A-FABP in Metabolic Diseases

Subjects: Endocrinology & Metabolism | Biochemistry & Molecular Biology
Contributor: Hang-Long Li

Adipocyte fatty acid-binding protein (A-FABP), which is also known as ap2 or FABP4, is a fatty acid chaperone that has been further defined as a fat-derived hormone. It regulates lipid homeostasis and is a key mediator of inflammation. Circulating levels of A-FABP are closely associated with metabolic syndrome and cardiometabolic diseases with imminent diagnostic and prognostic significance. Numerous animal studies have elucidated the potential underlying mechanisms involving A-FABP in these diseases. Recent studies demonstrated its physiological role in the regulation of adaptive thermogenesis and its pathological roles in ischemic stroke and liver fibrosis. Due to its implication in various diseases, A-FABP has become a promising target for the development of small molecule inhibitors and neutralizing antibodies for disease treatment. This review summarizes the clinical and animal findings of A-FABP in the pathogenesis of cardio-metabolic diseases in recent years.

A-FABP   metabolic syndrome   cardiovascular diseases

1. Introduction

Fatty acid-binding proteins (FABPs) belong to the lipocalin family and are a group of 14–15 kDa proteins involved in intracellular lipid homeostasis as well as metabolic and inflammatory pathways.[1][2] They are ubiquitously expressed in body organs/tissues, including the liver, intestine, heart, adipose tissue, epidermis, ileum, brain, myelin, and testis.[2] The isoforms were named according to the expression predominance or the organ where they were first identified. Different isoforms exhibit unique expression patterns and are mostly abundant in tissues involved in lipid metabolism.[1][2] Despite the considerable variation in protein sequences, FABPs share similar tertiary structures: a beta-barrel domain and an internal water-filled cavity, where hydrophobic ligands, such as long-chain fatty acid and eicosanoids, are bound to with high affinity.[3][4] FABPs function as lipid chaperones to transport lipids to specific organelles, such as the endoplasmic reticulum (ER) and mitochondria, within the cell.[1]

Adipocyte-FABP (A-FABP, also referred to aP2 or FABP4) is one of the most abundant cytosolic proteins in adipocytes and is also expressed in macrophages and endothelial cells.[5] Expression of A-FABP is induced during adipocyte differentiation.[6] Functionally, A-FABP regulates lipolysis by activating hormone-sensitive lipase (HSL) and by transporting HSL-derived fatty acids in adipocytes.[7][8] A-FABP is also elevated during the differentiation of monocytes into macrophages.[9] In macrophages, its expression can be induced by fatty acids, lipopolysaccharide (LPS), toll-like receptors (TLRs) agonist,[10] oxidized low-density lipoprotein (oxLDL),[11] and advanced glycation end products (AGEs).[12] A-FABP also promotes cholesterol ester accumulation and foam cell formation.[13][14] In endothelial cells, increased A-FABP induces endothelial dysfunction by modulating endothelial *NO* synthase (eNOS) nitric oxide (NO) signaling.[15] In addition to its intracellular effects, A-FABP is also recognized as a

hormone that is released into the circulation and exerts effects on target tissues, such as adipose tissue and endothelium.[16]

A-FABP contributes to the pathogenesis of a great variety of disorders/diseases, including metabolic syndrome,[17][18][19] atherosclerotic diseases,[20] heart failure,[21] and non-alcoholic steatohepatitis.[22] Recent findings also demonstrated the pathological roles of A-FABP in ischemic stroke and liver fibrosis[23][24] and implicated the potential of A-FABP as a sensitive predictor of the outcome of alcohol-induced acute-on-chronic liver failure.[25] In addition, the involvement of A-FABP in various cancer types, including bladder cancer,[26][27][28][29] prostate cancer,[30][31] breast cancer,[32] ovarian cancer,[33][34] cholangiocarcinoma,[35] hepatocellular carcinoma,[36][37][38] and leukemia[39][40] was also reported.

The potential of targeting A-FABP as a therapeutic strategy was elucidated in animal studies[41][42][43] (**central illustration**), while its clinical therapeutic implications are unclear.[1][44] This review aims to evaluate and summarize the existing evidence of A-FABP in the metabolic syndrome and cardiovascular diseases, and its potential therapeutic implications.

2. Metabolic Syndrome

Metabolic syndrome refers to a cluster of cardiovascular risk factors, including central obesity, insulin resistance, dyslipidemia, and hypertension.[45] A-FABP is a predictive circulating biomarker of components of metabolic syndrome.[17][18] Over the past 5 years, novel discoveries regarding the role of A-FABP in metabolic syndrome have been made (Table 1).

Table 1

Year	Diseases/Conditions	Subjects/Animals/Methods	Main Novel Findings	Reference
Metabolic syndrome				
2016	Type-2 diabetes/Obesity	48 non-obese subjects newly diagnosed with type 2 diabetes; 42 obese subjects newly diagnosed with type 2 diabetes; 30 simple obese subjects; and 30 matched normal subjects	1. Serum A-FABP levels were significantly correlated with HbA1c 2. Serum A-FABP levels correlated with levels of inflammatory cytokines (C-	Niu G et al. [46]

		reactive protein and IL-6) in obese diabetic subjects		
2017	Obesity	22 obese middle-aged men randomized to exercise training group or control group	Exercise training reduced A-FABP concentrations and improved glucose metabolism in obese middle-aged men	Bahrami Abdehgah E et al. [47]
2017	Lipotoxicity/ ER stress/Autophagy	Macrophages isolated from A-FABP knockout mice treated with palmitic acid and/or infected with adenoviruses over-expressing A-FABP	1. Prolonged treatment of palmitic acid enhanced the expression of A-FABP associating with increased endoplasmic reticulum stress and reduced autophagic flux in macrophages 2. A-FABP suppressed PA-induced JAK-dependent autophagy thus promoted ER stress and inflammation in macrophages.	Hoo RL et al. [48]
2017	Adaptive thermogenesis	A-FABP knockout mice were infused with	1. A-FABP levels were increased in both white and	Shu L et al. [49]

		recombinant A-FABP after HFD for 4 weeks	brown adipose tissue in response to thermogenic stimuli 2. A-FABP deficiency impaired adaptive thermogenesis in mice, which were reversed by replenishment of recombinant A-FABP 3. A-FABP induced the expression of type-II iodothyronine deiodinase in brown adipose tissue, promoting the conversion of thyroid hormones from its inactive form T4 to active form T3, thus enhancing thermogenic activity.	
2018	Glucose fluctuation on macrophage inflammation	Human monocytic THP-1 cells were exposed to normal, constant high, or intermittent high glucose	1. Intermittent high glucose induced A-FABP expression and release of pro-inflammatory cytokines. Treatment with constant high	Li H et al. [50]

			glucose showed similar effects but with less evident changes. 2. Inhibition of JNK signalling pathway inhibited glucose-induced A-FABP expression and production of pro-inflammatory cytokines	
2020	Lipolysis/ Pro-inflammation	Adipocytes were co-treated with recombinant A-FABP and A-FABP inhibitor (SB203580/I-9) or vehicle; Male mice were subcutaneous injected with recombinant A-FABP	1. Exogenous treatment of A-FABP resulted in anti-adipogenesis by inducing lipolysis (via p38/HSL signalling) and inflammation (via NF-κB signalling) 2. The pro-inflammatory and pro-lipolytic effects of exogenous A-FABP were reversed by A-FABP inhibitor	Dou HX et al. [51]
CVD				
2016	Cardiovascular mortality	950 male subjects with type 2 diabetes with an average follow-up for 22 years	Higher levels of A-FABP were significantly associated with	Liu G et al. [52]

			higher CVD mortality	
2016	Coronary atherosclerosis	Human macrophages and coronary artery-derived smooth muscle cells and endothelial cells were treated with exogenous A-FABP	1. Exogenous treatment with A-FABP stimulated the inflammatory response in vascular endothelial cells in a dose-dependent manner 2. Serum A-FABP levels were correlated with coronary sinus A-FABP 3. A-FABP in coronary sinus and aortic root independently predicted severity of coronary stenosis	Furuhashi M et al. [53]
2016	Macrophage inflammation	Macrophages from A-FABP knockout or wild-type mice	1. Sirtuin 3 was upregulated in A-FABP deficient macrophages 2. Elevated sirtuin 3 attenuated lipopolysaccharide-induced expression of inflammatory cytokines, inducible nitric oxide	Xu H et al. [54]

