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Expression, Significance, and Impact on Survival of Fatty Acid Binding Proteins 4 and 7 in Colorectal Cancer: A Tissue Microarray Study

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Abstract.

Background. Colorectal cancer (CRC) remains a major cause of cancer-related morbidity and mortality worldwide. Recently, the pathogenesis of CRC among other cancer types has been linked to lipid metabolism. Fatty acid-binding proteins (FABPs) are a protein-family expressed in multiple tissues and play a crucial role in lipid metabolism. A few recent studies have examined FABPs role in CRC. Our aims are to explore the immunohistochemical expression of fatty acid binding proteins (FABP) 4 and 7 in colorectal cancer, and correlate their expression levels with clinical, histopathological features, and survival.

Methods. A retrospective review of colorectal cancer biopsies over a 5-year period was conducted in our institute. Clinical and histological data were collected. Immunohistochemical staining for FABP 4 and 7 was performed using microarray and their expression was evaluated using the Histologic score (HS). The correlations between the expression of FABP 4 and 7 and clinicopathological parameters were determined by Fisher's exact test**.** The impact of the expression on the overall survival was determined using Kaplan–Meier survival analysis.

Results. 125 CRC tissue biopsy blocks were included. Median follow-up time was 35 months. High FABP4 expression was observed in 107 (85.60%). For FABP7, only 8.8% of cases (11/125) showed high expression. Co-expression of FABP4 and FABP7 occurred in 11 cases (8.8%). FABP7 expression correlated with age (p = 0.001). The median overall survival of patients with high expression of FABP4 was 43.00 ± 3.01 months, whereas patients showing low/negative expression reported a survival of 24.00 ± 6.24 months(p =0.041). No statistically significant association between FABP7 high expression and the overall survival was detected (Log-Rank test, p = 0.086).

Conclusion. FABP4 expression in CRC is higher than that of FABP7. FABP7 expression levels negatively correlate with the age of CRC patients. FABP4 expression is associated with a better survival in CRC. No significant association between FABP4 and 7 with tumor grade, stage, or other clinicopathological criteria has been found in this study.

Keywords: colorectal carcinoma; fatty acid-binding proteins; FABP4; FABP7; survival.

1. Introduction

CRC remains a major type of cancer in adults; and despite being studied for decades, it continues to be one of the leading causes of cancer mortality worldwide (Favoriti et al. 2016). In addition, about a third of CRC patients are diagnosed at an advanced stage, during which many cases are resistant to chemotherapy(Amiri et al. 2018)(Jaganathan et al. 2014)(Gupta et al. 2019). This dictates the need for novel treatments to manage CRC.

Understanding the molecular mechanisms involved in cancer development can aid in finding new treatment modalities. Some studies have found a relationship between the pathogenesis of certain cancers and lipid storage, uptake, and synthesis(Furuhashi M 2010)(Jung, Kim, and Koo 2015)(Amiri et al. 2018)(Kagawa et al. 2019). The effect of lipids on promoting tumor growth is mediated by inflammatory reactions and changes in the microenvironment, as well as by circulating inflammatory and metabolic mediators(H. Zhao et al. 2022). On the other hand, inhibition of lipid synthesis can suppress cancer development, as the inhibition of lipid storage may decrease the protection against reactive oxygen species toxicity, reduce cell survival exposed to hypoxia-reoxygenation in vitro, and hence may inhibit tumorigenesis in vivo (Bensaad et al. 2014)(McKillop, Girardi, and Thompson 2019).

Fatty acid-binding proteins (FABPs) belong to a protein family that exists in multiple tissues and plays a

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** **Abbreviations**: FABP: fatty acid binding, proteinCRC: colorectal cancer,TMA: Tissue microarray

crucial role in lipid metabolism (Coe and Bernlohr 1998). FABP4 (adipocyte FABP (A-FABP) or aP2)(Furuhashi M 2010) is a gene located on chromosome 8q21 and expressed in adipose tissues and other tissues (Amiri et al. 2018; Jung, Kim, and Koo 2015; McKillop, Girardi, and Thompson 2019). FABP7 (Brain typed FABP; Brain Lipid Binding Protein),(Furuhashi M 2010) is mainly identified in brain neural tissues.(Liu et al. 2010)(Alshareeda et al. 2012)(Jung, Kim, and Koo 2015).

