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ZNF750 facilitates carcinogenesis via promoting the expression of long non-coding RNA *CYTOR* and influences pharmacotherapy response in colon adenocarcinoma

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The epidermal cell differentiation regulator zinc finger protein 750 (ZNF750) is a transcription factor containing the Cys2His2 (C2H2) domain, the zinc finger structure of which is located at the N-terminal 25–46 amino acids of ZNF750. It can promote the expression of differentiation-related factors while inhibiting the expression of progenitor cell-related genes. ZNF750 is directly regulated by p63 (encoded by the *TP63* gene, belonging to the TP53 superfamily). The Krüppel-like factor 4 (KLF4), repressor element-1 (RE-1)-silencing transcription factor (REST) corepressor 1 (RCOR1), lysine demethylase 1A (KDM1A), and C-terminal-binding protein 1/2 (CTBP1/2) chromatin regulators cooperate with ZNF750 to repress epidermal progenitor genes and activate the expression of epidermal terminal differentiation genes (Sen et al., 2012; Boxer et al., 2014). Besides, ZNF750 and the regulatory network composed of bone morphogenetic protein (BMP) signaling pathway, long noncoding RNAs (lncRNAs) (anti-differentiation noncoding RNA (ANCR) and tissue differentiation-inducing non-protein coding RNA (TINCR)), musculoaponeurotic fibrosarcoma oncogene (MAF)/MAF family B (MAFB), grainy head-like 3 (GRHL3), and positive regulatory domain zinc finger protein 1 (PRDM1) jointly promote epidermal cell differentiation (Sen et al., 2012).

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Studies have shown that ZNF750 has an inhibitory effect on various tumors such as esophageal squamous cell carcinoma, oral squamous cell carcinoma, and nasopharyngeal carcinoma (Hao et al., 2016; Hazawa et al., 2017; Zhang et al., 2018). The compromised level of ZNF750 in squamous cell carcinoma cells was associated with poor clinical prognosis. In addition, ZNF750 promotes the expression of lncRNA TINCR (Hazawa et al., 2017). Zhang et al. (2018) confirmed that: (1) N^6-methyladenosine (m^6A) modification maintained the low level of ZNF750 in nasopharyngeal carcinoma; (2) ZNF750 directly regulates the transcription of fibroblast growth factor 14 (FGF14); and (3) the ZNF750-FGF14 signal axis inhibits the growth of nasopharyngeal carcinoma cells by promoting apoptosis. However, studies focused on the mechanistic functions of ZNF750 in colorectal adenocarcinoma have been very limited (Qu et al., 2020).

LncRNA cytoskeleton regulator (*CYTOR*), also known as *LINC00152*, is a widely reported differentially expressed lncRNA in cancers of different body parts such as the stomach, liver, colon, lung, gallbladder, kidney, breast, and oral cavity (Xu et al., 2017). Studies have shown that lncRNA *CYTOR* can promote the malignant phenotype of cancer cells (Deng et al., 2017), and facilitate the compromising of medication sensitivity (Yue et al., 2016, 2018; Bian et al., 2017). It was also related to the poor prognosis of patients. *CYTOR* can be transcriptionally activated by transcription factor 3 (TCF3) (Zheng et al., 2019), transcription factor Yin Yang 1 (YY1) (Shen et al., 2019), specificity protein 1 (SP1) (Cai et al., 2016), and

Yes-associated protein 1 (YAP1) (Ou et al., 2020). *CYTOR* competes with various microRNAs (miRNAs) such as miR-139-5p (Bian et al., 2017), miR-1182 (Zheng et al., 2019), miR-497 (Sun et al., 2019), miR-162 (Cai et al., 2018), miR-125b (Chen et al., 2018), miR-193a/b-3p (Ma et al., 2018; Wang et al., 2019), miR-138 (Cai et al., 2017), and miR-103a-3p (Yu MJ et al., 2017) as competing endogenous RNA (ceRNA) to regulate notch receptor 1 (NOTCH1) (Bian et al., 2017), cyclin-dependent kinase 14 (CDK14) (Zheng et al., 2019), brain-derived neurotrophic factor (BDNF) (Sun et al., 2019), protein kinase B (PKB)-β (AKT2)/nuclear factor-κB (NF-κB) (Cai et al., 2018), myeloid cell leukemia-1 (MCL-1) (Chen et al., 2018), cyclin D1 (CCND1) (Ma et al., 2018), E26 transformation-specific 1 (ETS1) (Wang et al., 2019), hypoxia-inducible factor-1α (HIF-1α) (Cai et al., 2017), FEZ family zinc finger 1 (FEZF1) (Yu MJ et al., 2017), and epidermal growth factor receptor-4 (ERBB4) (Yue et al., 2016). *CYTOR* interacts with thrombospondin-1 (THBS1) (Xia et al., 2014), SET and MYND domain protein 2 (SMYD2) (Shan et al., 2017), β-catenin (Shan et al., 2017; Yue et al., 2018), enhancer of zeste homolog 2 (EZH2) (Chen et al., 2017; Deng et al., 2017; Wang et al., 2017), lysine-specific demethylase 1 (LSD1) (Wang et al., 2017), trimethylated histone H3 lysine 27 (H3K27me3) (Wang et al., 2017), and other transcriptional and epigenetic factors to orchestrate downstream gene expression. *CYTOR* binds with the interleukin-24 (IL-24) (Chen et al., 2017) or epithelial cell adhesion molecule (EpCAM) (Ji et al., 2015) promoter to regulate their expression. According to the above results, *CYTOR* regulates signal pathways such as Wnt/β-catenin (Shan et al., 2017; Yue et al., 2018), NF-κB (Wang et al., 2018), phosphoinositide-3-kinase (PI3K)/AKT (Cai et al., 2016; Yu MJ et al., 2017), and mammalian target of rapamycin (mTOR) (Ji et al., 2015), which play vital roles in cancer biology (Yu Y et al., 2017; Xu et al., 2019; Ou et al., 2020).

