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Original Research Article

Effect of Curcumin-loaded Polystyrene Nanoparticles on Inhibiting the Generation of Lymphatic Vessels in Gastric Cancer Nude Mice Under Hypoxic Microenvironment

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Abstract

Background: In the treatment of gastric cancer, lymphangiogenesis under a hypoxic microenvironment has always been a current research hotspot.
Objectives: This study aimed to explore the mechanism of curcumin-loaded polystyrene nanoparticles (CUR/PS NPs) inhibiting the generation of lymphatic vessels in a hypoxic microenvironment of gastric cancer nude mice by interfering with phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling and reducing vascular endothelial growth factor (VEGF) expression.
Materials and Methods: CUR/PS NPs were prepared, a gastric cancer nude mouse transplanted tumor model was established, and the A549 group, Cu B group, and the Cu B-NPs group were set up to explore the molecular mechanism of Cu B-NPs in regulating autophagy and inhibiting the development of lung cancer; in addition, the Cu B-NPs+si-BECN1 group and the Cu B-NPs+pc-BECN1 group were used to analyze whether Cu B-NPs regulate autophagy through Beclin-1 (BECN1) to inhibit the development of lung cancer.
Results: (a) A subcutaneous transplanted tumor model was successfully constructed, a CUR/PS NPs composite material was successfully prepared, and the composite material had good dispersion stability. (a) CUR/PS NPs can significantly inhibit the formation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice transplanted tumors, and have an inhibitory effect on the development of gastric cancer. (c) CUR/PS NPs can inhibit the formation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice transplanted tumors by inhibiting PI3K/Akt/mTOR signaling, thereby delaying gastric cancer progression.
Conclusion: This study successfully prepared CUR/PS NPs, and the particles can reduce the expression of VEGF by inhibiting PI3K/Akt/mTOR signaling, thereby inhibiting the generation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice, delaying cancer progression.

Keywords

Gastric cancer, polystyrene nanoparticles, curcumin, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin, vascular endothelial growth factor, lymphangiogenesis

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Introduction

The pathogenesis of gastric cancer involves the long-term effects of various factors such as genetic factors, *Helicobacter pylori* infection, and chronic inflammation, leading to the gradual progression of gastric mucosa from atrophic gastritis to cancer; Epidemiology shows that gastric cancer has a high incidence rate in the world, especially in East Asia, and is more common in men and elderly people. Early symptoms of gastric cancer are insidious, and most patients are diagnosed in the middle to late stages, with limited treatment options that seriously affect their quality of life and prognosis. Therefore, it is very important to find new treatments for gastric cancer.

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Phosphatidylinositol 3-kinase (PI3K) plays an important role in cancer. It can interfere with the cell cycle and apoptosis to inhibit the growth of prostate cancer. In gastrointestinal stromal tumors (GIST), activating mutations of the PDGFRA gene are related, which will lead to PI3K activation (Yang et al., 2019). In gastric cancer, mutation or overexpression of the p110α subunit of class I PI3K may lead to abnormal PI3K activation (Mishra et al., 2021). PI3K inhibition may interfere with the survival and proliferation of tumor cells, and its activation will be achieved to a certain extent by the upstream activation of protein kinase B (Akt) kinase mediated by activating mutations such as c-KIT and PDGFRA (Song et al., 2019). Studies have shown (Ouyang et al., 2022) that MEK inhibitors affect the STAT3 signaling pathway in melanoma cells, which in turn affects the activation status of Akt, thus affecting cell invasion and metastasis capabilities. Mammalian target of rapamycin (mTOR/Akt) signaling activation in melanoma cells is related to the malignancy degree (Stanciu et al., 2022), and the expression of interleukin 24 (IL-24) can inhibit the activation of these pathways, thereby inhibiting the proliferation and survival of melanoma. At the same time, Akt can regulate the downstream target mTOR and participate in cell growth and metabolic regulation (Ma et al., 2021). Abnormal activation of mTORC1 in cancer can promote protein synthesis, cell growth, and metabolic reprogramming, thereby providing cancer cells with the survival advantage they need. Research has found (Szwed et al., 2021) that mTORC2 modulates macrophages by regulating vascular endothelial growth factor (VEGF) expression and inflammatory factors.

