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REVIEW

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

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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 cancer[10] 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 al[16] 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.

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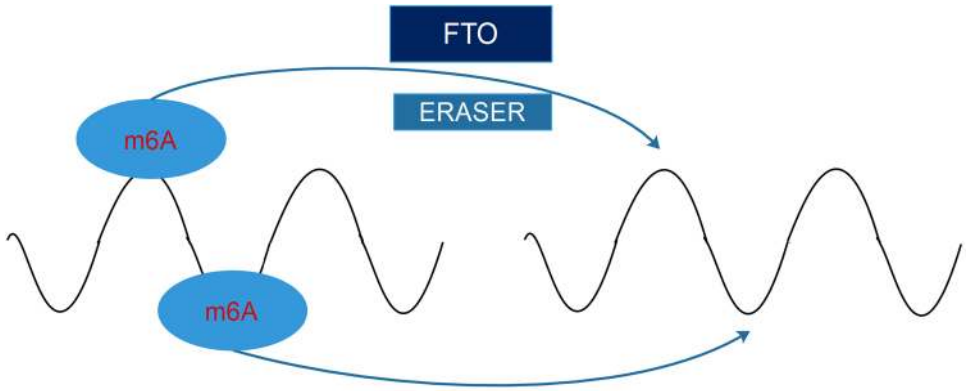

Figure 1 *FTO*, belonged to demethylase, termed as "erasers" and functioned to reverse the methylation.

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 maintenance[26] 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 al[28] 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 al[10] 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 al[30] 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 al[5] 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 al[38] 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.

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.

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 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 Up-regulated / Up-regulated	Oncogene Oncogene Oncogene Oncogene	Survival, colony formation Cell energy metabolism Proliferation Proliferation, colony formation, metastasis	*IRX3* *PI3K/AKT* *PI3K/AKT* *BNIP3*	45,46 48 31 47
Cervical Cancer	Up-regulated Up-regulated	Oncogene Oncogene	Chemo-radiotherapy resistance Proliferation, migration	*β-catenin, ERCC1* *E2F1, Myc*	21 67
Clear Cell Renal Cell Carcinoma	Down-regulated	Tumor suppressor	Cell growth, apoptosis, mitochondrial biogenesis, oxidative phosphorylation, oxidative stress	*PGC-1α*	62
Colorectal Cancer	/	Oncogene	Proliferation	/	20
Endometrial Carcinoma	Up-regulated Up-regulated	Oncogene Oncogene	Proliferation, invasion Proliferation	*PI3K/AKT* *MPAK* *mTOR*	25 78
Esophageal Squamous Cell Carcinoma	Up-regulated	Oncogene	Cell growth, migration, tumorigenicity	*MMP13*	24
Gastric Cancer	Up-regulated Down-regulated	Oncogene Tumor suppressor	Proliferation, migration, invasion /	/ /	8 57
Hepatocellular Carcinoma	Up-regulated Down-regulated	Oncogene Tumor suppressor	Proliferation, tumor growth, cell cycle /	*PKM2* /	11 60
Lung Cancer	Up-regulated Up-regulated	Oncogene Oncogene	Proliferation, colony formation, tumor growth Proliferation, invasion, apoptosis	*USP7* *MZF1*	12 52
Ovarian Cancer	Down-regulated	Tumor suppressor	Stemness	*cAMP*	27
Pancreatic Cancer	Up-regulated	Oncogene	Proliferation apoptosis	*cMYC*	22
Leukemia	Up-regulated Up-regulated	Oncogene Oncogene	Proliferation, viability, cell-cycle arrest, apoptosis Differentiation	*MYC/CEBPA* *ASB2,RARA*	87 81

FTO in Breast Cancer

In 2015, Tan et al[44] 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 al[47] 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 al[48] 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 al[31] 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

