Cellular Signalling 62 (2019) 109336

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Role of fatty acid binding proteins (FABPs) in cancer development and progression

Iain H. McKillop, Cara A. Girardi, Kyle J. Thompson*

Department of Surgery, Carolinas Medical Center, Atrium Health, Charlotte, NC 28203, USA

ARTICLE INFO

Keywords:
Fatty acid binding protein (FABP)
Cancer
Fatty acids
Lipid transport

ABSTRACT

Fatty acid binding proteins (FABPs) are small, water soluble proteins that bind long chain fatty acids and other biologically active ligands to facilitate intracellular localization. Twelve FABP family members have been identified to date, with 10 isoforms expressed in humans. Functionally, FABPs are important in fatty acid metabolism and transport, with distinct family members having the capacity to influence gene transcription. Expression of FABPs is usually cell/tissue specific to one predominant FABP family member. Dysregulation of FABP expression can occur through genetic mutation and/or environmental-lifestyle influences. In addition to intracellular function, exogenous, circulating FABP expression can occur and is associated with specific disease states such as insulin resistance. A role for FABPs is increasingly being reported in tumor biology with elevated exogenous FABP expression being associated with tumor progression and invasiveness. However, a less clear role has been appreciated for dysregulated FABP expression during cell transformation and early expansion.

1. Introduction

Lipids, including fatty acids (FAs), represent fundamental biochemical constituents of all cells and exhibit diverse biological functions that include serving as structural components of biological membranes, energy sources, and a range of signaling pathways that regulate cell function and homeostasis [1]. Cell lipid acquisition occurs through either *de novo* biosynthesis or uptake. However, the insoluble nature of FA in aqueous environments requires chaperones to bind and transport FAs between and within different cellular compartments and organelles, including the plasma membrane, mitochondria, lipid droplets, endoplasmic reticulum, and nucleus (Fig. 1) [1].

Fatty acid binding proteins (FABPs) are relatively small (14–15 kDa), water-soluble proteins that bind long-chain fatty acids (LCFA) and other ligands, including eicosanoids and thiazolidinediones [2].

Although FABP family members only exhibit modest sequence homology, the tertiary protein structures between different family members remain similar, comprising of 10 anti-parallel β-strands organized into two near-orthogonal β-sheets to form a β-barrel structure with an N-terminal helix-turn-helix motif that may also be involved in modulating LCFA binding [3]. Expansion of the FABP family is thought to have occurred largely through gene duplication events, as suggested by the number of FABPs (FABP 4, 5, 8 and 9) closely associated at chromosome 8q21 [4]. Although originally named for the tissue type in which FABP expression was first described, individual FABP members are often expressed in multiple tissues and can be co-expressed. This has given rise to multiple, sometimes misleading, nomenclatures (Table 1).

The dysregulation of lipid metabolism is a significant factor in the development and progression of a range of metabolic disorders, including obesity, diabetes, hepatic steatosis (non-alcoholic steatohepatitis (NASH) and/or alcoholic steatohepatitis (ASH)), and cardiovascular disease [5,6]. More recently, a role for aberrant FABP expression-function has been implicated as a potential mediator of tumorigenesis. The central focus of this review is to describe the known and emerging roles of FABP family members during initial cell transformation and subsequent tumor progression.

1.1. Fatty acid binding protein 1

The first FABP identified; fatty acid binding protein 1 (FABP1, alternative name liver-FABP (L-FABP)), was originally appreciated by Levi et al., as hepatic Z fraction and described for the capability of binding organic anions (such as bilirubin) in the liver [7]. Human FABP1 is located at chromosome 2p12-q11 and (as the nomenclature infers) is highly expressed in hepatocytes, as well as enterocytes, renal tubular cells, and the alveolar epithelium of the lung [8,9]. Unlike other members of the FABP family, the large hydrophobic binding pocket

* Corresponding author at: 404 Cannon Research Center, 1542 Garden Terrace, Charlotte, NC 28203, USA.
E-mail address: kyle.thompson@atriumhealth.org (K.J. Thompson).

https://doi.org/10.1016/j.cellsig.2019.06.001
Received 13 March 2019; Received in revised form 31 May 2019; Accepted 1 June 2019
Available online 03 June 2019
0898-6568/

