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REVIEW ARTICLE

Studies on the fat mass and obesity-associated (FTO) gene and its impact on obesity-associated diseases

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Abstract Obesity has become a major health crisis in the past ~50 years. The fat mass and obesity-associated (FTO) gene, identified by genome-wide association studies (GWAS), was first reported to be positively associated with obesity in humans. Mice with more copies of the FTO gene were observed to be obese, while loss of the gene in mice was found to protect from obesity. Later, FTO was found to encode an m^6A RNA demethylase and has a profound effect on many biological and metabolic processes. In this review, we first summarize recent studies that demonstrate the critical roles and regulatory mechanisms of FTO in obesity and metabolic disease. Second, we discuss the ongoing debates concerning the association between FTO polymorphisms and obesity. Third, since several small molecule drugs and micronutrients have been found to regulate metabolic homeostasis through controlling the expression or activity of FTO, we highlight the broad potential of targeting FTO for obesity treatment. Improving our understanding of FTO and the underlying mechanisms may provide new approaches for treating obesity and metabolic diseases.

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Introduction

Obesity, a condition of an abnormally high ratio of body fat, is a risk factor for type 2 diabetes, hypertension, cardiovascular diseases, and other metabolic illnesses.[1] Obesity and its associated sicknesses are expected to influence more than 1 billion people by the year 2030.[2] Researchers considered that the changes in dietary patterns and increasingly obesogenic environment might account for the obesity pandemic.[3] Moreover, the present costs of obesity are estimated at nearly $2 trillion annually from lost economic productivity and direct health care costs. These costs are equivalent to 2.8% of the world's gross domestic product (GDP).[4] Hence, to mitigate this epidemic and develop safer and more effective treatments, intensive research has been sparked to clarify the underlying mechanisms of obesity.

Over the past decades, however, strategies for obesity treatment and prevention, both at the population and individual level, have not hit the mark due to the complex pathogenesis of obesity.[1] To date, the fundamental drivers of obesity, which is caused by an intricate interplay between behavioral, genetic, environmental, epigenetic, physiological, socio-cultural, and economic factors, are widely considered the consequence of long-term energy disequilibrium between too much food intake and few physical activities (Fig. 1).[1,5–8] In 2007, four investigations for genetic risk factors in obesity have successfully associated single nucleotide polymorphism (SNPs) in the first intron of fat mass and obesity-associated *(FTO)* gene with obesity-related features concerning anthropometric traits, type 2 diabetes, early-onset and severe obesity.[9–12] Subsequently, the FTO protein was functionally confirmed as the first RNA demethylate targeting the substantial N^6-methyladenosine (m^6A) residues in RNA *in vitro*.[13] *FTO*-dependent m^6A demethylation was proved to be essential for adipogenesis.[14] Notably, the story of FTO research is interesting, intricate, and instructive: A large body of literatures on FTO has achieved controversial consequences.[15,16] For instance, although most studies confirmed a significant relationship between FTO and obesity, one study found that FTO deficient mice have comparable fat mass as the wild-type controls.[15,17–19] Besides, both FTO-overexpressing mice and FTO-knockout mice exhibited hyperphagia.[17,19]

In this review, we aim to summarize studies on the roles of FTO in adipogenesis and obesity-associated metabolic diseases. Special focus will be given to discuss the ongoing debates including the association between FTO polymorphisms and obesity. Considering the disproportional high expression of FTO and abundant epigenetic modification in the central nervous system,[20–22] we highlight the role of FTO in the control of energy balance. Moreover, the role of nutritional genomics containing epigenomic signatures is a young field with accumulating interest to uncover the causes of obesity and for precision nutrition to fight or prevent obesity and obesity-related diseases.[5,23–25] Thus, we also analyzed the potential of targeting FTO therapeutically by dietary compounds, especially polyphenols, for the management of obesity.

The history of FTO

In 1994, to explore the process of programmed cell death during limb development, the Fused toes (Ft) mouse was created by transgenic insertional mutagenesis involved in a 1.6 Mb deletion on mouse chromosome 8.[26,27] Heterozygous carriers for the Ft mutation displayed a fusion of forelimb.[27] Due to the deletion, the entire *IrxB* gene cluster (*Irx3*, *Irx5*, and *Irx6* from the Iroquois gene family) combined with three other genes (*FT1*, *Fasto*, *and Fantom*) were affected by the Ft mutation.[26] Among the three

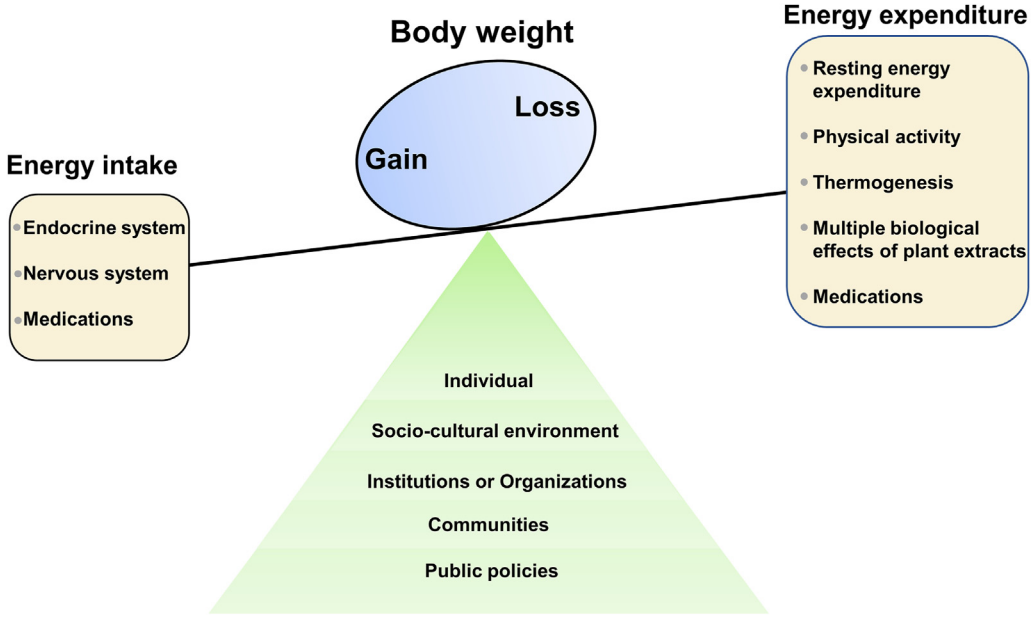

Figure 1 Key factors involved in the regulation of energy balance. Body weight will gain when energy intake exceeds energy expenditure.

genes, which were all largely unknown at that time, FT1 (now called Fts) has been detected in the first place.[28] Secondly, Peters et al reported the identification of Fasto (Fto) in the study of the Ft mouse as a result of exon trap analysis of a genomic clone encoding wild-type sequences.[29] The third gene, whose transcription initiation site was found very close to the initiation site of Fto, was labeled as Fantom (Ftm, also called KIAA1005 and RPGR interacting protein 1 [RPGRIP1L]) because its sequence was elusive to characterize technically.[11,26,30] When first cloned in 1999, Fto was found to express throughout embryonic development and speculated as a candidate gene related to the establishment of left-right asymmetry, craniofacial development, and programmed cell death.[29] In 2007, three independent genome-wide association studies (GWAS) showed a clear link between human obesity and variants within introns of FTO.[9–11] From then on, the mechanisms underlying the association between FTO and obesity have been extensively studied. Notably, great challenges were present at the very start. FTO was a gene of unidentified function with its expression throughout the whole body of both fetal and adult.[11,12,20] Besides, there was no clear genetic mechanism to elucidate how the genetic variation affected the expression or function of FTO. The possibility that the predisposing variants were involved in the development of obesity by affecting the expression or function of genes adjacent to FTO or more distant genes has existed from the very beginning.[11] It is also noteworthy, however, that FTO protein was subsequently confirmed to be a member of AlkB family of 2-oxyglutarate and Fe(II) dependent oxidative RNA/DNA demethylases.[31,32] Gerken et al reported that FTO catalyzed demethylation of 3-methylthymine in single-stranded DNA and was highly expressed in the brain, particularly in hypothalamic nuclei regulating energy balance.[20] Three following studies in the next three years further identified the association between FTO and obesity.[19,33,34] Afterward, He et al first identified FTO as an RNA demethylase,[13] thus initiating a wave of research on epigenetic modifications of RNA (Fig. 2). Since then, the diverse and complicated functions of FTO protein in the progress of metabolic diseases, especially obesity, have been gradually elucidated.

Figure 2 A brief timeline of discovery and exploration of FTO.

FTO expression in various species and tissues

FTO is a large gene containing more than 4,000 kb and 9 exons and is located on human chromosome 16q12.2.[35] The ancient evolutionary origin of this gene can be traced back to 450 million years ago.[36] Sequence homology comparisons have revealed that the *FTO* gene was found only in marine algae and vertebrates including fish, chicken, rabbits.[36–38] The pig *FTO* gene is located on chromosome 6 where numerous quantitative trait loci for the control of fat have been mapped.[39] The cDNA sequence of *FTO* in the pig shared nearly 80% homology with the cDNA sequences of both humans and mice.[40,41] The *FTO* gene of the human encodes a 505 amino-acid protein with its sequence highly conserved in organisms ranging from green algae to mammals.[20,42] While the mouse *FTO* protein contains 502 amino acids, with a molecular weight of 58,007 Da (Q8BGW1-1) compared with 58,282 Da in humans (Q9C0B1-1). The FTO protein consists of two well-defined domains: a C-terminal domain (residues 327–498, exons 6–9) (called CTD) and an N-terminal domain (residues 32–326, exons 1–5) (called NTD).[38,43] The CTD plays a critical role in stabilizing the conformation of the NTD.[43] NTD is composed of nucleotide recognition lids (NRL1 and NRL2), a highly conserved double-stranded β-helix (DBSH) domain and an extra loop.[43,44] Among the nine human AlkB homologs, FTO is the only member that contains this type of loop (Fig. 3).[45] The unique loop selectively blocks the ability of dsRNA/DNA to act as a physiological substrate for FTO.[46] The evolutionary conserved regions and structure of FTO protein have indicated that high similarity of whole-genome alignments exists between humans and mice.[47] It was reported that although FTO expressed widely in both mice and human tissues,[11,20,36] its mRNA was most abundant in the brain, particularly in hypothalamic nuclei regulating energy balance.[20] In human embryos, a nearly ubiquitous expression of FTO was observed, with higher expression in the liver and the central nervous system.[48] A strong expression of FTO in the mitral and semilunar valves, ventricular myocardium, pituitary, frontonasal and mandibular mesenchyme was also detected. This wide spatiotemporal expression pattern may related to the broad spectrum of clinical manifestations of many diseases like hypertonicity, ventricular septal defect and neuro sensory deafness.[48] FTO was first shown to be a nuclear protein,[20] but afterward, it was reported to exist in both the cytoplasm and cell nucleus in various mammalian cell lines.[49–51] Recent evidence from the pig model suggested that FTO protein also existed in the cytoplasm of specific tissues and cells, e.g., in the pancreatic β-cells in a pig model.[52] Abundant FTO protein expression was also found in the cerebellum, kidney, and salivary gland of adult pigs. However, FTO protein was not detected in bile, saliva, and blood.[52] Furthermore, FTO expression in tissues relies on energy intake, metabolic status, and age, although the mechanisms governing this dependency are unknown yet.[52]

RNA demethylase of FTO in adipogenesis

Although Gao et al found that FTO deficient mice had comparable fat mass as the wild type controls,[18] numerous studies have demonstrated that FTO plays a vital role in adipogenesis. *In vitro*, overexpression of FTO promotes adipogenesis in 3T3-L1 preadipocytes, porcine intramuscular preadipocytes and mouse embryonic fibroblasts (MEFs).[53–59] Overexpression of FTO led to an obese phenotype in mice,[17] while loss of FTO in mice generated by replacing exons 2 and 3 of the FTO gene caused a significant decrease in adipose tissue.[19,60,61] A recent study indicated that the protein expression level of FTO in the white adipose tissue of fat pigs is significantly higher than that in lean pigs.[62] However, its molecular mechanisms via which FTO affects adipogenesis remain largely unknown.