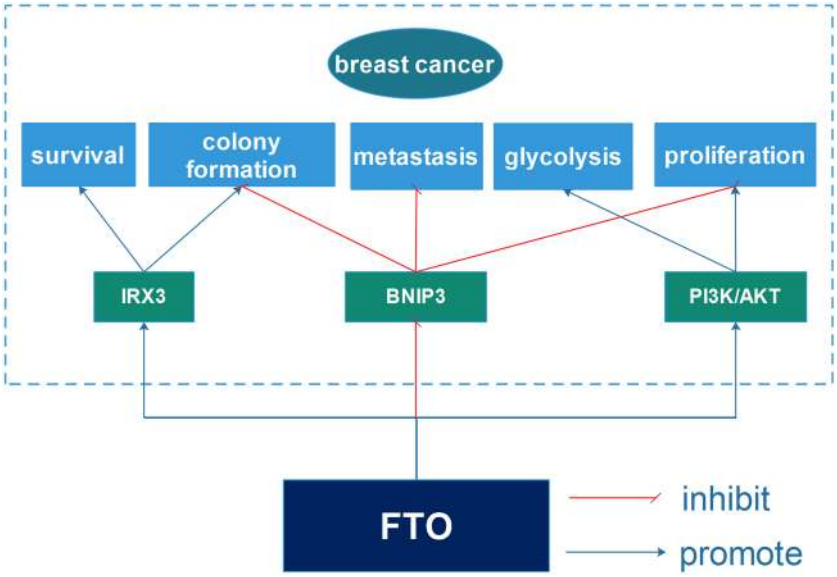

Figure 2 The specific mechanisms of *FTO* in breast cancer. *FTO* greatly participated in the survival, colony formation, metastasis, glycolysis and proliferation of breast cancer through targeting *IRX3*, *BNIP3* and *PI3K/AKT*.

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.

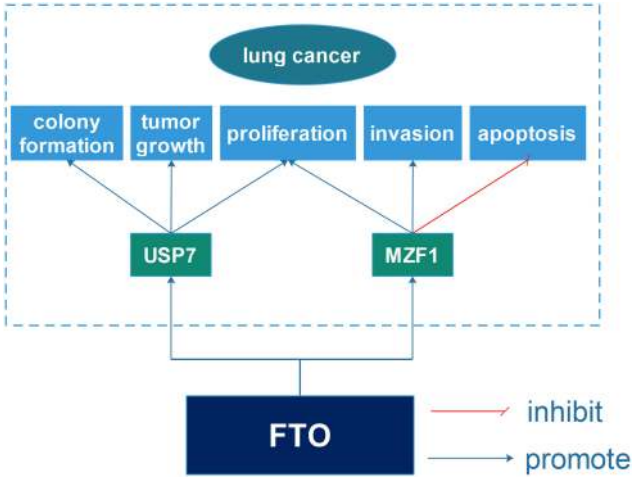

Figure 3 The specific mechanisms of *FTO* in lung cancer. *FTO* obviously promoted lung cancer cell colony formation, proliferation, invasion and tumor growth and inhibited apoptosis via promoting the expression of *USP7* and *MZF1*.

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 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 -al[57] 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 al[60] 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* severed to modulate mitochondrial activity, oxidative phosphorylation and cancer cell growth and apoptosis through demethylating the *PPARg 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

