



# Function of lipid binding proteins of parasitic helminths: still a long road

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## Abstract

Infections with parasitic helminths cause severe debilitating and sometimes lethal diseases in humans and domestic animals on a global scale. Unable to synthesize de novo their own fatty acids and sterols, helminth parasites (nematodes, trematodes, cestodes) rely on their hosts for their supply. These organisms produce and secrete a wide range of lipid binding proteins that are, in most cases, structurally different from the ones found in their hosts, placing them as possible novel therapeutic targets. In this sense, a lot of effort has been made towards the structure determination of these proteins, but their precise function is still unknown. In this review, we aim to present the current knowledge on the functions of LBPs present in parasitic helminths as well as novel members of this highly heterogeneous group of proteins.

**Keywords** Lipid binding proteins · FABPs · Nematodes · Platyhelminthes · FAR · NPAs

## Introduction

Knowing the biochemistry of parasitic helminths in detail may reveal differential enzymes or metabolic pathways that could represent an Achilles' heel for these organisms. Those proteins or enzymes could be targets for novel therapeutic strategies as well as molecular markers to be used in diagnostics. However, it is a really hard task to perform studies on the biochemistry of parasitic helminths, and many times it is almost impossible. This difficulty is based on the fact that these experiments may require keeping the complete life cycle (or at least part of it) under laboratory conditions, which can be complex and expensive, including welfare

protocols and keeping animals as alternative hosts. Although this has been achieved in some cases, e.g., for *Echinococcus multilocularis* (Spiliotis and Brehm 2009) and the hookworm *Necator americanus* (Jian et al. 2003), this is still not possible for many parasitic species. Particularly, those parasites affecting wild fauna where the collection of live samples depends on roadkill findings according to different country regulations. However, this is not the case for plant parasites where different biological approaches have been accomplished, and there is enough information to look into the possible biological function of different types of proteins (see below). In this regard, an impressive advance on helminthology has been achieved based on the massive data retrieved by whole genomic sequencing and genome-wide expression profiling methods at the level of the transcriptome and proteomes. All this data provides highly valuable information platforms to seek for alternative biochemical pathways, variations in certain canonical routes, different expression patterns, specific proteins, etc.

In particular, parasitic helminths present a restricted lipid metabolism; this means that many biochemical pathways are dampened or completely absent in different members of this group. The parasitic helminths considered in this review include species of the phylum Platyhelminth, commonly known as “flatworms” and phylum Nematoda or “roundworms”. Particularly, neither flatworms nor roundworms

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can synthesize fatty acid de novo (Barrett 1981). In some parasitic nematodes, the enzymes are present but with really low activity so no significant product is obtained (Barrett 2009). Nevertheless, incorporated fatty acids are involved in the synthesis of complex lipids such as triacylglycerol and phospholipids, suggesting their importance in maintaining different cellular structures. Although a partial mevalonate pathway is present for the synthesis of dolichol, quinones' side chains, and isoprenoids for protein prenylation (Hiepe et al. 2006), the complete de novo synthesis pathway of cholesterol is absent in both phyla (Barrett 1981; Frayha and Smyth 1983). In this sense, the acquisition and transport of several lipid molecules are crucial to these organisms, and the proteins and receptors involved in lipid transport and exchange may provide potential targets for chemo- and immunotherapy.

Lipid binding proteins (LBPs) of parasitic helminths have been studied for decades and are considered relevant because they are usually found in the excretion/secretion (E/S) products of these organisms. Most of them are structurally different from those of their host and as such they are usually targets of a strong immune response (Kennedy et al. 1990; Tomlinson et al. 1989). Hence, a lot of effort has been dedicated to study the structure of these proteins to improve novel drug design and the setting up of more specific diagnostic methods. Besides their possible utility, the precise biological functions of LBPs are still unknown. They have been proposed to participate in the acquisition and distribution of lipids within tissues of the parasite and/or modulation of the host's local tissue environment and its innate and acquired immune systems.

Addressing the function of these proteins is not a straightforward task, since they are not catalytic enzymes but carrier proteins. Hence, one of the few ways to assess LBPs' biological activity is to evaluate their binding capacity. A key step towards understanding the functions of these proteins might be to describe the ligands that are bound in their

natural environment, as well as studies performed on tissues from parasites or whole organisms. The most informative experiments used to unravel protein functions involve reverse genetics approaches. These would imply the knock-down (or knock out) expression of the protein of interest within the parasite. Unfortunately, this technique has been achieved successfully only in a few examples of parasitic species (Britton et al. 2016; Dutta et al. 2015; Guidi et al. 2015; Kimber et al. 2007; Lilley et al. 2012; MacDonald et al. 2014; Pérez et al. 2019). In this scenario, appropriate model organisms are needed to shed light on the functions. In this review, we highlight the improvements in the assessment of the biological functions of LBPs from parasitic helminths as well as the description of novel members of this diverse group.