FABPs act as intracellular lipid chaperones that play a role in the intake, transference, signal transduction, and packing of long-chain fatty acids (Coe and Bernlohr 1998). Several studies investigated the link of FABPs and lipid metabolism with neoplasia (Bensaad et al. 2014)

FABP 4 and 7 are expressed in several types of human malignancies, such as gliomas, renal cell carcinomas, breast cancers, and others (Mukherjee et al. 2020; Zeng, Sauter, and Li 2020; Sun and Zhao 2022)(Kagawa et al. 2019). The link between CRC and FABP4 and 7 expressions has not been adequately investigated. Few recent studies have shown that FABP4 and FABP7 may promote invasion and metastasis of CRC. The mechanism of promoting invasiveness maybe, in part, through improvingepithelial-mesenchymal transformation (EMT)of CRC cells, as documented by Tian et al withFABP4 overexpression leading to upregulation of Snail, matrix metalloproteinase (MMP-2 and MMP-9), and downregulation of E-cadherin. Moreover, Ma et al. have demonstrated that FABP7-overexpression activates CRC cell proliferation, and inhibits apoptosis, which are vital processes in cancer aggression and metastasis. On the contrary, FABP7 knockdown may negatively impact CRC cell proliferation and survival (Ma et al. 2018; Tian et al. 2020). FABP4 expression was found to be a risk factor for CRC progression , and it could be a biomarker for CRC diagnosis (Y. Zhang et al. 2019). Due to their role in tumor development, FABPs may become potential targets in cancer treatment (Sun and Zhao 2022).

The aims of this work are to define the rate of immunohistochemical expression of FABP4 and FABP7 in CRC, and to inspect the link with the clinical and histopathological features of CRC as well as with survival. The current study is the first of its kind in our population, and its significance is to explore the relationship of FABP 4 & 7, if any, with patient's survival, clinical, and histological parameters like CRC tumordifferentiation, stage, and lymph node invasion.

2. Materials and methods

This study is retrospective and cross sectional covering the period from 1/7/2016 until 31/12/ 2021. It includes 125 tissue samples obtained from colorectal carcinoma cases. The Institutional Review Board (IRB) approves the study in its decision no. (55-2022).

2.1. Patients and tissues.

One hundred and twenty-five cases diagnosed with CRC are retrospectively selected from the electronic database of the Department of Pathology. Inclusion criteria are: (*i*) adults above 18 years old; (*ii*) confirmed primary colorectal adenocarcinoma (*iii*) Paraffin blocks from CRC tissue biopsies or surgical resection specimens are available in our archives. Exclusion criteria are: (*i*) colon cancer other than adenocarcinoma (for example gastrointestinal stromal tumors and lymphomas), (*ii*) history of neoadjuvant or adjuvant therapy and (*iii*) paraffin tissue blocks that are not available or insufficient.

2.2. Tissue microarray construction (TMA).

Eight TMA blocks are constructed from the 125 archival paraffin blocks using a manual tissue microarrayer (Array mold Kit A, Catalogue # IW-110, IHC World/ USA). Representative tumor area is recognized on Hematoxylin and Eosin-stained slides and discerned on the paraffin blocks by two pathologists (N.A. and H.A.). Following instructions that are previously used in literature(Fowler et al. 2011), two cylindrical cores of 2-mm diameter each are removed from the blocks using a dermal biopsy punch and transferred to the TMA recipient blocks. Then *4*-micrometers (µm) sections are cut from each TMA block using an automatic rotary microtome *(*Microm HM355 S, Thermo Fisher Scientific Inc., USA) and are stained using immunohistochemistry.

