FTO gene, obesity and colon cancer: from epidemiological evidence to laboratory studies

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Abstract: Both epidemiological surveys and laboratory studies have demonstrated that obesity can increase colon cancer incidence and is one of factors leading to poor prognosis. However, the mechanisms for the association of obesity with colon cancer are not well elucidated although both genetic and other cancer risk factors have been reported to play an important role. The fat mass and obesity associated (FTO) gene is the first gene in which a common genetic variant is strongly associated with body mass index (BMI) in the general population. Over-expression of the FTO gene increases food intake, which in turn leads to obesity, one of the major risks to cancer incidences. Furthermore, people with different FTO genotypes show difference not only in the mean value but also in the variance of BMI. Recent studies have shown that genetic mutations in the FTO gene are associated with the carcinogenesis of several cancers including colon cancer. It has also been reported that the FTO-induced increase of cancer incidences is independent of obesity. Mechanistically, this is due to that FTO can activate different intracellular signalling pathways that are relevant to cancer development. Thus, FTO gene is related to the colon cancer incidence either through the obesity-dependent or the obesity-independent mechanisms. In this review, we summarize the evidence of FTO being involved in colon carcinogenesis and discuss the possible mechanisms as well as prevention approaches.

Keywords: Fat mass and obesity associated (FTO); food intake; obesity; colon cancer; intracellular signalling pathways

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Introduction

Cancers are a severe co-morbidity of obesity, which is recognised as a major health issue worldwide. As obesity is difficult to treat, obesity-associated cancers, are a major concern for healthcare, requiring greater attention. It is estimated that obesity accounts for about 14% of cancer-caused death (1). Thus, it is important to study obesity-associated cancer for cancer prevention. Published laboratory studies have demonstrated that many cancer risk factors altered in obesity, such as insulin, insulin-like growth factor, estrogen, leptin, adiponectin, IL-6, IL-17 and TNF-α, play key roles in obesity-associated cancers (2-5). Obesity has also been shown to be associated with poorer prognosis of many cancers which may be caused by the increase of drug resistance to chemotherapeutic agents (6,7). Multiple signalling pathways have been shown to be activated in obesity-associated cancers (8), which could be responsible for the increased cancer incidences and their poor prognosis.
It is not clear whether there is shared genetic basis between obesity and cancers. So far, more than 30 gene loci have been reported to be associated with obesity (9). Among them, fat mass and obesity associated (FTO) gene, a well known obesity-associated gene, is the first gene that has been confirmed to be related to the obesity (10). FTO protein is an AlkB-like 2-oxoglutarate—dependent nucleic acid demethylase with substrate specificity for 3-methylthymidine and 3-methyluracil in nuclear acids (11). It prefers single-stranded nuclear acids and thus methylated RNA rather than DNA (12,13). The molecular target of FTO has been identified to be N6-methyladenosine in mRNA (14). One of the physiological roles of the FTO has been identified to stimulate food intake as it is expressed highest in hypothalamic including arcuate (ARC), paraventricular (PVN), dorsomedial and ventromedial (VMN) nuclei (15-18), which are known to regulate satiety.

FTO genotype is strongly associated with fat mass in human bodies (19). Epidemiological studies have shown that FTO gene has a high frequency of gain-of-function mutations such as the mutation occurred at position rs9939609 (20-22). The FTO SNP rs9939609 is significantly associated with extremes of adiposity (23) in ascertained samples and body mass index (BMI) in general population (24). It has been demonstrated that homozygous “A” allele of FTO rs9939609 has 1.7 fold higher risk to be obese than that of “T” allele. Recently, Yang et al. reported that FTO affects not only the mean of BMI but also the variability of BMI (25). The association has been further demonstrated by laboratory studies. Over-expression of Fto in mice caused obesity (23) while knock out of Fto led to lean phenotype (26). In this review, we summarise the studies that investigated the role of FTO gene involved in obesity-associated colon cancer to discuss the possible molecular mechanisms of the colon carcinogenesis linking to the obesity.

