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Review Article

# Fatty Acid-Binding Proteins and Their Roles in Disease and Cancer

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**Abstract**

Fatty acid binding proteins (FABPs) are an evolutionarily conserved intracellular lipid binding protein family which facilitates lipid transport, metabolism and responses inside cells. Emerging evidence suggests dysregulated lipid metabolism and signalling may result in development of diseases and cancer. In this review, we described the FABP family proteins and summarised their association with different diseases. We have also described role of each FABP member played in development and malignant dissemination of different types of cancers.

## Introduction

Fatty acid-binding proteins (FABPs) are a group of molecules playing important roles in lipid transportation. FABPs are expressed in different configurations in numerous tissues and have diverse functions [1]. Transportation of fatty acids into cells is achieved either through membrane diffusion or via help of receptors like G-protein. FABPs act as a chaperone regulating all functions of cell lipid transportation and storage. Inside cells, FABPs send lipid to endoplasmic reticulum for signalling, to mitochondria for oxidative process, and to nucleus for transcription activity. All members of FABPs can bind long chain fatty acids, however; they differ in their selectivity, affinity and binding mechanism [2]. It is clear that the roles of FABPs are various and include the transportation of fatty acids to cells, participating in PPAR signal transduction, regulating enzyme activity, and controlling gene expression and cell growth. FABP family members are small protein molecules weighting from 14,208 (FABP1) to 15,565 Delton [3].

In humans, FABPs are classified as part of the intracellular lipid binding protein family. Since FABP10 and FABP11 are not seen in humans, and are expressed only in other species, such as zebrafish (Danio Rerio) and teleost fish (Solea senegalensis) [4, 5], this protein family is made up of 10 members: FABP1 to FABP9, and FABP12. Like other lipid metabolism factors, FABPs had been thought to be involved in transportation of lipids only until their importance in cancer pathogenesis was recognized with the findings of their differential expression patterns in cancer tumorigenesis and progression [4, 6]. The various actions of adipocytes, fatty acids and proteins in cancer progression have been revealed. Their roles range from being utilized as energy providers and cell signalling molecules to the regulations of cancer metabolisms, hence, to promote more aggressive cancer phenotypes by enabling the cancer cell relocation, infiltration, and self-renewal [7]. The degree of involvement of different FABPs in malignant progression of cancer cells varies from playing a crucial role to a non-direct role.

## FABP1

FABP1 is found mainly in the liver. It is also present in smaller amounts in intestines, kidneys and the stomach. Several ligands can bind to FABP1 to achieve its significant functions of cellular activities. Ligands include a variety of fatty acids and their metabolites to bilirubin and heme [8]. FABP1 has a proven relation to steatotic liver and non-alcoholic fatty liver disease. The down regulation of FABP1 activates the quiescent stellate cells in the liver leading to the secretion of collagen and proteins by the stellate cells and the subsequent hepatic fibrogenesis [4, 9]. Some studies were performed to find out whether FABP1 was related to cancer in organs it localised, such as Liver, intestine and Kidney. At least one study reported an association between FABP1 and

colon cancer; significant downregulation of FABP1 was found in circulating colon cancer cells [10]. Loss of FABP1 was identified as a major contributing factor to microsatellite unstable colorectal carcinomas [4, 11]. These studies seemed to suggest that FABP1 may be a tumour suppressor. In contrast, another study on the role of FABP1 in hepatocellular carcinomas (HCC) suggested that FABP1 may have a tumour promoting role. FABP1 induced vascular endothelial growth factor (VEGF) expression through its interaction with the VEGF receptor, leading to new blood vessels formation (angiogenesis). This investigation showed that the role of FABP1 in enhancing migration properties of the cancer cells via the VEGFR2 pathway, indicating a promoting role of FABP1 in the metastasis of HCC [12]. FABP1 was found to be highly upregulated in the HCC cells. The increased level of FABP1 was correlated to lymph node metastasis and the stage of the malignant progression [4, 13]. Further investigations are needed for a clear understand of the exact role of FABP1 in cancer development Table 1.