			synthase, and cyclo-oxygenase 2		
2016	Heart failure	Cardiomyocyte-specific A-FABP transgenic mice treated with A-FABP inhibitor (BMS309403)	1. Over-expression of A-FABP in cardiomyocytes activated ERK signaling pathway and upregulated the expression of cardiac hypertrophic marker genes 2. Aggravation of cardiac hypertrophy was alleviated with A-FABP inhibitor	Zhang J et al. [55]	
2017	Vascular Injury/ Neointima formation	1. A-FABP deficient mice and relative wild-type mice subjected to wire-induced vascular injury 2. Human coronary artery endothelial cells (HCAECs) and human coronary smooth muscle cells were infected with adenovirus-overexpressing A-FABP or treated with anti-A-FABP antibody.	1. A-FABP deficient mice exhibited decreased neointima formation in response to wire-induced vascular injury. 2. Human coronary artery endothelial cells secreted A-FABP 3. Adenovirus-mediated overexpression of A-FABP in human coronary artery	Fuseya T et al. [56]	

		endothelial cells increased inflammatory cytokines and reduced phosphorylation of nitric oxide synthase 3 4. Ectopic A-FABP increased proliferation and migration of human coronary smooth muscle cells and vascular endothelial dysfunction, which were attenuated by treatment with anti-A-FABP antibody	
2018	Carotid atherosclerosis	281 subjects without medication followed-up for 3 years	1. Serum A-FABP levels were significantly correlated with CIMT 2. Yearly changes in CIMT were positively associated with baseline levels of A-FABP	Furuhashi M et al. [57]
2017	Acute ischemic stroke	737 patients with acute ischemic stroke	1. A-FABP levels were associated with poor functional	Tu WJ et al. [58]

		outcome and mortality	
		2. Addition of A-FABP improved the prognostic accuracy of National Institutes of Health Stroke Scale score	
2020	Ischemic stroke	30 patients with acute ischemic stroke; A-FABP knockout or wild-type mice subjected to middle cerebral artery occlusion;	1. A-FABP levels were correlated with cerebral infarct volume and levels of matrix metalloproteinases-9 in patients with ischemic stroke 2. Ischemia-induced elevation of A-FABP in macrophages and microglial cells contributed to degradation of tight junction proteins and blood-brain barrier leakage by inducing metalloproteinases-9 expression	Liao B et al. [23]
2020	Heart failure; atherosclerotic cardiovascular diseases	176 patients with type 2 diabetes without established CVD followed-up for 28 months	1. A-FABP levels at baseline was associated with the development of left	Wu MZ et al. [59]

		ventricular hypertrophy and diastolic dysfunction 2. A-FABP levels at baseline predicted the development of major adverse cardiovascular events (composite of cardiovascular death, hospitalization for heart failure, non-fatal myocardial infarction, and stroke)	
2020	Metabolic syndrome; coronary artery disease	37 metabolic syndrome patients undergoing coronary artery bypass grafting (CABG) for underlying coronary artery disease and 23 patients without CAD undergoing heart valve surgery (control group)	1. A-FABP mRNA expression in epicardial adipose tissue was significantly elevated in patients with metabolic syndrome and coronary artery disease 2. The extent of coronary atherosclerosis was significantly associated with the level of expression of A-FABP mRNA in epicardial adipose tissue	Gormez et al. [60]

| 2021 | Heart failure | 50 patients with heart failure with preserved ejection fraction and 150 patients with elevated cardiometabolic risk | 1. A-FABP levels were associated with important hemodynamic indices, including higher central systolic and diastolic blood pressures

2. Compared to central hemodynamic information alone, the addition of A-FABP levels improved HF risk classification | Yen et al. [61] |

Abbreviations used in Table 1: A-FABP, adipocyte-fatty acid binding protein; HbA1c, glycated hemoglobin 1c; IL-6, interleukin-6; ER, endoplasmic reticulum; HFD, high-fat diet; CVD, cardiovascular disease; CIMT, carotid intima-media thickness.

2.1 Central Obesity

Central obesity, characterized by excessive accumulation of fat, especially in the abdominal region, resulting from a prolonged positive energy imbalance,[62] is the major risk factor of cardiovascular diseases (CVD).[62] Obesity is a chronic low-grade inflammatory state in which dysfunctional adipose tissue disrupts metabolic homeostasis through altering the secretion of cytokines and hormones, such as A-FABP, and impairing the metabolism of non-esterified fatty acid (NEFA).[62][63]

Xu et al. were among the first to show that circulation A-FABP levels were significantly higher in obese than in lean subjects.[17][18] A-FABP was positively correlated with indicators of adiposity, including body mass index (BMI), fat percentage, waist circumference, and waist-to-hip ratio.[17][18][64][65][66][67] A recent study identified that the higher serum A-FABP was negatively associated with the sensitivity to the thyroid hormone, which suggested that A-FABP may mediate the "cross-talk" between adipose tissue and the thyroid system.[68] In obese patients with concomitant

type 2 diabetes, A-FABP levels were further elevated and significantly correlated with levels of inflammatory cytokines, including C-reactive protein and interleukin-6 (IL-6).[46] In a cohort of obese women, a positive correlation between A-FABP and tumor necrosis factor (TNF) receptors was identified.[69] This evidence indicates the crucial role of A-FABP in mediating a pro-inflammatory state in obesity.

In addition to the clinical studies, animal and in vitro studies further revealed the sophisticated role of A-FABP in adipose tissue. In diet-induced or genetic models of obesity, A-FABP-deficient mice exhibited higher adiposity while they were more "metabolically healthy" with improved glucose and lipid metabolism[70][71] when compared to their wild-type littermates. Knockdown of A-FABP using the RNA interference technique also enhanced high-fat diet–induced body weight in mice, but the improvement in glucose metabolism was not observed possibly due to a partial knockdown of A-FABP using RNA interference compared to A-FABP knockout.[72] The increased susceptibility to diet-induced obesity despite protection against the development of insulin resistance might be attributed to the reduced lipolysis efficiency and improved insulin secretory response in A-FABP-deficient mice.[8][73] [74] Without altering the fatty influx/esterification and the expression of lipolysis-related proteins, A-FABP-deficient adipocytes exhibited diminished lipolysis and attenuated FFA efflux under basal condition or stimulation of isoproterenol or dibutyryl-cAMP.[73][74] Mechanistically, by interacting with hormone-sensitive lipase (HSL), the critical enzyme of lipolysis, A-FABP facilitates the out-trafficking of HSL-derived fatty acids, thus preventing the feedback inhibition of HSL by high FFA levels within cells.[8] This mechanism implicated the beneficial physiological effect of A-FABP in the context of starvation, which facilities lipid utilization. However, under obese conditions, the abundant A-FAPB provokes lipolysis leading to ectopic accumulation of lipids in other organs.[75] A-FABP-deficient mice also exhibited impaired insulin secretion in response to beta-adrenergic stimulation,[74] whereas A-FABP was demonstrated to regulate the FFA metabolism by altering the composition (reduction in both stearic and cis-11-eicoseneic acids and an increase in palmitoleic acid), thereby modulating the adipo-pancreatic axis-mediated insulin secretion.[74]

In addition to the studies using A-FABP-deficient mice/adipocytes, treatment recombinant of A-FABP protein also demonstrates its role in regulating lipolysis and inflammatory response. During differentiation of 3T3L1 preadipocytes to adipocytes, exogenous treatment of A-FABP inhibited the accumulation of lipids and suppressed the transcription of adipogenic marker genes, including PPARγ, C/EBPα, adiponectin, and A-FABP itself. On the other hand, the enhanced lipolysis was evidenced by the elevated levels of adipose triglyceride lipase (ATGL) and phosphorylated HSL (pHSL), the hallmark of lipolysis regulation.[51] Moreover, upregulation of MCP-1, TNFα, and IL-6 in adipocytes upon A-FABP treatment further implicates the role of A-FABP in pro-inflammatory response.[51] Mechanistically, A-FABP regulates lipolysis and inflammatory response through activation of p38/HSL and p38/NF-kB signaling pathways, respectively.[51] This study for the first time implicated the direct negative feedback regulation of adipocyte-derived A-FABP on adipose tissue expansion as well as its role in the initiation of adipose tissue inflammation.

Numerous studies have demonstrated the beneficial effect of enhanced adaptive thermogenesis in improving whole-body metabolism and body weight loss.[76] A-FABP was shown to stimulate adaptive thermogenesis.[49] On one hand, circulating A-FABP transports FFA to brown adipocytes as an energy substrate for FFA oxidation. On the

other hand, without altering the activity of sympathetic nervous system, A-FABP regulates the conversion of inactive thyroxine (T4) to active triiodothyronine (T3) in brown adipose tissue (BAT) by inducing the expression of enzyme type II iodothyronine deiodinase through promoting the proteasomal degradation of LXRα,[49] which is a crucial step in the activation of BAT-mediated thermogenesis.[77] Furthermore, replenishment with recombinant A-FABP increased whole-body energy expenditure by 1.5-folds in A-FABP-deficient mice when compared to those treated with vehicles.[49] This study emphasized the physiological role of circulating A-FABP in BAT-mediated adaptive thermogenesis implicating that systematic inhibition of A-FABP in treating obesity-related disorders might cause adverse effects and the tissue-specific function of A-FABP warrants further investigation.

