

The Potential Role of N6-Methyladenosine (m6A) Demethylase Fat Mass and Obesity-Associated Gene (FTO) in Human Cancers

This article was published in the following Dove Press journal:
OncoTargets and Therapy

Jin-yan Wang^{1,2}
Li-juan Chen¹
Ping Qiang³

¹Department of Obstetrics and Gynecology, Zhangjiagang First People's Hospital, Zhangjiagang Jiangsu 215600, People's Republic of China; ²Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, People's Republic of China; ³Department of Gynecology, Zhangjiagang First People's Hospital, Zhangjiagang Affiliated Hospital of Soochow University, Zhangjiagang, Jiangsu 215600, People's Republic of China

Abstract: N6-methyladenosine (m6A) demethylase *fat mass and obesity-associated gene* (*FTO*), previously recognized to be related with obesity and diabetes, was gradually discovered to be dysregulated in multiple cancers and plays an oncogenic or tumor-suppressive role. However, the specific expression and pro- or anti-cancer role of *FTO* in various cancers remained controversial. In this review, through summarizing the available literature, we found that *FTO* single nucleotide polymorphisms (SNPs) were closely related with cancer risk. Additionally, the dysregulation of *FTO* was implicated in multiple biological processes, such as cancer cell apoptosis, proliferation, migration, invasion, metastasis, cell-cycle, differentiation, stem cell self-renewal and so on. These modulations mostly relied on the communications between *FTO* and specific signaling pathways, including *PI3K/AKT*, *MAPK* and *mTOR* signaling pathways. Furthermore, *FTO* had great potential for clinical application by serving as a prognostic biomarker.

Keywords: *FTO*, biological function, cancers, prognosis

Introduction

Fat mass and obesity-associated gene (*FTO*) was previously recognized to be associated with the occurrence and development of childhood and adult obesity and type 2 diabetes (T2D).¹⁻³ Later, researchers found that the *FTO* A allele was not only associated with increased body mass index (BMI), but also associated with decreased risk of lung cancer and increased risk of kidney cancer.⁴ Accumulating studies revealed that there was a close connection between *FTO* and the risk of various human cancers, including breast cancer,^{5,6} colon cancer,⁷ gastric cancer,⁸ pancreatic cancer,⁹ prostate cancer¹⁰ and so on. Further studies discovered that the regulatory role of *FTO* in cancers might rely on *FTO*-mediated N6-methyladenosine (m6A) demethylation.^{11,12}

It was widely known that there were over 100 post-transcriptional modifications of RNA identified in living organisms, and these post-transcriptional modifications provided a functional diversity that allowed basic ribonucleotide residues to obtain various functions.¹³ M6A modification was first identified in mRNA-enriched RNA fractions from novikoff hepatoma cells in 1974.¹⁴ It was the most prevalent internal RNA modification and was a dynamic and reversible modification process in eukaryotic cells.¹⁵ With time going on, Dominissini et al¹⁶ presented in 2012 that m6A-seq, dependent on antibody-mediated capture and massively parallel sequencing, was able to landscape the human and mouse m6A modification in a transcriptome-wide manner.

Correspondence: Li-juan Chen
Department of Obstetrics and Gynecology, Zhangjiagang First People's Hospital, 68 W Jiyang Road, Zhangjiagang Jiangsu 215600, People's Republic of China
Email ljchen_doctor@163.com

Ping Qiang
Department of Gynecology, Zhangjiagang First People's Hospital, 68 W Jiyang Road, Zhangjiagang 215600 Jiangsu, People's Republic of China
Email pingqiang_doc_zjg@163.com

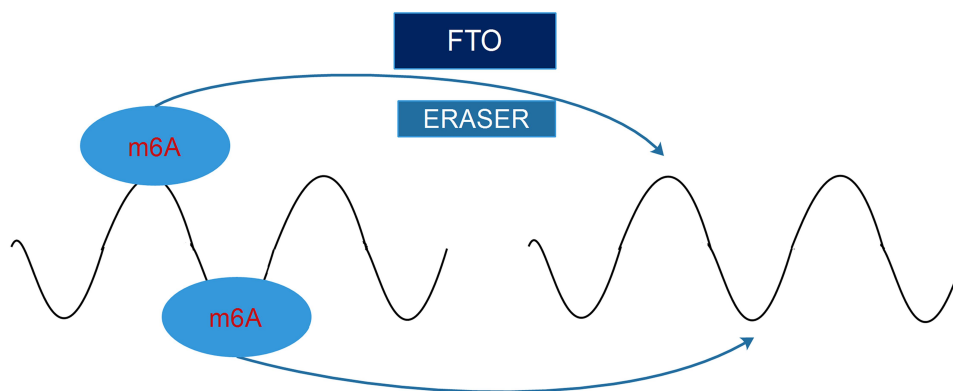


Figure 1 *FTO*, belonged to demethylase, termed as “erasers” and functioned to reverse the methylation.

With the application of the technology for monitoring m6A, insights into the potential mechanisms had been explored in recent decades. For example, existing evidence revealed that m6A modification was maintained by methyltransferase (MTase) complex and demethylase, and functionally regulated the eukaryotic transcriptome to affect mRNA splicing, export, localization, translation, and stability.¹⁷ MTase complex termed as “writers”, including *methyltransferase-like 3/14/16 (METTL3/14/16)*, *KIAA1429*, *wilms tumor 1 (WT1)-associated protein (WTAP)* and *RBM15*, and acted to add m6A-modified sites.¹⁸ However, *FTO* belonged to demethylase. Demethylase, termed as “erasers”, functioned to reverse the methylation and affect biological functions accordingly (Figure 1).¹⁹ In detail, *FTO* had been found to modify multiple RNAs, such as microRNAs (miRNAs)²⁰ and messenger RNAs (mRNAs).²¹ It was also significantly related with multiple biological functions of cancers, including cell cycle,¹¹ tumor growth,¹² proliferation,²² survival,²³ migration,²⁴ invasion,²⁵ stem cell maintenance²⁶ and self-renewal.²⁷

In order to better describe the role of *FTO* in various cancers, we first searched the literature about *FTO* and multiple cancers in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and classified them according to the types of cancers. After obtaining the literature, we focused on the relationship between *FTO* and cancer risks and the underlying mechanisms of *FTO* in various cancers.

FTO Single Nucleotide Polymorphism (SNP) with Cancer Risk

In 2010, Gaudet et al²⁸ first explored the relationship between *FTO* and cancer risk. Unfortunately, the results of genome-wide association scans indicated that there was

no association between *FTO* and endometrial cancer risk. Later, *FTO* variants, including rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002, rs11075995 and rs1121980 were found to be related with cancer risk.²⁹ Lewis et al¹⁰ carried out a genetic association study of the connection between *FTO* and prostate cancer risk. Interestingly, *FTO* rs9939609, which was a SNP known to be associated with obesity, was inversely related with low-grade prostate cancer risk, but positively related with high-grade prostate cancer. Salgado-Montilla et al³⁰ also discovered the same correlation between *FTO* rs9939609 and prostate cancer risk; nonetheless, the result was not statistically significant upon adjustment.

As for breast cancer, one research revealed that *FTO* might have a close connection with the risk of breast cancer.³¹ Kaklamani et al⁵ evaluated the role of four *FTO* SNPs, including rs7206790, rs8047395, rs9939609 and rs1477196 in breast cancer patients from Northwestern University in Chicago, Illinois. The results showed that all SNPs, especially *FTO* rs1477196, were significantly associated with breast cancer risk. Likewise, *FTO* rs1477196 significantly depressed breast cancer risk, and *FTO* rs16953002 significantly increased breast cancer risk in Chinese population.³² Additionally, *FTO* rs11075995 was closely connected with breast cancer risk, but this connection was eliminated with further adjustment for BMI.³³ However, in Iranian population, neither *FTO* rs1477196 nor *FTO* rs9939609 was statistically significantly related with the risk of breast cancer.³⁴ Similarly, *FTO* rs1121980 and rs9939609 did not show any significant association with breast cancer development.^{6,35} Another research genotyped two polymorphic sites located in *FTO* gene (rs993909 and rs9930506), and did not find any association between

FTO and breast cancer risk in patients from Copernicus Memorial Hospital in Lodz, Poland.³⁶ What is more, *FTO* rs3751812 was not significantly connected with breast cancer risk in Chinese population.³⁷ In conclusion, up to date, *FTO* rs7206790, rs8047395, rs9939609, rs1477196 and rs16953002 might be associated with breast cancer risk.

