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The Role of RNA Epitranscriptomics and the RNA Fat Mass and Obesity-Associated Demethylase in Triple Negative Breast Cancer

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Abstract

Breast cancer is one of the most commonly diagnosed cancers and one of the most significant sources of cancer mortality. Triple negative breast cancer (TNBC) is a particularly aggressive subtype that has proven difficult to treat with standard chemotherapies. Obesity has also been shown to exacerbate breast cancer, and diagnoses of these two diseases frequently overlap. Both conditions are regulated in part by the fat mass and obesity-associated (FTO) demethylase, an RNA demethylase which may drive breast cancers through epigenetic alterations to gene expression. Methods of inhibiting FTO have been researched *in vitro* and *in vivo* as an alternative or adjunct to chemotherapies in multiple cancers, including breast cancer. Translating knowledge of the role of FTO in breast cancer and the development of novel agents may allow for improvements in the treatment of this refractory cancer. This review therefore aims to provide an overview of existing and developing chemical inhibitors of FTO that could be innovatively studied for the treatment of TNBC and associated comorbidity.

Keywords

Breast Cancer, Obesity, Fat Mass and Obesity-Associated, Chemotherapy, Epigenetics, RNA

1. Breast Cancer Overview

Breast cancer comprised about 11.7% of diagnosed cancers in 2020 globally and was responsible for 6.9% of cancer deaths. Breast cancer is the greatest contributor to cancer mortality in women [1].

There are multiple types of breast cancer that vary in receptor expression and phenotypic characteristics. Luminal breast cancer is characterized by estrogen receptors (ER), ER regulation, or similarity to luminal epithelial cells. It's further divided into luminal types A and B. Human epidermal growth factor receptor 2 (HER-2) breast cancer subtypes are defined by their expression of HER-2 [2]. The normal-breast-like subtype, as the name suggests, has a less malignant phenotype and appears like normal breast tissue histologically. Basal-like breast cancer consists of normal and myoepithelial cells and does not express ER, progesterone receptor (PR), or HER-2 [2]. Basal-like phenotypes are one molecular subtype of triple negative breast cancer (TNBC) [3].

TNBC is common in pre-menopausal patients and is an especially concerning diagnosis. TNBC is associated with lower survival rates, quicker relapse, and higher metastatic potential, including metastasis to the brain [3]. This subtype does not respond to current endocrine and targeted molecular therapies since there is a lack of the relevant target receptors [3]. Consequently, TNBC requires additional and novel chemotherapies [4]. There are six types of TNBC: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR). The variation in abnormal genetic expression has been studied between subtypes. MYC is overexpressed in the BL1 subtype, whereas the MSL subtype shows significant increases in genes associated with stemness and mesenchymal cells [3]. Likewise, TNBC therapy is still selected broadly based on absence ER, PR, and HER2, although newer targets are approved, like programmed cell death ligand 1 (PDL-1) and immune checkpoint inhibitors, or emerging, like anti-androgen receptor therapies, and other molecular chemotherapeutics [3].

MYC, NOTCH, and Wnt family member (WNT)/epithelial-mesenchymal transition (EMT) are some of the most studied pathways in relation to breast cancer. MYC is a transcription factor implicated in stemness and cell cycle regulation as well as WNT and NOTCH signaling [5]. One resistance mechanism to treatment demonstrated by ER-positive breast cancers, specifically, may be attributed to MYC [6]. While tyrosine kinase inhibitors are one possible mechanism of decreasing MYC expression, this method appears unsuccessful in HER2-positive or ER-positive breast cancers [6].

The NOTCH group of proteins includes cell surface receptors implicated in angiogenesis, tumor immunity and maintenance of stemness. In particular, NOTCH1 and NOTCH4 impact angiogenesis in cancers, including breast cancer [7]. In TNBC, NOTCH1 and NOTCH2 cause enhancer of zeste homolog 2 (EZH2) to reduce the expression of phosphatase and tensin homolog deleted on chromosome ten (PTEN), a tumor suppressor, leading to worse outcomes [8]. In HER2-positive breast cancers, more proliferation and resistance to current treatments have also been attributed to decreased PTEN activity, via NOTCH1, and thus increased extracellular signal-related kinases 1 and 2 (ERK1 and ERK2) activity [9] [10].

WNT is another cell surface receptor heavily implicated in development, stemness, and migration of cancer cells whose activity is also elevated in breast cancer cells [11]. Mechanistically, methylation, and possibly other mechanisms, downregulate Dapper homolog 1 (DACT1) in breast cancer. This change in expression promotes WNT signaling [12]. Hypermethylation is also problematic because it can increase WNT by decreasing signaling antagonists like Aristaless-like homeobox-4 (ALX4), Dickkopf-3 (DKK3), and SRY-box 17 (SOX17) [13] [14] [15].

Like most aggressive cancers, TNBC seems driven by gene expression patterns that favor stemness and epithelial mesenchymal transition, such as the genes listed previously. Given the changes in gene expression that appear to underly breast cancer development and resistance to current treatments, understanding these mechanisms and potential ways of affecting them could be important to the development of new therapies.

