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Review

Emerging role of fatty acid binding proteins in cancer pathogenesis

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Summary. Fatty acid binding proteins (FABPs) are 15-kDa proteins responsible for the transport of fatty acids both intracellularly and extracellularly. Consisting of 12 different isoforms, some of the proteins have been found to be released in the serum and to be correlated with various diseases including cancer. Differential expression of these proteins has been reported to result in cancer pathogenesis by modulating various cancer signaling pathways; hence, in this review, we present the recent studies that have investigated the roles of different kinds of FABPs in different types of cancer and any possible underlying mechanisms to better understand the role of FABPs in cancer progression.

Key words: Adipocytes, Cancer, Drug resistance, FABPs, Metastasis

Emerging role of fatty acid binding proteins in cancer pathogenesis

Cancer is one of the deadliest and most common causes of deaths worldwide, with the number of cancer-related deaths rising in both developed and developing countries. Although the quest to understand cancer and the mechanisms of carcinogenesis and pathogenesis started a few decades ago, the complexity of the disease and its interrelationship with various other diseases make it difficult to develop new therapies for cancer. Globally, the World Health Organization has estimated an increase in the cancer-related mortality rate of approximately 70% over the next two decades, and currently, 1 in 6 deaths is caused by cancer, reflecting the high morbidity rate of cancer worldwide (World Health Organization, 2018). Intense research into the etiology and underlying mechanisms of cancer has revealed that, broadly, cancer mortality and relapse can be attributed to poor health diet, low levels of physical activity, alcoholism, genetic mutations of certain genes termed oncogenes and pre-existing conditions such as hepatitis, autoimmune diseases and polycystic syndrome (Blackadar, 2016). With a great deal of research on cancer mechanisms and the possible causes of cancer, scientists were able to develop more specific and effective therapies for patients; however, with the exponential rise in the incidence of cancer and the inability of the current therapies to effectively treat the diverse range of cancer phenotypes, it is essential to further understand the underlying mechanisms of cancer that result in the unique ability of cancer cells to thrive.

One of the recent interests in the field of cancer research is the crucial role played by fatty acid

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Abbreviations: Apolipoprotein E, ApoE; Protein Kinase B, Akt; DNA (cytosine-5)-methyltransferase 1, DNMTs; Epidermal growth factor receptor, EGFR; Epithelial mesenchymal transition, EMT; Fatty acid binding proteins, FABPs; Fatty acid synthase, FASN; Intestinal bile acid binding protein, I-FABP; Interleukin, IL; Krüppel-like Factor 2, KLF2; Matrix metalloproteinases, MMP; non-alcoholic fatty liver disease, NAFLD; Non-alcoholic steatohepatitis, NASH; Phosphoinositide 3-Kinase, PI3K; Peroxisome proliferator-activated receptors, PPARs; Vascular endothelial growth factors, VEGF; Vascular endothelial growth factor receptors, VEGFRs.

metabolism in cancer cell survival and pathogenesis. In recent decades, with the increase in cancer incidence, epidemiological data suggest there has also been an increase in obesity (Arroyo-Johnson and Mincey, 2016). A crucial study on the correlation between obesity and cancer mortality was reported revealing the existence of a strong correlation between cancer death rates and increased body weight (Calle et al., 2003). The paper also highlighted the fact that the effect of body weight on cancer was not restricted to only one type of cancer but remained valid for multiple cancers and for cancers at multiple sites. After the publication of that report, much research on lipid metabolism and the dependence of cancer cells on lipids for energy was conducted that revealed the diverse roles played by adipocytes, fatty acids and the secretome in cancer progression; these roles range from acting as sources of energy to initiating signaling pathways, modulating cancer metabolism and leading to aggressive cancer phenotypes by facilitating migration, invasion, and self-renewal, which lead to cancer progression (Duong et al., 2017). Lipid metabolism is a dynamic and complex pathway involving various kinds of proteins.

Among the proteins involved in lipid metabolism, fatty acid binding proteins (FABPs) are chaperone proteins that are expressed in different forms in various tissues and that help in the transport of fats. In humans, FABPs are categorized as part of the intracellular lipid binding family, which is composed of 10 members, including FABP1 to FABP9 and FABP12. FABP10 and FABP11 are not expressed in humans, but rather in other species, such as zebra fish (*Danio rerio*) and teleost fish (*Solea senegalensis*) (Haunerland and Spener, 2003). FABPs, like most of lipid metabolism constituents, was previously thought to be only involved in the transport of lipids; however, with the discovery of the differential expression pattern of FABPs in cancer tumorigenesis and progression, the importance of FABPs in cancer pathogenesis was revealed (Celis et al., 1996; Jing et al., 2000). The roles of different kinds of FABPs in different cancers has recently been investigated; this research has demonstrated that FABPs have many roles other than transporting fatty acids, and with the discovery that some FABPs are released into serum, the possibility of using FABPs for diagnostic purposes is also being investigated. In this review, we will investigate the emerging role FABPs are playing in the field of cancer research and the possible new insights into cancer energy metabolism and therapies it could provide.

