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Effect of demethyltransferase FTO on tumor progression

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Abstract: N^6-methyladenosine (m^{6}A) modification is the most widespread and conserved internal mRNA modification in mammalian cells. It greatly affects genetic regulation by enhancing the involvement of diverse cellular enzymes and thus, plays a significant role in basic life processes. Numerous studies on m^{6}A modification identified FTO as a crucial demethylase that participates in various biological processes. Not only does FTO play a pivotal role in obesity-related conditions, but it also influences the occurrence, development, and prognosis of several cancers, such as acute myeloid leukemia, breast cancer, liver cancer, and lung cancer. Moreover, FTO also shows a close association with immunity and viral infections. This article summarized the molecular mechanism of FTO in tumorigenesis and tumor progression.

Introduction

The N^6-methyladenosine (m^{6}A) modification is considered the most abundant internal modification of mammalian mRNAs identified in the 1970s (Wu *et al.*, 2019) and plays a significant role in regulating several cellular mechanisms involved in RNA stability, localization, splicing, transcription, and translation, as well as their interactions with other RNAs and proteins (Roundtree *et al.*, 2017; Genenncher *et al.*, 2018; Ke *et al.*, 2015; Li *et al.*, 2017a; Delaunay and Frye, 2019; Chen *et al.*, 2017). The abnormalities in m^{6}A modification may profoundly influence tumorigenesis and the development of multiple tumors. Although the exact molecular mechanism of m^{6}A modification is still ambiguous, due to the discovery of m^{6}A demethylases (FTO, ALKB5) and sequencing technologies (m^{6}A-seq, MeRIP-seq) (Molinie and Giallourakis, 2017; Zhang and Hamada, 2020), the molecular mechanism of m^{6}A modification in several cancers has been widely reported in recent years (Su *et al.*, 2018; Vu *et al.*, 2017; Ma *et al.*, 2017; Li *et al.*, 2017a).

The m^{6}A modification process is dynamic and reversible due to the combined actions of methylases, demethylasea, and m^{6}A-binding proteins (Duan *et al.*, 2019). As FTO was previously thought to be associated with debilitating diseases such as obesity and diabetes, it was first identified as a key demethylase instigating the m^{6}A modification in 2011 (Fig. 1), thus playing a modulatory role in multiple biological processes in a demethylase activity-dependent manner. For example, the FTO dysregulation might even aggravate major diseases like acute myeloid leukemia (AML) by carcinogenesis (Paris *et al.*, 2019), glioblastoma cell proliferation (Su *et al.*, 2018), and increased food intake and obesity by FTO overexpression (Jia *et al.*, 2008). The molecular structure characteristics, biological properties, and potential molecular functional mechanisms of FTO in various cancers were discussed in this article (Fig. 2).

Discovery, molecular structure, and functions of FTO

In 1994, van der Hoeven *et al.* (1994), for the first time, observed the deficiency of one of the six genes in the fused toe on chromosome 8 in mutant mice. A subsequent study in 2007 revealed a close association between a group of single nucleotide polymorphisms (SNPs) present in FTO with obesity in type2 diabetes patients by using genomic data and stated that obesity poses an influence on body mass index (BMI) (Frayling *et al.*, 2007). The fat mass and obesity-associated protein (FTO) is located on the long arm of chromosome 16 on position 12.2 and possesses a double helix structure that is 410.509 bp long with 9 exons and 410507 bases (Stratigopoulos *et al.*, 2008; Müller *et al.*, 2008). Robbens *et al.* (2008) revealed the widespread existence of FTO in vertebrates, Ostreococcus, and diatom species, while no signs of FTO were observed in other invertebrates (such as insects and fungi). Frayling *et al.* (2007) reported that FTO is extensively expressed in human systemic tissues, especially in the hypothalamus.

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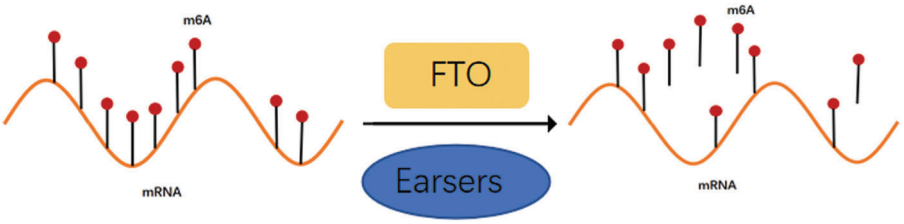

FIGURE 1. Demethylase FTO can reverse m^6A modification.