**Table 1:**

| Criterion | WOMAC | KOOS | OKS |
|---|---|---|---|
| Length | 24 items: 5 pain, 2 stiffness, 17 function [14]. | Length 42 items: 9 pain, 5 symptoms, 17 ADL difficulty, 5 sport, recreation and quality of life [5]. | Short, 12 items: 5 pain, 7 function [4]. |
| Origin date | 1982 | 1998 evaluation for knee injury & OA [5]. | 1998 for TKA outcome [4]. |
| Validity for TKA | Construct validity showed moderate to strong correlation with other measurements post-TKA (SF36, Nottingham health profile function scale, range of motion, radiology Kellgren rating) and disability scale [9]. | Construct validity shows high correlation between KOOS & SF36. Rs=.62 pain, .48 ADL. Low correlation with mental scores (convergent validity) [7]. | Construct validity shows moderate correlation pre-TKA with American knee society (AKS); significant agreement with SF36 & HAQ [4]. |
| Sensitivity/ responsiveness | Response rate at one year 90% | Significant improvement, p<.001, effect size for quality of life 2.86–3.54 at 6/12 months, pain 2.28–2.55 at 6/12 months, sport 1.18–1.08 at 6/12 months, respectively [7]. | Effect size 2.19, larger than SF36 [4]. |
| | Effect size 2.25 [8]. | | |
| Reliability for TKA | Acceptable ≥ .70 internal reliability for pain and stiffness, excellent ≥ .90-.95 for function. Test-retest reliability acceptable for pain and function, weak for stiffness (11). Correlation coefficients for pain, function and overall score 0.55, 0.50 and 0.55, respectively [13]. | ICC post-TKA 0.75 with no significant changes between two measures [7]. | Internal consistency: Cronbach's alpha .87 pre-TKA and .93 6 months post. |
| | | | Test-retest: r=.92, ± 0–4 points of differences [4]. |
| Time required | 11 minutes | 10 minutes [5] | 5 minutes |
| Accepted missing values | Not more than 5 pain, 2 stiffness, 4 function [14]. | Two–six items and substituted by average value for dimensions [6, 7]. | 2 items |
| Outcome categories | Improvement in pain & function ≥ 50% & absolute change ≥ 20. Responder if pain/ function/ global ≥ 20%, absolute ≥ 10. | 0–100: 0 extreme knee problems, 100 no knee problems. | Excellent >41, Good 34–41, Fair 27–33, Poor < 27. [4]. |
| MCID* | 15 points [14]. | 8–10 points [5], 6-9 points [16] | 5 points for 2 groups' estimations, 9, 7 points for cohorts & individuals [2,12]. |
| Floor effect | 14%. | 48% for sport & recreation section [1,7] | 7% (1), no effect [15] |
| Ceiling effect | **6 MONTHS:** 27% for pain, 51% for stiffness [10]; | **6 MONTHS:** 15% for pain, 16% for sport, | **6 MONTHS:** 5–14%; **12 MONTHS:** 7–22% (1), no effect [15]. |
| | **12 MONTHS:** 17% quality of life, 30% pain, 64% stiffness [10]. | **12 MONTHS:** 22% pain & 17% for quality of life [1, 7]. | |

## FABP2

FABP2, also known as intestinal fatty acid binding protein, is expressed exclusively in the small intestine, in which dietary lipids are absorbed. The part of the small intestine with highest levels of FABP2 is the jejunum. Saturated and unsaturated fats are known to be used for the triglyceride synthesis. When excessive fatty acids accumulate, FABP2 controls fatty acid transferring in order to prevent the alteration of membrane characteristics by un-esterified fatty acids build up [4]. A number of FABP2 polymorphism studies were carried out and revealed clues of the roles it has in the human intestine. A threonine substitution at amino acid 54 was identified and it resulted in disturbed lipid metabolism. Increased insulin resistance, hypertriglyceridemia and increased accumulation of triglycerides were described in the threonine variant [4]. FABP2 is related to the occurrence of certain diseases, some of which may

progress to the development of cancers. These diseases include diabetes, myocardial infarction, stroke, and gallbladder diseases [14]. Very few studies were carried out to detect the role of FABP2 in cancer progression. However, there is at least one study conducted in 2010 to investigate the association of FABP2 expression with dietary habits and lipid uptake in colorectal carcinoma. This study drew the attention to the negative correlation between FABP2 and fat uptake. Therefore, FABP2 is unlikely to be an accurate predictor of the risk of colorectal cancer [15].