FABPs: An introduction

FABPs are proteins that are 14-15 kDa in size and are composed of 126-134 amino acids. Even though the sequence homologies of FABPs are 25%-70%, the tertiary structures of this protein family are highly conserved (Zimmerman and Veerkamp, 2002). In general, the structure of FABPs is a ten-strand β-barrel. The barrel can be viewed as two antiparallel β sheets with five strands each, βA to βJ (Haunerland and Spener, 2004). In addition to the numerical naming of these FABP isoforms, another terminology is utilized based on the first tissue from which each FABP was isolated. As a result, there are a few names for each FABP member (Table 1). The prime physiological function of FABP is regulating fatty acid in cells. However, it is difficult to elucidate all the functions of each isoform due to the coexistence of several isoforms in the same tissue. When one of the isoforms is absent, the other isoforms may compensate for that absence by fulfilling their roles, which complicates the study of individual FABPs.

FABP1

FABP1 is mainly localized in the liver. FABP1 is also found at a comparatively lower concentration in the intestines, kidneys and stomach. FABP1 can bind different ligands to fulfil its important roles in cellular activities. These ligands range from fatty acids and their metabolites to bilirubin and heme (Wang et al., 2015). Therefore, the functions of FABP1 include but are not limited to transporting fatty acids to cells, participating in PPAR signal transduction, modulating enzymatic activity, and regulating gene expression and cell development. FABP1 has been proven to be related to steatotic livers and nonalcoholic fatty liver disease. Quiescent stellate cells in the liver are activated by the downregulation of FABP1, resulting in hepatic fibrogenesis due to collagen and proteins secreted by the stellate cells (Chen et al., 2013).

FABP2

FABP2 is solely expressed in the small intestine, where dietary lipids are absorbed. The jejunum is the segment of the small intestine in which FABP2 is most highly expressed. Saturated and unsaturated fats are used for triglyceride synthesis. When excessive fatty acids accumulate, FABP2 regulates fatty acid trafficking to avoid the alteration of membrane properties due to the accumulation of un-esterified fatty acids (Haunerland and Spener, 2004). FABP2 polymorphism studies have provided some clues as to the roles it plays in the human intestine. A threonine substitution at amino acid 54 was identified that resulted in disturbed lipid metabolism. Higher rates of insulin resistance and hypertriglyceridemia as well as increased accumulation of triglycerides were reported in the threonine variant (Baier et al., 1995; Levy et al., 2001).

FABP3

FABP3 is the most omnipresent FABP in the body, as it is found particularly in the heart and muscle tissue as well as the tissue of the lung, ovary, brain, placenta, mammary gland, and stomach (Veerkamp et al., 1990). To maintain a sufficient energy supply to these tissues with high energy expenditures, FABP3 acts as a lipid

carrier to direct fatty acids to mitochondria for use in energy production. However, elevated levels of FABP3 are suggested to provoke cardiac dysfunction by diminishing the calcium load in the sarcoplasmic reticulum (Li et al., 2017). FABP3 also accumulates in brain tissues 10-fold more than the brain FABP (FABP7) does, revealing its important role in neurological functioning. Compared to other FABPs in brains, FABP3 is detected in the later development of the brain, taking part in the synthesis of neurites and the maturation of synapses. Low FABP3 levels may be involved in some neural diseases including Down syndrome and Alzheimer's disease, which result from defects in signal transduction and alterations in membrane composition (Cheon et al., 2003).

FABP4

Both adipocytes and macrophages secrete FABP4 extracellularly. A drastic increase in FABP4 expression can be observed during adipocyte differentiation and the activation of macrophages. The secretion of FABP4 leads to different physiological effects including enhanced glucose production in hepatic cells, increased insulin secretion and decreased cardiomyocyte contraction (Lamounier-Zepter et al., 2009; Cao et al., 2013). Recent studies showed that FABP4 participated in the development of atherosclerosis in heart disease via inflammation and the accumulation of lipids in the macrophages or foam cells. When both ApoE and FABP4 are absent, a greater than 60% reduction in the blockage of coronary arteries was displayed in mice compared to the reduction with only ApoE missing, showing the importance of FABP4 in the development of atherosclerosis (Vasseur-Cognet and Lane, 1993; Makowski et al., 2001).

FABP5

Lipid synthesis is important in maintaining the function of the epidermis as a physical barrier against external invading microorganisms; therefore, FABP5 is

Table 1. Summary of different isoforms of FABPs with their alias and roles in different diseases (primarily focusing in cancer studies) as well as any inhibitory methods used to study their functions.

