Published in final edited form as:
Curr Opin Lipidol. 2005 October ; 16(5): 543–548.

The role of fatty acid binding proteins in metabolic syndrome and atherosclerosis

Liza Makowski[a] and **Gökhan S. Hotamisligil**[b]

[a]Sarah W. Stedman Nutrition and Metabolism Center, Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition, Duke University Medical Center, Durham, NC 27704, USA

[b]Department of Genetics and Complex Diseases, Harvard School of Public Health, Boston, MA 02115, USA

Abstract

Purpose of review—The global prevalence of obesity is increasing epidemically. Obesity causes an array of health problems, reduces life expectancy, and costs over US$100 billion annually. More than a quarter of the population suffers from an aggregation of co-morbidities, including obesity, atherosclerosis, insulin resistance, dyslipidemias, coagulopathies, hypertension, and a pro-inflammatory state known as the metabolic syndrome. Patients with metabolic syndrome have high risk of atherosclerosis as well as type 2 diabetes and other health problems. Like obesity, atherosclerosis has very limited therapeutic options.

Recent findings—Fatty acid binding proteins integrate metabolic and immune responses and link the inflammatory and lipid-mediated pathways that are critical in the metabolic syndrome. This review will highlight recent studies on fatty acid binding protein-deficient models and several fatty acid binding protein-mediated pathways specifically modified in macrophages, cells that are paramount to the initiation and persistence of cardiovascular lesions.

Summary—Adipocyte/macrophage fatty acid binding proteins, aP2 and mal1, act at the interface of metabolic and inflammatory pathways. These fatty acid binding proteins are involved in the formation of atherosclerosis predominantly through the direct modification of macrophage cholesterol trafficking and inflammatory responses. In addition to atherosclerosis, these fatty acid binding proteins also exert a dramatic impact on obesity, insulin resistance, type 2 diabetes and fatty liver disease. The creation of pharmacological agents to modify fatty acid binding protein function will provide tissue or cell-type-specific control of these lipid signaling pathways, inflammatory responses, atherosclerosis, and the other components of the metabolic syndrome, therefore offering a new class of multi-indication therapeutic agents.

Keywords

atherosclerosis; fatty acid binding protein; fatty acids; lipomics; macrophage

Introduction

Atherosclerosis is the leading cause of death in the United States [1–4]. At the core of this syndrome is the dysregulation of lipid metabolism and aberrant inflammatory responses [5].

Correspondence to Gökhan S. Hotamisligil, 665 Huntington Avenue, Building I, Room 207, Boston, MA 02115, USA, Tel: +1 617 432 1950; fax: +1 617 432 1941; ghotamis@hsph.harvard.edu.

Although mechanistic roles for fatty acids have been put forward in the formation of obesity and diabetes by modifying glucose and lipid metabolism as well as inflammatory cascades, little is known about the mechanisms that link fatty acids or other lipid signals to inflammatory responses and the formation of atherosclerotic lesions [6–8]. This review will focus on the biology of fatty acid binding proteins (FABPs) in several mouse models with targeted mutations in adipocyte/macrophage isoforms of these proteins. Although serum fatty acid levels are not reduced in these FABP-deficient models, they are strikingly and paradoxically protected from obesity, insulin resistance, type 2 diabetes, fatty liver disease and atherosclerosis [9–12,13••,14,15••,16–18]. This phenotype emphasizes the fact that total fatty acids may not be the primary pathogenic indicator, and that individual fatty acid or metabolite action at the intracellular level and the specific responses evoked by these signals are more relevant to the pathophysiology and outcomes of atherosclerotic disease than parameters classically measured.

