REVIEW

Unraveling the Complex Interactions between the Fat Mass and Obesity-Associated (*FTO*) Gene, Lifestyle, and Cancer

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ABSTRACT

Carcinogenesis is a complicated process and originates from genetic, epigenetic, and environmental factors. Recent studies have reported a potential critical role for the fat mass and obesity-associated (*FTO*) gene in carcinogenesis through different signaling pathways such as mRNA N6-methyladenosine (m6A) demethylation. The most common internal modification in mammalian mRNA is the m6A RNA methylation that has significant biological functioning through regulation of cancer-related cellular processes. Some environmental factors, like physical activity and dietary intake, may influence signaling pathways engaged in carcinogenesis, through regulating *FTO* gene expression. In addition, people with *FTO* gene polymorphisms may be differently influenced by cancer risk factors, for example, *FTO* risk allele carriers may need a higher intake of nutrients to prevent cancer than others. In order to obtain a deeper viewpoint of the *FTO*, lifestyle, and cancer-related pathway interactions, this review aims to discuss upstream and downstream pathways associated with the *FTO* gene and cancer. The present study discusses the possible mechanisms of interaction of the *FTO* gene with various cancers and provides a comprehensive picture of the lifestyle factors affecting the *FTO* gene as well as the possible downstream pathways that lead to the effect of the *FTO* gene on cancer. *Adv Nutr* 2022;13:2406–2419.

Keywords: *FTO*, lifestyle, m6A, carcinogenesis, signal transduction

Introduction

Cancer is a primary cause of death and is a complex and multifactorial disease. In 2020, 19.3 million new cancer cases and almost 10 million cancer deaths were estimated to have occurred globally (1). Recent developments in cancer research have reported some progress in the understanding of cancer etiology. This knowledge can lead to advances in prevention, early diagnosis, and treatment of cancer and finally, to a decline in cancer mortality (2, 3). Several studies have identified risk factors for cancer including intrinsic risk factors, e.g. cellular genetic changes, as well as endogenous nonintrinsic risk factors, e.g. epigenetic modifications, and exogenous nonintrinsic risk factors, e.g. improper lifestyle (4–8). These risk factors can influence each other and determine overall cancer risk. It has been reported that adherence to a healthy lifestyle may attenuate the overall cancer risk in individuals with high genetic susceptibility (9, 10). Consequently, a combination of genetic susceptibility and lifestyle constitute the main risk factors for cancer (11).

Recent studies have emphasized the role of the fat mass and obesity-associated protein (*FTO*) in the etiology of

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Abbreviations used: AA, amino acid; AML, acute myeloid leukemia; ASB2, ankyrin repeat and SOCS box containing 2; BC, breast cancer; BLCA, bladder cancer; CEBPA, CCAAT enhancer binding protein **α**; CRC, colorectal cancer; FTO, fat mass and obesity-associated; HCC, hepatocellular carcinoma; lncRNA, long noncoding RNA; LUSC, lung squamous cell carcinoma; MAL, myelin and lymphocyte protein; MALAT1, metastasis related to lung adenocarcinoma transcript 1; METTL3, methyltransferase like-3; mTORC1, mechanistic target of rapamycin complex 1; MZF1, myeloid zinc finger 1; NSCLC, nonsmall-cell lung cancer; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase-B; PK, pyruvate kinase; PRODH/POX, proline dehydrogenase/proline oxidase; PYCR1, pyrroline-5-carboxylate reductase 1; RARA, retinoic acid receptor, **α**; RTK, receptor tyrosine kinase; T2DM, type 2 diabetes; USP, ubiquitin specific peptidase; WC, waist circumference; YTHDF, YTH domain-containing family proteins.

multiple cancers (12, 13). FTO is a 2-oxoglutarate-dependent N6-methyladenosine DNA demethylase and regulates pre-mRNA splicing and mRNA translation (14). The location of the *FTO* gene is on human chromosome 16q12.2, it contains 9 exons and 8 introns, and its expression is ubiquitous with the highest expression in the hypothalamus (15). It has been demonstrated that polymorphisms of *FTO* such as rs9939609, rs178117449, rs3751812, rs9930506, rs7202116, and rs1421085 may influence the growth, proliferation, and function of cells, which are essential processes in cancer (16, 17). Most of these polymorphisms are located in an enhancer in intron 1 and are therefore likely to influence gene expression. In addition, it has been reported that the effect of *FTO* in the carcinogenesis process can be mediated by its m6A demethylase function, which can influence essential signaling pathways, such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin (PI3K/AKT/mTOR) (18, 19). FTO regulates m6A RNA modification, which is the most prevalent internal modification of mRNA and has a function in cellular processes (20). Dysregulation of m6A modification and its mediators such as FTO has been implicated in different physiological and pathological processes, particularly in cancer initiation and progression (5, 21, 22).

On the other hand, several recent studies have identified an association between lifestyle factors, including physical activity and dietary intake, and the level of *FTO* gene expression. For instance, a positive association was found between dietary carbohydrates, proteins, and fat intake with *FTO* expression (23, 24). Moreover, the association between the *FTO* gene and obesity might be modified by lifestyle factors (25). It is now well established that individuals who have a combination of the risk allele of *FTO* and an improper lifestyle are more susceptible to being obese, which is considered a risk factor for different cancer types (26, 27). A previous study has indicated the *FTO* genotype role in the impact of lifestyle changes on the expression of obesity-related genes (28).

However, the influence of lifestyle factors on *FTO* gene expression and their role in carcinogenesis beyond BMI is still not clear. This study aims to develop a more rigorous understanding of interactions between *FTO*, cancer, and lifestyle to gain deeper knowledge of the impact of lifestyle on cancer risk through *FTO* gene-dependent molecular mechanisms.

Interactions of lifestyle, cancer, and *FTO*

Lifestyle may, as an upstream factor, influence the association between cancer and the *FTO* gene. Some risk factors related to lifestyle, such as unhealthy diet, physical inactivity, and higher BMI, can provide the necessary conditions for the adverse effects of the *FTO* gene on carcinogenesis. The following are interactions between lifestyle factors, cancer, and the *FTO* gene.

