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Review Article

Multifaceted regulation and functions of fatty acid desaturase 2 in human cancers

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Abstract: As an important hallmark of metabolic reprogramming in cancer, a disruption in fatty acid metabolism contributes to tumor proliferation, cell migration and invasion, and other tumor cell behaviors. In recent years, more and more studies have been conducted on fatty acid desaturase 2 (FADS2), the first rate-limiting enzyme for the biosynthesis of polyunsaturated fatty acids. These studies have found that FADS2 is abnormally expressed in cancers of the breast, lung, liver, and esophagus; melanoma; leukemia; and other malignant tumors. Furthermore, its expression is significantly correlated with tumor proliferation, cell migration and invasion, clonal formation, angiogenesis, ferroptosis, resistance to radiotherapy, histological grade, metastasis to lymph nodes, clinical stage, and prognosis. The abnormal expression of FADS2 results in an imbalance of cell membrane phospholipids, which disrupts the fluidity of the membrane structure and the transmission of signals and promotes the production of proinflammatory factors and arachidonic acid (AA) metabolites, ultimately harming human health. This article aims to systematically review the structural characteristics of FADS2; its function, expression, and mechanism of action; and the factors affecting its activity. This review also provides new ideas and strategies for the development of treatments aimed at the metabolic reprogramming of tumors.

Keywords: Fatty acid desaturase 2, human cancer, expression, function, metabolism

Introduction

Cancer is the most severe public health problem and the leading cause of death worldwide [1]. There are approximately 4.3 million new cancer cases and 2.9 million new cancer deaths every year in China, and, compared with the United States and the United Kingdom, China has a lower cancer incidence but a 30% and 40% higher cancer mortality [2]. Despite significant advances in the treatment and diagnosis of cancer, the overall survival and prognosis remain poor. Therefore, the identification of new biomarkers and signaling pathways is crucial to the treatment of cancer.

A common phenomenon of tumor cells is metabolic reconstruction, which produces building blocks and energy for tumor cells to grow, divide, and survive. Several studies have reported that disruptions in glycolysis, as well as amino acid (mainly glutamine, serine, and glycine) and lipid metabolism promote the behavior of various malignant tumors by inducing cell proliferation, antiapoptosis, invasion, and metastasis [3], These findings have inspired researchers to explore new strategies for the treatment of various malignant tumors by targeting the metabolism of cancer cells. The breakdown of lipids provides sufficient building blocks and energy for tumor cells to synthesize the cell membrane and to perform other related functions during proliferation [4]. Studies have found that the key enzymes involved in lipid metabolism in tumor cells are acetyl-CoA carboxylase (ACC), fatty acid synthase (FASN), ATP-citrate lyase (ACLY), and fatty acid desaturase (FADS). The dysregulated expression and activity of these key enzymes directly affects the biosynthesis of fatty acids by tumor cells, which in turn interferes with tumor progression [4, 5].

As enzymes for fatty acid desaturation, the main function of FADS family is to catalyze the

conversion of lipids to regulate the metabolic balance of lipids. In mammals, the FADS family includes FADS1, FADS2, FADS3, FADS4 (SCD5), FADS5 (SCD1), FADS6, FADS7 (DEGS1), and FADS8 (DEGS2). Their amino acid sequences include three common conserved motifs (HX3H, HX2HH and HX2HHXFP), and the differences between them are substrates and sites of action. Among them, SCD has been proven to play an important role in tumor malignant behaviors through the YAP/TAZ pathway, the EGFR/PI3K/AKT pathway, EMT or ferroptosis [6-8], and it has been systematically summarized in several reviews [9, 10]. In addition, it has been shown that the common feature of many tumors is increased AA metabolites and increased synthesis of eicosanoids [11]. Omega-6 (n-6) polyunsaturated fatty acids, like arachidonic acid and its metabolites, play an important role in cell activity and physiological functions as components of the microenvironment. Among them, prostaglandin E2, leukotrienes, cyclooxygenase 2, etc. can promote the occurrence and progression of tumors through various mechanisms [12]. FADS2 among the members is a key enzyme that catalyzes the production of such polyunsaturated fatty acids, and changes in the expression and activity of FADS are related to hypertension, metabolic disorders, type 2 diabetes, cardiovascular diseases, inflammation, multiple sclerosis, neurological and mental diseases, and malignancy [13-15]. Although some reports have shown its important functions in cancers, there are few systematic reviews on it. There are fewer studies on other members of the FADS family in cancers. Therefore, the structure and physiological function of FADS2, as well as the role of FADS2 in human cancer, are systematically reviewed in this article.

