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Effect of Curcumin and Trichostatin A on the Expression of DNA Methyltransfrase 1 in Hepatocellular Carcinoma Cell Line Hepa 1-6

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Abstract

Background: Hepatocellular carcinoma (HCC), primary liver cancer, is a major health problem and the third most common cause of cancer-related deaths worldwide. Epigenetic modulations are essential for the maintenance of gene expression patterns in mammals. Disruption of these processes can lead to silenced gene and malignant cellular transformation. The current study was designed to compare the effect of curcumin with trichostatin A (TSA) on DNA methyltransferase 1 (DNMT1) gene expression, cell growth inhibition, and apoptosis induction in HCC Hepa 1-6 cell line.

Materials and Methods: Hepatocellular carcinoma Hepa 1-6 cell line was purchased from the National Cell Bank of Iran-Pasteur Institute, treated with curcumin (1, 5, 10, 25 and 50 μM) and TSA (0.5, 1, 2.5, 5 and 10 μM), and the MTT assay was performed. Then, flow cytometry assay and Real-Time RT-PCR analysis were performed with curcumin and TSA treatments. Statistical comparisons between groups were performed using ANOVA (one‑way ANOVA) and Turkey test. A significant difference was considered as $P < 0.05$.

Results: Both treatments showed significant inhibitory and apoptotic effects, besides reducing the expression of DNMT1. The relative expression of DNMT1 gene in the curcumin-treated groups were 0.7 to 0.3 ($P <0.001$) and in the TSA treated groups were 0.5 to 0.19 ($P <0.001$).

Conclusion: The curcumin and trichostatin A (TSA) can inhibit cell viability and induce apoptosis somehow through epigenetic modification. The curcumin indicated a more significant apoptotic effect than TSA.

Keywords: Apoptosis, Curcumin, DNMT1, Trichostatin A

Introduction

Hepatocellular carcinoma (HCC), primary liver cancer, is a major health problem and the third most common cause of cancer-related deaths worldwide. Major risk factors and etiologies of HCC include hepatitis B virus (HBV) and hepatitis C virus (HCV). In addition to these factors, high consumption of alcohol is the prevalent cause of the HCC in developed countries (1). Epigenetic modulations, which include changes in histone modifications, DNA methylation, and alteration in microRNA (miRNA) expression without any change in the DNA sequence, are essential for the maintenance of gene expression patterns in mammals. Disruption of these processes can lead gene silencing and malignant cellular transformation. Global epigenetic abnormalities are a hallmark of cancer

One of the most extensively studied epigenetic modifications is DNA methylation which provides a stable gene silencing mechanism, playing an important role in chromatin compaction (2). DNA methylation is achieved by a group of enzymes known as the DNA methyltransferases (DNMTs), including DNMT1, DNMT1b, DNMT1o, DNMT1p, DNMT2, DNMT3A, DNMT3b. DNMT1 maintenances methyltransferase activity leads to chromatin remodeling and regulation of gene expression. Besides, DNMT3A and DNMT3b are powerful de novo methyltransferases (3). To date, natural compounds such as curcumin and epigallocatechin gallate (EGCG) have been shown to increase the sensitivity of

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cancer cells to conventional agents and inhibit tumor cell growth (4). More recent studies have demonstrated that curcumin can exert its effect through epigenetic modification, including DNMTs, histone acetyltransferase (HAT), and histone deacetylase (HDAC). This agent has been known as a potential DNMT1 inhibitor resulting in hypomethylation of various genes (5, 6). Furthermore, trichostatin A (TSA), an antifungal antibiotic, is an inhibitor of HDAC activity in cultured mammalian cells which arrests cells in G1 and G2 phases of the cell cycle, induces cell differentiation, and reverts the transformed morphology of the cells in the cultured cell (7). It has been shown that HDAC inhibitor TSA in combination with curcumin has greater apoptotic and antiproliferative effects than either agent alone in breast cancer (8). Previously, we reported that TSA can inhibit proliferation and induce apoptosis by reducing the expression of DNMT1, DNMT3a, and DNMT3b in HCC HepG 2 cell line (9). Our previous results on estrogen receptor alpha (ERα) in HCC HepG 2 cell line (10) and the poptotic effect of DNA methyltransferase inhibitor genistein (GE) on HCC HepG2 (11) have encouraged us to investigate the effect of curcumin in combination to and in comparison with TSA on inactivation of DNA methyltransferase 1 gene expression, cell growth inhibition and apoptosis induction in hepatocellular carcinoma Hepa 1-6 cell line.

