3. Characterization of the JDP2 gene promoter region. (A) pGL3-basic and JDP2 5′-upstream region constructs (−4400/+177, −3600/+177, and −1192/+177) containing the luciferase gene were prepared and used in luciferase assays in F9 cells. (B) A series of sequential deletions were constructed and transfected into F9 cells. Luciferase assays were performed to identify the JDP2 basal promoter. (C) Confirmation of another JDP2 promoter recently identified. The bar graph shows the relative levels of luciferase activity. The luciferase activity of pGL3-basic was set to 1. The data shown are the mean ± SD from luciferase assays performed in triplicate.

3.5. Identification of the p53-responsive region within the JDP2 promoter

To identify the p53-responsive region within the JDP2 promoter, we cotransfected the pGL3−557/−302 construct with the wt-p53 expression vector or empty vector into HCT116 colon adenocarcinoma cells. The pGL3−557/−302 construct contains a previously identified strong promoter [22] (Fig. 3C). As shown in Fig. 4C, the luciferase activity of pGL3−557/−302 was markedly decreased by the ectopic expression of wt-p53 but not by expression of the empty vector, indicating that the wt-p53 responsive element lies between −557 and −302. To identify the minimal p53-responsive region, we made a series of further deletion mutations and transfected them into HCT116 cells. Wt-p53 significantly inhibited luciferase expression when deletion mutants pGL3Δ−486/−421, pGLSΔ−462/−384, and pGL3Δ−445/−326 were used, suggesting that the sequence between −486 and −326 is not required for wt-p53 reaction. Thus, the essential p53-responsive region may be located between −557 and −486 or between −326 and −302. A putative p53-binding site in the −550/−540 bp region was identified by prediction of transcription factor binding by PROMO software (Fig. 2B), suggesting that the essential p53-responsive region may lie between −557 and −486.

4. Discussion

We identified and characterized the basal promoter for the mouse JDP2 gene located between nt −343 and +177. We found that the region between nt −557 and −452 also shows promoter activity, which is consistent with a very recent observation by Yao et al. [22]. It has been demonstrated that the start site selection within many mouse core promoters varies between tissues [23]. Thus, multiple transcription initiation sites might contribute to the various transcripts of the JDP2 gene found in a number of different mouse tissues [3]. We identified this new site from embryonic carcinoma F9 cells. Multiple transcription initiation sites could be used to fine-tune JDP2 function at different developmental stages. In agreement with this hypothesis, a UCSC browser search showed high levels of histone H3 lysine 4 trimethylation, a marker of an active promoter, around the new transcription initiation site in embryo cells but not in other types of cells tested, supporting the idea that multiple initiation sites are used for tissue-specific expression of this gene.

Here, we found that wt-p53 repressed the JDP2 promoter in both H358 and HCT116 p53-null cell lines (Fig. 4). Other studies have shown that expression of wt-p53 reduces the activity of a variety of promoters, including those of the Fos, c-Jun genes [24]. Thus, p53 seems to display a broad type of repression of the promoters of AP-1 members including JDP2. The significance of the downregulation by p53 of these molecules with distinct functions deserves further investigation. In this study, we also found that mutant p53 resulted in the repression of the JDP2 promoter activity. One possible reason is that the mutant that we used contains only one point mutation in the DNA binding domain (R273H) of p53. Because some studies have shown that the transcriptional repression by p53 is also related to the other functional portions of p53 in addition to the DNA-binding domain, the R273H mutation could not completely abolish the function of transcriptional repression by p53. There is growing evidence that mutant p53s have gained functions that promote malignant progression [24–27]. The repression of JDP2 expression, a general inhibitor of AP1, may represent one gain of function of the R273H p53 mutant. We reported that JDP2 represses epithelial–mesenchymal transition (EMT) in pancreatic cells [7,13,14]. Intriguingly, Zhang et al. reported that EMT markers are highly induced by the ectopic

