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The effect of curcumin on cell adhesion of human esophageal cancer cell

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Abstract. – OBJECTIVE: Esophageal cancer is the 8th most common cancers worldwide and the 6th most common cause of death among cancers. Curcumin has been reported to have the function of anti-inflammatory, antioxidant, anti-rheumatoid, and anti-atherosclerosis role. It can also reduce lipid, eliminate free radicals and inhibit the growth of the tumor. Many reports had suggested that curcumin has shown great potential in the treatment of tumors by inducing apoptosis. Little is known about the effects of curcumin on cell adhesion of tumor cancer. Therefore, in this study, we attempted to look for a new approach to target resistant cells and improve efficacy without toxicity.

MATERIALS AND METHODS: Human esophageal cancer cell line (Eca-109 cells) was cultured. Cell adhesion was detected under a microplate reader. Reactive oxygen species were measured using Fluostar Omega Spectrofluorimeter. SOD activity and GSH content in cells were detected by commercial determination kit. The expression of p-JAK, p-STAT3 and STAT3 were measured by Western blot and RT-PCR.

RESULTS: Cell adhesion assay showed curcumin enhances cell-cell adhesion and cell-matrix adhesion in Eca-109 cells. ROS levels, SOD activity and total GSH content were detected and the results showed curcumin decreases intracellular ROS levels but increases SOD activity and total GSH content. Then, NAC (ROS inhibitor) and ICI (ER inhibitor) were pre-treated. Results showed ICI reversed the decreasing of intracellular ROS levels and the increasing of SOD activity and total GSH content affected by curcumin, but NAC had no such impact. Taken together, ER rather than ROS involves in cell adhesion affected by curcumin. Meanwhile, the downregulating of p-JAK, p-SATA3 and total STAT3 were caused by curcumin but NAC had no such influence. They were reversed by ICI, but NAC had no such influence.

CONCLUSIONS: Curcumin could increase cell adhesion through inhibiting JAK/STAT3 mediated by ER in Eca-109.

Key Words:
Curcumin, Cell adhesion, ROS, ER, JAK/STAT3, Cell adhesion molecules.

Introduction

Esophageal cancer is the 8th most common cancers worldwide and the 6th most common cause of death among cancers[1,2]. In recent 5 years, the survival rate of esophageal cancer was only 10 to 15% for the United States and 10% for Europe, despite advances in surgery and neoadjuvant therapy[3]. In recent years, many medical workers and researchers have devoted to the study of mechanism of esophageal cancer. The pathogenesis is still unclear. At present, chemotherapy, radiation therapy and esophagogastric resection are the current treatments, and chemotherapy is one of the most common methods for esophageal cancer treatment. Many studies showed chemotherapy drugs have side effects on human body. Therefore, it is necessary to look for a new approach to target resistant cells and improve efficacy without toxicity.

A number of natural products derived from edible plants have been reported to exhibit low toxicity and potential antitumor activity[4,5]. Curcumin is a kind of yellow pigment extracts from *zingiberaceae* plants, such as turmeric rhizome and so on. It also exists in other *zingiberaceae* plants. Modern researches have found that curcumin has the function of anti-inflammatory, antioxidant, anti-rheumatoid, and anti-atherosclerosis role[6,7]. It can also reduce lipid, eliminate free radicals and inhibit growth of tumor[8]. Many reports had suggested that curcumin has shown great potential in the treatment of tumors by inducing apoptosis[9-11].

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Adhesion, which includes cell-cell adhesion and cell-matrix adhesion, is an important process in tumor progression[12,13]. Little is known about the effects of curcumin on cell adhesion. Therefore, the effect of curcumin was explored on adhesion of esophageal cancer.

Cell-cell adhesion and cell-matrix are strictly controlled in normal cells. Cell adhesion is an important process in tumor progression and is frequently observed in cancer progression[12,13]. Cell adhesion rate is generally reduced in human cancer cells. The reduction of intercellular adhesiveness results in the destruction of histological and it is a morphological hallmark of malignant tumors[14,15]. Adhesion plays an important role in cell invasion and migration, and it has been used to assess the aggressive and malignant in cancer cells. The mechanism of adhesion is implicated[13,16]. Transduction of cell signals plays key roles in the initiation and progression of adhesion.

Oxidative stress is that the body is suffered from harmful stimulation, high activity molecules, such as reactive oxygen species free radicals (ROS) and reactive nitrogen free radicals (RNS) overproduces. Oxidation degree exceeds the removal of oxide, the oxidation system and antioxidant system imbalance, resulting in tissue damage. Mean molecular targets include estrogen receptors (ERs) and reactive oxygen species (ROS). Many reports indicate oxidative stress often expresses higher in cancer cells than normal cells[17-19].

JAK/STAT signaling pathway, which is short for Janus kinase/Signal transducers and activators of transcription, has been reported to involve in cancer cells[20]. When receptors are combined by cytokines, JAK (a tyrosine protein kinase) is activated by phosphorylation. Then monomer STAT3 of cytoplasm increases and p-STAT3 forms. p-STAT3 releases from receptors and enters the nucleus. In nucleus, p-STAT3 binds to special DNA sites and regulates the downstream target genes, thus promoting cell malignant transformation and tumorigenesis[21,22]. Many papers have reported JAK/STAT3 pathway is activated in cancer cells[23,24].

In this study, the effect of curcumin on cell adhesion in esophageal cancer (Eca-109 cells) was explored and the mechanism was verified. Results showed curcumin could increase cell adhesion through inhibiting JAK/STAT3 signal pathway mediated by ER in Eca-109. Therefore, curcumin has great potential in treating cancer.

