



Critical Enzymatic Functions of FTO in Obesity and Cancer

Xiaolan Deng^{1,2}, Rui Su¹, Savanna Stanford¹ and Jianjun Chen^{1*}

¹ Department of Systems Biology and The Gehr Family Center for Leukemia Research, Beckman Research Institute of City of Hope, Monrovia, CA, United States, ² School of Pharmacy, China Medical University, Shenyang, China

Fat mass and obesity-associated protein (FTO) single-nucleotide polymorphisms (SNPs) have been linked to increased body mass and obesity in humans by genome-wide association studies (GWAS) since 2007. Although some recent studies suggest that the obesity-related SNPs in *FTO* influence obesity susceptibility likely through altering the expression of the adjacent genes such as *IRX3* and *RPGRIP1L*, rather than *FTO* itself, a solid link between the SNP risk genotype and the increased *FTO* expression in both human blood cells and fibroblasts has been reported. Moreover, multiple lines of evidence have demonstrated that *FTO* does play a critical role in the regulation of fat mass, adipogenesis, and body weight. Epidemiology studies also showed a strong association of *FTO* SNPs and overweight/obesity with increased risk of various types of cancers. As the first identified messenger RNA *N*⁶-methyladenosine (*m*⁶A) demethylase, *FTO* has been shown recently to play *m*⁶A-dependent roles in adipogenesis and tumorigenesis (especially in the development of leukemia and glioblastoma). Given the critical roles of *FTO* in cancers, the development of selective and effective inhibitors targeting *FTO* holds potential to treat cancers. This mini review discusses the roles and underlying molecular mechanisms of *FTO* in both obesity and cancers, and also summarizes recent advances in the development of *FTO* inhibitors.

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*Correspondence:

Jianjun Chen
jianchen@coh.org

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INTRODUCTION

As the first genome-wide association studies (GWAS)-identified obesity susceptibility gene, the fat mass and obesity-associated gene (*FTO*) has been well known for the strong association of the multiple single-nucleotide polymorphisms (SNPs) located in its intron 1 with risk of obesity (1–10). Although there are some controversial reports regarding the association between *FTO* SNPs and *FTO* expression (11–13), mouse model studies have shown the pivotal role of *FTO* in the regulation of fat mass, adipogenesis, and body weight (14–20). The link between the SNP risk genotype and increased *FTO* expression in human fibroblasts and blood cells has also been demonstrated (21–23). Studies have demonstrated that a strong association exists between *FTO* SNPs and/or overweight/obesity with the increased risk of various types of cancers (24–29), implying a role of *FTO* in the pathogenesis of cancers. Indeed, the oncogenic role of *FTO* has been reported in leukemia and glioblastoma (GBM), where *FTO* is highly expressed (30–32). More importantly, *FTO* was reported as the first *N*⁶-methyladenosine (*m*⁶A) demethylase of eukaryotic messenger RNA (mRNA) (33), and the functions of *FTO* in adipogenesis and tumorigenesis have been linked to its *m*⁶A demethylase activity (30–32, 34). As the most abundant internal modification in eukaryotic mRNAs, *m*⁶A usually occurs at the consensus motif of

RRm⁶ACH ([G/A/U][G>A]m⁶AC[U>A>C]); enriched in 3' untranslated region (UTR), gene coding regions, and especially near stop codons (35, 36). The m⁶A modification is deposited by the METTL3-METTL14-WTAP methyltransferase complex (i.e., writer) (37–39) and can be removed by m⁶A demethylases (i.e., erasers) such as FTO and ALKBH5 (33, 40). The m⁶A modification functions as a post-transcriptional modulator of gene expression by decreasing or increasing mRNA stability, or promoting mRNA translation efficiency through its recognition of different m⁶A reader proteins (41–48). The roles of m⁶A modification and the associated machinery in the pathogenesis of various types of cancers have been reported recently (30–32, 48–59). This review focuses on the functions of FTO in both adipogenesis and tumorigenesis and on the underlying m⁶A-dependent mechanisms, along with a brief discussion of recent advance in the development of FTO inhibitors and their therapeutic potential to treat cancers.

