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The cytoplasmic fatty-acid-binding proteins: thirty years and counting

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Abstract. The interest in fatty-acid-binding proteins has produced about 1000 research papers since their discovery nearly 30 years ago. This review provides an entry to the mammalian and nonmammalian literature through a compendium of categorized review articles (nearly 60). Publications that have not yet been reviewed, particularly of function and modes of action, are presented and discussed in light of earlier reports. This large protein family may be integral in the relationship between lipid and carbohydrate metabolism.

Key words. Fatty-acid-binding protein; metabolism; nonmammalian; carbohydrate; glycolysis.

Introduction

The first consistent evidence of the physiological role for cytoplasmic fatty-acid-binding proteins ($FABP_C$s) was published recently. In reports [1–3] of work with knockout mice (nullizygous for heart $FABP_C$ gene and disrupted adipocyte $FABP_C$ gene) we have direct proof of the importance of $FABP_C$s in the uptake and transport of long-chain fatty acids (LCFAs), fuel preferenda and the interaction with other transport and enzyme systems. During the 30 years since their discovery in rat liver [4–6], there has been only indirect evidence of the functions of these proteins. The ubiquity and large concentration of this protein family in mammalian systems with many homologues in nonmammalian systems has been both a boon (the ease of isolation and physical study) and a conceptual difficulty: Why is there more than one type in some tissues? Perhaps a sign of some of the frustration of this field is the number of review articles published (at least 60) summarizing nearly 1000 publications for the last 15 years. Figure 1 shows the frequency of publications in the field: from the present until about 15 years ago this frequency relationship has been linear with a rate of increase of about 6 publications per year (data from Medline and Current Contents).

This review will attempt to facilitate the tyro's entrance to the extensive literature by providing a listing of reviews, the physical characteristics and structure of the protein family, the evolution and genetics of the family, the regulation of protein expression, the suggested functions of $FABP_C$s, the binding and delivery of ligands and a listing of reported nonmammalian $FABP_C$s. Recent publications will be discussed and linked to previous observations, and to interactions with nonlipid metabolism. Finally, a model of interactions of $FABP_C$s with glycolytic intermediates will be offered that may link LCFA trafficking to carbohydrate processing.

Signs of maturity of the field include a proposed nomenclature [8], a widening of focus to include nonmammalian species, and the application of protein to diagnosis and treatment of medical conditions. The proposed nomenclature [8] provides for the use of the general abbreviation, X-$FABP_C$ where X is the tissue of type predominance (liver, L; adipose, A; heart, H; muscle, M; brain, B; intestinal, I; epidermal, E; keratinocyte, K) and C indicates a cytoplasmic compartment. While medical applications of the knowledge base are important, they are outside the scope of this review. Interested readers are directed to reviews and recent papers of the direct medical applications of $FABP_C$s [9–21].

Before a deep understanding of the necessity of $FABP_C$s can be achieved, one must understand the biophysical properties of LCFAs and their interactions with the intracellular milieu. This has been approached at the theoretical level by a number of workers [22–32]. An-

other prerequisite for appreciation of the role of $FABP_C$s is the integration of lipid metabolism into general metabolism and in particular with carbohydrate catabolism. There are a number of reviews to which the reader is directed as an opening to this field of study [33–35].

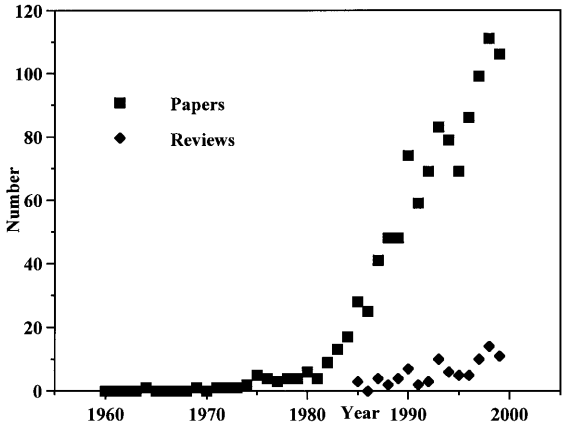

Figure 1. The frequency of publications and literature reviews dealing directly with the cytoplasmic FABPs. The data were culled from a combination of Current Contents and Medline databases and are current to 1 January 2000. The data for the number of papers fit well to an exponential curve, with an r^2 value of 0.94.

Table 1. A summary of the major foci of reviews of the biochemistry of cytoplasmic fatty acid binding proteins.

Topic	Literature reviews
General topics	7, 52–63, 65, 66, 72, 75, 80, 84–86, 88, 91, 95, 102, 104, 108
Occurrence/tissue	64–66, 79, 103, 108
Structure (3D)	53, 54, 57, 58, 65–67, 75, 76, 79, 87, 92, 97, 105–107, 109
Function	7, 52–54, 56, 61, 64–67, 69, 71–73, 75–78, 81, 85, 86, 88, 90–92, 95, 99, 100, 102, 105, 109–111
Ligands, K_d, specificity	7, 52–56, 61, 64–66, 69, 71, 72, 79, 104–106
Effect on enzymes, metabolism or development	52, 56, 59–61, 64, 65, 68, 72–74, 7781–83, 88, 93, 95, 98, 100, 110
Binding: dynamics, kinetics, thermodynamics	61, 65, 71, 74, 79, 85, 90, 99, 104–106
Evolution	7, 57, 61, 64, 92, 103, 104
Regulation of genes and expression	52, 55, 58, 59, 61, 64, 65, 70, 81, 87, 92, 96, 101
Sequences	54–57, 61, 65, 75, 79, 92, 103, 106, 107
Isoforms	52, 61, 71, 103
Medical (see also 'Introduction')	65, 73, 94, 100, 101
Nonmammalian FABPs	81, 89, 97