## A highly heterogeneous group

Altogether, parasitic helminths produce and secrete a broad range of different LBPs. At least five different types of LBPs have been described and they are distributed in different taxa as is summarized in Table 1. Below we describe in brief each type of LBP trying to address the most significant improvements on their biological functions.

### Hydrophobic ligand binding proteins (HLBPs)

HLBPs is a family of proteins that are specific to cestodes in phylum Platyhelminthes. This unusual family is composed of intracellular and extracellular members that bind a variety of fatty acids, retinoids, and some sterols as reviewed in Alvite and Esteves (2012). In their native state, HLBPs are described as lipoprotein particles that could reach a size of about 230 kDa. This complex structure consists of multiple small protein subunits of approximately 8 kDa (although this

**Table 1** Distribution of LBPs across groups of parasitic helminths

Type of LBP	Phylum <i>Platyhelminthes</i>		Phylum <i>Nematoda</i>				
	<i>Cestodes</i>	<i>Trematodes</i>	Clade I	Clade II	Clade III	Clade IV	Clade V
HLBP	✓						
FABP	✓	✓	✓	✓	✓	✓	✓
nemFABP				*	✓	✓	✓
FAR				✓	✓	✓	✓
NPAs				✓	✓	✓	✓
Dorylipophorin			✓				

Bibliographic references for each group are cited in each section. \*A search for nemFABPs has been done in clade II using Blast tool from WormBase Parasite (<https://parasite.wormbase.org/Tools/Blast?db=core>), and no hit was found with the presence of leader signal peptide. Nevertheless, there is only one species with a determined genome so we cannot rule out the presence of nemFABPs in the clade

might change within species) interacting with lipids (Lee et al. 2007; Silva-Álvarez et al. 2015).

One of the most studied examples is antigen B (EgAgB) from *Echinococcus granulosus* sensu lato (s. l.). EgAgB is one of the major molecules synthesized in large amounts by the cyst (metacestode larval stage), and it is present in most tissues of the parasite as well as in protoscoleces (infective stage for definitive host) (González et al. 1996; Oriol et al. 1971; Sanchez et al. 1991, 1993). From the molecular point of view, it conforms to a lipoprotein particle with a protein component consisting of 8 kDa subunits that are rich in amphipathic alpha-helices (Fernández et al. 1996; Lightowlers et al. 1989). For the case of *E. granulosus* s. l., these subunits are encoded by a multigene family, dubbed *EgAgB8/1–EgAgB8/5* (Arend et al. 2004; Chemale et al. 2001; Frosch et al. 1994; Haag et al. 2004; Kamenetzky et al. 2005; Muzulin et al. 2008; Zhang et al. 2010). The lipid moiety found to be interacting with native EgAgB showed that not only fatty acids and triacylglycerols are bound but also a wide range of other hydrophobic compounds like cholesterol esters, cholesterol, and phospholipids (Obal et al. 2012).

In vitro functional analysis of recombinant lipid-free rEgAgB8/2 and rEgAgB8/3 showed a selective capacity to bind lipids, showing affinity at least for 16- and 18-C fatty acids, but not for cholesterol, indicating that these components of the natural EgAgB lipoprotein particles would not interact directly with cholesterol (Silva-Álvarez et al. 2016). Additionally, the capacity of these subunits to transfer lipids to membranes was also assayed showing that different subunits of EgAgB8 are able to deliver their cargo to phospholipid membranes, supporting the hypothesis that EgAgB is involved in lipid transport between parasite and host tissues (Silva-Álvarez et al. 2015). However, the capacity of EgAgB particles to transfer fatty acids to the parasite or to the host's cells remains to be formally demonstrated. In this regard, assays performed with a related macromolecule found in *Taenia solium* metacestode strongly support this hypothesis (Lee et al. 2007).

Remarkably, EgAgB and particularly its predominant EgAgB8/1 apolipoprotein are potential ligands for monocyte and macrophage receptors as described in Silva-Álvarez et al. (2016). These receptors may also be involved in plasma lipoprotein recognition and induce an anti-inflammatory phenotype in macrophages upon recognition of EgAgB (Silva-Álvarez et al. 2016, 2018). Moreover, it has been proposed to be the most specific *Echinococcus* antigen for serodiagnosis (Siracusano et al. 2008).

Molecules of this type have also been described in other cestodes including *Moniezia expansa*, *Hymenolepis diminuta*, *Taenia crassiceps*, *Taenia solium*, and *Taenia hydatigena* (Barrett et al. 1997; Jia et al. 2011; Saghir et al. 2001; Sako et al. 2000; Zarlenga et al. 1994). A primary sequence comparison of HLBP found in these species

revealed that they are significantly diverse but present well-conserved molecular characteristics like two alpha-helical domains that are presumed to be involved in protein-membrane interactions (Lee et al. 2007). Notably, HLBP from *M. expansa* and *H. diminuta* do not show an N-terminal hydrophobic leader sequence indicating that they might exert their function intracellularly.

