Fatty acid-binding proteins at the inflammation-cancer interface: Isoform-specific metabolic-immune mechanisms and therapeutic implications (Review)

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Abstract. Fatty acid-binding proteins (FABPs) comprise ten mammalian isoforms (FABP1-FABP9 and FABP12), each a small intracellular lipid chaperone traditionally viewed as a mediator of fatty acid uptake, trafficking and metabolic partitioning. Evidence from metabolic disease, immunology and oncology indicates that selected FABP isoforms also regulate inflammatory signaling, immune-cell metabolism and tumor-stromal crosstalk. Prior reviews have mainly emphasized single isoforms of FABPs or single disease categories. The present narrative review organized FABP biology as a context-specific evidence map across the inflammation-cancer interface, in which each principal claim is reported together with the experimental system, with the outcome and limits of extrapolation described. The main mechanistic focus was FABP4, FABP5 and FABP7. The structural determinants of isoform specificity, ligand routing to nuclear receptors and the non-classical secretion of FABP4 as a circulating adipokine were summarized. The evidence supports a model in which FABPs may contribute to, rather than fully explain, the progression from metabolic stress to chronic low-grade inflammation, premalignant remodeling and the establishment of the tumor microenvironment. In the present model, FABP4 links adipocytes, macrophages, endothelial cells and tumor cells through fatty acid shuttling and inflammasome/cytokine signaling; FABP5 connects retinoic acid and peroxisome proliferator-activated receptor β/δ signaling with tumor-cell growth and T helper/regulatory T-cell balance; and FABP7 regulates neural-lineage tumor plasticity through ligand-dependent retinoid X receptor α signaling. In addition, translational evidence was stratified into clinically observed biomarkers, preclinical therapeutic targets and conceptual future technologies. Particular attention was paid to biomarker confounding by obesity, diabetes, age and sex, and to the therapeutic paradox in which FABP5 inhibition may suppress T helper 17 cell-driven inflammation while enhancing regulatory T-cell-mediated immunosuppression in cancer. This synthesis provides a restrained conceptual framework for stage-, isoform- and cell-type-specific FABP research.

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Abbreviations: AA, arachidonic acid; CRC, colorectal cancer; DHA, docosahexaenoic acid; EMT, epithelial-mesenchymal transition; FABP, fatty acid-binding protein; FAO, fatty acid oxidation; GBM, glioblastoma; GSC, GBM stem-like cell; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; LCFA, long-chain fatty acid; LPS, lipopolysaccharide; LXR, liver X receptor; MAFLD, metabolic dysfunction-associated fatty liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NLRP3, NLR family pyrin domain containing 3; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RA, retinoic acid; RXR, retinoid X receptor; STAM, stelic animal model; TAM, tumor-associated macrophage; TLR, Toll-like receptor; TME, tumor microenvironment; Treg, regulatory T cell; UCP2, uncoupling protein 2; VLDL, very low-density lipoprotein

Key words: fatty acid-binding proteins, inflammation-cancer interface, tumor microenvironment, adipokine, metabolic reprogramming, biomarker, therapeutic target

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1. Introduction

Overview of the fatty acid-binding protein (FABP) family. FABPs are a family of small (14-15 kDa) intracellular lipid-binding proteins abundantly expressed in tissues with high fatty acid metabolic activity (1). To date, 10 mammalian FABP isoforms (FABP1-9 and FABP12) have been identified, each exhibiting tissue-specific expression patterns while sharing a highly conserved tertiary structure (1). They form a β-barrel composed of two nearly orthogonal β-sheets capped by two short α-helical segments, creating an internal ligand-binding pocket that accommodates long-chain fatty acids (LCFAs) and other hydrophobic ligands (2,3). The conserved β-barrel architecture and the ligand-binding pocket common to all isoforms are illustrated in Fig. S1A, and the tissue distribution and functional grouping of the inflammation- and cancer-relevant isoforms are summarized in Table SI.

FABP isoforms differ not only in tissue distribution, but also in ligand-binding properties and intracellular functions. Liver-type FABP (FABP1 or L-FABP) is the only family member that can simultaneously bind two fatty acids or various other hydrophobic ligands due to its uniquely large binding pocket (4). By contrast, heart-type FABP (FABP3 or H-FABP), adipocyte-type FABP (FABP4 or A-FABP/aP2), epidermal-type FABP (FABP5 or E-FABP) and brain-type FABP (FABP7 or B-FABP) bind a single fatty acid with high affinity and perform distinct metabolic and signaling roles in their respective tissues (1). Notably, while FABPs were traditionally classified as intracellular proteins, studies have since demonstrated that several isoforms, including FABP4, are released extracellularly via non-classical secretion pathways and function as circulating adipokines (3,5).

Link between chronic inflammation and cancer. Over the past two decades, metabolic and inflammatory pathways have come to be regarded as tightly integrated, a relationship for which Hotamisligil (6) introduced the term 'metaflammation' and which has since been examined extensively in relation to FABP biology (7). Chronic metabolic disorders such as obesity, type 2 diabetes and atherosclerosis are accompanied by persistent low-grade inflammation, which serves as a common substrate for the development and progression of various cancer types (3). Signaling networks such as the PI3K/AKT axis further integrate metabolic and inflammatory inputs (8). Among the molecular nodes that connect this metabolism-inflammation-cancer axis, FABPs, particularly FABP4 and FABP5, which are co-expressed in adipocytes and macrophages, have emerged as central regulators that mediate both lipid metabolism and immune responses (3,9).

FABP4 knockout mice exhibit protection against insulin resistance and atherosclerosis under high-fat diet or genetic obesity conditions, indicating that FABP4 directly contributes to the pathophysiology of metabolic disease (9,10). Furthermore, in macrophages, FABP4 coordinates cholesterol trafficking and inflammatory activity by regulating the peroxisome proliferator-activated receptor (PPAR)γ and IKK pathways (11). Elevated circulating FABP4 levels correlate not only with obesity, insulin resistance and cardiovascular disease, but also with increased risk of obesity-associated cancer types, including breast cancer (7,12). Meanwhile, FABP5 is elevated relative to matched normal tissue in several tumor types, where higher expression has generally been associated with a poorer outcome, although the reported magnitude varies by tumor type and study (13). FABP5 promotes tumor growth and metastasis by transferring ligands to nuclear receptors such as PPARβ/δ and acts as a protumorigenic factor in prostate, cervical, breast and pancreatic neuroendocrine tumors (13,14). Notably, FABP5 also regulates lipid metabolism and T cell differentiation within the tumor microenvironment (TME), suggesting that FABP functions as a metabolic-immune integrator beyond its role as a simple lipid transporter (15).

However, the role of FABPs is neither uniform nor straightforward. Within the same family, isoforms can exhibit opposite functions depending on the tissue, cell type or disease stage. For example, FABP5 supports tumor growth in several tumor types, yet in colorectal cancer (CRC) the reported direction is contested, with one study identifying it as a tumor suppressor acting through FASN degradation and autophagy, and another describing tumor-intrinsic FABP5 as growth-promoting through hypoxia-inducible factor (HIF)-1α under hypoxia (16,17). Such context-dependent duality demands cautious interpretation when approaching FABPs as singular therapeutic targets.

Aims and structure. Previous FABP-related reviews have provided important foundations but have generally emphasized either a single isoform, a single disease category or a broad structural overview (3,7,9,13,14,18,19). This has left three practical gaps for molecular medicine. First, the same isoform can have divergent effects across cell types, for example, FABP5 in T helper 17 (Th17) cells, regulatory T cells (Tregs) and tumor cells. Second, circulating FABP4 is both a metabolic biomarker and an endocrine-like adipokine; but these two roles are often discussed separately. Third, therapeutic discussion has frequently grouped clinically observed biomarkers, preclinical inhibitors and future technologies into the same translational tier.

The present review addresses these gaps by organizing FABP biology as a context-specific evidence map across the inflammation-cancer interface rather than as a simple isoform catalogue. The primary emphasis is on FABP4, FABP5 and FABP7 as the mechanistic literature on inflammatory signaling, TME remodeling and tumor-cell plasticity is the most extensive and includes the most *in vivo* perturbation work. FABP1, FABP3 and FABP6 are discussed as contextual isoforms, whereas FABP2, FABP8, FABP9 and FABP12 are summarized in Table SI to avoid overextending claims beyond the available evidence.

The present review had three objectives. First, to map the isoform-specific and cell-type-specific roles of FABPs in inflammatory disease and cancer. Second, to evaluate FABPs as candidate metabolic-immune signaling integrators that may contribute to, rather than fully explain, transitions from metabolic stress to chronic inflammation and cancer. Third, to stratify clinical translation into observed biomarkers, preclinical therapeutic targets and conceptual future technologies, while highlighting therapeutic risks such as the FABP5-Treg paradox.

Earlier syntheses have addressed the FABP family from complementary angles, including metabolic and cardiovascular disease with an emphasis on FABP4 and FABP5 (3,9), peritumoral adipose tissue (18), FABP5 across tumor types (13) and the structural and ligand-binding biology of the family as a whole (1). The present review differs in scope rather than in quality of coverage as it examines the level of individual claims across isoforms, cell types and disease contexts, and reports for each claim what was measured and in what system.

The present review was prepared as a narrative synthesis supported by a structured, targeted literature search. PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov), Web of Science Core Collection (https://www.webofscience.com) and Scopus (https://www.scopus.com) were searched for peer-reviewed English language articles published from January 1990 to March 2026, with an emphasis on literature published after January 2020 and on landmark earlier studies that established FABP structure, knockout phenotypes, secretion biology or clinical biomarker associations. Search terms combined 'fatty acid-binding protein' or 'FABP' with individual isoforms (FABP1-FABP9 and FABP12) and disease or mechanism terms including 'inflammation', 'tumor microenvironment', 'cancer', 'adipokine', 'PPAR', 'NLRP3', 'MASLD', 'MASH', 'MAFLD', 'NAFLD', 'NASH', 'inflammatory bowel disease', 'colorectal cancer', 'psoriasis', 'skin cancer', 'breast cancer', 'biomarker' and 'therapeutic target'. Reference lists of relevant reviews and mechanistic primary articles were also screened.

Studies were prioritized if they provided the following direct mechanistic or translational evidence: i) Genetic or pharmacological perturbation of FABPs *in vivo*; ii) human tissue, circulating biomarkers or cohort data; iii) cell-type-specific *in vitro* validation; or iv) integrative reviews that clarified isoform function, ligand routing or therapeutic targeting. Conference abstracts without full peer-reviewed articles, non-English articles without accessible translations and studies lacking a direct connection to FABP biology were not considered central to the synthesis. The search aimed to support a focused conceptual review to balance breadth with mechanistic relevance, rather than to provide exhaustive enumerative coverage.

As the present article is a conceptual narrative review rather than a systematic review or meta-analysis, no prospective protocol, PRISMA flow diagram, formal risk-of-bias scoring or effect-size pooling were performed, and records of the number of items screened and excluded were not kept. Therefore, there was no attempt to express the weight of the evidence as a summary grade. A label such as 'strong' would have to be earned by studies that agree on the disease, on the cell type and on the outcome measured, and for most FABP circuits the available human association data, animal perturbation experiments and cell-based mechanistic work do not agree on all three. In place of grading, each principal claim in the present review was reported together with the system in which it was obtained, the manipulation performed, the outcome that was actually measured and the point at which extrapolation stops. Measured outcomes were kept distinct throughout and not combined, including inflammatory or immune phenotype, growth or spread of an already established tumor, premalignant change, cancer incidence and biomarker association in the absence of any perturbation. Table I sets out this mapping for the principal claims, and Table SII gives the study-level extraction from which it was built.

Section 5 (FABP networks at the inflammation-cancer interface: A context-specific evidence map) compares three disease contexts in which a preceding inflammatory or metabolic state has been linked to cancer: Metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC), obesity and breast cancer and inflammatory bowel disease (IBD) and CRC. These contexts permit comparison of where FABP-specific observations connect and where the evidence remains incomplete. They are not presented as three established FABP-mediated routes from inflammation to cancer. In the intestinal context, the inflammatory and neoplastic observations have not been experimentally connected in the studies discussed in the present review.

Section 6 (Clinical translation: Biomarkers, therapeutic targeting and readiness) distinguishes human biomarker observations, related early clinical registry records, preclinical interventions and conceptual approaches. This classification describes the setting and stage of investigation; it does not grade mechanistic certainty, clinical validity or efficacy. A common evidence grade was not assigned since the available studies differ in their biological systems, interventions and outcomes.