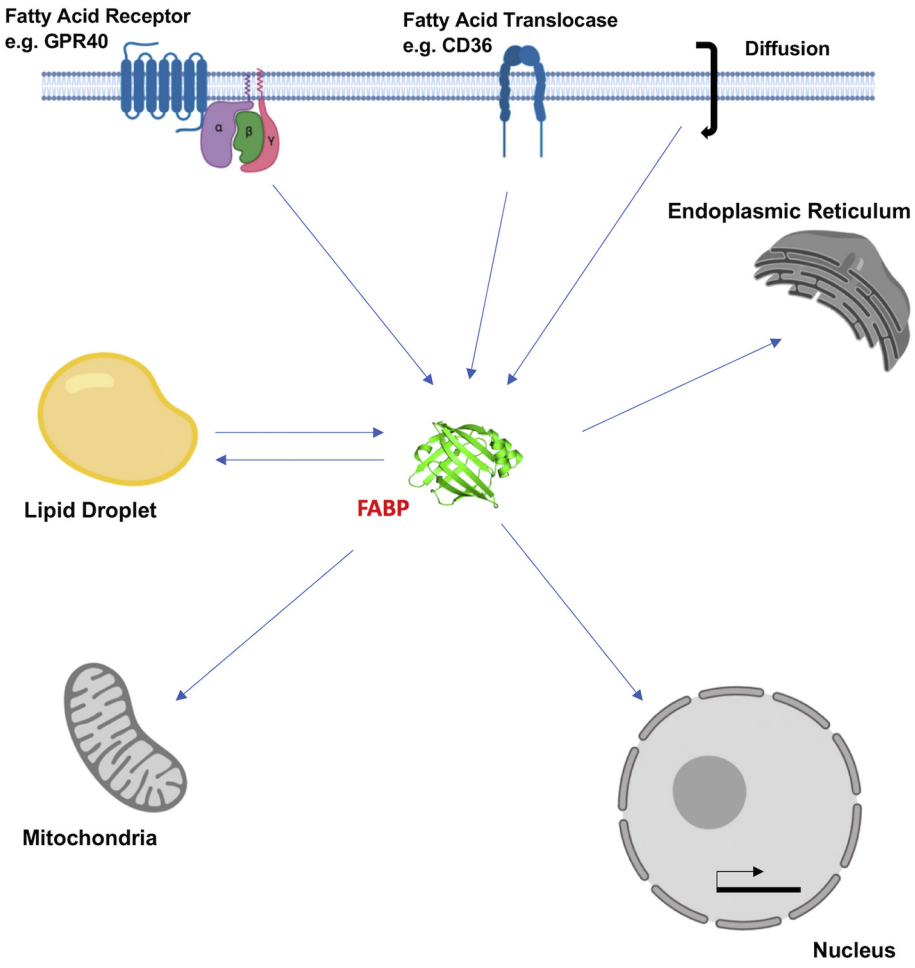

Fig. 1. Cellular functions of fatty acid binding proteins. Uptake of free fatty acids occurs by passive diffusion across membranes and *via* receptors such as the G-protein coupled free fatty acid receptors and fatty acid transport proteins. As lipid chaperones, fatty acid binding proteins (FABPs) have been proposed to play a role in the transport of lipids to specific compartments in the cell: to lipid droplets for storage; to the endoplasmic reticulum (ER) for signaling, trafficking and membrane synthesis; to the mitochondria for oxidation; to the nucleus (in the presence of an appropriate ligand) for the control of lipid-mediated transcriptional programs *via* nuclear hormone receptors (NHRs) or other transcription factors that respond to lipids; or outside the cell to signal in an autocrine or paracrine manner.

located in the FABP1 structure is capable of binding multiple ligands simultaneously [10]. Thus, in addition to binding LCFAs, FABP1 also exhibits the ability to bind a variety of xenobiotics including benzodiazepines, fibrates, β-blockers, and non-steroidal anti-inflammatory drugs [11]. Genetic knock-out of FABP1 in female mice reports increased weight gain (primarily as fat mass gain), hepatic cholesterol, and bile acid levels compared to wild-type counterparts when both groups are maintained on standard rodent diets (5% [*w/w*] calories derived from fat). However, when pair-matched animals were placed on a cholesterol-rich diet (5% [*w/w*] calories derived from fat supplemented with 1.25% [*w/w*] cholesterol), FABP1 deletion augmented weight gain and cholesterol levels, but did so in the setting of decreased bile acid levels [12].

Loss of FABP1 expression is frequently observed in hepatocellular adenoma (HCA), a benign hepatic malignancy most commonly associated with oral contraceptive use [13]. Downregulation of FABP1 is frequently associated with hepatic nuclear factor-1α (HNF-1α), a transcription factor which plays an important role in hepatocyte growth and differentiation [13]. Of note, HCAs deficient in HNF-1α are frequently characterized by steatosis, an unsurprising phenotype given the consequence of FABP1 gene deletion on hepatocyte fat accumulation in FABP1 knock-out mice [12]. Left untreated, HCA patients risk progression to malignant hepatocellular carcinoma (HCC), the most frequently occurring type of primary liver tumor diagnosed [14]. These HCAs are most commonly associated with β-catenin mutations; however, the risk of progression for HCA associated with HNF-1α loss is rare. Despite this finding, loss of FABP1 expression is observed in some HCC, suggesting FABP1 alone may play a role in HCC development and/or progression [15].

Although FABP1 expression can be decreased in HCC, upregulation of FABP1 expression has also been reported, and often correlates to vascular endothelial growth factor (VEGF) expression [16]. Expanding these observations using a mouse xenograft model, FABP1 was reported to increase HCC rates of tumor growth and metastasis, while *in vitro* studies indicate FABP1 interacts with the VEGF receptor 2 (VEGFR2) and Src *via* the focal adhesion kinase (FAK)/cell division control protein 42 homolog (cdc42) pathway. Additionally, FABP1 promoted expression of the angiogenic factor VEGF-A through hypoxia inducing factor-1α (HIF-1α) *via* an Akt/mammalian target of rapamycin (mTOR) signaling pathway [16]. Collectively, these data raise the possibility that FABP1 may be a potential target for chemotherapy in HCCs that overexpress FABP1.

In addition to HCA and HCC, FABP1 is upregulated in gastric cancer, with expression levels correlating with fatty acid synthase (FASN) expression [17]. Although FABP1 expression was not well correlated with tumor stage at time of treatment, presence of FABP1, cytokeratin 20 (CK20) and mucin 2 (MUC2) in peritoneal washings predicted gastric cancer recurrence [17,18].

Experiments with FABP1 knockout mice (using the APCMin/+FABP1(−/−) model of colorectal cancer) report diminished adenoma number and size compared to APCMin/+FABP1(+/+) mice. Concomitant with deletion of FABP1 were changes in lipid profile consisting of increased polyunsaturated fatty acid and decreased saturated fatty acid content [19]. FAPB1 deletion and reduced adenoma burden was also associated with altered eicosanoid profiles manifested as decreased levels of prostaglandin E_2, an arachidonic acid derivative frequently associated with increased tumorigenesis and progression in colorectal cancer models [20]. Of note, FABP1 has broad specificity

Table 1
Fatty acid binding protein nomenclature and distribution.