ASSOCIATION OF FTO WITH OVERWEIGHT/OBESITY AND ITS ROLE IN ADIPOGENESIS

Obesity and overweight populations have become a global crisis, with the numbers increasing every year in adults and children. In 2015, there were 603 million adults and 108 million children who were diagnosed obese in 195 countries, and the population suffering with obesity has increased two-fold in over 70 countries during 25 years (60). Obesity is commonly caused by inherited or behavioral factors (food intake, physical activities, etc.), and it may induce other chronic diseases: diabetes, heart disease, chronic kidney disease, bone disorders, and many types of cancer (10, 26, 60). SNPs of *FTO* in intron 1 was first found to be associated with human obesity in European populations in 2007 (1–3), and subsequently validated by different groups in other populations including Asians (4–6), Africans (7), Hispanics (8), and Native Americans (9, 10), demonstrating a strong association between *FTO* SNPs in intron 1 (rs9939609, rs17817449, rs3751812, rs1421085, rs9930506, and rs7202116) and overweight or obesity (61) (see **Figure 1**). People carrying *FTO* risk alleles typically have a high body mass index (BMI), which may be due to a higher food intake (62, 63) and diminished food satiety (64), but not related to energy expenditure (62). Meta-analysis studies (65–67) have validated and confirmed that the influence of *FTO* variants on obesity risk is attenuated through physical activities as well as dietary and drug-based interventions (68, 69), although the underlying mechanism remains elusive. Some recent studies have suggested that the association between *FTO* SNPs in intron 1 and obesity might be owing to their potential influence on expression of *IRX3*, *IRX5*, and *RPGRIP1L*, rather than on their

expression of *FTO* (11–13). However, there is also compelling evidence showing that such *FTO* SNPs are associated with increased expression of *FTO* (21–23, 70, 71). Moreover, animal model studies have shown that *FTO* plays a critical role in regulating fat mass, adipogenesis, and total body weight (14–20). For instance, *FTO*-deficient mice develop postnatal growth retardation and show a reduction in both adipose tissue and lean body mass (14). Conversely, overexpression of *FTO* in mice develops obesity by increased food intake (15), demonstrating the pivotal role of *FTO* expression itself in obesity (58). Therefore, there is no doubt that there is still a robust association of the *FTO* expression level/function with obesity and increased body mass, though the underlying mechanism has yet to be fully elucidated.

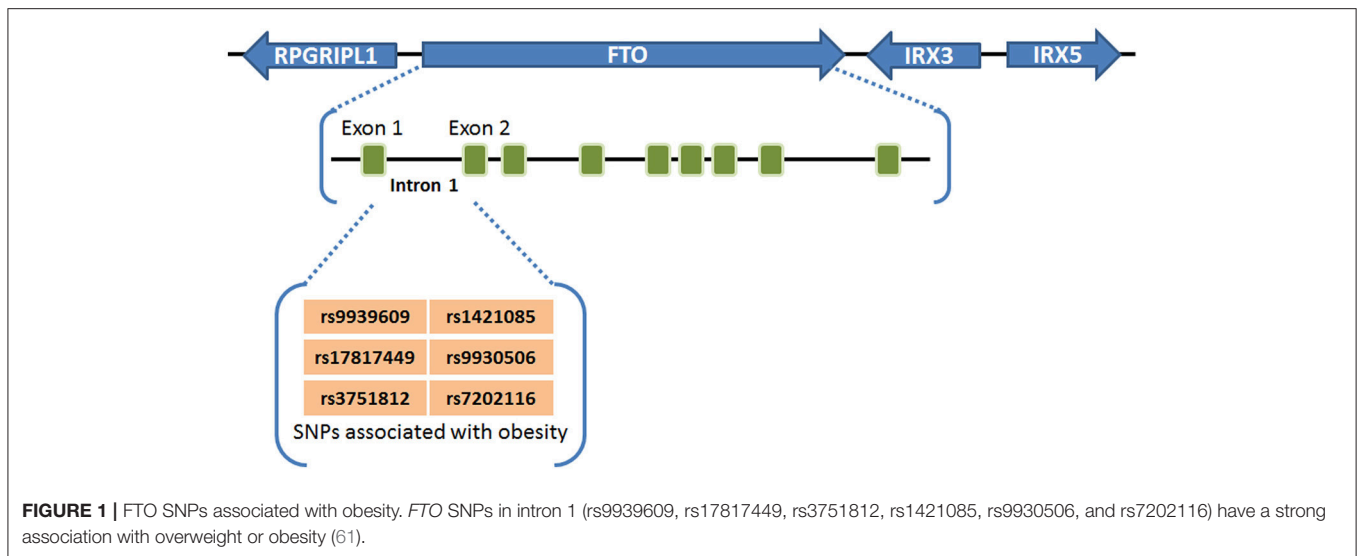
The recent discovery of *FTO* acting as an m⁶A eraser paved a novel way to reveal the molecular mechanism that links *FTO* with the increased susceptibility to overweight and obesity. A study in 2013 showed that the *FTO* obesity-risk allele (rs9939609 T/A) is associated with increased *FTO* expression, reduced m⁶A ghrelin mRNA methylation, and increased ghrelin expression (22). Ghrelin, the “hunger hormone,” is a key mediator of ingestive behavior, and its increased expression results in increased food intake and a preference for energy-dense foods, tending to lead to overweight and obesity (22, 72). A later study also reported that the *FTO* genotype (the AA (risk) genotype at the rs9939609 locus of *FTO*) impacts food intake and corticolimbic activation (73).