As for colorectal cancer, Yang et al³⁸ examined 677 *FTO* SNPs in patients from the Colon Cancer Family Registry, and did not find any evidence that *FTO* SNPs were related with colorectal cancer risk. Whereas, another research found that *FTO* rs1558902, rs8050136, rs3751812, and rs9939609 showed a positive association with colorectal cancer in Japanese population.⁷

Furthermore, *FTO* rs9939609 polymorphism might be associated with the susceptibility of pancreatic cancer and endometrial cancer, especially in Asian populations, while no statistical significance was found in other cancers.³⁹ A meta-analysis suggested that *FTO* rs9939609 was not significantly related with the increased risk of cancers, with the exception of pancreatic cancer.^{33,40} A case-control study in Japan revealed that *FTO* rs9939609 was correlated with pancreatic cancer risk and possibly independent of obesity.⁹ Additionally, although *FTO* rs9939609 was associated with increased risk of endometrial carcinoma, this association was eliminated after adjusting for BMI in white non-Hispanic women.⁴¹

In other cancers, researches revealed that *FTO* was not only associated with a decreased risk of lung cancer but also associated with a weak increased risk of kidney cancer.⁴ And *FTO* rs8047395 was closely associated with papillary thyroid cancer in German population.⁴² All associations between *FTO* SNPs and cancer risk are listed in Table 1.

The Biological Functions and the Underlying Mechanisms of *FTO* in Multiple Cancers

According to the existing researches, the association between *FTO* SNPs and the risk of various cancers might rely on the molecular mechanisms of *FTO*, which played a critical role in cancer tumorigenesis.⁴³ For instance, the expression of *FTO* was dramatically dysregulated in cancers and took a great part in the growth of cancer cells through modulating cellular metabolic pathways, including *phosphoinositide 3-kinases/protein kinase B (PI3K/AKT)* and *adenosine monophosphate-activated*

Table 1 The Associations Between *FTO* SNPs and Various Cancers

Cancer	SNPs	Population	Association	Ref
Prostate cancer	rs9939609	/	+	10
	rs9939609	/	/	30
Breast cancer	rs7206790 rs8047395 rs9939609 rs1477196	Patients from Northwestern University in Chicago	+	5
	rs1477196 rs16953002	Chinese population	+	32
	rs11075995	/	/	33
	rs1477196 rs9939609	Iranian population	/	34
	rs1121980 rs9939609	/	/	6
	rs993909 rs9930506	Patients from Copernicus Memorial Hospital in Poland	/	36
	rs3751812	Chinese population	/	37
Colorectal cancer	rs1558902 rs8050136 rs3751812 rs9939609	Japanese population	+	7
Pancreatic cancer	rs9939609	Asian population	+	39
		/	+	9
Endometrial cancer	rs9939609	Asian population	+	39
		White non-Hispanic population	/	41
Papillary thyroid cancer	rs8047395	German population	+	42

Notes: +: indicated significantly related. /: indicated not significantly related.

protein kinase(AMPK) signaling pathways.²³ Next, we would further explore the detailed molecular mechanisms of *FTO* in the occurrence and progression of cancers. The expression, clinical significance and biological functions of *FTO* in various cancers are shown in Table 2.

Table 2 Expression, Clinical Significance and Biological Functions of *FTO* in Various Cancers

Cancer	Expression	Role	Biological Function	Target	Ref
Bladder Cancer	Down-regulated	Tumor suppressor	Proliferation, migration, cytotoxicity	/	61
Breast Cancer	Up-regulated	Oncogene	Survival, colony formation	<i>IRX3</i>	45,46
	Up-regulated	Oncogene	Cell energy metabolism	<i>PI3K/AKT</i>	48
	/	Oncogene	Proliferation	<i>PI3K/AKT</i>	31
	Up-regulated	Oncogene	Proliferation, colony formation, metastasis	<i>BNIP3</i>	47
Cervical Cancer	Up-regulated	Oncogene	Chemo-radiotherapy resistance	<i>β-catenin, ERCC1</i>	21
	Up-regulated	Oncogene	Proliferation, migration	<i>E2F1, Myc</i>	67
Clear Cell Renal Cell Carcinoma	Down-regulated	Tumor suppressor	Cell growth, apoptosis, mitochondrial biogenesis, oxidative phosphorylation, oxidative stress	<i>PGC-1α</i>	62
Colorectal Cancer	/	Oncogene	Proliferation	/	20
Endometrial Carcinoma	Up-regulated	Oncogene	Proliferation, invasion	<i>PI3K/AKT</i>	25
	Up-regulated	Oncogene	Proliferation	<i>MPAK</i> <i>mTOR</i>	78
Esophageal Squamous Cell Carcinoma	Up-regulated	Oncogene	Cell growth, migration, tumorigenicity	<i>MMP13</i>	24
Gastric Cancer	Up-regulated	Oncogene	Proliferation, migration, invasion	/	8
	Down-regulated	Tumor suppressor	/	/	57
Hepatocellular Carcinoma	Up-regulated	Oncogene	Proliferation, tumor growth, cell cycle	<i>PKM2</i>	11
	Down-regulated	Tumor suppressor	/	/	60
Lung Cancer	Up-regulated	Oncogene	Proliferation, colony formation, tumor growth	<i>USP7</i>	12
	Up-regulated	Oncogene	Proliferation, invasion, apoptosis	<i>MZFI</i>	52
Ovarian Cancer	Down-regulated	Tumor suppressor	Stemness	<i>cAMP</i>	27
Pancreatic Cancer	Up-regulated	Oncogene	Proliferation apoptosis	<i>cMYC</i>	22
Leukemia	Up-regulated	Oncogene	Proliferation, viability, cell-cycle arrest, apoptosis	<i>MYC/CEBPA</i>	87
	Up-regulated	Oncogene	Differentiation	<i>ASB2,RARA</i>	81

FTO in Breast Cancer

In 2015, Tan et al⁴⁴ first explored the association between *FTO* and breast cancer. The results showed that the expression of *FTO* was significantly higher in breast cancer tissues, especially *HER2*-overexpressed breast cancer. Furthermore, *FTO* inhibitor obviously suppressed the survival and colony formation of panresistant triple-negative inflammatory breast cancer cells, this regulation might depend on obesity-associated cis-acting elements in non-coding region of *FTO*, which acted to modulate the expression of *IRX3* gene and activate obesity networks.^{45,46} Niu et al⁴⁷ also found that *FTO* was elevated in breast cancer cell lines and tissues, and enhanced cancer cell proliferation, colony formation and metastasis through regulating m6A demethylation in the 3'UTR of

*BNIP3*mRNA, which was a tumor suppressor, and inducing its degradation by a *YTHDF2*independent mechanism.