Type	Alternative names	Tissues	Related diseases apart from Cancer	Overexpression	Downregulation	Inhibitors/ Inhibited by	References
FABP1	L-FABP	Liver, intestine, kidney, stomach, pancreas	Liver steatosis, nonalcoholic fatty liver disease	Colon Gastric HCC	Esophagus Colon HCC	siRNA	Chen et al., 2013
FABP2	I-FABP	Intestine	Higher insulin resistant rate, hypertriglyceridemia, increased triglyceride accumulation	N/A	N/A	N/A	Baier et al., 1995; Levy et al., 2001
FABP3	H-FABP M-FABP MDGI	Heart, kidney, skeletal muscle, lung, ovary, brain, placenta, mammary gland	Down Syndrome, Alzheimer disease	NSCLC; Ovarian; Gastric Melanoma; Leiomyosarcoma; Gastric Cancer; Uterine	Breast Embryonic Lung Adenocarcinoma	N/A	Chen et al., 2013
FABP4	A-FABP ALBP aP2	Adipocyte	Atherosclerosis	Uterine; Cholangiocarcinoma; Prostate; Breast; Leukemia; Ovarian (stroma); Glioblastoma	Lung adenocarcinoma Urothelial Bladder Gastric	BMS309403/shRNA/siRNA	Vasseur-Cognet and Lane, 1993; Makowski et al., 2001; Huang et al., 2017; Harjes et al., 2016
FABP5	E-FABP KLBP cFABP mal1	Skin, adipose tissue, brain, heart, muscle, kidney, lung, testis	Failed in keratinocyte migration	Gastric; Liver; Prostate; Cervical; Colorectal; Breast; Oral		SBP5I26/siRNA	Kusakari et al., 2006; Al-Jameel et al., 2017; Zhao et al., 2017
FABP6	I-FABP IL-FABP ILBP I-BABP Gastrotropin	Ileal	Fatty liver	Colorectal		N/A	Agellon et al., 2007
FABP7	B-FABP R-FABP	Central nervous system	Down Syndrome, schizophrenia	Adenoid Cystic; Carcinoma; Renal Cell Carcinoma; Breast Glioblastoma; Melanoma	Renal carcinoma cell line Breast Melanoma	siRNA	Slipicevic et al., 2008; Watanabe et al., 2008
FABP8	M-FABP; mP2; Myelin P	Peripheral nervous system	Guillain-barré syndrome				Kadlubowski et al., 1984
FABP9		Testis	Sperm head malformation				Selvaraj et al., 2010
FABP12		Testis	Prostate cancer				AL-Bayati et al., 2017

actively expressed in the skin (Khnykin et al., 2011). In addition, FABP5 can regulate insulin responses, inflammation and water permeability. Studies showed that keratinocyte migration was affected in FABP5 knockout mice, indicating that the loss of FABP5 may delay the regeneration of the epidermis in the wound healing process (Kusakari et al., 2006). In addition to being expressed in the skin, FABP5 is abundant in brain tissues, and less abundant but present in the lungs, kidneys, liver and mammary glands (Khnykin et al., 2011). FABP5 in the brain has ligands for binding with PPAR beta/gamma, which strengthens the transcriptional activity, resulting in energy homeostasis, neuronal differentiation, and neurogenesis (Yu et al., 2012).

FABP6

FABP6 has an alternate name, intestinal bile acid binding protein (I-FABP), because of its high affinity for bile acid (Zimmerman and Veerkamp, 2002). FABP6 is commonly found in the ileum, binding bile acid to perform its major function of acting as a surfactant to aid in lipid digestion, controlling bile acid and lipid homeostasis. Males lacking FABP6 have been shown to be more prone to fatty liver disease (Agellon et al., 2007).

FABP7

FABP7 is expressed mainly in the central nervous system. Its ligands are saturated, monounsaturated and polyunsaturated fatty acids, such as docosahexaenoic acid, arachidonic acid and stearic acid, which are the essential fatty acids in early development (Liu et al., 2010). The expression level of FABP7 is greater in the fetal brain than in the adult brain, implying that FABP7 plays important roles in the developing brain. This protein is involved in nerve cell and neuroglia differentiation (Kurtz et al., 1994; Sellner at al., 1995). To support the neuronal migration necessary for the normal interaction of neurons, FABP7 aids in radial glial fiber formation and regulates Schwann cells (Miller et al., 2003). Intellectual disability is always connected with neuronal damage. As an important protein in brain development, FABP7 is associated with several psychiatric disorders, namely, Down syndrome and schizophrenia (Watanabe et al., 2008).