Without a change in the DNA sequence, epigenetics mainly affects the functions and characteristics of genes through controlling the translation or transcription processes.[63,64] The study of epigenetics and its involvement in adipogenesis and metabolic diseases is a young research

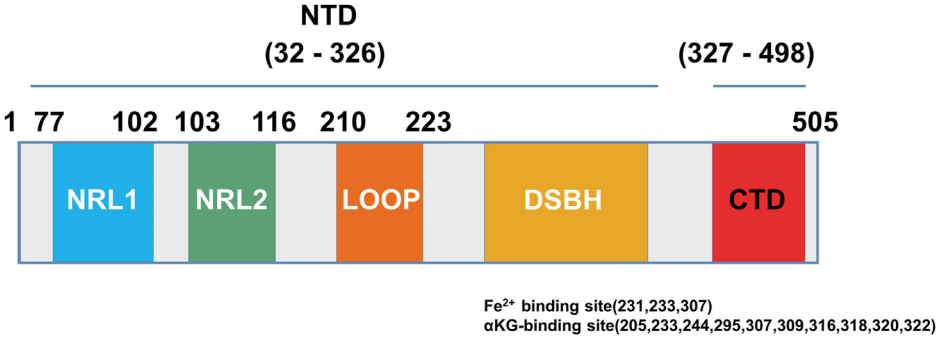

Figure 3 Functional domains of the human FTO protein. FTO contains 505 amino acids and consists of an N-terminal domain (called NTD) (residues 32–326) and a C-terminal domain (called CTD) (residues 327–498). The catalytic core of the NTD is mainly composed of a highly conserved double-stranded β-helix (DSBH) fold which is homologous to those of Fe(II)/2-oxoglutarate-dependent oxygenase (for a review of structural information of these enzymes, see ref. 41). NTD also possesses two nucleotide recognition lids (NRL1 and NRL2). Residues of NRL1 (residues 77–102), NRL2 (residues 103–116), DSBH, CTD (residues 327–498) and the unique loop of FTO (residues 210–223) are labeled with bule, green, brown, red, and orange, respectively. The highly conserved residues His 231, Asp 233 and His 307 are coordinated to Fe^{2+}. Residues (Asn205, Asp 233, Val 244, Tyr 295, His 307, Val 309, Arg 316, Ser 318, Thr 320, Arg 322) involved in interactions with α-KG analog N-oxalylglycine (NOG) are also described.

field.[24,25,65] In the last few decades, more attention has been paid to RNA modification with the help of modern high throughput sequencing techniques. N^6-methyladenosine (m^6A), accounting for more than 80% of all RNA base methylations, is the most prevalent modification in eukaryotic mRNAs with a highly conserved architecture across mice and humans.[66,67] Since the FTO protein was confirmed as an RNA demethylase,[13] whether FTO influences adipogenesis by controlling m^6A modification has been hypothesized by our group. To verify this, we have conducted a series of studies and established the central role of the RNA demethylase FTO in adipogenesis. For example, we found that deficiency of m^6A demethylase FTO attenuated adipogenesis in porcine and mouse preadipocytes through Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3)/transcription coactivators CCAT/enhancer-binding protein β (C/EBPβ) signaling.[56] Mechanistically, knockdown of FTO inhibited JAK2 expression and STAT3 phosphorylation, causing debilitated transcription of C/EBPβ which is necessary for adipocyte differentiation in the early stage. Furthermore, it was forced expression of wild-type (FTO-WT) plasmid, not catalytic inactive mutant FTO (FTO-MUT, R96Q) plasmid that can dramatically enhance JAK2 protein expression and stimulate STAT3-C/EBPβ signal pathway in porcine preadipocytes at the early stage of differentiation.[56] Similarly, it has been shown that FTO could influence adipogenesis during the process of mitotic clonal expansion (MCE), a prerequisite for adipocyte differentiation, which also appears at an early stage after adipogenic stimulation.[54] The effect of FTO overexpression on MCE appears to be mediated via increased expression of the pro-adipogenic S inform of runt related transcription factor 1 (RUNX1T1).[54] While our group discovered that the negative effect of FTO knockdown on MCE may partly attribute to impaired cell cycle progression at the early stage of adipogenesis.[57] The expression of cyclin A2 (CCNA2) and cyclin-dependent kinase 2 (CDK2), two pivot cell cycle regulators promoting cells from S phase to G2 phase,[68,69] was drastically decreased by FTO knockdown in preadipocytes, leading to a delayed entry of MDI-induced cells into S phase.[57] Unregulated m^6A levels of CCNA2 and CDK2 mRNA and decreased triglyceride (TG) deposition were observed following FTO knockdown.[57] These results suggest that high m^6A levels lead to less lipid accumulation (Fig. 4). Indeed, our group recently has identified m^6A is negatively related to fat deposition in muscle tissue by using pigs as a model.[70] To explore the effects of m^6A on the adipogenesis of intramuscular preadipocytes and associated mechanisms, we compared m^6A methylome of the longissimus dorsi muscles (LDMs) between Jinhua pigs (obese-type breed) and Landrace pigs (lean-type breed).[70] The LDM of Jinhua (J-LDM) pigs had a higher intramuscular fat content than that of Landrace (L-LDM) pigs, whereas the m^6A/A ratio was higher for L-LDM than for J-LDM. Consistently, the expression level of FTO was higher in J-LDM than in L-LDM.[70]

Just like many other chemical modifications on biological macromolecules, m^6A can also be recognized by specific readers.[71,72] For instance, our group found that deficiency of m^6A modification on family with sequence similarity 134 member B (FAM134B) enhanced its protein abundance through m^6A reader YTHDF2-dependent manner

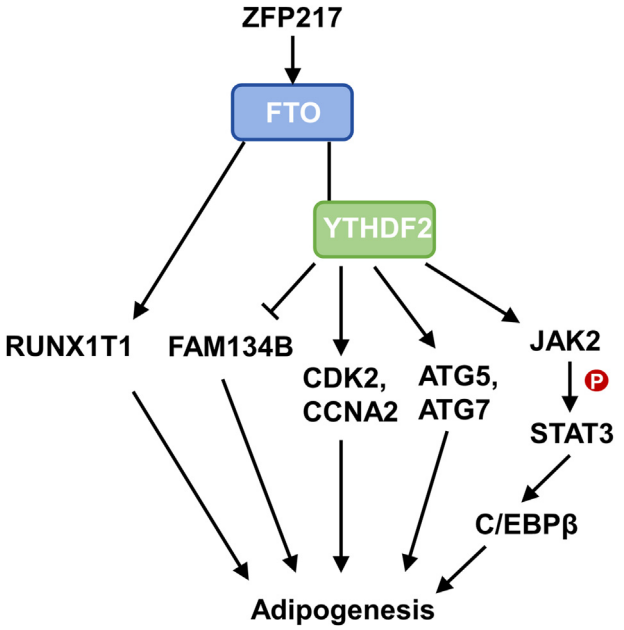

Figure 4 The regulation of gene expression by m^6A modification in adipogenesis. The diagram describes how FTO (blue) and YTHDF2 (green) are engaged in the regulation of various pathways and genes in adipogenesis (modified from ref. 26).

and stimulated differentiation of porcine preadipocytes (Fig. 4).[73] A recent study by our group showed that FTO could cooperate with YTHDF2, the first identified m^6A binding reader,[74] to regulate the progress of adipogenesis.[75] FTO played an important role in regulating macroautophagy and adipogenesis through targeting autophagy related 5 (ATG5) and ATG7. Knockdown of FTO caused an increase in the m^6A levels of ATG5 and ATG7 with their transcripts captured by m^6A-binding protein YTHDF2, which resulted in mRNA degradation and reduction of protein expression. As a result, autophagy and adipogenesis were alleviated (Fig. 4).[75] In brief, our group uncovered molecular mechanisms responsible for the regulatory role of FTO in adipogenesis which may be potentially significant in the development of new prevention or treatment modalities for obesity.

FTO and energy homeostasis

FTO was highly enriched in neurons and widely expressed in the brain, paraventricular, hypothalamic arched, ventromedial nucleus, dorsomedial, which were engaged in the regulation of energy homeostasis and food intake.[20,76] Global loss of FTO as well as neural-specific FTO knockout mice both had postnatal growth retardation with altered energy intake and expenditure. FTO-deficient mice had apparent hyperphagia.[19] Evidence up-to-date showed that variants in FTO influence appetite and increase food intake through impaired central nervous system satiety processing.[77–79] In addition, within the arcuate nucleus, the expression of FTO was decreased nearly 60% following a fasting period of 48 h and increased after 10 weeks of consuming a high-fat diet.[20,80] Moreover, although the role

of FTO in neurogenesis and neurodevelopment is still largely unknown, FTO deficiency in mice led to reduced proliferation and neuronal differentiation of adult neural stem cells and exhibited impaired dopaminergic function which may potentially affect body-weight regulation and energy homeostasis.[81,82] Taken together, these investigations support the apparent primacy of the function of FTO, particularly in modulating energy homeostasis, is partly mediated by the brain. Furthermore, a recent study by our group provided new insight into understanding the relationship between FTO and energy balance.[83] Adipose-specific deletion of FTO predisposed mice to prevent high-fat diet (HFD)-induced obesity by enhancing energy expenditure. Additionally, loss of FTO *in vitro* promoted thermogenesis and white to beige adipocytes transition. Mechanistically, FTO deficiency increased the m^{6}A levels of hypoxia inducible factor 1 A (HIF1A) mRNA, which is recognized and bound by m^{6}A-binding protein YTHDC2, thus facilitating mRNA translation and protein abundance. HIF1A activated transcription of thermogenic genes including PR domain containing 16 (PRDM16), and peroxisome proliferator activated receptor gamma (PPARG), thereby promoting UCP1 expression and browning process.[83] Collectively, these results unveiled an epigenetic mechanism by which m^{6}A-mediated HIF1A expression controls browning of white adipocytes and thermogenesis, providing an attractive target to counteract obesity and metabolic diseases.

