FABP5 as a novel molecular target in prostate cancer

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Abstract

Emerging evidence suggests that dysregulated lipid signaling is a key factor in prostate cancer (PC), through fatty acid activation of the nuclear receptors peroxisome proliferator-activated receptors (PPARs), leading to the upregulation of protumoral genes. Fatty acid-binding proteins (FABPs) are intracellular lipid-binding proteins that transport fatty acid to PPARs, facilitating their activation. FABP5 is overexpressed in PC, and correlates with poor patient prognosis and survival. Genetic knockdown or silencing of FABP5 decreases the proliferation and invasiveness of PC cells in vitro, and reduces tumor growth and metastasis in vivo. Pharmacological FABP5-specific inhibitors also reduce tumor growth and metastases, and produce synergistic effects with taxanes. In this review, we present current data supporting FABP5 as a novel molecular target for PC.

Introduction

PC is the most common cancer in men. Around 1.1 million men are found to have PC annually and three out of every four cases are diagnosed in men over 65. Almost all men who have local or regional PC will survive more than 5 years after diagnosis. However, this figure falls to ~30% for PC diagnosed as distantly metastasized. Some men with PC do not respond well or become unresponsive to hormone therapy, which is known as castration-resistant prostate cancer (CRPC). CRPC is identified by rising levels of prostate-specific antigen (PSA) despite chemical castration, and >90% of patients with CRPC develop bone metastases. The average survival for patients with CRPC is only 2–3 years. Consequently, there is an urgent need to develop novel pharmacotherapeutics to treat metastatic CRPC and prolong survival.

Lipids and prostate cancer

Epidemiological studies have shown a positive relationship between the consumption of dietary fats, lipid metabolism, and the development of PC. Linoleic acid, a common component of dietary fat, and its metabolic derivative, arachidonic acid (AA), have both been associated with prostate tumor progression [1]. Prostate adenocarcinomas show a preference for lipids to fuel their growth, and dysregulated lipid signaling and metabolism is
observed is suggested to be a key feature in PC cell survival [2]. Elevated lipid metabolism is also observed in patients with PC relapse, and is associated with greater mortality [3].

*De novo* fatty acids are synthesized by fatty acid synthase (FASN), and monoacylglycerol lipase (MAGL) cleaves 2-monoacylglycerols to generate free fatty acids. Increased FASN and MAGL activities (generating increased local levels of fatty acids) promote tumorigenesis in multiple cancer types [3–6]. Fatty acids can be used as a crucial energy source for proliferating cancer cells [7]. Fatty acids and their metabolites also serve as agonists at nuclear receptor peroxisome proliferator-activated receptors (PPARs). The PPARγ isoform regulates the expression of proangiogenic genes within a cell. Similar to FASN and MGL, PPARγ is overexpressed in metastatic prostate adenocarcinomas, promoting tumorigenicity, and this overexpression is associated with shorter patient survival times [8–10]). Fatty acid-derived ligands also activate the PPARβ/δ isoform, which similarly promotes cancer cell survival and tumor growth [11,12]. These results link fatty acid signaling to cancer aggression, and disruption of this signaling network could constitute a novel approach to treat metastatic PC.

**FABPs**

FABPs are a class of intracellular lipid-binding proteins that transport hydrophobic lipids throughout cellular compartments, including to peroxisomes, mitochondria, endoplasmic reticulum, and the nucleus (reviewed in [13,14]). FABPs are small cytosolic proteins comprising a central water-filled binding pocket surrounded by a beta barrel (a tubular protein structure). FABPs have broad specificity, including the ability to bind long-chain fatty acids, eicosanoids, bile salts, and peroxisome proliferators. FABP delivery of lipids and their derivatives to the nucleus facilitates the activation of PPARs and the transcription of PPAR-regulated genes [8,15–17]. There are ten FABP isoforms expressed in humans, most of which have restricted tissue expression patterns [15].