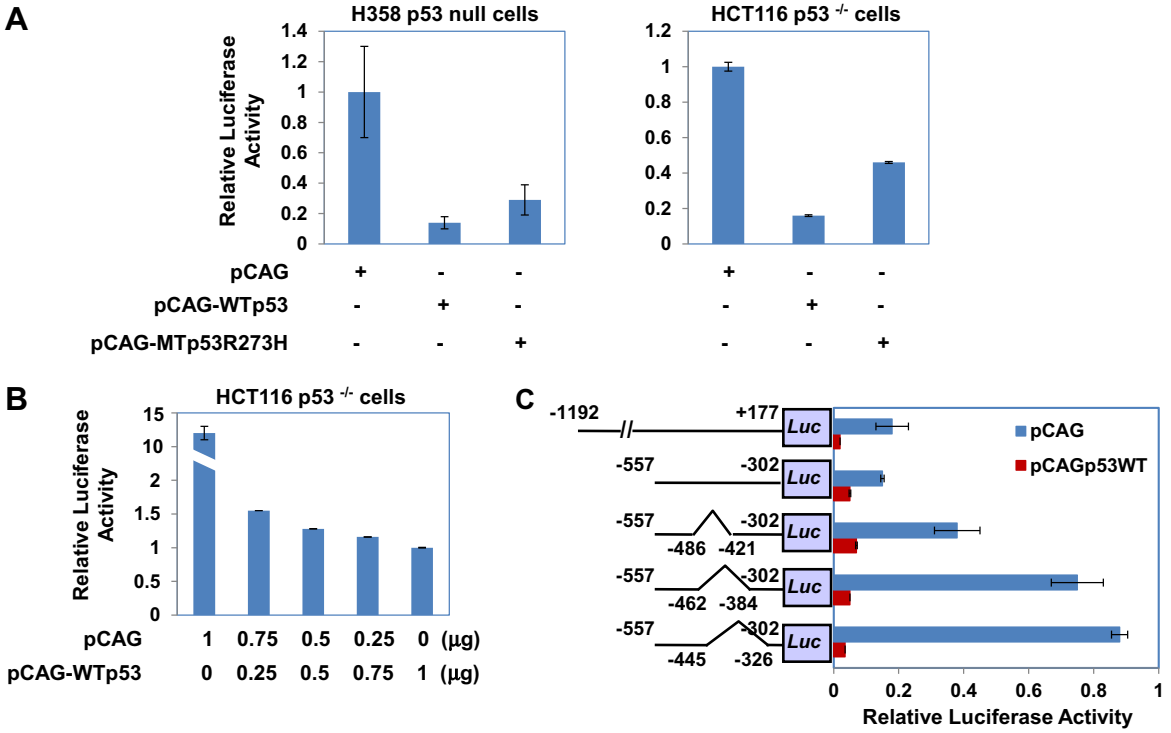

Fig. 4. Regulation of the JDP2 gene promoter by p53. (A) pGL3−1172/+177 was cotransfected with the pCAG empty vector, wt-p53 or p53R273H mutant plasmid into two different p53-null cell lines, and luciferase expression was measured. The bar graph shows the relative levels of luciferase activity normalized to empty vector control. The data shown are the mean ± SD from luciferase assays performed in triplicate. (B) Dose-dependent repression of the JDP2 promoter activity by wt-p53. Increasing amounts of wt-p53 plasmid was cotransfected with the pGL3−1192/+177 luciferase reporter gene into HCT116 p53 null cells, and luciferase assays were performed in triplicate. The data shown are the mean ± SD. (C) Identification of the p53-responsive region. The JDP2 promoter reporter (−1192/+177 and −557/−302) and different internally deleted promoters as indicated (−557/−302) were used to transfect F9 cells. The blue bars represent luciferase expression in the control (empty vector) cells. The red bars indicate luciferase expression in wt-p53-transfected cells. Luc; luciferase. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

expression of the R273H p53 mutant [27], suggesting that inhibition of JDP2 expression may contribute to the p53 mutant gain of function such as during the EMT. It would be interesting to determine whether other p53 mutants also downregulate JDP2 expression and, if so, what impact these p53 mutants have on the EMT.

Unlike the activation of gene expression, the mechanism of repression by wt-p53 is not well defined, and p53 has been shown to repress transcription by different mechanisms [28]. These mechanisms include: (1) binding of p53 to TATA-binding proteins; (2) recruitment of mSin3a and histone deacetylases by p53 to the gene promoter; (3) sequence-specific DNA binding of p53 to the consensus sequence present in the regulatory region of genes; and (4) interactions of p53 with other *cis*-acting elements, including SP-1, CCAAT, and AP-1. The 5′-flanking sequence of the JDP2 gene is TATA-less and contains potential p53-binding sites and several SP-1 binding sites. In the future, we will determine which motif within the JDP2 promoter is responsible for the regulation of JDP2 transcription by p53.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2014.07.034.

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