Materials and Methods

Materials

Roswell Park Memorial Institute 1640 (RPMI 1640) and fetal bovine serum (FBS) were obtained from Gibco (Grand Island, NY, USA). Penicillin/streptomycin and pancreatin were from Sigma-Aldrich (St. Louis, MO, USA). Dimethyl sulfoxide (DMSO) was purchased from Sigma-Aldrich (St. Louis, MO, USA). N-acetyl-l-cysteine (NAC, the scavenger of ROS) was obtained from Beyotime Institute of Biotechnology (Nantong, Jiangsu, China). ER inhibitor ICI 182780 and 2', 7'-dichlorofluorescein diacetate (DCFH-DA) were from Sigma-Aldrich (St. Louis, MO, USA). Western lysis buffer, BCA protein kit and enhanced chemiluminescence (ECL) kit were from Beyotime Institute of Biotechnology (Nantong, Jiangsu, China). Antibodies for p-JAK1 (Tyr 1022), p-STAT3 (Ser 727) and STAT3 were purchased from BBI (Sangon Biotech, Shanghai, China). α-tubulin was from Sigma-Aldrich (St. Louis, MO, USA).

Cell Culture and Drug Treatments

Human esophageal cancer cell line (Eca-109) was obtained from the Institute of Biochemistry and Cell Biology (SIBS, CAS, Shanghai, China). Eca-109 was maintained in RPMI-1640 medium (HyClone, South Logan, UT, USA). Media was supplemented with 10% fetal bovine serum (FBS) (Boster, Wuhan, China) and 1% penicillin/streptomycin (Solarbio, Beijing, China) at 37°C in a 5% CO_2 humidified cell culture incubator.

Cell-matrix Adhesion Assay

Eca-109 cells were digested with trypsin (0.1%) and re-suspended with RPMI-1640 medium. Cells were seeded at a density of 1×10^4 cells/well in flat-bottomed 96-well plate and incubated for 0.5 h, 1 h, 1.5 h and 2 h, respectively at 37°C. Non-adherent cells were removed and washed by phosphate-buffered saline (PBS) and adherent cells were fixed with paraformaldehyde solution (4%, 50 μL) at room temperature for 15 min. Wells were washed with PBS for three times and cells were stained with 1% crystal violet at room temperature for 15 min. Then, excess dye was removed and intracellular stain was solubilized by 1% SDS (50 μL). Absorbance was determined at 570 nm under a microplate reader. Cell-matrix adhesion ratio was calculated on the following formula: (A_{570} Experiment/ A_{570} Control) ×100%.

Cell-cell Adhesion Assay

Eca-109 cells were digested with trypsin (0.1%) and re-suspended with RPMI-1640 medium. Cells were seeded at a density of 1×10^4 cells/well in flat-bottomed 96-well plate. The plate was placed at a 37°C shaker (rotated at 80 rpm) for 1 h. Then, the number of single and aggregates cells was counted under a hemacytometer. Cell-cell adhesion ratio was calculated on the following formula: Nd/Nc. Nc is the number of single cells forming aggregation in control and Nd is the group cells detected in cultures at various time points.

Measurement of ROS Generation

The generation of ROS was determined by DCFH-DA, which is a cell-permeable, nonfluorescent probe. This probe is cleaved by intracellular esterase into a highly fluorescent dichlorofluorescein upon reaction with H_2O_2. Eca-109 cells were plated in at a density of 1×10^6 cells/well in flat-bottomed 6-well plate and treated with curcumin (5, 20 and 50 μM) for 24 h, NAC (5 mmol, 2 h) in RPMI-1640 medium alone or composite processing. Control group was treated with PBS in medium. Cells were stained with DCFH-DA (10 μmol/L) at 37°C for 30 min. The generation of ROS was determined by dichlorofluorescein fluorescence. Fluorescence intensities were determined at an excitation of 488 nm and an emission of 525 nm using Fluostar Omega Spectrofluorimeter (Thermo Fisher Scientific, Waltham, MA, USA).

Determinations of Oxidative Stress-Related Parameters

SOD activity and GSH content in cells were detected by commercial determination kit (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China) dichlorofluorescein fluorescence. Eca-109 cells were seeded in flat-bottomed 6-well plate at a density of 1×10^6 cells/well and treated with curcumin (5, 20 and 50 μM) for 24 h, NAC (5 mmol, 2 h) in RPMI-1640 medium alone or composite processing. Control group was treated with PBS in medium. Cells were dissolved in physiological and disrupted using ultrasound equipment and then centrifuged at 6000 rpm for 10 min. The supernatants were used to determined enzyme activity.

Western Blot Analysis

The cells were lysed with Western lysis buffer (containing 1% phenylmethylsulfonyl fluoride (PMSF)) for 10 min at 4°C and centrifuged at 13000 rpm under a high speed refrigerated (Eppendorf, Hamburg, Germany) at 13000 rpm, 4°C for 15 min to precipitate the insoluble material. Protein concentration was detected by bicinchoninic acid (BCA) protein kit. An equal amount of protein (80 μg) was loaded and separated by 12% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred to PVDF (polyvinylidene fluoride) membranes. The membrane was blocked in Tris buffered-saline (TBS) containing 5% milk and Tween-20 for 1 h. The membrane was incubated with anti-p-JAK1, anti-p-STAT3, STAT3 and α-tubulin overnight at 4°C. The membrane was washed with TBST (Tris buffered saline containing Tween-20) and incubated with the appropriate horse radish peroxidase (HRP)-conjugated secondary antibody (Abcam, Cambridge, MA, USA). Finally, the protein was detected by chemiluminescence.

Reverse Transcription-Quantitative Polymerase Chain Reaction (RT-PCR)

Quantitative Real-time PCR (qRT-PCR) was performed using an Applied Biosystems platform (Applied Biosystems, Foster City, CA, USA). In brief, total RNA in cells was isolated and column purified using a RNeasy Mini Kit (Qiagen, Suzhou, Jiangsu, China) and reverse-transcribed with 250 μM dNTPs, 12.5 ng/μL oligo$(dT)_{12\text{-}18}$ primer, 75 ng/μL random primers, 10 mM dithiothreitol, 1 U/μL RNaseOUT, and 5 U/μL SuperScript II reverse transcriptase (Invitrogen, Carlsbad, CA, USA). Real-time polymerase chain reaction (PCR) amplification using 20 ng worth of total RNA, 1×Platinum SYBR Green qPCR SuperMix-UDG (Invitrogen, Carlsbad, CA, USA), and 0.2 μM both forward and reverse primers were performed on the Corbett Rotor-Gene 6000 (Qiagen, Suzhou, Jiangsu, China). GAPDH mRNA amplified from the same samples served as an internal control. Relative expression of targeted gene was normalized by subtracting the corresponding GAPDH threshold cycle (Ct) values using the $^{\Delta\Delta}$Ct comparative method.