**FABPs and prostate cancer**

Given that FABPs are regulators of fatty acid metabolism and fatty acids are critical in PC progression, researchers have investigated the expression and role of the various FABP isoforms in many cancers [18–20], including PC (summarized in Table 1). To date, the best evidence supports a significant role for FABP5 in PC. FABP5 [also known as epidermal FABP (isoform), keratinocyte FABP (K-FABP), and psoriasis-associated-FABP (PA-FABP)] is found in the epidermis, tongue, adipocytes, macrophage, dendritic cells, mammary glands, brain, stomach, intestine, kidney, liver, lung, heart, skeletal muscle, testis, retina, lens, spleen, and placenta. FABP5 has a generic role of FA binding and trafficking, lipid metabolism, and regulating cell growth [14]. Moderately high FABP5 expression in PC is associated with significantly reduced patient survival [8,21]. FABP5 is one of 15 signature genes the upregulation of which can predict PC [22] and, as part of a panel of biomarkers, can distinguish between PC and adjacent benign tissues with sensitivities and specificities of ∼90–100% [23].
FABP5 expression levels in PC

The normal prostate lacks, or has minimal, FABP5 expression, but tumor levels of FABP5 are significantly increased in PC (Table 1). Adamson et al. showed increased staining for FABP5 in samples from prostatic carcinomas compared with benign hyperplasia [17], a result that was confirmed in independent studies [23,24]. Morgan et al. showed that FABP5 expression (cytoplasmic and nuclear) was increased in patients with PC compared with patients with benign hyperplasia and this was associated with decreased survival time [25]. A >20-fold upregulation of FABP5 is also observed in lymph node metastases compared with the primary tumor [24,26,27]. Most recently, Nitschke and colleagues showed that FABP5 was overexpressed in patients with radical prostatectomy or palliative transurethral resection, but this was independent of tumor (T) Stage, Gleason score, nodal status, or PSA levels [28]. In this study, FABP5 overexpression was also associated with SPOP and FOXA1 (genes that show frequent point mutations in primary PC) mutations, and with increased PPARγ signaling.

Increased FABP5 expression is observed in PC cell lines, with nonaggressive or weakly aggressive cell lines lacking FABP5 expression and highly aggressive cells demonstrating high FABP5 expression levels [29–31]. FABP5 is also upregulated in cadmium-induced prostate epithelial cells [32].

FABP5 expression is transcriptionally regulated (Figure 1). The FABP5 promoter is methylated in benign PC cell lines and normal prostate tissue, but becomes hypomethylated and transcriptionally active in aggressive PC cell lines and prostate tumors, resulting in elevated FABP5 expression [31] In breast cancer, NF-kappaB (NF-κB) induces the expression of FABP5 through two response elements in the promoter of the epidermal growth factor receptor [33], and PPARγ activation increases FABP5 expression. The expression of FABP5 is downregulated by the anticarcinogenic Krüppel-like factor KLF2 [33,34].

FABP5 genetic silencing in PC

In preclinical models, it has been widely demonstrated that genetic modulation of FABP5 regulates PC progression. Overexpression of FABP5 in benign PC cell lines increases, whereas FABP5 downregulation reduces, the migratory and invasive potential of PC cells in vitro, typically by ~50% [9,12,25,31,35–37]. FABP5 overexpression promotes, whereas its inhibition attenuates, the primary tumor growth and metastasis of PC cells orthotopically implanted into mice or rats [17,25,29,38,39].

