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# The role of hepatocyte nuclear factor 4 $\alpha$ (HNF4 $\alpha$ ) in tumorigenesis

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Hepatocyte Nuclear Factor 4 Alpha (HNF4 $\alpha$ ) is a master transcription factor mainly expressed in the liver, kidney, intestine and endocrine pancreas. It regulates multiple target genes involved in embryonic development and metabolism. HNF4 $\alpha$ -related diseases include non-alcoholic fatty liver disease (NAFLD), obesity, hypertension, hyperlipidemia, metabolic syndrome and diabetes mellitus. Recently, HNF4 $\alpha$  has been emerging as a key player in a variety of cancers. In this review, we summarized the role and mechanism of HNF4 $\alpha$  in different types of cancers, especially in liver and colorectal cancer, aiming to provide additional guidance for intervention of these diseases.

## KEYWORDS

HNF4 $\alpha$ , tumorigenesis, liver cancer, colorectal cancer, transcription factor

## Introduction

HNF4 $\alpha$  is a critical transcription factor (TF) during development. Its silencing and dysfunction could lead to stunted development in gastrula formation (1), liver (2) and kidney (3). Interestingly, enforcing expression of HNF4 $\alpha$ , in cooperation with Forkhead Box Protein A3 (FOXA3) and Hepatocyte Nuclear Factor 1-Alpha (HNF1 $\alpha$ ), could even reverse the hepatocellular carcinoma (HCC) cells into normal hepatocyte-like cells (4). Furthermore, HNF4 $\alpha$  binds to different gene clusters between undifferentiated state and differentiated state during embryonic development (5), which may be a reason why HNF4 $\alpha$  has opposite functions in different types of malignancies.

Another vital role of HNF4 $\alpha$  is the regulation of metabolic homeostasis. Most HNF4 $\alpha$ -related diseases have abnormal insulin secretion such as occurrence of diabetes mellitus (including Type I and Type II diabetes mellitus), while the

underlying molecular mechanism remains elusive (6, 7). It has been shown that HNF4 $\alpha$  interacts with Circadian Locomotor Output Cycles Protein Kaput (CLOCK)/BMAL1 to regulate a series of metabolic genes involved in lipid, glucose and amino acid homeostasis. It was known that the circadian rhythm of metabolism was controlled by HNF4 $\alpha$  through repression of transcriptional activity of CLOCK/BMAL1 (8). Knockout of BMAL1 attenuated the genome-wide binding of HNF4 $\alpha$  in the liver possibly *via* transcriptional downregulation of HNF4 $\alpha$  (9). In addition, HNF4 $\alpha$  regulated energy metabolism and inflammation through recruiting glucocorticoid receptors (10).

Similarly, HNF4 $\alpha$  has been shown to promote glycolysis, glucose uptake, lactic acid production and ATP levels in neuroblastoma cells, and the underlying mechanism involved hexokinase 2 (HK2) and Solute Carrier Family 2 Member 1 (SLC2A1) and the heterogeneous nuclear ribonucleoprotein U (hnRNP) (11). In pancreatic cancer, HNF4 $\alpha$  deletion led to a glycolytic energy metabolism transition from typical pancreatic adenocarcinoma to squamous pancreatic cancer, in which Fructose-Bisphosphate Aldolase A (ALDOA), Hexokinase 1 (HK), and Glycogen Synthase Kinase 3 Beta (GSK3 $\beta$ ) genes are upregulated. The downstream Wingless-Type MMTV Integration Site Family, Member 7A (WNT7A) and Protein Kinase AMP-Activated Catalytic Subunit Alpha 1 (AMPK) signal activation further led to drug resistance in squamous pancreatic cancer (12).

Here, we review the role and the mechanism of HNF4 $\alpha$  in various cancers, try to emphasize the importance of HNF4 $\alpha$  in tumorigenesis and look forward to helping with the treatment and prevention of cancer.

## The expression of HNF4 $\alpha$ in different tumors

HNF4 $\alpha$  has been demonstrated to be a tumor suppressor in certain types of tumors but act as an oncogene in other forms of cancers. We also analyzed the expression levels of HNF4 $\alpha$  in different tumors from the TCGA database and found that HNF4 $\alpha$  is upregulated in most gastrointestinal tumor tissues when compared to their matched normal tissues, including colon and rectal adenocarcinoma, esophageal cancer, stomach cancer and pancreatic cancer. However, HNF4 $\alpha$  expression level is downregulated in cholangiocarcinoma and kidney chromophobe tissues compared to their normal counterparts (Figure 1). Although we did not see significant change of HNF4 $\alpha$  expression in HCC and prostate cancer (Figure 1), HNF4 $\alpha$  plays an important role in HCC and prostate cancer (see below).