Due to the role of *FTO* in metabolism, Liu et al⁴⁸ assessed the effect of *FTO* on the energy metabolism of breast cancer cells. Mechanism researches found out that *FTO* inhibitor restrained pyruvate kinase and hexokinase activity and suppressed breast cancer cell glycolysis, partly through lowering the levels of *PI3K*, *p-PI3K*, *Akt* and *p-Akt*, which were members of *PI3K/AKT* signaling pathway. It was also disclosed by Gholamalizadeh et al³¹ that *FTO* functioned to activate the *PI3K/Akt* signaling pathway and promote breast cancer cell proliferation in estrogen receptor positive breast cancer patients. Additionally, the association of *FTO* and breast cancer was affected by the status of estrogen receptors

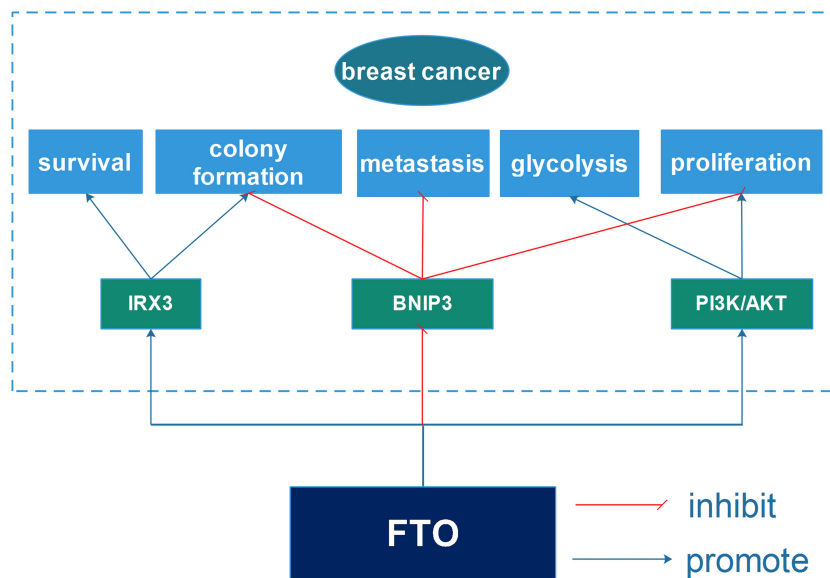


Figure 2 The specific mechanisms of *FTO* in breast cancer. *FTO* greatly participated in the survival, colony formation, metastasis, glycolysis and proliferation of breast cancer through targeting *IRX3*, *BNIP3* and *PI3K/AKT*.

and estrogen might exert its influence on breast cancer through *FTO*. The specific mechanisms of *FTO* in breast cancer are displayed in Figure 2.

FTO in Lung Cancer

FTO was up-regulated in non-small cell lung cancer (NSCLC) tissues and cell lines, and *FTO* knockdown decreased the proliferation rate, inhibited the colony formation ability of cancer cells and retained tumor growth in vivo via increasing mRNA stability of *ubiquitin-specific protease (USP7)*.¹² *USP7* was recognized to regulate the activities of numerous proteins and known as tumor suppressors, DNA repair proteins, immune responders, viral proteins, and epigenetic modulators.^{49–51} *FTO* was also drastically overexpressed in lung squamous cell carcinoma (LUSC), and loss-of-function assays indicated that the knockdown of *FTO* effectively retained the proliferation and invasion of cancer cells, while enhanced the apoptosis, via targeting *myeloid zinc finger protein 1 (MZF1)*.⁵² *MZF1* was a member of the SCAN-Zinc finger transcription factor family and had been proved to facilitate lung adenocarcinoma (LUAD) progression.⁵³ The specific mechanisms of *FTO* in breast cancer are displayed in Figure 3.

FTO in Gastrointestinal Cancer

FTO in Esophageal Squamous Cell Carcinoma (ESCC)

FTO was obviously up-regulated in ESCC tissues and functional assays revealed that *FTO* silence retained

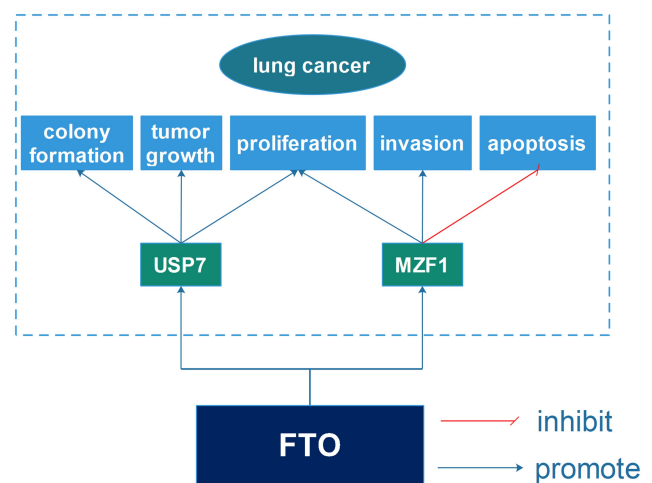


Figure 3 The specific mechanisms of *FTO* in lung cancer. *FTO* obviously promoted lung cancer cell colony formation, proliferation, invasion and tumor growth and inhibited apoptosis via promoting the expression of *USP7* and *MZF1*.

ESCC cell growth, migration and tumorigenicity through regulating *matrix metalloproteinases 13 (MMP13)*, and *FTO* overexpression exhibited the opposite results.²⁴ *MMP13* was an important member of *MMPs*, who were a family of Zn^{2+} -dependent endopeptidases, mainly existed in connective tissue and had a significant influence on tumor genesis and biological behavior.^{54–56}

FTO in Gastric Cancer (GC)

The mRNA and protein expression of *FTO* was up-regulated in GC tissues and contributed to cancer cell

proliferation, migration and invasion.⁸ However, Li et al⁵⁷ disclosed that as opposed to the mRNA level, *FTO* protein level was significantly down-regulated in signet ring cells and GC tissues.

FTO in Hepatocellular Carcinoma (HCC)

Overexpressed *FTO* in the HCC tissues and cells modulated cancer cell proliferation, cell cycle and in vivo tumor growth, mechanically through triggering the demethylation of *pyruvate kinase (PKM2)* mRNA and accelerating the translation.¹¹ *PKM2* was one of the key glycolysis pyruvate kinase isoenzyme and transformed the glucose metabolism from the normal respiratory chain to lactate production in tumor cells, thus contributing to tumorigenesis.^{58,59} However, it was claimed by Zhao et al⁶⁰ that *FTO* mRNA and protein levels were significantly down-regulated in HCC tissues.

FTO in Pancreatic Cancer and Colorectal Cancer

It was proved that *FTO* was overexpressed in pancreatic cancer cell lines, and *FTO* knockdown promoted cancer cell apoptosis and inhibited proliferation partly via communicating with *cMYC* proto-oncogene, which was a critical mediator in regulating cell entry into S phase of cell cycle.²² *FTO*, targeted by microRNA-1266, promoted proliferation of colorectal cancer cell lines.²⁰ The specific mechanisms of *FTO* in gastrointestinal cancer are displayed in Figure 4.

FTO in Urological Cancer

FTO in Bladder Cancer

The mRNA and protein expression level of *FTO* were decreased in bladder cancer cell lines and bladder urothelial carcinoma tissues compared with the normal control.⁶¹ Further cell counting kit-8 and wound healing assays revealed that *FTO* knockdown enhanced cancer cell proliferation and migration, and cisplatin-induced cytotoxicity of bladder cancer cells could be rescued by a highly selective inhibitor of *FTO*. However, further mechanism explorations had not been conducted.

FTO in Clear Cell Renal Cell Carcinoma (ccRCC)

The expression of *FTO* is suppressed in ccRCC tissues and *FTO* seemed to modulate mitochondrial activity, oxidative phosphorylation and cancer cell growth and apoptosis through demethylating the *PPARγ coactivators (PGC)-1α* mRNA.⁶² *PGC-1α* was a member of transcriptional coactivators, which acted to be a central regulator of mitochondrial biogenesis and oxidative phosphorylation, and played a tumor-suppressive and pro-tumorigenic role in variant cancers.^{63–66} The specific mechanisms of *FTO* in urological cancer are shown in Figure 5.

