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Research Progress of Fatty Acid Synthase in Digestive Tract Tumors

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Abstract: Fatty acid synthase (FAS) is a key enzyme in the synthesis of endogenous fatty acids. It consists of two identical polypeptide chains connected in a head-to-tail manner to form a dimer, which constitutes the catalytic center of the enzyme. It is composed of seven enzymatic active domains, and catalyzes the synthesis of fatty acids by acetyl-CoA and malonyl-CoA. The main product of FAS is palmitic acid, which is not only one of the main components of the cell membrane structure, but also an important substrate for cell energy metabolism. It stores energy, synthesizes phospholipids, and participates in cell membrane structure, intracellular signal transduction and protein acylation and many other functions. In normal tissue cells, FAS is expressed at low activity, while FAS is highly expressed in many tumor tissue cells. The level of FAS activity in vivo is of great significance to fatty acid synthesis and body fat deposition. The application of FAS inhibitors can eliminate the proliferation and migration of tumor cells and become a new therapeutic target. In recent years, scholars at home and abroad have carried out a lot of research on FAS on fat synthesis, metabolic regulation and tumor tissue. This article reviews the structure, function, origin and distribution of FAS, as well as the research progress in digestive tract tumors, correctly understands the biological characteristics of FAS and its mechanism of action in tumors, and studies new FAS inhibitors, so as to provide insights into the digestive tract. The diagnosis of tumor provides a theoretical basis and new ideas for the successful prevention and treatment of tumors.

Keywords: Fatty Acid Synthesis, Biological Characteristics, Gastrointestinal Cancer

1. Introduction

The three major nutrients of the human body include carbohydrates, proteins and fats, which can be ingested through food or synthesized in the body and transformed into each other to jointly maintain various physiological activities of the body. Among them, lipids are one of the most important nutrients in the human body, including fats, lipids and their derivatives. Fat, or triglyceride, is an energy substance for the body's energy supply and storage. Lipids mainly include phospholipids, glycolipids, cholesterol, etc., which are important components of biological membranes and are mainly involved in cell recognition and information transmission. Therefore, lipid metabolism is not only related to cell energy supply, but also closely related to the maintenance of cell membrane structure and cell signal transduction. Therefore, lipid metabolism is not only related to cell energy supply, but also closely related to the maintenance of cell membrane structure and cell signal transduction. The body has a set of finely regulated lipid metabolism network, which regulates the lipid metabolism process to maintain the normal structure and function of cells [1]. A large number of research data show that lipid metabolism disorders are related to various diseases such as tumors, diabetes, and cardiovascular diseases, especially the occurrence and development of malignant tumors [2]. In recent years, the research on the relationship between lipid metabolism and tumor has received great attention from scholars at home and abroad. Fatty acid synthesis (FAS) is a key enzyme in fatty acid synthesis and plays an important role in the synthesis of endogenous fatty acids. With the deepening

of the research on the relationship between FAS and tumor, the current research on FAS has become a hot spot. In this paper, the biological characteristics of FAS and its research progress in digestive tract tumors are reviewed as follows.

2. FAS Overview

2.1. The Structure and Function of FAS

Fatty acid synthase, also known as fatty acid synthase, is a macromolecular protein complex isolated and purified from animal liver homogenate by scholars such as Wakil SJ in 1957. Its molecular weight is as high as 540 kDa. A large number of studies have confirmed that mammalian FAS is a multifunctional complex enzyme, which is a key enzyme in the synthesis of fatty acids [3], and plays a key role in the synthesis of endogenous fatty acids. FAS is located in the cytoplasm. The human FAS gene is located on the 5th region (17q25) of the long arm of chromosome 17. Its DNA is about 20kb in length, including 42 introns and 43 exons, and consists of 7512 nucleosides. The acid encodes 2504 amino acids, 2 identical 270kda peptide chains, which form dimers in a head-to-tail manner [4], constituting the catalytic center of enzymatic activity, the latter consisting of condensation, transacylation, reduction and dehydration, etc. 7 Enzyme activity domain composition. The FAS enzyme activity domain is linearly related from the C-terminus to the N-terminus, including the C-terminal enolreductase domain, the β-ketoacylreductase domain, the acyl carrier protein and the thioesterase domain, and the N-terminal β-ketoacyl acyl synthesis Enzyme domains, acetate/malonyl monoacid transferase and beta-hydroxyacyldehydratasedomains. There are also two additional non-enzymatic regions, pseudoketoreductase and pseudomethyltransferase, which may be conserved parts of the genetic methyltransferase domain and are involved in maintaining the function of some related polyketide synthases [5]. Therefore, FAS has multiple catalytic functions, among which acetyl/malonyltransferase is involved in substrate reaction, β-ketoacyl synthase is involved in synthesis reaction, and thioesterase is involved in termination reaction of carbon chain synthesis.