Inhibition of mTORC2 leads to downregulation of VEGF expression, thereby affecting inflammatory response and angiogenesis. In addition, in lung adenocarcinoma (Hu et al., 2021), miR-409-3p inhibits tumor cell growth by downregulating VEGFA expression, and the mTOR pathway regulates VEGFA expression. Research has found (Li, Shan et al., 2020) that melatonin plays a protective role against ischemia/reperfusion injury by regulating the mTOR and VEGF pathways. Therefore, these provide a good foundation for the development of new cancer drugs.

In recent years, the research on traditional Chinese medicine in anti-tumor has received more and more attention, among which curcumin (CUR) has been widely studied in the treatment of cancer (Peng et al., 2021). CUR has powerful antioxidant properties that can neutralize free radicals, reduce oxidative stress, and protect cells from oxidative damage, thereby helping to inhibit the growth of cancer cells. CUR can not only regulate cell cycle proteins and reduce deoxyribonucleic acid (DNA) synthesis and other pathways, but also interfere with the proliferation signaling pathways of cancer cells to inhibit tumor growth (Cui et al., 2022). Studies have shown (Deng et al., 2021) that CUR can also regulate processes such as apoptosis, inflammation, and oxidative stress by inhibiting key proteins such as AKT and mTOR in PI3K signaling. Although CUR can inhibit PI3K/Akt/mTOR signaling to treat cancer, its specific mechanism of action is still unclear, and whether it can treat gastric cancer by regulating the tumor microenvironment remains to be further studied. However, although CUR has many pharmacological activities, its bioavailability is low, which means that its absorption and distribution in the body are limited, and it is easily decomposed or affected by light *in vitro*, resulting in reduced stability. Polystyrene nanoparticles (PS NPs) are a technology that prepares polystyrene materials into nanoscale particles. Wrapping CUR in nanoparticles can not only improve its bioavailability and make it easier to be absorbed by the body, but also protect CUR from external environmental influences and prolong its stability. In addition, the use of nanoparticles can achieve a slow release of drugs and control the distribution and activity of drugs in the body, thereby increasing the effect of drug treatment (Romagnoli et al., 2021).

Therefore, this study uses CUR/PS NPs to treat gastric cancer, aiming to explore whether it can reduce the expression of VEGF by interfering with PI3K/Akt/mTOR signaling, thereby inhibiting the generation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice, thus inhibiting the progression of gastric cancer.

Materials and Methods

Experimental Materials

Human gastric cancer SGC-7901 cell line, Akt antibody, mTOR antibody (Fenghui Bio); CUR (specification: 100 g, purity: ≥98%) (Ita Bio); PI3K antibody (Aimei Jie Technology); Matrigel (Corning Life Sciences); LY294002 and 740 Y-P (Shanghai Yuanye); hematoxylin (Shanghai Kaiyin Chemical); eosin dye (Changsha Hanchen Biotechnology).

Animal: Nude mice (thymus-free mice, 6–8 weeks old, weighing approximately 20–25 g), provided by Jiangsu Huachuang Xinnuo Pharmaceutical Technology Ltd., license number SCXK (Su) 2020-0009. All animals are raised and handled in accordance with guidelines approved by the Animal Ethics Committee to ensure compliance with internationally recognized animal care standards. Place the nude mice in a specific pathogen-free (SPF) environment, maintain a room temperature of 20°C–25°C, control the relative humidity at 40%–60%, and follow a 12-h light/12-h dark cycle, with each mouse free to eat and drink.

Preparation and Characterization of CUR/PS NPs

Preparation of CUR/PS NPs

Add an appropriate amount of CUR to distilled water and stir to fully dissolve it to obtain a uniform CUR solution; then pour the polystyrene solution into an ultrasonic cleaner to remove bubbles and insoluble impurities to form a uniform polystyrene precursor solution. Transfer the cleaned solution to a water bath, keep the temperature at 70°C–80°C, and continue stirring to further diffuse the polystyrene molecular

chains and form nanoparticles. Add the CUR extract to the prepared polystyrene solution and mix evenly. Ultracentrifugation was used to remove unreacted substances, and finally, the nanoparticle sample was dried to obtain a composite sample of CUR/PS NPs.

