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A role for adipocyte lipid-binding protein in atherosclerosis

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Fatty acid binding proteins (FABPs) are members of a multigene family that consists of small (~15 kDa) cytoplasmic proteins that bind long-chain fatty acids, and facilitate their solubilization and transport within the cell [1–4]. Currently, at least nine FABPs are known, each expressed in a selective tissue-specific pattern. Of these, FABP4, or the adipocyte lipid-binding protein (ALBP; also known as aP2), has been extensively investigated for its role in the regulation of carbohydrate and lipid metabolism [5–9].

Targeted disruption of the *Ap2* gene results in no obvious phenotypic changes in C57BL/6 mice [5]. However, in mice challenged with a high-fat diet a deficiency in ALBP is beneficial, as evidenced by decreased levels of fasting plasma glucose, insulin, cholesterol and triglycerides compared with wild-type mice [5,6]. In addition, *Ap2*^{−/−} mice maintain insulin sensitivity, whereas wild-type mice develop insulin resistance after fat-feeding [5,7,8]. In spite of such overall metabolic changes, the *Ap2*^{−/−} and wild-type mice have similar body mass and develop comparable diet-induced obesity [5,9]. Thus, deficiency in ALBP results in uncoupling of the insulin resistance syndrome from obesity [5]. This is an interesting finding and is worthy of consideration in the treatment of diabetes. A comparison of the levels of ALBP between diabetic and normal individuals should reveal any correlations between diabetes and ALBP.

Apart from its metabolic functions, ALBP also participates in cell-signaling pathways [2,4]. In this role, ALBP targets fatty acid second messengers to various gene regulatory elements. It has been suggested that ALBP binds to 15-deoxy-Δ^{12,14}-prostaglandin J₂ and thiozolidinediones [natural and synthetic ligands, respectively, of peroxisome proliferator-activated receptor (PPAR)-γ, a nuclear hormone receptor and transcription factor [10,11•]. In turn, activation of PPAR-γ induces expression of *Ap2* messenger RNA [12]. PPAR-γ is expressed in a differentiation-dependent manner in both adipocytes and macrophages, and has been implicated in atherosclerosis [13,14]. Until recently it was believed that ALBP is expressed exclusively in adipocytes [2,4]. Recent studies [15,16••] demonstrated that the 5.4 kilo-base enhancer/promoter element of the *Ap2* gene drives the expression of ALBP in differentiated macrophages as well.

The discovery that ALBP is expressed in macrophages and the interactions between PPAR-γ and ALBP have led to investigations into the role of macrophage ALBP in atherosclerosis [16••,17••]. Two recent reports support a proatherosclerotic role for ALBP. Perrella *et al.* [17••] demonstrated that ALBP messenger RNA is expressed in atherosclerotic lesions from hypercholesterolemic apolipoprotein E knockout mice, but not in normal mice. Similarly, ALBP protein was detected in macrophage foam cells from aortic lesions of *Ap2*^{−/−} mice but not in *Ap2*^{+/+} mice [16••]. Macrophage ALBP expression is induced by oxidized LDL, a prominent contributor to the atherogenic process [17••]. Makowski *et al.* [16••] reported that macrophages from *Ap2*^{−/−} mice accumulate significantly less cholesterol esters after exposure

to oxidized LDL than do wild-type macrophages. Additional experiments in genetically engineered mouse models established that a deficiency of macrophage *Ap2* protects against atherosclerosis [16••,17••]. Because mice do not develop significant size lesions in the presence of apoE, *Ap2*^{-/-} mice were intercrossed with apolipoprotein-E-deficient mice. In two independent studies and in all diet and sex groups, mice that lacked *Ap2* developed significantly smaller lesions than did *Ap2*^{+/+} mice [16••,17••].

