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CHFR enhances the drug sensitivity of paclitaxel in oral cancer cells

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Abstract: **Background**: Paclitaxel is used in oral cancer treatment, but drug sensitivity remains a concern. CHFR has been implicated in tumor regulation, yet its role in modulating paclitaxel sensitivity in oral cancer requires further investigation. **Objectives**: This study aimed to evaluate the effect of CHFR on enhancing the drug sensitivity of paclitaxel in oral cancer cells. **Methods**: A rat oral tumor model was established, followed by paclitaxel intervention. Observations included tongue tissue morphology, immune function, cell cycle, apoptosis, and the expression levels of NF-κB and CHFR proteins and mRNAs. **Results**: The modeling success rate was 100%, with visible tongue masses and ulceration. CHFR protein expression increased in the CHFR mimic group. The high-dose paclitaxel group showed the highest immune indices, increased G0/G1 phase cell proportion, and significantly decreased tumor cell viability. The CHFR mimic group exhibited the smallest tumor volume, marked tumor cell death, and active proliferation. CHFR downregulated NF-κB expression; CHFR mRNA was higher, and NF-κB mRNA lower, compared to the high-dose paclitaxel and CHFR mimic groups. **Conclusion**: CHFR enhances paclitaxel sensitivity in oral cancer cells by downregulating NF-κB, effectively inhibiting tumor cell activity and suppressing tumor progression.

Keywords: Apoptosis; CHFR; Oral cancer; Proliferation; Paclitaxel

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INTRODUCTION

The head and neck of the human body are the predilection sites for oral cancer. Globally, oral cancer causes 377,713 new cases per year, with a 5-year mortality rate of nearly 50%, which seriously affects patients' life quality (Yete *et al*., 2020). It has become a global health problem (Li *et al*., 2020; Kijowska *et al*., 2024). However, oral cancer is a rare malignant tumor in western countries with several risk factors, such as smoking (Abati *et al*., 2020). At present, the treatment methods for oral cancer mainly include: surgical treatment, radiotherapy and chemical treatment. However, the therapeutic effect cannot meet clinical expectations, mainly because the conventional treatment methods have strong toxic and side effects, resulting in a decrease in the overall therapeutic efficacy (Liu *et al*., 2022). Therefore, it is an urgent clinical problem to actively seek effective treatment methods.

Cancer is a kind of genomic instability caused by gene mutations such as proto-oncogenes, tumor suppressor genes and other regulatory genes, which in turn leads to the occurrence and development of cancer (Hausman *et al*., 2019; Dakal *et al*., 2024). Mitotic prophase checkpoint with forkhead associated and ring finger do-main (CHFR) is a new premitotic checkpoint gene (Wahner *et al*., 2021). Clinical studies have shown that CHFR is a gene with a good tumor suppressor effect and various studies have confirmed that it is highly expressed in various normal tissues of the body. However, it is often expressed in various cancers such as lung cancer and colon cancer. The phenomenon of inactivation occurs (Maekawa *et al*., 2020). The CHFR gene was discovered by two scholars, SCOINICK and HALAZONETIS, through experimental research in 2000. They found that it is a gene that can detect the division state of healthy cells during division and control it (Scolnick *et al*., 2000). In addition, the CHFR gene is one of the most popular genes in cancer research today and the abnormal methylation of the CHFR gene is one of the important reasons for its silencing (Baretti *et al*., 2021). In the study of Nair *et al*. (Nair *et al*., 2020), it was also shown that the occurrence of some cancers is related to the CHFR gene. Paclitaxel is an important chemical substance extracted from the bark of Yew brevifolia. This substance has a relatively novel chemical structure and a unique mechanism of action. Combined, it promotes the aggregation and stability of microtubules in tumor cells, inhibits tumor cell mitosis and further hinders tumor growth. It is known as one of the three important achievements of anticancer drugs in the 1990s (Al-Mahayr *et al*., 2021; Yu *et al*., 2022). However, there are few research reports on the effect of paclitaxel on the occurrence and development of oral cancer cells through CHFR. Therefore, this study intervened oral cancer rats with different concentrations of paclitaxel to explore whether CHFR can affect oral cancer cells in Tianjin Stomatological Hospital (Tianjin, China). The research idea map is shown in Fig. 1.

