Journal of Cancer Research and Clinical Oncology (2019) 145:19–29
https://doi.org/10.1007/s00432-018-2796-0

REVIEW – CANCER RESEARCH

Novel positioning from obesity to cancer: FTO, an m^{6}A RNA demethylase, regulates tumour progression

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Received: 23 June 2018 / Accepted: 13 November 2018 / Published online: 21 November 2018

Abstract

Purpose The fat mass- and obesity-associated (FTO) gene on chromosome 16q12.2 shows an intimate association with obesity and body mass index. Recently, research into the FTO gene and its expression product has attracted widespread interest due to the identification of FTO as an N6-methyladenosine (m6A) demethylase. FTO primarily regulates the m6A levels of downstream targets via their 3′ untranslated regions. FTO not only plays a critical role in obesity-related diseases but also is involved in the occurrence, development and prognosis of many types of cancer, such as acute myeloid leukaemia, glioblastoma and breast cancer. Currently, studies indicate that FTO is a crucial component of m6A modification, it regulates cancer stem cell function, and promotes the growth, self-renewal and metastasis of cancer cells. In this review, we summarized and analysed the data regarding the structural features and biological functions of FTO as well as its association with different cancers and possible molecular mechanisms.

Methods We systematically reviewed the related literatures regarding FTO and its demethylation activity in many pathologic and physiological processes, especially in cancer-related diseases based on PubMed databases in this article.

Results Mounting evidence indicated that FTO plays a critical role in occurrence, progression and treatment of various cancers, even acting as a cancer oncogene in acute myeloid leukaemia, research on which is no longer restricted to metabolic diseases such as obesity and diabetes.

Conclusion Considering FTO's critical role in many diseases, FTO may become a new promising target for the diagnosis and treatment of various diseases in the near future, especially for specific types of cancers, such as acute myeloid leukaemia, glioblastoma and breast cancer.

Keywords FTO · M^{6}A RNA demethylase · Tumourigenesis · Oncogene · Proliferation · Chemo-radiotherapy resistance

Abbreviations

FTO	Fat mass and obesity-associated
BMI	Body mass index
T2DM	Type 2 diabetes mellitus
SNPs	Single-nucleotide polymorphisms
m^{6}A	*N*^{6}-methyladenosine
GWAS	Genome-wide association studies
XPO2	Exportin 2
UTRs	Untranslated regions
2-OG	2-oxoglutarate
3-meT	3-methylthymidine
AML	Acute myeloid leukaemia
MLL	Mixed lineage leukaemia
3-meU	3-methyluracil
CSC	Cancer stem cell
DNMT	DNA methyltransferases
IRX3	Iroquois-related homeobox 3
circRNAs	Circular RNAs
mRNAs	Messenger RNAs
lncRNAs	Long non-coding RNAs
METTL14	Methyltransferase-like 14
METTL3	Methyltransferase-like 3
WTAP	Wilms' tumour 1-associating protein
ALKBH5	AlkB homologue 5
ASB2	Ankyrin-repeat SOCS box-containing protein 2
RARA	Retinoic acid receptor alpha
ATRA	All-trans-retinoic acid
R-2HG	R-2-hydroxyglutarate
IDH1/2	Isocitrate dehydrogenase ½
CEBPA	CCAAT enhancer-binding protein alpha

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GSCs	Glioblastoma stem cells
FOXM1	Forkhead box transcription factor M1
ERCC1	Excision repair cross-complementation group 1

Basic information for FTO

FTO gene discovery

In 1994, Van der Hoeven et al. (1994) first discovered a deletion, up to 1.6 Mb, on chromosome 8 in the fused-toe (Ft) mutant mouse that was created by insertional mutagenesis. A follow-up study reported that the deletion comprises three genes of unknown function (FTS, FTM and FTO) and another three genes from the Iroquois gene family (IRX3, IRX5 and IRX6) (Anselme et al. 2007). In 2007, during a study of type 2 diabetes mellitus (T2DM) in Europe, Frayling et al. (2007) found a cluster of single-nucleotide polymorphisms (SNPs) in the first intron of the FTO gene, which was associated with obesity as it affected the body mass index (BMI) in genome-wide association studies (GWAS), and the gene was later officially named the fat mass- and obesity-associated protein (FTO). The FTO gene exists only in vertebrates and marine algae, while no expression is observed in plants, fungi or invertebrate animals (Robbens et al. 2008). At present, studies have demonstrated that FTO is located in both the nucleus and cytoplasm and that a mobile fraction shuttles between both cellular compartments, possibly via a mechanism mediated by one of the Exportin 2 (XPO2) family of proteins (Gulati et al. 2014). Subsequent accumulating evidence suggested that the FTO gene was closely related to the occurrence and development of obesity (Dina et al. 2007; Scuteri et al. 2007; Zhang et al. 2010). However, the study of FTO is not limited to the obesity field. Recent research shows that this protein is likely to predispose patients to the onset and development of certain tumours, such as acute myeloid leukaemia (AML).