FTO in Gynecological Cancer

FTO in Cervical Cancer

Up-regulated *FTO* enhanced the chemo-radiotherapy resistance of cervical squamous cell carcinoma (CSCC) partly through reducing m6A level of *β-catenin* mRNA transcripts

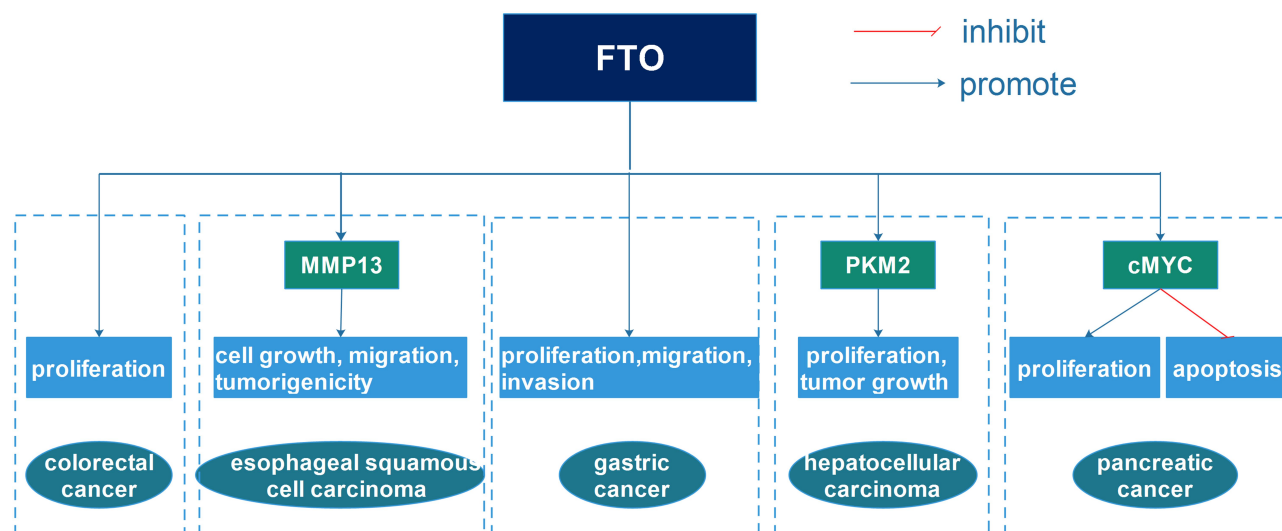


Figure 4 The detailed mechanisms of *FTO* in gastrointestinal cancer. *FTO* promoted colorectal and gastric cancer cell proliferation, migration and tumor growth. *FTO* also advanced cancer cell growth, migration and tumorigenicity through up-regulating *MMP13* in esophageal squamous cell carcinoma, and enhanced cancer cell proliferation and tumor growth via up-regulating *PKM2* in hepatocellular carcinoma. Finally, *FTO* promoted pancreatic cancer cell proliferation and inhibited apoptosis by regulating the expression of *cMYC*.

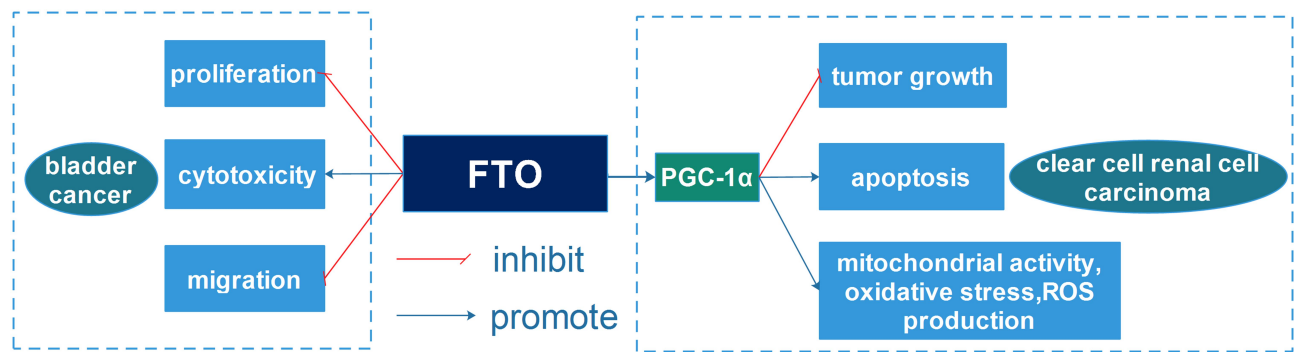


Figure 5 The specific mechanisms of *FTO* in urological cancer. *FTO* advanced bladder cancer cell proliferation and migration and suppressed cytotoxicity. Additionally, *FTO* greatly participated in cancer cell apoptosis, mitochondrial activity, oxidative stress, ROS production and tumor growth through modulating *PGC-1α* in clear cell renal cell carcinoma.

and in turn increasing *excision repair cross-complementation group 1 (ERCC1)* activity.²¹ *ERCC1* was a significant regulator of nucleotide excision repair and positively associated with chemo-radiotherapy resistance of CSCC. Likely, *FTO* served as a positive modulator of cervical cancer cell proliferation and migration through affecting the translation efficiency of *E2F1* and *Myc*.⁶⁷

FTO in Endometrial Cancer

In *FTO* in Breast Cancer, we found that there was a mutual relationship between *FTO* and estrogen in breast cancer. As far as we know, aberrant estrogen metabolism was also greatly involved in endometrial cancer growth and metastasis.^{68–70} Zhang et al²⁵ first explored the association between *FTO* and estrogen in endometrial cancer, they found that *β-estradiol (E2)* up-regulated *FTO* expression, thus enhancing endometrial cancer cell proliferation, migration and invasion via activating *phosphatidylinositol-3-kinase (PI3K)/protein kinase b (AKT)* and *mitogen-activated protein kinase (MAPK)* signal pathways. *PI3Ks* were key regulators of intracellular signaling in response to the extracellular stimulators. The activation of *PI3K/AKT* signaling pathway was one of the most common events in human cancers.^{71–73} *MAPK* pathway was also a pivotal bridge in the switch from extracellular signals to intracellular responses and frequently involved in oncogenesis, tumor progression and drug resistance.^{74–77} It was also proved by Zhu et al⁷⁸ that estrogen promoted *FTO* nuclear localization and advanced *mammalian target of rapamycin (mTOR)* signaling pathway in endometrial carcinoma, thus promoting proliferative activity of cancer cells. *mTOR* signaling pathway was often activated in tumors, and acted to modulate cell proliferation, immune cell differentiation, tumor metabolism through affecting gene transcription and protein synthesis.^{79,80}

FTO in Ovarian Cancer

However, *FTO* was down-regulated in ovarian tumors and inhibited the self-renewal of ovarian cancer stem cells (CSC) and suppressed tumorigenesis in vivo via blocking *cAMP* signaling.²⁷ The detailed mechanisms of *FTO* in gynecological cancer are shown in Figure 6.

FTO in Leukemia

Similarly, *FTO* was extremely overexpressed in acute myeloid leukemia (AML) with t(11q23)/*MLL* rearrangements, t(15;17)/*PML-RARA*, *FLT3-ITD*, and/or *NPM1* mutations. Mechanically, *FTO* enhanced leukemogenesis, cell proliferation and transformation, and suppressed apoptosis through modulating m6A level in *ASB2* and *RARA* mRNA transcripts.⁸¹ *ASB2* and *RARA* had an anti-leukemic effect via degrading *MLL* during hematopoietic differentiation via ubiquitination.^{82–86} Furthermore, *R-2-hydroxyglutarate (R-2HG)* inhibited leukemia cell proliferation/viability and promoted cell-cycle arrest and apoptosis via increasing m6A RNA modification in the sensitive cells, modulating the stability of *MYC/CEBPA* transcripts and thus suppressing relevant pathways.⁸⁷ *CEBPA* was a vital hematopoiesis-related transcription factor which was essential for leukemogenesis.^{88–90} The specific mechanisms of *FTO* in leukemia are displayed in Figure 7.