2.2 Insulin Resistance

Insulin resistance refers to the impaired response of targeted cells to insulin action. Among the risk factors, obesity is the most critical one, as the aberrant release of adipose tissue-derived NEFA, glycerol, adipokines, and proinflammatory cytokines contribute to insulin resistance and eventually causes pancreatic β-cell dysfunction.[78]

Clinical studies identified strong positive correlations between A-FABP, insulin resistance, and type 2 diabetes,[17][18][22][65][66][67][79][80][81][82] suggesting A-FABP as a biomarker of insulin resistance. Carriers of genetic variant (rs77878271) of T-87C polymorphism in the functional promoter of A-FABP gene with reduced A-FABP expression had a lower risk of developing type 2 diabetes.[83] A study investigating the effects of exercise training on insulin resistance in middle age obese men also showed that improvement in glucose metabolism was significantly correlated with reduction in circulating A-FABP.[47]

Animal studies also supported that A-FABP acts as a mediator of insulin resistance. In the context of DIO, A-FABP-deficient mice showed improvement in insulin sensitivity and glucose-stimulated insulin secretion.[70][84][85] The protection against the development of insulin resistance by A-FABP deficiency could be attributed to several mechanisms. A-FABP deficiency generates a lipid environment that is highly favorable for insulin action: mice lacking A-FABP had altered lipid composition in muscular tissue (upregulation of shorter chain [12:0 and 14:0] fatty acids, and downregulation of longer chain [16:0 and 18:0] fatty acids), leading to an upregulation in insulin-stimulated phosphorylation of Akt and protecting against high-fat-induced insulin resistance, thus enhancing the insulin signaling cascade.[84] The basal level and leptin-stimulated activity of AMP-K-α1, an important energy sensor in muscular tissue, were also elevated in A-FABP-deficient mice when compared to wild-type mice.[84] Furthermore, A-FABP-deficient DIO mice not only exhibited attenuation in beta-adrenergic-stimulated lipolysis[74][85] but also shown reduced secretion of inflammatory cytokines, such as TNFα,[70] when compared to their relative controls. The treatment of human THP-1 macrophages with intermittent high glucose stimulated the expression of A-FABP, which subsequently mediated inflammatory cytokine (TNF-α and IL-1β) secretion through activating TLR4/p-JNK signaling cascade,[50] which implicates the additional regulatory effect of A-FABP on inflammation in response to glucose fluctuation under insulin resistance.

2.3 Dyslipidemia

Dyslipidemia includes increased low-density lipoproteins (LDLs), decreased high-density lipoproteins (HDLs), and increased fasting and postprandial triglyceride (TG)-rich lipoproteins (very-low-density lipoproteins [VLDL] and chylomicrons).[86][87] The mechanism through which dyslipidemia develops is closely related to insulin resistance, [88] as unrestrained lipolysis leads to an increased hepatic flux of FFA, contributing to increased hepatic TG, hence VLDL production.[89][90] Lipid overload in non-adipose tissues causes cellular dysfunction and apoptotic cell death, leading to lipotoxicity.[91] Clinical studies have shown a positive correlation of A-FABP with hypertriglyceridemia and LDL, as well as an inverse correlation with HDL.[17][18][65][66][67][79][81][83]

Aside from the effects of A-FABP on lipolysis, it also potentiates dyslipidemia-related lipotoxicity and chronic inflammation. In macrophages, A-FABP promotes toxic lipid-induced ER stress, leading to the exaggeration of inflammation via suppressing Janus kinase (JAK) 2-dependent autophagy.[48] Palmitic acid-mediated elevation of A-FABP in macrophages downregulated the autophagy-related protein 7, leading to the suppression of autophagy and increase of ER stress.[48] On the contrary, in A-FABP deficient macrophages, the phagocytic activity was significantly higher, the LPS-INFγ-induced M1 macrophage polarization was attenuated, while the IL4-induced M2 markers were markedly enhanced.[48] These findings implicate that A-FABP is a critical player in lipotoxicity-related inflammatory disorders.

2.4 Hypertension

Hypertension is defined as a prolonged period of high blood pressure with systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg.[92] Multiple mechanisms, including endothelial dysfunction, endothelin-1 overexpression due to dysregulated secretion of adipokines,[93][94] and the associated unrestricted vasoconstriction,[95] contribute to the development of hypertension. Other contributory mechanisms include the anti-natriuretic effect of insulin,[96][97] a positive feedback loop between an upregulated renin–angiotensin system and an overactive sympathetic nervous system[98][99] as well as a dysregulated autonomic nervous system–associated volume overload. A-FABP was identified to be a key mediator in these pathophysiological pathways involved in the development of hypertension, including being associated with endothelial dysfunction through mediating endothelial nitric oxide pathways[100] as well as activation of the sympathetic nervous system.[101] Indeed, ample human evidence has demonstrated the correlation between A-FABP and blood pressure. Circulating levels of A-FABP are positively correlated with systolic/diastolic blood pressure.[17][18][67][79] Ota et al. further identified that increased circulating A-FABP was associated with increased blood pressure, and the elevation of A-FABP was predisposed by a family history of hypertension.[81]

3. Cardiovascular Diseases

Cardiovascular disease (CVD), including myocardial infarction (MI), stroke, and peripheral vascular disease, are the leading causes of death worldwide.[102] Atherosclerosis is the predominant cause of these medical conditions. [103] In multiple long-term follow-up studies of various patient cohorts, circulating levels of A-FABP were shown to

predict the development of CVD and cardiovascular mortality.[52][79][104][105] The important findings on the role of A-FABP in CVD in recent years are summarized in Table 1.

3.1 Atherosclerosis

Atherosclerosis is characterized by the narrowing/hardening of arteries caused by the buildup of plaque, which is made up of substances, including fats and cholesterol.[103] Risk factors, such as endothelial dysfunction, dyslipidemia, hypertension, and type 2 diabetes, contribute to the pathogenesis of atherosclerosis.[106][107] The mechanisms through which atherosclerosis develops are manifold. Mechanistically, endothelial dysfunction-associated reduction of nitric oxide (NO) production, generation of reactive oxidative species (ROS), and increase in oxLDL trigger an inflammatory response, thus leading to atherosclerosis.[15] Apart from metabolic risk factors, smoking is also another major contributory factor for the development of atherosclerosis through multiple mechanisms, including promoting the formation of ROS, causing endothelial dysfunction, and inducing a systemic inflammatory state.[108] Indeed, A-FABP has been implicated in the development of endothelial dysfunction through mediating production of nitric oxide as well as systemic inflammation.[100] Although no prior studies have comprehensively evaluated the association between A-FABP and cigarette smoking, A-FABP levels were found to be higher among women exposed to polycyclic aromatic hydrocarbons, a major constituent in cigarettes that triggers an inflammatory reaction.[109]

Human studies have shown a strong association between A-FABP and atherosclerotic conditions (Table 2). Circulating levels of A-FABP are closely associated with carotid intima-media thickness (CIMT), a well-established marker of atherosclerosis.[57][110][111] In Chinese cohorts, serum A-FABP levels were independently associated with CIMT in women but not in men,[110][111] which might be due to lower levels of A-FABP in men. Higher basal levels of A-FABP were also associated with larger changes in CIMT, suggesting that A-FABP predicts the progression of atherosclerosis.[57] Moreover, expression of A-FABP was elevated in carotid plaques in patients with CVD and was associated with plaque vulnerability.[112][113] Patients with higher baseline levels of A-FABP had an increased risk of subclinical atherosclerosis in a cohort of Chinese patients.[114] A recent study also showed a significant association between A-FABP expression levels in epicardial adipose tissue and the extent of coronary atherosclerosis in patients with metabolic syndrome and coronary artery disease (CAD).[60] On the contrary, patients with T-83C polymorphism exhibited lower A-FABP expression in carotid plaques and adipose tissue, had a lower prevalence of carotid plaques, reduced CIMT, and a reduced risk of developing CAD and MI.[83][113] By using coronary thrombectomy specimens from patients with acute myocardial and autopsy coronary artery and specimens from patients with ischemic heart disease, the elevated expression of A-FABP was identified in macrophages within atherosclerotic lesions and epicardial/perivascular adipocytes.[53]

Table 2. Summary of human studies showing an association between adipocyte-fatty acid binding protein (A-FABP) and atherosclerotic cardiovascular disease.

