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FTO: a critical role in obesity and obesity-related diseases

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Abstract

In recent years, obesity is a growing pandemic in the world and has likely contributed to increasing the incidence of obesity-related diseases. Fat mass and obesity-associated gene (*FTO*) is the first gene discovered which has a close connection with fat. Recent studies suggested that *FTO* gene has played an important role in the molecular mechanisms of many diseases. Obesity is considered to be a hereditary disease and can evoke many kinds of diseases, including polycystic ovary syndrome (PCOS), type 2 diabetes mellitus (T2DM), cancer, etc., whose exact possible molecular mechanisms responsible for the effect of *FTO* on obesity and obesity-related diseases remain largely unknown. In this review, we comprehensively discuss the correlation between *FTO* gene and obesity, cancer, PCOS, T2DM, as well as the molecular mechanism involved in these diseases.

Key words: *FTO*: SNP: Obesity: PCOS: Cancer: Type 2 diabetes mellitus

The prevalence of obesity has risen sharply last several years and has become one of the most severe health issues in the world. It is estimated that obesity may be considered as a heritable trait[1]. The SNP are the common genetic variations in human genomes[2]. To date, it is found that 23 715 susceptibility SNP (including 283 index SNP) are located in the enhancer regions of obesity-related cell lines[3], and various genes such as *LEP*, *LEPR*, *NPY*, *ADIPOQ*, *FTO*, *MC4R*, *PCSK1* and *POMC* are implicated and have a direct role in obesity[4]. Among these genes, the fat mass-associated gene (*FTO*) is considered as the first and strongest related gene causing obesity in multiple populations of different countries[5].

FTO gene is a DNA/RNA methylase that encodes Fe(II)/2-OG-dependent demethylase, which is the ninth AlkB family protein (also known as *ALKBH9*)[6]. The *FTO* gene was firstly cloned from the identification of a fusion toe mutant mouse which phenotypically caused by a 1·6-Mb deletion of six genes, including *FTO*[7]. In 2007, *FTO* was described as the first gene which was associated with the common obesity. Because *FTO* has a strong preference for 3-methylthymine (3-meT) and 3-methyluracil (3-meU) single-stranded DNA and RNA[6], it has been demonstrated that *FTO* can oxidise demethylated 3-meT and 3-meU in single-stranded DNA (ssDNA) and single-stranded RNA (ssRNA) *in vitro*[8]. *FTO* also can demethylate N6-methyladenosine (m^6A) and N6, 2'-O-methyladenosine (m^6A_m) in mRNA, m^6A in U6RNA, m^6A_m in snRNAs and N1-methyladenosine (m^1A) in tRNA[9]. *FTO* has been reported to be associated with many diseases, including type 2 diabetes mellitus (T2DM), polycystic ovary syndrome (PCOS) and various malignancies such as breast[10], thyroid[11] and endometrial cancer[12].

Molecular mechanisms

FTO have an effect on the molecular mechanisms of diseases mainly through regulating the expression levels of m^6A in the relative diseases. The insulin resistance, obesity, hyperandrogenism, etc., are the major features of PCOS; previous study reported that *FTO* is the positive regulator of FLOT2 in KGN cells and decreases m^6A levels in mRNA of FLOT2 and increases the

Abbreviations: *FTO*, fat mass-associated gene; HCC, hepatocellular carcinoma; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

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stability of FLOT2 mRNA to enhance the expression of FLOT2 so that it promotes cell proliferation, inhibits cell apoptosis and reduces GLUT4 membrane transport by insulin induced in KGN cells. The deletion of FLOT2 may weak the influence of *FTO* overexpression to GCs cell proliferation/apoptosis and insulin resistance[13]. *FTO* variation may impact the baseline lipid oxidation in PCOS patients[14], and obesity PCOS women rose the lipid oxidation level in the condition with insulin induced[15]. It is reasonable to assume that *FTO* gene might be one of the underlying mechanisms in the weight of PCOS patients. Moreover, *FTO* variation may play a significant role in hyperandrogenism state, and the high free testosterone levels have a significant association with rs9939609 A allele in *FTO*[16].

