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HOXC11 functions as a novel oncogene in human colon adenocarcinoma and kidney renal clear cell carcinoma

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Abstract

Aims: Accumulating evidence has confirmed the involvement of the homeobox (HOX) gene family in carcinogenesis. HOXC11, belongs to the homeobox-C (HOXC) gene cluster, has been reported to play important roles in the development of several cancers. However, its expression and clinical value in pan-cancer remain elusive.

Materials and Methods: Bioinformatics analysis, CCK-8 assay, Flow cytometry and Western blot were use to analyze gene expression and patient survival, cell proliferation, cell apoptosis and protein level, respectively.

Key Findings: In this study, we comprehensively analyzed the expression profile and prognostic value of HOXC11 in human pan-cancer using online The Cancer Genome Atlas (TCGA) databases. HOXC11 was widely up-regulated in tumor tissues when compared with the normal tissues in pan-cancer across nine cancer types. In addition, high mRNA level of HOXC11 predicted poor overall survival (OS) of patients with adrenocortical carcinoma (ACC), colon adenocarcinoma (COAD), kidney renal clear cell carcinoma (KIRC), mesothelioma (MESO) and pancreatic adenocarcinoma (PAAD), respectively. By comparative analysis, we found that HOXC11 was up-regulated and closely correlated patient OS in COAD and KIRC. Functionally, down-regulation of HOXC11 inhibited cell proliferation but promoted apoptosis of

COAD and KIRC *in vitro*. Mechanistically, HOXC11 promoted cell proliferation of COAD and KIRC might by inactivating the peroxisome proliferator-activated receptor gamma (PPARγ) signaling pathway.

Significance: Our findings suggest that HOXC11 may act as a tumor driving gene in COAD and KIRC.

Key words: Homeobox-C 11; Pan-cancer; The Cancer Genome Atlas; Prognosis; PPARγ

Introduction

Homeobox (HOX) gene encodes a series of transcription factors that play critical roles in human pathological and physiological processes. The HOX family consists of four gene clusters termed HOXA, HOXB, HOXC and HOXD, which located on Chromosome 7, Chromosome 17, Chromosome 12 and Chromosome 2, respectively. HOX genes control numerous cancer related biological behaviors, such as cell differentiation, proliferation, metastasis and apoptosis [1-3]. HOXC gene cluster contains nine members, namely, HOXC4, HOXC5, HOXC6, HOXC8, HOXC9, HOXC10, HOXC11, HOXC12 and HOXC13.

Previous studies showed that dysregulated HOXC genes contributed to the initiation and development of various types of cancer and had certain clinical values. For example, up-regulation of HOXC5 inhibits HeLa cell growth both *in vitro* and *in vivo* by decreasing Human telomerase reverse transcriptase (hTERT) expression [4]. HOXC6 is over-expressed in glioma, cervical cancer and non-small cell lung cancer, knockdown of HOXC6 inhibits cancer progression via specific signaling pathways [5-7]. HOXC8-mediated up-regulation of matrix Gla protein (MGP) promotes cell proliferation, invasion and epithelial-mesenchymal transition (EMT) in triple-negative breast cancer [8]. High expression of HOXC9 is associated with worse patient overall survival in colorectal cancer [9]. Increased HOXC10 facilitates cell proliferation and predicts poor prognosis in glioblastoma [10]. These studies imply that the HOXC genes may participate in human tumorigenesis and be potentially useful for the prognostic evaluation of cancer patients.

HOXC11, a member of the HOXC gene cluster, was also previously reported to be involved in the development of several types of cancer. HOXC11 was found to promote cell proliferation in both clear cell renal cell carcinoma and non-small cell lung cancer [11-12]. But its expression, clinical values and function in pan-cancer are still largely unknown. In this study, we report that HOXC11 is a potential therapeutic target and (or) prognostic biomarker in multiple types of cancer based on the comprehensive bioinformatics analysis using online TCGA databases. Our results highlight the oncogenic role of HOXC11 in COAD and KIRC.

Materials and methods

Bioinformatics analysis

Three online TCGA analysis databases including GEPIA [13] (http://gepia.cancer-pku.cn/index.html), UALCAN [14] (http://ualcan.path.uab.edu/) and starBase v3.0 [15] (http://starbase.sysu.edu.cn/index.php) were used to observe the transcriptional levels of HOXC11 in human pan-cancer. Three online TCGA analysis databases including GEPIA, starBase v3.0 and LinkedOmics [16] (http://www.linkedomics.org) were utilized to analyze the relationship between gene expression and patient overall survival (OS). The co-expressed genes of HOXC11 in COAD and KIRC were obtained from LinkedOmics. Gene Set Enrichment Analysis of HOXC11-related genes in COAD and KIRC based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) was analyzed by the WebGestalt [17] (http://www.webgestalt.org/) tool.

Cell culture and siRNA transfection

The human COAD cell line (SW480) and KIRC cell line (Caki-1) were all maintained in RPMI 1640 medium containing 10% FBS (Gibco, USA) and cultured in a cell incubator at 37℃ with 5% CO_2. The specific siRNAs for HOXC11 (si-HOXC11) (5'-CGAUGUUUAACUCGGUCAACC-3'; 5'-UUGACCGAGUUAAACAUCGUU-3') and PPARγ (si-PPARγ) (5'-CAGUGGUUGCAGAUUACAAGU-3'; 5'-UUGUAAUCUGCAACCACUGGA-3') as well as the negative control siRNAs (si-NC) were transfected into cell using the

INTERFERin regent (Polyplus Transfection, France).

CCK-8 assay

Cell counting kit-8 (CCK-8) (Solarbio, China) was used to detect cell proliferative ability. Briefly, transfected cells were seeded into 96-well plates, 10 μL of CCK-8 solution was added into each well. After incubation at 37℃ for 4 hours, the absorbance of each well at 450 nm was detected by a SpectraMax microplate reader (Molecular Devices, USA).

Flow cytometry

The procedures were following the user's instructions of the Annexin V-FITC/PI kit (7sea biotech, China). In brief, after transfection, cells were collected in a clean tube and resuspended in binding buffer. Annexin V-FITC and PI were added in turn to each tube. Then, cell apoptosis was examined by Flow cytometry.