2. Breast Cancer and the Fat Mass- and Obesity-Associated Protein

The fat mass- and obesity-associated (FTO), originally determined through genome-wide association studies to contribute to obesity, is a member of the alpha-ketoglutarate-dependent hydroxylases, which includes the group of enzymes that demethylates nucleic acids [16] [17]. FTO removes methyl groups from mRNA, specifically at m^6A and m^6Am sites [18] [19] [20]. Azzam *et al.* (2022) reviews how FTO demethylation and single nucleotide polymorphisms (SNPs) in the gene contribute to obesity and cancer. FTO activity may be inhibited by oncometabolites as well as other molecules [21]. FTO has been reported to be elevated in breast cancer tissues obtained from mastectomy samples, especially in cases of HER-2 positive cancers, suggesting it may function as an oncogene [22]. Conversely, FTO has been suggested to have some tumor suppressive qualities in other cancers, like ovarian cancer [23].

2.1. Correlation between Obesity and Breast Cancer

Clinical studies have revealed overlaps between obesity and cancer in the patient population. Obesity was associated with about 40% of patients developing cancer, according to United States Cancer Statistics data from 2014 [24] [25]. Experiencing an increase in weight post-menopause and having diabetes were correlated with breast cancer and related mortality risk [26] [27] [28]. Obesity may further complicate the efficacy of current therapies for breast cancer [29].

Breast tissue is made up of a complex interplay of fatty tissues, immune and vascular cells, stromal tissues and mammary glandular tissues. Like all complex organs, there are intracellular communications between the cells in both normal tissues and in the cancers that derive from these organs. For example, adipose tissue macrophages may be influenced by the abnormal microenvironment in obesity and contribute to aggressive behavior of tumors, metastasis, and an im-

mune-suppressive microenvironment [30]. Similarly, cross talk from the adipocytes in obesity also seems to promote fibrosis, aggressiveness and metastasis in breast cancer and other obesity-associated cancers [31].

Mechanistically, ongoing studies have revealed FTO's contributions to signaling pathways with downstream impacts related to both obesity and cancer. For instance, FTO supports the mammalian target of rapamycin complex 1 (mTORC1) pathway, thereby limiting autophagy and potentially protecting against obesity. However, FTO may have a problematic function in cancer since this mTORC1 pathway seems to contribute to oncogenesis [32] [33]. FTO is also involved in phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling in breast cancer, thereby increasing energy metabolism. This process was suggested to be active prominently in those who are ER-positive, and estrogen is deemed to be a postmenopausal risk factor for breast cancer [34] [35].

2.2. Single Nucleotide Polymorphisms, Mutations, and Breast Cancer

SNPs are single nucleotide mutations in genes that may alter gene expression and therefore impact cancer susceptibility depending on the regions the SNPs localize to in introns, exons, promotors, 5'- and 3'-UTRs, or other gene regulatory elements [36]. SNP mutations in FTO have been examined for their involvement in breast cancer and obesity development, as described in-depth by Hernandez-Caballero and Sierra-Ramírez (2015) and Lan *et al.* (2020) [25] [37]. SNP rs9939609 and others in FTO's first intron are relevant and may relate to gene expression, with effects varying based on the type of SNP, type of mutation, and type of receptor [28] [38].

Data from breast cancer patients and controls showed that SNP rs1477196 and rs9939609, independently and together, as well as rs1477196 contribute to breast cancer risk [28]. Rs9939609 is correlated with patients who are HER-2-negative [39]. Evidence is mixed about whether rs9939609 is important in the development of breast cancer in those who are overweight and whether rs1477196 correlates with a diagnosis of stage 1 breast cancer [28] [35] [40] [41].

Other pertinent SNPs include rs720690 and rs8047395. According to analyses that considered SNPs in the context of their interactions with other SNPs, these SNPs are significant in breast cancer [28]. *In vitro* data on metastatic triple negative breast cancer has suggested SNP rs8050136 and rs1421085 activity that relates back to obesity [21] [42]. However, other studies have not found a correlation between metastatic breast cancers and FTO SNPs [37].

Several SNPs categorized as non-body-mass-index(BMI)-related, including those in FTO's intron 8, have also been identified in breast cancers. ER− and ER+ breast cancers were linked to rs11075995 and rs17817449, respectively [37] [43] [44]. Certain mutations in FTO SNPs rs1121980 and rs9939609 alongside the MC4R SNP rs17782313 have been shown to significantly affect breast cancer [37] [45].

2.3. Fat Mass- and Obesity-Associated Protein Demethylation in Breast Cancer

In addition to SNPs, FTO's function as a demethylase has also been associated with breast cancer. FTO is thought to cause 3' demethylation of BCL2 interacting protein 3 gene (*BNIP*3) transcripts, resulting in breakdown of the mRNA. This process inhibits apoptosis and allows for breast cancer growth [21] [25] [46]. Furthermore, in triple negative breast cancer, methylation from methyltransferase-like 3 (METTL3) decreases collagen type III alpha 1 (COL3A1) levels, inhibiting metastasis. It was found that increased FTO activity—and thus demethylation—did have the opposite effect by increasing onset of evident metastasis [47]. Our own laboratory has identified FTO inhibition to impact stemness gene expression and cancer aggressiveness (unpublished data). Further study is needed to explore the impact of FTO demethylation on breast cancer development, especially considering the study of related mechanisms in other cancers.