Possible link between FTO and colon cancer

Epidemiological studies have shown that the genetic variants at the FTO gene locus are associated with several cancers including breast cancer, endometrial cancer, pancreatic cancer and colon cancer (27). Kaklamani et al. reported that FTO single nucleotide polymorphisms (SNPs) are associated with increased risk of breast cancer (28). In a case-control study with 354 breast cancer cases and 364 controls, the associations of SNPs of intron 1 of FTO including rs7206790, rs8047395, rs9939609 and rs1477196 with breast cancer risk were examined (27). It was found that all four SNPs examined were significantly associated with breast cancer risk with the SNP rs1477196 showing the strongest association. FTO is expressed both in normal and malignant breast tissue and FTO genotypes could be one of breast cancer risk factors.

Endometrial cancer is a cancer which is highly associated with obesity (29). Lurie et al. found that FTO rs9939609 is a susceptibility marker for white non-Hispanic women at higher risk of endometrial cancer (30). In a study with 832 cases of endometrial cancer patients and 2,049 controls, genetic variants at 7 obesity-related genes (SEC16B/RASAL, TMEM18, MSRA, SOX6, MTH2, FTO, and MC4R) were found to be associated with endometrial cancer after adjustment of BMI (31), suggesting a potential role of these genes in endometrial cancer which is independent of obesity.

Genetic variants at FTO locus have also been associated with pancreatic cancer. In a meta-analysis study which includes 13 studies with 16,277 cases and 31,153 controls, FTO rs9939609 is also associated with pancreatic cancer (32). However, most of the participating studies do not take the BMI/obesity factor into account. Thus, it is unclear whether the association between FTO and pancreatic cancer is obesity-dependent or not. Tang et al. observed that FTO IVS1-2777AC/AA genotype is associated with pancreatic cancer but only limited in overweighted people (33).

Relatively fewer studies have reported that the FTO variant is associated with colon cancer. Nock et al. investigated the involvement of FTO in obesity-associated colorectal cancer in 759 Caucasians and 469 African-Americans and found that FTO variants are positively associated with colorectal cancer in African-Americans (34). However, Lim et al. examined the direct effect of polymorphisms of 15 loci (BDNF, FAIM2, FTO, GNPDA2, KCTD15, LYPLAL1, MC4R, MSRA, MTH2, NEGR1, NRXN3, SEC16B, SH2B1, TEAP2B and TMEM18) in 2,033 colorectal cancer cases and 9,640 controls, and found that only 3 loci (KCTD15 rs29941 and MC4R rs17782313) were associated with colorectal cancer independent of obesity (35). The sample size used in this study may be not big enough to make solid conclusion.

Taken together, epidemiological studies provide evidence to support that genetic variants at the FTO locus are associated with several cancers including colon cancer. The mechanisms could be obesity dependent or
expression of Fto and thus increase food intake (16,53,54). Starvation in Wistar rats resulted in an increase of both Fto mRNA and protein in neurons of paraventricular and ventromedial nucleus (53). This also provides evidence that FTO is involved in satiety regulation in normal conditions.

FTO can decrease monoamine such as noradrenaline, serotonin and dopamine, which repress food intake (55-59). In Fto null mice, catecholamine was increased (26). Hess demonstrated that FTO knock out resulted in disruption of dopamine pathway (60). On the other hand, FTO can also increase orexigenic hormones. FTO has been shown to increase these hormones including ghrelin, neuropeptide Y (NPY) and oxytocins (58,61,62). Olszewski et al. studied the effect of overexpression of FTO on mRNA expression of oxytocins, NPY and agouti-related peptide (AgPR). It was found that overexpression of FTO up-regulated oxytocins but not NPY and AgPR (61). Addition of oxytocins into cell culture of hypothalamic cells did not change FTO protein expression, suggesting the lack of feedback. Karra et al. showed that one allele of the FTO variant increased expression of ghrelin, which is known to increase food-intake (62).