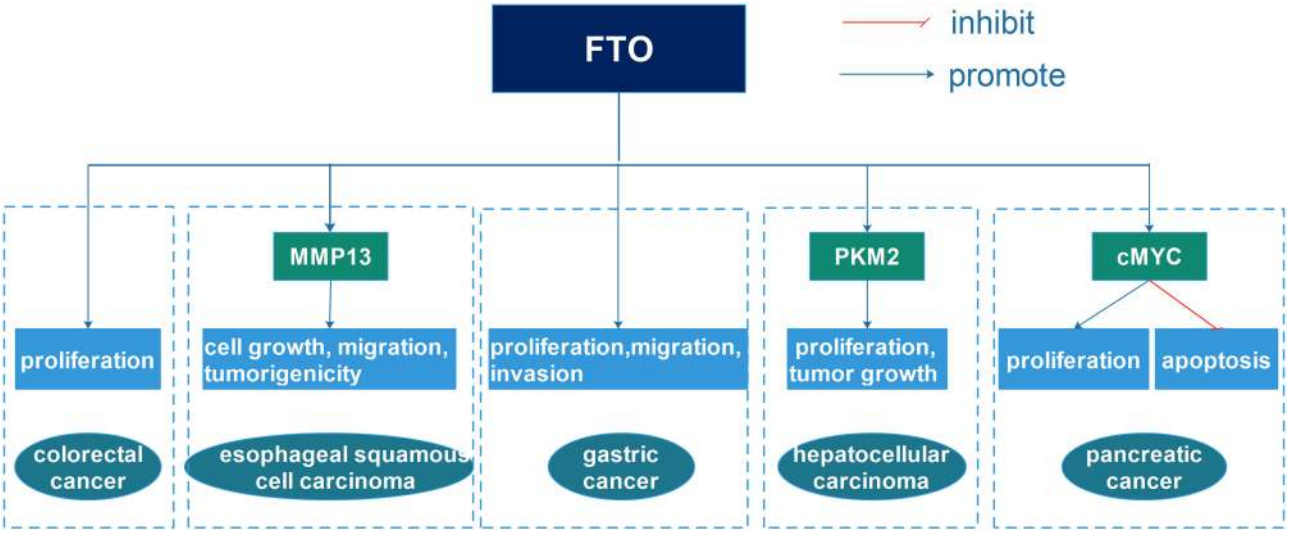

Figure 4 The detailed mechanisms of *FTO* in gastrointestinal cancer. *FTO* promoted colorectal and gastric cancer cell proliferation, migration and tumor growth. *FTO* also advanced cancer cell growth, migration and tumorigenicity through up-regulating *MMP13* in esophageal squamous cell carcinoma, 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*.

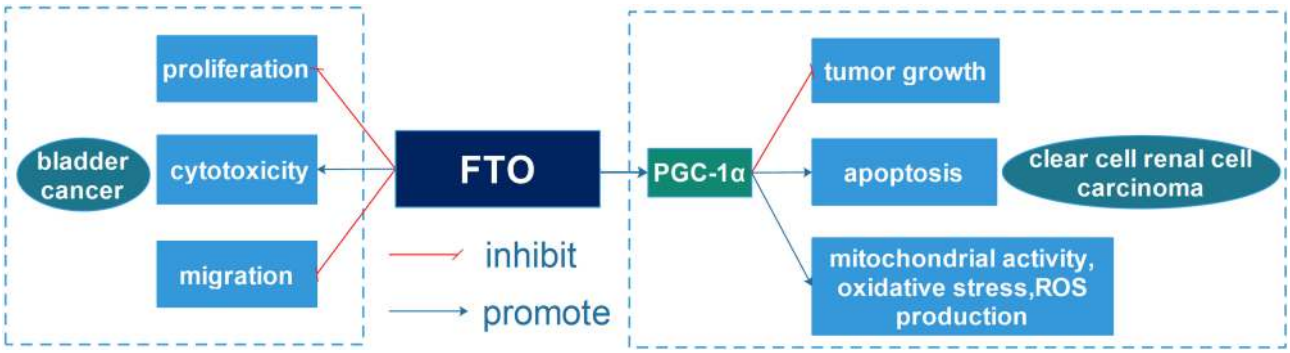

Figure 5 The specific mechanisms of *FTO* in urological cancer. *FTO* advanced bladder cancer cell proliferation and migration and suppressed cytotoxicity. Additionally, *FTO* greatly participated in cancer cell apoptosis, mitochondrial activity, oxidative stress, ROS production and tumor growth through 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 al[25] 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 al[78] 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