Name	Alternative name	Gene	Chromosomal location (Hu)	Tissue expression	Reference
FABP1	Liver-FABP (L-FABP)	*FABP1*	2p12-q11	Hepatocytes; Enterocytes); Renal tubular cells; Alveolar epithelium.	[7,8,9]
FABP2	Intestinal-FABP (I-FABP)	*FABP2*	4q28-q31	Intestine.	[20,21]
FABP3	Heart-FABP (H-FABP); Mammary-derived growth inhibitor (MDGI); Ovary-FABP (O-FABP)	*FABP3*	1p33-p31	Myocardium; Skeletal muscle; Mammary gland; Brain; Lung; Stomach.	[26,27]
FABP4	Adipocyte FABP (A-FABP); Adipocyte protein 2 (aP2).	*FABP4*	8q21	White adipose tissue; Brown adipose tissue; Monocytes; Macrophages.	[6]
FABP5	Epidermal-FABP (E-FABP); Cutaneous-FABP (C-FABP); Psoriasis associated FABP	*FABP5*	8q21.13	Epidermis; Liver; Kidney; Lung; Brain Adipocytes; Mammary glands	[75]
FABP6	Ileal bile acid binding protein (I-BABP); Gastrotropin; Keratinocyte-FABP (K-FABP),	*FABP6*	5q23-q25	Ileal enterocytes; Ovary; Placenta; Adrenal glands	[96,97]
FABP7	Brain FABP (B-FABP), Brain lipid-binding protein (BLBP) Mammary-derived growth inhibitor-related gene (MRG)	*FABP7*	6q22-q23	Brain development- post-natal cerebellum	[108,109]
FABP8	Peripheral Myelin Protein 2 (PMP2); Myelin- FABP (M-FABP); Myelin P2 Protein (MP2)	*FABP8*	8q21.3-q22.1.	Peripheral nervous system - Schwann cell myelin; spinal cord; brain stem	[132]
FABP9	Testis-FABP (T-FABP); PERF15	*FABP9*	8q21.13	Testis	[135,136]
FABP10	None	*FABP10*	XXX		
FABP11	None	*FABP11*	XXX		
FABP12	None	*FABP12*	8q21.13		[4,140]

towards other prostaglandins such as growth promoting PGE_1 and PDG_2, as well as growth-inhibitory PGA_1, PGA_2, d12-PGJ_2 and PGJ_2 [21]. Given the significance of eicosanoids in cancer biology ([151,152,153,154]) and the identification of eicosanoids as FABP ligands [20,21], a better understanding of the interaction of FAPBs and these specific ligands during carcinogenesis, and the impact of altered FABP expression in cancer development and progression represents an attractive area of research.

1.2. Fatty acid binding protein 2

Fatty acid binding protein 2 (FABP2, alternative name intestinal FABP (I-FABP)), is located on chromosome 4q28-q31 [22]. Expression of FABP2 is extensive throughout the intestine and mediates absorption of dietary fats through binding and transporting of LCFAs. Other FABPs are located in intestine; however, expression varies by anatomical location, with FABP2 expression primarily in the tips of villi, whereas FABP1 is localized to intestinal crypts [23]. Genetic polymorphisms of FABP2 are associated with human disease development. For example, Ala54Thr is a missense FABP2 variant associated with dyslipidemia, insulin resistance, and obesity [24]. Coupled with evidence linking hyperinsulinemia and central obesity with increased risk for developing colorectal cancer, this makes the Ala54Thr genotype of FABP2 an attractive candidate for investigation. However, it should be noted, the Ala54Thr genotype alone was not associated with elevated risk for colorectal cancer development [25], and these data were confirmed by an additional study series that reported colorectal cancer risk was not significantly different in Ala54Thr genotype compared to individuals without the mutation (OR 1.01; 95% CI 0.86–1.45). However, subjects with the AA genotype with low fat intake diets had a significantly higher risk for colorectal cancer than subjects with either the AT or TT genotype [26].

Beyond the intestinal environment other investigators have addressed the role for FABP2 in cancer progression. For example, an *in vitro* study by Lopes-Cohelo and colleagues examining cross talk between fibroblasts and breast cancer cells, reports decreased FABP2 expression when lipids were added to breast cancer cells conditioned with fibroblast media. Concomitant with this decrease was an increase in fatty acid transport protein-1 (FATP1) expression, facilitating uptake of FA from fibroblasts, while down regulating fatty acid synthase (FASN) activity [27]. These data suggest lipid transport between cells within the tumor microenvironment may play a role in tumor progression following transformation.

1.3. Fatty acid binding protein 3

Fatty acid-binding protein 3 (FABP3, alternative names heart fatty acid binding protein (H-FABP), mammary-derived growth inhibitor (MDGI), and ovarian fatty acid binding protein (O-FABP)) is located on chromosome 1p33-p31 [28]. Expression of FABP3 is high in myocardium and skeletal muscle, with lower expression observed in mammary gland, brain, lung and stomach tissue [29]. In skeletal muscle, FABP3 plays a critical role in delivery of FAs to mitochondria to facilitate energy production *via* β-oxidation. During terminal differentiation of mouse cardiomyocytes, FABP3 is upregulated and inhibits proliferation of the mouse embryonic P19 cell line [30,31]. More recently, the rapid release of FABP3 from damaged myocardium into circulation has led to interest in the use of serum FABP3 levels as a potential early biomarker for acute myocardial infarction [32], and these studies have led to exploration of FABP3 as a similar potential early biomarker for other critical clinical conditions such as pulmonary embolism and traumatic brain injury, in which FABP3 may be rapidly released into the circulation following acute injury [33,34].

With relation to cancer biology, proteomic analysis of uveal melanoma tissue, the most common intraocular malignancy diagnosed in adults, revealed upregulation of FABP3, a result that was confirmed by

immunohistochemical (IHC) analysis [35]. Follow-up experiments using an siRNA approach to deplete FABP3 expression in the 92.1 primary human uveal melanoma cell line reported decreased invasion and motility, suggesting FABP3 may have a role in uveal melanoma metastasis [36]. Similarly, FABP3 expression was reported to be significantly increased in a subset (19%) of gastric carcinomas by IHC, and FABP3-positive staining was associated with increased depth of invasion, vascular invasion, metastases/cancer stage, and decreased survival when compared to FABP3-negative gastric adenocarcinomas. Conversely, no FABP3 expression was detected in gastric adenomas [37].

Analysis of patients diagnosed with non-small cell lung cancer (NSCLC), the most common form of lung cancer diagnosed, also report elevated FABP3 mRNA expression compared to pair-matched, adjacent non-cancerous tissue, a finding confirmed at the protein level by IHC in resected NSCLC tissue. As with uveal melanoma, elevated FABP3 expression in NSCLC was linked to worse overall survival compared to patients with low NSCLC-FABP3 expression [38]. Similarly, microarray analysis of stage I human lung adenocarcinoma samples by Ludovini and colleagues reported elevated FABP3 expression correlated to diminished disease-free survival [39].

Altered FABP3 expression has also been associated with uterine sarcomas, whereby increased FABP3 expression (detected by IHC in resected samples) was clinically diagnostic in differentiating low-grade endometrial stromal sarcoma (LG-ESS; FABP3-negative) from uterine leiomyosarcoma (LMS; FABP3-positive). However, this study did not report any significant differences in outcomes between FABP3 expression levels in LMS *versus* LG-ESS patients [40].