## FABP3

FABP3 is expressed predominantly in the heart and muscle tissue, as well as the tissue of the lung, ovary, brain, placenta, mammary gland, and stomach [8]. In order to provide enough energy to these tissues with high energy expenditures, FABP3 transfers fatty acids to mitochondria to produce energy. However, elevated levels of FABP3 may evoke cardiac dysfunction by reducing calcium level in the sarcoplasmic reticulum [16]. FABP3 accumulates in the brain tissue 10-fold more than the brain FABP [FABP7]. This indicates its significant action of neurological performances. When compared to other FABPs of the brain, FABP3 is found in its later development stage. It acts in the production of neurites and the maturation of synapses. Lower levels of FABP3 may be associated with some neurological disorders such as Down syndrome and Alzheimer's disease, which are caused by deficiencies in signal transduction and alterations in membrane structure [17]. The role of FABP3 in cancer is not yet fully understood, there are debates on whether it promotes or suppresses cancer. Previous studies found that FABP3 was overexpressed in 4 types of cancers: non-small cell lung carcinoma [18], gastric cancer [19], leiomyosarcoma [20] and melanoma [21]. Conversely, FABP3 was found to facilitate the suppression of breast cancer [22, 23], lung adenocarcinoma [24], lymphomas [25], and embryonic cancers [20].

## FABP4

FABP4 secretion leads to several physiological effects including greater glucose production in hepatic cells, augmented insulin secretion and reduced cardiomyocyte contraction [26, 27]. It was reported that FABP4 has a paracrine/endocrine signalling function; thus it acts on nearby or distant organs after it is released from adipose tissue to change metabolism and cell function [1]. Recent studies have revealed that FABP4 can participate in the elaboration of atherosclerosis in heart disease via inflammation and the accumulation of lipids in the macrophages or foam cells. A study on mice revealed that a more than 60% reduction in the blockage of coronary arteries is observed with the absence of both ApoE and FABP4 when compared to the absence of ApoE alone. This shows an important role of FABP4 in the development of atherosclerosis [28, 29]. A number of studies had demonstrated the involvement of FABP4 in the aggressiveness of various cancers such as prostate cancer [30], breast cancer [31], cholangiocarcinoma [32], glioblastoma [33], and leukaemia [32]. Recent evidence suggests that FABP4 can be used as a novel molecular marker for the investigation, prediction, and the monitoring of bladder cancer during therapy as well as a potential novel therapeutic target [34]. The role of FABP4 in the epithelial-mesenchymal transition (EMT) of cancer cells was reported. FABP4 overexpression has been correlated to EMT transition in cholangiocarcinoma [32] and cervical cancer [35].

## FABP5

FABP5, also named E-FABP or PA-FABP, is a 15 kDa cytosolic protein, which binds with a high affinity to medium and long chain fatty acids. FABP5 has a wide range distribution in the body: epidermis, mammary gland, brain, liver, kidney, lung, adipocyte, macrophage, tongue, and testis [2, 4]. Like other FABP family members, it binds and traffics fatty acids, in addition to the keratinocyte differentiation. It was suggested that FABP5 may have an association with obesity, abnormal lipid and insulin levels [2, 36]. FABP5 is an anandamide transporter, and a FABP5 inhibitor was used to manipulate the brain anandamide levels and thus to produce analgesia effect [37, 38]. Although over-expression of FABP5 in some cancer cells was noticed long-time ago, the molecular identification and functional characterisation of FABP5 as a tumour-promoter and a metastasis-inducer were first confirmed in prostate and breast cancer cells [6, 39]. FABP5 is expressed in high level in cancer cells, contributing to the aggressive phenotypes of cancer, promoting proliferation, invasion, tumorigenicity and metastatic ability of the cancer cells. High level of FABP5 expression was also related to the resistance to therapy and poor prognosis in various cancers such as gastric cancer [19, 40], melanoma [41], cervical cancer [42], breast cancer [43], prostate cancer [6, 44, 45], cholangiocarcinoma [46], oral cancer [47] and HCC [44]. Amongst all different cancer types, the role of FABP5 in promoting prostate cancer was studied most. Numerous studies proved FABP5 promoted tumor invasiveness both in vitro and in vivo [1]. A cohort study reported expression of FABP5 in triple negative breast cancer, the high level was associated with aggressive disease and low survival. The authors hypothesized that FABP5 exerted its effects via altering extracellular matrix to allow the tumor cells invading nearby organs [43].