The transmembrane movement of LCFAs has been a contentious issue (see [7, 23, 25, 27, 31, 36–39]). There are data suggesting that nonmediated transmembrane movement of LCFAs is of sufficient rate to supply cellular needs [40–42], whereas other evidence shows that entrance of LCFAs into the cell is mediated by membrane proteins [43–48]: fatty acid translocator (FAT), fatty acid transport protein (FATP) and plasma membrane fatty-acid-binding protein (FABPpm) facilitate transmembrane transport, particularly in mammalian placental tissue [49]. The coexpression of these protein systems in rat heart and skeletal muscle [48] and the presence in human skeletal muscle [50] provide evidence that membrane protein transportation is an important module in LCFA homeostasis. It is important to note that in the $FABP_C$ knockout mouse heart [1, 2] β-oxidation and cell uptake of LCFA did not decrease to zero. Dual transmembrane pathways may have implications on the LCFA load that the cell must manage and implicates the degree of saturation of the intracellular $FABP_C$s since it is known that the rate of hydration of membrane bound amphiphiles is rapid [51]. This aspect of LCFA metabolism is larger than the scope of this review, but it appears as if both the passive and protein mediated transport can occur.

Previous reviews

The preponderance of literature relating to the family of cytoplasmic fatty-acid-binding proteins can be daunting. Table 1 summarizes the major aspects of published reviews relating directly to $FABP_C$s. Every attempt has been made to cite all reviews since 1985 that deal directly the $FABP_C$s (excluding the cellular-retinoid-binding proteins, CRBPs).

$FABP_C$ structure

Because of the abundance and ease of isolation of $FABP_C$s, the study of three-dimensional structures is more sophisticated than our understanding of $FABP_C$ function. Table 2 lists the $FABP_C$ structures that have been reported. The first reported crystallographic studies to enter the literature were of recombinant rat I-$FABP_C$ [110, 111]. A recent review of $FABP_C$ (and other lipid-binding proteins) structures (table 1 in [3]) listed five solved crystal structures (heart, intestinal, *Manduca sexta* protein, adipocyte, myelin P2).

The picture that emerges is remarkably consistent over the various $FABP_C$ types and across phyla. The reader is referred to any of the protein databases from which published structures can be downloaded in a number of formats. The molecule is compact ($\sim 250 \times 350 \times 400$ nm) and, although generally referred to as a β-clam

Table 2. A list of 3D structure of FABPs deduced from X-ray crystallography or NMR solution studies. Studies with recombinant $FABP_C$ are indicated by (recomb). When the structure was determined by crystallography the resolution (in Ångstroms) is given in parentheses. Whether the structure solution was carried out with protein bearing ligand is indicated (halo or apo) in parentheses after the protein type. The table does not include various mutated $FABP_C$ structures.

Year	Organism	FABP type	Method	Reference
1989	Rat	I (recomb) halo	X-ray (2.0)	110
1989	Rat	I (recomb) apo	X-ray (1.96)	111
1990	RatL	Apo	X-ray (?)	112
1992	Bovine	H apo	NMR	113
1992	Mouse	A apo	X-ray (2.5)	114
1993	Bovine	H halo	NMR	115
1994	Human	M apo	X-ray (1.4)	116
1994	Locust	M apo	X-ray (2.2)	117
1995	Bovine	H halo	NMR	118
1995	Rat	I apo	NMR	119
1996	Rat	I halo	NMR	120
1997	Human	I (recomb) apo	NMR	121
1997	Rat	L (recomb) apo, halo	X-ray (2.3)	122
1998	Rat	L apo	NMR	123
1999	Human	E (recomb) apo*	X-ray (2.05)	124
1999	Chicken	L apo	NMR	125

* There is an unusual disulfide linkage in the epidermal protein between Cys120 and Cys127 not seen in other $FABP_C$s.