3. RNA Methylation Regulates Gene Expression

The path from gene to protein includes the DNA messages (the genome), the epigenome (which includes histone modifications and DNA methylation), the RNA message (the transcriptome), RNA modifications including RNA methylation (the RNA epitranscriptome), protein expression and the protein post translational modifications that make up the proteome. In addition to the chemical modifications made to DNA that impact genetic expression through epigenetics by modulating transcription, post-transcriptional changes contribute to expression downstream by helping to regulate the fate of RNA transcripts. Epitranscriptomics looks at chemical variations on RNAs. These include predominantly the presence of methyl groups at N6-methyladenosine (m^6A) sites [18]. Methylations specific to the 5' end of RNAs are referred to as 2'-O-methyladenosine (m^6Am) modifications. These changes in mRNAs can have a direct, gene-specific impact on translation and contribute to alternate splicing [48]. Studies indicate associations between mRNA methylation and bodily systems, including the central nervous and reproductive systems. Their regulation is also implicated in disease states such as cancer and obesity [49]. The addition, recognition, and removal of m^6A and m^6Am are carried out by methyltransferases, binding proteins, and demethylases, respectively; accordingly referred to as writers, readers, and erasers [49].

3.1. "Writers": Methyltransferases

Known human methyltransferases include METTL3, methyltransferase-like 14 (METTL14), and methyltransferase-like 16 (METTL16), which individually or combined with each other and other proteins partake in m^6A methylation in mRNAs [50]. The DRACH motif is methylated by a complex consisting of METTL3, METTL14, and the Wilms tumor 1 associating protein (WTAP) [50].

Expression, and thereby activity, of these enzymes have been found to have prognostic implications. For example, reduced levels of METTL3 and METTL14, corresponding to less methylation, decreased acute myeloid leukemia growth [51] [52], but increased glioblastoma growth [53]. Meanwhile, mRNA cap adenosine N6-methyltransferase is responsible for methylating m^6Am sites [50] **Figure 1**.

3.2. "Readers": Binding Proteins

The YTH domain family (YTHDF) proteins and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) are responsible for recognizing methylation

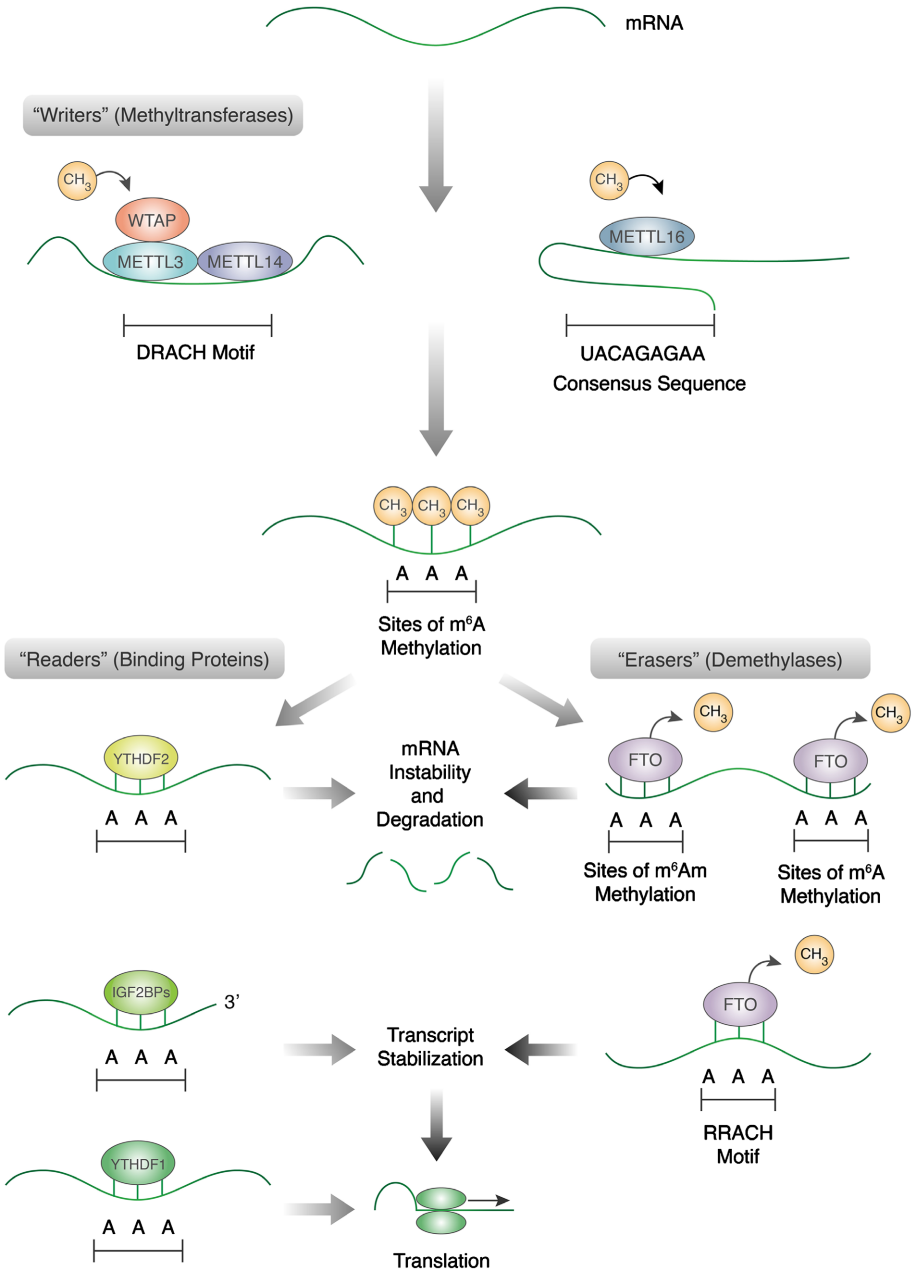

Figure 1. Epitranscriptomic functions of methyltransferases, binding proteins and demethylases [18] [19] [20] [50] [54] [55] [57] [59]-[64].