Structure of FTO

The FTO gene is 410.50 kb, contains 9 exons and is located on chromosome 16q12.2. This gene is widely expressed in many tissues at various development phases, especially in the brain regions (Frayling et al. 2007). As research has progressed, the understanding of the FTO gene, its expression products, its structure and its function have been further developed. Gerken et al. (2007) first showed that the FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase that catalyses the demethylation of 3-methylthymine in single-stranded DNA using Fe(II) and 2-oxoglutarate (2-OG) while producing succinate, formaldehyde and carbon dioxide. The FTO protein, consisting of an amino-terminal AlkB-like domain and a carboxy-terminal domain with a novel fold, which shows high sequence conservation, was identified as an AlkB-like DNA/RNA demethylase that has high affinities for 3-methylthymidine (3-meT) in single-stranded DNA and 3-methyluracil (3-meU) in single-stranded RNA (Gerken et al. 2007; Han et al. 2010; Sanchez-Pulido and Andrade-Navarro 2007; Jia et al. 2008a). Compared with other AlkB members, an extra loop in the FTO structure covers one side of the conserved jelly-roll motif, which allows it to specifically compete with unmethylated double-stranded DNA for binding to FTO (Han et al. 2010). The evidence suggests that this special structure plays a significant role in limiting the binding of FTO to double-stranded nucleic acids. Subsequent groundbreaking research indicated that the FTO protein has a high affinity for N^6-methyladenosine (m^6A) in messenger RNA (mRNA) and shows efficient demethylation activity (Jia et al. 2011). This FTO mRNA demethylase activity is currently gaining increased notoriety, which is drawing additional attention to its roles in various diseases.

Regulation of the FTO gene in obesity

At present, the FTO gene is generally considered a susceptibility gene that is strongly linked to obesity. In 2007, through a GWAS analysis among 490,032 autosomal single-nucleotide polymorphisms in Britons, 10 SNPs were identified (represented by rs9939609) in the FTO gene region on chromosome 16 (Frayling et al. 2007). This study found that adults carrying the rs9939609 A allele weighed approximately 1.5 kg more than adults without the allele and that the dominant homozygous allele increased the average weight by almost 3 kg, with a 1.67-fold increased odds ratio of obesity, compared to those without this risk allele (Frayling et al. 2007). Meanwhile, Dina et al. (2007) found that the FTO gene may contribute to early-onset and severe obesity in children and adults of European ancestry. In fact, the SNP sites in FTO show diverse characteristics in people from different regions, such as Africa, Spain, Australia, India, Japan and China (Chang et al. 2008; Hotta et al. 2008; Gonzalez-Sanchez et al. 2009; Fang et al. 2010; Grant et al. 2008; Ningombam et al. 2018). In general, the prevalence of the risk allele is obviously lower in Asian populations than that in European populations. Strangely, another study reported that three FTO variants (rs8050136, rs9939609, and rs9930506) seemed to be unrelated to obesity in the Chinese Han population (Li et al. 2008). The discrepancies in this study remain to be further confirmed by additional evidence.

In regard to the proposed mechanisms through which the FTO genetic polymorphisms are involved in triggering obesity, current evidence indicates that the correlation between FTO genetic polymorphisms and obesity is mostly driven by increased energy intake rather than by energy expenditure, as

the carriers of the risk allele tend to consume high-calorie diets. The FTO gene is highly expressed in the hypothalamus, which is the critical region that regulates feeding and energy expenditure, implying that it may modulate the function of the feeding centre (Frayling et al. 2007; Gerken et al. 2007; McTaggart et al. 2011). Leptin functions to stimulate metabolism and facilitate weight loss. It was proven that some FTO obesity risk alleles (rs17817449 and rs9939609) are connected with lower serum levels of the satiety-enhancing adipokine leptin (Qi et al. 2008; Benedict et al. 2014), while other researchers take an opposing view of the related evidence (Arrizabalaga et al. 2014; Do et al. 2008). Therefore, whether leptin plays a role in the effect of FTO polymorphisms on obesity has not been thoroughly elucidated to date. Moreover, a decline in exercise levels was observed to enhance the risk of obesity. Andreasen et al. (2008) found that lack of physical activity might fortify the effect of the FTO rs9939609 polymorphism on body fat accumulation. To summarize, the association between the FTO gene and obesity may depend on appetite-regulating hormones and physical activity, but the related concrete mechanism is complicated and warrants further research.