Nanoparticle Characterization

Dip a small amount of the nanoparticle dispersion liquid and evenly drop it on the conductive adhesive. After natural drying, spray gold for 1 min. Then, use transmission electron microscopy (TEM) to observe the shape and structure of the nanoparticles, and analyze their potential with dynamic laser scattering.

Establishment and Grouping of Gastric Cancer Nude Mouse Transplanted Tumor Models

Before the operation, the nude mice were fasted for 12 h and were anesthetized via intraperitoneal injection of 2% sodium pentobarbital. After disinfection, an incision was made at the subcutaneous area of the xiphoid process of the mouse, with a length of about 1.5 cm, and then cut from the white line. Open the peritoneum, pull out the mouse's stomach slightly, select an area rich in blood vessels, cut the serosa layer of the stomach in a "-" shape, and press to separate the subserosa layer to form a groove, and then remove the human gastric cancer The SGC-7901 cell line was planted here, and after it was firmly adhered, it was put back into the abdominal cavity, the abdomen was closed, and the culture continued.

The nude mice that were successfully modeled were included in the model group. Mice intragastrically received 50 mg kg^{-1} CUR and were designated as the CUR group. Mice received initially the same dose of PS NPs and CUR/PS NPs, which were designated as the PS NP group and CUR/PS NPs, respectively. CUR/PS NPs group. The effect of CUR/PS NPs on inhibiting the formation of lymphatic vessels and delaying tumor progression in the hypoxic microenvironment of gastric cancer nude mice was analyzed. In addition, a CUR/PS NPs+LY294002 group and a CUR/PS NPs+740 Y-P group were set up to analyze whether CUR/PS NPs inhibit the generation of lymphatic vessels in gastric cancer nude mice transplanted tumors and delaying tumor progression in a hypoxic microenvironment was related to its ability to inhibit PI3K/Akt/mTOR signaling pathway and reduce VEGF expression.

Lymphangiogenesis

Take gastric cancer tissue sections and fix them in neutral formalin. Slowly thaw the frozen Matrigel to 4°C and keep it refrigerated on ice. Select lung cancer cells that grow well, wash them, adjust to 1×10^6 cells/mL, evenly apply pre-cooled Matrigel on the bottom of the culture dish or 96-well plate, and then add the cells with the adjusted concentration. The suspension was added to the coated Matrigel. After incubation, immunofluorescence staining was performed, and the morphology of blood vessels was observed using a light microscope.

Cell Apoptosis Detection

After 24 h, the supernatant was first discarded, then washed with phosphate-buffered saline (PBS) solution, then 0.25% trypsin was added for digestion, and centrifuged to collect the cell pellet. Wash the cells three times with PBS solution, and then add 500 μL of binding buffer solution (cell density is 1×10^6 cells/mL). Then, add 5 μL of Annexin V-FITC (Wuhan Punosai) under dark conditions and incubate. Then, add 5 μL of propidium iodide (PI) and continue to incubate under the same conditions for 10 min. Finally, the flow cytometer was immediately used to detect cell apoptosis.

Polymerase Chain Reaction (PCR) Detection

Gastric cancer tissue was ground and homogenized using liquid nitrogen, and total messenger ribonucleic acid (mRNA) was extracted and transcribed into complementary DNA (cDNA). The analysis was performed by real-time PCR system analysis (Shanghai Unico), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was selected as a reference. Relative levels were estimated using the $2^{-\Delta\Delta Ct}$ method. Table 1 lists the primers and primer sequences.

Western Blotting Analysis of Protein Expression

Total protein was extracted with TriZol reagent, and its concentration was detected. The electrophoresed total protein was heated, electrophoresed (120 V, 100 min), transferred to a polyvinylidene fluoride (PVDF) membrane, and blocked, followed by incubation with PI3K, Akt, mTOR, hypoxia-inducible factor 1-alpha (HIF-1α), VEGF-C, VEGF-D, and GAPDH

Table 1. Polymerase Chain Reaction (PCR) Primers and Primer Sequences.

Primers		Sequences
HIF-1α	Forward primer	5′-ACTTCTGGATGCTGGTGATTTG-3′
	Reverse primer	5′-GCTTCGCTGTGTGTTTTGTTCT-3′
GAPDH	Forward primer	5′-ACGGCAGGTCATCACTATTG-3′
	Reverse primer	5′-TGGATGCCACAGGATTCCAT-3′

Note: GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; HIF-1α: Hypoxia-inducible factor 1-alpha.

antibody and then with secondary antibody (1:10,000). Wash with PBS, repeat three times, and observe the ImageJ images.