2.2. The Source and Distribution of FAS

There are two sources of fatty acids in the human body, one is the direct intake of exogenous fatty acids, and the other is the self-synthesis of endogenous fatty acids. Under normal circumstances, most of the fatty acids used in the synthesis of biofilms in human cells come from exogenous sources. FAS is an important synthase for the synthesis of endogenous fatty acids. The specific process of fatty acid synthesis in the body is: the basic substance is catalyzed by acetyl-CoA synthase to synthesize acetyl-CoA, and the latter is catalyzed by acetyl-CoA carboxyl pure enzyme to generate malonyl CoA, and then the reduced nicotinamide adenine dinuclear and nucleotide phosphate generating enzymes provide hydrogen, and FAS catalyzes the synthesis of long-chain fatty acids. There is obvious heterogeneity in the distribution of FAS in normal body. The higher expression of FAS is concentrated in: (1) tissues with high lipid metabolism, such as adipose tissue, liver, sebaceous glands; (2) hormone-sensitive tissues, such as breast, anterior pituitary, adrenal cortex, endometrium, prostate, seminal vesicles, etc.; (3) cells in a state of proliferation, such as gastroduodenal epithelial cells, colonic absorptive cells, proliferating epithelial cells of fetal digestive and respiratory systems [6]. In order to meet the rapid proliferation of malignant cells, in order to provide lipids for the formation of cell membranes, the de novo synthesis of fatty acids is enhanced, so FAS is highly expressed in tumor cells.

2.3. The Role and Function of FAS

The main role of FAS in the process of fat metabolism is to be responsible for the synthesis of endogenous fatty acids, and to polymerize acetyl-CoA and malonyl-CoA into long-chain fatty acids to store energy in the form of triglycerides. Under physiological conditions, human tissues mainly use exogenous fatty acids to synthesize structural lipids, and as the key enzyme in the synthesis of endogenous fatty acids, excess energy is stored in adipose tissue in the form of triacylglycerols. Synthesis is at a low level. Therefore, in normal tissue cells, FAS is in a state of low activity and low expression, and its expression is closely related to hormones, diet and growth factors [7]. The main product of FAS is palmitic acid, which is one of the main components of the cell membrane structure and an important substrate for cell energy metabolism. and protein acylation. Normal cells mainly utilize dietary lipid molecules [8]. The fatty acid metabolism of cancer cells is different from that of normal cells. The fatty acids synthesized by itself account for 93% of all fatty acids in triglycerides. According to the transfer rate of fatty acids in free fatty acids and plasma triglycerides from host cells to tumor cells, it is further clarified that The synthesis of endogenous fatty acids is an important source of fatty acids for tumor cell growth [9]. A large number of studies have shown that FAS is continuously highly expressed in aggressive tumor tissues, which is an adaptation to endogenous fatty acid synthesis and cell proliferation, and is not regulated by regulatory signals in normal cells, and self-synthesizes endogenous fatty acids to synthesize large amounts of lipids. It is used for the construction of cell membrane structure to meet the energy needs of cell proliferation and the excessive demand of tumor cells to form cell membrane lipids due to rapid proliferation of tumor cells.

3. FAS and Gastrointestinal Tumors

The digestive tract is one of the most common sites of human malignant tumors. With the change of people's diet structure and lifestyle, the incidence of digestive tract tumors is increasing year by year [10]. The results of the third retrospective sampling survey on causes of death in my country in 2008 showed that the incidence of malignant tumors increased at an average annual rate of 3% to 5%. Gastrointestinal tumors [11]. According to the latest global

cancer statistics released by the American Cancer Society in 2011, the incidence and mortality of digestive tract tumors such as esophagus, stomach, liver, and colorectum are among the top 10 in developing countries [12]. Because the early symptoms of digestive tract tumors are not typical, most of them have entered the middle and late stages when they are diagnosed, and the 5-year mortality rate of comprehensive treatment is over 90% [13], which seriously endangers human health. Therefore, early diagnosis and early treatment are the keys to improving the survival rate of patients, and the search for tumor markers with high sensitivity and specificity for early diagnosis is the focus and focus of current research. There are many commonly used clinical tumor markers of the digestive system, but the sensitivity and specificity are not ideal. Therefore, it is of great clinical value to find tumor markers with ideal prognosis for early diagnosis or monitoring [10]. In recent years, the detection of FAS expression and serum level in gastrointestinal tumor tissue has been carried out clinically, which has opened up a new way for the diagnosis and prognosis detection of gastrointestinal tumors.