FTO SNPs and physical activity

The first two GWAS for obesity-related genes that confirmed the FTO gene as a promising candidate identified different SNPs in the gene's first intron significantly associated with BMI.[9,11] Subsequently, the association between multiple FTO SNPs and obesity was further identified by a myriad of population-based European studies.[84–89] Studies have also identified the association between FTO SNPs and BMI in non-European populations, specifically, Asian populations,[90–93] Africans,[94] and African-Americans.[95] After the wave of association studies were followed by reports considering how do these FTO SNPs exert their effect on BMI and whether FTO SNPs are associated with physical activity and food intake, the two main mediators of energy balance. Evidence supporting a link between physical activity and FTO on BMI is increasing and has been reviewed.[96–100] Data from observational studies in human beings reported that the FTO SNPs effect on adiposity could be modified by physical activity (PA) level.[100,101] A meta-analysis of 218,166 adults and 19,268 children concluded that the relevance of the FTO rs9939609 variant with the odds of obesity was decreased in physically active adults.[101] In another study, European adolescents who meet the daily PA recommendations (exercising for 60 min per day or longer) could abolish the deleterious effect of the FTO rs9939609 on body fat estimates.[102] In Korean, active exercise in humans carrying rs9939609 (AT + AA) genotypes also reduced the risk of obesity by nearly 2-fold compared with those carrying the wild type (TT) homozygote.[103] Recently, a meta-analysis of 200,452 adults discovered robust evidence of interaction with PA for the strongest known obesity-risk locus in the FTO gene region, of which the body mass-increasing effect is decreased by nearly 30% in physically active individuals compared to inactive individuals.[104] Notably, the adverse impacts of the FTO rs1421085 on BMI may also be overcome by PA.[105] The association with PA and rs1421085 has been observed in a multi-ethnic prospective cohort that included 17,423 people from 17 countries who were followed for 3.3 years.[105] Moreover, low PA has been reported to accentuate the effect of the FTO polymorphism on body fat accumulation.[106,107] In sum, these data provide evidence for genetic variability in response to vigorous PA on weight loss, although clinical applications of these studies require further explorations.

FTO SNPs and food intake

Since time immemorial, the regulation of body weight and food intake has been simply considered as an issue of willpower instinct and self-control.[108,109] After all, Gluttony is one of the Seven Deadly Sins which not only involved a habitual excess of eating and drinking but also referred to being fussy about food and drink. So as obesity is becoming increasingly prevalent,[1] public in turn blame these patients with obesity for a lack of moral principle.[108,109] "Rectify your eating habits and do more exercise" so the advice for patients with obesity goes. However, this sage piece of advice, as far as goes, is distinct not working.[108,110] For the public, two complex and meaningful problems to be settled urgently are: why some people eat more than others and why do we prefer some food over others. Nowadays, an increasing number of genetics-related researches provided new insights into understanding these issues and suggested that the FTO SNPs are related to increased energy intake,[77,111,112] food preference,[33,113] overeating,[114] increased intake of dietary fat or protein.[115,116] For example, a GWAS conducted by Tanaka et al for macronutrient intake in more than 70,000 participants confirmed variants in FTO to be significantly relevant to increased protein intake.[116] Chuang et al firstly reported the pleiotropic longitudinal effects of the FTO gene and its influence on personality, brain function, and diet in an older population.[117] FTO rs1421085 was associated with decreased brain function in the medial prefrontal cortex which mediated a greater preference for dietary fat over time during aging.[117] In addition, a study carried on 196 overweight adults of Iran reported that carriers of the rs9939609 AA genotype had significantly higher carbohydrate, calorie, and fat intake than the carriers of the TT genotype.[115] While the FTO rs9939609 AA subjects in Emirati were reported to have higher carbohydrate but lower fat intake compared to those with other genotypes.[118] Mechanically, decreased levels of ghrelin and IL6 postprandially in individuals with rs9939609 AA genotype may be responsible for their increased energy intake.[119] Moreover, a recent study using cross-sectional data from 985 older people found that serum levels of leptin were inversely related to the number of FTO C risk alleles in participants with distinct rs17817449 genotypes.[120] Taken together, the present findings suggest that FTO SNPs may affect weight gain by shifting the endocrine balance and are highly associated with food intake.

FTO SNPs and genes adjacent to FTO

The obesity-associated FTO region is located within a large topologically associated domain of approximately 2 Mb containing FTO, the IRXB cluster, and RPGRIP1L which encodes a protein localized at the transition zone of the primary cilium.[121–124] As a result of this arrangement, the obesity-associated SNPs may affect the regulation of all or any of these genes. The possibility that the mechanistic basis of interactions between FTO SNPs and obesity involved neighboring genes was raised right from the start.[11] Recently, there is some evidence to support this possibility. For example, FTO and RPGR1P1L were both regulated by isoforms P110 and P200 of the transcription factor cut-like homeobox 1 (CUX1) whose binding site overlapped SNP rs8050136 in intron 1 of FTO,[9] which in turn affected binding affinities of P200 and P110.[125] In mice, homozygosity for a null allele of RPGR1P1L was embryonically lethal.[126] While mice heterozygous for a null allele of RPGR1P1L would be fatter than wild-type animals.[127] Moreover, *Rpgrip1l*$^{+/-}$ mice displayed diminished suppression of food intake in response to leptin administration.[127] Mechanistically, the number of type III adenylyl cyclase (ACIII)-positive cilia in the axonemal part of the cilium was diminished in the hypothalamus of *Rpgrip1l*$^{+/-}$ mice, accompanied by diminished pStat3 in response to leptin and impaired convening of the leptin receptor to the vicinity of the cilium.[127] Smemo et al also supported this possibility by demonstrating that the promoters of the homeobox gene IRX3, as well as FTO, directly interacted with the obesity-associated FTO region in the human, mouse, and zebrafish genomes.[128] Furthermore, obesity-associated SNPs were related to the expression of IRX3, but not FTO, in human brains.[128] The expression of IRX3 was positively linked to regulation of body mass and composition demonstrated by a bodyweight reduction of 25% or more in Irx3-deficient mice, primarily through the increase in basal metabolic rate with browning of white adipose tissue and loss of fat mass.[128] Most recently, Laber et al engineered a deletion of the rs1421085 conserved cis-regulatory module (CRM) in mice and identified that the CRM affects mitochondrial function and Irx3 and Irx5 gene expression in an adipose depot–dependent manner.[129] The CRM also modulated physical phenotypes that were associated with obesity, including decreased whole-body fat mass and high-fat diet-induced weight gain.[129] Interestingly, data from an unpublished study indicated that the rs1421085 variant within FTO may promotes thermogenic capacity and was potentially associated with human migration.[130] Notably, all these results concerning FTO rs1421085 were consistent with previous data from human subcutaneous adipocyte model systems which indicated that adipocyte thermogenesis regulation involving AT-rich interaction domain 5B (ARID5B), rs1421085, IRX3, and IRX5.[131] However, these data did not offer an explanation immediately for the well-known association of variants within FTO with food preference and eating behavior.[33,78,131] To address this question and ascertain the pattern of interactions between the obesity-associated region and genes in the FTO-IRXB locus, a recent study performed by Sobreira et al found that obesity-resistant *Irx3*$^{-/-}$ mice exhibited a decreased preference for sucrose, but not protein or lipid, compared with WT animals.[132] It has also established a central nervous system role of IRX3 in the regulation of metabolism and eating behavior analogous to phenotypes associated with allelic variants of obesity-associated SNPs within FTO in humans.[132] Nonetheless, there are two important limitations of the study. Firstly, the selection of immortalized cell lines, but not primary cells, for the reporter assays may mask the allelic effects of SNPs seen in primary cells.[132] Secondly, the manipulation of candidate genes in mice may cause organismal phenotypes that are quantitatively and qualitatively different from the small-effect phenotypes elicited by allelic variants of SNPs associated with the human trait.[132] Moreover, in which cell groups of the brain, the expression of IRX5 and IRX3 was determined by allelic variants and enhancers in the obesity-associated region are unknown yet. Further studies are needed to address this outstanding and critical question.[132]

FTO and Type 2 diabetes

Type 2 diabetes (T2D), accounting for approximately 90% of diabetes mellitus, is a complicated metabolic disease characterized by dyslipidemia and hyperglycemia.[133] At the first time, FTO was reported to be strongly associated with T2D in an adiposity-dependent manner in the UK and Finnish populations.[11,134,135] Later, one study found that FTO gene expression was not increased in subcutaneous adipose tissues (SAT) and visceral adipose tissues (VAT) from individuals with T2D. Furthermore, VAT FTO mRNA expression was related only to fasting glucose, but not to insulin action.[136] While some other studies found evidence that levels of FTO were increased in skeletal muscle and adipose tissue from patients with T2D and observed no correlation of both omental adipose tissues (OAT) and SAT FTO expression with either fasting glucose or insulin levels.[137,138] The discrepancy of these studies is difficult to interpret, but it is worth noting that small sample sizes and ethnic differences may account for part of these discrepancies observed.

Yang et al showed that the FTO mRNA expression in white blood cells was positively correlated with fasting glucose and negatively connected with the m^{6}A content in all 102 participants with T2D.[139] FTO expression in patients with T2D with hyperglycemic emergency was significantly higher than those with hypoglycemic emergency. A previous study has shown that m^{6}A strongly stimulates glucose oxidation in adipocytes of rats.[140] Recent research showed that the m^{6}A content in RNA in patients with T2D and diabetic rats was strongly decreased.[141] These data suggest that the dynamic m^{6}A level regulated by FTO is related to blood glucose. However, the effect of high-glucose stimulation on FTO expression is still controversial. Hepatic FTO mRNA levels were increased in fasting mice which are influenced by reduced blood glucose levels and body weight.[142] Correspondingly, level of FTO mRNA in liver was significantly lesser in hyperglycemic mice compared to normoglycemic mice.[143] In humans, levels of FTO mRNA and protein were significantly higher in livers of patients with nonalcoholic fatty liver disease (NAFLD) who are also hyperglycemic compared to healthy patient controls.[144]

Specie differences may account for these inconsistent results. Additional investigations should be done to thoroughly explore the effect of long and short-term hyperglycemia on FTO expression in liver tissue.

Forkhead box protein O1 (FOXO1), FASN, glucose-6-phosphatase-alpha (G6PC), and diacylglycerol O-acyltransferase 2 (DGAT2) are involved in glucose and lipid metabolism.[145–148] The transcription factor FOXO1 plays a critical role in the insulin and insulin-like growth factor 1 (IGF-1) signaling pathway.[149] FASN is known to have a key role in T2D.[146] G6PC catalyzes the hydrolysis of the intracellular glucose-6-phosphate to glucose in the final step of gluconeogenesis.[150] DGAT catalyzes the terminal step in the major pathway of triacylglycerol biosynthesis.[147] The expression of FTO was positively relevant to FOXO1, FASN, G6PC, and DGAT2 in HepG2 cells.[139] Meanwhile, previous data from m^{6}A-Seq in HepG2 cells have indicated that FASN and FOXO1 have 2 and 5 m^{6}A loci, respectively.[67] To sum up, these data imply that FTO may participate in the process of T2D by controlling the expression of these genes.

