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REVIEW ARTICLE

FTO as an epigenetic regulator in metabolic and inflammatory diseases

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Abstract

Obesity has emerged as a global health crisis in the 21st century, driven by rising obesity rates and associated metabolic disorders. The genome-wide association studies led to the identification of a gene associated with obesity and thus named the fat mass and obesity-associated (*FTO*) gene. In humans, the *FTO* gene is expressed in various tissues, including the brain, liver, and adipose tissue. It is known to play a major role in regulating energy balance, appetite, and body fat mass. *FTO* encodes an N6-methyladenosine RNA demethylase that regulates key biological processes, including adipogenesis, energy homeostasis, and glucose metabolism, through a dynamic RNA modification process involving splicing, export, decay, and/or translation. Polymorphisms in the *FTO* gene, particularly within intron 1, are strongly associated with increased risk of body mass index and obesity. In addition, *FTO* has been implicated in the pathogenesis of type 2 diabetes mellitus, cardiovascular disease, chronic kidney disease, and various cancers, where it could function both as an oncogene and a tumor suppressor gene. Pre-clinical studies have established the functional relevance of FTO, where its overexpression promotes obesity, whereas its deletion allows maintenance of a normal body phenotype. This review covers the recent advances in the development of specific FTO inhibitors and highlights their potential as therapeutic agents for obesity and metabolic disorders, although their development is still in its early stages. Despite the significant progress made in understanding the role of FTO in metabolic diseases, further research is needed to elucidate the precise mechanisms linking *FTO* variants to specific pathological outcomes and to optimize targeted therapies.

Keywords: FTO; N6-methyladenosine; Metabolic dysfunction-associated steatotic liver disease; Obesity; RNA demethylase; Inhibitors; Single nucleotide polymorphisms; RNA demethylation

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1. Introduction

Overweight and obesity pose significant health risks that are characterized by abnormal or excessive accumulation of adipose tissue, both in size (hypertrophy) and number (hyperplasia).[1] These conditions are commonly classified based on body mass index (BMI), where BMI >25 is defined as overweight, and BMI >30 is categorized as obese.[2] According to the World Health Organization (WHO), the prevalence of overweight and obesity has continued to rise in both adults and children, and over 1 billion people worldwide will become obese by 2030.[3]

Obesity is a chronic multifactorial disease that adversely affects overall health and quality of life. It is influenced by genetic predisposition, physiological mechanisms, environmental factors, and lifestyle choices, including diet and physical activity levels.[4] The primary underlying cause is sustained energy imbalance, wherein excessive caloric intake leads to lipid accumulation and adipocyte hypertrophy, resulting in increased secretion of pro-inflammatory cytokines.[1] Chronic inflammation contributes to insulin resistance and impaired glucose and lipid metabolism, leading to metabolic syndrome (MetS), a key factor in obesity-related complications.[5,6] Obesity is associated with increased risk of numerous medical conditions, including cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), hypertension, dyslipidemia, nonalcoholic fatty liver disease, and several malignancies.[5] Besides, it has profound psychological and psychosocial consequences that affect self-esteem and mental health.[6]

The genome-wide association studies have shown that the fat mass and obesity-associated (*FTO*) gene has a strong association with the obesity risk.[7,8] Genetic variations in the *FTO* gene are strongly associated with increased BMI and obesity risk, as well as a higher risk of developing different cancers in diverse populations.[8] The role of single-nucleotide polymorphisms (SNPs) in the pathophysiology of obesity and cancer is increasingly becoming clear.[2,9] At the molecular level, it involves dynamic regulation of N6-methyladenosine (m6A) modifications in nucleic acids, particularly RNAs.[9] FTO is a member of the Fe(II) and 2-oxoglutarate (2OG)-dependent oxygenase superfamily,[7] primarily functioning as an oxidative demethylase by catalyzing the conversion of m6A to N6-hydroxymethyladenosine and then to adenosine through N6-formyladenosine intermediate (Figure 1).[10]

Recently, FTO has gained attention as a potential RNA demethylase or an "eraser" that has a profound influence on mRNA stability, protein translation, and disease development (Figure 2). The FTO protein selectively interacts and co-localizes with RNA-binding proteins and splicing factors in an RNA-independent manner across the transcriptome, facilitating m6A demethylation in proximity to splicing factor, proline-, and glutamine-rich (SFPQ) binding sites.[11] SFPQ binds and interacts with the CUGUG consensus sequence on RNA and recruits FTO. The C-terminal domain (CTD) of FTO facilitates this interaction, enhances RNA substrate selectivity, and mediates localized demethylation. The reversible nature of m6A marks in gene transcripts makes it a promising therapeutic target for FTO-related interventions.

Significant efforts have focused on developing small-molecule inhibitors to block the demethylase activity of FTO and regulate gene expression involved in pathophysiological changes. However, the clinical relevance of FTO in obesity and metabolic diseases is still unclear. This review explores the key roles of FTO in health and disease and in managing metabolic disorders.

2. *FTO* gene and protein

2.1. Discovery of the *FTO* gene

The *FTO* gene was originally discovered as one of six genes that naturally localized within a 1.6 Mb region on chromosome 8 in a fused toe (Ft) mouse model.[7] Earlier, it was known as *Fatso*, on account of its large size, but was later dubbed as *FTO* (Figure 3).[10,12]

2.2. Origin and evolution of the *FTO* gene

The evolutionary lineage of the *FTO* gene spans approximately 450 million years. Sequence homology analyses across species, from mammals to unicellular organisms (such as diatoms and green algae), reported good sequence conservation at both the nucleotide and amino acid levels.[7,8] *FTO* is present as a single copy gene with no variants or isoforms in all vertebrates, except for humans (based on the National Center for Biotechnology Information [NCBI] database). Homology analysis of the FTO protein revealed a high degree of sequence conservation among different vertebrate species, each of which carries two conserved protein sequence motifs, namely "MAVSWHHDENLV" and "PRFSSTHRVA," in the middle region (NCBI database; Figure 4). The human and mouse *FTO* genes share a close sequence alignment, with each containing nine exons. While the *FTO* gene is localized on chromosome 16q12.2 in humans, it is present on chromosome 8 in mice.[7] Sequence homology between mouse and human FTO proteins is approximately 87%, whereas mouse and rat FTO proteins share 96% similarity (NCBI database). In addition, the human FTO protein and its vertebrate homologs are globular in structure and contain a nuclear localization signal, indicating a primary nuclear function.[12]

The *FTO* gene is expressed in various animal tissues and is widely dispersed across a variety of biological taxa.[10] Notably, it is highly expressed in the skeletal muscle and adipose tissue.[10,12] Its most prominent expression is observed in the hypothalamic arcuate nucleus, which is crucial for regulating energy balance and may play a key role in appetite regulation and metabolic processes.[7,10] The *FTO* gene encodes a protein with RNA demethylase activity essential for controlling a wide range of biological and metabolic processes. The gene is highly polymorphic, with many variations listed in the NCBI dbSNP database. FTO polymorphisms, especially those found in intron 1, are associated with (MetS; Table 1). These genetic loci are