In contrast to uveal melanoma, gastric tumors, NSCLC, and LMS, but in a similar manner as that described for FABP2, FABP3 expression was diminished in breast cancer cells *in vitro* by the presence of cancer-associated fibroblast-conditioned media and lipids [27]. Of note, this finding appears consistent with the molecular profiling of breast cancer samples that reported hypermethylation of the FABP3 promoter, an event typically associated with diminished expression [41].

1.4. Fatty acid binding protein 4

Fatty acid binding protein 4 (FABP4, alternative names adipocyte-fatty acid binding protein (A-FABP) and adipocyte protein 2 (aP2)) is located at chromosome 8q21. High FABP4 expression is found in white and brown adipose tissue, monocytes and macrophages [6], with FABP4 expression being regulated by FAs, peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, and insulin [42]. Following synthesis, FABP4 binds long-chain FAs and other lipid derivatives such as eicosanoids [43]. Unlike most members of the FABP family, FABP4 is able to form both a functional nuclear localization signal (NLS) and nuclear export signal (NES) as a result of conformational changes that occur following the binding of specific ligands (*e.g.* linoleic acid and troglitazone) to facilitate nuclear delivery and influence gene transcription [44]. Dysregulation of FABP4 is associated with a number of disease states in humans including obesity, diabetes, and insulin resistance. Genetic ablation of FABP4 using a knockout mouse model results in the uncoupling of insulin resistance from obesity, suggesting a role for FABP4 in the progression of this disease [45]. Of further interest, FABP4 is reported to act as an adipokine-like paracrine/endocrine signaling molecule, whereupon release from adipose tissue leads to FABP4 acting on adjacent or distant organs to alter metabolic homeostasis and cell function [46].

Abdominal tumors, including ovarian cancer, have a high propensity for metastasis to the omentum, which is largely comprised of adipocytes [47], and protein array data report elevated FABP4 expression in ovarian cancer omental metastases, but not in primary tumors [48]. Further analysis, using IHC to localize FABP4 expression identified increased FABP4 expression in ovarian cancer cells in proximity to adipocytes, suggesting FABP4 may be involved in transporting FAs to cancer cells to facilitate tumor growth/progression [48]. In contrast, employing a FABP4 genetic knockout mouse model reported significantly decreased ovarian cancer omental metastases [47]. The potential role of FABP4 in ovarian cancer progression is also evidenced clinically, Gharpure et al., reporting significantly decreased overall and progression-free survival of ovarian cancer patients with high *versus* low FABP4 expression levels [49]. Expanding on these studies, the authors also identify potential mechanisms whereby FABP4 expression may be regulated as a result of hypoxia (leading to a reduction in miR-409-3p and increased FABP4 expression *via* hypoxia-inducible factor 1 alpha (HIF-1α) activity), and a potential role for Tamoxifen (selective estrogen receptor modulator) in reducing FABP4 expression, FA uptake, and migratory potential in ovarian cancer cells *in vitro* [49].

In addition to breast cancer, Adipocyte-derived FABP4 is implicated in the invasion, migration, and epithelial-mesenchymal transition (EMT) potential of cholangiocarcinoma (CCA) cells *in vitro* and *in vivo*, with BMS309403 (a pharmacological inhibitor of FABP4) significantly impairing adipocyte-induced CCA metastasis and EMT phenotypes [50].

A role for adipocyte-derived FABP4 has also been identified in the progression of other tumor types. In prostate cancer, FABP4 secreted by periprostatic adipose tissue is taken up by prostate cancer cells and is suggested to play a role in enhancing FA availability as an energy source for tumor cells to promote invasive and growth potential [51]. In contrast to peritumor-derived FABP4, studies examining FABP profiles in human prostate cancer cell lines and biopsy samples report a significant decrease in FABP4 expression in tumor *versus* normal prostate epithelial cells/tissue [52,53], and transfection of prostate cancer cells to over-express FABP4 *in vitro* promoted apoptosis *via* increased tumor necrosis factor-alpha (TNF-α) and decreased transforming growth factor-alpha (TGF-α) expression/activity [54]. The potential role(s) of FABP4 in prostate cancer progression are further evidenced when considering metastatic disease, in which elevated FABP4 expression is reported in prostate cancer bone metastases in an obese mouse model [55]. In this study, the authors also exposed metastatic prostate cancer cells to adipocyte-conditioned media *in vitro*, and report increased FABP4, hemeoxygenase-1 (HMOX1) and IL-1β [55] expression, concomitant with increased tumor cell invasiveness, an effect attenuated by blocking FABP4 and/or IL-1β [55]. Similarly, Uehara et al., report FABP4 promotes prostate cancer cell invasion *in vitro via* a phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, and pharmacological inhibition of FABP4 reduced growth of subcutaneous and lung metastatic prostate tumors, effects associated with increased cleaved caspace-3 and cleaved Poly (ADP-ribose) polymerase (PARP) expression [56].

Along with the direct effects of FABP4 on prostate cancer cells, additional reports suggest FABP4 is capable of promoting disease progression indirectly by altering matrix metalloproteinases (MMP) activity and stromal cytokine production. Studies using the PC-3 prostate cancer cells, a cell line that endogenously expresses FABP4 and promotes invasiveness by activation of prostate stromal cells (PrSC) to secrete IL-6 and IL-8, report invasiveness is diminished by treatment with an FABP4 inhibitor (BMS309403) [57]. Furthermore, FABP-4 dependent invasiveness was further increased by upregulation of MMP-9 and MMP-2 gelatinase activity, events that occurred *via* Akt and extracellular signal-regulated kinase (ERK)1/2 dependent signaling pathways [57].