The biological regulation of islet cells, especially pancreatic β-cells, is critical for glucose homeostasis.[151] mRNA m^{6}A methylation has been demonstrated to be vital for β-cell biology and neonatal β cell mass establishment and contribute significantly to the pathogenesis of T2D.[152,153] It was reported that m^{6}A modification can also regulate mature β-cells insulin secretion and survival.[154,155] Depletion of m^{6}A levels in EndoC-βH1 cells caused cell cycle arrest and impaired insulin secretion by decreasing pancreatic duodenal homeobox 1 (PDX1) protein levels and AKT serine/threonine kinase (AKT) phosphorylation.[152] As the only hormone in the human body that can lower blood glucose, insufficient secretion of insulin in β-cells is the culprit of T2D. Several cell lines have been used as a useful model to exploit the biological function of FTO in the pancreatic β cells and the interrelated molecular mechanism. The FTO protein was proved to have a quick turnover in the clonal β-cell line INS-1 and its overexpression enhanced insulin secretion.[156] By contrast, the insulin secretion of MIN6 cells was significantly inhibited by FTO overexpression which promoted reactive oxygen species (ROS) production and nuclear factor-kappaB (NF-κB) activation, but FTO silence did not affect insulin secretion. Inhibition of intracellular ROS production could alleviate NF-κB activation and normalize insulin secretion.[157] Recent studies have illustrated that FTO expression was reduced in islets from donors with T2D and that knockdown of FTO expression in GRINCH cells attenuated insulin secretion stimulated by glucose.[158] These contradictory results could be explained by the reasons that cell lines are isolated from different tissues and cells, and as a result, often differ genetically and phenotypically from each other. Thus, data only generated from cell lines should be interpreted cautiously since it could not fully represent the results obtained from *in vivo* studies. Collectively, these studies implied that the levels of FTO in the pancreas may directly influence insulin release from beta cells. Additional investigations should pinpoint the exact role of the FTO gene as a regulator of pancreatic β-cell function.

FTO and nonalcoholic fatty liver disease

NAFLD is a common co-morbidity related to obesity.[159] Excess fat accumulation is the contributor and common feature of this disease.[159] The expression of FTO was considerably increased in the liver of both animal models and patients with NAFLD.[144,160,161] Increased hepatic FTO mRNA and protein levels in patients with NAFLD were reported to be involved in lipid deposition and oxidative stress, which characterize NAFLD.[160] Overexpression of FTO led to increased triglyceride accumulation in both HepG2 and L02 cells and caused increased malondialdehyde (MDA) levels and decreased superoxide dismutase (SOD) activity which were both studied as markers of tissue injury and oxidative stress in L02 cells.[160,162,163] However, the precise regulatory mechanisms via which FTO controls oxidative stress remain unknown. In conclusion, up-regulation of FTO may contribute to the pathogenesis and progression as well as increased liver damage of NAFLD. Indeed, FTO could enhance lipid accumulation by FTO/Sterol regulatory element binding protein-1c (SREBP1c)/cell death-inducing DNA fragmentation factor-α-like effector c (CIDEC) signaling pathway in hepatocytes in a demethylation-dependent manner. FTO overexpression significantly upregulated the transcriptional levels of SREBP cleavage-activating protein (SCAP) and site 2 proteases (S2P) which are involved in the processing and nuclear translocation of SREBP1c.[163] Levels of key regulatory factors in lipogenesis such as SREBP1c, CIDEC, fatty acid synthase (FASN), and stearoyl-CoA desaturase (SCD1) were improved followed by transfection of FTO, but not catalytically inactive FTO mutant (R316A).[163] Consistently, a recent study revealed that FTO reduced mitochondria content, decreased m^{6}A levels, and promoted lipid deposition, but the FTO (R316A) mutant did not have this effect.[162] Mechanistically, overexpression of FTO in HepG2 cells enhanced expression levels of mitofusin 1/2 (MFN1/2) and OPA1 mitochondrial dynamin like GTPase (OPA1) (related to mitochondrial fusion), but inhibited expression levels of mitochondrial fission 1 (FIS1), dynamin related protein 1 (DRP1), and mitochondrial fission process protein 1 (MTP18) (regulation of mitochondrial fission), and decreased expression of PPARγ coactivator 1 alpha (PGC-1α) and mitochondrial transcription factor A (TFAM) (involved in mitochondrial biogenesis) (Fig. 5). Taken together, FTO may modulate mitochondrial content by inhibiting mitochondria fission and promoting mitochondrial fusion. Long-term exposure to excessive glucocorticoids (GC) might have a pathogenic role in the progression of NAFLD.[164] Recently study discovered that FTO also participates in the GC-induced NAFLD in a chicken model.[165] Glucocorticoid receptor (GR)-mediated m^{6}A modification on mRNA of lipogenic genes and transactivation of FTO contributed to the accumulation of lipids in primary chicken hepatocytes induced by oleic acid/dexamethasone and lipogenic gene activation in corticosterone-induced chicken fatty liver.[165] These studies suggest the possibility that inhibition of FTO expression and/or activity may serve as a new therapeutic method to treat NAFLD.

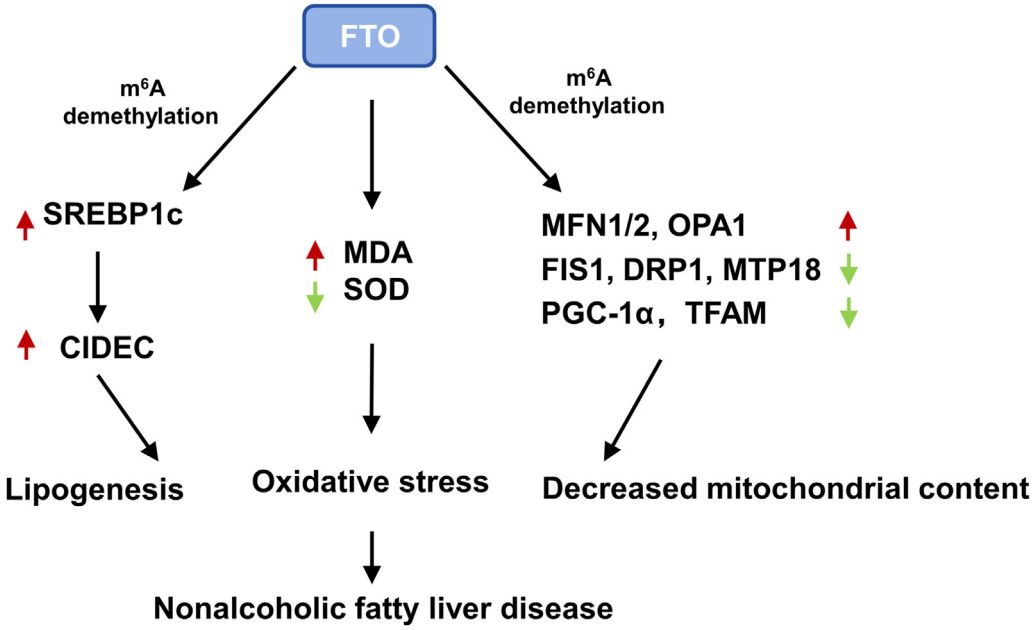

Figure 5 Role of FTO in the development of nonalcoholic fatty liver disease (NAFLD). FTO-mediated m^{6}A demethylation controls lipogenesis and mitochondrial content. One study indicated that FTO-mediated m^{6}A demethylation enhanced the expression of SREBP1c and CIDEC and promoted lipogenesis, resulting in increased lipid accumulation. Another study showed that FTO-mediated m^{6}A demethylation promoted expression levels of MFN1/2 and OPA1, but inhibited expression levels of FIS1, DRP1, and MTP18, and decreased expression of PGC-1α, TFAM, thereby reducing mitochondrial content. For oxidative stress, MDA and SOD, the biomarkers of oxidative stress, are changed in the development of NAFLD accompanied by increase expression of FTO. Red arrow: Stimulation. Green arrow: Inhibition.

FTO and cardiovascular diseases

Cardiovascular diseases (CVD) are the leading cause of global mortality and a principal contributor to disability.[166] Although m^{6}A has long been considered as the most abundant chemical mRNA posttranscriptional modification in mammalian cells and has an impact on various fundamental bioprocesses, the effect of this process in the heart remains largely unknown. Very recently, Doen et al (2019) identified that m^{6}A methylation was essential for normal hypertrophic response in cardiomyocytes indicating that m^{6}A also takes part in the cardiac homeostasis.[167] Notably, increased levels of m^{6}A were associated with significantly reduced expression of FTO in the ischemic heart.[168] It is also interesting to note that FTO has been associated with many cardiac defects including heart hypertrophy,[169] atrioventricular defects,[48] arrhythmias,[170] and coronary heart disease.[171] Moreover, cardiac ventricular levels of FTO in human embryos were higher in addition to brain and liver tissues even though FTO is expressed ubiquitously.[48] Therefore, the cardiac FTO mRNA expression level may relate to the physiological state of the heart. Recently study showed that FTO expression was decreased in failing mammalian hearts and hypoxic cardiomyocytes. Forced expression of FTO could block ischemia-induced m^{6}A increase and rescued myocardial contractile function by selectively demethylating transcriptions associated with cardiac contraction, controlling Ca^{2+}, and stabilizing mRNA to affect myocardial dynamics.[172] Importantly, FTO overexpression in mouse models of myocardial infarction resulted in decreased fibrosis and enhanced angiogenesis.[172] Transgenic overexpression of FTO caused an upregulation of myosin heavy chain associated RNA transcript (Mhrt) and reduced m^{6}A modification of Mhrt in the hypoxia/reoxygenation (H/R)-treated myocardial cells.[173] FTO upregulation repressed apoptosis of H/R-treated myocardial cells, implying that FTO may be a potential target gene for heart failure treatment.[173] Correspondingly, FTO deficiency leads to diminished heart function.[169] Global knockout of the mouse FTO gene will lead to an imbalance of the autonomic neural modulation of cardiac function and a higher risk for the proarrhythmic remodeling of electrical and structural properties of the mouse heart.[170] Collectively, the regulation of m^{6}A modification on the transcription process may be a target for the treatment of cardiovascular diseases.