Materials and Methods

Cell culture

The current experimental study was performed in a research center for non-communicable diseases, Jahrom University of medical sciences with Ethic code of "ir.Jums.rec.1395.075". Human hepatocellular carcinoma (Hepa 1-6) cells were purchased from the National Cell Bank of Iran‑Pasteur Institute and maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 1% antibiotics, including penicillin G sodium (Sigma), streptomycin sulfate, and amphotericin B (Sigma) at 37°C in 5% CO2 to promote attachment. The cells were treated with agents (curcumin and TSA) after they attached and reached > 80 % confluence. The drugs, including curcumin and TSA were purchased from Sigma-Aldrich (St. Louis, MO, USA) and dissolved in dimethyl sulfoxide (DMSO) in order to prepare a stock solution and then all drug concentrations were prepared by diluting the stock solution. Other compounds, including fetal bovine serum (FBS), trypsin-EDTA, and phosphate-buffered saline (PBS) were purchased from the best available company and also Annexin-V-(FITC) and propidium iodide were obtained from Sigma (PI, Becton-Dickinson, San Diego, CA).

Cell growth and viability assay

The effects of curcumin and TSA on the cell viability were measured using MTT assay. First, the cells were cultured at a density of 5×10^5 cells per well into 96-well plates overnight and then culture medium was removed and a medium containing different concentrations of curcumin (1, 5, 10, 25 and 50 μM) and TSA (0.5, 1, 2.5, 5 and 10 μM) were added, controls were incubated with DMSO only. After 24, 48, and 72 h, the cells were washed twice with FBS, maintained in a medium containing MTT for 4 h, and then the culture media were discarded, 200 μL of DMSO was added to each well and finally, the optical density was measured at 570 nm with a microplate reader.

Cell apoptosis assay

For apoptotic effect determination, the Hepa 1-6 cells were seeded in 24-well plates at a density of 4×10^5 cells/well and incubated for 24 h before treating with agents.

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On the second day, the cells treated with curcumin (5 μM) and TSA (2.5 μM) based on IC50 values, at mentioned times (24, 48, and 72 h). After treatment, the culture medium was removed and all the adherent treated or untreated cells were harvested by trypsinization, washed with cold PBS, and then the cells was re-suspended in 0.5 ml of a binding buffer (1x). Finally, Annexin-V-(FITC) and propidium iodide (PI) were added to stain the cells according to the protocol and the apoptotic cells were counted by FACScan flow cytometry (Becton Dickinson, Heidelberg, Germany).

Real-Time quantitative reverse-transcription polymerase chain reaction (qRT-PCR) analysis

To determine whether curcumin and TSA could reactivate the DNMT1 gene expression, qRT-PCR was performed. In this regard, the cells were cultured and treated with curcumin and TSA (5 and 2.5μM respectively, based on IC5o values) for 24, 48 and 72 h and total RNA from the cells was extracted using the RNeasy kit (Qiagen, Valencia, CA) according to the protocol and treated by RNase-free DNase (Qiagen) to eliminate the genomic DNA before cDNA synthesis. The RNA concentration and purity were determined using a BioPhotometer (Biowave II Germany). By using the RevertAid™ First Strand cDNA Synthesis Kit (Fermentas, K1622 for 100 reactions), total RNA (100 ng) was reverse transcribed to complementary DNA (cDNA) using oligo-dT primers and Superscript II Reverse Transcriptase according to the protocol. Real-time RT-PCR reactions for cDNA amplification were performed on Applied Biosystems StepOneTM Real-Time PCR System using Maxima SYBR Green RoxqPCR master mix kit (Fermentas). DNMT1 primers were obtained from our previous work (9) which their sequences are shown in the Table I. GAPDH was used as an endogenous control. Data were analyzed using the comparative Ct (ΔΔct) method; the relative expression level of DNMT1 was calculated by determining a ratio between the amount of the gene and that of endogenous control.