Gene location and structural characteristics of FADS2

Fatty acid desaturase 2 (FADS2, D6D, des6, llcdl2, fadsd6, tu13, delta-6-desaturase, delta (6) fatty acid desaturase) is encoded by the *FADS2* gene on chromosome 11 (11q12-q13.1) [16]. The *FADS2* gene has been identified in more than 200 species, including bacteria, fungi, plants, and animals (**Table 1**) [17-49]. Human FADS2 is a membrane-binding protein of 444 amino acids with a molecular weight of 52.2 kDa; it contains a cytochrome b_5-like domain, two transmembrane domains, and three histidine-rich domains (regions I, II, III). Regions I (HX3H) and II (HX_2HH) are located between the two transmembrane domains, and region III (HH) is located at the C-terminus (**Figure 1**) [18]. FADS2 is expressed in the brain, liver, lungs, heart, and other tissues in humans [18].

Physiological functions of FADS2

FADS2 plays both physiological and pathological roles in different organisms. Wang et al. studied *Antheraea pernyi* and reported that FADS2 biosynthesis is involved in the mating and communication of these insects [36]. In mice, FADS2 inhibition reduces AA synthesis, thereby reducing inflammation [50], Furthermore, *FADS2* gene knockout eliminates the first enzymatic step of the polyunsaturated fatty acid (PUFA) cascade, leading to sexual dysfunction and infertility in male and female mice [51]. Another study has reported that FADS2 regulates the synthesis of PUFAs and the breakdown of triglycerides in dairy goat mammary glands [52]. FADS2 overexpression in zebrafish not only increases the production of PUFAs, but also stimulates antibacterial and anti-inflammatory activity [53].

FADS2 mainly plays a role in desaturation by introducing a double bond at the δ6 position of the fatty acid chain, and this is the first rate-limiting enzyme for the conversion of upstream fatty acids into PUFAs (AA and eicosatetraenoic acid). In baboons, a recent study has revealed that in addition to δ6-dehydrogenase activity, FADS2 also possesses δ8-dehydrogenase activity in the desaturation of 20:3n-3 and 20:2n-6 to stearidonic acid (SDA) and γ-linolenic acid (GLA) [54]. FADS2 exhibits desaturase activity toward at least seven substrates (18:2n-6, 18:3n-3, 20:2n-6, 20:3n-3, 24:4n-6, 24:5n-3, 16:0) [55], the major metabolic processes that FADS2 is involved in are shown in **Figure 2A**. Presently, there is no unified standard for representing the activity of FADS2. Cho et al. used the ratio of ETA/α-linolenic acid (ETA/ALA) and AA/linoleic acid (AA/LA) to represent FADS2 activity [18]. Pender-Cudlip et al. and Gardiner et al. used the ratio of total metabolites of linoleic acid (GLA; DGLA, dihomo-γ-linolenic acid; AA) to LA to express the activity of FADS2 [56, 57]. FADS2 activity has also been estimated from the ratio of the percentage of DGLA to the percentage of LA (i.e. % DGLA/% LA) [3] and the

Table 1. FADS2 in different species

Species name	Amino acid length coded by ORF	Reference
Cyanobacteria PCC6803	359	[19]
Spirulina platensis	368	[20]
Glossomastix chrysoplasta	465	[21]
Phaeodactylum tricornutum	477	[22]
Mortierella alpina	457/458	[23-25]
Mucor rouxii	523	[26]
Mucor circinelloides	467	[27]
Pythium irregulare	459	[28]
Borago officinalis	448	[29]
Echium plantagineum	448	[30]
E. gentianoides and E. pitardii	438	[31]
Anemone rivularis	446	[32]
Marchantia polymorpha	481	[33]
Primula farinosa	453	[34]
Primula vialii	453	[34]
Caenorhabditis elegans	443	[35]
Antheraea pernyi	316	[36]
Physcomitrella patens	525	[37]
Ceratodon purpureus	520	[38]
Oncorhynchus mykiss	454	[39]
Sparus aurata	445	[40]
Cyprinus carpio	445	[41]
Psetta maximus	445	[41]
Pleuronectiformes	445	[41]
Cyprinus carpio	444	[41, 42]
Gadus morhua	447	[43]
Siganus canaliculatus	445	[44]
Dicentrarchus labrax L.	445	[45]
Anguilla japonica	444	[46]
Epinepheluscoioides	445	[10]
Rachycentron canadum (Linnaeus)	247	[9]
Eriocheir sinensis	442	[47]
Mus musculus	444	[48]
Homo sapiens	444	[18]
Capra hircus	444	[49]

ratio of GLA to LA (GLA:LA) [58]. In addition, many factors influence FADS2 activity. These factors are related to different physiological and pathological conditions, such as aging, diet (high alcohol intake; high cholesterol level; deficiencies of zinc, magnesium, and vitamins C, B_3, B_5, B_6; and high trans fatty acid levels), hypertension, diabetes, cardiovascular disease, cancer, viral infections, hormone levels, and allergic dermatitis. FADS2 activity can also be affected by other regulatory genes and single nucleotide polymorphisms, as well as radiation [58-62], (**Figure 2B**).