motif, resembles no clam this author has observed, as one 'side' is pinched inwards—a β barrel with a waist. There are 10 antiparallel β strands (βA–βJ) with βA–βE and βF–βJ forming the two 'faces' of the barrel. The strands of two sheets (βA–βE and βG–βJ) are nearly orthogonal to each other. All β strands are hydrogen-bonded to the preceding and succeeding strands except βD and βE. This rift in the continuous surface of the barrel, the 'gap', allows flexibility of the barrel structure without significant disruption of the H-bonded strands around the rest of its circumference. At the 'top' of the gap region (the structure is usually oriented with the helix-turn-helix motif at the top and back) is the portal region where the base of the helix-turn-helix and right turns of βCD and βEF are proximal. It is through the portal region that the ligand probably enters and exits the internal binding site. The internal cavity within the barrel contains a number of hydrophilic side chains that form charge/charge interactions and a H-bonded lattice that interacts directly with the carboxylate moiety of the ligand. The internal volume to accommodate ligands has been determined (cf. [79, 122]) and can vary from about 250 to 440 A^3 with the largest observed for L-$FABP_C$ that accommodates two rather than the usual single LCFA [122]. When bound, the LCFA carboxylate interacts directly with Arg-126 in a salt bridge deep in the protein interior. The alkyl tail of the fatty acid is bent with the end of the tail outside the protein exposed to the solvent. L-$FABP_C$ has a second LCFA, bound tail-first in the cavity [122], that interacts with both the protein side groups lining the cavity and the alkyl tail of the first internalized fatty acid. The carboxylate group of the second fatty acid ligand, exiting the portal region, appears fully exposed. A comparison of 31 engineered mutant I-$FABP_C$s with wild type [126] has extended suggestions [79] and outlines a possible mechanism by which oleate and linoleate enter and exit the binding cavity. This proposal sees an initial interaction between the carboxylate and Arg-56 (present in CRABP II, CRABP, CRBP, CRBP II and I-$FABP_C$ [79]) or Lys-56 (myelin P2, H-$FABP_C$, shark L-$FABP_C$, schistosome $FABP_C$ and rat L-$FABP_C$ [79]), since alterations in this site alter LCFA-binding kinetics, and inhibition of binding by increased ionic strength appears to result from masking of the charge on this amino acid site. Position 56 is on the outer surface of the βD strand, near the portal region. Similar binding activation energies for adipocyte, heart and intestinal proteins were suggested to indicate similarities in the initial interaction of ligand with protein and correspond to very similar conformation of the portal regions of these proteins [127]. The proposal suggests that after the initial complex formation in which there is a carboxylate/guanidino (or quaternary ε-NH_3^+) interaction, the LCFA moves to the interior of the protein taking up its bent conformation, associating the carboxylate now with Arg-126 along with release of cavity water. The exit of ligand is seen as reversing the entry trajectory. A human H-$FABP_C$ mutant with an altered portal region (Phe-16) showed significantly decreased oleate binding affinity [128] consistent with the proposed interaction mechanism.

Evolution, genes and chromosome location

Analysis of $FABP_C$ evolution emerged as soon as amino acid sequences and cDNA sequences became available [129–131]. The picture drawn is of an ancient precursor that was probably the initial solution to solubilizing and mobilizing hydrophobic resources at least 10^9 years ago. The precursor that gave rise to the liver/intestine/ileal grouping emerged from the heart/adipose/myelin P2 lineage about 700 millions of years ago, prior to the vertebrate/invertebrate divergence. While muscle type $FABP_C$ has been found in locust [81, 97], no liver/intestinal types have been reported for invertebrates. The retinoid binding proteins appear to have diverged from the liver/intestinal line about 500 millions of years ago. It has been suggested that the multiple CRBP genes of mammals arose from gene duplication events after the split with amphibian lines: *Xenopus* has only one CRBP gene (reviewed in [61]).

The lineage and interrelationships of this protein family have been discussed in a number of reviews (see table 1) with the most detailed analysis to date, comparing 51 related sequences [132] clarifying our understanding but at the same time indicating at least 14 gene duplications. Work with nonmammalian systems (table 4 for refs) indicates the divergence of liver function and what $FABP_C$ type is present echos the metabolic poise of the tissue. Lamprey express an H-type in their livers, whereas some bony fish can produce L- and H-types hepatically. The suggestion [148] that divergence of liver function in lower vertebrates and the transition from L, to L plus H, to H, moving from higher vertebrates, to teleosts, to lower pisciformes is consistent with the proteins expressed, the cartilaginous/bony fish boundary and the finding of a mammalian type L-$FABP_C$ in liver of an amphibian (*Rana catesbeiana*). This suggestion is not consistent with the presence of liver type $FABP_C$ in shark liver (*Halaetunus bivius*). To illustrate further the differences in lower vertebrates, both heart and adipose type $FABP_C$s are expressed in Antarctic fish cardiac tissue and may reflect the reliance on large lipid content of these hemoglobin-less fish. On the other hand, rainbow trout heart (*Salmo gairdneri*), more similar to the mammalian system in physiology, shows a heart type with only 75% identity with mammalian H-$FABP_C$. Clearly, comparison of mammalian and nonmammalian lipid storage and intracellular lipid transport will tell us much.

The structures of fatty-acid-binding protein genes are remarkably similar, with four exons separated by three introns (detailed descriptions reviewed in [61, 132, 133] and with positioning of the introns very similar relative to the coding regions, although there is considerable variability in the intron length. The exception to this organization is the two-intron, three-exon structure of locust flight muscle $FABP_C$ [81, 97]. The chromosomal locations of $FABP_C$/CRBP genes have been reported for four animals, with most studies being performed with mice (reviewed in [99, 133]). Table 3 shows the known chromosomal positions for murine, rat, porcine and human genes.

Regulation of $FABP_C$ production

The expression of $FABP_C$ genes has developmental aspects, responds to levels of lipids presented to cells and is under hormonal influence. From recent work it is clear that LCFAs induce both translation and transcription, probably through interactions with peroxisome-proliferator-activated receptors (PPARs) and concomitant interaction with promoter regions of

Table 3. Chromosomal locations of fatty-acid and retinoid-binding proteins. Locations on the chromosome are listed where known. (H/M, heart/muscle; A, adipocyte; L, liver; I, intestinal; B, brain; K, keratinocyte; E, epidermal; CRBP, cellular retinol-binding protein; CRABP, cellular retinoic acid-binding protein.)