2.3. Immunohistochemistry (IHC).

A standardized IHC protocol is performed in accordance to literature(Walker 2006; Taylor and Levenson 2006) and manufacturer's instructions. 4-µm-thick paraffin-embedded tissue sections (PETS) are de-waxed with xylene (twice for 5 minutes) then rehydrated by descending alcohol series (100%, 95%, and70% alcohol, 5 minutes each). Antigen unmasking is performed using a water bath for 15 minutes at 95°C in Coplin jars containing sodium citrate buffer for FABP7 (pH=6.0) and Tris/ethylene diamine tetra-acetate buffer for FABP4 (pH=9.0). Next, PETS are rinsed with phosphate-buffered saline (PBS;pH=7.2) and with 3% hydrogen peroxide (H2O2) for 10 minutes at room temperature to ablate endogenous peroxidase. Next, PETS are incubated with serum blocking reagent G (CTS005; R&D Systems, Minneapolis, MN) in PBS for 60 minutes to prevent non-specific binding. The sections are incubated with rabbit polyclonal anti-FABP4 (1:750, NBP1-89218, Novus biological/ USA) and rabbit polyclonal anti-FABP7 (1:600, NBP1-88648, Novus biological/ USA) for 90 minutes at room temperature. After rinsing with PBS buffer, sections are then incubated for 30 minutes with anti-rabbit HRP secondary antibody (ab236466, Abcam, Cambridge, UK). The chromogenic reaction is performed with 3-diaminobenzidine solution (CTS005; R&D Systems, Minneapolis, MN/USA) at room temperature in darkness for 7 min. After rinsing with PBS buffer, the sections are counterstained with Mayer's Hematoxylin solution, for 4 min at room temperature. Finally, the sections are dehydrated with ascending alcohol (70%, 95%, and 100%) and mounted with dibutyl phthalate in xylene mounting media (BCBX0183, Sigma/ Germany) and cover-slipped.

Thyroid cancer and nevus tissue samples are used as positive controls for FABP4 and FABP7, respectively(Coe and Bernlohr 1998)(Hewitt et al. 2014). PBS is utilized as a negative control.

2.4. IHC scoring.

Two pathologists using an Olympus CX41 upright light microscope (Olympus / Tokyo / Japan) evaluated the IHC results. Expression of FABP4 and FABP7 is scored

according to cytoplasmic staining intensity (0 points = no staining, 1 = weak, 2 = moderate, and 3 = strong staining) and percentage of positive cells (0 points (0-25%), 1 point (26-50%), 2 points (51-75%), and 3 points (76-100%)). The total Histological Score (HS) is calculated by multiplying the staining intensity score and percentage score. Using comparable methodology to the previous studies, (Chen et al. 2021; Zang et al. 2021; C. Zhang et al. 2020) we considered HS scores of 3 or less as low expression, while HS that is equal to or greater than 4 as high expression.

2.5. Statistical analysis.

The relationship of FABP4/ FABP7 expression and the clinicopathological features is determined using Fisher's exact test (two-sided). Overall survival time is calculated from the date of surgical resection of CRC to the date of death from any cause or last follow-up date. Survival probabilities of patients based on theexpression status of FABP4 and FABP7 are estimated using the Kaplan-Meier approach and compared with the log-rank test. Two-tailed P values ≤0.05 are considered statistically significant. Analyses are made using Statistical Package for Social Sciences (SPSS) version 26 software (SPSS Inc., Chicago, Illinois, United States).

3. Results

3.1. Demographical and clinicopathological characteristics of the study patients.

One hundred and twenty five CRC tissue samples belonging to 125 patients are included in this study. The median patients' age is 55.14 years (range: 18–85). 71 (56.8%) patients are males with a male-to-female ratio of 1.3:1. Pathological evaluation shows that 105 (84%) tumors are colorectal adenocarcinoma, and 20 (16%) tumors are mucinous colorectal adenocarcinoma. Both Demographical and clinicopathological characteristics are summarized in Table 1.

Table 1. Demographic and clinicopathological characteristics of study population.

Feature		Number	Percentage
Age (Years)	<50	52	41.6
	≥50	73	58.4
Gender	Female	54	43.2
	male	71	56.4
Histological type	Adenocarcinoma	105	84.0
	Mucinous carcinoma	20	16.0
Grade (differentiation)	Well	10	8.0
	moderate	104	83.2
	poor	11	8.8
Tumor T Stage	T1	1	0.8
	T2	17	13.6
	T3	75	60.0
	T4	32	25.6
Lymph node metastasis	Present	74	59.2
	Absent	51	40.8
Lymphovascular invasion	Present	46	36.8
	Absent	79	63.2
Perineural invasion	Present	19	15.2
	Absent	106	84.8

3.2. Expression of FABP4 and FABP7 in CRC.

Overall, high FABP4 immuno-expression in tumor cells is observed in 107/125 (85.60%) (Figure 1A). Low/negative FABP4 immuno-expression in tumor cells is observed in 18/125 (14.4%) (Figure 1B). On the other hand, only 8.8% of cases (11/125) show high expression of FABP7 (Figure 1C). Low/negative FABP7 expression in tumor cells is observed in 114/125 (91.2%) (Figure 1D). Co-expression of FABP4 and FABP7 proteins is ascertained in 11 cases (8.8%). Figure 2 demonstrates IHC staining intensity for FABP 4 and 7.