Fatty acids and eicosanoids in signaling

Fatty acids and cholesterol are involved in the basic maintenance of the cell structure and energy metabolism, but are also vital in cell signaling [19,20]. Many transcription factors are regulated by lipids, including the families of peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs), which play central roles in lipid metabolism, cell differentiation, and the inflammatory response [21]. In addition, fatty acids can transmit a stress response through the activation of multiple kinases such as the inhibitor of kappa kinase (IKK) and c-jun NH2-terminal kinase (JNK), which have been linked to insulin resistance and other aspects of the metabolic syndrome including atherosclerosis [22]. Furthermore, fatty acids can be metabolized into a diverse family of more than 100 bioactive lipid mediators called eicosanoids, which may function as pro and anti-inflammatory mediators [19,23]. In particular, the cyclopentenone prostaglandins (PGA_1, PGA_2, and PGJ_2) have potent anti-inflammatory effects through the inhibition of inflammatory kinase pathways, and are beneficial in rodent models of inflammation [24]. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) is a controversial lipid mediator, which has been shown to be anti-inflammatory, but some suggest that it is not produced in substantial quantities to be truly effective [24]. However, 15d-PGJ_2 should not be disregarded as it was recently detected in human atherosclerotic lesions and is produced in and secreted from macrophages [25]. The role of fatty acids and eicosanoids in inflammation and atherosclerosis deserves special consideration in light of the clinical profile of cyclo-oxygenase 2-specific inhibitors and the increased incidence of heart disease [26].

Transcriptional pathways and cholesterol trafficking in the macrophage

Several key steps of cholesterol uptake and efflux in the macrophage are regulated by the nuclear hormone receptors PPAR-γ and LXR-α [21]. When modified LDL is taken up and degraded, fatty acids and eicosanoid ligands for PPAR-γ are generated, driving PPAR-γ transcription, which plays a role in macrophage biology as it relates to atherosclerosis by regulating cholesterol trafficking and the inflammatory response [21,27,28,29•]. PPAR-γ-driven scavenger receptor CD36 upregulation results in enhanced lipoprotein entry, which triggers a protective mechanism via the PPAR-γ–LXR-α–ATP binding cassette (ABC) A1 cholesterol efflux pathway [27,30,31]. Briefly, the transcription factor LXR-α is positively regulated upon the activation of PPAR-γ and by oxysterol ligands [21]. LXR-α activation leads to an increase in the cholesterol transporters ABCA1 and apolipoprotein E, which drive free cholesterol efflux from macrophages to acceptors such as apolipoprotein A1 or HDL [30–32]. The activation of PPAR-γ and LXR-α, or the overexpression of ABCA1 and apolipoprotein E result in decreased atherosclerosis, whereas blocking or deleting these genes resulted in greater atherosclerosis in mice [21,33]. Early clinical results also suggest a

protective effect of PPAR-γ ligands in humans [34]. In addition, PPAR-γ and LXR-α have been linked to anti-inflammatory action [21,35–38]. However, the impact of the PPAR-γ pathway on inflammatory responses has not yet been fully established.

A very poorly understood part of lipid-activated transcription factors has been the upstream mechanisms controlling their access to ligands. Recent discoveries have indicated a critical role for FABPs in this important regulation [13••] (also see below).

Lipids and pro-inflammatory kinase pathways in the macrophage

The IKK–nuclearfactor kappa B (NF-κB) and JNK-AP-1 pathways are two important intermediaries in the control of macrophage pro-inflammatory activity as well as insulin receptor signaling and insulin action [22,39,40]. For example, the IKK–NF-κB pathway has been shown to be highly sensitive to inactivation by certain lipids; α-lipoic acid, 15d-PGJ_2, PGA_1, and PGA_2 block NF-κB activity through inhibition of IKK and directly hinder transcription by blocking the ability of NF-κB to bind to DNA [24,41]. Many of the pro-inflammatory components downstream of NF-κB have been shown to be essential to the formation of the atherosclerotic lesion. For example, when monocyte chemoattractant protein 1 or its receptor are deleted from a mouse model prone to develop atherosclerotic lesions, the size of the lesions is reduced [42,43]. Similarly, JNK is regulated by lipids and plays a critical role in both type 2 diabetes and atherosclerosis [22]. The targeted disruption of JNK-1 provides strong protection against insulin resistance associated with obesity, whereas JNK-2 deficiency results in a significant reduction in vascular lesions associated with an apolipoprotein E-deficient model of atherosclerosis [44,45]. These show that manipulations in the pro-inflammatory processes controlled by these and other lipid-responsive pathways may lead to substantial benefits for the prevention of atherosclerosis. Interestingly, both of these pathways are also regulated by FABPs [13••].