Primer sets (Invitrogen, Carlsbad, CA, USA) were designed using DNASTAR software (Promega, Madison, WI, USA).

E-cadherin-Fw: 5' AGGACCAGGTGACCACCCTAGA3', E-cadherin-Rw: 5'ATGCCCAAGATGGCAGGAAC3', N-cadherin-Fw: 5'TCCATGTGCCGGATAGC3', N-cadherin-Rw: 5'AGTTCAGTCATCACCTCCACCATACA3', CD29-Fw: 5'AATGAAGGGCGTGTTGGTAG3', CD29-Rw: 5'CTGCCAGTGTAGTTGGGGTT3', GAPDH-Fw: 5'GCACCGTCAAGGCT-

GAGAAC3', GAPDH-Rw: 5'TGGTGAAGACGC-CAGTGGA3'

Statistical Analysis

The results were analyzed by SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). All data were presented as the mean±SD and analyzed with ANOVA with Tukey's multiple comparison tests. A value < than 0.05 ($p<0.05$) and 0.01 ($p<0.01$) were considered statistically significant and highly significant, respectively.

Results

Curcumin Enhanced Cell-Cell Adhesion and Cell-matrix adhesion in Eca-109 Cells

To investigate the effect of curcumin on cell adhesion of human esophageal cancer cell line, Eca-109 cells were treated with curcumin (5, 20 and 50 μM) for 24 h, NAC (5 mmol, 2 h) in Roswell Park Memorial Institute-1640 (RPMI -1640) medium alone or composite processing. Then, cells were digested with trypsin (0.1%) and re-suspended with RPMI-1640 medium. Eca-109 cells were plated at a density of 1×10^4 cells/well in flat-bottomed 96-well plate and treated according to the above-described steps. Results showed the cell-cell adhesion was enhanced after treated with curcumin in dose-dependent manner (Figure 1A). Quantitative analysis of cell-cell adhesion was also detected and results indicated that curcumin significantly increased the ratio of cell-cell adhesion. The ratio of cell-cell adhesion was increased to 192% in 50 μM curcumin-treated cells compared with the control (Figure 1B). The result showed cells were adhered quickly after treated with curcumin compared with the control (Figure 1C). Meanwhile, results showed the effect of curcumin on cell adhesion ratio reached the biggest in 50 μM curcumin-treated for 1.5 h. Above all, curcumin enhances cell-cell adhesion and cell-matrix adhesion in Eca-109 cells.

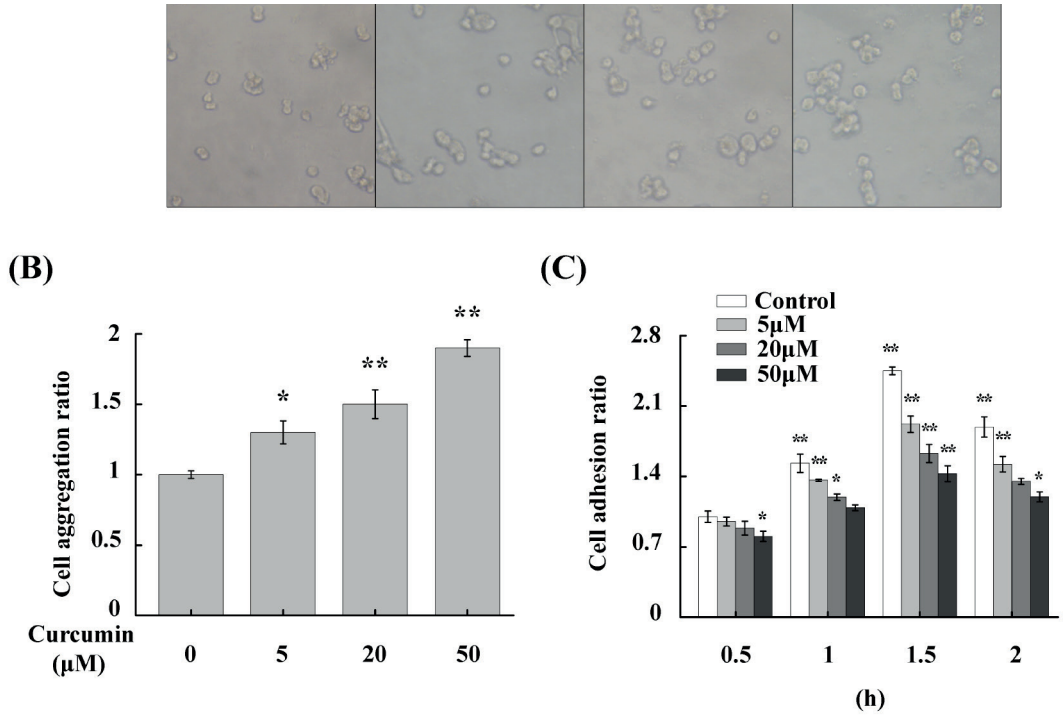

Figure 1. Effect of curcumin on the cell-cell adhesion and cell-matrix adhesion of Eca-109 cells. Eca-109 cells were treated with curcumin (5, 20 and 50 μM) for 24 h. Then, cells were digested and seeded at a density of 1×104 cells/well in flat-bottomed 96-well plate. ***(A)*** The plate was placed at a 37°C shaker (rotated at 80 rpm) for 1 h. Then the number of single and aggregates cells was counted under a hemacytometer. ***(B)*** Quantitative analysis of cell-cell adhesion was calculated. ***(C)*** Cells were incubated for 0.5 h, 1 h, 1.5 h and 2 h, respectively at 37°C. Cell-matrix adhesion ratios are detected under a microplate reader. In ***(A)***, ***(B)*** and ***(C)***, values are percent as the mean ± SD of three independent experiments. $0.01 <^{*}p <0.05$ and $^{**}p <0.01$ vs. control.