Statistical analysis

The database was setup with the SPSS (version 16.0) for analysis. The data were acquired from three tests and were shown as means ± standard deviations. Statistical comparisons between groups were performed with ANOVA (one-way ANOVA) and Turkey tests. A significant difference was considered as $P < 0.05$.

Results

Effect of curcumin and TSA on viability of Hepa 1-6 cells

The Hepa 1-6 cells were cultured in 96-well plates (at a density of 5×10^5 per well), treated with curcumin (1, 5, 10, 25 and 50 μM) and TSA (0.5, 1, 2.5, 5 and 10 μM) for 1, 2, and 3 days, and evaluated by MTT assay to measure drugs effects on cell viability. The results are shown in Figure 1, comparing the percentage of cell viability in treated cells with untreated control groups. As shown in Figure 1, curcumin decreased cell viability in a time and dose-dependent manner significantly, ($P < 0.001$). Similar results were observed by TSA as shown in Figure 2 ($P < 0.001$). The result of MTT assay demonstrated that curcumin and TSA inhibited cell growth with an IC50 of ~5 and ~2.5 Mμ, respectively.

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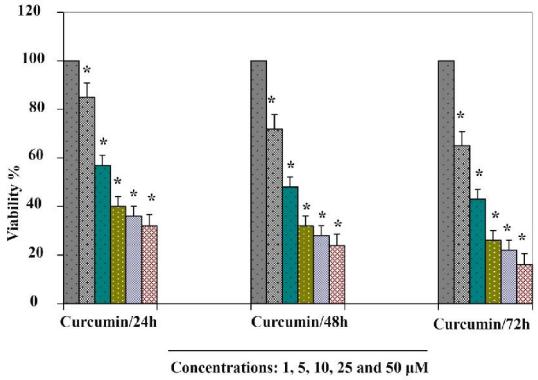

Figure1. The effect of curcumin (1, 5, 10, 25 and 50 µM) on the Hepa 1-6 cell viability determined by the MTT assay. Data are presented as mean ± SD from at least triplicate wells and 3 independent experiments. Significant differences between treated cell groups and the control groups are indicated by asterisks (*). The first column of each belongs to the control group.

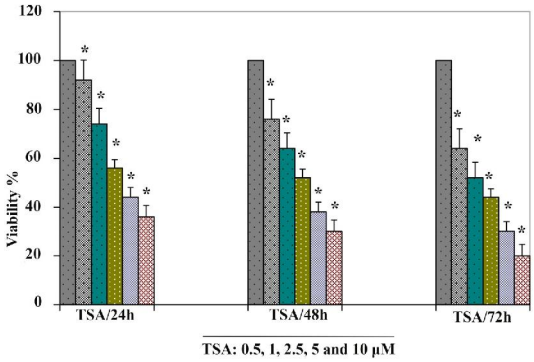

Figure 2. The effect of TSA with concentrations of 0.5, 1, 2.5, 5 and 10 µM on the Hepa 1-6 cell viability. The effect of the drug was determined by the MTT assay. Data are presented as mean ± SD from at least triplicate wells and 3 independent experiments. Significant differences between treated cell groups and the control groups are indicated by asterisks (*). The first column of each group belongs to the control group.