More importantly, obesity is a risk factor for certain cancers, which suggests that FTO may be an important link between obesity and tumourigenesis. Obesity is considered to be closely related to more than 10 types of cancer, including colon cancer, post-menopausal breast cancer, endometrial cancer, pancreatic cancer, and advanced-stage prostate cancer (Pischon et al. 2008). An updated meta-analysis has demonstrated that FTO rs11075995 is associated with breast cancer and that this connection depends on BMI (Kang et al. 2017). The main factors connecting obesity to cancer are classified into three functional classes, including the insulin-IGF-1 axis, sex hormones, and adipokines (such as leptin and adiponectin), which are all involved in the secretion and regulation of adipose tissue (Pischon and Nimptsch 2016). Obesity-related inflammation may increase tumour burden and promote tumour growth, development and metastasis (Deng et al. 2016). Recently, FTO was shown to affect obesity and breast cancer, possibly through similar mechanisms, by regulating the Iroquois-related homeobox 3 (IRX3) gene expression level (Akbari et al. 2018). In fact, there is no clear molecular mechanism through which FTO affects obesity-mediated tumourigenesis and tumour progression. However, FTO seems to increase the risk of some cancers by promoting obesity.

Epigenetic research on the FTO gene

Epigenetic regulation of FTO gene expression

In recent years, research on the role of epigenetic regulation in various biological functions and in the pathogenesis of diseases has gained extensive attention. Epigenetic mechanisms, including DNA methylation, play critical roles in the regulation of gene expression. In mammals, more than 70% of the CpG (5′-C-phosphate-G-3′) cytosine residues in promoter regions are methylated (Jabbari and Bernardi 2004; Saxonov et al. 2006). Generally, CpG islands are hypomethylated in normal cells. It has been demonstrated that SNPs in intron 1 of FTO are associated with increased levels of FTO expression that affect the primary transcript levels, at least in blood cells and skin fibroblasts (Berulava and Horsthemke 2010). A number of studies have found that variations in DNA methylation at clusters of CpG methylation sites correlate with the susceptibility to T2DM. Toperoff et al. (2012, 2015) demonstrated that a CpG site in the first intron of the FTO gene exhibited small but significant hypomethylation in T2DM patients compared to controls; the same results were also found in peripheral blood leukocytes. It is notable that decreased methylation of FTO CpG11 sites correlates with increased FTO mRNA expression (Liu et al. 2016). Therefore, the data are convincing that the hypomethylation of specific CpG sites in the FTO gene promotes FTO expression (Melnik 2015) and that increased FTO expression is connected with the occurrence of some metabolic diseases and cancers. FTO expression is influenced by many factors. Previous research has demonstrated that milk functions as an epigenetic regulator by promoting the expression of FTO via transfer of exosomal miRNA-29, which downregulates the expression DNA methyltransferases (DNMT) and suppresses DNA CpG methylation (Melnik 2015). Moreover, FTO expression is regulated by essential amino acids (Gulati and Yeo 2013). In the presence of amino acids, FTO acts as a nutrient sensor that, via its demethylation activity, induces decreased activation of the mammalian target of the rapamycin complex 1 (mTORC1) signalling pathway, which is vital for the regulation of mRNA translation rates and cell growth (Yeo 2014; Gulati et al. 2013). Follow-up studies found that the role of FTO in nutrient regulation seems to be connected to its cellular localization, as it shuttles between the nucleus and cytoplasm, possibly via a mechanism mediated by XPO2 (Gulati et al. 2014). Recently, Aas et al. (2017) identified an N-terminal nuclear localization signal (NLS) and a C-terminal nuclear transport signal in FTO that participate in nucleocytoplasmic shuttling; however, this behaviour is not influenced by short-term amino acid starvation or by manipulation of autophagy. However, the mechanisms underlying FTO nucleocytoplasmic shuttling and its physiological functions remain to be further elucidated. Mechanistically, recent studies have found that FTO facilitates the activation of mTOR via increasing the mRNA level of TSC1, through which it is involved in insulin defects related to Alzheimer's disease (Li et al. 2018).

Recently, it has been proposed that FTO may be associated with the regulation of telomere length (TL), through which it

affects ageing and stress-related diseases including obesity, T2DM and certain types of cancer (Zhou et al. 2017). Shorter telomeres may be connected to increased BMI and adiposity (Tzanetakou et al. 2012). The 2-OG-dependent dioxygenase catalytic activity of FTO may regulate gene transcription or TL regulation by affecting nucleic acid demethylation (Zhou et al. 2017; Lister et al. 2009). However, further exploration is needed to understand the correlations between epigenetic modification by FTO and TL regulation.