In T2DM, the reduction of expression levels of m^6A in diabetes and obesity patients is negatively correlated with the increasing expression of *FTO*[17]. The high demethylases (*FTO* and ALKBH5) may cause a decrease in m^6A RNA expression and result in obesity[18]. FTO protein may induce the mRNA expression of four genes (FOXO1, FASN, G6PC and DGAT2) involved in glycolipid metabolism. High-glucose-enhanced FTO mRNA expression resulted in the up-regulated methyltransferase to abate the m^6A levels, and the up-regulated expression levels in those four genes were closely associated with the hyperglycaemia and dyslipidemia in T2DM patients[19]. There was a 2·797-fold increased risk of T2DM with a one-unit increase in *FTO* mRNA level, and the enhancement of *FTO* mRNA levels may be responsible for the reduction of m^6A in T2DM, which can further trigger the complications of T2DM[20]. In the aggregate, *FTO* may involve in the molecular mechanisms of T2DM.

N^6-methyladenosine (m^6A) also plays a pivotal role in tumorigenesis. The main pathway is up-regulated the mRNA and protein levels of m^6A-related genes through down-regulating the expression of *FTO* protein to inhibit tumorigenesis. It has been proved that m^6A demethylase includes *FTO* protein and ALKBH5. A study emphasised a decrease in the percentage of total RNA m^6A in the hepatocellular carcinoma (HCC) tissues compared with normal samples[21]. The ectopic overexpression of *FTO* protein not only suggested poor prognosis but also associated with low m^6A content in HCC[21] (Fig. 1(c)). *FTO*-mediated n-6,2-O-dimethyladenosine (m^6A_m) demethylation played a minimal role in *FTO*-induced inhibition of proliferation and activation of apoptosis in acute myelogenous leukemia cells[22]. The modification of m^6A in RNA reduced the proliferation and cell viability of melanoma cells, which confirmed that m^6A could inhibit the growth of melanoma[23]. *FTO*, as a m^6A demethylase, played a crucial role in promoting melanoma development and anti-pd-1 resistance. *FTO* protein inhibition and anti-pd-1 blockade might reduce the drug resistance of melanoma immunotherapy. Additionally, m^6A content was increased by knock-out *FTO* to inhibit the proliferation of A549 lung cancer cells[24]. The growth of cancer cells can be inhibited by regulating the m^6A level so as to target cancer therapy.

The functions of *FTO* SNP

Different *FTO* SNP caused the accumulation of fat in various parts of the body. Individuals of *FTO* rs17817449 TT genotype have easier fat deposition in the thoracic and breast region[25]. *FTO* rs1421085 C/C alleles inhibit the expression of mitochondrial and thermogenesis genes, and human adipose-derived stromal cells from the different position of human neck keep differing propensity for adipocyte browning by the influence of the alleles[26]. The mRNA levels of *FTO* rs9939609 A allele are up-regulated with peripheral protein and the expression of peripheral protein, which elucidated the most significant associations for *FTO* in regulating lipoclasis and total body fat[27].

FTO SNP may have underlying associations with the children and pregnant women. In children, *FTO* SNP rs8050136 took part in the risk of adjusting attention-deficit/hyperactivity disorder, especially who were not exposed in maternal smoking during pregnancy[28]. Among the pregnant women, the maternal and infant AA genotype of the obesity-associated *FTO* rs9939609 SNP associates with increased risk for small-for-gestational-age pregnancy and spontaneous preterm birth, and the SNP might play a significant role in calculating the risk of pregnancy complications and subsequent vascular diseases[29]. *FTO* rs9939609 TA genotype only related with the risk reduction of intra-uterine growth restriction in male offspring[30].