Dietary macronutrients and expression of *FTO*

We found in a previous study that there is a relation between the level of *FTO* gene expression in the hypothalamus and macronutrient concentrations (29). As suggested by additional evidence, *FTO* mutually interacts with the consumption of dietary macronutrients. For instance, dietary carbohydrates have been proposed to influence *FTO* gene expression in the hypothalamus (30), and hypothalamic *FTO* gene expression can be increased by a higher intake of carbohydrates such as glucose (31). Another study reported that supplementation with high glycemic index foods can increase hypothalamic *FTO* gene expression (32). In a previous study, we consistently indicated that the increased consumption of carbohydrates caused significant upregulation of *FTO* gene expression in peripheral blood ($P = 0.001$) (23). Interestingly, we previously found that there was a positive relation between the amount of dietary carbohydrate and peripheral blood *FTO* gene expression only in people with the GG genotype of *FTO* rs9930506, indicating a possible function of the *FTO* genotype in the relation between *FTO* gene expression and dietary intake (33). Moreover, a recent study found that in subcutaneous adipose tissues, there is a direct association between higher fructose intake and high *FTO* mRNA expression in obese individuals, whereas there is an inverse association between a higher intake of sucrose, sugar, lactose, and glucose with *FTO* gene expression (34). Further, we found in a previous study that women with high-grade breast cancer (BC) had a higher intake of carbohydrates compared with women with early-grade BC (35). In addition, concerning the effect of different monosaccharides and disaccharides on BC risk, a previous study found the potential role of some types of dietary carbohydrates, such as total carbohydrates, sucrose, maltose, fructose, and simple sugar in developing BC (36). This is in accordance with a previous study that reported an association between high sugar consumption after the detection of cancer and a higher mortality rate in females with colorectal cancer (CRC) (37). Moreover, we found in previous studies that dietary carbohydrate can influence cell growth and survival through regulating the expression level of cancer-related genes such as *FTO* (29, 38). The exact mechanism of the impact of dietary carbohydrates on *FTO* gene expression is not yet clear. It has been established that in cancer cells, high dietary carbohydrates can affect *FTO* gene expression through elimination of the inhibitory impact of adenosine monophosphate-activated protein kinase (AMPK) on *FTO* gene expression. In turn, high *FTO* expression can promote cell growth and survival via the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signaling pathway (38). Moreover, Speakman et al. indicated that the AA and AT genotypes of rs9939609 in the *FTO* locus had a higher appetite and had higher daily calorie intake compared with the TT genotype carriers (39). Thus, different genotypes of *FTO* gene polymorphisms may affect the amount of calorie intake. In addition, *FTO* genotype differences can affect the proliferation and metabolism of cells and the impact of dietary interventions on BC patients (40). This

confirms our previous findings, which showed the potential relation between the *FTO* gene rs9939609 polymorphism and BC in obese individuals after adjusting for lifestyle factors, including the consumption of alcohol, smoking, or dietary intake (41). We also found in a previous study that the intake of calories, carbohydrate, and fat is significantly higher in carriers of the AA genotype of rs9939609 of the *FTO* gene compared with the TT genotype carriers after adjustment of sex and age (42). It is important to note that the polymorphisms in *FTO* that are highly related to BMI may affect obesity by influencing the expression of other genes besides *FTO*. For example, a landmark study found that *FTO* polymorphisms act through modulating expression of the distant *IRX3* and *IRX5* genes, influencing the fate of developing adipocytes (with obesity promoting alleles shifting adipocyte development from brown fat to white fat) (43). On the other hand, the *FTO* genotype may affect expression of *FTO* and *RPGRIP1L* in the brain, contributing to obesity by affecting leptin signaling (44, 45). Thus, the *FTO* genotype may regulate different genes in different tissues, highlighting that studies concerning the *FTO* genotype may be independent from those directly examining the effects of *FTO* mRNA or protein concentrations.

Regarding dietary proteins, a recent study found significant effects of genetic risk alleles and dietary protein intake on waist circumference (WC) and triglyceride concentrations (46). In individuals with the *FTO* rs3751812 polymorphism risk allele (allele A), more beneficial results in weight reduction were obtained when dietary protein was <18% of the total daily calorie intake (27). Other previous studies confirmed that genetic impacts of *FTO* variants on BMI and body weight can be modulated by high-protein diets (47, 48). Moreover, it was reported that in individuals with the risk allele of the *FTO* gene for BMI, lower protein intake (13% of the total daily calorie intake) was related to lower WC and serum triglyceride concentration (46). In addition, regarding the effect of the amino acid (AA) leucine on *FTO* expression, Olszewski et al. reported reduced *FTO* expression in hypothalamus organotypic cultures via leucine intake 48 h after intervention (49). In contrast, Johansson et al. reported increased *FTO* expression via leucine intake in hypothalamus organotypic cultures 48 h after intervention (50). Another study on murine and human cell lines found a reduction of *FTO* expression by total AA deprivation (51). A possible role for the *FTO* gene is acting as an AA sensor promoting translation and growth. Essential amino acids (EAAs) may regulate the expression of *FTO*, and the *FTO* gene couples AA concentrations to mechanistic target of rapamycin complex 1 (mTORC1) signaling through a demethylation-dependent mechanism. (52, 53). FTO triggers the demethylation of pyruvate kinase 2 (PKM2) mRNA and accelerates its translation. Overexpression of *PKM2* activates mTORC1 signaling through phosphorylation-mediated inactivation of the mTORC1 inhibitor AKT1 substrate 1 (AKT1S1) (54). Remarkably, in a previous study we found that in AA/AG carriers of *FTO* rs9930506, there was a positive relation between dietary protein and *FTO* expression in peripheral blood (23). This indicates that the influence of dietary protein on *FTO* expression can be affected by genotype of *FTO*.