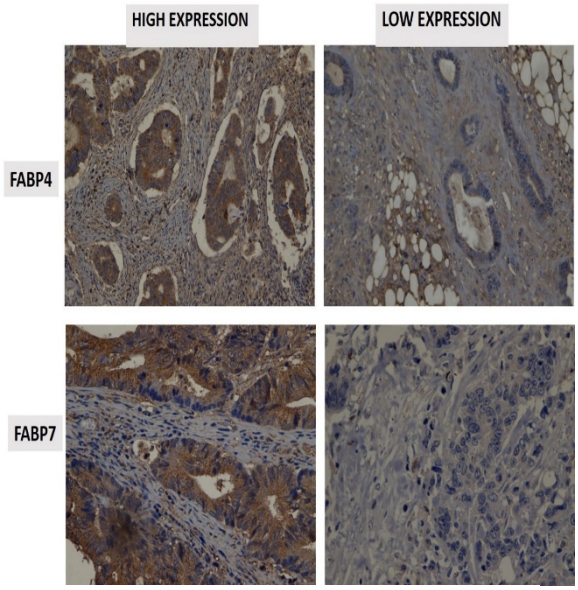

***Figure** 1.* Representative images of immunohistochemistry for FABP4 and FABP7 protein expression in colorectal cancer tissue samples. Light microscopy; original magnification upper panel 200X, and lower panel 400X.

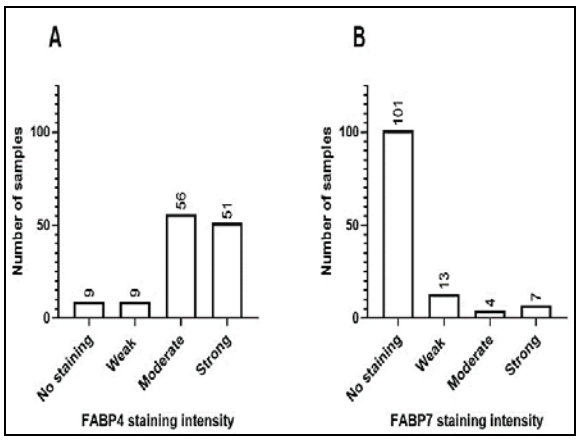

Figure 2. Staining intensity results for FABP4 and FABP7 protein in colorectal cancer cells.

3.3. Correlation between FABP4 and FABP7 expression with clinicopathological characteristics.

Table 2 details the correlation between FABP4 and FABP7 expression and the clinico-pathological features.

There is a significant difference of FABP7 expression in patients below 50 years of age (19.2% high expression rate) and those aged fifty and above (1.4% high expression rate), ($p = 0.001$). However, there is no statistical significance of FABP7 expression with respect to gender, tumor grade, T stage, and lymph node metastasis or perineural or lymphovascular invasion.

There is no significant correlation between FABP4 expression and any of the clinico-pathological variables.

Table 2. Clinicopathological variables and the expression of FABP4 and FABP7 in corresponding colorectal carcinoma tissue samples.