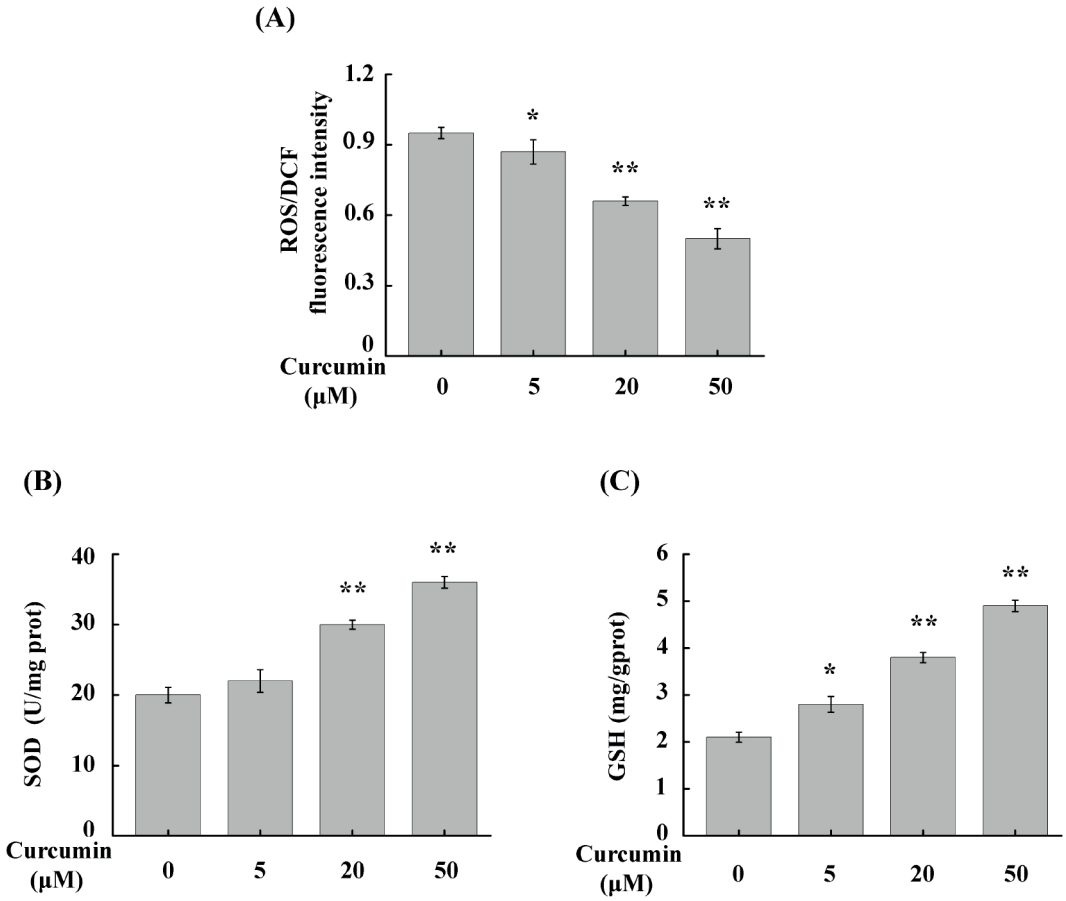

Figure 2. Effect of curcumin on oxidative stress in Eca-109. Eca-109 cells were plated in at a density of 1×106 cells/well in flat-bottomed 6-well plate and treated with curcumin (5, 20 and 50 μM) for 24 h. ***(A)*** Cells were stained with DCFH-DA (10 μmol/L) at 37°C for 30 min. The generation of ROS was determined by dichlorofluorescein fluorescence. Meanwhile, cells were dissolved in physiological and disrupted using ultrasound equipment and then centrifuged at 6000 rpm for 10 min. The supernatants were used to determined SOD activity (B) and GSH content ***(C)***. In ***(A)***, ***(B)*** and ***(C)***, values are percent as the mean ± SD of three independent experiments. $0.01 < {}^{*}p < 0.05$ and ${}^{**}p < 0.01$ vs. control.

ER Rather Than ROS Involved in Cell-Cell Adhesion and Cell-Matrix Adhesion were Affected by Curcumin

It had been reported that oxidative stress involved in cell adhesion and assessed the mechanism of cell adhesion induced by curcumin, intracellular ROS levels, SOD activity and total GSH content of Eca-109 were detected after treated by curcumin. Results showed curcumin decreased intracellular ROS levels but increased SOD activity and total GSH content (Figure 2). These results indicated that curcumin inhibits the oxidative stress of Eca-109 cells. In order to further study the function of ROS and ER in the adhesion affected by curcumin, NAC (ROS inhibitor) and ICI (ER inhibitor) were pre-treated. As shown in Figure 3, ICI reversed the decreasing of intracellular ROS levels and the increasing of SOD activity and total GSH content affected by curcumin, but NAC had no such impact. Meanwhile, ICI reversed the enhancement of cell-cell adhesion and cell-matrix adhesion induced by curcumin. (Figure 4) Taken together, ER rather than ROS involves in cell-cell adhesion and cell-matrix adhesion affected by curcumin.

Curcumin Inhibited JAK/STAT3 Signal Pathway in Eca-109 cells

JAK/STAT3 pathway had been reported to involve in the occurrence and development of cancer. Therefore, the effect of JAK/STAT3 signal pathway was investigated on the adhesion regulation affected by curcumin. Eca-109 cells were seeded in 60 mm dishes (1×10^6 cells/dish) and incubated overnight. After 24 h, Eca-109 cells were treated with curcumin (5, 20 and 50 μM) for 24 h.