Western blot

RIPA buffer containing protease inhibitor was utilized to extract total protein of each sample. After denatured at 100℃ for 10 min, total protein of each sample was used for SDS-PAGE, PVDF membrane transfer and blocking in 5% skim milk. Then, the membranes were incubated with diluted primary antibodies (GAPDH, Abcam, USA; HOXC11, Santa, USA; PPARγ, Santa, USA) and secondary antibody, respectively. After incubated with ECL regent for seconds, the immunoreactive protein bands were detected by the imaging system (Bio-Rad, USA).

Statistical analysis

For the prognosis analysis of gene, patients with cancer were divided into low expression group and high expression group based on the median mRNA level of interest gene in each database, log-rank p less than 0.05 was regarded to be statistically significant. Data of *in vitro* experiments are expressed as mean ± SD. SPSS 19.0 was used for statistical analysis (student's t-test and one-way ANOVA). *P* value less than 0.05 was considered to be statistically significant.

Results

HOXC11 is highly expressed in human pan-cancer

Three online TCGA analysis databases were used to examine the expression profile of HOXC11 in human pan-cancer. The GEPIA database contains information of 33 types of cancer. In GEPIA, HOXC11 was found to be up-regulated in 19 (ACC, BLCA, BRCA, CESC, COAD, DLBC, ESCA, GBM, HNSC, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, PAAD, READ, STAD and UCS) but down-regulated in 3 types of cancer (KICH, SKCM and TGCT) as compared with the normal tissues (Fig. 1). The UALCAN database contains information of 24 types of cancer. In UALCAN, HOXC11 was found to be up-regulated in 14 (BLCA, BRCA, CESC, COAD, ESCA, HNSC, KIRC, KIRP, LUAD, LUSC, PAAD, READ, SARC and STAD) but down-regulated in 2 types of cancer (KICH and UCEC) as compared with the normal tissues (Supplementary Fig. 1). The starBase v3.0 database contains information of 32 types of cancer. In this database, HOXC11 was found to be up-regulated in 10 types of cancer (BRCA, COAD, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC and STAD) but down-regulated in KICH as compared with the normal tissues (Supplementary Fig. 2). Then, we compared these data (Fig. 1, Supplementary Fig. 1 and Supplementary Fig. 2) and found that HOXC11 was evidently dysregulated in 10 types of cancer (BRCA, COAD, ESCA, KIRC, KICH, KIRP, LUAD, LUSC, HNSC and STAD) in the three databases (Fig. 5A).

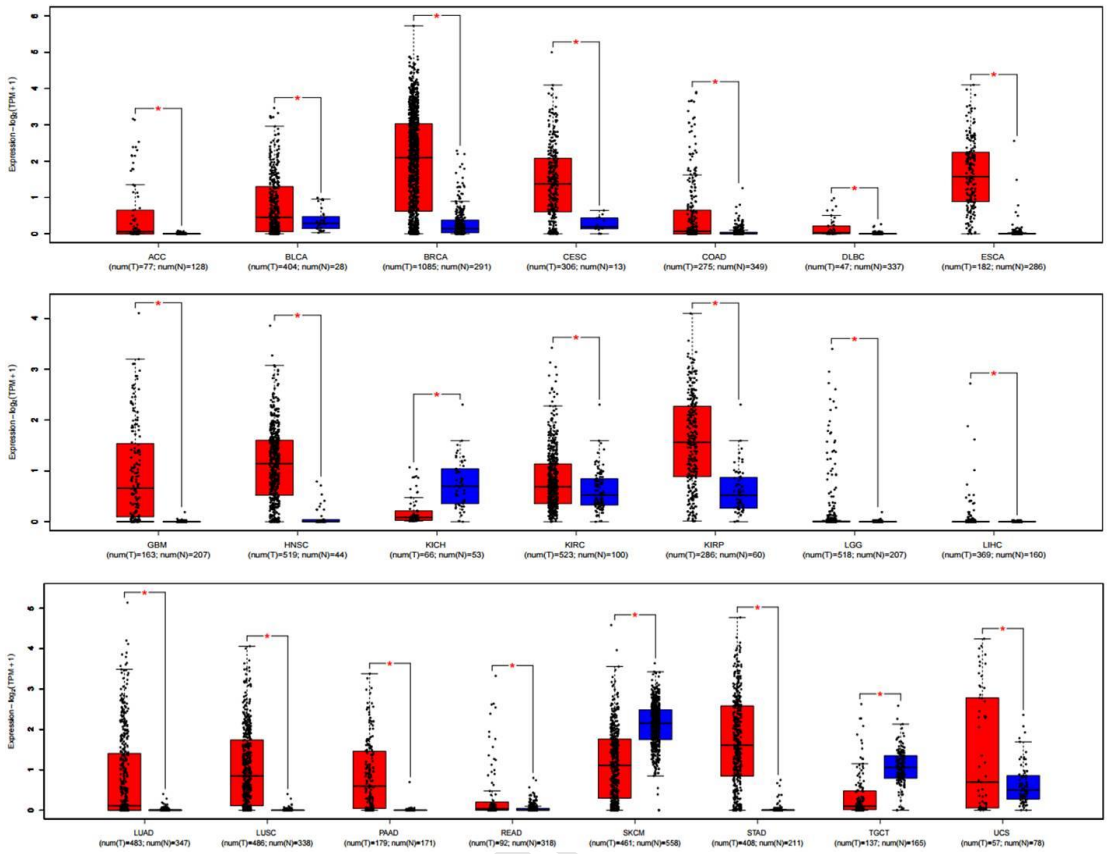

Fig. 1 The transcriptional level of HOXC11 in human pan-cancer HOXC11 is dysregulated in 22 types of cancer (GEPIA). Red bar graph refers to tumor tissues (T) and blue bar graph refers to normal tissues (N). *p ＜ 0.05.