Fatty acid binding proteins

The recent expansion of mechanistic insights into FABP action demonstrated that these lipid chaperones serve as upstream and critical modulators of many lipid-signaling cascades. FABPs are abundant cytoplasmic proteins that reversibly bind hydrophobic ligands such as saturated and unsaturated long chain fatty acids, plus eicosanoids such as hydroxyeicosatetraenoic acid, leukotrienes and prostaglandins [46,47]. FABPs may actively facilitate the transport of lipids to specific compartments in the cell: such as to the mitochondria for oxidation; to the lipid droplet for storage; to enzymes for mediating activity; to the nucleus for lipid-mediated transcriptional regulation; or outside the cell to signal in an autocrine or paracine fashion. Overexpression and anti-sense studies in cultured cells have suggested potential roles in fatty acid import, storage, and export, as well as cholesterol and phospholipid metabolism [47]. Furthermore, FABPs are involved in the conversion of fatty acids to eicosanoid intermediates and in the stabilization of leukotrienes [48–50,51•]. In addition, aP2 has been shown to modify hormone-sensitive lipase activity through direct protein–protein interaction [52]. Finally, movement of FABPs into the nucleus and interaction with nuclear hormone receptors is possible, and this mechanism might potentially deliver ligands to this protein family [53–55]. Overall, FABPs act to sequester or distribute ligands to regulate signaling processes and enzymatic activity. Clear evidence on the specific impact of FABPs on cell biology and lipid metabolism in complex systems had been lacking until FABP-deficient mice models were created.

aP2$^{-/-}$ model and atherosclerosis

Adipocyte/macrophage FABP, also designated aP2 or FABP4, is an important contributor to the maintenance of systemic glucose metabolism and adipocyte biology [14,17,18]. As a

result of alterations in insulin sensitivity and serum lipids in aP2-deficient mice, we investigated the role of aP2 in atherosclerosis in the apolipoprotein $E^{-/-}$ model with the goal of exploring the link between insulin resistance and atherosclerosis in an experimental model. Strikingly, mice deficient in aP2 exhibited as much as 88% reduction in vascular lesions compared with $aP2^{+/+}$ controls on the apolipoprotein $E^{-/-}$ background, independent of any effects on insulin signaling or serum lipids [12]. The extent of protection from atherosclerosis by aP2 deficiency exceeds most, if not all, reported models of anti-atherogenic activity. The aP2 deficiency-mediated protection from atherogenesis in the apolipoprotein $E^{-/-}$ background persists even when these animals are kept on a hypercholesterolemic Western diet [9]. It thus appeared that additional, and probably inflammatory, pathways are also targeted by FABPs in the regulation of atherosclerosis.

At this stage, we and others observed the presence of aP2 in macrophages, and have shown that expression can be induced in monocytes by phorbol myristate acetate-induced differentiation and activation, lipopolysaccharide/Toll receptor activation, PPAR-γ agonists, oxidized LDL, and rapamycin inhibitor treatments, and decreased by treatment with a cholesterol-lowering statin [12,56–59,60•]. Parallel patterns also exist in humans, with a similar relationship to atherosclerotic lesions (unpublished observations and Damcott *et al*. [61]). On the basis of these findings, we designed experiments to test the impact of macrophage aP2 deficiency in atherosclerosis directly. Bone marrow transplantation studies demonstrated that despite the adipocyte being the major site of aP2 expression, macrophage-specific action of aP2 is the predominant contributor to vascular lesion formation [12]. At the cellular level, aP2-deficient macrophages have increased free fatty acids and decreased cholesterol and cholesterol esters [13••]. In a gain of function model, the overexpression of aP2 in human macrophage cell lines drives the accumulation of cholesterol esters and foam cell formation [62]. We hypothesized that the modulation of intracellular fatty acids by aP2 leads to changes in lipid-mediated signaling pathways that modify cholesterol metabolism and inflammatory responses in the macrophage. Our data show that aP2 is a critical regulator of the PPAR-γ–LXR-α–ABCA1 pathway and contributes to foam cell formation [11,13••]. PPAR-γ activity is elevated in $aP2^{-/-}$ macrophages with stimulation of downstream targets including LXR-α, ABCA1, and apolipoprotein E expression [13••]. This has dramatic consequences on cholesterol trafficking in macrophages, with the lack of aP2 resulting in enhanced efflux of cholesterol [11,13••]. In parallel, aP2 coordinates the inflammatory activity of macrophages [11,13••]. In $aP2^{-/-}$ macrophages, several inflammatory signaling responses are suppressed, including cytokine and chemokine secretion, such as TNF-α and pro-inflammatory enzyme production and function including inducible nitric oxide synthase and cyclo-oxygenase 2 [13••]. We have also demonstrated that aP2 deficiency results in modified inflammatory responses and the inhibition of the IKK–NF-κB pathway, well upstream of transcriptional activity [11,13••]. Consequently, the overall reduction in foam cell formation and modified inflammatory responses of $aP2^{-/-}$ macrophages is highly beneficial against the formation of atherosclerosis.