FTO and obesity

Obese patients are influenced by diet intakes and living habits, which are generally associated with a specific *FTO* polymorphisms. SNP are the main form of variation that regulates gene expression in the DNA sequence of the human genome. The A (risk) allele of rs9939609 in the *FTO* gene was strongly associated with greater obesity[31]. High-fibre diets may have positive effects on anthropometric parameters but may also worsen lipid profiles dependent on the *FTO* genotypes[32]. *FTO* rs1421085 TC + CC genotypes were associated with fat intake[33]. Moreover, *FTO* rs1421085 C-allele was linked with the degree of abdominal fat accumulation in adolescent males and females, but the effect of *FTO* rs1421085 risk allele C on obesity was not mediated by daily energy intake, macronutrient intake or physical activity[34]. *FTO* gene polymorphisms may play a significant role in dietary habits, which might associate with *FTO* SNP. For example, the decline in emotional eating with age was greater in the rs9939609 *FTO* polymorphism of AA + AT genotype group[35]. Individuals with minor allele carriers of rs9939973, rs8050136, rs1781749 and rs3751812 had lower risk of obesity when they had higher Mediterranean dietary score, compared with wild-type homozygote genotype carriers[36]. Med Diet adherence can be useful for the prevention or treatment of obesity phenotypes in subjects with *FTO* risk alleles[36].

Weight gain in obese patients is influenced by the frequency of various *FTO* gene polymorphisms. Obese patients were remarkably associated with *FTO* (rs9939609) AA genotype compared with non-obese patients, not only the frequencies of rare *FTO* alleles (A) in obese patients were conspicuously higher than those in non-obese controls, but also the frequencies of (TA + AA) genotype in obese patients were also significantly higher than those in non-obese controls[37]. Similarly, SNP rs9939609 A allele carrier subjects (AT/AA) who had dramatically higher BMI ($P = 0{\cdot}001$) and fat mass index ($P = 0{\cdot}002$) compared with SNP rs9939609 TT homozygote carriers and carriers