The alternative splicing effects of FTO play a crucial role in mRNA processing events. The connection between FTO binding, activity and pre-mRNA processing mediated by m^{6}A have been demonstrated (Bartosovic et al. 2017). Bartosovic et al. (2017) discovered that FTO preferentially binds to pre-mRNAs and mediates m^{6}A removal in introns. Substantial changes in pre-mRNA splicing occurred after FTO knockout, exhibiting a clear prevalence of exon-skipping events that were negatively correlated with METTL3 knockdown, revealing the involvement of m^{6}A. Moreover, extensive pre-mRNA back-splicing generates numerous circular RNAs (circRNAs) rich in consensus m^{6}A motifs in the human transcriptome. This m^{6}A-driven translation requires initiation factor eIF4G2 and the m^{6}A reader YTHDF3 and is enhanced by the methyltransferase METTL3/14 and inhibited by the demethylase FTO (Yang et al. 2017). With respect to FTO degradation, related studies are lacking to a great extent. It has been previously described that ubiquitin proteasome-mediated degradation of FTO can be restrained by overexpression of protein kinase Cβ (PKCβ) (Tai et al. 2017). A recent study showed that FTO may undergo active ubiquitination on the evolutionarily conserved Lys-216 residue, routing FTO to proteasomal degradation (Zhu et al. 2018). These findings provide new insights into FTO protein turnover, but the precise mechanism requires further investigation.

Association between the FTO gene and RNA m^{6}A demethylation

Chemical modification plays a critical role in DNA, RNA and histone metabolism by introducing or removing various groups, such as methyl, phosphate and acetyl groups. These modifications enrich the functions and genetic polymorphisms of DNA to a great extent. The N^6-methyladenosine (m^{6}A) modification is one of the most common modifications in messenger RNAs (mRNAs) and long non-coding RNAs (lncRNAs) in eukaryotes, accounting for approximately 80% of all methylations, and this process is regulated by methyltransferases (METTL3, METTL14 and WTAP), RNA-binding proteins (YTH Domain) and demethylases (FTO and ALKBH5) (Zhao et al. 2017; Wei et al. 1975; Desrosiers et al. 1974; Bokar et al. 1997; Liu et al. 2014; Ping et al. 2014; Wang et al. 2014; Liao et al. 2018). m^{6}A is enriched in the 3′-untranslated regions (3′-UTRs) around the stop codon and the start codon (Schwartz et al. 2013; Meyer et al. 2012; Luo et al. 2014), and such modifications play critical roles in RNA splicing, degradation, translation and RNA–protein interactions (Wang et al. 2014, 2015; Yang et al. 2017a; Liu et al. 2015; Alarcon et al. 2015). Therefore, the m^{6}A modification is engaged in widespread fundamental processes, including cell differentiation, tissue development, stem cell differentiation, circadian cycles, and fertility (Geula et al. 2015; Wang et al. 2014a; Zheng et al. 2013; Fustin et al. 2013).

Studies related to the m^{6}A modification have stagnated for some time due to the lack of information on the relevant demethylases. However, the role of m^{6}A modification in mRNA has recently gained renewed attention due to the breakthrough discoveries of two RNA demethylases, the fat mass- and obesity-associated protein (FTO) and the alkylation repair homologue protein 5 (ALKBH5) (Jia et al. 2011; Zheng et al. 2013). These discoveries indicate that the modification is reversible and dynamic, similar to the epigenetic modifications of DNA and histone proteins. He et al. (2011) found that siRNA-mediated knockdown of FTO enhanced m^{6}A levels in mRNA and that upregulated expression of the FTO gene suppressed m^{6}A methylation, revealing the demethylation activity of FTO. These researchers subsequently found that FTO partially co-localized with nuclear speckles, providing evidence of m^{6}A in nuclear RNA as a physiological substrate of FTO (Jia et al. 2011). An earlier study found that the FTO protein targets certain m^{6}A sites in mRNA, which may be an effect of the extra loop covering one side of the conserved jelly-roll motif, as revealed through its crystal structure (Han et al. 2010). Recently, Zou et al. (2016) indicated that m^{6}A serves as a ‘conformational marker’ by inducing different conformational outcomes in RNAs that depend on sequence context, which then regulate the substrate specificity of the m^{6}A demethylases. Nevertheless, these data fail to explain the differences in the substrate selectivity between FTO and ALKBH5; thus, more convincing evidence is needed.