3.1. FAS and Esophageal Cancer

Esophageal cancer (EC) is one of the ten most common malignant tumors in the world and one of the leading causes of tumor-related death worldwide [14]. The global statistical report of the International Center for Cancer Research shows that in 2020, there will be 604,000 new cases of esophageal cancer worldwide, and the standardized incidence rate of the world's standard population is 63/10,000, ranking 8th in the world in the incidence of malignant tumors. The number of deaths from esophageal cancer increased to 544,000, ranking sixth in the global cancer death spectrum. In 2020, the crude death rate of esophageal cancer was 7.0/10,000, and the world standardized population death rate was 5.6/10,000 [15]. China is a high-incidence area of esophageal cancer, more than 90% of which are squamous cell carcinoma. In 2020, there will be 324,000 new cases of esophageal cancer, accounting for more than 50% of the new cases in the world. The standardized incidence rate of the world standard population is 13.8/100,000. It ranks sixth in the incidence of malignant tumors in China; in 2020, the number of new esophageal cancer deaths in China will be 301,000, accounting for more than 50% of global deaths. 4th cause of death. The number of esophageal cancer incidence and deaths in my country is 477,900 and 375,000 respectively, ranking first in the world. Esophageal squamous cell carcinoma (ESCC) is the main histological subtype of esophageal cancer, accounting for 5% of EC. more than 90 percent. The occurrence and development of esophageal cancer is a multi-step and multi-stage process, which is related to the activation or function enhancement of proto-oncogenes, the inactivation or loss of function of tumor suppressor genes, apoptotic genes and abnormal DNA repair. Although progress has been made in surgical treatment, chemoradiotherapy, and targeted therapy, the prognosis of ESCC patients remains poor. Therefore, it is very important to find more effective prognostic indicators for ESCC patients, among which molecular marker research and intervention of cancer cells have always been an effective means of tumor diagnosis and treatment.

Nemoto et al [16] used immunohistochemistry to detect the expression of FAS in 80 cases of ESCC, 6 cases of other types of esophageal cancer, 14 cases of dysplastic esophagus lesions and 4 cases of normal esophageal mucosal tissue, and found that FAS only occurs in the stroma of normal esophageal mucosal tissue. It is weakly expressed in the cytoplasm of the layer of esophagus, and is obviously expressed in dysplasia and esophageal cancer tissues. Its positive expression rate is 92.9% and 96.5%, respectively. FAS can be detected in almost all esophageal cancer tissue cells, and its high expression is similar to that of esophageal cancer. The pathological features of esophageal cancer have nothing to do with prognosis, indicating that FAS may be involved in the whole process of esophageal cancer from early to middle and late stages. RuanZheng et al [17] reported that the positive expression rate of FAS in esophageal cancer tissues was 78% (35/45), of which 23 cases were positive, 9 cases were strongly positive, and 3 cases were very strong; 6 cases were moderate, The positive rate of esophageal mucosa with severe dysplasia was 50%, with 2 cases of positive expression and 1 case of strong positive expression; 10 cases of normal esophageal mucosa of 12 cases were negative for FAS, and 2 cases were weakly positive. The results showed that the expression of FAS in esophageal cancer tissues was significantly increased, which was significantly different from that of dysplasia and normal esophageal mucosa ($P<0.01$), but had nothing to do with tumor size, lymph node metastasis and clinical stage. It is suggested that FAS may play an important role in the carcinogenesis of esophageal squamous cells. Ishimura et al [18] reported that FAS is highly expressed in Barrett's esophageal lesions and is associated with clinicopathological features, suggesting that abnormal expression of FAS may be one of the mechanisms leading to the pathogenesis of esophageal cancer. Zhou et al. [19] found that FAS is mainly located in the esophageal cancer cell cytoplasm, while the normal esophageal mucosa is not stained. The positive rate of ESCC is 95.0% (57/60), of which the high expression rate is 31.7%, which is similar to that of normal esophageal mucosa. There was a significant difference in expression ($P<0.05$). Wu et al. [9] transfected chemically synthesized FAS small interfering RNA (siRNA) with liposome Lipofectamine2000 into human esophageal cancer TE13 cell line, and detected FASN mRNA expression by reverse transcription-polymerase chain reaction (RT-PCR). Blot detection of FAS protein expression and the expression of cell proliferation-related protein CCND1 after siRNA interference, CCK-8 detection of cell proliferation, and transwell assay to detect cell migration ability. It was found that the FAS gene and protein levels of esophageal cancer TE13 cell line were higher than those of normal esophageal epithelial cells, and FAS gene and protein levels were significantly down-regulated after FAS-siRNA transfection ($P<0.05$), which could significantly inhibit the migration ability of TE13 cells ($P<0.05$). It is suggested that the application of FAS-siRNA in vitro can inhibit the expression of FAS in esophageal cancer cells, thereby