## HNF4 $\alpha$ function in hepatocellular carcinoma

The important role of HNF4 $\alpha$  in development and metabolism, especially in liver tissues, led to the initial research focusing on HNF4 $\alpha$  in liver cancer. HNF4 $\alpha$  was shown to play an inhibitory role in the development of liver cancer, and was significantly correlated with genes related to drug absorption, distribution, metabolism and excretion in patients with liver cancer (13). Mutations in the Catenin Beta 1 (CTNNB1) exon 3 region were detected in 54 of 59 samples (92%) of pediatric hepatoblastoma; In such tumors, Wnt

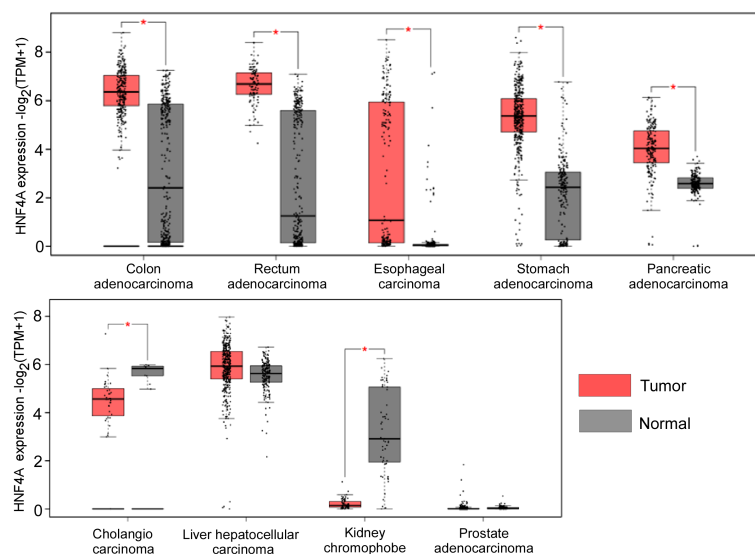


FIGURE 1  
HNF4 $\alpha$  expression levels in different types of cancer tissues and their matched normal counterparts. \*indicates  $p < 0.05$ . The raw data are from <http://gepia2.cancer-pku.cn>.

signaling and cell cycle pathways are usually upregulated. Moreover, in more malignant genotypes, HNF4 $\alpha$ /CEBP $\alpha$  (CCAAT Enhancer Binding Protein Alpha) binding regions of the genome is highly methylated, and HNF4 $\alpha$ /CEBP $\alpha$  transcriptional activity is inhibited (14).

HCC associated with hepatitis B virus (HBV) showed that E2F Transcription Factor 1(E2F1) acts as an active UR (upstream regulator), to positively regulate cell cycle and DNA replication, while HNF4 $\alpha$  and HNF1 $\alpha$  function as inhibitor URs. In alcoholic HCC, Erb-B2 Receptor Tyrosine Kinase 2 (ERBB2) is activated, while HNF4 $\alpha$  and Nuclear Transcriptional Regulator Protein 1(NUPR1 are inhibited) (15).

Taniguchi, H. et al. provided evidence that the HNF4 $\alpha$  gene mutations G79C, F83C and M125I (Zn DNA domain) are loss-of-function mutations that would lead to decreased expression of HNF1 $\alpha$  and Apolipoprotein B (ApoB) genes and increased risk of liver tumor (16). HNF1 $\alpha$  and HNF4 $\alpha$  had positive feedback regulation, mutations of Y122C, R229Q and V259F in the POU domain of HNF1 $\alpha$  inhibited its activity and disrupted the binding to the HNF4 $\alpha$  promoter, resulting in down-regulation of HNF4 $\alpha$  and other HNF1 $\alpha$  target genes, as well as disruption of HNF4 $\alpha$ -HNF1 $\alpha$  transcriptional network, thus triggering the development of HCC (17). In addition, Lysine Demethylase 8(KDM8) is a potential tumor suppressor downregulated in HCC and is a downstream target of HNF4 $\alpha$  signaling (18). Furthermore, Mitochondrial Amidoxime Reducing Component 2 (MARC2)-HNF4 $\alpha$  forms a positive feedback loop to inhibit the progression of HCC (19).