While both FTO and ALKBH5 belong to the AlkB family of dioxygenases, FTO has a high affinity for 3-meT in ssDNA and 3-meU in ssRNA, while ALKBH5 only catalyses the N-demethylation of m^{6}A ssRNA and ssDNA (Gerken et al. 2007; Xu et al. 2014; Jia et al. 2008). Their reaction pathways and functions appear to be different. FTO-mediated m^{6}A demethylation generates two intermediates, N^6-hydroxymethyladenosine (hm^{6}A) and N^6-formyladenosine (f^{6}A). However, ALKBH5 converts m^{6}A to hm^{6}A without any intermediate (Chen et al. 2014; Fu et al. 2013). Furthermore, the FTO gene is widely expressed in many tissues including the hypothalamus, skeletal muscle and adipose tissue (Fan et al. 2009). The expression product of ALKBH5 mainly exists in the testis and lung, where it plays critical roles in RNA metabolism and impaired fertility (Zheng et al. 2013). It is important to note that the complexities of the demethylation-regulating activities of FTO and ALKBH5 remain to be further elucidated

owing to the uncertain regulatory mechanisms of many physiological and pathological processes.

The role of FTO as a specific eraser of m^6A tags on RNA has recently been challenged (Mauer and Jaffrey 2018; Mauer et al. 2017). In 2017, Mauer et al. (2017) proposed a new viewpoint on the actual substrate of FTO. They suggested that FTO preferentially demethylates m^6Am rather than m^6A and that m^6Am tends to stabilize mRNA. Their findings showed that the demethylation activity of FTO was approximately 100 times higher towards m^6Am than towards m^6A. Moreover, the depletion of FTO showed no obvious effect on m^6A levels, while the m^6Am levels were more clearly enhanced in response to the changes in FTO levels. These results implied that the substrate of FTO was likely to be m^6Am, which starkly differed from the results of a previous study by He et al., who discovered that m^6A in mRNA serves as the substrate of FTO (Jia et al. 2011; Fu et al. 2013). Notably, the total amount of internal m^6A is at least tenfold higher than that of m^6Am in different cell lines; thus, the absolute level of m^6A demethylation may be higher (Wei et al. 1975, 2018). The latest research conducted by He et al. revealed that the distribution of FTO varies between the nucleus and cytoplasm in different cell lines and that m^6A seems to be the primary polyadenylated RNA substrate of FTO in the nucleus, while FTO preferentially targets m^6Am in the cytoplasm (Wei et al. 2018).

The involvement of demethylation by FTO in many physiological and pathological processes, including RNA modification, transcriptome regulation and translation, is being gradually revealed. Wu et al. (2017) discovered that FTO-dependent demethylation, regulated by the AMPK pathway, suppresses mRNA m^6A methylation and lipid accumulation in skeletal muscle cells. Recently, another study indicated that FTO reduced the mitochondrial content and thus increased the fat deposition in the liver by downregulating m^6A levels (Kang et al. 2018). These results provide evidence for an association between FTO and fat metabolism. In addition, as an m^6A demethylase, FTO is reported to play a key role in various cancers, such as leukaemia, breast cancer, glioblastoma, a topic that is now gaining attention (Li et al. 2017; Kaklamani et al. 2011; Cui et al. 2017) and is described below.

Briefly, m^6A modification, which is regulated by various regulatory proteins, is universal and complicated in eukaryotes. FTO, which serves as a critical component of m^6A modification, is related to the dysregulation of pathways that may underlie serious diseases, although the exact functions and concrete mechanisms remain to be explored.

Role of the FTO gene in various cancers

Although studies related to the role of the FTO gene in cancer are in the early stages, increasing evidence shows an association between FTO and the occurrence, development and prognosis of various cancers. Considering that cancer is always multifactorial, the role of FTO tends not to be the sole cause, and the recognition of the relevant pathogenesis is challenging. Through its function as an m^6A demethylase, FTO seems to be attracting more attention in the cancer field because of the growing awareness of the role of the m^6A modification in cancer. In this review, we describe the recent progress in understanding the function of FTO in cancer.

