

# Does not *hUTP14a* promoter form a regulation feedback loop with P53?

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**Objective:** We previously found that hUTP14a binds P53 and promotes P53 degradation. However, if *hUTP14a* is a downstream gene of P53 remains to be determined. This study aimed to identify the promoter of *hUTP14a* and investigate if *hUTP14a* is regulated by P53.

**Methods:** The *hUTP14a* promoter region was cloned into pGL3-Basic-luciferase reporter plasmid to get pGL3-hUTP14a-luc. The reporter plasmid was transfected into 293T cells and luciferase activity was evaluated by the Dual-Luciferase Reporter Assay System. Putative transcription factors were identified through searching MatInspector Professional and Algorismica i Genetica databases. Either pGL3-hUTP14a-luc or *p21* promoter reporter plasmid was co-transfected with increasing dose of *p53* plasmid, and luciferase activity was evaluated. A series of deletion constructs of pGL3-hUTP14a-luc were constructed and minimal promoter region of *hUTP14a* was determined. Differences of the luciferase activities between different groups were assessed by statistical analysis.

**Results:** The *hUTP14a* gene promoter reporter construct was correctly cloned and was demonstrated to possess promoter activity. The transcription of *hUTP14a* was not regulated by P53. The minimal promoter region of *hUTP14a* gene is located between -203 to -100 of the transcription initiation site.

**Conclusion:** Unlike other P53-interacting proteins such as MDM2, Pirh2 and Cop I which promote P53 degradation and whose transcriptions are regulated by P53, does not hUTP14a transcription form a regulation feedback loop with P53.

**Keywords:** hUTP14a; luciferase activity; promoter; P53; transcription factor

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## Introduction

The U3 proteins (U Three Proteins, UTPs) are found to be part of a large ribonucleoprotein (RNP) complex containing the U3 snoRNA (1) and are part of the active pre-rRNA processing complex. This large RNP complex has been termed the small subunit (SSU) processome (1). We previously identified a member of UTP family, the human UTP14a (hUTP14a) by demonstrating that hUTP14a is nucleolar, associated with U3 small nucleolar RNA, and that knockdown of hUTP14a inhibits 18S rRNA processing (2). In the same study, we also found that

hUTP14a caused protein degradation of P53 (2).

P53 is a tumor suppressor protein, which is encoded by the *TP53* gene in humans (3-5). The tumor suppressor P53 is mutated in more than 50% of human cancers (6,7). P53 acts as a transcription factor, which can promote cell cycle arrest, apoptosis and senescence via regulating the expression of various downstream genes (8-10). Thus, it is of great importance to keep this protein under tight control. Under normal, non-stressed conditions, P53 is an unstable protein with a short half-life ranging from 5 to 30 min, which is maintained at low level through its predominant

regulator the mouse double minute 2 protein (MDM2, or HDM2 for the human ortholog) (11-13). MDM2 is an E3 ligase and promotes P53 degradation through a ubiquitin dependent pathway (14). MDM2 transcription is negatively regulated by P53 and thus MDM2 and P53 forms an autoregulatory negative feedback loop (15). Moreover, several other E3 ligases have been identified, such as P53-induced RING-H2 protein (Pirh2) (16), constitutively photomorphogenic 1 (COP1) (17), and ARF binding protein 1 (ARF-BP1) (18). Among them, P53 activates Pirh2 and COP1 transcription in stressed cells, thus P53 forms a regulation loop with these two P53 E3 ligases, while the transcription of ARF-BP1 is not regulated by P53 (19).

We found that *hUTP14a* is up-regulated in various types of human cancer tissues (our unpublished data) suggesting that *hUTP14* protein might function as an oncogene and play a significant role in tumorigenesis. We thereafter wanted to know if *hUTP14a* forms a regulation loop with P53 as MDM2 does. To address this issue, we set out to investigate if the transcription of *hUTP14a* is regulated by P53.