However, the role of lncRNA *CYTOR* in colorectal cancer (CRC) is still controversial. Studies have shown that the level of *CYTOR* increases in colon malignant tissues, and its expression level is positively correlated with the clinical stage of the tumor and lymph node metastasis (Yue et al., 2016, 2018; Yu Y et al., 2017). Further studies have found that *CYTOR* not only enhances the tumorigenicity of colon cancer cells, but also is related to CRC chemotherapy resistance by interacting with β-catenin protein and forming a positive feedback loop (Yue et al., 2018). The YAP1/*CYTOR* axis facilitates the progression of CRC (Ou et al., 2020). *CYTOR* works as ceR binding to miR-193a-3p, upregulating the expression of the *ERBB4* oncogene, which further activates the PKB/AKT signaling pathway and reduces the sensitivity of colon cancer cells to chemotherapy drugs (Yue et al., 2016). The *CYTOR*-nucleolin-Sam68/KHDRBS1 heterotrimeric complex activates the NF-κB pathway and epithelial-mesenchymal transition (EMT) to potentiate CRC progression (Wang et al., 2018). Meanwhile, some studies have shown that upregulating the expression of *CYTOR* decreases the activity of colon cancer cells and increases apoptosis, suggesting that *CYTOR* may suppress tumorigenesis in colon cancer cells (Zhang et al., 2016). These studies indicated that *CYTOR* may play a dual role of tumor promoter gene and tumor suppressor gene. Further research should be untaken to reveal the functional role of *CYTOR* in colon cancer progression and the underlying mechanism.

In the present study, we found that ZNF750 expression was higher in colon adenocarcinoma (COAD) tissue than in the normal colonic mucosal tissue in The Cancer Genome Atlas (TCGA)-COAD cohort (Fig. 1a). The receiver operating characteristic (ROC) curve analysis showed that ZNF750 is a good predictor of COAD (Fig. 1b). Low ZNF750 expression was a good prognostic marker in both the TCGA-COAD and GSE39582 datasets (Fig. 1c).

In order to assess the function of ZNF750 in CRC progression, we detected the expression of ZNF750 using western blotting in various COAD cells, among which the human colon cancer cell line SW620 showed the highest ZNF750 expression level, and human colon cancer cell lines (HCT116, CACO2, and SW480) showed moderate expression levels (Fig. 2a). Next, ZNF750 expression was either increased or reduced in HCT116 cell lines using overexpression constructs or short hairpin RNA (shRNA) constructs. The expression levels of ZNF750 were effectively altered (Fig. 2b). The cell proliferation assay revealed that ZNF750 overexpression improved the growth speed, whereas ZNF750 silencing slowed it down (Figs. 2c and 2d). Furthermore, the colony formation assays demonstrated that ZNF750 overexpression had an augmentation effect, while ZNF750 silencing exerted a weakening effect on the cloning formation and