MATERIALS AND METHODS

Reagents and instruments

Paclitaxel (Sichuan Taiji); mouse anti-human CHFR antibody (Beijing Zhongshan Biotechnology); CCK-8 and cDNA synthesis kit (Beijing Tiangen Biochemical); PCR

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primers (Shanghai Invitrogen); GAPDH (Shanghai Viall Biotechnology); Protein extraction and BCA assay kit (Shanghai Beyontian); paraffin embedding machine (Beixiaogan Hongye); neutral gum (Sinopharm Group); Westernblot (Shanghai Beyontien).

Animals

SD rats, 30 males (Beijing Weitong Lihua), were bred under constant temperature, constant humidity, light and darkness for 12 hours respectively. This study was approved by the ethical committee of Tianjin Stomatological Hospital.

Construction of rat oral cancer model

First, the rats were anesthetized, the rat tongue was pulled out and fixed and 200 μL of 1.67×10-1/L Walk-er256 tumor cell suspension was injected into the sublingual right side 8 mm and the concentration of the cancer cells suspension was kept within a certain range and a tumor tissue with uniform volume was formed under the tongue of the rat. The success rate of making animal models is 100%. On the 8th day after the establishment of the rat model, a distinct lump appeared on the rat's tongue and there were also damaged ulcers on the oral surface. Subsequently, one modeled rat and one unmodeled rat were randomly selected for immunofluorescence staining of their tongue tissues. The results showed that the CHFR protein content in the rat CHFR simulation group increased (Fig. 2), which also confirmed that the establishment of the rat model of oral cancer was successful.

Experimental grouping and drug intervention treatment

The five groups were the blank control group, the CHFR simulation group, the low-dose paclitaxel group, the medium-dose paclitaxel group, and the high-dose paclitaxel group, with six rats in each group. The blank control group did not require modeling, while the rest constructed oral cancer rat models in the above-mentioned way. Paclitaxel solutions of 1, 3 and 6 mg/kg were injected intraperitoneally into all rats in the paclitaxel low-dose group, paclitaxel middle-dose group and paclitaxel high-dose group, respectively. The chemical molecular structure of paclitaxel is shown in Fig. 3

Immunofluorescence staining detection

The tongue tissue was embedded in paraffin and sectioned and then dewaxed. The dewaxed preparation was washed in 0.1 mol/L phosphate buffered saline 3 times, 5 min each time. Then soaked in 3% donkey serum and block for 120min; add anti-Iba1 at a ratio of 1:100 and then put it in an incubator at 4°C for incubation for one day; added the corresponding donkey-derived fluorescently labeled secondary antibody at a ratio of 1:400 and place it at room temperature The cell nuclei were labeled after being placed in DAPI and then mounted, observed and recorded under a fluorescence microscope and the fluorescence intensity was detected by ImageJ 1.5.0 analysis software.

ELISA

The peripheral blood of rats was collected and the levels of CD3+, CD4+ and CG4+/CD8+ in serum were determined by ELISA.

Tongue tissue cell culture

Rat tongue tissue cells were extracted and cultured in DMEM at 37°C with 10% fetal bovine serum as the medium.

Gene knockout by CRISP-Cas9 technology

According to literature reports and operating guidelines (Back *et al*., 2019; Easmin *et al*., 2019), CRlSPR/Cas9 gRNA technology mainly includes the following steps: design and selection of gRNA library, PCR amplification of gRNA library, lentiviral packaging and infection of gRNA library, identification of gRNA library and screening, exponential amplification by PCR and NGS sequence determination and analysis. The details are as follows: use the gene editing technology CRISPR/Cas9 system to design and construct the sgRNA targeting the second exon of CHFR of the target gene and at the same time T7 RNA polymerase was used to transcribe Cas9 mRNA *in vitro*. After the cell line was transfected with sgRNA and Cas9 mRNA *in vitro*, the target gene was knocked out.