In terms of dietary FAs and *FTO* expression, recent evidence reported a positive correlation between total FA intake and *FTO* mRNA expression in subcutaneous ($P = 0.020$) and visceral ($P = 0.037$) adipose tissues (55). These findings are in agreement with previous in vivo animal research, which showed higher *FTO* expression in both subcutaneous and visceral adipose tissues in rats with a high-fat diet (56). As reported by Nowacka-Woszuk et al., a high intake of dietary fats may result in *FTO* overexpression in visceral and subcutaneous adipocytes of rats (57). In contrast with these findings, Zhong et al. indicated a lack of influence of a high-fat diet on the *FTO* expression in the adipose tissue of mice (58). The quantity of FA intake and its type (for example, ω-6 versus ω-3 FAs) may influence their effects on the regulation of *FTO* expression (24). Moreover, the *FTO* gene plays a critical role in fat metabolism and *FTO* risk allele carriers had lower fat cell lipolysis compared with others (59). We found in a previous meta-analysis that carriers of the A allele of the *FTO* rs9939609 polymorphism had higher body fat % (BF%) (60). This finding is consistent with that of Timpson et al., who reported that people with the rs9939609 minor allele had a higher intake of dietary fats than those with the TT genotype (61). In addition, previous studies have shown that homozygotes for the rs9939609 risk allele (A) showed significantly lower serum HDL cholesterol and higher serum leptin concentrations compared with the TT genotype (62, 63).

Physical activity and expression of *FTO*

Regarding the association between the level of physical activity and *FTO* expression, in a previous study we found that the *FTO* impact on obesity can be intensified by lower physical activity, which is a risk factor for various diseases and cancer (64). As reported by Atici et al., lower physical activity is significantly related to lower concentrations of adiponectin in people with the minor allele A of the *FTO* rs9939609 polymorphism (25). Adiponectin is a hormone produced and released by adipose tissue that has antihyperglycemic, anti-inflammatory, antiatherogenic, and cardioprotective effects (65). Dysregulation of adipokine production has been shown to have a strong association with the onset of different types of metabolic abnormalities such as CVD and cancer (66). In addition, it has been observed that in subjects carrying the AA or AT genotype of rs9939609, active exercise reduced the risk of obesity ~2-fold more than in those with the TT genotype (67). It has been demonstrated that BMI is higher in sedentary individuals with the AA/AT genotypes than those with the homozygous T allele of *FTO* rs9939609 (68). In line with these results, Rampersaud et al. indicated that rs147719 and rs1861868 polymorphisms of *FTO* in individuals with lower physical activity are related to higher BMI after adjusting for sex and age, whereas those with above average physical activity did not show such a relation (69); thus, the impact of the *FTO* gene on obesity can be adjusted by physical activity. Importantly, Danaher et al. found that

high-intensity physical activity downregulates *FTO* mRNA expression in skeletal muscle, which can be due to a role of *FTO* as an energy sensor (70). However, in a previous study we indicated that *FTO* gene expression in PBMCs was not affected by exercise (28). These differences can be explained by age, gender, period of intervention, and different cell types.

BMI and the *FTO* gene

The relation between BMI and *FTO* gene expression has been widely investigated. For example, Wang et al. examined 110 subjects with type 2 diabetes (T2DM) and demonstrated that serum FTO protein expression is significantly related to BMI as one of the risk factors for T2DM (71). These results were in line with those of Abd El Gayed et al. who found a positive relation between *FTO* expression and its serum protein concentration with obesity indices such as BMI (72). In addition, Czogala et al., in a cohort of 16 obese and 10 healthy children, reported a significant increased expression of *FTO* in PBMCs of obese children compared with healthy children. They also found that the overexpression of *FTO* in obese children was associated with their biochemical and anthropometric characteristics (73). Moreover, higher *FTO* expression in human adipose tissue has been established, indicating that increased subcutaneous fat deposition was associated with the subcutaneous expression of *FTO* (74). Importantly, it has been noted that BMI can influence the genome-wide DNA methylation pattern in human adipose tissue. Altered DNA methylation has an essential role in the incidence of some diseases, such as T2DM, cancer, obesity, and CVD (75). These results are in agreement with the findings of other studies, in which there was a relation between obesity and the upregulation of *FTO* expression in adipocytes (15, 76). In addition, *FTO* overexpression in the peripheral adipose tissue of obese people has been reported (77). In a previous study we found that the *FTO* genotype can influence the relation between the expression of *FTO* and body composition. The upregulation of *FTO* expression was associated with an increased percentage of skeletal muscle in male adolescents with the AG or AA genotype of *FTO* rs9930506 (78).

Various studies have investigated the relation between BMI and the rs9930506 polymorphism of the *FTO* gene, and a positive correlation has been found between BMI and the GG genotype of the rs9930506 polymorphism. For instance, Scuteri et al. evaluated the polymorphisms related to obesity, and found the strongest relation with BMI was observed in rs9930506 risk allele carriers (79). In addition, Sentinelli et al. conducted a study to determine the rs9930506 polymorphism impact on BMI, and they reported an association between the rs9930506 polymorphism and higher BMI and early initiation of childhood obesity (80). In this context, we found a strong association between a haplotype (rs9930506, rs9930501, and rs9932754) in the first intron of the *FTO* gene and obesity indices in Iranian male adolescents after adjusting for physical activity and calorie intake. It is proposed the *FTO* genotype exerts its impact on anthropometric measurements of adolescents as a haplotype and by mechanisms other than calorie intake and calorie expenditure, possibly by influencing the expression of other genes, such as *IRX3* (81, 82). Furthermore, animal model studies have revealed that *FTO* is involved in the regulation of adipogenesis and total body weight (30, 56, 83–85). *FTO*-deficient mice, for example, demonstrate postnatal growth retardation and a decrease in both adipose tissue and lean body mass (30). The overexpression of *FTO*, on the other hand, causes obesity in mice by increasing food consumption, highlighting the critical function of *FTO* expression in obesity (56). As a result, *FTO* expression has frequently been reported to be associated with obesity and increased body mass, however, the underlying mechanism has yet to be fully understood (86).