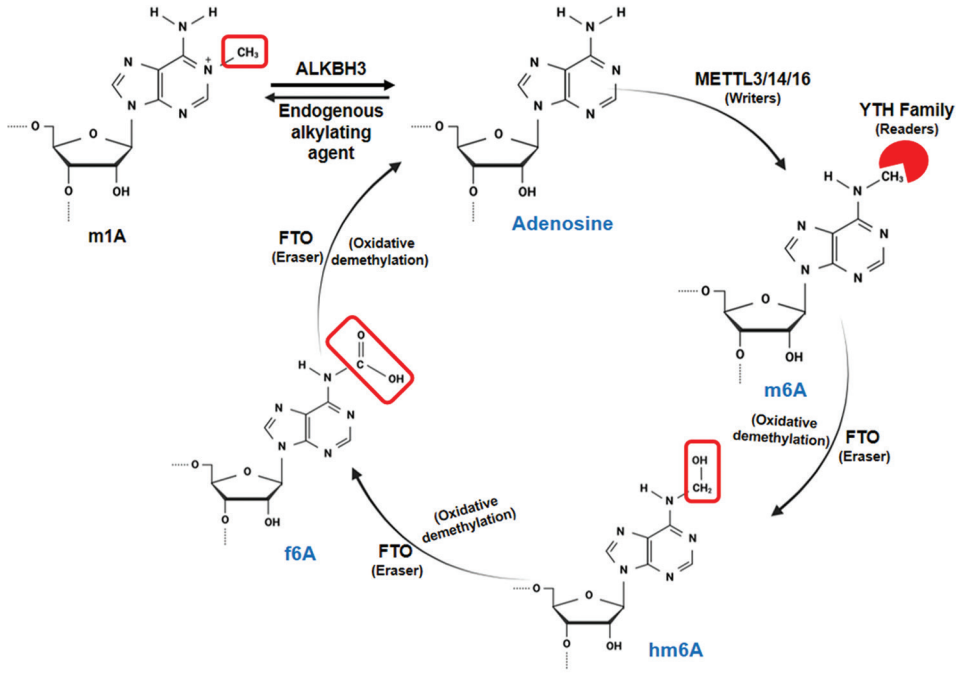


Figure 1. Biochemistry of the N6-methyladenosine (m6A) demethylation process. Adenosine undergoes methylation at the sixth position, a process facilitated by N6-adenosine methyltransferase-like 3/14/16 (METTL3/14/16) enzymes. Fat mass and obesity-associated protein catalyzes oxidative demethylation reactions of m6A. The N6-methyl group undergoes oxidation in the presence of Fe(II) and α-ketoglutarate, leading to the formation of N6-hydroxymethyladenosine (hm6A) and N6-formyladenosine (f6A). In contrast, methylation at the first position of adenosine occurs through an endogenous alkylating agent and can be reversed by alpha-ketoglutarate-dependent dioxygenase alkB homolog 3 demethylase. Figure was created with BioRender.com (https://BioRender.com/z9rg2dy).
Abbreviation: m1A: N1-methyladenosine.

Table 1. *FTO* single-nucleotide polymorphisms (SNPs) and their associated diseases

SNP	Location in gene	Associated traits/diseases	References
rs9939609	Intron 1	Increased BMI, obesity, T2DM, metabolic syndrome, CVD, CAD, atherogenic lipid profile, elevated C-reactive protein, hypertension, increased risk of certain cancers (lung, renal, breast, prostate, pancreatic, endometrial, and melanoma)	9,15-17
rs1421085	Intron 1	Increased BMI, obesity, T2DM, metabolic syndrome	17
rs17817449	Intron 1	Increased BMI, obesity, T2DM, metabolic syndrome, CVD	9,17
rs8043757	Intron 1	Increased BMI, obesity	2

Abbreviations: BMI: Body mass index; CAD: Coronary artery disease; CVD: Cardiovascular disease; T2DM: Type 2 diabetes mellitus.

categorized as intronic polymorphisms (e.g., rs9939609 and rs17817449), exonic polymorphisms (e.g., rs79206939), and promoters (e.g., rs62048369).[13] Moreover, strong correlations have also been found between obesity and MetS biomarkers, such as waist circumference, blood pressure, and levels of triglycerides, high-density lipoprotein, and fasting blood glucose, in association with variations within intron 1, such as rs993960976.[14]

2.3. Structure and function of *FTO* protein

The *FTO* gene variants exhibit a significant variability in their structure, size, and function. The human *FTO* gene encompasses 12 known isoforms, whereas mice have only one isoform, reflecting the complexity of FTO regulation in humans. The function and expression of mouse FTO protein (502 aa) share a similar pattern to that of human FTO-3 (505 aa). The domain structure of the FTO protein was elucidated after the resolution of the crystal structure of the human FTO isoform 3.[10] This isoform carried a catalytic core N-terminal domain (NTD) with demethylase activity (amino acids 32–325). The CTD (amino acids 326–505) adopts a three-helix bundle configuration, one end of which interacts extensively with the NTD to provide structural stability and to regulate the enzymatic

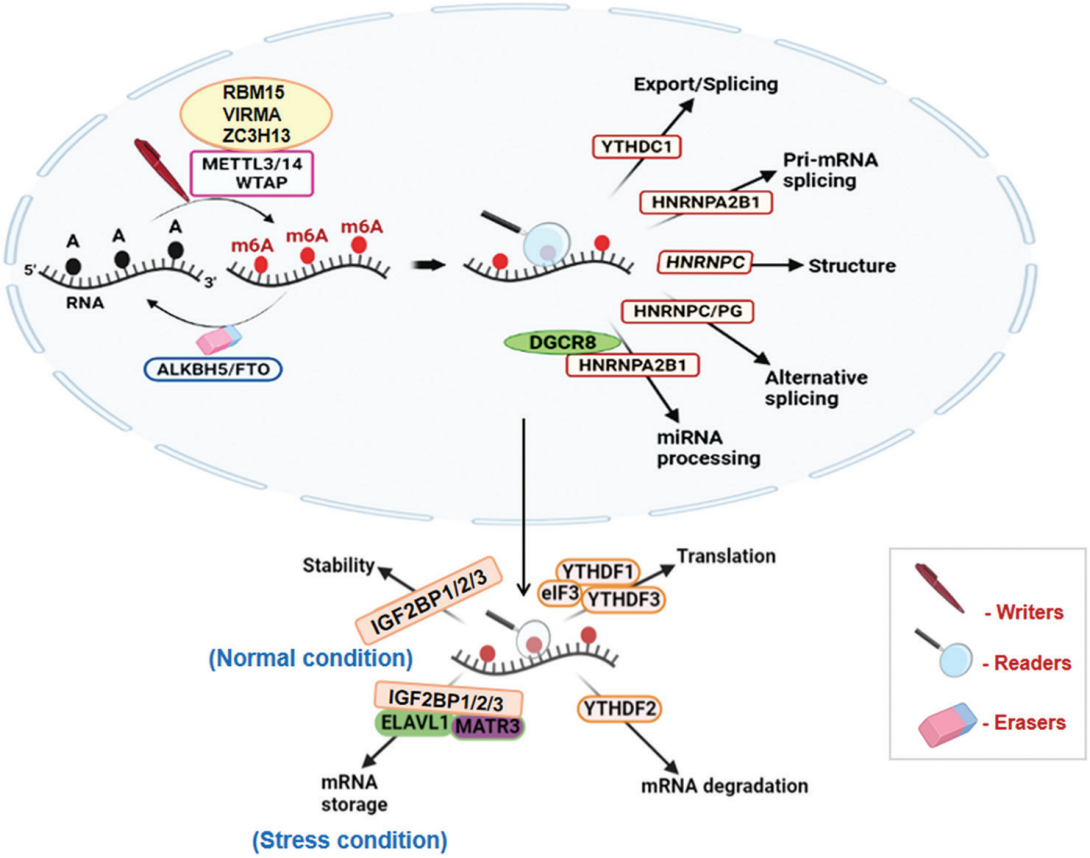


Figure 2. Dynamic regulation of N6-methyladenosine (m6A) modification in mRNA. Methyltransferases, including N6-adenosine methyltransferase-like 3/14 and WT1-associated protein, behave as writers and incorporate m6A signatures into gene transcripts. Demethylases such as fat mass and obesity-associated protein and alpha-ketoglutarate-dependent dioxygenase alkB homolog 5 act as erasers by removing m6A signatures from transcripts, whereas readers such as YTH family and others determine the transcript fate. Figure was created with BioRender.com (https://BioRender.com/eei3fb1).
Abbreviations: DGCR8: DiGeorge syndrome critical region 8; IGF2BP1: Insulin-like Growth Factor 2 mRNA Binding Protein 1; eIF3: Eukaryotic translation initiation factor 3; ELAVL1: ELAV-like protein 1; HNRNP: Heterogeneous nuclear ribonucleoproteins;; MATR3: Matrin-3; mRNA: Messenger RNA; miRNA: micro RNA; RBM15: RNA-binding protein 15; VIRMA: vir like m6A methyltransferase associated; YTHDC1: YTH domain-containing protein 1; YTHDF: YTH domain-containing family protein; ZC3H13: Zinc finger CCCH domain-containing protein 13.

