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Recent Advances in Fibrinogen Research in Colorectal Cancer

Wenjing Jiang[1], Di Wang[1], Junyan Yu[2*]

[1]Changzhi Medical College, Changzhi, China
[2]Department of Oncology, Heping Hospital of Changzhi Medical College, Changzhi, China
Email: *hanbing398@163.com

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Abstract

Colorectal Cancer (CRC) is a common malignant tumour of the gastrointestinal tract in China, with increasing morbidity and mortality rates year by year. Most patients are in the middle and late stage when diagnosed, and its high mortality and poor prognosis have seriously threatened the health and life. Fibrinogen (FIB) is mainly used as a coagulation factor in the body to participate in the process of coagulation and haemostasis, and is the main protein in the coagulation process. In recent years, studies at home and abroad have shown that FIB levels correlate with the diagnosis, outcome prediction and prognosis of CRC, and some of the findings are still controversial. This article aims to review the related research and new progress of the relationship between FIB and CRC in recent years.

Keywords

Fibrinogen, Colorectal Cancer, Coagulation Function

1. Introduction

According to the 2020 China Cancer Statistics Report, Colorectal Cancer (CRC) incidence and mortality in China ranked 2nd and 5th among all malignant tumours, with 555,000 new cases and 286,000 deaths, respectively, and the overall incidence and mortality of CRC in China showed an obvious upward trend [1]. The search for effective indicators for CRC diagnosis, efficacy prediction and prognostic assessment can help in early clinical diagnosis, dynamic monitoring and early intervention in CRC recurrence or metastasis, thus improving patient outcomes and prognosis. It has been reported in the literature that tumour cells can activate the coagulation and fibrinolytic systems of the body, and patients with malignant tumours often have varying degrees of coagulation abnormali-

ties, and coagulation disorders may be the first sign of malignancy [2]. The hypercoagulable state of blood in patients with malignant tumours may be associated with tumour invasion and metastasis [3]; Adams found a close relationship between fibrinogen (FIB) and the growth and metastasis of colorectal cancer [4]. This article summarizes the progress of research related to FIB and CRC as follows.

2. Structure and Function of the FIB

FIB is a glycoprotein with coagulation function produced by hepatocytes, a precursor of fibrin, with a molecular weight of 340 kD and a molecular length of about 450 A. FIB is a covalent dimer containing two identical subunits, each subunit consisting of three peptide chains, α, β and γ, which are connected by disulfide bonds. The two subunits combine at the N-terminus of the peptide chain through disulfide bonds to form an intermediate globule, which consists of the six N-termini of two alpha chains, two beta chains and two gamma chains, and the N-termini of the six peptide chains combine to form two strands of a coiled helix structure. FIB consists of a central structural domain and two symmetrical structural domains, the central structural domain of FIB is called the E structural domain and contains the N-termini of the six peptide chains. The globular domain formed from the two strands of the E structural domain is called the D structural domain (**Figure 1**) [5] [6]. The three peptide chains of FIB are encoded by the FGA, FGB and FGG genes located in a 50 kb region on chromosome 4 (4q31.3-q32.1), with the beta chain encoded by FGB being the rate-limiting step in the synthesis of the FIB molecule and an important factor in the level of FIB [7] [8].

FIB is a sensitive indicator of the fibrinolytic system and hypercoagulability. During coagulation, FIB is transformed into stable fibrin by thrombin and encapsulates the blood's tangible fractions to form a solid thrombus. In addition, numerous studies have found a close association between FIB and malignancy. FIB regulates the expression of E-calmodulin and waveform proteins through the Akt/mTOR signalling pathway, inducing epithelial-mesenchymal transition (EMT), thereby enhancing the ability of tumour cells to proliferate, infiltrate and metastasise [9]. FIB interacts with vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2) can enhance the pro-angiogenic effect of VEGF and FGF-2, thereby promoting tumour neovascularisation [10].

3. FIB and Colorectal Cancer

Malignant tumour cells secrete VEGF, tissue factor (TF), cancer procoagulant (CP) and tumour necrosis factor (TNF) leading to a hypercoagulable state of blood and increased plasma FIB levels [11]. FIB forms fibronectin through a series of reactions and acts as a scaffold for the growth, infiltration and metastasis of malignant tumour cells [4] [12]. Palumbo [13] found that the incidence of metastasis was significantly reduced in FIB-deficient mice, but primary tumour growth was not affected. In contrast, Adams concluded that colon cancer growth