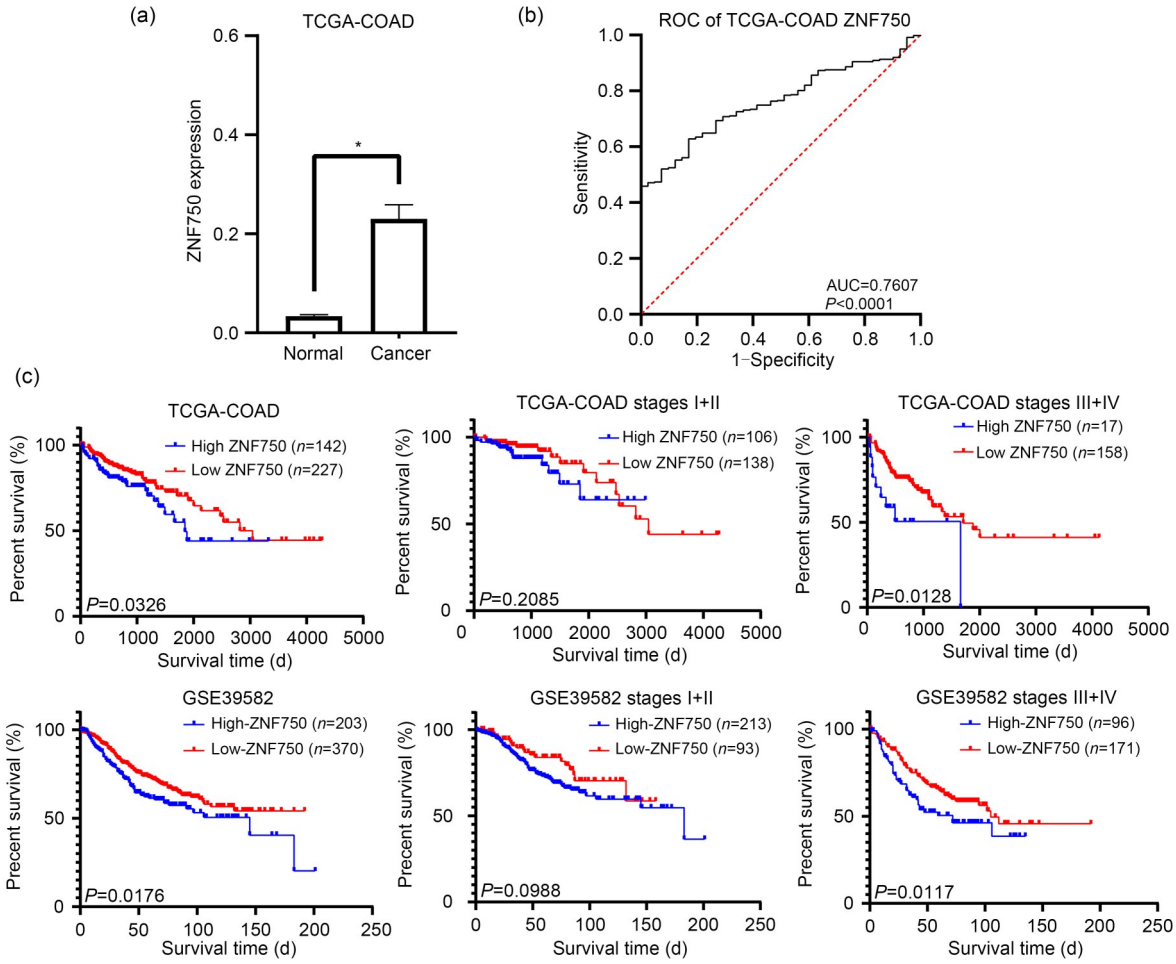

Fig. 1 Potential diagnostic and prognostic values of zinc finger protein 750 (ZNF750) expression level in colon adenocarcinoma (COAD). (a) Differential expression of ZNF750 in normal colon and COAD tissues. The values are expressed as mean±standard error of the mean (SEM) (n=41 for normal, n=473 for cancer). * P<0.05. (b) Evaluation of the sensitivity and specificity of COAD diagnosis by receiver operating characteristic (ROC) curves. (c) Survival curves of overall survival for patients in all stages (left panel), stages I+II (middle panel), and stages III+IV (right panel) according to the ZNF750 in The Cancer Genome Atlas (TCGA)-COAD (upper panel) cohort or GSE39582 (lower panel) dataset.

proliferation capacity of CRC cells (Fig. 2e). The transwell assays indicated the increased migration and invasion of HCT116 cells with ZNF750 overexpression, and reduced migration and invasion in HCT116 cells with ZNF750 silencing (Figs. 2g and 2h). Furthermore, we injected HCT116 ZNF750-silencing cells or control cells subcutaneously into nude mice. The tumor volume measurements showed that the ZNF750-silencing group generated smaller tumors compared with the controls (Fig. 2f; n=3, where one failed to form a subcutaneous tumor).

In order to explore the molecular mechanism by which ZNF750 directly promotes the malignant CRC type, we performed RNA sequencing (RNA-seq) to investigate the transcription level alterations occurring along with ZNF750 overexpression. The results showed that the expression levels of multiple genes changed with the alteration of ZNF750, among which 277 genes were upregulated and 291 genes were downregulated in HCT116 cells (P<0.05). According to Gene Set Enrichment Analysis (GSEA) in the HCT116 cell line, ZNF750 regulates subsets of genes highly enriched in the tumor necrosis factor-α (TNF-α) signaling via NF-κB, EMT, hypoxia, transforming growth factor-β (TGF-β) signaling, and hypoxia (Fig. S1a). The GSEA results of TCGA-COAD dataset were similar to those of RNA-seq in the HCT116 cell line (Fig. S1b).