FTO SNPs related to different types of cancer

Several single-nucleotide polymorphisms (SNPs) in the FTO gene within a strong linkage disequilibrium block appear to be involved in many cancers. Considering the complexity of the samples and underlying causes, associations between FTO SNPs and the risk of some cancers are always controversial. The rs9939609, rs6499640, rs19079260, and rs8050136 variants in the FTO gene have been identified as being associated with endometrial cancer risk, and rs9939609 is also related to susceptibility to pancreatic cancer (Delahanty et al. 2011; Huang et al. 2017; Lurie et al. 2011). The results of two studies showed no significant association between FTO rs9939609 and the risk of prostate cancer (Salgado-Montilla et al. 2017; Lewis et al. 2010). Interestingly, it has been demonstrated that an inverse association between diabetes and prostate cancer exists (Jian Gang et al. 2015; Kasper and Giovannucci 2006) and that FTO was one of the susceptibility markers of this connection; however, the relevant mechanism remains unclear (Machiela et al. 2012). The role of FTO in breast cancer has been described by many studies. It is generally acknowledged that obesity increases the risk of breast cancer, which is associated with poorer prognosis, greater tumour size, faster metastasis, and higher malignancy (Trentham-Dietz et al. 1997; Renehan et al. 2008; Hernandez-Caballero and Sierra-Ramirez 2015; Calle and Kaaks 2004). Compared with adjacent breast tissues, FTO expression is highly expressed in breast cancer tissues, especially in those that are hormone receptor (HR)-negative and show HER2 amplification (Tan et al. 2015). Previously, it was shown that SNPs located in intron 1 of the FTO gene played a vital role in breast cancer, especially rs1477196, rs9939609, rs7206790 and rs8047395 (Kaklamani et al. 2011). Garcia-Closas et al. (2013) discovered that another SNP, rs11075995, showed activity in both normal and triple-negative breast cancer cells, which was correlated to patient BMI. However, the genetic polymorphisms in the FTO gene vary by ethnicity. The FTO SNPs rs1477196 and rs9939609 have no relationship with increased risk of breast cancer in Iranian women (Mojaver et al. 2015). Furthermore, whether the FTO-associated increase in the risk of breast cancer is mediated by obesity in different breast cancer subtypes is largely unknown.

In summary, certain FTO SNPs are associated with cancer susceptibility, possibly by regulating related gene expression. This association provides evidence for us to understand the roles of FTO in cancer, even if uncovering the relevant relationships is not easy. Although numerous loci associated with different cancers have been identified, further functional studies are needed to explore the concrete mechanisms.

FTO functions as a cancer oncogene

Studies on the role of FTO in cancer are rapidly accumulating. It was recently reported that FTO plays a critical oncogenic role in haematopoietic cell transformation and acute myeloid leukaemia (AML) as an m^{6}A demethylase (Li et al. 2017). Li et al. (2017) found that the FTO gene, which is mediated by certain oncogenic proteins, is highly expressed in certain subtypes of AMLs, including *t*(11q23)/MLL-rearranged, *t*(15;17), FLT3-ITD, and/or NPM1-mutated AMLs. FTO improves the viability and proliferation of human AML cells and exerts anti-apoptosis effects (Li et al. 2017). Moreover, by targeting the critical downstream genes (ASB2 and RARA) and by reducing their m^{6}A levels, mainly in the UTRs, FTO reinforces leukaemic oncogene-mediated cell transformation and leukaemogenesis and inhibits the progression of all-trans-retinoic acid (ATRA)-induced *t*(15;17) AML cells towards granulocytic and monocytic differentiation (Li et al. 2017). Therefore, using targeted FTO signalling inhibitors in combination with an all-trans-retinoic acid (ATRA) treatment may become an effective therapeutic strategy for leukaemia. Studies have emphasized the critical role of m^{6}A modification in cancer and suggested that FTO acts as an oncoprotein. Nevertheless, a Cancer Genome Atlas Research Network (TCGA) AML study suggests that ALKBH5, also an m^{6}A demethylase, shows frequent copy number loss that results in non-carcinogenic effects in AML, in contrast to FTO (Kwok et al. 2017). Approximately 10–20% of AML patients present recurrent somatic mutations in isocitrate dehydrogenase 1/2 (IDH1/2), leading to high levels of R-2-hydroxyglutarate (R-2HG) (Mardis et al. 2009). Recently, Su et al. (2018) discovered that R-2HG exerts effects in AML by suppressing FTO function, thereby promoting the accumulation of m^{6}A on the MYC and CEBPA transcripts, decreasing their mRNA stability and expression, and eventually exhibiting antitumour activity. The discovery of this FTO/m^{6}A/MYC/CEBPA signalling pathway offers insight into the concrete role of FTO in AML.

Cancer stem cells (CSCs) are widely considered to drive tumour progression through self-renewal and multipotent differentiation. A study performed by Cui et al. (2017) indicated a key role for m^{6}A modification in the self-renewal and tumourigenesis of glioblastoma stem cells (GSCs), the tumour heterogeneity and treatment resistance of which tend to be the main causes of refractory glioblastoma (Huang et al. 2010; Satchi-Fainaro et al. 2012; Bao et al. 2006). FTO, as an m^{6}A demethylase, exerts a positive effect on glioblastoma progression. The FTO inhibitor MA2 markedly suppresses GSC growth and self-renewal in vitro and lengthens the survival time of GSC-grafted mice, while the knockdown of METTL3 or METTL14, the key elements of the m^{6}A methyltransferase complex, promotes GSC growth and self-renewal (Cui et al. 2017). Meanwhile, Zhang et al. (2017) discovered that ALKBH5 also maintained GSC proliferation and tumourigenesis by maintaining the methylation and expression of FOXM1. These findings emphasize a critical oncogenic role for FTO in CSCs by regulating the occurrence and development of the related tumour. However, to date, research into the effect FTO on CSCs is scarce.