Statistical Analysis

The data obtained in each of the above experiments were analyzed using SPSS 21.0 and GraphPad Prism software. If there are no special requirements, $p < .05$ is used as the test standard.

Results

Successfully Constructed a Subcutaneous Transplanted Tumor Model and Successfully Prepared CUR/PS NPs Composite Materials

All nude mice survived during the modeling process. The mice in the model group had obvious tumor growth, local parts of the abdomen turned purple–brown, significantly reduced eating and drinking, poor mental status, decreased exercise ability, and drowsiness. Compared with the model group, the tumor growth rate of nude mice treated with cisplatin and artesunate was significantly reduced, and they had good appetite, exercise volume, mental state, slow movement, and mild lethargy. After combined treatment with the two drugs, the tumor formation rate in nude mice was the lowest, and there was no significant impact on their appetite, movement, spirit, or reaction.

TEM images show that the morphology of the prepared C/PS NPs composite is spherical (see Figure 1A), and the mean zeta potential is −26.4 ± 3.1 mV (see Figure 1B), indicating that the nanoparticles have good stability.

CUR/PS NPs Can Significantly Inhibit the Formation of Lymphatic Vessels in the Hypoxic Microenvironment of Transplanted Tumors in Nude Mice with Gastric Cancer, and Have an Inhibitory Effect on Gastric Cancer

After the successful modeling, the mice were sacrificed, and the abdominal cavity was opened. It was found that round/oval solid tumors were seen, with protruding nodules on the surface. They were large in size and almost occupied the entire stomach (Figure 2A). Gastric cancer cells grew abnormally and actively. The intracellular nuclei were enlarged, dark in color, and irregular in shape (Figure 2B). Compared with the above situation, after drug intervention, the tumor volume decreased, and gastric cancer cells gradually experienced nuclear pyknosis, fragmentation, and necrosis. The cell's growth is inhibited. In addition, in order to analyze the tumor suppressor effect of CUR/PS NPs, we used it to culture SGC-7901 and found that HIF-1α was abnormally highly expressed in human gastric cancer cells. After CUR/PS NPs intervention, its level dropped sharply, indicating that CUR/PS NPs can improve the hypoxic microenvironment in cancer cells (Figure 2C). In addition, through the observation of the expression of VEGF-C and VEGF-D, it was found that CUR/PS NPs intervention caused a significant decrease (Figure 2D); among the apoptosis results, the CUR/PS NPs group had the highest apoptosis rate (Figure 2E). The protein expression of the pathway is the lowest (Figure 2F), which is contrary to the Model, indicating that the anti-cancer effect of CUR/PS NPs may be related to the PI3K/Akt/mTOR pathway.

CUR/PS NPs Can Inhibit the Formation of Lymphatic Vessels in the Hypoxic Microenvironment of Gastric Cancer Nude Mice Transplanted Tumors by Inhibiting P3K/Akt/mTOR Signaling

We further tested PI3K/Akt/mTOR mRNA expression. We found that its expression was abnormally low under the intervention of CUR/PS NPs and LY294002 (Figure 3A and B), reflecting that CUR/PS NPs can mediate the reduction of PI3K/Akt/mTOR signaling. Under the intervention of CUR/PS NPs+LY294002, the expression levels of HIF-1α, VEGF-C, and VEGF-D proteins were reduced (Figure 3C), and the density of microvessels and lymphatic microvessels was also significantly reduced (see Figure 3D). In the immunohistochemistry results, the positive expression of cleaved caspase-3 appeared as brown–yellow particles in the tumor tissue. After the intervention of CUR/PS NPs+LY294002, the brown–yellow particles further increased (Figure 3F), and the