High expression of HOXC11 predicts poor overall survival in pan-cancer

The relationship between HOXC11 expression and patient OS was analyzed by three independent online TCGA tools. First, we observed that high HOXC11 expression was an unfavorable factor for patient OS (p = 0) in pan-cancer (33 types of cancer, GEPIA) (Fig. 2). Results from GEPIA also showed that high expression of HOXC11 was closely associated with worse OS in ACC (p = 6.4E-8), CESC (p = 0.021), COAD (p = 0.021), KIRC (p = 0.02), MESO (p = 0.0082) and PAAD (p = 0.0043) but with well OS in STAD (p = 0.012) (Fig. 2). In addition, high HOXC11 expression was also an unfavorable factor for patient OS (p = 0.018) in these 6 types of cancer (Fig. 2). Results from LinkedOmics showed that high expression of HOXC11 was closely associated with worse OS in ACC (p = 7.6E-8), CHOL (p = 1.0E-9), COAD (p = 0.031), GBM (p = 0.032), KIRC (p = 1.7E-4), MESO (p = 0.0047) and PAAD (p = 0.017) but with well OS in THYM (p = 0.016) (Fig. 3). Results from starBase v3.0

showed that high expression of HOXC11 predicted poor OS in ACC (p = 6.1E-8), COAD (p = 0.019), KIRC (p = 0.0056), MESO (p = 0.019) and PAAD (p = 0.01) (Fig. 4). Then, we compared these results (Fig. 2, Fig. 3 and Fig. 4) and found that high expression of HOXC11 indicated poor OS in 5 types of cancer (ACC, COAD, KIRC, MESO and PAAD) in the three databases (Fig. 5B).

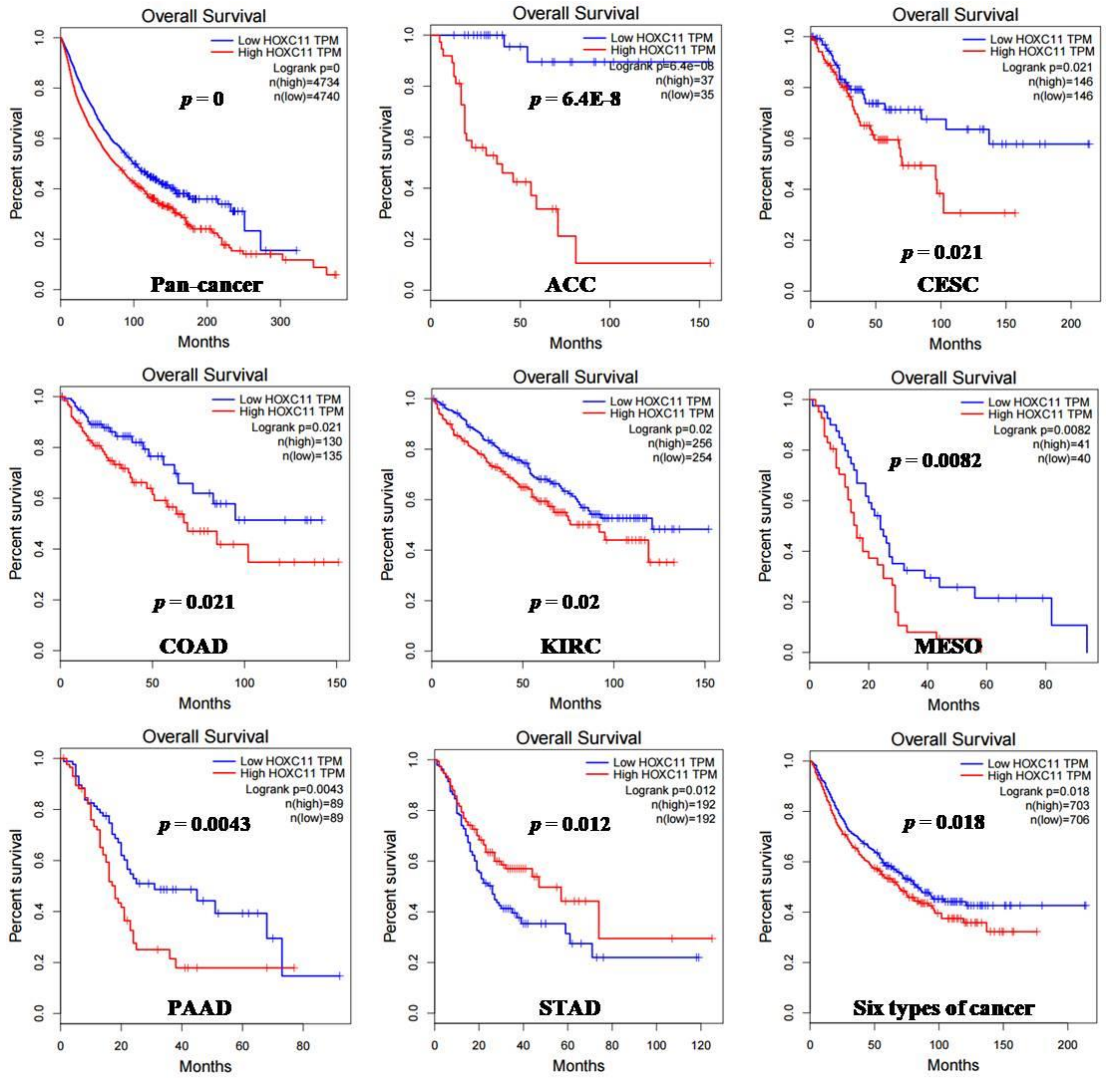

Fig. 2 The prognostic values of HOXC11 in pan-cancer were analyzed from GEPIA database

Six types of cancer refers to ACC, CESC, COAD, KIRC, MESO and PAAD.