	FABP4			FABP7		
Variables	Low/no expression	High expression		Low/ no expression	High expression	
	n (%)	*n* (%)	*P Value*	*n* (%)	*n* (%)	*p Value*
Age (years)						
≦50	8 (15.4)	44 (84.6)	0.801	42 (80.8)	10 (19.2)	0.001*
>50	10 (13.7)	63 (86.3)		72 (98.6)	1 (1.4)	
Gender						
Female	5 (9.3)	49 (90.7)	0.201	50 (92.6)	4 (7.4)	0.756
Male	13 (18.3)	58 (81.7)		64 (90.1)	7 (9.9)	
Histologic type						
Adenocarcinoma	15 (14.3)	90 (85.7)	1.000	96 (91.4)	9 (8.6)	0.689
Mucinous	3 (15.0)	17 (85.0)		18 (90.0)	2 (10.0)	
Degree of differentiation						
Well	3 (30.0)	7 (70.0)		9 (90.0)	1 (10.0)	1.000
Moderate	13 (12.5)	91 (87.5)	0.221	95 (91.3)	9 (8.7)	
Poor	2 (18.2)	9 (81.8)		10 (90.9)	1 (9.1)	
Tumor T-Stage						
T1	0 (0.0)	1 (100.0)		1 (100.0)	0 (0.0)	0.345
T2	2 (11.8)	15 (88.2)	0.677	16 (94.1)	1 (5.9)	
T3	13 (17.3)	62 (82.7)		70 (93.3)	5 (6.7)	
T4	3 (9.4)	29 (90.6)		27 (84.4)	5 (15.6)	
Lymph node metastasis						
Absent	7 (13.7)	44 (86.3)	1.000	47 (92.2)	4 (7.8)	1.000
Present	11 (14.9)	63 (85.1)		67 (90.5)	7 (9.5)	
Lymphovascular invasion						
Absent	12 (15.2)	67 (84.8)	0.798	72 (91.1)	7 (8.9)	1.000
Present	6 (13.0)	40 (87.0)		42 (91.3)	4 (8.7)	
Perineural invasion						
Absent	14 (13.2)	92 (86.8)	0.475	97 (91.5)	9 (8.5)	0.674
Present	4 (21.1)	15 (78.9)		17 (89.5)	2 (10.5)	

3.4. Survival analysis.

The impact of FABP4/ FABP7 protein expression on overall survival is investigated using Kaplan–Meier survival analysis. The Median follow-up time after surgical resection is 35 months, and 16 deaths (12.8%) are documented. The median overall survival of patients with high expression of FABP4 is 43.00 ± 3.01 months, which is significantly better than that of patients with low/negative expression of FABP4 (24.00 ± 6.24 months, p =0.041). On another hand, Kaplan–Meier analysis exposes no significant association between FABP7 expression and overall survival (Log-Rank test, p = 0.086) (Figure 3).

Univariate and multivariate Cox proportional hazards regression are calculated to detect impact of FABP4 and 7 expression along with other variables on overall survival of CRC patients (Tables 3 and 4).

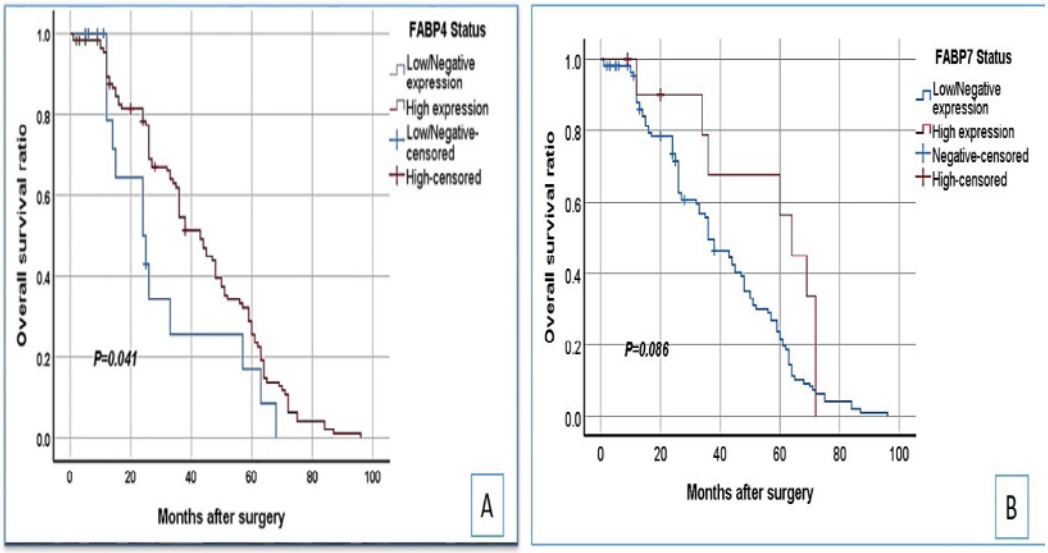

Figure 3. Kaplan-Meier survival analysis for patients with colorectal cancer according to FABP4 status (A) and FABP7 status (B).