Determination of cell viability by CCK-8

After 4 hours of seeding cells in 96-well plate, DMED medium containing 10% CCK-8 was added for 1 hour. The growth of the cells on day 1, 2, 3, 4 and 5 was measured with the CCK-8 kit and the growth curve was determined.

Transwell migration experiment

Prepare each group of cells to 1×10^5/ml and inoculate them in upper chamber of Transwell, put the serum-free culture medium containing SDF-1α in the lower chamber, incubate for 12 hours, remove and wash, fix with paraformaldehyde, stain with crystal violet and absorb the floating color to measure absorbance at 565 nm.

Flow cytometry analysis

After cells in experimental group were cultured, they were collected according to the number of cells higher than 1×10^6 and then 500 μl of 70% ethanol was added to fix the cells. Place at 4°C for 12h. The fixed cells were washed with PBS solution. After washing, use a centrifuge to remove the liquid, then add 10mg/l PI 0.5ml, put it at room temperature, away from light, for 60min and use a flow cytometer to detect the apoptosis rate after staining.

qRT-PCR

Rat tongue tissue total RNA was extracted and cDNA double strands were prepared by RT-PCR method according to the RT-PCR method of Roche Company. Subsequently, using cDNA as a template, real-time PCR technology was used to realize the real-time detection of the gene in a system including 10 μL of SYBR Green PCR

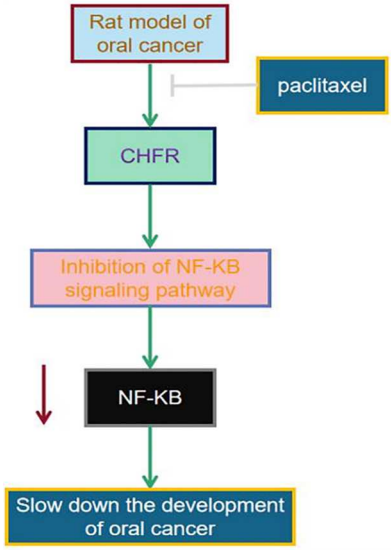

Fig. 1: CHFR increases the sensitivity of paclitaxel chemotherapy drugs, further inhibits the NF-KB signaling pathway, down-regulates the wild level of NF-KB, and slows down the occurrence and development of the disease.

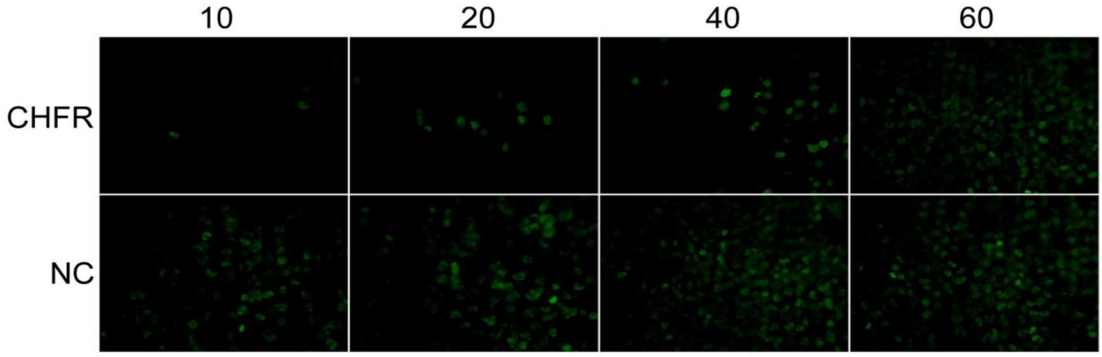

Fig. 2: Construction characteristics of oral cancer rat model. (Observation by immunofluorescence staining; n=1)

Master Mix, 1 μL of eDNA and 200 nmol/L of primers and conditions: 95°C 5 min, 94°C 15 s, 56°C 30 s and 72°C 30 s, a total of 40 cycles. Finally, using GAPDH as a reference, the 2-1ΔCt method was used to quantitatively analyze the expression of target genes. The primers and primer sequences are listed in Table 1.

