© IJHG 2022 Int J Hum Genet, 22(3): 118-127 (2022)
PRINT: ISSN 0972-3757 ONLINE: ISSN 2456-6330 DOI: 10.31901/24566330.2022/22.03.810

Research on Diagnosis and Prognosis of Cervical Cancer in FOXD1

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KEYWORDS Cervical Cancer. Connective Tissue Growth Factor. Diagnosis. FOXD1 (Human) Recombinant Protein (P01). Prognosis

ABSTRACT The aim of the present study was to investigate the diagnostic and prognostic value of FOXD1 in cervical carcinoma. 24 patients with cervical carcinoma were the sample for this study. Human cervical carcinoma cell lines (AV3, Hela229, CaSki and Hela cells) and cervical normal cell line (UVECs) were used in this study for vitro model. FOXD1 mRNA expression level was up-regulated in the tissue of cervical cancer, compared with paracancerous tissue group. FOXD1 mRNA expression level in I-II patients with cervical cancer was lower than those of III-IV patients with cervical cancer. Overall survival (OS) and disease-free survival (DFS) of FOXD1 high expression were lower than those of FOXD1 low expression. FOXD1 mRNA expression level was induced in cervical cancer cell lines, compared with UVECs cell. In conclusion, serum FOXD1 expression was the diagnostic and prognostic value for cervical carcinoma, and promotes cell growth and metastasis via Warburg effect by CTGF.

INTRODUCTION

Cervical cancer is a serious threat to women's health and life. It is one of the main malignant tumors endangering women's health (Beekman et al. 2021). In 2018 global cancer statistics show that there are 8.6 million new cases of female cancer worldwide, accounting for 6.6 percent of cervical cancer. There were 4.2 million female cancer deaths, and cervical cancer accounted for 7.5 percent. It ranks fourth in the incidence and death causes of female malignant tumors. The incidence rate and mortality of cervical cancer vary greatly among countries (Ge et al. 2021). The world cancer burden data in 2013 shows that the incidence rate and mortality of cervical cancer in developing countries are 1.64 times and 2.10 times higher than those in developed countries respectively (Ge et al. 2021). The prevalence of cervical cancer in China is not optimistic. According to the data of China cancer registration annual report, in 2015, there were 111000 new cases of cervical cancer and 34000 deaths of cervical cancer, ranking sixth and eighth in the order of incidence and cause of death of female malignant tumors in China (Ge et al. 2021). Studies have shown that the age standardized mortality of cervical cancer is significantly lower than 30 years ago, but it began to rise in rural areas after 2005 and cities after 2008. The harm of cervical cancer to women's health and its prevention and treatment are important public health problems all over the world (Gul et al. 2021; Ribeiro et al. 2021).

Connective tissue growth factor (CTGF) is a member of the immediate early gene CCN family. CTGF is widely expressed in many human tissues and organs (Hashiguchi et al. 2021). CTGF is widely expressed in liver, lung, heart and other organs, which can promote cell proliferation, collagen synthesis and formation, and the expression of adhesion molecules. CTGF is an early immediate response protein, which affects the activity of fibroblasts and plays an important role in the occurrence and development of fibrosis (Hashiguchi et al. 2021). It has biological functions such as promoting cell proliferation, mediating cell adhesion, stimulating cell migration and promoting angiogenesis (Chu et al. 2008; Kim et al. 2020).

Many members of the forkhead box (Fox) gene family have been proved to be related to cancer and play an important regulatory role in the process of tumour formation (Fu et al. 2019). They mainly control the expression of other

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genes through transcription factors and participate in tumour cell growth, differentiation, apoptosis, proliferation, migration, invasion and angiogenesis (Gao et al. 2020). FoxD1 is a member of the Fox family and is expressed in human embryonic tissues (Li et al. 2019). Studies have reported that the abnormal expression of FOXD1 is closely related to the occurrence of prostate cancer, breast cancer and clear cell sarcoma of the kidney (Li et al. 2019; Wu et al. 2021).

Objective of the Study

This study considered that FOXD1 might regulate cell growth and metastasis of cervical carcinoma. The aim of the present study was to investigate the diagnostic and prognostic values of FOXD1 in cervical carcinoma.

MATERIAL AND METHODS

Establishment of Patients with Cervical Carcinoma

This study was approved by the Human Ethics Committees of our hospital. Informed consent was obtained from all patients in the study. Tissue samples were collected and immediately stored at -80°C. 24 patients with cervical carcinoma were obtained from May 2015 to July 2016.