$mal1^{-/-}$ model and atherosclerosis

Interestingly, another minor adipocyte FABP, mal1 (FABP5), is also present in macrophages. In the $aP2^{-/-}$ model, mal1 expression is dramatically upregulated in the adipocytes; however, this level of compensatory regulation has not been observed in the macrophages [12,17]. In addition, although being the minor isoform in adipocytes, mal1 protein levels are comparable to aP2 in normal macrophages. To address the role of mal1 in the metabolic syndrome, we generated a mouse model with a targeted mutation in the mal1 gene [16]. Unlike aP2-deficient animals, $mal1^{-/-}$ animals on a high fat diet or in the setting of genetic obesity exhibited only a slight protection from the development of insulin resistance [16]. As mal1 is not markedly regulated upon aP2 deficiency in the macrophages,

and the atherosclerosis phenotype appears to be predominantly regulated by aP2 in this cell type, mal1 alone may not be a major player in atherosclerosis but may rather enhance the biology of aP2 (see below). In any case, accumulating evidence demonstrates that there must be as yet undiscovered functional differences between aP2 and mal1. Studies to address these questions and the specific role of mal1 in macrophages and atherosclerosis are currently underway.

aP2-mal1$^{-/-}$ model and atherosclerosis

Our laboratory has recently generated mice with combined aP2-mal1 deficiency (aP2-mal1$^{-/-}$) to remove all FABP activity from adipocytes and macrophages, and address the issue of FABP function in these target cells without compensation as a confounding effect. The aP2-mal1$^{-/-}$ mouse model has striking resistance to the formation of the metabolic syndrome, with improved parameters for multiple components including decreased hypertension, cholesterol, triglycerides, insulin, and glucose [15••]. On a high fat diet, aP2-mal1$^{-/-}$ mice exhibit alterations in tissue fatty acid composition and do not develop insulin resistance, type 2 diabetes or fatty liver disease, demonstrating that the protective phenotype of this model far exceeds that of individual FABP mutants [15••]. Similarly, when intercrossed to the apolipoprotein E$^{-/-}$ model, aP2-mal1$^{-/-}$ mice develop dramatically less atherosclerosis compared with aP2 null and wild-type mice on the same background [10]. Remarkably, aP2-mal1$^{-/-}$ animals also have significantly increased survival in the apolipoprotein E$^{-/-}$ background even when fed a Western-type hypercholesterolemic diet for 12 months, probably because of the increased stability of plaques [10].

To understand how FABPs expressed in only a few tissue depots can have such wide-reaching systemic benefits, an in-depth fatty acid profiling of muscle, liver and adipose tissues was performed. This indicated that in the absence of both FABPs, there are increased short chain fatty acids in the muscle and adipose tissues of aP2-mal1$^{-/-}$ mice, which favored enhanced insulin receptor signaling, AMP-activated kinase activity, fatty acid oxidation, and insulin-stimulated glucose uptake [15••]. There were also alterations in liver fatty acid composition, which differed from other sites and favored lipid mobilization over storage and suppressed stearoyl coenzyme A desaturase and sterol-regulatory element-binding protein activities, thus reducing hepatosteosis [15••]. This phenomenal mouse model has shed new light on the role of FABPs in regulating intracellular fatty acid profiles and how these alterations are linked to specific biochemical pathways critical in metabolic homeostasis.