In this study, we defined the promoter of *hUTP14a* gene and explored the role of P53 on regulating the *hUTP14a* promoter. These findings will help us to understand the fundamental molecular mechanisms by which *hUTP14a* functions in the tumorigenesis.

## Materials and methods

### Bioinformatics

The transcriptional initiation site was identified using the NCBI (<http://www.ncbi.nlm.nih.gov/mapview/>) and UCSC Genome (<http://genome.ucsc.edu/>) bioinformatics analysis. Potential binding sites of transcription factors within the promoter region of *hUTP14a* gene were performed with MatInspector Professional ([http://genomatix.de/cgi-bin/matinspector\\_prof/mat\\_fam.pl](http://genomatix.de/cgi-bin/matinspector_prof/mat_fam.pl)) and Algorismica i Genetica ([http://algggen.lsi.upc.es/cgi-bin/promo\\_v3/promo/](http://algggen.lsi.upc.es/cgi-bin/promo_v3/promo/)) web softwares.

### Cloning of *hUTP14a* promoter reporter vectors

To obtain the 2,422 bp putative *hUTP14a* promoter region, a polymerase chain reaction (PCR) on human genomic DNA was performed in a 50 uL reaction mixture. The oligonucleotide sequences of the primers used in the PCR are as following: F-1: 5'-CTAGGAAGCAATGGGACA-3',

R-1: 5'-GGCTGGATCGCGGAAAATA-3'. After an initial denaturation step at 94 °C for 5 min, the PCR was carried out for 35 cycles at 94 °C for 15 s, 60 °C for 30 s, and 68 °C for 2 min 30 s, with a final extension at 68 °C for 10 min. The PCR product was purified with glass milk and cloned into pGL3-Basic reporter vector (Promega, Madison, WI) at the *Nhe I/Hind III* sites. The constructed plasmid pGL3-*hUTP14a*-luc was verified by DNA sequencing.

Series deletion mutants of *hUTP14a* promoter were cloned into the pGL3-Basic vector by PCR-cloning as described above to get the following plasmids: pGL3-*hUTP14a*(-1400/+173)-luc, pGL3-*hUTP14a*(-745/+173)-luc, pGL3-*hUTP14a*(-320/+173)-luc, pGL3-*hUTP14a*(-203/+173)-luc, pGL3-*hUTP14a*(-100/+173)-luc and pGL3-*hUTP14a*(-17/+173)-luc. The oligonucleotide sequences used as primers in the PCRs are listed in *Table 1*. The constructed plasmids were verified by DNA sequencing.

### Cell culture, transient transfection and luciferase assay

U2OS and 293T cells were obtained from the American Type Culture Collection (ATCC) and were grown in Dulbecco Modified Eagle Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS) according to the instructions of the ATCC. Cells were incubated in a humidified atmosphere with 5% CO<sub>2</sub> at 37 °C.

Transfections were performed with Lipofectamine<sup>TM</sup> 2000 Reagent (Invitrogen) according to the manufacturer's instructions. 293T cells were seeded at a density of 1×10<sup>5</sup> cells per well in a 24-well plate before transfection. Cells were transfected with various *hUTP14a* promoter constructs or pGL3-basic control plasmid, and a *Renilla* luciferase control reporter vector (Promega) was used for normalizing transfection efficiency. After 24 h of transfection, the cells were harvested in 100 uL of Passive Lysis Buffer (Promega) and luciferase activity was assayed using the Dual-Luciferase Reporter Assay System (Promega) using Berthold luminometer (Berthold, Wildbad, Germany) according to the manufacturer's recommendations. Data were presented as relative luciferase activity compared with the pGL3-Basic control, which is normalized to 1.0. Experiments were repeated at least three times in triplicates.