Role of FADS2 in cancer

FADS2 and breast cancer

Lane et al. detected FADS2 expression in breast cancer cells and tissues and reported that FADS2 was expressed in the breast cancer cell line MCF-7 but not in the highly invasive triple-negative breast cancer cell MDA-MB-231. In addition, FADS2 expression in breast cancer tissues was significantly lower than that in paracancerous tissues (6.2 ± 2.1 copies/50 ng RNA vs. 15.4 ± 8.2 copies/50 ng RNA, $P <$

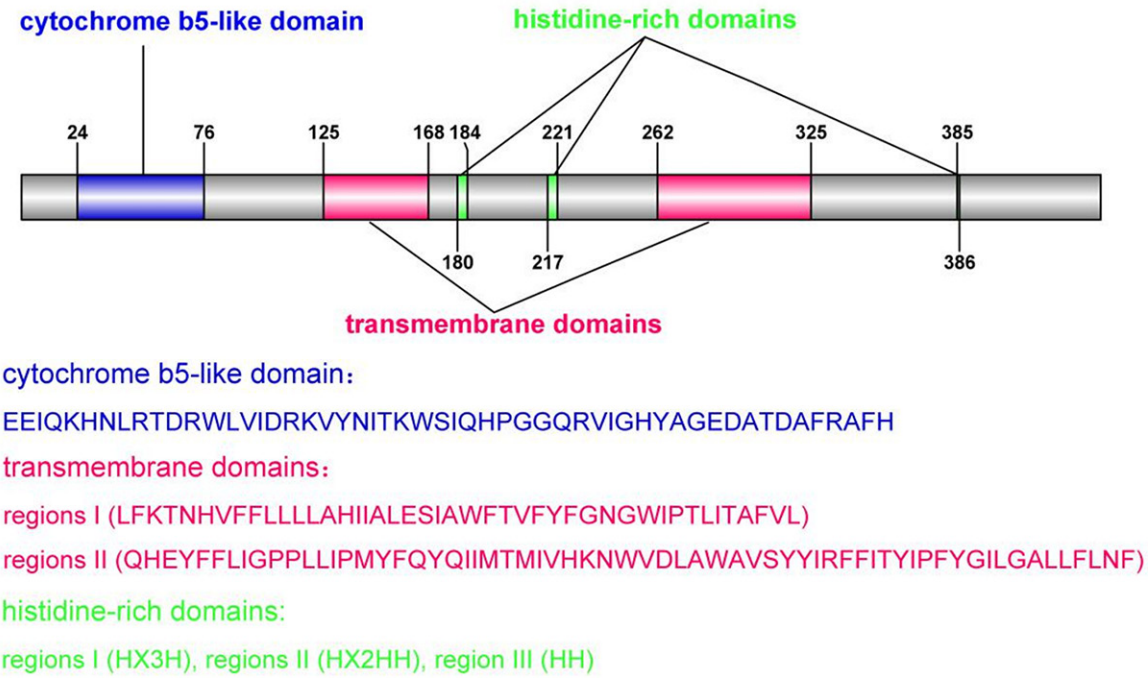


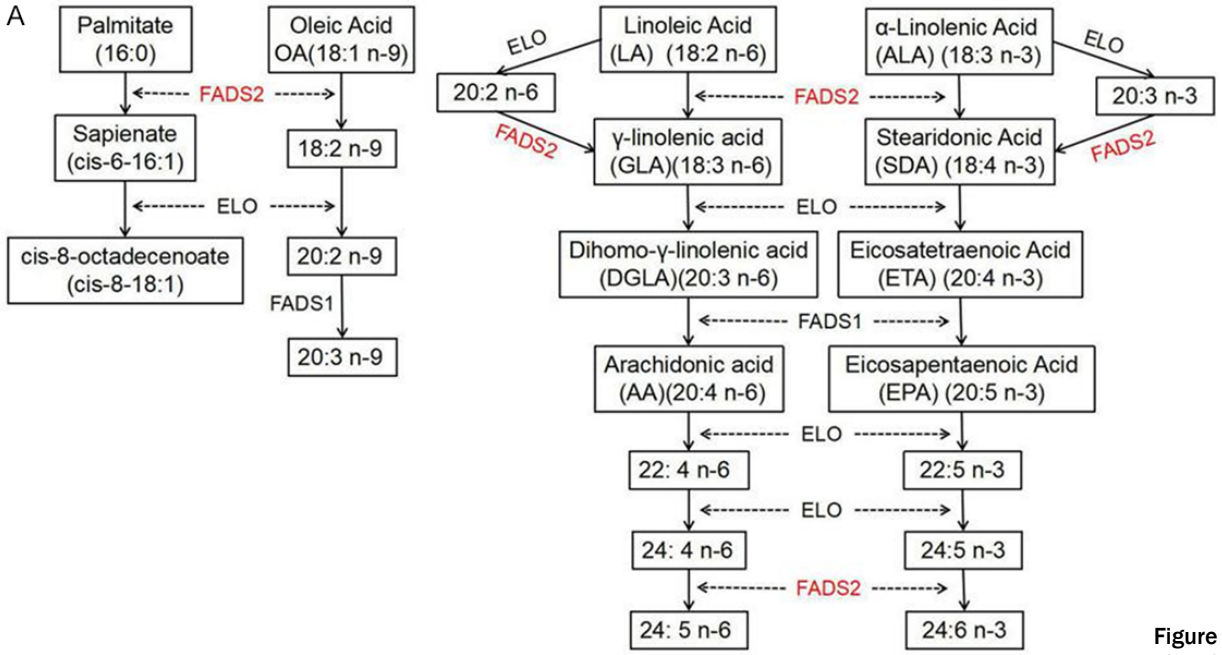
Figure 1. The structure of human FADS2. The blue area is the cytochrome b5-like domain, the red area is the transmembrane domain, and the green area is the histidine-rich domain (region I, II, and III).

0.05), and it was even lower in breast cancer patients with poor prognoses [63], suggesting that FADS2 is weakly expressed in breast cancer, and low FADS2 expression is significantly correlated with poor prognosis. Vriens et al. found that stearoyl COA destruction (SCD) inhibitor significantly inhibited the proliferation of breast cancer cells MDA-MB-468 and T47D, and FADS2 overexpression restored proliferation. However, FADS2 expression in these two breast cancer cell lines was significantly lower than that in the normal breast epithelial cell line MCF-10A ($P < 0.005$) [64].