inhibiting their proliferation and migration, becoming a new target for FAS-targeted therapy for esophageal cancer. The application of synthetic FAS inhibitor C75 can significantly inhibit and induce apoptosis of ESCC TEl3 cell line [19]. The above research results show that the expression of FAS in esophageal cancer tissue is significantly increased and may play an important role in the occurrence and development. C75 inhibitor can significantly inhibit the proliferation of tumor cells and induce apoptosis, which may provide a new target for the treatment of esophageal cancer. point. However, there is no report on the correlation between serum FAS levels and esophageal cancer.

3.2. FAS and Gastric Cancer

Gastric cancer (GC) is one of the most common malignant tumors in the digestive tract, and its morbidity and mortality are second only to lung cancer. The incidence of GC in my country is relatively high. In 2015, the incidence and mortality of GC were as high as 679.1/100,000 and 4.980/100,000, respectively, and the age of onset showed a younger trend. Due to the insidious early symptoms, most patients are already in the middle and late stages at the time of diagnosis. Local invasion and distant metastasis lead to poor treatment effect and prognosis. The 5-year survival rate is 20% lower, which seriously affects human health and the quality of life of patients [20, 21]. In recent years, clinical studies have been carried out on the relationship between the expression of FAS in tissue and serum of GC patients, diagnosis and treatment and prognosis, but the results are not the same.

Kusakabe et al [22] performed immunohistochemical staining on 626 cases of GC, 51 cases of gastric adenomas and adjacent normal mucosal tissues, and found that more than 70% of GC tissues were positive for FAS, especially in well-differentiated, male and over 51-year-old patients. FAS was highly expressed in well-differentiated GC-related gastric tubular adenomas and intestinal metaplasias, while no or low expression of FAS was found in paracancerous mucosal tissues. It indicated that the expression of FAS is closely related to the occurrence and development of gastric cancer, which can occur in the early stage of the tumor and precancerous lesions, but has nothing to do with the depth of tumor invasion, vascular and lymphatic distant metastasis and prognosis. Ito et al [23] detected serum FAS levels in 47 GC patients and 150 healthy controls by ELISA, and found that serum FAS levels in GC patients were significantly higher than those in healthy controls, with 95% CIs of 30.37-52.46 and 1.331-2.131, respectively. Taking serum FAS=6.0ng/ml as the best critical value for the diagnosis of GC, its sensitivity and specificity were 93.62% and 93.33%, respectively, and its sensitivity was higher than that of commonly used markers of CA199 and CA724, and serum FAS of early GC patients Levels also increased. Lin et al [24] reported that the serum FAS level [(5.25±0.48) ng/mL] in 53 GC patients was significantly higher than that in 52 chronic superficial gastritis [(3.24±0.37) ng/mL] and 51 healthy controls. Group [(2.82±0.28) ng/mL] ($P<0.05$). Taking serum FAS=3.78ng/mL as the best critical value for diagnosing GC, the ROC curve analysis showed that the serum FAS [(5.83±1.37) ng/mL] level in 29 patients with stage III and IV GC was significantly higher than that in 24 patients with I. and stage II [(4.04±0.35) ng/mL] ($P<0.05$). 10 patients had serum FAS>3.78ng/mL before surgery, of which 7 patients had decreased to below 3.78ng/mL after surgery ($P<0.05$). It is suggested that the increase of serum FAS level is related to the occurrence and development of GC, and the detection of serum FAS content is helpful for the diagnosis and follow-up of GC.