activity of FTO (Figure 5).[7] Highly conserved residues, such as His231, Asp233, and His307, within the double-stranded β-helix of the NTD play a crucial role in Fe^{2+} chelation. Although the structure–function relationship of FTO-3 has been investigated in detail, the functions and sites of expression of other isoforms remain unknown. Nevertheless, these findings offer structural insights into FTO's substrate specificity and establish a framework for the rational design of FTO inhibitors.[10]

The NCBI database suggests that among the 12 FTO isoforms in humans, FTO-1 is the longest (526 aa) isoform, whereas FTO-11 (334 aa) is the shortest isoform containing an "unstab_antitox" module (Figure 6). However, the organ-specific functions of FTO isoforms in obesity-associated diseases need to be investigated as their biological functions remain poorly understood.

3. Roles of *FTO* in metabolic regulation and disease susceptibility

3.1. *FTO* and insulin resistance

Insulin is the only hormone that lowers blood glucose levels.[18] Impaired β-cell function and insufficient insulin production in the body lead to insulin resistance (a hallmark of T2DM), glucose-sensitive organ damage, and vital function impairment. It has been reported that obesity and higher BMI increase the risk of developing T2DM.[19-21] Excess body fat increases the release of free fatty acids, inflammatory cytokines, and other metabolic byproducts that disrupt insulin signaling, leading to insulin resistance[20] (Figure 7). In animal models, hepatic *FTO* mRNA levels were increased in fasting mice with reduced body weight and low blood glucose levels,[7] whereas

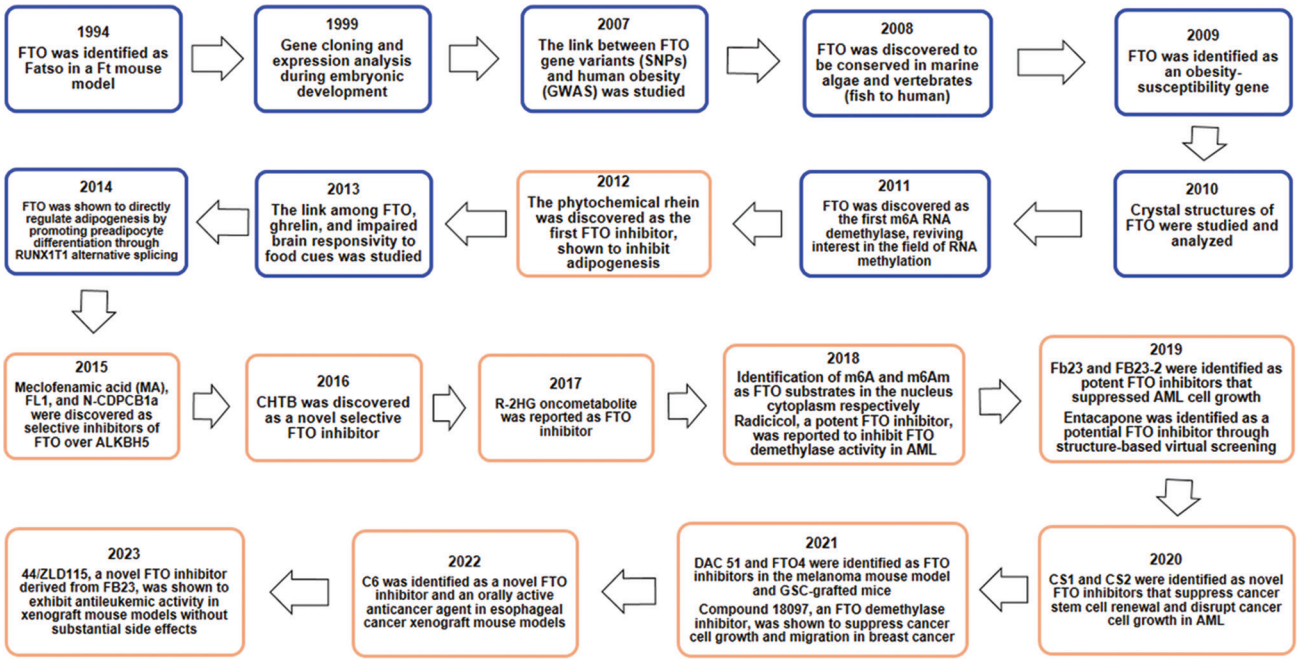


Figure 3. Timeline of fat mass and obesity-associated (*FTO*) gene and protein research. The events related to FTO discovery and biology are shown in blue boxes. Novel and FTO-selective inhibitors are shown in brown boxes. Image created by the authors using Microsoft PowerPoint.
Abbreviations: ALKBH5: Alpha-ketoglutarate-dependent dioxygenase alkB homolog; AML: Acute myeloid leukemia; CHTB: 4-Chloro-6-(6'-chloro-7'-hydroxy-2',4',4'-trimethyl-chroman-2'-yl)benzene-1,3-diol; FL1: Floricaula/leafy homolog 1; Ft: Fused toe; GWAS: Genome-wide association studies; GSC: glioblastoma stem cells; m6A: N6-methyladenosine; m6Am: N6, 2-O-dimethyladenosine; N-CDPCB1a: N-(5-chloro-2,4-dihydroxyphenyl)-1-phenylcyclobutanecarboxamide; R-2HG: (R)-2-hydroxyglutarate; RUNX1T1: RUNX1 partner transcriptional co-repressor 1; R-2HG: R-2-hydroxyglutarate; SNP: Single-nucleotide polymorphism.

hyperglycemic mice showed reduced levels of hepatic *FTO* mRNA than the normoglycemic controls.[19] In contrast, humans with hyperglycemia and metabolic dysfunction-associated steatotic liver disease (MASLD) showed higher *FTO* mRNA and protein levels than healthy individuals.[7] In addition, the dual function of FTO in controlling adipose tissue, as well as energy balance, is linked to the progression of obesity to diabetes.[20,21]

In patients with T2DM, glucose increases FTO expression and decreases global m6A content. The m6A methylation in gene transcripts plays a crucial role in β-cell biology, neonatal β-cell mass development, T2DM pathogenesis,[7] and glucose homeostasis regulation by pancreatic β-cells.[22,23] It also influences the maturation of β-cell insulin secretion and cell survival.[7] It has been shown that the downregulation of FTO impairs autophagy, suggesting FTO as a biomarker and therapeutic target in diabetic wound healing.[24] Furthermore, FTO influences the expression of several metabolism-associated genes, such as *FOXO1*, *FASN*, *G6PC*, and *DGAT2*, which in turn affects the pathophysiology of T2DM.[7,19,25] Research has demonstrated a negative correlation between m6A content and *FTO* mRNA expression and a positive correlation between fasting glucose levels and FTO mRNA expression in white blood cells.[7]