The Role of *FTO* Inhibitors

As the promoting role of *FTO* in leukemogenesis, Huang et al^{19,91} developed a promising *FTO* inhibitor, termed as FB23-2, which directly bound to *FTO* and selectively retained m6A demethylase activity. Further functional assays revealed that FB23-2 could remarkably inhibit the proliferation and advance the differentiation/apoptosis of AML cells, thus inhibiting the progression of AML. Considering the oncogenic

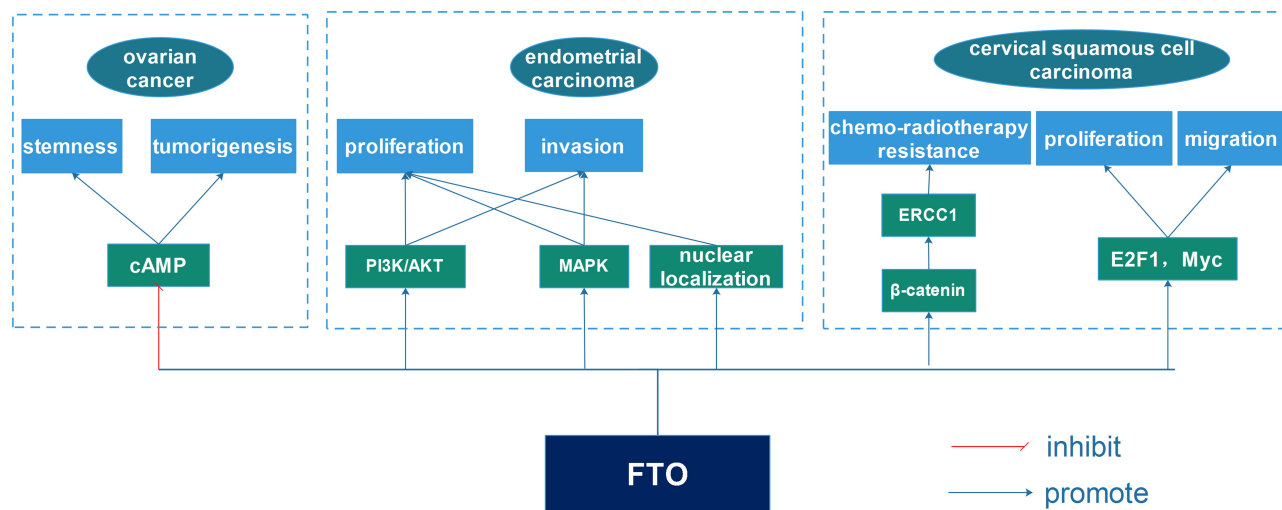


Figure 6 The specific mechanisms of *FTO* in gynecological cancer. *FTO* greatly influenced ovarian cancer cell stemness and tumorigenesis via suppressing the expression of *cAMP*. *FTO* also affected endometrial carcinoma cell proliferation and invasion by modulating *PI3K/AKT* and *MAPK* signaling pathways and nuclear localization. Finally, *FTO* played an important role in the chemo-radiotherapy resistance of cervical squamous cell carcinoma and cancer cell proliferation and migration through up-regulating β -catenin, *E2F1* and *Myc*.

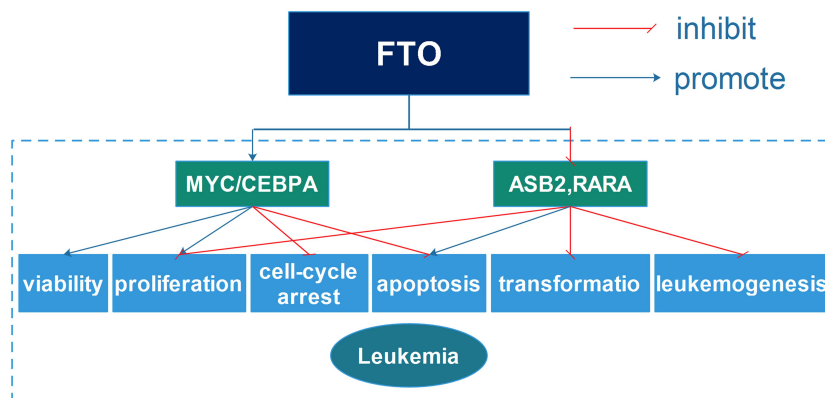


Figure 7 The detailed mechanisms of *FTO* in leukemia. *FTO* up-regulated *MYC/CEBPA* and down-regulated *ASB2* and *RARA*, thus promoting leukemia cell viability, proliferation, transformation and leukemogenesis and inhibiting cell-cycle arrest and apoptosis.

roles of *FTO* in kinds of cancers, Su et al²⁶ also developed two potent small-molecule *FTO* inhibitors, which proclaimed prominent anti-tumor effects in multiple cancers. In detail, inhibitors of *FTO* took a great part in cancer stem cell self-renewal and immune evasion by mediating the expression of immune checkpoint genes, especially *LILRB4*. In conclusion, the discovery of *FTO* inhibitors highlighted the broad potential of targeting *FTO* for cancer therapy.

FTO in Cancer Prognosis

High level of *FTO* was significantly correlated with lower survival rates in patients with advanced stage of breast cancer and patients with ER negative breast cancer.⁴⁷ In addition, high expression of *FTO* was associated with poor

prognosis and early relapse of endometrial carcinoma.⁷⁸ Overexpression of *FTO* predicted the lower survival rate in HCC patients.¹¹ High expression of *FTO* was also positively correlated with low differentiation, lymph node metastasis, high TNM stage and poor prognosis in gastric cancer patients.⁸ It was also observed in lung cancer that higher expression of *FTO* was significantly related with poor prognosis.⁵² Li et al⁵⁷ revealed that although higher mRNA level of *FTO* was associated with poor overall survival (OS), further immunohistochemistry (IHC) staining and evaluation found that lower *FTO* protein expression was associated with shorter OS in GC patients. ESCC patients with high *FTO* expression had shorter OS, despite the statistical significance was absent.²⁴ The prognostic

value of *FTO* in OSCC patients for OS is dependent on the expression of β -catenin.²¹

However, in ccRCC patients, low expression of *FTO* was significantly associated with poor survival, such as shortened OS and disease-free survival (DFS).^{62,92,93} Additionally, HCC patients with decreased *FTO* expression had shorter OS and progression-free survival (PFS).⁶⁰

Discussion

FTO was dysregulated and played a tumor-suppressive or oncogenic role in human cancers, including breast cancer, bladder cancer, cervical cancer, renal cell carcinoma, endometrial cancer, esophageal carcinoma, gastric cancer, hepatocellular carcinoma, lung cancer, leukemia and so on. Through m6A modification, *FTO* regulated cancer cell apoptosis, proliferation, viability, migration, invasion, metastasis, cell-cycle, differentiation, stem cell self-renewal, colony formation, chemo-radiotherapy resistance and so on. These effects were achieved by regulating various pathways, such as *mTOR* signaling pathway, *PI3K/AKT* and *MPAK* signal pathways. In addition, miRNAs and estrogen could modulate the expression of *FTO*. Given that *FTO* patterns in RNA transcripts play important roles in multiple cancers, researchers focused on the rational design of potent and specific *FTO* inhibitors in medicine use and several *FTO* inhibitors had been developed, which might have extensive application for cancer therapy. What is more, *FTO* had great potential for clinical application by serving as prognostic targets. However, further studies are still needed to clarify *FTO* patterns in human cancers and pave the way for research into the discovery and development of *FTO*-specific drugs.

Data Sharing Statement

All the relevant references can be searched in PubMed (<https://pubmed.ncbi.nlm.nih.gov/>).

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Funding

This work was supported by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD, JX10231802 to Jinyan Wang),

Postgraduate Research and Practice Innovation Program of Jiangsu Province (SJCX17_0387 to Jinyan Wang), the Science Foundation of Jiangsu Health vocational college (JKC201948 to Jinyan Wang), the Science and Technology Development Fund of Nanjing Medical University (NMUB2019235 to Jinyan Wang) and Jiangsu province maternal and child health association research project (ZKY201737 to Ping Qiang).

