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Valproic acid suppresses telomerase activity and downregulates hTERT expression in human colorectal cancer cells

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Abstract

Background: Colorectal cancer (CRC) is a leading cause of cancer-related mortality, underscoring the need for novel therapies targeting key drivers of tumor progression. Telomerase, which is reactivated in 85 - 90% of CRCs, confers unlimited replicative potential and represents a promising therapeutic target. Valproic acid (VPA), a histone deacetylase inhibitor with documented anticancer properties, has unclear effects on telomerase activity and human telomerase reverse transcriptase (hTERT) expression in CRC.

Methods: Six human CRC cell lines (HCT116, HT-29/219, LS180, SW1116, SW480, and SW742) were treated with 1.5 mM VPA for 72 hours. Telomerase activity was evaluated using a non-isotopic TRAP assay in both intact cells and cell-free systems. hTERT mRNA expression was quantified by real-time RT-PCR and normalized to GAPDH using the 2-ΔΔCt method. Statistical significance was assessed using the t-test or ANOVA, with $P < 0.05$ considered statistically significant.

Results: VPA significantly reduced telomerase activity in SW480 (27.7 ± 6.24%), SW742 (33.2 ± 12.34%), HT-29/219 (18.6 ± 4.6%), and LS180 (21.8 ± 5.32%) cells ($P < 0.05$), but not in HCT116 or SW1116 cells. No inhibition was observed in cell-free systems treated with 1.5 - 5 mM VPA, indicating an indirect mechanism of action. hTERT mRNA expression was significantly downregulated in HCT116 (38.0 ± 8%), LS180 (49.3 ± 10.18%), and HT-29/219 (34.8 ± 14.2%) cells ($P < 0.05$), while changes in the remaining cell lines were not statistically significant.

Conclusion: VPA indirectly inhibits telomerase activity in a subset of CRC cell lines, primarily through transcriptional repression of hTERT. These findings suggest that transcriptional regulation is a key underlying mechanism, although post-transcriptional or post-translational processes may also contribute in a cell line-specific manner. Overall, the results highlight the therapeutic potential of VPA for targeting telomerase in CRC, particularly as part of combination strategies with telomere-shortening agents.

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Highlights

What is current knowledge?

Valproic acid (VPA) is a known histone deacetylase inhibitor with anticancer properties, and telomerase is reactivated in most colorectal cancers (CRCs) and regulated epigenetically; however, the effects of VPA on telomerase activity in CRC have not been clearly established.

What is new here?

This study demonstrates indirect, cell line-dependent suppression of telomerase activity and hTERT expression in CRC cells, identifying transcriptional repression as the primary mechanism with a possible contribution from post-transcriptional regulation. These findings support the potential role of VPA in targeted CRC therapy.

Introduction

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide due to its high global prevalence. Despite significant advances in early detection and therapeutic strategies, survival rates for advanced CRC remain poor (1,2). This underscores the urgent need for novel therapeutic approaches that specifically target the molecular mechanisms underlying tumor progression and survival.

Progressive telomere shortening occurs with each round of cell division in somatic cells, primarily as a result of the end-replication problem and insufficient telomerase activity. Telomerase is a reverse transcriptase enzyme that restores telomere length by adding nucleotide repeats to the ends of chromosomes (3). In normal somatic cells, telomerase activity is largely suppressed; however, it is reactivated in approximately 85 - 90% of human tumors, including colorectal carcinoma. This reactivation allows cancer cells to evade cellular senescence and acquire unlimited replicative potential (4). Moreover, telomerase activity is strongly correlated with the degree of malignant progression (5). Telomerase confers cellular immortality by extending the replicative lifespan of normal human cells, particularly following transfection with hTERT, the catalytic subunit of human telomerase (6,7).