Published Year	Cohort	Country	Follow-Up	Main Findings	Conclusion	Reference

			Years			
2007	479 subjects	China	/	1. Serum A-FABP levels were higher in women than in men 2. Serum A-FABP levels were positively correlated with CIMT in both sexes, but an independent association was only observed in women 3. Serum A-FABP levels were independently associated with age and hypertension in women	A-FABP levels are independently associated with carotid atherosclerosis in women	Yeung DC et al. [110]
2010	125 subjects with CAD and 120 control subjects	Japan	/	1. CAD patients had higher A-FABP levels compared to controls 2. Serum A-FABP levels were independently associated with plaque volume in CAD patients	Increased serum A-FABP is significantly associated with a greater coronary plaque burden	Miyoshi T et al. [20]

				3. Serum A-FABP levels were positively correlated with BMI, IL-6, and hsCRP, and were negatively correlated with HDL-cholesterol and serum adiponectin in CAD patients		
2013	1847 subjects without previous CVD	China	12 years	1. Higher baseline levels of A-FABP were associated with development of CVD 2. Addition of A-FABP to the traditional risk factor model improved the predictive performance	Circulating A-FABP level independently predicts the development of CVD	Chow WS et al. [79]
2013	104 overweight/obese women (BMI ≥ 25 kg/m^2) and 76 age-matched healthy controls (BMI < 25 kg/m^2)	Poland	/	1. A-FABP concentration was correlated with insulin resistance 2. A-FABP was an independent predictor of	A-FABP is a predictor of atherogenic risk profile	Mankowska-Cyl A et al. [82]

				triglyceride and HDL-cholesterol 3. A-FABP discriminated overweight/obese patients from healthy individuals	
2014	2253 CVD-free subjects with normal glucose tolerance	China	/	A-FABP levels correlated with CIMT in men and in women (both premenopausal and postmenopausal), but an independent association was only observed in women	Serum A-FABP levels are independently associated with subclinical atherosclerosis in pre- and post-menopausal women with normal glucose tolerance	Hao Y et al. [111]
2018	170 subjects with newly diagnosed type 2 diabetes	China	8 years	Patients with higher baseline levels of A-FABP had an increased risk of developing subclinical atherosclerosis at 8 years	Circulating A-FABP levels independently predict the development of subclinical atherosclerosis in type 2 diabetes patients	Xiao Y et al. [114]
2018	281 subjects without medication	Japan	3 years	1. Serum A-FABP levels were significantly	A-FABP concentration is an	Furuhashi M et al. [57]

				correlated with CIMT 2. Yearly changes in CIMT were positively associated with baseline levels of A-FABP	independent predictor of the progression of carotid atherosclerosis	
2020	176 patients with type 2 diabetes without established CVD followed-up for 28 months	China	28 months	1. A-FABP levels at baseline was associated with the development of left ventricular hypertrophy and diastolic dysfunction 2. A-FABP levels at baseline predicted the development of major adverse cardiovascular events (composite of cardiovascular death, hospitalization for heart failure, non-fatal myocardial infarction, and stroke)	A-FABP is able to predict adverse cardiovascular outcomes in diabetic patients	Wu MZ et al. [59]

Abbreviations used in Table 2: A-FABP, adipocyte-fatty acid binding protein; CIMT, carotid intima-media thickness; CAD, coronary artery disease; BMI, body mass index; IL-6, Interleukin-6; hsCRP, high-sensitive C-reactive protein; HDL, high-density lipoprotein; CVD, cardiovascular disease.

Animal studies showed that A-FABP mediates the pathogenesis of atherosclerosis via inducing endothelial dysfunction, [15][100] vascular smooth muscle cell invasion,[53][56][115] foam cell formation,[11][100] and inflammatory response.[13][115] On the contrary, A-FABP deficiency in apolipoprotein E (ApoE)–deficient mice protected against atherosclerosis[9][116][117] and even high-fat diet–induced advanced atherosclerosis[118].

In ApoE$^{-/-}$ mice, who developed atherosclerotic plaques spontaneously, the presence of A-FABP was observed in the aortic endothelium from 12 weeks, while pharmacological inhibition of A-FABP by BMS309403 significantly improved endothelial function through rescuing the eNOS-NO signaling pathway.[15] Consistent with in vivo studies, lipid-induced elevation of A-FABP in human microvascular endothelial cells was accompanied with reduced phosphorylated eNOS and NO production, which was reversed upon BMS309403 treatment.[15] A-FABP was also induced in endothelial cells of the hyperplastic neointima of mice subjected to wire-induced vascular injury.[56] In human coronary artery endothelial cells (HCAECs), A-FABP expression was induced upon vascular endothelial growth factor (VEGF) or hydrogen peroxide (H_2O_2) treatment.[56] Adenovirus-mediated A-FABP overexpression inhibited the VEGF or insulin-stimulated eNOS phosphorylation and induced pro-inflammatory cytokine/adhesion molecules expression.[56] In human vascular endothelial cells (HUVECs), exogenous treatment of recombinant A-FABP (rA-FABP) also reduced the level of phosphorylated eNOS.[53] Upon palmitic acid treatment, rA-FABP not only further reduced the p-eNOS, but also upregulated the expression of pro-inflammatory cytokines, including MCP-1, IL-6, and TNFα.[53] Moreover, r-A-FABP treatment impaired the insulin-mediated eNOS pathway in vascular endothelial cells by inhibiting insulin receptor substrate 1 (IRS1) and Akt activation,[100] which implicates the mechanistic linkage between circulating A-FABP and endothelial cell dysfunction in diabetes. Furthermore, rA-FABP stimulated cell proliferation and migration of human coronary artery smooth muscle cells (HCASMCs) through upregulating cell cycle regulations (cyclin D1, CCL2, and MMP2) via activating c-jun and c-myc in a MAPK-dependent manner.[116] It also induced pro-inflammatory cytokine expression in HCASMCs.[53][56][115]

A-FABP plays a critical role in foam cell formation and the subsequent development of cholesterol-rich lesions. In ApoE$^{-/-}$ mice with macrophage-specific A-FABP deficiency, the reduction in atherosclerotic lesions was comparable with ApoE$^{-/-}$ mice with global A-FABP deficiency, suggesting the independent role of macrophage A-FABP in the pathogenesis of atherosclerosis.[9] In macrophages, A-FABP is induced by LPS[9][13][14] through activating JNK-c-Jun signaling[13] and oxLDL via activating NF-κB and PKC signaling pathways and PPARγ.[11][117] A-FABP-deficient macrophages not only exhibited a reduced capacity for inflammatory cytokine production[9][14] but also showed reduced total cholesterol and cholesterol ester content, due to accelerated cholesterol efflux.[14] A-FABP regulates cholesterol trafficking through mediating the PPARγ-LXRα-ABCA1 pathway.[14]

In addition, A-FABP promotes atherosclerosis by mediating inflammatory responses in macrophages, T cells, and dendritic cells.[13][115] A-FABP-deficient mice exhibited a significantly reduced expression of inflammatory cytokines[119] and inflammasome activation.[54][120] In macrophages, A-FABP mediates the inflammatory response induced by various stimulators. In response to LPS, A-FABP forms a positive feedback loop with JNK/AP-1, thereby upregulating the expression of inflammatory cytokines in macrophages.[13] On the other hand, in response

to LPS or CD154 stimulation, A-FABP activates the IκB/NF-κB pathway, thus inducing the inflammatory activity of macrophages.[14] Upon the stimulation of palmitic acid, elevated A-FABP provoked the toxic lipid-induced ER stress via inhibiting the JAK2-dependent autophagy, which in turn triggered M1 macrophage polarization and the inflammatory cytokine expression.[48] In response to intermittent high glucose treatment, the activation of TLR4/p-JNK cascade upregulated both A-FABP expression and inflammatory cytokine secretion, which implicates that A-FABP might also be involved in the glucose fluctuation-associated inflammatory response.[50] A-FABP also activates the IκB/NF-κB pathway in T cells and dendritic cells, thus inducing inflammatory cytokine secretion.[115]

3.2 Ischemic Stroke

A-FABP has long been implicated in the progression and severity of ischemic stroke (IS). There is concrete evidence showing the association between A-FABP and the risk factors/poor prognostic markers of ischemic stroke, such as type 2 diabetes, hypertension, dyslipidemia, arterial stiffness, higher levels of high-sensitivity C-reactive protein, and cerebral embolization from carotid atherosclerosis.[17][121][122][123] Circulating A-FABP levels are elevated after acute ischemic stroke and are positively correlated with early death and poor functional outcome.[58][124]

A recent finding demonstrated that A-FABP mediates the ischemia-induced blood–brain barrier (BBB) disruption, contributing to cerebral ischemia injury.[23] Briefly, by using middle cerebral artery occlusion (MCAO)–induced ischemic stroke model, researchers identified the elevation of A-FABP in peripheral monocytes and microglia.[23] Mechanistically, on one hand, via activating the JNK/c-Jun signaling cascade, A-FABP upregulates the expression of matrix metalloproteinase-9 (MMP-9) in bone marrow-derived macrophage (BMDM). BMDM-derived MMP-9 degrades the extracellular matrix and tight junction proteins of the BBB and allows the infiltration of blood-borne immune cells into the brain.[23] Elevated A-FABP also enhances the production of inflammatory cytokines from microglia, which further provoke ischemic injury. The upregulation of cytokines, such as TNFα and IL-1β, might also induce MMP-9 expression.[125] All these factors lead to post-ischemic inflammation and poor functional recovery.[23][126][127]