2. Structural and functional foundations of FABPs

Conserved β-barrel structure. Although FABPs share only 20-70% sequence identity, their tertiary structures are nearly superimposable and highly conserved (20-23). The first cytosolic FABP was identified in intestinal and hepatic tissue by Ockner *et al* (24), and subsequent work revealed the broader physiological importance of this protein family in cellular fatty acid uptake and partitioning (25). The conserved β-barrel fold, evolutionary relationships among the 10 mammalian isoforms and their chromosomal organization are summarized in Fig. S1. All FABP isoforms are small proteins of 126-134 amino acids (14-15 kDa) that form a β-barrel composed of 10 antiparallel β-strands organized into two nearly orthogonal β-sheets (20,21). One end of the β-barrel is capped by a short helix-loop-helix motif, and the interior contains a water-filled cavity that accommodates hydrophobic ligands (4,20,26).

The gene structures of FABPs are also highly conserved. Most FABP genes consist of four exons and three introns, and several isoforms cluster within the same chromosomal region (20). For example, FABP4, FABP5, FABP8, FABP9 and FABP12 form a gene cluster on the same chromosome, suggesting that they evolved through tandem duplication of a common ancestral

Table I. Claim-level evidence map for FABPs at the inflammation-cancer interface.

Claim and context[a]	Experimental evidence (system, manipulation, outcome measured)	Human data	What is not established	(Refs.)
FABP4 amplifies macrophage inflammatory output (inflammatory phenotype)	Mouse macrophages; FABP4 deletion and BMS309403. Outcomes measured: NF-κB- and AP-1-dependent cytokine production, UCP2-dependent mitochondrial ROS, NLRP3 priming and IL-1β release.	Circulating FABP4 correlates with obesity, insulin resistance, type 2 diabetes and cardiovascular disease.	That this macrophage phenotype contributes to human cancer initiation. All perturbation data are murine and the outcome measured is inflammation, not tumor incidence.	(11,46-53)
FABP4 is released non-classically and acts as a circulating adipokine (inflammatory phenotype; biomarker association)	Mouse adipocytes; lipolytic stimulation and fasting; antibody neutralization. Outcomes measured: Secretion, hepatic glucose production and glucose tolerance.	Serum FABP4 rises with adiposity. Mendelian randomization supports adiposity as a cause of higher FABP4, placing the protein downstream of the adipose state.	Whether the tumor state itself raises circulating FABP4. Post-resection decline in colorectal cancer is confounded by surgery, resolving inflammation and altered metabolic state.	(5,71-75,123)
Circulating FABP4 and colorectal cancer risk (cancer incidence)	Not applicable; human observational and genetic epidemiology.	Prospective nested case-control, 1,324 incident cases: RR 1.01 (0.92-1.12) per SD after adjustment for body size. Two-sample Mendelian randomization, 58,131 cases: OR 1.10 (0.95-1.27); cis-only estimate 1.56 (1.09-2.23) in women, not surviving correction for multiple testing.	A causal contribution of circulating FABP4 to colorectal cancer risk. The analysis was powered to detect an OR of about 1.17 per SD, so a small effect is not excluded. No equivalent analysis exists for breast cancer or for colitis-associated disease.	(119)
FABP4 in the adipocyte-macrophage-tumor axis supports growth of established tumors (established tumor growth)	Mouse mammary tumor models; FABP4 deficiency; TAM subset analysis; adipocyte co-culture. Outcomes measured: Tumor growth, metastasis, IL-6/STAT3 signaling, triglyceride synthesis and lipid droplet accumulation. In a direct test using mice lacking mature peritoneal adipocytes, ovarian tumor growth and carboplatin response were unaffected; endothelial-specific FABP4 deletion reduced omental tumor growth whereas myeloid-specific deletion did not.	Higher tumoral FABP4 associates with a poorer breast cancer survival.	Any contribution to tumor initiation. Every perturbation experiment measures growth or spread of an already established tumor; none measures incidence. Whether adipocyte-derived supply is required, as distinct from sufficient; the dominant FABP4-expressing compartment differs between tumor types.	(12,44,84-86)

Table I. Continued.

Claim and context[a]	Experimental evidence (system, manipulation, outcome measured)	Human data	What is not established	(Refs.)
FABP4-mediated lipid uptake drives $CD8^+$ T-cell senescence in adipocyte-rich tumors (established tumor growth; inflammatory phenotype)	Ovarian cancer models; BMS309403 or FABP4 knockdown. Outcomes measured: Lipid peroxidation, senescence markers and antitumor function in combination with chemotherapy.	Not established beyond descriptive association in human tissue.	Generalization beyond adipocyte-rich tumors. BMS309403 engages FABP3, FABP4 and FABP5, so the effect is not attributable to FABP4 alone. In the same niche, mature adipocytes are not required for tumor growth, so the adipocyte-to-T-cell fatty acid route has not been shown to be necessary.	(147)
FABP5 routes retinoic acid and fatty acids to PPARβ/δ and supports tumor-cell growth in several tumor types (established tumor growth)	Prostate, cervical and breast cancer cell lines and xenografts; FABP5 knock-down or knockout; manipulation of the FABP5:CRABPII ratio. Outcomes measured: Proliferation, invasion, VEGF and MMP expression and xenograft growth.	Tissue FABP5 associates with poor prognosis in several tumor types.	That this applies across tumor types; see the two rows below. Ligand routing was established largely in cell systems and no human intervention data exist.	(13,14,34, 36-38,87-90)
FABP5 in colorectal cancer: reported direction is opposite between studies (established tumor growth)	Normoxic monolayer and subcutaneous xenograft (HCT116, SW620): stable FABP5 overexpression increases FASN ubiquitination, lowers FASN, suppresses mTOR, induces autophagy and reduces tumor growth; stable knock-down does the reverse. Hypoxic monolayer and three-dimensional spheroid (HCT116, WiDr): transient FABP5 silencing lowers hypoxia-induced HIF-1α and its target genes and reduces spheroid growth. Both studies used HCT116, so cell line does not explain the difference. A third report adds a distinct axis: p53-induced FBXO2 directs FABP5 to chaperone-mediated autophagy, lowering poly-unsaturated fatty acids and conferring resistance to ferroptosis, so FABP5	FABP5 protein is lower in 90 paired carcinoma specimens than in adjacent tissue and higher FABP5 associates with longer survival. FABP5 mRNA is higher in the paired series used by the opposing study, but that series (GSE8671) is a colorectal adenoma set, not carcinoma.	Which variable sets the direction. Disease stage, analyte, oxygen tension and perturbation kinetics all differ and none have been tested as the determining factor. The HIF-1α arm has no *in vivo* experiment and tested loss of function only.	(16,17,92)

Table I. Continued.

Claim and context[a]	Experimental evidence (system, manipulation, outcome measured)	Human data	What is not established	(Refs.)
	sensitizes colorectal cells to ferroptosis; the *in vivo* arm manipulated FBXO2 rather than FABP5.			
FABP5 in myeloid cells restricts tumor growth (established tumor growth)	Mouse tumor models; E-FABP knock-out and a small-molecule E-FABP activator. Outcomes measured: Tumor growth and IFN-β response in tumor-associated macrophages.	Not established in human tissue.	How this antitumor myeloid direction relates to the protumorigenic roles described for tumor-cell FABP5. The two have not been tested in the same system and should not be summed.	(59,61)
Acute loss of FABP5 function in regulatory T cells raises IL-10-dependent suppressive capacity (inflammatory phenotype)	Mouse *in vitro*-differentiated and *ex vivo* regulatory T cells; acute BMS309403 (engaging FABP3, FABP4 and FABP5) or FABP5 knockdown; dependence on cGAS, STING and IFNAR shown by knockdown or knock-out. Outcomes measured: oxidative phosphorylation, cristae structure, cytosolic mtDNA, IL-10 and suppression assay.	*In vitro*-expanded human regulatory T cells show the same metabolic and suppressive shift in four donors. Reanalysis of published human breast-carcinoma regulatory T-cell transcriptomes shows higher FABP5, IL-10 and interferon-stimulated genes than blood regulatory T cells.	Tumor regulatory T cells express more, not less, FABP5; the reconciling proposal is that lipid scarcity in the tumor interstitium produces a functional deficit. FABP5 was not perturbed *in vivo* in tumor-bearing animals, direct type I interferon production by tumor regulatory T cells was not shown, tumor data rest on one transplantable model, and no independent replication was identified in the literature searched.	(67)
FABP7 delivers polyunsaturated fatty acids to RXRα and supports glioblastoma stem-like plasticity (established tumor growth)	Patient-derived glioblastoma stem-like cells and cell lines; FABP7 knock-down; arachidonic-acid-rich vs. docosahexaenoic-acid-rich conditions. Outcomes measured: SOX2 and ZEB1 induction, proliferation and migration.	FABP7 expression and subcellular localization associate with glioma grade and with selected breast cancer phenotypes.	Any role outside neural-lineage tumors. The mechanism has not been tested in premalignant lesions of liver, colon, skin or breast and must not be presented as a shared premalignant pathway.	(96-102)

Table I. Continued.

Claim and context[a]	Experimental evidence (system, manipulation, outcome measured)	Human data	What is not established	(Refs.)
FABP6 in the intestine: The physiological and the cancer-associated observations are not connected (inflammatory phenotype; biomarker association)	Intestinal-epithelium-specific FABP6 deletion; rescue by *Ligilactobacillus murinus* or taurodeoxycholic acid. Outcome measured: Colitis severity, which is worsened by loss of FABP6.	FABP6 mRNA is elevated in most paired colorectal cancer samples and is detectable from the adenoma stage; expression only, with no perturbation.	Any link between the two. No experiment has tested FABP6 manipulation in a colitis-associated carcinogenesis model, and the only loss-of-function phenotype available runs opposite to the direction a driver role would predict.	(116,117)

[a]Outcome classes are stated in parentheses after each claim and are not combined: Inflammatory or immune phenotype; growth or spread of an already established tumor; premalignant change; cancer incidence; and biomarker association in the absence of perturbation. AP-1, activator protein 1; cGAS, cyclic GMP-AMP synthase; CRABPII, cellular retinoic acid-binding protein II; E-FABP, epidermal FABP; FABP, fatty acid-binding protein; FASN, fatty acid synthase; FBXO2, F-box protein 2; HIF-1α, hypoxia-inducible factor 1α; IFNAR, interferon α/β receptor; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; NLRP3, NLR family pyrin domain containing 3; OR, odds ratio; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; ROS, reactive oxygen species; RR, relative risk; RXRα, retinoid X receptor α; SD, standard deviation; STING, stimulator of interferon genes; TAM, tumor-associated macrophage; UCP2, uncoupling protein 2; VEGF, vascular endothelial growth factor; ZEB1, zinc finger E-box binding homeobox 1.

gene (1,27). Phylogenetic analysis indicates that the FABP family arose ~1 billion years ago, after the divergence of animals from plants and fungi, and diversified into tissue-specific isoforms through successive gene duplications (1,28,29).

Ligands are hypothesized to enter the binding pocket through the dynamic region of the β-barrel, specifically the entrance formed between α-helix II and the loops between βC-βD and βE-βF; a model termed the 'portal hypothesis' (21). The majority of FABPs bind a single LCFA (C16-C20) with high affinity and binding affinity, increasing with ligand hydrophobicity (21,30). FABP1 is a notable exception, possessing a relatively wide binding pocket that can simultaneously accommodate two LCFAs or other hydrophobic ligands such as bile acids, heme, monoacylglycerols and endocannabinoids (4,31).

FABP5 carries six cysteine residues, two of which, Cys120 and Cys127, form a disulfide bridge within the ligand-binding cavity; at present this is the only intramolecular disulfide reported among mammalian intracellular lipid-binding proteins (32). Cys120 is also the principal site at which the lipid peroxidation product 4-hydroxynonenal covalently modifies the protein, a reaction potentiated by bound fatty acid. Cells lacking FABP5 show increased 4-hydroxynonenal modification of other proteins, which has been taken to indicate a redox-buffering function (33). This evidence comes from retinal and retinal pigment epithelial tissue; whether the same function operates in epidermis has not been established directly.

Tissue distribution and ligand preferences. FABP isoforms have historically been named after the tissues in which they were first identified or are most abundant (9,20). Currently, the 10 mammalian isoforms include FABP1 (L-FABP), FABP2 (I-FABP), FABP3 (H-FABP), FABP4 (A-FABP/aP2), FABP5 (E-FABP), FABP6 (Il-FABP), FABP7 (B-FABP), FABP8 (M-FABP/PMP2), FABP9 (T-FABP) and the more recently identified FABP12 (1,27). The numbering is not continuous, and FABP10 and FABP11 were described in teleost fish rather than in mammals (29). However, this nomenclature does not imply exclusivity of expression. In fact, most tissues express multiple FABP isoforms, which has previously caused confusion (9,34).