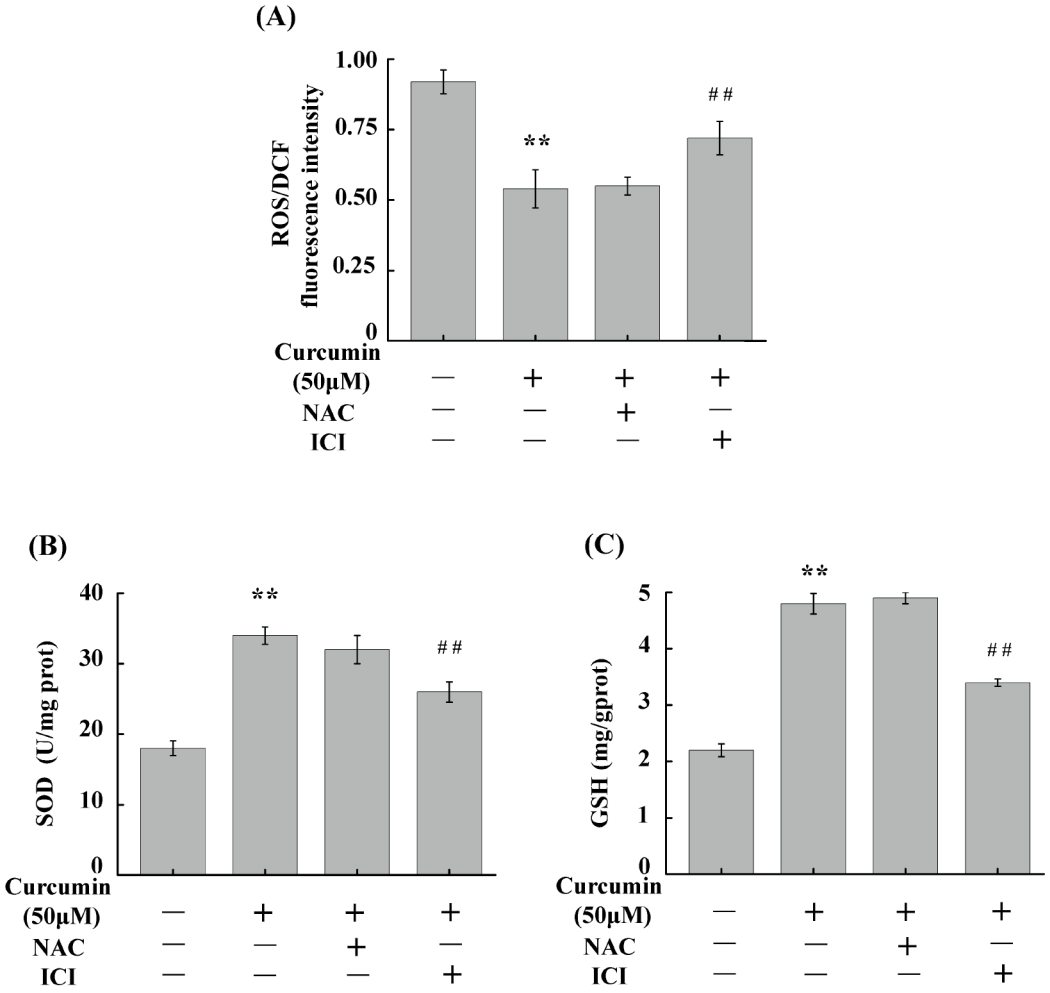

Figure 3. Oxidative stress affected by curcumin were inhibited by ICI not NAC in Eca-109. Eca-109 cells were plated in at a density of 1×106 cells/well in flat-bottomed 6-well plate and incubated with curcumin (5, 20 and 50 μM) for 24 h with or without NAC and ICI. ***(A)*** ROS levels, (B) SOD activity, and ***(C)*** GSH content were assessed as described in figure 2. In ***(A)***, ***(B)*** and ***(C)***, values are percent as the mean ± SD of three independent experiments. $0.01 < {}^{*}p < 0.05$ and ${}^{**}p < 0.01$ vs. control. $0.01 < {}^{\#}p < 0.05$ and ${}^{\#\#}p < 0.01$ vs. curcumin alone.

The expression of p-JAK, p-SATA3 and STAT3 were detected using Real-time PCR and Western blot. Results showed curcumin significantly down-regulated the expression of p-JAK, p-SATA3 and STAT3 compared to the control (Figure 5). These results indicated curcumin inhibits JAK/STAT3 signal pathway in Eca-109.

Curcumin Inhibited JAK/STAT3 Signal Pathway via Down-regulated ER

The experimental results had showed ER and JAK/STAT3 signal pathway were both inhibited after treated by curcumin in Eca-109. Therefore, the possible correlation between ER and JAK/STAT3 pathway in Eca-109 cells after treated was detected. Eca-109 cells were pre-treated with NAC and ICI and incubated with curcumin (50 μM) for 24 h. The expression of p-JAK, p-SATA3 and STAT3 were detected using Real-time PCR and Western blot. Results indicated supplement ICI reversed the downregulating of p-JAK, p-SATA3 and total STAT3 caused by curcumin; NAC had no such influence (Figure 6). Taken together, these results suggested curcumin inhibits JAK/STAT3 signal pathway via down-regulating ER not ROS.