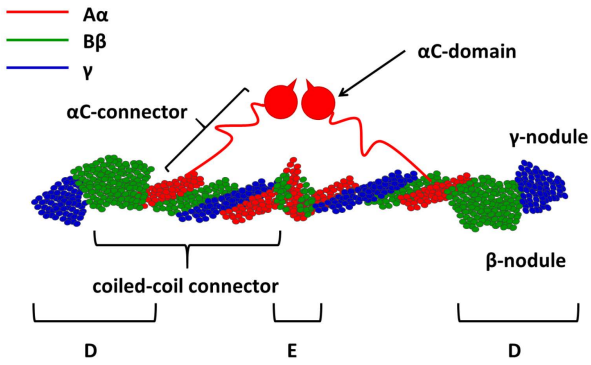

Figure 1. Fibrinogen model diagram [6].

and metastasis were significantly reduced in FIB-deficient mice [4]. A recent study [14] found that FIB promotes ubiquitination of the tumour suppressor P53 by activating adherens spot kinase (FAK), leading to reduced expression of the P53 downstream genes P21 and 14-3-3σ, ultimately leading to accelerated tumour cell proliferation and inhibition of tumour cell senescence, suggesting that inhibition of the interaction between FIB and FAK may inhibit tumour progression and therefore may be a potential therapeutic potential therapeutic target. Fibrinogen-like protein 2 (FGL2), a member of the FIB family involved in the regulation of coagulation as well as immunomodulatory functions, has been found to be upregulated in CRC tissues, suggesting that FGL2 may be related to the pathogenesis of CRC, where the mitogen-activated protein kinase (MAPK) signaling pathway is activated in CRC patients, and the MAPK signaling pathway promotes the proliferation, migration and invasion of CRC cells by regulating FGL2 expression, resulting in upregulation of its expression level, thereby promoting proliferation, migration and invasion of CRC cells [15]. Therefore, inhibition of FGL2 expression may serve as a potential therapeutic target for the treatment and prevention of CRC metastasis.

Steinbrecher [16] found that the interaction of FIB with leukocyte integrin αMβ2 promotes the progression of colitis and colitis-associated colon cancer (CAC) by establishing a mouse model, and also leads to altered inflammatory cell function in tumour tissue, thereby promoting the growth of colonic adenomas. Therefore, this study suggests that selective blockade of FIB interaction with leukocyte integrin αMβ2 is both an effective anti-inflammatory and reduces the growth of adenomas. It has been reported in the literature [17] that the frequency of FGBβ-148T allele and mutant gene in CRC patients were higher than that in normal controls, and the frequency of -148T allele in CRC patients and healthy controls was 30.9% and 17.6%, respectively. The FIB concentration of the mutant type carrying -148T gene in the metastatic group and the non-metastatic group of CRC patients was higher than that of the wild type. In the tumor metastasis group, the FIB concentration of the mutant type and the wild type were 3.83 ± 1.10 g/L and 3.22 ± 1.05 g/L, respectively. In the non-metastasis group, the FIB concentration of mutant and wild type was 3.71 ± 1.25 g/L and 2.87 ± 0.51 g/L, respectively. The results suggest that FGBβ-148C/T polymorphism may

be one of the reasons for the change of FIB concentration in CRC patients. Some scholars examined the plasma FIB concentration and gene polymorphism at the FGBβ-148C/T locus in elderly progressive colorectal cancer, and found that the altered polymorphism at the FGBβ-148C/T locus may be one of the causes of the elevated FIB concentration in elderly progressive colorectal cancer patients, and the probability of thrombotic events was higher in the mutant group, but the association of this locus with patient prognosis has not been confirmed correlation [18].

3.1. FIB and CRC Diagnosis

Most clinical studies have confirmed the value of FIB in differentiating CRC from benign colorectal disease, contributing to the early detection and diagnosis of CRC. A single-centre prospective cohort study showed that preoperative FIB levels helped to differentiate CRC from benign adenoma [19]. Chen Yu [20] also concluded that FIB has some value in differentiating colon cancer from benign colon lesions, and that FIB has a diagnostic efficacy comparable to that of carcinoembryonic antigen (CEA) and carbohydrate antigen199 (CA199), and that the combination of FIB, neutrophil-to-lymphocyte ratio (NLR), CA199 and CEA can improve the diagnostic efficacy of colon cancer. Zhou Ting [21] showed that FIB in the serum of CRC patients was significantly higher than that of colorectal polyps and healthy controls, while the difference between the colorectal polyp group and healthy controls was not statistically significant. One study found [22] that FIB was more sensitive than CEA and CA199 in identifying benign and malignant colorectal diseases. Tingting Lu [23] compared the positive rate of FIB in serum of CRC patients with that of tumour markers and found that the positive rate of FIB was lower than that of CEA and higher than that of carbohydrate antigen 125 (CA125), carbohydrate antigen 724 (CA724), carbohydrate antigen (CA153) and alpha-fetoprotein (AFP.) It has been reported in the literature that FIB, platelet to lymphocyte It has been reported in the literature that FIB, platelet-to-lymphocyte ratio (PLR) has some predictive value in colorectal inflammation-cancer transition in elderly patients, and the combination of FIB, PLR and CEA can improve the detection rate of CRC in the elderly [24].