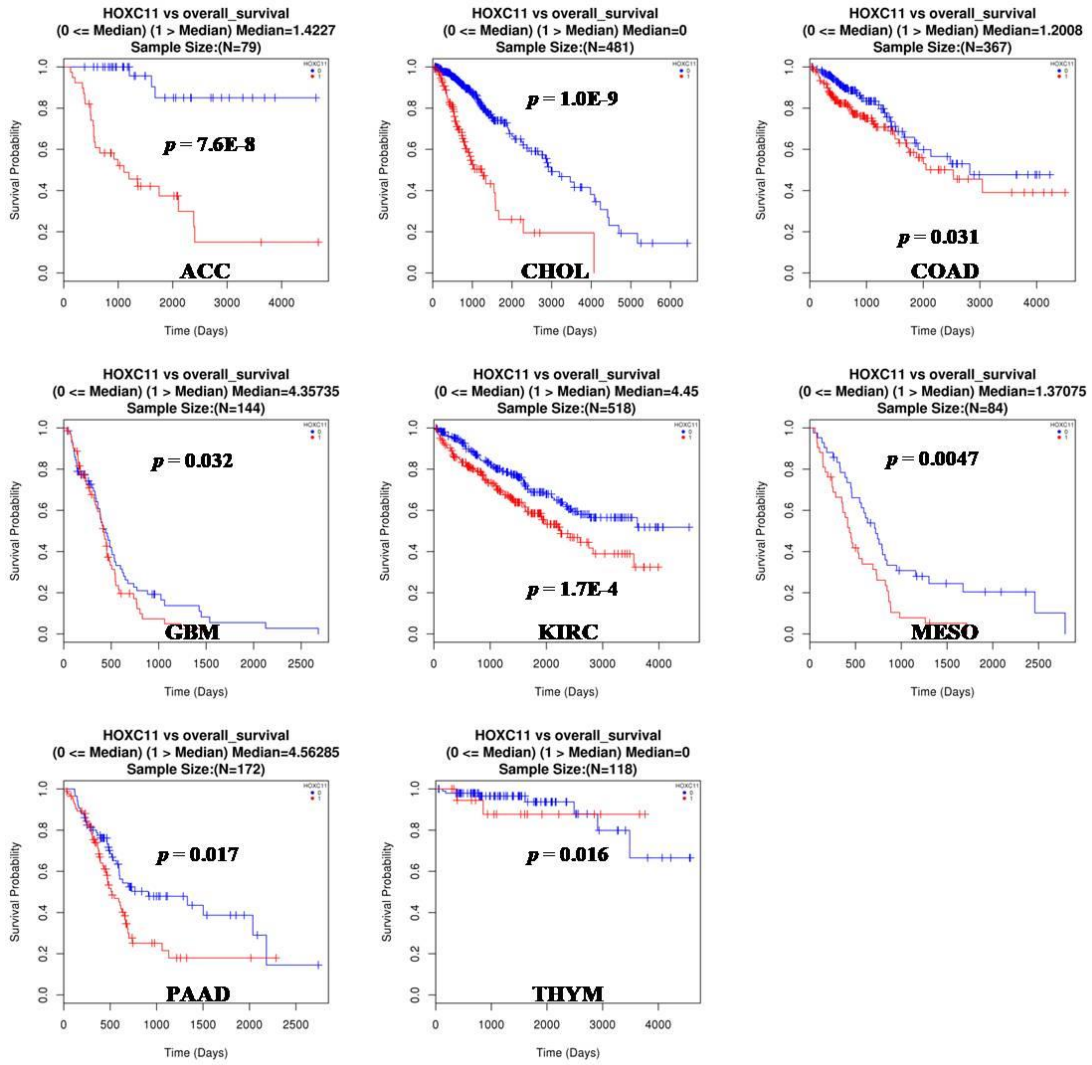

Fig. 3 The prognostic values of HOXC11 in pan-cancer were analyzed from LinkedOmics database High expression of HOXC11 predicts poor OS of ACC, CHOL, COAD, GBM, KIRC, MESO and PAAD, but well OS of THYM.