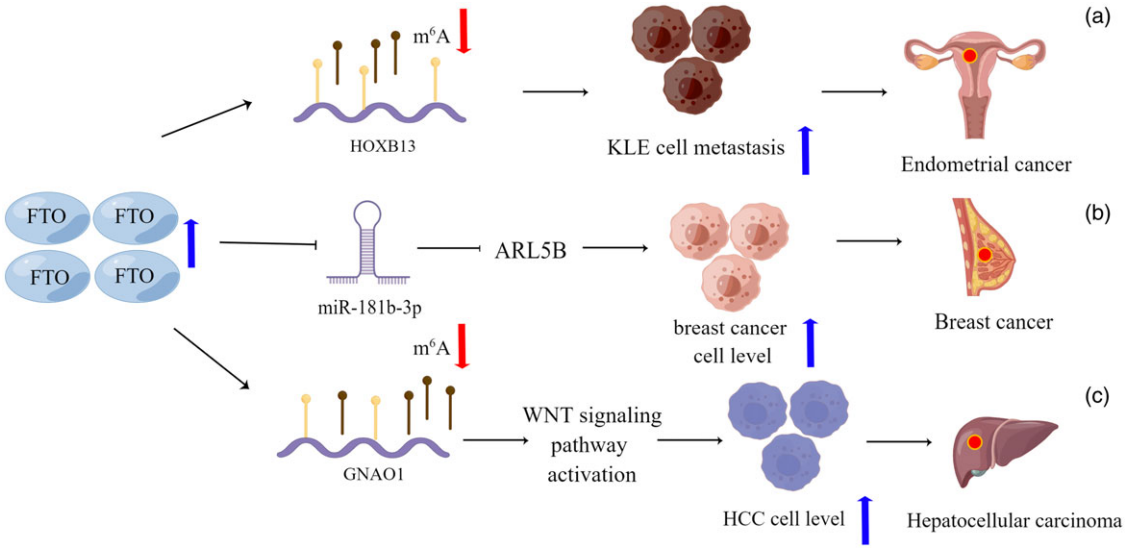

Fig. 1. FTO overexpression promotes tumorigenesis via different signal pathways by Figdraw (www.figdraw.com). (a) Enhancing the expression of FTO in human endometrial cancer cells (KLE) and the m^{6}A of HOXB13 mRNA decreases to activate the WNT signalling pathway so that the ability of migration and invasion was significantly increased. (b) FTO upregulates ARL5B by inhibiting miR-181b-3p. The carcinogenic activity of FTO/MIR-181B-3P/ARL5B signalling pathway promotes invasion and migration in breast cancer cells. (c) FTO overexpression downregulates the m^{6}A of GNAO1 mRNA to increase the HCC cells level and HCC tumorigenesis. HCC, HCC, hepatocellular carcinoma.

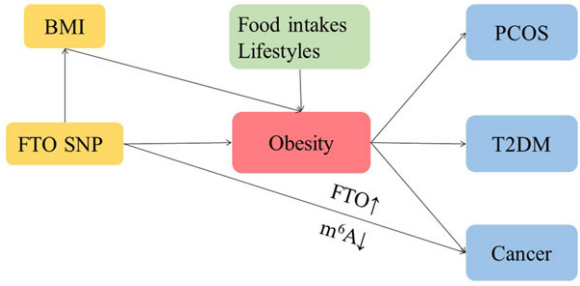

Fig. 2. The relationships between *FTO* SNP and obesity with its diseases. PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.

of T allele in SNP rs10163409 had a higher risk of central obesity than carriers of AA genotype of SNP rs10163409 in the Turkish population[38]. The total fat content of rs9939609 AA genotype individuals was higher in Turkey[39]. The higher is the frequency of AA genotype in SNP rs9939609 A/T, the more is the obese individual in population.

FTO polymorphisms have genetic difference among obese population according to the difference of sex, ethnic group and region. Women carrying the minor allele of rs9930506 variant have a significant increase in BMI by year, which indicates that rs9930506 exhibited positive interactions with age and BMI in a sex-dependent manner[40]. Male carrying *FTO* (rs8050136) risk A allele would even lose more weight than non-carriers after exercise intervention but not in females[41]. The *FTO* SNP rs1421085 is a genetic factor associated with obesity in Mayan school-aged children, and *FTO* SNP rs1421085 and rs9939609 affect genetic susceptibility for obesity only in girls; however, SNP rs8057044 is associated with overweight status only in boys[42]. The *FTO* rs1558902 and rs1421085 variations had robustly effected on obesity in women, and overweight may be regulated by different genetic patterns depending on sex[43]. *FTO* contributed to obesity susceptibility in Caucasian, Chinese, African American and Hispanic population[44]. *FTO* rs9939609 A allele and rs1421085 C risk allele increased the risk of obese in Balinese[45], and the *FTO* variant rs1421085 CT genotype was associated to raise the risk of overweight/obesity (BMI ≥ 25 kg/m^2 for overweight and BMI ≥ 30 kg/m^2 for obesity) to 1·583 times in Pakistani individuals[46]. The severe obesity in Brazilian population was strongly related to *FTO* rs9939609 allele (A)[47].

FTO and polycystic ovary syndrome

PCOS is a common endocrine and metabolic disorder in women of childbearing age, which is characterised by polycystic ovary, hypomenorrhea or amenorrhea, clinical or biochemical hyperandrogenism and insulin resistance. Due to the majority of patients with PCOS is obese, it is reasonable to assume that *FTO* gene might play a central role in the pathogenesis of PCOS.