Since the RNA-seq data only contain the information of messenger RNA (mRNA) with poly-A tail, we further analyzed the expression of ZNF750 and

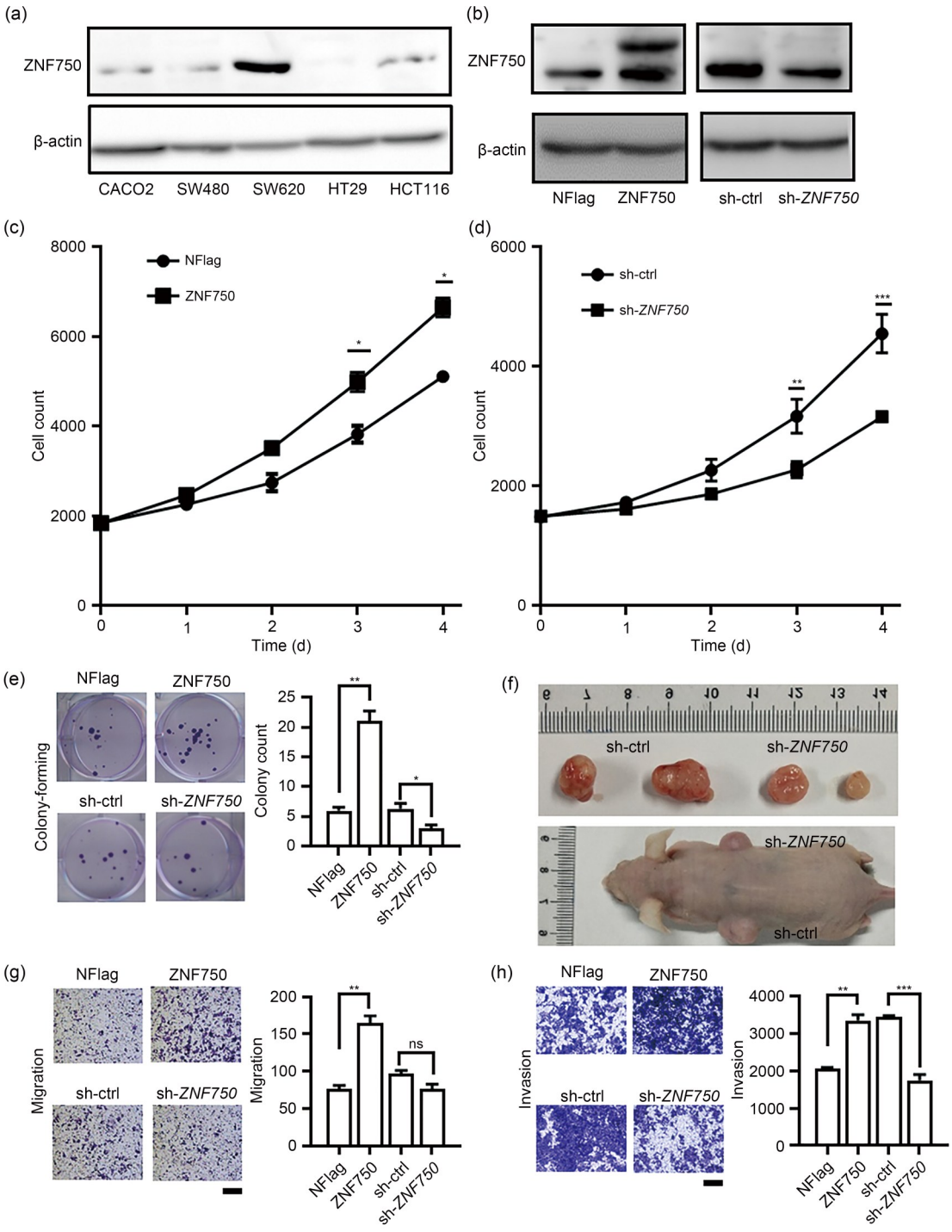

Fig. 2 Effects of zinc finger protein 750 (ZNF750) on proliferation, colony formation, migration, and invasion in HCT116 cells. (a) ZNF750 expression in colon cancer cell lines CACO2, SW480, SW620, HT29, and HCT116, as detected by western blotting. (b) The expression level of ZNF750 in HCT116 cells using overexpression constructs (NFlag, ZNF750) or short hairpin RNA (shRNA) constructs (sh-ctrl, sh-*ZNF750*) at the protein level. (c, d) Cell proliferation assays in HCT116 cells with ZNF750 overexpression (c) or silencing (d). (e) Colony formation assays in HCT116 cells with ZNF750 overexpression (upper panel) or silencing (lower panel). (f) HCT116-derived subcutaneous xenograft tumor in nude mice with ZNF750 silencing. (g, h) Transwell assays without (g) or with (h) BD Matrigel™ in HCT116 cells with ZNF750 overexpression (upper panel) or silencing (lower panel). Scale bar=250 μm. The data are shown as mean± standard error of the mean (SEM) of triplicate experiments. ^{ns} $P\geqslant0.05$; * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

lncRNA in the TCGA-COAD datasets. ZNF750 is positively correlated with 15 lncRNAs and negatively correlated with four lncRNAs in the TCGA-COAD datasets (Fig. 3a). *CYTOR* is one of lncRNAs positively correlated with ZNF750 in the TCGA-COAD dataset (P<0.001; Fig. 3b). The chromatin immunoprecipitation (ChIP)-quantitative real-time polymerase chain reaction (qPCR) results confirmed the binding of ZNF750 in the gene region of *CYTOR* in SW620 cells, which has been detected in the ChIP-seq data numbered SRR1287820 (Figs. 3c and 3d). Furthermore, the reverse transcription (RT)-qPCR experiment confirmed that the expression of lncRNA-*CYTOR* decreased with ZNF750 silencing in HCT116 cells (Fig. 3e). Taken together, these results revealed that ZNF750 transcriptionally regulates *CYTOR* expression.