The effect of the *FTO* genotype on adolescents' anthropometric indices, such as obesity, can be considered as a chronic inflammatory stimulus in carcinogenesis. In this regard, a previous study has shown that the A allele of the rs9939609 polymorphism of the *FTO* gene is positively associated with a higher predisposition to CRC in Iranian patients, possibly via the role of the *FTO* gene in obesity (87). However, we found no association between this polymorphism of *FTO* with CRC in a previous meta-analysis study of articles published from 2000 to 2019 (17). This suggests that this association may be affected by other factors, such as race/ethnicity or lifestyle of subjects. In total, *FTO* gene expression is associated with food intake, energy expenditure, and BMI. There is also an association between several single-nucleotide polymorphisms in the *FTO* gene and human body weight, and their abnormal regulation can elevate the risk of carcinogenesis indirectly through obesity. Similar molecular mechanisms may play a role in the development of cancer and obesity (88).

FTO gene expression impact on regulation of m6A and other cancer-related pathways

Epigenetic alteration is one of the essential mechanisms involved in the carcinogenesis process. RNA posttranscriptional modification has recently been considered to be one of the pivotal epigenetic mechanisms of gene expression regulation. m6A is the most common internal alteration of mRNAs among all the modifications, which is a reversible and dynamic process and is observed in multiple cellular processes as well as in various cancers (5). The regulatory elements of m6A modification constitute writers, erasers, and readers working together in concert to maintain a steady-state equilibrium of m6A modification in the cell (89). The m6A writers, such as methyltransferase like-3 (METTL3) and its homolog METTL14 are methyltransferases catalyzing the delivery of a methyl group to the N-6 position of adenosine (A) from S-adenosyl methionine (SAM) (90). The first detected m6A eraser was FTO and the role of FTO as an m6A demethylase proved its relation with the regulation of gene expression (91, 92). Finally, the

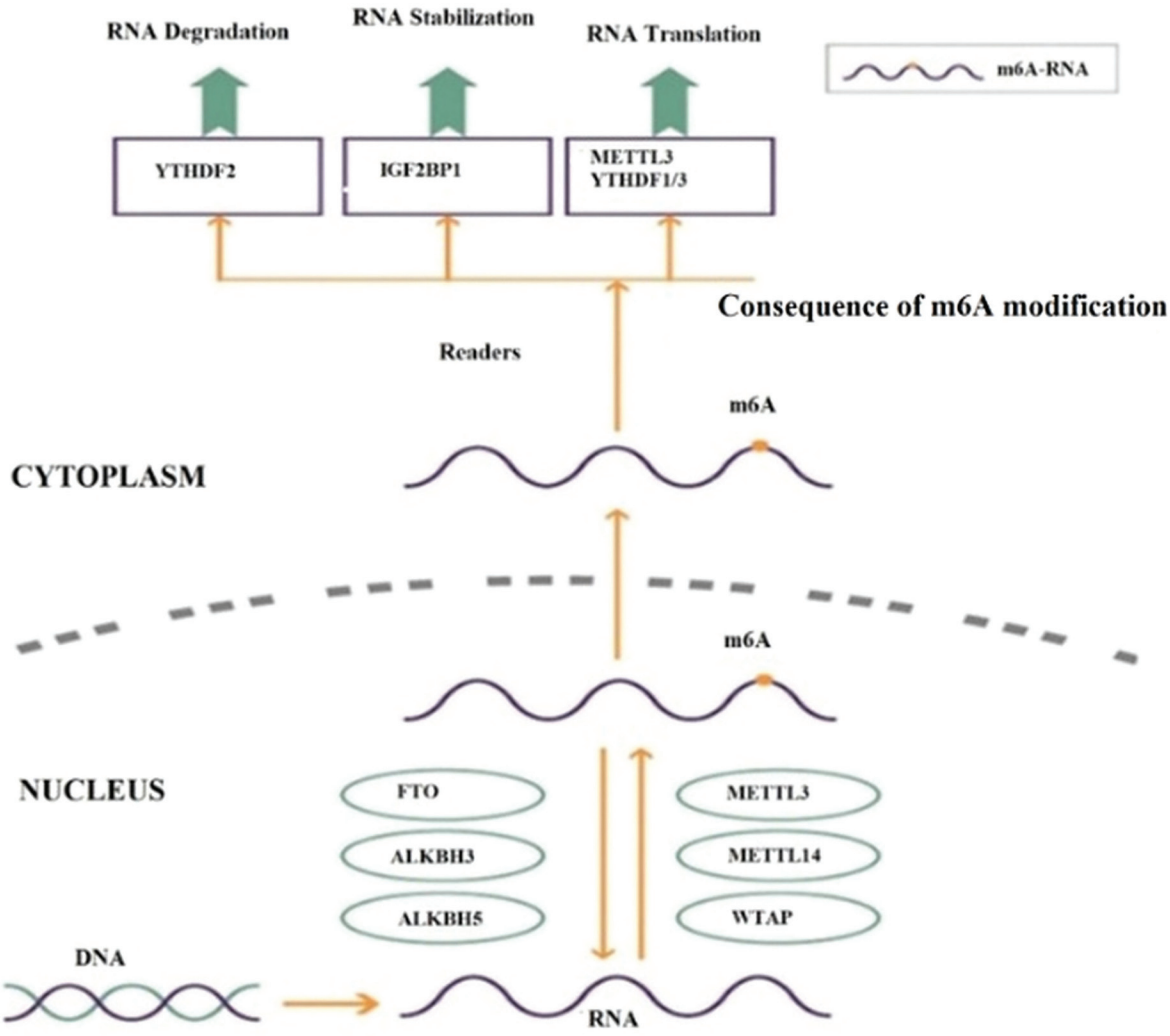

FIGURE 1 m6A modification and its regulators. FTO: Fat mass and obesity associated, ALKBH: Alpha-ketoglutarate-dependent dioxygenase homologs, METTL: methyltransferase-like, WTAP: Wilms tumor 1 associated protein, YTHDF: YTH domain-containing family proteins, IGF2BP1: insulin-like growth factor 2 mRNA binding protein 1

m6A readers determine the functional outcomes of the modifications caused by writers and erasers. It should be noted that the reader proteins have a functional diversity, for example, after recognizing m6A modified transcripts, insulin-like growth factor-2 mRNA binding proteins 1, 2, and 3 (IGF2BP1–3) can stabilize them by protecting from degradation. In addition, the YTH domain-containing family proteins 1 (YTHDF1) recognize the m6A modification and facilitate mRNA translation, whereas YTHDF2 accelerates their degradation. Thus, erasers, readers, and writers have vital roles in discovering the biological function and fate of m6A modified transcripts (93–95) (**Figure 1**).