The expression of hydroxysteroid 17- $\beta$  dehydrogenase 6 (HSD17B6) in HCC is lower than that in the normal liver and is associated with HCC stage and grade. HNF4 $\alpha$  has been shown to bind to the enhancer and promoter regions of the HSD17B6 gene to activate its transcription, and the methylation of the HSD17B6 promoter negatively regulates its expression even in the presence of HNF4 $\alpha$  (20).

Accumulating evidence indicates that ferroptosis is closely associated with liver cancer. Zhang, X. et al. showed that HNF4 $\alpha$  is a controller of ferroptosis down-regulated factors (FDF), which inhibits iron death by affecting the synthesis of GSH. In response to ferroptosis, dissociation of histone acetyltransferase Lysine Acetyltransferase 2B (KAT2B) blocks the binding of HNF4 $\alpha$  to the FDF promoter (21).

For HNF4 $\alpha$ -based targeting therapeutics in HCC, HNF4 $\alpha$  and HNF1 $\alpha$  have been used to inhibit HCC cell proliferation and eliminate tumor-specific features. Takashima, Y et al. showed that the combined transduction of three liver TFs: HNF4 $\alpha$ , HNF1 $\alpha$  and FOXA3 could stably inhibit HCC cell proliferation and tumor stem cell renewal (22). Oligo-fucoidan, a sulfated polysaccharide, inhibited HCC growth by binding to the Asialoglycoprotein Receptor (ASGR) which led to Signal Transducer And Activator of Transcription 3 (STAT3) phosphorylation, and then p-STAT3 induced the transcription of the HNF4 $\alpha$  (23). The mRNA of HNF4 $\alpha$  encapsulated by lipid

nanoparticles can reduce the liver damage (fibrosis and cirrhosis) in various mouse models. Paraoxonase1 is a direct target of HNF4 $\alpha$  and participates in the weakening of liver fibrosis mediated by HNF4 $\alpha$  (24).

In conclusion, HNF4 $\alpha$  maintains homeostasis of liver, and the mutations of HNF4 $\alpha$  or epigenetic modifications of promoter regions of its targeting genes lead to the loss of function of HNF4 $\alpha$ . Elevated expression of HNF4 $\alpha$  has a good prognosis in patients with HCC. In the progression of liver cancer, HNF4 $\alpha$  is regulated by factors such as STAT3 and KAT2B, and function as tumor suppressor through HSD17B6, HNF1 $\alpha$ , FOXAs, MARC2. Some HCC phenotypes can even be reversed by overexpression of HNF4 $\alpha$ .

Interestingly, not all studies support the point that HNF4 $\alpha$  inhibits liver cancer. In a recent study on the effect of SNPs in liver cancer, the rs73613962 (T > G) site at the Protein Arginine Methyltransferase 7 (PRMT7) gene has allele-specific enhancer activity. HNF4 $\alpha$  preferentially binds to this enhancer region with the risk allele G to activate PRMT7 transcription, and elevated PRMT7 promotes malignant phenotypes of HCC through inhibition of the p53 signaling cascade (25). Another study revealed that HNF4 $\alpha$  bound to the -1409 to -1401 region of the circRNA\_104075 promoter to induce its expression. Upregulated circRNA\_104075 increased the expression of Yes1 Associated Transcriptional Regulator (YAP1), a target of mir-582-3p, by acting as a sponge of mir-582-3p, ultimately promoting the initiation of liver cancer (26).

## HNF4 $\alpha$ functions in colorectal cancer

HNF4 $\alpha$  also plays a pivotal role in CRC through regulation of several major oncogenic pathways. In 2009, genomic-wide association scanning on 2361 cases of ulcerative colitis and 5417 control cases revealed that HNF4 $\alpha$  was related to the progression of ulcerative colitis (27). The Cancer Genome Atlas (TCGA) analysis of colon and rectal tumors showed that HNF4 $\alpha$ , TOMM34 (outer mitochondrial membrane translocation enzyme 34) and SRC (non-receptor tyrosine kinase) were overexpressed in colorectal cancer (28).