on RNAs and may then have roles in degradation or stabilization of bound transcripts. YTH domain family 2 (YTHDF2) partakes in mRNA degradation. Wang *et al.* (2014) specifically showed how YTHDF2 is associated with the m^{6}A sites of mRNA in HeLa cells [54]. It has also been proposed that METTL14 methylates mRNAs that are targets of YTHDF2, thereby bringing in this reader [55]. Its binding may then transfer the mRNA to cellular locations where it can be degraded. This mRNA-YTHDF2 interaction was correlated with less survival of the mRNA, indicating that YTHDF2 helps break it down [54]. In a study by Su *et al.* (2018) on acute myeloid leukemia cells, reduced YTHDF2 expression stabilized MYC mRNA [56]. Meanwhile, evidence suggests that YTH domain family 1 (YTHDF1) increases translation by binding at m^{6}A sites, primarily at the GRAC motif, guiding mRNAs to ribosomes, and then helping to instigate translation [57]. YTHDF1 activity is exhibited through associated MYC expression following increased m^{6}A methylation in lung adenocarcinoma cells [58]. IGF2BPs also associate with m^{6}A sites, especially near the 3' end of mRNA, to stabilize MYC transcripts *in vitro* [59] (**Figure 1**).

3.3. "Erasers": Demethylases

Demethylases, including FTO and AlkB Homolog 5 (ALKBH5) proteins, remove methyl groups from RNA transcripts. FTO and ALKBH5 act on the m^{6}A sites of mRNA and interact with post-transcriptional splicing factors in nuclei [19] [20] (**Figure 1**). FTO has the additional capability of m^{6}Am demethylation [18]. Demethylase activity may alter mRNA expression by inducing mRNA breakdown through splicing or by stabilizing transcripts. This varies based on the associated reader and the location of the m^{6}A on the transcript [60]. While not a universal rule, decreased stability has been linked to demethylation at 3' end sites or 5' m^{6}Am. The latter is potentially due to lost integrity of the 5' cap. Interestingly, FTO also has stabilizing activity at the internal m^{6}A of transcripts like MYC in acute myeloid leukemia cells and like CAP-Gly domain containing linker protein 3 (CLIP3) in glioblastoma cells [60] [61] [62] [63]. FTO is known to target specific sequences, including RRACH and GAC [64]. At the RRACH consensus motif in glioblastoma cells, Zepecki *et al.* (2021) proposed coordinated activity between FTO, argonaut 1 (AGO1), and interleukin enhancer binding factor 3 (ILF3). The association between the three proteins, mediated by microRNA-145, is hypothesized to incite demethylation and subsequent translation of the CLIP3 tumor suppressor in the cells. Thus, there is a potential mRNA-stabilizing role for AGO1, which is commonly incorporated into the RNA-induced silencing complex (RISC) [62].

4. Fat Mass- and Obesity-Associated Demethylase Activity and Inhibition across Obesity and Cancers

4.1. Roles in Obesity

While FTO has been increasingly studied in the context of a variety of diseases,

one of its signature functions pertains to obesity.

Studies illustrate that elevated FTO is accompanied by weight gain, fat mass, and energy storage, such as through adipogenesis. Conversely, decreasing FTO yields the opposite observations [37] [65] [66] [67]. Locations involved in the usage and storage of energy, such as the hypothalamus, adipose tissue, and skeletal muscle, exhibit FTO expression [25] [63] [68]. Genetic differences in the FTO gene's first intron can correspond to higher BMI, as well as other measures of obesity. There is an association with FTO and type 2 diabetes that is known to be stimulated by obesity [37] [68] [69]. Accordingly, reducing expression of FTO decreases BMI. This suggests that FTO may contribute to obesity onset, potentially through its influence on other molecules' efficacy [21].

Loss of FTO activity hinders adipogenesis by interfering with the energy-harboring cofactor nicotinamide adenine dinucleotide phosphate (NADPH)'s function [70]. Less FTO function similarly reduced autophagy and adipogenesis by increasing m^6A methylation on the autophagy related 5 and 7 (ATG5 and ATG7) transcripts, which have been associated with obesity-related metabolism, and thereby decreasing expression of these proteins, possibly through the involvement of YTHDF2 and mRNA degradation [71]. Indirectly, inhibiting FTO was shown to increase thermogenesis in adipocytes, indicated by elevated uncoupling protein 1 (UCP1) [72]. Collectively, these data suggest that FTO is involved in mechanisms that could contribute to obesity if in excess, but inhibiting FTO may consequently be a means of moderating this activity experimentally.

FTO's impact also depends on its sequence variability as determined by single nucleotide polymorphisms (SNPs). Some SNPs differentially regulate FTO or nearby gene expression and may contribute to obesity [21] [28] [38] [69]. Studies have suggested that, in FTO's first intron, the SNP rs8050136 decreases retinitis pigmentosa GTPase regulator interacting protein 1 like (RPGRIP1L) protein expression, thereby attenuating the body's response to leptin and increasing feeding [25] [73]. The SNP also increases retinoblastoma-like 2 (RBL2) levels, which is known to contribute to preadipocyte growth [25] [74]. A handful of other SNPs, including rs1421085 mutations, have been linked to greater Iroquois homeobox 3 (*IRX3*) expression, more white adipose and energy storage, and less thermogenesis, heightening obesity characteristics [21] [25] [75] [76].