Effect of FTO on the growth, proliferation and metastasis of cancer

As mentioned above, FTO enhances the growth and proliferation of human AML cells and clearly promotes leukaemic cell transformation and immortalization (Li et al. 2017). Moreover, another AML study revealed that FTO activity is inhibited by R-2HG, which decreases the stability of MYC/CEBPA transcripts by increasing m^{6}A mRNA levels, thereby suppressing leukaemia-cell proliferation and promoting cell-cycle arrest (Su et al. 2018). In addition, FTO functions in cancers such as endometrial cancer and gastric cancer. FTO is connected to the PI3K/AKT and MAPK signalling pathways in oestrogen-driven endometrial cancer, where it induces cancer cell growth and invasion (Zhang et al. 2012). In addition, it has been demonstrated that oestrogen promotes FTO nuclear localization and increases endometrial cancer cell proliferation via the mTOR signalling pathway, which is involved in energy metabolism; however, how ERα mediates FTO nuclear accumulation is unknown (Zhu et al. 2016). A recent study on gastric cancer revealed that FTO was also highly expressed in tumour regions, which promotes the occurrence of gastric cancer by enhancing the proliferation and migration of gastric cancer cell lines and lymph node metastasis (Xu et al. 2017). However, studies related to the molecular mechanism of this aspect of gastric cancer are lacking. Due to the significant role of FTO in the growth, proliferation and metastasis of cancer cells, research into the molecular and cellular mechanisms are urgently needed for improving cancer treatments and prognoses.

Impact of FTO on chemo-radiotherapy resistance and prognosis

FTO is also involved in chemo-radiotherapy resistance and may give rise to poor cancer prognoses. Cancer stem

cells (CSCs) are often a crucial factor regulating treatment resistance. Cui et al. (2017) discovered that m^{6}A RNA modification exerted a critical effect on the self-renewal and tumourigenesis of glioblastoma stem cells (GCSs). The FTO inhibitor MA2 extended the lifespan of GSC-engrafted mice, implying that m^{6}A modification may be a target for suppressing tumour progression and reversing resistance to radiotherapy and chemotherapy in glioblastoma. In AML, all-trans-retinoic acid (ATRA) treatment is an important treatment regimen (Hu et al. 2009; Wang and Chen 2008). Li et al. (2017) discovered that FTO suppressed all-trans-retinoic acid (ATRA)-triggered AML cell differentiation by decreasing m^{6}A levels in some mRNA transcripts, including ASB2 and RARA, indicating that FTO plays a positive role in the poor prognosis conferred by AML. Recently, it was illustrated that FTO participates in regulating chemo-radiotherapy resistance in cervical squamous cell carcinoma (CSCC) (Zhou et al. 2018). As an m^{6}A demethylase, FTO confers chemo-radiotherapy resistance in CSCC by targeting β-catenin, an EMT marker that indicates resistance to anticancer treatment and is upregulated by excision repair cross-complementation group 1 (ERCC1), a downstream modulator of FTO (Zhou et al. 2018). In addition, high expression of FTO is reported to be closely associated with the poor prognosis conferred by gastric cancer by promoting gastric cancer cell migration and invasion and lymph node metastasis (Xu et al. 2017). In fact, studies on how FTO regulates chemo-radiotherapy resistance are still in the initial stages. Further functional studies are needed to verify the roles of FTO in different cancers, especially for a deep understanding of the related mechanisms. Accurate knowledge of the function of FTO and m^{6}A modifications in cancer is of great significance for making accurate diagnoses, understanding therapy sensitivity and improving the prognoses of the related diseases.

In summary, these findings indicate that the relevant modulators involved in m^{6}A modification have notable impacts on various cancers. As seen below, it can be concluded that FTO plays critical roles in tumour germination, development and chemo-radiotherapy resistance, exerting its effects to a large extent via its m^{6}A demethylase activity (Fig. 1). Furthermore, FTO serves as an oncogene in AML and glioblastoma. As FTO was only recently identified as a demethylase, much remains to be explored with regard to its functions and mechanisms in different cancers.

