

Signal Transducer and Activator of Transcription 3 (STAT3) Regulates Human Telomerase Reverse Transcriptase (hTERT) Expression in Human Cancer and Primary Cells

Liza Konnikova, Marina C. Simeone, Matthew M. Kruger, Maciej Kotecki, and Brent H. Cochran

Department of Physiology, Tufts University, Boston, Massachusetts

Abstract

Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that plays a critical role in cytokine and growth factor signaling and is frequently activated in human tumors. Human telomerase reverse transcriptase (hTERT) is also often overexpressed in tumor cells and mediates cellular immortalization. Here we report that STAT3 directly regulates the expression of hTERT in a variety of human cancer cells. Moreover, STAT3 activity is required for the survival of many human tumors, and hTERT expression contributes to the survival of STAT3-dependent tumor cells. In addition, we find that growth factors and cytokines stimulate hTERT expression in primary human cells in a STAT3-dependent manner. Thus, STAT3 is a key regulator of hTERT expression in both normal and tumor cells. (Cancer Res 2005; 65(15): 6516-20)

Introduction

The signal transducer and activator of transcription (STAT) family of transcription factors are direct mediators of signaling from the cell membrane to the nucleus. Upon stimulation by a wide variety of growth factors and cytokines, STATs become phosphorylated by Src and Jak family kinases on a unique tyrosine and thereby acquire high-affinity DNA-binding activity. They subsequently translocate to the nucleus where they regulate transcription of specific target genes (1). Of the seven human STAT genes, *STAT3* has drawn the most interest for its involvement in cancer (2). An activated form of STAT3 is sufficient to transform fibroblasts in culture. Additionally, a dominant-negative STAT3 can inhibit v-src-mediated transformation. Targeted knockout of STAT3 in the mouse epidermis prevents chemical induction of skin tumors (3). Moreover, STAT3 is constitutively activated in a wide variety of human tumors and tumor cell lines. Inhibition of STAT3 activity in these tumor cell lines typically leads to either growth inhibition or the rapid onset of apoptosis (2). Here we find that STAT3 is able to regulate the expression of the cancer hallmark gene, the catalytic subunit of human telomerase reverse transcriptase (*hTERT*), in both tumor and normal cells.

Materials and Methods

Cell lines and culture conditions. The human cell lines A172, U87, AGS, HS27, and MDA-435S were obtained from the American Type Culture Collection (Rockville, MD). The U251-MG cell line was donated by Dr. George Perides (Tufts New England Medical Center, Boston, MA). Human airway smooth muscle cells (HASMC) were kindly provided by

Dr. Reynold Panettieri (University of Pennsylvania). All cells were cultured in DMEM (American Type Culture Collection) supplemented with 10% FCS.

Small interfering RNA treatment. Cells were treated with small interfering RNA (siRNA) for either 48, 72, or 96 hours. Transfections with siRNAs were done overnight with oligofectamine (Invitrogen, Carlsbad, CA) in Opti-MEM (Invitrogen) and supplemented with serum the next morning. The concentration of siRNA ranged from 200 to 600 nmol/L depending on the experiment. hTERT siRNA used was a smart pool obtained from Dharmacon Research (Lafayette, CO). The sequence for STAT3i-1 siRNA was previously published (4). STAT3i-2 was a sequence identified from the STAT3 smart pool (Dharmacon Research). The sequence is CCACTTTGGTGTTCATAA.

Immunoblotting. For Western blot analysis, cells were harvested and lysed with radioimmunoprecipitation assay buffer [0.15 mol/L NaCl, 1% NP40, 0.01 mol/L desoxycholate, 0.1% SDS, 0.05 mol/L Tris-HCl (pH 8.0), 1 mmol/L sodium orthovanadate, 1 mmol/L phenylmethylsulfonyl fluoride, and 10 µg/mL each of aprotinin, pepstatin, and leupeptin]. Anti-phospho-STAT3, anti-STAT3, and anti-cleaved caspase 3 were obtained from Cell Signaling (Beverly, MA). Anti-STAT1 and anti-hTERT were obtained from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA) Anti-β-actin antibody was obtained from Sigma (St. Louis, MO). Anti-myc (9E10) monoclonal antibodies were obtained from the GRASP Digestive Diseases Research Center (Tufts New England Medical Center).

