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ORIGINAL ARTICLE

Curcumin Mediates the Proliferation and Apoptosis of Colorectal Cancer Cells by Downregulating the Expression of Interleukin-1β through the Nuclear Factor-κB Signaling Pathway

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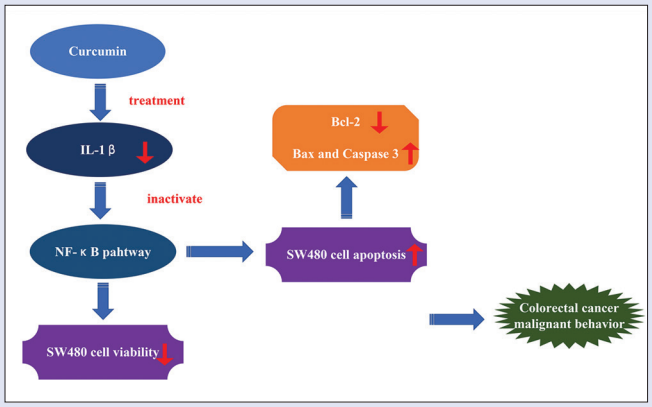
ABSTRACT

Background: Colorectal cancer (CRC) is a frequently occurring malignant tumor, which is mainly observed in elderly men with no significant symptoms at the early stage. Among the malignant tumors of the digestive system, the incidence and mortality of CRC rank second only to hepatic and gastric cancer. Curcumin is an antioxidant and anti-inflammatory compound extracted from the roots of *Curcuma longa* plant. The antitumor effects of curcumin have been widely reported for various types of cancers, including CRC. **Objective:** In this study, we aimed to elucidate the protective effects and mechanism of interleukin (IL)-1 β on curcumin-induced apoptosis in SW480 cells. **Materials and Methods:** Expression levels of IL-1 β in CRC tissues and cells were detected by the quantitative reverse transcription polymerase chain reaction and Western blot assays. Followed by the incubation of cells with curcumin, the effect on IL-1 β was measured. Moreover, after transfection, the effects of IL-1 β on curcumin-induced SW480 cellular processes were analyzed by cell counting kit-8 and flow cytometric analysis. **Results:** According to the results of this study, IL-1 β was significantly increased in CRC tissues and cells. However, after incubation of the cells with curcumin, IL-1 β was downregulated and overexpression of IL-1 β counteracted the antitumor functions of curcumin in SW480 cells. Further studies have shown that curcumin could promote apoptosis of SW480 cells by inhibiting nuclear factor-κB (NF-κB) signaling pathway. **Conclusion:** Our study validated that curcumin inhibits SW480 cell proliferation but promotes apoptosis by downregulating the expression of IL-1 β probably through NF-κB signaling pathway. IL-1 β may an important target for the treatment of CRC.

Key words: Colorectal cancer, curcumin, interleukin-1 beta, nuclear factor-κB pathway

SUMMARY

- Curcumin, a well-known phytochemical, is the bioactive pigment of turmeric which has a variety of pharmacological activities. Curcumin is a familiar and effective anticancer component in the field of cancer, including colorectal cancer (CRC). Cumulative evidence supports the fact that inflammatory factors such as cytokines are key mediators involved in regulating the growth of CRC. Interleukin (IL)-1β, a crucial member of the IL-1 family of cytokines, functioning as an important mediator in the inflammatory response while playing a vital role in many cellular activities, including cell proliferation, apoptosis, and differentiation. IL-1β has been thought to be associated with CRC progression and development. Meanwhile, other studies have pointed out that inhibition of nuclear factor-κB (NF-κB) signaling pathway may promote cancer cell apoptosis and restrain proliferation in CRC.
- In this study, we found that IL-1β was significantly increased in CRC tumor tissues and cells. After incubating with curcumin, the expression level of IL-1 β was significantly decreased. Moreover, curcumin suppressed SW480 cell proliferation but promoted apoptosis by inhibition of IL-1β through the NF-κB signaling pathway.