The effect of FTO on BMI can account for the increased cancer incidence in patients with FTO SNPs. Obesity is known to play an important role in colon cancer via increased cancer risks in obesity including insulin, estrogen, adipokines and inflammatory factors (63). These factors can activate several signalling pathways such as PI3K/Akt, MAPK and STAT3 which are known to play key roles in carcinogenesis of colon cancer. Therefore, inhibition of these pathways by specific small molecule inhibitors or phytochemicals can be used for the prevention and treatment of obesity-associated colon cancer (8,64,65). Leptin is one of the major cancer risk factors in obesity. It has been shown to increase blood levels of leptin (66). This could be a mediator for the link between FTO mutations and cancer risk. It has been demonstrated that FTO-increased leptin increase is via obesity (66).

The mediate effect of obesity in FTO-increased colon cancer incidence can be further evidenced by the association of FTO with other obesity-associated diseases. It has been shown that FTO is significantly associated with osteoarthritis, a disease highly related with obesity (67). In animal models, it has been demonstrated that obesity increases osteoarthritis incidence and accelerates its progression (68). Leptin is of critical role in obesity-associated osteoarthritis (68-70).

**Mechanisms for FTO in obesity-associated colon cancer**

FTO protein is highly expressed in hypothalamus, a food intake regulating organ, indicating its possible role in satiety (16,18). Genetic variants at FTO locus have been found to be associated with satiety (36). Further studies have demonstrated that FTO affects the food intake rather than the energy expenditure (18,37-41). For example, a particular allele of the FTO SNP rs9939609 has an effect to repress satiety and increase food intake (42-46). Church et al. reported that over-expression of Fto in mice increased food intake and obesity in both standard food feeding and high-fat diet (HFD) feeding (47). In contrast, deletion or missense mutations of FTO lead to leanness (48-51).

It has been shown that nutrition state affects the expression of FTO and other food intake-related genes including Etr5, Faim2 and Negr1 (52). Based on the studies on postpradial response of Fto in mice, fasting can increase

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**Figure 1** Possible link between FTO and colon cancer. Overexpression of FTO protein could increase colon cancer incidence via obesity dependent and independent pathways. FTO increases food intake via satiety hormones and thus results in obesity, which is known to increase colon cancer incidence. FTO could also activate cellular signalling molecules STAT3, cyclin D1 and MMPs to increase cancer incidence. FTO, Fat mass and obesity associated; STAT3, signal transducer and activator of transcription 3; MMPs, matrix metalloproteinases; NPY, neuropeptide Y.
The role of FTO in multiple intracellular signalling pathways

Evidences have also shown that FTO is directly associated with cancer independent of obesity. Kikuchi et al. demonstrated that the FTO SNP rs9939609 is associated with pancreatic cancer risk in Japanese subjects, possibly through a mechanism that is independent of obesity (71). Iles et al. provided evidence that FTO variant increased melanoma independent of BMI [66]. The study showed a genetic variant in intron 8 of FTO, which is not linked with BMI, is associated with increased melanoma incidence. It is known that the BMI associated FTO variant is located in intron 1 (72).

Previous studies have shown that FTO can stimulate several intracellular signalling pathways important in carcinogenesis including signal transducer and activator of transcription 3 (STAT3), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), cyclin D1 and matrix metalloproteinases (MMPs) (73,74). The direct effect of FTO on these pathways is evidence that FTO can increase cancer incidence independent of obesity.

FTO and STAT3

STAT3 is a transcription factor that functions as a signal transducer and activator. STAT3 is also considered as an oncogene because it promotes cell survival/proliferation, motility and immune tolerance. In obesity-associated colon cancer, STAT3 is activated (2). Activated STAT3 can promote carcinogenesis by mediating the functions of the downstream proteins through its signaling pathway. FTO has been demonstrated to increase the activity of STAT3. Over-expression of Fto in rats increased STAT3 mRNA expression in the arcuate nucleus of the hypothalamus (58). The role of FTO in the STAT3 pathway in colon cells, however, is yet to be elucidated.