FTO polymorphisms are closely related to the risk of PCOS, in which rs9939609 is the most important factor, followed by rs1421085, rs17817449, rs8050136, rs8060136, rs1588413, etc. Li *et al.*[48] and Yuan *et al.*[49] demonstrated that *FTO* rs9939609 risk allele A was associated with PCOS in obese Chinese women. The association was influenced by BMI, while the connection was weakened after the adjustment for BMI. *FTO* risk allele A was associated with measurements of IR traits and weight gain; however, the obesity risk allele A of the *FTO* variant rs9939609 was lower frequency in polycystic ovary patients than that in PCOS patients without polycystic ovary[50]. *FTO* polymorphisms were associated with PCOS susceptibility, and both the *FTO* polymorphisms and PCOS susceptibility were observably related with BMI. The A allele of rs9939609 variation in *FTO* gene

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was associated with PCOS susceptibility in Chinese population, possibly because of its influence on BMI[51]. Likewise, the A risk allele of SNP rs9939609 has been indicated to increase the susceptibility to PCOS[52]. The G/G genotype (rs1421085), the C/C genotype (rs17817449) and the A/A genotype (rs8050136) variations of *FTO* gene were associated with PCOS susceptibility, hyperandrogenemia and a higher BMI in young Korean women, which suggests that these results might be caused by obesity[53]. In contrast, neither *FTO* rs9939609 (T/A) and *FTO* rs8050136 (A/C) nor its haplotypes were associated with PCOS in Brazilian women[54].

FTO gene variation rs9939609 is associated with metabolic disorders of PCOS in different ethnic populations. A study firstly provided the evidence that *FTO* genes were associated with metabolic syndrome, which is also a characteristic of PCO, especially impacted on impaired glucose tolerance in Caucasian women[55]. The *FTO* rs9939609 was associated with hyperandrogenism and the metabolic manifestations of PCOS in women of Sri Lankan origin. The A risk allele of SNP rs9939609 has been shown to increase the susceptibility to PCOS, and serum adiponectin and leptin were independent markers of PCOS diagnosis, which depended on BMI status[56]. The risk alleles of both rs9939609 (TA/AA) and rs8050136 (AA/AC) in *FTO* gene were proposed to be associated with higher fasting glucose levels in Brazilian women[57]. *FTO* genes played a strong role in PCOS through their effects on obesity or metabolic complications in Central European populations[58]. *FTO* polymorphisms were closely associated with the metabolic syndrome of PCOS patients, which is always shown as the higher fasting glucose levels and impaired glucose tolerance.

In conclusion, both *FTO* polymorphisms raise the risk of obesity in PCOS, and these vital polymorphisms are closely associated with BMI, metabolic syndrome, hyperandrogenemia, impaired glucose tolerance, lipid metabolism disorder, etc., in PCOS.

FTO and cancer

Cancer prevalence is increasing worldwide. The occurrence and development of cancer are closely related to many factors, such as environments, heredity, living habits, and diets. *FTO* is a demethylase which connects with cancer. There are many cancers which are induced by obesity, including breast cancer[57], HCC[21], oesophageal cancer[59], etc. Interestingly, *FTO* gene has been reported to be closely associated with cancer. Not only the *FTO* polymorphisms are associated with the risk of cancer and DNA demethylation, but also *FTO* proteins regulate those specific mechanisms of carcinosis, and *FTO* glycosidases seem to play a major role in cancer by regulating the expression of *FTO*. Thus, *FTO* has been demonstrated to cause a variety of cancers, such as bladder, liver and breast cancer, and there are different pathological mechanisms for different cancers.