Reverse Transcription quantitative Polymerase Chain Reaction (RT qPCR)

The total RNA was extracted from serum and cell samples using a TRIZOL reagent (Life Technologies Inc.). qRT PCR assays were performed using Light Cycler® 480 SYBR Mix (Roche, Germany) using LightCycler® 480 real time PCR system. The expression levels of mRNA were normalised to the GAPDH expression using the $2^{-\Delta\Delta ct}$ method.

Cell Culture and RNA Interference

The human cervical carcinoma cell lines (AV3, Hela229, CaSki and Hela cells) and cervical normal cell line (UVECs) were cultured in RPMI 1640 medium (Gibco, Carlsbad, CA, USA) supplemented with ten percent foetal calf serum (FCS, Gibco, Carlsbad, CA, USA) in a humidified atmosphere of five percent carbon dioxide at 37°C. Plasmids were transfected into PBMCs using Lipofectamine 2000. After 48 hours of transfection, cells were used other experiments.

Analysis of Cell Growth and Metastasis

After 48 hours of transfection, 1×10^3 cells/well were seeded in 96-well plate. After culturing at indicated time (0, 6, 12, 24 and 48 day), the cellular proliferation was detected using Cell Counting Kit-8 (CCK-8, Beyotime, Beijing, China) by CellTiter-GloR Luminescent Cell Viability Assay according to manufacturer's instructions.

After 48 hours of transfection, 1×10^3 cells/well were seeded in 96-well plate. Ethynyl deoxyuridine (EdU) (10 mM) was added to each well and cells were fixed with four percent formaldehyde for 30 minutes. After washing, EdU was detected with Click-iTR EdU Kit and images were visualised using fluorescent microscope (Olympus).

Western blot assay: In this assay, cell samples or tissue samples were extracted total protein using Radio Immunoprecipitation Assay (RIPA) and PMSF reagent (Beyotime, Beijing, China). SDS-PAGE was conducted to transfer the protein to polyvinylidene difluoride membranes. The membranes were blocked with non-fat-milk (5%) for 2 hours at room temperature and incubated with ant-FOXD1 antibody, anti-CTGF antibody and anti-â-actin antibody at 4°C. The membranes were incubated with horseradish peroxide-coupled sheep anti-mouse secondary antibody at room temperature for 2 hours. The bound antibodies were detected using enhanced chemiluminescence (ECL) with β-actin used as a control.

Statistical Analysis

IBM SPSS Statistics (version 24.0, IBM Corp., Armonk, NY, USA) was used for data analysis. $P<0.05$ was considered statistically significant. Measurement data are expressed as mean ± standard deviation. Multiple groups were compared by two-way repeated-measures analysis of variance (ANOVA), date between two groups were compared using Student's t tests.

RESULTS

Expression of FOXD1 in Patients with Cervical Carcinoma or Cervical Carcinoma Cell Lines

The researchers screened microarray datasets of cervical cancer and FOXD1 may be an important target (Fig. 1A). FOXD1 mRNA expression level was up-regulated in tissue of cervical cancer, compared with paracancerous tissue group (Fig. 1B). FOXD1 mRNA expression level in I-II patients with cervical cancer was lower than those of III-IV patients with cervical cancer (Fig. 1C). FOXD1 protein expression level was induced in tissue of cervical cancer, compared with paracancerous tissue group (Fig. 1D). OS and DFS of FOXD1 high expression were lower than those of FOXD1 low expression (Fig. 1E-1F). FOXD1 mRNA expression levels was induced in cervical cancer cell lines, compared with UVECs cell (Fig. 1G). Taken together, the data suggests that FOXD1 played a repair factor in occurrence and development of cervical cancer.

FOXD1 Promoted Cell Growth and Metastasis of Cervical Carcinoma

To investigate the function of FOXD1 in cell growth and metastasis of cervical cancer, the researchers examined cell growth and migration of cervical cancer cell lines by over-expression of