Excessive accumulation of adipose tissue under obese condition is a main mechanism for storage of excess energy (61). It has been reported that a positive correlation exists between the *FTO* level in subcutaneous adipose tissue and BMI, with a higher *FTO* mRNA level in adipose tissue from obese individuals than that in control populations (61, 74, 75). Zhao et al. demonstrated that *FTO*-mediated m⁶A demethylation regulates mRNA splicing and plays a critical role in the regulation of adipogenesis (34). They showed that *FTO* expression is inversely correlated with the m⁶A level during adipogenesis, and *FTO* depletion blocks differentiation and wild-type *FTO* (but not *FTO* mutant) restores adipogenesis; mechanistically, *FTO* mediates differentiation through the regulation of m⁶A levels around splice sites, thereby controlling the exonic splicing of the adipogenic regulator factor *RUNX1T1* (34, 76). Similarly, another study also revealed that the demethylase activity of *FTO* is functionally required for pre-adipocyte (3T3-L1) differentiation (77). Furthermore, Merkestein et al. showed *FTO* regulates adipocyte differentiation *in vivo*, and further revealed that *FTO* enhances adipocyte numbers during mitotic clonal expansion at an early stage of adipogenesis (19). The compelling evidence of these studies supports *FTO*-mediated m⁶A demethylation playing a pivotal role on adipogenesis regulatory.

ASSOCIATION OF FTO WITH CANCERS AND ITS ONCOGENIC ROLE IN BOTH TUMORIGENESIS AND DRUG RESPONSE

Epidemiology studies show that *FTO* SNPs (including rs9939609, rs17817449, rs8050136, rs1477196, rs6499640, rs16953002,

Abbreviations: FTO, the fat mass and obesity-associated protein; SNP, single-nucleotide polymorphism; GWAS, genome-wide association study; mRNA, messenger RNA; m⁶A, N⁶-methyladenosine; GBM, glioblastoma; UTR, untranslated region; BMI, body mass index; CSCC, cervical squamous cell carcinoma; AML, acute myeloid leukemia; R-2HG, R-2-hydroxyglutarate; GSCs, glioblastoma stem(-like) cells; ATRA, all-trans-retinoic acid; AZA, azacitidine; αKG, α-ketoglutarate; MA, meclufenamic acid.



rs11075995, and rs1121980) and overweight/obesity are strongly associated with an increased risk of various types of cancers, including breast cancer, prostate cancer, kidney cancer, endometrial cancer, pancreatic cancers, lymphoma, and leukemia (24–29). For instance, several SNPs of intron 1 of FTO (including rs7206790, rs8047395, rs9939609, and rs1477196) are all significantly associated with breast cancer risk, and rs1477196 shows the strongest association (29). Notably, SNPs outside of intron 1 of FTO could also be associated with cancer risk. For example, rs16953002 of intron 8 of FTO has been identified to be significantly associated with melanoma risk (28). It is possible that the obesity-associated SNPs lead to increased expression of FTO, which in turn contributes (at least to some extent) to an increased susceptibility to overweight and obese, as well as an increased risk of cancer development (30). Indeed, several recent studies have suggested that FTO plays an oncogenic role in various types of cancers such as leukemia, brain tumor, breast cancer, gastric cancer, endometrial carcinoma, and cervical squamous cell carcinoma (CSCC) where it is overexpressed (30–32, 78–82). Li et al. provided the first *in vivo* animal model study demonstrating a critical oncogenic role of FTO in cancer (30). They reported that FTO is highly expressed in certain subtypes of acute myeloid leukemias (AMLs) such as those carrying t(11q23)/*MLL*-rearrangements, t(15;17)/*PML-RARA*, *FLT3-ITD*, and/or *NPM1* mutation (30). They further showed that forced expression of FTO significantly promoted human AML cell survival and proliferation and inhibited human AML cell differentiation and apoptosis, and forced expression of FTO significantly promoted leukemogenesis in mice (30). The opposite was true when endogenous expression of FTO was depleted (30). Subsequently, Su et al. reported that by the inhibition of FTO's oncogenic role, R-2-hydroxyglutarate (R-2HG), a previously well-recognized oncometabolite (83–90), actually exhibits a broad and intrinsic antitumor activity in AML and GBM (31). Cui et al. reported that targeting glioblastoma stem(-like) cells (GSCs) with a FTO inhibitor in mice could

significantly inhibit the development of GSC-initiated tumor *in vivo* (32). It was also reported that the depletion of FTO expression significantly inhibited cell proliferation, migration, and invasion of human gastric cancer cell lines, and the opposite phenomenon was observed when FTO was forced expressed (80).