Quantitative PCR. RNA from cells was isolated using Trizol (Invitrogen). RNA was treated with DNase I (Invitrogen) for 30 minutes at 37°C. cDNA was made using SuperScript III (Invitrogen) according to manufacturer's instructions. Quantitative PCR was done using the QuantiTect SYBR Green PCR Kit (Qiagen, Valencia, CA). All fold differences in expression are expressed relative to β-actin expression in the corresponding sample.

PCR primers sequences: human *β-actin*, top primer CCTGGGCATG-GAGTCTCTGTGG and bottom primer CTGTGTTGGCGTACAGGTCTT; human *STAT3*, top primer ACCTGCAGCAATACCATTTGAC and bottom primer AAGGTGAGGGACTCAAATGC; human *c-myc*, top primer TTCGGGTAGTGGAAAACCCAG and bottom primer CAGCAGCTCGAATTTCTTCC; human *TERT* sequence 1, top primer CGTGGTTTCTGTGTGGTGTGTC and bottom primer CCTTGTGCGCTGAGGAGTAG; human *TERT* sequence 2, top primer CGGAAGAGTGTCTGGAGCAA and bottom primer GGATGAGCG-GAGTCTGGA.

Cell number assay. For cell proliferation assays, cells were incubated for 72 hours in 96-well plates in quadruplicates. Viable cell number was determined by using 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt assay according to the manufacturer's instructions (CellTiter 96 AQ Nonradioactive proliferation kit, Promega Biosciences, San Luis, CA). The absorbance was measured at 490 nm with a 96-well plate reader.

Fluorescence-activated cell sorting analysis. Cells were treated with siRNA as described above. After 96 hours, cells were isolated and stained with Annexin V/EGFP (BD Biosciences Clontech, Palo Alto, CA). Cells were analyzed using fluorescence-activated cell sorting (FACS) for green fluorescent protein (GFP) fluorescence of Annexin V-positive cells. The fraction of Annexin V-positive cells in the siRNA-treated population was determined using WinList software (Verity Software House, Topsham, ME).

Chromatin immunoprecipitation. The promoter of human TERT was analyzed for putative STAT3-binding sites. Primer sets were designed flanking the possible STAT3 binding regions. Untreated A172 cells were grown to confluence, crosslinked, lysed, and sheared. Chromatin

Requests for reprints: Brent Cochran, Department of Physiology, Tufts University, 136 Harrison Avenue, Boston, MA 02111. Phone: 617-636-0442; Fax: 617-636-0445; E-mail: cochran@cochranlab.org.

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immunoprecipitation (ChIP) was done according to manufacturer's instructions (Upstate, Waltham, MA). The immunoprecipitated DNAs were amplified by PCR with the primers indicated below.

Primer sequences: *hTERT* promoter primer sequence 1, top primer CCAAACCTGTGGACAGAACC and bottom primer AGACTGACTGCCTC-CATCGT; *hTERT* promoter primer sequence 2, top primer GGGGTGTC-TTCTGGGTATCA and bottom primer AAGGGCTGTGTTGTGAATTG.

Results

In an effort to identify genes that may mediate the effects of STAT3 on oncogenesis, we investigated whether STAT3 could regulate hTERT expression. To assess this, we initially transfected siRNA against STAT3 into the human A172 glioblastoma cell line and then immunoblotted extracts for expression of hTERT and STAT3 (4). As shown in Fig. 1A, STAT3 siRNA not only reduced expression of STAT3 but was also able to knockdown expression of hTERT. Two different siRNAs against STAT3 reduced hTERT protein expression while having no effect on the expression of STAT1 or c-myc proteins (Fig. 1A). Mock transfection or transfection with an siRNA against GFP had no effect on hTERT expression (Fig. 1). Thus, the observed hTERT knockdown is correlated with decreased STAT3 expression and is not likely due to off-target effects of the siRNAs. STAT3 knockdown, as shown by quantitative reverse transcription-PCR analysis, reduced expression of the hTERT mRNA by 90% relative to the effect of a GFP control siRNA (Fig. 1B), suggesting hTERT expression is regulated at the transcriptional level. Additionally, this data shows that the