In order to reveal the possible role of the ZNF750-*CYTOR* axis in COAD development, the difference in the RNA expression of *CYTOR* in COAD and normal tissues was evaluated. *CYTOR* expression was higher in COAD tissue than in paired normal tissue in accordance with ZNF750 (Fig. 4a). The ROC curve

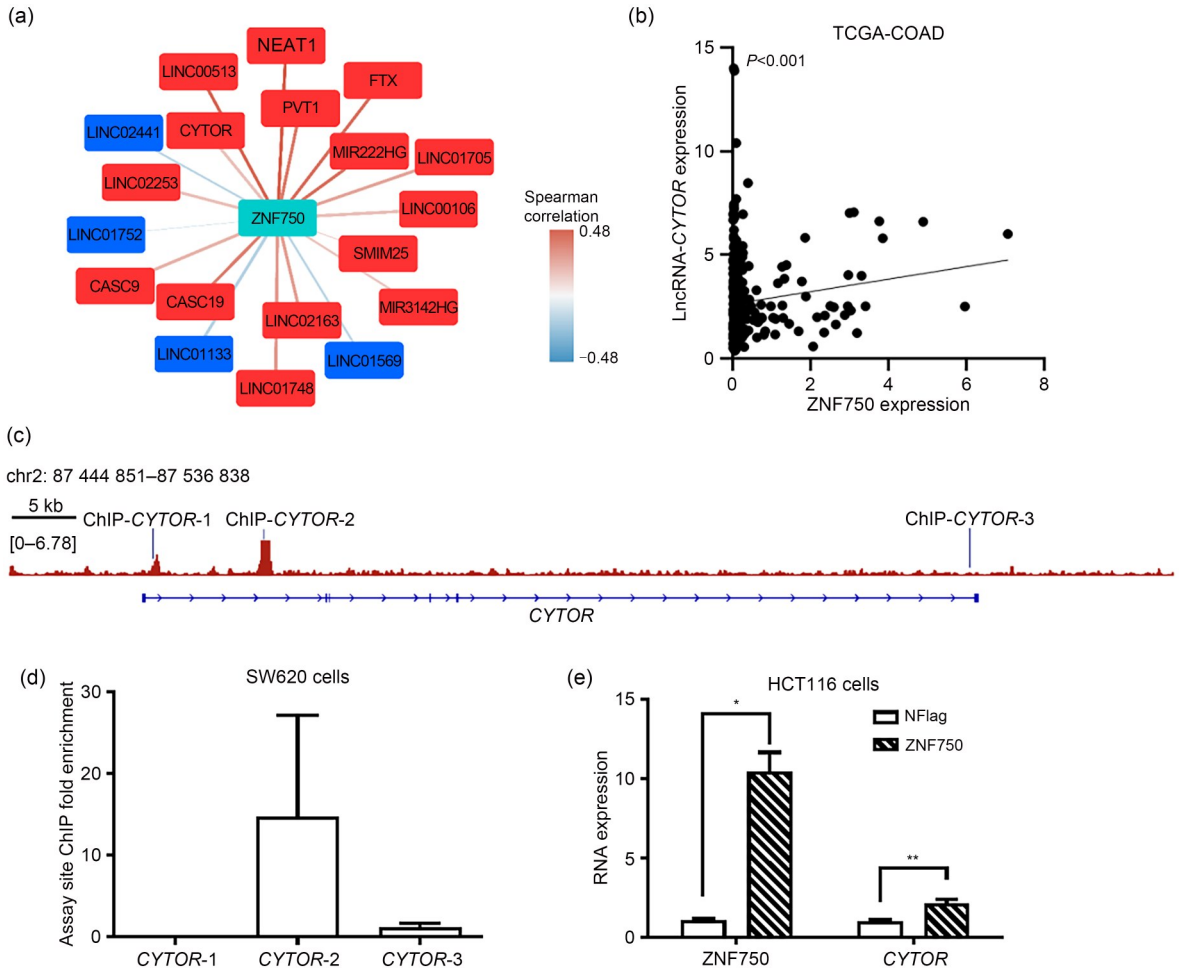

Fig. 3 Binding of ZNF750 at the *CYTOR* gene loci and regulation of *CYTOR* expression. (a) Correlation between ZNF750 and lncRNA expression in the TCGA-COAD cohort (red means positive correlation with tumor and blue stands for negative correlation with tumor). (b) Spearman correlation of ZNF750 with *CYTOR* in the TCGA-COAD cohort. (c, d) ZNF750 binding region at the lncRNA-*CYTOR* gene loci: (c) ChIP-seq IGV view of ZNF750 ChIP-seq data (SRR1287820) at lncRNA-*CYTOR* in keratinocytes (data range=0–6.78 normalized read counts); (d) ZNF750 ChIP-qPCR in SW620 cells validated the binding of ZNF750 at the ChIP-*CYTOR*-2 primer binding site. (e) The RT-qPCR experiment confirmed that the expression of *CYTOR* increased with ZNF750 overexpression in HCT116 cells. The data are shown as mean±standard error of the mean (SEM) of triplicate experiments. * P<0.05; ** P<0.01. ZNF750: zinc finger protein 750; *CYTOR*: cytoskeleton regulator; LncRNA: long non-coding RNA; TCGA: The Cancer Genome Atlas; COAD: colon adenocarcinoma; ChIP-seq: chromatin immunoprecipitation-sequencing; IGV: Integrative Genomics Viewer; RT-qPCR: reverse transcription-quantitative real-time polymerase chain reaction.

analysis revealed that *CYTOR* is a good predictor of COAD (Fig. 4b). Although low ZNF750 expression was a good prognostic marker, there was no significant survival advantage in the low *CYTOR* expression group in the TCGA-COAD dataset (Fig. 4c; left panel). However, when classified by stages, low *CYTOR* expression was a good prognostic marker for patients in stages I+II in the TCGA-COAD dataset (Fig. 4c; middle panel).

The RNA-seq results mentioned above revealed that the TNF-α_SIGNALING_VIA_NF-κB is the most significant GSEA item influenced by ZNF750 overexpression in HCT116 cells. Moreover, NF-κB signaling is a vital regulatory pathway involved in tumor growth and at the same time is one of the linking hubs between chronic inflammation and neoplastic development. Prompted by this finding, the potential immune modulation roles of ZNF750 and *CYTOR* in TCGA-COAD data were analyzed. In COAD, the abundance of cluster of differentiation 4-positive ($CD4^+$) cells, macrophages, neutrophils, and dendritic cells correlated positively with ZNF750; $CD8^+$ cells, macrophages, neutrophils, and dendritic cells correlated positively with *CYTOR* expression (Fig. S2a). ZNF750 and *CYTOR* expression levels were both positively linked to immune checkpoint genes, including programmed death-ligand 1 (*PD-L1*), *CD86*, *PD-L2*, and cytotoxic T-lymphocyte antigen-4 (*CTLA4*) (Fig. S2b). These genes are immune checkpoints and efficacy-related influencers of immunotherapy. The assessment of the potential roles of ZNF750 and *CYTOR* in immunotherapy requires further investigation by new cohorts using immunotherapy.

In order to explore the possible roles of altered ZNF750-*CYTOR* expression in response to guideline-recommended medication, survival analysis was applied to validate the survival differences between patients treated with specific medications. For those who underwent leucovorin or oxaliplatin therapy, the death risk in the high ZNF750/*CYTOR* group was smaller than that in the low ZNF750/*CYTOR* group (Figs. 5a–5c). These results indicated that ZNF750-*CYTOR* may serve as a prognostic marker of specific chemotherapy.