Hu et al [25] detected serum FAS and pepsinogen (PG) levels in 74 cases of GC, 45 cases of benign gastric disease and 75 cases of healthy controls by ELISA and immunoturbidimetry, and found that the ratio of serum PGI and PGI/PGII in GC patients decreased., serum FAS was significantly increased, and the difference was statistically significant compared with the control group ($P<0.05$). Combined detection of PG and FAS, the area under the ROC curve was 0.972, and the sensitivity and specificity of GC diagnosis were 95.50% and 92.32%, respectively, which were higher than those of the two alone. It is suggested that the combined detection of serum PG and FAS can improve the diagnostic efficiency of GC and contribute to the early diagnosis of GC. Li [26] detected serum FAS levels in 30 cases of GC, chronic atrophic gastritis (CAG), other digestive tract tumors (ODT) and healthy control groups, and found that serum FAS levels in GC patients were significantly higher than those in the control group ($P< 0.01$), also higher than the CAG group ($P < 0.05$), and the difference in FAS between the GC group and the CAG group was also statistically significant ($P < 0.05$). However, there were no significant differences in FAS levels between the GC group and the ODT group, between the ODT group and the CAG group, and between the ODT group and the CAG group and the control group ($P>0.05$). The results showed that serum FAS levels in GC patients were significantly increased and could be differentiated from CAG patients, but there was no significant difference in FAS levels between GC patients and ODT patients. Duan et al [27] analyzed the correlation between FAS expression and clinicopathology in 167 GC patients by immunohistochemistry, and found that FAS overexpression was associated with overall survival [P=0.008, hazard ratio (HR) 4.412, 95% confidence interval (CI) 1.463-13.305] and the recurrence rate (P=0.014, HR 1.705, 95% CI 1.116-2.606). FAS protein in GC tissue was associated with age (P=0.032), clinical stage ($P<0.001$), gastric wall invasion (P=0.014), lymph node metastasis ($P<0.001$) and distant metastasis ($P<0.001$), FASN mRNA and The protein level was overexpressed in GC tissue, and there was a significant difference compared with adjacent non-cancerous tissue ($P<0.05$), but no gender difference ($P>0.05$). The results showed that the expression of FAS in GC tissue was higher than that in normal control tissue, and was closely related to tumor clinical stage, pathological grade, and overall survival. In conclusion, the expression level of FAS in GC tissue is closely related to the clinical stage, pathological grade and overall survival of GC. As a biomarker of GC, serum FAS

level has high sensitivity and specificity, and has a good value for the diagnosis of GC, and the tumor starts to increase in the early stage, which is expected to become an indicator for early screening, diagnosis and prognosis of GC. It plays an important role in the diagnosis and treatment of GC.

3.3. FAS and Liver Cancer

Hepatocellular carcinoma (HCC) is the most common pathological type of primary hepatocellular carcinoma (PHC), which ranks the second in the mortality of malignant tumors in the world. The incidence of HCC has been increasing in recent years. Human life and health are seriously threatened due to active angiogenesis, rapid proliferation, high propensity for metastasis, recurrence and poor prognosis [28]. Using RNA as a template, Xu et al [29] found that mRNA content in HCC tissues was significantly higher than that in adjacent normal tissues ($p < 0.05$) by RT-PCR reaction and gel imaging system analysis, the results showed that the levels of FAS nucleic acid and protein in hepatoma cells were significantly higher than those in normal hepatoma cells, and the over-expression of FAS suggested that the hepatoma cells had an enhanced ability to synthesize endogenous fatty acids. It was confirmed that the expression of FAS was abnormally high in HCC tissues and human highly metastatic hepatocellular carcinoma cell line HCCLM3, and with the increase of the expression level, FAS directly affected the proliferation and growth of HCC cells. C75 could inhibit the growth of hepatoma cells. With the increase of concentration of C75, the expression of FAS in hepatoma cells and the proliferation of hepatoma cells were obviously decreased, which indicated that the expression of FAS was abnormally high in primary hepatoma cells, it can promote the Fatty acid metabolism of hepatoma cells, accelerate the proliferation and growth of hepatoma cells, and provide relevant targets and new clues for the study of its therapy and pathogenesis. Liu et al [30] used ELISA to detect serum AFP and FAS levels. The results showed that serum AFP levels were elevated in 75.0% (45/60) of HCC patients and FAS expression was significantly up-regulated in 71.7% (43/60) of HCC patients, the level of AFP (36.83±10.52) mg/L was significantly higher than that of the control group (11.3±7.21) mg/L ($p<0.05$). 91.7% (55/60) of AFP levels were increased and/or FAS expression was up-regulated. FAS expression was up-regulated in 33 (73.3%) of 45 serum AFP-positive HCC patients (33/45) and in 10 (76.9%) of 15 serum AFP-negative HCC patients (10/15). It is suggested that the increase of serum FAS expression may be related to the invasion and metastasis of tumor cells. The combined detection of FAS and AFP can obviously increase the detection rate of HCC and may increase the early diagnosis rate of HCC. χ^2 test showed that there was no significant correlation between up-regulation of FAS expression and AFP level. It is suggested that serum FAS may be a new marker for early diagnosis and prediction of metastasis of hepatocellular carcinoma, and may be one of the molecular targets for the prevention and treatment of hepatocellular carcinoma. Hao et al. [31] found that Fas was highly expressed in HCC tissues and HCC cell lines, and the expression of FAS in high metastatic HCC cell lines was significantly higher than that in low metastatic HCC cell lines. Fas could promote the proliferation, invasion and migration of HCC cells, it is suggested that FAS may be involved in the occurrence and metastasis of HCC. Inhibition of FAS expression inhibited cell proliferation, migration and invasion, but had no effect on apoptosis of HCC cells. Inhibition of FASN expression may be a promising approach for the treatment of HCC [32]. Animal experiments have found that pharmacological blockade of Fas expression in mouse liver cancer can activate Akt signaling pathway and inhibit tumor growth, which may provide a new theoretical basis for the treatment of liver cancer [33]. In vitro studies have been performed on the full range of gene expression, lipid profiles, and human HCC cell lines from wild-type and Fas knockout mice with sgPten/c-MetHCC [34]; It was found that FAS ablation could significantly delay the hepatocarcinogenesis induced by SGPT/c-Met in mice. Blockade of cholesterol synthesis by a dominant-negative form of Srebp2 (dnSrebp2) completely prevents the development of hepatoma driven by FAS Spgten/c-Met in knockout mice; FAS silencing induced SREBP2 activation and increased expression of hydroxyl-3-methyl-glutaryl-CoA (HMG-CoA) reductase (HMGCR) in human HCC cell lines. Inhibition of FAS-mediated Fatty acid synthesis and HMGCR-driven cholesterol production can affect the growth of HCC cells. It is suggested that abnormal fat and cholesterol biosynthesis may influence each other's biosynthetic pathway of hepato-carcinogenesis, and their concomitant inhibition may be a new method for the treatment of HCC.