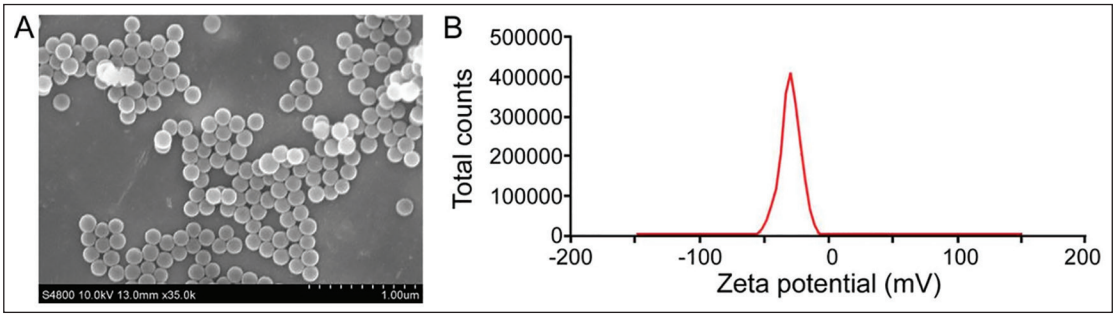


Figure 1. Characterization of Curcumin-loaded Polystyrene Nanoparticles (CUR/PS NPs) Composites.

Note: (A) Morphological characteristics of CUR/PS NPs composite materials under transmission electron microscopy (TEM); (B) Potential analysis results.