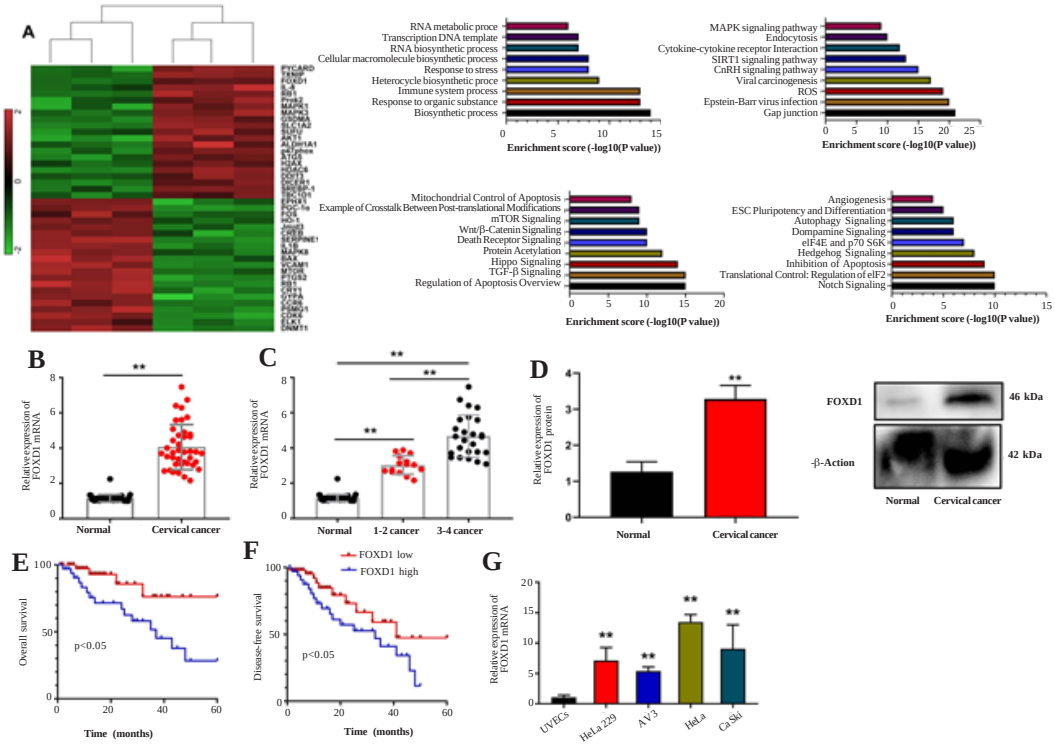

Fig. 1. The expression of FOXD1 in cervical carcinoma
(A) Microarray analysis and result analysis
(B) FOXD1 mRNA expression in patients
(C) FOXD1 mRNA expression in patients using pathological grading
(D) FOXD1 protein expression in patients with cervical carcinoma
(E and F) overall survival and disease free survival
(G) FOXD1 mRNA in cervical carcinoma cell lines
**p<0.01 compared with normal group or UVECs

FOXD1 or down-regulation of FOXD1. The researchers found that FOXD1 plasmid increased the expression of FOXD1 mRNA expression level in cervical cancer cell line (AV3, Fig. 2A). Over-expression of FOXD1 promoted cell growth, increased migration rate and the number of EDU cells of cervical cancer cell line (Figs. 2B-2D). Si-FOXD1 reduced FOXD1 mRNA expression level in cisplatin resistance of cervical cancer cell line (Hela cells, Fig. 2E). Down-regulation of FOXD1 reduced cell growth, inhibited migration rate and the number of EDU cells of cervical cancer cell line (Figs. 2F-2H). Therefore, the researchers focused on FOXD1 promoted cell growth and metastasis of cervical carcinoma.

FOXD1 Promoted Warburg Effect of Cervical Carcinoma and Si- FOXD1 Reduced Warburg Effect of Cervical Carcinoma

The researchers observed that FOXD1 controls Warburg effect to affect cell growth of cervical carcinoma. Over-expression of FOXD1 promoted the glucose consumption, lactate production and ATP quantity in cervical carcinoma cell (Figs. 3A-3C). Down-regulation of