The effect of ALBP on atherosclerosis appears to be independent of its metabolic functions, because in the apolipoprotein-E-knockout background both *AP2*^{-/-} and *Ap2*^{+/+} mice had elevated but comparable levels of total plasma cholesterol and triglycerides, and the two groups did not differ in insulin sensitivity and glycemic control [16••]. Additionally, using the technique of bone marrow transplantation, Makowski *et al.* [16••] obtained mice whose adipocytes were *Ap2*^{+/+} but whose macrophages were *Ap2*^{-/-}, also in the apolipoprotein-E-deficient background. Even in mice with macrophage-specific *Ap2*-deficiency, aortic lesions were significantly reduced as compared with mice with *Ap2*^{+/+} macrophages. Similarly, carotid arteries transplanted from another mouse strain into *Ap2*^{-/-} mice developed transplant-associated atherosclerosis, presumably because of the presence of endogenous *Ap2* in the transplanted arteries [17••].

ALBP may influence atherosclerosis by modulating the macrophage inflammatory response and cell-signaling functions. The expression of inflammatory cytokines, including tumor necrosis factor- α , interleukin-6 and interleukin-1 β , was negligible in *Ap2*^{-/-} as compared with *Ap2*^{+/+} macrophages [16••]. Similarly, *Ap2*^{-/-} macrophages secreted significantly lower levels of monocyte chemotactic factor-1 as compared with wild-type mice [16••]. Earlier studies indicated that PPAR- γ is a negative modulator of those cytokines in macrophages [18,19]. Given the ability of ALBP to activate PPAR- γ , it is unclear why ALBP deficiency leads to repression of cytokine secretion by macrophages. It is likely that regulatory mechanisms distinct from PPAR- γ also contribute to precipitating the proatherogenic effects of ALBP.

These studies clearly indicate that the metabolic and inflammatory effects of ALBP may be independent of each other. This presents an opportunity to develop novel therapeutic approaches to combat selectively either the metabolic syndrome or atherosclerosis by targeted inactivation of adipocyte or macrophage ALBP. In any case, a deficiency in ALBP appears to be beneficial at both levels. However, further studies are warranted to investigate whether removal of ALBP may compromise the intracellular transport of long-chain fatty acids and adversely affect normal physiology at the cellular level.

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17. Perrella MA, Pellacani A, Layne MD, et al. Absence of adipocyte fatty acid binding protein prevents the development of accelerated atherosclerosis in hypercholesterolemic mice. *FASEB J* 2001;15:1774–1776. [PubMed: 11481226]
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Recommended reading

20. Chiu KC, Chuang LM, Chu A, Yoo C. Fatty acid binding protein 2 and insulin resistance. *Eur J Clin Invest* 2001;31:521–527. [PubMed: 11422402] This is a similar study to that by Galluzzi *et al.* (2001), conducted to determine any correlation between the A54T polymorphism of liver FABP and insulin resistance. In a population of 71 healthy, normotensive and glucose-tolerant Caucasian persons, only five were found to be homozygous for the polymorphism, but approximately 50% were heterozygous carriers. Insulin sensitivity and β -cell function was determined based on oral glucose tolerance tests. The authors report no effect of this polymorphism on β -cell function, whereas insulin sensitivity was in fact slightly increased. This is a very interesting finding considering the fact that complete deficiency of ALBP was found to be protective against diet-induced insulin resistance in mice. Similar analysis of any correlation between ALBP and the insulin resistance syndrome is required.
21. Galluzzi JR, Cupples LA, Meigs JB, et al. Association of the Ala54-Thr polymorphism in the intestinal fatty acid-binding protein with 2-h post-challenge insulin levels in the Framingham Offspring Study. *Diabetes Care* 2001;24:1161–1166. [PubMed: 11423496] A A54T mutation in liver FABP has been associated with insulin resistance in various populations. In this study, the presence of this polymorphism was investigated in participants in the Framingham Offspring Study. It was determined that this mutation did not associate with fasting glucose and insulin levels or with the prevalence of type 2 diabetes.