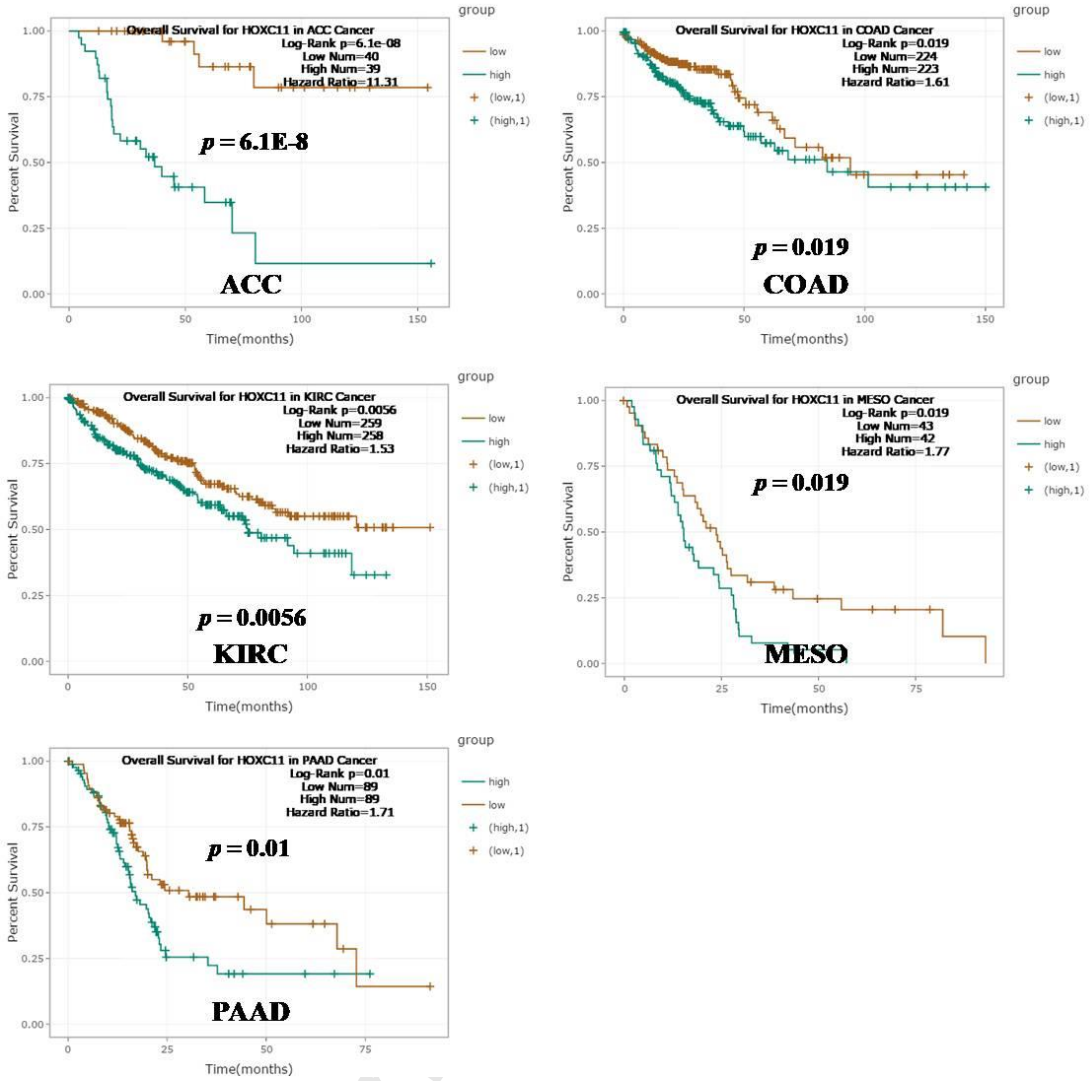

Fig. 4 The prognostic values of HOXC11 in pan-cancer were analyzed from starBase v3.0 database High expression of HOXC11 predicts poor OS of ACC, COAD, KIRC, MESO and PAAD.

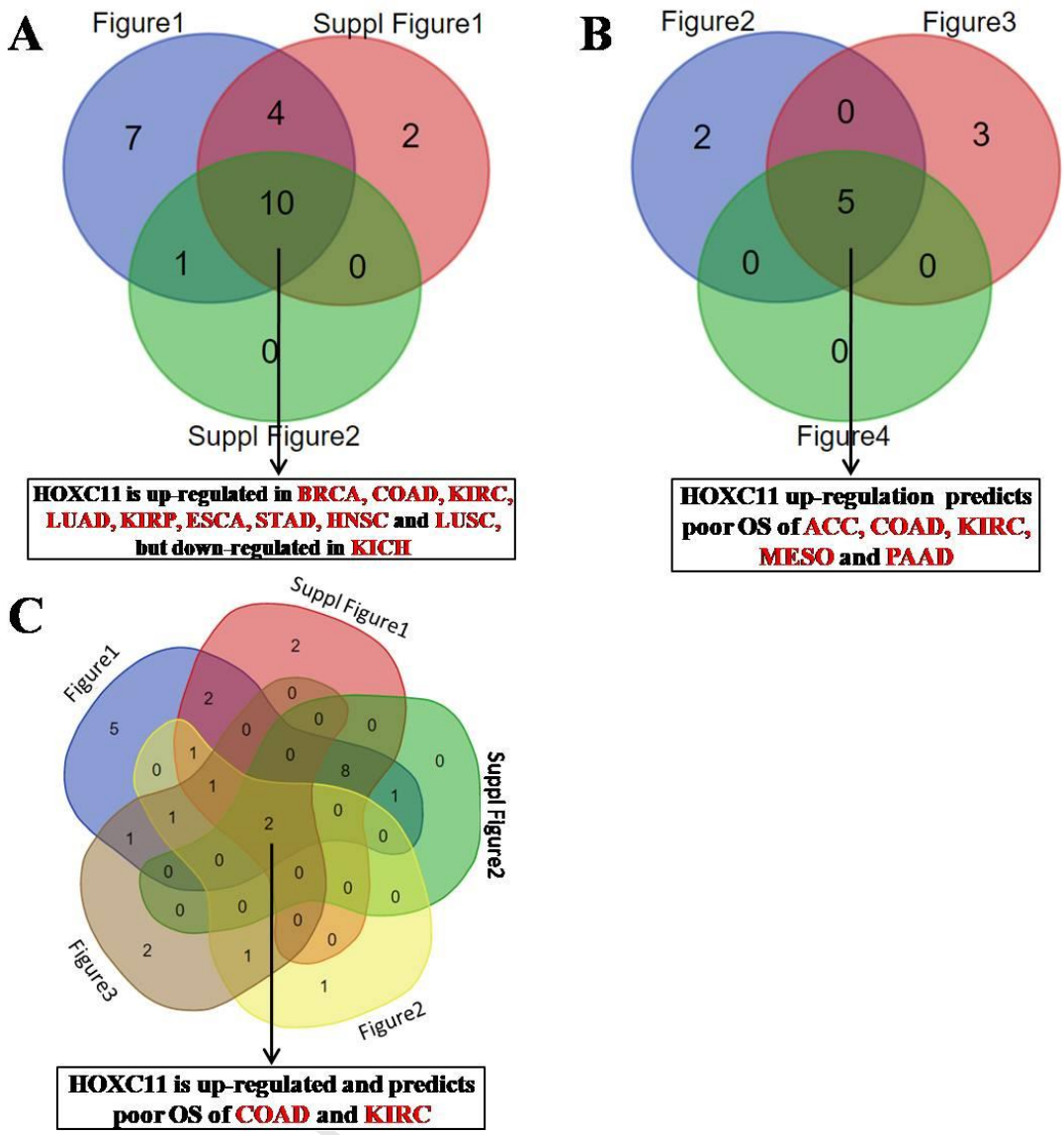

Fig. 5 Data comparison was shown as Venn diagram (A) Data comparison of Fig. 1, Supplementary Fig. 1 and Supplementary Fig. 2. (B) Data comparison of Fig. 2, Fig. 3 and Fig. 4. (C) Data comparison of Fig. 1, Supplementary Fig. 1, Supplementary Fig. 2, Fig. 2 and Fig. 3.

HOXC11 functions as an oncogenic gene to promote cell proliferation of COAD and KIRC

Next, the five datasets of Fig. 1, Supplementary Fig. 1, Supplementary Fig. 2, Fig. 2 and Fig. 3 were compared. We found that HOXC11 was not only dramatically up-regulated but also closely associated with worse patient OS in COAD and KIRC (Fig. 5C). Therefore, we speculated that HOXC11 may work as an oncogene in these two cancer types. To confirm this, we examined the effects of HOXC11 knockdown on cell proliferation and apoptosis of COAD and KIRC *in vitro*. The results showed

that down-regulation of HOXC11 could significantly suppress cell proliferation (Fig. 6A, 6C) but promote apoptosis (Fig. 6B, 6D) in SW480 and Caki-1 cells. These results indicate that HOXC11 functions as an oncogenic gene in both COAD and KIRC.