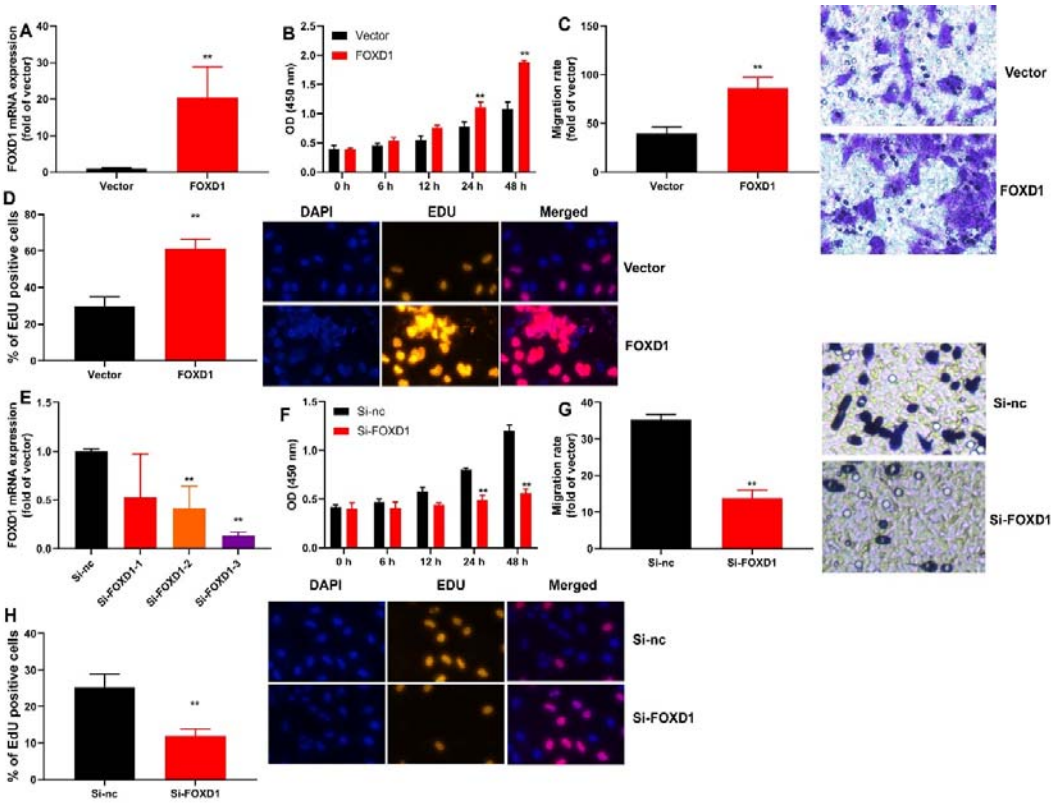

Fig. 2. FOXD1 promoted cell growth and metastasis of cervical carcinoma
(A) FOXD1 mRNA expression
(B) Cell growth (CCK-8)
(C) Migration rate (C)
(D) EDU assay in vitro model of cervical carcinoma by over-expression of FOXD1
(E) FOXD1 mRNA expression
(F) Cell growth (CCK-8)
(G) Migration rate
(H) EDU assay in vitro model of cervical carcinoma by down-regulation of FOXD1
**p<0.01 compared with negative control group or si-negative control group

FOXD1 reduced glucose consumption, lactate production and ATP quantity of cervical carcinoma cell (Figs. 3A-3C). Furthermore, over-expression of FOXD1 promoted extracellular acidification rate (ECAR) and OCR relative level of cervical carcinoma cell (Figs. 3D, 3F). Down-regulation of FOXD1 reduced ECAR and OCR relative levels of cervical carcinoma cell (Figs. 3E, 3G). These results suggest that FOXD1 could increase Warburg effect to promote cell growth of cervical carcinoma.

FOXD1 Gene Induced CTGF Protein Expression and Reduced Ubiquitination of CTGF Protein

The study directly examined the mechanism of FOXD1 regulated cell growth of cervical carcinoma cells. Over-expression of FOXD1 induced CTGF mRNA expression level in cervical carcinoma cells, and down-regulation of FOXD1 suppressed CTGF mRNA expression level in cervical carcinoma cells (Figs. 4A-4B). Over-expression of FOXD1 induced FOXD1 and CTGF protein expressions in cervical carcinoma cells (Figs. 4C, 4D, 4G). Down-regulation of FOXD1 suppressed FOXD1 and CTGF protein expressions in cervical carcinoma cells (Figs. 4E, 4F, 4H). Over-expression of FOXD1 reduced ubiquitination of CTGF protein expressions in cervical carcinoma cells, and down-regulation of FOXD1 promoted ubiquitination of CTGF protein expressions in cervical carcinoma cells (Fig. 4I).