FABP type	Source organism			
	Mouse	Rat	Porcine	Human
H/M*	4, 8 [61, 138, 143]	5q36 [134]	6 [135, 140]	1p32–1p33 [144] 1 1pter-q31 [145]
A	3 [61]		4 [136]	8 q21.3-q22.1 [99, 141]
L	6 [61]		-	2 [147] p12-q11 [61]
I	3 [61]		4 q28-q31 [61]	
Ileal				5 [142]
B	6 q22–23 [139]			
K†	3 [137]			
E†	3A1-3 [134]			
CRBP	9 [61]			3 3p11-3qter [61, 146]
CRBP II	9 [61]			3 [61]
CRABP				3 [61]

* MDGI (H-$FABP_C$) has been reported on chromosome 4 [138].
† K (keratinocyte)- and E (epidermal)-$FABP_C$s are frequently reported as if distinct, but are identical.

$FABP_C$ genes. Thus, the metabolism of lipids appears to be enmeshed in an elaborate feedback system.

Since it is clear that the amount of $FABP_C$ in a tissue corresponds to cellular (or tissue) flux of fatty acids (see references in table 1), it is consistent that regulation during animal development is important. In the rat [133], H-$FABP_C$ is present in the 19-day embryonic heart at 20% of adult levels and up to 60% of adult levels at term. The appearance of the protein tracks the appearance of the enzymes for fatty acid metabolism. In developing locust flight muscle (reviewed in [97]), $FABP_C$ messenger RNA (mRNA) appears immediately after adult ecdysis, increases to a maximun at 7 days post-ecdysis and then decreases to a steady state level at 15 days. M-$FABP_C$ appears shortly after ecdysis (2–3 days) and increases to 13% of total cytosolic protein by 10 days, the time required before the insect can perform long-term flight. This temporal expression pattern was not under direct hormonal control but was coincident with metamorphosis in an unknown way. By way of contrast to the locust, I-$FABP_C$ in developing *Xenopus* is downregulated by thyroid hormone [149] but increases later. Developmental quieting of the $FABP_C$ system may also have been observed in adult marine echinoderms, molluscs and crustaceans, whose preadult forms have significant fluxes of LCFAs [150]. Developmental aspects are also apparent at the tissue level: quiescent mammary tissue contains very little H-$FABP_C$ but increases the protein content manifold upon initiation of lactation [151]. There are also indications that aging alters the expression of fatty-acid-binding proteins in mouse brain [152]

A number of other hormones have been implicated in the expression of the $FABP_C$ system. Both in vivo and in vitro experiments with liver from hypophysectomized rats indicate that bovine growth hormone (bGH) increases L-$FABP_C$ and its mRNA 2- to 5-fold over a 7-day course of treatment [153], but insulin or insulin-like growth factor I had no effect in vivo. In vitro experiments showed bGH plus insulin increased L-$FABP_C$ mRNA and bGH increased transcription within 3 h. Since actinomycin D eliminated the effect of bGH, the authors concluded that the effect was at the transcriptional level. Glucagon decreased L-$FABP_C$ mRNA in hepatocytes.

Norepinephrine appears to mimic the effect of low-temperature exposure on rat brown adipose tissue [154], where H-$FABP_C$ increases 100-fold whereas A-$FABP_C$ in the same tissue remains unchanged. Such differential effects suggest different promotion of gene expression. There were no effects on the $FABP_C$s of white adipose tissue of cold-treated animals. There are indications that testosterone and endurance training can increase $FABP_C$ in heart and muscle [155].

The amount of $FABP_C$ expressed by a tissue is a function of its health. The decrease of lipid metabolism (lipolysis, lipogenesis, reesterification and β-oxidation) in infected or inflamed tissue is mediated, in part, by a downregulation of the $FABP_C$ system [156]. Bacterial endotoxin (lipopolysaccharide, LPS) and tumor necrosis factor α (TNF-α) and interleukin 1β (IL-1β, cytokines) decreased β-oxidation in Syrian hamster liver and heart. Part of this curtailment was LPS-mediated decreases in L-$FABP_C$ (41%) and its mRNA (72%) within 24 h. In muscle, LPS decreased H-$FABP_C$ 49% and its mRNA 60%, whereas in heart, H-$FABP_C$ mRNA decreased 65%. The cytokines did not alter muscle H-$FABP_C$ or its mRNA but decreased the L-$FABP_C$s in liver (TNF-α, 30%; IL-1β, 45%).

The effect of diet on the levels of $FABP_C$ in various tissues has been recognized for a number of years (see 'General', table 1). Recent work indicated how such upregulation occurs and how the levels of LCFAs can induce differentiation in, for example, adipocytes [157], through actions on plasma-membrane-bound adipose differentiation related protein. In hepatic tissue LCFAs trigger a fourfold increase in L-$FABP_C$, a sevenfold increase of its mRNA within 16 h of exposure, whereas octanoate had no effect [158]. The time- and dose-dependent effect of LCFAs was eliminated by cycloheximide, leading the authors to conclude that the control was, at least partially, transcriptional. Similar upregulation at the transcriptional level was also implied earlier by work with muscle [159] and with small intestine [160].