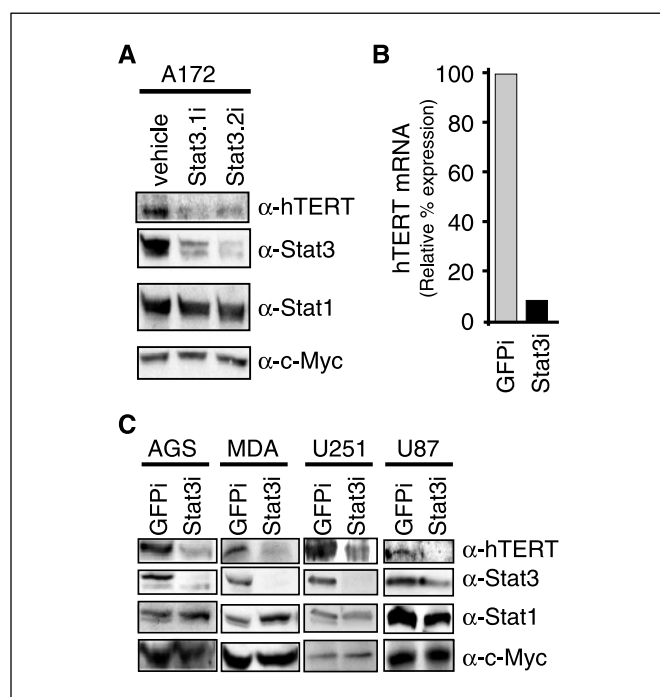


Figure 1. STAT3 regulates hTERT expression in human cancer cell lines. **A**, A172 glioblastoma cells were either mock transfected with oligofectamine or transfected with one of two of Stat3 siRNAs for 48 hours. Cells were lysed and processed for immunoblotting with antibodies against hTERT, STAT3, STAT1, or c-myc. **B**, quantitative reverse transcription-PCR analysis of hTERT mRNA in A172 cells after STAT3 or GFP siRNA treatment. Relative hTERT expression is shown after normalization to β -actin mRNA levels. **C**, the indicated tumor cell lines (AGS, gastric; MDA-435s, breast; U251 and U87, glioblastoma) were transfected with STAT3 siRNA or transfected with GFP siRNA, and after 72 hours, lysates were prepared for Western blotting with the indicated antibodies.

decrease in hTERT expression is not mediated through down-regulation of c-myc expression (Fig. 1A). This is of note, because it has previously been shown that STAT3 can sometimes regulate c-myc and that c-myc can regulate hTERT expression (5, 6).

To determine whether STAT3 regulation of hTERT expression in cancer cells is a more general phenomenon, we investigated the effect of STAT3 knockdown on a number of other tumor cell lines expressing activated STAT3. STAT3 siRNA suppressed hTERT expression in two other glioblastoma cell lines, U251 and U87, a breast cancer cell line, MDA-435S, and a gastric tumor line, AGS (Fig. 1C). The increase in STAT1 expression upon STAT3 knockdown observed in the gastric and breast tumor lines may be a compensatory effect similar to that seen in targeted STAT3 knockouts in mice (7). These results indicate that STAT3 controls hTERT expression in a variety of STAT3-dependent cancers.