FABP1, FABP3, FABP4, FABP5, FABP6 and FABP7 are of relevance to the inflammation-cancer axis. FABP1 is expressed in the liver, small intestine, pancreas and kidney, and contributes to hepatic β-oxidation, bile acid metabolism and very low-density lipoprotein (VLDL) biogenesis through its unique capacity to bind two fatty acids simultaneously (4,20). FABP3 is abundantly expressed in the heart, skeletal muscle and mammary gland, where it transports LCFAs for mitochondrial β-oxidation (4). FABP4 and FABP5 are primarily expressed in adipocytes and epidermal cells, respectively, but their co-expression in immune and vascular cells, including macrophages, dendritic cells and endothelial cells, is of pathophysiological importance (3,9). Double-knockout mice for FABP4 and FABP5 exhibit more pronounced protection against insulin resistance, metabolic syndrome and various inflammatory diseases compared with single-knockout mice, indicating functional compensation between the two isoforms (4,35). FABP6 mediates ileal bile acid reabsorption and has been implicated in CRC (20). FABP7 is expressed in

the brain and neural stem cells, where it regulates neurodevelopment and contributes to the maintenance of cancer stem cells in glioblastoma (GBM) and other neural tumors (1,4). Table I summarizes the principal claims by experimental system and measured outcome; Table SI provides a broader family overview.

The ligand spectrum of FABPs extends beyond LCFAs. Studies have shown that FABPs bind various bioactive lipids, including eicosanoids, retinoic acid (RA), endocannabinoids, heme, bile acids and lysophosphatidic acid (1,3). Notably, FABP5 binds RA with high affinity and delivers it to the nuclear receptor PPARβ/δ, thereby inducing genes related to cell survival (34,36). The FABP5/CRABPII expression ratio determines the fate of RA; a higher ratio directs RA toward the PPARβ/δ pathway, whereas a lower ratio favors the classical RA receptor (RAR) pathway (34,37,38). This ligand-specific partitioning mechanism provides a molecular basis for the protumorigenic role of FABP5 in cancer such as in triple-negative breast cancer (TNBC) (34,37).

Subcellular localization and secretion. The functional diversity of FABPs is expanded by their dynamic subcellular localization. Although FABPs were previously classified as cytosolic proteins, several isoforms have been shown to translocate to the nucleus and directly participate in transcriptional regulation. In particular, FABP1, FABP4 and FABP5 act as 'ligand delivery' proteins that activate PPAR family nuclear receptors under specific conditions (4,39,40). FABP4, in its ligand-bound holo form, undergoes continuous nucleocytoplasmic shuttling to transcriptionally activate PPARγ (3,41), and acts as an inter-compartmental shuttle for PPARγ agonists. Ligand binding promotes its nuclear accumulation, but its interaction with PPARγ is ligand-independent and involves both the DNA- and ligand-binding regions of the receptor (42). By contrast, FABP5 transfers RA to PPARβ/δ, a pathway closely associated with cell survival, proliferation and tumor progression (4,13).

FABP4 has been reported both to activate PPARγ and reduce its abundance. These findings are not measured on the same variable and describing them only as 'opposing' does not include information regarding the manner in which they coexist. Ligand-loaded FABP4 raises PPARγ transcriptional output (3,41). Separately, FABP4 promotes the ubiquitination of PPARγ, shifting it from mono- to polyubiquitinated forms and accelerating its proteasomal degradation. FABP4 upregulation lowers both basal and agonist-induced PPARγ transactivation, and PPARγ protein is higher in FABP4-null adipocytes (43). This is consistent with the earlier observation that PPARγ activity is elevated in FABP4-null macrophages (11).

A total of two structural observations make a single architecture plausible. The FABP4-PPARγ interaction does not require a ligand and engages regions of the receptor outside the ligand-binding domain, so binding is not conditional on FABP4 being in the holo form. Therefore, ligand binding alters the nuclear accumulation of FABP4 itself (42). The interaction also occurs through a site on FABP4 distinct from its fatty-acid-binding pocket (43). Together these data are consistent with FABP4 acting as a constitutive partner of PPARγ that both delivers the ligand to the receptor and marks it for turnover, a negative-feedback arrangement in which net transcriptional output depends on the ratio of ligand supply to receptor degradation rather than on either function alone (43). This is offered as an interpretation that accommodates the published measurements rather than as a tested model. The experiment that would test it, measuring PPARγ occupancy, transactivation and protein half-life in parallel across a range of FABP4:PPARγ ratios and ligand concentrations in a single cell system, has not been reported.

The non-classical secretion pathway of FABPs is a particularly important discovery for understanding inter-organ FABP signaling. Despite lacking a typical secretory signal peptide, FABP4 is released from adipocytes via a non-classical secretion pathway upon lipolytic stimulation or fasting (5,7). Circulating FABP4 functions as an adipokine that stimulates hepatic glucose production and impairs systemic insulin sensitivity, exerting widespread effects on distant tissues (3,5). In obese mice and humans, circulating FABP4 levels are markedly elevated and independently correlate with insulin resistance, type 2 diabetes, cardiovascular disease and an increased risk of obesity-associated cancer types, including breast cancer (7,44). Therefore, circulating FABP4 has been re-evaluated as an active signaling mediator linking the metabolism-inflammation-tumor axis, beyond its role as a mere biomarker (5).

In summary, FABPs perform a central role at the intersection of lipid metabolism and signal transduction through three layers of functional diversity: i) Binding of diverse lipid ligands via the highly conserved β-barrel structure; ii) fine-tuning of tissue-specific expression and ligand preference among isoforms; and iii) dynamic localization spanning the cytoplasm, nucleus and extracellular compartments. This molecular foundation provides the structural rationale for the divergent or convergent isoform-specific roles of FABPs in inflammation and tumorigenesis.

3. FABPs and inflammation

The key feature of the FABP family in inflammation is that function varies depending on the isoform and, even within a single isoform, on the cell of expression and biological context. This section organizes these properties along four axes: i) FABP4, a proinflammatory member; ii) FABP5, which modulates inflammation differently across cell contexts; iii) FABP1 and FABP3, which can play protective roles under certain conditions; and iv) circulating FABP4, which mediates inflammation at distant tissues following secretion. The divergent isoform- and context-specific inflammatory mechanisms discussed below are summarized schematically in Fig. 1.

FABP4 in macrophage-adipocyte inflammation. FABP4 has been firmly established as a representative 'proinflammatory' FABP co-expressed in adipocytes and macrophages (3,9,45); it functions as a key molecular node in metaflammation, integrating lipid accumulation, lipolysis and the production of inflammatory cytokines (7).

In macrophages, FABP4 inhibits the PPARγ/liver X receptor (LXR)α/ABCA1 axis to promote cholesterol ester accumulation and foam cell formation, while simultaneously activating the IKK/NF-κB and JNK/AP-1 pathways to upregulate proinflammatory cytokines such as TNF-α, IL-6

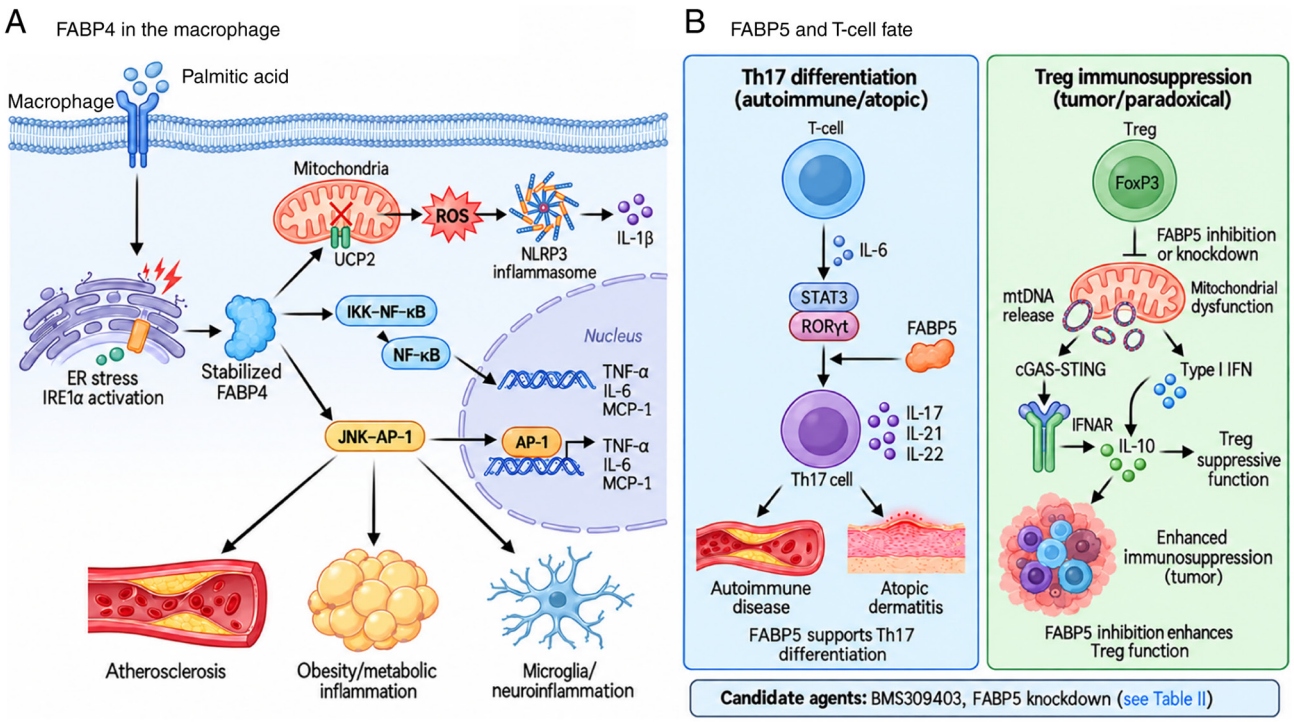

Figure 1. Isoform- and context-specific roles of FABPs in inflammation. (A) FABP4 in the macrophage. Palmitic acid induces ER stress and IRE1α activation, stabilizing FABP4 (56-58). FABP4 suppresses UCP2, raising mitochondrial reactive oxygen species and priming the NLRP3 inflammasome for IL-1β release (52,53), and activates IKK/NF-κB and JNK/AP-1 to increase TNF-α, IL-6 and MCP-1 (7,11,46,47). This circuit has been described in atherosclerotic plaque macrophages (11,48,50), obesity-associated metabolic inflammation (3,9,10) and microglia (55). (B) FABP5 and T-cell fate, reported here in three separate evidence layers. Observed: Tumor-infiltrating Tregs express high FABP5, and tumor interstitial fluid is lipid-poor (67). Functional experiment: Acute loss of FABP5 function in differentiated Tregs, by BMS309403 (which engages FABP3, FABP4 and FABP5) or by FABP5 knockdown, impairs mitochondrial integrity and triggers mtDNA release, cGAS-STING-dependent type I IFN signaling and IFNAR-dependent IL-10 production, increasing suppressive capacity *in vitro* (67). Not yet tested: whether lipid scarcity phenocopies this *in vivo*, and the net effect on antitumor immunity. On the left, IL-6/STAT3/RORγt-driven FABP5 supports Th17 differentiation in autoimmune and atopic settings (63-65,153,166). Not shown: In macrophages, FABP5 activity has instead been reported to restrict tumor growth through IFN-β (59,61). Candidate agents are listed in Table II. Arrows and symbols: Solid black, direction of signaling or of a downstream consequence; blunt-ended connector, inhibition (pharmacological inhibition or knockdown of FABP5); cross on UCP2 in (A), FABP4-dependent suppression of UCP2. AP-1, activator protein 1; cGAS, cyclic GMP-AMP synthase; ER, endoplasmic reticulum; FABP, fatty acid-binding protein; IFNAR, IFN α/β receptor; IKK, IκB kinase; IRE1α, inositol-requiring enzyme 1α; MCP-1, monocyte chemoattractant protein 1; mtDNA, mitochondrial DNA; NLRP3, NLR family pyrin domain containing 3; RORγt, retinoic acid receptor-related orphan receptor γt; ROS, reactive oxygen species; STING, stimulator of interferon genes; Th17, T helper 17; Treg, regulatory T cell; UCP2, uncoupling protein 2.

and MCP-1 (7,11,46,47). The transrepressive activity of PPARγ on inflammatory gene promoters, which is disrupted when FABP4 sequesters PPARγ ligands, provides an additional molecular basis for the proinflammatory consequences of FABP4 induction (48,49). Macrophage-specific FABP4 deletion induces an anti-inflammatory phenotype that confers marked protection against atherosclerotic plaque formation in ApoE-deficient mouse models (7,50). Pharmacological inhibition of aP2/FABP4 with small-molecule inhibitors similarly protects against diabetes and atherosclerosis in mouse models, providing the earliest preclinical evidence that FABP4 is a druggable target (51). Mechanistically, FABP4 uncouples lipid metabolism from inflammation by regulating mitochondrial redox signaling through uncoupling protein 2 (UCP2) (52).