3.3 Heart Failure

Heart failure is a chronic syndrome representing the inability of the heart to pump sufficient blood to meet the oxygen demand of the body.[128] Coronary atherosclerosis and components of metabolic syndrome are the risk factors contributing to left ventricular systolic/diastolic dysfunction, increasing the risk of heart failure.[128]

Human studies have identified an association between A-FABP and various cardiac abnormalities that predispose heart failure. Circulating A-FABP levels were associated with myocardial perfusion abnormalities,[129] positively correlated with left ventricular mass and hypertrophy[126][127] and were strongly correlated with N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), a well-established biomarker of heart failure.[130] Circulating A-FABP was identified as an independent risk factor in left ventricular dysfunction [21][131] and a 10-year prospective study of over 4000 patients showed that A-FABP levels predicted the development of heart failure.[132] A recent study identified that A-FABP levels predicted the development of left ventricular hypertrophy, diastolic dysfunction, and adverse cardiovascular events in patients with type 2 diabetes without established cardiovascular diseases in a

median follow-up duration of 28 months.[59] Further, another recent study identified a significant association between A-FABP levels and key hemodynamic indices and showed that the accuracy of HF risk classification models could be improved by incorporating A-FABP levels.[61] Thus, A-FABP has been proposed as a biomarker and predictor for heart failure.[133]

In animal studies, several mechanisms linking A-FABP and heart failure have been proposed. A-FABP exhibits cardio-depressant properties, as it suppresses myocardial contractility, contributing to systolic dysfunction.[134][135] Without modulating the action potential duration and the L-type Ca^{2+} channel activity, adipocyte-derived A-FABP represses the cardio-depressant activity in a dose-dependent manner.[134] Specifically, the N-terminal of A-FABP confers cardio-depressive properties.[134] The mechanism of cardio-depressant effects may be related to the fact that fatty acids are the main energy source for cardiomyocytes and that A-FABP binds fatty acid with high affinity, thus disrupting energy supply and contractile function.[136] The overexpression of A-FABP exacerbated pressure-induced heart hypertrophy in mice by upregulating the expression of cardiac hypertrophic marker genes, while treatment with BMS309403 reversed the condition.[55] A-FABP deficiency also attenuated ischemia/reperfusion-induced myocardial injury and improved left ventricular function in mice.[137]

References

1. Masato Furuhashi; Gökhan S. Hotamisligil; Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets. *Nature Reviews Drug Discovery* **2008**, *7*, 489-503, 10.1038/nrd2589.

2. Rebecca L Smathers; Dennis R Petersen; The human fatty acid-binding protein family: Evolutionary divergences and functions. *Human Genomics* **2011**, *5*, 170-91, 10.1186/1479-7364-5-3-170.

3. A. W. Zimmerman; J. H. Veerkamp; New insights into the structure and function of fatty acid-binding proteins. *Cellular and Molecular Life Sciences* **2002**, *59*, 1096-1116, 10.1007/s00018-002-8490-y.

4. Agata Chmurzyńska; The multigene family of fatty acid-binding proteins (FABPs): Function, structure and polymorphism. *Journal of Applied Genetics* **2006**, *47*, 39-48, 10.1007/bf03194597.

5. B M Spiegelman; H Green; Control of specific protein biosynthesis during the adipose conversion of 3T3 cells.. *Journal of Biological Chemistry* **1980**, *255*, 8811-18.

6. Masato Furuhashi; Shigeyuki Saitoh; Kazuaki Shimamoto; Tetsuji Miura; Fatty Acid-Binding Protein 4 (FABP4): Pathophysiological Insights and Potent Clinical Biomarker of Metabolic and Cardiovascular Diseases. *Clinical Medicine Insights: Cardiology* **2014**, *8s3*, CMC.S17067-33, 10.4137/cmc.s17067.

7. Anne J. Smith; Mark A. Sanders; Brittany E. Juhlmann; Ann V. Hertzel; David A. Bernlohr; Mapping of the Hormone-sensitive Lipase Binding Site on the Adipocyte Fatty Acid-binding

Protein (AFABP). *Journal of Biological Chemistry* **2008**, *283*, 33536-33543, 10.1074/jbc.m806732 200.

8. Wen-Jun Shen; Kunju Sridhar; David A. Bernlohr; Fredric Kraemer; Interaction of rat hormone-sensitive lipase with adipocyte lipid-binding protein. *Proceedings of the National Academy of Sciences* **1999**, *96*, 5528-5532, 10.1073/pnas.96.10.5528.

9. Liza Makowski; Jeffrey B. Boord; Kazuhisa Maeda; Vladimir R. Babaev; K. Teoman Uysal; Maureen A. Morgan; Rex A. Parker; Jill Suttles; Sergio Fazio; Gökhan S. Hotamisligil; et al.MacRae F. Linton Lack of macrophage fatty-acid–binding protein aP2 protects mice deficient in apolipoprotein E against atherosclerosis. *Nature Medicine* **2001**, *7*, 699-705, 10.1038/89076.

10. Mahmood R. Kazemi; Carol M. McDonald; Judy K. Shigenaga; Carl Grunfeld; Kenneth R. Feingold; Adipocyte Fatty Acid–Binding Protein Expression and Lipid Accumulation Are Increased During Activation of Murine Macrophages by Toll-Like Receptor Agonists. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2005**, *25*, 1220-1224, 10.1161/01.atv.0000159163.52632.1b.

11. Y Fu; N Luo; M F Lopes-Virella; Oxidized LDL induces the expression of ALBP/aP2 mRNA and protein in human THP-1 macrophages.. *Journal of Lipid Research* **2000**, *41*, 2017-2023.

12. Xiao Qun Wang; Ke Yang; Yu Song He; Lin Lu; Wei Feng Shen; Receptor Mediated Elevation in FABP4 Levels by Advanced Glycation End Products Induces Cholesterol and Triacylglycerol Accumulation in THP-1 Macrophages. *Lipids* **2011**, *46*, 479-486, 10.1007/s11745-011-3542-4.

13. Xiaoyan Hui; Huiying Li; Zhiguang Zhou; Karen S. L. Lam; Yang Xiao; Donghai Wu; Ke Ding; Yu Wang; Paul M. Vanhoutte; Aimin Xu; et al. Adipocyte Fatty Acid-binding Protein Modulates Inflammatory Responses in Macrophages through a Positive Feedback Loop Involving c-Jun NH2-terminal Kinases and Activator Protein-1*. *Journal of Biological Chemistry* **2010**, *285*, 10273-10280, 10.1074/jbc.m109.097907.

14. Liza Makowski; Katherine C. Brittingham; Joseph M. Reynolds; Jill Suttles; Gökhan S. Hotamisligil; The Fatty Acid-binding Protein, aP2, Coordinates Macrophage Cholesterol Trafficking and Inflammatory Activity. *Journal of Biological Chemistry* **2005**, *280*, 12888-12895, 10. 1074/jbc.m413788200.

15. Mary Yk Lee; Huiying Li; Yang Xiao; Zhiguang Zhou; Aimin Xu; Paul M Vanhoutte; Chronic administration of BMS309403 improves endothelial function in apolipoprotein E-deficient mice and in cultured human endothelial cells. *British Journal of Pharmacology* **2011**, *162*, 1564-1576, 10.11 11/j.1476-5381.2010.01158.x.

16. Gökhan S. Hotamisligil; David A. Bernlohr; Metabolic functions of FABPs—mechanisms and therapeutic implications. *Nature Reviews Endocrinology* **2015**, *11*, 592-605, 10.1038/nrendo.201 5.122.

17. Aimin Xu; Yu Wang; Jian Yu Xu; David Stejskal; Sidney Tam; Jialiang Zhang; Nelson M. S. Wat; Wai Keung Wong; Karen S. L. Lam; Adipocyte Fatty Acid–Binding Protein Is a Plasma Biomarker Closely Associated with Obesity and Metabolic Syndrome. *Clinical Chemistry* **2006**, *52*, 405-413, 10.1373/clinchem.2005.062463.

18. Aimin Xu; Annette W.K. Tso; Bernard M.Y. Cheung; Yu Wang; Nelson M.S. Wat; Carol H.Y. Fong; Dennis C.Y. Yeung; Edward D. Janus; Pak C. Sham; Karen S.L. Lam; et al. Circulating Adipocyte–Fatty Acid Binding Protein Levels Predict the Development of the Metabolic Syndrome. *Circulation* **2007**, *115*, 1537-1543, 10.1161/circulationaha.106.647503.

19. Annette W.K. Tso; Aimin Xu; Pak C. Sham; Nelson M.S. Wat; Y. Wang; Carol H.Y. Fong; Bernard M.Y. Cheung; Edward D. Janus; Karen S.L. Lam; Serum Adipocyte Fatty Acid Binding Protein as a New Biomarker Predicting the Development of Type 2 Diabetes: A 10-year prospective study in a Chinese cohort. *Diabetes Care* **2007**, *30*, 2667-2672, 10.2337/dc07-0413.