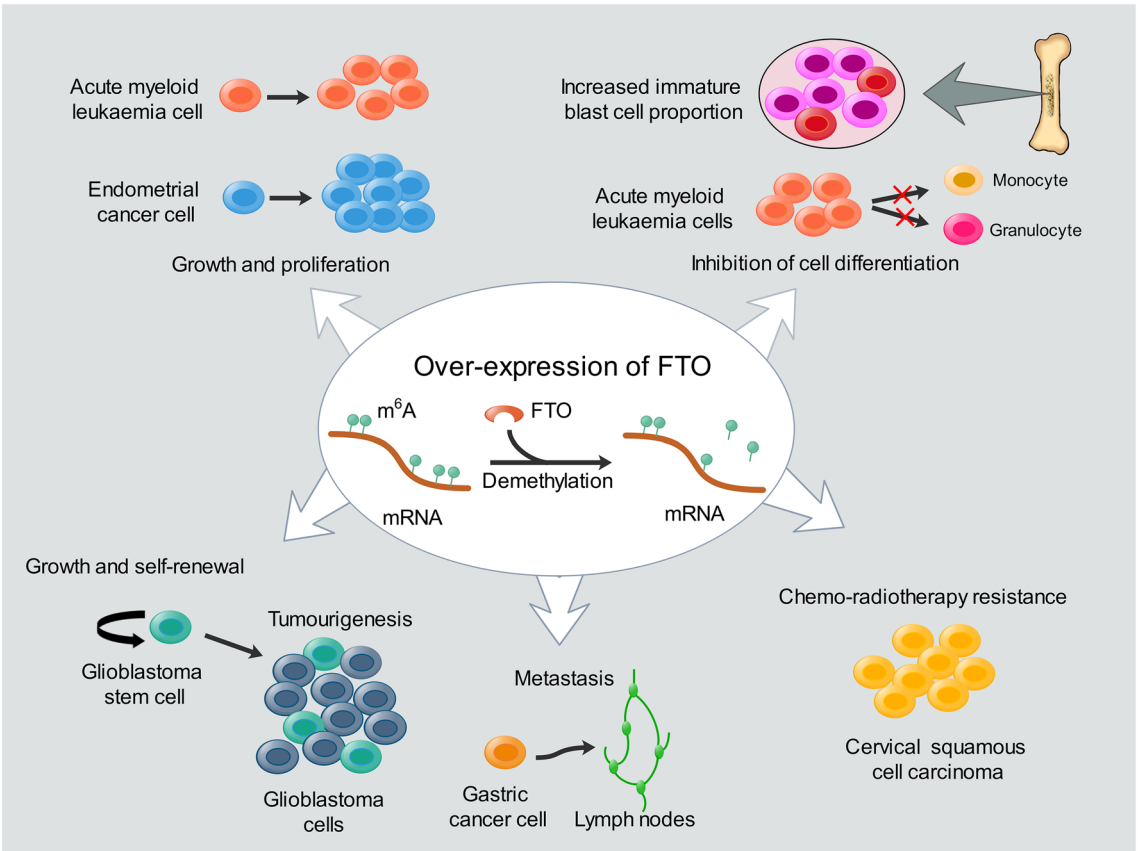

Fig. 1 Role of FTO in tumourigenesis and progression. The upregulated expression of FTO, an m^{6}A demethylase, contributes to cancer cell proliferation, tumour metastasis, chemo-radiotherapy resistance and cancer stem cell tumourigenesis

Conclusions

The FTO gene was initially identified as a susceptibility gene strongly linked to obesity. It has been demonstrated that FTO plays critical roles in fat metabolism, energy regulation and other physiological activities and that it exerts positive effects on the occurrence and development of lipid metabolism-related diseases, including obesity and T_2DM. As studies progressed, it was discovered that FTO is an m^6A demethylase that regulates the m^6A levels in mRNA, which are involved in many fundamental physiological processes. More importantly, FTO plays key roles in the occurrence, progression and treatment of various cancers, such as leukaemia, breast cancer, and glioblastoma. FTO exhibits both cancer-inhibiting and -promoting activities. Nevertheless, comprehensive and systematic studies on the exact roles and molecular mechanisms underlying the roles of FTO in cancer are incomplete. Therefore, finding more convincing evidence to define the detailed roles of FTO is desperately needed to analyse and understand the similarities and differences between various cancers. Considering FTO's critical role in many diseases, FTO may become a new promising target for the diagnosis and treatment of various diseases in the near future, especially for specific types of cancers, such as AML, glioblastoma and breast cancer.

Acknowledgements This study was supported by the National Natural Science Foundation of China (China; 31201028, 81872893), the Fundamental Research Fund for the Central Universities (China; 21617462), the Guangzhou Science Technology and Innovation Commission (China; 201707010099), the Medical Scientific Research Foundation of Guangdong Province (China; A2017574) and the Provincial Undergraduates' Innovation and Entrepreneurship Training Programs (China; 82618257).

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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