Abbreviations used: CRC: Colorectal Cancer; IL-1β, Interleukin-1β; NF-κB: Nuclear Factor-κB

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INTRODUCTION

Colorectal cancer (CRC) is the third most common type of cancer worldwide,[1] and its morbidity ranks second in China.[2] To date, treatment modalities used for CRC include surgery, radiation therapy, chemotherapy, and targeted therapy.[3] However, due to the characteristics of high recurrence and poor prognosis, the clinical treatment effect of CRC is greatly compromised.

Curcumin, a well-known phytochemical, is the bioactive pigment of turmeric which has a variety of pharmacological activities.[4] It is a potential cure for several diseases. For instance, curcumin is used as a

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cardioprotective agent for the treatment of myocardial ischemia.[5] A recent report suggests that curcumin shows beneficial effects on hepatic injury and cirrhosis.[6] Curcumin is a familiar and effective anticancer component in the field of cancer.[7] Prior studies demonstrate the effectiveness of curcumin against different types of tumors,[8-10] including CRC.[11] However, the detailed mechanisms of curcumin-mediated CRC progression remain unclear.

Cumulative evidence supports the fact that inflammatory factors such as cytokines are key mediators involved in regulating the growth of CRC.[12,13] Interleukin (IL)-1 β, a crucial member of the IL-1 family of cytokines, functioning as an important mediator in the inflammatory response while playing a vital role in many cellular activities, including cell proliferation, apoptosis, and differentiation.[14,15] IL-1 β has been thought to be associated with CRC progression and development.[16] A previous study revealed that IL-1 β may exert inflammatory activities by activating NK-κB signaling in CRC.[17] Meanwhile, other studies have pointed out that inhibition of nuclear factor-κB (NF-κB) signaling pathway may promote cancer cell apoptosis and restrain proliferation in CRC.[18-20] However, the underlying mechanisms of IL-1 β/NF-κB axis regulated by curcumin in the CRC micro-environment are not fully understood.

In this study, we found that IL-1 β was significantly increased in CRC tumor tissues and cells. After incubating with curcumin, the expression level of IL-1 β was significantly decreased. Moreover, curcumin suppressed SW480 cell proliferation but promoted apoptosis by inhibition of IL-1 β through the NF-κB signaling pathway.

MATERIALS AND METHODS

Samples

A total of 30 pairs of CRC samples and their matched adjacent normal samples were collected between June 2015 and September 2017 at the Taizhou People's Hospital (Hailing South Road No. 399, Taizhou 225300, Jiangsu, China) and preserved in liquid nitrogen. All samples were obtained from patients with CRC who had undergone surgical resections without undergoing any chemotherapy, radiation, or other adjuvant therapy. The protocol of this study was approved by the Ethics Committee of Taizhou People's Hospital and informed consent was obtained from each patient.

Cell culture

The HCoEpiC, HT29, HCT116, and SW480 cell lines were purchased from Shanghai Institution for Biological Sciences (Shanghai, China) and cultured in Dulbecco's Modified Eagle medium (DMEM; Gibco, CA, USA) with 10% fetal bovine serum (FBS; Hyclone, Shanghai, China) containing penicillin/streptomycin at 37°C in a humidified incubator with 5% CO_2.

Cell viability assay

Cell viability was measured using Cell Counting Kit-8 (CCK-8 kit; Beyotime, Hangzhou, China). Briefly, SW480 cells were seeded in a 96-plate well at a density of 0.5×10^4 cells/well under a humidified atmosphere containing 5% CO_2 at 37°C. Following this, 20 μM curcumin and IL-1 β (Recombinant Human IL-1 β; LT-0111-010; 10 ng/mL) were added to the plate and further incubated for 24, 48, and 72 h, respectively. CCK-8 reagent was added into each well, and the culture was carried out for another 50 min. The absorbance of each well was read at 490 nm using a microplate reader (TECAN Infinite M1000; TECAN, Shanghai, China).