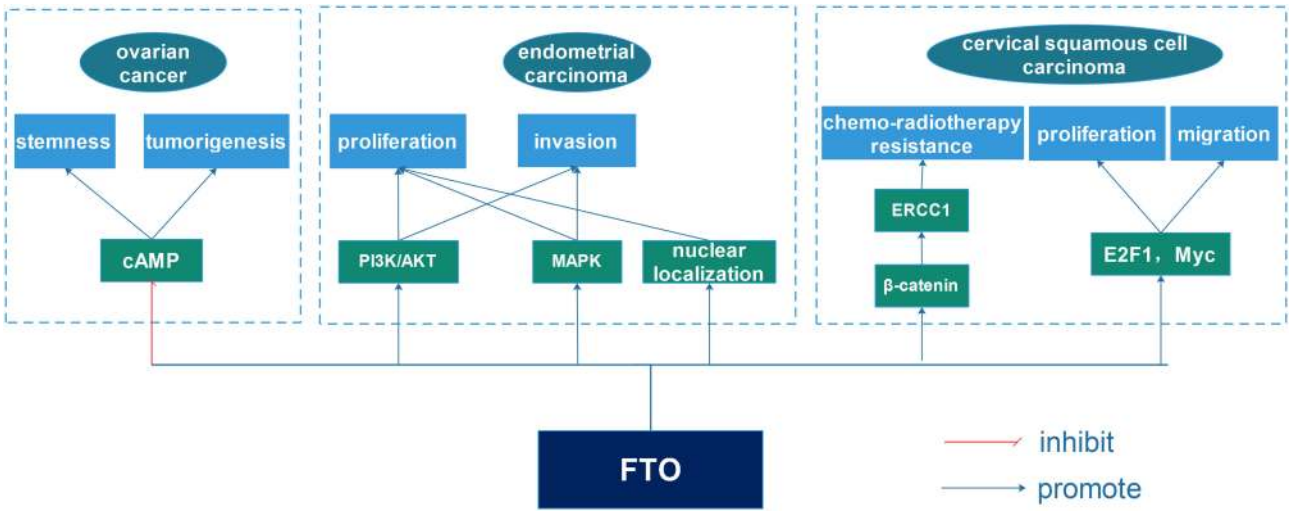

Figure 6 The specific mechanisms of *FTO* in gynecological cancer. *FTO* greatly influenced ovarian cancer cell stemness and tumorigenesis via suppressing the expression of *cAMP*. *FTO* also affected endometrial carcinoma cell proliferation and invasion by modulating *PI3K/AKT* and *MAPK* signaling 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*.

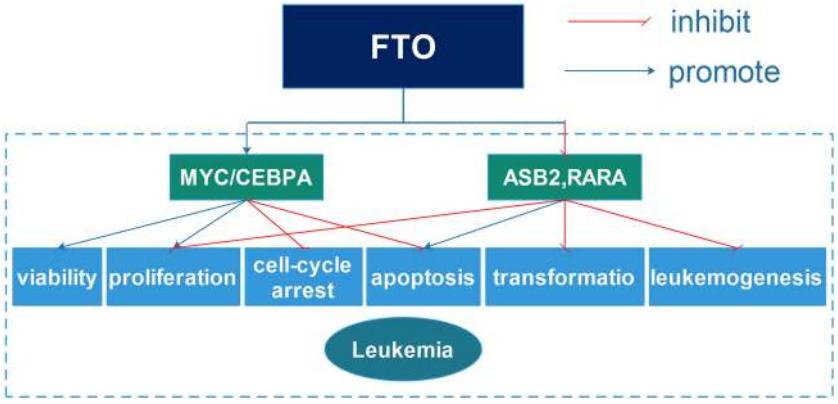

Figure 7 The detailed mechanisms of *FTO* in leukemia. *FTO* up-regulated *MYC/CEBPA* and down-regulated*ASB2*and *RARA*, thus promoting leukemia cell viability, proliferation, transformation and leukemogenesis and inhibiting cell-cycle arrest and apoptosis.

roles of *FTO* in kinds of cancers, Su et al[26] 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 al[57] 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.

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Disclosure

The authors declare that they have no competing interests.

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