We have previously reported that knockdown of STAT3 induces apoptosis of glioblastoma cells (4). Because hTERT expression is also necessary for the survival of some tumor cells, we examined the possibility that hTERT expression may mediate part of the prosurvival activity of STAT3 in STAT3-dependent tumors. Using hTERT siRNA, we inhibited hTERT expression in A172 cells and observed a decrease in cell number comparable with that observed in response to inhibition of STAT3 expression (Fig. 2A). A Western blot showing the knockdown of hTERT expression is shown in Fig. 2C. Visually, hTERT siRNA-transfected cells were much sparser than GFP siRNA-treated cells. In addition, they exhibited a number of characteristics consistent with apoptosis such as cell rounding, shrinkage, and blebbing (data not shown). Glioblastoma cells treated with hTERT siRNA also exhibited more apoptotic cells as judged by Hoechst 33258 staining (Fig. 2B; ref. 4). In addition, glioblastoma cells treated with hTERT siRNA, had elevated levels of phospho-histone H2B (Ser¹⁴), a marker of apoptosis, compared with cells treated with GFP siRNA (Fig. 2C). FACS analysis of cells stained with Annexin V/GFP also showed an increased number of cells undergoing apoptosis when treated with hTERT siRNA with respect to the control GFP siRNA-treated cells (Fig. 2E; GFPi, 25%; hTERTi, 55%; STAT3i, 43%). Taken together these data show that A172 cells require hTERT expression for survival. Because STAT3 can regulate hTERT expression and knockdown of hTERT induces apoptosis, it is likely that STAT3 siRNA-induced apoptosis is at least in part due to the down-regulation of hTERT expression.

To determine whether the apoptosis observed might be secondary to hTERT knockdown and telomere shortening, average telomere length was measured by telomere restriction fragment (TRF) assay. Figure 2D shows that there is no detectable change in telomere length over the time course of this assay. This result was expected given the rapid onset of apoptosis after STAT3 knockdown.

In addition to its presence in cancer cells, telomerase expression can be detected in normal human somatic cells (8). We therefore examined the possibility that STAT3 might regulate hTERT expression in primary, nontransformed cells. Growth factors, such as platelet-derived growth factor (PDGF) and interleukin-6 (IL-6) that activate STAT3, were found to rapidly up-regulate hTERT in primary fibroblasts (HS27) and primary HASMC at both the protein and mRNA levels (Fig. 3A and B). Oxidative stress can also activate STAT3 (9). Accordingly, we have found that H₂O₂ induces hTERT expression in HASMC (Fig. 3B and E). Moreover, siRNA knockdown of STAT3 substantially diminished the amount of hTERT that could be induced at both the protein and mRNA levels by the gp130 signaling STAT3 activating cytokines (10), IL-6, and oncostatin M, or peroxide treatment (Fig. 3C-E). These results show that hTERT