Previous work has identified FABP4 as an upstream regulator of NLR family pyrin domain containing 3 (NLRP3) inflammasome activation. Steen *et al* (53) demonstrated that loss of FABP4 in macrophages reduces oxidative modification of mitochondrial cysteine residues and upregulates antioxidant enzymes (SOD2, catalase and methionine sulfoxide reductase A). This redox rebalancing attenuates the mitochondrial unfolded protein response, thereby reducing cleaved caspase-1 and NLRP3 expression and substantially suppressing IL-1β secretion. Notably, this anti-inflammatory effect is partially reversed upon UCP2 silencing, indicating that the FABP4/UCP2 axis is a key pathway regulating mitochondrial reactive oxygen species (ROS) and inflammasome activation.

The proinflammatory activity of FABP4 has been confirmed in additional vascular contexts. In homocysteine-induced macrophage inflammation, FABP4 activates the JAK2/STAT2 pathway via Rap1a-dependent c-Src Tyr416 phosphorylation and membrane translocation; an effect negatively regulated by SOCS1 (54). Microglia, the resident macrophages of the central nervous system, also exhibit FABP4-mediated ROS and TNF-α production, JNK phosphorylation, increased Toll-like receptor (TLR) 4 expression and decreased UCP2 in response to lipopolysaccharide (LPS), all of which are reversed by genetic silencing or BMS309403 treatment (55). These findings indicate that the proinflammatory function of FABP4 is conserved across the macrophage lineage.

Moreover, FABP4 expression itself is amplified by inflammatory stimuli in a positive feedback loop, and macrophage FABP4 acts as a central hub linking endoplasmic reticulum

(ER) stress, lipotoxicity and autophagy dysregulation (56,57). Palmitic acid increases macrophage FABP4 protein levels (independent of mRNA levels) via ER stress and IRE1α activation, and elevated FABP4, in turn, inhibits PPARγ and LXRα function, suppressing SIRT3, UCP2 and PGC-1α expression, and amplifying mitochondrial ROS production (58). This circuit provides a molecular basis for the mechanism by which saturated fatty acids sustain chronic low-grade inflammation in obesity.

FABP5 and T cell differentiation. FABP5 (E-FABP) adopts a fold that is nearly superimposable on that of FABP4 but is expressed far more widely, including in macrophages, dendritic cells and T cells (7,59). The inflammatory regulatory function of FABP5 resembles that of FABP4 in macrophages but displays a markedly more complex, context-dependent behavior in T cells.

In macrophages, FABP5 expression is induced by TLR4 (LPS) and TLR2 (zymosan) agonists (60) and has been linked to fatty acid oxidation (FAO), ROS production, inflammasome activation, IL-1β upregulation and lipid droplet formation (59,61). However, the same studies report an antitumor consequence of this activity, whereby FABP5 promotes IFN-β responses in tumor-associated macrophages (TAMs) and restricts tumor growth, and a small-molecule activator of FABP5 inhibits tumor growth in mouse models (59,61). This myeloid antitumor direction is not readily reconciled with the protumorigenic roles described for tumor-cell FABP5 below, and the two should not be summed into a single directional statement for the isoform. FABP5 also participates in cross-talk between dietary polyunsaturated fatty acid (PUFA) availability and macrophage polarization. FABP5 deletion suppresses atherosclerosis in VLDL receptor-deficient mice by reducing IL-6 and COX-2 expression and by CCR2-dependent inhibition of macrophage recruitment (62).

However, in T cells FABP5 function is far more nuanced. Li *et al* (63) reported that E-FABP-deficient $CD4^+$ T cells exhibit markedly reduced Th17 differentiation and increased $FoxP3^+$ Treg differentiation. Mechanistically, E-FABP deficiency impairs IL-6-induced expression of IL-21, RORγt and RORα while increasing PPARγ, which in turn suppresses STAT3 activity and blocks the Th17 program (63). In experimental autoimmune encephalomyelitis, FABP5-deficient mice are protected from disease through reduced Th17 differentiation (63,64). However, FABP5 expression promotes Th17 polarization in mouse models and patient samples of atopic dermatitis (65), whereas FABP5 deficiency has no effect on antigen-specific $CD4^+$ or $CD8^+$ T cell generation in a *Listeria monocytogenes* infection model (66). These divergent results illustrate that the T cell-regulatory role of FABP5 depends on stimulus, tissue context and disease stage.

From a Treg perspective, FABP5 creates one of the most important therapeutic paradoxes in the FABP field. Field *et al* (67) demonstrated that pharmacological or genetic inhibition of FABP5 in Tregs causes mitochondrial dysfunction, including decreased oxidative phosphorylation, impaired lipid metabolism and loss of cristae structure. These mitochondrial defects promote mtDNA release and cGAS-STING-dependent type I interferon signaling, thereby increasing IL-10 production and enhancing Treg suppressive function. Thus, the same FABP5 blockade that may attenuate Th17-driven autoimmune inflammation could reinforce immunosuppression in a tumor-bearing host.

This paradox means that FABP5 inhibition cannot be interpreted as uniformly anti-inflammatory or antitumor. The desired effect may be Th17 suppression in psoriasis, atopic dermatitis or autoimmunity, whereas the undesired oncological effect may be strengthened Treg-mediated immune evasion. Preclinical evaluation of FABP5-targeted agents should therefore include immunocompetent syngeneic tumor models, Treg depletion or rescue experiments, cell-type-specific knockout approaches and combination studies with immune checkpoint blockade before clinical translation in cancer or premalignant high-risk settings.

FABP1 and FABP3. Not all FABPs act in a proinflammatory manner. Some isoforms attenuate inflammation under specific conditions or protect tissues from oxidative stress. FABP1 is highly expressed in the liver, small intestine and kidney, and serves as a fatty acid buffering and safe transport protein owing to its unique ability to bind two fatty acids simultaneously (4). FABP1-deficient mice display reduced hepatic β-oxidation efficiency and bile acid homeostasis disturbances. However, paradoxically, these animals can also exhibit exacerbated oxidative stress and lipotoxicity, suggesting that FABP1 functions as a 'buffer protein' that safely partitions excess fatty acids (4,68).

FABP3 (H-FABP) plays a central role in delivering LCFAs to mitochondria for β-oxidation in the heart and skeletal muscle (4). FABP3 deficiency switches cardiac fuel selection from fatty acids to glucose and induces cardiac hypertrophy in aged mice (4). During myocardial ischemia-reperfusion injury, FABP3 is rapidly released into the bloodstream and serves as an early biomarker of acute myocardial infarction (1). Recent work has shown that FABP3, FABP7 and FABP8 also bind cholesterol and facilitate its egress from lysosomes, contributing to intracellular lipid trafficking homeostasis (69). However, in the nervous system, FABP3 has been implicated in pathogenic processes such as α-synuclein aggregation and mitochondrial damage in Parkinson's disease, illustrating that even within a single isoform, tissue-specific functional divergence is pronounced (70).

These isoform-specific functional divergences indicate that a binary 'proinflammatory vs. protective' classification of the FABP family is untenable. Rather, each isoform appears optimized for the physiological demands of its expressing tissue (fuel supply, toxicity buffering and signal transduction), and the directionality of inflammation is determined when these normal functions become deregulated under pathological conditions (1).

Circulating FABP4 as an adipokine. The most recently described aspect of FABP-mediated inflammatory regulation is the existence of extracellular circulating FABP. Despite lacking a typical secretory signal peptide, FABP4 is released into the extracellular space via a non-classical secretion pathway upon lipolytic stimulation or fasting (71-73). Secreted FABP4 is a bioactive adipokine that stimulates hepatic glucose production and influences systemic insulin sensitivity in experimental models (3,5).

Circulating FABP4 levels are markedly elevated in obese humans and mice, and correlate strongly and independently with type 2 diabetes, hypertension, heart failure and atherosclerosis (5,7). Notably, circulating FABP4 is not merely a disease biomarker but an active mediator that proactively induces inflammation in distant tissues; it upregulates the ERK/JNK/STAT1 pathway and downregulates eNOS and SDF-1 signaling in human coronary endothelial cells, inducing endothelial dysfunction (74). Moreover, antibody-mediated neutralization of aP2 improves glucose tolerance and insulin sensitivity in obese mice, demonstrating that circulating FABP4 is a neutralizable therapeutic target (3,75).

The concept of circulating FABP4 supports the view of FABPs as metabolic-immune signaling integrators. FABP4 is secreted from obese adipose tissue and reaches the liver, vasculature and potentially distant TMEs to coordinate inflammation and metabolic rewiring across organs, providing an integrative framework explaining the obesity-chronic inflammation-cancer continuum. Specifically, Hao *et al* (12) reported that circulating FABP4 is a novel link underlying obesity-associated breast cancer development; a topic that directly connects with the role of FABPs in the TME discussed below.

A total of two features of this section carry into the next. The directionality of FABP-dependent inflammation is set by the combination of ligand, cell type and disease context, so an isoform cannot be labeled proinflammatory or anti-inflammatory on its own; and circulating FABP4 extends this biology beyond the cell in which the protein is made. The next sections examine how far these circuits operate in tumors, and where the evidence for that stops.

4. FABPs in cancer

The aforementioned inflammatory regulatory functions of FABPs acquire new dimensions in the context of tumor biology. Beyond their use as biomarkers in cancer, FABPs also act as drivers that mediate intercellular lipid shuttling and metabolic rewiring within the TME. FABP4, FABP5 and FABP7 each have distinct pathological roles in cancer due to their isoform-specific properties. A schematic overview of the isoform-specific mechanisms discussed below, covering FABP4 in adipocyte-macrophage-tumor crosstalk and the omental endothelial niche, FABP5 ligand routing in tumor cells and FABP7 in GBM stem-like cells, is provided in Fig. 2.

FABP4 in obesity-associated cancer types. FABP4 has emerged as the most potent protumorigenic FABP in various obesity-associated cancer types. FABP4 is upregulated in numerous solid tumors, including breast, ovarian, prostate, hepatic, pancreatic and lung cancer, and this upregulation is generally associated with a poor prognosis (18,76,77). Dysregulated adipose-tumor crosstalk is a shared feature of these obesity-associated malignancies (78). Notably, FABP4 is expressed not only in tumor cells, but also across stromal components of the TME, including adipocytes, TAMs and endothelial cells, where it contributes to intercellular lipid exchange (19). In ovarian cancer, adipocyte-induced FABP4 expression in tumor cells promotes metastasis and carboplatin resistance (76).

The adipocyte-tumor cell fatty acid shuttle represents the most representative model of FABP4-mediated tumorigenic mechanisms and was originally delineated in the omental niche of ovarian cancer metastasis (79,80). Adipocytes supply fatty acids to tumor cells during metastasis to the omentum, inducing FABP4 expression in tumor cells and simultaneously increasing both metastatic potential and carboplatin resistance (19,76). A parallel CD36-driven fatty acid import axis, induced by adipocyte coculture, further amplifies this metastasis-initiating program (81,82). Intraperitoneal injection of FABP4-high ovarian cancer cells into FABP4$^{-/-}$ mice markedly reduces tumor growth and metastasis, and FABP4 inhibitors such as BMS309403 effectively suppress both early and established metastases (76). A similar pattern is observed in breast cancer, where adipocyte cancer cell co-culture simultaneously upregulates CD36 and FABP4 expression, with their direct interaction integrally coordinating fatty acid uptake, intracellular trafficking and delivery to mitochondria and peroxisomes (82-84). This process promotes metabolic reprogramming toward FAO and is associated with adipocyte-induced epithelial-mesenchymal transition (EMT) and stemness, in part through CD36-FABP4 interaction (84).