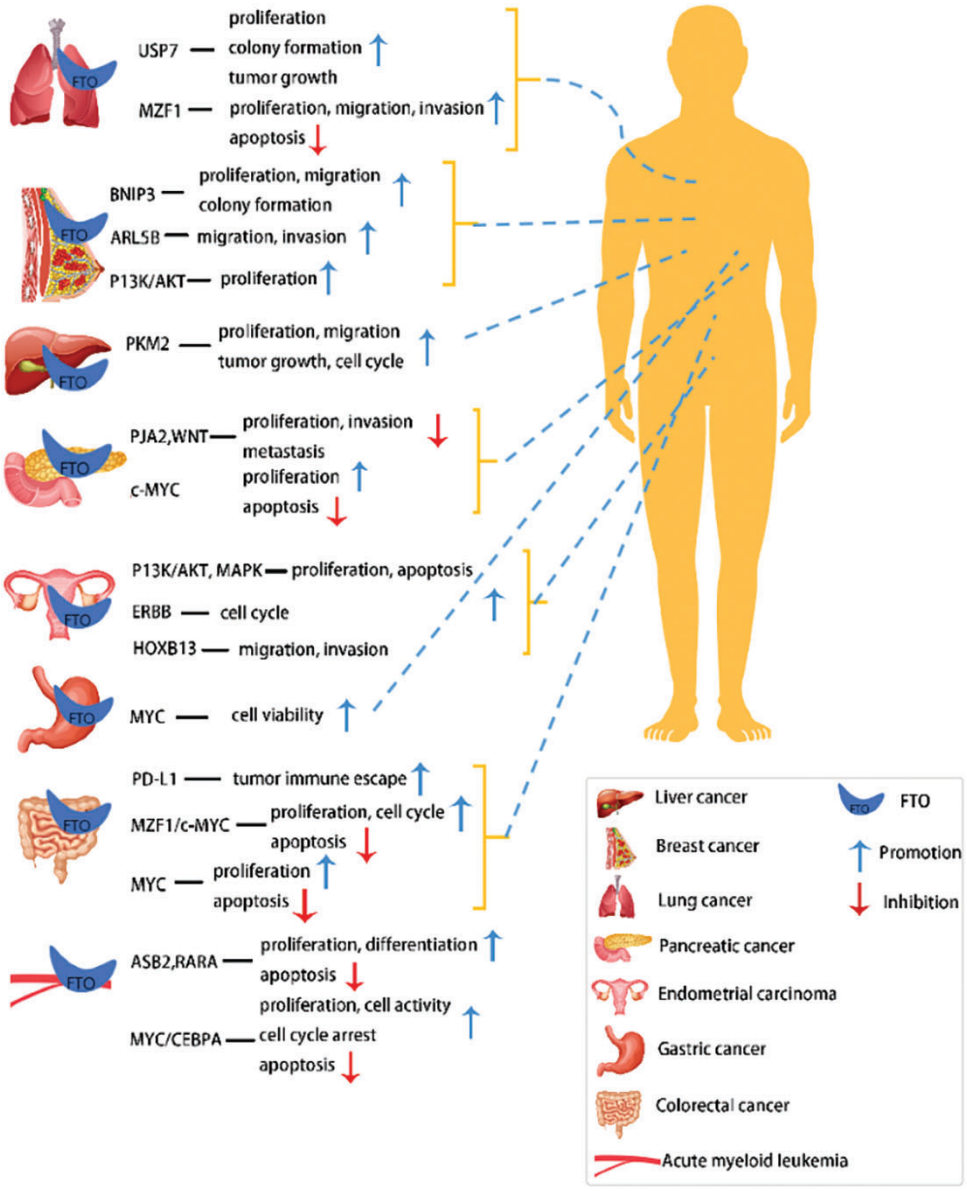

FIGURE 2. Targets and biological functions of FTO in different tumors.