## Fatty acid binding proteins (FABPs)

FABPs are small intracellular proteins (around 15 kDa) that reversibly bind fatty acids and other hydrophobic ligands. Members of this family have been found throughout the animal kingdom, both in invertebrates and vertebrates, but no counterparts have been found in plants or fungi (Hauerland and Spener 2004). Ancestral intracellular FABP genes are supposed to have arisen after the separation of animals from fungi and plants (Schaap et al. 2002).

The first FABP from invertebrates was found in *Schistosoma gregaria* (Hauerland and Chisholm 1990), almost 20 years after the first vertebrate FABP was described. After this finding, many proteins of the family have been described in nematodes, insects, mollusks, and flatworms (Esteves and Ehrlich 2006). The first flatworm FABP to be described was Sm14 from *Schistosoma mansoni* (Moser et al. 1991), followed by FABPs of *S. japonicum*, *Fasciola hepatica*, *Fasciola gigantica*, and *E. granulosus* s.l. (Becker et al. 1994; Esteves et al. 1993; Estuningsih et al. 1997; Rodríguez-Pérez et al. 1992). As in vertebrate's FABPs, the sequence identity between different FABPs from invertebrates varies significantly, but they still share their overall 3D protein structure. It consists of a  $\beta$ -barrel, composed of ten antiparallel  $\beta$ -strands ( $\beta$ A- $\beta$ J), capped with two  $\alpha$ -helices ( $\alpha$ I and  $\alpha$ II). The barrel is solvent accessible, and the helices have been proposed as a gate that regulates the entrance or exit of ligands see Fig. 1 (Hauerland and Spener 2004; Scapin et al. 1992; Storch and Corsico 2008; Storch and McDermott 2009; Zimmerman and Veerkamp 2002).

FABPs from vertebrates are grouped into four subfamilies based on their primary sequence analysis (Marcelino et al. 2006) and each of these characteristically binds certain types of ligands. When compared to mammalian FABPs, proteins from parasitic helminths show higher similarity to those that belong to subfamily IV (Esteves and Ehrlich 2006; Marcelino et al. 2006; Smathers and Petersen 2011). Group IV is the largest subfamily and includes FABP3, FABP4, FABP5, FABP7, FABP8, FABP9, and FABP12 (Liu et al. 2008) from vertebrates and binds a variety of ligands including long-chain fatty acids, eicosanoids, and retinoids. In particular, there is a high conservation of a triad of residues that play a central role in the mechanism of binding of fatty acids to those FABPs. In relation to the genetic structure, it is worth mentioning that the position of the introns in



**Fig. 1** X-ray structure of EgFABP1 (PDB: 108 V) from *Echinococcus granulosus*. Copurifying ligand, palmitic acid, is depicted in green

invertebrate FABPs seems to be substantially conserved, although their number and length vary considerably (Esteves and Ehrlich 2006).

Recently, data mining in genomes from the parasitic plathelminthes, *Echinococcus multilocularis* and *E. granulosus s.l.*, revealed that this family of proteins is far more complex than previously reported in cestodes. Six genes with different coding sequences for FABPs were found in each organism, with the sole exception of EmFABP1.1 and EmFABP1.2, in *E. multilocularis*, that are identical to one another (Pórfido et al. 2020). All of these variants have been cloned and produced recombinantly presenting structural features (inferred from spectroscopic data as well as in silico prediction) that resemble those of previously reported FABPs from vertebrates and invertebrates (Bélgamo et al. 2020; Pórfido et al. 2020). Notably, for EmFABP4, the most striking feature is that the primary sequence is considerably longer (176 amino acids) than that for a regular FABP (around 130 amino acids). In this case, a typical FABP fold is predicted, but no specific structure is assigned to the C terminus of the protein (Pórfido et al. 2020). Surprisingly, EmFABP4 was purified

as a dimer, and this state is stable in solution (Bélgamo et al. 2020). However, whether it exists as a dimer in its biological environment remains to be elucidated. It is noticeable that a large subfamily of FABPs, including some with C-terminal extensions, has also been reported in *Fasciola* spp. (Bélgamo et al. 2020; Morphew et al. 2016). Interestingly, these longer variants are different from the so-called nemFABPs (see below) since the unusual extensions in flatworms' FABPs are exclusively on the C-terminal sequence.

Published transcriptomic information on *E. multilocularis* and *E. granulosus s.l.* suggest that all *fabp* genes are transcribed in different stages of these organisms (Huang et al. 2016; Tsai et al. 2013; Zheng et al. 2013a, b). Moreover, according to the different sets of data, *emfabp1.1* and *emfabp1.2* are the most highly expressed FABP genes in *E. multilocularis* (Pórfido et al. 2020).