22. Liou HL, Storch J. Role of surface lysine residues of adipocyte fatty acid-binding protein in fatty acid transfer to phospholipid vesicles. *Biochemistry* 2001;40:6475–6485. [PubMed: 11371211] This nice structural study was conducted to determine the structure–function relationship of ALBP. It is well known that the tertiary structure of all FABPs consists of a β -barrel with a hydrophobic binding cavity that encloses a single fatty acid molecule. Additionally, a helical domain may act as a channel for the entry and exit of the fatty acid. This study further elaborates on the requirements for interaction of ALBP with membrane phospholipids. Using site-directed mutagenesis these authors demonstrate that a positively charged surface lysine residue is required for ionic interactions with negatively charged membrane phospholipids.
23. Makowski L, Boord JB, Maeda K, et al. Lack of macrophage fatty-acid-binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nat Med* 2001;7:699–705. [PubMed: 11385507] This paper examines the role of macrophage ALBP in atherosclerosis. The authors used *Ap2^{-/-}* mice intercrossed with *apoE^{-/-}* mice to demonstrate that ALBP deficiency protects against atherosclerosis. Based on biochemical assays and glucose tolerance tests, they conclude that the protection against atherosclerosis is independent of the metabolic state of the animals. To back this hypothesis, they generated mice with macrophage-specific deficiency of ALBP by bone marrow transplantation, demonstrating that macrophage ALBP regulates atherosclerosis independent of adipocyte ALBP. The paper also reports decreased levels of cytokine secretion and cholesterol ester accumulation by macrophages from *Ap2^{-/-}* mice.
24. Margareto J, Larrarte E, Marti A, Martinez JA. Up-regulation of a thermogenesis-related gene (UCP1) and down-regulation of PPARgamma and aP2 genes in adipose tissue: possible features of the antiobesity effects of a beta3-adrenergic agonist. *Biochem Pharmacol* 2001;61:1471–1478. [PubMed: 11377376] This paper examines the mechanisms by which certain β -adrenergic agents regulate adipogenesis. The authors demonstrate that treatment of obese mice with the β -adrenergic agonist tertatolol significantly reduces obesity and that this reduction is correlated with an inhibition of the expression of both PPAR- γ 2 and ALBP. Their results suggest PPAR- γ and ALBP are important factors in adipogenesis.
25. Miki H, Yamauchi T, Suzuki R, et al. Essential role of insulin receptor substrate 1 (IRS-1) and IRS-2 in adipocyte differentiation. *Mol Cell Biol* 2001;21:2521–2532. [PubMed: 11259600] This research was conducted to investigate the role of insulin-receptor substrates (IRSs) 1 and 2 in adipocyte differentiation. The authors developed embryonic fibroblast cells deficient in either one or both forms of IRS, and then examined the effect on various genes of the adipose tissue. They demonstrated that cells deficient in both IRS-1 and IRS-2 lose their ability to differentiate into adipocytes. Coincident with this phenotype is a dramatic reduction in PPAR- γ messenger RNA and protein levels. Additionally, the level of ALBP protein is also greatly reduced. These studies establish a clear function for ALBP and PPAR- γ in adipogenesis.
26. Perrella MA, Pellacani A, Layne MD, et al. Absence of adipocyte fatty acid binding protein prevents the development of accelerated atherosclerosis in hypercholesterolemic mice. *FASEB J* 2001;15:1774–1776. [PubMed: 11481226] This paper investigates the role of ALBP in atherogenesis in mice. The authors demonstrate the presence of Ap2 messenger RNA in aortic lesions of apolipoprotein-E-deficient mice. They compared lesion size in *Ap2^{-/-}*, *apoE^{-/-}* mice with that in *apoE^{-/-}* mice, and show a definite protection against atherosclerosis in the double-null mice. They also reported that ALBP deficiency does not protect against transplant-induced atherosclerosis in carotid arteries transplanted from *Ap2^{+/+}* mice into *Ap2^{-/-}* mice.
27. Wolfrum C, Borrmann CM, Borchers T, Spener F. Fatty acids and hypolipidemic drugs regulate peroxisome proliferator-activated receptors alpha- and gamma-mediated gene expression via liver fatty acid binding protein: a signaling path to the nucleus. *Proc Natl Acad Sci USA* 2001;98:2323–2328. [PubMed: 11226238] This paper demonstrates the colocalization of PPAR- α and liver FABP to the nucleus of hepatocytes. A similar distribution of PPAR- γ and ALBP may be expected in macrophages. Additionally, the authors demonstrate a correlation between PPAR activation and concentration of FABP, supporting the hypothesis that FABP modulates ligand availability to PPAR.