Discussion

Esophageal cancer is the 8th most common cancer worldwide. In recent 5 years, the survival rate of esophageal cancer was still low for the United

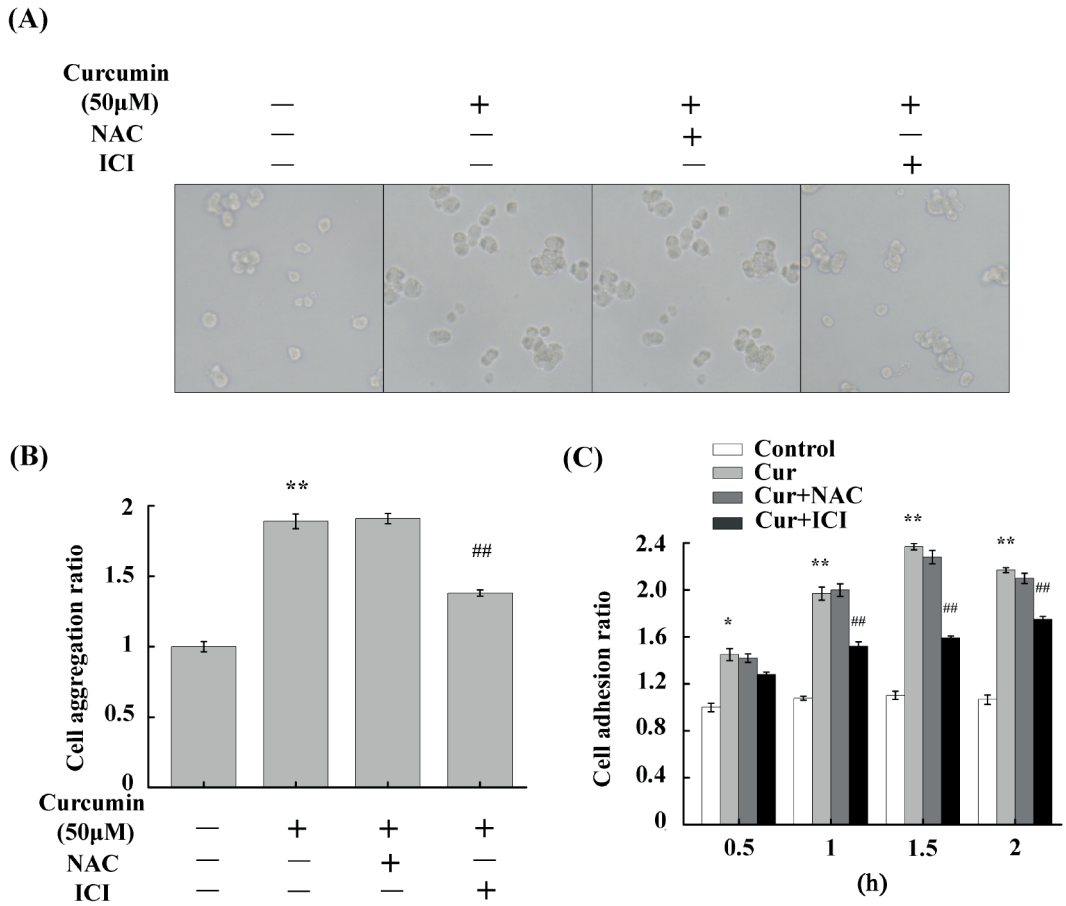

Figure 4. Cell adhesion affected by curcumin were inhibited by ICI not NAC in Eca-109. Eca-109 cells were incubated with curcumin (5, 20 and 50 μM) for 24 h with or without NAC and ICI. Then cells were digested and seeded at a density of 1×104 cells/well in flat-bottomed 96-well plate. ***(A)*** Morphological photo of cell-cell adhesion, ***(B)*** quantitative analysis of cell-cell adhesion, and ***(C)*** cell-matrix adhesion ratio were detected as described in figure 1. In (A), (B) and (C), values are percent as the mean ± SD of three independent experiments. 0.01 $<^{*}p<0.05$ and $^{**}p<0.01$ vs. control. 0.01 $<^{\#}p<0.05$ and $^{\#\#}p<0.01$ vs. curcumin alone.

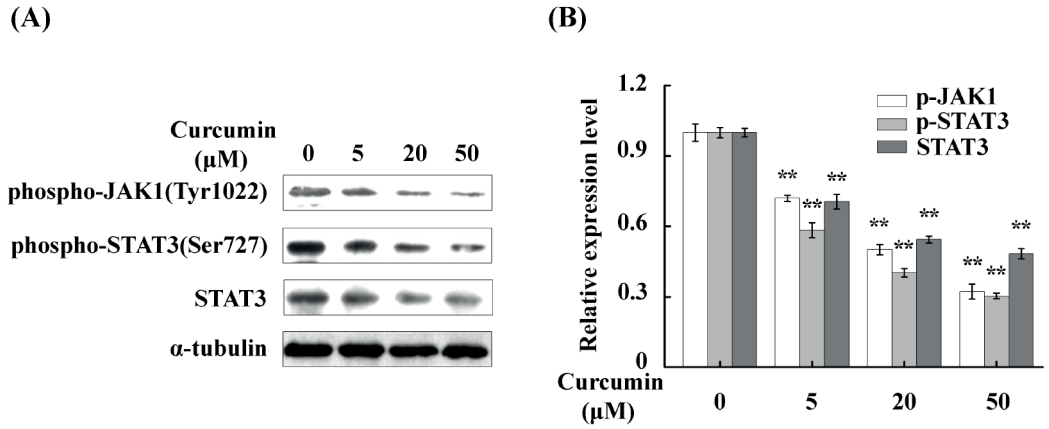

Figure 5. Effect of curcumin on JAK/STAT3 signal patyway in Eca-109. Eca-109 cells were seeded in 60 mm dishes (1×106 cells/dish) and incubated overnight. After 24 h, Eca-109 cells were treated with curcumin (5, 20 and 50 μM) for 24 h. The expression of p-JAK, p-SATA3 and STAT3 were detected using Western blot (A) and Real-time PCR ***(B)***. In ***(A)*** and ***(B)***, values are percent as the mean ± SD of three independent experiments. 0.01 $<^{*}p<0.05$ and $^{**}p<0.01$ vs. control.