In contrast to the aforementioned results, Zhao et al. analyzed gene expression in human breast cancer and normal tissues by microarray analysis, and the FADS2 mRNA level was more than two times higher in breast cancer tissues than in normal tissues [65]. Pender-Cudlip et al. also showed that FADS2 activity was significantly higher in breast cancer tissues than in paracancerous tissues (1.18 vs. 0.78, $P < 0.001$), and it was significantly higher in ER− breast cancer tissues than in ER+ breast cancer tissues (1.87 vs. 0.98, $P < 0.01$), suggesting that the FADS2 expression level may be related to the ER expression level in breast cancer. The discrepancy in the results reported by Lane et al. and others may be attributed to differences in detection methods. Proinflammatory factors, such as PEG2, produced during metabolic processes can alter the inflammatory status of the tumor microenvironment, thereby promoting tumor progression. Pender-Cudlip et al. reported that the amount of PGE2 produced in breast cancer tissues was significantly higher than that in paracancerous tissues (30.81 vs. 6.33 ng/g, $P < 0.001$), and the amount in ER-breast cancer tissues was significantly higher than that in related paracancerous tissues ($P < 0.01$). However, in different ER-responsive breast cancer tissues, there was no significant difference in the amount of proinflammatory factors [56], therefore, proinflammatory metabolites are associated with higher FADS2 activity and higher PGE2 expression in more aggressive ER-breast cancer. In conclusion, abnormal FADS2 expression in breast cancer may result in metabolic disorders, which may impact the development and progression of breast cancer.