FTO has also been analyzed in obesity for its role as an RNA demethylase that can impact transcript processing and translation [72]. *In vitro* and *in vivo* data have shown that demethylation at m^6A promotes transcription factor forkhead box protein O1 (FOXO1), which elevates energy storage through hepatic gluconeogenesis and simultaneously reduces thermogenesis by decreasing uncoupling protein 1 (UCP1) levels [21] [72]. Removal of m^6A from ghrelin hormone's mRNA promotes ghrelin expression and thus a pathway associated with obesity [25] [77]. The SNP rs9939609 was associated with this observation [77]. Additionally, demethylation by FTO prompts exon removal, likely mediated by regulator proteins like serine/arginine-rich splicing factor 2 (SRSF2) [78]. The effects of such splicing activity, as well as transcription factors and cellular pathways associated

with FTO, modulate adipogenesis [25]. The AMP-activated protein kinase signaling pathway reduces FTO and m^{6}A demethylation, minimizing lipid build up [21] [79]. Loss of FTO also induces downregulation of ATG5 and ATG7 through transcript degradation, lessening adipogenesis and autophagy and potentially helping to prevent obesity [71]. Meanwhile, zinc finger protein 217 gene (ZNF217) (the murine homolog is Zfp217) spurs FTO transcriptional activity and promotes adipocyte proliferation, exemplifying the complex role of FTO in obesity and cancer [21] [80].

4.2. Roles in Cancer

In addition to breast cancer, FTO is implicated in other cancers including lung, endometrial, pancreatic, gastric, colorectal, bladder, acute myeloid leukemia, glioblastoma multiforme, cutaneous squamous cell carcinoma, and melanoma [18] [21] [81]. Estrogen receptor (ER)-mediated PI3K/AKT and mitogen-activated protein kinase (MAPK) activity was shown to stimulate FTO and thereby proliferation and invasion of endometrial cancer cells [82]. Zhu *et al.* (2016) identified specifically mTOR signaling, which is associated with PI3K, as an instigator for FTO activity in the nucleus and proliferation in this cancer [83]. FTO may then target homeobox B13 (HOXB13) transcripts, with demethylation at the 3' end increasing expression, leading to WNT signaling, and enabling the cancer to spread [84]. In gastric cancer, FTO is linked to cancer growth and proliferation through its involvement in the epithelial-mesenchymal transition [81].

In lung cancer, FTO was shown to promote oncogenesis and proliferation by stabilizing and activating Myeloid Zinc Finger Protein 1 (MZF1) and ubiquitin-specific protease 7 (USP7), respectively [85] [86]. These mechanisms suggest connections between FTO and breast cancer since HER2/Erb-B2 receptor tyrosine kinase (ERBB2) has been observed to promote MZF1 activity in breast cancers, and USP7 may also contribute to breast cancer cell survival, growth, and replication [87] [88]. FTO is also involved in the polarization of macrophages, which is associated with signal transducer and activator of transcription 1 (STAT1) levels. STAT1 expression may indicate worse outcomes in breast cancers, in part due to its impact on macrophages [18] [89] [90].

FTO displays both oncogenic and tumor suppressive activity in pancreatic cancer. By improving MYC stability, FTO propagates cancer by assisting cellular replication [91]. An opposing mechanism has been suggested in lung adenocarcinoma, whereby FTO demethylation reduces MYC expression, so Wnt signaling promotes oncogenesis by decreasing FTO transcription [58]. FTO also exhibited tumor suppressive nature in ovarian cancer. Having destabilizing demethylation of the 3' end of phosphodiesterase 1C (PDE1C) and phosphodiesterase 4B (PDE4B) transcripts in these cells decreases expression, enhancing cAMP signaling, and thus reducing stemness and cancer cell growth [23].

FTO may also regulate metabolic reactions, such as glycolysis and mitochondrial activity. This activity can positively and negatively impact cancer progression and may depend upon the relative roles of m^{6}A writers, readers, and deme-

thylases in the specific cancer [18].

4.3. Inhibitors

With FTO having shown to possess such widespread regulation of obesity and cancer-related processes, research has attempted to inhibit the demethylase using repurposed and novel molecules to prevent or reverse the effects [21] (**Table 1**, **Figure 2**).

4.3.1. Natural Oncometabolite Inhibitors

2-oxoglutarate (2-OG) analogs comprise one such category of inhibitors. The oncometabolite R-2-hydroxyglutarate (R-2HG) acts as a competitive inhibitor

Table 1. Fat mass and obesity-associated (FTO) inhibitors under study.