Western blot

The tongue cells were lysed and the total tissue protein was extracted. SDS-PAGE electrophoresis supernatant containing 50 μg protein, the gel obtained in the previous step was slowly moved onto PVDF. Then, 5% human serum albumin was effectively added to PVDF and it was effectively blocked in a constant temperature environment of 25°C. After storage for 1 hour, the operator used the primary antibody (diluted 1:800), the secondary antibody (diluted 1:1000) was used to incubate the samples obtained in the above steps. Using GAPDH as an internal reference, the cultured photographs developed by ECL reagents and gel imaging system were quantitatively analyzed using ImageJ14.0 software to detect the protein levels of NF-KB and CHFR.

Statistical analysis

Data were processed using SPSS 29.0 and GraphPad Prism 10.6. The measurement data were represented by mean ± SD, conforming to the normal distribution and meeting the homogeneity of variance; the measurement data were represented by (%) and assessed by LSD method. $P<0.05$ refers to a difference.

RESULTS

Through ELISA to detect the immune function of rats, we found that all the immune function indicators of rats were positively correlated with the concentration (vs other groups, $p<0.05$, Fig. 4A-C), indicating that paclitaxel can improve the immune function of rats and slow down oral cancer development. Through further research, we found that under the intervention of CHFR mimics, compared with the other three groups, the number of cells in G0/G1 phase increased ($P<0.001$, Fig. 4D&G) and the viability of tumor cells decreased significantly ($p<0.05$, Fig. 4E), meanwhile, the tumor volume in CHFR mimic group was

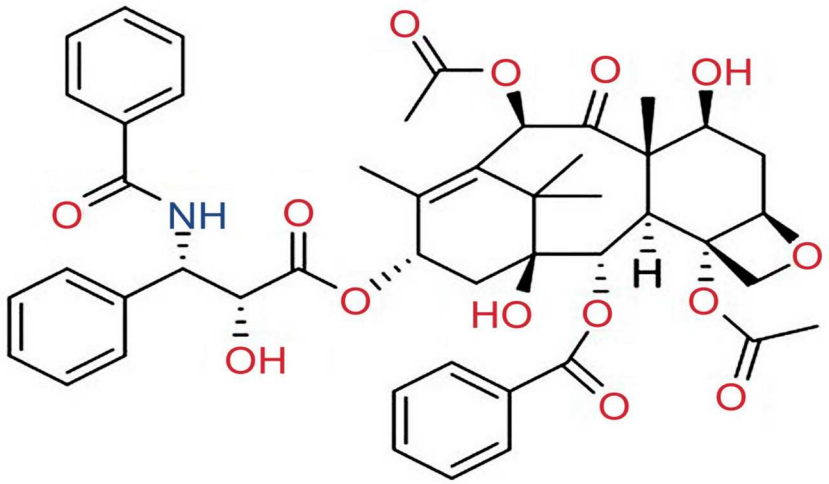

Fig. 3: Molecular structure of paclitaxel.