A study [25] showed that FIB levels in patients with CRC with concurrent peritoneal metastases were higher than those in patients without peritoneal metastases, suggesting that FIB ≥ 4.13 g/L is valuable for the diagnosis of CRC with concurrent peritoneal metastases and may help clinicians provide some guidance for the early preoperative diagnosis and surgical planning of CRC patients. A recent study [26] found that serum levels of FIB and fibrinogen to albumin ratio (FAR) were significantly higher in patients with CRC than in patients with colorectal adenoma, and that a predictive model for the diagnosis of CRC using FAR is valuable for differentiating colorectal adenoma from CRC. Preoperative fibrinogen to pre-albumin ratio (FPR) has certain guiding significance in distinguishing early CRC from benign colorectal polyps. FPR can be used to identify patients with stage II CRC with a high risk of clinical recurrence. In addition,

FPR combined with CEA can improve the diagnostic efficacy of early CRC [27]. The sensitivity of FPR in diagnosing CRC is greater than that of CEA and CA199, but the specificity is lower than that of CEA and CA199, and the combination of the three improves the diagnostic efficacy [28].

3.2. Judgement of FIB on the Efficacy of Chemotherapy

Chemotherapeutic drugs can lead to apoptosis of tumour cells and endothelial cells and release of cytokines, resulting in increased release and activity of tissue factor (TF), leading to abnormal coagulation and increased FIB levels [29]. The blood of tumour patients is often hypercoagulable, which leads to reduced blood flow and slower entry of drugs into tumour cells, thus affecting the efficacy of chemotherapeutic drugs [30]. The efficacy of chemotherapy for CRC is often assessed by reference to the response evaluation criteria in solid tumours (RECIST) [31]. It can be classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The specific evaluation criteria are as follows: CR: disappearance of the target lesion and reduction of the short diameter of all pathological lymph nodes (either target or non-target lymph nodes) to less than 10 mm; PR: reduction of the total diameter of the target lesion by more than 30% of the total diameter of the target lesion using the sum of the baseline diameter of the target lesion as a reference; SD: the sum of the smallest diameters of the target lesion as a reference, the degree of reduction does not meet the criteria for PR and the degree of increase does not meet the criteria for PD; PD. An increase of more than 20% in the sum of the diameters of the target lesions compared to the sum of the minimum diameters of the lesions after treatment, and an increase of more than 5 mm in absolute value, or the appearance of new lesions. In patients with metastatic CRC, patients with higher levels of FIB have a poorer response to chemotherapy [32]. A retrospective study found that FIB was significantly lower after chemotherapy [33]. Many studies in recent years have shown that FIB combined with pre-albumin may provide some guidance in assessing the efficacy of chemotherapy in CRC patients, and that this index may assist in screening patients with colon cancer who would benefit from chemotherapy [34] [35]. A multicentre prospective study enrolling 2917 eligible CRC patients with a 3-year follow-up concluded that FPR was significantly associated with chemotherapy efficacy in patients with stage III and VI CRC, with patients with FPR < 15 having better chemotherapy efficacy, patients with FPR < 20 having lower chemotherapy sensitivity and patients with FPR ≥ 20 being prone to chemoresistance. Therefore, FPR can be used as an indicator to differentiate eligible patients for chemotherapy and predict chemotherapy efficacy [35]. A prospective study of 1181 patients undergoing surgery for stage I-III CRC showed that patients with high FPR had a lower survival rate after chemotherapy than patients with low FPR on the same course of treatment, but better than those who did not undergo chemotherapy after surgical resection, and concluded that chronic high-intensity inflammation could reduce the sensitivity of chemotherapy and lead to a poor prognosis for patients with stage III CRC, providing a

basis for targeted anti-inflammatory therapy combined with adjuvant chemotherapy, provide new ideas for the clinical application of targeted anti-inflammatory therapy in patients with high FPR [36].