FABP8

FABP8 has several alternate names, such as peripheral myelin protein 2, mP2 and M-FABP. It can bind with cholesterol, retinol and retinoic acids. FABP8 is present in the peripheral nervous system and regulates the fatty acid content in the myelin membrane and Schwann cells. During inflammation, FABP8 also participates in the re-modeling process of the major histocompatibility complex (Stettner et al., 2014). Studies on the distribution of FABP8 in the nervous system have indicated that there is a correlation between FABP8 and the lesions in Guillain-Barré Syndrome, an autoimmune disease with impaired peripheral neuritis (Kadlubowski et al., 1984).

FABP9

FABP9 is found in testicular germ cells. FABP9 participates in processes in the male reproductive system, especially spermatogenesis. This protein prevents the oxidation of fatty acids in sperm. In addition, it determines germ cell fates and maintains sperm cell quality (Kido et al., 2005) Sperm head malformation was reported due to the absence of FABP9, although the sperm cells remained fertile (Selvaraj et al., 2010).

FABP12

FABP12 is the most recently discovered member in the family. It is commonly found in the testes. Recent research showed that FABP12 expression was increased in prostate cancer, implying its role in promoting cancer development (Al-Bayati et al., 2017). Like FABP9, however, limited studies have focused on this FABP, and its functional roles in the human body remain undiscovered.

The roles of FABPs in cancer

FABP1 and cancer

FABP1, also known as L-FABP, has been primarily described as being present in the liver and related to liver disease pathology such as that of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) (Tanaka et al., 2017). Primarily studied in hepatocellular carcinoma (HCC) (Chan et al., 2016), the expression of the protein has also been widely studied in various other cancers such as esophagus (Srivastava et al., 2017), colon (Alix-panabières et al., 2017), and gastric (Jiang et al., 2016) cancers. Although widely studied in both cell lines and clinical samples in various cancer types, the expression trend has been found to vary among different cancer types. There have also been reports suggesting varied expression patterns of the protein at different stages of the same cancer type. For instance, circulating colon cancer specimens demonstrated significant downregulation of FABP1 (Onstenk et al., 2016). Loss of FABP1 in microsatellite unstable colorectal carcinoma (Wood et al., 2017). However, a stable cell line from circulating colorectal carcinoma showed upregulation of FABP1, linking it to the development of stemness properties in the circulating cancer cells (Alix-panabières et al., 2017). Likewise, in HCC, many reports have suggested the possible role of FABP1 in tumor suppression, as immunohistochemistry analysis of various samples demonstrated the loss of FABP1 in cancerous tissue compared to the

corresponding noncancerous tissue (Graham et al., 2016) In contrast, a report on the role of FABP1 on HCC demonstrated a tumor promoting role of FABP1, whereby it promoted angiogenesis by inducing VEGF expression through its interaction with the VEGF receptor and demonstrated the role of FABP1 in enhancing migration properties via the VEGFR2/Src pathway, hinting at a role played by FABP1 in the metastasis of HCC (Ku et al., 2016). With more epidemiological evidence correlating NAFLD and HCC, reports highlighting the enhanced expression of FABP1 in steatosis induction (the first step of NAFLD) (Mukai et al., 2017), and the important role of the protein in liver lipid accumulation resulting from a high fat diet (Milligan et al., 2018), the role of FABP1 in HCC could be further investigated. In a gastric cancer cohort, FABP1 was reported to be highly upregulated in cancer tissues, with the increased expression correlated with lymph node metastasis and metastasis stage (Jiang et al., 2016). They also demonstrated the co-expression of FABP1 with fatty acid synthase (FASN), further establishing the relationship of FABP1 with lipid accumulation and lipogenesis and suggesting the possible role of lipid homeostasis in gastric cancer progression. Apart from abdominal cancers, FABP1 expression level was also investigated in esophageal cancer, with clinical evidence indicating the loss of FABP1 expression upon the development of esophageal adenocarcinoma from its premalignant condition (Srivastava et al., 2017). The team also demonstrated the translocation of FABP1 from the surface epithelium in Barrette's esophagus to much deeper glands in dysplasia and adenocarcinoma. The expression site directly correlated with the progression of the disease; hence, the expression site of FABP1 is a promising tool in diagnosing the progression of the disease and providing appropriate therapy based on the stage.

FABP2 and cancer

Fatty acid binding protein 2, also known as intestinal fatty acid binding protein, has been linked to the development of various diseases that can lead to the development of cancers, from diabetes to myocardial infarction, stroke and gallbladder disease (Furuhashi et al., 2014). Not much research has been conducted on the role of FABP2 in cancer disease progression. However, a study conducted on the correlation of FABP2 expression with dietary habits and lipid uptake in colorectal cancer illustrated a negative correlation between FABP2 and fat uptake; therefore, FABP2 is not considered an accurate predictor of the risk of colorectal cancer (Kato et al., 2010).