A genome-wide screen for T2DM susceptibility genes has identified several FTO variants that predispose individuals to obesity through their effect on BMI.[26,27] For example, FTO variants rs8050136 and rs9939609A>C are strongly associated with important markers of inflammation, obesity, and insulin resistance in an adiposity-dependent manner.[26]

3.2. *FTO* in appetite and energy balance

The prevalence of overweight and obesity has reached pandemic levels worldwide, affecting 60–70% of the adult population in industrialized nations, with numbers continuing to rise.[19] Among the genetic factors linked to obesity, the *FTO* gene has been implicated in the development of obesity and related metabolic disorders.[28] It was the first gene to be conclusively linked to obesity through GWAS, which identified SNPs within the gene that correlates with BMI, body fat rate, waist and hip circumference, as well as energy intake.[9]

FTO expression in the arcuate nucleus of the hypothalamus is regulated by feeding and fasting cycles[9] and has been shown to influence food intake in rats when selectively altered.[19] Inhibition of hypothalamic FTO activates signal transducer and activator of transcription

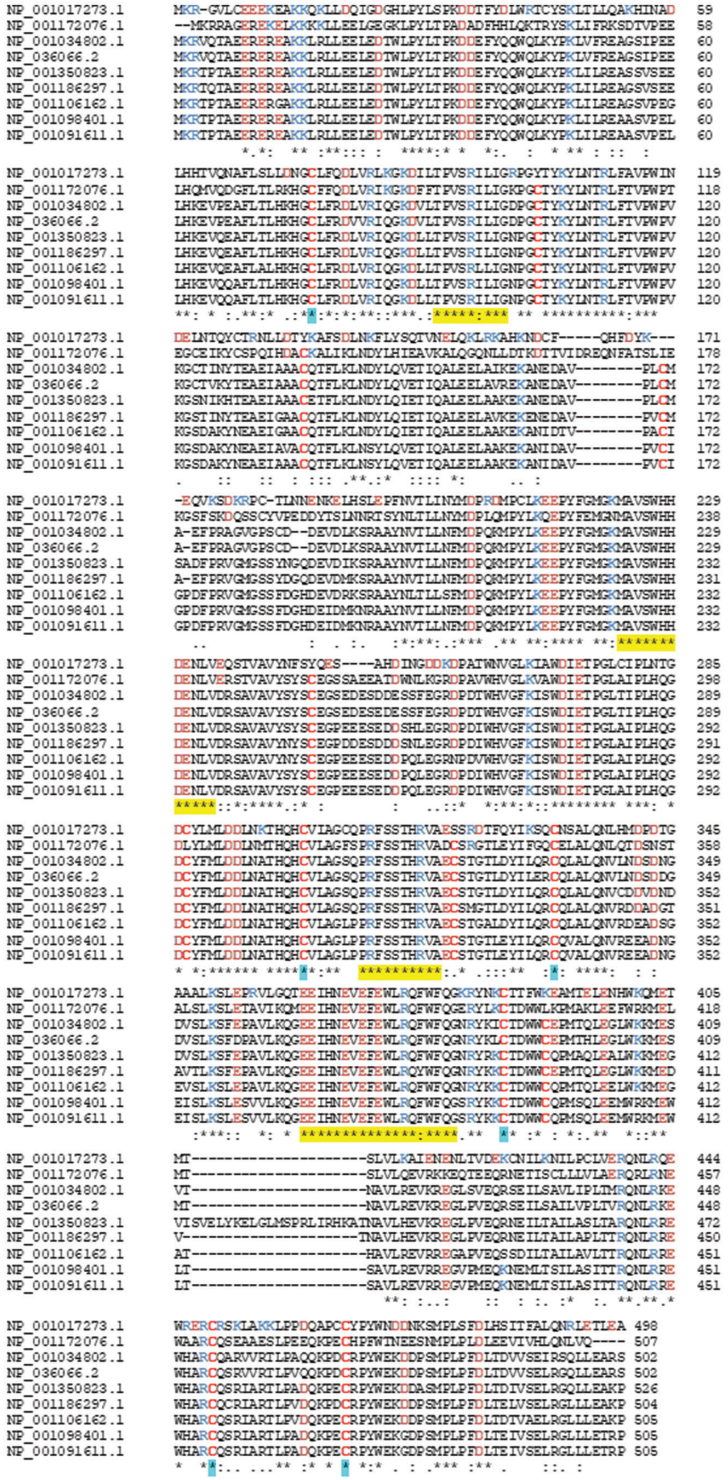


Figure 4. Sequence homology of the fat mass and obesity-associated (FTO) protein from representative vertebrate species. Alignment of amino acid sequences of the nine FTO proteins using the Clustal Omega (version 1.2.4; http://www.clustal.org/) multiple sequence alignment software. Gaps (--) were introduced to optimize the alignment of identical amino acid residues. All species encode two conserved protein sequence motifs, "MAVSWHHDENLV" and "PRFSSTHRVA" (highlighted in yellow), and six conserved cysteine residues (highlighted in blue). The gene accession numbers for the nine different FTO sequences are NP_001017273.1-frog (498 aa), NP_001172076.1-chicken (507 aa), NP_001034802.1-rat (502 aa), NP_036066.2-mouse (502 aa), NP_001350823.1-human FTO 1 (526 aa), NP_001186297.1-rabbit (504 aa), NP_001106162.1-pig (505 aa), NP_001098401.1.1-sheep (505 aa), and NP_001091611.1-cattle (505 aa). Note: Data retrieved and modified from National Center for Biotechnology Information database (https://www.ncbi.nlm.nih.gov).

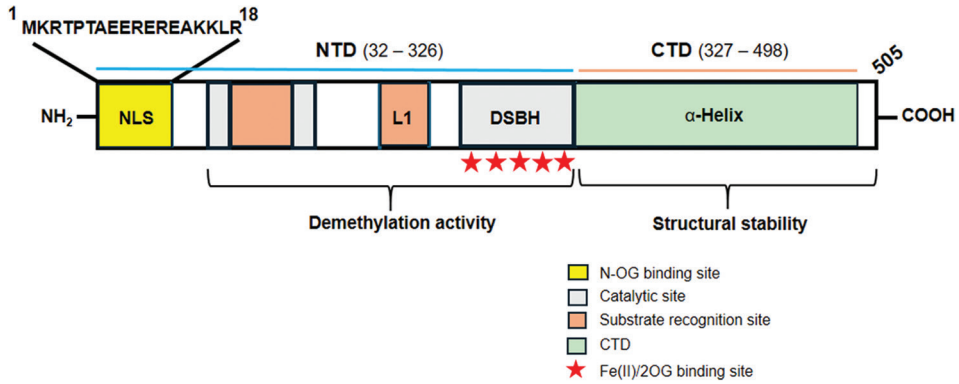


Figure 5. Functional domains of the fat mass and obesity-associated (FTO) protein. The human FTO protein, comprising 505 amino acids, contains two primary domains: the N-terminal domain (NTD) spanning 32–326 aa residues and the C-terminal domain (CTD) covering 327–498 aa residues. NTD also contains nuclear localization signals (NLS) rich in K (lysine) and R (arginine) spanning from 1 to 18, two distinct substrate recognition lids encompassing 77–102 aa residues and 103–116 aa residues, and a unique loop (L1) exclusive to FTO located between residues 210 and 223, mediating substrate specificity. The catalytic core within the NTD features a highly conserved double-stranded β-helix (DSBH) fold, resembling the structural characteristics of Fe(II)/2-oxoglutarate (OG)-dependent oxygenase. CTD interacts with the OG-binding domain in NTD for demethylation activity and maintains the structural stability of the protein. Image created by the authors using Microsoft PowerPoint.