Annexin V-FITC/PI double staining assay

The cell apoptosis rate was determined using an Annexin V-FITC/PI apoptosis kit (Dojindo Molecular Technologies, Inc., Kumamoto, Japan) according to the manufacturer's protocol. Briefly, the cells were seeded at a density of 1×10^5 cells/well in a six-well plate and treated with 20 μM curcumin and IL-1 β. After 24 h of incubation, the cells were harvested by centrifugation at 1000 rpm for 5 min and stained with propidium iodide and Annexin V. FACSCalibur (BD Bioscience, Shanghai, China) was used to analyze the apoptotic cells.

Protein extraction and western blotting

Total protein was extracted from the tissues and cells using radioimmunoprecipitation assay (Solarbio, Beijing, China) buffer. Following this, the protein content was determined using a bicinchoninic acid protein assay kit according to the manufacturer's instructions. The proteins were resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and transferred onto a PVDF membrane, which was blocked in 5% non-fat milk for 50 min. The membranes were incubated at 4°C overnight with primary antibodies (IL-1 β, Bcl-2, phosphate-NF-κB, Bax, Caspase-3, and GAPDH), whereas GAPDH functioned as the endogenous control for protein loading. Afterward, the membranes were incubated at 37°C for another 2 h with horseradish peroxidase-conjugated secondary antibodies followed by ECL™ Western blotting detection reagent (Thermo Fisher Scientific, Rockford, IL, USA). Data were analyzed using Image Lab software (BioRad Laboratories, CA, USA).

RNA isolation and quantitative reverse transcription polymerase chain reaction

Total RNA was extracted with TRIzol reagent (Invitrogen, CA, USA). All primers were designed and synthesized by Genscript (Nanjing, China) according to the manufacturer's instructions. Subsequently, RNA was reverse transcribed into cDNA with SuperScript reagent (Invitrogen, MA, USA). Quantitative reverse transcription polymerase chain reaction (RT-qPCR) was performed with TaqMan PCR reagent kit (Applied Biosystems, NJ, USA) as per the manufacturer's instructions. The reaction procedure was as follows: 52°C for 2 min, 94°C for 10 min; 30 cycles of 94°C for 10 s, and 52°C for 30 s. GAPDH was used as an endogenous control. The expression level of IL-1 β in CRC tissues was measured according to the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

All the results were presented as mean ± standard deviation. SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Significant differences among the groups were evaluated by the Student's *t*-test or one-way analysis of variance followed by the Newman–Keuls method. $P < 0.05$ was considered statistically significant.

RESULTS

The expression level of interleukin-1 β is upregulated in colorectal cancer tissues

Through RT-qPCR and Western blot assays, the expression of IL-1 β in 30 sets of paired tissues was determined. As demonstrated in Figure 1a, a remarkably high level of IL-1 β mRNA and protein was found in the CRC tissues [Figure 1b].

Curcumin suppresses the expression of interleukin-1 β in SW480 cells

To corroborate the basic function of curcumin on IL-1 β expression, we first detected the expression of IL-1 β in four cell lines. As demonstrated in Figure 2a, a significantly high level of expression of IL-1 β was measured in SW480 cell lines. After treatment with 20 μM curcumin, the expression of IL-1 β mRNA and protein was significantly [Figure 2b and c].

Curcumin suppresses SW480 cell proliferation by inhibition of interleukin-1 β expression

In this study, the CCK-8 assay was performed to detect the proliferation of SW480 cells. As demonstrated in Figure 3, the proliferation of SW480 cells was remarkably decreased after treatment with curcumin. However, the reduction in proliferation was partially reversed by the upregulation of IL-1 β expression.