This model has since been tested directly and requires verification. In mice congenitally lacking mature adipocytes within the peritoneal cavity, ovarian tumors still seeded adipose-associated regions, peritoneal expansion was not impaired and the response to carboplatin was unchanged, whereas removal of the adipocyte-free omentum did reduce tumor burden (85). The earlier evidence rested on whole-body FABP4 deletion, which cannot separate adipocyte FABP4 from its expression in other compartments. Single-cell analysis of mouse and human omentum placed the highest FABP4 expression in endothelial cells. Endothelial-specific deletion reduced omental tumor expansion by ~29% during exponential growth and lowered tumor-associated vascular branching, whereas myeloid-specific deletion had no effect in this model (85). Therefore, adipocyte-derived fatty acid supply may be sufficient to support tumor growth in this niche without being required for it, and the dominant FABP4-expressing compartment appears to differ between tumor types, whereby myeloid FABP4 is required in breast models (44,86), but not in this ovarian model.

FABP4 in TAMs illustrates the mechanisms by which the inflammatory functions of immune-cell FABPs may be repurposed in the TME. Hao *et al* (44) reported that a CD11b^{+}F4/80^{+}MHCII^{-}Ly6C^{-} TAM subset in breast tumors expresses high levels of FABP4, and that FABP4 in these cells is associated with activation of the NF-κB/microRNA (miR)-29b/IL-6/STAT3 axis. In the same study, FABP4 deficiency reduced mammary tumor growth and metastasis, and higher FABP4 expression was associated with poorer breast cancer survival (44). More recently, Yorek *et al* (86) demonstrated that unsaturated fatty acids, particularly linoleic acid, promote FABP4/CEBPα-dependent triglyceride synthesis and lipid droplet accumulation in TAMs, and that FABP4-dependent lipid mobilization in TAMs supports breast cancer cell migration and metastasis. Together, these findings support a role for FABP4-positive TAMs in metabolic crosstalk that contributes to breast cancer progression (44,86).

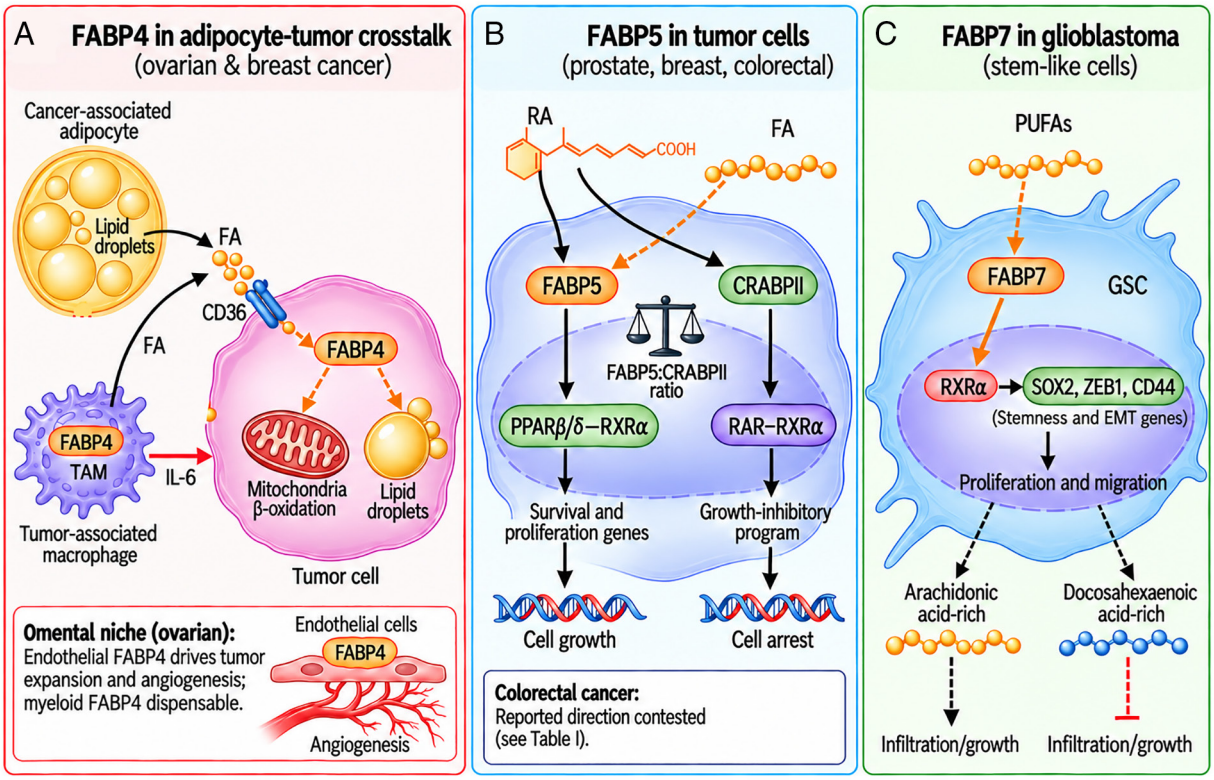

Figure 2. Isoform-specific contexts in cancer. Three contexts are shown separately since the evidence does not support a single shared pathway. (A) FABP4 acts in more than one compartment, and which one dominates differs by tumor type. Cancer-associated adipocytes and FABP4-high TAMs supply FAs to tumor cells, and the TAMs also supply IL-6 (44,79,80,86); within tumor cells CD36-mediated uptake feeds FABP4, which partitions FAs to β-oxidation and lipid droplets (84). However, in the omental niche, mature adipocytes are not required for ovarian tumor growth. Endothelial cells are the principal FABP4-expressing population and endothelial-specific deletion reduces tumor expansion and angiogenic branching whereas myeloid-specific deletion does not (85). (B) FABP5 in tumor cells. FABP5 delivers RA and FAs to PPARβ/δ-RXRα, inducing survival and proliferation genes, whereas RA routed instead to CRABPII-RAR activates a growth-inhibitory program; the FABP5:CRABPII ratio sets which of the two receptors the ligand reaches, and lowering it suppresses tumor growth in mammary carcinoma models (13,14,34,36-38,87). In colorectal cancer the reported direction is contested (Table I). (C) FABP7 in glioblastoma. FABP7 delivers PUFAs to RXRα, inducing SOX2, ZEB1 and CD44 and supporting proliferation and migration of GSCs; arachidonic-acid-rich and docosahexaenoic-acid-rich environments have opposite effects (96,101). This has been demonstrated in GSCs and has not been tested in premalignant lesions of other tissues. Arrows and symbols: Solid black, release of FAs from adipocytes and macrophages in (A), movement of RA in (B) and downstream transcriptional or phenotypic output in (B) and (C); dashed orange, uptake or intracellular movement of FA; solid orange in (C), delivery of PUFAs to RXRα; solid red in (A), IL-6 signaling; dashed black in (C), an outcome conditional on the surrounding lipid composition; dashed red blunt-ended connector in (C), suppression of that outcome; balance symbol in (B), the FABP5:CRABPII ratio that determines which receptor the ligand reaches. CRABPII, cellular retinoic acid-binding protein II; EMT, epithelial-mesenchymal transition; FA, fatty acid; FABP, fatty acid-binding protein; GSC, GBM stem-like cell; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; PUFA, polyunsaturated fatty acid; RA, retinoic acid; RAR, retinoic acid receptor; RXRα, retinoid X receptor α; TAM, tumor-associated macrophage; ZEB1, zinc finger E-box binding homeobox 1.

Circulating FABP4 may extend the fatty acid shuttle model to a systemic context. Hao *et al* (12) reported that obesity-associated adipose-derived FABP4 was linked to the development of distant breast/mammary tumors, suggesting a potential molecular connection between obesity and breast cancer. These observations support the possibility that the aforementioned 'FABP4 as adipokine' concept (circulating FABP4 as an adipokine) may be relevant not only to metabolic disease but also to systemic processes that influence tumor progression.

FABP5 and the PPARβ/δ axis. FABP5, along with FABP4, is among the most studied isoforms in cancer research. FABP5 is elevated relative to matched normal tissue in several tumor types, and higher expression has generally been associated with a poorer outcome, although the reported magnitude varies by tumor type and study (13). The protumorigenic mechanisms of FABP5 can be summarized along two main axes: i) Ligand-nuclear receptor delivery; and ii) metabolic rewiring.

The core of the ligand-nuclear receptor delivery axis is the function of FABP5 to deliver fatty acids and RA to PPARβ/δ, thereby inducing genes involved in tumor survival, proliferation and angiogenesis (VEGF, MMPs and Akt) (13,14,87). This pathway is particularly well-established in prostate cancer. In castration-resistant prostate cancer, the FABP5/PPARγ/VEGF axis progressively replaces the androgen receptor (AR)-mediated pathway, and FABP5 knockout markedly suppresses proliferation, invasion and colony formation of PC3-M cells (88). Notably, deletion of FABP5 results in a complete loss of expression of the AR splice variant ARV7, which is characterized by the absence of the ligand-binding domain. This finding highlights FABP5 as a promising target for addressing resistance to antiandrogen therapy (88).

In breast cancer, FABP5 plays a complementary role to FABP4. Both isoforms are prominently expressed in breast tissue and exhibit distinct expression patterns across molecular subtypes (19). The FABP5/CRABPII ratio is a key switch that determines the fate of RA, whereby a higher ratio directs RA

toward the protumorigenic PPARβ/δ pathway, and a lower ratio favors the tumor-suppressive RAR pathway (36). Reducing the FABP5/CRABPII ratio in TNBC redirects RA from PPARβ/δ to RAR, thereby suppressing tumor growth (38).

Along the metabolic rewiring axis, FABP5 shows tight connections with FASN and hypoxia signaling. In cervical cancer, FABP5 facilitates lymph node metastasis by reprogramming fatty acid metabolism, which correlates with elevated MMP-2 and MMP-9 expression (89,90). In pancreatic neuroendocrine tumors, FABP5 interacts directly with FASN, modulating its stability via the ubiquitin-proteasome pathway and activating the WNT/β-catenin signaling cascade to promote tumor progression (91). Notably, the direction of this coupling is the opposite of that reported in colorectal cells, where FABP5 stabilizes FASN in pancreatic neuroendocrine neoplasia, but promotes its ubiquitination in CRC (16,91). The two reports come from the same group and appeared within weeks of each other, share the same interaction partner and ubiquitin-proteasome read-out and neither addresses the other. Rather than a contradiction, this is the clearest available indication that the FABP5-FASN relationship is tumor-type dependent and cannot be stated as a single rule.

FABP5 in CRC: An unresolved directional conflict. Reports on FABP5 in CRC have opposing results, and the discrepancy is informative rather than incidental. Seo *et al* (17) showed that transient FABP5 silencing lowered hypoxia-induced HIF-1α protein and its target transcripts (VEGF, CA9, LOX, PDK1 and BNIP3L) in HCT116 and WiDr cells, and that FABP5-silenced HCT116 spheroids grown on an oxygen-permeable three-dimensional chip remained smaller than the controls over 7 days. Ye *et al* (16), also working with the HCT116 cell line, reported the converse, whereby FABP5 protein was lower in 90 paired colorectal carcinoma specimens than in adjacent tissue, higher FABP5 was associated with longer survival, stable FABP5 overexpression suppressed proliferation, migration and xenograft growth while stable knockdown enhanced them, and the effect was traced to FABP5-dependent ubiquitination of FASN with downstream inhibition of mTOR and induction of autophagy.

These are four differences between the two studies which may account for the discrepancies; however, none have been further studied. First, the lesions differ, whereby the paired expression series analyzed by Seo *et al* (17) (GSE8671) comprised colorectal adenomas, while Ye *et al* (16) sampled established carcinoma. Therefore, the two tissue observations may describe different points on the adenoma-carcinoma sequence, rather than opposite findings in the same lesion. Second, the analytes differ, with transcript vs. protein. Third, oxygen tension is central to one mechanism and absent from the other, in which the FABP5/HIF-1α axis was defined under hypoxia and in spheroids that develop an internal hypoxic region, whereas the FASN/mTOR/autophagy axis was characterized in normoxic monolayers and subcutaneous xenografts. Fourth, the perturbations differ in kinetics and in direction, with transient silencing in one case against stable overexpression and knockdown in the other; only the latter tested both directions, and no *in vivo* experiment has been reported for the HIF-1α arm.

A third report adds a distinct axis rather than adjudicating between these two. In colorectal cells, p53 induces FBXO2, which binds FABP5 and directs it to chaperone-mediated autophagy. The resulting fall in PUFAs reduces lipid peroxidation and confers resistance to ferroptosis; arachidonic acid (AA) supplementation reverses it (92). FABP5 sensitizes cells to ferroptosis, which again places it on the tumor-restraining side, although the outcome measured is ferroptosis susceptibility rather than proliferation and the *in vivo* arm manipulated FBXO2 rather than FABP5. Therefore, two of the three colorectal reports describe a restraining role, but the one that does not was conducted under hypoxia and in three-dimensional culture, so oxygen tension remains the most testable candidate for the discrepancy.