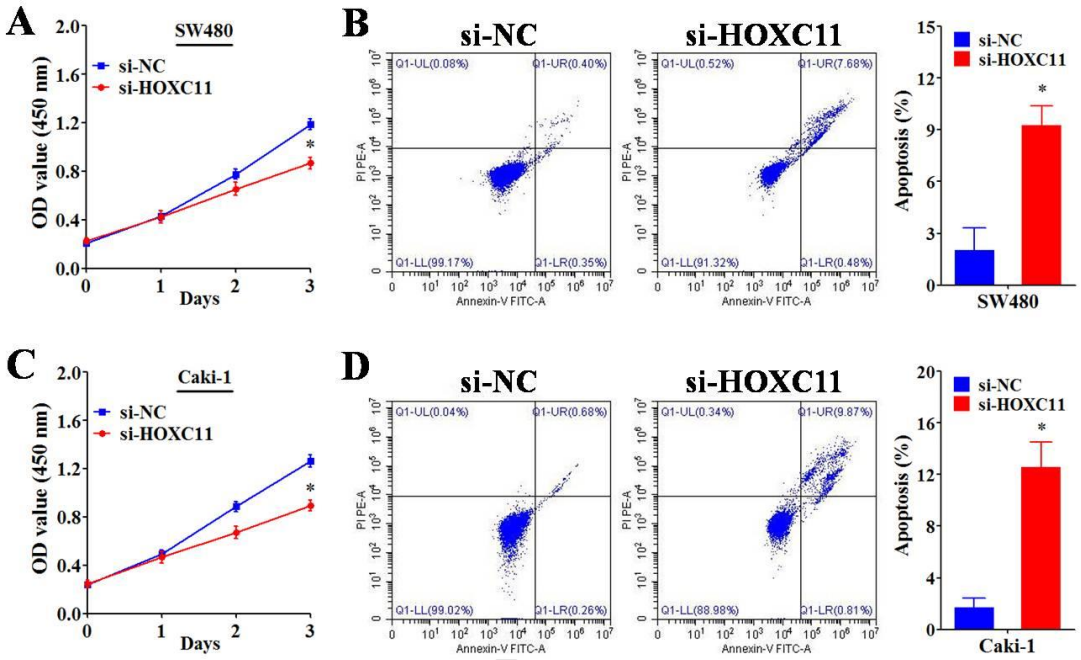

Fig. 6 The effects of HOXC11 knockdown on cell proliferation and apoptosis in COAD and KIRC *in vitro* (A, C) CCK-8 assay was used to detect the effect of HOXC11 knockdown on cell proliferation of SW480 (A) and Caki-1 (C) cells, $*p < 0.05$. (B, D) Flow cytometry was used to detect the effect of HOXC11 knockdown on cell apoptosis of SW480 (B) and Caki-1 (D) cells $*p < 0.05$.

HOXC11 promotes cell proliferation of COAD and KIRC via down-regulating PPARγ

Next, we intend to investigate the potential mechanism of HOXC11 in the development of COAD and KIRC. To this end, we obtained the co-expressed genes of HOXC11 in COAD and KIRC from the LinkedOmics. The overall closely co-expressed genes of HOXC11 in COAD (Fig. 7A) and KIRC (Fig. 7D) were shown as volcano plots. The top-50 positively and negatively co-expressed genes of HOXC11 in COAD were shown as heat maps (Fig. 7B-C), respectively. The top-50 positively and negatively co-expressed genes of HOXC11 in KIRC were shown as

heat maps (Fig. 7E-F), respectively. GSEA, which based on the KEGG database, was used to explore the potential signaling pathways mediated by HOXC11 in both COAD and KIRC. The results displayed that HOXC11 were mainly involved in the regulation of fatty acid degradation (p = 0, FDR = 0, NES = -2.25), glycolysis (p = 0, FDR = 0, NES = -2.12) and PPAR (p = 0, FDR = 0.0009, NES = -2.03) pathways in COAD (Fig. 8A). In KIRC, HOXC11 was mainly related to the fatty acid metabolism (p = 0, FDR = 0.001, NES = -2.06), PPAR (p = 0, FDR = 0.009, NES = -1.87) and mTOR (p = 0, FDR = 0.009, NES = -1.87) pathways (Fig. 8B).

Given that HOXC11 may be involved in the same PPAR pathway in both COAD and KIRC. We next focused on observing the effect of PPAR signaling on HOXC11-mediated cell proliferation of COAD and KIRC. Result of Western blot showed that the protein level of PPARγ was elevated in SW480 and Caki-1 cells after knockdown of HOXC11 (Fig. 9A). The effects of HOXC11 knockdown on cell proliferation, apoptosis and HOXC11 level were partially rescued by down-regulation of PPARγ (Fig. 9A-E) (p < 0.05). Collectively, our data suggests that HOXC11 may fulfill its oncogenic role in both COAD and KIRC through inactivating the PPARγ signaling.