FTO and PI3K/Akt pathway

PI3K/Akt is an important survival pathway in many cancers including colon cancer (75-78). Its activation in obesity by various factors is responsible for the increased carcinogenesis and drug resistance. FTO has been shown to regulate Akt in both neurons and adipocytes. siRNA silencing of Fto resulted in increased pAkt while pAMPK, a negative regulator of pAkt was decreased (79). However, how FTO protein acts on the PI3K/Akt pathway is not clear. The possibility of FTO-regulated PI3K/Akt pathway may be involved in obesity-associated colon cancer and warrant further studies.

FTO and Cyclin D1

Increased cell proliferation is a major hall marker of carcinogenesis (80,81). A major regulator of cell proliferation is cyclin D1; increase of cyclin D1 can promote cell cycle and thus increase cell proliferation (82). Cyclin D1 has been shown to play a key role in the carcinogenesis associated with adenomatous polyposis coli (APC), a tumour suppressor gene (83). The loss of APC gene is closely associated with colon cancer. Loss of APC will lead to accumulation of beta-catenin, which in turn interact with TCF/LEF family to increase gene transcription including cyclin D1.

FTO has been shown to involve in the regulation of cell proliferation. Knockout of FTO resulted in decreased cyclin D1 and thus reduced cell cycle and cell proliferation in endometrial cells (84). This is evidence that FTO may involve in cell proliferation directly. However, the effect of FTO on cyclin D1 in colon cells has not been studied and warrants further studies.

FTO and MMPs

MMPs are enzymes that degrade the extra cellular matrix and thus play a key role in physiological activities such as extracellular matrix remodelling during growth (85,86). They have been demonstrated to play key roles in cancer metastasis through facilitating the detachment of cancer cells from original sites (85,86). MMPs can also change microenvironment of cancer cells to promote growth (87). MMPs can increase vascular endothelial growth factor (VEGF), a known factor in angiogenesis of tumour growth (86).

FTO has been shown to regulate MMPs to promote cell migration in endometrial cancer cell line Ishikawa. Treatment of Ishikawa cells with estrogen at concentration of 10^-7 M up-regulated protein expression of FTO and MMPs via estrogen-receptors (84). Knockdown of FTO by siRNA resulted in decreased MMP2 and MMP9 and thus reduced cell migration in endometrial cells, indicating regulatory role of FTO in MMP production. Thus, it is proposed to target FTO for treatment of cancer.

FTO, estrogen and cancer risk

It has been shown that estrogen can stimulate FTO expression
in both mRNA and protein levels via PI3K/Akt and MAPK pathways in endometrial cancer cells (84). Endometrial cancer can be estrogen-dependent or independent (88). This study showed that FTO was a target protein of estrogen in estrogen-dependent endometrial cancer (84). Estrogen can bind estrogen receptor-alpha to increase cell proliferation and decrease apoptosis. There are several down-stream pathways to mediate such an effect. FTO could be one of them. Increased expression of FTO in turn promotes cell proliferation via cyclin D1. In colon cancer the role of estrogen is complicated; it has different effects when it binds to estrogen receptor-alpha and estrogen receptor-beta (89). Estrogen receptor-beta has protective effect and estrogen receptor-alpha can promote carcinogenesis. It will be interesting to study the role of FTO in estrogen-mediated effects in colon cancer cells.

**FTO in HFD fed mouse model of obesity-associated colon cancer**

HFD is a common model for obesity and obesity-associated colon cancer studies. Several studies have demonstrated that HFD-induced obesity increased colon cancer incidence in mouse and rat models (90-92). Various mechanisms have been proposed. For example, leptin and adiponectin are the two major adipocytokines, which have been considered to be major factors in obesity-associated cancer (2,93). These changes could affect intracellular signalling pathways to increase colon cancer incidence (2).

FTO alterations have been found in HFD-feeding animals. Short-term HFD-feeding decreased FTO while long term HF-feeding increased FTO (58,94). It indicates FTO expression is involved in increased colon cancer incidence in this model. However, it is not known how important FTO is in the HFD-induced obesity-associated colon cancer compared to other cancer risk factors.