It is worth mentioning that specific inhibitors of mammalian FABP4 have been developed and employed as effective therapeutic agents of diseases such as diabetes and atherosclerosis (Barf et al. 2009; Furuhashi et al. 2007; Wang et al. 2016). Based on the degree of conservation between FABPs from helminths to group IV from vertebrate FABPs, members of this family from *E. multilocularis* and *E. granulosus* are being considered as druggables (Bélgamo et al. 2020), and this could also be extended to FABPs from other helminth species as well.

As expected, FABPs are also present in both parasitic and free-living nematodes. Particularly, in the free-living species, *Caenorhabditis elegans*, there are nine isoforms of FABPs (dubbed *lbp-1* to *lbp-9*) with tissue specific expression patterns (Plenefisch et al. 2000). As previously said, it is difficult to perform reverse genetic experiments on most parasitic helminths, but in the case of nematodes, the use of *C. elegans* as a model to study protein function is an excellent option. In this sense, knockdown experiments on *lbp-5* of *C. elegans* have shown strong physiological disruptions (Xu et al. 2011). *lbp-5* knockdown causes a decrease in expression of  $\beta$ -oxidation genes, by affecting NHR-49 signaling (homolog of mammalian NHR-4 and functional homolog of PPAR- $\alpha$ ), which contributes to fat storage increase. An analysis of the localization of LBP-5 in cells from *C. elegans* revealed that it is found both in the nucleus and the cytoplasm, suggesting a possible role in transporting fatty acids into the nucleus regulating the expression of genes involved in fat metabolism (Xu et al. 2011).

### The particular case of “nemFABPs”

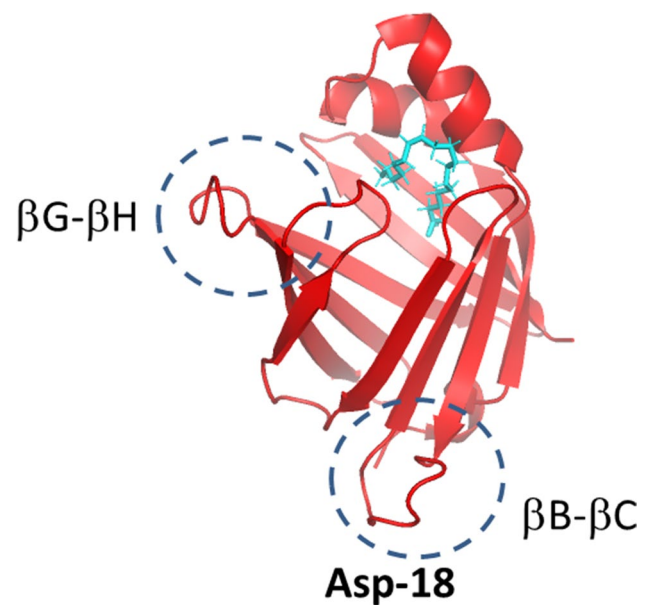
All the FABPs described so far in nematodes form two distant groups suggesting at least two different phylogenetic origins (Plenefisch et al. 2000; Zheng et al. 2013a, b). One of these groups includes sequences related with muscle-type intracellular FABPs from vertebrates as is the case of

LBP-5 mentioned above (Plenefisch et al. 2000). The other group includes some FABPs that present particular characteristics that are found almost exclusively in the phylum Nematoda; hence, they were dubbed “nemFABPs.” One of the most striking differences found in “nemFABPs” is the presence of a cleavable secretion signal leader peptide, and hence they are secreted from the cell, presumably by traditional secretory pathways (Mei et al. 1997). Until now, only FABPs genes from *Trichinella spiralis* are found to be the exception to the two groups mentioned before. This is an interesting finding, since *T. spiralis* is a member of Clade I of nematodes which is quite an underrepresented group and may show interesting features (Blaxter and Koutsovoulos 2015).

As in vertebrate cytosolic FABPs, “nemFABPs” present the characteristic beta barrel fold with an alpha-helical cap. The first of these to be described from nematodes were Asp-18 from the large intestinal roundworm, *Ascaris suum*, and Bm-FAB-1 from the agent of lymphatic filariasis, *Brugia malayi* (Michalski et al. 2002). These proteins are not only produced by human and animal parasites (Zheng et al. 2013a, b) but, as already mentioned, are also found in free-living forms like *C. elegans*. These proteins were found to be gender specific as well as developmentally regulated and have been proposed to be associated with reproduction since they are found in the perivitelline fluid of nematode eggs harboring the embryos (Li et al. 2004; Mei et al. 1997; Michalski et al. 2002; Michalski and Weil 1999; Plenefisch et al. 2000). One of these, Ce-LBP-1, appears only to be synthesized and secreted by developing embryos within the egg (Plenefisch et al. 2000).