FABP5 mechanism of action in PC

The mechanisms through which FABP5 promotes tumorigenesis in several cancer types have been partially elucidated, and primarily originate through the delivery of fatty acid agonists to PPARs (both PPARγ and β/δ) to activate these nuclear receptors and upregulate a variety of protumoral genes that promote cell survival, growth, and migration (summarized in Figure 1). FABP5 upregulates vascular endothelial growth factor (VEGF) in PC, a key factor that promotes angiogenesis and metastasis [9,17,25,40]. FABP5 upregulates matrix
metalloproteinases (MMPs), enzymes that degrade the extracellular matrix and promote cellular migration and metastasis [41]. FABP5 also enhances epithelial–mesenchymal transition in hepatocellular carcinoma, a phenotypic change that promotes cancer growth and metastasis [42]. FABP5 induces de novo fatty acid synthesis in highly aggressive PC and breast cancer cells [37]. In mammary tumor stroma, FABP5-expressing macrophages produce high levels of IFN-β, which can further enhance the recruitment of tumoricidal effector cells [43]. FABP5 also induces inflammation and cytokine production through NF-κB, activated by reactive oxygen species and protein kinase C [36]. Knockdown of FABP5 downregulates survivin and high mobility group protein A1 expression [44]. Together, these changes in gene expression increase cancer cell growth and survival, migration and invasiveness, angiogenesis and inflammation (Figure 1). The increase in some of these protumoral proteins (e.g., NF-κB and EGFR) acts to further increase the expression of FABP5.

Pharmacological inhibition of FABP5 in PC

Al-Jameel and colleagues were the first to show that FABP5 inhibition using the small molecule SBFI26 developed by Stony Brook University decreased the proliferation, migration, and invasiveness of CRPC \textit{in vitro} (75–100 mM) and \textit{in vivo} (1 mg/kg) by decreasing fatty acid uptake and PPARγ levels [38]. SBFI26 contains an α-truxillic acid core related to incarvillateine, a natural antinociceptive compound (Figure 2). They showed that SBFI26 interferes with the FABP5-PPARγ signaling pathway at the initial stage of the signal transduction by binding competitively to FABP5. This prevents fatty acids from activating downstream cancer-promoting genes. More potent or more selective FABP5 inhibitors developed by Stony Brook University, SBFI102 and SBFI103 (Figure 2), are also cytotoxicin PC3, DU-145, and 22Rv1 cells \textit{in vitro} (IC\textsubscript{50} 3.1–11.4 μM depending on cell type) and reduced tumor growth \textit{in vivo} (20 mg/kg, intraperitoneally, once daily) in PC3 implanted BALB/c nude mice [45]. The Stony Brook University compounds have been licensed and are being developed by Artelo Biosciences, Inc. (the lead compound is called ART26.12).

Al-Jameel and colleagues recently described a recombinant FABP5 inhibitor (dmrFABP5) where two of the three amino acids in the fatty acid-binding motif of FABP5 were altered, losing its ability to bind fatty acids. dmrFABP5 significantly suppressed the proliferation, migration, invasion, and colony formation of PC3-M \textit{in vitro} (0.5 μM), and mice treated with dmrFABP5 (20 mg/kg) had a reduction in metastatic rates and the size of primary tumors. Similar to other FABP5 inhibitors, dmrFABP5 suppressed the cancer cells by blocking fatty acid stimulation of PPARγ [46]. Together, these studies show that the antitumoral effect of FABP5 inhibition in PC is a class effect and not specific to particular molecules.

Although indirect, it has also been shown that polyphenol proanthocyanidins from grape stem extracts and adzuki beans suppress the proliferation of PC3 cells and suppress FABP5 mRNA [47]. In breast cancer, the polyphenol extract curcumin suppresses the expression level of FABP5 and PPARβ/δ in triple-negative mammary carcinoma cells, also decreasing VEGF [48]. In colon cancer, the antitumoral effects of pterostilbene (a stilbenoid chemically related to resveratrol found in almonds and blueberries) are mediated by FABP5.
Thus, the antitumoral effects of other natural compounds appear to rely on FABP5 inhibition and/or downregulation (the first Stony Brook University compound SBFI26 was based on the chemical structure of incarvillateine, which comes from the plant *Incarvillea sinensis*).

