The Relationship Between FTO and Female Reproduction System Diseases: Focusing on PCOS, Endometriosis and Cancer and Targeted Therapy Strategy

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Abstract. Fat mass and obesity-related (FTO) proteins are indispensable key enzymes in the dynamic regulation of RNA epigenetic transcriptome modification, which significantly affect the RNA life cycle process. In recent years, the involvement of RNA epigenetic modifications in the underlying mechanisms of female reproductive disorders has been extensively researched. Several m6A regulators, including METTL3, FTO are involved in the processes and development of reproduction. FTO-involved m6A modification has been implicated in endometriosis, polycystic ovary syndrome (PCOS), and frequent gynecological cancers include ovarian and endometrial cancer. The pleiotropic effect of FTO has been revealed to be involved in many female diseases, which exert tumor suppressive effects by affecting the IGF1/PI3K-AKT axis and EMT pathway. In ovarian cancer, FTO expression showed distinct associations with tumor growth, with pleiotropic effects. This paper summarizes the association between the m6A modification process of FTO and recent female reproductive diseases——endometriosis, PCOS and cancer, aiming to explore the clinical application and research direction of female reproduction and pathophysiology, increase the current understanding of the cellular mechanism of female reproductive system diseases, diagnostic biomarkers and explore the treatment plan of reproductive system diseases with FTO target as the core.

Keywords: FTO, PCOS, Endometriosis, Gynecological cancer, m6A.

1. Introduction

FTO, which consists of nine exons is a sizable gene that spans over 4000 kb. It is situated on human chromosome 16q12.2 and plays a significant role in the advancement of lipogenesis. Recent research has identified a significant link between the common single nucleotide polymorphism (SNP rs9939609) in the FTO and the likelihood of developing obesity. The FTO rs9939609 SNP has been demonstrated to be connected to various metabolic disorders [1]. The main biological substrate of FTO was not known until 2011, when it was reported that FTO has effective oxidative demethylation activity towards m6A. In recent years, RNA modifications have come into the public eye. Numerous RNA modifications exist, with over 170 different types identified to date, and the most common and abundant internal modification is m6A. The m6A modification relies on a various dynamic regulatory proteins encoded, known as eraser, readers, and writers. The primary focus of this paper is the FTO, which acts as an eraser in the m6A regulatory process. FTO facilitates the demethylation of m6A through enzymatic reactions that depend on both Fe (II) and α-ketoglutarate [2].

FTO affects the prognosis of female reproductive system diseases through different aspects, including endocrine regulation, inflammation, glucose and lipid metabolism, and oxidative stress. FTO is reduced in several types of epithelial cancers, which impacts the m6A modification and 3'-end processing of mRNA associated with Wnt signaling, thereby facilitating tumor advancement. The information indicates that the down-regulation of FTO accelerates the invasion and metastasis of cancer cells in vivo. The role of FTO as a tumor suppressor extends to other epithelial cancers, among which is endometrial carcinoma [2]. Additionally, studies demonstrate that FTO influences cell proliferation, and the movement of endometriotic stromal cells through the ATG 5/PKM 2 pathway [3]. These results highlight the significance of the m6A demethylation of FTO in the regulation of

cancer cells and endometriosis, enhancing the comprehension of this biological mechanisms and playing a crucial role in the creation of treatment methods.

Although significant progress has been made in research, there is currently a lack of a comprehensive summary of the relationship between FTO and female reproductive system diseases. Therefore, the objectives of this paper are: 1) Outlining the connection between FTO and PCOS; 2) summarizing the relationship between endometriosis and FTO; 3) emphasizing the impact of FTO in genital system tumors. In recent decades, the rates of infertility and tumors in the female genital system have been rising consistently around the globe. And targeted drug therapy is a significant form of treatments, but their different tissue distribution and off-target effects may cause negative side effects, so it is urgent to study the mechanisms that affect the occurrence of diseases in women to explore better treatments methods. Up to now, the etiopathogenesis of endometriosis and PCOS remains unclear, and effective treatment strategies still need to be studied. Therefore, a deeper understanding of the relationship between FTO and female reproductive system diseases will help us to identify new molecule targets to create more effective therapeutic approaches.