LCFA upregulation of the $FABP_C$ system has been clarified by work with neonate cardiomyocytes [161]. Incubation of myocytes with oleate or palmitate did not change cell morphology or the amount of glucose transporter (GLUT4), hexokinase II or glyceraldehyde 3-phosphate dehydrogenase but induced a four fold increase in mRNA for H-$FABP_C$ along with mRNA for FAT, acylcoenzyme A (CoA) synthetase and long-chain acylCoA dehydrogenase. Additionally, there was a a 60% increase in β-oxidative capacity. The action of LCFAs was most likely at the level of PPAR-α. How the PPAR signal translates into action on gene transcription was suggested by the identification of a 1.2-kbp promoter region in the 5′ flanking region of the H-$FABP_C$ gene [162] that controls tissue expression patterns for this gene.

Function of $FABP_C$s

Since the discovery of $FABP_C$s with a strong affinity for LCFAs and their presence at large concentrations in tissues that produce large fluxes of LCFAs, it has been clear that they perform a transport function (see reviews

in table 1). Since that time, there have been many refinements of this hypothesis as information became available. It was suggested [79], with little opposition, that the expression of more than one type of $FABP_C$ in a tissue is a strong predictor that $FABP_C$s perform functions other than bulk transport. Additionally, the presence of true isoforms (with amino acid substitutions and distinct mRNAs such as seen in bovine H-$FABP_C$, reviewed in [103]) may indicate either very subtle functional refinements or the development of two homologous genes in progress. It should be noted that although there have been a number of variants of the types of $FABP_C$s reported as isoforms, most result from posttranslational modifications or the presence of bound ligands (this was well addressed [103]). The functions suggested for the $FABP_C$ family are increasing transport across plasma membrane; solubilizing LCFAs and facilitating their diffusion; 'buffering' LCFA concentrations to prevent toxic and/or detergental effects and mediating partitioning of LCFAs between membrane and solublized pools; targeting LCFAs to intracellular sites and specific enzyme systems; mediating cell signaling metabolites (eicanosoids, prostaglandins, leukotrienes and thromboxanes); behaving as an LCFA sensor in regulation of $FABP_C$ mRNA expression. Recent and still tentative additions to the list of possible functions include modulation of aspects of protein synthesis and integrating carbohydrate and fatty acid metabolism. Most of the functions and the evidence presented to support these views have been reviewed many times (see table 1, 'Functions'), with the most recent appearing during the last 2 years [7, 99].

Transmembrane transport of fatty acid

The contentious issues raised from studies of transport of LCFAs across the plasma membrane are summarized in the Introduction. Cell cultures, transfected to overexpress $FABP_C$s, increase the uptake of LCFAs in some cases, but not all. Data from such experiments have been summarized (table 2 in [7]). Whereas some experiments show no increase in LCFA uptake as in A-$FABP_C$ transfection L6 myoblasts [163], human breast cancer cells transfected with H-$FABP_C$, increased palmitate uptake 67% with no changes in targeting of ligand to complex lipid synthesis [164]. Similar increases in palmitate uptake have been reported in rat hepatocytes [165], but overexpression of I-$FABP_C$ in Caco-2 cells inhibited LCFA absorption by 34%, again with no alteration in the triglyceride pool [166]. In mouse heart and cardiomyocytes nullizygous for the H-$FABP_C$ gene, uptake of fatty acid decreased 80% in the former, and uptake of an LCFA analogue decreased 45% in the latter [1, 2]. Disruption of the A-$FABP_C$ gene in mouse resulted in no changes in LCFA influx or esterificaton patterns [3]. Clearly, the role of $FABP_C$ in movement of LCFAs into cells is not fully understood. Whether the increase in uptake, where it occurs, is the result of steeper concentration gradients across the membrane as a strictly physical process (as suggested by Weisiger [29]), or whether there is specific or nonspecific docking of the $FABP_C$ with the interior of the plasma membrane, is not clear.

Cytoplasmic transport of fatty acids

There are probably two LCFA transport processes in the cytoplasm that may contribute to fatty acid flux at least in terms of rates relative to slow lateral membrane diffusion. Effective diffusion coefficients for lateral membrane diffusion ($Deff = 10^{-10}$ cm^2 s^{-1}) are smaller [29] than $FABP_C$-bound ligand ($Deff < 2.6 \times 10^{-9}$ cm^2 s^{-1}) [167] and free LCFAs (e.g. palmitate $Deff = 3 \times 10^{-6}$ cm^2 s^{-1} [168]), and the transit time for a 20-μm cell has been estimated to be 10,000 s, >110 s and 0.1–1 s, respectively [29] for the three contributions. Clearly, the concentration of LCFA in each pool must be the important factor: unfortunately, the intracellular distribution of LCFA in whole cells has not been adequately addressed. It is probably adequate to assume that protein-bound LCFA is the major contributor because of the low solubility of LCFAs in aqueous systems. The self-diffusion of LCFA may be sufficient to supply low-flux tissues such as seen in peroxisomal LCFA oxidation of $FABP_C$-less marine invertebrates [150]. It is clear that assessment of intracellular transport of LCFAs must appreciate the complexity of viscoelasticity, tortuosity and cytoarchitecture [28, 29].