Neither direction of the FABP5 effect is therefore treated as established across CRC. A comparison using the same colorectal cell models, bidirectional FABP5 perturbation and matched oxygen conditions, with FASN, HIF-1α and autophagy assessed in parallel, could test whether oxygen tension or pathway interactions explain the discrepancy. Stage-matched human tissue would address the separate question of disease-stage associations. These explanations remain untested.

In cervical cancer, FABP5 promotes EMT, lymphangiogenesis and lymph node metastasis by reprogramming fatty acid metabolism. This includes FABP5-driven lipolysis and *de novo* fatty acid synthesis which increase intracellular fatty acid levels that activate the NF-κB signaling pathway and FABP5 expression, which independently predicts lymph node metastasis and poor prognosis (90). Additionally, FABP5 serves as an intracellular carrier of anandamide and related N-acylethanolamines in the brain, delivering them to fatty acid amide hydrolase for hydrolysis, such that pharmacological FABP inhibition elevates brain anandamide levels and produces analgesia (93). From the perspective of antitumor immune evasion, FABP5 illustrates the manner in which the aforementioned Treg-regulatory function is exploited oncologically. In tumor-infiltrating Tregs, FABP5 inhibition activates the mtDNA leakage cGAS/STING/IL-10 pathway, paradoxically enhancing the Treg immunosuppressive function (67). This raises a fundamental dilemma in the clinical application of FABP5 inhibitors in autoimmune disease (where inhibition is beneficial) vs. cancer (where inhibition may reinforce immunosuppression). Meanwhile, in $CD8^+$ T cells, FABP5 promotes linoleic acid uptake and induces ROS-mediated T cell death, thereby reducing TME $CD8^+$ T cells and accelerating tumor growth under high-fat-diet conditions (15,94).

FABP7 in nervous system tumors. FABP7 (B-FABP) is the most studied FABP in nervous system tumors, including GBM. In the normal brain, FABP7 functions as a marker for radial glial cells and neural stem cells and is essential for establishing the radial glial fiber system during neurogenesis (95,96). The transformation of this normal neurodevelopmental role into the maintenance of 'cancer stemness' in oncological contexts is a unique mechanism of FABP7.

Although FABP7 is predominantly expressed in neural lineage tissues, aberrant FABP7 expression has also been reported in breast cancer subtypes, where its subcellular localization correlates with clinical outcomes (97). FABP7 is most

characteristically associated with GBM stem-like cells (GSCs). FABP7 is highly enriched in patient-derived GSCs and localizes to both the cytoplasm and nucleus (98). Differentiation of GSCs by serum addition markedly reduces FABP7 expression, and $FABP7^{+}Sox2^{+}$ tumor cells are significantly increased in WHO grade IV GBM compared with grade II and III tumors (98). siRNA-mediated FABP7 downregulation reduces both proliferation and migration of GBM-derived neurospheres, and FABP7 expression increases after radiation, suggesting an association with radioresistance (99). This behavior places FABP7 among the lipid-handling mediators that contribute to immune evasion by cancer stem cells (100).

Mechanistically, recent work has demonstrated that FABP7 delivers PUFAs to the nuclear receptor retinoid X receptor (RXR)α, activating a PUFA/FABP7/RXRα neurogenic pathway (96). This pathway induces SOX2 (a key stemness regulator) and ZEB1 (an EMT transcription factor), driving the 'stationary-to-migratory' transition in GSCs (96). Notably, the role of FABP7 is bidirectional depending on the fatty acid microenvironment. In an AA-rich environment, FABP7 promotes GBM growth and infiltration, while in a docosahexaenoic acid (DHA)-rich environment, FABP7 may inhibit tumor infiltration through increased DHA uptake and utilization (101). Therefore, FABP7 has been proposed as a candidate vulnerability of GBM neural stem-like cells, suggesting that FABP7-targeted therapy may need to be combined with manipulation of the ligand environment (101).

Limitations in FABP7 inhibitor development have also been noted, as the existing drug SBFI-26 displays low selectivity, targeting both FABP5 and FABP7, and its blood-brain barrier permeability has not been evaluated (102). This underscores the need for isoform-selective and tissue-specific FABP inhibitors.

FABP1 and FABP6 in gastrointestinal cancer. FABP1 (L-FABP) shows opposing roles in liver and CRC depending on tissue context. In some HCC cases, FABP1 promotes tumor growth and angiogenesis by upregulating VEGF-A through the VEGFR2/Akt/mTOR pathway (103), whereas in another study, FABP1 expression is downregulated in poorly differentiated HCC and associated with poor prognosis (104). In CRC, FABP1 has been reported as a differentiation marker downregulated at the adenoma stage but is upregulated again in advanced cancer (1). Such stage- and context-dependent expression changes indicate that FABP1 cannot be classified simply as a tumor-promoting or -suppressing factor. Therefore, FABP1 and FABP6 exert mechanistically distinct gastrointestinal effects, whereby FABP1 modifies tumor cell phenotype in a stage-dependent manner through cell-intrinsic lipid buffering, whereas FABP6 contributes through an epithelial bile acid-microbiota interaction that is more clearly tied to chronic intestinal inflammation. Both isoforms are summarized alongside FABP4/FABP5/FABP7 in Table I, which states for each claim the system in which it was obtained, the outcome measured and what remains untested.

A total of two points from this section are relevant to the subsequent discussion. FABPs act both within tumor cells and in the surrounding compartments, and the compartment that matters is not fixed, as it differs between tumor types. As the same isoform can alter tumor metabolism and immune function in opposite directions, antitumor and immunomodulatory effects must be assessed separately rather than assumed to align.

5. FABP networks at the inflammation-cancer interface: A context-specific evidence map

The previous sections outlined that FABPs can regulate inflammatory signaling and tumor metabolism in a highly isoform- and cell-type-dependent manner. The present section integrates these observations but does not claim a deterministic linear pathway from inflammation to cancer. Instead, it sets out for each context what has been measured and in what system, so that the point at which the chain of evidence stops is visible.

Each context is considered using the same logic: i) The established inflammation-cancer link; ii) the FABP isoforms implicated; iii) the relevant cell types; iv) what has been measured, in which system, and what has not been measured; v) unresolved questions; and vi) translational implications. This structure is intended to separate causal *in vivo* evidence from associative biomarker evidence and hypotheses that remain to be directly tested. Of these, three disease contexts were selected for comparison. Each has a chronic inflammatory or metabolic precondition that is epidemiologically linked to cancer, each has FABP-specific mechanistic evidence and each has human data that can be set against the experimental work rather than simply added to it. Other clinically important FABP-related cancer contexts, such as adipocyte-rich ovarian cancer and FABP7-dependent GBM, are addressed primarily in previous sections and Fig. 2 rather than as integrative contexts in this section.

Metabolic liver axis: MASLD/MASH-to-HCC

Terminology requires clarification. The current nomenclature uses MASLD and MASH, replacing much of the older non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) terminology; metabolic dysfunction-associated fatty liver disease (MAFLD) is a related but not identical metabolic-definition framework (105,106). In the present review, MASLD/MASH is used for current conceptual discussion, while NAFLD/NASH is retained when referring to the terminology used in older studies.

Established link. MASLD can progress through steatosis, MASH, fibrosis, cirrhosis and HCC, particularly in the presence of obesity, insulin resistance and type 2 diabetes (106-108). This makes the metabolic liver axis one of the strongest examples of an inflammation-cancer continuum discussed in the present review.

FABP evidence and what has been measured. Human association studies indicate that hepatic and circulating FABP4 levels rise during NAFLD/NASH and correlate with inflammation and fibrosis, supporting FABP4 as a biomarker of disease activity rather than of cancer (109,110). Mechanistic evidence is stronger in experimental models, whereby the LPL/FABP4/CPT1 fatty acid metabolic axis is activated during the MASH/NASH-to-HCC transition in stelic animal model (STAM) mice, and pharmacological inhibition of this axis reduces progression to HCC (111). In addition, adipocyte-derived FABP4 promotes HCC stemness and drug

resistance through ITGB1-mediated β-catenin activation, and FABP4 deficiency delays tumor development in diet- and carcinogen-driven models (112). In both cases the outcome measured was tumor development in mice. For FABP4, this is the context in which three types of study, namely human cohort association, pharmacological inhibition in mice and genetic deficiency in mice, come closest to addressing the same question. However, no human study has tested whether altering FABP4 changes HCC incidence, so the human and causal evidence remain on different outcomes. For FABP1, the hepatic homeostatic functions are well characterized (4,68), but no experiment has tested a stage-specific role in the transition to HCC, and the cancer associations are based on expression data.

Unresolved issues and implications. It remains unclear whether FABP4 is necessary for all metabolic liver cancer contexts or primarily modifies risk in obesity- and lipotoxicity-dominant subtypes. FABP4-directed interventions should therefore be evaluated as risk-modifying or progression-modifying strategies in defined metabolic settings rather than as general HCC therapeutics.

Intestinal axis: IBD-to-CRC

Established link. Chronic IBD, especially long-standing ulcerative colitis, increases the risk of CRC and represents a classical inflammation-driven cancer model (113,114). In this setting, epithelial barrier disruption, dysbiosis, bile acid remodeling and cytokine signaling converge on epithelial regeneration and malignant transformation.

FABP evidence and what has been measured. FABP6 is the most relevant local intestinal isoform as it mediates ileal bile acid transport and enterohepatic recycling (1,115). Intestinal epithelium-specific FABP6 knockout alters bile acid composition, shifts microbiota composition and exacerbates dextran sulfate sodium-induced colitis; rescue by *Ligilactobacillus murinus* or taurodeoxycholic acid supports a functional bile acid-microbiota-barrier mechanism (116). The outcome measured was colitis severity, and loss of FABP6 makes the condition worse. Separately, FABP6 mRNA is elevated in most paired human CRC samples and is detectable from the adenoma stage (117); the measured outcome was expression, with no perturbation. The two FABP6 observations on this axis point in different directions and have not been joined. No experiment has tested FABP6 manipulation in a colitis-associated carcinogenesis model. Therefore, there is no evidence that FABP6 drives the transition, and the only loss-of-function phenotype available runs opposite to the direction such a role would predict.

For FABP4 the evidence on this axis is of a different type. Circulating FABP4 and FABP6 are elevated in patients with CRC and fall after radical resection (118), which is a biomarker observation that is compatible with the tumor state raising FABP4 rather than the reverse. In a prospective analysis of 1,324 incident cases and a two-sample Mendelian randomization study using 58,131 cases, neither measured nor genetically predicted that circulating FABP4 was associated with CRC risk overall (119). These analyses concern the circulating protein and CRC as a whole; they were not designed to address colitis-associated disease, and do not speak to tissue FABP4.

Unresolved issues and implications. The major unresolved question is whether FABP6 is a causal driver of colitis-associated tumor initiation or a marker of epithelial bile acid stress. Future studies should test FABP6 manipulation in colitis-associated CRC models and evaluate microbiota, bile acid species and immune infiltration as linked readouts.

Obesity-breast cancer axis

Established link. The epidemiological association between obesity and breast cancer risk, recurrence and outcomes is well-established, particularly in postmenopausal disease (120-122). The molecular connection involves chronic adipose inflammation, adipokine signaling, insulin/IGF signaling, estrogenic effects and altered lipid availability.

FABP evidence and what has been measured. FABP4 accounts for most of the FABP-specific work on this axis. Circulating FABP4 secreted from obese adipose tissue promotes mammary tumor stemness and aggressiveness through an IL-6/STAT3/ALDH1-linked mechanism (12). In the TME, FABP4 expression in a $CD11b^{+}F4/80^{+}MHCII^{-}Ly6C^{-}$ TAM subpopulation promotes breast cancer progression through a CEBPα/NF-κB/miR-29b/IL-6/STAT3 circuit (44). FABP4 also participates in adipocyte-tumor cell fatty acid transfer and CD36-linked fatty acid uptake in breast cancer cells (84,86). For FABP4 the different types of study converge more closely than elsewhere. Every perturbation experiment on this axis measures the growth or spread of an already established tumor, and the adipocyte-to-tumor supply route on which the mechanism rests has been shown to be dispensable in the analogous ovarian niche (85); none measures tumor incidence, and no human study has tested whether altering FABP4 changes breast cancer risk. Circulating FABP4 is also not cancer-specific, as it is confounded by body mass index, insulin resistance, diabetes, age, sex and cardiovascular disease, and Mendelian randomization indicates that adiposity raises FABP4 rather than the reverse (123), so an elevated level is at least partly a consequence of the adipose state it is being used to interrogate.