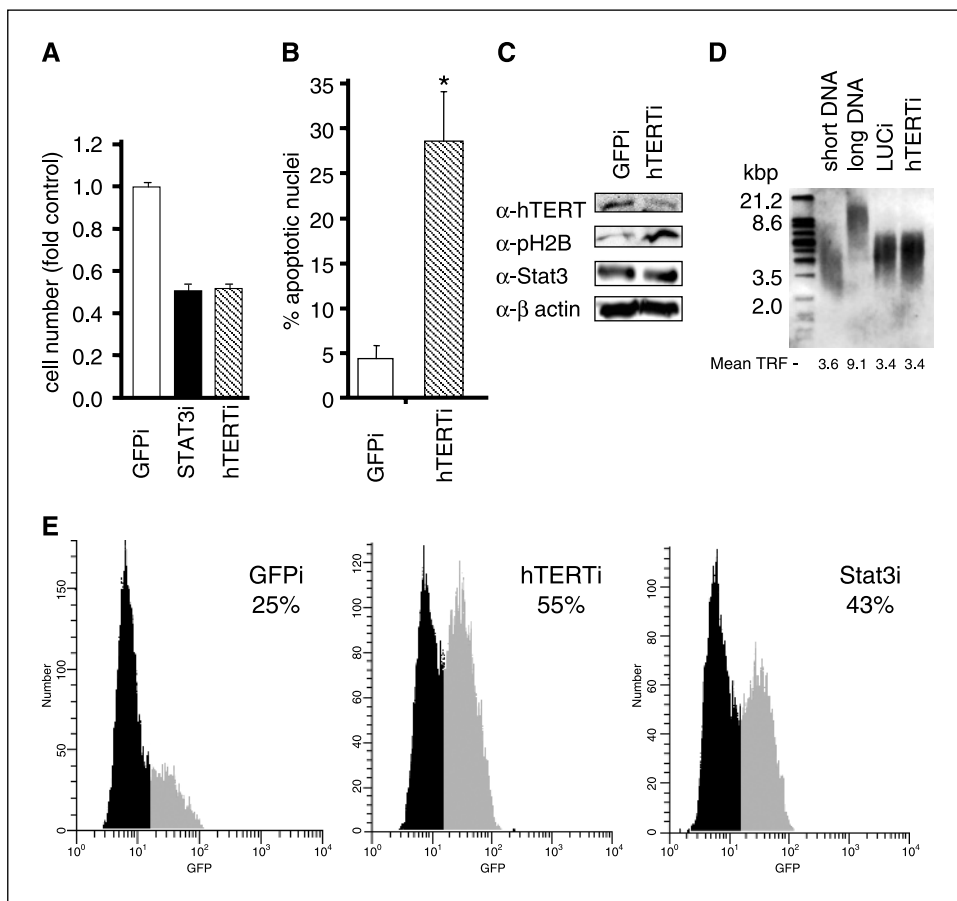


Figure 2. hTERT siRNA induces apoptosis of glioblastoma cells. *A*, A172 cells were treated with either GFP, STAT3, or hTERT siRNA for 72 hours and an 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxy-phenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt assay was used to determine relative viable cell number. *B*, A172 cells treated with GFP or hTERT siRNA for 72 hours were fixed in 4% paraformaldehyde and stained for apoptosis with Hoechst 33258 dye as previously described (4). Percentage of apoptotic-positive nuclei (i.e., those positive for Hoechst dye staining) is plotted. *C*, cells treated as in (*B*) were lysed and subjected to Western blotting with the indicated antibodies. *D*, to measure telomere length, DNA was isolated from A172 cells treated for 72 hours with either luciferase or hTERT siRNA. Relative telomere length was measured using the Telo TAGGG Telomere Length Assay kit (Roche Applied Science, Mannheim, Germany) according to the manufacturer's instructions. Long and short DNAs are controls for TRF length. The numbers below each lane are the mean TRF length in kilobases. *E*, A172 cells were treated with siRNA against GFP, STAT3, or hTERT for 72 hours and stained with Annexin V/GFP and GFP-positive cells were sorted by FACS. Percentage of Annexin V-positive cells is given in each panel.

can be induced in nontransformed primary cells upon cytokine signaling or by oxidative stress in a STAT3-dependent fashion.

The findings that PDGF, IL-6, oncostatin M, and H₂O₂ can induce hTERT expression within minutes of stimulation suggest that STAT3 directly regulates the *hTERT* gene. Consistent with this, we identified three consensus STAT3-binding sites (TTCNNGAA) in

the *hTERT* promoter (Fig. 4A; refs. 11, 12). Chromatin immunoprecipitation (ChIP) assays were done with all of the putative STAT3-binding sites. In A172 cells, STAT3 was found to associate with site 1 within the *hTERT* promoter (Fig. 4B). Moreover, STAT3 can be found bound to the same site of the *hTERT* promoter in primary cells (Fig. 4C). IL-6 stimulation of HS27 fibroblasts for 15 minutes