FTO Inhibitor	Inhibitor Characteristics			
	Mechanism of Action	Experimental Conditions	IC50 (μM)	Study
R-2-hydroxyglut-arate (R-2HG)	Competetive inhibitor	*In vitro* and *in vivo* for leukemia; *in vitro* for GBM	N/A but 300 used to show inhibition	Su *et al.* (2018), Qing *et al.* (2021)
Entacapone	Competetive inhibibitor	*In silico;* *in vitro* for hepatocytes; *in vivo* for metabolic study	3.5	Peng *et al.* (2019)
MA	Studied alone and in combination with an EGFR TKI (Gefitinib)	*In vitro* assay [92] [93]; *in vitro* for lung cancer; clinical trials for GBM	4 - 12.5	Chen *et al.* (2022), Huang *et al.* (2015), Huff *et al.* (2021), Zeyen *et al.* (2022)
MA derivative: FB23-2	Direct inhibition, higher affinity than MA	*In silico;* *in vitro* and *in vivo* for AML	2.6 ± 0.5	Huang *et al.* (2019)
MA derivative: MA2	Competetive inhibitor	*In vitro* and *in vivo* for gastric cancer and GBM; *in vitro* for HeLa cells	N/A but 20 - 120 used to show inhibition	Cui *et al.* (2017), Shimura *et al.* (2022), Huang *et al.* (2015)
FTO-04	Selective competetive inhibitor	*In* silico; *in vitro* for GBM	3.4	Huff *et al.* (2021)
Bisantrene (CS1) and Brequinar (CS2)	Tight, direct FTO inhibition	*In silico*; *in vitro* and *in vivo* for AML and breast cancer; bisantrene phase II clinical trials for AML; *in vitro* for GBM	CS1: 0.02 - 0.8; CS2: 0.06 - 10	Su *et al.* (2020), Canaani *et al.* (2021)
Rhein	Inhibitor	*In vitro* assay; *in vivo* for TNBC	30	Chen *et al.* (2012), Niu *et al.* (2019)
MO-I-500	Inhibitor	*In vitro* for TNBC	8.7	Singh *et al.* (2016)

Table 1 Select FTO inhibitors and their pharmacologic characteristics in oncology studies. List of FTO inhibitors, their mechanisms of action if known, experimental conditions under which published results showing inhibition were obtained (*in vitro*, *in vivo*, *in silico*, or clinical trial and condition type), IC50 if known, and source of the data. AML = acute myeolid leukemia, EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor, GBM = glioblasotma multiforme, GSC = glioma stem cells, MA = meclofenamic acid, TNBC = triple negative breast cancer.

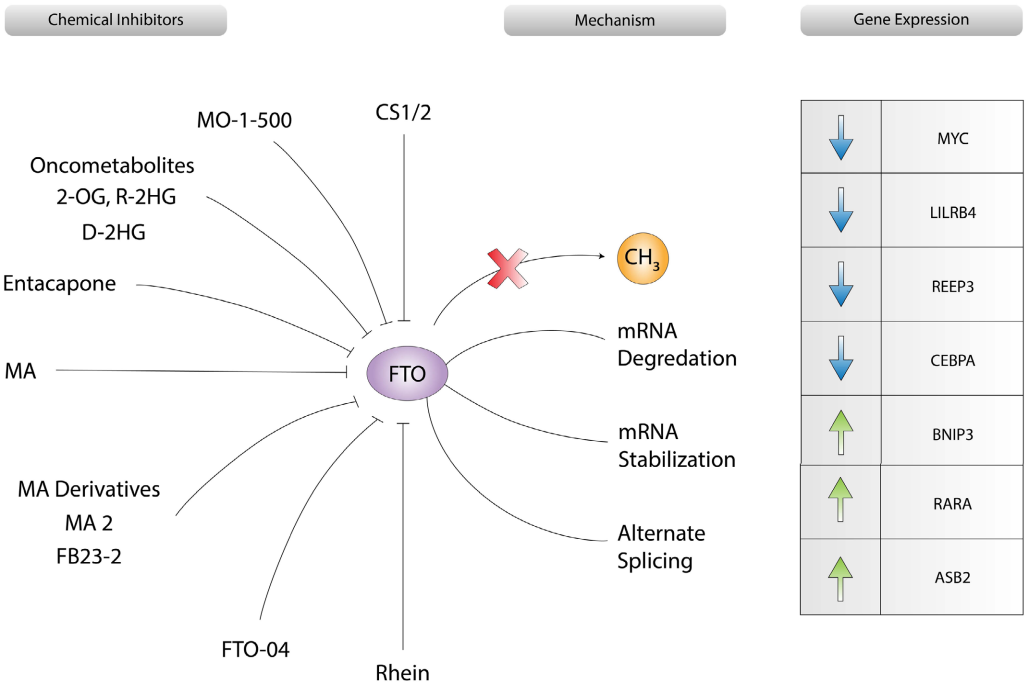

Figure 2. FTO inhibitors, associated mechanisms of action and gene expression changes [18] [21] [25] [42] [46] [53] [56] [72] [81] [92] [93] [95] [101] [102] [103] [104] [106].

and indirectly reduces MYC, curtailing growth of some cancers like leukemia and glioblastoma (GBM) [18] [56]. The molecule also blocks the expression of some enzymes responsible for aerobic glycolysis necessary and specific to acute myeloid leukemia (AML) viability and growth: phosphofructokinase platelet (PFKP) and lactate dehydrogenase B (LDHB) [94]. Research suggests that D-2-hydroxyglutarate (D-2-HG), produced by isocitrate dehydrogenase (IDH), has similar potential to help kill cancer cells by inhibiting FTO [95]. However, if patients also have a mutation in the gene for IDH, these inhibitors may promote cancer by acting on other enzymes, like ten-eleven translocation methylcytosine dioxygenase 2 (TET2) [18] [95]. In gliomas, IDH mutations and D-2-HG activity together aid tumor growth, and IDH inhibitors thus also have clinical potential for this disease [95] [96] [97].