Disclosure

The authors declare that they have no competing interests.

References

- Dina C, Meyre D, Gallina S, et al. Variation in *FTO* contributes to childhood obesity and severe adult obesity. *Nat Genet.* 2007;39:724–726. doi:10.1038/ng2048
- Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science.* 2007;316:889–894. doi:10.1126/science.1141634
- Tschritter O, Preissl H, Yokoyama Y, Machicao F, Häring HU, Fritsche A. Variation in the *FTO* gene locus is associated with cerebrocortical insulin resistance in humans. *Diabetologia.* 2007;50:2602–2603. doi:10.1007/s00125-007-0839-1
- Brennan P, McKay J, Moore L, et al. Obesity and cancer: mendelian randomization approach utilizing the *FTO* genotype. *Int J Epidemiol.* 2009;38(4):971–975. doi:10.1093/ije/dyp162
- Kaklamani V, Yi N, Sadim M, et al. The role of the fat mass and obesity associated gene (*FTO*) in breast cancer risk. *BMC Med Genet.* 2011;12:52. doi:10.1186/1471-2350-12-52
- da Cunha PA, de Carlos Back LK, Sereia AF, et al. Interaction between obesity-related genes, *FTO* and *MC4R*, associated to an increase of breast cancer risk. *Mol Biol Rep.* 2013;40:6657–6664. doi:10.1007/s11033-013-2780-3
- Yamaji T, Iwasaki M, Sawada N, Shimazu T. Fat mass and obesity-associated gene polymorphisms, pre-diagnostic plasma adipokine levels and the risk of colorectal cancer: the Japan Public Health Center-based Prospective Study. 2020;15:e0229005.
- Xu D, Shao W, Jiang Y, Wang X, Liu Y, Liu X. *FTO* expression is associated with the occurrence of gastric cancer and prognosis. *Oncol Rep.* 2017;38:2285–2292. doi:10.3892/or.2017.5904
- Lin Y, Ueda J, Yagyu K, et al. Association between variations in the fat mass and obesity-associated gene and pancreatic cancer risk: a case-control study in Japan. *BMC Cancer.* 2013;13:337. doi:10.1186/1471-2407-13-337
- Lewis SJ, Murad A, Chen L, et al. Associations between an obesity related genetic variant (*FTO* rs9939609) and prostate cancer risk. *PLoS One.* 2010;5:e13485. doi:10.1371/journal.pone.0013485
- Li J, Zhu L, Shi Y, Liu J, Lin L, Chen X. m6A demethylase *FTO* promotes hepatocellular carcinoma tumorigenesis via mediating PKM2 demethylation. *Am J Transl Res.* 2019;11:6084–6092.
- Zhe H, Li J, Han Y, et al. The m6A demethylase *FTO* promotes the growth of lung cancer cells by regulating the m6A level of *USP7* mRNA. *Mol Carcinog.* 2019;512:479–485.
- Boccalletto P, Machnicka MA, Purta E, et al. MODOMICS: a database of RNA modification pathways. 2017 update. *Nucleic Acids Res.* 2018;46:D303–d7. doi:10.1093/nar/gkx1030
- Desrosiers R, Friderici K, Rottman F. Identification of methylated nucleosides in messenger RNA from Novikoff hepatoma cells. *Proc Natl Acad Sci U S A.* 1974;71:3971–3975. doi:10.1073/pnas.71.10.3971