Table 3. *Univariate Cox proportional hazards regression* to detect the influences *FABP4 and FABP7 expression and other variables on overall survival of CRC patients.*

Univariate Cox proportional hazards regression					
Variable		Odd ratio	95% C.I.		p
			Lower	Upper	
FABP4 expression	High vs Low	3.622	1.221	10.745	0.020
FABP7 expression	High vs Low	0.694	0.156	3.076	0.630
Age	< 50 vs ≥ 50	1.141	0.412	3.158	0.799
Gender	Female vs Male	0.624	0.226	1.721	0.362
Lymphovascular invasion	Present vs Absent	0.807	0.287	2.268	0.684
Perineural invasion	Present vs Absent	0.445	0.141	1.401	0.166
Lymph node metastasis	Present vs Absent	1.176	0.426	3.249	0.754
Degree of differentiation	Well vs Moderate vs Poor	1.392	0.414	4.683	0.593
Tumor T-Stage	T1 vs T2 vsT3 vsT4	2.589	1.092	6.137	0.031

Table 4. *Multivariate Cox proportional hazards regression* to detect influences *of FABP4, FABP7 protein expression and other variables on overall survival of colorectal cancer patients.*

Multivariate Cox proportional hazards regression					
Variables		Odd ratio	95.0% CI		p
			Lower	Upper	
FABP4 expression	High vs Low	0.176	0.053	0.586	0.005
FABP7 expression	High vs Low	1.880	0.318	11.105	0.486
Age	< 50 vs ≥ 50	1.994	0.684	5.818	0.206
Gender	Female vs Male	1.016	0.317	3.257	0.979
Lymphovascular invasion	Present vs Absent	1.328	0.428	4.121	0.623
Perineural invasion	Present vs Absent	1.665	0.505	5.495	0.402
Lymph node metastasis	Present vs Absent	0.451	0.141	1.443	0.180
Degree of differentiation	Well vs Moderate vs Poor	1.029	0.284	3.735	0.965
Tumor T-Stage	T1 vs T2 vsT3 vsT4	3.373	1.190	9.560	0.022

4. Discussion

The current work has utilized TMA(Camp, Neumeister, and Rimm 2008)(Hutchins and Grabsch 2018)as the method for tissue processing; and IHC for studying FABP 4/ 7 expression. This technique has been in use for 2 decades in oncology research. TMA proves to be a cost-effective and rapid scheme to examine large sample numbers. TMA has been utilized in colorectal cancer diagnostic and prognostic studies (Knösel et al. 2005).

This study proposes that 58.6% of CRC cases show high FABP4 expression but only a minority (8.8%) exhibit high expression of FABP7**.** It also demonstrates that expression of FABP7 correlates with younger patient's age (p = 0.001). Interestingly, the overall survival is

statistically longer with high expression compared to low expression of FABP4 (p =0.041). We observe no association between FABP4 or FABP7 expression and other clinicopathological characteristics. No significant association is detected between FABP7 expression and overall survival (Log-Rank test p = 0.086).

Our results are compatible with those of Prayugo et al (Prayugo et al. 2021) who studied FABPs' Gene expression analysis in CRC. They showed that, among other genes, FABP 4 gene has a higher expression levels in CRC tissues as matched to normal colon (Prayugo et al. 2021).Meanwhile, their results do not show statistical significance of FABP7 expression in CRC tissues compared to normal colon. Nevertheless, our results are the opposite of theirs regarding the relationship of FABP4 expression and overall survival. We have found the median overall survival to be statistically longer with high expression contrasted to low/negative expression of FABP4.On the other hand, our results contradict with other papers such as the one by Ma et al(Ma et al. 2018), since we observe negative/low expression of FABP7 in the majority of our cases.(Ma et al. 2018; Tian et al. 2020)

It has been previously postulated that FABP4 has a role in the early development of CRC, as it activates the Wnt/-catenin pathway, which plays a chief role in CRC evolution. (H. Zhao et al. 2022; Oliveira, Predes, and Borges 2022; Prayugo et al. 2021) Moreover, a high blood level of FABP4 has been detected in CRC patients (Y. Zhang et al. 2019). A recent study proposes that FABP4 overexpression can enhance invasiveness of CRC through activating lipid metabolism. (Ma et al. 2018; Tian et al. 2020)

FABP 4 is a gene that is located on chromosome 8q21 and it is expressed in adipose tissues and other tissues. EndogenousFABP4 acts as a tumor suppressor and exogenous FABP4 enhances cancer development. Fatty acids regulate FABP4 expression as its levels are higher in obese than in non-overweight patients (Hancke et al. 2010). FABP4 is found to be involved in lipid metabolism and pathogenesis in some cancers (McKillop, Girardi, and Thompson 2019).