Curcumin promotes SW480 cell apoptosis by inhibition of interleukin-1 β expression through the nuclear factor-κB signaling pathway

To demonstrate the effects of curcumin on SW480 cell apoptosis, we performed flow cytometry and Western blot analysis. As demonstrated in Figure 4, curcumin-induced apoptosis in SW480 cells could be reversed by increasing the expression of IL-1 β. Furthermore, after treatment with curcumin, the expression levels of IL-1 β, Bcl-2, and p-p65 were significantly downregulated, whereas the expression level of Bax and Caspase-3 were upregulated [Figure 5]. However, the variation of Bcl-2, p-p65, Bax, and Caspase-3 induced by curcumin could be partially counteracted by IL-1 β

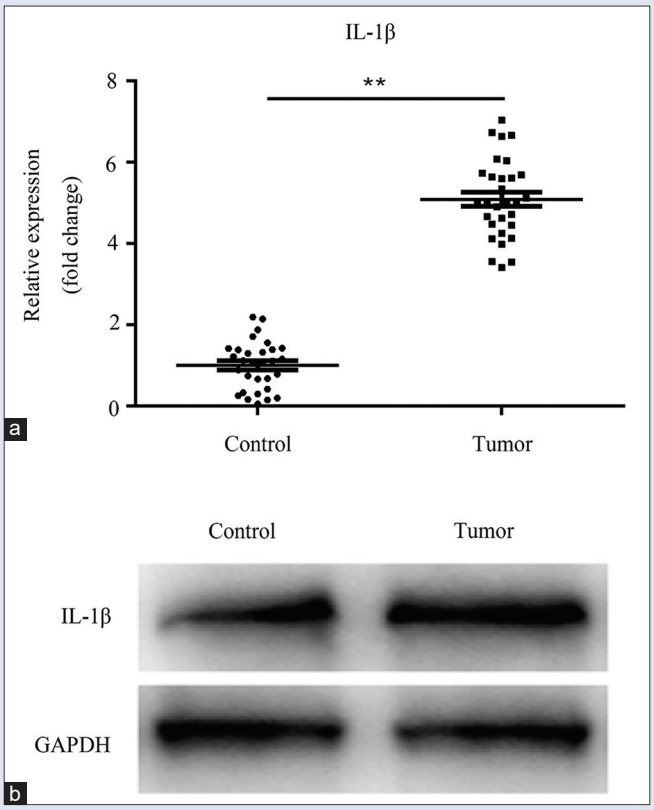

Figure 1: Interleukin-1 β expressions were up-regulated in colorectal cancer samples. (a) Significantly higher mRNA levels of interleukin-1 β expression were found in the colorectal tumor samples compared with adjacent non-tumor samples ($P < 0.01$). (b) Significantly higher protein levels of interleukin-1 β expression were found in the colorectal tumor samples compared with adjacent nontumor samples. **$P < 0.01$, tumor versus control

DISCUSSION

IL-1 β, a primary pro-inflammatory cytokine, functions as a pleiotropic agent in tumorigenesis, tumor growth, and metastasis.[21,22]