### Statistical analysis

All statistical analyses were carried out using SPSS software 17 version (SPSS Inc., Chicago, IL, USA). All data were shown as  $\bar{x} \pm s$ . Data assessing the luciferase activity of

**Table 1** Primers for series deletion mutants of *bUTP14a* luciferase reporter constructs

	Primer sequences
pGL3-hUTP14a(-1400/+173)-luc	Forward: 5'-GAATAATGGGGCAAAGCAA-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'
pGL3-hUTP14a(-745/+173)-luc	Forward: 5'-ACTCCAGCCTGAACGACACAGCA-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'
pGL3-hUTP14a(-320/+173)-luc	Forward: 5'-ACCGTCGCCCTAAGCTAA-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'
pGL3-hUTP14a(-203/+173)-luc	Forward: 5'-ACAGCCGTTTCATCTCAGGCCTC-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'
pGL3-hUTP14a(-100/+173)-luc	Forward: 5'-CGAGCGATTGACGGAAA-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'
pGL3-hUTP14a(-17/+173)-luc	Forward: 5'-AGAAGCTGGCTGCTGAAA-3' Reverse: 5'-GGCTGGATCGCGGAAAATA-3'

*bUTP14a* promoter were compared using the Student's *t*-test, and the identification of *bUTP14a* minimal promoter was compared with one-way analysis of variance (ANOVA) in different groups.  $P < 0.05$  was considered statistically significant.

## Results

### Structure analysis and cloning of *bUTP14a* promoter region

In order to clone the promoter region of *bUTP14a*, we used the NCBI and UCSC Genome Bioinformatics to analyze the 5' upstream sequence of *bUTP14a* gene. A database search against the human genomic DNA database was performed using *bUTP14a* sequence (GenBank accession No. NC\_000023) as a query. A genomic DNA fragment that spans position -2248 to +173 including the initiation codon ATG of the *bUTP14a* gene was chosen as the putative promoter region of *bUTP14a* gene and this DNA fragment was amplified by PCR (Figure 1A). Figure 1B shows the PCR product which is about 2,500 bp in size. The amplified DNA fragment was cloned into pGL3-Basic reporter vector at the *Nhe I/Hind III* site (Figure 1C) to get pGL3-hUTP14a-luc plasmid. The constructed plasmid was verified by DNA sequencing (Figure 1D). Figure 1E shows the database search against the human genomic DNA database using the DNA sequence of pGL3-hUTP14a-luc plasmid as a query, which demonstrates that the genomic DNA fragment spanning -2248 to +173 of *bUTP14a* gene was successfully cloned.

### Verification of *bUTP14a* promoter by luciferase activity

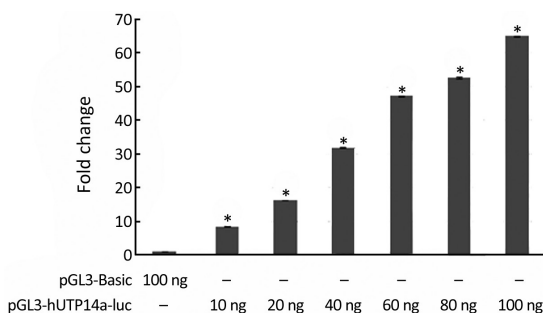
In order to verify if pGL3-hUTP14a-luc reporter construct possesses activity of a promoter, pGL3-hUTP14a-luc plasmid was transiently co-transfected into 293T cells along with *Renilla* luciferase control reporter vector. The luciferase assay was performed 24 h after transfection. The results showed that the luciferase activity of pGL3-hUTP14a-luc reporter plasmid increased in a dose-dependent manner as compared to the pGL3-Basic empty vector in 293T cells ( $P < 0.05$ ), indicating that an active *bUTP14a* promoter construct (Figure 2) was obtained.