FABP3 and cancer

Fatty acid binding protein 3 is also known as heart fatty acid binding protein. Most reports have demonstrated the upregulation of FABP3 in most of the cancer types investigated, with the high expression of the protein being linked to invasion (Hashimoto et al., 2004), tumor stage (Hashimoto et al., 2004; Tang et al., 2016) and overall metastasis (Hashimoto et al., 2004); however, in some cancers, FABP3 plays a key role in interfering with the cancer signaling pathway, making cancer cells more sensitive to drugs and thus aiding in tumor suppression and hindering tumor growth and metastasis (Nevo et al., 2009). FABP3 has been found to be overexpressed in non-small cell lung carcinoma (Tang et al., 2016), gastric cancer (Hashimoto et al., 2004), leiomyosarcoma (Davidson et al., 2013) and melanoma (Linge et al., 2012); however, FABP3 was found to aid in the suppression of tumors in breast cancer (Huynh et al., 1996; Nevo et al., 2009), lung adenocarcinoma (Okano et al., 2007), lymphomas (Wu et al., 2008) and embryonic cancers (Tang et al., 2016). Although the mechanism by which FABP3 acts is not yet fully understood, FABP3 overexpression has been reported to be linked to resistance to anti-EGFR therapy in lung cancer (Okano et al., 2007).

FABP4 and cancer

Fatty acid binding protein 4, also known as adipocyte fatty acid binding protein, has been found to be abundantly expressed in adipocytes and macrophages. Like other fatty acids, it aids in the transport of fatty acids, is highly expressed in adipocytes and is considered to be a hallmark of adipocyte differentiation. Most interestingly, this protein is released into the serum and is associated with various metabolic disorders (Furuhashi et al., 2014). With various epidemiological and experimental results suggesting the crucial role of FABP4 in metabolic disorders such as diabetes, insulin resistance, cirrhosis and others, which are hypothesized to lead to the development of various types of cancer, FABP4 has garnered interest from cancer researchers in recent years. Since FABP4 is highly expressed and secreted from adipocytes, researchers investigated the correlation of serum levels of FABP4 with the obese breast cancer patient phenotype; the data showed high serum levels of FABP4 in obese breast cancer patients and demonstrated the correlation of the serum levels of FABP4 with tumor size (Hancke et al., 2010). FABP4 has been reported to be involved in cancer aggressiveness in various cancers such as prostate cancer (Uehara et al., 2014), breast cancer (Guaita-Esteruelas et al., 2017a,b), cholangiocarcinoma (Nie et al., 2017), glioblastoma (Cataltepe et al., 2012), and leukemia (Yan et al., 2017). FABP4, a well-known chaperone of fatty acids, was previously thought to play a role in the provision of fatty acids as a source of energy, resulting in cancer progression and has therefore been studied in relation to fatty acid metabolism; however, recent studies have highlighted roles in cancer progression played by FABP4 independent of fatty acids, including acting as a transcription factor (Yan et al., 2017), participating in the inflammatory response (Hao et al.,

2018), and modulating the microenvironment (Guaita-Esteruelas et al., 2017a,b). Epithelial to mesenchymal transition (EMT) is one of the hallmarks of the development of circulating cancer cells, resulting in metastasis of cancer and, hence, it is one of the largest hurdles in cancer therapy. Drivers of EMT have been widely studied and targeted for cancer therapy. FABP4 has also been reported to play a role in EMT transition of cancer cells, as the overexpression of FABP4 has been shown to promote EMT transition in cholangiocarcinoma (Nie et al., 2017) and cervical cancer (Jin et al., 2018). Overexpression of FABP4 in cancer cells has been reported to activate DNA (cytosine-5)-methyltransferase 1 (DNMT1) via upregulation of IL-6/STAT3 axis in AML cells (Yan et al., 2017). They further demonstrated the upregulation of the serum level FABP4 with the development of obesity. Consistently, FABP4$^{-/-}$ mice demonstrated great reduction in the tumor burden and better survival in mouse model. In addition, they also demonstrated deficiency of FABP4 led to decreased white blood cell counts and decreased metastasis to lungs and liver.