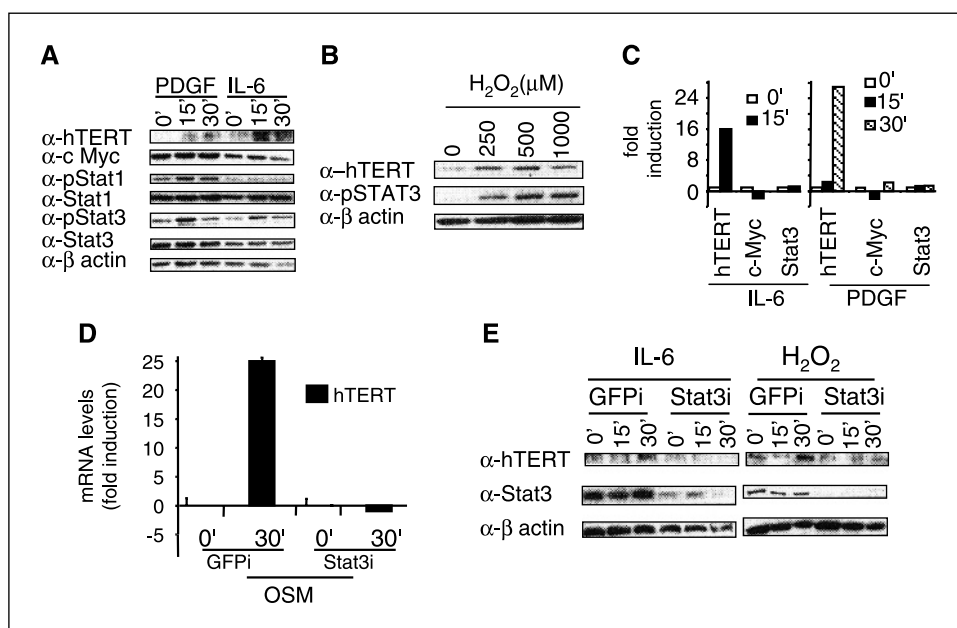


Figure 3. Growth factor stimulation of hTERT expression in somatic cells is STAT3 dependent. *A*, primary HASMC were stimulated with PDGF (25 ng/mL), IL-6 (20 ng/mL), or (*B*) H₂O₂ for the indicated doses for 30 minutes and processed for either Western blotting with the indicated antibodies or (*C*) lysed in trizol for RNA extraction and analyzed for the expression of the indicated genes by quantitative reverse transcription-PCR. Fold induction is relative to untreated cells after normalization to β-actin expression. *D*, quantitative reverse transcription-PCR analysis of hTERT mRNA in HS27 primary foreskin fibroblasts cells after STAT3 or GFP siRNA treatment and stimulation with oncostatin M (OSM, 20 ng/mL) for the indicated amount of time. *E*, HS27 or HASMC cells were pretreated with either STAT3 siRNA, oligofectamine (vehicle), or GFP siRNA for 72 hours before stimulation with IL-6 (20 ng/mL, HS27) or H₂O₂ (1 mmol/l, HASMC) as indicated for 0, 15, or 30 minutes. Cells were lysed and processed for immunoblotting with anti-hTERT, anti-STAT3, or anti-β-actin antibodies.