In addition to the role of adipocyte-derived FABP4 in tumorigenesis, emerging studies suggest FABP4 may play a direct role in tumor formation and progression in cancers arising from cells not normally associated with FABP4 expression. For example, FABP4 mRNA and protein was not detected in hepatocytes of mice maintained on normal rodent chow diets, yet FABP4 was robustly detected in hepatocytes of pair-matched mice in a model of dietary obesity-associated HCC progression [58]. Furthermore, serum from tumor-bearing mice

maintained on the high fat diet, as well as patients with obesity-associated HCC, revealed significant increases in circulating FABP4 levels compared to non-obese mice and patients respectively [58]. Additional *in vitro* studies demonstrated addition of exogenous FABP4 to human HCC cells stimulated proliferation and migration [58]. Collectively, these data suggest that in the setting of obesity-induced metabolic stress (hepatosteatosis), liver-derived FABP4 may act independently, or in parallel with, adipocyte-derived FABP4 to promote hepatocarcinogenesis. In contrast to these findings, Yu et al., report decreased FABP4 expression in the BEL-7404 hepatoma cell line *versus* the immortalized, non-tumorigenic L-02 hepatic cell line [59], while Zhong and colleagues report decreased cell proliferation in HCC cell lines that have been transfected with an FABP4 overexpressing plasmid [60]. Furthermore, when these human, FABP-4 expressing HCC cells were injected (subcutaneously) in a nude mouse model, it resulted in decreased tumor size compared to mock-transfected cells [60]. One possible explanation of these findings may lie with the use of specific immortalized tumor and non-tumor cell lines, whereby "baseline" expression profiles differ markedly from the *in vivo* environment in which HCC normally develops and expands. Similarly, the use of molecular biology approaches to express "endogenous" FABP4 in cell lines that do not normally express FABP4, may indicate the function of FABP4 in hepatic tumor progression is context-dependent, whereby elevated exogenous FABP4 (hepatic or adipocyte-derived) enhances HCC progression, while endogenous (tumor-derived FABP4) impairs tumor progression.

Obesity is a significant risk factor/comorbid risk factor for the development and progression of a number of commonly diagnosed cancers, including breast cancer. As with other types of cancer, this has led to investigations as to the relative role of FABP4 (whether originating from distant adipose tissue, peritumoral adipose tissue, or tumor cells *per se*) as a paracrine-endocrine signaling molecule during disease development and progression. For example, analysis of serum from breast cancer patients demonstrated elevated FABP4 levels *versus* healthy individuals independently of obesity status, with increased serum FABP4 being associated with elevated risk for developing breast cancer (1.038; 95%; CI 1.001–1.72) [61]. Conversely, while Jung et al., did not demonstrate a correlation between FABP4 expression and breast cancer metastasis [62], Kim et al., by sorting breast cancers by subtype, report FABP4 tissue expression was elevated in human epidermal growth factor receptor 2 (HER2) subtypes and was lowest in luminal A subtype, with breast cancer FABP4 expression levels being associated with both decreased disease free survival, and overall survival [63].

As discussed for other tumor types, the expression and [apparent] function of tumor and peritumor-derived FABP4 in breast cancer can appear contradictory. Experiments using exogenous FABP4 (to model elevated FABP4 serum levels in breast cancer patients) stimulated proliferation, but not migration, of MCF-7 and MDA-MB-231 breast cancer cells *in vitro*, effects mediated *via* AKT and MAPK signaling pathways [64]. Examination of single nucleotide polymorphisms (SNP) associated with triple-negative breast cancer (TNBC; estrogen receptor- [ER-], progesterone receptor- [PR-], human epidermal growth factor receptor 2- [HER2-]) found a rs1054135 SNP in the 3′ untranslated region (UTR) of FABP4 associated with outcomes. The G allele of rs1054135 was linked to reduced risk of progression and prolonged disease-free survival time. For subjects possessing the rs1054135 SNP with the AA/AG genotype, tumor recurrence risk for overweight patients (BMI $\geq 25\ kg/m^2$) was significantly elevated (2.53; 95%CI 1.06–6.03) [65]. Staining of adipocytes adjacent to TNBC showed expression of FABP4 was significantly lower in patients with the rs1054135-GG genotype [65].

While these data suggest FABP4 may exert either direct or indirect effects on breast cancer cells depending on the clinical study group or experimental model employed, other studies reveal potential synergy between breast tumor progression and adipocyte function that may provide additional targets for therapeutic intervention. Breast cancer is frequently associated with overexpression and secretion of cathepsin-D [66], an aspartyl lysosomal protease involved in tumor metastasis, and an independent marker of poor disease prognosis. Cathepsin-D is also expressed in adipose tissue, and silencing of cathepsin-D inhibits markers of adipocyte function such as PPAR-γ activity, and expression of FABP4 and hormone-sensitive lipase (HSL) [67].

In contrast to those cancers in which FABP4 is implicated in promoting disease progression, decreased FABP4 expression is reported in primary tumors and metastatic liver disease in colorectal cancer [68,69] and bladder cancer patients with increased levels of tumor invasiveness and advanced disease staging [70]. Using a murine model of bladder cancer, in conjunction with an FABP4 knock-out mouse model, Celis et al., report compensatory increases in the expression of other FABP family members, an event not mirrored in human tumor samples [45,71,72]. While the mechanisms that underlie down-regulation of FABP4 in bladder cancer still need to be fully elucidated, it is of interest that PPAR-γ (a regulator of FABP4 expression [70]) was unchanged in bladder tumors, indicating a pathway independent of its activity [73]. In contrast, *in vitro* studies using bladder cancer cell lines suggest PPAR-α, PPAR-β, and PPAR-γ agonists upregulate FABP4 expression, suggesting a clearer understanding of the regulatory mechanisms by which FABP4 expression is controlled may provide a therapeutic approach to reduce bladder cancer invasiveness [70].

The potential role(s) and impact of FABP4 in the cancers discussed thus far are somewhat unusual, in that they focus on tumors that arise in cell populations that do not "classically" express FABP4 (prostate, liver, bladder, breast). While there is little evidence to suggest that FABP4 plays a role in liposarcoma, a recent case report did identify strong FABP4 expression in a rare pleiomorphic bone liposarcoma concomitant with uncoupling protein 1 (UCP1) expression (a marker of brown adipose tissue) [74]. In addition to adipose tissue, FABP4 is robustly expressed in macrophages [75], and there is an established role for tumor-associated macrophages (TAM) in breast cancer progression, a high density of TAMs in the intra-tumoral environment being associated with poor outcomes and diminished survival [76]. Thus, it is of interest to note that expression of FABP4 in a subset of CD11b+, F4/80+, MHCII-, Ly6C-TAMs promotes breast cancer progression, with FABP4 deficiency resulting in decreased tumor volume and metastasis [76]. Furthermore, expression of FABP4 in TAMs promoted interleukin 6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) signaling *via* a nuclear factor-kappaB (NF-κB)/miR-29b pathway [76], data that provides additional insights into potential mechanisms that underlie the regulation of FABP4 expression.