Epigenetic events, particularly histone modifications, play a central role in the regulation of hTERT expression (8), making telomerase an attractive target for cancer chemoprevention. Among epigenetic-modifying agents, histone deacetylase (HDAC) inhibitors have attracted considerable attention due to their ability to reverse aberrant gene silencing in malignant cells. Valproic acid (VPA), a well-characterized drug traditionally used to treat neurological disorders, has recently gained increasing interest in cancer research because of its HDAC inhibitory activity (9). As a key epigenetic regulator, VPA can modify chromatin structure, leading to the reactivation of tumor suppressor genes and the suppression of oncogenic pathways (10). In addition, VPA modulates the expression of genes involved in cell cycle regulation, DNA repair, and apoptosis (11,12). Despite these promising antineoplastic properties, the specific effects of VPA on telomerase activity and hTERT expression in CRC cells remain insufficiently explored, representing an important knowledge gap that this study seeks to address.

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Given that HDAC inhibitors such as VPA influence chromatin architecture and that hTERT expression is epigenetically regulated, VPA represents a promising candidate for telomerase-targeted cancer therapy. Accordingly, this study aimed to evaluate the effects of VPA on telomerase activity and hTERT expression in human CRC cell lines and to determine whether these effects result from direct enzymatic inhibition or indirect intracellular mechanisms.

Methods

All chemicals and reagents were purchased from Sigma-Aldrich (Munich, Germany) unless otherwise specified. Cell culture reagents were obtained from Gibco/Invitrogen (Paisley, UK). The histone deacetylase (HDAC) inhibitor valproic acid (VPA; Depakine) was supplied by Sanofi-Aventis (Paris, France).

Cell culture and VPA solution preparation

Human colorectal cancer (CRC) cell lines HCT116, HT-29/219, LS180, SW1116, SW480, and SW742 were obtained from the National Cell Bank of Iran (Pasteur Institute, Tehran, Iran). The cells were cultured in RPMI 1640 or DMEM (LS180 only), supplemented with 10% fetal bovine serum (FBS), 2 mM L-glutamine, penicillin (100 U/mL), and streptomycin (100 µg/mL). All cell lines were maintained at 37°C in a humidified atmosphere containing 5% CO_2.

A 200 mM stock solution of VPA was prepared in phosphate-buffered saline (PBS) and stored at -20°C. For experimental treatments, the stock solution was diluted in the appropriate culture medium to achieve a final concentration of 1.5 mM. Cells were treated with 1.5 mM VPA for 72 hours (13,14), while control groups received an equivalent volume of PBS as the vehicle control.

Evaluation of telomerase activity by non-radioactive TRAP assay

Telomerase activity in response to VPA treatment was evaluated in both intact cells and cell-free systems. Telomerase activity was assessed using a non-isotopic TRAP (Telomere Repeat Amplification Protocol) assay, adapted from the method described by Nemos et al. (15) and performed as previously reported (16). Briefly, cell lysates were prepared from 1×10^6 cells (VPA-treated and untreated control groups) using 200 µL of ice-cold NP-40 lysis buffer (10 mM Tris-HCl, pH = 7.5; 1 mM $MgCl_2$; 1 mM EGTA; 0.5% NP-40; 10% glycerol; 5 mM β-mercaptoethanol; and 0.1 mM PMSF). Samples were incubated on ice for 30 minutes and then centrifuged at 12,000 × g for 20 minutes at 4°C. All solutions were prepared using DEPC-treated, RNase-free water.

Protein concentrations were determined using the Bradford assay. For the TRAP assay, 0.2 µg of protein extract was incubated with 0.1 µg of the TS primer at 30°C for 30 minutes to allow telomeric repeat extension. Subsequently, CX, NT, and TSNT primers (100 ng/µL each) and 0.25 µL of Taq DNA polymerase (5 U/µL) were added, followed by 32 cycles of PCR amplification. Primer sequences are provided in Table 1. PCR products (20 µL) were separated on 12.5% non-denaturing polyacrylamide gels at 100 V for 2 hours, stained with GelRed, and visualized under ultraviolet light. Telomerase-positive samples exhibited a characteristic ladder pattern, whereas negative samples showed only the 36-bp internal control band.

