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Ockner R K, Manning J A, Poppenhausen R B & Ho W K L. A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium, and other tissues. *Science* 177:56-8, 1972.
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This paper described the binding of long-chain fatty acids to a low molecular weight protein in cytosol of intestinal mucosa, liver, myocardium, adipose tissue, and kidney. Binding was noncovalent, and the apparent affinity was greater for unsaturated than for saturated and medium-chain fatty acids. [The *SCI*® indicates that this paper has been cited in more than 310 publications.]

Fatty Acid Binding Proteins: Considerable Progress—More Ground to Cover

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Our description of the cytosolic binding activity and subsequent isolation and characterization of a specific intestinal fatty acid binding protein (FABP) have largely withstood the test of time and have generated new questions. One of my coauthors, Joan A. Manning, remains a member of the research team; her excellent contributions have played a major role in its subsequent accomplishments.

Although our early studies confirmed the hypothesis that prompted them, as well as the immediately ensuing prediction that FABP would also be found in other tissues exhibiting substantial fatty acid transport or metabolism, two important facts were not evident at the time. First, the FABP in four of the tissues we examined, namely, intestine, liver, myocardium, and adipose tissue, proved to be distinct but closely related proteins. Second, the abundance of FABP in the enterocyte reflects nearly equal expression of the liver and intestinal forms (L-FABP and I-FABP). The significance of this prominent expression of two distinct and independently regulated FABPs in one cell remains unknown. It has also become evident that the FABPs are members of a multigene family that includes the myelin P2 protein, the cytosolic retinol and retinoic acid binding proteins, mammary-derived growth inhibitor, and gastrotropin, a constituent of ileal cytosol.[1]

The paper's relatively frequent citation probably reflects the fact that it, along with a nearly simultaneously published study by S. Mishkin, et al.,[2] provided the first evidence that, as in plasma, intracellular long-chain fatty acids are largely bound to specific soluble proteins. Our original hypothesis, that this interaction would participate in intracellular transport and metabolism of long-chain fatty acids, may prove to be correct, but no function of the FABP has been conclusively established, despite the efforts of a growing number of laboratories over nearly 20 years.

Moreover, evidence that FABP expression may increase in response to increased tissue fatty acid flux rather than, as a precondition suggests, along with other evidence, a possibly cytoprotective role.[1,3] Recent findings also suggest that FABP may be involved in extramitochondrial (e.g., peroxisomal) fatty acid oxidation, growth regulation, signal transduction, and heme and cholesterol metabolism.[1,3-5] In addition, J.I. Gordon and colleagues,[6] in their studies of the structure and molecular genetics of liver, intestinal, and heart FABP, and B.M. Spiegelman and associates,[7] in elucidating the regulation of the adipocyte form of FABP (aP2) during the preadipocyte to adipocyte transition, have addressed fundamental issues in the control of tissue-specific gene expression and cell differentiation. Current research in this rapidly growing area was the subject of the First International Workshop on Fatty Acid Binding Proteins, held in September 1989 in Maastricht, The Netherlands.[8]

From its inception, investigation of the FABP has led to many unexpected turns and the need to address increasingly fundamental questions. This unpredictability seems likely to persist, given our incomplete understanding of these proteins and of the interactions of their fatty acid ligands with the cell. With continuing pursuit of these issues, we can expect to gain a clearer picture of both the biology of the FABPs and of their implications for health and disease.

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