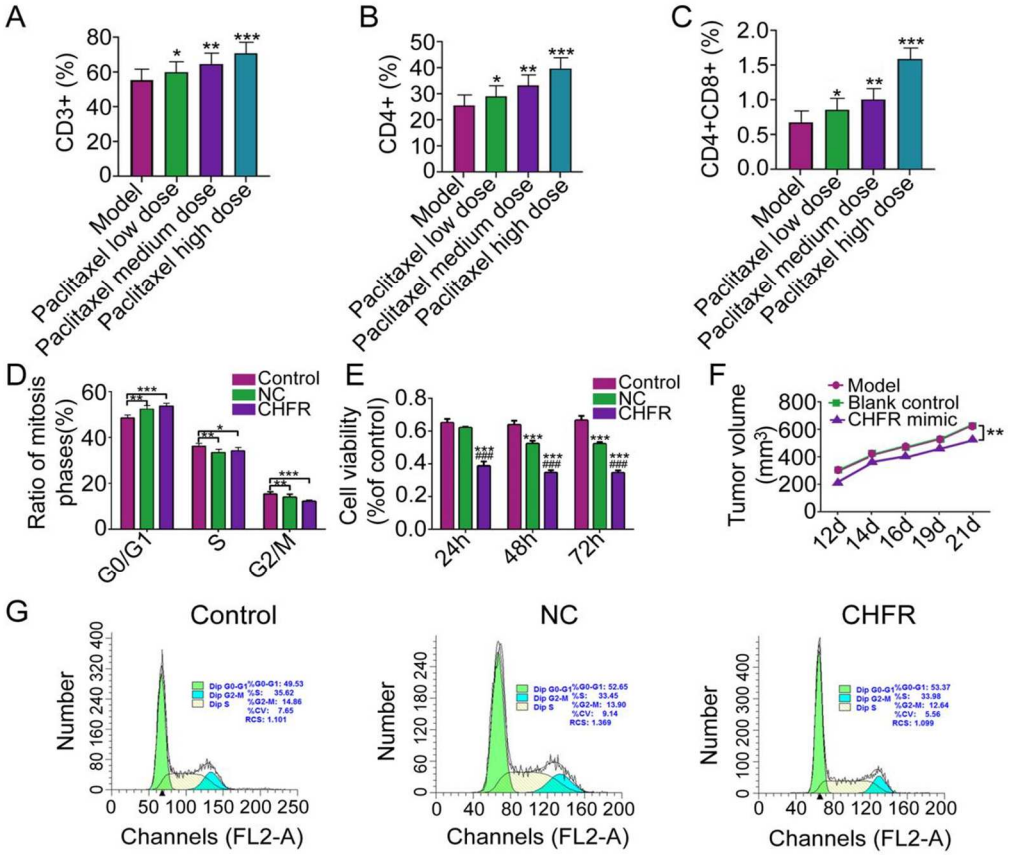

Fig. 4: Paclitaxel has a certain degree of improvement in oral cancer.(A, B, C): ELISA was used to detect the immune function of rats; (D, E, G): Flow cytometry was used to detect the viability of tumor cells in rats; (F): Compared with the model group, *P<0.05; Compared with paclitaxel low-dose group, **P<0.05; compared with paclitaxel medium-dose group, ***P<0.05; compared with model group, **P<0.05, ***P<0.05; and blank Compared to the control group, ## #P<0.05; n=6). NC: negative control.

the lowest (p<0.05, Fig. 4F), which also fully demonstrated that the improvement effect of paclitaxel on oral cancer may be through regulating CHFR. Under CHFR intervention, the apoptosis of cells in the CHFR mimic group was significant (p<0.05, Fig. 5A&D); after knocking out CHFR gene, the tumor cells proliferated actively (p<0.05, Fig. 5B) and the migration ability was enhanced (p<0.05, Fig. 5C). Further analysis of the reason found that CHFR could down-regulate the expression of NF-KB (p<0.05, Fig. 5E&F), the expression of NF-KB decreased and the proliferation and apoptosis of tumor cells were inhibited.