The role of FABP4 in the metastasis of ovarian cancer was demonstrated using mice models by Nieman and group in 2011 which demonstrated that the provision of fatty acid, with the help of FABP4, from the omental adipocytes to the cancer cells resulted in omental metastasis (Nieman et al., 2011). They demonstrated the potential role of FABP4 in the tumor microenvironment and the possible role that circulating FABP4 could play in cancer metastasis and progression. Following this discovery, recombinant FABP4 was established and used to study its role in cancer progression; FABP4 has been reported to promote prostate cancer progression by aiding in proliferation and invasion via modulating the PI3K/Akt pathway (Uehara et al., 2014) and to promote the progression of breast cancer (Guaita-Esteruelas et al., 2017a,b). Both reports highlighted the independent role of FABP4 in cancer progression, although FABP4 was previously thought to be a chaperone for fatty acids and to be mostly involved in fat metabolism by aiding in the transport of fat to cancer cells. Apart from directly modulating cancer cells, FABP4 overexpression in the microenvironment and in circulating and associated cells such as macrophages and fibroblasts and adipocytes has been reported to create a niche for the development of aggressive cancer phenotypes, with the expression of FABP4 in these cells linked to poor survival and therapy response, as shown in breast (Hao et al., 2018) and prostate cancer (Huang et al., 2017). The study also demonstrated the production of inflammatory signals by the stromal cells in response to FABP4, enhancing the production of matrix metalloproteinase-2 and -9, which have been reported to aid in metastasis in prostate cancer, contributing to cancer migration (Xu et al., 2005). Fig. 1 shows a schematic drawing of the proposed mechanism of the role of FABP4 in cancer progression with the overexpression of FABP4 in various cancer cells and the exogenous supply of FABP4 to cancer cells resulting in cancer progression. FABP4, apart from its overexpression in cancer cells has also been found to be overexpressed in endothelial cells in response to VEGF expression, resulting in cell proliferation and facilitating angiogenesis (Elmasri et al., 2009). In contrast to the results of various experiments that have provided supporting evidence demonstrating the role that the upregulation of FABP4 plays in cancer progression, the analysis of urothelial cancer cohorts showed that the downregulation of FABP4 was correlated with the development of cancer and invasive lesions (Celis et al., 1996; Boiteux et al., 2009). Downregulated expression in tumorigenesis was also observed in gastric cancer, further confirming different roles of FABP4 in different cancer types and indicating the need for more research to verify its role in different kinds of cancer (Karim, 2016). A schematic drawing of the known mechanism is illustrated in Fig. 1A.

FABP5 and cancer

Fatty acid binding protein 5, also known as epidermal fatty acid binding protein, like other lipid chaperones, is exclusively involved in retinoic acid transport. Like FABP4, this protein has been widely studied in cancer research. This protein has been reported to be highly expressed in cancer cells, contributing to the aggressive phenotypes of cancer cells such as proliferation, invasiveness, tumor burden, insensitivity to therapy and poor survival correlation in various cancers such as gastric cancer (Hashimoto et al., 2017; Zhao et al., 2017), melanoma (Levi et al., 2013), cervical cancer (Wang et al., 2016), breast cancer (Powell et al., 2015), prostate cancer (Kawaguchi et al., 2016; Myers et al., 2016; Al-Jameel et al., 2017), cholangiocarcinoma (Jeong et al., 2012), oral cancer (Fang et al., 2010) and HCC (Ohata et al., 2017). One of the striking features of FABP5 is its correlation with epidermal growth factor receptor, which is one of the key features of cancer metastasis. Powell et al. (2015) and Levi et al. (2013) both demonstrated the critical role of FABP5 in stabilizing epidermal growth factor receptor (EGFR) in breast cancer, which is involved in the prevention of the proteasomal degradation of the receptor; this role is supported by the decrease in the level of the EGFR protein and its phosphorylation upon FABP5 knockout (Levi et al., 2013; Powell et al., 2015). EGFR is a well-known signaling molecule in cancer metastasis and the delay in the abrogation of the signaling pathway results in cancer pathogenesis. Interestingly, one paper also demonstrated an EGFR/FABP5/PPARβ/δ relationship, in which EGFR was found to promote FABP5, which is negatively regulated by Krüppel-like Factor 2 (KLF2) (Kannan-Thulasiraman et al., 2010). Further strengthening the significant role of fatty acids in cancer progression is the fact that the inability of FABP5 to uptake fatty acids in prostate cancer has been shown to decrease the tumor burden in the malignant progression of castration-

resistant prostate cancer (Al-Jameel et al., 2017). Interestingly, FABP5 is most widely reported as being upregulated in the nucleus of most cancer cells, suggesting a possible mechanism wherein FABP5 modulates the transcription factors of oncogenic genes, although such a mechanism has yet to be elucidated. Given all the evidence that points to FABP5 as a specific target for cancer therapy, the mechanism of its interaction with the cancer microenvironment has yet to be explored. A schematic drawing of the potential mechanism is illustrated in Fig. 1B.

FABP6 and cancer

Fatty acid binding protein 6, also known as ileal fatty acid binding protein, has mostly been reported as being involved in the transport of bile acids. Although little research has been conducted regarding the role of this protein in cancer except in colon cancer, where bile acid metabolism plays a critical role in carcinogenesis, FABP6 was found to be upregulated in a cohort of patients; however, the expression level was greatly reduced in cases of node metastasis, indicating the possible role of FABP6 in carcinogenesis rather than metastasis (Ohmachi et al., 2006). However, a study on the influence of bile acid homeostasis and the role of FABP6 as the chaperone of bile acid in colon cancer tumorigenesis demonstrated the deregulation of FABP6 expression upon the fluctuation of bile acid homeostasis, resulting in colon cancer tumorigenesis (Dermadi et al., 2017). A cohort analysis of renal cell carcinoma reported differential expression of IL-FABP, with its overexpression in the metastatic cohort indicating better survival (Tölle et al., 2011).