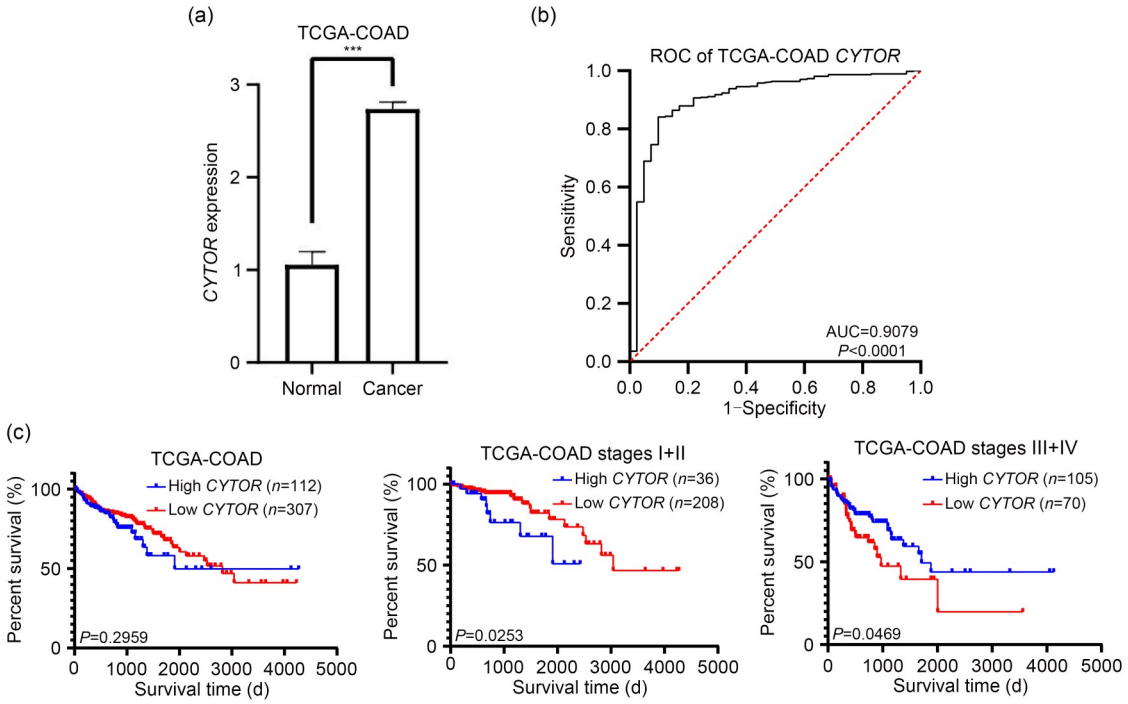

Fig. 4 Relationship between *CYTOR* expression and clinicopathological data. (a) Differential expression of *CYTOR* in normal colon and colon cancer tissues. The values are expressed as mean±standard error of the mean (SEM) (*n*=41 for normal, *n*=473 for cancer). * *P*<0.001. (b) Evaluation of the sensitivity and specificity of colon cancer diagnosis by ROC curves. (c) Survival curve of 12-year OS for patients in all stages, stages I+II, and stages III+IV according to the *CYTOR* in TCGA-COAD cohort. *CYTOR*: cytoskeleton regulator; ROC: receiver operating characteristic; OS: overall survival; TCGA: The Cancer Genome Atlas; COAD: colon adenocarcinoma; AUC: area under the curve.**