In order to expand from small clusters of transformed foci, tumors must avoid hypoxia, nutrient depravation, and accumulation of waste products as they extend beyond the original blood source [77]. Expression of FABP4 may also contribute to progression of cancers through the ability to promote angiogenesis. Experiments employing human vascular endothelial (HUVEC) cells report expression of FABP4 is linked to mTORC1 activity, and FABP4 expression was linked to important pro-angiogenic signals such as p38 MAPK, endothelial nitric oxide synthase (eNOS), and stem cell factor (SCF)/c-kit [78]. Conversely, studies employing FABP4-deficient mice report decreased VEGF-induced angiogenesis with concomitant changes in eNOS expression [79]. Expression of FABP4 in the presence of VEGF has also been linked to the delta-like ligand (DLL) 4-NOTCH signaling pathway [80] and targeted inhibition of endothelial FABP4 in a model of ovarian cancer progression resulted in marked decreases in angiogenesis and tumor growth/metastasis of xenografts [81]. Collectively, these data suggest FABP4, and potentially other FABP isoforms, may play an integral role in tumor cell growth *per se*, as well as other components of the tumor expansion process following initial cell transformation.

1.5. Fatty acid binding protein 5

Fatty acid-binding protein 5 (FABP5, alternative names epidermal-FABP (E-FABP), cutaneous fatty-acid-binding protein (C-FABP) or

psoriasis associated fatty-acid-binding protein) is found on chromosome 8q21.13. Of the FABP family members, FABP5 is the most widely expressed and is readily detectable in the epidermis, liver, kidney, lung, adipocytes, brain, and mammary glands [82]. Like other FABP family members, FABP5 binds long-chain FAs and other ligands and similar to FABP4, FABP5 possess a functional NLS outside of its primary sequence that facilitates nuclear translocation in response to binding specific ligands. Studies using genetic deletion of FABP4 result in compensatory upregulation of FABP5 in adipocytes, suggesting an important role in lipid and glucose homeostasis [45].

Given the wide range of tissue distribution, it is not surprising that FABP5 is frequently dysregulated in cancer. In a screening of normal, benign prostate hypertrophy (BPH) and prostate cancer samples, no FABP5 staining was detected in normal tissue, whereas FABP5 positive staining was present in > 70% of prostate cancer samples [83,84]. Transfection of antisense therapy against FABP5 into the (highly invasive) PC-3 prostate cancer cell line significantly decreased invasiveness *in vitro* and following injection into a nude mouse model (compared to mock-transfected cells), with decreased tumor burden using FABP5-deficient cell lines also being associated with decreased VEGF expression [83]. Similarly, in patients with lymph node metastatic prostate cancer, expression of FABP5 was upregulated in both tissue and serum compared to patients with localized pancreatic cancer [85].

Because FABP5 is endogenously expressed in untransformed cells, the mechanisms by which changes in expression and function of FABP5 in cancer cells often appears to be tissue specific. From a functional perspective, FABP5 preferentially delivers retinoic acid (RA) to its alternate intracellular receptors, PPAR-β/δ, as opposed to cellular RA-binding protein II (CRABP-II, which delivers RA to the retinoic acid receptor (RAR)) [86]. In the setting of the FABP5-RA-PPAR-β/δ pathway, PPAR-β/δ drives the transcription of target genes associated with survival and growth/proliferation (such as VEGF and pyruvate dehydrogenase kinase 1 (PDK1)) as opposed to cell cycle arrest and differentiation [87]. In prostate cancer cells, disruption of either FABP5 or its nuclear target, PPAR-β/δ inhibits PC3 cell growth [88]. Furthermore, FABP5 expression is regulated *via* a positive-feedback loop, wherein FABP5-dependent activation of PPAR-β/δ promotes increased transcription of the *FABP5* gene [88]. Experiments detailing the relationship between FABP5 and PPAR-γ in prostate cancer report significant decreases in proliferation when blocking PPAR-γ, an effect associated with diminished VEGF production [89]. Pharmacological targeting of this interaction, through competitive binding of FABP5 to prevent uptake of FAs (and other ligands), diminishes progression of castration-resistant PC3-M cells [90].

As with prostate cancer, disruption of the RA-RAR axis can also occur in breast cancer due to the elevated ratio of FABP5 to CRABP-II, and diminishing this ratio resulted in decreased proliferation of breast cancer cells derived from *MMTV-neu* mice tumors when treated with RA [91]. Of further note, expression of FABP5 in breast cancer cells is regulated, at least in part, by the epidermal growth factor receptor (EGFR), and treatment of breast cancer cells with an EGFR ligand stimulated FABP5 expression *via* PI3K and ERK-MAPK signal transduction pathways, culminating in activation of NF-κB [92]. In TNBC, FABP5 expression is upregulated *via* EGFR signaling associated with RA signaling and correlated with poorer disease-free survival and overall survival when compared to low FABP5-expressing tumors [93,94]. More recently, studies report a role for CRABP-I, a member of the same RA-binding family as CRABP-II, and while CRABP-I expression is significantly down-regulated in ER + ve breast tumors, expression is maintained in TNBC. Persistence of CRABP-I in cytoplasm of TNBC cells effectively sequesters RA to the cytoplasm, thus facilitating growth and proliferation [95]. High FABP5/CRABP-II ratios are also observed in other cancers, including recurrent craniopharyngiomas, cutaneous squamous cell carcinoma, thyroid cancer, glioblastomas, and pancreatic cancer [95–98].

Kruppel-like factor 2 (KLF2) is a transcription factor with anti-carcinogenic activity that is commonly down-regulated in breast cancer, whereby KLF2 expression (in breast cancer) correlates positively with survival. KLF2 likely exerts its effects by inducing expression of CRABP-II, inhibiting expression of FABP5, and promoting growth arrest [94]. Another approach evaluated FA treatment to overcome FABP5/RA signaling and discovered treatment with saturated FA led to increased binding to FABP5 and permitting RA to signal through PPAR-β/δ while treatment with unsaturated FA promoted FABP5/RA signaling [99]. Of note, therapeutic approaches using curcumin to overcome FAPB5-RA signaling report restoration of RA sensitivity in TNBC cells, possibly through suppression of the p65 subunit of NF-κB [100].