FABP7 and cancer

Fatty acid binding protein 7 is also called brain fatty acid binding protein. FABP7 is also widely studied in cancer, particularly in glioblastoma in which the

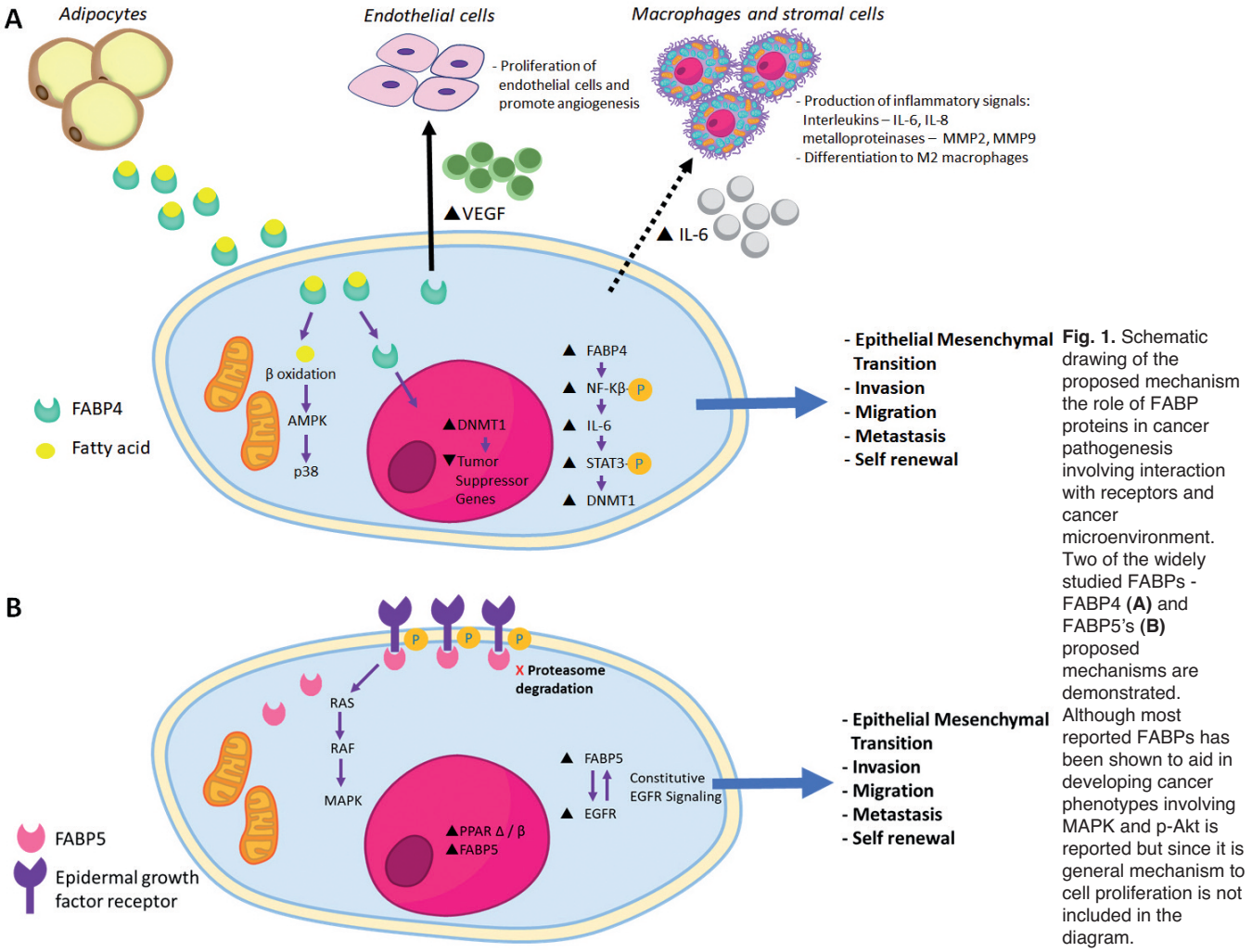

Fig. 1. Schematic drawing of the proposed mechanism the role of FABP proteins in cancer pathogenesis involving interaction with receptors and cancer microenvironment. Two of the widely studied FABPs - FABP4 **(A)** and FABP5's **(B)** proposed mechanisms are demonstrated. Although most reported FABPs has been shown to aid in developing cancer phenotypes involving MAPK and p-Akt is reported but since it is general mechanism to cell proliferation is not included in the diagram.