3 (STAT3) through extracellular signal-regulated kinase 1/2 signaling, resulting in reduced food intake and body weight.[29] In addition, FTO has been implicated in the regulation of ghrelin, a hunger hormone. *FTO*-knockout mice exhibit elevated circulating ghrelin levels after prolonged fasting, whereas *FTO* overexpression in cell cultures shows reduced m6A methylation of *Ghrl* mRNA, thereby increasing ghrelin production.[13] A similar pattern is observed in humans carrying high-risk *FTO* alleles, where peripheral blood cells show increased *FTO* and *Ghrl* mRNA expression.[19] Together, these findings underscore the role of FTO in the regulation of appetite and energy balance.

3.3. *FTO* in adipogenesis

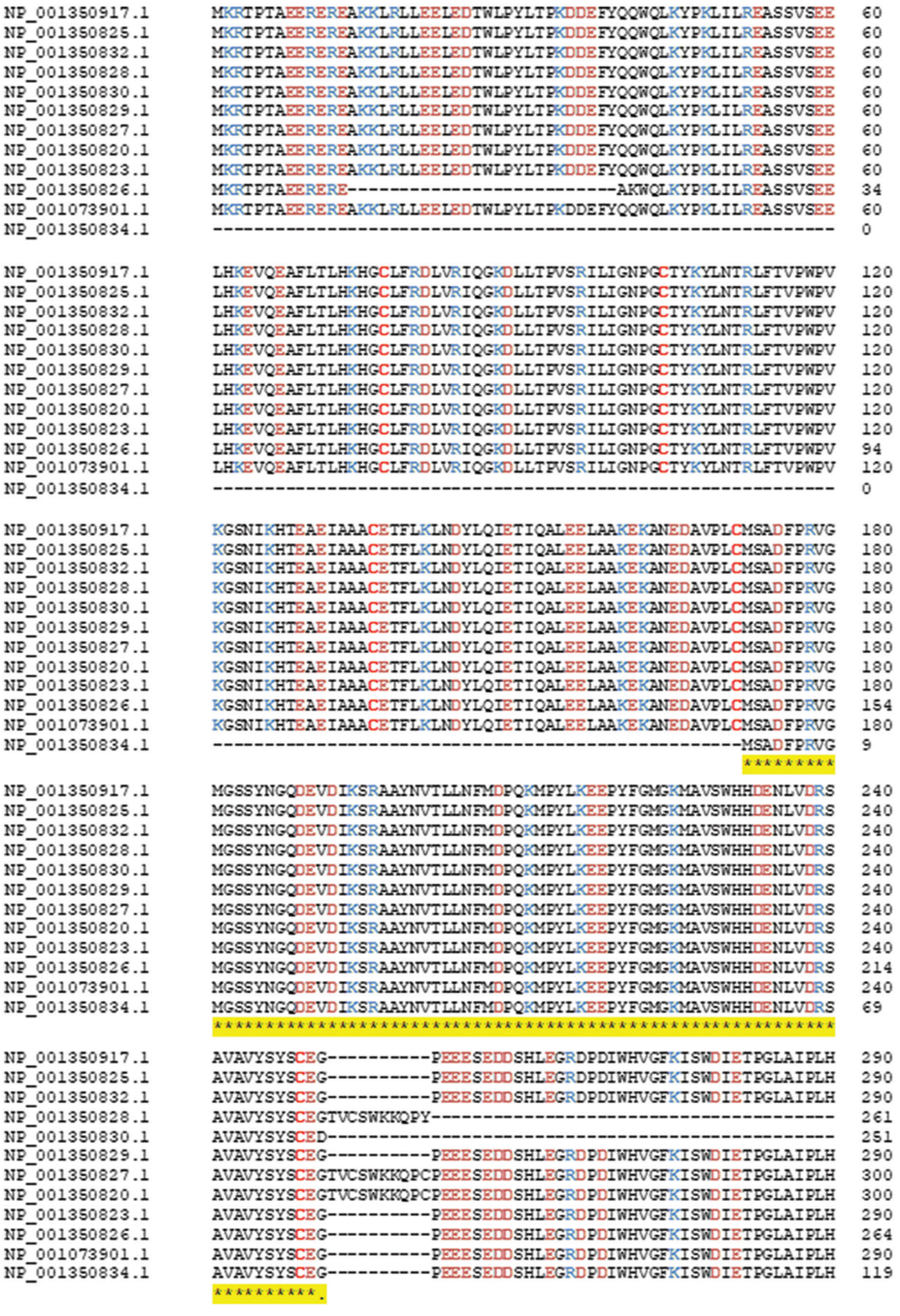
In addition to its role in regulating food intake and satiety, FTO is also involved in adipogenesis. During adipocyte differentiation, FTO expression progressively declines, whereas m6A methylation levels show a steady increase.[14] Observational studies on humans have suggested that the degree of physical activity may influence the effect of *FTO* SNPs on adiposity.[7] Notably, polymorphisms found in introns 1 (rs17817449, rs1421085, rs8050136, rs1558902, rs7206790, and rs1861868) and intron 8 (rs11644943) are strongly associated with waist circumference.[13] These associations underscore the genetic contribution of *FTO* polymorphisms to adiposity and metabolic traits, especially during early developmental stages.

It has been shown that FTO regulates important signaling pathways that control the differentiation of fat cells. Its deficiency inhibits adipogenesis in pre-adipocytes of both pig and mouse by suppressing the Janus kinase 2 (JAK2)–STAT3–CCAAT/enhancer-binding protein-beta (C/EBPβ) signaling cascade.[10] Early adipocyte differentiation depends on C/EBPβ transcription, which is mechanistically reduced in the absence of FTO due to decreased expression of JAK2 and impaired STAT3 phosphorylation. Under normal physiological conditions, skeletal muscle is the main peripheral organ involved in lipid metabolism.[23] Increased m6A methylation promotes lipid accumulation in skeletal muscle by upregulating genes linked to lipid synthase and downregulating genes linked to oxidation and lipolysis.[10,30] These results suggest FTO as a potential therapeutic target for the treatment of obesity and metabolic disorders.

In a high-fat diet mouse model, FTO overexpression leads to increased production of sterol regulatory element-binding protein 1 (SREBP1) and carbohydrate-responsive element-binding protein, promoting lipogenesis.[31] The result indicates that FTO acts as a transcriptional co-activator along with SREBP1c on the promoters of lipogenesis-related genes, thereby contributing to disease progression and severity.