In order to clarify the mechanism of paclitaxel intervening in CHFR to improve oral cancer and carry out more in-depth research on it, the levels of CHFR and NF-KB under paclitaxel intervention are similar to the results of CHFR mimic intervention ($p<0.05$, Fig. 6A-D), while CHFR mRNA level was increased (vs paclitaxel high-dose group, $p<0.05$, Fig. 6A) and the expression of NF-KB mRNA was decreased (vs paclitaxel high-dose group) after adding CHFR mimics on the basis of paclitaxel dose group, $p<0.05$, Fig. 6B) and the expression of CHFR mRNA was significantly higher than that of paclitaxel high-dose group and CHFR mimic group and the expression of NF-KB mRNA was lower than paclitaxel high-dose group and CHFR mimic group, confirming that CHFR can increase Sensitivity to paclitaxel, enhanced therapeutic effect.

DISCUSSION

Paclitaxel, one of the broad-spectrum anticancer compounds mainly derived from the bark of the Pacific yew tree (Taxus brevifolia) is used today as therapeutic drug for various cancers (Hu *et al*., 2021; Zhou *et al*., 2021; Sati *et al*., 2021; Zhang *et al*., 2025). However, there are some difficulties due to limited solubility, recrystallization upon dilution and toxicity caused by co-solvents. In addition, CHFR also has strong anti-tumor activity. Hagiwara *et al*., (Hagiwara *et al*., 2022) that CHFR promoter methylation was positively correlated with the inhibition of colon cancer by SN38 in HDRA, which indicated that CHFR had a strong inhibitory effect on colon cancer tumor cells. At the same time, in the study of Jiang *et al*., (Jiang *et al*., 2021), it was also shown that CHFR plays a tumor suppressor role in various cancer types. The above studies have confirmed the tumor suppressor effect of CHFR. However, previous studies mostly focused on the antitumor effect of paclitaxel and the current application mechanism of paclitaxel interfering with CHFR in tumor chemotherapeutic drug resistance is not clear. This experiment aims to explore whether CHFR can affect oral cancer cells activities, thereby delaying the progression of the disease and In-depth discussion of its mechanism will provide an important theoretical basis for relevant clinical research.

In this study, we successfully constructed a rat model of oral cancer and used it in this study. On the 8th day after the establishment of the rat model, an obvious lump appeared on the tongue of the rat and there were also damaged ulcers on the surface of the lump.

Afterwards, the tongue tumor was infiltrating and other tissues of the rat tongue were infiltrated, which also confirmed the successful modeling of oral cancer in rats. In the study of Kawaharada M *et al*., (Kawaharada *et al*., 2022), a rat model of oral cancer was also successfully constructed. At the same time, Fazli *et al*., (Fazli *et al*., 2022) showed that local (sustained release) and systemic curcumin nano-antioxidants have effects on oral cancer. Oral cancer in rats has a certain degree of preventive effect. The above research confirms the reliability and authenticity of our research model construction. Further analysis found that under the intervention of different concentrations of paclitaxel, the various immune function indexes of rats showed an upward trend, which was concentration-dependent and the index levels of the high-dose paclitaxel group were the highest, indicating that paclitaxel can improve the immune function of rats. Immune function in rats slows the development of oral cancer. According to the report of Meng *et al*., (Meng *et al*., 2021), chemotherapeutic drugs such as paclitaxel and cisplatin have now become the first-line choice for patients with oral squamous cell carcinoma. And Cabezas-Camarero (Cabezas-Camarero *et al*., 2021) also showed in the study that patients with oral cancer had a durable response to paclitaxel and carboplatin. The above studies also confirmed that paclitaxel can slow down the development of oral cancer. Cai *et al*., (Cai *et al*., 2022) also studied that the extract of paclitaxel has obvious anticancer activity on A549 xenografted BALB/C nude mice. The reason is that paclitaxel has a synergistic effect with flavonoids or lignin. Lignin contribute to its anticancer effects by simultaneously improving enterocyte absorption of paclitaxel and cytotoxicity of paclitaxel. This study further confirms that paclitaxel is suitable for the treatment of various cancers.