Notably, their primary sequences are typically 10–19 residues longer than other FABPs, and it was proposed that some of these additional residues are accommodated in extended loops (Mei et al. 1997). The structure of Asp-18 has been solved at the atomic level by X-ray crystallography and NMR confirming the presence of two extended loops, one immediately adjacent to the ligand portal and another distantly located on the opposite side of the molecule see Fig. 2. Additionally, the triad of amino acid side chains that tether bound fatty acids is differently arranged and composed compared to what is found in mammalian FABPs (Ibáñez-Shimabukuro et al. 2019). A preliminary analysis of their ligand preferences in a biological context such as *E. coli* showed that Asp-18 binds exclusively fatty acids, particularly 18 carbons vaccenic acid with the highest affinity (Ibáñez-Shimabukuro et al. 2019).

The fact that some nemFABPs are found in eggs, more precisely in the perivitelline fluid allows us to hypothesize that they might be involved in the uptake of lipids from perivitelline fluid. Unfortunately, no further functional experiments have been performed other than in vitro assays.



**Fig. 2** X-ray structure of Asp-18 (PDB: 6I8X) from *Ascaris suum* in complex with vaccenate (depicted in light blue). Extended loops are shown in dashed circles

### Fatty acid and retinol binding proteins (FAR)

The FAR family is a novel class of proteins, also exclusively found in nematodes. They have an approximate size of 20 kDa and are able to bind both fatty acids and retinol. Genes encoding FAR proteins have been described in many nematode species, both free-living and parasitic forms (Garofalo et al. 2002; Kennedy et al. 1997) and each species produces several isoforms. FARs are present in ES products, as is the case of Ac-FAR-1 from the intestinal hookworm *Ancylostoma caninum* (Basavaraju et al. 2003; Kennedy et al. 1997). The study of FAR proteins started in 1995 with Ov-FAR-1 (Tree et al. 1995), a protein secreted by *Onchocerca volvulus*, a causative agent of river blindness. Since then, the FAR family has expanded greatly; being described not only in filarial species but also in hookworms, plant parasites, and the free-living nematode *C. elegans*, as well as other *Caenorhabditis* species. Notably, none of these proteins are found in clade I of phylum Nematoda. The knowledge we have about them nowadays seems vast but also dispersed, with many studies done in separated groups of proteins within the family.

From the molecular point of view, FARs range from 17 to 30 kDa in size and have relatively conserved glycosylation sites, but glycosylation patterns vary from one protein to another (Nirmalan et al. 1999). They also have potential sites of phosphorylation for conserved type II casein kinase (Prior et al. 2001). They are rich in alpha-helices, show high stability, and do not have structural analogues in other animal groups. To date, the crystallographic structure of FAR

proteins has been resolved for two members of the family, Ce-FAR-7 from *C. elegans* (Jordanova et al. 2009) and Na-FAR-1 from *Necator americanus* (Rey-Burusco et al. 2015) (see Fig. 3). Ce-FAR-7 presents two discrete cavities in which it could locate different types of ligands; however, based on its sequence identity, this protein might not be representative of parasite proteins. The overall structure is a flattened ellipsoid which seems to adopt different degrees of expansion depending on whether ligands are absent or bound to the central cavity. Recent studies using in silico techniques compared Na-FAR-1 with classical  $\beta$ -barrel FABPs. Particularly, the use of extended molecular dynamics simulations and principal component analysis allowed to identify different conformations adopted by each system during the simulations. Na-FAR-1 encompasses a complex highly flexible internal ligand-binding domain that allows reversible switching between distinct states in the protein. Besides, the ligand inside the cavity experiences large conformational changes between bent and stretched conformations. These changes in the ligand conformation follow changes in the cavity size dictated by the transient protein conformation. On the contrary, protein–ligand complex in  $\beta$ -barrel FABPs fluctuates around a unique conformation (Barletta et al. 2019). These results are in agreement with the observations that FAR proteins bind a broad range of hydrophobic ligands while FABPs bind almost uniquely fatty acids.

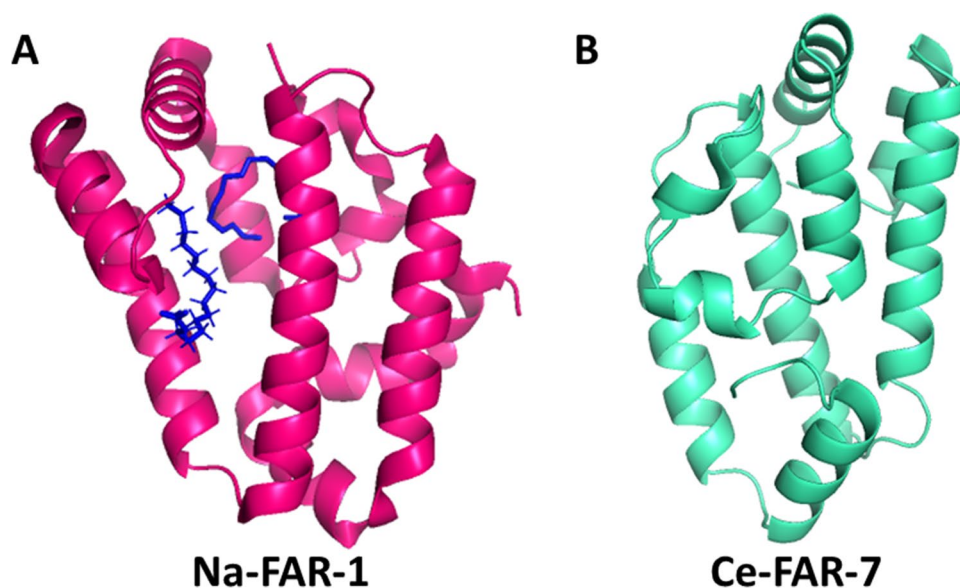
Na-FAR-1 and possibly other FARs may have a wider repertoire for hydrophobic ligand binding; this is supported by the fact that a range of neutral and polar lipids co-purify with the bacterially expressed recombinant protein (Rey-Burusco et al. 2015). Many studies show that these proteins are able to bind fatty acids (mainly oleic acid) and retinol, but recent evidence shows phospholipids as other possible ligands (Rey-Burusco et al. 2015). As observed with FABPs,