20. Toru Miyoshi; Go Onoue; Atsushi Hirohata; Satoshi Hirohata; Shinichi Usui; Kazuyoshi Hina; Hiroshi Kawamura; Masayuki Doi; Kengo Fukushima Kusano; Shozo Kusachi; et al.Yoshifumi Ninomiya Serum adipocyte fatty acid-binding protein is independently associated with coronary atherosclerotic burden measured by intravascular ultrasound. *Atherosclerosis* **2010**, *211*, 164-169, 10.1016/j.atherosclerosis.2010.01.032.

21. Takahiro Fuseya; Masato Furuhashi; Satoshi Yuda; Atsuko Muranaka; Mina Kawamukai; Tomohiro Mita; Shutaro Ishimura; Yuki Watanabe; Kyoko Hoshina; Marenao Tanaka; et al.Kohei OhnoHiroshi AkasakaHirofumi OhnishiHideaki YoshidaShigeyuki SaitohKazuaki ShimamotoTetsuji Miura Elevation of circulating fatty acid-binding protein 4 is independently associated with left ventricular diastolic dysfunction in a general population. *Cardiovascular Diabetology* **2014**, *13*, 1-9, 10.1186/s12933-014-0126-7.

22. Young-Choon Kim; Yong-Kyun Cho; Won-Young Lee; Hong-Joo Kim; Jung-Ho Park; Dong Il Park; Chong-Il Sohn; Woo-Kyu Jeon; Byung-Ik Kim; Se-Eun Park; et al. Serum adipocyte-specific fatty acid-binding protein is associated with nonalcoholic fatty liver disease in apparently healthy subjects. *The Journal of Nutritional Biochemistry* **2011**, *22*, 289-292, 10.1016/j.jnutbio.2010.02.007.

23. Boya Liao; Leiluo Geng; Fang Zhang; Lingling Shu; Ling Wei; Patrick K K Yeung; Karen S L Lam; Sookja K Chung; Junlei Chang; Paul M Vanhoutte; et al.Aimin XuKai WangRuby L C Hoo Adipocyte fatty acid-binding protein exacerbates cerebral ischaemia injury by disrupting the blood–brain barrier. *European Heart Journal* **2020**, *41*, 3169-3180, 10.1093/eurheartj/ehaa207.

24. Xiaoping Wu; Lingling Shu; Zixuan Zhang; Jingjing Li; Jiuyu Zong; Lai Yee Cheong; Dewei Ye; Karen S. L. Lam; Erfei Song; Cunchuan Wang; et al.Aimin XuRuby L. C. Hoo Adipocyte Fatty Acid Binding Protein Promotes the Onset and Progression of Liver Fibrosis via Mediating the Crosstalk

between Liver Sinusoidal Endothelial Cells and Hepatic Stellate Cells. *Advanced Science* **2021**, *8*, 2003721, 10.1002/advs.202003721.

25. Anand V. Kulkarni; Mithun Sharma; Pramod Kumar; Venu Simhadri; Tirumalige R. Sowmya; Sasikala Mitnala; Duvvuru Nageshwar Reddy; Padaki Nagaraja Rao; Adipocyte Fatty Acid–Binding Protein as a Predictor of Outcome in Alcohol-induced Acute-On-Chronic Liver Failure. *Journal of Clinical and Experimental Hepatology* **2021**, *11*, 201-208, 10.1016/j.jceh.2020.07.010.

26. Guillaume Boiteux; Isabelle Lascombe; Emmanuelle Roche; Marie-Laure Plissonnier; Anne Clairotte; Hugues Bittard; Sylvie Fauconnet; A-FABP, a candidate progression marker of human transitional cell carcinoma of the bladder, is differentially regulated by PPAR in urothelial cancer cells. *International Journal of Cancer* **2009**, *124*, 1820-1828, 10.1002/ijc.24112.

27. Christel Mathis; Isabelle Lascombe; Franck Monnien; Hugues Bittard; François Kleinclauss; Isabelle Bedgedjian; Sylvie Fauconnet; Séverine Valmary-Degano; Down-regulation of A-FABP predicts non-muscle invasive bladder cancer progression: investigation with a long term clinical follow-up. *BMC Cancer* **2018**, *18*, 1-13, 10.1186/s12885-018-5137-4.

28. Gita Ohlsson; Jose Moreira; Pavel Gromov; Guido Sauter; Julio E. Celis; Loss of Expression of the Adipocyte-type Fatty Acid-binding Protein (A-FABP) Is Associated with Progression of Human Urothelial Carcinomas. *Molecular & Cellular Proteomics* **2005**, *4*, 570-581, 10.1074/mcp.m500017-mcp200.

29. J E Celis; M Ostergaard; B Basse; A Celis; J B Lauridsen; G P Ratz; I Andersen; B Hein; H Wolf; T F Orntoft; et al.H H Rasmussen Loss of adipocyte-type fatty acid binding protein and other protein biomarkers is associated with progression of human bladder transitional cell carcinomas.. *Cancer Research* **1996**, *56*, 4782-4790.

30. R Das; R Hammamieh; R Neill; M Melhem; M Jett; Expression pattern of fatty acid-binding proteins in human normal and cancer prostate cells and tissues.. *Clinical Cancer Research* **2001**, *7*, 1706-1715.

31. Marta L De Santis; Rasha Hammamieh; Rina Das; Marti Jett; Adipocyte-fatty acid binding protein induces apoptosis in DU145 prostate cancer cells.. *Journal of Experimental Therapeutics and Oncology* **2004**, *4*, 91-100.

32. Bing Li; Jiaqing Hao; Xiaofang Yan; Maiying Kong; Edward R. Sauter; A-FABP and oestrogens are independently involved in the development of breast cancer. *Adipocyte* **2019**, *8*, 379-385, 10.1080/21623945.2019.1690827.

33. Kristin Nieman; Hilary A Kenny; Carla V Penicka; Andras Ladanyi; Rebecca Buell-Gutbrod; Marion R Zillhardt; Iris Romero; Mark S Carey; Gordon B Mills; Gökhan S Hotamisligil; et al.S Diane YamadaMarcus Ernst PeterKatja GwinErnst Lengyel Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nature Medicine* **2011**, *17*, 1498-1503, 10.1038/nm.2492.

34. Kshipra M. Gharpure; Sunila Pradeep; Marta Sans; Rajesha Rupaimoole; Cristina Ivan; Sherry Y. Wu; Emine Bayraktar; Archana S. Nagaraja; Lingegowda S. Mangala; Xinna Zhang; et al.Monika HaemmerleWei HuCristian Rodriguez-AguayoMichael McGuireCelia Sze Ling MakXiuhui ChenMichelle TranAlejandro Villar-PradosGuillermo Armaiz PenaRagini KondetimmanahalliRyan NiniPranavi KoppulaPrahlad RamJinsong LiuGabriel Lopez-BeresteinKeith BaggerlyLivia S. EberlinAnil K. Sood FABP4 as a key determinant of metastatic potential of ovarian cancer. *Nature Communications* **2018**, *9*, 1-14, 10.1038/s41467-018-04987-y.

35. Jihua Nie; Jingying Zhang; Lili Wang; Lunjie Lu; Qian Yuan; Fangmei An; Shuyu Zhang; Yang Jiao; Adipocytes promote cholangiocarcinoma metastasis through fatty acid binding protein 4.. *Journal of Experimental & Clinical Cancer Research* **2017**, *36*, 183, 10.1186/s13046-017-0641-y.

36. Kyle J. Thompson; Rebecca Garland Austin; Shayan S. Nazari; Keith S. Gersin; David A. Iannitti; Iain H. McKillop; Altered fatty acid-binding protein 4 (FABP4) expression and function in human and animal models of hepatocellular carcinoma. *Liver International* **2017**, *38*, 1074-1083, 10.1111/liv.13639.

37. Cheng-Qian Zhong; Xiu-Ping Zhang; Ning Ma; Er-Bin Zhang; Jing-Jing Li; Ya-Bo Jiang; Yu-Zhen Gao; Yan-Mei Yuan; Shi-Qian Lan; Dong Xie; et al.Shu-Qun Cheng FABP4 suppresses proliferation and invasion of hepatocellular carcinoma cells and predicts a poor prognosis for hepatocellular carcinoma. *Cancer Medicine* **2018**, *7*, 2629-2640, 10.1002/cam4.1511.

38. Samira Laouirem, Aurélie Sannier, Emma Norkowski, François Cauchy, Sabrina Doblas, Pierre Emmanuel Rautou, Miguel Albuquerque, Philippe Garteiser, Laura Sognigbé, Jerôme Raffenne, Bernard E. van Beers, Olivier Soubrane, Pierre Bedossa, Jerôme Cros, Valérie Paradis; Endothelial fatty liver binding protein 4: A new targetable mediator in hepatocellular carcinoma related to metabolic syndrome. *Oncogene* **2019**, *38*, 3033-3046.