Considering the m6A modification role in regulation of gene expression, m6A probably contributes to carcinogenesis via down- or upregulation of key components of cellular pathways. **Figure 2** lists examples of crucial signaling pathways that are abnormally activated/inactivated/expressed in various cancers caused by *FTO* gene upregulation as an m6A modification eraser.

FTO and metastasis related to lung adenocarcinoma transcript 1

A large part of the genome contains noncoding DNA that produce noncoding RNAs, which are classified into 3 categories based on the sequence length: short, medium, and long chain (96). Previous research has discovered that noncoding RNAs play a role in various human biological processes, such as gene splicing, transcription interference, cell cycle regulation, and transcription regulation (97). Some of these molecular markers, including short noncoding RNAs (miRNAs) and long noncoding RNAs (lncRNAs), have been identified in pathological changes and tumorigenesis in various human organs (98). For example, overexpression of lncRNA metastasis related to lung adenocarcinoma transcript 1 (MALAT1) has been shown in individuals

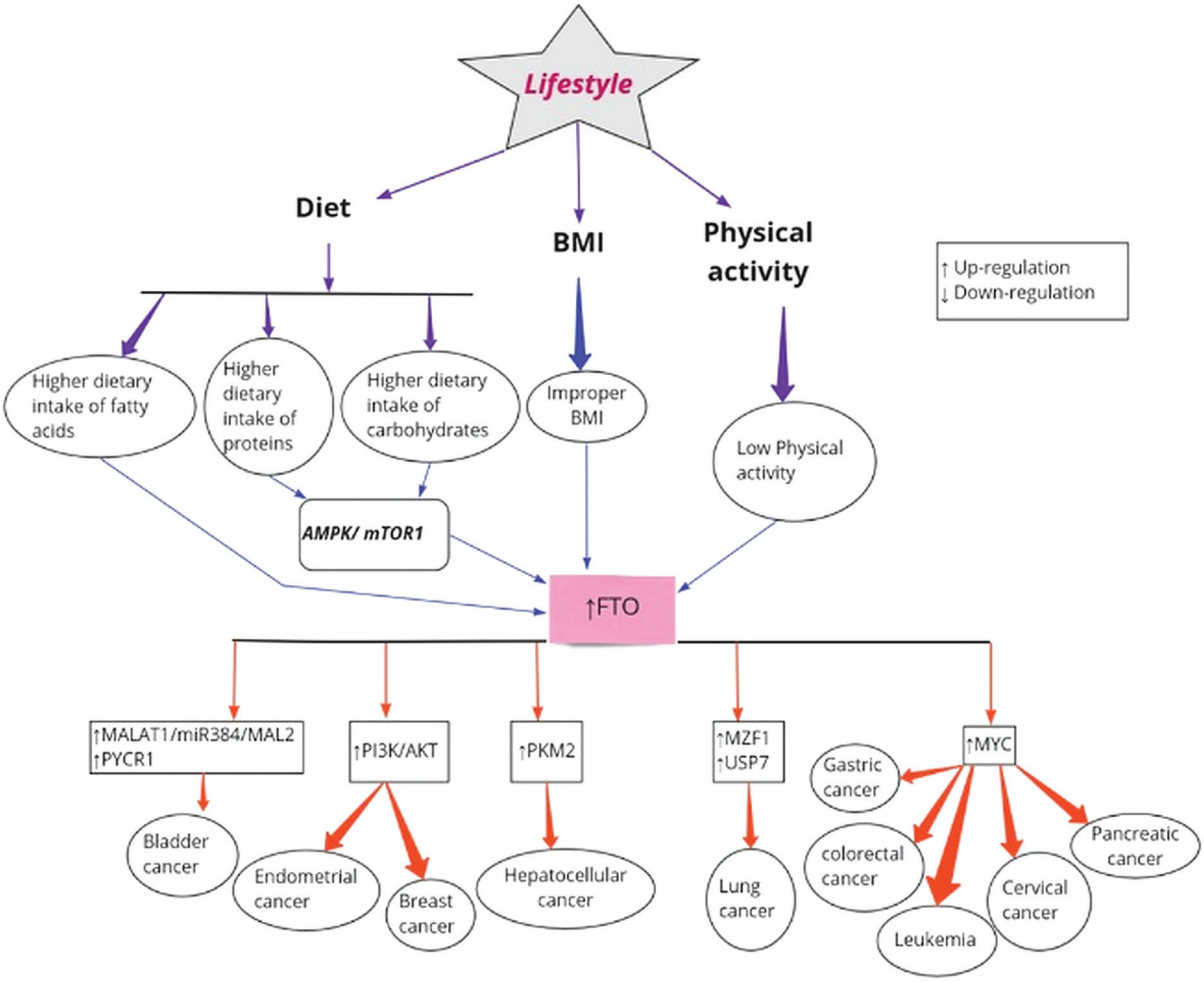

FIGURE 2 Interplay between lifestyle, *FTO*, and different types of cancers. AMPK: adenosine monophosphate-activated protein kinase, mTOR1: mammalian target of rapamycin complex 1, FTO: fat mass and obesity associated, MALAT: metastasis-associated-lung-adenocarcinoma-transcript, PKM2: pyruvate kinase 2, USP: ubiquitin specific peptidase, MZF: myeloid zinc finger, PI3K: phosphatidylinositol 3-kinase, AKT: protein kinase-B.