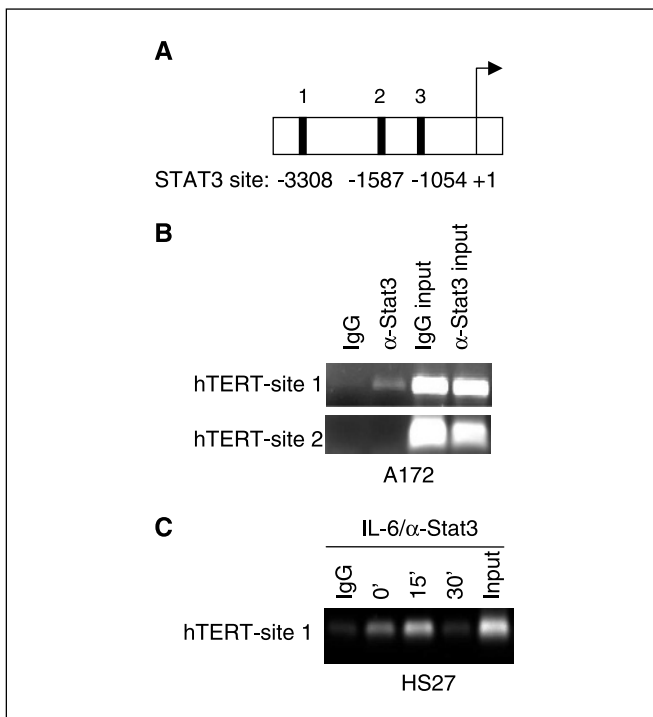


Figure 4. STAT3 binds to the hTERT promoter region. The promoter region of the *hTERT* gene was analyzed for consensus STAT3-binding sites. Primer sets were designed flanking the putative STAT3-binding sites. A, diagram of hTERT promoter with location of consensus STAT3-binding sites indicated. B, untreated A172 cells were grown to confluency and lysed. ChIP was done on the lysates using equal portions of anti-STAT3 and anti-(pTyr⁷⁰⁵)STAT3 antibodies or IgG (control) and protein-A agarose beads as described in Materials and Methods. Results for sites 1 and 2 are shown. No binding of STAT3 to site 3 was detected (data not shown). Input samples are DNAs amplified from lysates before immunoprecipitation. C, HS27 cells were stimulated with IL-6 (20 ng/mL) for the indicated amounts of time, and ChIP analysis was done as in (A).

leads to an increased recruitment of STAT3 to the promoter followed by down-regulation after 30 minutes of treatment. The ChIP data is consistent with the quantitative PCR data that show an increase of hTERT expression after 15 minutes of induction with IL-6. These data suggest that STAT3 directly regulates hTERT expression.

Discussion

Here we have shown that STAT3 is an important regulator of hTERT expression in both human primary and tumor cells. These findings strengthen the notion that STAT3 is a key mediator of critical cancer cell processes. Previous work has shown that STAT3 can regulate growth-promoting genes (*cyclin D* and *c-myc*), angiogenic genes (*VEGF*), antiapoptotic genes (*survivin* and *bcl-xl*), and genes associated with tumor invasion (*LIV-1*; refs. 4, 6, 13–16). Thus, it is perhaps not surprising that STAT3 is frequently found to be activated in many human tumors and that its inhibition typically

leads to growth inhibition or apoptosis of these tumors (2). The finding that STAT3 regulates hTERT expression and that hTERT knockdown also induces apoptosis in a STAT3-dependent tumor cell line further suggests that hTERT is an important effector of STAT3-mediated cell survival along with antiapoptotic genes such as *survivin* and *bcl-xl* that it also regulates (4).

It has previously been reported that replicative senescence due to shortening of telomeres can induce apoptosis (17). However, our data suggests that hTERT siRNA-induced apoptosis is likely to occur independently of telomere shortening. All of the apoptotic assays were done within 96 hours of initial treatment with hTERT siRNA and we detected no average telomere shortening within this time frame. Therefore, it is unlikely that replicative senescence is the signal for apoptosis in these assays. Consistent with this, we have not observed senescence associated β -galactosidase expression in these cells after hTERT knockdown (data not shown). This suggests that hTERT has a role in maintaining cell survival that is independent of its role in maintaining telomere length as has recently been found by others as well (18).

A somewhat surprising result here is that growth factors and cytokines regulate hTERT in nonimmortalized primary somatic cells. However, recent data indicates that hTERT expression can be regulated in somatic cells (8). Whereas it is not certain what the role of STAT3 regulation of hTERT is in normal cell function, there are a number of clues from previous work. In somatic cells, hTERT may serve to protect telomere caps from cell stress induced by both mitogens and oxidative stress (19). Thus, STAT3 induction of hTERT by these agents may serve to protect telomeres during times of physiologic stress such as the oxidation burst in response to growth factors. Additionally, it is known that STAT3 is an important mediator of self-renewal in murine embryonic stem (ES) cells (20). LIF, like IL-6 and oncostatin M, is a gp130 signaling cytokine that signals through STAT3 and is widely used to culture and maintain ES cells. Telomerase is expressed in ES cells and is known to be important for the maintenance of their self renewal potential. Because we have shown that gp130 signaling cytokines up-regulate hTERT in a STAT3-dependent fashion, it would be interesting to determine whether LIF can regulate expression of hTERT in human ES cells as well.

In conclusion, our finding that STAT3 regulates hTERT expression further strengthens the notion that STAT3 is a key mediator of the transformed state in human cancer. Recent studies demonstrating the efficacy of STAT3 inhibitors against human tumors grown in mice further strengthen this idea (21).

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