39. F Yan; N Shen; J X Pang; Y W Zhang; E Y Rao; A M Bode; A Al-Kali; D E Zhang; M R Litzow; B Li; et al.S J Liu Fatty acid-binding protein FABP4 mechanistically links obesity with aggressive AML by enhancing aberrant DNA methylation in AML cells. *Leukemia* **2016**, *31*, 1434-1442, 10.1038/leu.2016.349.

40. F Yan; N Shen; J X Pang; N Zhao; Y W Zhang; A M Bode; A Al-Kali; M R Litzow; B Li; S J Liu; et al. A vicious loop of fatty acid-binding protein 4 and DNA methyltransferase 1 promotes acute myeloid leukemia and acts as a therapeutic target. *Leukemia* **2017**, *32*, 865-873, 10.1038/leu.2017.307.

41. Hong Lan; Cliff C. Cheng; Timothy J. Kowalski; Ling Pang; Lixin Shan; Cheng-Chi Chuang; James Jackson; Alberto Rojas-Triana; Loretta Bober; Li Liu; et al.Johannes VoigtPeter OrthXianshu YangJr. Gerald W. ShippsJoseph A. Hedrick Small-molecule inhibitors of FABP4/5 ameliorate dyslipidemia but not insulin resistance in mice with diet-induced obesity. *Journal of Lipid Research* **2011**, *52*, 646-656, 10.1194/jlr.m012757.

42. Ann V. Hertzel; Kristina Hellberg; Joseph Reynolds; Andrew C. Kruse; Brittany E. Juhlmann; Anne J. Smith; Mark A. Sanders; Douglas H. Ohlendorf; Jill Suttles; David A. Bernlohr; et al. Identification and Characterization of a Small Molecule Inhibitor of Fatty Acid Binding Proteins. *Journal of Medicinal Chemistry* **2009**, *52*, 6024-6031, 10.1021/jm900720m.

43. Tjeerd Barf; Fredrik Lehmann; Kristin Hammer; Saba Haile; Eva Axen; Carmen Medina; Jonas Uppenberg; Stefan Svensson; Lena Rondahl; Thomas Lundbäck; et al. N-Benzyl-indolo carboxylic acids: Design and synthesis of potent and selective adipocyte fatty-acid binding protein (A-FABP) inhibitors. *Bioorganic & Medicinal Chemistry Letters* **2009**, *19*, 1745-1748, 10.1016/j.bmcl.2009.01.084.

44. Masato Furuhashi; Fatty Acid-Binding Protein 4 in Cardiovascular and Metabolic Diseases. *Journal of Atherosclerosis and Thrombosis* **2019**, *26*, 216-232, 10.5551/jat.48710.

45. K G Alberti; R H Eckel; S M Grundy; P Z Zimmet; J I Cleeman; K A Donato; J C Fruchart; W P James; C M Loria; S C.Jr Smith; et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Forceon Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World HeartFederation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Obesity and metabolism* **2010**, *7*, 63-65, 10.14341/2071-8713-5281.

46. Guifen Niu; Jian Li; Huaiguo Wang; Yuan Ren; Jie Bai; Associations of A-FABP with Anthropometric and Metabolic Indices and Inflammatory Cytokines in Obese Patients with Newly Diagnosed Type 2 Diabetes. *BioMed Research International* **2016**, *2016*, 1-6, 10.1155/2016/9382092.

47. 47. Bahrami Abdehgah, E.; Abdollahpur, N.; Hosseini, F; Effects of 8 weeks combined resistance and endurance training on A-FABP in obese middle age men. *J Phys Act Horm* **2017**, *1*, 11-12.

48. Ruby L. C. Hoo; Lingling Shu; Kenneth K. Y. Cheng; Xiaoping Wu; Boya Liao; Nghai Wu; Zhiguang Zhou; Aimin Xu; Adipocyte Fatty Acid Binding Protein Potentiates Toxic Lipids-Induced Endoplasmic Reticulum Stress in Macrophages via Inhibition of Janus Kinase 2-dependent Autophagy. *Scientific Reports* **2017**, *7*, 40657, 10.1038/srep40657.

49. Lingling Shu; Ruby L. C. Hoo; Xiaoping Wu; Yong Pan; Ida P. C. Lee; Lai Yee Cheong; Stefan R Bornstein; Xianglu Rong; Jiao Guo; Aimin Xu; et al. A-FABP mediates adaptive thermogenesis by promoting intracellular activation of thyroid hormones in brown adipocytes. *Nature Communications* **2017**, *8*, 14147, 10.1038/ncomms14147.

50. Hui Li; Han-Ying Luo; Qing Liu; Yang Xiao; Lin Tang; Feng Zhong; Gan Huang; Jun-Mei Xu; Ai-Min Xu; Zhi-Guang Zhou; et al.Ru-Ping Dai Intermittent High Glucose Exacerbates A-FABP Activation and Inflammatory Response through TLR4-JNK Signaling in THP-1 Cells. *Journal of Immunology Research* **2018**, *2018*, 1-9, 10.1155/2018/1319272.

51. Hui-Xia Dou; Ting Wang; Hai-Xia Su; Ding-Ding Gao; Ye-Chun Xu; Ying-Xia Li; He-Yao Wang; Exogenous FABP4 interferes with differentiation, promotes lipolysis and inflammation in adipocytes. *Endocrine* **2019**, *67*, 587-596, 10.1007/s12020-019-02157-8.

52. Gang Liu; Ming Ding; Stephanie Chiuve; Eric B. Rimm; Paul W. Franks; James B. Meigs; Frank B. Hu; Qi Sun; Plasma Levels of Fatty Acid–Binding Protein 4, Retinol-Binding Protein 4, High-Molecular-Weight Adiponectin, and Cardiovascular Mortality Among Men With Type 2 Diabetes. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2016**, *36*, 2259-2267, 10.1161/atvbaha.116.308320.

53. Masato Furuhashi; Takahiro Fuseya; Masaki Murata; Kyoko Hoshina; Shutaro Ishimura; Tomohiro Mita; Yuki Watanabe; Akina Omori; Megumi Matsumoto; Takeshi Sugaya; et al.Tsuyoshi OikawaJunichi NishidaNobuaki KokubuMarenao TanakaNorihito MoniwaHideaki YoshidaNorimasa SawadaKazuaki ShimamotoTetsuji Miura Local Production of Fatty Acid–Binding Protein 4 in Epicardial/Perivascular Fat and Macrophages Is Linked to Coronary Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2016**, *36*, 825-834, 10.1161/atvbaha.116.307225.

54. Hongliang Xu; Ann V. Hertzel; Kaylee A. Steen; David A. Bernlohr; Loss of Fatty Acid Binding Protein 4/aP2 Reduces Macrophage Inflammation Through Activation of SIRT3. *Molecular Endocrinology* **2016**, *30*, 325-334, 10.1210/me.2015-1301.

55. Ji Zhang; Congzhen Qiao; Lin Chang; Yanhong Guo; Yanbo Fan; Luis Villacorta; Y. Eugene Chen; Jifeng Zhang; Cardiomyocyte Overexpression of FABP4 Aggravates Pressure Overload-Induced Heart Hypertrophy. *PLOS ONE* **2016**, *11*, e0157372, 10.1371/journal.pone.0157372.

56. Takahiro Fuseya; Masato Furuhashi; Megumi Matsumoto; Yuki Watanabe; Kyoko Hoshina; Tomohiro Mita; Shutaro Ishimura; Marenao Tanaka; Tetsuji Miura; Ectopic Fatty Acid–Binding Protein 4 Expression in the Vascular Endothelium is Involved in Neointima Formation After Vascular Injury. *Journal of the American Heart Association* **2017**, *6*, e006377, 10.1161/jaha.117.006377.

57. Masato Furuhashi; Satoshi Yuda; Atsuko Muranaka; Mina Kawamukai; Megumi Matsumoto; Marenao Tanaka; Norihito Moniwa; Hirofumi Ohnishi; Shigeyuki Saitoh; Kazuaki Shimamoto; et al.Tetsuji Miura Circulating Fatty Acid-Binding Protein 4 Concentration Predicts the Progression of Carotid Atherosclerosis in a General Population Without Medication. *Circulation Journal* **2018**, *82*, 1121-1129, 10.1253/circj.cj-17-1295.

58. Wen-Jun Tu; Xian-Wei Zeng; Aijun Deng; Sheng-Jie Zhao; Ding-Zhen Luo; Guo-Zhao Ma; Hong Wang; Qiang Liu; Circulating FABP4 (Fatty Acid–Binding Protein 4) Is a Novel Prognostic Biomarker in Patients With Acute Ischemic Stroke. *Stroke* **2017**, *48*, 1531-1538, 10.1161/strokeaha.117.017128.