### *bUTP14a* promoter activity was not regulated by P53

The prediction of transcription factors on *bUTP14a* promoter revealed a number of putative binding sites for transcription factors. It is a particular interest that P53 was the most frequently found transcription factor on the *bUTP14a* promoter (Figure 1A), which prompted us to evaluate the transcription regulation of P53 on *bUTP14a* promoter. To determine the role of P53 in regulating *bUTP14a* promoter, different amounts of *p53* were co-transfected with *bUTP14a* promoter reporter construct pGL3-hUTP14a-luc into 293T cells. As shown in Figure 3A, the luciferase activity of pGL3-hUTP14a-luc did not show a dose-dependent change when an increasing amount of P53 was ectopically co-expressed. In comparison, the luciferase activity of *p21* promoter containing the P53 binding site showed a dose-dependent increase when P53 was co-expressed (Figure 3B). These results indicated that

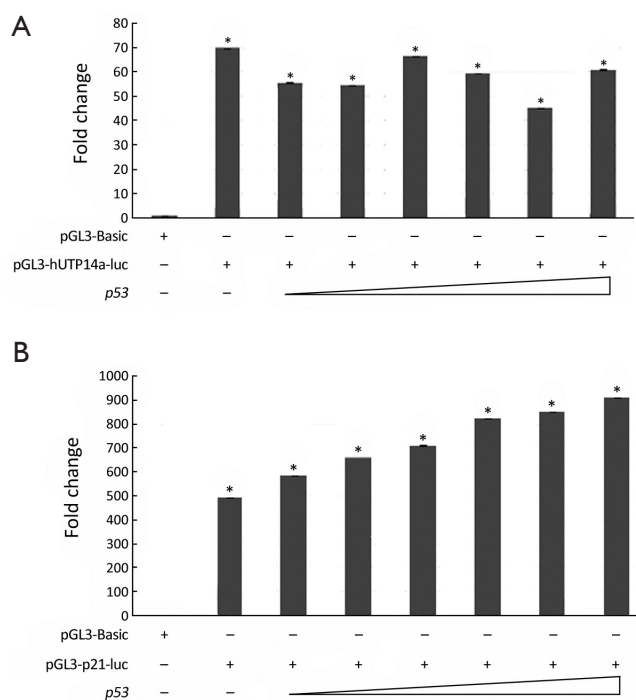






**Figure 2** Luciferase activity of the *hUTP14a* promoter. pGL3-Basic control plasmid or indicated amounts of *hUTP14a* promoter construct pGL3-hUTP14a(-2248/+173)-luc were transfected into 293T cells, respectively. Luciferase activity was measured 24 h after transfection. Luciferase activity in 293T cells is represented by the black histogram. All of the constructs were co-transfected with the PRL-SV40 plasmid for normalizing transfection efficiency. Statistical significance was analyzed using one-way ANOVA. \*, P<0.05 vs. pGL3-Basic control.

control reporter vector into 293T cells. Luciferase activities were evaluated 24 h after transfection. As shown in *Figure 4* (right), the *hUTP14a* promoter reporter construct and its deletion mutants including pGL3-hUTP14a-luc, pGL3-hUTP14a(-1400/+173)-luc, pGL3-hUTP14a(-745/+173)-luc, pGL3-hUTP14a(-320/+173)-luc and pGL3-hUTP14a(-203/+173)-luc showed fairly high luciferase activities compared to the pGL3-Basic vector. In addition, a significant increase of promoter activity was found between pGL3-hUTP14a-luc and pGL3-hUTP14a(-1400/+173)-luc, pGL3-hUTP14a(-745/+173)-luc and pGL3-hUTP14a(-320/+173)-luc, pGL3-hUTP14a(-320/+173)-luc and pGL3-hUTP14a(-203/+173)-luc, indicating that negative regulatory element(s) may lie between -2248 and -1400, -745 and -203 of *hUTP14a* gene promoter region. Whereas, a significant decrease of luciferase activity was found between pGL3-hUTP14a(-1400/+173)-luc and pGL3-hUTP14a(-745/+173)-luc, pGL3-hUTP14a(-203/+173)-luc and pGL3-hUTP14a(-100/+173)-luc, suggesting that positive regulatory element(s) may exist between -1400 and -745, -203 and -100 of *hUTP14a* gene promoter region. These results showed that deleting each of all putative P53 binding sites caused different changes of *hUTP14a* promoter reporter activity, demonstrating again that *hUTP14a* transcription is not regulated by P53. It is of notable that the luciferase activity of pGL3-hUTP14a(-100/+173)-luc dropped dramatically compared to that of pGL3-hUTP14a(-203/+173)-luc. This result suggested that the DNA sequence between -203 and -100 to the transcription