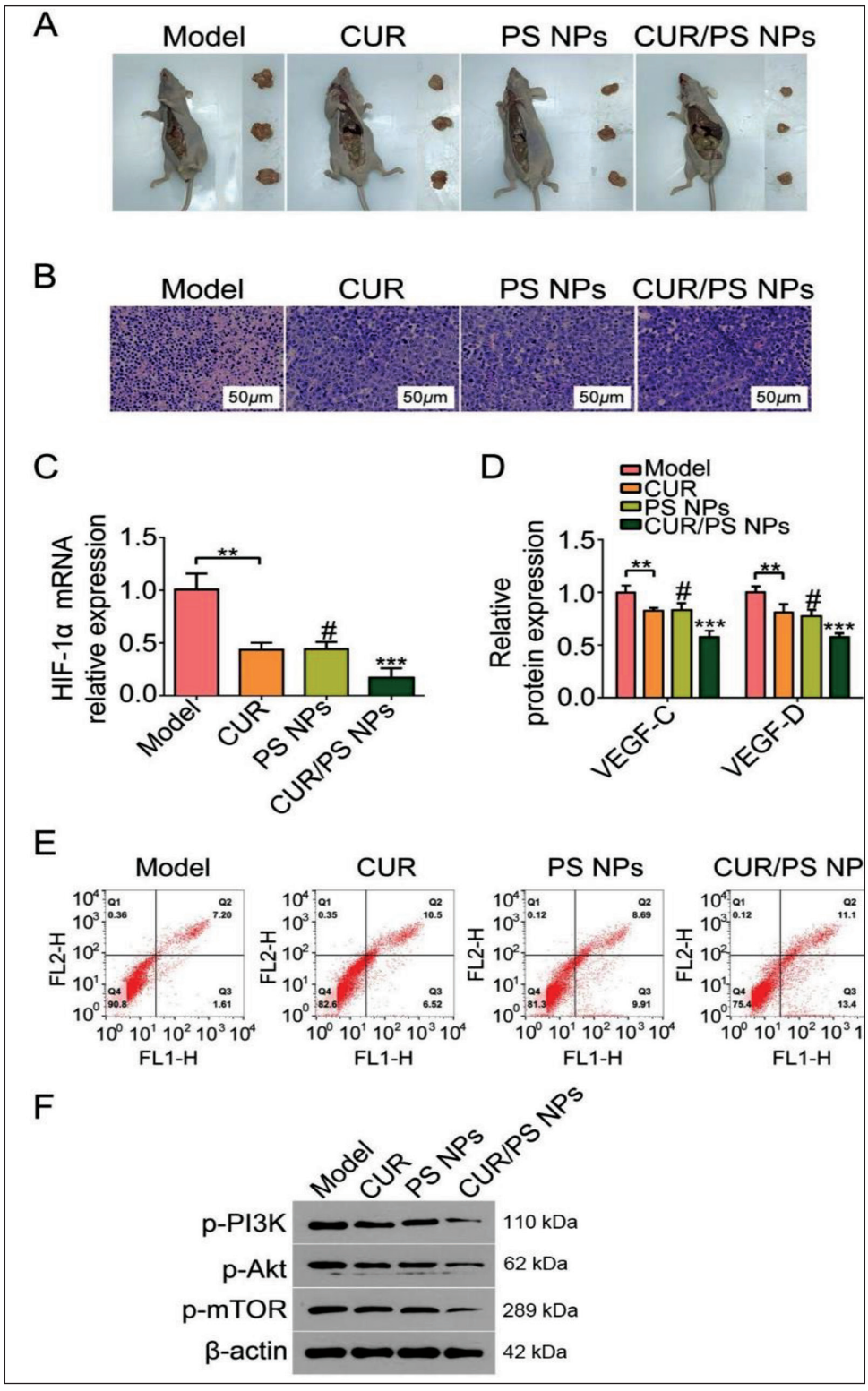


Figure 2. Curcumin-loaded Polystyrene Nanoparticles (CUR/PS NPs) Inhibit the Formation of Lymphatic Vessels in the Hypoxic Microenvironment of Transplanted Tumors in Nude Mice with Gastric Cancer and Inhibit the Development of Gastric Cancer.

Note: (A) Size of gastric cancer orthotopic transplanted tumors in nude mice; (B) hematoxylin and eosin (HE) staining to observe the pathological tissue of transplanted tumors. Arrows represent nuclear pyknosis, arrowheads represent nuclear fragments, and asterisks represent necrotic areas; (C) polymerase chain reaction (PCR) detects hypoxia-inducible factor 1-alpha (HIF-1α) messenger ribonucleic acid (mRNA) expression in nude mouse cells; (D) Western blot (WB) detects vascular endothelial growth factor (VEGF)-C and VEGF-D protein expression in nude mouse cells; (E) flow cytometry detects cell apoptosis in nude mice; (F) WB detects the expression of pathway-related proteins in nude mouse cells; compared with the CUR group, #$p > .05$; compared with the PS NPs group, **$p < .01$, ***$p < .001$.