According to bioinformatics analysis, the protein encoded by FTO is a member of the AlkB dioxygenase family, further categorized as deoxyribonucleic acid demethylase (Han *et al.*, 2010). Unlike other members, FTO mainly exerts its effects on single-stranded DNAs and RNAs and produces a distinctive demethylating effect on 3-methylthymine and 3-methyluracil in single-stranded DNAs and RNAs, respectively (Jia *et al.*, 2008; Han *et al.*, 2010). However, there is a substrate specificity of FTO that is exhibited in different demethylase activities and is dominated by m^6A and N^6, 2-O-dimethyladenosine (m^6Am) in the cytoplasm and m^6A in the nucleus (Wei *et al.*, 2018).

Obesity, as one of the major risk factors for cancer development, induces tumorigenesis and progression of diverse tumors such as colorectal cancer, breast cancer, pancreatic cancer, and endometrial cancer (Akbari *et al.*, 2018). Deng *et al.* (2016) revealed that obesity-related inflammatory factors could facilitate tumor cell production, growth, and migration. It is suggested that SNPs in the FTO gene show a possible correlation with tumorigenesis and tumor development; obesity-related FTO polymorphism rs8050136 is specifically associated with endometrial carcinogenesis, while rs9939609 is related to pancreatic cancer (Huang *et al.*, 2017; Lurie *et al.*, 2011). The

regulatory mechanism of FTO gene variation remains elusive to date. The FTO post-transcriptionally regulates the expression of its critical target genes; thus, affecting the occurrence and development of tumors as depicted in Table 1.

Functional mechanism of FTO in tumors

Acute myeloid leukemia

Acute myeloid leukemia (AML) is the most common malignant tumor in the bone marrow and lymphatic system. FTO plays a key role in oncogene-mediated cell transformation and apoptosis of blood cells. FTO is overexpressed in certain AML subtypes carrying several oncogenes, like PML-RARA, FLT3-ITD, and NPM1 mutations leading to an accelerated AML onset and development. Subsequently, it also promotes tumor cell growth in AML and suppresses the differentiation induced by all-trans retinoic acid (ATRA) by targeting ankyrin repeat and SOCS box containing 2 (ASB2) protein-coding gene and retinoic acid receptor alpha (RARA) (Li *et al.*, 2017b), that show anti-leukemic effects (Guibal *et al.*, 2002; Glasow *et al.*, 2005).

Additionally, the FTO inhibitor, R-2-hydroxyglutarate (R-2HG), elevates m^{6}A mRNA levels, reduces the stability of c-MYC-CEBPA transcripts, inhibits FTO demethylase activity, and limits AML cell proliferation and survival by directly binding to FTO protein; thus, exerting anti-leukemia activity in tumor cells with FTO low expression (Glasow *et al.*, 2005). Hence, it can be inferred that R-2HG has an innate potential to effectively suppress leukemia and produce evident anti-tumor effects in patients with FTO overexpression. Thus, the production of corresponding FTO inhibitors (Huang *et al.*, 2019) that inhibit FTO demethylase activity decrease m^{6}A demethylation, and suppress AML cell proliferation, and growth lead to the development of novel therapeutic targets exhibiting anti-leukemic activity.

Huang *et al.* (2019) developed two likely inhibitors of FTO, namely FB23 and FB23-2, which after binding to FTO, specifically inhibited FTO demethylase activity, among which FB23-2 showed better anti-proliferative ability than FB23 and could repress cancer cell proliferation, promote normal cell differentiation, and delay AML progression. Therefore, it was suggested that FTO inhibitors in AML downstream target genes such as c-MYC, CEBPA, ASB2, and RARA that might help in formulating effective therapies against AML (Su *et al.*, 2018; Li *et al.*, 2017b). According to recent evidence, Rhein, an FTO inhibitor, can competitively bind to the FTO active site and directly jeopardize FTO binding to the m^{6}A substrate, thereby inhibiting FTO-dependent m^{6}A demethylation (Chen *et al.*, 2012). In addition, Zheng *et al.* (2014) also designed multiple chemical compounds designated as FTO inhibitors which selectively suppressed FTO demethylase activity to increase cellular m^{6}A methylase activity.