It was reported that significantly high FABP5 levels in both prostate cancer cells and prostate carcinoma tissues [48]. It was found that the increased FABP5 expression was significantly associated with reduced patient survival time. When the level of FABP5 was suppressed via RNAi in prostate cancer cells, their tumorigenicity and metastatic ability was greatly suppressed both in vitro and in vivo [49]. During the extensive studies on the molecular mechanisms involved in the malignancy-promoting role of FABP5, a novel signal transduction pathway initiated by the stimulation of fatty acids transported by FABP5 was discovered. The detailed route for this signal transduction pathway is like following: the increased level of FABP5 transports a large amount of fatty acids into the cytoplasm, and most of the fatty acids were used as new sources of energy supply for the cells, whereas some excessive amount of fatty acids was delivered to their nuclear receptor PPARγ. The activated PPARγ can trigger a series of

molecular events or a chain of molecular reactions, including up-regulating some cancer promoting genes, such as VEGF; and down-regulating possible tumor-suppressor genes, and hence to facilitate the malignant progression of the cancer cells [50-53]. Recently, effort has been made for further exploring the FABP5-related signal transduction pathway in castration-resistant prostate cancer cells and for inhibiting the malignant progression of the cancer cells through targeting FABP5 [54].

## FABP6

FABP6 is also known by its alternate name: intestinal bile acid binding protein and I-FABP, because of its high affinity for bile acid [55]. FABP6 is expressed mainly in the ileum, binding bile acid to give its major role as a surfactant to facilitate in lipid digestion, thus controlling bile acid and lipid homeostasis. The lack of expression of FABP6 in male mice renders them more susceptible to fatty liver disease [56]. Several attempts have been made to examine FABP6's role in colorectal cancer. Since it is expressed widely in ileum, one study identified that FABP6 was highly expressed in colorectal carcinomas comparing to benign tissues. However, tissues from metastatic sites had low FABP6 levels [4]. Thus, more studies are required to determine the exact role of FABP6 in colorectal cancer and other cancer cells.

## FABP7

FABP7 is expressed in glia cells of the nervous system [57], it was hypothesized that it contributes to central nervous system development by supplying fatty acids during cellular maturation [2]. One study suggested that FABP7 was associated with several psychiatric disorders, specifically, Down syndrome and schizophrenia [58]. More research is needed to understand its role. These neurological diseases may develop as a result of abnormal fatty acids binding and energy supply. FABP7 plays an important role in Notch1 signalling pathway. It has also been widely examined in breast cancer, in which a FABP7-positive cohort was associated with the triple negative breast cancer group. This correlated with poor survival outcome, high tumour grade and increased proliferation [59]. In 2008, Slipicevic et al. published a paper on melanoma in which they described a high expression of FABP7 in both primary and metastatic tissues and the FABP7 level was correlated to increased tumour size and a decreased relapse-free survival period [4, 60]. However, the true role of FABP7 is not yet completed clear.

## FABP8

FABP8 is called myelin protein or M-FABP due to its predominance in peripheral nervous system myelin [61]. Despite decades of research, the role of M-FABP is unidentified; few studies had reported that it may be essential for myelin stabilizing and biogenesis [2, 62]. Until recently, there has been no reliable evidence of FABP8's involvement in any types of carcinomas; more work is necessary to decide the role of FABP8 in cancer cells.

## FABP9

It was proposed that FABP9 is one of major protein components of mammalian sperm [63]; it was assumed that it attributes to sperm protection [2, 64], however more studies are needed to understand its exact role.

The possible involvement of FABP9 in prostate cancer was assessed in 2016 [65]. It was reported that FABP9 is overexpressed in both prostate cancer cells and tissues. This expression was correlated with increased malignancy and poor patient survival time. Thus, it is suggested that FABP9 could be bio-marker for predicting tumour malignancy and patient outcome, with a similar reliability with the combined Gleason scores. When FABP9 mRNA was knocked down by RNA interference and tested in vitro, it was suggested that the suppression of FABP9 expression produced significant inhibition on invasiveness of the cancer cells, but it did not seem to have significantly affected the cell proliferation, anchorage-independent growth which is an indication of tumorigenicity, and the migration rate [65]. More investigation is needed to decide whether FABP9 has a promotive role in cancer.

## FABP12

It is the most recently discovered member of FABP family, little information is currently available, and it was detected in high level in human retinoblastoma cells [8]. FABP12 expression at both mRNA and protein levels were increased in malignant cell lines and the FABP12 increase is closely associated with increasing degree of malignancy. FABP12 was barely detectable in BPH, but its immunohistological staining in prostate carcinomas was significantly stronger than that in BPH. The staining intensity was increased as the increasing combined Gleason scores and the increased FABP12 is significantly associated with patient survival. Therefore, FABP12 may play an important promoting role in malignant progression of prostate cancer [66].