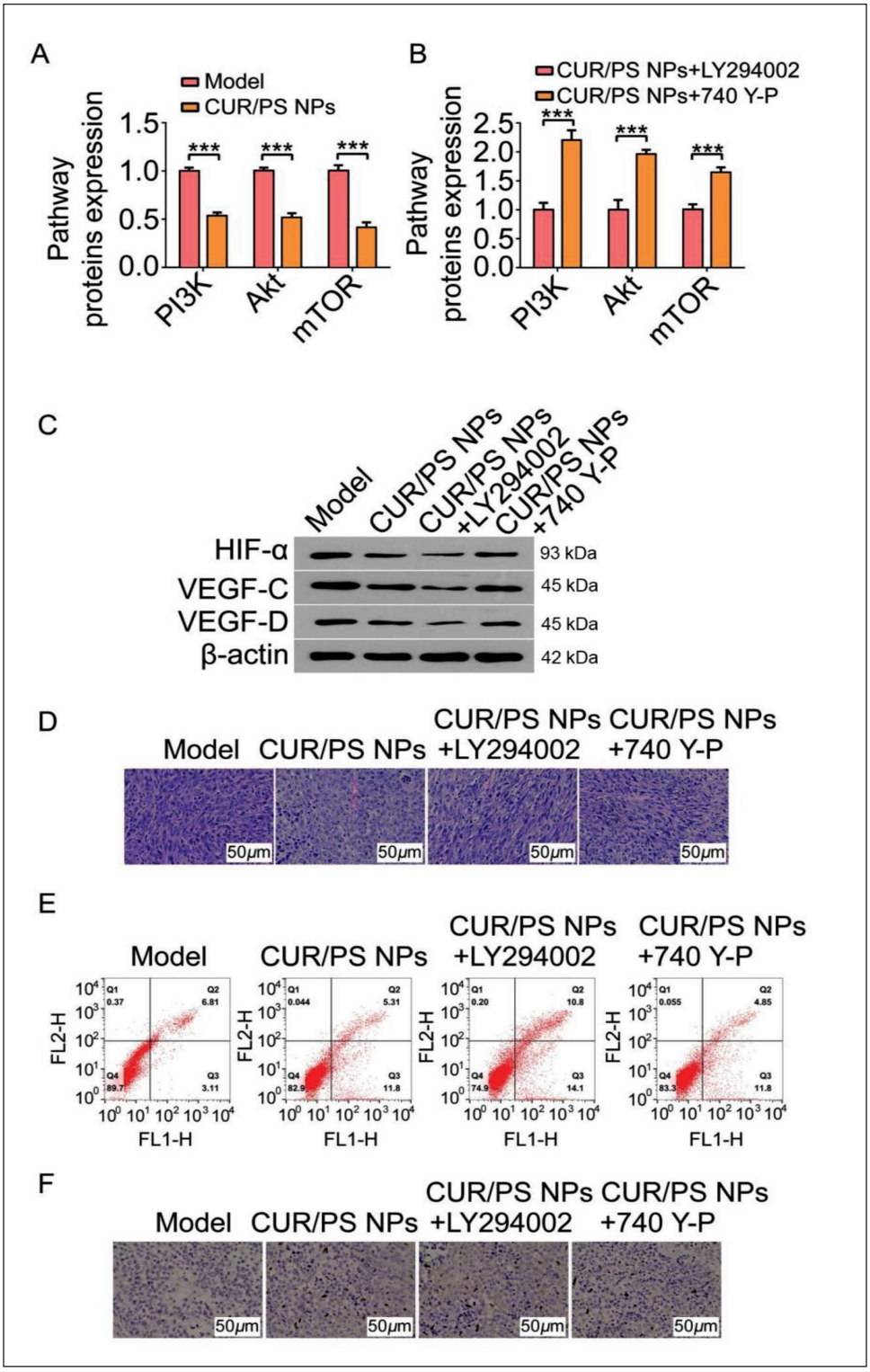


Figure 3. Curcumin-loaded Polystyrene Nanoparticles (CUR/PS NPs) Inhibit the Formation of Lymphatic Vessels in the Hypoxic Microenvironment of Gastric Cancer Nude Mice Transplanted Tumors by Inhibiting the Activity of the Phosphatidylinositol 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/Akt/mTOR) Signaling Pathway, Thereby Inhibiting Gastric Cancer Metastasis.

Note: (A) Western blot (WB) detects the expression of two groups of pathway-related proteins; (B) WB detects the expression of two groups of pathway-related proteins after inhibiting/activating the pathway; (C) WB detects hypoxia-inducible factor 1-alpha (HIF-1α) and vascular endothelial growth factor (VEGF) in nude mouse cells-C and VEGF-D protein expression; (D) lymphangiogenesis in nude mice in each group; (E) flow cytometry to detect cell apoptosis in nude mice in each group; (F) immunohistochemical staining to detect transplantation cleaved caspase-3 expression in tumor tissue; compared with control group, $^{***}p < .001$.

apoptosis rate also increased (Figure 3E). After combining CUR/PS NPs with 740 Y-P, the above phenomenon was significantly reversed.

Discussion

Studies have reported (Zhang et al., 2019) that curcumin can inhibit the degradation of inhibitor of nuclear factor kappa B (IκBα), and keep nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in the cytoplasm, thereby reducing its activity, thereby inhibiting inflammatory responses and the growth of cancer cells. In addition, curcumin can inhibit the expression of VEGF-C and VEGF-D by inhibiting the SMYD3 pathway, thereby affecting the formation of lymphatic vessels in gastric cancer (Wada et al., 2020). Because curcumin is insoluble in water and will decompose under the influence of factors such as light, oxygen, and temperature, it has low bioavailability or even loses activity. Therefore, we use nano drug delivery technology to improve its shortcomings and achieve a directional delivery function to reduce the impact on surrounding healthy tissues. In this study, we successfully prepared CUR/PS NPs composite materials. In order to prove the effect of CUR/PS NPs on lymphatic vessels in the hypoxic microenvironment of gastric cancer transplanted tumors, animal experiments were conducted, and it was found that after drug intervention, tumor growth was inhibited, indicating that CUR has an inhibitory effect on gastric cancer. To further explore the tumor-suppressor effect of CUR/PS NPs, we used it to culture SGC-7901 and found that CUR/PS NPs could reduce HIF-1α expression in human gastric cancer cells, thereby improving the hypoxic microenvironment of gastric cancer.