Telomerase activity inhibition was quantified using ImageJ software. Band intensities from VPA-treated samples were summed and normalized to untreated controls, which were set at 100%, and the results were expressed as relative telomerase activity.

To assess direct enzymatic inhibition, cell-free lysates from SW742 and SW480 cells - selected based on their strong antitelomerase response - were treated with VPA at concentrations ranging from 1.5 to 5 mM and incubated at 37°C for 1 hour prior to TRAP analysis. This approach allowed differentiation between direct inhibition of telomerase activity and indirect intracellular mechanisms, thereby providing insight into the mechanism of action of VPA in CRC.

Assessment of hTERT gene expression using quantitative RT-PCR

Total RNA was extracted from sub-confluent CRC cells using the RNA isolation reagent Biozol (Bioflux, Japan). Complementary DNA (cDNA) synthesis was performed using 2 µg of total RNA, oligo(dT) primers, and M-MuLV reverse transcriptase (MBI Fermentas, Lithuania) in a final reaction volume of 20 µL, in accordance with the manufacturer's instructions. To prevent amplification of genomic DNA, PCR primers (Table 1) were designed to span exon-exon junctions. Quantitative real-time RT-PCR analysis of hTERT expression was performed in triplicate using SYBR Green Master Mix (Ampliqon, Denmark) on an ABI 7500 Real-time PCR System (Applied Biosystems, USA). hTERT mRNA expression levels were normalized to the housekeeping gene GAPDH using the 2-ΔΔCt method (17).

Statistical analysis

Statistical analyses were performed using SPSS version 23 (SPSS Inc., Chicago, Illinois, USA). Student's t-test was applied for pairwise comparisons between control and VPA-treated groups within each cell line. One-way analysis of variance (ANOVA), followed by Tukey's post-hoc test, was used for multiple group comparisons, such as those involving cell-free dose-response data. GraphPad Prism software was used for data visualization.

Table 1. Primer sequences used for TRAP assay and real-time RT-PCR

Assay	Primer	Sequence	Annealing temperature (°C)	Product size (bp)
RT-PCR	hTERT-F hTERT-R	5′-CGGAAGAGTGTCTGGAGCAA-3′ 5′-GGATGAAGCGGAGTCTGGA-3′	60	146
	GAPDH-F GAPDH-R	5′-CGACCACTTTGTCAAGCTCA-3′ 5′-AGGGGTCTACATGGCAACTG-3′	60	232
TRAP	Ts ACX	5′-AATCCGTCGAGCAGAGTT-3′ 5′-GCGCGG[CTTACC]$_3$CTAACC-3′	58	NA
	NT TSNT	5′-ATCGCTTCTCGGCCTTTT-3′ 5′-AATCCGTCGAGCAGAGTTAAAAG GCCGAGAAGCGAT-3′	58	36

F: Forward; R: Reverse; NA: Not Applicable

Results

Effect of VPA on telomerase activity in intact cells and cell-free systems

CRC cell lines were treated with 1.5 mM VPA for 72 hours, and telomerase activity in cellular extracts was assessed using the TRAP assay. As shown in Figure 1, telomerase activity was visualized as a characteristic ladder of amplified DNA fragments. The extent of VPA-induced inhibition was determined by quantifying relative band intensities and comparing them with those of untreated control samples. VPA reduced telomerase activity in a cell line-dependent manner. Significant inhibition was observed in SW480 (27.7 ± 6.24%), SW742 (33.2 ± 12.34%), HT-29/219 (18.6 ± 4.6%), and LS180 (21.8 ± 5.32%) cells ($P < 0.05$). In contrast, no significant reduction in telomerase activity was detected in SW1116 or HCT116 cells ($P > 0.05$). Among the responsive cell lines, SW742 exhibited the strongest inhibition, whereas SW1116 and HCT116 appeared resistant to VPA-induced telomerase suppression.