FAR proteins have a well described and conserved structure but have a wide range of sequence similarity even between isoforms. For example, Na-FAR-1 has a sequence identity that ranges from 44 to 60% with FARs from other nematodes from the *Rhabditida* (*Ancylostoma*, *Ostertagia*, and *Caenorhabditis*) class, but this identity descends to 25–38% with other classes like *Spirurida* (*Onchocerca*, *Brugia*, *Acanthocheilonema*) and *Diplogasterida* (*Globodera* and *Meloidogyne*) (Rey Burusco, 2014). For *C. elegans*, Ce-FAR-8 and Ce-FAR-7 are so divergent (19–23%) that has even led to cataloging them as outliers, disregarding their importance.

In regard to expression levels, different isoforms are found through all developmental stages, some are highly expressed during infective stages other during reproductive or prereproductive stages. An important note is that no FAR proteins are highly expressed in eggs. Moreover, in most cases, more than one FAR isoform is found at the same stage and they show a different pattern of expression, as is clear for the case of *C. elegans* (Garofalo et al. 2002). This evidence suggests that FAR proteins might fulfill different roles through development rather than having one static biological function.

FARs are the major components of human, animal, and plant parasite secretions (Basavaraju et al. 2003; Kennedy et al. 1997). As an example, we have the case of Na-FAR-1, found in ES products thanks to immunological assays with antibodies against the recombinant protein (Rey-Burusco et al. 2015). A proteogenomic analysis of ES products revealed that FAR proteins are among the top 10 most abundant protein families in the ES products of adult *N. americanus* (Logan et al. 2020). These findings have made it possible to use FAR proteins as diagnostic tools for some parasitic diseases (Burbelo et al. 2009). This raises the hypothesis that they could play roles in the interaction with

**Fig. 3** X-ray structures of **A** Na-FAR-1 (PDB: 4XCP) from *Necator americanus* and **B** Ce-FAR-7 (PDB: 2W9Y) from *Caenorhabditis elegans*. For Na-FAR-1, the ligands (palmitic acid) are depicted in blue



the host and in pathogenesis by interfering with host defense signals (Bradley et al. 2001; Hewitson et al. 2009; Iberkleid et al. 2015). In fact, recent results demonstrated that injecting recombinant FAR proteins from entomopathogenic nematode *Steinernema carpocapsae* can reduce survival of host *Drosophila melanogaster* when exposed to bacterial infections, showing that these proteins can interfere with immune response. Although further studies are needed, the mechanism seems to indeed involve sequestering lipidic signals, thus disrupting the normal functioning of host defenses (Parks et al. 2021). Apart from this, it should be noted that Ace-FAR-1 from *Ancylostoma ceylanicum* has been shown to be potentially useful as a vaccine because it is capable of conferring immunity in challenge tests in laboratory animals (Fairfax et al. 2009). On the other hand, these parasitism-focused hypotheses fall short when we look at the eight FAR proteins described for *C. elegans*, where seven of them present a signal peptide with Ce-FAR-7 lacking this sequence. It is thus important to formulate new hypotheses including the possible function of these secreted proteins in free-living worms.

### FAR proteins in plant parasites

The first example we have is Gp-FAR-1 from *Globodera pallida*. From its molecular description, analyses of its binding specificity (encompassing linoleic and linolenic acid) and localization in the hypodermis of J2 stage (invasive stage of the parasite) suggested a crucial role in countering plant defense mechanisms. Lipoxygenase-mediated peroxidation of linolenic acid is an early step in the octadecanoid signaling pathway, which leads to the synthesis of the systemic plant defense signal transducer jasmonic acid. A pronounced inhibition of lipoxygenase-mediated breakdown of linoleic acid was observed in the presence of recombinant Gp-FAR-1 (Prior et al. 2001).