Expression of P1-/P2-promoter-driven nuclear HNF4 $\alpha$  is significantly correlated with cytoplasmic  $\beta$ -catenin in colitis-associated tumor and sporadic CRC. Depletion of HNF4 $\alpha$  reduces  $\beta$ -catenin expression (29). HNF4 $\gamma$ , a paralog of HNF4 $\alpha$ , and Nuclear Receptor Subfamily 1 Group F Member 3 (RORC) along with HNF4 $\alpha$  are also up-regulated in CRC tissues (30). Due to the compensatory role of HNF4 $\gamma$  in intestinal tissues, ablation of HNF4 $\alpha$  did not cause changes in HDL level in serum or lipoprotein gene expression in ileum (31). Furthermore, transcription factors such as Heat Shock Transcription Factor 1 (HSF1) and Double-Strand-Break Repair Protein Rad21 Homolog (RAD21) play a regulatory role with HNF4 $\alpha$  in colorectal cancer metastasis (32). In addition, HNF4 $\alpha$  was identified as a positive

regulator of oxidoreductase related genes that involved in regulation of ROS level. Knockdown of HNF4 $\alpha$  increases and ectopic expression of HNF4 $\alpha$  reduces ROS production in CRC cells. Both HNF4 $\alpha$  and oxidoreductase related genes are overexpressed in colorectal cancers (33). It has also been found that Nuclear Factor Kappa B Subunit 1 (NF- $\kappa$ B) regulates transcriptional activation of Carboxylesterase 1 (CES1) through HNF4 $\alpha$  in invasive CRC (34). These findings suggest that HNF4 $\alpha$  functions as an oncogene in CRC.

Contrary to the conclusion above, the expression of HNF4 $\alpha$  in colon cancer leads to the decreased expression of oncogenic factors Lysine Demethylase 1 (ALSD1), SET Domain Containing 1A, Histone Lysine Methyltransferase (SETD1A), Protein Arginine Methyltransferase 1 (PRMT1), FOXM1, Protein Tyrosine Kinase 2 (FAK) and Snail Family Transcriptional Repressor 1(SNAI1), and inhibits the tumor-formation of HCT116 cells (35).

To sum up, HNF4 $\alpha$  is a key player in CRC while the underlying mechanism is largely unknown. Further investigation of the role and the specific mechanism of HNF4 $\alpha$  in the development and progression of CRC is of great significance for establishing HNF4 $\alpha$  as a therapeutic target in CRC.

## HNF4 $\alpha$ functions in gastric cancer

HNF4 $\alpha$  promotes gastrointestinal adenocarcinoma proliferation and survival in a genealogy-specific manner through transcriptional activation of many downstream targets, including HNF1 $\alpha$  and interleukin signaling factors (36). The promoter and three distal enhancers of HNF4 $\alpha$  are activated by four key transcription factors, ELF3, GATA-Binding Factor 4 (GATA 4), GATA6, and Kruppel Like Factor 5 (KLF5).

HNF4 $\alpha$  is highly expressed in both primary gastric cancer and metastasis from gastric cancer to mammary gland, but not in breast cancer, which should be a good marker to distinguish primary and metastatic gastric cancer from breast cancer (37). The same conclusion was confirmed by Saad, DZ. HNF4 $\alpha$  was overexpressed in 22 of 23 cases of primary gastric adenocarcinoma and in 15 of 16 cases of metastatic gastric adenocarcinoma, but not in 25 cases of primary breast cancer and 17 cases of metastatic breast cancer, suggesting HNF4 $\alpha$  as a valuable biomarker (38). Moreover, HNF4 $\alpha$  binds to Mucin 5AC, Oligomeric Mucus/Gel-Forming (MUC5AC) promoter and transcriptionally induces MUC5AC expression. Thus, HNF4 $\alpha$  correlates with MUC5AC mucin expression during stomach development and in GC cells (39).

Furthermore, different HNF4 $\alpha$  subtypes derived from two different promoters (P1 and P2) determine the malignancy degree in gastric cancer. Overexpression of P1-HNF4 $\alpha$  rather than P2-HNF4 $\alpha$  induces tumor growth, and Chemokine Ligand 15 (CCL15) was a direct target of P1-HNF4 $\alpha$  in GC (40). In addition, X Inactive Specific Transcript (XIST), a long-strand

non-coding RNA, increases enrichment of HNF4 $\alpha$  in the promoter region of EPH Receptor A1 (EPHA1), contributing to the deterioration of GC (41).

In conclusion, HNF4 $\alpha$  plays a role as a promoter in GC, but underlying mechanism remains elusive, and P1-HNF4 $\alpha$  subtype could drive a more malignant phenotype than P2-HNF4 $\alpha$  in GC.