Studies have shown (Maracci et al., 2022; Romagnoli et al., 2021) that when mTOR is activated, it is beneficial to release eIF4E and phosphorylate the Thr37 and Thr46 sites of 4E-BP1, resulting in their dissociation, allowing eIF4E to bind to eIF4G, thereby promoting protein Initiation of synthesis. Both VEGF antibodies and their inhibitors can interfere with the VEGF pathway to inhibit the production of VEGF and prevent the binding of VEGF to its receptors, thereby reducing the biological activity of VEGF and inhibiting the biological process of tumors. In addition, anti-inflammatory cytokines reduce VEGF production by inhibiting the NF-κB pathway, thereby inhibiting cancer (Chen et al., 2022; Pan et al., 2020).

Therefore, during the above experimental process, we found that the intervention of CUR/PS NPs significantly reduced the levels of VEGF-C and VEGF-D, and the apoptosis rate in this group was the highest, indicating that CUR/PS NPs can reduce VEGF and thus exert Inhibits the formation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice transplanted tumors. In addition, PI3K, Akt, mTOR, and other protein levels were lowest during this process, suggesting that PI3K/Akt/mTOR signaling is also involved in gastric cancer treated with CUR/PS NPs. This finding provides valuable clues for further studying the molecular mechanism of CUR/PS NPs and their therapeutic potential for gastric cancer.

Other studies have found (Cretella et al., 2019; Liang et al., 2021) that PTEN inhibits the activation of PI3K by dephosphorylating PIP3, thereby inhibiting the activation of Akt, promoting apoptosis, and thus inhibiting the development of cancer. TSC1 and TSC2 can inhibit mTOR by inhibiting Rheb, thereby inhibiting the activation of p70S6K and 4EBP1, leading to effective ribosome binding and an increase in protein synthesis, thereby inhibiting biological processes such as tumor growth and immune response (Li, Guan et al., 2020; Zhang et al., 2022). In addition, the use of cariporide to inhibit NHE1 can reduce the levels of Ki67, MMP2, and MMP9 by inhibiting the PI3K/AKT/mTOR pathway, significantly increasing the levels of CD_4^+ and CD_4^+/CD_8^+, thus inhibiting the activities of lung cancer cells and lifting immune suppression and then exerting anti-cancer effects (Yu et al., 2022).

In this study, we used LY294002 and 740 Y-P. Through the detection of PI3K/Akt/mTOR mRNA expression, we found that LY294002 showed abnormally low expression after the intervention of CUR/PS NPs. This may be due to the intervention of CUR/PS NPs. This is achieved through the interaction between PS NPs and PI3K/Akt/mTOR signaling. Moreover, the levels of HIF-1α, VEGF-C, and VEGF-D in this group were reduced, the density of microvessels and lymphatic microvessels was also significantly reduced, and the apoptosis rate was increased, indicating that CUR/PS NPs can mediate PI3K/Akt/mTOR The activity of the signaling pathway is reduced, and the combined effect of CUR/PS NPs and LY294002 inhibits the formation of new blood vessels and lymphatic vessels in tumors, thereby affecting tumor growth and metastasis. After combining CUR/PS NPs with 740 Y-P, the above phenomenon was significantly reversed. This shows that CUR/PS NPs can inhibit the formation of lymphatic vessels in the hypoxic microenvironment of gastric cancer nude mice transplanted tumors by inhibiting PI3K/Akt/mTOR signaling. However, this study can also consider the combined application of CUR/PS NPs with other antitumor drugs or treatments, combined with immunotherapy or radiotherapy, which may produce more significant therapeutic effects.

Conclusion

In summary, while CUR/PS NPs improve drug efficacy, they also significantly enhance the inhibitory effect on PI3K/Akt/mTOR signaling and reduce VEGF expression, thus inhibiting the hypoxia-induced microbiome in lymphatic vessels of gastric cancer nude mice transplanted tumors. Generation in the environment. This nanoparticle is expected to be applied in treating gastric cancer and related diseases, and further clinical studies will help determine its potential use in cancer treatment.

Abbreviations

AKT: Protein kinase B; BECN1: Beclin-1; CUR/PS NPs: Curcumin-loaded polystyrene nanoparticles; PI3K: Phosphoinositide 3 kinase; mTOR: Mammalian target of rapamycin; VEGF: Vascular endothelial growth factor.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the ethics committee of The First People's Hospital of Shuangliu District.

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Informed Consent

Not applicable.

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