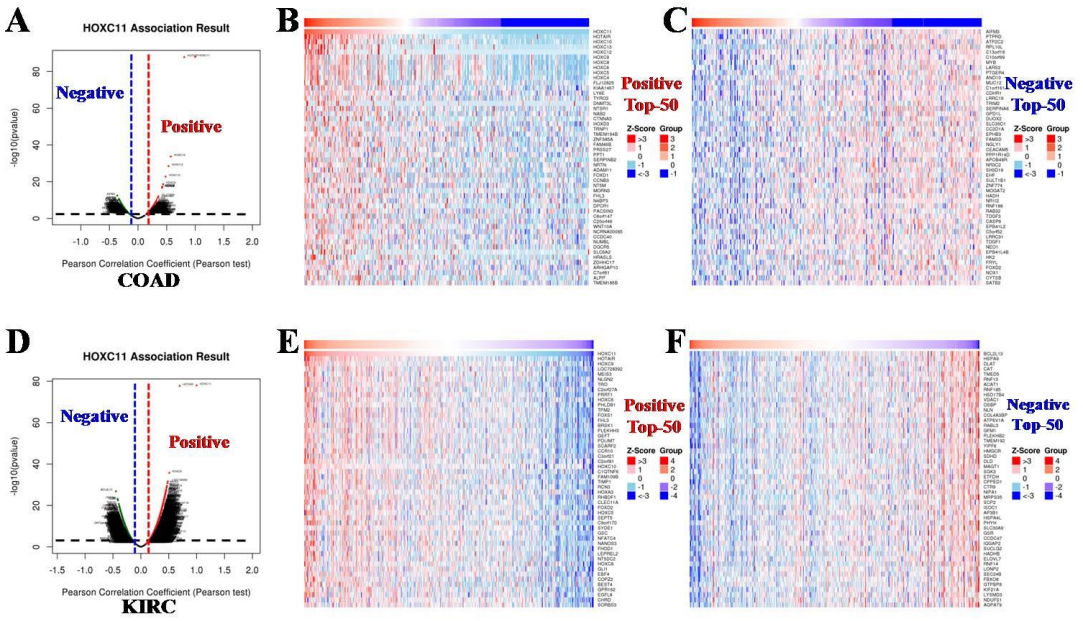

Fig. 7 The co-expressed genes of HOXC11 in COAD The overall closely co-expressed genes of HOXC11 in COAD (A) and KIRC (D) were shown as volcano plots. The positively (B) and

negatively (C) co-expressed top-50 genes of HOXC11 in COAD were shown as heat maps. The positively (E) and negatively (F) co-expressed top-50 genes of HOXC11 in KIRC were shown as heat maps.

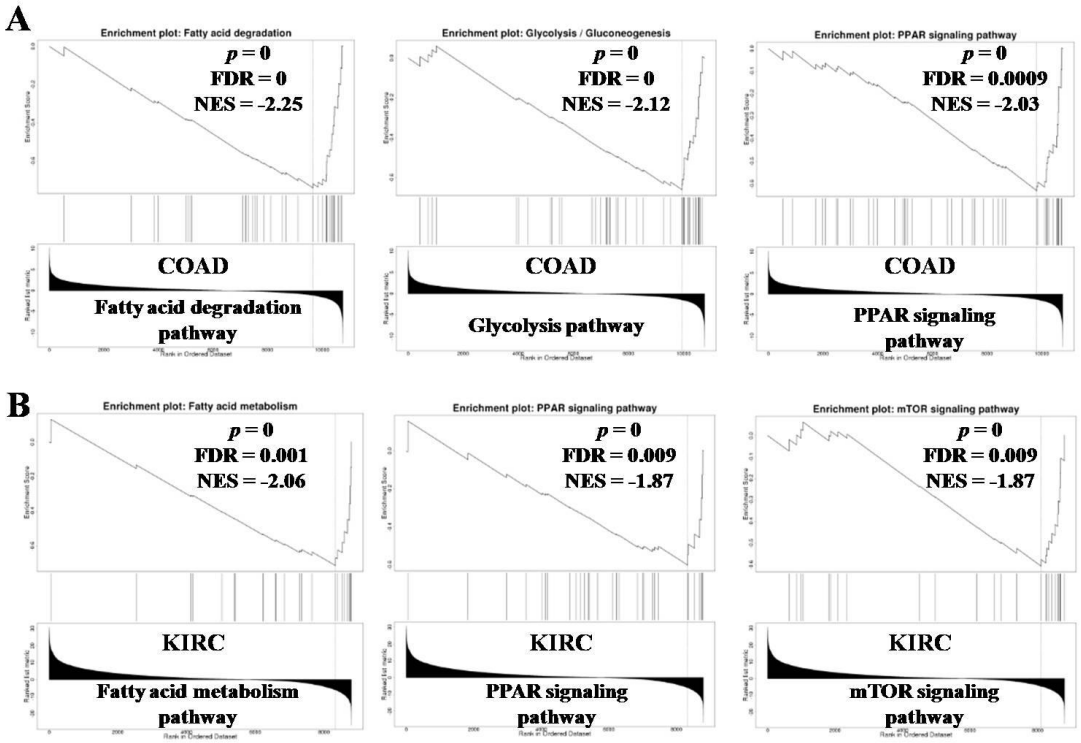

Fig. 8 GSEA analysis of HOXC11 co-expressed genes in COAD and KIRC (A) Three pathways (fatty acid degradation, glycolysis and PPAR) were closely correlated with HOXC11 in COAD. (B) Three pathways (fatty acid metabolism, PPAR and mTOR) were closely correlated with HOXC11 in KIRC. FDR refers to false discovery rate and NES refers to normalized enrichment score.