Conclusion

FABP-mediated lipid metabolism is closely linked to both metabolic and inflammatory processes through modulating critical lipid-sensitive pathways in target cells; macrophages and adipocytes. The lack of aP2 alters the intracellular lipid milieu such that lipid-sensitive targets including nuclear hormone receptors and inflammatory kinases have broad ranging protective consequences on macrophage biology. The absence of aP2 and mal1 has even more remarkable protection from atherosclerosis and the metabolic syndrome through fatty acid-mediated alterations in kinase and transcriptional activity. The phenotypes observed in the absence of adipocyte/macrophage FABPs illustrate the integrating role played by these proteins in metabolic and inflammatory responses, and establish these genes as a strong example of the ‘thrifty’ gene family. Finally, these models illustrated further networks of bioactive lipid signals between adipocytes and macrophages, and muscle and liver tissues, the identification of which should be highly informative. Bone marrow transplantation and genetic loss of function studies are currently under way to determine the effect of mal1 and aP2-mal1 macrophage and adipocyte-specific deficiency on atherosclerosis to dissect their biology in detail. Further investigation of fatty acid profiles, eicosanoid synthesis, the

partitioning of fatty acids into various cellular domains, and the identification of target genes should aid in clarifying the exact function of FABPs in macrophages and other cell types.

Our findings, as well as recent developments in the field, invite a deeper examination of the relevance of fatty acids and eicosanoids in metabolism and disease. There are hundreds of biologically active lipid derivatives that may act as signaling molecules. A fundamental shift in our approach to lipid signaling is necessary so that we no longer simply bulk all fatty acids into one parameter, but consider each one and its metabolites individually. This requires investigation by large scale, high throughput lipomic and metabolomic approaches, coupled with mechanistic and functional studies to address how FABPs expressed in limited tissues can have such wide-ranging effects on atherosclerosis and the metabolic syndrome. These questions notwithstanding, targeting adipocyte/macrophage FABPs, particularly aP2, by small molecule inhibitors offers highly attractive therapeutic opportunities for the management of atherosclerosis and other components of the metabolic syndrome.

Acknowledgments

Sponsorship: Studies on FABP function in macrophages and atherosclerosis are the result of ongoing collaborations between G.S. Hotamisligil (Harvard University), M. Linton (Vanderbilt University) and J. Suttles (Louisville University) laboratories and are funded by joint grants from National Institutes of Health (NIH; HL65405 and AI048850). Other studies on FABP in Hotamisligil laboratory are supported by NIH (DK064360), ADA (7-02-RA-38) and Sandler Foundation (03-0148). L.M. is funded by NIH NRSA F32 HL075970-01 and NIH Loan Repayment Program

Abbreviations

ABC	ATP binding cassette
15d-PGJ$_2$	15-deoxy-$\Delta^{12,14}$-prostaglandin J_2
FABP	fatty acid binding protein
IKK	inhibitor of kappa kinase
LXR	liver X receptor
NF-κB	nuclear factor kappa B
PPAR	peroxisome proliferator-activated receptor

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

1. Hedley AA, Ogden CL, Johnson CL, et al. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA. 2004; 291:2847–2850. [PubMed: 15199035]
2. Olshansky SJ, Passaro DJ, Hershow RC, et al. A potential decline in life expectancy in the United States in the 21st century. N Engl J Med. 2005; 352:1138–1145. [PubMed: 15784668]
3. Moller DE, Kaufman KD. Metabolic syndrome: a clinical and molecular perspective. Annu Rev Med. 2005; 56:45–62. [PubMed: 15660501]
4. American Heart Association. Heart disease and stroke statistics – 2005 Update. Dallas, TX: American Heart Association; 2005.

5. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med. 1999; 340:115–126. [PubMed: 9887164]
6. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. Trends Immunol. 2004; 25:4–7. [PubMed: 14698276]
7. Hotamisligil, GS. Inflammation, TNFalpha, and insulin resistance. In: LeRoith, DTS.; Olefsky, JM., editors. Diabetes mellitus – a fundamental and clinical text. 3rd ed.. New York: Lippincott, Williams and Wilkins; 2004. p. 953-962.
8. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005; 352:29–38. [PubMed: 15635110]
9. Boord JB, Maeda K, Makowski L, et al. Adipocyte fatty acid-binding protein, aP2, alters late atherosclerotic lesion formation in severe hypercholesterolemia. Arterioscler Thromb Vasc Biol. 2002; 22:1686–1691. [PubMed: 12377750]
10. Boord JB, Maeda K, Makowski L, et al. Combined adipocyte-macrophage fatty acid-binding protein deficiency improves metabolism, atherosclerosis, and survival in apolipoprotein E-deficient mice. Circulation. 2004; 110:1492–1498. [PubMed: 15353487]
11. Makowski L, Hotamisligil GS. Fatty acid binding proteins – the evolutionary crossroads of inflammatory and metabolic responses. J Nutr Suppl : Nutr Gene Regul. 2004; 134:2464S–2468S.
12. 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]
13. Makowski L, Brittingham KC, Reynolds JM, et al. The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity: macrophage exression of aP2 impacts peroxisome proliferator-activated receptor γ and IκB kinase activities. J Biol Chem. 2005; 280:12888–12895. [PubMed: 15684432] This report presents the role of aP2 in regulating two key pathways related to atherogenesis: PPAR-γ–LXR-α–ABCA1 cholesterol trafficking and IKK–NF-κB-mediated inflammation in macrophages.
14. Hotamisligil GS, Johnson RS, Distel RJ, et al. Uncoupling of obesity from insulin resistance through a targeted mutation in aP2, the adipocyte fatty acid binding protein. Science. 1996; 274:1377–1379. [PubMed: 8910278]
15. Maeda K, Cao H, Kono K, et al. Adipocyte/macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes. Cell Metabolism. 2005; 1:107–119. [PubMed: 16054052] This study demonstrates that aP2-mal1-combined deficiency has a dramatic effect on all aspects of the metabolic syndrome, with a potential mechanism through altered fatty acid profiles in target tissues and the regulation of key metabolic activities outside adipocytes such as in muscles and the liver.
16. Maeda K, Uysal KT, Makowski L, et al. Role of the fatty acid binding protein mal1 in obesity and insulin resistance. Diabetes. 2003; 52:300–307. [PubMed: 12540600]
17. Scheja L, Makowski L, Uysal KT, et al. Altered insulin secretion associated with reduced lipolytic efficiency in $aP2^{-/-}$ mice. Diabetes. 1999; 48:1987–1994. [PubMed: 10512363]
18. Uysal KT, Scheja L, Wiesbrock SM, et al. Improved glucose and lipid metabolism in genetically obese mice lacking aP2. Endocrinology. 2000; 141:3388–3396. [PubMed: 10965911]
19. Funk CD. Prostaglandins and leukotriens: advances in eicosanoid biology. Science. 2001; 294:1871–1875. [PubMed: 11729303]
20. Vanden Heuvel JP. Diet, fatty acids, and regulation of genes important for heart disease. Curr Atheroscler Rep. 2004; 6:432–440. [PubMed: 15485588]
21. Castrillo A, Tontonoz P. Nuclear receptors in macrophage biology: at the crossroads of lipid metabolism and inflammation. Annu Rev Cell Dev Biol. 2004; 20:455–480. [PubMed: 15473848]
22. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. J Clin Invest. 2005; 115:1111–1119. [PubMed: 15864338]
23. Linton MF, Fazio S. Cyclooxygenase-2 and inflammation in atherosclerosis. Curr Opin Pharmacol. 2004; 4:116–123. [PubMed: 15063354]
24. Scher JU, Pillinger MH. 15d-PGJ2: the anti-inflammatory prostaglandin? Clin Immunol. 2005; 114:100–109. [PubMed: 15639643]