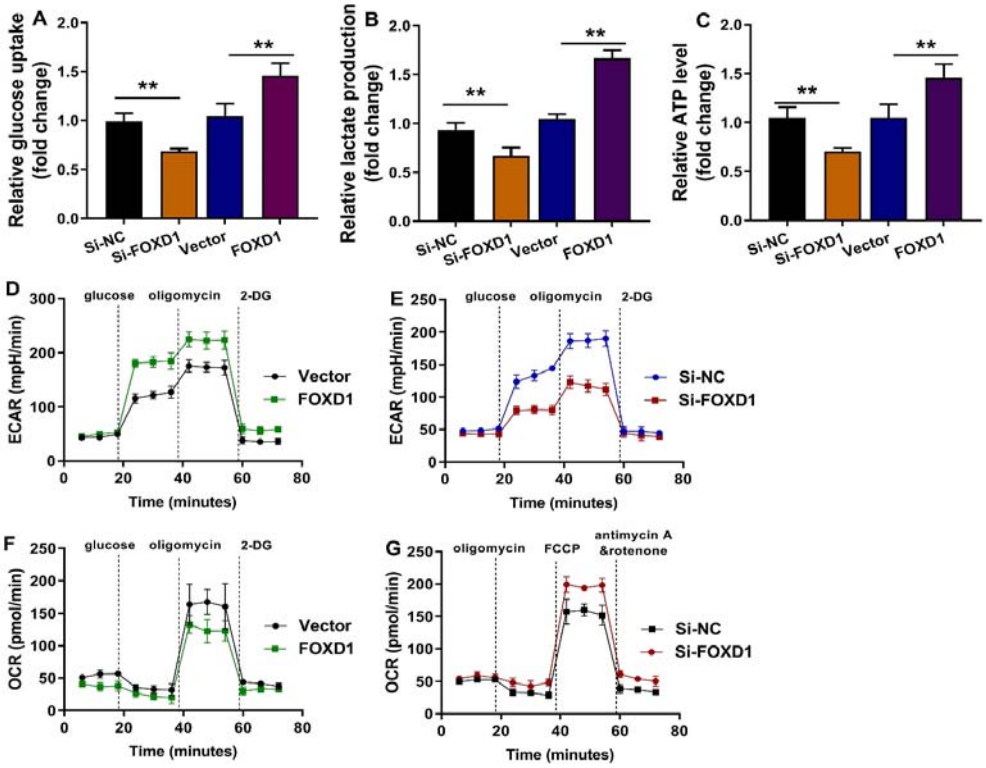

Fig. 3. FOXD1 promoted Warburg effect of cervical carcinoma
(A) the glucose consumption
(B) revealed the lactate production
(C) the ATP quantity
(D and E) lactate-induced acidification of the medium surrounding cells
(F and G) mitochondrial respiratory capacity was conducted using Seahorse XFp assay
****p<0.01 compared with negative control group or si-negative control group.**

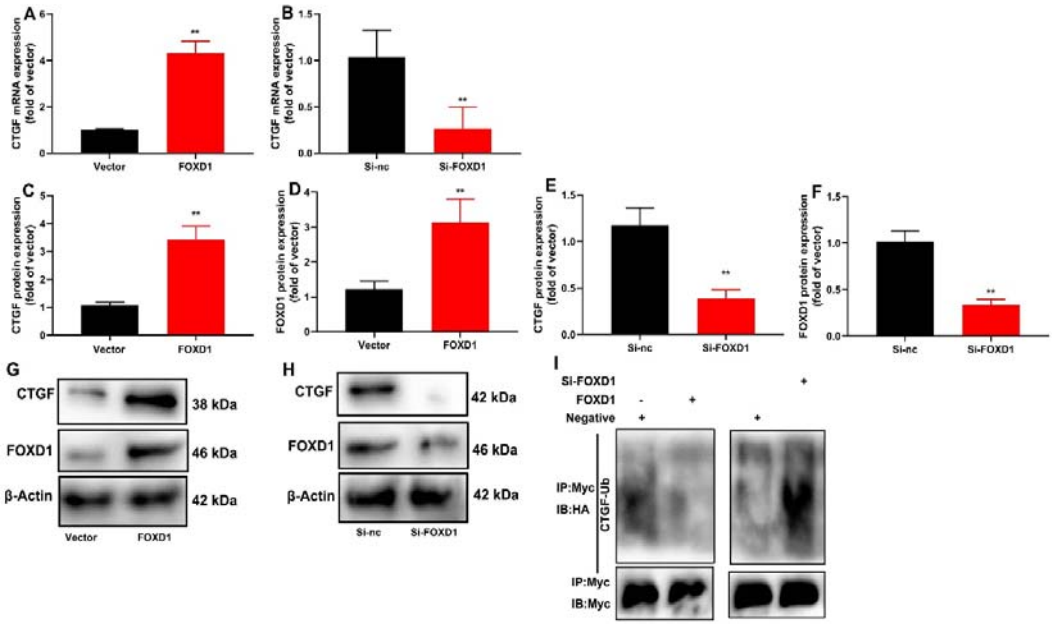

Fig. 4. FOXD1 induced CTGF protein expression and reduced Ubiquitination of CTGF protein
(A and B) FOXD1 mRNA expression by over-expression of FOXD1 or down-regulation of FOXD1
(C, D and G) FOXD1 and CTGF protein expressions by over-expression of FOXD1
(E, F and H) FOXD1 and CTGF protein expressions by down-regulation of FOXD1
(I) Ubiquitination of CTGF protein
**p<0.01 compared with negative control group or si-negative control group.