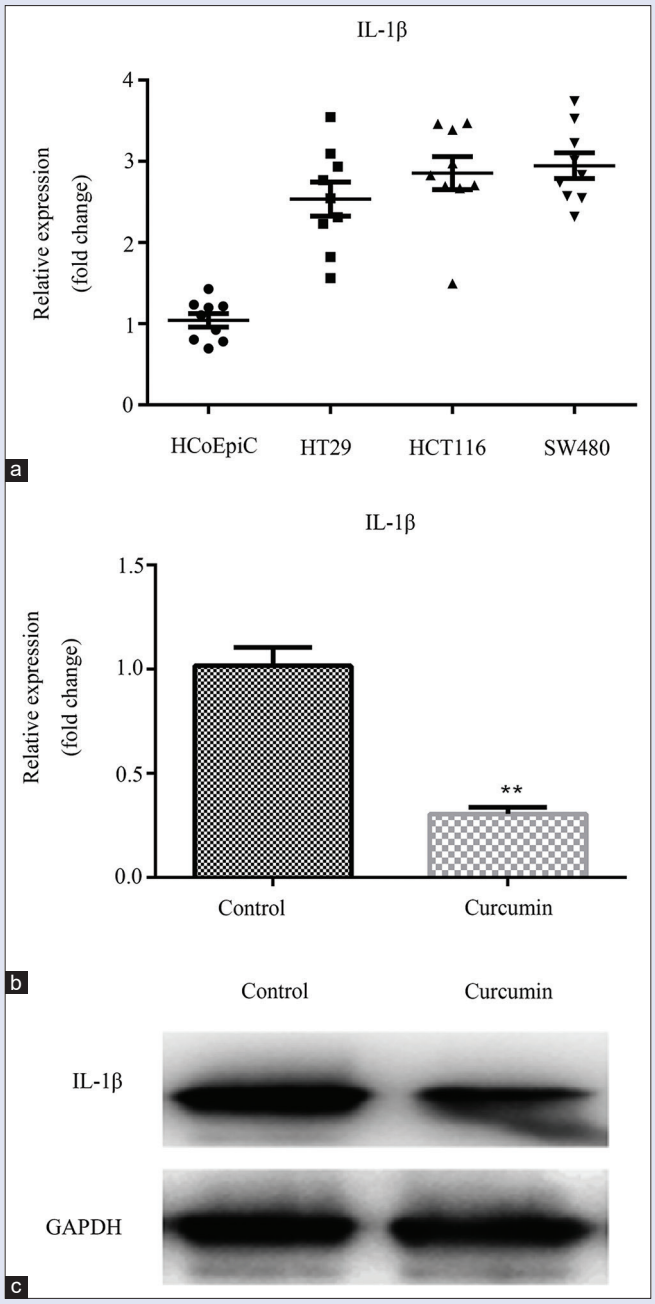

Figure 2: Curcumin inhibits the expression levels of interleukin-1 β in colorectal cancer cells. (a) Significantly higher expression levels of interleukin-1 β were found in SW480 cells. (b) Curcumin inhibits the mRNA expression levels of interleukin-1 β in SW480 cells ($P < 0.01$). (c) Curcumin inhibits the protein expression levels of interleukin-1 β in SW480 cells. **$P < 0.01$, curcumin versus control

Previous studies have shown that the expression of IL-1 β is elevated in CRC tissues,[23] which is compatible with the findings of this study, indicating that IL-1 β acts as an oncogene in CRC cells. In addition, in keeping with previous results, we were able to demonstrate that IL-1 β expression was suppressed by curcumin.[24,25] Since curcumin is an upstream stimulator of IL-1 β in CRC *in vitro*, we further evaluated the functions of the curcumin/IL-1 β axis in the regulation of CRC cell progression. We found that curcumin may suppress proliferation but increase apoptosis of SW480 cells by the inhibition of IL-1 β, suggesting that IL-1 β functions as an oncogenic protein in CRC development.

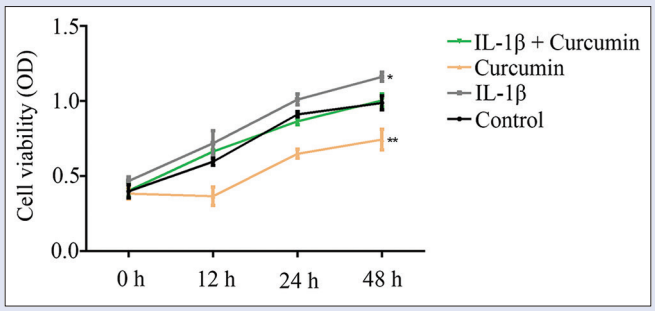

Figure 3: Curcumin inhibits SW480 cell proliferation by decreasing interleukin-1 β expression. The cell viability of SW480 measured by cell counting kit-8 assay in different groups. $^{**}P < 0.01$, $^{*}P < 0.05$, interleukin-1 β versus control, curcumin versus control, interleukin-1 β + Curcumin versus interleukin-1 β

Cumulative evidence highlighted the value of IL-1 β in the development of malignant types of cancer cells. For instance, the downregulation of expression of IL-1 β may suppress cell invasiveness in breast cancer.[26] As in CRC, IL-1 β promotes colon cancer cell growth as well as invasion.[27] Curcumin is widely used in ancient medicine and has been shown to induce cell apoptosis in CRC,[28] indicating its potential value as a tumor suppressor in CRC. In agreement with these reports, we found that IL-1 β may increase cell proliferation but inhibit apoptosis of CRC, the effect of which was reversed by curcumin.