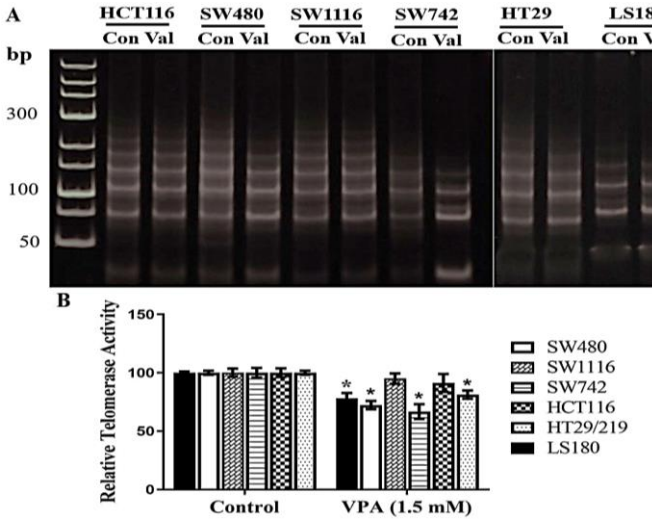

Figure 1. Effect of VPA on telomerase activity in intact CRC cell lines: (A) Tumor cell lines were incubated with 1.5 mM VPA for 72 hours, after which telomerase activity was assessed in cell lysates using the TRAP assay. VPA treatment resulted in a cell line-specific reduction in telomerase activity, as evidenced by a decreased number and intensity of the characteristic telomeric ladder bands compared with untreated control cells. (B) Quantitative analysis of relative telomerase activity. The intensities of telomerase ladder bands were quantified, normalized to the corresponding untreated controls (Set at 100%), and expressed as mean ± standard deviation from three independent experiments. Statistical significance was determined using student's t-test ($P < 0.05$ compared with untreated control cells; M, Molecular weight marker).

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To distinguish between direct and indirect inhibitory effects of VPA, telomerase activity was also evaluated in cell-free systems. Cell lysates derived from SW480 and SW742 cells were treated with increasing concentrations of VPA (1.5, 3, and 5 mM) and incubated at 37°C for 1 hour. Telomerase activity was then measured using the TRAP assay, as described in the Materials and Methods section. No significant inhibition of telomerase activity was observed in any of the VPA-treated lysates (Figure 2). Telomerase activity remained at 97.1 ± 4.3% in SW742 and 98.4 ± 2.78% in SW480 following treatment with 1.5 mM VPA; at 95.3 ± 7.8% in SW742 and 96.8 ± 10.18% in SW480 with 3 mM VPA; and at 93.6 ± 5.2% in SW742 and 94.7 ± 3.4% in SW480 with 5 mM VPA. None of these values differed significantly from those of the untreated controls. As illustrated in Figure 2, even the highest concentration of VPA did not result in complete or substantial inhibition of telomerase activity in the cell-free system.

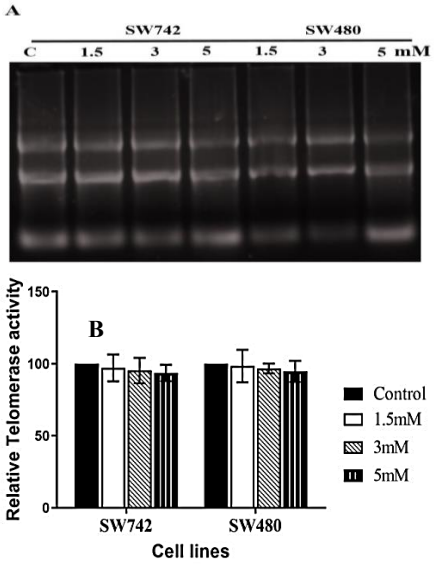

Figure 2. Effect of VPA on telomerase activity in cell-free extracts: (A) CRC cell lysates (0.2 µg protein) were incubated with 1.5 mM VPA and subsequently analyzed for telomerase activity using the TRAP assay, as described in the materials and methods section. (B) Relative telomerase activity was quantified based on ladder band intensities, normalized to the untreated control (Set as 100%), and expressed as mean ± standard deviation from at least two independent experiments. Statistical significance was determined using student's t-test.