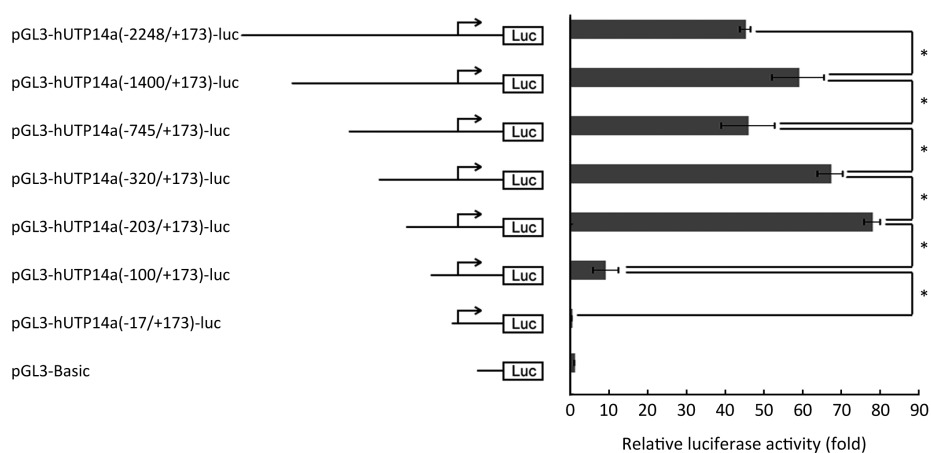


**Figure 3** Effect of ectopically expressed P53 on *hUTP14a* promoter. (A) Various indicated amounts of *p53* and equal dose of *hUTP14a* promoter construct pGL3-hUTP14a-luc were transfected into 293T cells, respectively. Luciferase activity was measured 24 h after transfection. Luciferase activity is represented by the black histogram. All of the constructs were co-transfected with the PRL-SV40 plasmid for normalizing transfection efficiency; (B) increasing amounts of *p53* as indicated and equal dose of *p21* promoter construct were transfected into 293T cells, respectively. Luciferase activity was measured 24 h after transfection. Luciferase activity is represented by the black histogram. All of the constructs were co-transfected with the PRL-SV40 plasmid for normalizing transfection efficiency.

initiation site of *hUTP14a* gene is mainly required for the minimal transcription activity and the positive regulatory element for basal transcription activity is mainly located in the region between -203 and -100.

**Discussion**

Our previous study showed that *hUTP14a* expression caused P53 protein degradation, knockdown of *hUTP14a* inhibits cell growth and induces apoptosis (2). In addition, *hUTP14a* is up-regulated in various types of human cancer tissues (our unpublished data). However, little is known about the transcriptional mechanisms controlling *hUTP14a* gene expression. To find out the mechanisms of *hUTP14a*



**Figure 4** Determination of the *bUTP14a* minimum promoter. Schematic illustration of the deletion mutants of *bUTP14a* promoter constructs are illustrated in the left. The estimated transcription initiation site is indicated with an arrow. The luciferase activity for the individual construct was calculated as the fold over pGL3-Basic control in the right. *bUTP14a* promoter deletion mutant constructs or pGL3-Basic control plasmid were transfected into 293T cells, respectively. Luciferase activity was measured 24 h after transfection. Luciferase activity in 293T cells is represented by the black histogram. All of the constructs were cotransfected with the PRL-SV40 plasmid for normalizing transfection efficiency. Statistical significance was analyzed using Student's *t*-test. \*,  $P < 0.05$ .

gene transcriptional regulation, we first constructed the *bUTP14a* promoter.