Experiments profiling simvastatin (ZOCOR; a statin prescribed to lower cholesterol/triglyceride levels) treatment of melanocytes led to identification of FABP5-dependent delivery of 15d-PGJ_2 to PPAR-γ, leading to cell cycle arrest and apoptosis. Disruption of this pathway *via* knockdown of FABP5 abolished PPAR-γ activation but amplified the apoptotic response. These simvastatin-dependent effects were not observed in primary melanocytes, suggesting targeting of FABP5 expression and/or activity could be used to amplify the activity of 15d-PGJ_2 to treat melanoma [101]. Expression of FABP5 was also identified as a mediator of inflammation *via* PGE_2 through NF-κB induction of microsomal PGE synthase-1, and may represent a novel approach to limit inflammation-associated carcinogenesis and tumor progression [102].

1.6. Fatty acid binding protein 6

Fatty acid-binding protein 6 (FABP6, alternative names ileal bile acid binding protein (I-BABP), gastrotropin and keratinocyte-FABP (K-FABP)), is located on chromosome 5q23-q25 [103,104]. Expression of FABP6 occurs mainly in ileal enterocytes, with lesser expression in adrenal glands, ovaries, and the placenta [105]. Unlike the majority of other FABP family members, FABP6 has greater affinity for bile acids (BAs) than FAs, and can cooperatively bind more than one BA ligand within its hydrophobic core, suggesting a role in the entero-hepatic circulation of BAs [106]. From a functional standpoint, experiments with FABP6-deficient mice suggest the major role of FABP6 is to facilitate apical-basolateral transport of BAs through the cytosol [107].

Previous studies have identified links between BAs and colorectal carcinogenesis in animal models [108]. Exposure of the colonic epithelium to BAs can promote carcinogenesis through several mechanisms, including oxidative stress with DNA damage/genomic instability, apoptosis, epigenetic changes, and changes in the gut microbiota [46,109–111]. These findings, as well as the observation that BA leads to dramatic increases in FABP6 expression, led to the examination of genes associated with BA homeostasis that may be associated with development of colorectal cancer [112]. Expression of FABP6 mRNA was significantly elevated in 75 of 78 subjects with pair-matched colorectal tumor and adjacent non-tumor tissue. Elevated FABP6 levels were also associated with smaller tumor size, decreased invasion (into the bowel wall), and preferential localization to the left colon, while metastatic lesions were associated with diminished FABP6 expression [113]. These observations were further supported in a study that examined the gene expression profile of sessile serrated adenomas/polyps, a precursor to colorectal cancer development from benign microvesicular hyperplastic polyps. These analyses report FABP6 was upregulated approximately 10-fold from normal colonic tissue, and > 20-fold from microvesicular hyperplastic polyps [114]. A similar study analyzing renal cell carcinoma tissue revealed elevated FABP6 mRNA (> 39-fold) compared to normal tissue. However, expression was not confirmed at the protein level, and no correlation with outcomes was reported [115].

1.7. Fatty acid binding protein 7

Fatty acid binding protein 7 (FABP7, alternative names brain FABP (B-FABP), brain lipid-binding protein (BLBP) and mammary derived

growth inhibitor-related gene (MRG)), has been identified at chromosome 6q22-q23 [116]. Expression of FABP7 is greatest during mouse brain development, with the highest expression in the post-natal cerebellum and lower levels in the young adult and further declining in adults [117]. Experiments utilizing FABP7 knockout mice report no gross morphological or histological features, although FABP7 deletion negatively impacted brain development, learning, memory, and emotion [82]. Although FABP7 can bind both ω-3 and ω-6 fatty acids, greater affinity is observed for the former and may be important in cancer progression [118].

Malignant gliomas are the most common adult brain cancers diagnosed and are associated with frequent recurrence and high mortality. Lipid dysregulation is often observed in gliomas and is associated with worse prognosis [119,120]. Compared to normal brain tissue and low-grade astrocytomas, FABP7 is up-regulated in glioblastoma [121,122], and increased nuclear localization of FABP7 in glioblastoma is associated with EGFR amplification and poorer outcomes [123,124]. The expression of FABP7 is also linked to enhanced cell motility and migration, with a decreasing docosahexaenoic acid (*DHA*, [ω-3]) -arachidonic acid (*AA*, [ω-6]) ratio appearing to govern these effects, perturbing the normal, tightly regulated ratio of fatty acids in brain tissue and providing increased substrate for prostaglandins such as PGE2 to promote progression [125–127].

Increased expression of FABP7 in malignant gliomas is associated with expression of glial fibrillary acidic protein (GFAP), a protein normally expressed in astrocytes [128]. Studies report reduced phosphorylation of NF-I proteins is associated with FABP7 and GFAP in a subset of malignant glioma cell lines [129], and the dephosphorylation of NF-I proteins appears to be a result of the phosphatase activity of a cleaved form of calcineurin found in malignant glioma cells [130]. RNA interference experiments suggest NF-IA and NF-IB isoforms are most relevant NF-I isoforms in driving GFAP and FABP7 co-expression in malignant glioma cells *in vitro* [131]. Additionally, FABP7 over-expression in malignant glioma cells can be significantly reduced by knockdown of PAX6 expression; however, over-expression of PAX6 could not induce endogenous FABP7 expression in FABP7-negative glioma cell lines [132]. Additionally, migration of glioma cell lines could be reduced by targeting FABP7 expression using pharmacological inhibitors for PPAR-γ [133].

The upregulation of FABP7 is also linked to increased proliferation and invasiveness of superficial spreading melanoma (SSM) compared to nodular melanoma [134], and increased FABP7 expression is associated with thicker lesions and decreased duration of relapse-free survival [135]. While the mechanisms that underlie the role of FABP7 in SSM remain to be fully elucidated, it is reported that phorbol-12-myristate-13-acetate (PMA) mediated protein kinase C (PKC) activation of a MAPK-ERK1/2 signaling pathway enhanced proliferation and reduced apoptosis of melanoma cells *in vitro* [136]. However, in a separate study, inhibition of PKC and ERK1/2 signaling decreased FABP7 expression, yet PMA treatment downregulated FABP7 in the presence of activated ERK1/2, suggesting an alternative PKC-mediated, MAPK/ERK1/2 independent pathway(s) may also be present [135].