4.3.2. Drug Inhibitors

Entacapone, currently approved for treatment of Parkinson's activity because of its ability to inhibit catechol-O-methyltransferase (COMT), has also been explored as an FTO inhibitor [98]. This molecule has an IC50 of approximately 3.5 μM in its interactions with FTO, and *in vitro* studies have failed to indicate crossover inhibition of the ALKBH5 demethylase or ten-eleven translocation methylcytosine dioxygenase 1 (TET1) [72]. *In vivo* treatment with entacapone reduced obesity-related measures and activity, including fat mass ratio, cholesterols and triglycerides, and gluconeogenesis, while increasing energy expenditure and possibly thermogenesis [21] [72].

Meclofenamic acid (MA), a nonsteroidal anti-inflammatory drug (NSAID)

used to treat some conditions related to pain, arthritis and bleeding, is another FTO inhibitor whose derivatives have been analyzed in several cancers [92] [99]. MA itself was not particularly effective *in vitro* for lung cancer, though, in conjunction with an epidermal growth factor receptor tyrosine kinase inhibitor, it prompted apoptosis [100]. Derivatives may hold more promise as individual therapeutic agents. For example, FB23 and FB23-2 reduced acute myeloid leukemia growth and cell survival *in vitro*, with FB23-2 having a relatively low IC50 of around 2.6 μM and showing anti-tumor effects *in vivo*, as well, potentially through pathways governing cancer cell differentiation [18] [21] [101]. The derivative MA2 has anti-proliferative effects and reduces cancer cell movement in gastric cancer, as elucidated through *in vivo* and *in vitro* experiments [81]. For GBM, this same compound was shown to increase survival *in vivo* and help control MYC activity and cancer development alongside treatment with the existing chemotherapeutic temozolomide (TMZ) [18] [53] [102].

A multitude of other novel inhibitors have been developed and assessed for their efficacy against cancers. Huff *et al.* (2021) found that FTO-04 could successfully inhibit FTO in glioma stem cells (GSCs) and restrain cell growth *in vitro* [18] [93]. The molecule rhein was studied in neuroblastoma, but its implications for the progression of cancer remain to be determined [103]. Su *et al.* (2020) tested the efficacy of CS1 and CS2, also called bisantrene and brequinar, in AML [104]. The compounds were shown to be specific to FTO, acting primarily in cancerous cells. *In vitro* data indicated less cell division and more apoptosis in treated AML stem cells. *In vivo* findings also pointed to a reduction in cancer cells. Mechanistically, this inhibition of FTO may downregulate and destabilize leukocyte immunoglobulin-like receptor subfamily 4 (LILRB4), which increases cells' susceptibility to immune system defenses. It may also lessen the MYC and CCAAT enhancer binding protein alpha (CEBPA) pathways and promote retinoic acid receptor alpha (RARA) and ankyrin repeat and SOCS box containing 2 (ASB2), corroborating the epigenetic effects observed with FTO inhibition using FB23-2 [101] [104]. CS1 has progressed to clinical trials for AML patients [105]. Both compounds also showed some efficacy in reducing GBM tumor growth [104].

5. Potential Role of Fat Mass- and Obesity-Associated Protein Inhibitors in Breast Cancer Therapy

5.1. Monotherapies

Among the potential breast-cancer therapeutics targeting FTO that are under study *in vitro* and *in vivo* are inhibitors whose effects have been examined independent of any other concurrent treatments. In triple-negative breast cancer, 2-oxogluterate oxygenase has been studied but may not be readily translatable to therapies given numerous anticipated downstream effects aside from FTO inhibition [18]. Rhein successfully diminished tumor growth *in vivo* [46]. MO-I-500 prevented cell growth *in vitro*, though this result was dependent on the me-

dium and thus may not be as applicable to resistant TNBC cells [25] [42] [46]. MO-I-500, which has an IC50 of 8.7 μM, resulted in the survival of fewer TNBC metastatic-like cells without glutamine for metabolism. However, there was no significant inhibition of cell growth in cells adapted to this environment, suggesting that such treatments may need to be provided early. IRX3 and FTO decreased in surviving cells, which could have been a causal response or could imply that cells with less FTO or IRX3 are less impacted by the FTO inhibitor [42].

With regards to obesity, rhein has also been associated with decreased levels of receptor expressing-enhancing protein 3 (REEP3), which may be a mechanism of attenuating adipogenesis [21] [106]. This suggests disparate but potentially mutual beneficial effects through different pathways. Nevertheless, more promising are the FTO inhibitors CS1 and CS2, which were shown to decrease the rate of breast tumor growth *in vivo,* had IC50s of 1 μM and lower concentrations in most cell lines tested *in vitro*, and have been deemed relatively safe [104].

5.2. Combination Therapies

The aforementioned monotherapies and other FTO inhibitors have also revealed promising results in cancer research, including breast cancer, when applied in combination with current treatments. In glioblastoma, FTO inhibition decreases resistance to temozolomide (TMZ) by improving the chemotherapy's efficacy [18] [102]. A clinical trial of the FTO inhibitor MA in combination with TMZ is in development [107]. FTO also seems to have an adverse association with obesity through ATG5 and ATG7 activity [71]. Han *et al.* (2020) found that targeting ATG5 in breast cancer may decrease resistance to the prescribed breast cancer therapy trastuzumab [108]. The overlap in the mechanisms proposed in these two studies suggests that reducing ATG5 function through FTO inhibition could reduce both breast cancer and obesity. This could be beneficial in patients with both conditions, especially in cases of interdependency.