FADS2 and melanoma

In a mouse model, He et al. reported that FADS2 mRNA and protein levels, as well as its activity, were significantly higher in melanoma



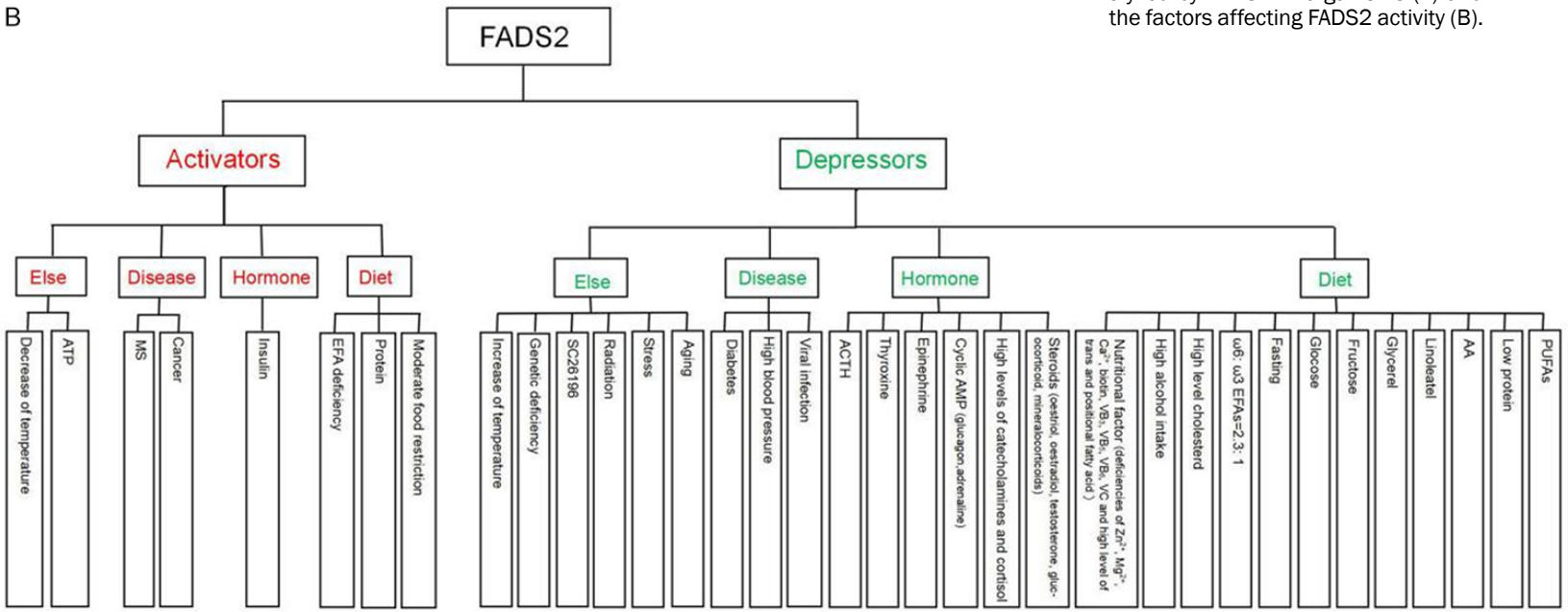


Figure 2. The metabolic pathways catalyzed by FADS2 in organisms (A) and the factors affecting FADS2 activity (B).

B16 tissues than in paracancerous tissues ($P < 0.01$). FADS2 protein was hardly detected in paracancerous tissues, whereas the FADS2 mRNA level, as well as its activity, were positively correlated with the size of B16 tumors (ETA/LA: $P = 0.0015$, $R^2 = 0.58$; AA/LA: $P = 0.0025$, $R^2 = 0.55$; mRNA: $R^2 = 0.93$, $P = 0.0017$). The content of AA in B16 tumors was four times higher than that in paracancerous tissues, and suppression of FADS2 activity with an inhibitor (SC-26196) or by RNA interference significantly suppressed the growth of B16 tumors ($P < 0.01$) and significantly reduced the AA content ($P < 0.01$). Furthermore, protumor metabolite levels derived from AA also decreased by 80%-95%, and the levels of angiogenesis-related genes and inflammatory factors (IL-6 and TNF-α) in B16 tumors were also significantly inhibited. These results indicate that FADS2 is a key factor in the progression of melanoma, and it regulates the release of inflammatory factors and the synthesis of proinflammatory metabolites in the tumor microenvironment [66].