Regulation of CTGF Affected the Function of FOXD1 in Cervical Carcinoma

Based on these results, CTGF plasmid increased CTGF mRNA expressions in cervical carcinoma cells (Fig. 5A). Si-CTGF suppressed CTGF mRNA expressions in cervical carcinoma cells (Fig. 5B). Then, si-CTGF suppressed the effects of FOXD1 on CTGF protein expression in cervical carcinoma cells (Figs. 5C-5D). CTGF plasmid also reversed the effects of si-FOXD1 on CTGF protein expression in cervical carcinoma cells (Figs. 5E-5F). In general, data suggests that CTGF is one important targets of FOXD1 in cervical carcinoma cells.

Regulation of CTGF Affected the Function of FOXD1 on Warburg Effect of Cervical Carcinoma

The study determined the role of CTGF in the control effects of FOXD1 on Warburg effect of cervical carcinoma cells. Next, the researchers found that si-CTGF reversed the effects of FOXD1 on cell growth, migration rate and number of EDU cells in cervical carcinoma cells, compared with FOXD1 group (Figs. 6A-6E). CTGF plasmid recovered cell growth, migration rate and number of EDU cells in cervical carcinoma cells by si- FOXD1, compared with si-FOXD1 group (HS683 cells, Figs. 6F-6J).

Si-CTGF reduced the effects of FOXD1 on the glucose consumption, lactate production and ATP quantity in cervical carcinoma cell (Figs. 7A, 7C, 7E). CTGF plasmid increased the effects of si-FOXD1 on glucose consumption, lactate production and ATP quantity of cervical carcinoma cell (Figs. 7B, 7D, 7F). Furthermore, si-CTGF reduced the effects of FOXD1 on extracellular acidification rate (ECAR) and OCR relative level of cervical carcinoma cell (Figs. 7G, 7I). CTGF plasmid increased the effects of si-FOXD1 on ECAR and OCR relative levels of cervical carcinoma cell (Figs. 3E, 3G). These results sug-

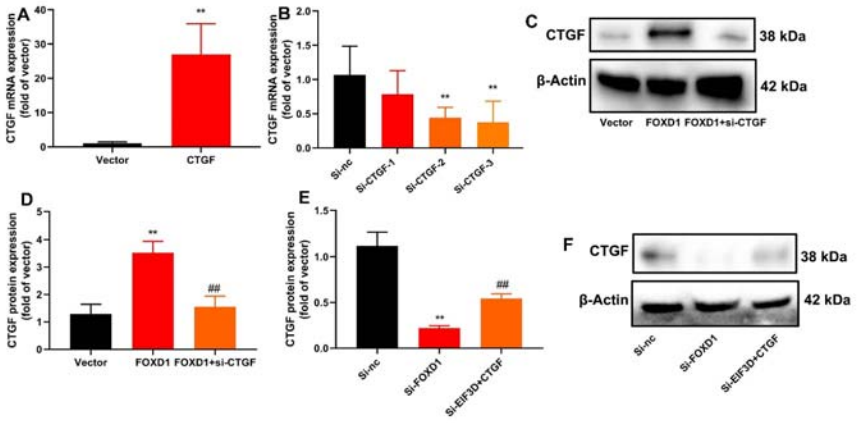

Fig. 5. The regulation of CTGF affected the function of FOXD1 in cervical carcinoma
(A) CTGF mRNA expression
(B) CTGF protein expression in vitro model of FOXD1 and si-CTGF
(C) CTGFmRNA expression
(D) CTGF protein expression in vitro model of si-FOXD1 and CTGF
**p<0.01 compared with negative control group or si-negative control group;
$^{\#\#}$p<0.01 compared with over-expression of FOXD1 group or down-regulation of FOXD1 group.