FTO has also been reported to affect the response of cancer cells to drug treatment. Li et al. showed that a knockdown of FTO could significantly enhance the response of human AML cells to all-trans retinoic acid (ATRA) treatment and promote ATRA-induced AML cell differentiation (30). Su et al. reported that analogous to FTO depletion, R-2HG treatment also sensitized human AML cells to standard chemotherapeutic agents such as ATRA, azacitidine (AZA), Decitabine, and Daunorubicin *in vitro* (31). They further showed that R-2HG treatment also sensitized human AML cells to Decitabine and Daunorubicin *in vivo* in immunodeficient xenotransplantation recipient mice (31). Similarly, Zhou et al. reported that FTO enhanced the resistance of CSCC cells to chemo-radiotherapy (82). Consistent with the function of FTO in drug resistance, it was reported that overexpression of FTO is a marker for poor prognosis in cancers such as gastric cancer and endometrial carcinoma (80, 81).

Mechanistically, the roles of FTO in tumorigenesis and drug response have been linked to its m⁶A demethylase activity. Li et al. reported that FTO negatively regulates expression of a set of tumor suppressor target genes, such as *ASB2* and *RARA* [two genes implicated in leukemia cell proliferation and drug response (91–93)], through post-transcriptionally modulating m⁶A abundance of the target mRNA transcripts and thereby affecting their stability (30). Su et al. further reported that FTO also positively regulates expression of a set of oncogenic targets such as *MYC* and *CEBPA* through an m⁶A-dependent mechanism (31). The suppression effect of the FTO inhibitor on GSC growth/proliferation and survival is also believed to be owing to the inhibition of the m⁶A demethylase activity of FTO (32). In CSCC, FTO has been

reported to enhance chemo-radiotherapy both *in vitro* and *in vivo* through positively regulating expression of β -catenin (CTNNB1) via an m^6A -dependent mechanism (82). Collectively, evidence is emerging that FTO plays critical oncogenic roles in various types of cancers as an m^6A demethylase, and post-transcriptionally regulates expression of a number of functionally important target genes through m^6A -dependent mechanisms.

IDENTIFICATION OF SMALL MOLECULE INHIBITORS TARGETING FTO

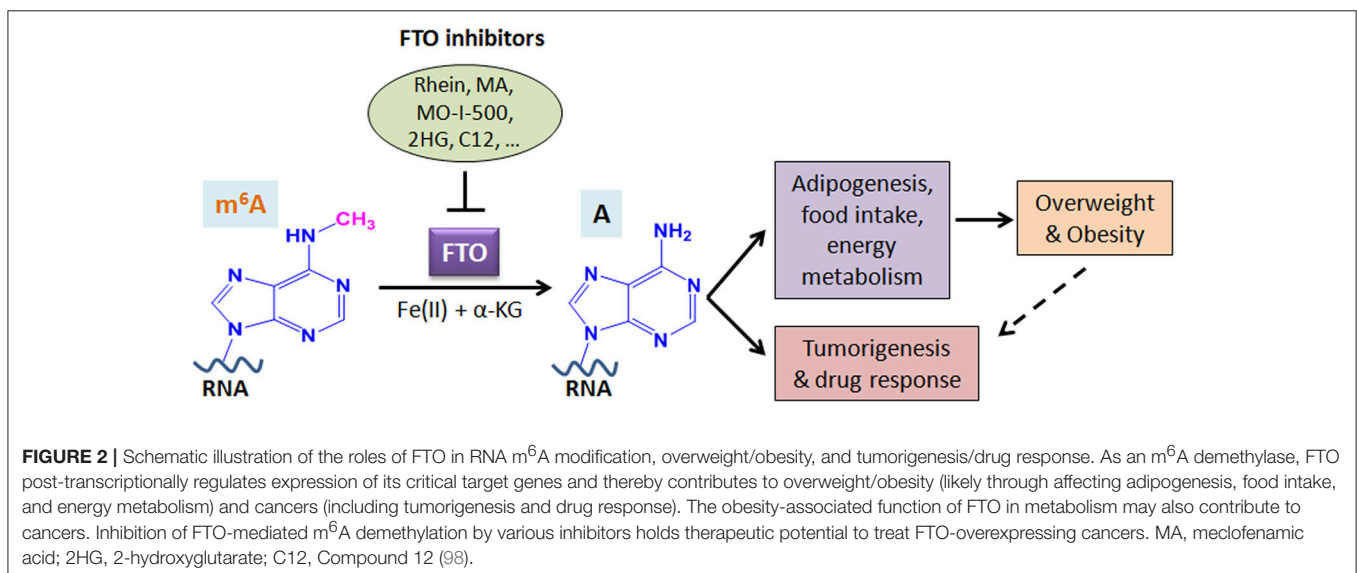
Since the discovery of FTO as an m^6A demethylase in 2011 (33), efforts have been made to identify selective small-molecule inhibitors targeting FTO's m^6A demethylase activity (94–98). FTO belongs to the AlkB family, and the crystal structure of FTO resolved in 2010 (99) shows a strong Fe (II) and α -ketoglutarate (α KG) dependent activity as a dioxygenase, at N-terminals. Chen et al. reported in 2012 that rhein, a natural product, competitively binds to an FTO active site, and exerts an inhibitory activity on FTO-dependent m^6A demethylation in cells, through directly disrupting the bindings between FTO and the m^6A substrate (94). In 2014, Zheng et al. developed a selective FTO inhibitor that also selectively inhibits the m^6A demethylase activity of FTO and increases the m^6A levels in cells (95); a later study showed that this FTO inhibitor (i.e., MO-I-500) could significantly inhibit the survival and/or colony formation of human SUM149 cells, a triple-negative inflammatory breast cancer cell line (97). Meclofenamic acid (MA), a nonsteroidal anti-inflammatory drug, was discovered to specifically inhibit FTO's m^6A demethylase activity, while paring ALKBH5 (96). MA has been further proved to effectively inhibit the survival and growth of GBM cells through suppression of the m^6A demethylase activity of FTO (32). In addition, Compound 12 has been developed based on a α -KG tethering strategy, which could selectively inhibit FTO