FADS2 and lung cancer

He et al. suggested that FADS2 mRNA and protein levels, as well as activity, were significantly higher in mouse Lewis lung cancer (LCC) tissues than in paracancerous tissues ($P < 0.01$), and FADS2 protein was undetectable in paracancerous tissues. Furthermore, the FADS2 mRNA level and the enzyme activity were positively correlated with the size of LCC tumors (ETA/LA: $P = 0.0001$, $R^2 = 0.70$; AA/LA: $P = 0.0017$, $R^2 = 0.54$; mRNA: $P = 0.0139$, $R^2 = 0.81$). The content of AA in LCC was two times higher than that in paracancerous tissues, and the suppression of FADS2 activity with an inhibitor (SC-26196) or by RNA interference significantly suppressed the growth of LCC tumors ($P < 0.05$). Furthermore, the synthesis of AA and AA-derived protumor metabolites in LCC tumors was reduced ($P < 0.05$), and the levels of angiogenesis-related genes and inflammatory factors were also inhibited [66]. Jiang et al. showed that *FADS2* knockdown significantly suppressed lung cancer growth ($P < 0.001$), thereby resulting in a significant increase in the levels of Fe and lipid reactive oxygen species in lung cancer cells and a significant decrease in the levels of ferroptosis-related genes, which ultimately induces ferroptosis. Survival analysis showed that FADS2 expression is related to the overall survival of lung cancer patients, whereas another mechanistic study found that the expression of LSH in lung cancer positively regulated the expression of the target gene FADS2, and WDR76 increased the expression of FADS2 via epigenetic modifications that require dependence on LSH [67]. Vriens et al. measured the expression of FADS2 in 10 pairs of non-small cell lung cancer/paracancerous tissues and found that the expression of FADS2 in 8 pairs of lung cancer tissues was significantly higher than that in the corresponding paracancerous tissues [64]. In addition to the critical role that FADS2 plays in lung cancer, the circular RNA-circFADS2 produced by abnormal splicing also plays a vital role in lung cancer. Zhao et al. found that the expression of circFADS2 in non-small cell lung cancer tissues and cells was significantly upregulated ($P < 0.05$), and its high expression was significantly related to poor prognosis, high TNM grade, lymph node metastasis, and poor differentiation of non-small cell lung cancer ($P < 0.05$). Another study revealed that *circFADS2* promotes lung cancer development by regulating miR-498 expression [68]. These findings indicate that the effects of FADS2 on lung cancer cell growth and ferroptosis are regulated by other factors.

FADS2 and brain cancer

Researchers have examined human tissues by microarray and reported that the *FADS2* mRNA level in brain tumor tissues was twice as high as that in normal brain tissues [69]. The FADS2 level was also related to the radiotherapy sensitivity of tumors. Wang et al. demonstrated that FADS2 inhibitor SC-26196 decreased the proliferation rate by >45%, decreased the colony formation rate by >40%, and increased the apoptotic rate by 30%-40% for U-87 MG and LN-229 cells under radiotherapy *in vitro*, and significantly increased the lack of response of tumor growth to radiotherapy in xenograft tumor in mice (66.8 ± 28.3 mm^3 vs. 151.6 ± 15.1 mm^3). Another study revealed that SC26196 reverses the radioresistance of PGE2-ID1-dependent glioblastoma by blocking the synthesis of AA and PGE2 [70], indicating that FADS2 may be involved in the development of tumor resistance.

FADS2 and liver cancer

Vriens et al. reported that FADS2 mRNA and protein levels are significantly higher in HUH7 liver cancer cells than in normal cells, and the FADS2 level was higher in three out of four pairs of liver cancer tissues than in paracancerous tissues [64]. SCD is a key regulator of various processes such as tumor growth, programmed cell death and carcinogenesis [7]. Vriens et al. also demonstrated that the growth of certain cells was not inhibited when SCD was blocked, and the authors classified the tumor cells as SCD-independent, partially SCD-dependent, and SCD-dependent. The FADS2 level in SCD-independent and partially SCD-dependent tumor cells was significantly higher than that in SCD-dependent tumor cells. In a mechanistic study, liver cancer cells that do not rely on SCD desaturase could synthesize sapienate through FADS2, which is an alternative fatty acid desaturation pathway, to support biofilm synthesis during tumor cell proliferation. This complemented the reduction of fatty acid desaturation caused by the decrease of SCD activity and promoted the proliferation of cancer cells [64], indicating that the FADS2 desaturation pathway plays a key role in promoting the behaviors of certain cancers. However, Horrobin et al. reported no FADS2 expression in human liver cancer [71].

FADS2 and colon cancer

After SC-26196 treatment, tumors in $Apc^{Min/1}$ mice were reduced by 36%-37%, and the size of primary tumors arising from colon cancer cell HT-29 xenografts in nude mice were reduced by 35% ($P < 0.05$). Moreover, the LA level in the phospholipids of tissues was significantly increased, and the AA level was decreased. Furthermore, AA supplementation in the diet could eliminate the effects of SC-26196 on the fatty acid composition and tumorigenesis of $Apc^{Min/1}$ mice, indicating that the effect of this FADS2 inhibitor on the fatty acid composition of these two types of intestinal cancer cell are related to the synthesis of AA [72].