Effect of VPA on hTERT gene expression

To elucidate the mechanism underlying VPA-induced telomerase inhibition, the effect of VPA on hTERT transcript expression was evaluated in CRC cells. Cells were treated with 1.5 mM VPA for 72 hours, after which total RNA was extracted from both treated and untreated control cells. hTERT mRNA levels were quantified using real-time RT-PCR. VPA treatment resulted in a significant reduction in hTERT mRNA expression in HCT116 (38.0 ± 8.0% of control), LS180 (49.3 ± 10.4%), and HT-29/219 (34.8 ± 14.2%) cell lines compared with untreated controls ($P < 0.05$; Figure 3). In contrast, only modest and non-significant decreases in hTERT expression were observed in SW480 (17.4 ± 8.2%), SW742 (13.8 ± 12.2%), and SW1116 (14.5 ± 10.4%) cells ($P > 0.05$).

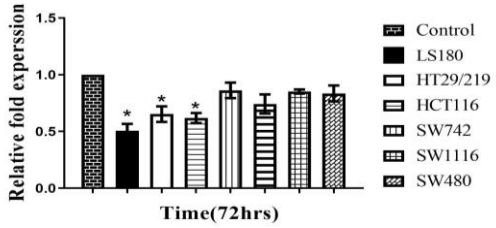

Figure 3. Effect of VPA on hTERT gene expression in human CRC cell lines: CRC cell lines were treated with 1.5 mM VPA for 72 hours. Subsequently, hTERT mRNA levels were quantified by real-time RT-PCR. Expression values were normalized to GAPDH as the housekeeping gene, and relative expression levels are presented in comparison with untreated control cells (Set as 1). Data represent the mean ± standard deviation from two independent experiments performed in duplicate. Statistical analysis was conducted using one-way ANOVA followed by Tukey's post-hoc test (* $P < 0.05$).

Discussion

The results of this study indicate that VPA, a well-established HDAC inhibitor, exerts a significant inhibitory effect on telomerase activity in human CRC cells in a cell line-dependent manner. Our findings show that telomerase activity was significantly reduced after 72 hours of treatment with 1.5 mM VPA compared with untreated controls in SW742 (33.2 ± 12.34%), SW480 (27.7 ± 6.24%), LS180 (21.8 ± 5.32%), and HT-29/219 (18.6 ± 4.6%) cell lines, whereas resistance to VPA-induced telomerase inhibition was observed in HCT116 and SW1116 cells. Importantly, results from the cell-free TRAP assay demonstrated that VPA does not directly inhibit telomerase activity, as even higher concentrations (Up to 5 mM) failed to suppress telomerase activity in lysates from sensitive cell lines (SW480 and SW742). These findings strongly suggest that the inhibitory effect of VPA on telomerase is indirect and requires an intact cellular context, likely mediated through epigenetic or transcriptional regulatory mechanisms.

The hTERT gene expression results further support the presence of an indirect mechanism. Treatment with VPA led to a significant downregulation of hTERT mRNA levels compared with untreated controls in HCT116 (38.0 ± 8% of control; $P = 0.023$), LS180 (49.3 ± 10.4% of control; $P = 0.008$), and HT-29/219 (34.8 ± 14.2% of control; $P = 0.014$) cells. A strong correspondence between transcriptional suppression of hTERT and inhibition of telomerase activity in LS180 and HT-29/219 cells suggests that downregulation of hTERT transcription represents the primary mechanism underlying telomerase inhibition in these cell lines.