**Possible co-operation between FTO and other obesity-associated genes**

It is now recognised that many genes may involve in the regulation of fat accumulation in body. More than 30 genes have been identified to involve in BMI in European decent (9,95,96). Dorajoo et al. showed that Asians including Chinese, Indian and Malay share some of obesity-associated gene mutations (96). Each gene may only contribute a small percentage. The outcome of obesity and obesity-associated cancer may be due to the co-operation of several obesity-associated genes.

Except FTO, other genes important in obesity have been identified by GWAS. Kilpelainen et al. identified IRS1 and SPRY2 are associated with adipocyte physiology (95). Fox et al. studied subcutaneous adipose tissue and visceral adipose tissue in 5,560 women and 4,997 men (97). It was found that the association between visceral/subcutaneous adipose tissue (VAT/SAT) ratio and rs11118316 at LPLAL1 gene is the most significant while SNP in the FTO gene was most associated with SAT. In addition, rs1659258 near THNSL2 gene is associated with VAT in women but not men (97). Okada et al. analysed 62,245 east Asian subjects and found several genes were associated with obesity including previously known SEC16B, BDNF, FTO, MC4R and GIPR loci as well as newly identified loci including CDAKL1 locus at 6q22 (rs2206734) and the KLIF9 locus at 9q21 (rs1142387) (98).

GWAS has also identified several other genes which are associated with BMI and cancer such as HHEX gene rs1111875 mutation (99) and MC4R rs17782313 (30). MC4R rs17782313 is linked to increased endometrial cancer risk (30). The polymorphisms in HHEX have also linked with endometrial cancer risk although the effect was weak (100). A metastasis analysis showed that the association of FTO, MC4R, TMEM18, SDCCAG8, and TNKS/MRSA mutations with early-onset obesity were very strong (101). It could be an interesting topic to elucidate how these genes co-operate each other to affect cancer incidence.

**Prevention**

Although there are abundant evidences that FTO is associated with increased cancer incidence including colon cancer, there are no prevention approaches at present. It has been proposed to take some preventive approaches such as targeting FTO in the population with over-expression of FTO (47). A question is that FTO is also necessary for physiological function of human body. It has been shown that an inactivating mutation of FTO (resulting in the p.Arg316Gln alteration) in humans caused an autosomal recessive lethal syndrome (102). Mice lacking Fto gene or dominant mutation (resulting in p.Ile367Phe) had reduced fat mass and thus prevented from obesity (103,104). However, increased postnatal lethality and postnatal growth retardation were also found. Therefore it may be not practical to ablate FTO for the prevention of obesity. Inhibition of FTO downstream pathways may be a better choice. The advantage for inhibition of pathways
is that it may also decrease the effect of other gene defects which may also activate the similar intracellular signalling pathways.

Phytochemicals could be used to disrupt the association between $\textit{FTO}$ and cancer. They are not expensive with low toxic and thus ideal compounds for disrupting $\textit{FTO}$ and obesity-induced activation of intracellular signalling pathways important for carcinogenesis (64). In addition, some phytochemicals such as beta-glucans can increase immune responses which can facilitate the early elimination of abnormal cells. Phytochemicals have now extensively studied for the prevention of cancer. Some of them may be applied to obesity-associated colon cancer such as EGCG, curcumin and genistein (64,89,105,106). How these phytochemicals act on $\textit{FTO}$-signalling pathways has not been well studied and warrant further exploration.

**Conclusions**

Epidemiological studies indicate that $\textit{FTO}$ may be involved in obesity-associated colon cancer. Over-expression of $\textit{FTO}$ can increase food intake, leading to obesity, which can increase colon cancer risk and result in poorer prognosis and drug resistance. $\textit{FTO}$ protein may also act on different molecules in several survival signalling pathways such as cyclin D1, MMPs, STAT3 and PI3K/Akt, which play a crucial role in carcinogenesis. Over-expression of $\textit{FTO}$ protein has been shown to mediate other cancer risk factors such as estrogen and HFD to increase cell proliferation. Preventive approaches may be taken in those people with over-expression of $\textit{FTO}$. Phytochemicals could be suitable for the prevention as they can inhibit $\textit{FTO}$-induced signalling pathways.

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