FADS2 and esophageal adenocarcinoma

Wang et al. reported that FADS2 mRNA and protein levels were significantly higher in esophageal adenocarcinoma tissues than in paracancerous tissues ($P < 0.05$), and the high expression of FADS2 in esophageal adenocarcinoma was significantly correlated with late stage, lymph node metastasis, and poor prognosis ($P < 0.001$). *In vitro*, FADS2 overexpression significantly promoted esophageal adenocarcinoma cell proliferation ($P < 0.05$), and enhanced anchorage- independent colony formation ($P < 0.05$), and migration and invasion ($P < 0.001$) [59], indicating that FADS2 may serve as a biomarker of esophageal adenocarcinoma.

FADS2 and other cancers

The results of microarray analysis of human tissues show that the *FADS2* mRNA level in cervical cancer tissue is twice as high as that in normal cervical tissue [73]. Vriens et al. reported that FADS2 mRNA and protein levels in the prostate cancer cell line DU145 were significantly higher than those in normal prostate cells [64]. FADS2 activity in renal cell carcinoma was significantly higher than that in healthy renal tissue [74]. Apart from the aforementioned solid tumors, Agatha et al. found a significant increase in FADS2 indexes of membrane phospholipids in children with acute lymphoblastic leukemia (1.21 ± 0.39 vs. 0.27 ± 0.04; $P < 0.001$). However, there was no significant difference in FADS2 indexes of membrane phospholipids in children with acute myelogenous leukemia (0.26 ± 0.08 vs. 0.27 ± 0.04). FADS2 activity related to n-6 and n-3 pathways in blood cells of patients with acute lymphoblastic leukemia increased by 3.8-fold and 2.5-fold compared to the healthy control group, respectively. However, there was no significant change in FADS2 activity in blood cells of patients with acute myelogenous leukemia [75]. In addition to the abnormal expression in leukemia cells, inhibition of FADS2 could suppress the growth of various leukemia cells [76]. These data indicate that changes in FADS2 expression and activity in cervical cancer, prostate cancer, renal carcinoma, and acute lymphoblastic leukemia may be related to the development and progression of tumors.

Discussion and conclusion

The studies reviewed in this article indicate that FADS2 overexpression promotes tumor proliferation, clonal formation, migration and invasion, and lymph node metastasis, and it is related to the tumor microenvironment, poor prognosis, radiotherapy resistance, and ferrop-

tosis. However, some researchers have reported that inhibition of the FADS2 level in tumor cells *in vitro* cannot suppress the proliferation of tumor cells. For example, in the study conducted by He et al., tumor cell growth was not suppressed after inhibition of FADS2 by SC-26196 and RNA interference in B16 melanoma and LCC lung cancer, which may be attributed to the fact that inhibiting FADS2 is not directly toxic to tumor cells. Instead, it may affect the behavior of tumor cells by regulating the production of metabolites in the tumor microenvironment or altering the phospholipid composition of the tumor cell membrane [66]. Vriens et al. indicated that silencing *FADS2* in HUH7 cells promotes proliferation, which may be the result of an alternative pathway of FADS2 fatty acid metabolism in tumor cells [64]. This article also summarizes studies in which FADS2 activity was up- or downregulated, and studies in which the expression in certain cancers, such as breast cancer and liver cancer, resulted in different conclusions (**Table 2**). Discrepancies may be related to the timespan between specific studies and available detection methods at the times they were performed.