Previous studies show that FABP4 expression plays an vital role in some cancers including breast cancer; where higher FABP4 serum levels indicate a worse prognosis (Xie et al. 2020). Moreover, FABP4 is increased in fatty tissue and is continually released in blood of obese persons. Thus, inhibition of FABP4 activity may provide a new treatment strategy for obesity-associated breast cancer (Zeng, Sauter, and Li 2020).

FABP4 is documented to play a role in prostate cancer, (Huang et al. 2017; Amiri et al. 2018) bladder cancer, and lung cancer . FABP4 expression in lung cancer is found to be related to advanced lymph node metastasis (Tang et al. 2016).

FABP7 is identified mainly in evolving and mature neural tissues (brain astrocytes, cerebellar glial cells, and retinal cone photoreceptor cells)(Kagawa et al. 2019). It is also identified in liver Kupffer cells, reticular cells in lymph nodes and melanocytes. FABP7 seems to be expressed in several malignant tumors, such as gliomas, renal cell carcinomas, breast cancers, and others (Shi et al. 1997).

The role of FABP7 expression in carcinogenesis is the subject of several studies that show controversial results. For instance, De Rosa et al propose that FABP7 expression has a negative impact on prognosis in gliomas (De Rosa et al. 2012). Similarly, FABP7 expression correlates with unfavorable prognosis in Renal cell carcinoma.(Tan et al. 2014). However, contradictory results are found in breast cancer with better survival in cases with higher expression levels. A possible explanation of worsened prognosis maybe because FABP7 overexpression leads to activated cell proliferation and migration of tumor cells (Kagawa et al. 2019). Some studies demonstrate that FABP7 shortage decreases cultured astrocytes proliferation (Sharifi et al. 2011).

Prayugo et al results do not show significant discrepancy of FABP7 gene expression between normal colon and CRC tissues (Prayugo et al. 2021). Moreover, the expression does not correlate with prognosis in CRC patients. The current study demonstrates similar findings on the protein expression level using IHC testing.

Adding to the controversy, Ma et al. (Ma et al. 2018) have found FABP7 expression to be stronger in CRC tissues in comparison to normal colon tissues, suggesting possible involvement in CRC carcinogenesis. Furthermore, their investigations display that FABP7 overexpression stimulates neoplastic proliferation and inhibits apoptosis. Moreover, FABP7 knockdown has a negative effect on cell proliferation (Ma et al. 2018).

Due to their role in tumor development, FABPs may become potential targets in cancer treatment (Sun and Zhao 2022). FABP4 has been embattled using several methods, such as small molecules like Polyphenols that are derivatives of natural plant sources and act as therapeutic substitutes for cancer therapy(Oliveira, Predes, and Borges 2022). These small molecules are synthesized by plants and are found in multiple sources such as seeds, leaves, and roots. Small molecule inhibitors (siRNAs) and short hairpin RNAs are also recently examined as potential cancer therapy agents (Mukherjee et al. 2020). In their animal experiment, Mukherjee et al. utilizea small-molecule inhibitor (BMS309403), an antagonist of FABP4 that interacts with its lipid-binding pocket. Interestingly, they document substantial reduction in the number and size of metastatic lesions in ovarian cancer with BMS309403 treatment. Similar trials have been performed in animal models of CRC. For example, it is proposed that miR-211 may reduce cell migration, invasiveness, and EMT via targeting FABP4 (D. Zhao et al. 2019).

Presently, however, no published research on human subjects or clinical trials to evaluate the usefulness of FABP4 inhibition is so far available. Future studies and clinical trials are needed to prove that FABPs may become promising targets of cancer therapy.

5. Conclusions

This study shows high expression of FABP4 in CRC, and that it may have an influence on survival. On the other hand, FABP7 is expressed in a minority of cases and high expression is not predictive of outcome.

The current work has several limitations including a relatively small sample size, and utilizing immunohistochemistry as a sole method to investigate FABP4 and FABP7 expression without molecular or genetic studies. Further studies and clinical trials are required to ascertain the relationship of FABP and CRC.

The emphasis of such studies should be placed on the impact of FABPs on patient's outcome, along with the potential role of FABP inhibitors in targeted therapy for CRC patients, expanding the opportunities of therapeutic approaches in the clinical practice.

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