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Introduction: lipid-binding proteins: novel aspects

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Abstract. Lipid-binding proteins function to transport lipids across membranes and aqueous phases and act to solubilise their cargo, protect it from chemical damage and probably also to define its destination. As such, they have been adapted to carry out a broad spectrum of biological functions in addition to their classical roles in energy metabolism and the transmission or blocking of retinoid-based signalling. The set of reviews in this issue of CMLS is designed to draw attention to some newly understood aspects and principles of their biology and structure, and concentrates on the proteins involved in transport of fatty acids and retinoids.

Key words. Fatty-acid-binding proteins; lipocalins; trans-membrane fatty acid transporters; placenta; retinol; protein:protein interaction; protein:membrane interaction, uterocalin.

Lipid transporter proteins are attracting considerable and increasing interest from scientists active in a wide range of subjects from protein dynamics and energy mobilisation, to embryonic development, and the biological adaptations of organisms that undergo prolonged migrations, hibernation or aestivation. The following set of short reviews is intended to draw attention to some new aspects of thinking about the structure and function of these proteins, which have otherwise been the focus of several excellent reviews in recent years. Two articles will deal with cytosolic lipid binding proteins of the FABP/P2/CRBP/CRABP family of small (~ 14 kDa) lipid intracellular transporters, one on transmembrane proteins (in particular the recently described form from the placenta) and one on a novel lipocalin which supports pregnancy in the horse (a novel function for a lipocalin).

Proteins of the FABP/P2/CRBP/CRABP family are often termed FABP (from *f*atty *a*cid *b*inding *p*rotein), but this has caused some confusion because such a binding propensity is a property of many different types of protein (e.g. serum albumins and some lipocalins), and some members of the family do not bind fatty acids. Instead of 'FABP', some authors have instead used the term 'cLBP', for *c*ytosolic *l*ipid *b*inding *p*rotein, and the authors in the following set of reviews use either convention.

There has been a dramatic increase in interest in the family of cLBPs in recent years, as reflected by the exponential growth in the number of papers on them, and they have now been described widely amongst the animal phyla, from vertebrates to insects and parasitic worms of different kinds. The expectation is that they will eventually be found universally amongst the animal phyla, and there is already evidence, particularly from nematodes, that their role in the biology of animals is broader than previously suspected. The number of reviews on cLBPs is also undergoing a steady increase, and a review set such as published here could easily be reiterative. So, what follows is a selection of topics on the general theme of lipid binding/transporter proteins which was designed around the imperative to find new things to say and point out recently described novelties in their biological functions which may point in the direction of potentially expansive avenues of investigation.

First in an article on the cLBPs (= FABPs) by Jack Stewart (Sackville, Canada) which reviews progress in the understanding of the proteins themselves, and their role in biological systems. A particularly important aspect to note is the author's own recent contributions to the role of cLBPs in metabolic regulations and how they have been adapted for the life of animals living in extreme environments or conditions.

But the cLBPs do not exist in isolation—they must interact with other cellular components, such as integral membrane proteins, cytosolic proteins or directly with membranes, and it is conceivable that some types of FABPs interact with more than one of these entities. One cellular component which is clearly of immediate importance to the ingress of lipids is membrane-associated proteins involved in the capture and transport of fatty acids across the plasma membrane. This is dealt with by Asim Dutta-Roy's (Aberdeen, Scotland) article, in which the evidence for several different types of trans-membrane transporters is reviewed, with particular emphasis on that of the human placenta, which is specialised to capture and transport the particular types of fatty acids which are essential to fetal growth and development, particularly for the developing brain.

Continuing on the developmental biological theme, Francesca Stewart (Cambridge, England) discusses an entirely novel function for the extracellular counterpart of the cLBPs—the lipocalins. The lipocalins are known to be involved in a broader range of biological functions than even the cLBPs, such as the transport of vitamin A in plasma or milk, coloration in insects, solubilising the lipid in tears, capture of odorants in olfaction and the dispersal of pheromones, and now provisioning the early embryo of horses with lipids before placentation occurs. The latter function appears to be carried out by a protein discovered in the Stewart laboratory, the protein being currently named P19, but probably to be renamed 'uterocalin'. One might justifiably speculate that proteins homologous to P19 may be involved in the support of the early conceptus of other mammals, and perhaps even in humans, but the brief period before placentation in mammals other than equids has made their detection less likely.

Given that cLBPs must interact with one or more cellular components, it is conceivable that there are external features of cLBPs which are critical to such interactions. Such features may be crucial to the interactions concerned (e.g. protein:membrane or protein:protein), and may determine the specificity of such events. The traffic in lipids within cells for the purposes of, for instance, energy metabolism and the delivery of cellular and gene activation signals is so extensive that it might fail or be seriously compromised by cross-talk between transporter pathways unless some mechanisms exist to impose specificity. Whilst this can be achieved by specifying the type of lipid a particular protein can carry (e.g. fatty acids or retinoids), some cLBPs with similar binding specificities exist in the cytoplasm of the same cell type at considerably different concentrations, and appear to be under separate gene activation control. If they have different functions within the cells, then there must be mechanisms to discriminate their carrying and delivery of ligands—from where they are loaded with ligand to where it is deposited—in other words, addressing. Discussing this is the function of the final article, which is the most speculative of the set, deliberately so, and suggests a role for the unusual protruding bulky hydrophobic side chains known from crystallographic and nuclear magnetic resonance studies to project into solvent adjacent to the presumed portal of cLBPs.

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