The study of the root knot nematode, *Meloidogyne javanica*, and its FAR proteins Mj-FAR-1 and Mj-FAR-2 was the first work to place FAR proteins from plant parasites as a unique node in a phylogenetic tree showing a clear evolutionary adaptation to plant parasitism. Mj-FAR-1 accumulates in the cuticle and is secreted by hypodermis, being found in the intercellular space between the parasite and the host (Iberkleid et al. 2013, 2015). These findings so far are aiming towards an immunomodulatory function, disrupting plant defense mechanisms, and facilitating parasitism. On the other hand, Mi-FAR-1 from *Meloidogyne incognita* is expressed in J2, J3, and J4. In this last stage, it might be playing a role in the pre-reproductive stage, presenting the possible relationship with development, egg-laying, and reproduction. This was also supported by the silencing of Mi-FAR-1 with RNAi that showed a decreased number of females as well as the fertility and production of eggs when

exposed to bacteria (Phani et al. 2017). This decrease in fertility was also seen in Ab-FAR-1 from *Aphelenchoides besseyi*, “white tip nematode”, where the retinol binding capabilities of FAR proteins could be related to the needs of retinol for the synthesis of collagen and egg development (Cheng et al. 2013; Wang et al. 2018).

In accordance with both hypotheses, FAR proteins in *Bursaphelenchus mucronatus* are among the genes with increased expression in the more virulent strains of this plant parasite. A silencing experiment showed a decrease of infective capacity and offspring, associating FARs with both development and reproduction functions as well as disturbing inter-intracellular defense signals in plants (Zhou et al. 2016). Similar experiments and results are presented with Pp-FAR-1 from *Pratylenchus penetrans* (Vieira et al. 2015), highly expressed during infection and showing a significant reduction in reproduction upon silencing, and Rs-FAR-1 from *Radopholus similis* (Zhang et al. 2015), as this protein regulates expression of allene oxide synthase and it is upregulated during early infection in *Arabidopsis thaliana*.

At last, work done in *Heterodera avenae* described two FAR proteins, Ha-FAR-1 and Ha-FAR-2, with different molecular structures (Le et al. 2016). While Ha-FAR-1 has the conserved phosphorylation site and no glycosylation site, Ha-FAR-2 has a glycosylation site and no phosphorylation site, also showing weaker binding capabilities. Expression of both is seen in hypodermis, suggesting secretion, but Ha-FAR-1 is greater than Ha-FAR-2, and although they are expressed through all stages, Ha-FAR1 is predominant in the J4 stage (prereproductive), and Ha-FAR2 is predominant in J2 (post-parasitic). Structurally, they show a 28% similarity, a difference also seen in their weight, 17 kDa for Ha-FAR-1, and 30kDa for Ha-FAR-2; and isoelectric point, 5.62 for Ha-FAR-1 and 9.02 for Ha-FAR-2, which might indicate that they work in different environments (Le et al. 2016).

### FAR proteins in *Caenorhabditis* genus

Recent studies done in *Caenorhabditis bovis*, a close relative of *C. elegans*, have rekindled the interest in FAR-8, an outlier of the FAR protein family (Garofalo et al. 2002), as a possible factor in the evolution towards parasitic behavior. *C. bovis* is unusual for a *Caenorhabditis* species, as it has been isolated several times from the outer auditory canals of Zebu cattle in Eastern Africa and Gyr cattle in South America, presenting a deeply different habitat (Cardona et al. 2010; Kiontke and Sudhaus 2006). *C. bovis* is believed to be the causative agent of bovine parasitic otitis. However, there is not enough information about the biology to classify it as a “true” parasite; *C. bovis* might instead be an opportunistic colonizer of niches created by other pathogens. The publication of the genome of *C. bovis* showed that the genome and gene set of *C. bovis*, compared to *C. elegans* is smaller

but at least three gene families have undergone an expansion and all of them have been related to parasitism (Stevens et al. 2020). The FAR family of genes in *C. bovis* has been almost completely lost, except for FAR-8 which is repeated two times. This suggests that there might be a relationship between the adaptation to a completely different niche and the conservation and expansion of this FAR protein. These findings indicate how poorly understood these proteins are and that molecular analysis alone provides little information of the possible biological functions and role of these proteins in the major plot that is the evolution in nematodes.

### Nematode polyprotein antigens/allergens (NPAs)

Nematodes present yet another well-described LBP group, the NPAs. These proteins are found in the pseudocoelomic fluid and connective tissue of nematodes, as well as in the E/S products where they induce a highly immunogenic response from the host (Kennedy 2011).

NPAs present a quite particular translation mechanism since they are produced as a large polypeptide that is post-translationally cleaved by proteases rendering globular units of 15 kDa (Kennedy 2011). These units are helix-rich and can present similar or divergent amino acid sequences, depending on the species (Kennedy et al. 1995; Kuang et al. 2009).