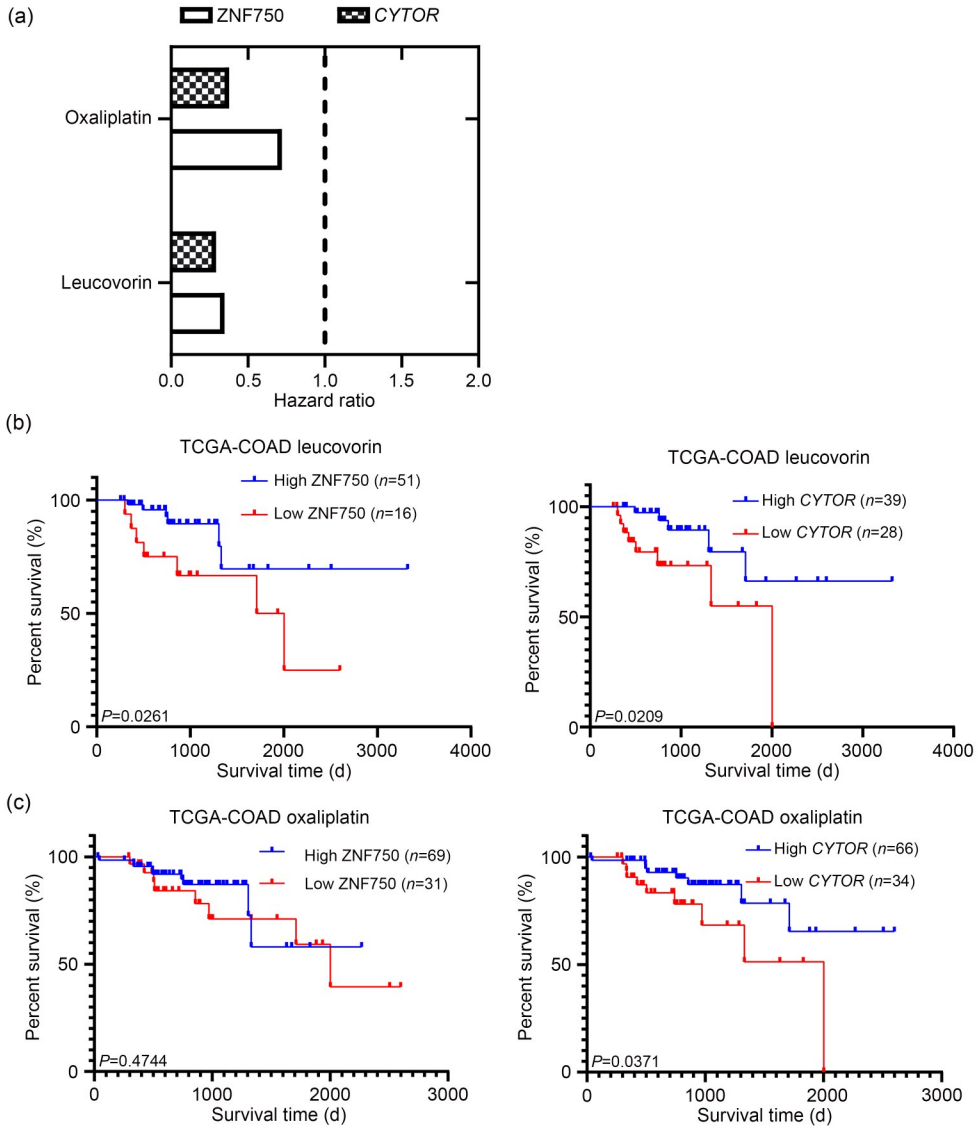

Fig. 5 Effects of ZNF750 and *CYTOR* on the chemotherapy resistance of colon cancer in TCGA-COAD cohorts. (a) The hazard ratio of survival analysis in patients subjected to different treatments. (b, c) ZNF750 and *CYTOR* Kaplan-Meier curves for overall survival in the TCGA-COAD cohort subgroups treated with leucovorin (b) or oxaliplatin (c). ZNF750: zinc finger protein 750; *CYTOR*: cytoskeleton regulator; TCGA: The Cancer Genome Atlas; COAD: colon adenocarcinoma.

In squamous cell carcinoma, ZNF750 is a lineage-specific tumor suppressive transcription factor. However, little evidence has shown its role in COAD or as a therapeutic target (Wen et al., 2021). In the present study, we demonstrated that ZNF750 may promote carcinogenesis and progression either through modulating ZNF750 expression in vitro and in vivo, or the correlation analysis of ZNF750 and clinical pathological studies. Evidence shows that lncRNA modulates cancer progression (Chen and Shen, 2020). LncRNA *CYTOR* plays a crucial role in COAD development, which has been reviewed previously.

It is now clear that tumors orchestrate certain immune checkpoint pathways as a major mechanism of immune resistance. A plethora of immune checkpoint regulators have been identified (Pardoll, 2012), among which two have been studied the most intensively: CTLA4 binding to CD80 or CD86 and programmed cell death protein 1 (PDCD1, also called PD1) binding to CD274 (also known as PD-L1) or PDCD1 ligand 2 (PDCD1LG2). Microsatellite instability-high (MSI-H), tumor mutational burden (TMB), and PD-L1 simultaneously exist in 12.8% of CRC cases, which is much higher than that in all cancers (2.9%) mentioned in

European Society of Medical Oncology (ESMO) recommendations. Besides, TMB and MSI-H show strong correlation in 44.2% of CRC (Luchini et al., 2019). These clinical data indicate tremendous possibilities of immunological therapy in CRC. The ZNF750-*CYTOR* axis shows strong correlation with currently known immune therapy indicators (Fig. S2), prompting the notion that ZNF750-*CYTOR* participates in immune therapy.

Radical surgical resection and adjuvant therapy are the primary treatment methods for advanced COAD. In the present study, patients with a high expression of ZNF750/*CYTOR* had different prognosis results depending on the received therapy, which indicates that the prediction value of whether ZNF750/*CYTOR* is a good potential medication target or therapeutic efficacy predictor varies by the specific kind of drug applied. So far, no study has shown that ZNF750 can serve as a therapeutic target for tumors. Hence, further work should be undertaken to explore whether ZNF750 is an appropriate target for the therapy of different kinds of cancer.