2. FTO and PCOS/endometriosis

2.1. FTO and PCOS

PCOS is a prevalent hormonal disease that impacts 6-12% of women who are of reproductive age, with hyperandrogenism, ovulation dysfunction, menstrual menstruation or absence of menstruation, clinical or biochemical signs of hyperandrogenism. Besides causing infertility, PCOS is also closely linked to type 2 diabetes, endometrial cancer, and heart disease. The disease was first reported in 1935, but the cause of it is still unclear. Study shows one of the significant factors influencing the onset and the progression of PCOS is FTO. It may play a significant role in controlling the aging of granulosa cells via m6A-YTHDF2-dependent mechanisms, and it reduces AMH expression through the m6A-YTHDF2 axis suppresses follicle maturation (Table 1) [4].

In recent years, over 100 candidate genes, including the FTO gene have been proposed to explore the association between single nucleotide polymorphisms (SNPs) and PCOS [4]. FTO plays a significant role in type 2 diabetes mellitus by influencing insulin resistance. It simultaneously affects the process of obesity development. Meanwhile, obesity and PCOS, are closely related. FTO variants have been shown to be a key risk for PCOS. The FTO rs9939609 polymorphism affects the Kiss1/kisspeptin/GPR54 pathway in PCOS, whose variants have been associated with insulin resistance and abnormal glucose tolerance in PCOS patients. The relationship between FTO and MC4R genetic variations has been found to have a notable link to PCOS. This is manifested by the fact that SNPs in FTO and MC4R correlate with BMI in women with PCOS [11].

In addition, the influence of FTO in the sensitivity to PCOS seems to be induced through its implication in the likelihood of obesity and the amount of body fat, in a manner resembles the relationship between FTO variants and susceptibility to type 2 diabetes. In PCOS, the common SNP (rs9939609) and T to A changes within the initial intron of the FTO gene are extensively researched. However, the results of the different researches are disputable. The positive correlation between FTO and PCOS has been proved to exist, while the opposite relationship has also to be found. Meta-analysis indicated that the FTO rs9939609 polymorphism has been linked to an increased risk of PCOS in East Asian populations but this association was not observed in the general population [4]. The variant rs9939609 in FTO is related to PCOS that occurs among Chinese females. This association was disclosed in both the obese and non-obese groups. Nevertheless, further in-depth research is required to clarify the biological function of FTO in the relationship between obesity and PCOS.

Table 1. Function of the FTO in diseases of female genital system

Disease	Research subject	Changes in the FTO expression	Main regulation mechanism	Functional impact	Ref.
POF	POF mouse model	↓	Reducing FTO expression suppresses impaired cell proliferation and increases apoptosis by regulating BNIP3 expression	Lower BNIP3 expression to enhance the viability of granule cells following cisplatin treatment	[5]
PCOS	Granular cells	↓	Reducing AMH expression through the m6A-YTHDF2 axis suppresses follicle maturation	Follicle development is stagnated and androgen synthesis is increased	[6]
Endometriosis	EESCs	Negative correlation	ATG5/PKM2	Regulates glycolysis, proliferation, metastasis of EESCs	[3]
Endometrial carcinoma	Tumor tissue	↓	AKT	Activation of the AKT pathway leads to enhanced growth and tumorigenicity of endometrial cancer cells	[7]
	Mouse	↓	Increasing the modification levels of m6A of EMT transcription factors	Drive invasion and cancer cell metastasis	[2]
	Tumor patients	↓	IGF1 and IRS1, IGF2BP1	Hyperinsulinemia increases the risk of developing endometrial cancer	[8]
Adenomyosis	Epithelium	↓	Elevated expression of the IGF1 and DDT genes	Epithelial proliferation and cell migration	[9]
Abortion	Chorionic cells	↓	MEG3-TGF-β	Suppressed the trophoblast invasion and proliferation of URSA trophoblast cells	[10]