**FABP5 inhibitors and taxanes produce synergistic inhibition in PC**

Taxanes, such as docetaxel and cabazitaxel, are standard treatment regimens for chemotherapy-naïve CRPC, although resistance to these drugs can develop [50]. Ideally, new pharmacological treatments in PC would work alongside or even synergize with taxanes. This was recently shown for taxanes and pharmacological FABP5 inhibitors in cell and mouse PC models. The second-generation Stony Brook University inhibitors SBFI102 and SBFI103 combined with docetaxel or cabazitaxel produced synergistic cytotoxicity in PC3, DU-145, and 22Rv1 cells in vitro [51]. Furthermore, the in vivo administration of docetaxel with either SBFI102 or SBFI103 (20 mg/kg, administered at the same time, from day 15 after PC3 implantation) potentiated the antitumoral effects of docetaxel (5 mg/kg) in nude mice implanted with PC3 cells. The ability of these FABP5 inhibitors to synergize could lead to exciting new combination therapies with anticancer efficacy, with the potential to reduce taxanes doses and, thus, the associated adverse effects.

**Rationale for targeting FABP5 in PC**

As discussed in this review, aggressive PC is characterized by the upregulation of multiple components of fatty acid metabolism and signaling pathways (i.e., FASN, FABP5, and PPARγ), which are independently associated with reduced patient survival [10,24,25,29,52]. Therefore, what advantage does FABP5 present over lipid-metabolizing enzymes? As an example, FASN has emerged as a target to treat PC and related malignancies [53] and at least one FASN compound (TVB-2640) has entered into clinical testing in nonsmall cell lung cancer (NCT03808558), colon cancer (NCT02980029), breast cancer (NCT03179904), astrocytoma (NCT03032484), or solid tumors (NCT02223247) (but not PC as yet). However, other enzymes, such as MAGL [6], can also simultaneously generate fatty acid pools (see Figure 1) that promote tumor growth and metastasis; thus, inhibiting FASN alone might not be sufficient to reduce fatty acid levels. There is also evidence that exogenous fatty acids contribute to lipid synthesis in PC [54], and that prostate tumors upregulate proteins and increase their rates of fatty acid oxidation [55–57]. Consequently, therapeutics targeting singular lipid-metabolizing enzymes might be limited in their efficacy. By contrast, the robust upregulation of FABP5 in advanced PC coupled with its key role in promoting prostate tumor growth and metastasis elicited by both endogenous and exogenous lipid pools [39] positions this protein as a major node in lipid-driven metastasis and an attractive target to treat metastatic PC. In parallel to its key role in transporting lipids to prometastatic nuclear receptors, FABP5 also regulates cytosolic lipid pools (e.g., lipid droplets) that enhance cancer cell survival. Therefore, FABP5 inhibition targets lipid metabolism and signaling at distinct sites to suppress PC cell survival, tumor growth, and metastasis. Based on these findings, we suggest that FABP5 emerges as a clear target for the development of pharmacotherapeutic interventions to mitigate PC growth and metastasis.
Future research

The identification of FABP5 as a molecular target in PC is still early in the drug development process, and there might be challenges because of its ubiquitous expression. Early experiments revealed that the small molecule developed by Stony Brook University New York SBF126 (now ART26.12) has a half-life of ~3 h [58], does not inhibit hERG, causes no significant inhibition of CYPs (1A2, 2A6, 2C9, 2C19, 2D6, or 3A4), does not show activity at a range of other molecular targets, is negative in in vitro genotoxicity studies, and has low addictive potential [59]. Future work will examine acute and chronic toxicity screening in vivo, and the development of robust clinical trial protocols to assess the use, and monitor the consequences, of FABP5 inhibitors in PC in combination with taxanes.

Concluding remarks

In light of growing evidence in this field, we suggest that FABP5 inhibition in prostate cancer is a compelling concept. With specific and selective inhibitors now available, future preclinical research and well-designed clinical trials are warranted to assess this molecular target in humans.

Acknowledgments

Conflict of interest

S.E.O’S is an independent consultant and works as a paid scientific advisor to Artelo Biosciences, who paid her for her time in the preparation of this manuscript. M.K. is a co-inventor of the FABP5 inhibitors developed by Stony Brook University, and is funded in this area by research grants from Artelo and NIH grants DA035949 and CA237154.