Convergent signaling pathways. As aforementioned, across these disease contexts, FABP isoforms appear to converge on four recurring signaling modules and are summarized in the present review to highlight cross-context recurrence rather than to re-describe individual mechanisms. First, FABP-nuclear receptor routing links lipid availability to transcriptional programs, whereby FABP4 interacts with PPARγ-related signaling, FABP5 can route RA or fatty acids toward PPARβ/δ and FABP7 can regulate ligand-dependent RXRα signaling (13,34,41,43,96). Second, inflammatory cytokine modules involving NF-κB, IL-6 and STAT3 recur in macrophage and TAM contexts (11,44,124,125). Third, mitochondrial metabolism, ROS and inflammasome activation connect lipid chaperoning with innate immune activation (53,67). Fourth, hypoxia-linked metabolic rewiring has been described for FABP5 and HIF-1α in hepatic and CRC cells (17,126). In colorectal cells this has been shown under hypoxia and in three-dimensional culture, without *in vivo* confirmation, and it coexists with a report of the opposite direction under normoxia (16); it should therefore be read as a

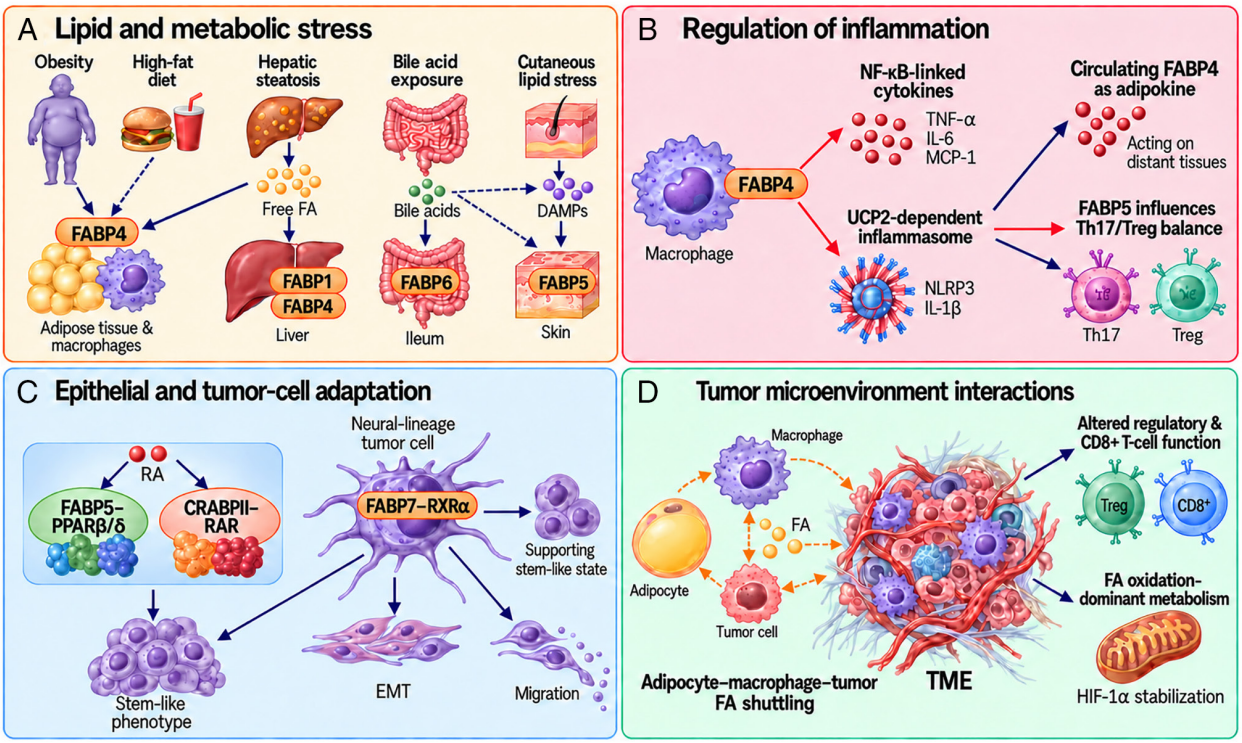

Figure 3. Domains in which FABPs have been implicated at the inflammation-cancer interface. The four domains are shown as related areas rather than as sequential stages, as the evidence does not establish a single ordered progression. Solid connectors mark links supported by perturbation experiments; dashed connectors mark links that have not been directly tested. (A) Lipid and metabolic stress. Obesity, high-fat diet, hepatic steatosis, bile acid exposure and cutaneous lipid stress are associated with tissue-specific FABP induction: FABP4 in adipose tissue and macrophages, FABP1 and FABP4 in liver, FABP6 in the ileum and FABP5 in skin. Principal mediators are free fatty acids, bile acids and damage-associated molecular patterns. (B) Regulation of inflammation. FABP4 amplifies NF-κB-linked cytokine production and UCP2-dependent inflammasome activation, circulating FABP4 acts at a distance as an adipokine, and FABP5 influences the Th17/Treg balance. (C) Epithelial and tumor-cell adaptation. RA is partitioned between FABP5-PPARβ/δ and CRABPII-RAR; in neural-lineage tumors FABP7-RXRα supports a stem-like state. Reported outputs are stem-like phenotype, epithelial-mesenchymal transition and migration. (D) Tumor microenvironment interactions. Adipocyte-macrophage-tumor fatty acid shuttling, altered regulatory and $CD8^+$ T-cell function and fatty-acid-oxidation-dominant metabolism with HIF-1α stabilization. Arrows: dark blue, induction of a FABP or a downstream consequence, with solid and dashed forms as defined above; red in (B), FABP-dependent amplification of inflammatory output; dashed orange in (D), fatty acid movement between adipocytes, macrophages and tumor cells, where the dashed form denotes lipid movement rather than evidence status. CRABPII, cellular retinoic acid-binding protein II; DAMP, damage-associated molecular pattern; EMT, epithelial-mesenchymal transition; FA, fatty acid; FABP, fatty acid-binding protein; HIF-1α, hypoxia-inducible factor 1α; MCP-1, monocyte chemoattractant protein 1; NLRP3, NLR family pyrin domain containing 3; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; RA, retinoic acid; RAR, retinoic acid receptor; RXRα, retinoid X receptor α; Th17, T helper 17; TME, tumor microenvironment; Treg, regulatory T cell; UCP2, uncoupling protein 2.

condition-specific observation rather than a general property of FABP5 in this tumor type.

These convergent modules provide a mechanistic rationale for the model in Fig. 3, but they should be interpreted as context-dependent routes rather than universal FABP-driven cascades. In some settings, FABPs appear causal, in others, they are modifiers or may serve mainly as biomarkers of metabolic or inflammatory stress.

Integrative framework. Synthesizing these observations, Fig. 3 presents them as a conceptual framework. Fig. 3A involves lipid and metabolic stress, including obesity, lipotoxicity, bile acid exposure or cutaneous lipid stress, which may induce tissue-specific FABP expression, including FABP4 in adipose tissue and macrophages, FABP1/FABP4 in the liver, FABP6 in the ileum and FABP5 in skin. Fig. 3B involves the regulation of inflammation, whereby selected FABPs can amplify inflammatory signaling through PPAR-dependent, NF-κB-linked or inflammasome-related pathways, with circulating FABP4 providing a systemic adipokine route. Fig. 3C involves epithelial and tumor-cell adaptation, whereby FABP-linked lipid routing and nuclear receptor signaling may support survival, stemness or plasticity of stressed epithelial or tumor cells. Fig. 3D involves TME interactions, whereby FABP4/5/7-related circuits may support fatty acid shuttling, immune evasion, TAM activity, Treg function or tumor-cell plasticity.

The clinical implication is not that FABP targeting is already a validated stage-specific therapy, but that the stage of disease, dominant cell type and immune context should determine the manner in which FABP biomarkers or inhibitors are tested. FABP4 inhibition for MASLD/MASH-HCC prevention, FABP5 inhibition for Th17-driven inflammation or selected PPARβ/δ-driven tumors and FABP7 targeting for neural-lineage tumor plasticity are testable hypotheses rather than clinical recommendations.

6. Clinical translation: Biomarkers, therapeutic targeting and readiness

The maturity of the clinical translation evidence differs sharply by application. Therefore, this section separates the three categories of evidence that are easily conflated: i) Biomarkers

observed in humans; ii) agents tested only preclinically; and iii) approaches that remain conceptual. Table II gives the development status of each strategy and the next validation requirement.

ClinicalTrials.gov was searched again at revision (Data S1). No study has evaluated an agent developed as an FABP-directed therapeutic, in any indication. However, one interventional oncology study is relevant. Specifically, XL114, a CARD11/BCL10/MALT1 pathway inhibitor registered by its sponsor under the key word 'Fatty Acid Binding Protein 5', was tested in a first-in-human phase I study in non-Hodgkin lymphoma (trial no. NCT05144347). It was terminated after enrolling two participants for sponsor reasons and has not posted results and therefore provides no clinical information about FABP5 as a target. Only one registered study addresses an FABP as a cancer-related biomarker; it is recruiting and has no results (trial no. NCT07114614).

Biomarkers and interpretive limitations. FABP4 is the most developed circulating FABP biomarker, and also the most difficult to interpret. Serum FABP4 is consistently associated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease (5,7,127-132), which makes it a useful index of systemic metabolic-inflammatory burden, but limits its specificity for cancer.

A total of three directional questions must be distinguished, since conflating them would allow an association that is downstream of adiposity to be read as evidence that FABP4 contributes to cancer. First, adiposity is a cause of higher circulating FABP4 rather than the reverse, as shown by Mendelian randomization of body mass index against the plasma proteome (123); therefore, an elevated level is in part a consequence of the adipose state it is being used to interrogate. Second, whether the tumor itself raises circulating FABP4 has not been established. Levels fall after radical resection in CRC (118), which is compatible with a tumor contribution but is equally compatible with the effects of surgery, of resolving inflammation and of altered metabolic state. Third, the circulating protein and tissue FABP4 are different compartments, and genetic epidemiology of the former does not speak to the latter.

Where the causal question has been tested directly, the result was null. Neither measured nor genetically predicted circulating FABP4 was associated with CRC risk in a prospective analysis of 1,324 incident cases combined with two-sample Mendelian randomization in 58,131 cases (119). That analysis was powered to detect an odds ratio of ~1.17/standard deviation. Therefore, a small effect is not excluded, but a large causal contribution is.

Tissue FABP5 and FABP7 are more effectively supported as expression markers than as circulating ones, and both remain exploratory pending standardized assays and independent cohorts (13,14,87-90,96-102); for FABP5 the prognostic direction is contested in CRC (Table I). FABP3 and FABP1 have established roles in myocardial and renal or hepatic injury (133-139), but this established biomarker status does not extend to oncological applications.

Preclinical therapeutic approaches. BMS309403 remains the best-characterized small-molecule FABP inhibitor, although it engages the binding pockets of FABP3, FABP4 and FABP5 rather than FABP4 alone (140-143). In mouse models it improves atherosclerosis and endothelial function, reduces ovarian cancer burden and carboplatin resistance, prevents progression from steatohepatitis to HCC, and reduces FABP4-dependent $CD8^+$ T-cell senescence in adipocyte-rich tumors (51,76,111,142,144-147). As the compound is not isoform-selective, none of these results attributes the effect to a single FABP with confidence.

FABP4-neutralizing antibodies are mechanistically distinct as they act on the extracellular pool while leaving intracellular FABP4 intact (3,75,112,148). SBFI-26 and related compounds are the main tools for FABP5 and FABP7, but their limited selectivity between those two isoforms, and the absence of independently confirmed blood-brain barrier penetration, mean that the reported effects in prostate cancer and GBM are proof of concept rather than isoform-specific validation (14,102).

Intervening on FABP5 in an immune context requires particular caution. Acute loss of FABP5 function in Tregs increases IL-10-dependent suppressive capacity *in vitro*, which would be an unwanted effect in a tumor-bearing host (67). That finding rests on a single primary report, whereby its pharmacological arm used the aforementioned non-selective inhibitor, and FABP5 was not perturbed *in vivo* in tumor-bearing animals; independent replication is the first requirement.

Barriers to translation. Isoform selectivity is the most fundamental barrier. FABP3, FABP4, FABP5 and FABP7 share a conserved β-barrel and partially overlapping ligand pockets. Therefore, complete selectivity is difficult, and dual or pan-FABP inhibition risks disrupting cardiac FAO, hepatic lipid buffering, epithelial barrier function or neural lipid handling (1,143).