In light of the significance of FTO in carcinogenesis and drug resistance, the best therapeutic strategy for combating AML might be the implementation of stable and effective FTO inhibitors. Although clinical FTO inhibitors for therapeutic application are available nowadays, more selective and effective FTO inhibitors are greatly needed to control AML pathogenesis and progression.

Breast cancer

An estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020, as indicated by the Global Cancer Statistics database, 2020 (Sung *et al.*, 2021). Breast cancer (BC) ranked first in cancer incidence worldwide, with an estimated 2.3 million newly emerged cases (11.7%) in 2020. In China, BC is now considered as the second leading health burden in terms of incidence next to lung cancer, colorectal cancer, and gastric cancer. The risk factors of BC included genetic predisposition (Braithwaite *et al.*, 2018), age (Spreafico *et al.*, 2020), reproductive and hormonal factors (Fan *et al.*, 2014; Nelson *et al.*, 2012; Sun *et al.*, 2017), obesity (Eliassen *et al.*, 2006; Jiralerspong and Goodwin, 2016), and unhealthy lifestyles (Nelson *et al.*, 2012; Kerr *et al.*, 2017). Distant metastases and chemoresistance are a few major contributors to the surging mortality rate of BC patients. Moreover, incorporating early targeted cancer interventional therapy in current BC treatment modalities might prevent invasive metastasis; thus, increasing the survival rates and projecting a favorable prognosis.

Niu *et al.* (2019) observed that a higher FTO expression in MCF7 and MDA-MB231 cell lines facilitated BC cell proliferation and colony formati-on, inhibited cancer cell apoptosis, and promoted tumorigenesis and development by suppressing m^{6}A demethylation of a pro-apoptotic gene, BNIP3 3' untranslated regions(3'UTRs). Consequently, the inhibition of FTO expression in BC can inhibit tumor cell proliferation and migration (Niu *et al.*, 2019). However, beyond that, a study by Kaklamani *et al.* (2011) confirmed a significant association of rs1477196 SNP in the intron 1 region of the FTO gene with BC carcinogenesis, which was further suggestive of a direct correlation between FTO SNPs with BC risks. Moreover, FTO promotes BC cell migration and invasion by upregulating ARL5B that shows carcinogenic activity in BC cells (Xu *et al.*, 2020). Therefore, the clinical applications of FTO can be utilized as the potential novel therapeutic target as well as a prognostic biomarker for BC treatment.

Endometrial cancer

Endometrial cancer (EC) is the most commonly diagnosed invasive gynecological cancer and a leading cause of cancer-related deaths in American females. More than 60,000 women were diagnosed with endometrial cancer in 2018, with nearly 10,000 deaths reported annually (Brooks *et al.*, 2019). Recent years have seen a more remarkable surge in the incidence and mortality rates of EC, which might be due to the decline of resection rates in benign uterine diseases. Relative to other countries, China has reported fewer EC cases but has witnessed a significant rise in its incidence lately. Despite recent advances, the exploration for additional reliable therapeutic targets in EC is of utmost importance for reducing EC incidence and mortality rates.

The genome-wide association studies revealed a close correlation between obesity-related SNPs and EC (Delahanty *et al.*, 2011). The bioinformatics analysis on multiple databases by Zhang and Yang (2021) reflected the abnormal expression of enzymes involved in m^{6}A modification in EC, among which YTHDF1, YTHDF2, and METTL3 had upregulated expressions, whereas METTL14,