In contrast, although SW480 and SW742 cells exhibited the most pronounced inhibition of telomerase activity, only modest reductions in hTERT mRNA levels were observed (17.4 ± 8.18% and 13.8 ± 12.18% of control, respectively). These discordant patterns between hTERT mRNA expression and telomerase activity across different cell lines highlight the complexity of VPA's mechanism of action and suggest the involvement of post-transcriptional or post-translational regulatory pathways in certain cellular contexts, particularly in SW480 and SW742 cells. This dissociation implies that, in these cell lines, VPA may exert its inhibitory effects through mechanisms such as modulation of hTERT protein stability, phosphorylation status, or nuclear translocation. Collectively, these findings indicate that, in specific cellular settings, HDAC inhibitors such as VPA can regulate hTERT function beyond transcriptional control, acting through post-transcriptional mechanisms.

The differential cellular responses observed in this study are consistent with the well-documented heterogeneity of tumor responses to HDAC inhibitors across different cancer models (18,19). Such variability is thought to arise from differences in epigenetic landscapes, HDAC isoform expression, and transcription factor profiles among tumor types (18). For example, trichostatin A (TSA) has been reported to exert opposing effects on telomerase activity: Takakura et al. (2001) demonstrated that TSA upregulates telomerase activity in normal human keratinocytes by inducing hTERT expression, suggesting a potential pro-immortalization effect in non-malignant cells (20). In contrast, TSA and other HDAC inhibitors, including VPA, have been shown to suppress telomerase activity in cancer cell lines such as HeLa and MCF-7 (21,22). Furthermore, Nakamura et al. reported that VPA inhibits telomerase activity in hepatoma cells through transcriptional downregulation of hTERT mediated by histone hyperacetylation and recruitment of repressive complexes (23). Our findings in CRC cell lines support the role of VPA as a context-dependent inhibitor of telomerase, consistent with its broader antitumor activity (24).

This study has several limitations that should be acknowledged. First, a single concentration and exposure duration of VPA were applied across all cell lines, which may have limited the detection of optimal responses in less sensitive models. Second, although our data support transcriptional repression of hTERT, the proposed involvement of post-transcriptional or post-translational regulatory mechanisms - particularly in SW480 and SW742 cells - remains speculative and warrants further investigation. Notably, we did not directly assess hTERT protein expression, phosphorylation status, or subcellular localization, which would be necessary to substantiate these hypotheses. Third, mechanistic differences among cell lines, such as variations in HDAC isoform expression, were not explored in this study. Future research addressing these limitations is needed to further clarify the mechanisms underlying VPA-mediated telomerase regulation.

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Conclusion

In conclusion, this study provides compelling evidence that VPA functions as a potent indirect inhibitor of telomerase in a subset of CRC cell lines. Its primary mechanism appears to involve transcriptional repression of hTERT, likely through modulation of the hTERT promoter complex, with additional contributions from post-transcriptional regulatory processes in certain cellular contexts. Despite heterogeneous responses among the examined cell lines, the robust inhibition of telomerase activity and hTERT expression observed in responsive models underscores the therapeutic relevance of VPA in CRC, particularly as part of synergistic treatment strategies that target telomere maintenance mechanisms and promote replicative senescence.

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Ethical statement

This in vitro study utilized commercially available human colorectal cancer cell lines and did not involve human participants, animals, or clinical samples; therefore, ethical approval was not required.

Conflicts of interest

The authors declare no conflicts of interest.

Author contributions

Mohsen Tatar: Methodology, Software, Validation, Formal analysis, Investigation, Data curation, and Original draft preparation; Fatemeh Lotfi Asrami and Mehdi Khorami: Resources, Visualization, Manuscript review, and Editing; Fakhraddin Naghibalhossaini: Supervision and Project administration.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon justified request.

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