The analysis of cytoplasmic diffusion processes, aside from being far more complex than generally appreciated, also indicates that the 'snapshot' view of $FABP_C$ binding of LCFAs may not be adequate when referring to the proposed 'buffering' functions of the protein. The static view leads to estimates that a significant fraction of the protein does not carry ligand and, hence, could mediate transient increases in cytoplasmic LCFA concentration. The dynamic view, taking into consideration the flux of ligand, protein and protein/ligand complex, indicates that with the metabolic fluxes of, for example, heart tissue, the protein pool would be saturated in about 1 min [29]. This must be addressed, since work with enterocytes [169] is consistent with diffusion being the sole process and provides no evidence for convectional transport.

One aspect of intracellular LCFA transport that has not been adequately addressed in the literature is the role of nonspecific protein binding. Theoretically, any protein that binds LCFAs and can diffuse could facilitate or at

least add to the LCFA flux. With H-$FABP_C$ nullizygous mouse heart, a significant proportion of both LCFA uptake and oxidation still occurs [1, 2]. The possibility that other proteins could bind LCFAs was shown in the detection of a high-affinity saturable binding site for *cis*-parinarate and oleate on bovine heart hexokinase ($K_d = 3.5 + 0.4$ μM and $1.47 + 0.24$ μM, respectively) [170], and a low-affinity site with an inhibition constant of about 70 μM. An assessment of the non-$FABP_C$ protein contribution to LCFA transport would be possible with the nullizygous mouse, since no true isoforms are known for protein [103].

Delivery of LCFAs to organelles and enzyme systems

There is evidence that $FABP_C$s target intracellular membranes such as the mitochondria and endoplasmic reticulum: these processes have been reviewed recently [7, 99] and are referred to in table 1, 'Functions'. When coupled with reports from Storch and her group (see below), and arguments for the establishment of intracellular gradients of LCFA/$FABP_C$ [29], it is most likely that $FABP_C$s target membranes or receptors on membranes to deliver their cargo.

Transfer of fluorescent LCFA analogues from $FABP_C$s to membrane targets appears to involve collision of the holoprotein with anionic membranes (reviewed in [71, 90]). This mechanism operates with A- [171–173] and H-$FABP_C$s [171, 174, 175], but not L-$FABP_C$ [175, 176]. The adsorption and desorption of fluorescent probes from L-$FABP_C$ appears diffusion limited and is about 50-fold slower than the collisional mechanism [175]. Electrostatic interactions between the protein and negatively charged membranes indicate portal lysine residues are involved [177]. This hypothesis received strong confirmation in work where A-$FABP_C$ with acetylated lysines reverted to a diffusionally restrained mechanism [178], as did a helixless mutant of I-$FABP_C$ [179, 180]. Reevaluaton of the diffusional mechanism for L-$FABP_C$ is suggested by observations that recombinant rat L-$FABP_C$ binds to, and delivers fluorescent fatty acids to, anionic phospholipid vesicles [181]. The results indicate a role for the N-terminal region of L-$FABP_C$ in membrane adsorption, but lack of N-terminal acetylation of the recombinant protein would leave a formal positive charge on the N-terminus and must be considered in assessing this work.

To date, it is not clear how collisional $FABP_C$s adsorb ligands from cell membranes, if they do. Presumably, thermodynamics of the collision process favours membrane uptake. The transfer of LCFAs from phospholipid vesicles to proteins, while spontaneous, is slow enough that transient increases in membrane-soluble LCFAs produced from lipolysis [182] may be significant to LCFA uptake. While these data may be used in examining hepatic fatty acid transport, it is unfortunate that one of the $FABP_C$s purported to operate by a collisional mechanism was not studied. It is peculiar that I-$FABP_C$ did not increase uptake of a fluorescent stearate analogue in transfected fibroblasts, whereas L-$FABP_C$, presumably not operating though a direct collisional mechanism, did, by 1.7-fold [183]. In this study, both the L- and the I-$FABP_C$ types increased cytoplasmic diffusion rates in single cells.

$FABP_C$s have been implicated in targeting specific enzymes in ways other binding proteins (e.g. serum albumin) do not. The ability of L-, I-, A- and H-$FABP_C$ to influence glyceride synthesis is through stimulation of microsomal and mitochondrial glycerol 3-phosphate acyltransferase and lysophosphatidylphosphate acyltransferase (reviewed in [103]). L-$FABP_C$ stimulates acylCoA synthetase of rat liver endoplasmic reticulum (reviewed in [99]). Since some $FABP_C$s (liver, keratinocyte) can bind signalling metabolites (eicosanoids, prostaglandins and so on.) there have been suggestions that $FABP_C$s mediate cell processes. Also, $FABP_C$ modulates enzymes involved in signal metabolite production (reviewed in [72] and [83, 184]) and mediates mitogenic cascades in liver (reviewed in [22]). Presumably, any factor that modulates the binding of such ligands to $FABP_C$s could have implications in affecting cell processes on a much wider scale. In keeping with the regulatory functions, it was suggested [99] that $FABP_C$s are part of a control loop relating lipid and protein levels by acting as sensors of intracellular lipid levels. A novel finding may further complicate and provide unexpected roles of the protein family: cell-free protein synthesis was inhibited by delipidated myelin P2, I-, H- and B-$FABP_C$s, but not A-, L- or E-$FABP_C$s [185].