TABLE 1

Expression level, biological functions and targets of FTO in tumors

Cancer	Expression	Targets	Role	Biological function	Reference
Leukemia	Increased	ASB2, RARA	Oncogene	Differentiation, proliferation, apoptosis	Li *et al*., 2017b
	Increased	MYC/CEBPA	Oncogene	Proliferation, activity, cycle arrest, apoptosis	Su *et al*., 2018
Breast cancer	Increased	BNIP3	Oncogene	Cell proliferation, colony formation, migration	Niu *et al*., 2019
	Increased	ARL5B	Oncogene	Migration, invasion	Xu *et al*., 2020
	/	PI3K/AKT	Oncogene	Proliferation	Gholamalizadeh *et al*., 2020
Endometrial cancer	Increased	PI3K/AKT, MAPK	Oncogene	Proliferation, invasion	Zhang *et al*., 2012
	Increased	ERBB	Oncogene	Cell cycle	Zhang and Yang, 2021
	Increased	HOXB13	Oncogene	Invasion, migration, proliferation	Zhang *et al*., 2021a
Liver cancer	Increased	PKM2	Oncogene	Migration, cell cycle, tumor growth	Li *et al*., 2019b
	Increased	/	Oncogene	Proliferation, migration, invasion	Ye *et al*., 2020
Lung cancer	Increased	USP7	Oncogene	Cell proliferation, colony formation, tumor growth	Li *et al*., 2019a
	Increased	MZF1	Oncogene	Cell proliferation, invasion, apoptosis	Liu *et al*., 2018
Gastric cancer	Increased	c-MYC	Oncogene	Cell activity	Yang *et al*., 2021
Colorectal cancer	/	PD-L1	Oncogene	Tumor escape	Tsuruta *et al*., 2020
	Increased	MZF1/c-MYC	Oncogene	Cell proliferation, cell cycle, apoptosis	Zhang *et al*., 2021b
	Increased	c-MYC	Oncogene	Cell proliferation	Yue *et al*., 2020
Bladder cancer	Increased	PYCR1	Oncogene	Cell proliferation, migration	Song *et al*., 2021
	Increased	MALAT	Oncogene	Cell activity, tumor growth	Tao *et al*., 2021
	Increased	CDK6	Oncogene	Cell migration, invasion	Zhou *et al*., 2021
Esophageal squamous cell carcinoma	Increased	MMP13	Oncogene	Cell growth, migration, tumorigenicity	Liu *et al*., 2020
	Increased	LINC00022	Oncogene	Cell cycle, proliferation	Cui *et al*., 2021
Pancreatic cancer	Decreased	PJA2, WNT	Cancer suppressor	Cell proliferation and migration	Zeng *et al*., 2021
	Increased	c-MYC	Oncogene	Cell proliferation, apoptosis	Tang *et al*., 2019

FTO, and ALKBH5 showed downregulated expressions. A subsequent Cox survival analysis demonstrated that aberrant FTO expression was negatively correlated with the total survival rates. Although these database findings are beneficial for exploring other novel biological targets, their effectiveness and potency may require further validation in experimental and clinical research.

Additionally, FTO overexpression can also enhance proliferative and invasive abilities of tumor cells through the PI3K/AKT and MAPK pathways (Zhang *et al*., 2012; Zhu *et al*., 2016), promote tumor progression by activating the WNT pathway (Zhang and Hamada, 2020), and alter the tumor cell cycle in EC via the ERBB pathway (Zhang and Yang, 2021). Endometrial cancer, as one of the most common gynecologic cancer (Siegel *et al*. 2019; Ito *et al*., 2007), requires further investigation into the intrinsic molecular mechanisms of its tumorigenesis and progression. There is an increased demand for new therapeutic targets that will improve the prevention and treatment of EC.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver cancer (European Association for the Study of the Liver, 2018), with a high incidence and mortality rate worldwide (Gong and Qin, 2018; Torre *et al*., 2015). There are several etiologic factors for HCC like chronic hepatitis B virus infection (Rawla *et al*., 2018), liver cirrhosis, alcoholic liver disease, non-alcoholic fatty liver disease, aflatoxin exposure (Piñeros *et al*., 2018), obesity, and metabolic syndrome, reported in the Western countries (Younossi *et al*., 2019). Despite the recent diagnostic, therapeutic, and preventive advances, most patients are diagnosed at an advanced stage of the disease, making them more susceptible to relapse. Liver cancer remains the second leading cause of cancer-related death due to an 18% 5-year survival rate (Torre *et al*., 2015; Forner *et al*., 2018; Jemal *et al*., 2017), which necessitates the search for new prognostic biomarkers and therapeutic targets for reducing cancer-related mortality.