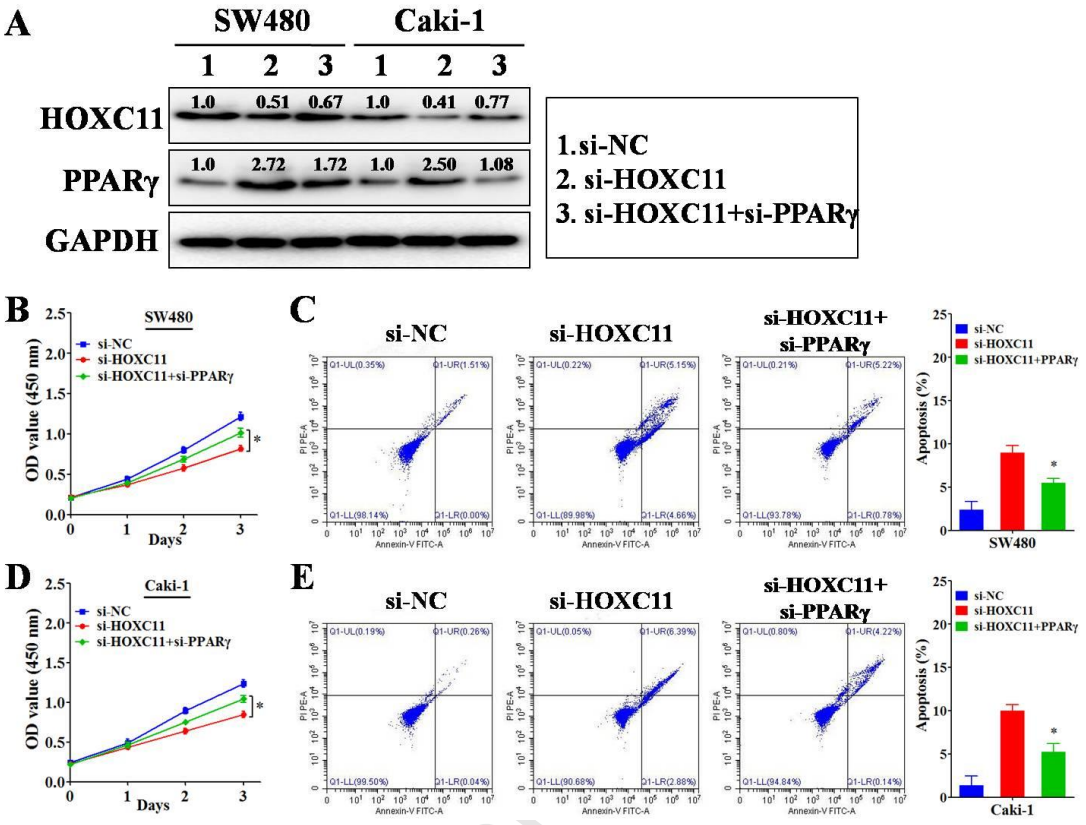

Fig. 9 Down-regulation of PPARγ abolishes the effects of HOXC11 knockdown on cell proliferation and apoptosis in COAD and KIRC (A) Protein levels of HOXC11 and PPARγ in each group of SW480 and Caki-1 cells were examined by Western blot. (B, D) Cell proliferation of SW480 (B) and Caki-1 (D) was detected by CCK-8 assay, $*p < 0.05$. (C, E) Cell apoptosis of SW480 (C) and Caki-1 (E) was detected by flow cytometry, $*p < 0.05$.

Discussion

HOXC11, located on chromosome 12q13.13, was first reported to act as an essential gene for metanephric kidney induction [17]. In recent years, it has been shown that HOXC11 played a role in the development and prognosis in several human cancers. In clear cell renal cell carcinoma, over-expression of HOXC11 promotes cancer cell proliferation and negatively correlates with patient prognosis [11]. In non-small cell lung cancer, HOXC11 cooperates with microRNA-1197 and regulates cell proliferation and migration [12]. But the expression profile and prognostic value of HOXC11 in pan-cancer remains largely unclear. Herein, we for the first time report that HOXC11 may be a prognostic biomarker for multiple cancer types and functions

as a tumor driving gene in COAD and KIRC.

As far as we know, only a few studies have investigated the expression and clinical significance of HOXC11 in several types of cancer. In breast cancer, HOXC11 was expressed at a lower level in cancer tissues than adjacent normal tissues [18], HOXC11 interacted with steroid receptor co-activator SRC-1 and promoted resistance to endocrine therapy [19]. High expression of HOXC11 predicted poor patient prognosis in breast cancer and cervical cancer [19-20]. In this study, we observed the expression landscape and prognostic value of HOXC11 in pan-cancer across thirty-three cancer types, and found that HOXC11 was abnormally expressed in ten types of cancer and correlated with patient OS in five cancer types. Thus, further studies regarding the expression of HOXC11 in body fluid and its correlation with patient clinical characteristics may help in developing HOXC11 as a clinical biomarker for these malignancies.

Considering that HOXC11 was significantly up-regulated and closely correlated with patient OS in both COAD and KIRC based on our bioinformatics analysis. We focused on explore the function and possible regulatory pathway of HOXC11 in COAD and KIRC. By *in vitro* functional experiments, we found that down-regulation of HOXC11 enhanced cancer cell apoptosis but inhibited cell proliferation. In previous studies, HOXC11 was found to promote cell proliferation in both KIRC and non-small cell lung cancer [11-12]. Therefore, our study confirmed the role of HOXC11 in KIRC growth and provided first-hand evidence for the oncogenic function of HOXC11 in COAD.

Through GSEA enrichment analysis, HOXC11 was found to be mainly involved in the negative regulation of the same PPAR signaling pathway in both COAD and KIRC. PPARγ, one member of the PPAR gene family, was reported to be the master regulatory factor in adipogenesis [21]. Recent studies highlight its important role in human tumorigenesis [22-23]. In COAD, PPARγ was a necessary pathway involved in the antitumor activity of drugs such as embelin [24]. In KIRC, PPARγ acted as a crucial mediator in the cancer progression [25]. We then speculated that HOXC11 contributed to cell proliferation of COAD and KIRC via regulating PPARγ. To test this hypothesis,

we performed a series of rescue experiments *in vitro*. Our data displayed that HOXC11 negatively regulated the expression of PPARγ in both SW480 and Caki-1 cells. The effects of HOXC11 knockdown on cell proliferation and apoptosis were rescued in part by down-regulation of PPARγ in both SW480 and Caki-1 cells. These data suggests that HOXC11 may contribute to development of COAD and KIRC via PPARγ signaling.

In summary, this study comprehensively analyzed the expression profile and prognostic values of HOXC11 in pan-cancer based on bioinformatics analysis, and investigated the function of HOXC11 in COAD and KIRC through *in vitro* experiments. Our data provided some clues for the development of HOXC11 as a clinical biomarker for some cancer types, such as ACC, COAD, KIRC, MESO and PAAD. Our findings suggest that HOXC11 may function as a tumor driving gene in both COAD and KIRC. The specific role and the precise mechanism of HOXC11 in the initiation and progression of these two malignancies need to be further extensively explored.

Authors' contributions

YBC conceived this study and wrote the manuscript. CYZ, YPW, SSM and WC participated in the in vitro experiments, draft writing and data analysis. FXG provided assistance for revising the manuscript. All authors read the manuscript and approved for publication.

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Competing interests

No.

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