However, there is an ongoing conflict for the role of FTO in body weight and obesity with some investigations revealing either negative or positive association for FTO with body mass.[128,131] In the context of the negative effects of obesity on almost all the major CVD risk factors,[174] although serval studies showed the possible cardioprotective function of FTO,[169,172] a deeper understanding of the impact of FTO in body mass is needed to make the best of its clinical potential for the treatment of human heart diseases. Furthermore, the learning of m^{6}A methylation in myocardial fibers is unknown, and it is a field to be investigated urgently.[175]

RNA m^{6}A demethylase FTO: a new bridge between nutrition and health

Because of the obtainable and edible- and medicinal-safety properties, extracts from plants, such as vegetables, tea, fruits, have been attracted attention for their potential in the prevention and treatment of metabolic diseases for decades.[8] Recently, several studies showed that plant-derived polyphenols may regulate adipogenesis and attenuate obesity in an m^{6}A-dependent manner. Due to the dynamic and reversible nature of m^{6}A modification, understanding more about the mechanisms responsible for their anti-obesity effects will help to develop new approaches or medicines for treating obesity-related disorders.

1) Since 2006, using resveratrol as a small molecule was proven to improve health and survival of middle-aged mice on a high-calorie diet and shift their physiology,[176] the naturally occurring polyphenol has been continuously studied. Dietary resveratrol supplementation affected liver function and changed the hepatic m^{6}A abundance in piglets.[177] Currently, the beneficial outcome of resveratrol on high-fat diet-induced lipid metabolism disorder was proved that may be due to a decrease of m^{6}A RNA methylation and a significant increase of peroxisome proliferator-activated receptor α (PPARα) mRNA.[178] Resveratrol supplementation of high-fat diet-fed mice decreased the level of YTH domain family 3 (YTHDF3) and m^{6}A abundance, whereas it upregulated the transcript levels of methyltransferase like 3 (METTL3), alkB homolog 5 (ALKBH5), FTO, and YTH domain family 2 (YTHDF2) in the liver.[178]
2) The anti-obesity properties of curcumin, a yellow-colored polyphenol from the curcuminoids, are similar to resveratrol, through inhibiting adipocyte differentiation, lipogenesis in adipose tissue.[179] Na Lu and colleagues observed that dietary curcumin affected the expression of METTL14, METTL3, FTO, ALKBH5, and YTHDF2 mRNA, and improved the abundance of m^{6}A in the liver of piglets.[180] Further investigations are required to explore the precise mechanisms of the effect of curcumin on the profile of gene-specific m^{6}A RNA methylation. Most recently, our group reported that curcumin prevents HFD-induced obesity by decreasing the expression of m^{6}A demethylase, ALKHB5, which leads to higher m^{6}A-modified TNF receptor-associated factor 4 (TRAF4) mRNA. TRAF4 with higher m^{6}A modification was bound and recognized by YTHDF1 resulting in enhanced translation of TRAF4 which inhibits adipogenesis owing to the improved degradation of adipocyte differentiation regulator PPARγ by a ubiquitin-proteasome pathway.[181] Our group has also reported that Epigallocatechin gallate (EGCG), the most biologically active and abundant polyphenols in green tea,[182] inhibited adipogenesis by blocking the MCE at the initial stage of adipocyte differentiation.[183] EGCG decreased the expression of FTO and increased the m^{6}A levels of CCNA2 and CDK2 mRNA in 3T3-L1 cells. Interestingly, EGCG increased the expression of YTHDF2, which recognized and decayed the methylated CCNA2 and CDK2 mRNA, resulting in decreased protein levels of CCNA2 and CDK2.[183]

Conclusion

Genetic variation in the first intron of FTO is largely related to adiposity.[11,12] Despite many exciting and profound scientific breakthroughs have been made (Fig. 2), there are still some outstanding questions: what are the mechanisms linking FTO SNPs to obesity and the relevant cell types and target genes? Do sequences of the intronic regions of the FTO gene regulate the expression of genes associated with whole body energy balance? If or how does FTO-determined changes in IRX3 expression influence whole body energy metabolism? Is there a possibility for targeting IRX3 and/or other FTO neighboring genes as a therapeutic strategy against obesity? Do the FTO risk alleles influence the FTO protein or not? Further studies should provide advances in the detailed characterization of these problems. Nevertheless, FTO undoubtedly plays an important part in the development of obesity and contributes to many metabolic diseases. N^6-Methyladenosine (m^{6}A), found in the mid-1970s,[184,185] is the most abundant internal modification in eukaryotic mRNA.[186] m^{6}A has been reported to impact various biological and pathological processes.[186–190] The discovery of FTO as an m^{6}A demethylase has revealed the significance of FTO in epigenetic regulation. Developing effective inhibitors to target FTO's m^{6}A demethylase activity or searching for plant extracts to inhibit the expression of FTO may serve as a feasible way to remedy obesity and associated diseases. Intriguingly, several small-molecule FTO inhibitors have been studied and they exhibit powerful anti-tumor effects in multiple types of cancers.[191–194] In addition, entacapone, a Food and Drug Administration-approved drug, was confirmed as a potent FTO chemical inhibitor by using biochemical and structural experiments. Entacapone administration lowered fasting blood glucose concentrations and decreased body weight in diet-induced obese mice.[195] These investigations provide evidence in targeting FTO for metabolic disorders therapy. However, considering that the ubiquitous expression of FTO and the negative phenotype in humans and mice with FTO deficiency,[48,82,196] further explorations are needed to dig into the underlying mechanisms between FTO and metabolic diseases in-depth, which could help to develop more FTO inhibitors or/and other efficacious drugs to propel the field of epitranscriptomics forward.

Conflict of interests

There is no conflict of interests to declare.

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Author contributions

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References

1. Blüher M. Obesity: global epidemiology and pathogenesis. *Nat Rev Endocrinol*. 2019;15(5):288—298.
2. Lempradl A, Pospisilik JA, Penninger JM. Exploring the emerging complexity in transcriptional regulation of energy homeostasis. *Nat Rev Genet*. 2015;16(11):665—681.
3. Sturm R, An R. Obesity and economic environments. *CA Cancer J Clin*. 2014;64(5):337—350.
4. Swinburn BA, Kraak VI, Allender S, et al. The global syndemic of obesity, undernutrition, and climate change: the lancet commission report. *Lancet*. 2019;393(10173):791—846.
5. González-Muniesa P, Mártinez-González MA, Hu FB, et al. Obesity. *Nat Rev Dis Prim*. 2017;3:17034.
6. Gadde KM, Martin CK, Berthoud HR, Heymsfield SB. Obesity: pathophysiology and management. *J Am Coll Cardiol*. 2018;71(1):69—84.
7. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med*. 2017;376(3):254—266.
8. Wang HN, Xiang JZ, Qi Z, Du M. Plant extracts in prevention of obesity. *Crit Rev Food Sci Nutr*. 2022;62(8):2221—2234.
9. Scuteri A, Sanna S, Chen WM, et al. Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet*. 2007;3(7):e115.
10. Hinney A, Nguyen TT, Scherag A, et al. Genome wide association (GWA) study for early onset extreme obesity supports the role of fat mass and obesity associated gene (FTO) variants. *PLoS One*. 2007;2(12):e1361.
11. Frayling TM, Timpson NJ, Weedon MN, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*. 2007;316(5826):889—894.
12. Dina C, Meyre D, Gallina S, et al. Variation in FTO contributes to childhood obesity and severe adult obesity. *Nat Genet*. 2007;39(6):724—726.
13. Jia G, Fu Y, Zhao X, et al. N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. *Nat Chem Biol*. 2011;7(12):885—887.
14. Zhao X, Yang Y, Sun BF, et al. FTO-dependent demethylation of N6-methyladenosine regulates mRNA splicing and is required for adipogenesis. *Cell Res*. 2014;24(12):1403—1419.
15. Tung YCL, Yeo GSH, O'Rahilly S, Coll AP. Obesity and FTO: changing focus at a complex locus. *Cell Metab*. 2014;20(5):710—718.
16. Speakman JR. The 'fat mass and obesity related' (FTO) gene: mechanisms of impact on obesity and energy balance. *Curr Obes Rep*. 2015;4(1):73—91.
17. Church C, Moir L, McMurray F, et al. Overexpression of FTO leads to increased food intake and results in obesity. *Nat Genet*. 2010;42(12):1086—1092.
18. Gao X, Shin YH, Li M, Wang F, Tong Q, Zhang P. The fat mass and obesity associated gene FTO functions in the brain to regulate postnatal growth in mice. *PLoS One*. 2010;5(11):e14005.
19. Fischer J, Koch L, Emmerling C, et al. Inactivation of the FTO gene protects from obesity. *Nature*. 2009;458(7240):894—898.
20. Gerken T, Girard CA, Tung YCL, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science*. 2007;318(5855):1469—1472.
21. Meyer KD, Saletore Y, Zumbo P, Elemento O, Mason CE, Jaffrey SR. Comprehensive analysis of mRNA methylation reveals enrichment in 3′ UTRs and near stop codons. *Cell*. 2012;149(7):1635—1646.
22. McTaggart JS, Lee S, Iberl M, Church C, Cox RD, Ashcroft FM. FTO is expressed in neurones throughout the brain and its expression is unaltered by fasting. *PLoS One*. 2011;6(11):e27968.
23. Wang DD, Hu FB. Precision nutrition for prevention and management of type 2 diabetes. *Lancet Diabetes Endocrinol*. 2018;6(5):416—426.
24. Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. *Cell Metab*. 2019;29(5):1028—1044.
25. Wu R, Wang X. Epigenetic regulation of adipose tissue expansion and adipogenesis by N6-methyladenosine. *Obes Rev*. 2021;22(2):e13124.
26. Peters T, Ausmeier K, Dildrop R, Rüther U. The mouse Fused toes (Ft) mutation is the result of a 1.6-Mb deletion including the entire iroquois B gene cluster. *Mamm Genome*. 2002;13(4):186—188.
27. van der Hoeven F, Schimmang T, Volkmann A, Mattei MG, Kyewski B, Rüther U. Programmed cell death is affected in the novel mouse mutant Fused toes (Ft). *Development*. 1994;120(9):2601—2607.
28. Lesche R, Peetz A, van der Hoeven F, Rüther U. Ft1, a novel gene related to ubiquitin-conjugating enzymes, is deleted in the Fused toes mouse mutation. *Mamm Genome*. 1997;8(12):879—883.
29. Peters T, Ausmeier K, Rüther U. Cloning of Fatso (FTO), a novel gene deleted by the Fused toes (Ft) mouse mutation. *Mamm Genome*. 1999;10(10):983—986.
30. Delous M, Baala L, Salomon R, et al. The ciliary gene RPGRIP1L is mutated in cerebello-oculo-renal syndrome (Joubert syndrome type B) and Meckel syndrome. *Nat Genet*. 2007;39(7):875—881.
31. Trewick SC, Henshaw TF, Hausinger RP, Lindahl T, Sedgwick B. Oxidative demethylation by *Escherichia coli* AlkB directly reverts DNA base damage. *Nature*. 2002;419(6903):174—178.
32. Falnes PØ, Johansen RF, Seeberg E. AlkB-mediated oxidative demethylation reverses DNA damage in *Escherichia coli*. *Nature*. 2002;419(6903):178—182.
33. Cecil JE, Tavendale R, Watt P, Hetherington MM, Palmer CNA. An obesity-associated FTO gene variant and increased energy intake in children. *N Engl J Med*. 2008;359(24):2558—2566.
34. Speakman JR. FTO effect on energy demand versus food intake. *Nature*. 2010;464(7289):E1. discussion E2.
35. Tews D, Fischer-Posovszky P, Wabitsch M. FTO — friend or foe? *Horm Metab Res*. 2010;42(2):75—80.
36. Fredriksson R, Hägglund M, Olszewski PK, et al. The obesity gene, FTO, is of ancient origin, up-regulated during food deprivation and expressed in neurons of feeding-related nuclei of the brain. *Endocrinology*. 2008;149(5):2062—2071.
37. Robbens S, Rouzé P, Cock JM, Spring J, Worden AZ, Van de Peer Y. The FTO gene, implicated in human obesity, is found only in vertebrates and marine algae. *J Mol Evol*. 2008;66(1):80—84.
38. Zhang GW, Gao L, Chen SY, et al. Single nucleotide polymorphisms in the FTO gene and their association with growth and meat quality traits in rabbits. *Gene*. 2013;527(2):553—557.
39. Fan B, Du ZQ, Rothschild MF. The fat mass and obesity-associated (FTO) gene is associated with intramuscular fat content and growth rate in the pig. *Anim Biotechnol*. 2009;20(2):58—70.
40. Fontanesi L, Scotti E, Buttazzoni L, Davoli R, Russo V. The porcine fat mass and obesity associated (FTO) gene is associated with fat deposition in Italian Duroc pigs. *Anim Genet*. 2009;40(1):90—93.
41. Sanchez-Pulido L, Andrade-Navarro MA. The FTO (fat mass and obesity associated) gene codes for a novel member of the non-heme dioxygenase superfamily. *BMC Biochem*. 2007;8:23.