with nonsmall cell lung cancer (NSCLC) (99). Further, it has been previously indicated that the expression of MALAT1 accelerates cancer cell proliferation, metastasis, and invasion in several cancers such as breast, pancreas, colon, liver, and lung (100–103). It has been reported that MALAT can affect the growth and spread of cancer via promoting the epithelial-mesenchymal transition, increasing AKAP9 (A-kinase anchoring protein 9) expression, and modulating the β-catenin pathway (104–106). Apart from that, MAL (myelin and lymphocyte protein) is a lipid raft-associated membrane protein that is engaged in protein apical transport in polarized epithelial cells. Previous studies have indicated overexpression of MAL2, as a new member of the MAL proteolipids, in multiple human cancers, such as ovarian, colorectal, and lymphomas (107). Although it is uncertain how this proteolipid might have a role in cancer progression, more recent studies have suggested a signaling counterpart, such as cytoplasmic tyrosine kinases (ZAP-70), small GTPases, cellular receptors (TCR), phospholipases (PLC-γ), and others that may mediate the carcinogenic activity of MAL (107, 108). In addition, MAL2 is known to interact with the tumor protein D52, modulating the tumorigenicity of a variety of human cancers (109, 110). It should be noted that both *MALAT1* and MAL2 can be targeted by microRNAs, such as miR-384, and their expression can be suppressed. In turn, this downregulation can reduce the viability of the malignancies (111–113).

On the other hand, *FTO*'s important involvement in cellular metabolism is thought to be a key element in cancer etiology (86). *FTO* can regulate the posttranscriptional modification of relevant genes (92, 114). *FTO* plays an oncogenic role as an m6A demethylase. The m6A alteration of mRNA can influence cancer-related gene expression at the posttranscriptional stage by either boosting mRNA stability or increasing mRNA translation efficiency by recognizing m6A reader proteins (115, 116). Tao et al. indicated that through the MALAT1/miR-384/MAL2 axis, *FTO* enhances

bladder cancer (BLCA) cell viability and tumor growth. They illustrated that *FTO* can reduce miR-384 transcript levels that result in upregulation of MAL2 expression as well as MALAT1. Thus FTO/MALAT1/miR384/MAL2 can be an essential pathway in BLCA cell development (117).

FTO and pyrroline-5-carboxylate reductase 1

PYCR1 (pyrroline-5-carboxylate reductase 1) catalyzes the conversion of pyrroline-5-carboxylate to proline in the presence of NAD(P)H (118). Proline is an AA that is abundantly available in the cellular microenvironment. There is an association between the synthesis and metabolism of proline and the urea cycle, pentose phosphate pathway, and tricarboxylic acid cycle; hence, the synthesis and metabolism of proline are crucial for tumor cells (119). The first step in proline catabolism is catalyzed by proline dehydrogenase/proline oxidase (PRODH/POX), and its function in tumors has drawn attention because it has been identified as the *P53*-induced gene in tumor cell lines (120). Downregulation of PRODH/POX is observed in various types of human tumors, in particular, those in the colon, kidney, rectum, and stomach. It acts as a mitochondrial tumor suppressor mainly via inhibition of cell proliferation, apoptosis induction, and suppression of hypoxia-inducible factor 1 signaling (121); however, the proline synthesis function in cancer is still unclear. The last step of proline synthesis is catalyzed by PYCR, and 3 human genes encode 3 isozymes of PYCR. Individuals with autosomal-recessive cutis laxa type 2 show a mutation in *PYCR1*, which indicates the vital role of proline in normal development (122). Several studies revealed *PYCR1* overexpression in many cancers, such as prostate cancer, NSCLC, BLCA, and BC (123, 124). Moreover, it has been reported that *PYCR1* has an oncogenic role by increasing proliferation and decreasing apoptosis through its interaction with *myelocytomatosis (MYC)* or some cell cycle checkpoints (123).

Although the carcinogenic role of *FTO* has long been appreciated, the underlying mechanism via RNA m6A demethylation remained unclear until it was first demonstrated as a prevalent demethylase of RNA and DNA in 2011 (92). It was then indicated that *FTO* directs gene expression via altering the mRNA m6A methylation level, acting to promote oncogenesis (125). Song et al. described the FTO role in BLCA. They discovered high expression of the FTO protein, but not mRNA, in BLCA tissues and cell lines because of ubiquitin specific peptidase 18 (USP18)-imposed posttranslational deubiquitination on the N-terminal protein domain. m6A methylation on the *PYCR1* gene was reduced by stabilized FTO, and the *PYCR1* mRNA half-life was extended to promote BLCA cell migration and proliferation in vitro and tumor growth in vivo. Moreover, they concluded that the *FTO/PYCR1* signaling network can be a vital network for cell proliferation, migration, and tumor onset and progress (124).

FTO and phosphatidylinositol 3-kinase/protein kinase-B signaling pathway

The PI3K/AKT (phosphatidylinositol 3-kinase/protein kinase-B) signaling pathway is an essential interconnected signaling pathway, which regulates several essential cellular processes, such as survival, cell growth, differentiation, cellular metabolism, nutrient uptake, and anabolic reactions in response to various signals, including G-protein-coupled receptor signaling and growth factor receptor tyrosine kinases (RTKs) (126, 127). Importantly, this signaling pathway interacts with oncoproteins and tumor suppressors, which are involved in metabolic/signaling dysregulations characteristic of human cancer cells. Abnormal PI3K/AKT activation has been observed in multiple human malignancies, which is related to tumor growth, angiogenesis, and survival (128, 129). The PI3K/AKT pathway can be aberrantly activated by RTKs, somatic mutation in vital elements of the pathway, and abnormalities of AKT and rat sarcoma virus (RAS) (130, 131).