Through further research, we found that under the intervention conditions of CHFR, the apoptosis of cells in the CHFR mimic group was significant; after gene knockout of CHFR, the tumor cells proliferated actively and their migration ability was enhanced. The analysis of the reasons found that CHFR can down-regulate NF-KB, which reduces NF-KB and inhibits the proliferation and apoptosis of tumor cells. Luo *et al*., (Luo *et al*., 2021) found that CHFR regulates the chemotherapy resistance of triple-negative breast cancer by destabilizing ZEB1 through the process of exploring the main reason for the failure to treat triple-negative breast cancer. Wu *et al*., (Wu *et al*., 2021) also found in their study that CHFR-mediated degradation of RNF126 endows triple-negative breast cancer cells with sensitivity to PARP inhibitors. In addition, Wang *et al*., (Wang *et al*., 2022) also found through related research that Circ CHFR can promote vascular smooth muscle cells activities through mir-149-5p/NRP2. To assess the mechanism of paclitaxel intervening CHFR to improve oral cancer and carry out more in-depth research on it, the levels of CHFR and NF-KB under paclitaxel intervention are similar to the results of CHFR mimic intervention, while on the basis of high dose paclitaxel with addition of CHFR mimics, CHFR mRNA increased significantly and NF-KB mRNA decreased significantly and CHFR mRNA was higher than paclitaxel high-dose group and CHFR mimic group and NF-KB mRNA was lower.

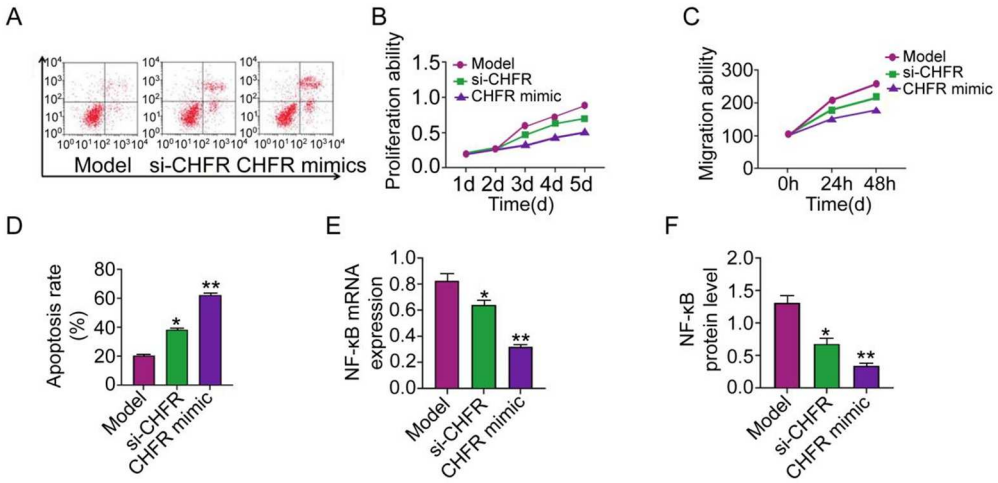

Fig. 5: CHFR can down-regulate the expression of NF-KB to inhibit the proliferation of oral cancer cells and promote cancer apoptosis.(A): Flow cytometry detection of rat tumor cell apoptosis; (B): CCK detection of rat tumor cell proliferation quantification; (C): Transwell detection of rat tumor cell migration quantification; (D): Quantification of tumor cell apoptosis in rats detected by flow cytometry; (E): NF-KB mRNA expression in rats detected by PCR; (F): NF-KB protein expression detected by Western blot; compared with the model group, *p<0.05; compared with si-CHFR group, **P<0.05; n=6. siCHFR: Small interfering RNA targeting CHFR.