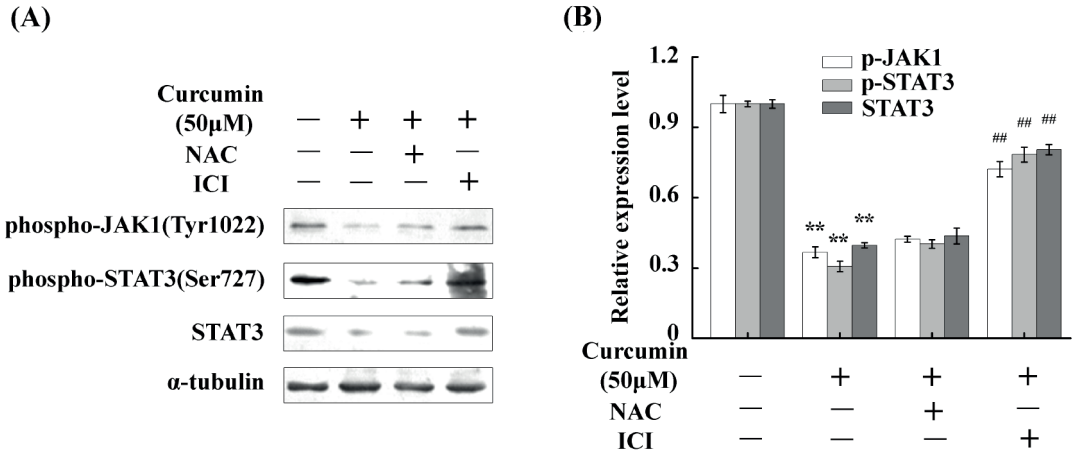

Figure 6. JAK/STAT3 signal pathway affected by curcumin were inhibited by ICI not NAC in Eca-109. Eca-109 cells were seeded in 60 mm dishes (1×106 cells/dish) and incubated overnight. After 24 h, Eca-109 cells were incubated with curcumin (5, 20 and 50 μM) for 24 h with or without NAC and ICI. The expression of p-JAK, p-SATA3 and STAT3 were detected using Western blot (A) and Real-time PCR (B). In (A) and (B), values are percent as the mean ± SD of three independent experiments. 0.01 $<^{*}p<0.05$ and $^{**}p<0.01$ vs. control. 0.01 $<^{\#}p<0.05$ and $^{\#\#}p<0.01$ vs. curcumin alone.

States and Europe despite advances in surgery and neoadjuvant therapy[1,2]. Curcumin has the function of anti-inflammatory, antioxidant, anti-rheumatoid, and anti-atherosclerosis role.

Furthermore, it can also reduce lipid, eliminate free radicals and inhibit growth of tumor[7,9]. Adhesion, including cell-cell and cell-matrix adhesive, has been reported to play an important role in tumor progression[8]. Furthermore, little is known about the effects of curcumin on cell adhesion. Therefore, the effect of curcumin was explored on cell adhesion of human esophageal cancer cell line (Eca-109). Results showed curcumin could enhance cell-cell adhesion and cell-matrix adhesion in Eca-109 cells in dose-dependent. Many reports have showed oxidative stress involves in cell adhesion and plays a key role in cancer cells. Therefore, the relationship between oxidative stress and curcumin-induced increasing of cell adhesion was investigated. Results indicated ER rather than ROS involves in cell-cell adhesion and cell-matrix adhesion affected by curcumin. JAK/STAT3 pathway has been reported to be activated in cancer cells. After JAK is activated by phosphorylation, p-STAT3 is released from receptors and enters the nucleus, thus regulating the metabolism of tumor cells[19,27,28]. The expression of JAK/STAT3 was detected in protein and gene level. Results indicated curcumin inhibits JAK/STAT3 signal pathway in Eca-109. Meanwhile, ICI (ER inhibitor) could reverse the downregulating of p-JAK, p-SATA3 and total STAT3 induced by curcumin, but NAC (ROS inhibitor) had no such influence. Above all, curcumin inhibits JAK/STAT3 signal pathway via down-regulating ER not ROS.

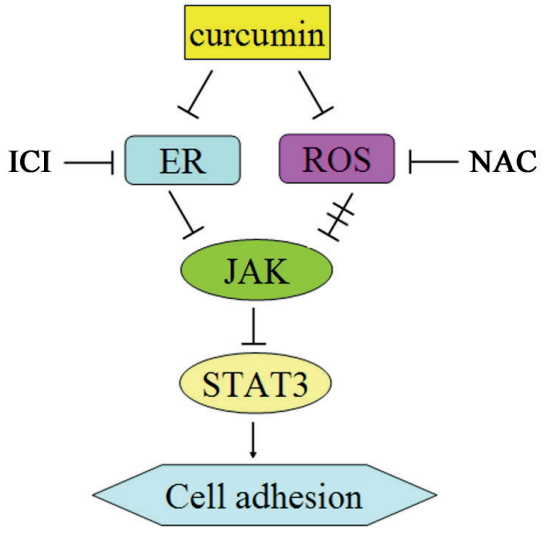

Figure 7. Proposed mechanism of curcumin enhances cell adhesion of human esophageal cancer cell. Incubate of curcumin firstly inhibits ER and suppresses oxidative stress. Next, it decreases phosphorylation of JAK and then phosphorylation of represses STAT3, which impacts cell adhesion of human esophageal cancer cell.

Conclusions

Curcumin could increase cell adhesion by inhibiting ER-mediated JAK/STAT3 signal pathway

and has great potential in against cancer. Briefly, incubate of curcumin firstly inhibits ER and suppresses oxidative stress. Next, it decreases phosphorylation of JAK and then phosphorylation of represses STAT3, which impacts cell adhesion of human esophageal cancer cell (Figure 7).

Conflict of Interest

The Authors declare that they have no conflict of interest.