over other AlkB subfamilies (including ALKBH5) and α -KG oxygenases (98). Su et al. showed that R-2HG is also an inhibitor of FTO that binds direct to FTO protein and significantly inhibits the m^6A demethylase activity of FTO in a dose-dependent manner, leading to a significant increase of global m^6A abundance in R-2HG-treated sensitive leukemia cells (31).

DISCUSSION AND CONCLUSIONS

A growing body of evidence suggests that FTO plays critical roles in both overweight/obesity and cancers. As the first m^6A demethylase identified, FTO has been shown to regulate expression of a number of important target genes through post-transcriptionally reducing their m^6A levels and thereby affecting the stability and/or splicing of target mRNAs, in turn leading to promoting adipogenesis, tumorigenesis, and drug resistance of cancer cells. Therefore, although FTO may regulate expression of distinct sets of target mRNAs in different cell types, it affects overweight/obesity and cancers likely through similar, m^6A demethylase activity-dependent mechanisms (see **Figure 2**). The strong association between FTO SNPs or overweight/obesity with an increased risk of cancers suggests that the obesity-associated function of FTO in metabolism may also contribute to its effects in cancers (**Figure 2**). Indeed, the FTO gene variant related to cancer risk is unlikely independent of adiposity (100). In addition, it was reported that by targeting the PI3K/AKT signaling, FTO influences breast cancer cell energy metabolism including lactic acid, ATP, pyruvate kinase activity, and hexokinase activity (79).

Given the essential role of FTO in cancer development and drug resistance, targeting FTO holds therapeutic potential in treating cancers in which FTO is overexpressed. Thus far, FTO inhibitors have been tested *in vitro* and *in vivo*, and show potent antitumor effects in treating both GBM and breast cancer (32, 97). Similarly, Su et al. showed that by targeting



FTO directly, R-2HG exhibits a strong antitumor effect in both leukemia and GBM, especially when in combination with standard chemotherapeutic agents (31). These studies provide proof-of-concept evidence demonstrating that FTO is a realistic druggable target in treating cancers. In the near future, when more effective and selective inhibitors of FTO are developed, they could be applied, especially in combination with other therapeutic agents, into the clinic to treat various types of cancers. On the other hand, although FTO also plays a role in obesity, it was argued that FTO might not be a good pharmaceutical target to treat obesity, because the factors leading to obesity might be more complex (101, 102). Thus, a deeper understanding of the factors contributing to obesity could lead to the development of therapeutics targeting obesity.

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XD and JC drafted and revised the manuscript, while RS and SS contributed to the revision of the manuscript.

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Conflict of Interest Statement: A patent has been filed by JC and RS based on their work on R-2HG/FTO.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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