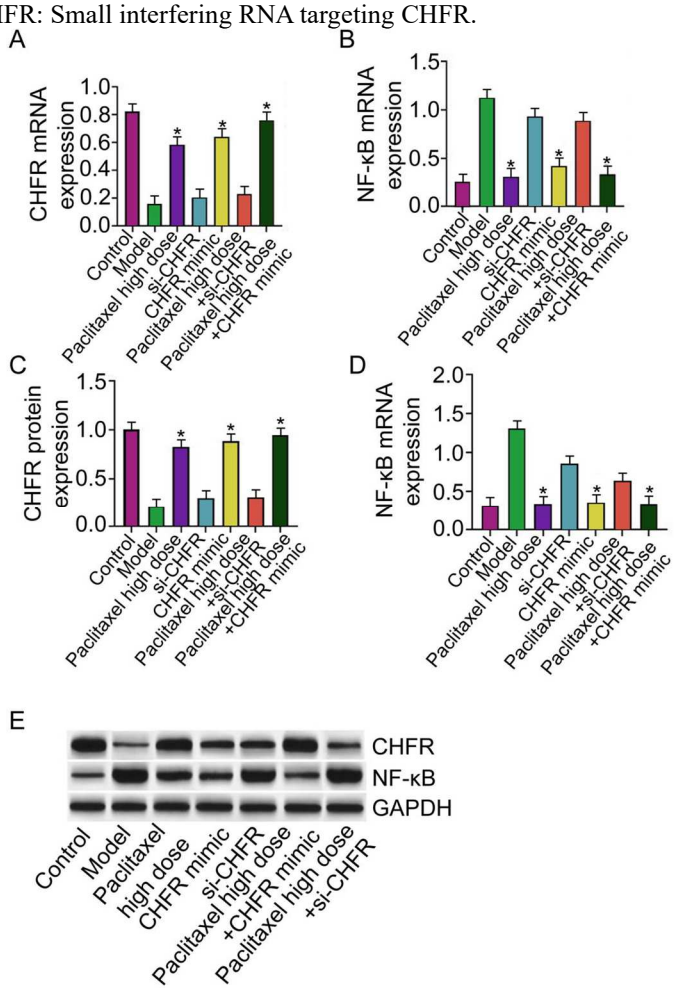

Fig. 6: Paclitaxel can affect CHFR to further improve oral cancer. (A and B): PCR detection of mRNA expression of CHFR and NF-KB in rats; (C, D, E): Western blot detection of protein expression of CHFR and NF-KB; compared with model group, *p<0.05; n=6.

Table 1: Primer sequences.

Gene	Primer	Sequences
NF-KB	Forward	5'-AGTTGAGGGGACTTTCCC AGGC-3'
	Reverse	5'-TCA ACTCCCCTG AAAGGGTCCG-3'
CHFR	Forward	5′-AGGAAGTGGTCCCTCTGTG-3′
	Reverse	5′-TTTGGGCATTTCTACGC-3′
GAPDH	Forward	5′-TGGCACCCAGCACAATGAA-3′
	Reverse	5′-CTAAGTCATAGTCCGCCTAGAAGCA-3′

It was confirmed that CHFR can increase the sensitivity of paclitaxel and enhance the therapeutic effect. In the study by Li *et al*., (Li *et al*., 2020) we were able to show that loss of CHFR sensitizes gastric tumor cells to PARP inhibitor treatment. This study also further confirmed the research point of view of this paper.

CONCLUSION

In summary, CHFR can inhibit NF-KB signaling and further inhibit oral cancer cells activities and slow down the development of oral cancer, indicating that it might be a novel approach for the treatment of oral cancer.

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Authors' contributions
Yuan Gao: Writing - original draft
Tianzheng Deng: Writing – original draft
Ying Li: Conceptualization
Chengxiong Cai: Formal analysis
Chufan Ma: Writing - review & editing

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Data availability statement
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval
This study was approved by the Ethical Committee of Air Force Medical Center (Ethical Approval NO: 2023-088-PJ01).

Conflict of interest
There are no conflicts to declare.

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