Overexpression of FTO protein promotes proliferation in cancer cells, while down-regulation of FTO protein inhibits proliferation in cancer cells. FTO expression was apparently increased in oral squamous cell carcinomas cell lines and tissues, and high expression of FTO was closely correlated with poor prognosis[60]. FTO protein was up-regulated in HCC tissues and cells[21]. In addition, the m^6A levels in HCC cells were increased when FTO protein was silenced, and FTO protein as an oncogene might regulate mRNA demethylation in HCC tumorigenesis[21]. The ability of migration was distinctly increased after enhancing FTO protein expression in human endometrial cancer cells (KLE)[61]. In contrast, cell migration was tremendously decreased after silencing FTO protein expression in KLE cells[62]. Meanwhile, FTO protein was closely related with the occurrence and development of endometrial cancer[59]. FTO protein was overexpressed in transmissible endometrial cancer cells, which promoted migration and invasion of endometrial cancer cells *in vivo* and *in vitro*[59] (Fig. 1(a)). FTO protein was up-regulated in ovarian cancer tissues compared with non-cancerous ovarian tissues, which clearly improved the viability and autophagy but reduced apoptosis of ovarian cancer cells[60]. However, FTO protein expression was down-regulated, which promoted tumour growth and metastasis and negatively correlated with poor survival in lung adenocarcinoma patients[63]. Those researches revealed that up-regulated FTO protein expression in majority tumour cells promotes proliferation and differentiation of cancer cells, but the FTO protein overexpression inhibits the growth of cancer cells in some cancers, which demonstrated that the pathogenic mechanisms mediated by FTO were evidently different in cancers.

Different FTO protein signalling pathways for each type of cancer may provide new targets for cancer therapy. The carcinogenic activity of *FTO*/MIR-181B-3P/ARL5B signalling pathway promoted invasion and migration of breast cancer cells[57]. FTO protein enhanced ARL5*B* expression, while miR-181b-3p inhibited ARL5B expression[57] (Fig. 1(b)). The 2-hydroxyglutarate (2HG) inhibited the proliferation/survival of FTO protein high-expression cancer cells by targeting the *FTO*/m^6A/*MYC*/CEBPA signalling pathway[62]. FTO protein was the direct target of R-2-hydroxyglutarate (R-2HG) and the main mediator of R-2HG-induced growth inhibition in leukemic cells[62]. The down-regulation of FTO protein expression obviously increased m^6A levels in a large number of genes of mRNA in key pathways, especially in metabolic pathway genes such as *MYC*[61]. The level of m^6A on *MYC* mRNA was increased to recruit YTHDF1 binding and enhance glycolysis, tumour cell proliferation and tumorigenesis[61]. As such, the down-regulation of FTO protein expression is negatively correlated with survival rates of lung adenocarcinoma patients, which may promote tumour growth and metastasis.

FTO and diabetes

T2DM is a common polygenic disease and complex metabolic disease, which is caused by many genetic factors, environment, obesity and epigenetic regulation and accompanied by co-morbidity. Obesity is a major risk factor for the development of type 2 diabetes, and *FTO* polymorphisms are not only associated with obesity but also a main cause of type 2 diabetes.

FTO polymorphisms are differently expressed in various populations, and the different alleles of *FTO* cause diabetes. The SNP on the first intron of *FTO* gene was associated with T2DM[64]. *FTO* rs9939609 gene variation is the predictor of T2DM in the future, which would use to further study the predictive model

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of T2DM in Vietnam[65]. The *FTO* gene rs9940128 A/G polymorphism was investigated to be associated with type 2 diabetes in North Indians[66]. The allele A at the rs9939609 locus is highly associated with type 2 diabetes in South Asian Indians[67], and the association with type 2 diabetes was still significant after adjusting BMI, waist circumference and other body measurement variables. The *FTO* rs9939609 polymorphism was associated with a family history of diabetes in the northeastern Iranian population[68]. Not only *FTO* variants were related with type 2 diabetes, but also some variants were robustly connected with hormones and androgens in obese women in Iran[64]. The *FTO* rs141115189, rs9926289 and rs9939609 polymorphisms were apparently associated with T2DM in the general population. The *FTO* rs9939609 A allele was associated with an increased risk of diabetes and obesity in White people, and only the rs1421085 C allele was found to be protective against diabetes in African Americans[45]. In the same way, the homozygosity or heterozygosity of the T allele in *FTO* rs9939609 had a protective effect, decreasing T2DM risk by inheriting collectively with C/C for the *PPARγ* rs1801282 and C/C for melanocortin 4 receptor (*MC4R*) rs2229616 or C/C for *PPARγ* rs1801282 and C/T *MC4R* rs2229616[69]. However, when the AA genotype of *FTO* rs9939609 was combined with CC genotype in *PPARγ* rs1801282 or CC *MC4R* rs2229616 genotype, it had a positive effect on the development of T2DM[69]. Diabetics differently affected BMI in different races or regions, which may have a certain relationship with age. The *FTO* variation changed the risk of type 2 diabetes and increased the weight before adulthood of patients in Ahvaz, in which BMI also played an indispensable role[70]. The studies of Indians in South Asia[71] and Karachi in Pakistan[72] demonstrated that the population with the minor allele A at the rs9939609 were predisposed to type 2 diabetes, and the variation may influence on BMI. However, *FTO* rs8050136 had no association with T2DM in Saudi people[73]. In sum, *FTO* gene can increase the risk of T2DM in different ages, races and regions. Next studies should be conducted according to the different influencing factors. Some research results were not completely consistent between *FTO* SNP and diabetes, and a large sample research is very necessary in multiple centres in the future.