2.2. FTO and endometriosis

As a gynecological disorder, endometriosis which is an estrogen-dependent inflammatory disorder is not uncommon and its mechanism is complex. The main feature of endometriosis is that the endometrium appears in the pelvic peritoneum or ovary, resulting in menstrual cramps that get progressively worse, menstrual abnormalities, severe abdominal pain. The pathogenesis of this disease still remains unexplored and unexplained. At present, the generally accepted mechanisms are the menstrual blood return hypothesis as well as epigenetic factors. As a modification of RNA, m6A methylation is very common and important which may participate in the development and advancement of endometriosis. Research has demonstrated that the m6A methyltransferase METTL3 could be significantly involved in the onset and progression of endometriosis, along with two other regulators, FTO and IGF2BP2, which also play a role. Related studies have pointed out that methylation modification of human HOX genes play a crucial role in the development of the endometrium, and that improper regulation of certain HOX genes may contribute to the onset of endometriosis. [12]. It was demonstrated by vitro functional assays that FTO influences glycolysis, cell proliferation, and metastasis of EESCs through ATG 5/PKM 2 axis. These results highlight the crucial role of the m6A methylation process involving FTO in controlling the progression of endometriosis. [3].

From an immunological perspective, HNP 1-3 (human neutrophilic peptide 1, 2, and 3) neutrophils are associated with early immunopathogenesis of endometriosis through formation of angiogenesis and adjustment of the partial inflammatory infiltration. HNRNPA2B1 and HNRNPC which may serve as useful diagnostic biomarkers for endometriosis may be related to the immune response. HNRNPA2B1 and HNRNPC may have an effect on immune cell infiltration and immunologic process which play a significant role in endometriosis.

In addition to endocrine diseases, the regulatory role of FTO in gynecologic malignancies has received increasing attention, and it plays a crucial role in important processes like immune suppression, the development of malignant tumors, resistance to drugs, epithelial-mesenchymal transition (EMT), metastasis, and the development of cancer cells. Due to FTO's significant involvement in various processes, it presents a valuable target for identifying and treating gynecological tumors.

3. FTO and gynecological cancer

FTO is improperly expressed in cancer and is associated with the clinical outcomes of numerous cancer patients. Gynecological cancers, particularly endometrial and ovarian cancers, have increasingly become a focal point of research. A growing body of research indicates that the m6A demethylase is a crucial enzyme and is involved in gynecological cancers.

3.1. FTO and endometrial cancer

Endometrial cancer is an estrogen-dependent tumor, its occurrence and development are closely related to metabolic abnormalities and epigenetic disorders, and it is a common gynecological cancer in which the m6A modification of FTO plays a key role. Initial findings indicate that DNA methylation biomarkers may be useful for the early detection and risk assessment of individuals at high risk for endometrial cancer. FTO has an impact on the survival of patients with endometrial adenocarcinoma by regulating connective tissue development, catabolic processes, temperature homeostasis and the energy metabolism of IRS1, IGF1, LARP1, CBFA2T3 and RBM24, demonstrating that FTO is critical for the progression and prognosis of endometrial cancer [13]. m6A RNA methylation promotes the growth and tumor formation of endometrial cancer by regulating the activity of AKT. Seventy percent of endometrial tumors exhibit reduced m6A methylation, potentially due to mutations in METTL14 or a reduction in the expression of METTL3, another part of the methyltransferase complex [7]. Alternatively, low expression of FTO promotes epithelial tumor progression mediated by the progress of EMT and it also enhances the susceptibility to Wnt inhibitors.

Mechanistically, down-regulation of FTO induces EMT procedures by modifying the 3'-end processing of the mRNA within the Wnt signaling pathway. An increase in the m6A modification level of EMT transcription factors enhances the stability of their mRNA, which in turn facilitates the invasion and metastasis of cancer cells [2]. FTO has low expression in endometrial cancer tissues. It can enhance the expression of β -catenin by increasing the m6A levels and reduce the chemotherapy sensitivity of CSCC cells, which is closely linked to the unfavorable prognosis of endometrial cancer [14].