Ye *et al.* (2020) observed a significantly higher expression of FTO in 330 HCC cases than the normal liver tissues through immunohistochemical analysis and revealed that FTO facilitated cancer cell proliferation, migration, and invasion, inhibited apoptosis, and accelerated liver cancer progression in the human liver cancer cell line (HepG2). Additionally, Li *et al.* (2019b) also found that FTO overexpression in HCC cells could modulate m^6A level in PKM2 mRNA to enhance the PKM2 expression and facilitate tumor cell proliferation and migration. A subsequent Kaplan-Meier analysis also confirmed an important correlation between the FTO overexpression and poor prognosis of HCC patient.

Lung cancer

Presently, lung cancer remains the leading cause of cancer death and a global threat to public health. Non-small cell lung cancer (NSCLC) accounts for nearly 80% of all lung cancer types (Siegel *et al.*, 2020; Siegel *et al.*, 2018) and consists of two major subtypes, squamous cell carcinoma of the lung and pulmonary adenocarcinoma. Due to an unsatisfactory survival rate, 21 million people were newly diagnosed with lung cancer in 2018 and 18 million deaths worldwide in 2019 (Siegel *et al.*, 2018). Moreover, the functional mechanisms of FTO in lung squamous cell carcinoma are still not fully understood and require in-depth investigation for further validation.

In lung cancer, FTO enhances the stability of deubiquitinated ubiquitin-specific protease 7 (USP7) mRNA level and accelerates the progression of NSCLC (Li *et al.*, 2019a), while FTO demethylase activity plays a key role in increasing USP7 expression, thus, denoting a close association of FTO-USP7 signaling axis with NSCLC occurrence and its potential as a therapeutic target in lung cancer treatment. Furthermore, Liu *et al.* (2018) investigated the association of FTO expression with poor prognosis in patients with non-squamous cell carcinoma in the TCGA database and discovered FTO overexpression in cancer tissues. Furthermore, FTO facilitates the proliferation, migration, and colony formation of lung cancer cells and produces a carcinogenic effect by inhibiting m^6A levels in myeloid zinc finger protein 1 (MZF1) mRNA transcripts as well as upregulating the MZF1 expression.

Gastric cancer

Gastric cancer (GC) is the fifth most common cancer globally and the third most common cause of cancer-related mortality (McGuire *et al.*, 2016; Figueiredo *et al.*, 2017; Ferro *et al.*, 2014). Although GC incidence is relatively low in China, it remains a common malignancy accounting for 10% of all malignant tumors (Jackson and Giraud, 2009). Various genetic and environmental factors, including GC family history, *Helicobacter pylori* infection, excessive salt intake, and chronic gastropathy, play vital roles in inducing GC (Fuccio *et al.*, 2010). Due to the development of the latest biological technology, the discovery of intrinsic molecular mechanisms in inducing GC occurrence and progression along with sustained investigation and exploration will contribute substantially to the early diagnosis and prognosis of GC.

As indicated in a previous study (Xu *et al.*, 2017), FTO overexpression plays a contributory role in GC cell proliferation, migration, and invasion, while a Kaplan-Meier analysis on the same a negative correlation between the 5-year survival rate of GC patients and FTO expression. Similarly, Li *et al.* (2019c) and Guan *et al.* (2020), through Kaplan-Meier analysis and TCGA databases, revealed a close association between low FTO expressions and the shorter overall survival rate of GC patients. Hence, it can be duly inferred that FTO overexpression is directly correlated with the development and poorer prognosis of GC.

The forkhead transcription factor (Foxa2) directly binds to the FTO promoter region and inversely modulates the activity and expression of the FTO promoter (Guo *et al.*, 2012). Furthermore, histone deacetylase 3 (HDAC3) overexpression in GC significantly inhibits Foxa2 protein expression and activates the FTO/m^6A/MYC axis, promoting tumor cell proliferation, migration, and migration invasion, consequently contributing to GC (Yang *et al.*, 2021). These findings confirmed that HDAC3 induces tumor cell activity in GC by modulating Foxa2-mediated FTO/m^6A/MYC axis and provided a theoretical foundation for targeted genetic modification therapy.

According to a study by Su *et al.* (2019), m^6A modified demethylase FTO can serve as a potential prognostic marker for GC. Based on GO enrichment and TCGA database analysis results, FTO expression is related to various immune cell genotypes, which further affects the immune microenvironment of tumor cells (Xu *et al.*, 2021). There is increasing evidence that FTO has the potential to become a promising noninvasive biomarker for GC treatment leading to a better prognosis and survival rate.

