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Review

Invertebrate intracellular fatty acid binding proteins ☆

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Abstract

Fatty acid binding proteins are multigenic cytosolic proteins largely distributed along the zoological scale. Their overall identity at primary and tertiary structure is conserved. They are involved in the uptake and transport of hydrophobic ligands to different cellular fates. The precise functions of each FABP type remain imperfectly understood, since sub-specialization of functions is suggested. Evolutionary studies have distinguished major subfamilies that could have been derived from a common ancestor close to vertebrate/invertebrate split. Since the isolation of the first invertebrate FABP from *Schistocerca gregaria* in 1990, the number of FABPs isolated from invertebrates has been increasing. Differences at the sequence level are appreciable and relationships with vertebrate FABPs are not clear, and lesser among invertebrate proteins, introducing some uncertainty to infer functional relatedness and phylogenetic relationships. The objective of this review is to summarize the information available on invertebrate FABPs to elucidate their mutual relationships, the relationship with their vertebrate counterparts and putative functions. Structure, gene structure, putative functions, expression studies and phylogenetic relationships with vertebrate counterparts are analyzed. Previous suggestions of the ancestral position concerning the heart-type of FABPs are reinforced by evidence from invertebrate models.

Keywords: Fatty acid binding proteins; *Schistocerca gregaria*; Invertebrate

Contents

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1. Introduction

Fatty acid binding proteins (FABPs) are small (14–15 kDa) cytosolic proteins that bind non-covalently hydrophobic ligands mainly fatty acids. Several tissue-specific types of FABPs have been identified in vertebrates each named after the tissue in which they predominantly occur: heart (H-FABP) (Billich et al., 1988), adipocyte (ap2) (Bernlohr et al., 1984), liver (L-FABP) (Lowe et al., 1985; Chan et al., 1985), brain/retina (B-FABP/R-FABP) (Shimizu et al., 1997), intestine (I-FABP) (Alpers et al., 1984), epidermis (E-FABP) (Siegenthaler et al., 1993), Schwann cells (myelin P2 protein) (Narayanan et al., 1988), and ileum (gastrotropin) (Fujita et al., 1995). The family also includes the cellular retinol (CRBP) and retinoic acid binding proteins I and II (CRABPs).

Depending on the structural elements and database considered for classification, FABPs can be included in the following families: cytosolic fatty-acid signature containing proteins (PS00214, PROSITE, www.expasy.org/prosite), lipid binding proteins (SCOP, www.mrc-lmb.cam.uc.uk/scop), lipid binding proteins, code 2.40.128.20 or binding proteins, code 2.40.128.30 (CATH, www.biochem.ucl.ac.uk.bsm/cath). They were also included in different super-families: calycins (PROSITE), lipocalins (SCOP) or retinol transporters (CATH).

FABPs isolated from the same tissue, from different vertebrate species, consistently display sequence identities higher than 70%, while FABPs from different tissues of a given species share identities as low as 20%. Despite of their variable sequence identity all FABPs have the same general tertiary fold structure comprising 10 anti-parallel β-strands forming a β-barrel and a helix turn helix "cap", delimiting a cavity where the ligand is bound. Amino acids involved in binding through ligand carboxylate head, are also conserved (Zimmerman and Veerkamp, 2002).

Fatty acid binding proteins are involved in transport of fatty acids (FA) from the plasmalemma to the intracellular sites of conversion. Some members have been implicated in the modulation of cell growth and proliferation (Madsen et al., 1992; Yang et al., 1994; Shimizu et al., 1997; Wang et al., 2003). The precise function of each FABP type remains imperfectly understood since sub-specialization of functions is suggested by the complex diversity of distinct members that display striking tissue and temporal specificity of expression, in addition to ligand preferences.

The mechanisms underlying the extra-cellular FA uptake and transport are incompletely known despite decades of extensive search. The traditional view of FA transport across biological membranes considers a passive diffusion. Evidence is accumulating showing that several membrane associated proteins (mammalian FAT/CD36, FABPpm, FAT) are involved in the traffic across the membrane (Van der Vusse et al., 2002). Moreover, membrane-associated proteins may also play a crucial role in the release of FA from the inner leaflet of the plasma membrane into the cytoplasm by a collisional interaction with FABPs or into the water layer adjacent to the membrane prior to binding to FABPs conforming a diffusional mechanism (Glatz and Storch, 2001; Van der Vusse et al., 2002). The different members of the FABP family may differ in the uptake mechanism: it was reported that the collisional mechanism may be applicable to proteins of the H-FABP and I-FABP subgroups (Herr et al., 1995; Herr et al., 1996; Corsico et al., 1998; Thumser and Storch, 2000), while the diffusional process was described for the L-FABP subfamily (Kim and Storch, 1992; Thumser and Storch, 2000). The α-helical domain of FABPs could be implicated in fatty acid transfer by interacting with membrane anionic phospholipids and proteins (Liou and Storch, 2001).

The first FABP was reported in 1972 by Ockner et al., purified from intestinal mucosa; 20 years later, an invertebrate fatty acid binding-like protein was isolated (Haunerland and Chisholm, 1990). Since that time the number of proteins of this family isolated from invertebrate organisms and tissues has been increasing; at present about 31 invertebrate FABPs have been reported showing low sequence identities among them.

Early evolutionary studies analyzing vertebrate FABPs have distinguished major subfamilies (H-FABPs/ ap2/myelin P2, I/L-FABPs and CRABPs/CRBPs) that could be raised by gene duplication from a common ancestor closer to vertebrate/ invertebrate split (Chan et al., 1985; Matarese et al., 1989; Medzihradsky et al., 1992; Schaap and Glatz, 2002). When the number of FABP sequences increased, despite that more complex relationships appeared, the basic sub-family organization in vertebrates was maintained. Nevertheless, the progressive inclusion of invertebrate members, which do not share extensive sequence motifs with vertebrate FABPs, blurred the dendrogram topologies (Esteves et al., 1997).

The objective of this review is to summarize the information available on invertebrate members of the FABP family, in order to understand their evolutionary relationships and putative functions.

2. Climbing the tree of life

2.1. Archaebacteria and fungi

A sequence coding for a hypothetical fatty acid transporter from a hyper-thermophilic archaebacterium *Pyrococcus horikoshii* has been reported (NP-143498). This sequence codes for a putative protein of 483 amino acids. The cytosolic fatty acid binding protein signature is present