Three recent publications have provide direct and clear evidence of the role of $FABP_C$s [1–3]. In mice with a disrupted A-$FABP_C$ gene, there was no difference in uptake or in esterification of delivered LCFAs from the wild type. Basal lipolysis and glycerol release from adipose tissue decreased 40 and 35% respectively, and the basal efflux of fatty acids was elevated threefold in the null condition. This was consistent with a 300% increase in LCFA in adipose tissue (525 nmol/g vs. 1474 nmol/g in null animals). The experiments with mice with both copies of the gene for H-$FABP_C$ disabled [1, 2] proved very illuminating. In cardiomyocytes from the nullizygous ($-/-$) mice, palmitate uptake decreased 45%, whereas cytosol oleate binding capacity decreased 55%. Uptake of ^{125}I-15-(*p*-iodophenyl)-3(*R*,*S*)-methylpentadecanoic acid was unaltered in brain, liver, and kidney that contained other $FABP_C$ gene products but decreased fivefold in heart and a small amount in soleus muscle. At the same time, uptake of ^{14}C-deoxyglucose was increased fivefold only in heart tissue of

−/− mice. Concomitant with decreased cardiac uptake of LCFAs was increased circulating LCFA and β-hydroxybutyrate, presumably from increased liver β-oxidation. The increase in glucose uptake was not a function of increased GLUT4 transporters (protein or mRNA) or of hexokinase mRNA. Finally, there were no differences between knockout and wild-type mice for activities of citrate synthase, β-hydroxyacylCoA dehydrogenase, lactate dehydrogenase, acylCoA synthetase (mRNA), carnitine palmitoyltransferase I or acylCoA-binding protein. Also, there were no detectable differences in the complement of membrane LCFA transport proteins. Thus, there was neither reorganization of the components of FA metabolism nor reorganization of organelle distribution in −/− mice. The amount of triacylglyceride did not differ between the two phenotypes, indicating no reorganization of the targeting of FAs. In myocytes, the rate of palmitate oxidation was 65% lower, whereas the rate of glucose oxidation increased 80%. Electrical pacing of myocytes resulted in an increase (2×) in +/+ myocytes, but not in −/− derived myocytes, indicating that glycolysis was probably at maximal flux. Along with increased glucose uptake and oxidation, glycogen content was increased from 49.5 to 78.3 μmol/g dry weight. This would indicate that an uninhibited glycolytic flux still maintained enough glucose 6-phosphate (G6P) to produce glycogen and suggests that the normal glycolytic control systems were displaced, probably by hexokinase and phosphofructokinase inhibition being lifted. These experiments may connect observations of interactions between hexokinase and fatty acids [170] and between glycolytic metabolites, LCFA binding to rat L-$FABP_C$ and toad M-$FABP_C$, and substrate cycling [186, 187].

A new proposition in the regulatory aspects and perhaps an integrating role for the proteins has been made from observations that the binding of LCFAs to $FABP_C$s can be modulated by nonlipid metabolites and physiological states. Early work with an $FABP_C$ from the heart of the teleost *Macrozoarces americanus* (ocean pout) [188] showed calcium ion caused a maximum in fatty acid binding at 0.5 mM not related to ionic strength changes since NaCl did not elicit binding changes. Binding was also specific to $FABP_C$s since albumin was not calcium responsive. It is not clear how activation of LCFA binding occurs, but recent reports indicate that such aspects may be important. E-$FABP_C$ can bind the protein S100A7 (function unknown) to form a complex that can bind fatty acid in a manner that is modulated by divalent cations [189]. Although heme is normally kept at very low concentrations, ferriheme and ferroheme can compete LCFAs from rat L-$FABP_C$ isosterically with the K_i for ferroheme threefold smaller than the Fe III state [190]. In light of these observations it may be useful to examine various porphyrias for dislocations in lipid metabolism: an acquired porphyria cutanea tarda (PCT) [191] resulted in hepatic lipid infiltration, whereas an essential fatty acid deficiency mimicked PCT photosensitivity and skin lesions [192]. The binding of LCFAs to rat L-$FABP_C$ and spadefoot toad M-$FABP_C$ is modulated by nonlipid metabolites. Rat L-$FABP_C$ increases binding of oleate and *cis*-parinarate in the presence of physiologically relevant concentrations of D-glucose and glucose 6-phosphate (6 mM and 0.2 mM, respectively), but not glucose 1-phosphate or phosphate ion [186]. The apparent $K_{0.5}$ for G6P (the effect was saturable) was 0.12 mM in activating [1-^{14}C]oleate binding and 0.26 mM for activating the binding of *cis*-parinarate. It was suggested that this ability may affect carbohydrate flux through hepatic glycolysis since both glucokinase [193] and phosphofructokinase [194] are inhibited by LCFAs or their derivatives. Additionally, cardiac hexokinase is inhibited by LCFAs and contains saturable LCFA binding sites [170]; it may also represent another aspect of the Randle cycle (glucose/fatty acid cycle) [195, 196]. In a study examining the behaviour of muscle $FABP_C$ from estivating spadefoot toad (*Scaphiopus couchii*) [187], G6P and fructose 1,6-phosphate (F1,6P2) altered the binding of the *cis*-parinarate but glucose, fructose-6-phosphate, phosphoenolpyruvate and fructose 2,6-bisphosphate did not. As with rat L-$FABP_C$, G6P increased LCFA binding to the toad protein (40%), but F1,6P2 decreased binding to M-$FABP_C$ by 40% by increasing the K_d for *cis*-parinarate 2.3-fold. Glucose did not affect toad M-$FABP_C$. The inhibition constant of F1,6P2 for the toad protein was 25 μM and within physiological concentrations. The reciprocal interaction of the substrate and product of hexokinase and L-$FABP_C$ and LCFAs with hexokinase, and the interaction of F1,6P2 with M-$FABP_C$, whereas LCFAs are inhibitory to phosphofructokinase [194], have led to a working model [187] in which glycolytic flux and intracellular LCFA flux might be connected and may produce amplified effects through shifts in these two substrate cycles. If such phenomena are common with other $FABP_C$s, and if the effects are different with different types of $FABP_C$s, it is possible that $FABP_C$s of different types within one tissue may respond differently to modulation by nonlipid metabolites and may provide a clue to the multiple expression of different $FABP_C$ genes within single tissues.