3.4. *FTO* in metabolic dysfunction-associated steatotic liver disease

Nearly 25% of the adult population worldwide is affected by MASLD—the most common chronic liver disease, surpassing both T2DM and obesity in prevalence.[32] Although MASLD is highly prevalent worldwide, higher rates have been observed in countries with lower Human Development Index scores.[32,33] MASLD is also a major cause of liver-related mortality, yet no Food and Drug Administration (FDA)-approved treatment is currently


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NP_001350825.1 MKRTPTAEERERERAKKLRLLEELEDTWLPYLTPKDDEFYQQWQLKYPKLILREASSVSEE 60
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NP_001350917.1 AVAVYSYSCEG----------PEEESEDDSHLEGRDPDIWHVGFKISWDIETPGLAIPLH 290
NP_001350825.1 AVAVYSYSCEG----------PEEESEDDSHLEGRDPDIWHVGFKISWDIETPGLAIPLH 290
NP_001350832.1 AVAVYSYSCEG----------PEEESEDDSHLEGRDPDIWHVGFKISWDIETPGLAIPLH 290
NP_001350828.1 AVAVYSYSCEGTVCSWKKQPY---------- 261
NP_001350830.1 AVAVYSYSCED---------- 251
NP_001350829.1 AVAVYSYSCEG----------PEEESEDDSHLEGRDPDIWHVGFKISWDIETPGLAIPLH 290
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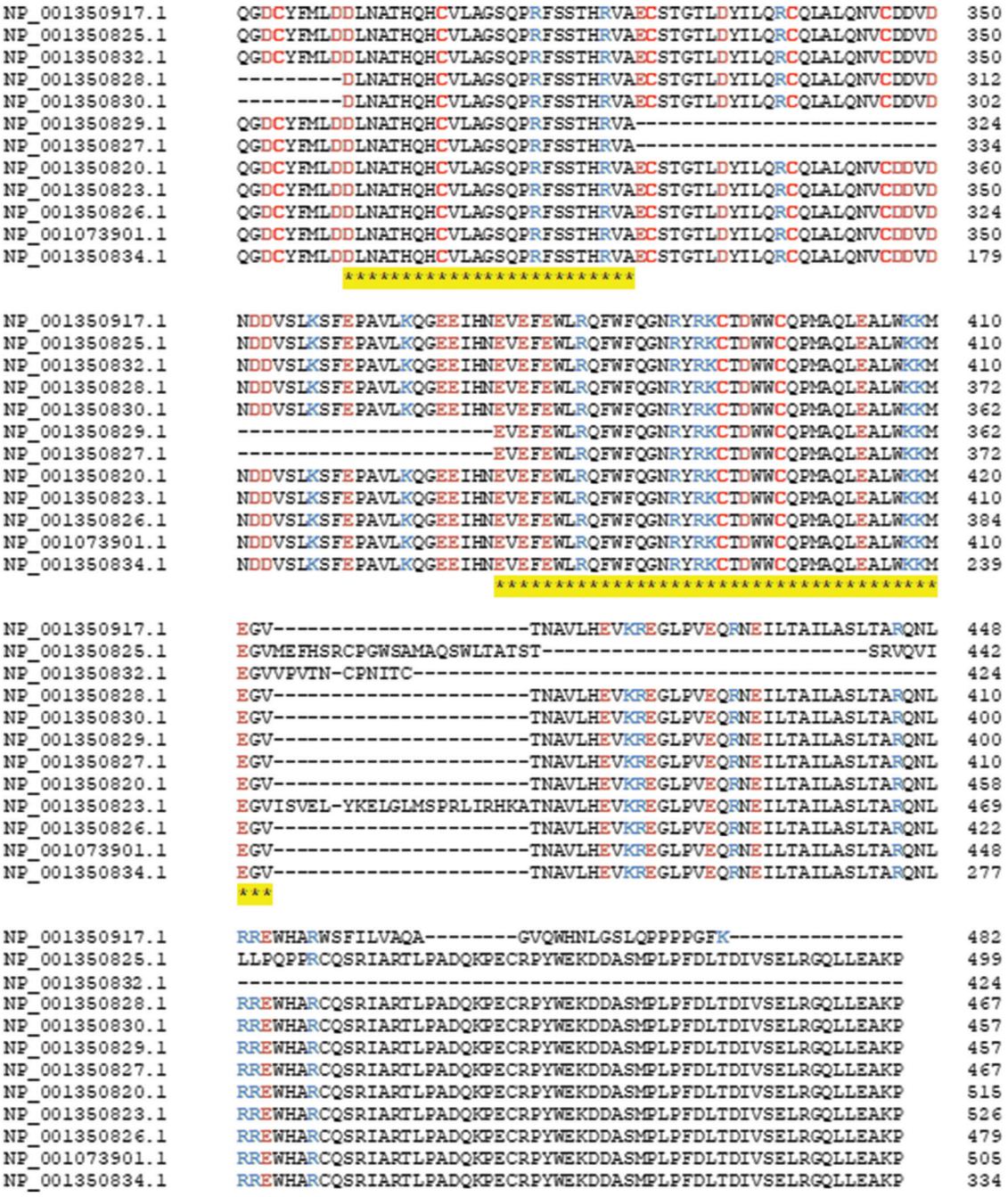


Figure 6. Sequence homology of the human fat mass and obesity-associated (FTO) protein isoforms. Alignment of amino acid sequences of the 12 human FTO isoforms using the Clustal Omega (version 1.2.4; http://www.clustal.org/) multiple sequence alignment software. Gaps (--) were introduced to optimize the alignment of identical amino acid residues. All isoforms encode three conserved protein sequence motifs (highlighted). The N-terminal motifs "MSADFPRVGMGSSYNGQDEVDIKSRAAY NVTLLNFMDPQKMPYLKEEPYFGMGKMAVSWHHDENLVDRS" and "DLNATHQHCVLAGSQPRFSSTHRVA" are catalytic domains that exhibit demethylase activity. Sequences shown in bold are conserved in the FTO protein of all vertebrates (Figure 4). The C-terminal motif—EVEFEWLRQFWFQGNRYRKCTDWWCQPMAQLEALW KKMEGV—includes the EF-hand calcium-binding domain and cyclic adenosine monophosphate-dependent protein kinase phosphorylation site (shown in bold). The gene accession numbers for the 12 different FTO isoforms are: NP_001350823.1-FTO isoform 1 (526 aa), NP_001350820.1-FTO isoform 2 (515 aa), NP_001073901.1-FTO isoform 3 (505 aa), NP_001350825.1-FTO isoform 4 (499 aa), NP_001350826.1-FTO isoform 5 (479 aa), NP_001350827.1 -FTO isoform 6 (467 aa), NP_001350828.1-FTO isoform 7 (467 aa), NP_001350829.1-FTO isoform 8 (457 aa), NP_001350830.1-FTO isoform 9 (457 aa), NP_001350832.1-FTO isoform 10 (424 aa), NP_001350834.1-FTO isoform 11 (334 aa), and NP_001350917.1-FTO isoform 12 (482 aa).
Note: Data retrieved and modified from National Center for Biotechnology Information database (https://www.ncbi.nlm.nih.gov).