Diabetes can also cause a variety of complications, including diabetic nephropathy, CVD, high blood pressure and depression, etc. The T2DM patients with inflammation had an increased risk of arteriosclerosis. The inflammatory state of T2DM patients played a stronger role in developing arteriosclerosis problems than the influence on CVD by obesity[70]. The C allele of *FTO* gene polymorphism rs7204609 contributed to genetic predisposition of chronic kidney disease[74]. Chronic kidney disease patients with central obesity, hypertension, high proteinuria and diabetes are more common than patients with chronic kidney disease alone. Taira's study for the first time identified the association between the G/A alleles of rs56094641 in *FTO* and susceptibility to diabetic nephropathy in T2DM patients in Japan[75]. Moreover, the results suggested that cognitive decline and dementia could be prevented by controlling blood sugar and depression. *FTO* promoted inflammatory response to stimulate the pathogenesis of diabetic kidney disease through the *FTO*/SOCS1/JAK-STAT axis, and *FTO* expression evidently decreased in the diabetic kidney disease tissue; thus, *FTO* overexpression can obviously reduce kidney inflammation[76].

Conclusions

Many studies have proved the relationship between *FTO* and obesity. The obesity is affected not only by *FTO* gene but also by individuals eating habits. *FTO* SNP are also closely related to the increase of PCOS risk. However, the susceptibility of PCOS will also be related to BMI. Different regions, races and sexes have different genetic patterns of *FTO*. There are different sensitivities to BMI, and the complications of diabetes are related to *FTO* alleles among diabetic patients in Caucasians and South Asian Indians. The relationship of *FTO* gene with cancer shows that *FTO* overexpression can promote the proliferation of numerous cancer cells. On the contrary, it can inhibit the proliferation of cancer cells by down-regulating FTO expression and up-regulating mRNA and protein levels of m^6A-related genes in other cancers (Fig. 2).

There are still limitations in studies. The scale of research objects is relatively small, and large-scale researches are needed to confirm the association and difference between *FTO* SNP and various races with regions. Secondly, the regulation mechanism of *FTO* gene is still obscure, and it is necessary for further researches to focus on the regulation mechanism of *FTO* as well as its polymorphisms on obesity. The current researches may help to understand the potential role of *FTO* polymorphism variation in different population of races and regions. However, in order to find the potential mechanisms of *FTO*-induced diseases, further researches should closely pay attention to the mechanism of tumorigenesis and other diseases in *FTO* risk alleles.

In a word, *FTO* gene may help to define the susceptibility of obesity or other metabolic complications in PCOS high-risk population through its association with metabolic syndrome and its components to provide a predictive genetic marker. The role of *FTO* in the development of cancers is to provide potential targets for the diagnosis, prognosis and treatment of various cancers. A comparative study of *FTO* between different races and regions, including functional genomics and epigenetics analysis, may be helpful to understand the key mechanism mediated by *FTO* gene of obesity and obesity-related diseases.

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