## Competing Interest

The authors declare no conflict of interest.

## References

1. McKillop IH, Girardi CA, Thompson KJ (2019) Role of fatty acid binding proteins (FABPs) in cancer development and progression. Cellular Signaling 62: 109336.
2. Smathers RL, Petersen DR (2011) The human fatty acid-binding protein family: evolutionary divergences and functions. Hum Genomics 5(3): 170-191.
3. Molecular weight of FABPs [online] powered by cell signaling technology.
4. Gurung S, Chung KPS, Lee TK (2019) Emerging role of fatty acid binding proteins in cancer pathogenesis. Histol Histopathol 34(1): 1-12.
5. Haunerland NH, Spener F (2003) Properties and physiological significance of fatty acid binding proteins. Advances in Molecular and Cell Biology. Elsevier p. 99-122.
6. Jing C, Beesley C, Foster CS, Rudland PS, Fujii H, Ono T, et al. (2000) Identification of the messenger RNA for human cutaneous fatty acid-binding protein as a metastasis inducer. Cancer Res 60(9): 2390-2398.

7. Duong MN, Geneste A, Fallone F, Li X, Dumontet C, et al. (2017) The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance. Oncotarget 8(34): 57622-57641.

8. Veerkamp JH, Paulussen RJA, Peeters RA, Maatman RGHJ, van Moerkerk HTB, van Kuppevelt THMSM (1990) Detection, tissue distribution and (sub)cellular localization of fatty acid-binding protein types. Molecular and Cellular Biochemistry 98(1-2): 11-18.

9. Chen A, Tang Y, Davis V, Hsu FF, Kennedy SM, Song H, et al. (2013) Liver fatty acid binding protein (L-FABP) modulates murine stellate cell activation and diet-induced nonalcoholic fatty liver disease. Hepatology 57(7): 2202-2212.

10. Onstenk W, Sieuwerts AM, Mostert B, Lalmahomed Z, Bolt-de Vries JB, van Galen A, et al. (2016) Molecular characteristics of circulating tumor cells resemble the liver metastasis more closely than the primary tumor in metastatic colorectal cancer. Oncotarget 13(37): 59058-59069.

11. Wood SM, Gill AJ, Brodsky AS, Lu S, Friedman K, Karashchuk G, et al. (2017) Fatty acid-binding protein 1 is preferentially lost in microsatellite instable colorectal carcinomas and is immune modulated via the interferon gamma pathway. Mod. Pathol 30(1): 123-133.

12. Ku CY, Liu YH, Lin HY, Lu SC, Lin JY (2016) Liver fatty acid-binding protein (L-FABP) promotes cellular angiogenesis and migration in hepatocellular carcinoma. Oncotarget 7(14): 18229-18246.

13. Jiang Z, Shen H, Tang B, Yu Q, Ji X, Wang L (2017) Quantitative proteomic analysis reveals that proteins required for fatty acid metabolism may serve as diagnostic markers for gastric cancer. Clin Chim Acta 464: 148-154.

14. Furuhashi M, Hotamisligil GS (2008) Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. Nat Rev Drug Discov 7(6): 489-503.

15. Kato I, Land S Fau-Majumdar AP, Majumdar Ap Fau-Barnholtz-Sloan J, Barnholtz-Sloan J Fau - Severson RK, Severson RK (2010) Functional polymorphisms to modulate luminal lipid exposure and risk of colorectal cancer. Cancer Epidemiol 34(3): 291-297.

16. Li W, Zhang S, Zhou S, Jiang L, Wang W (2017) Cardiac Fatty Acid Binding Protein (FABP3) Depletes SR Calcium Load in Ventricular Myocytes. Biophysical Journal 112: 424a.

17. Cheon MS, Kim SH, Fountoulakis M, Lubec G (2003) Heart type fatty acid binding protein (H-FABP) is decreased in brains of patients with Down syndrome and Alzheimer's disease. J Neural Transm Suppl 67:225-2234.

18. Tang Z, Shen Q, Xie H, Zhou X, Li J, Feng J, et al. (2016) Elevated expression of FABP3 and FABP4 cooperatively correlates with poor prognosis in non-small cell lung cancer (NSCLC). Oncotarget 7(29): 46253-46262

19. Hashimoto T, Kusakabe T Fau - Sugino T, Sugino T Fau - Fukuda T, Fukuda T Fau - Watanabe K, Watanabe K Fau - Sato Y, et al. (2004) Expression of heart-type fatty acid-binding protein in human gastric carcinoma and its association with tumor aggressiveness, metastasis and poor prognosis. Pathobiology 71(5): 267-273.