42. Sebert S, Salonurmi T, Keinänen-Kiukaanniemi S, et al. Programming effects of FTO in the development of obesity. *Acta Physiol*. 2014;210(1):58—69.
43. Han Z, Niu T, Chang J, et al. Crystal structure of the FTO protein reveals basis for its substrate specificity. *Nature*. 2010;464(7292):1205—1209.
44. Xiao MZ, Liu JM, Xian CL, Chen KY, Liu ZQ, Cheng YY. Therapeutic potential of ALKB homologs for cardiovascular disease. *Biomed Pharmacother*. 2020;131:110645.
45. Zhang X, Wei LH, Wang Y, et al. Structural insights into FTO's catalytic mechanism for the demethylation of multiple RNA substrates. *Proc Natl Acad Sci U S A*. 2019;116(8):2919—2924.
46. Bayoumi M, Munir M. Structural insights into m6A-erasers: a step toward understanding molecule specificity and potential antiviral targeting. *Front Cell Dev Biol*. 2021;8:587108.
47. Chang JY, Park JH, Park SE, Shon J, Park YJ. The fat mass- and obesity-associated (FTO) gene to obesity: lessons from mouse models. *Obesity*. 2018;26(11):1674—1686.
48. Boissel S, Reish O, Proulx K, et al. Loss-of-function mutation in the dioxygenase-encoding FTO gene causes severe growth retardation and multiple malformations. *Am J Hum Genet*. 2009;85(1):106—111.
49. Aas A, Isakson P, Bindesbøll C, Alemu EA, Klungland A, Simonsen A. Nucleocytoplasmic shuttling of FTO does not affect starvation-induced autophagy. *PLoS One*. 2017;12(3):e0168182.
50. Gulati P, Avezov E, Ma M, et al. Fat mass and obesity-related (FTO) shuttles between the nucleus and cytoplasm. *Biosci Rep*. 2014;34(5):e00144.
51. Wei J, Liu F, Lu Z, et al. Differential m^6A, m^6A_m, and m^1A demethylation mediated by FTO in the cell nucleus and cytoplasm. *Mol Cell*. 2018;71(6):973—985.
52. Ferenc K, Pilžys T, Garbicz D, et al. Intracellular and tissue specific expression of FTO protein in pig: changes with age, energy intake and metabolic status. *Sci Rep*. 2020;10(1):13029.
53. Zhang M, Zhang Y, Ma J, et al. The demethylase activity of FTO (fat mass and obesity associated protein) is required for preadipocyte differentiation. *PLoS One*. 2015;10(7):e0133788.
54. Merkestein M, Laber S, McMurray F, et al. FTO influences adipogenesis by regulating mitotic clonal expansion. *Nat Commun*. 2015;6:6792.
55. Chen X, Luo Y, Jia G, Liu G, Zhao H, Huang Z. FTO promotes adipogenesis through inhibition of the Wnt/β-catenin signaling pathway in porcine intramuscular preadipocytes. *Anim Biotechnol*. 2017;28(4):268—274.
56. Wu R, Guo G, Bi Z, et al. m6A methylation modulates adipogenesis through JAK2-STAT3-C/EBPβ signaling. *Biochim Biophys Acta Gene Regul Mech*. 2019;1862(8):796—806.
57. Wu R, Liu Y, Yao Y, et al. FTO regulates adipogenesis by controlling cell cycle progression via m^6A-YTHDF2 dependent mechanism. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018;1863(10):1323—1330.
58. Chen X, Zhou B, Luo Y, et al. Tissue distribution of porcine FTO and its effect on porcine intramuscular preadipocytes proliferation and differentiation. *PLoS One*. 2016;11(3):e0151056.
59. Wang X, Zhu L, Chen J, Wang Y. mRNA m6A methylation downregulates adipogenesis in porcine adipocytes. *Biochem Biophys Res Commun*. 2015;459(2):201—207.
60. Church C, Lee S, Bagg EAL, et al. A mouse model for the metabolic effects of the human fat mass and obesity associated FTO gene. *PLoS Genet*. 2009;5(8):e1000599.
61. McMurray F, Church CD, Larder R, et al. Adult onset global loss of the FTO gene alters body composition and metabolism in the mouse. *PLoS Genet*. 2013;9(1):e1003166.
62. Wang X, Sun B, Jiang Q, et al. mRNA m6A plays opposite role in regulating UCP2 and PNPLA2 protein expression in adipocytes. *Int J Obes*. 2018;42(11):1912—1924.
63. Bird A. Perceptions of epigenetics. *Nature*. 2007;447(7143):396—398.
64. Bi Z, Liu Y, Zhao Y, et al. A dynamic reversible RNA N^6-methyladenosine modification: current status and perspectives. *J Cell Physiol*. 2019;234(6):7948—7956.
65. Lee JE, Schmidt H, Lai B, Ge K. Transcriptional and epigenomic regulation of adipogenesis. *Mol Cell Biol*. 2019;39(11):e00601-18.
66. Wang X, Wang Y. From histones to RNA: role of methylation in signal proteins involved in adipogenesis. *Curr Protein Pept Sci*. 2017;18(6):589—598.
67. Dominissini D, Moshitch-Moshkovitz S, Schwartz S, et al. Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq. *Nature*. 2012;485(7397):201—206.
68. Li X, Kim JW, Grønborg M, Urlaub H, Lane MD, Tang QQ. Role of cdk2 in the sequential phosphorylation/activation of C/EBPbeta during adipocyte differentiation. *Proc Natl Acad Sci U S A*. 2007;104(28):11597—11602.
69. Hochegger H, Takeda S, Hunt T. Cyclin-dependent kinases and cell-cycle transitions: does one fit all? *Nat Rev Mol Cell Biol*. 2008;9(11):910—916.
70. Jiang Q, Sun B, Liu Q, et al. MTCH2 promotes adipogenesis in intramuscular preadipocytes via an m^6A-YTHDF1-dependent mechanism. *FASEB J*. 2019;33(2):2971—2981.
71. Lee Y, Choe J, Park OH, Kim YK. Molecular mechanisms driving mRNA degradation by m^6A modification. *Trends Genet*. 2020;36(3):177—188.
72. Zhao YL, Liu YH, Wu RF, et al. Understanding m^6A function through uncovering the diversity roles of YTH domain-containing proteins. *Mol Biotechnol*. 2019;61(5):355—364.
73. Cai M, Liu Q, Jiang Q, Wu R, Wang X, Wang Y. Loss of m^6A on FAM134B promotes adipogenesis in porcine adipocytes through m^6A-YTHDF2-dependent way. *IUBMB Life*. 2019;71(5):580—586.
74. Wang X, Lu Z, Gomez A, et al. N^6-methyladenosine-dependent regulation of messenger RNA stability. *Nature*. 2014;505(7481):117—120.
75. Wang X, Wu R, Liu Y, et al. m^6A mRNA methylation controls autophagy and adipogenesis by targeting Atg5 and Atg7. *Autophagy*. 2020;16(7):1221—1235.
76. Ho AJ, Stein JL, Hua X, et al. A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proc Natl Acad Sci U S A*. 2010;107(18):8404—8409.
77. Melhorn SJ, Askren MK, Chung WK, et al. FTO genotype impacts food intake and corticolimbic activation. *Am J Clin Nutr*. 2018;107(2):145—154.
78. Ranzenhofer LM, Mayer LES, Davis HA, et al. The FTO gene and measured food intake in 5- to 10-year-old children without obesity. *Obesity*. 2019;27(6):1023—1029.
79. Abdella HM, El Farssi HO, Broom DR, Hadden DA, Dalton CF. Eating behaviours and food cravings; influence of age, sex, BMI and *FTO* genotype. *Nutrients*. 2019;11(2):377.
80. Tung YC, Ayuso E, Shan X, et al. Hypothalamic-specific manipulation of FTO, the ortholog of the human obesity gene FTO, affects food intake in rats. *PLoS One*. 2010;5(1):e8771.
81. Hess ME, Hess S, Meyer KD, et al. The fat mass and obesity associated gene (FTO) regulates activity of the dopaminergic midbrain circuitry. *Nat Neurosci*. 2013;16(8):1042—1048.
82. Li L, Zang L, Zhang F, et al. Fat mass and obesity-associated (FTO) protein regulates adult neurogenesis. *Hum Mol Genet*. 2017;26(13):2398—2411.
83. Wu R, Chen Y, Liu Y, et al. m6A methylation promotes white-to-beige fat transition by facilitating Hif1a translation. *EMBO Rep*. 2021;22(11):e52348.
84. Graff M, Ngwa JS, Workalemahu T, et al. Genome-wide analysis of BMI in adolescents and young adults reveals