It has been reported that there is altered expression of the PI3K/AKT pathway components in connection with m6A mRNA methylation alterations in different types of cancer. As already mentioned, the *FTO* gene has an eraser role in m6A modification, which can influence target genes via demethylase activity (5). It has also been reported that decreased m6A methylation due to increased *FTO* expression can lead to the augmentation of PI3K/AKT, which can be associated with tumorigenesis in gastric cancer (132). In addition, *FTO* caused activation of PI3K/AKT in estrogen-receptor-positive BC cells, promoting the production of lactic acid and glycolysis, as well as cell proliferation (133). Similarly, a previous study found a possible significant relation between *FTO* and BC risk, with the status of estrogen receptors affecting the relation between BC and *FTO* gene polymorphisms (134). BC cell proliferation can be promoted by estrogen through upregulating *FTO* expression and activating the PI3K/AKT signaling pathway in estrogen-receptor-positive cases (134). Further, upregulation of *FTO* in estrogen-induced endometrial cancer was observed, and PI3K/AKT signaling pathway activation increased the invasion and proliferation of endometrial cancer cells (135).

FTO and PKM2

Pyruvate kinase (PK) is an important enzyme for glycolysis, which is encoded by 4 subtypes from 2 groups of genes, although the expression of the M2 subtype of *PKM2* occurs mostly during embryonic development in healthy humans, and is associated with tissue regeneration and repair. PKM2 can be aggregated into dimeric and tetrameric states and may have a role in tumor tissues. PKM2 in the dimeric form has the ability to enter the nucleus for the regulation of gene expression; the transformation between them importantly plays a role in epithelial-mesenchymal transition (EMT), tumor cell energy supply, metastasis, invasion, and cell proliferation (136). *PKM2* overexpression is observed in a broad range of human cancers, e.g. gastrointestinal cancer,

cervical cancer, and CRC (137–139). Wong et al. reported the role of PKM2 in regulating cancer metabolism and noted that posttranscriptional modification of PKM2 leads to regulation of its activity and the Warburg effect can promote tumorigenesis (140).

As mentioned above, FTO is a vital demethylase in the dynamic and reversible modification of m6A, which regulates several biological processes, such as RNA stability, alternative splicing, and mRNA translation (141). According to Li et al., upregulation of *FTO* occurred in hepatocellular carcinoma (HCC) tissue and cells, with the m6A concentration in the HCC cells increasing when *FTO* was silenced, which was in accordance with its role as a demethylase. In their investigation, the functional assay indicated that knockdown of *FTO* could repress HCC progression by influencing proliferation and apoptosis. In an in vivo mouse assay, they found that knockdown of *FTO* could repress tumor growth, suggesting that *FTO* functions as an oncogene in HCC oncogenesis, possibly through its function of regulating the demethylation of mRNA. They showed that FTO triggered the demethylation of *PKM2* mRNA and accelerated its translation. These results suggest that *FTO* co-ordinately targets *PKM2* to regulate HCC progression (142).

FTO and myeloid zinc finger 1

Myeloid zinc finger 1 (MZF1) belongs to the SCAN-Zinc Finger (SCAN-ZF) transcription factor family, which plays a role in myeloid differentiation and leukemia and also in the etiology of major solid tumors, including cervical, lung, colorectal, and BC (143, 144). The location of the human *MZF1* gene is on the end of chromosome 19q and telomere shortening in aging cells may influence the biology of *MZF1*. Moreover, the influence of *MZF1* on tumorigenesis can be related to its ability to encode multiple transcripts with different characteristics. The effect of *MZF1* on malignant cell migration and invasiveness can be dependent on its posttranslational modification (145).

The relation between *MZF1* m6A posttranslational modification and FTO with demethylase activity has been reported by Liu et al. in lung squamous cell carcinoma (LUSC) (146). They first showed the prognostic value of FTO in LUSC, they then reported that FTO can reduce *MZF1* m6A concentrations, resulting in increasing mRNA stability of the *MZF1* transcript, leading to oncogenic functions related to *MZF1*. Thus, they concluded that m6A demethylase induced by FTO facilitates tumor progress in LUSC by regulating *MZF1* expression (146). Furthermore, available studies have indicated that *MZF1* may enhance proto-oncogene *c-Myc* expression (147), with a potential contribution to the occurrence of CRC (148). Consistent with these results, Zhang et al. indicated that the *MZF1*/*c-MYC* axis can be affected by *FTO* in CRC. They showed that FTO, through m6A demethylase, can increase *MZF1* and subsequently the *c-MYC* proto-oncogene. Thus, *FTO* may cause proliferation of CRC cells by upregulating the *MZF1*/*c-Myc* axis (149).

FTO and USP7

USP7 was originally discovered as a partner of the herpes simplex virus type 1 (HSV-1) regulatory protein infected cell polypeptide 0 (ICP0) (150). USP7 has extensive roles in several cellular pathways (151), including regulation of the activities of proteins characterized as tumor suppressors, immune responders, DNA repair proteins, epigenetic modulators, and viral proteins. In addition, USP7 has a vital role in genome stability and regulating the *p53*/*Mdm2* signaling axis. As a result of USP7 inhibition, the oncogenic E3 ligase mouse double minute 2 homolog (MDM2) is degraded, resulting in re-activation of the tumor suppressor *p53* in different types of cancer (152). Moreover, through USP7-mediated regulation of the *MDM2-p53* pathway, WD-repeat domain 79 (WDR79) promotes the proliferation of NSCLC cells (153). Additionally, according to reports, USP7 inhibitors downregulate coiled-coil domain containing 6 (*CCDC6*), leading to the sensitization of lung neuroendocrine cancer cells to poly ADP-ribose polymerase (PARP) inhibitor drugs (154).