Elevated FABP7 expression has also been reported in a subset (15.6%) of cases with the basal phenotype of breast cancer, and FABP7 expression was associated with decreased lymph node stage and increased survival [137]. A separate study confirmed the association of FABP7 with the basal phenotype of breast cancer, and specifically in TNBC lesions [138], with the association between FABP7 and higher grade-worse prognosis being linked to increased FABP7 nuclear translocation and elevated EGFR expression [138]. While this study did not report links between FABP7 expression-localization and outcomes, a more recent study by Alshereeda et al., addressed this issue and reported nuclear FABP7 localization was associated with improved disease-free interval compared to cytoplasmic-only localization, or cytoplasmic and nuclear expression of FABP7. It is of particular note that these findings for breast cancer appear to contradict the apparent role of FABP7 in malignant gliomas, suggesting additional factors beyond FABP7 nuclear localization may underlie these phenotypic difference(s) [139].

Dramatic upregulation of FABP7 is also reported in adenoid cystic adenocarcinoma (ACC), an aggressive neoplasia arising in the salivary glands. Expression of FABP7 in ACC is linked to significantly worse survival compared to low-expression FABP7 ACC tumors, and diffuse FABP7 localization (cytoplasmic and nuclear) was specifically associated to poorer survival compared to nuclear- or cytoplasmic-specific FABP7 localization [140]. In a similar manner, a study of patients with ACC reports poorer outcomes in patients with high expression of Notch1, and its target; FABP7 [141].

1.8. Fatty acid binding protein 8

Fatty acid binding protein 8 (FABP8, alternative names peripheral myelin protein 2 (PMP2), myelin fatty acid binding protein (M-FABP) and myelin P2 protein (MP2), is located on chromosome 8q21.3-q22.1. FAPB8 is one of the major proteins found in Schwann cell myelin of the peripheral nervous system, with lower expression levels observed in the spinal cord and brain stem [142]. Ligands for FABP8 include LCFAs, cholesterol, oleic acid, and retinoid [142]. Studies with FABP8 knockout mice revealed a role for lipid homeostasis in myelin, but no overt defect in function was observed [143]. There have been no studies to our knowledge that have linked aberrant FABP8 expression or function to tumorigenesis, although FABP8 has been used as an antigen to induce experimental autoimmune neuritis in an animal model for Guillain-Barré syndrome [144].

1.9. Fatty acid binding protein 9

Fatty acid binding protein 9 (FABP9, alternative names testis-FABP (T-FABP) or PERF15), is located at chromosome 8q21.13 in humans [145]. FABP9 is highly expressed in the inner acrosomal membrane of sperm and is associated with germ cell apoptosis [146]. Deletion of FABP9 results in increased sperm head abnormalities; however, there is no loss of fertility [147]. From a cancer perspective, the majority of FABP studies in prostate cancer have focused on FABP5. However, profiling of prostatic cancer cell lines has demonstrated elevated FABP9 mRNA and protein expression in malignant (compared to benign) cell lines, and suppressing FABP9 expression in highly malignant (PC3-M) cells inhibited invasive potential. Expanding this study to analyze human prostate cancer samples using an IHC approach revealed FABP9 staining intensity was significantly greater in carcinomas *versus* benign cases and correlated with reduced patient survival time. [148].

1.10. Fatty acid binding proteins 10 and 11

The Expression of fatty acid binding protein 10 (FABP10) and 11 (FABP11) have not been identified in mammalian species; FABP10 having been detected in avian, crustacean and fish species, whereas FABP11 is restricted to fish. Phylogenetic analysis of both genes are cited as evidence of evolutionary decent of FABP members from a single ancestral gene [149].

1.11. Fatty acid binding protein 12

Fatty acid binding protein 12 (FABP12) is the most recently identified member of the FABP family, and relatively little data currently exists regarding its functional properties. Chromosomal mapping reveals FABP12 to be located in the same chromosomal region as FABP4, FABP5, FABP8 and FABP9 (8q21.13) [4], and FABP12 mRNA expression has been reported in human, mouse, and rat tissue (high levels in retinal and testis tissues, lower expression in the cerebral cortex, kidney and epididymis), but not in the genomes of chicken, or zebrafish [4,150]. From a cancer perspective, analysis of human retinoblastoma

cell lines indicate expression of FABP12 in four lines [4], and in malignant prostatic epithelial cell lines compared to a benign cell lines [148].

2. Concluding remarks

The FABPs are a class of intracellular lipid transporters which are highly expressed in tissues associated with high metabolic activity and/or lipid storage. Although their individual functions remain relatively unknown, dysregulated FABP are increasingly appreciated as promoters of human disease, including cancer. Given the diversity of ligands associated with carcinogenesis and/or chemoprevention-therapy that can be bound by FABPs, including n-3 and n-6 (eicosanoids) fatty acids, further studies to characterize the role of FABPs in governing these pathways may led to additional therapeutic strategies.

Almost universally, overexpression of exogenous (extracellular/circulating) FABPs are associated with growth promotion and invasiveness of cancers; however, the role of overexpressed endogenous (intracellular) FABPs are less clear. While some studies report loss of FABP with increased progression and worse outcomes, other studies have reported increased tumor aggressiveness associated with elevated endogenous FABP levels. The resolution of this discrepancy may lie within the context of endogenous FABP overexpression. For example, the forced expression of FABP is often associated with diminished tumor aggressiveness, perhaps as a result of a lack of fatty acid ligands as a means to promote growth. In cancers where there is an abundance of lipid, such as in the obese state or disease metastasis to adipose tissue, endogenous FABP expression is induced rather than forced, suggesting FABP are responding to energy availability in the form of fatty acids to promote growth and tumorigenesis. As tumors outgrow their oxygen and nutrient supply, hypoxia promotes VEGF-induced angiogenesis *via* FABP4 activity. Future studies to resolve the discrepancies between intracellular and extracellular changes in FABP expression, as well as a better understanding of how FABPs signal to promote growth are needed to provide greater insight into their role in tumorigenesis and raise the potential of developing novel therapeutic targets for cancer treatment.

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