20. Davidson B, Abeler Vm Fau - Hellesylt E, Hellesylt E Fau - Holth A, Holth A Fau - Shih I-M, Shih IeM Fau - Skeie-Jensen T, et al. (2013) Gene expression signatures differentiate uterine endometrial stromal sarcoma from leiomyosarcoma. Gynecol. Oncol 128(12): 349-355.

21. Linge A, Kennedy S Fau - O'Flynn D, O'Flynn D Fau - Beatty S, Beatty S Fau - Moriarty P, Moriarty P Fau - Henry M, et al. (2012) Differential expression of fourteen proteins between uveal melanoma from patients who subsequently developed distant metastases versus those who did Not. Invest Ophthalmol Vis Sci 53(8): 4634-4643.

22. Huynh H, Alpert L Fau - Pollak M, Pollak M (1996) Silencing of the mammary-derived growth inhibitor (MDGI) gene in breast neoplasms is associated with epigenetic changes. Cancer Res 56(21): 4865-4870.

23. Nevo J, Mattila E, Pellinen T, Yamamoto DL, Sara H, et al. (2009) Mammary-derived growth inhibitor alters traffic of EGFR and induces a novel form of cetuximab resistance. Clin Cancer Res 15(21): 6570-6581.

24. Okano T, Kondo T, Fujii K, Nishimura T, Takano T, Ohe Y, et al. (2007) Proteomic signature corresponding to the response to gefitinib (Iressa, ZD1839), an epidermal growth factor receptor tyrosine kinase inhibitor in lung adenocarcinoma. Clin Cancer Res 13(3): 799-805.

25. Wu C-H, Sahoo D, Arvanitis C, Bradon N, Dill DL, Felsher DW (2008) Combined analysis of murine and human microarrays and ChIP analysis reveals genes associated with the ability of MYC to maintain tumorigenesis. PLoS genetics 4(6): e1000090-e90.

26. Cao H, Sekiya M, Ertunc ME, Burak MF, Mayers JR, et al. (2013) Adipocyte lipid chaperone AP2 is a secreted adipokine regulating hepatic glucose production. Cell metabolism 17(5): 768-778.

27. Lamounier-Zepter V, Look C Fau - Alvarez J, Alvarez J Fau - Christ T, Christ T Fau - Ravens U, Ravens U Fau - Schunck W-H, et al. (2009) Adipocyte fatty acid-binding protein suppresses cardiomyocyte contraction: a new link between obesity and heart disease. (1524-4571 (Electronic)). Circ Res 105(4): 326-334.

28. Makowski L, Boord JB, Maeda K, Babaev VR, Uysal KT, Morgan MA, et al. (2001) Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. Nat Med 7(6): 699-705.

29. Vasseur-Cognet M, Lane MD (1993) Trans-acting factors involved in adipogenic differentiation. Curr Opin Genet Dev 3(2): 238-245.

30. Uehara H, Takahashi T, Oha M, Ogawa H, Izumi K (2014) Exogenous fatty acid binding protein 4 promotes human prostate cancer cell progression. Int J Cancer 135(11): 2558-2568.

31. Guaita-Esteruelas S, Guma J, Masana L, Borras J (2018) The peritumoural adipose tissue microenvironment and cancer. The roles of fatty acid binding protein 4 and fatty acid binding protein 5. Mol Cell Endocrinol 462: 107-118.

32. Nie J, Zhang J, Wang L, Lu L, Yuan Q, An F, et al. (2017) Adipocytes promote cholangiocarcinoma metastasis through fatty acid binding protein 4. J Exp Clin Cancer Res 36(1): 183.

33. Cataltepe O, Arikan Mc Fau - Ghelfi E, Ghelfi E Fau - Karaaslan C, Karaaslan C Fau - Ozsurekci Y, Ozsurekci Y Fau - Dresser K, et al. (2012) Fatty acid binding protein 4 is expressed in distinct endothelial and non-endothelial cell populations in glioblastoma. Neuropathol Appl Neurobiol 38(5): 400-410.

34. Boiteux G, Lascombe I, Roche E, Plissonnier ML, Clairotte A, Bittard H, et al. (2009) A-FABP, a candidate progression marker of human transitional cell carcinoma of the bladder, is differentially regulated by PPAR in urothelial cancer cells. Int J Cancer 124(8): 1820-1828.