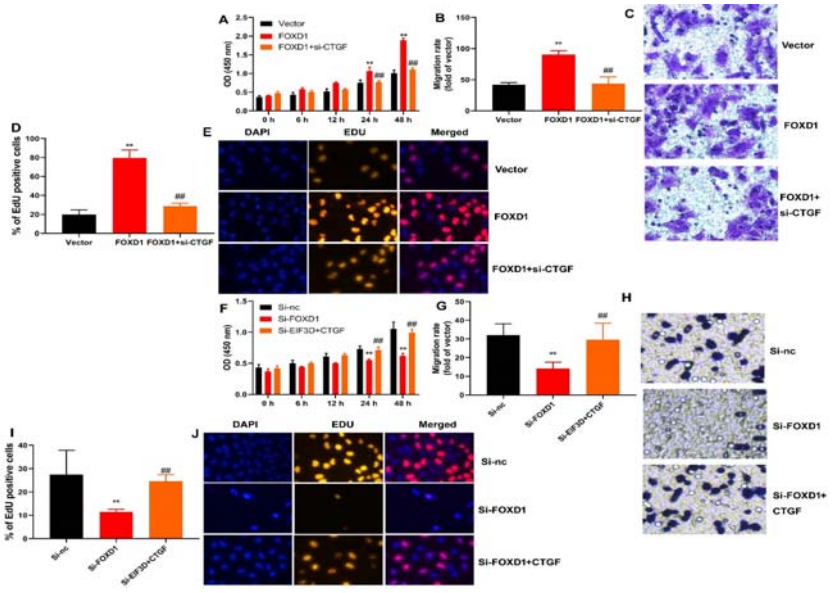

Fig. 6. The regulation of CTGF affected the function of FOXD1 on cell growth and metastasis of cervical carcinoma
(A) Cell growth (CCK-8)
(B and C) EDU assay
(D and E) Migration rate in vitro model of glioma in vitro model of FOXD1 and si-CTGF
(F) Cell growth (CCK-8)
(G and H) EDU assay
(I and J) Migration rate in vitro model of si-FOXD1 and CTGF
**p<0.01 compared with negative control group or si-negative control group;
$^{\#\#}$p<0.01 compared with over-expression of FOXD1 group or down-regulation of FOXD1 group