3.4. FAS and Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is the main type of pancreatic cancer, accounting for 80%~90%. Its incidence ranks 10th among all malignant tumors, but its mortality ranks 4th, and it isexpected to jump to 2nd by 2030 [35]. Pancreatic cancer is one of the malignant tumors with the highest malignant degree and the worst prognosis in the digestive system. From 2005 to 2015, the incidence and mortality of pancreatic cancer in males in my country were higher than those in females, and higher in urban areas than in rural areas [36]. According to the 2020 cancer statistics, new cases of pancreatic cancer worldwide account for the 14th place in all malignant tumors, accounting for 2.6% of new malignant tumors. Based on the public data of the 2019 Global Burden of Disease Study (GBD2019), using Joinpoint software to analyze the trend of incidence and mortality of pancreatic cancer, it was found that the incidence and mortality of pancreatic cancer in my country showed a significant upward trend from 1990 to 2019, especially among men and the elderly, bviously [37]. Pancreatic cancer is also the seventh leading cause of death from malignant tumors in both men and women worldwide, with a 5-year survival rate of only 9% [38]. This is related to late discovery and easy transfer [39]. Walter et al [40] reported that FAS protein was overexpressed in the ductal epithelium of primary pancreatic cancer and intraductal papillary mucinous neoplasm (IPMN) [(86.0%, 343/399) VS

(28/30, 93.3%)], the expression rate of islet and ductal cells in chronic pancreatitis tissue was 5.6% (3/54), while the normal ductal epithelium had no FAS expression. The serum FAS (ng/mL) levels in 102 pancreatic adenocarcinomas, 42 IPMNs, 27 chronic pancreatitis and 39 healthy controls were 22.0±4.5, 20.7±9.4, 31.1±11.9 and 0±0, respectively, which were all significantly higher in the healthy control group. Preoperative serum FAS was elevated in 9 patients with pancreatic cancer, and FAS level decreased in 8 patients after operation. Serum FAS levels are elevated in pancreatic cancer and IPMN patients and are associated with tumorigenic overexpression of FAS. High-level expression of FAS contributes to the diagnosis of pancreatic cancer [41]. Bian et al [42] found that patients with abnormally high expression of FAS in PDAC tissue had a poor prognosis. Knockout or inhibition of endogenous FAS gene can inhibit the proliferation of PDAC cells and promote their apoptosis. With the increase of C75 concentration, the inhibitory effect on FAS was enhanced, the expression of FAS protein in pancreatic cancer cells was significantly decreased, and the level of apoptosis was increased. The level of Caspase-3 in the C75-treated group was significantly higher than that in the control group, while the level of Bcl-2 decreased ($P<0.05$) [43]. It is suggested that FAS participates in the process of apoptosis in pancreatic cancer cell line PANC-1 through Bcl-2 and Caspase-3 molecules. Many studies have shown that abnormal lipid metabolism and FAS expression in pancreatic cancer are related to its drug resistance, indicating that FAS may become an effective target for diagnosis, treatment and prognosis [41]. By interfering with FAS, inhibiting the growth of pancreatic cancer cells may provide a new drug target for treatment.