Compensation between isoforms is a distinct problem and not confined to the FABP4-FABP5 pair. FABP5 rises when FABP4 is deleted in adipocytes yet does not substitute for it in macrophages (3,35,76). In Tregs, FABP4/FABP5 double-knockout cells show a metabolic phenotype opposite to that of acute pharmacological inhibition, attributed to compensatory FABP3 (67). Therefore, germline deletion and acute inhibition are not interchangeable read-outs, and a target validated by one may behave differently under the other.

Delivery separates the strategies, whereby antibody-mediated neutralization reaches only the extracellular pool, whereas intracellular FABP5 or FABP7 targeting requires exposure inside tumor or immune cells, with central nervous system penetration decisive for GBM and hepatic exposure for metabolic liver disease.

Safety is structural rather than incidental, whereby FABPs are homeostatic lipid chaperones, not cancer-specific oncoproteins, and sustained inhibition could alter PPAR signaling, mitochondrial fuel selection, lipid storage, barrier function or immune-cell differentiation.

The limitations of isoform selectivity, delivery and safety require the target isoform, target cell and disease context to be defined before an agent is tested. Antitumor effects should be measured together with immune and metabolic consequences in the same experimental system.

Table II. FABP-directed biomarkers and therapeutic strategies: development status, limitations and next validation requirements.

Strategy[a]	Target and level	Development status[b]	Principal limitation	Next validation requirement
Circulating FABP4 measurement	Secreted adipokine; systemic, not tissue	Early translational for cardiometabolic risk; exploratory in oncology	Not cancer-specific. Confounded by body mass index, insulin resistance, diabetes, age, sex, renal function and cardiovascular disease. Mendelian randomization gives no support for a causal contribution to colorectal cancer risk and indicates that adiposity raises FABP4 rather than the reverse.	Prospective cohorts with standardized assay platforms, predefined cut-offs, cancer-specific sensitivity and specificity and adjustment for cardiometabolic confounders, before any cancer-specific claim is made.
Tissue FABP5 or FABP7 expression	Tumor tissue; immunohistochemistry or transcript	Exploratory	Association only, with no perturbation. Assay platform and scoring are not standardized. For FABP5 the prognostic direction is contested in colorectal cancer.	Independent cohorts with standardized immunohistochemistry or transcriptomic scoring, analyzed separately by tumor type rather than pooled.
BMS309403	Pocket inhibitor; engages FABP3, FABP4 and FABP5	Preclinical	Not isoform-selective, so effects cannot be attributed to a single FABP. Off-target effects reported. No human safety data.	Isoform-selective comparators, and cell-type-specific genetic models to establish which isoform carries each effect in each tissue.
FABP4-neutralizing monoclonal antibody	Extracellular and circulating FABP4 only	Preclinical	Does not reach intracellular tumor-cell FABP4, so it addresses only the adipokine pool.	Immunocompetent tumor models in which the dominant FABP4-expressing cell type has been defined in advance, with metabolic safety assessed over a relevant duration.
SBFI-26 and related compounds	Dual FABP5 and FABP7	Preclinical	Low selectivity between the two target isoforms. Blood-brain barrier penetration has not been independently confirmed, so on-target neural effects cannot be separated from peripheral FABP5-mediated immune effects.	Separation of the FABP5 and FABP7 contributions using cell-type-specific deletion and confirmed central nervous system exposure before any glioma study.
FABP5-directed intervention in an immune context	FABP5 in T cells	Preclinical hypothesis	Acute loss of FABP5 function raises regulatory T-cell suppressive capacity *in vitro*, which would be unwanted in a tumor-bearing host. The evidence rests on a single primary report; its pharmacological arm used a non-selective inhibitor; and FABP5 was not perturbed *in vivo* in tumor-bearing animals.	Independent replication first, then immunocompetent syngeneic tumors with T-cell-specific deletion, regulatory T-cell depletion or rescue and combination with immune checkpoint blockade.

[a]Interface-directed blockers of FABP4-CD36, FABP5-PPARβ/δ or FABP7-RXRα, targeted protein degradation and nanoparticle or antibody-drug-conjugate delivery have been proposed for this family but have no FABP-specific *in vivo* validation and are therefore not listed as separate strategies (158-165). [b]Development status: Early translational, supported by human association data together with mechanistic or preclinical validation but not in routine use; preclinical, supported mainly by cell and animal models; exploratory, limited human or model-system evidence requiring validation; preclinical hypothesis, a mechanism proposed from existing data but not yet tested as an intervention. These categories record what has been done with an intervention and are not a ranking of biological plausibility. FABP, fatty acid-binding protein; PPARβ/δ, peroxisome proliferator-activated receptor β/δ; RXRα, retinoid X receptor α.

7. Therapeutic paradoxes, open questions and future perspectives

The aforementioned framework remains incomplete. Future FABP research should prioritize mechanistic tests that distinguish driver, modifier, biomarker and downstream-correlate roles. A total of four challenges are particularly important, including therapeutic paradoxes, isoform compensation, single-cell heterogeneity and emerging microbiota/drug-design technologies. The minimum preclinical checkpoints required to address the most pressing of these paradoxes are summarized in Table II, which is intended as a decision aid for FABP-targeted preclinical development.

Therapeutic paradoxes as a design principle. The FABP5-Treg paradox should be treated as a design principle rather than a minor caveat. Desired anti-inflammatory effects, such as Th17 suppression, may conflict with antitumor immunity if FABP5 inhibition enhances IL-10-producing Tregs. Conversely, FABP4 inhibition may restore exhausted or senescent $CD8^+$ T-cell function in adipocyte-rich tumors (147). These opposing immune effects require preclinical testing in immunocompetent systems, with cell-type-specific FABP deletion, Treg depletion/rescue and immune checkpoint combinations before human cancer studies.

Unresolved questions about compensation. It has not yet been elucidated in which tissues and under what conditions inter-isoform compensation operate, and whether compensatory upregulation limits the durability of therapeutic inhibition. This can only be addressed with conditional tissue-specific deletion and simultaneous silencing of more than one isoform. At present, whether the less-studied FABP9 and FABP12 can substitute in any context remains unknown (1).

FABP heterogeneity at single-cell resolution. Existing FABP research has predominantly been conducted at the bulk tissue level, failing to capture heterogeneity in cell-by-cell FABP expression within the same tissue. However, recent single-cell RNA sequencing studies have revealed notable differences in FABP expression by cell subpopulation. For example, only the $CD11b^+F4/80^+MHCII^-Ly6C^-$ subpopulation of TAMs in breast cancer highly expresses FABP4 (44), and only the $CD8^+$ T cell subpopulation adjacent to the adipocyte-rich microenvironment in ovarian cancer exhibits the FABP4-mediated senescence phenotype (147). Single-cell analysis of GBM has revealed notable differences in FABP7 expression between tumor core and infiltrating margins (102).

This cell subpopulation-level FABP heterogeneity provides an opportunity to refine the 'inflammation-cancer continuum' model with spatial and temporal resolution. At present, integrated single-cell RNA sequencing analysis pipelines enable unified comparison of FABP expression patterns across disease contexts (149), and the rapid maturation of spatial transcriptomics technologies (150,151) provides an unprecedented opportunity to map FABP-mediated niches. Multicellular program discovery approaches such as DIALOGUE (152) could be particularly powerful in identifying coordinated FABP-driven states across adipocytes, macrophages and tumor cells. Future research should capture the spatial distribution of $FABP^+$ cells within the TME, interaction patterns with neighboring cells and dynamic changes during treatment response through spatial transcriptomics and multiplex protein imaging techniques such as CODEX/MIBI. Such data will form the foundation of patient stratification and precision FABP-targeted therapy.

Gut microbiota/bile acid/FABP axis. The aforementioned FABP6/bile acid/microbiota axis is an actively expanding emerging area of FABP research. The intestinal dysbiosis-exacerbated colitis phenotype in Fabp6ΔIEC mice (116) suggests that FABPs may participate in host-microbe interactions, extending their role beyond intracellular lipid handling. However, this axis is not limited to FABP6. FABP4 may also be involved in the systemic circulation of microbial metabolites (short-chain fatty acids and lipopolysaccharides) through intestinal lymphatics and adipose tissue, and FABP5 may be a link between cutaneous microbiota changes and psoriasis progression (153).

Causal evidence from humanized gnotobiotic models demonstrates that gut microbiota from obese hosts is sufficient to transmit metabolic phenotypes (154), and microbial metabolites have been established as central mediators of host-microbiota communication (155,156). Bile acid derivatives have been shown to directly control the Th17/Treg axis, which is also central to FABP5 biology (157). Future research should address: i) Which microbial metabolites act as ligands for each FABP isoform; ii) the mechanisms by which gut microbiota composition regulate FABP expression and function; and iii) whether probiotics, prebiotics or fecal microbiota transplantation can modulate FABP-mediated inflammation-cancer pathways. A study by Kwon *et al* (116) demonstrated alleviation of colitis in Fabp6ΔIEC mice through oral administration of *L. murinus*, which represents the first practical example of such microbiota-mediated modulation of the FABP pathway and suggests the possibility of therapeutic strategies combined with dietary interventions.

Emerging approaches. Interface-directed inhibition, targeted protein degradation, selective delivery and artificial intelligence-assisted structural analysis are possible research approaches (158-165). The cited technology literature motivates their consideration but does not, by itself, establish FABP-specific target engagement or antitumor efficacy. Predicted binding requires biochemical and cellular validation, followed by appropriate *in vivo* exposure and safety studies. These approaches are therefore discussed as future research directions.

Cutaneous FABP5: An instructive limit. FABP5 amplifies IL-17-associated inflammation in psoriasis models (153,166), which has invited the inference that it also promotes psoriasis-associated skin cancer. However, a cutaneous carcinogenesis experiment reported a different direction, whereby E-FABP-deficient mice developed DMBA/TPA-induced tumors earlier and in greater number than wild-type littermates, whereas FABP4-deficient mice did not, with protection traced to E-FABP-dependent IFN induction, enhanced p53 responses and suppression of SOX2 in keratinocytes (167). Inflammatory amplification and carcinogenic direction are separate questions for this isoform, and

cutaneous inflammation is not treated as a FABP5-driven route to skin cancer.

FABPs in endocrine-metabolic aging. Finally, emerging evidence suggests that FABP function may extend beyond the aforementioned inflammation-cancer continuum. The role of FABP4 as an aging biomarker (168), together with observations that other FABP isoforms participate in neural and behavioral regulation (1,70), hints at broader biological roles. These emerging dimensions intersect with the metaflammation framework, particularly via the concept of inflammaging in obesity-associated endocrine dysfunction. Further investigation of the FABP network as a common molecular substrate of metaflammation and inflammaging represents a logical extension of the aforementioned framework.

8. Conclusion

The main conclusions of the present review are three-fold. First, FABP biology at the inflammation-cancer interface is isoform- and cell-type-specific, whereby FABP4 most strongly links adipose inflammation, macrophage activation and obesity-associated tumor biology; FABP5 connects epithelial/T-cell lipid metabolism with tumor growth and immune balance; and FABP7 contributes to neural-lineage tumor plasticity in a ligand-dependent manner.

Second, FABPs should not be framed uniformly as oncogenic drivers. Depending on context they may act as causal contributors, risk modifiers, biomarkers or downstream correlates, and the present review has separated those possibilities rather than summing them into a single verdict/isoform. A total of three cases illustrate the range of these possibilities. For FABP4 in obesity-associated breast cancer, human association, circulating biomarker data and *in vivo* perturbation all point the same way, yet every perturbation experiment measures the growth of an established tumor and none measures incidence. For FABP5 in CRC the reported direction is opposite between studies and remains unresolved, and myeloid FABP5 has been reported to restrict rather than promote tumor growth. For FABP6 in the intestine, the inflammatory and the neoplastic observations have not been connected by any experiment, and the available loss-of-function phenotype is the opposite of what a tumor-driving role would predict.

Third, clinical translation requires restraint. FABP4, FABP5 and FABP7 remain promising molecular targets, but isoform selectivity, biomarker specificity, metabolic safety and the FABP5-Treg paradox must be resolved before FABP-targeted diagnostics or therapeutics can be used in precision oncology.

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Authors' contributions

YSH contributed to the conceptualization of the present review, performed the literature search and wrote, reviewed and edited the manuscript. YTJ and SJL performed the literature search, screened and extracted data from the included articles and wrote, reviewed and edited the manuscript. JH performed the literature search, designed and constructed the figures and tables and wrote, reviewed and edited the manuscript. SJK contributed to the conceptualization of the present review, supervised and administered the project and wrote, reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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