Nonmammalian $FABP_C$s

Since the last review of nonmammalian $FABP_C$s in 1996 [88], where 10 species were listed (birds, amphibians, fish and flukes), the phyletic ubiquity of this protein family is now established. table 4 lists 29 additional

Table 4. Nonmammalian FABPs. Where more than two types have been reported, the number of types is outside the bracket with the types, and number of that type, noted inside the bracket. The types are liver, L; heart, H; muscle, M; adipose, A; intestine, I; brain, B.

Organism	Tissue	Type	Reference
Amphibians			
Axolotl (*Ambistoma mexicanum*)	Liver, intestine	2[L, Lb]*	205
Bullfrog (*Rana catesbeiana*)	Liver	2L,	206
Spadefoot toad (*Scaphiopus couchii*)	Muscle	M	187
Toad (*Bufo aranum*)	Liver	L	207
	Heart	-	207
	Intestine	-	207
Wood frog (*Rana sylvatica*)	Liver	L	[Stewart, unpublished]
Xenopus laevis	Intestine	I	149
Birds			
Barnacle goose (*Branta leucopsis*)	Muscle	M	208
Canary (*Serinus* sp)	Brain	B	209
Chicken (*Gallus domesticus*)	Embryo/serum	Ex-FABP†	202
Western sandpiper (*Calidris mauri*)	Muscle	2[H]	203
	Heart	2[H]	203
Fish			
Catfish (*Rhamdia sapo*)	Liver	3[B, H, L]	197, 198
Elephant fish (*Callorhynchus callorhynchus*)	Liver	5[3H, I, L]	119
Antarctic icefish‡ (*Chaenocephalus acerata*)	Heart	2[A, H]	210
(*Notothenia corticeps*)	Heart	2[A, H]	210
(*Parachaenichthys charcoti*)	Heart	2[A, H]	210
(*Gobionothus gibberifrons*)	Heart	2[A, H]	210
Lamprey (*Entosphenus japonica*)	Liver	H	148
Rainbow trout (*Salmo gairdneri*)	Heart	H	211
Shark (*Halaetunus bivius*)	Liver	L	200
Invertebrates			
Cestode (*Echinococcus granulosus*)	-	-	212
Flukes (*Schistosoma japonicum*)	-	-	213
(*Fasciola gigantica*)	-	-	18
(*Fasciola hepatica*)	-	-	214
Mites(*Acarus sero*)	-	-	215
(*Blomia tropicalis*)	-	-	14
Nematodes (*Caenorhabditis elegans*)	-	-	216
(*Ascaris suum*)	-	Ex-FABP‡	217
Locust (*Locusta migratoria*)	Muscle	M	218

* One mammalian L-type; one similar to L-type in chicken, catfish and iguana liver (Lb).
† These FABPs are, unusually, expressed extracellularly. The chicken protein, despite having the descriptor 'FABP', appears to be a lipocalin, whereas that of nematodes is a true FABP-type protein, albeit possessing a secretory leader peptide and possible modifications to the conserved FABP structure.
‡ An FABP has also been reported in gill tissue that does not metabolize fatty acids [201].

incidences of $FABP_C$s. The pattern of tissue expression is unlike that seen in mammalian systems. For example, the livers of catfish [197, 198] and elephant fish [199] express, as well as a liver type, H- and B-types, and H- and I-types, respectively. Whereas the gills of an icefish express $FABP_C$, this tissue has little capacity to process fatty acids [201]. Avian embryos express an extracellular fatty-acid-binding protein, but this appears to be a lipocalin rather than an FABP-type protein [202]. The largest measured concentrations of $FABP_C$ reported are from pectoralis muscle (14% of soluble protein) and heart (23% of soluble protein) of migrating Western sandpiper, which fuels its migrational flight with LC-FAs [203]. Such divergences from mammalian $FABP_C$s may teach us the subtle interactions and interplays of lipid metabolism. The most thoroughly studied of invertebrate $FABP_C$s is that of migrating locust (reviewed in [97]). This protein is developmentally expressed to large concentrations (13% of soluble protein) and has had its crystal structure determined. One curiosity is the absence of detectable $FABP_C$s in all marine invertebrates that have been investigated (echinoderms, molluscs, crustaceans) [150], although we are now probing for $FABP_C$ genes in these animals. Nematodes, however, appear to have FABPs which, so far uniquely to these organisms, are secreted from the synthesizing cell, and also appear to be slight modifications of the conserved FABP structure [217]. It is clear that the presence and use of $FABP_C$ is more diverse and probably more complex than in mammals. The continued study of

$FABP_C$s across the phyla will inform evolutionary studies and adaptation of the protein to unusual physiological states such as in estivating toads [187] or hibernators [204].

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