Recent evidence suggests that hyperinsulinemia increases the risk of endometrial cancer, and on the one hand, FTO promotes the advancement of endometrial adenocarcinoma through the function of IGF1 and IRS1. The FTO-mediated stability of IGF1 and IRS1 increases in patients with hyperinsulinemia, and this increased stability further exacerbates the proliferative and anti-apoptotic capacity of endometrial cancer cells [13]. Meanwhile, an independent prognostic evaluation revealed that IGF2BP1 serves as a universal prognostic regulator in endometrial cancer [8]. On the other hand, insulin exhibits both mitogenic and anti-apoptotic properties, and the endometrial cancer cells have a high-affinity insulin receptor. The annual incidence of central precocious puberty is gradually increasing, with some short-term and long-term effects on women, and an increasing risk of endometrial cancer in adulthood. Meanwhile, estrogen is associated with cell growth dysregulation and the spread of cancer in the early stages of endometrial cancer development. It regulates the amount of body fat and obesity-related genes through PI3K/AKT signaling pathways, which in turn enhances glycolysis, aids in the production of cancer cells, and stimulates the growth of cancer cells [15]. Clinical data identified the function of FTO in endometrial cancer is tissue-specific and disease stage-dependent. A relationship was observed between FTO expression and six types of immune-infiltrating cells and immune checkpoint genes in cancer. TCGA database analysis found significantly reduced TCL cell invasion and decreased the expression of PD-L1 in tumor microenvironment of endometrial cancer patients with low expression of FTO. In addition, FTO may influence immunotherapy response by modulating immune checkpoint molecules. Intercepting PD-L1/PD-1 coactions can markedly heighten the immune response against tumors. It represents a significant advancement in cancer therapy [16]. FTO is involved in immune-related pathways and can be used as prognostic markers and immune biomarkers.

3.2. FTO and ovarian cancer

It was pointed out that FTO controls m6A of HOXB13 mRNA, denies YTHDF2-mediated degradation of HOXB13, and speeds up the metastasis of EC cell. HOXB13 induces SLUG expression, encourages the process of EMT of OC, and enhances the tumor metastasis ability [17]. Up-regulation of FTO in human ovarian tumor tissues promotes the development of OC by restraining apoptosis, initiating autophagy and accelerating proliferation. FTO, a crucial regulator, is up-regulated and influences the prognosis of OC by enhancing the P53 signaling pathway, which can promote the apoptosis of OC cells. [18]. Moreover, recent studies suggest that FTO triggers NLRP3/Caspase-1/GSDMD-dependent pyro ptosis. And by this way it enhances DDP sensitivity and hinder the progress of ovarian cancer cells. Therefore, improving the effectiveness of immunological therapy for ovarian cancer and addressing resistance to chemotherapy could provide a novel approach for the optimizing therapeutic method of OC.

In addition, other studies have shown that the cAMP pathway has emerged as a novel target for FTO in ovarian cancer, related to tumor suppression function. FTO reduces the m6A levels and the mRNA stability of two phosphodiesterase genes (PDE1C and PDE4B) by inhibiting cAMP signaling, and inhibits the self-renewal of ovarian cancer stem cells, thus delaying the growth of ovarian tumor [19]. FTO is down-regulated with increased m6A levels in epithelial ovarian cancer, and inhibition of SNAI1 expression by FTO attenuates the development and dissemination of EOC cells in a manner dependent on m6A IGF2BP2, indicating that the FTO-IGF2BP2-SNAI1 pathway could be a promising target for therapy in epithelial ovarian cancer [20]. And m6A up-regulates the Wnt/β-

catenin pathway by stabilizing FZD 10 and promotes BRAC deficiency to resist PARP inhibitors in ovarian epithelial cancer cells.

FTO has been implicated in the prognosis of endometrial and ovarian cancer patients as well as tumor immune invasion, and can be used as a novel and potential prognostic and immune biomarker. FTO affects the growth, invasion, and immune escape of cancer cells through the m6A regulatory mechanism, providing fresh perspectives on understanding the molecular process of gynecological cancer.

4. Therapeutic strategies

Table 2. Combination therapy for female genital system disorders

Types of treatment	Intervention means	Target of action	Experimental model	Effects	Research stage	Ref.
Medication	Dac51	FTO	In vitro cell model of uLMS	Inhibiting uLMS proliferation	Preclinical	[21]
	Rhein		In vitro biochemical experiments	Rhein inhibits FTO by attaching to the catalytic domain to a single-stranded RNA substrate	Preclinical	[22]
	MA		Virtual screening	MA binds to FTO and stabilizes FTO	Preclinical	[23]
	2OG analogues		Crystallographic analysis	Inhibiting FTO by competing with the metal ion chelating group using 2 OG.	Pharmaprojects	[24]
	FB23		AML cell lines	Anti-tumor cell proliferation	Preclinical	[23]
Gene editing	Ythdf1$^{-/-}$	YTHDF1	Mouse	YTHDF1 increases the translation of lysosomal cathepsins in DC	Experimental verification	[25]
	Mettle3 defect	Mettl3	Mouse	PD-1 checkpoint blockade is reduced	Experimental verification	[26]
Immunization therapy	Naboliumab and dostarlimab	PD-1		With promising results in patients with advanced endometrial cancer	Clinical application	[27]