Previous studies have shown that curcumin shows its antioxidant, anti-inflammatory, and anti-tumor properties by targeting specific signaling pathways such as NF-κB, Nrf2, and PTEN pathways.[29-32] NF-κB is present in almost all animal cell types and plays a crucial role in regulating the immune response to infection.[33,34] Previous studies have reported that abnormal regulation of the NF-κB signaling pathway is related to inflammatory and tumor progression.[35,36] Furthermore, cumulative evidence has confirmed that its abnormal activation is a key factor in the progression of CRC.[37,38] Accumulating evidence suggests that curcumin inhibits the NF-κB signaling pathway to regulate the cellular processes in cervical cancer,[39] squamous cell carcinoma,[40] esophageal cancer,[41] and breast cancer.[42] In this study, we found that the upregulation of IL-1 β markedly increased the expression level of Bcl-2 and p-p65 and decreased the expression level of Bcl-2, Bax, and Caspase; however, the variation could be reversed by curcumin. These results suggest that curcumin is involved in the regulation of growth and development of CRC by the inhibitory effect of IL-1 β through the NF-κB signaling pathway.

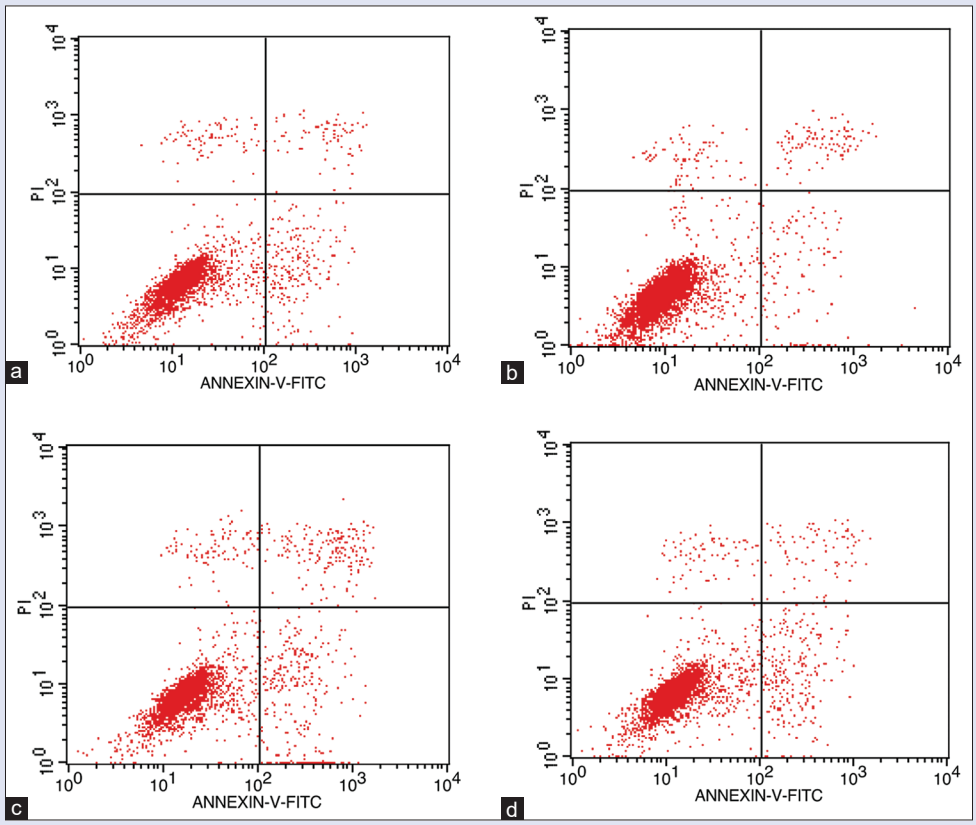

Figure 4: Curcumin promotes SW480 cell apoptosis by decreasing interleukin-1 β expression. (a) Control group; (b) interleukin-1 β group; (c) Curcumin group; (d) interleukin-1 β + curcumin group