Oral squamous cell carcinoma

Oral cancer is the sixth most common cancer globally, with a high mortality rate (Hussein *et al.*, 2017). Oral squamous cell carcinoma (OSCC) is the most common malignancy in the mouth and accounts for 90% of all oral cancers. Due to inconspicuous clinical manifestations in the early stages, most patients are diagnosed in the later stages (Valdez and Brennan, 2018), accompanied by cervical lymph node and distant metastasis (Mupparapu and Shanti, 2018). Although several progressions have been made in the treatment strategies, the 5-year survival rate remains as low as 50% due to a higher recurrence rate (Diao *et al.*, 2018; Zanoni *et al.*, 2019). Therefore, the functional mechanism of tumorigenesis and tumor progression should be accurately investigated for better patient outcomes.

Wang *et al.* (2021) observed a significant rise in FTO expression in OSCC cells while FTO knockdown leads to downregulated eIF4G1, increased autophagy flux, apoptosis inhibition, and consequently, tumorigenesis. Furthermore, FTO upregulation in oral squamous cell carcinoma causes further tumor progression, whereas FTO downregulation remarkably represses tumor cell proliferation, colony formation and tumor growth (Li *et al.*, 2021a). The *in vivo* assays in mice indicated that FTO knockdown slows down tumor growth (Li *et al.*, 2021b). Subsequently, FTO might act as an effective therapeutic target against OSCC. However, the regulatory action of FTO in OSCC has not been fully clarified and requires further exploratory measures.

Glioma

Glioma is the most common primary intracranial malignant tumor, accounting for 80% of malignant brain tumors (Ostrom *et al.*, 2014; Neglia *et al.*, 2006). It mainly originates from neuroglial stem cells or progenitor cells (Weller *et al.*, 2015; Jones *et al.*, 2018). Pediatric low-grade gliomas and WHO grade I or II gliomas are generally benign tumors. The WHO grade I or II gliomas rarely show malignant transformation with a good prognosis. However, WHO grade III or IV high-grade gliomas are usually malignant tumors with a rapid rate of progression and poor prognosis, with a five-year survival rate of 20% (Bush *et al.*, 2017; Louis *et al.*, 2016).

Most researchers argue that high-dose ionizing radiation is the cause of the disease (Vienne-Jumeau *et al.*, 2019; Davis, 2018). The effect of other pathogenic factors such as lifestyle, dietary habits, and genetic factors on glioma should also be further studied (Davis, 2018).

Many genetic factors were determined to be glioma risk factors. Genome-wide association studies (GWASs) have found a large number of SNPs related to glioma risk-related susceptibility polymorphisms, such as CDKN2B, RTEL1, CCDC26, PHLDB1, EGFR, and TP53 (Wrensch *et al.*, 2009; Shete *et al.*, 2009; Melin *et al.*, 2017; Kinnersley *et al.*, 2015). Studies on the mechanism of the effect of FTO on glioma are increasing. Some studies have shown that SNPs of the FTO gene can affect tumor risk (Sigurdson, *et al.*, 2016). He *et al.* (2021) detected a significant negative correlation between FTO rs8047395 and glioma susceptibility. Cui *et al.* (2017) showed that knocking out FTO inhibits the growth and self-renewal of glioblastoma stem cells. In glioma, ectopic high expression of FTO can improve the stability of MYC and promote the proliferation of glioma cells (Wang *et al.*, 2018). Tao *et al.* (2020) found that the protein level of FTO in glioma tissues was significantly lower compared to that in brain tissues. Subsequent experiments revealed that the inhibitory effect of FTO on glioma might be related to its interaction with FOXO3a, thus promoting the expression of FTO target genes. The above results indicate that FTO can be used as an effective biological therapeutic target for treating gliomas and further improving the survival rate of gliomas.