NOTCH1 and the melanoma cell adhesion molecule (MCAM), which are active in breast cancer, also correlate to TNBC patient mortality, migration, and invasion of breast cancer cells [109]. NOTCH1 has been studied as a contributor to TNBC and basal-type breast cancers and is associated with EMT genes [110]. EMT is, in turn, associated with metastasis and growth of stem cells [81] [110]. *In silico, in vitro*, and *in vivo* breast cancer results showed that blocking NOTCH1 downregulates MCAM, thereby decreasing proliferative EMT. The ultimate result of this pathway is a reduction in chemoresistant TNBC, particularly with cisplatin [109]. Of note, ER-negative breast cancer also shows high levels of NOTCH1 and MCAM [109], suggesting potential relevance of mitigating this pathway in multiple types of breast cancer. Breast cancer gene 1 (BRCA1) deficiency also induces NOTCH1 and is linked to more severe breast cancer [110]. More specifically, BRCA1 loss was shown to increase ICN1 activity experimentally, which was representative of NOTCH1 activity. This causes ATR to promote CHK1 activity, which increases cancer cell survival [110]. Inhibiting NOTCH1

may therefore stop uncontrolled cell growth in TNBC [110].

Given this data, BRCA1, NOTCH1, MCAM, ATR serine/threonine kinase (ATR), and checkpoint kinase 1 (CHK1) could all be plausible sites of therapeutic targeting to inhibit this pathway towards oncogenesis and metastasis, though off-target effects and interactions with standard treatments must be considered. Chemotherapy has been a preferred treatment for TNBC, with cisplatin being selective for BRCA1-deficient cancers [109] [110]. CHK1 and ATR inhibitors worked in tandem with cisplatin *in vitro* and ATR inhibitors worked *in vivo*, as well [110], indicating a potential benefit in reducing activity of the NOTCH1-induced pathway alongside treatment with chemotherapy.

While the research on the connection between NOTCH1 and FTO is limited, a loose association can be extrapolated from Yi *et al.* (2021), who showed how FTO in bladder cancer yields changes in m^6A levels at NOTCH1 transcripts, among some other genes [111]. Further research is necessary to determine whether a direct connection can be established in other cancers, including breast cancer, and whether targeting FTO could take advantage of this pathway, potentially in combination with other treatments.

Lastly, MA was studied in lung cancer in combination with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) to decrease resistance via inhibition of the FTO pathway. These findings may hold implications in breast cancer since the breast cancer resistance protein (BCRP) is one of the proteins responsible for the lack of effectiveness of EGFR inhibition in lung cancer [100]. Trying to directly inhibit EGFR in TNBC patients previously was ineffective [3]. However, BCRP levels dropped with MA treatment in lung cancer experiments. The most likely explanation is the reduction of its transcription factor MYC because of more m^6A methylation of MYC transcripts following FTO inhibition [100]. Perhaps such therapies could consequently be applied to breast cancer to improve upon the unsuccessful outcomes.

6. Discussion

Breast cancer, especially TNBC, is a significant contributor to mortality that necessitates improved therapies [1] [3]. The severity and resistance of the disease can be attributed to the molecular mechanisms responsible for breast cancer growth and development. These are rooted in the expression of certain genes that induce downstream effects promoting attributes like stemness, cancer cell growth, and metastasis [6]. Such gene expression is regulated by epigenetic changes like m^6A methylation, which is controlled by methyltransferases, "reader" proteins, and demethylases [18] [49].

The demethylase FTO contributes to obesity and breast cancer by influencing expression and suppression of various genes. In obesity, increases in FTO correlate to higher BMI, obesity-associated disorders like type 2 diabetes, and changes in molecular processes driving obesity, such as increased autophagy and adipogenesis and decreased thermogenesis [21] [37] [63] [65] [66] [67] [68] [69] [72].

Among the cancers affected by FTO are endometrial, lung, and pancreatic cancer, which involve receptors and pathways that are also notable in breast cancer, such as MYC and estrogen-receptor-related signaling [82] [91] [100]. FTO SNPs and demethylation patterns have been linked to the onset and development of breast cancer [21] [25] [28] [46].

Since obesity can contribute to breast cancer [29], the importance of FTO in the progression of both diseases suggests that targeting FTO could be an effective means of therapy. A variety of FTO inhibitors have already been studied *in vitro* and *in vivo* to determine their impacts on cancers. These compounds include repurposed drugs, like entacapone, bisantrene and brequinar, and novel therapies, like FTO-04 [18] [21] [72] [93] [104]. Some studies have specifically assessed the effects of such FTO inhibitors in breast cancer, alone or in tandem with other inhibitors or current chemotherapies [18] [42] [104] [108].

Nonetheless, applicability of FTO inhibitors as a treatment is still in the early stages of research and more studies are needed to understand their mechanisms of action, side effects, interactions with other drugs, and their safety and efficacy in human patients. If identified, an appropriate drug candidate that takes advantage of FTO activity could benefit breast cancer patients who currently see grim outcomes, especially those who have comorbid obesity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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