The 2,422 bp fragment, which was originally obtained from human genomic DNA by PCR, was found to contain the promoter region of the *bUTP14a* gene. The *bUTP14a* promoter luciferase reporter construct showed a dose-dependent luciferase activity, indicating that the *bUTP14a* promoter we obtained possesses an active promoter activity.

Our previous study found that hUTP14a binds P53 and promotes P53 degradation (2). Given that the transcription of MDM2 (14), Pirh2 (16) and COP1 (17), which are P53-binding proteins and promote P53 degradation, is regulated by P53, therefore these proteins form an autoregulatory feedback loop with P53. In addition, bioinformatics analysis of transcription factors' binding sites on *bUTP14a* promoter revealed several potential P53 binding sites. We thus wanted to know if P53 regulates *bUTP14a* promoter. *bUTP14a* promoter was transfected into 293T cells with *p53* and pGL3-Basic control plasmid, and luciferase activity was determined. To our surprise, the result showed that ectopic expression of P53 failed to regulate the *bUTP14a* promoter activity. In comparison, the luciferase activity of *p21* promoter containing the P53 binding site was stimulated by P53 in a dose-dependent way. Collectively, these data indicate that the *bUTP14a* promoter is not regulated by P53.

In order to define the minimal regulatory region in the *bUTP14a* promoter and to confirm that hUTP14a

transcription is not regulated by P53, we generated a series of deletion mutants of the *bUTP14a* luciferase reporter construct according to the position of putative P53 binding sites. The results of luciferase activity indicated that negative regulatory element(s) may lie in the two regions, one is the region between -2248 and -1400, the other is between -745 and -203 of *bUTP14a* gene promoter, while positive regulatory element(s) may exist in the regions including the DNA fragment from -1400 to -745 and that from -203 to -100 of *bUTP14a* gene promoter region. Deletion of each putative P53 binding sites displayed different luciferase activity changes, which demonstrated again that hUTP14a transcription is not regulated by P53. It is of importance that a 103 bp region (-203 to -100) was found to be the uppermost element for the transcriptional activity of the *bUTP14a* promoter. Further study is to identify specific transcriptional regulation factors of hUTP14a in the promoter region between -203 to -100.

Several specific E3 ubiquitin ligases such as MDM2 (14), Pirh2 (16,20), COP1(17,21) and ARF-BP1 (18) play as E3 ligases for P53 and mediate P53 degradation through an ubiquitin-dependent pathway. Among them, transcriptions of MDM2, Pirh2 and COP1 are regulated by P53 and thus these E3 ligases form a feedback regulation loop with P53 when cells are under stressed conditions (19). However, the transcription of ARF-BP1 is not regulated by P53 under either unstressed or stressed conditions so far (19).

We previously found that hUTP14a failed to promote P53 polyubiquitination though it promotes a proteasomal degradation of P53 (2). In this study, we demonstrate that transcription of hUTP14a is not regulated by P53 under unstressed condition. Whether P53 regulates hUTP14a transcription under stressed conditions needs further study.

The other possibility that P53 has no effect on *bUTP14a* promoter can also be attributed to the cell lineage. There is endogenous expression in 293T cells, which may influence the interaction between the exogenous P53 and *bUTP14a* promoter. Human Saos2 osteosarcoma cells, which harbor a homozygous deletion of the P53 locus and do not produce P53 protein, will be used in the further study to investigate whether P53 functions on the *bUTP14a* promoter. In addition, wild-type *p53* or mutant *p53* along with *bUTP14a* promoter construct will be co-transfected into the human Saos2 cells to see if P53 regulates *bUTP14a* promoter.

In conclusion, we cloned the *bUTP14a* promoter and defined its minimal promoter. The *bUTP14a* promoter is not regulated by P53 under unstressed conditions. The essential transcriptional factors of *bUTP14a* gene may exist in the promoter region between -203 and -100. Further understanding of the transcriptional regulation of the *bUTP14a* gene will provide important information about functions of hUTP14a in tumorigenesis.

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