Non-neoplastic diseases

FTO not only regulates the occurrence, development, and prognosis of tumors but also plays an important role in non-neoplastic diseases. Epidemiological studies showed that type 2 diabetes is a risk factor for Alzheimer's disease (Vagelatos and Eslick, 2013). *In vitro* animal experiments showed that FTO expression was significantly lower in the brain tissues of diabetic, aged, and Alzheimer's disease (AD) mice, which indicated that FTO might be closely related to diabetes and AD (Li *et al.*, 2018). Additionally, bioinformatics analysis showed that FTO may also be associated with chronic obstructive pneumonia (COPD). Furthermore, correlation analyses showed that FTO expression was negatively correlated with the expression of several genes, such as BCL2A1, CYP1A1, and CYP1B1. These genes are enriched in signaling pathways that promote the development of COPD and are closely related to the development and progression of chronic obstructive pulmonary disease (Huang *et al.*, 2020). In bronchial asthma, FTO deletion decreases the stability of the mRNA encoding the ciliary transcription factor FOXJ1 (Kim *et al.*, 2021), which induces the development of asthma. Through mouse experiments, Mathiyalagan *et al.* (2019) demonstrated that FTO expression levels were significantly downregulated in mice within 4 h of myocardial infarction caused by the coronary arteries on the left side of the heart. Cardiac remodeling was performed a short while after myocardial infarction, and high expression of FTO for about a week was shown to repair the function of cardiomyocytes (Mathiyalagan *et al.*, 2019). Shen *et al.* (2021) showed that overexpression of FTO enhanced cardiac function and inhibited cardiomyocyte apoptosis, thereby delaying heart failure. This demonstrated an important role of FTO in regulating cardiac function and cardiac remodeling in heart failure and suggested that the role of epigenetics of FTO in myocardial infarction needs to be further studied.

Conclusion and prospects

To summarize, FTO exhibits dual effects such as carcinogenic and anti-carcinogenic manifestation in human tissues. For instance, FTO participates in liver cancer cell proliferation, migration, and cell cycle and is associated with tumor growth. Similarly, FTO downregulation as an anti-tumor gene inhibits the WNT pathway and suppresses pancreatic cancer cell proliferation and migration, while FTO upregulation as an oncogene activates the c-MYC pathway and promotes cancer cell proliferation. Correspondingly, FTO as an oncogene facilitates AML progression, whereas several effective FTO inhibitors like Rhein, FB23-2, and R-2HG delay the development of AML.

With the advances made in the high-throughput sequencing and bioinformatics technique, m^6A modification has attracted a lot of attention due to its universal existence in mammals and close associations with certain diseases, especially malignant tumors. Recent explorations have documented different roles of diverse regulatory factors like METTL3, METTL14, WTAP, FTO, and YTH families in different tumors and their corresponding pathways. Hence, m^6A modification is a complex process of molecular interaction with indispensable functions in tumorigenesis and development. Multiple regulatory factors related to m^6A modification can be applied as noninvasive biomarkers for detecting oncogenesis as well as a better prognosis. On the one hand, oncogenesis is a complex pathologic process manipulated by a variety of molecules, which makes it difficult for tumors to be fully cured; on the other hand, it might be feasible to activate the tumor-suppressive pathways and inhibit the oncogenic pathways via certain regulatory factors for arresting tumor progression and increasing the survival rates.

m^6A modification has now been proved as a double-edged sword in tumor progression, excessive m^6A modification of several genes can promote tumorigenesis and development, while the lack of m^6A modification in some genes facilitates tumor cell proliferation, migration, and invasion. The role of m^6A methylation in non-neoplastic diseases is similar to that in cancer. This article elucidated the role of FTO in several

tumors but still faced some limitations in the investigation of some diseases. For example, studies regarding FTO expression in GC are rare. The complex molecular mechanism of FTO as an oncogene in GC requires further investigations to provide reliable biological therapeutic targets for its clinical management and prognosis. This article also identified several carcinogenic and anti-carcinogenic effects of FTO via activating and inhibiting some common tumor-related pathways (PI3K/AKT, WNT, and c-MYC) yet the regulatory role of FTO in other tumor-related pathways remains unknown. Owing to the complex causes of non-neoplastic diseases, new effective therapeutic targets can significantly improve the quality of life of non-neoplastic patients. Furthermore, it is imperative to conduct several in-depth studies for studying the m^6A modification in tumors or non-tumors to extract potential therapeutic targets for novel disease treatment strategies.

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