Regulation of *USP7* at the posttranscriptional level through m6A demethylation by FTO and its relation to cancer has been demonstrated by Li et al. (155). They found upregulation of *FTO* in human NSCLC tissues in comparison with noncancer tissues and in cancer cell lines in comparison with normal lung epithelial cells. They also showed that as a result of the downregulation of *FTO*, cell proliferation and colony formation of lung cancer cells in vitro and growth of lung cancer cells in vivo were repressed. In their study, the overexpression of *FTO* led to increased stability of *USP7* mRNA through demethylation of its mRNA. Finally, they introduced the *FTO-USP7* axis as an essential pathway involved in human NSCLC (155).

FTO and *MYC*

Frequent deregulation of the *MYC* proto-oncogene in human cancers has been reported, which can promote the growth and proliferation of tumor cells. Altered metabolism induced by deregulation of the *MYC* proto-oncogene is characterized by improved glycolysis, increased nutrient uptake, increased FA and nucleotide synthesis, and glutaminolysis, which is the mark of *MYC*-driven cancers. In addition, metabolism is altered by *MYC* via posttranscriptional and transcriptional regulation (156). Indeed, it has been shown that *MYC* signaling can enable tumor cells to escape the host immune response and dysregulate their microenvironment (157).

FTO overexpression, in terms of its m6A demethylase role, has been demonstrated in certain subtypes of acute myeloid leukemia (AML) (158). Li et al. indicated enhancement of the proliferation, transformation, and viability of AML cells by *FTO* via reducing m6A modification in AML cells and elevating *MYC*/CEBPA (CCAAT Enhancer Binding Protein α) transcript stability and suppressing relevant gene transcription such as ASB2 (ankyrin repeat and SOCS box containing 2) and RARA (retinoic acid receptor, α) (159). CEBPA is a vital hematopoiesis-related transcription factor that is essential for leukemogenesis (160). ASB2

and RARA had an antileukemic effect through degrading MLL during hematopoietic differentiation via ubiquitination (161). Therefore, through upregulation of *MYC*/CEBPA and downregulation of ASB2 and RARA, *FTO* promotes leukemia cell viability, proliferation, transformation, and leukemogenesis, and inhibits cell-cycle arrest and apoptosis (18). In addition, the *FTO*/m6A/*MYC* signaling pathway has been proposed in gastric cancer cells. As indicated by Yang et al., increased *FTO* and decreased m6A methylation in gastric cancer cells can promote the stability of *MYC* mRNA, enhancing the metastasis and invasion of gastric cancer cells (162). These findings broadly support the work of other studies in this area linking *FTO* and m6A demethylase modification with upregulation of *MYC* as an underlying pathway in cancers such as cervical, colorectal, and pancreatic (22, 163, 164).

Small molecule inhibitors targeting *FTO*

Since the identification of FTO as an m6A demethylase in 2011 (92), researchers have been working to find small molecule inhibitors that specifically target FTO's m6A demethylase activity. FTO has a strong Fe(II) and alpha-ketoglutarate (Alpha-KG)-dependent dioxygenase activity at the N-terminals (165). Chen et al. reported that rhein, a natural substance, competitively binds to an FTO active site and inhibits FTO-dependent m6A demethylation in cells by breaking the bindings between FTO and the m6A substrate (166). In 2014, Zheng et al. developed a selective FTO inhibitor (i.e. MO-I-500), which selectively inhibits the m6A demethylase activity of FTO and increases the concentration of m6A in cells (167). In addition, this FTO inhibitor could significantly inhibit the survival and/or colony formation of human SUM149 cells, a triple-negative inflammatory BC cell line (168). Meclofenamic acid (MA), a nonsteroidal anti-inflammatory drug, has been found to block FTO's m6A demethylase activity while reducing ALKBH5 expression (169). Furthermore, compound 12, created via an alpha-KG tethering method, may have the potential to selectively inhibit FTO over other AlkB subfamilies (including ALKBH5) and alpha-KG oxygenases (170). Su et al. discovered that R-2HG is a direct FTO inhibitor that inhibits the m6A demethylase activity of FTO in a dose-dependent manner, resulting in a considerable increase in global m6A abundance in R-2HG-treated sensitive leukemia cells (171). In addition, 4-chloro-6-(6′-chloro-7′-hydroxy-2′,4′,4′-trimethyl-chroman-2′-yl) benzene-1,3-diol (CHTB) is supposed to be another inhibitor of *FTO* which contributes to the regulation of mRNA splicing and adipogenesis by modulating m6A concentrations (172). Recently, Huang et al. developed 2 FTO inhibitors, FB/FB23, that specifically reduce FTO's m6A demethylase activity. They showed antiproliferative and proapoptotic effects in AML cell lines in vitro, as well as extending the survival of AML animal models in vivo (173). Finally, the discovery of FTO inhibitors may demonstrate the vast therapeutic promise of targeting *FTO* in cancer.

Conclusion

A growing body of evidence suggests that there is a significant association between individual lifestyle factors, such as dietary intake, physical activity, and BMI with *FTO* expression. An overall improper lifestyle such as the overconsumption of foods, sedentary lifestyle, and higher BMI were associated with *FTO* overexpression (23–25). Moreover, some polymorphisms of *FTO* can influence the association between lifestyle and *FTO* expression (23, 39, 60, 67, 78). On the other hand, FTO with m6A demethylase activity has been shown to regulate the expression of a number of important target genes through posttranscriptionally reducing their m6A concentrations and thereby affecting the stability and/or splicing of target mRNAs, in turn, promoting adipogenesis, tumorigenesis, and drug resistance of cancer cells (86). More importantly, increasing proof reveals the dysregulation of FTO in terms of its role in m6A demethylation in cancer development, such as acute myeloid leukemia (159), melanoma (174), BC (175), and lung cancer (155). Therefore, *FTO* seems to be a mediator player between an improper lifestyle and cancer-related pathways (Figure 2). However, there is no clear knowledge regarding the precise relation between lifestyle and *FTO* expression as well as the exact function of *FTO* and molecular mechanisms in cancer, much work is still required. Further knowledge in this context will provide essential insights into the better management of cancer.

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Data Availability

The data of this article will be made available by the authors, if they are requested, to any qualified researcher.

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