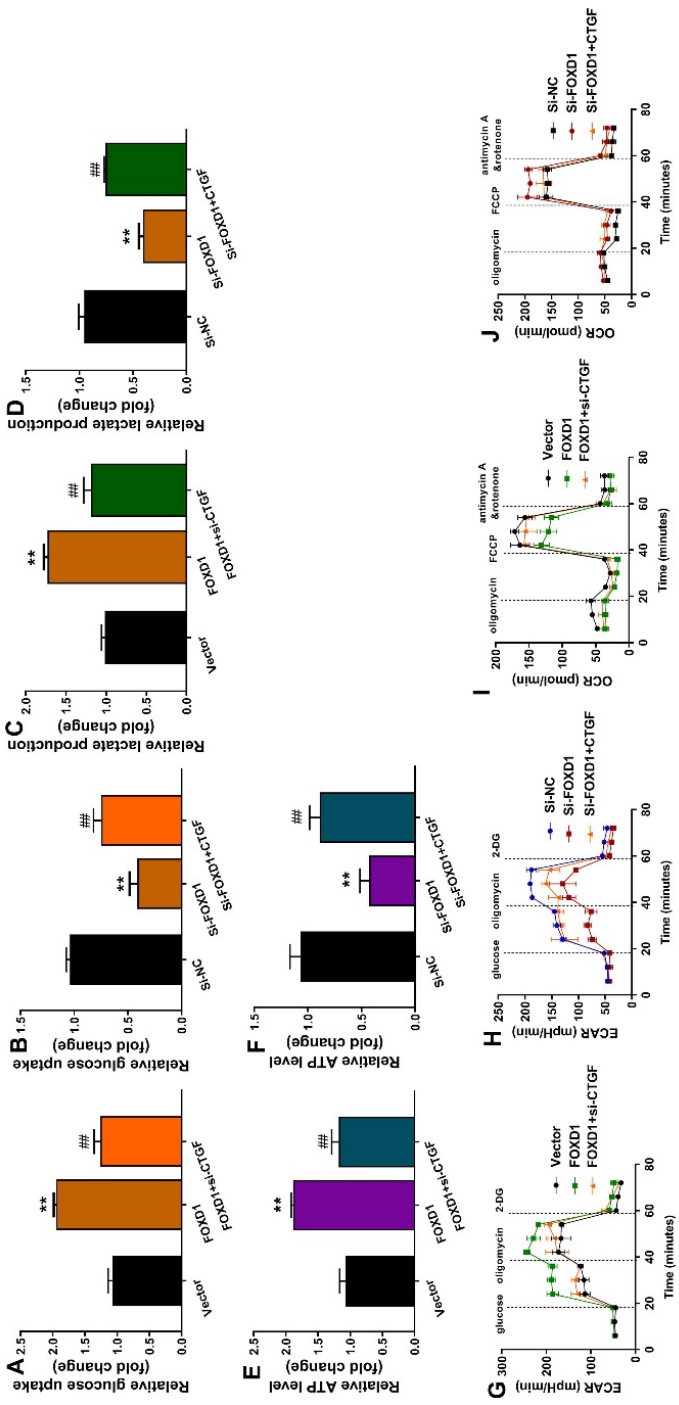

Fig. 7. The regulation of CTGF affected the function of FOXD1 on Warburg effect of cervical carcinoma
(A) the glucose consumption
(B) the lactate production
(C) the ATP quantity
(D and E) lactate-induced acidification of the medium surrounding cells
(F and G) mitochondrial respiratory capacity was conducted using Seahorse XFp assay

gest that FOXD1/CTGF signal pathway could increase Warburg effect to promote cell growth of cervical carcinoma.

DISCUSSION

Despite the popularisation of cervical cancer screening and the continuous improvement of early diagnosis technology, cervical cancer is still one of the most common malignant tumours leading to female death (Kim and Kim 2021). Cervical cancer is a common gynaecological malignant tumour (Kim and Kim 2021). Every year, more than 200,000 women die from cervical cancer in the world. About 510,000 cases of cervical cancer die in China every year. China accounts for about thirty percent of the new cases in the world (Li et al. 2021). More than 200,000 women die from cervical cancer in the world every year, and about 53,000 women die from cervical cancer in China every year (Li et al. 2021). Cervical cancer is a key disease to be prevented and controlled in China (Li et al. 2021; Oishi et al. 2021). At present, FOXD1 mRNA expression level was up-regulated in tissue of cervical cancer, compared with paracancerous tissue group. FOXD1 mRNA expression level in I-II patients with cervical cancer was lower than those of III-IV patients with cervical cancer. OS and DFS of FOXD1 high expression were lower than those of FOXD1 low expression. Wu et al. (2021) showed that FOXD1 promotes gastric cancer progression and colorectal cancer (Chen et al. 2019). The researchers suggest that FOXD1 may precisely control cervical cancer progression.

FOX gene family members play an important regulatory role in tumour formation (Chen et al. 2019). They control the expression of other genes through transcription factors and participate in tumour cell growth, differentiation, apoptosis, proliferation, migration, invasion and angiogenesis (Jin et al. 2019; Lin et al. 2020). On the basis of this, the present study showed that FOXD1 promoted cell growth and metastasis, and increased Warburg effect of cervical carcinoma. Zhao et al. (2015) suggest that FOXD1 promotes breast cancer proliferation. Moreover, FOXD1 could increase Warburg effect to promote cell growth of cervical carcinoma.

Recent studies have shown that the expression level of CTGF is closely related to the occurrence and progression, invasion and metastasis, tumour angiogenesis and prognosis of a variety of malignant tumours (Hofsjö et al. 2019; Hellinger et al. 2020). But the specific mechanism of CTGF gene in the occurrence and development of cervical cancer is not clear (Ladwa et al. 2011; Lun et al. 2018). The results of this study showed that FOXD1 induced CTGF protein expression and reduced Ubiquitination of CTGF protein. The regulation of CTGF affected the function of FOXD1 in cervical carcinoma. Sun et al. (2021) reported that FOXD1 promotes dedifferentiation in melanoma by CTGF expression (24). This may lead to FOXD1 promoted cell growth of cervical carcinoma by CTGF.

CONCLUSION

Taken together, FOXD1 in patients with cervical carcinoma was the diagnostic and prognostic value, and promotes cell growth and metastasis via CTGF. Thus, FOXD1 played a protective role for cervical carcinoma, and the present study may act as a reference for the clinical treatment of cervical carcinoma.

RECOMMENDATIONS

In order to prevent and treat cervical cancer, the diagnostic and prognostic value of FOXD1 for cervical cancer patients should be actively recommended.

ABBREVIATIONS LISTS

FOXD1: FOXD1 (Human) Recombinant Protein (P01)
CTGF: Connective tissue growth factor
WHO: World Health Organization
ECL: enhanced chemiluminescence
RIPA: Radio Immunoprecipitation Assay

FUNDING

This study was funded by the Jiaxing City Science and Technology Plan Project (2020AD30116).

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Paper received for publication in November, 2021
Paper accepted for publication in April, 2022