3.5. FAS and Intestinal Cancer

Colorectal cancer (CRC) is a common malignancy with more than 1.8 million new cases (ranked 4th) and 860000 deaths (ranked 2) worldwide each year [44]. In recent years, the incidence and mortality of malignant tumors in China have been increasing year by year, and they have become the leading cause of death among Chinese residents. According to a tumor registry data in 2015, CRC is the malignant tumor with the fastest increasing incidence and mortality in China in the past decade, and its morbidity and mortality ranks third among all types of cancer [45]. In 2018, the standardized incidence of CRC in China was 23.7/100,000 (ranking third), and the standardized mortality rate was 10.9/100,000 (ranking fifth) [44]. The incidence of colon cancer in my country has been increasing year by year and has become younger, from 12 cases/100,000 in the 1970s to 56 cases/100000 in 2015, with an average annual growth rate of 4.2%, significantly higher than the international level [46]. Although the mortality rate of colon cancer has decreased significantly in the past 20 years and ranks 4th among the global causes of cancer-related death, the incidence rate is still high, and the incidence of CRC has increased by 2 to 4 times. Invasion and metastasis are also important causes of death [21]. Therefore, finding key genes affecting colon cancer has become a reliable means of long-term colon cancer treatment.

Rashid et al [47] reported that the FAS positive, positive and weak positive rates in 130 colon cancer tissues were 53%, 38% and 9%, respectively. Scattered adenomas, family-related adenomatous polyps and hyperplastic polyps also expressed FAS. increased, while normal colonic mucosa stained only weakly with FAS. It shows that FAS is not only expressed in malignant tumors, but also in precancerous lesions. It was also found that the FAS enzyme activity in the cancer tissue was 2-7 times that of the surrounding tissue ($P=0.006$), and 6-16 times that of the mesenteric tissue ($P=0.01$). The enzyme activity was significantly correlated with the positive expression of immune-histochemistry (Spearinan grade). Correlation coefficient = 0.85, $p < 0.001$). FAS has enzymatic activity in tumor cells, and its overexpression suggests that tumor cells synthesize endogenous fatty acids increased. In poorly differentiated carcinomas or those with more than four lymph node metastases, the strong positive rate of FAS tends to increase, but there is no statistical significance between the survival time of patients and the intensity of FASstaining. Notarnicola et al [48] used ELISA to detect serum FAS levels in 67 CRC patients, and used the Kruskal-Wallis test and χ^2 trend analysis to analyze the levels of 14.46±10.43 ng/mL for stage I-II and 23.0±12.07 ng/mL for stage III, IV was 34.24±11.88 ng/mL, and there were significant differences in FAS levels among the three groups. The serum FAS levels in stage III and IV were significantly higher than those in stages I-II ($P=0.003$). The serum FAS level increased from stage I-II to stage III-IV ($p = 0.001$), suggesting that the level of FAS is related to the pathological grade of colorectal cancer.

Lu et al. [49] analyzed the relationship between serum FAS levels and clinicopathological characteristics of CRC patients and found that serum FAS levels in CRC (20.77±10.56 mg/L) were significantly higher than those in healthy controls (10.33±5.65 mg/L). Statistical significance ($P<0.05$), the FAS levels in stages I-II, III and IV were 13.24±11.43, 24.20±11.87 and 35.44±12.18mg/L, respectively, and the differences between the groups were statistically significant ($P<0.05$), with the progression of tumor stage, the level of FAS increased ($P=0.001$). The FAS levels of patients with high, moderate and low differentiation were 16.46±10.58, 20.38±11.87 and 25.84±10.88 mg/L, respectively. The higher the degree of tumor differentiation, the lower the FAS level, but the difference was not statistically significant ($P>0.05$). The results showed that serum FAS levels may have a certain relationship with the occurrence and development of colorectal cancer. Long et al [50] reported that the serum FAS level in CRC patients was significantly higher than that in healthy controls, and there was a significant difference between the two groups. The serum FAS level was related to tumor extent, lymph node and distant metastasis, and clinical stage. The 5-year overall survival rate and 5-year disease-free survival rate of patients with low serum FAS level were significantly higher than those of patients with high serum FAS level ($p=0.003$). Elevated serum FAS levels are an independent predictor of advanced colorectal cancer and shorter survival and may be a potentially useful tumor marker.