additional insight into the effects of genetic loci over the life course. *Hum Mol Genet*. 2013;22(17):3597—3607.
85. Bradfield JP, Taal HR, Timpson NJ, et al. A genome-wide association meta-analysis identifies new childhood obesity loci. *Nat Genet*. 2012;44(5):526—531.
86. Meyre D, Delplanque J, Chèvre JC, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet*. 2009;41(2):157—159.
87. Scherag A, Dina C, Hinney A, et al. Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and German study groups. *PLoS Genet*. 2010;6(4): e1000916.
88. Wheeler E, Huang N, Bochukova EG, et al. Genome-wide SNP and CNV analysis identifies common and low-frequency variants associated with severe early-onset obesity. *Nat Genet*. 2013;45(5):513—517.
89. Willer CJ, Speliotes EK, Loos RJF, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet*. 2009;41(1):25—34.
90. Yajnik CS, Janipalli CS, Bhaskar S, et al. FTO gene variants are strongly associated with type 2 diabetes in South Asian Indians. *Diabetologia*. 2009;52(2):247—252.
91. Ramya K, Radha V, Ghosh S, Majumder PP, Mohan V. Genetic variations in the FTO gene are associated with type 2 diabetes and obesity in south Indians (CURES-79). *Diabetes Technol Ther*. 2011;13(1):33—42.
92. Vasan SK, Fall T, Neville MJ, et al. Associations of variants in FTO and near MC4R with obesity traits in South Asian Indians. *Obesity*. 2012;20(11):2268—2277.
93. Li H, Kilpeläinen TO, Liu C, et al. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. *Diabetologia*. 2012; 55(4):981—995.
94. Monda KL, Chen GK, Taylor KC, et al. A meta-analysis identifies new loci associated with body mass index in individuals of African ancestry. *Nat Genet*. 2013;45(6):690—696.
95. Nock NL, Plummer SJ, Thompson CL, Casey G, Li L. FTO polymorphisms are associated with adult body mass index (BMI) and colorectal adenomas in African-Americans. *Carcinogenesis*. 2011;32(5):748—756.
96. Xiang L, Wu H, Pan A, et al. FTO genotype and weight loss in diet and lifestyle interventions: a systematic review and meta-analysis. *Am J Clin Nutr*. 2016;103(4):1162—1170.
97. Yang Q, Xiao T, Guo J, Su Z. Complex relationship between obesity and the fat mass and obesity locus. *Int J Biol Sci*. 2017;13(5):615—629.
98. Sonestedt E, Roos C, Gullberg B, Ericson U, Wirfält E, Orho-Melander M. Fat and carbohydrate intake modify the association between genetic variation in the FTO genotype and obesity. *Am J Clin Nutr*. 2009;90(5):1418—1425.
99. Scott RA, Bailey MES, Moran CN, et al. FTO genotype and adiposity in children: physical activity levels influence the effect of the risk genotype in adolescent males. *Eur J Hum Genet*. 2010;18(12):1339—1343.
100. Young AI, Wauthier F, Donnelly P. Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. *Nat Commun*. 2016;7:12724.
101. Kilpeläinen TO, Qi L, Brage S, et al. Physical activity attenuates the influence of FTO variants on obesity risk: a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med*. 2011;8(11):e1001116.
102. Ruiz JR, Labayen I, Ortega FB, et al. Attenuation of the effect of the FTO rs9939609 polymorphism on total and central body fat by physical activity in adolescents: the HELENA study. *Arch Pediatr Adolesc Med*. 2010;164(4):328—333.
103. Cho HW, Jin HS, Eom YB. The interaction between FTO rs9939609 and physical activity is associated with a 2-fold reduction in the risk of obesity in Korean population. *Am J Hum Biol*. 2021;33(3):e23489.
104. Graff M, Scott RA, Justice AE, et al. Genome-wide physical activity interactions in adiposity — a meta-analysis of 200,452 adults. *PLoS Genet*. 2017;13(4):e1006528.
105. Reddon H, Gerstein HC, Engert JC, et al. Physical activity and genetic predisposition to obesity in a multiethnic longitudinal study. *Sci Rep*. 2016;6:18672.
106. Cauchi S, Stutzmann F, Cavalcanti-Proença C, et al. Combined effects of MC4R and FTO common genetic variants on obesity in European general populations. *J Mol Med*. 2009;87(5): 537—546.
107. Andreasen CH, Stender-Petersen KL, Mogensen MS, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes*. 2008; 57(1):95—101.
108. Hall KD, Guo J. Obesity energetics: body weight regulation and the effects of diet composition. *Gastroenterology*. 2017; 152(7):1718—1727.
109. Puhl RM, Peterson JL, DePierre JA, Luedicke J. Headless, hungry, and unhealthy: a video content analysis of obese persons portrayed in online news. *J Health Commun*. 2013; 18(6):686—702.
110. Dulloo AG, Miles-Chan J, Schutz Y, Montani JP. Targeting lifestyle energy expenditure in the management of obesity and health: from biology to built environment. *Obes Rev*. 2018;19(suppl 1):3—7.
111. Qi Q, Downer MK, Kilpeläinen TO, et al. Dietary intake, FTO genetic variants, and adiposity: a combined analysis of over 16,000 children and adolescents. *Diabetes*. 2015;64(7): 2467—2476.
112. Speakman JR, Rance KA, Johnstone AM. Polymorphisms of the FTO gene are associated with variation in energy intake, but not energy expenditure. *Obesity*. 2008;16(8):1961—1965.
113. Brunkwall L, Ericson U, Hellstrand S, Gullberg B, Orho-Melander M, Sonestedt E. Genetic variation in the fat mass and obesity-associated gene (FTO) in association with food preferences in healthy adults. *Food Nutr Res*. 2013;57.
114. Cameron JD, Tasca GA, Little J, et al. Effects of fat mass and obesity-associated (FTO) gene polymorphisms on binge eating in women with binge-eating disorder: the moderating influence of attachment style. *Nutrition*. 2019;61:208—212.
115. Mehrdad M, Doaei S, Gholamalizadeh M, Eftekhari MH. The association between FTO genotype with macronutrients and calorie intake in overweight adults. *Lipids Health Dis*. 2020; 19(1):197.
116. Tanaka T, Ngwa JS, van Rooij FJ, et al. Genome-wide meta-analysis of observational studies shows common genetic variants associated with macronutrient intake. *Am J Clin Nutr*. 2013;97(6):1395—1402.
117. Chuang YF, Tanaka T, Beason-Held LL, et al. FTO genotype and aging: pleiotropic longitudinal effects on adiposity, brain function, impulsivity and diet. *Mol Psychiatry*. 2015;20(1): 133—139.
118. Saber-Ayad M, Manzoor S, Radwan H, et al. The FTO genetic variants are associated with dietary intake and body mass index amongst Emirati population. *PLoS One*. 2019;14(10): e0223808.
119. Magno FCCM, Guaraná HC, Fonseca ACP, et al. Influence of *FTO* rs9939609 polymorphism on appetite, ghrelin, leptin, IL6, TNFα levels, and food intake of women with morbid obesity. *Diabetes Metab Syndr Obes*. 2018;11:199—207.
120. Benedict C, Axelsson T, Söderberg S, et al. Fat mass and obesity-associated gene (FTO) is linked to higher plasma levels of the hunger hormone ghrelin and lower serum levels

of the satiety hormone leptin in older adults. *Diabetes*. 2014; 63(11):3955—3959.
121. Dixon JR, Selvaraj S, Yue F, et al. Topological domains in mammalian genomes identified by analysis of chromatin interactions. *Nature*. 2012;485(7398):376—380.
122. Hunt LE, Noyvert B, Bhaw-Rosun L, et al. Complete resequencing of a 2Mb topological domain encompassing the FTO/IRXB genes identifies a novel obesity-associated region upstream of IRX5. *Genome Med*. 2015;7:126.
123. Williams CL, Li C, Kida K, et al. MKS and NPHP modules cooperate to establish basal body/transition zone membrane associations and ciliary gate function during ciliogenesis. *J Cell Biol*. 2011;192(6):1023—1041.
124. Liu L, Zhang M, Xia Z, Xu P, Chen L, Xu T. Caenorhabditis elegans ciliary protein NPHP-8, the homologue of human RPGRIP1L, is required for ciliogenesis and chemosensation. *Biochem Biophys Res Commun*. 2011;410(3):626—631.
125. Stratigopoulos G, LeDuc CA, Cremona ML, Chung WK, Leibel RL. Cut-like homeobox 1 (CUX1) regulates expression of the fat mass and obesity-associated and retinitis pigmentosa GTPase regulator-interacting protein-1-like (RPGRIP1L) genes and coordinates leptin receptor signaling. *J Biol Chem*. 2011;286(3):2155—2170.
126. Vierkotten J, Dildrop R, Peters T, Wang B, Rüther U. Ftm is a novel basal body protein of cilia involved in Shh signalling. *Development*. 2007;134(14):2569—2577.
127. Stratigopoulos G, Martin Carli JF, O'Day DR, et al. Hypomorphism for RPGRIP1L, a ciliary gene vicinal to the FTO locus, causes increased adiposity in mice. *Cell Metab*. 2014; 19(5):767—779.
128. Smemo S, Tena JJ, Kim KH, et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. *Nature*. 2014;507(7492):371—375.
129. Laber S, Forcisi S, Bentley L, et al. Linking the *FTO* obesity rs1421085 variant circuitry to cellular, metabolic, and organismal phenotypes in vivo. *Sci Adv*. 2021;7(30):eabg0108.
130. Zhang Z, Chen N, Liu R, et al. The rs1421085 variant within *FTO* promotes but not inhibits thermogenesis and is potentially associated with human migration. *bioRxiv*. 2021. https://doi.org/10.1101/2021.08.13.456245.
131. Claussnitzer M, Dankel SN, Kim KH, et al. FTO obesity variant circuitry and adipocyte browning in humans. *N Engl J Med*. 2015;373(10):895—907.
132. Sobreira DR, Joslin AC, Zhang Q, et al. Extensive pleiotropism and allelic heterogeneity mediate metabolic effects of *IRX3* and *IRX5*. *Science*. 2021;372(6546):1085—1091.
133. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. *Nat Rev Dis Prim*. 2015;1:15019.
134. Zeggini E, Weedon MN, Lindgren CM, et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science*. 2007;316(5829):1336—1341.
135. Scott LJ, Mohlke KL, Bonnycastle LL, et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science*. 2007;316(5829):1341—1345.
136. Samaras K, Botelho NK, Chisholm DJ, Lord RV. Subcutaneous and visceral adipose tissue FTO gene expression and adiposity, insulin action, glucose metabolism, and inflammatory adipokines in type 2 diabetes mellitus and in health. *Obes Surg*. 2010;20(1):108—113.
137. Bravard A, Lefai E, Meugnier E, et al. FTO is increased in muscle during type 2 diabetes, and its overexpression in myotubes alters insulin signaling, enhances lipogenesis and ROS production, and induces mitochondrial dysfunction. *Diabetes*. 2011;60(1):258—268.
138. Bravard A, Veilleux A, Disse E, et al. The expression of FTO in human adipose tissue is influenced by fat depot, adiposity, and insulin sensitivity. *Obesity*. 2013;21(6):1165—1173.
139. Yang Y, Shen F, Huang W, et al. Glucose is involved in the dynamic regulation of m6A in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2019;104(3):665—673.
140. Souness JE, Stouffer JE, de Sanchez VC. Effect of N6-methyladenosine on fat-cell glucose metabolism: evidence for two modes of action. *Biochem Pharmacol*. 1982;31(24): 3961—3971.
141. Shen F, Huang W, Huang JT, et al. Decreased N(6)-methyladenosine in peripheral blood RNA from diabetic patients is associated with FTO expression rather than ALKBH5. *J Clin Endocrinol Metab*. 2015;100(1):E148—E154.
142. Poritsanos NJ, Lew PS, Mizuno TM. Relationship between blood glucose levels and hepatic Fto mRNA expression in mice. *Biochem Biophys Res Commun*. 2010;400(4):713—717.
143. Mizuno TM, Lew PS, Luo Y, Leckstrom A. Negative regulation of hepatic fat mass and obesity associated (Fto) gene expression by insulin. *Life Sci*. 2017;170:50—55.
144. Guo J, Ren W, Li X, et al. Altering of FTO in the serum and livers of NAFLD patients: a correlation analysis. *Int J Clin Exp Med*. 2018;11(6):6046—6053.
145. Lei KJ, Shelly LL, Pan CJ, Sidbury JB, Chou JY. Mutations in the glucose-6-phosphatase gene that cause glycogen storage disease type 1a. *Science*. 1993;262(5133):580—583.
146. Menendez JA, Vazquez-Martin A, Ortega FJ, Fernandez-Real JM. Fatty acid synthase: association with insulin resistance, type 2 diabetes, and cancer. *Clin Chem*. 2009;55(3): 425—438.
147. Buhman KK, Chen HC, Farese Jr RV. The enzymes of neutral lipid synthesis. *J Biol Chem*. 2001;276(44):40369—40372.
148. Li Y, Ma Z, Jiang S, et al. A global perspective on FOXO1 in lipid metabolism and lipid-related diseases. *Prog Lipid Res*. 2017;66:42—49.
149. Dong XC, Copps KD, Guo S, et al. Inactivation of hepatic Foxo1 by insulin signaling is required for adaptive nutrient homeostasis and endocrine growth regulation. *Cell Metab*. 2008; 8(1):65—76.
150. Chou JY, Jun HS, Mansfield BC. Glycogen storage disease type I and G6Pase-β deficiency: etiology and therapy. *Nat Rev Endocrinol*. 2010;6(12):676—688.
151. De Jesus DF, Kulkarni RN. Epigenetic modifiers of islet function and mass. *Trends Endocrinol Metab*. 2014;25(12): 628—636.
152. De Jesus DF, Zhang Z, Kahraman S, et al. m6A mRNA methylation regulates human β-cell biology in physiological states and in type 2 diabetes. *Nat Metab*. 2019;1(8):765—774.
153. Wang Y, Sun J, Lin Z, et al. m^6A mRNA methylation controls functional maturation in neonatal murine β-cells. *Diabetes*. 2020;69(8):1708—1722.
154. Liu J, Luo G, Sun J, et al. METTL14 is essential for β-cell survival and insulin secretion. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(9):2138—2148.
155. Men L, Sun J, Luo G, Ren D. Acute deletion of METTL14 in β-cells of adult mice results in glucose intolerance. *Endocrinology*. 2019;160(10):2388—2394.
156. Russell MA, Morgan NG. Conditional expression of the FTO gene product in rat INS-1 cells reveals its rapid turnover and a role in the profile of glucose-induced insulin secretion. *Clin Sci*. 2011;120(9):403—413.
157. Fan HQ, He W, Xu KF, Wang ZX, Xu XY, Chen H. FTO inhibits insulin secretion and promotes NF-κB activation through positively regulating ROS production in pancreatic β cells. *PLoS One*. 2015;10(5):e0127705.
158. Taneera J, Prasad RB, Dhaiban S, et al. Silencing of the FTO gene inhibits insulin secretion: an in vitro study using GRINCH cells. *Mol Cell Endocrinol*. 2018;472:10—17.
159. Fan JG, Kim SU, Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol*. 2017;67(4):862—873.