References

1) Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108.
2) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
3) Sant M, Aareleid T, Berrino F, Bielska LM, Carli PM, Faivre J, Grosclaude P, Hedelin G, Matsuda T, Moller H, Moller T, Verdecchia A, Capocaccia R, Gatta G, Micheli A, Santaquilani M, Roazzi P, Lisi D. EUROCARE-3: survival of cancer patients diagnosed 1990-94-results and commentary. Ann Oncol 2003; 5: v61-118.
4) Song L, Jiao C, Zhuoyu L. A serine protease extracted from Trichosanthes kirilowii induces apoptosis via the PI3K/AKT-mediated mitochondrial pathway in human clolrectal adenocarcinoma cells. Food Funct 2016; 7: 843-854.
5) Sharif T, Stambouli M, Burrus B, Emhemmed F, Dandache I, Auger C, Etienne N, Schini Vb, Fuhrmann G. Bioactive compound contents and antioxidant activity in aronia (Aronia melanocarpa) leaves collected at different growth stages. J Funct Foods 2013; 5: 1244-1252.
6) Schraufstatter E, Bernt H. Antibacterial action of curcumin and related compounds. Nature 1949; 164: 456-467.
7) Anand P, Kunnumarkkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm 2007; 4: 807-818.
8) Subash CG, Sridevi P, Wonil K, Bharat BA. Discovery of curcumin, a component of the golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol 2012; 39: 283-299.
9) Dharmalingam S, Sivapriya P, Prabhu R, Richard JB, Shrikant A, Prateek S. Curcumin induces cell death in esophageal cancer cells through modulating notch signaling. PLoS One 2012; 17: 1-11.
10) Hartojo W, Silvers AL, Thomas DG, Seder CW, Lin L, Rao H, Wang Z, Greenson JK, Giordano TJ, Orringer Mb, Rehemtulla A, Bhojani MS, Beer DG, Chang AC. Curcumin promotes apoptosis, increases chemosensitivity, and inhibits nuclear factor kappaB in esophageal adenocarcinoma. Transl Oncol 2010; 3: 99-108.
11) Li L, Ahmed B, Mehta K, Kurzrock R. Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. Mol Cancer Ther 2007; 6: 1276-1282.
12) Beaussart A, Eikiratchatel S, Sullan RM, Alsteens D, Herman P, Derclaye S, Dufrene YF. Quantifying the forces guiding microbial cell adhesion using single-cell force spectroscopy. Nat Protoc 2014; 9:1049-1055.
13) Yves FD. Sticky microbes: forces in microbial cell adhesion. Trends Microbiol 2015; 23: 376-382.
14) Bourboulia D, Sterlerstevenson WG. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs): positive and negative regulators in tumor cell adhesion. Semin Cancer Bio 2010; 20: 161-168.
15) Hirohashi S, Kanai Y. Cell adhesion system and human cancer morphogenesis. Cancer Sci 2003; 94: 575-581.
16) Silvafilho AF, Sena WL, Lima LR, Carvalho LV, Pereira MC, Santos LG, Santos RV, Tavares LB, Pitta MG, Rego MJ. Glycobiology modifications in intratumoral hypoxia: the breathless side of glycans interaction. Cell Physiol Biochem 2017; 41: 1801-1829.
17) Wang ZC, Qi J, Liu LM, Li J, Xu HY, Liang B, Li B. Valsartan reduce AT1-AA- induced apoptosis through suppression oxidative stress mediated ER stress in endothelial progenitor cells. Eur Rev Med Pharmacol Sci 2017; 21: 1159-1168.
18) Wang X, Meng L, Zhao L, Wang Z, Liu G, Guan G. Resveratrol ameliorates hyperglycemia-induced renal tubular oxidative stress damage via modulating the SIRT1/FOXO3a pathway. Diabetes Res Clin Pract 2016; 126: 172-181.
19) Ahamed M, Ali D, Alhadlaq HA, Akhtar MJ. Nickel oxide nanoparticles exert cytotoxicity via oxidative stress and induce apoptotic response in human liver cells (HepG2). Chemosphere 2013; 93: 2514-2522.
20) Schindler CW. Series introduction: JAK-STAT signaling in human disease. J Clin Invest 2002; 109: 1133-1137.
21) Li WC, Ye SL, Sun RX, Liu YK, Tang ZY, Kim Y, Karras JG, Zhang H. Inhibition of growth and metastasis of human hepatocellular carcinoma by antisense oligonucleotide targeting signal transducer and activator of transcription3. Clin Cancer Res 2006; 12: 7140-7148.
22) Xiaoting J, Meilan C, Li S, Hanqing LI, Zhuoyu L. The evaluation of p,p'-DDT exposure on cell adhesion of hepatocellular carcinoma. Toxicology 2014; 322: 99-108.
23) Rivat C, Dewever O, Bruyneel E, Mareel M, Gespach C, Attoub S. Disruption of STAT3 signaling leads to tumor cell invasion through alterations of homotypic cell-cell adhesion complexes. Oncogene 2004; 23: 3317-3327.
24) Wei RC, Cao X, Gui JH, Zhuo XM, Zhong D, Yan QL, Huang WD, Qian QJ, Zhao FL, Liu XY. Augmenting the antitumor effect of TRAIL by SOCS3 with double-regulated replicating oncolytic adenovirus in

hepatocellular carcinoma. Hum Gene Ther 2011; 22: 1109-1119.

25) Sadeghzadeh J, Vakili A, Bandegi AR, Sameni HR, Zahedi KM, Darabian M. Lavandula reduces heart injury via attenuating tumor necrosis factor-alpha and oxidative stress in a rat model of infarct-like myocardial injury. Cell J 2017; 19: 84-93.

26) Suntiparpluacha N, Tammachote N, Tammachote R. Triamcinolone acetonide reduces viability, induces oxidative stress, and alters gene expressions of human chondrocytes. Eur Rev Med Pharmacol Sci 2016; 20: 4985-4992.

27) Aneknan P, Kukongviriyapan V, Prawan A, Kongpetch S, Sripa B, Senggunprai L. Luteolin arrests cell cycling, induces apoptosis and inhibits the JAK/STAT3 pathway in human cholangiocarcinoma cells. Asian Pac J Cancer Prev 2014; 15: 5071-5076.

28) Lu X, Zhu Z, Jiang L, Sun X, Jia Z, Qian S, Li J, Ma L. Matrine increases NKG2D ligand ULBP2 in K562 cells via inhibiting JAK/STAT3 pathway: a potential mechanism underlying the immunotherapy of matrine in leukemia. Am J Transl Res 2015; 7: 1838-1849.