The differential expression of FTO in gynecological disease is of great clinical significance, so the creation of specific small molecule inhibitors for FTO targets holds considerable scientific importance and practical utility. Moreover, previous research indicates that m6A is crucial in the development of malignant biological behaviors such as tumor development, invasion and metastasis, differentiation, energy metabolism and angiogenesis. Therefore, the creation of targeted inhibitors holds significant clinical importance and scientific value, and play an important role in tumor treatment [14]. Combination therapies for FTO——drug therapy, gene editing, immunotherapy may be a tailored and appealing approach for gynecologic cancer patients [13]. FTO has been identified as a potential therapeutic target in various cancer types and experimental models. As a result, multiple FTO inhibitors have been created, including GS1, Rhein, FB 23-2, C6 and Dac51, showing potent inhibition as FTO inhibitors (Table 2). Moreover, these drug inhibitors showed antitumor effects in inhibiting FTO m6A methylation. PD-L1/MSI/TMB, the three immunotherapy indicators approved for solid tumors, have been recommended by endometrial cancer guidelines (Table 2). Such as envafolimab, tislelizumab, serplulimab and a series of PD-1 drugs, they have been included in the "CSCO Guidelines for the Diagnosis and Treatment of endometrial cancer" second-line treatment recommendations.

5. Conclusion and prospects

FTO, as an m6A demethylase, presents a pleiotropic effect in the female reproductive system. FTO rs9939609 polymorphism exacerbate insulin resistance and hyperandrogenism in PCOS patients, while in endometrial cancer, FTO exerts a cancer-inhibiting effect. However, in ovarian cancer, there are different opinions regarding the expression of FTO and its related biological processes, which can both suppress cancer and promote cancer. FTO is a potential biomarker for specific types of tumors, and FTO inhibitors with other drugs or therapies could lead to combined effects, and improve treatment effectiveness. FTO inhibitors such as Rhein, MA, FB23, 2OG and Dac51 have shown significant antitumor effects in preclinical studies, and have the potential for synergistic therapy with immunotherapy.

Because of the variable expression patterns and contradictory roles that FTO displays in various tumors, more comprehensive studies are warranted. In future studies, it is expected to focus on the following aspects: 1) the tissue-specific mechanism of FTO, and to analyze the molecular basis of FTO in the endometrium and ovary; 2) Combination therapies targeting FTO to promote treatment effects and extend survival could be a tailored and appealing treatment option for individuals with endometrial cancer. Combining chemotherapy with immunotherapy and focusing on developing precision treatment strategies is warranted. Due to the functional differences between FTO-201 and FTO-202, targeted FTO selective inhibitors can be developed for FTO-201 and FTO-202, and the combination of these selective inhibitors and immunotherapy such as PD-1/PDL-1 inhibitors can be explored; 3) Combine single-cell sequencing and spatial transcriptome technology to map the dynamics of the FTO-mediated m6A modification network in the tumor microenvironment. In recent years, epitome editing has shown potential for precise intervention in functional gene transcription. The benefits of targeting the RNA epigenetic transcriptome in terms of safety and efficiency can greatly improve the efficiency of basic research through the discovery of inhibitors and the progress in gene editing technology. Furthermore, although FTO inhibitors present a novel target for the treatment of gynecological tumors in clinical settings, their different tissue distribution and off-target effects may cause serious side effects. Numerous challenges remain to be addressed in the clinical implementation of FTO-targeted therapy. Therefore, it is necessary to promote the personalized treatment of stratified patients based on biomarkers. According to the level of FTO in serum exosomes, patients are stratified and different treatment strategies are adopted.

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