35. Jin J, Zhang Z, Zhang S, Chen X, Chen Z, Hu P, et al. Fatty acid binding protein 4 promotes epithelial-mesenchymal transition in cervical squamous cell carcinoma through AKT/GSK3beta/Snail signalling pathway. Mol Cell Endocrinol 2018, 461: 155-164.

36. Yeung DC, Wang Y, Xu A, Cheung SC, Wat NM, Fong DY, et al. (2008) Epidermal fatty-acid-binding protein: a new circulating biomarker associated with cardio-metabolic risk factors and carotid atherosclerosis. Eur Heart J 29(17): 2156-2163.

37. Berger WT, Ralph BP, Kaczocha M, Sun J, Balius TE, Rizzo RC, et al. (2012) Targeting fatty acid binding protein (FABP) anandamide transporters - a novel strategy for development of anti-inflammatory and anti-nociceptive drugs. Plos One 7(12): e50968.

38. Kaczocha M, Rebecchi MJ, Ralph BP, Teng Y-HG, Berger WT, et al. (2014) Inhibition of Fatty Acid Binding Proteins Elevates Brain Anandamide Levels and Produces Analgesia. Plos One 9: e94200.

39. Jing C, Beesley C, Foster CS, Chen H, Rudland PS, West DC, et al. (2001) Human cutaneous fatty acid-binding protein induces metastasis by up-regulating the expression of vascular endothelial growth factor gene in rat Rama 37 model cells. Cancer Res 61(11): 4357-4364.

40. Zhao G, Wu M, Wang X, Du Z, Zhang G (2017) Effect of FABP5 gene silencing on the proliferation, apoptosis and invasion of human gastric SGC-7901 cancer cells. Oncol Lett 14(4): 4772-4778.

41. Levi L, Lobo G Fau - Doud MK, Doud Mk Fau - von Lintig J, von Lintig J Fau - Seachrist D, Seachrist D Fau - Tochtrop GP, et al. (2013) Genetic ablation of the fatty acid-binding protein FABP5 suppresses HER2-induced mammary tumorigenesis. Cancer Res 73(15): 4770-4780.

42. Wang W, Chu HJ, Liang YC, Huang JM, Shang CL, et al. (2016) FABP5 correlates with poor prognosis and promotes tumor cell growth and metastasis in cervical cancer. Tumour Biol 37(11): 14873-14883.

43. Powell CA, Nasser MW, Zhao H, Wochna JC, Zhang X, et al. (2015) Fatty acid binding protein 5 promotes metastatic potential of triple negative breast cancer cells through enhancing epidermal growth factor receptor stability. Oncotarget 6(8): 6373-6385.

44. Kawaguchi K, Kinameri A, Suzuki S, Senga S, Ke Y, et al. (2016) The cancer-promoting gene fatty acid-binding protein 5 (FABP5) is epigenetically regulated during human prostate carcinogenesis. Biochem J 473(4): 449-461.

45. Myers JS, von Lersner AK, Sang QX (2016) Proteomic Upregulation of Fatty Acid Synthase and Fatty Acid Binding Protein 5 and Identification of Cancer- and Race-Specific Pathway Associations in Human Prostate Cancer Tissues. J Cancer 7(11): 1452-1464.

46. Jeong CY, Hah YS, Cho BI, Lee SM, Joo YT, et al. (2012) Fatty acid-binding protein 5 promotes cell proliferation and invasion in human intrahepatic cholangiocarcinoma. Oncol Rep 28(4): 1283-1292.

47. Fang LY, Wong Ty Fau - Chiang W-F, Chiang Wf Fau - Chen Y-L, Chen YL (2010) Fatty-acid-binding protein 5 promotes cell proliferation and invasion in oral squamous cell carcinoma. J Oral Pathol Med 39(4): 342-348.

48. Adamson J, Morgan EA, Beesley C (2003) High-level expression of cutaneous fatty acid-binding protein in prostatic carcinomas and its effect on tumorigenicity. Oncogene 22(18): 2739-2749.

49. Morgan EA, Forootan SS, Adamson J, Foster CS, Fujii H, et al. (2008) Expression of cutaneous fatty acid-binding protein (C-FABP) in prostate cancer: potential prognostic marker and target for tumorigenicity-suppression. Int J Oncol 32(4): 767- 775.