160. Guo J, Ren W, Li A, et al. Fat mass and obesity-associated gene enhances oxidative stress and lipogenesis in nonalcoholic fatty liver disease. *Dig Dis Sci*. 2013;58(4):1004—1009.
161. Lim A, Zhou J, Sinha RA, et al. Hepatic FTO expression is increased in NASH and its silencing attenuates palmitic acid-induced lipotoxicity. *Biochem Biophys Res Commun*. 2016; 479(3):476—481.
162. Kang H, Zhang Z, Yu L, Li Y, Liang M, Zhou L. FTO reduces mitochondria and promotes hepatic fat accumulation through RNA demethylation. *J Cell Biochem*. 2018;119(7):5676—5685.
163. Chen A, Chen X, Cheng S, et al. FTO promotes SREBP1c maturation and enhances CIDEC transcription during lipid accumulation in HepG2 cells. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2018;1863(5):538—548.
164. Candia R, Riquelme A, Baudrand R, et al. Overexpression of 11β-hydroxysteroid dehydrogenase type 1 in visceral adipose tissue and portal hypercortisolism in non-alcoholic fatty liver disease. *Liver Int*. 2012;32(3):392—399.
165. Hu Y, Feng Y, Zhang L, et al. GR-mediated FTO transactivation induces lipid accumulation in hepatocytes via demethylation of m^6A on lipogenic mRNAs. *RNA Biol*. 2020;17(7):930—942.
166. Roth GA, Mensah GA, Fuster V. The global burden of cardiovascular diseases and risks: a compass for global action. *J Am Coll Cardiol*. 2020;76(25):2980—2981.
167. Dorn LE, Lasman L, Chen J, et al. The N^6-methyladenosine mRNA methylase METTL3 controls cardiac homeostasis and hypertrophy. *Circulation*. 2019;139(4):533—545.
168. Mathiyalagan P, Liang Y, Sassi Y, et al. Abstract 12:M6A modification in RNA regulates cardiomyocyte and cardiac function in heart failure. *Circ Res*. 2017;121(suppl 1):A12.
169. Berulava T, Buchholz E, Elerdashvili V, et al. Changes in m6A RNA methylation contribute to heart failure progression by modulating translation. *Eur J Heart Fail*. 2020;22(1):54—66.
170. Carnevali L, Graiani G, Rossi S, et al. Signs of cardiac autonomic imbalance and proarrhythmic remodeling in FTO deficient mice. *PLoS One*. 2014;9(4):e95499.
171. Gustavsson J, Mehlig K, Leander K, et al. FTO genotype, physical activity, and coronary heart disease risk in Swedish men and women. *Circ Cardiovasc Genet*. 2014;7(2):171—177.
172. Mathiyalagan P, Adamiak M, Mayourian J, et al. FTO-dependent N^6-methyladenosine regulates cardiac function during remodeling and repair. *Circulation*. 2019;139(4):518—532.
173. Shen W, Li H, Su H, Chen K, Yan J. FTO overexpression inhibits apoptosis of hypoxia/reoxygenation-treated myocardial cells by regulating m6A modification of Mhrt. *Mol Cell Biochem*. 2021;476(5):2171—2179.
174. Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. *Nat Rev Cardiol*. 2018;15(1):45—56.
175. Li X, Yang Y, Chen S, Zhou J, Li J, Cheng Y. Epigenetics-based therapeutics for myocardial fibrosis. *Life Sci*. 2021;271: 119186.
176. Baur JA, Pearson KJ, Price NL, et al. Resveratrol improves health and survival of mice on a high-calorie diet. *Nature*. 2006;444(7117):337—342.
177. Gan Z, Wei W, Wu J, et al. Resveratrol and curcumin improve intestinal mucosal integrity and decrease m^6A RNA methylation in the intestine of weaning piglets. *ACS Omega*. 2019;4(17):17438—17446.
178. Wu J, Li Y, Yu J, et al. Resveratrol attenuates high-fat diet induced hepatic lipid homeostasis disorder and decreases m^6A RNA methylation. *Front Pharmacol*. 2020;11:568006.
179. Meydani M, Hasan ST. Dietary polyphenols and obesity. *Nutrients*. 2010;2(7):737—751.
180. Lu N, Li X, Yu J, et al. Curcumin attenuates lipopolysaccharide-induced hepatic lipid metabolism disorder by modification of m^6A RNA methylation in piglets. *Lipids*. 2018;53(1):53—63.
181. Chen Y, Wu R, Chen W, et al. Curcumin prevents obesity by targeting TRAF4-induced ubiquitylation in m^6A-dependent manner. *EMBO Rep*. 2021;22(5):e52146.
182. Patra SK, Rizzi F, Silva A, Rugina DO, Bettuzzi S. Molecular targets of (-)-epigallocatechin-3-gallate (EGCG): specificity and interaction with membrane lipid rafts. *J Physiol Pharmacol*. 2008;59(suppl 9):217—235.
183. Wu R, Yao Y, Jiang Q, et al. Epigallocatechin gallate targets FTO and inhibits adipogenesis in an mRNA m^6A-YTHDF2-dependent manner. *Int J Obes*. 2018;42(7):1378—1388.
184. Wei CM, Gershowitz A, Moss B. Methylated nucleotides block 5′ terminus of HeLa cell messenger RNA. *Cell*. 1975;4(4): 379—386.
185. Wei CM, Gershowitz A, Moss B. 5′-Terminal and internal methylated nucleotide sequences in HeLa cell mRNA. *Biochemistry*. 1976;15(2):397—401.
186. Lee M, Kim B, Kim VN. Emerging roles of RNA modification: m(6)A and U-tail. *Cell*. 2014;158(5):980—987.
187. Zhou J, Wan J, Gao X, Zhang X, Jaffrey SR, Qian SB. Dynamic m(6)A mRNA methylation directs translational control of heat shock response. *Nature*. 2015;526(7574):591—594.
188. Zheng G, Dahl JA, Niu Y, et al. ALKBH5 is a mammalian RNA demethylase that impacts RNA metabolism and mouse fertility. *Mol Cell*. 2013;49(1):18—29.
189. Boles NC, Temple S. Epimetronomics: m6A marks the tempo of corticogenesis. *Neuron*. 2017;96(4):718—720.
190. Yoon KJ, Ringeling FR, Vissers C, et al. Temporal control of mammalian cortical neurogenesis by m^6A methylation. *Cell*. 2017;171(4):877—889.
191. Su R, Dong L, Li Y, et al. Targeting FTO suppresses cancer stem cell maintenance and immune evasion. *Cancer Cell*. 2020;38(1):79—96.
192. Huang Y, Su R, Sheng Y, et al. Small-molecule targeting of oncogenic FTO demethylase in acute myeloid leukemia. *Cancer Cell*. 2019;35(4):677—691.
193. Liu Y, Liang G, Xu H, et al. Tumors exploit FTO-mediated regulation of glycolytic metabolism to evade immune surveillance. *Cell Metab*. 2021;33(6):1221—1233.
194. Deng X, Su R, Stanford S, Chen J. Critical enzymatic functions of FTO in obesity and cancer. *Front Endocrinol*. 2018;9:396.
195. Peng S, Xiao W, Ju D, et al. Identification of entacapone as a chemical inhibitor of FTO mediating metabolic regulation through FOXO1. *Sci Transl Med*. 2019;11(488):eaau7116.
196. Wang X, Huang N, Yang M, et al. FTO is required for myogenesis by positively regulating mTOR-PGC-1α pathway-mediated mitochondria biogenesis. *Cell Death Dis*. 2017;8(3): e2702.