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FIGURE 1.
The role of fatty acid-binding protein 5 (FABP5) in regulating cancer cell survival and progression through fatty acid activation of nuclear receptors. Abbreviations: EGFR, epidermal growth factor; FA, fatty acid; IFN-γ, interferon gamma; MMP, matrix metalloproteinases; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PPAR, peroxisome proliferator-activated receptor; VEGF, vascular endothelial growth factor.
FIGURE 2.
Chemical structures, potency, and selectivity of small-molecule fatty acid-binding protein 5 (FABP5) inhibitors based on an α-truxillic acid core related to incarvillateine developed by Stony Brook University now licensed and being developed by Artelo Biosciences Inc.
| FABP  | Expression in PC                                                                 | Role/function in PC                                      | Effect of inhibition/knockdown                                                                 | Refs                      |
|-------|---------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------|
| FABP1 | Elevated in LNCaP, PC3, and DU145                                               | Not known                                               | Knockdown decreases proliferation and apoptosis                                                 | [60,61]                  |
| FABP2 | Increased and decreased expression in PC cell lines                            | Not known                                               | Not known                                                                                        | [60-62]                  |
| FABP3 | Decreased in LNCaP, PC3M, and DU145                                            | Not known                                               | Not known                                                                                        | [60-62]                  |
| FABP4 | Evidence for increased and decreased expression in PC cell lines; mean serum FABP4 level (not tumor expression) higher in patients with PC | Transfection of FABP4 into DU145 cells blocks growth and induces apoptosis | Upregulation induces apoptosis and increases cytokine secretion; downregulation decreases cytokine secretion and reduced invasive capacity of PC-3 cells | [60,61,63,64]            |
| FABP5 | Overexpressed in various PC cell lines and patient samples; correlated with survival rates and sometimes with Gleason score; overexpression can be caused by hypomethylation of FABP5 promoter region, increasing its transcription; also upregulated by PPAR activation | Increased delivery of fatty acids to the nucleus causes activation of PPARγ and PPARα/β and estrogen receptor α. Together, this increases survival genes, VEGF metabolic genes, NF-kB signaling, and pro-invasiveness of PC | Knockdown of FABP5 decreases proliferation, apoptosis, and invasiveness (in multiple cells types) in vitro via AMPK-FOXO3A signaling, and reduces tumor growth and metastasis in vivo. This is associated with decreased VEGF. FABP5 deficiency impairs endothelial cell proliferation, chemotactic migration, and angiogenic sprouting. Pharmacological inhibition of FABP5 by SBFI26 in vitro (75–150 μM) decreases PC3 cell viability and invasiveness and in vivo (1 mg/kg for 25 days) decreases tumor growth and metastases. FABP5 inhibitors SBFI-102 and SBFI-103 are cytotoxic and increase cytotoxic and tumor-suppressive effects of taxanes in vitro and in vivo. | [8,9,16,17,21,23,29,31,35-40,45,51,52,65,66] |
| FABP6 | Expressed in most PC cell lines, and is upregulated in PC3 cells and human patient samples | Not known                                               | Not known                                                                                        | [61,62]                  |
| FABP7 | Upregulated in LNCaP, 22RV-1, PC3, and PC3-M cells                             | Not known                                               | Not known                                                                                        | [60,61]                  |
| FABP8 | Upregulated in PC3 cells and downregulated in 22RV-1 cells                     | Not known                                               | Not known                                                                                        | [61]                     |
| FABP9 | Upregulated in 22RV-1, PC3, and PC3-M cells and patient samples                | Not known                                               | Knockdown in PC3-M cells inhibits their invasive potential                                        | [61]                     |
| FABP12| Upregulated in LNCaP, 22RV-1, and PC3−M cells                                  | Not known                                               | Not known                                                                                        | [61]                     |