15. Yue Y, Liu J, He C. RNA N6-methyladenosine methylation in post-transcriptional gene expression regulation. *Genes Dev.* 2015;29:1343–1355. doi:10.1101/gad.262766.115
16. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, et al. Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. *Nature.* 2012;485:201–206. doi:10.1038/nature11112
17. Maity A, Das B. N6-methyladenosine modification in mRNA: machinery, function and implications for health and diseases. 2016;283:1607–1630.
18. Sun T, Wu R, Ming L. The role of m6A RNA methylation in cancer. *Biomed Pharmacother.* 2019;112:108613. doi:10.1016/j.biopha.2019.108613
19. Huang Y, Su R, Sheng Y, et al. Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia. *Cancer Cell.* 2019;35:677–91.e10. doi:10.1016/j.ccell.2019.03.006
20. Shen XP, Ling X, Lu H, Zhou CX, Zhang JK, Yu Q. Low expression of microRNA-1266 promotes colorectal cancer progression via targeting FTO. *Eur Rev Med Pharmacol Sci.* 2018;22:8220–8226.
21. Zhou S, Bai ZL, Xia D, Zhao ZJ, Zhao R, Wang YY. FTO regulates the chemo-radiotherapy resistance of cervical squamous cell carcinoma (CSCC) by targeting β -catenin through mRNA demethylation. 2018;57:590–597.
22. Tang X, Liu S, Chen D, Zhao Z, Zhou J. The role of the fat mass and obesity-associated protein in the proliferation of pancreatic cancer cells. *Oncol Lett.* 2019;17:2473–2478.
23. Doaei S, Gholamalizadeh M, Akbari ME, et al. Dietary carbohydrate promotes cell survival in cancer via the up-regulation of fat mass and obesity-associated gene expression level. *BJU Int.* 2019;26:8–17.
24. Liu S, Huang M, Chen Z, et al. FTO promotes cell proliferation and migration in esophageal squamous cell carcinoma through up-regulation of MMP13. *Exp Cell Res.* 2020;389:111894.
25. Zhang Z, Zhou D, Lai Y, et al. Estrogen induces endometrial cancer cell proliferation and invasion by regulating the fat mass and obesity-associated gene via PI3K/AKT and MAPK signaling pathways. *Cancer Lett.* 2012;319:89–97. doi:10.1016/j.canlet.2011.12.033
26. Su R, Dong L, Li Y, et al. Targeting FTO suppresses cancer stem cell maintenance and immune evasion. *Cancer Cell.* 2020;38(1):79–96. e11. doi:10.1016/j.ccell.2020.04.017
27. Huang H, Wang Y, Kandpal M. FTO-dependent N6-methyladenosine modifications inhibit ovarian cancer stem cell self-renewal by blocking cAMP signaling. 2020.
28. Gaudet MM, Yang HP, Bosquet JG, et al. No association between FTO or HHEX and endometrial cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2010;19(8):2106–2109. doi:10.1158/1055-9965.EPI-10-0515
29. Hernández-Caballero ME, Sierra-Ramírez JA. Single nucleotide polymorphisms of the FTO gene and cancer risk: an overview. *Mol Biol Rep.* 2015;42(3):699–704. doi:10.1007/s11033-014-3817-y
30. Salgado-Montilla JL, Rodríguez-Cabán JL, Sánchez-García J, Sánchez-Ortiz R, Irizarry-Ramírez M. Impact of FTO SNPs rs9930506 and rs9939609 in prostate cancer severity in a cohort of puerto rican men. *Arch Cancer Res.* 2017;5.
31. Gholamalizadeh M, Jarrahi AM, Akbari ME, et al. Association between FTO gene polymorphisms and breast cancer: the role of estrogen. *Expert Rev Endocrinol Metab.* 2020;15:115–121. doi:10.1080/17446651.2020.1730176
32. Zeng X, Ban Z, Cao J, et al. Association of FTO mutations with risk and survival of breast cancer in a Chinese population. *Dis Markers.* 2015;2015:101032. doi:10.1155/2015/101032
33. Kang Y, Liu F, Liu Y. Is FTO gene variant related to cancer risk independently of adiposity? An updated meta-analysis of 129,467 cases and 290,633 controls. *Oncotarget.* 2017;8(31):50987–50996. doi:10.18632/oncotarget.16446
34. Chen J, Davuluri RV, Matei D, et al. Specific TaqMan allelic discrimination assay for rs1477196 and rs9939609 single nucleotide polymorphisms of FTO gene demonstrated that there is no association between these SNPs and risk of breast cancer in Iranian women. *Cancer Res.* 2015;4:136.
35. Tsugane S, Jafari Nedooshan J, Kargar S, et al. Lack of association of the fat mass and obesity associated (FTO) Gene rs9939609 polymorphism with breast cancer risk: a systematic review and meta-analysis based on case-control studies. *PLoS One.* 2017;18:1031–1037.
36. Kusinska R, Górniak P, Pastorczak A, et al. Influence of genomic variation in FTO at 16q12.2, MC4R at 18q22 and NRXN3 at 14q31 genes on breast cancer risk. *Mol Biol Rep.* 2012;39(3):2915–2919. doi:10.1007/s11033-011-1053-2
37. Zhu RM, Lin W, Zhang W, et al. Modification effects of genetic polymorphisms in FTO, IL-6, and HSPD1 on the associations of diabetes with breast cancer risk and survival. *J Cancer Res Clin Oncol.* 2017;12:e0178850.
38. Yang B, Thrift AP, Figueiredo JC, et al. Common variants in the obesity-associated genes FTO and MC4R are not associated with risk of colorectal cancer. *Cancer Epidemiol.* 2016;44:1–4. doi:10.1016/j.canep.2016.07.003
39. Huang X, Zhao J, Yang M, Li M, Zheng J. Association between FTO gene polymorphism (rs9939609 T/A) and cancer risk: a meta-analysis. *Eur J Cancer Care (Engl).* 2017;26.
40. Li G, Chen Q, Wang L, Ke D, Yuan Z. Association between FTO gene polymorphism and cancer risk: evidence from 16,277 cases and 31,153 controls. *Tumour Biol.* 2012;33(4):1237–1243. doi:10.1007/s13277-012-0372-9
41. Lurie G, Gaudet MM, Spurdle AB, et al. The obesity-associated polymorphisms FTO rs9939609 and MC4R rs17782313 and endometrial cancer risk in non-Hispanic white women. *PLoS One.* 2011;6(2):e16756. doi:10.1371/journal.pone.0016756
42. Sigurdson AJ, Brenner AV, Roach JA, et al. Selected single-nucleotide polymorphisms in FOXE1, SERPINA5, FTO, EVPL, TICAM1 and SCARB1 are associated with papillary and follicular thyroid cancer risk: replication study in a German population. *Carcinogenesis.* 2016;37(7):677–684. doi:10.1093/carcin/bgw047
43. Deng X, Su R, Stanford S, Chen J. Critical enzymatic functions of FTO in obesity and cancer. *Front Endocrinol (Lausanne).* 2018;9:396. doi:10.3389/fendo.2018.00396
44. Tan A, Dang Y, Chen G, Mo Z. Overexpression of the fat mass and obesity associated gene (FTO) in breast cancer and its clinical implications. *Int J Clin Exp Pathol.* 2015;8:13405–13410.
45. Singh B, Kinne HE, Milligan RD, Washburn LJ, Olsen M, Lucci A. Important role of FTO in the survival of rare panresistant triple-negative inflammatory breast cancer cells facing a severe metabolic challenge. *PLoS One.* 2016;11(7):e0159072. doi:10.1371/journal.pone.0159072
46. Akbari ME, Gholamalizadeh M, Doaei S, Mirsafa F. FTO gene affects obesity and breast cancer through similar mechanisms: a new insight into the molecular therapeutic targets. *Nutr Cancer.* 2018;70(1):30–36. doi:10.1080/01635581.2018.1397709
47. Niu Y, Lin Z, Wan A, et al. RNA N6-methyladenosine demethylase FTO promotes breast tumor progression through inhibiting BNP13. 2019;18:46.
48. Liu Y, Wang R, Zhang L, Li J, Lou K, Shi B. The lipid metabolism gene FTO influences breast cancer cell energy metabolism via the PI3K/AKT signaling pathway. *Oncol Lett.* 2017;13:4685–4690.
49. Bojagora A, Saridakis V. USP7 manipulation by viral proteins. *Virus Res.* 2020;286:198076. doi:10.1016/j.virusres.2020.198076
50. Li P, Liu HM. Recent advances in the development of ubiquitin-specific-processing protease 7 (USP7) inhibitors. *Eur J Med Chem.* 2020;191:112107. doi:10.1016/j.ejmech.2020.112107