25. Shibata T, Kondo M, Osawa T, et al. 15-deoxy-delta 12,14-prostaglandin J2. A prostaglandin D2 metabolite generated during inflammatory processes. J Biol Chem. 2002; 277:10459–10466. [PubMed: 11786541]
26. Maxwell SR, Webb DJ. COX-2 selective inhibitors – important lessons learned. Lancet. 2005; 365:449–451. [PubMed: 15705439]
27. Tontonoz P, Nagy L, Alvarez JG, et al. PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell. 1998; 93:241–252. [PubMed: 9568716]
28. Forman BM, Tontonoz P, Chen J, et al. 15-Deoxy-delta 12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPAR gamma. Cell. 1995; 83:803–812. [PubMed: 8521497]
29. Li AC, Binder CJ, Gutierrez A, et al. Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARalpha, beta/delta, and gamma. J Clin Invest. 2004; 114:1564–1576. [PubMed: 15578089] A thorough study of PPAR-α, β and γ ligands in foam cell formation and atherosclerosis.
30. Chinetti G, Lestavel S, Bocher V, et al. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med. 2001; 7:53–58. [PubMed: 11135616]
31. Chawla A, Boisvert WA, Lee CH, et al. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell. 2001; 7:161–171. [PubMed: 11172721]
32. Akiyama TE, Sakai S, Lambert G, et al. Conditional disruption of the peroxisome proliferator-activated receptor gamma gene in mice results in lowered expression of ABCA1, ABCG1, and apoE in macrophages and reduced cholesterol efflux. Mol Cell Biol. 2002; 22:2607–2619. [PubMed: 11909955]
33. Levin N, Bischoff ED, Daige CL, et al. Macrophage liver X receptor is required for antiatherogenic activity of LXR agonists. Arterioscler Thromb Vasc Biol. 2005; 25:135–142. [PubMed: 15539622]
34. Haffner SM, Greenberg AS, Weston WM, et al. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation. 2002; 106:679–684. [PubMed: 12163427]
35. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature. 1998; 391:82–86. [PubMed: 9422509]
36. Joseph SB, Castrillo A, Laffitte BA, et al. Reciprocal regulation of inflammation and lipid metabolism by liver X receptors. Nat Med. 2003; 9:213–219. [PubMed: 12524534]
37. Ricote M, Li AC, Willson TM, et al. The peroxisome proliferator-activated receptor-gamma is a negative regulator of macrophage activation. Nature. 1998; 391:79–82. [PubMed: 9422508]
38. Marx N, Sukhova G, Murphy C, et al. Macrophages in human atheroma contain PPARgamma: differentiation-dependent peroxisomal proliferator-activated receptor gamma (PPARgamma) expression and reduction of MMP-9 activity through PPARgamma activation in mononuclear phagocytes *in vitro*. Am J Pathol. 1998; 153:17–23. [PubMed: 9665460]
39. Shoelson SE, Lee J, Yuan M. Inflammation and the IKK beta/I kappa B/NF-kappa B axis in obesity- and diet-induced insulin resistance. Int J Obes Relat Metab Disord. 2003; 27(Suppl. 3):S49–S52. [PubMed: 14704745]
40. Karin M, Yamamoto Y, Wang QM. The IKK NF-kappa B system: a treasure trove for drug development. Nat Rev Drug Discov. 2004; 3:17–26. [PubMed: 14708018]
41. Zhang WJ, Frei B. Alpha-lipoic acid inhibits TNF-alpha-induced NF-kappaB activation and adhesion molecule expression in human aortic endothelial cells. FASEB J. 2001; 15:2423–2432. [PubMed: 11689467]
42. Gu L, Okada Y, Clinton SK, et al. Absence of monocyte chemoattractant protein-1 reduces atherosclerosis in low density lipoprotein receptor-deficient mice. Mol Cell. 1998; 2:275–281. [PubMed: 9734366]
43. Boring L, Gosling J, Cleary M, Charo IF. Decreased lesion formation in $CCR2^{-/-}$ mice reveals a role for chemokines in the initiation of atherosclerosis. Nature. 1998; 394:894–897. [PubMed: 9732872]

44. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. Nature. 2002; 420:333–336. [PubMed: 12447443]
45. Ricci R, Sumara G, Sumara I, et al. Requirement of JNK2 for scavenger receptor A-mediated foam cell formation in atherogenesis. Science. 2004; 306:1558–1561. [PubMed: 15567863]
46. Hertzel AV, Bernlohr DA. The mammalian fatty acid-binding protein multigene family: molecular and genetic insights into function. Trends Endocrinol Metab. 2000; 11:175–180. [PubMed: 10856918]
47. Haunerland NH, Spener F. Fatty acid-binding proteins – insights from genetic manipulations. Prog Lipid Res. 2004; 43:328–349. [PubMed: 15234551]
48. Raza H, Pongubala JR, Sorof S. Specific high affinity binding of lipoxygenase metabolites of arachidonic acid by liver fatty acid binding protein. Biochem Biophys Res Commun. 1989; 161:448–455. [PubMed: 2500117]
49. Widstrom RL, Norris AW, Spector AA. Binding of cytochrome P450 monooxygenase and lipoxygenase pathway products by heart fatty acid-binding protein. Biochemistry. 2001; 40:1070–1076. [PubMed: 11170430]
50. Ek BA, Cistola DP, Hamilton JA, et al. Fatty acid binding proteins reduce 15-lipoxygenase-induced oxygenation of linoleic acid and arachidonic acid. Biochim Biophys Acta. 1997; 1346:75–85. [PubMed: 9187305]
51. Zimmer JS, Dyckes DF, Bernlohr DA, Murphy RC. Fatty acid binding proteins stabilize leukotriene A4: competition with arachidonic acid but not other lipoxygenase products. J Lipid Res. 2004; 45:2138–2144. [PubMed: 15342681] An exciting work demonstrating a direct link between FABPs and leukotriene stability. The half life of LTA_4 is stabilized from mere seconds to 20 min in the presence of FABPs.
52. Shen WJ, Sridhar K, Bernlohr DA, Kraemer FB. Interaction of rat hormone-sensitive lipase with adipocyte lipid-binding protein. Proc Natl Acad Sci U S A. 1999; 96:5528–5532. [PubMed: 10318917]
53. Huang H, Starodub O, McIntosh A, et al. Liver fatty acid-binding protein colocalizes with peroxisome proliferator activated receptor alpha and enhances ligand distribution to nuclei of living cells. Biochemistry. 2004; 43:2484–2500. [PubMed: 14992586]
54. Helledie T, Antonius M, Sorensen RV, et al. Lipid-binding proteins modulate ligand-dependent trans-activation by peroxisome proliferator-activated receptors and localize to the nucleus as well as the cytoplasm. J Lipid Res. 2000; 41:1740–1751. [PubMed: 11060343]
55. Tan NS, Shaw NS, Vinckenbosch N, et al. Selective cooperation between fatty acid binding proteins and peroxisome proliferator-activated receptors in regulating transcription. Mol Cell Biol. 2002; 22:5114–5127. [PubMed: 12077340]
56. Kazemi MR, McDonald CM, Shigenaga JK, et al. Adipocyte fatty acid-binding protein expression and lipid accumulation are increased during activation of murine macrophages by Toll-like receptor agonists. Arterioscler Thromb Vasc Biol. 2005; 25:1220–1224. E-pub 10 February 2005. PMID: 15705927. [PubMed: 15705927]
57. Liu QY, Nambi P. Sirolimus upregulates aP2 expression in human monocytes and macrophages. Transplant Proc. 2004; 36:3229–3231. [PubMed: 15686734]
58. Pelton PD, Zhou L, Demarest KT, Burris TP. PPARgamma activation induces the expression of the adipocyte fatty acid binding protein gene in human monocytes. Biochem Biophys Res Commun. 1999; 261:456–458. [PubMed: 10425206]
59. Fu Y, Luo N, Lopes-Virella MF. Oxidized LDL induces the expression of ALBP/aP2 mRNA and protein in human THP-1 macrophages. J Lipid Res. 2000; 41:2017–2023. [PubMed: 11108735]
60. Llaverias G, Noe V, Penuelas S, et al. Atorvastatin reduces CD68, FABP4, and HBP expression in oxLDL-treated human macrophages. Biochem Biophys Res Commun. 2004; 318:265–274. [PubMed: 15110783] In foam cells, this statin reduces aP2 expression.
61. Damcott CM, Moffett SP, Feingold E, et al. Genetic variation in fatty acid-binding protein-4 and peroxisome proliferator-activated receptor gamma interactively influence insulin sensitivity and body composition in males. Metabolism. 2004; 53:303–309. [PubMed: 15015141]

62. Fu Y, Luo N, Lopes-Virella MF, Garvey WT. The adipocyte lipid binding protein (ALBP/aP2) gene facilitates foam cell formation in human THP-1 macrophages. Atherosclerosis. 2002; 165:259–269. [PubMed: 12417276]