Zaytseva et al [51] found that high expression of FAS was associated with advanced CRC and liver metastasis, suggesting that it may play a role in the progression of CRC to metastatic disease and is likely to be involved in distant metastasis of rectal cancer. Ogino et al [52] et al used two independent cohorts to study the association between body mass index (BMI) and CRC risk in 647 patients. Univariate and multivariate analysis found that FASN overexpression was associated with a significant reduction in colon cancer mortality. The effect of BMI on mortality was different, with adjusted mortality of 0.63 for patients with BMI less than 27.5 kg/m^2 and 2.91 for patients with BMI≥27.5 kg/m^2. The adverse effect of moderate overweight/obesity on overall survival was limited to FAS-positive individuals. In non-obese colon cancer patients, FAS overexpression in tumor tissue was associated with improved survival, while in moderately overweight or obese patients (BMI ≥ 27.5 kg/m^2), FAS overexpression may predict decreased survival. Increased FAS expression in rectal cancer patients was associated with increased mortality in rectal cancer patients with high BMI, but not in patients with low BMI. Crispino et al [53] found that the high expression of FAS in CRC tissues easily leads to lymphatic and distant metastasis and more advanced clinical phenotypes. In the CRC cohort, there was a positive correlation between FSA expression and Wnt signaling marker gene expression. Knockout of FAS in SW480 and HT29CRC cell lines inhibited cancer cell proliferation by down-regulating unique genes (Wnt5a, Wnt5b, Fzd2) of the Wnt signaling pathway. Invasion and metastasis. It is suggested that FSA is a key factor in the process of CRC carcinogenesis and becomes a potential therapeutic target. Kuchiba et al [54] explored the association of BMI with CRC risk by following up the expression of FAS in 1351 rectal cancers in 109051 prospectively studied women. The age-adjusted risk of CRC was found to be related to whether FAS was positive or not. The incidence of FAS-positive and FASN-negative were 10.9 and 7.1 per 100,000 people/year, respectively, and the difference between the two groups was statistically significant (p=0.033). It is suggested that the overexpression of FAS is also closely related to rectal cancer.

Wang et al [55] found that FAS was abnormally overexpressed in both CRC tissues and cell lines, resulting in lymph node and distant metastasis and a more advanced clinical phenotype. Using shRNA interference technology, the FAS gene in CRC cell lines SW480 and HT29 was knocked out. By down-regulating Wnt5a, Wnt5b, Fzd2 and other specific genes, the Wnt signaling pathway was weakened, and the migration and invasion of colorectal cancer cells were significantly inhibited, and tumor metastasis was slowed down. There was a positive correlation between FAS and Wnt signaling marker gene expression in 43 colorectal cancer tissues. Lee et al [56] used western blotting and reverse transcription-PCR to detect FAS gene and protein expression, and explored the regulatory effect of emodin on FAS gene expression and enzymatic activity in human colon cancer cell lines, and found that emodin significantly down-regulated human colon cancer HCT116 The expression of FAS protein in the cell line significantly inhibited the proliferation of HCT116 cells, and the expression of FAS protein was higher. Emodin also inhibited intracellular FAS enzymatic activity, decreased free fatty acid levels, and enhanced anti-proliferative and apoptotic effects in a dose and time-dependent manner. Emodin also alters signaling pathways including phosphatidylinositol 3-kinase/AKT and mitogen-activated protein kinase/extracellular signal-regulated kinase FSN. The results suggest that emodin can mediate cell growth and apoptosis by inhibiting the expression of FAS, providing a molecular basis for the treatment of colon cancer. The results of clinical and experimental studies show that FAS is a key factor in the occurrence and development of CRC, and inhibiting the expression of FAS opens up a new way for the treatment of CRC.

4. Conclusion

The results show that abnormal lipid metabolism is closely related to the occurrence and development of tumors. Many research have shown that the levels of FAS in many malignant tumor tissues and serum are elevated, and there is an increasing trend in the early stage of some digestive tract tumors, which indicates that FAS plays an important role in the formation of early digestive tract tumors, so it can be used for can be used for early diagnosis. The expression level of FAS is also closely related to tumor progression, pathological grade, the presence or absence of lymph node or distant metastasis, and survival. Therefore, the expression level of FAS can be used to judge the prognosis of digestive tract tumors. Serum FAS level changes synchronously with clinical stage and survival period, and serum FAS level is simpler and easier to detect than FAS expression in tumor cells, suggesting that serum FAS can be used as an important independent predictor for evaluating tumor invasiveness, and dynamic monitoring can be used to judge the digestive tract Tumor progression and prognosis, especially for patients after radical tumor surgery, can be used as effective indicators to evaluate postoperative efficacy. The results of clinical and experimental studies show that FAS is a key factor in the process of tumorigenesis and development, and its expression regulation in tumor tissue is a complex process. By controlling FAS gene transcription, controlling RNA stability and its translation level to regulate gene expression, the research on effectively controlling the synthesis of fat in the body in tumors is bound to make a breakthrough. At present, although the biological significance and role of tissue and serum FAS levels in digestive tract tumors are still unclear, further exploration of its expression regulation mechanism and research on new FAS inhibitors will provide theoretical basis and new drug targets for tumor prevention and treatment of tumor.

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