3.3. Application of FIB Levels in the Prognostic Assessment of Colorectal Cancer

Some studies have shown that have shown the value of FIB in assessing the prognosis of CRC, and it is expected to be one of the predictors of CRC clinical progression. Preoperative FIB levels can be used as an indicator to monitor postoperative lymph node metastasis and venous invasion in patients with colon cancer [37], but some studies have shown no correlation between high FIB levels and lymph node metastasis [23] [38]. The results of some studies on the value of FIB levels in CRC patients for prognostic assessment are controversial. It has been reported in the literature [23] that FIB correlates with age, site of tumour, size of tumour, degree of differentiation, distant metastases and the older the age, the larger the diameter of the tumour, the less differentiated the tumour and the presence of distant metastases, the higher the FIB level. Independent of gender, lymph node metastasis, peripheral nerve invasion, extra-nodal tumor implantation, vascular cancer thrombosis and growth pattern, the results of multifactorial survival analysis showed no significant correlation between high or low preoperative FIB levels and overall survival (OS) in CRC. This is inconsistent with the results of the study by Wang Jing [39] which collected clinical data from 158 patients who underwent surgical treatment for colorectal cancer, followed up and recorded the 5-year survival rate of the patients. The study showed that FIB level was correlated with tumour size, lymph node metastasis and tumor-node-metastasis (TNM) classification, independent of gender, age, tumour site and differentiation; among them, FIB level was positively correlated with TNM stage, and patients with high level of FIB The 5-year survival rate of patients with high level of FIB is lower and is an independent risk factor affecting prognosis, and it is believed that there is a correlation between FIB level and the prognosis of CRC patients. Some reports have shown that FIB levels correlate with the prognosis of patients with non-metastatic CRC. This study concluded that 3.64 g/L could be used as a threshold value for FIB to assess prognosis [38]. FIB was compared across different TNM stages of CRC and the differences were statistically significant, with FIB levels significantly higher in stages III and IV than in stage I and in stage IV than in stage II [21].

Many studies in recent years have shown the value of fibrinogen combined with prealbumin in assessing the prognosis of CRC patients. High FPR often indicates the presence of hypercoagulation, hypoproteinemia, wasting and malnutrition in CRC patients. The results of a multicentre, prospective study suggest that FPR levels correlate with tumour size, depth of infiltration and the presence of distant metastases, and that the prognosis is worse in the high FPR group than in the low FPR group. FPR is an independent risk factor for the prognosis of CRC patients [35]. FPR is also an independent prognostic factor for left-sided

metastatic colorectal cancer, with higher FPR values suggesting lower progression-free survival (PFS) and OS. However, for patients with right-sided metastatic colorectal cancer, FPR is not associated with survival [40]. Patients with high FPR have a higher complication rate, and high FPR is an independent risk factor for postoperative complications, especially in patients with stage I CRC, and FPR is a potential predictor of immediate and long-term prognosis in patients undergoing surgical resection for stage I-III CRC [41]. FPR can also be used as a monitor for postoperative recurrence in patients with stage I-III colorectal mucinous FPR can also be used as an indicator of postoperative recurrence in patients with stage I-III colorectal mucinous adenocarcinoma [42]. A retrospective study identified albumin-to-fibrinogen ratio (AFR) as an independent risk factor affecting the long-term prognosis of patients undergoing surgical treatment for CRC, and the AFR-based Nomogram prediction model can be used to assess PFS and OS in CRC patients at 1 - 5 years, and the AFR-based Nomogram prediction model has been shown to have better predictive power and accuracy compared with TNM staging [43]. Yin Weiwei found that preoperative AFR is valuable in assessing the prognosis of patients undergoing radical surgery for open colorectal cancer, and this study concluded that a preoperative AFR < 9.89 may be an independent risk factor for survival at 3 years after surgery [44]. A meta-analysis of 17 articles involving 6863 CRC patients showed that higher pre-treatment FIB levels were associated with shorter OS and shorter disease-free survival (DFS) in CRC patients, but there was no significant correlation between FIB levels and DFS in CRC patients who had developed metastases [45]. In patients with metastatic colorectal cancer, increased FIB levels were associated with mortality [32]. Colon cancer is most prone to liver metastasis [46], and it has been suggested that FGB, a major component of FIB, is involved in the process of liver metastasis in colorectal cancer, and that FGB could be a potential target for the treatment and prevention of colorectal cancer metastasis [47].

4. Summary and Outlook

The occurrence and metastasis of CRC are closely related to FIB levels, and FIB is an economical, simple, reproducible and easy-to-obtain test that has potential applications in the diagnosis, outcome prediction and prognosis of CRC. However, there are still several questions regarding the study of FIB and CRC: 1) whether elevated FIB is a cause of CRC or a consequence of CRC progression; 2) there is no consensus on the concentration reference values for diagnosis, efficacy prediction and prognosis assessment of FIB and CRC; 3) whether the level of FIB can be included in the CRC staging system; 4) whether treatment to reduce FIB is beneficial in reducing the recurrence rate and mortality of CRC.

Therefore, future multicentre and larger prospective studies are needed to further confirm whether the prevention and treatment of hypercoagulable blood in CRC patients can benefit patients, and the specific timing, type and mode of dosing needs to be further explored. In addition, there is a need to investigate whether FIB is a causative factor for CRC at the genetic level, which could help

to achieve early prediction and diagnosis of CRC. There is also a need to further investigate the characteristics of the coagulation pathway in CRC patients and to combine the coagulation characteristics with the molecular mechanisms of CRC, so as to provide new ideas and targets for the prognosis assessment and treatment of CRC patients.

Conflicts of Interest

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

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