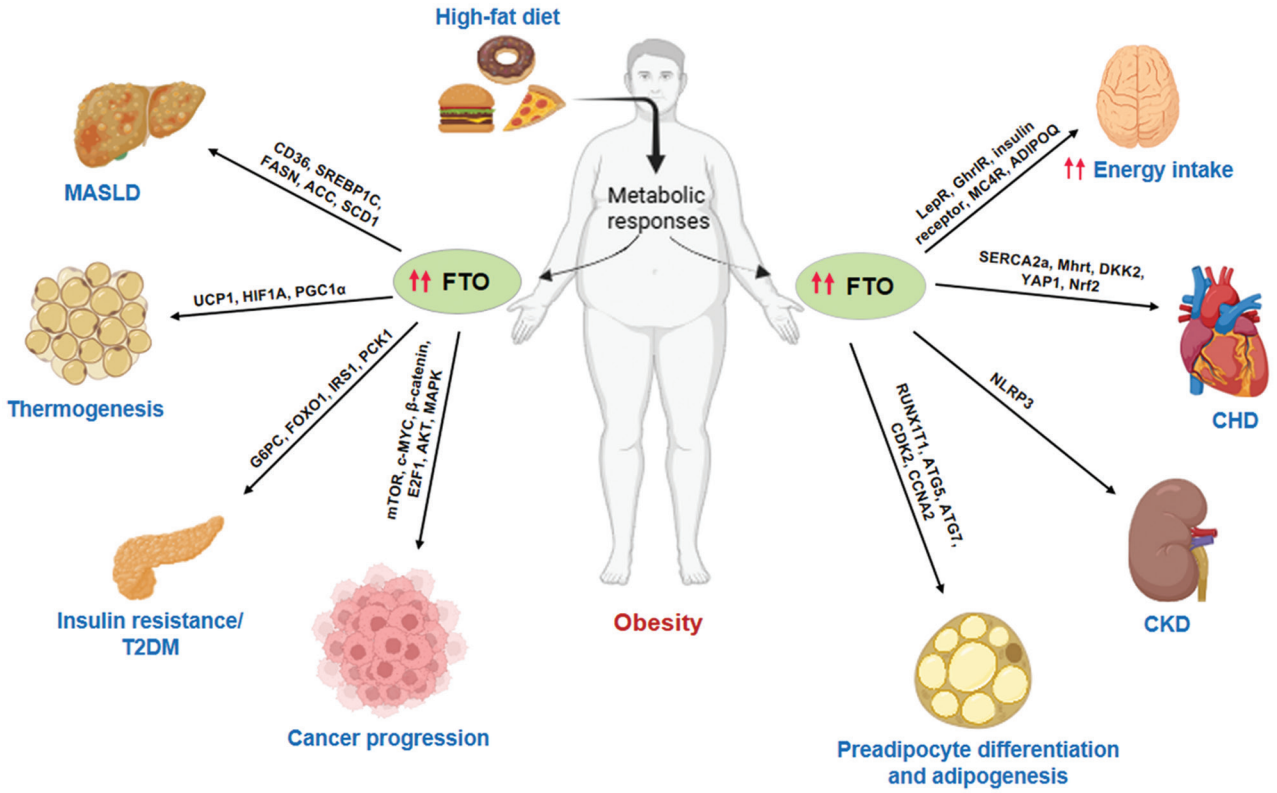


Figure 7. Dysregulation of FTO in obesity-associated diseases. The FTO protein plays a significant role in various physiological and pathological processes, with its altered expression influencing multiple metabolic functions. It is implicated in the regulation of energy balance and adipogenesis, mediated through pathways such as the leptin receptor, Ghrelin receptor, RUNX1 partner transcriptional co-repressor 1, and cyclin-dependent kinase 2/cyclin A2 signaling cascade. In addition, it contributes to the pathophysiology of insulin resistance and MASLD through modulation of the forkhead box protein O1 in gluconeogenesis and sterol regulatory element-binding protein-1c in lipogenesis. FTO also affects cardiac function by regulating sarcoplasmic/endoplasmic reticulum Ca 2+ ATPase 2a, myosin heavy chain-associated RNA transcript, and yes-associated protein 1. Moreover, it contributes to the pathophysiology of CKD through the modulation of NLR family pyrin domain containing 3. Furthermore, its oncogenic role has been associated with the activation of the phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin pathway and the c-MYC oncogene. The broad impacts of FTO on these diverse cellular processes underscore its importance in various disease conditions. Figure was created with BioRender.com (https://BioRender.com/pe6akt9).
Abbreviations: ADIPOQ: Adiponectin; CHD: Coronary heart disease; CKD: Chronic kidney disease; FTO: Fat mass and obesity-associated; MASLD: Metabolic dysfunction associated steatotic liver disease; T2DM: Type 2 diabetes mellitus.

available.[33] Despite extensive research, the mechanisms underlying MASLD pathogenesis are largely unknown. The defining characteristic of MASLD is increased hepatic triglyceride production, primarily due to increased activity of lipogenic enzyme regulators.[34-36]

Elevated FTO level plays its role in MASLD and metabolic dysfunction-associated steatohepatitis, potentially by altering m6A patterns, underscoring m6A's influence on liver disease progression.[7,15] In a glucocorticoid-induced chicken model, FTO was shown to contribute to the development of MASLD, specifically through glucocorticoid receptor-mediated m6A modifications of lipogenic mRNAs.[7] These findings suggest that targeting FTO may be a promising therapeutic approach for the treatment of MASLD.

3.5. *FTO* in CVD

According to a WHO report, CVD remains the foremost cause of death worldwide, accounting for nearly 18 million fatalities annually.[19] Among the main risk factors, obesity plays a pivotal role in promoting myocardial fat accumulation and fostering a pro-inflammatory and pro-thrombotic environment.[37] Heart failure is primarily driven by the loss of cardiomyocytes and their impaired contractility. Therefore, targeting the apoptotic pathways to mitigate cardiomyocyte loss may be a promising therapeutic strategy in the management of heart failure.[16]

The *FTO* gene has been identified as an important modulator of cardiovascular health.[10] Experimental studies have shown that FTO-mediated hypermethylation

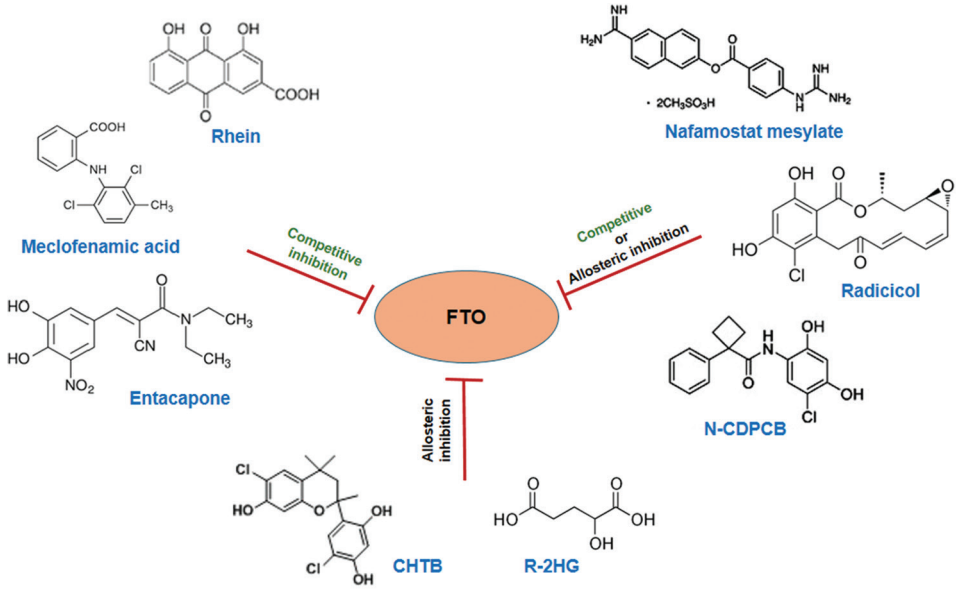


Figure 8. Chemical structures of fat mass and obesity-associated protein inhibitors and their mode of action. Image created by the authors using standard chemical structures and Microsoft PowerPoint.
Abbreviations: CHTB: 4-Chloro-6-(6'-chloro-7'-hydroxy-2',4',4'-trimethyl-chroman-2'-yl)benzene-1,3-diol; N-CDPCB: N-(5-chloro-2,4-dihydroxyphenyl)-1-phenylcyclobutanecarboxamide; R-2HG: R-2-hydroxyglutarate.

plays a significant role in metabolic disturbances, leading to myocardial dysfunction, cardiomyocyte fibrosis, and apoptosis through the mitochondria-dependent apoptotic pathway.[10] Moreover, elevated FTO levels protect myocardial cells from apoptosis under hypoxic and reoxygenation conditions by modulating the m6A modification of myosin heavy chain-associated gene transcripts, ultimately improving heart failure outcomes.