50. Bao Z, Malki MI, Forootan SS, Adamson J, Forootan FS, et al. (2013) A novel cutaneous fatty acid-binding protein-related signaling pathway leading to malignant progression in prostate cancer cells. Genes Cancer 4(7-8): 297-314.

51. Forootan FS, Forootan SS, Gou X, Yang J, Liu B, Chen D, et al. (2016) Fatty acid activated PPARgamma promotes tumorigenicity of prostate cancer cells by up regulating VEGF via PPAR responsive elements of the promoter. Oncotarget 7(8): 9322-9339.

52. Waseem Al-Jameel, Xiaojun Gou, Shiva S, Forootan, Majed Saad Al Fayi, Philip R Rudland, et al. (2017) Inhibitor SBFI26 suppresses the malignant progression of castration-resistant PC3-M cells by competitively binding to oncogenic FABP5. Oncotarget 8(19): 31041-31056.

53. Waseem Al-Jameel, Xiaojun Gou, Xi Jin, Jiacheng Zhang, Qiang Wei, et al. (2019) Inactivated FABP5 suppresses malignant progression of prostate cancer cells by inhibiting the activation of nuclear fatty acid receptor PPARγ. Genes & Cancer 10(3-4): 80-96.

54. Abdulghani AA Naeem, Saud A Abdulsamad, Philip S Rudland, Mohammed I Malki, Youqiang Ke et al. (2019) FABP5-related signal transduction pathway in castration resistant prostate cancer: A possible therapeutic target. Invited review article. Precision Clinical Medicine 2(8): 192-196.

55. Zimmerman AW, van Moerkerk HT, Veerkamp JH (2001) Ligand specificity and conformational stability of human fatty acid-binding proteins. Int J Biochem Cell Biol 33(9): 865-876.

56. Agellon LB, Drozdowski L, Li L, Iordache C, Luong L, Clandinin MT, et al. (2007) Loss of intestinal fatty acid binding protein increases the susceptibility of male mice to high fat diet-induced fatty liver. Biochim Biophys Acta 1771(10): 1283-1288.

57. Amiri M, Yousefnia S, Seyed Forootan F, Peymani M, Ghaedi K, et al. (2017) Diverse roles of fatty acid binding proteins (FABPs) in development and pathogenesis of cancers. Gene 676: 171-183.

58. Watanabe A, Toyota T, Owada Y, Hayashi T, Iwayama Y, et al. (2007) Fabp7 maps to a quantitative trait locus for a schizophrenia endophenotype. PLoS Biol 5(11): e297.

59. Xie M, Wu X, Zhang J, He C, Wei S, Huang J, et al. (2018) The Prognostic Significance of Notch1 and Fatty Acid Binding Protein 7 (FABP7) Expression in Resected Tracheobronchial Adenoid Cystic Carcinoma: A Multicenter Retrospective Study. Cancer Res Treat 50(4): 1064-1073.

60. Slipicevic A, Jørgensen K, Skrede M, Rosnes AK, Trøen G, et al. (2008) The fatty acid binding protein 7 (FABP7) is involved in proliferation and invasion of melanoma cells. BMC Cancer 8: 276.

61. Veerkamp JH, Maatman RG (1995) Cytoplasmic fatty acid-binding proteins: their structure and genes. Prog Lipid Res 34(1): 17-52.

62. Zimmerman AW, van Moerkerk HT, Veerkamp JH (2001) Ligand specificity and conformational stability of human fatty acid-binding proteins. Int J Biochem Cell Biol 33(9): 865-876.

63. Farkhondeh P, Tahereh K, Mahmood JT, Mojgan B, Jamileh G, et al. (2009) A Novel Human Lipid Binding Protein Coding Gene: PERF15, Sequence and Cloning. J Reprod Infertil 10(1): 199-205.

64. Kido T, Arata S, Suzuki R, Hosono T, Nakanishi Y, et al. (2005) The testicular fatty acid binding protein PERF15 regulates the fate of germ cells in PERF15 transgenic mice. Dev Growth Differ 47(1): 15-24.

65. Al Fayi MS, Gou X, Forootan SS, Al-Jameel W, Bao Z, et al. (2016) The increased expression of fatty acid-binding protein 9 in prostate cancer and its prognostic significance. Oncotarget 7(50): 82783-8297.

66. Asmaa AL-Bayati, MajedAL-Fayi, Waseem Al-Jameel, Jiacheng Zhang, Youqiang Ke (2017) Increased FABP12 expression in prostate cancer and its possible promoting role in malignant progression. Eur J Surg Oncol 43: 2208.

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