Effect of curcumin and TSA on cell apoptosis

The propidium iodide (PI) and Annexin-V/FITC staining was done to determine the apoptotic effects of curcumin and TSA on Hepa 1-6 cells treated with curcumin (5 Mµ) and TSA (2.5 Mµ) for 24, 48, and 72 h. The cells were stained with both propidium iodide (PI) and Annexin-V/FITC in the calcium-HEPES buffer as recommended by the manufacturer protocol and the percentage of apoptotic cells was determined by flow cytometry. Flow cytometric demonstrated that both agents indicated significant apoptotic effects in all different-time treated groups as shown in the figure 3 and Figure 4 ($P < 0.001$). As seen in the Figure 5, curcumin indicated a more significant apoptotic effect than TSA ($P < 0.002$). The percentage of apoptotic cells were shown in table II.

Effect of curcumin and TSA on DNMT1 gene expression

To determine the mechanism of curcumin (5 Mµ) and TSA (2.5 Mµ), RT-PCR was done to test the DNMT1 gene expression quantity during treatment with these compounds at different time periods. As shown in the Figure 6, the DNMT1 gene expression quantity was decreased significantly by treatment with curcumin and TSA. The relative expression of DNMT1 gene in the curcumin-treated groups were 0.5 ($P <0.003$), 0.3 ($P <0.001$), and 0.19 ($P <0.001$) and in the TSA treated groups were 0.7 ($P <0.396$), 0.4 ($P <0.004$), and 0.32 ($P <0.001$) at different times, respectively. The effect of curcumin was stronger than TSA.

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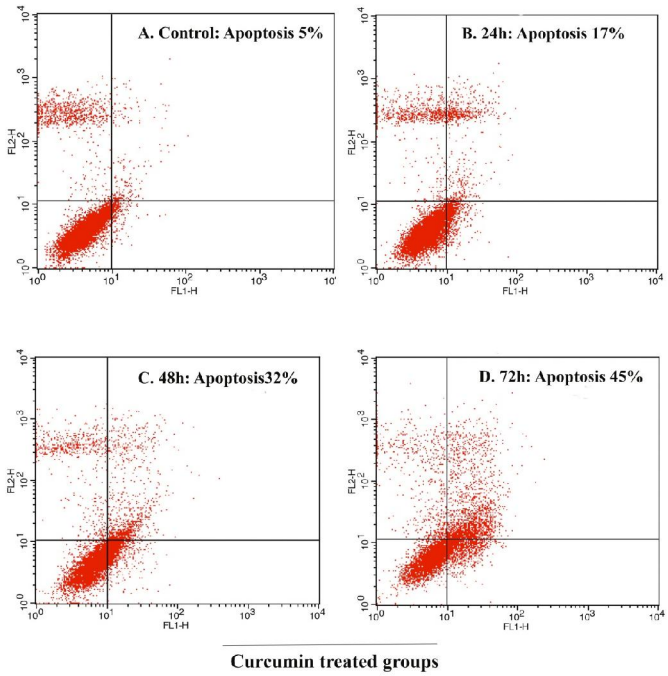

Figure 3. Flow cytometry analysis of annexin V- (FL1-H) and PI- (FL2-H) Hepa 1-6 cell line labeled cells treated with curcumin. The cells were treated with curcumin with the concentration of 5 µM for 24, 48, and 72 h. Data are presented as a mean ± standard error of the mean from at least three different experiments. Asterisks (*) indicate significant differences between treated cell groups and the control cell groups.