Thus far, there are two main mechanisms of action of FADS2 in cancer: (1) Metabolite-related mechanisms in which FADS2 modulates the tumor microenvironment or the fluidity of cell membranes by regulating the synthesis of PUFAs during fatty acid metabolism. For example, Scanferlato et al. found that the production of sapienic acid is related to apoptosis and necrosis in colon cancer cells CaO2 [78]. Furthermore, FADS2 supports the synthesis of cell membranes during tumor cell proliferation by catalyzing the conversion of palmitic acid to sapienate and its extended product, *cis*-8-octadecenoic acid [64]. FADS2 inhibitors can reverse PGE2-ID1-dependent radioresistance in glioblastoma cells by blocking the synthesis of AA and PGE2 [70]. Pender-Cudlip et al. suggest that the AA synthesis pathway (AA and PGE2 production), which involves FADS2, may be related to breast cancer [56]. He et al. demonstrate that FADS2 may impair the tumor microenvironment by regulating the synthesis of AA and AA-derived eicosanoids (PGs, LTs, EETs), and thus affects tumor growth [66]. PUFAs can also regulate the expression of various transcription factors, including PPAR α/β/γ1/γ2, SREBP-1c, HNF-4α/γ, RXRα, LXRα, and NF-κB by directly binding transcription factors or regulating signal transduction pathways that control expression, phosphorylation, ubiquitination, or proteolysis in the liver [79]. Furthermore, AA-derived products such as prostaglandins, thromboxane, leukenoic acid, and 5-hydroxyeicosapentaenoic acid play important roles in cancer and other diseases [12]. (2) Molecular regulation-related mechanisms in which FADS2 expression or activity is regulated by other factors. Wy14643, an activator of transcription factor PPARα, synergistically induces *FADS2* transcription [80]. WDR76 and WD40 proteins can increase the expression of FADS2 through the epigenetic modification of the TSSs of the FADS2 promoter [67]. SREBP-1 and PPAR-α are involved in fatty acid biosynthesis by regulating *FADS2* transcription [81, 82]. As a key transcription factor in fatty acid metabolism, SREBP can be activated by mTOR signaling [83], and HIF-1α can stimulate SREBP-1c expression under hypoxia [84]. PUFAs, metabolites of FADS2, can also regulate the nuclear abundance of SREBP-1 and PPARα in liver and regulate the expression of FADS2 through a feedback mechanism [85, 86]. He et al. hypothesized the possible molecular regulatory mechanism of FADS2 expression in cancer, namely, hypoxia/reactive oxygen species-HIF-1α-SREBP-1c-FADS2 [66]. Recently, a research showed that SREBP-1/2 and mTOR signaling can regulate the expression of FADS2 and the production of its metabolite sapienate in cancer cells, just as we guessed [87]. The molecular mechanism of FADS2 in tumors needs further experimental exploration.

This review illustrates the important roles of FADS2 in the development, progression, metabolism, and death of various cancer cells. However, in studies on the relationship between FADS2 and cancer, the mechanisms by which FADS2 regulates tumor cells are rarely addressed. Thus, the expression, function, and specific mechanism of FADS2 in specific cancers need to be further explored. The regulation of FADS2 may have potential anti-inflammatory and antitumor effects in different pathological conditions. Therefore, it is important to explore the association between FADS2 and other clinicopathological factors in cancer patients such as age, lifestyle, menopause status, histological grade, and genotypes. Drug

Table 2. The association between FADS2 expression and the malignant tumors and its functions

Cancer type	FADS2 expression level	Function	Reference
Breast cancer	Downregulated (mRNA and activity)	Low FADS2 expression was related to poor prognosis of breast cancer patients and high TNM grade of tumor.	[63, 64, 77]
	Upregulated (mRNA and activity)	High expression promoted the synthesis of the pro-inflammatory metabolite PGE2 in breast cancer, which may promote the occurrence of inflammation.	[56, 65]
Melanoma	Upregulated (mRNA, protein and activity)	High expression promoted the growth of B16 melanoma and could lead to enhanced n-6 AA and AA-derived tumor, promoting metabolites production, as well as the gene expression of angiogenesis and inflammatory factors.	[66]
Lung cancer	Upregulated (mRNA, protein and activity)	High expression promoted the growth of lung cancer and could lead to enhanced n-6 AA and AA-derived tumor, promoting metabolites production, as well as the gene expression of angiogenesis and inflammatory factors. Inhibiting FADS2 could induce ferroptosis by increasing the level of Fe and lipid ROS in lung cancer cells. Patients with high FADS2 expression had poorer prognosis.	[64, 66, 67]
Brain cancer	Upregulated (mRNA)	Inhibition of FADS2 could improve the sensitivity of tumor cells to radiotherapy and block the synthesis of AA and PGE2 *in vitro* and *in vivo*.	[69, 70]
Liver cancer	Loss	--	[71]
	Upregulated (mRNA and protein)	FADS2 promoted the proliferation of cancer cells by synthesizing sapienate and used it for membrane biosynthesis of cancer cell.	[64]
Colon cancer	--	Inhibition of FADS2 could inhibit the growth of colon cancer and the synthesis of AA.	[72]
Esophageal carcinoma	Upregulated (mRNA and protein)	High expression was related to clinicopathological parameters such as late stage, lymph node metastasis, and poor prognosis. High expression promoted tumor cell proliferation, non-anchored clonal formation, migration and invasion.	[59]
Cervical cancer	Upregulated (mRNA)	--	[73]
Prostate cancer	Upregulated (mRNA and protein)	--	[64]
Renal cell carcinoma	Increased (activity)	--	[74]
Acute lymphoblastic leukemia	Increased (activity)	High activity promoted the growth of different types of leukemia cells.	[75, 76]

research and nutritional interventions for the breakdown of fatty acids, which is catalyzed by FADS2, may provide new strategies for cancer prevention and treatment.

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Disclosure of conflict of interest

None.

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