overexpression of FABP7 has been found to be involved in proliferation and invasion (Rosa et al., 2012). FABP7 has also been reported to be associated with the EGFR status in glioblastoma, as its overexpression is linked to EGFR amplification and invasive phenotypes of cancer, eventually leading to shorter survival times of the patients (Kaloshi et al., 2007). In glioblastoma, FABP7 has also been reported to be a marker for stem cells, with its high expression in grade IV glioblastoma and loss upon differentiation further confirming a vital role played by FABP7 in brain tumors (Morihiro et al., 2013). Found in both the cytoplasm and the nucleus, the exact mechanism by which FABP7 acts in brain tumors have yet to be elucidated; however, there have been studies suggesting both transcriptional and mechanistic roles played by FABP7 in cancer progression. In adenoid cystic carcinoma, co-expression of Notch 1 and FABP7 was correlated with the shortest survival times in patients, indicating that FABP7 may further support the tumorigenic role of the Notch1 signaling pathway (Xie et al., 2018). FABP7 has also been widely studied in breast cancer, in which the FABP7-positive cohort was associated with the triple negative breast cancer group, correlating with poor prognosis, high tumor grade and increased proliferation (Liu et al., 2012). However, another study identified various expression levels of FABP7 in cellular compartment in a breast cancer cohort where the cytoplasmic expression of FABP7 was found to be associated with poorer prognosis than the nuclear expression, even though nuclear expression of FABP7 was linked to high histologic grade, tumor stage and triple negative phenotype (Alshareeda et al., 2012). In some cancers, expression of FABP7 has been observed in the primary site, with gradual loss of expression in metastatic sites and high tumor grades. This phenomenon was observed by another team who examined a melanoma cohort in which 69% of the primary melanomas were found to express FABP7, while the metastatic sites did not; however, FABP7-positive metastatic tissues were found to correlate with poorer survival and higher relapse rates, hinting that although FABP7 is lost in most cases upon metastasis, the expression at a later stage could aid in cancer progression (Goto et al., 2010). The team suggested this loss could be due to the genetic instability of chromosome 6, where the FABP7 gene is located, in melanoma. However, another study on melanoma reported high expression of FABP7 in both primary and metastatic tissues that was correlated to increased tumor size and shorter relapse-free survival time (Slipicevic et al., 2008). Similar dynamic changes in the expression of FABP7 were reported in renal cancer, and FABP7 was found to be significantly upregulated in renal cell carcinoma, although the expression decreased with increasing tumor grade (Tölle et al., 2009). Although FABP7 has been reported as being overexpressed in most cancer cells, and knockdown assays have confirmed its link with cancer cell invasion and proliferation, the full mechanism by which FABP7 acts in cancer is yet to be elucidated.

FABP8, FABP9, and FABP12 and cancer

FABP8, FABP9 and FABP12 have not yet been widely studied in cancer because of their relatively recent discovery. As their names suggest, they are indeed lipid chaperones and have been reported as assisting in the uptake of lipids. Among these three proteins, FABP9 has been recently studied in prostate cancer and was found to have high expression levels in both clinical samples and malignant prostate cancer cell lines. The paper also reported the correlation of high expression of FABP9 with a reduced patient survival rate and the possible role of FABP9 in the acquisition of invasive properties by the cancer cells, suggesting a potential role of FABP9 in the metastasis of prostate cancer (Fayi et al., 2016). FABP12, the newest member of the FABP family, was reported to be expressed in human retinoblastoma cell lines (Liu and Godbout, 2008).

Conclusion

FABPs are of great interest to cancer researchers because of the twelve different kinds with different sites of expression and the recent discovery of their involvement in various kinds of physiological processes including cancer metastasis. FABPs were previously only thought to be lipid chaperones and were considered to be vehicles for fatty acid uptake; however, recent reports have suggested a transcriptional role played by FABPs, indicating the diverse roles of FABPs in cancer pathogenesis. With the rise in the obese population and the dependence of the current population on high fat diets and fats in general, it would not be incorrect to say that the role of FABPs is crucial in maintaining lipid metabolism in our body. Furthermore, with more epidemiological evidence supporting a strong relationship between cancer and obesity, it is important to study the many pathways involved in lipid metabolism and cancer. In addition, with reports indicating diverse roles of FABPs in cancer, it is time to understand FABPs and their mechanisms of action in cancer. Additionally, the release of some FABPs into the serum and the correlation of that release with different cancer stages suggests that FABPs could also be used as biomarkers for cancer prognosis and the response to various therapies. FABPs, as mentioned above, not only modulate cancer phenotypes but have been reported to alter cancer niches by regulating other cells such as endothelial, macrophage, stellate cells to support cancer niches by stimulating a favorable cancer environment, further highlighting the role FABPs could play not only in supporting aggressive cancer phenotype changes but also in modulating the environment, which would be difficult for current therapies to decipher in order to address cancer in its niche. Therefore, it is of great importance to study FABPs and their possible mechanisms of action in cancer pathogenesis.

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