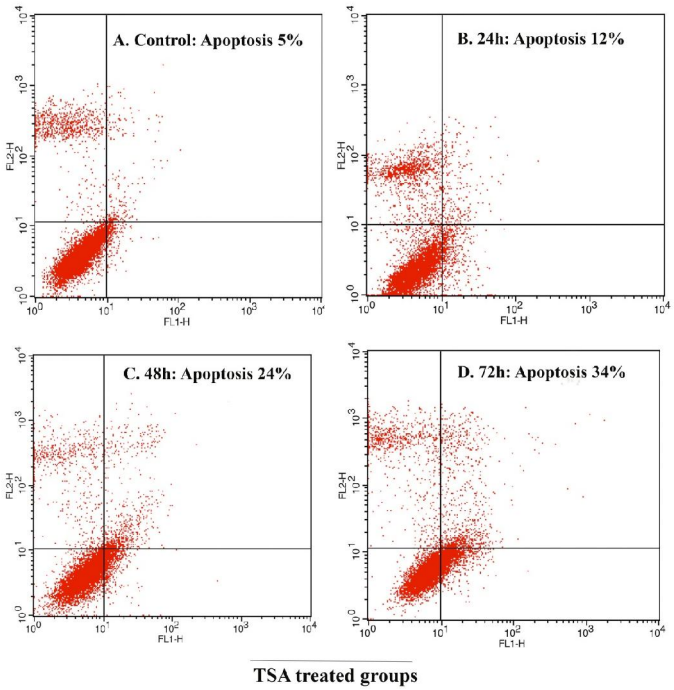

Figure 4. Apoptotic effect of TSA (2.5 µM) on Hepa 1-6 cell line. The cells were treated with TSA (2.5 µM) for 24, 48, and 72 h. Data are presented as a mean ± standard error of the mean from at least three different experiments. Asterisks (*) indicate significant differences between treated cell groups and the control cell groups.

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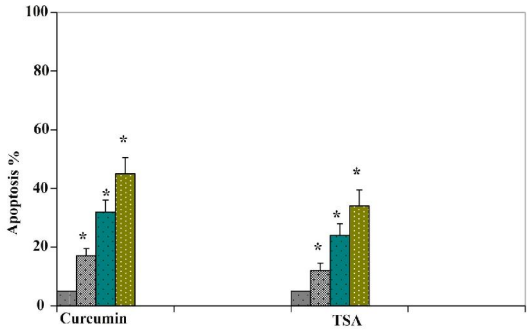

Figure 5. Apoptotic effect of curcumin and TSA on Hepa 1-6 cell line

The cells were treated with curcumin (5 µM) and TSA (2.5 µM) for 24, 48, and 72 h. Data are presented as a mean ± standard error of the mean from at least three different experiments. Asterisks (*) indicate significant differences between treated cell groups and the control cell groups. Besides, the apoptotic effect of curcumin was more significant that of the TSA.

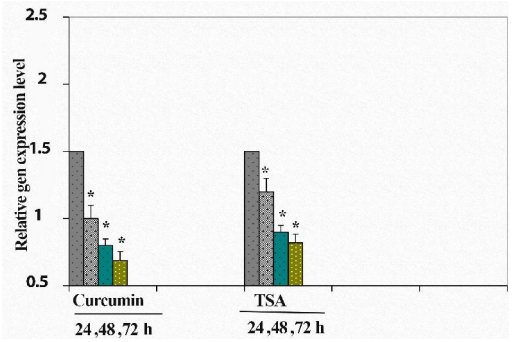

Figure 6. The relative expression level of DNMT1

As can be seen above, curcumin (5 Mµ) and TSA (2.5 Mµ) decreased DNMT1 gene expression significantly. Data were analyzed using the comparative Ct (ΔΔct) method and are presented as a mean ± standard error of the mean from at least three different experiments. It should be noted that the effect of curcumin was stronger than TSA. Asterisks (*) indicate significant differences between treated cells and the control group.

Table I. Real time polymerase chain reaction primers (DNMT1 and GAPDH) used in this study

Primer name	Primer name Primer sequences (5' to 3')
DNMT1 Forward: Reverse:	 GAG GAA GCT GCT AAG GAC TAG TTC ACT CCA CAA TTT GAT CAC TAA ATC
GAPDH Forward: Reverse:	 AAC GTG TCA GTO GTG GAC CTG GGG TGT CGC TGT FGA AGT

Table II. The percentage of apoptosis in the groups treated with curcumin and TSA at different time periods.