51. Zhou J, Wang J, Chen C, Yuan H, Wen X, Sun H. USP7: target validation and drug discovery for cancer therapy. *Med Chem*. 2018;14:3–18.
52. Liu J, Ren D, Du Z, Wang H, Zhang H, Jin Y. m 6 A demethylase FTO facilitates tumor progression in lung squamous cell carcinoma by regulating MZF1 expression. *Biochem Biophys Res Commun*. 2018;502(4):456–464. doi:10.1016/j.bbrc.2018.05.175
53. Tsai LH, Wu JY, Cheng YW, et al. The MZF1/c-MYC axis mediates lung adenocarcinoma progression caused by wild-type Ikb1 loss. *Oncogene*. 2015;34:1641–1649.
54. Qu Y, Dou P, Hu M, Xu J, Xia W, Sun H. circRNA-CER mediates malignant progression of breast cancer through targeting the miR-136/MMP13 axis. *Mol Med Rep*. 2019;19:3314–3320.
55. Zhang H, Yang Q, Lian X, Jiang P, Cui J. Hypoxia-inducible Factor-1 α (HIF-1 α) promotes hypoxia-induced invasion and metastasis in ovarian cancer by targeting matrix metalloproteinase 13 (MMP13). *Med Sci Monit*. 2019;25:7202–7208. doi:10.12659/MSM.916886
56. Zhang R, Zhu Z, Shen W, Li X, Dhoomun DK, Tian Y. Golgi Membrane Protein 1 (GOLM1) promotes growth and metastasis of breast cancer cells via regulating matrix metalloproteinase-13 (MMP13). *Med Sci Monit*. 2019;25:847–855. doi:10.12659/MSM.911667
57. Li Y, Zheng D, Wang F, Xu Y, Yu H, Zhang H. Expression of demethylase genes, FTO and ALKBH1, is associated with prognosis of gastric cancer. *Mol Cancer*. 2019;64:1503–1513.
58. Zahra K, Dey T, Ashish MSP, Pandey U. Pyruvate Kinase M2 and cancer: the role of PKM2 in promoting tumorigenesis. *Front Oncol*. 2020;10:159. doi:10.3389/fonc.2020.00159
59. Zhang Z, Deng X, Liu Y, Liu Y. PKM2, function and expression and regulation. 2019;9:52.
60. Zhao Y, You S, Yu YQ, et al. Decreased nuclear expression of FTO in human primary hepatocellular carcinoma is associated with poor prognosis. *Int J Clin Exp Pathol*. 2019;12:3376–3383.
61. Wen L, Pan X, Yu Y, Yang B. Down-regulation of FTO promotes proliferation and migration, and protects bladder cancer cells from cisplatin-induced cytotoxicity. *BMC Urol*. 2020;20:39. doi:10.1186/s12894-020-00612-7
62. Zhuang C, Zhuang C, Luo X, et al. N6-methyladenosine demethylase FTO suppresses clear cell renal cell carcinoma through a novel FTO-PGC-1 α signalling axis. *J Cell Mol Med*. 2019;23:2163–2173. doi:10.1111/jcmm.14128
63. Panajatovic M, Singh F, Duthaler U, Krähenbühl S, Bouitbir J. Role of PGC-1-alpha-associated mitochondrial biogenesis in statin-induced myotoxicity. *Eur Cardiol*. 2020;15:e35. doi:10.15420/eur.2020.15.1.PO12
64. Safdar A, Little JP, Stokl AJ, Hettinga BP, Akhtar M, Tarnopolsky MA. Exercise increases mitochondrial PGC-1 α content and promotes nuclear-mitochondrial cross-talk to coordinate mitochondrial biogenesis. *J Biol Chem*. 2018;293:4953. doi:10.1074/jbc.EC118.002682
65. Jones AW, Yao Z, Vicencio JM, Karkucinska-Wieckowska A, Szabadkai G. PGC-1 family coactivators and cell fate: roles in cancer, neurodegeneration, cardiovascular disease and retrograde mitochondria-nucleus signalling. *Mitochondrion*. 2012;12:86–99. doi:10.1016/j.mito.2011.09.009
66. Zhang S, Liu X, Liu J, Guo H, Xu H, Zhang G. PGC-1 alpha interacts with microRNA-217 to functionally regulate breast cancer cell proliferation. *Biomed Pharmacother*. 2017;85:541–548. doi:10.1016/j.biopha.2016.11.062
67. Zou D, Dong L, Li C, Yin Z, Rao S, Zhou Q. The m(6)A eraser FTO facilitates proliferation and migration of human cervical cancer cells. *Cancer Cell Int*. 2019;19:321. doi:10.1186/s12935-019-1045-1
68. Tian W, Teng F, Gao J, et al. Estrogen and insulin synergistically promote endometrial cancer progression via crosstalk between their receptor signaling pathways. *Horm Cancer*. 2019;16:55–70.
69. Yang B, Chen R, Liang X, et al. Estrogen enhances endometrial cancer cells proliferation by upregulation of prohibitin. *J Cancer*. 2019;10:1616–1621. doi:10.7150/jca.28218
70. Rodriguez AC, Blanchard Z, Maurer KA, Gertz J. Estrogen signaling in endometrial cancer: a key oncogenic pathway with several open questions. 2019;10:51–63.
71. Noorolyai S, Shajari N, Baghban E, Sadreddini S, Baradaran B. The relation between PI3K/AKT signalling pathway and cancer. *Gene*. 2019;698:120–128. doi:10.1016/j.gene.2019.02.076
72. Roncolato F, Lindemann K, Willson ML, Martyn J, Mileskin L. PI3K/AKT/mTOR inhibitors for advanced or recurrent endometrial cancer. *Cochrane Database Syst Rev*. 2019;10:CD012160.
73. Wanigasooriya K, Tyler R, Barros-Silva JD, Sinha Y, Ismail T, Beggs AD. Radiosensitising cancer using Phosphatidylinositol-3-Kinase (PI3K), Protein Kinase B (AKT) or mammalian target of rapamycin (mTOR) Inhibitors. *Cancers (Basel)*. 2020;12.
74. Braicu C, Buse M, Busuioc C, et al. A comprehensive review on MAPK: a promising therapeutic target in cancer. *Int J Mol Sci*. 2019;11.
75. Dreas A, Mikulski M, Milik M, Fabritius CH, Brzózka K, Rzymiski T. Mitogen-activated Protein Kinase (MAPK) interacting Kinases 1 and 2 (MNK1 and MNK2) as targets for cancer therapy: recent progress in the development of MNK inhibitors. *Cancers (Basel)*. 2017; 24:3025–3053.
76. Lee S, Rauch J. Targeting MAPK signaling in cancer: mechanisms of drug resistance and sensitivity. 2020;21.
77. Stramucci L, Pranteda A, Bossi G. *Insights of Crosstalk Between P53 Protein and the MKK3/MKK6/P38 MAPK Signaling Pathway in Cancer*. 2018:10.
78. Zhu Y, Shen J, Gao L, Feng Y. Estrogen promotes fat mass and obesity-associated protein nuclear localization and enhances endometrial cancer cell proliferation via the mTOR signaling pathway. *Oncol Rep*. 2016;35:2391–2397. doi:10.3892/or.2016.4613
79. Mirza-Aghazadeh-Attari M, Ekrami EM, Aghdas SAM, et al. Targeting PI3K/Akt/mTOR signaling pathway by polyphenols: implication for cancer therapy. *Cell Biosci*. 2020;255:117481.
80. Zou Z, Tao T, Li H, Zhu X. mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. 2020;10:31.
81. Li Z, Weng H, Su R, et al. FTO plays an oncogenic role in acute myeloid leukemia as a N(6)-Methyladenosine RNA Demethylase. *Cancer Cell*. 2017;31:127–141. doi:10.1016/j.ccell.2016.11.017
82. Glasow A, Prodromou N, Xu K, von Lindern M, Zelent A. Retinoids and myelomonocytic growth factors cooperatively activate RARA and induce human myeloid leukemia cell differentiation via MAP kinase pathways. *Blood*. 2005;105:341–349. doi:10.1182/blood-2004-03-1074
83. Guibal FC, Moog-Lutz C, Smolewski P, et al. ASB-2 inhibits growth and promotes commitment in myeloid leukemia cells. *J Biol Chem*. 2002;277:218–224. doi:10.1074/jbc.M108476200
84. Kohroki J, Fujita S, Itoh N, et al. ATRA-regulated Asb-2 gene induced in differentiation of HL-60 leukemia cells. *FEBS Lett*. 2001;505:223–228. doi:10.1016/S0014-5793(01)02829-0
85. Sakamoto K, Imamura T, Yano M, et al. Sensitivity of MLL-rearranged AML cells to all-trans retinoic acid is associated with the level of H3K4me2 in the RAR α promoter region. *Blood Cancer J*. 2014;4:e205. doi:10.1038/bcj.2014.25
86. Wang J, Muntean AG, Hess JL. ECSASB2 mediates MLL degradation during hematopoietic differentiation. *Blood*. 2012;119:1151–1161. doi:10.1182/blood-2011-06-362079
87. Su R, Dong L, Li C, et al. R-2HG exhibits anti-tumor activity by targeting FTO/m(6)A/MYC/CEBPA signaling. *Cell*. 2018;172:90–105.e23. doi:10.1016/j.cell.2017.11.031
88. D'Altri T, Wilhelmson AS, Schuster MB, et al. The ASXL1-G643W variant accelerates the development of CEBPA mutant acute myeloid leukemia. *Haematologica*;2020. haematol.2019.235150. doi:10.3324/haematol.2019.235150

89. Maxson JE, Schmidt L, Heyes E, Scheiblecker L, Eder T. CEBPA-mutated leukemia is sensitive to genetic and pharmacological targeting of the MLL1 complex. *Nat Commun.* 2019;33:1608–1619.
90. Braun TP, Okhovat M, Coblenz C, Carratt SA. Myeloid lineage enhancers drive oncogene synergy in CEBPA/CSF3R mutant acute myeloid leukemia. 2019;10:5455.
91. Van Der Werf I, Jamieson C. The Yin and Yang of RNA methylation: an imbalance of erasers enhances sensitivity to FTO demethylase small-molecule targeting in leukemia stem cells. *Cancer Cell.* 2019;35:540–541. doi:10.1016/j.ccell.2019.03.011
92. Wen L, Yu Y, Lv H, He Y, Yang B. FTO mRNA expression in the lower quartile is associated with bad prognosis in clear cell renal cell carcinoma based on TCGA data mining. *Ann Diagn Pathol.* 2019;38:1–5. doi:10.1016/j.anndiagpath.2018.10.009
93. Strick A, von Hagen F, Gundert L, et al. The N(6)-methyladenosine (m(6)A) erasers alkylation repair homologue 5 (ALKBH5) and fat mass and obesity-associated protein (FTO) are prognostic biomarkers in patients with clear cell renal carcinoma. 2020;125:617–24

OncoTargets and Therapy

Dovepress

Publish your work in this journal

OncoTargets and Therapy is an international, peer-reviewed, open access journal focusing on the pathological basis of all cancers, potential targets for therapy and treatment protocols employed to improve the management of cancer patients. The journal also focuses on the impact of management programs and new therapeutic

agents and protocols on patient perspectives such as quality of life, adherence and satisfaction. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/oncotargets-and-therapy-journal>