Only one of these proteins has its structure determined by nuclear magnetic resonance (NMR), ABA-1A from *Ascaris suum* (Meenan et al. 2011). This protein adopts a novel seven-helical fold comprising a long central helix that participates in two four-helical bundles. There are two discrete hydrophobic ligand-binding pockets, one in each of the N-terminal and C-terminal bundles (Fig. 4). It is important to note that this is the first structure of a unit of any tandemly repetitive polyprotein yet reported. To date, the structure and ligand-binding characteristics of these proteins have been demonstrated only for single units of the polyprotein, but not for two or more units in tandem from the same polyprotein array as these functions might change if interactions with other subunits are present.

From the functional point of view, NPAs bind small lipids such as fatty acids and retinol as has been demonstrated using in vitro fluorescence experiments (Moore et al. 1999). Additionally, it has been shown that NPAs, particularly ABA-1A, physically interact with membranes and they unload their lipid cargo by releasing it into the aqueous phase (McDermott et al. 2002). They have been described in several species of disease-causing nematodes, including *Ascaris lumbricoides*, *A. suum* and *B. malayi* of humans, and *Dictyocaulus viviparus*, *Ostertagia ostertagi*, *Haemonchus contortus*, and *Dirofilaria immitis* of domestic animals (Britton et al. 1995; Kuang et al. 2009; Poole et al. 1996; Selkirk et al. 1993; Solovyova et al. 2003; Xia et al. 2000).



**Fig. 4** NMR structure of ABA-1A (PDB: 2XV9) from *Ascaris suum*. Black arrows are showing the two described ligand binding sites

Notably, as with other LBPs, NPAs are also found in free-living species from the phylum. Indeed the *npa-1* gene from *C. elegans* has been involved in some morphological, and life span phenotypes obtained in gunshot RNAi experiments (Ceol and Horvitz 2004; Curran and Ruvkun 2007). Unfortunately, no further functional experiments have been performed on these extremely interesting proteins.

### Novel LBPs of parasitic helminths: a bottomless pit

It is well known that we are still in a lack of knowledge of novel species across the biodiversity worldwide and hence a lot of biomolecules are still to be described. A good example is the case of the dorylipophorin (GeneBank: MW014827.1) isolated from the pseudocoelomic fluid of *Dioctophyme renale*, the giant kidney worm (Giorello et al. 2017). To date, *D. renale* is a clade I nematode that has no genomic, transcriptomic, or proteomic data, yet it is an important parasitic infection affecting domestic and wild fauna, not mentioning that it is a zoonosis (Eiras et al. 2021; Paras et al. 2018). The phylogenetically closest species for which genomic data is available is *Sobolyphyme baturini* that belongs to the same subclass Dorylaimia but is a member of an entirely different family of nematode parasites. It is important to note that other members of clade I include the human parasites *Trichuris trichiura* and *Trichinella spiralis*.

Dorylipophorin has proven to selectively bind fatty acids from a highly heterogeneous environment (Giorello et al.



2017). N-terminal and internal peptide amino-acid sequences of this protein indicate a relationship with a cysteine- and histidine-rich protein of unknown function from *Trichinella spiralis* and *Trichuris muris* which are found to be the major component of E/S products (Radoslavov et al. 2010; Tritten et al. 2017). Recently, the structure of P43, the major secreted protein from *T. muris*, was resolved to the atomic level, and it was shown to bind the signaling molecule interleukin-13 (Bancroft et al. 2019). Since dorylipophorin and P43 present 50% sequence identity, these observations give room to hypothesize that dorylipophorin might be important in the attenuation of host's immune response. Notably, within the five clades that conform phylum Nematoda, clade I only presents FABPs and now this novel family of LBPs which seems to be clade specific.

## Concluding remarks

Different members of LBPs are present in all parasitic helminths. In some cases, they can be found broadly distributed like FABPs, but in other cases, they are highly specific of a particular group as is the case of HLBP or the clade I from phylum Nematoda, to which P43 and dorylipophorin belong. LBPs are usually found in multigenic families where function might vary even in the same species, as more than one LBP protein might be present and its expression could change through the developmental stages.

Regardless of the enormous amount of information available, a specific function cannot be strictly associated with any of these families of proteins yet. As stated before, LBPs have been proposed to participate in the acquisition and distribution of lipids within tissues of the parasite; and/or in the modulation of the host's immune systems. To date, experiments performed with HLBP and FAR proteins (exclusively found in cestodes and nematodes, respectively) presented strong evidence about their role in the modulation of the host's immune response. On the other hand, FABPs might be involved in the distribution and storage of lipids in nematodes. Whether this is also the case for cestodes remains to be determined. For nemFABPs and NPAs, detailed knowledge about their structure and possible natural ligands is available, but there are no direct functional experiments.

Finally, the HLBPs are the only LBPs with a detailed description of their cargo obtained from their natural environment; this is clearly a missing block of information that needs attention in order to decipher the metabolic routes these proteins are related to.

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