Drug	Dose/ µM	Duration/ h	Apoptosis %	P-value
Curcumin	5	24	17	P < 0.001
	5	48	32	P < 0.001
	5	72	45	P < 0.001
TSA	2.5	24	12	P < 0.001
	2.5	48	24	P < 0.001
	2.5	72	34	P < 0.001

Discussion

DNA methylation plays a significant role in chromatin remodeling and transcriptional regulation in mammalian cells. DNA hypomethylation has been well documented in various cancers. Aberrant DNA methylation can be involved in tumorigenesis as a result of repression of gene transcription by methylation of the CpG islands of specific genes, such as tumor-suppressor genes (12). In addition to hypermethylation, histone deacetylation plays a major role in tumorigenesis and is a common hallmark of human cancer (13). In mammals, DNA methylation is mediated at CpG dinucleotides by DNMTs. Histone modifications are modified by HATs and HDACs. Fortunately, epigenetic changes such as DNA hypermethylation and histone

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deacetylation are reversible by DNMTs inhibitors and HDAC inhibitors (14). Previously, we indicated that DNMT1 inhibitor genistein can induce apoptosis in human HCC PLC/PRF5 (15), HepG2 (11, 16), and Hepa1-6 (17) cell lines. Besides, we reported that histone deacetylase inhibitor valproic acid can induce apoptosis in HCC WCH 17 cell line (18). Furthermore, we demonstrated that GE and trichostatin A act through inactivation of DNMT1, DNMT3a, and DNMT3b gene expression in HCC Hep G2 cell line (9).

In the present study, we indicated that curcumin and TSA can inhibit cell growth and induce apoptosis in Hepa 1-6 cells and that curcumin induces a more significant apoptotic effect than TSA. Besides, our result indicated that both agents can reduce the expression of DNMT1 significantly. The effect of curcumin on DNMT1 down-regulation was stronger than that of TSA.

Similar to our study, it has been reported that curcumin inhibits proliferation and induces apoptosis of HCC cells in a concentration-dependent manner. Other studies have shown that curcumin covalently blocks the catalytic thiolate of C1226 of DNMT1 to exert its inhibitory effect (19). One of the mechanisms of curcumin in HCC is Wnt signaling interruption by decreasing β-catenin activity, which suppresses the expression of β-catenin target genes (VEGF, c-myc, and cyclin D1) (20).

In acute myeloid leukemia (AML), curcumin reduces the expression of positive regulators of DNMT1, including p65 and Sp1, which correlates with a reduction in binding of these factors to the DNMT1 promoter region (21). Curcumin inhibits cell cycle progression and cell proliferation by accumulating cells at the G2/M-phase with a decreased expression level of DNMT1 and enhanced expression of p21 in melanoma cells (22). Another pathway of the apoptotic effect of curcumin includes NF-KB activity inhibition which leads to cellular apoptotic response (23).

As mentioned above, TSA inhibited proliferation and induced apoptosis in the current study. In agreement with our report, it has been shown that TSA increases the levels of acetylated histones H3 and H4, up-regulates liver-specific functions and liver-enriched transcription factors resulting cell growth inhibition and G0 /G1 arrest induction in both HCC HepG2 and Huh-7 (24). It has been indicated that TSA induces G2/M-phase arrest by upregulation of p2lcip/waf, cyclin A, bax, and (pro)-caspase 3 and down-regulation of bcl-2 in hepatoma cells HepG2 (25). Similar studies have reported that it enhances the expression of p21, cyclin E, cyclin A, CBP, Bax, and Bak, cleaves PARP (85kDa) protein, and reduces the expression of HDAC1, E2F-1, E2F-4, p53, and hyperphosphorylated Rb protein in human oral and gastric carcinoma cell lines (26-28). In the current study, we did not evaluate the combined effect of agents and also the apoptotic factors such as expression of the cyclin-dependent kinase inhibitor p21cip1/waf1, acetylation status of p53, and phosphorylation of the cell cycle regulator retinoblastoma protein (Rb). The evaluation of these factors and the combination effect is recommended.

Conclusion

In conclusion and in accordance with our findings, curcumin and TSA were able to restore the epigenetic regulation and appeared as attractive preventive and/or therapeutic candidates against human hepatocellular carcinoma.

Acknowledgment

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Conflict of interest

Authors declared no conflict of interst.

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