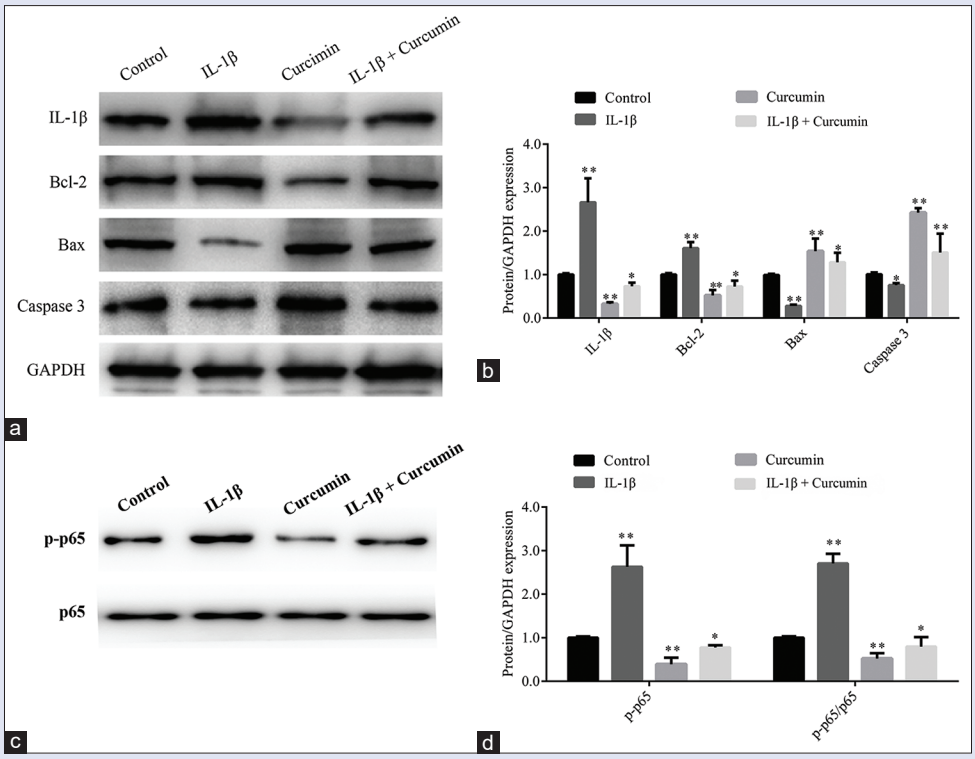

Figure 5: Curcumin increases interleukin-1 β expression via nuclear factor-κB signaling pathway. (a) Expressions of interleukin-1 β and apoptosis-related factors measured by western blot assay. (b) Quantified results of A were presented. (c) Expressions of p-p65 measured by western blot assay. (d) Quantified results of C were presented. $^{**}P < 0.01$, $^{*}P < 0.05$, interleukin-1 β versus control, Curcumin versus control, interleukin-1 β + Curcumin versus interleukin-1 β

This study has some limitations. First, the sample size of our experiment is small and we need to recruit more participants in order to obtain more accurate results. Second, we will conduct further experiments by inhibiting IL-1 β expression to verify whether NF-κB is directly regulated by IL-1 β. Last but not the least, immunolabeling and *in vivo* experiments need to be conducted in the future.

CONCLUSION

In general, our study elucidates the effects of curcumin as a crucial therapeutic option in CRC treatment. Furthermore, the overexpression of IL-1 β in CRC samples and cells could partially counteract the effect of curcumin in restoring the proliferation or promoting the apoptosis of SW480 cells. In summary, our study suggests that curcumin may regulate the proliferation and apoptosis of SW480 cells by the suppression of IL-1 β via NF-κB pathway.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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