## HNF4 $\alpha$ functions in other cancers

Apart from HCC, CRC, and GC, HNF4 $\alpha$  has been shown to have significant role in many other cancer types.

### Lung cancer

Activation of HNF4 $\alpha$  in lung cancer leads to higher lung cancer grade and shorter survival (42). HNF4 $\alpha$  has also been found to be elevated in lung adenocarcinoma (43) and induce mucin MUC3 expression in Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) mutated lung mucinous adenocarcinoma (44). In addition, HNF4 $\alpha$  recognizes the SNP site RS401681, which can interact with Telomerase Reverse Transcriptase (TERT) promoter to increase lung cancer risks (45).

### Pancreatic cancer

Although the TCGA database showed that HNF4 $\alpha$  expression level was elevated in pancreatic cancer tissues, Camolotto's results demonstrated that HNF4 $\alpha$  inhibited tumor growth and promoted epithelial development through directly inhibiting expression of *Sine Oculis Homeobox Homolog (SIX) 4* and *SIX1*, two markers of mesodermal/neuronal lineage expressed in basal-like subtypes (46). KRAS (G12D) -driven pancreatic tumors develop after GATA6 deletion, which is accompanied by the loss of HNF1 $\alpha$  and HNF4 $\alpha$  (47).

### Prostate cancer

It has been revealed that HNF4 $\alpha$ -mediated AMPK/mTOR pathway promotes prostate cancer progression (48). A previous study showed that selenium-binding protein 1(SBP1) inhibits prostate cancer growth by reducing oxygen consumption and increasing the activation AMPK, and that HNF4 $\alpha$  binds to the promoter of SBP1 to restrain SBP1 transcription (49). In addition, exposure to bisphenol A (BPA) caused prostate preneoplasia, HNF4 $\alpha$ -regulated gene networks were altered by BPA, which include nuclear factor- $\kappa$ B, ERK1/2 and insulin-related signaling (50). However, one report indicated HNF4 $\alpha$  as a tumor suppressor of prostate cancer by promoting p21-driven senescence (51).

## Renal cell carcinoma

HNF4 $\alpha$  function as a tumor suppressor in clear cell renal cell carcinoma (ccRCC). HNF4 $\alpha$  has been shown to regulate two metabolic enzymes ABAT and ALDH6A1 leading to inhibition of cell proliferation and migration, and impaired lactate production (52). In addition, HNF4 $\alpha$  restrains the development of renal cell carcinoma by transcriptional activation of NR\_023387 (53) and inhibition of E-cadherin (54). Moreover, ALDH2 can enhance anthracycline sensitivity of RCC and activates the transcription of HNF4 $\alpha$  (55), and HNF4 $\alpha$  also increased the chemosensitivity of RCC cells to oxaliplatin and 5-FU (56).

## Cervical, bladder, esophageal and breast cancer

There are few reports about the roles of HNF4 $\alpha$  in these tumors. In cervical cancer, HNF4 $\alpha$  inhibits the tumorigenic potential *in vivo* and induces the tumor cell G0/G1 arrest through suppression of the Wnt/ $\beta$ -catenin pathway (57). A recent study showed that expression of HNF4 $\alpha$  reduced cell proliferation and enhanced cisplatin sensitivity by activation of ALDH6A transcription in bladder cancer (58) and triggered malignant transformation in esophageal carcinoma (59). In addition, upregulation of HNF4 $\alpha$  under hypoxia contributes to adriamycin resistance in breast cancer (60).

## Conclusions and future perspectives

The important role of HNF4 $\alpha$  in development and metabolism also directly reflect the tumor process. However, the regulation of HNF4 $\alpha$  in tumor is not only dependent on metabolic and developmental pathways. In HCC, HNF4 $\alpha$  has been demonstrated to inhibit malignant phenotype, while the effect of HNF4 $\alpha$  in colon cancer is quite opposite. In addition, a few studies have shown that overexpression of HNF4 $\alpha$  promoted the development of gastric and lung cancer and inhibited the development of pancreatic ductal carcinoma. Sporadic studies have shown that HNF4 $\alpha$  played a certain regulatory role in all types of tumors. Further investigations of the role of the of HNF4 $\alpha$  in different tumor types will greatly enhance the

understanding HNF4 $\alpha$  biological function and also will be important for development of HNF4 $\alpha$ -based therapeutics.

## Author contributions

LS and JWS were responsible for the study concept and design. LS, XW and WB drafted the manuscript. JLS, YZ, and JWS revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

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