This study has certain limitations. The exact mechanisms of ZNF750-*CYTOR* axis affecting tumor-infiltrating lymphocyte (TIL) infiltration and the modulating efficacy of immune checkpoint blocker regents require further experiments to explore. In addition, new immunotherapy information for COAD to verify the role of ZNF750-*CYTOR* axis through additional clinical experiments would prove useful. Beyond these limitations, this is the first study to demonstrate that ZNF750-*CYTOR* promotes tumor malignant phenotypes and influences chemotherapy response.

In conclusion, this paper has revealed that ZNF750 positively regulates *CYTOR* expression through in vitro experiments. ZNF750-*CYTOR* promotes the malignant phenotypes in COAD cells. Furthermore, studies based on TCGA or Gene Expression Omnibus (GEO) COAD cohorts have indicated three vital relevancies between the ZNF750-*CYTOR* axis and clinical features: first, the ZNF750-*CYTOR* axis is upregulated during carcinogenesis and cancer progression; second, ZNF750-*CYTOR* positively correlates with the TILs and is related to the expression of immune checkpoint genes; third, ZNF750-*CYTOR* may be a pharmacotherapy response predictor of COAD for several kinds of conventional chemotherapy.

Materials and methods

Detailed methods are provided in the electronic supplementary materials of this paper.

Acknowledgments

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Author contributions

Lu XIA performed the experimental research and data analysis, wrote and edited the manuscript. Hexin LIN performed the data analysis. Yanming ZHOU performed the establishment of animal models. Jiabian LIAN contributed to the study design, writing and editing of the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Lu XIA, Hexin LIN, Yanming ZHOU and Jiabian LIAN declare that they have no conflict of interest.

All institutional and national guidelines for the care and use of laboratory animals were followed. The animal experiments were carried out according to the guidelines of the Laboratory Animal Research Center of Xiamen University by the Ethical Committee on Animal Research at Xiamen University (No. XMULAC20180066), Xiamen, China.

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Supplementary information

Figs. S1 and S2; Materials and methods