Considering that obesity is a well-established contributor to CVDs, FTO is believed to play a crucial role in their onset and progression.[38] A meta-analysis evaluating the relationship between the *FTO* rs9939609 variant and CVD confirmed a significant association, independent of BMI, and other conventional CVD risk factors.[39] Moreover, this variant has been linked to both CVD and coronary heart disease, independent of established risk factors, and diabetes-related measures. These findings collectively indicate that FTO influences cardiovascular health through multiple molecular pathways, beyond its known role in obesity.

3.6. *FTO* in coronary artery disease (CAD)

CAD and its severe complication, myocardial infarction (MI), are major contributors to global morbidity and mortality, arising from a combination of environmental and genetic risk factors. Well-documented risk factors include smoking, excessive alcohol consumption, abnormal lipid profiles, obesity, hypertension, and T2DM.[40] Recently, FTO has been implicated in the pathogenesis of various CVDs, including atherosclerosis, CAD, and MI.[41] FTO protects against atherosclerosis by modulating lipid metabolism, inhibiting lipid uptake, increasing cholesterol efflux, and reducing the formation of macrophage-derived foam cells. Its upregulation improves cardiac contractility, lowers fibrosis, and promotes angiogenesis in ischemic myocardium.[40] Collectively, these results indicate that FTO plays a critical role in the pathophysiology of MI and CAD.

3.7. *FTO* in chronic kidney disease (CKD)

Nearly 20–40% of diabetic patients develop CKD.[42] It has become a major public health concern due to its increasing incidence, high medical expenses, and compromises on life expectancy and quality of life. While environmental and genetic factors play a key role, epigenetic modifications and genetic variations are also associated with the development and progression of CKD. Notably, a positive correlation between the FTO polymorphism rs7204609 and CKD has been established. Moreover, a reduced expression of FTO is observed in CKD patients, while its overexpression promotes cell growth and inhibits pyroptosis.[42] FTO shows protective effects on kidney function by modulating interleukin expression and pyroptosis-related protein levels in kidney tissue. Mechanistically, FTO influences CKD progression by modulating the expression of the *NLRP3* gene through m6A modifications and regulating the NACHT, LRR, and PYD domains-containing protein 3/Parkin signaling pathway.[43]

Apart from its role in metabolic diseases, FTO also plays an important role in pain sensitivity (hyperalgesia). It regulates the expression of P2X purinoceptor 3 receptors (P2X3Rs) through m6A modifications, key mediators of pain signaling.[44] In lumbar disc herniation, both FTO and P2X3R are upregulated in dorsal root ganglion neurons, contributing to increased neuronal excitability and hyperalgesia. Thus, targeting FTO or P2X3R presents a potential therapeutic strategy for alleviating pain sensitivity in lumbar disc herniation and related neuropathic conditions.

4. Inhibitors of FTO enzymatic activities

The active site of FTO includes three binding pockets—the 2OG binding site, which is crucial for its catalytic activity, as well as the Fe(II) binding site and substrate binding site, both of which offer a valuable framework for chemical intervention.[45] Therefore, the development of small molecules capable of targeting various functional domains of FTO and its expression holds considerable potential for developing new therapeutic strategies. Emerging studies on m6A regulation suggest a significant correlation between the extent of m6A modification and obesity-associated metabolic disorders, as well as between m6A modification and tumor development and progression.

The development of synthetic chemical inhibitors, as well as the identification of plant-derived molecules capable of targeting the m6A demethylase activity of FTO, represents a promising therapeutic approach for managing obesity and related metabolic disorders. Over the past decade, intensive research efforts on FTO inhibitors have led to the identification of several molecules that have shown promising results as anti-obesity and antitumor activities both *in vitro* and *in vivo* (Figure 8).

For example, rhein is a bioactive anthraquinone derivative isolated from rhubarb (*Rheum* species) and routinely used as a traditional Chinese medicinal herb. It is a strong FTO inhibitor (IC_{50} = 30 μM) that competitively binds to its catalytic domain and interferes with its interaction with single-stranded RNA substrates.[46]

Epigallocatechin gallate, a predominant catechin found in green tea, has been extensively studied for its potential anti-obesity and anti-adipogenic properties. It binds to the catalytic site of FTO and inhibits the demethylation of downstream targets cyclin-A2 and cyclin-dependent kinase 2, preventing the proliferation and differentiation of pre-adipocytes into mature adipocytes by effectively blocking mitotic clonal expansion and adipogenesis.[47]

Meclofenamic acid (MA), a non-steroidal anti-inflammatory molecule, was identified as a specific inhibitor of FTO demethylase activity, functioning through competitive binding at the catalytic site (IC_{50} = 8.6 μM).[48] Later, MA2 was developed as an ethyl ester derivative of MA, demonstrating enhanced FTO inhibition and increased m6A methylation of gene transcripts in a dose-dependent manner.[9] Based on the structural insights gained from MA, researchers have used structure-guided design strategies to develop more potent and selective FTO inhibitors.

A novel compound FB23 was synthesized using a dichloride-substituted benzene, resulting in an over 100-fold increase in its inhibitory potency (IC_{50} = 0.06 μM) compared to MA. Another potent FTO inhibitor, Dac51, was developed through structural optimization of FB23.[49] Dac51 showed enhanced inhibitory activity (IC_{50} = 0.4 μM) and maintained effective interactions within the FTO active site. Further chemical modifications of Dac51 led to the development of another FTO inhibitor, Dac85 (IC_{50} = 0.7 μM). In addition, another FTO inhibitor, ZLD115, was designed using a flexible alkaline side-chain-substituted benzoic acid structure derived from FB23. It showed improved pharmacological characteristics compared to earlier inhibitors, including FB23 and Dac85.

The therapeutic potential of the FDA-approved drug entacapone in metabolic disorders has been observed in a high-fat diet-induced obese mouse model, where it reduced body weight and blood glucose levels.[50] However, further research and comprehensive clinical validation are necessary to fully establish its efficacy and therapeutic value.

5. Conclusion

Obesity is a complex, multifactorial condition and a growing global epidemic linked to metabolic diseases, such as T2DM, CVDs, and certain cancers. While lifestyle and environmental factors are critical contributors to obesity, genetic predisposition also plays an equally important role. *FTO* encodes an m6A RNA demethylase that regulates gene expression through epitranscriptomic modifications essential for normal biological functions. Its reversible nature makes m6A a promising therapeutic target for FTO-related interventions. Understanding the FTO regulatory mechanisms may pave the way for the treatment of obesity, metabolic disorders, and cancer. Future research should focus on optimizing FTO modulators, exploring their structure–activity relationships, and assessing their clinical efficacy in managing complex diseases.

As illustrated in Figure 7, the dysregulation of FTO activity has been implicated in the development of obesity, metabolic disorders, and cancer. Therefore, targeting FTO using small-molecule inhibitors is a novel therapeutic

strategy. With its high expression in the brain, FTO influences energy intake and expenditure by mediating the demethylation of m6A RNA, thereby affecting the stability and translation of key genes involved in adipogenesis, energy balance, and metabolic homeostasis. In addition to its role in metabolic disorders, FTO is a crucial factor in cancer progression, making FTO a promising therapeutic target. Significant efforts have focused on developing small-molecule inhibitors that block FTO demethylase activity and modulate gene expression.

Some FTO inhibitors have shown promising antitumor effects in preclinical cancer models and have been shown to enhance insulin sensitivity and reduce adipogenesis in metabolic disorders. Despite their promise, further studies are required to evaluate the long-term safety, efficacy, and clinical relevance of FTO inhibitors.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization: All authors
Visualization: All authors
Writing – original draft: Sunita Giri
Writing – review & editing: Vijay Kumar

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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