59. Mei-Zhen Wu; Chi-Ho Lee; Yan Chen; Shuk-Yin Yu; Yu-Juan Yu; Qing-Wen Ren; Ho-Yi Carol Fong; Pui-Fai Wong; Hung-Fat Tse; Siu-Ling Karen Lam; et al.Kai-Hang Yiu Association between adipocyte fatty acid-binding protein with left ventricular remodelling and diastolic function in type 2 diabetes: a prospective echocardiography study. *Cardiovascular Diabetology* **2020**, *19*, 1-11, 10.1 186/s12933-020-01167-5.

60. Selcuk Gormez; Refik Erdim; Gokce Akan; Barıs Caynak; Cihan Duran; Demet Gunay; Volkan Sozer; Fatmahan Atalar; Relationships between visceral/subcutaneous adipose tissue FABP4 expression and coronary atherosclerosis in patients with metabolic syndrome. *Cardiovascular Pathology* **2019**, *46*, 107192, 10.1016/j.carpath.2019.107192.

61. Chih-Hsuan Yen; Jiun-Lu Lin; Kuo-Tzu Sung; Cheng-Huang Su; Wen-Hung Huang; Yun-Yu Chen; Shih-Chieh Chien; Yau-Huei Lai; Ping-Ying Lee; Yen-Yu Liu; et al.Jui-Peng TsaiCheng-Ting TsaiCharles Jia-Yin HouYing-Ju ChenYu-Jou HsiehChung-Lieh HungTa-Chuan HungHung-I. Yeh Association of free fatty acid binding protein with central aortic stiffness, myocardial dysfunction and preserved ejection fraction heart failure. *Scientific Reports* **2021**, *11*, 16501, 10.1038/s41598-021-95534-1.

62. Jean-Pierre Després; Isabelle Lemieux; Abdominal obesity and metabolic syndrome. *Nature* **2006**, *444*, 881-887, 10.1038/nature05488.

63. Gokhan Cildir; Semih Can Akıncılar; Vinay Tergaonkar; Chronic adipose tissue inflammation: all immune cells on the stage. *Trends in Molecular Medicine* **2013**, *19*, 487-500, 10.1016/j.molmed.2 013.05.001.

64. D. Stejskal; Michal Karpisek; Adipocyte fatty acid binding protein in a Caucasian population: a new marker of metabolic syndrome?. *European Journal of Clinical Investigation* **2006**, *36*, 621-625, 10.1111/j.1365-2362.2006.01696.x.

65. Bernhard M. Kaess; Danielle M. Enserro; David D. McManus; Vanessa Xanthakis; Ming-Huei Chen; Lisa M. Sullivan; Cheryl Ingram; Christoper J. O'donnell; John F. Keaney; Ramachandran S. Vasan; et al.Nicole L. Glazer Cardiometabolic Correlates and Heritability of Fetuin-A, Retinol-Binding Protein 4, and Fatty-Acid Binding Protein 4 in the Framingham Heart Study. *The Journal of Clinical Endocrinology & Metabolism* **2012**, *97*, E1943-E1947, 10.1210/jc.2012-1458.

66. Jang Hyun Koh; Young Goo Shin; Soo Min Nam; M. Young Lee; Choon Hee Chung; Jang Yel Shin; Serum Adipocyte Fatty Acid-Binding Protein Levels Are Associated With Nonalcoholic Fatty Liver Disease in Type 2 Diabetic Patients. *Diabetes Care* **2008**, *32*, 147-152, 10.2337/dc08-1379.

67. Shutaro Ishimura; Masato Furuhashi; Yuki Watanabe; Kyoko Hoshina; Takahiro Fuseya; Tomohiro Mita; Yusuke Okazaki; Masayuki Koyama; Marenao Tanaka; Hiroshi Akasaka; et al.Hirofumi OhnishiHideaki YoshidaShigeyuki SaitohTetsuji Miura Circulating Levels of Fatty Acid-Binding Protein Family and Metabolic Phenotype in the General Population. *PLoS ONE* **2013**, *8*, e81318, 10.1371/journal.pone.0081318.

68. Ms. Xiaomin Nie; Xiaojing Ma; Yiting Xu; Yun Shen; Yufei Wang; Yuqian Bao; Increased Serum Adipocyte Fatty Acid-Binding Protein Levels Are Associated with Decreased Sensitivity to Thyroid Hormones in the Euthyroid Population. *Thyroid* **2020**, *30*, 1718-1723, 10.1089/thy.2020.0011.

69. Ximena Terra; Yunuen Quintero; Teresa Auguet; Jose Antonio Porras; Mercé Hernández; Fatima Sabench; Carmen Aguilar; Anna María Luna; Daniel Del Castillo; Cristobal Richart; et al. FABP 4 is associated with inflammatory markers and metabolic syndrome in morbidly obese women. *European Journal of Endocrinology* **2011**, *164*, 539-547, 10.1530/eje-10-1195.

70. Gökhan S. Hotamisligil; Randall S. Johnson; Robert J. Distel; Ramsey Ellis; Virginia E. Papaioannou; Bruce M. Spiegelman; Uncoupling of Obesity from Insulin Resistance Through a Targeted Mutation in aP2, the Adipocyte Fatty Acid Binding Protein. *Science* **1996**, *274*, 1377-1379, 10.1126/science.274.5291.1377.

71. Ann V. Hertzel; Lisa Ann Smith; Anders H. Berg; Gary W. Cline; Gerald I. Shulman; Philipp E. Scherer; David A. Bernlohr; Lipid metabolism and adipokine levels in fatty acid-binding protein null and transgenic mice. *American Journal of Physiology-Endocrinology and Metabolism* **2006**, *290*, E814-E823, 10.1152/ajpendo.00465.2005.

72. R Yang; G Castriota; Y Chen; M A Cleary; K Ellsworth; M K Shin; J-Lv Tran; T F Vogt; M Wu; S Xu; et al.X YangB B ZhangJ P BergerS A Qureshi RNAi-mediated germline knockdown of FABP4 increases body weight but does not improve the deranged nutrient metabolism of diet-induced obese mice. *International Journal of Obesity* **2010**, *35*, 217-225, 10.1038/ijo.2010.128.

73. Natalie Ribarik Coe; Melanie A. Simpson; David A. Bernlohr; Targeted disruption of the adipocyte lipid-binding protein (aP2 protein) gene impairs fat cell lipolysis and increases cellular fatty acid levels. *Journal of Lipid Research* **1999**, *40*, 967-972, 10.1016/s0022-2275(20)32133-7.

74. L. Scheja; L. Makowski; K. T. Uysal; S. M. Wiesbrock; D. R. Shimshek; D. S. Meyers; M. Morgan; R. A. Parker; G. S. Hotamisligil; Altered insulin secretion associated with reduced lipolytic efficiency in aP2-/- mice. *Diabetes* **1999**, *48*, 1987-1994, 10.2337/diabetes.48.10.1987.

75. Kacey J. Prentice; Jani Saksi; Gökhan S. Hotamisligil; Adipokine FABP4 integrates energy stores and counterregulatory metabolic responses. *Journal of Lipid Research* **2019**, *60*, 734-740, 10.1194/jlr.s091793.

76. Alexander Bartelt; Joerg Heeren; Adipose tissue browning and metabolic health. *Nature Reviews Endocrinology* **2013**, *10*, 24-36, 10.1038/nrendo.2013.204.

77. Federica Cioffi; Alessandra Gentile; Elena Silvestri; Fernando Goglia; Assunta Lombardi; Effect of Iodothyronines on Thermogenesis: Focus on Brown Adipose Tissue. *Frontiers in Endocrinology* **2018**, *9*, 254, 10.3389/fendo.2018.00254.

78. Steven E. Kahn; Rebecca Hull; Kristina M. Utzschneider; Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature* **2006**, *444*, 840-846, 10.1038/nature05482.

79. Wing Sun Chow; Annette Wai Kwan Tso; Aimin Xu; Michele Mae Ann Yuen; Carol Ho Yi Fong; Tai Hing Lam; Su Vui Lo; Hung Fat Tse; Yu Cho Woo; Chun Yip Yeung; et al.Bernard Man Yung CheungKaren Siu Ling Lam Elevated Circulating Adipocyte-Fatty Acid Binding Protein Levels Predict Incident Cardiovascular Events in a Community-Based Cohort: A 12-Year Prospective Study. *Journal of the American Heart Association* **2013**, *2*, e004176, 10.1161/jaha.112.004176.

80. M. E. Trujillo; P. E. Scherer; Adiponectin - journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *Journal of Internal Medicine* **2005**, *257*, 167-175, 10.1111/j.1365-2796.2004.01426.x.

81. Hideki Ota; Masato Furuhashi; Shutaro Ishimura; Masayuki Koyama; Yusuke Okazaki; Tomohiro Mita; Takahiro Fuseya; Tomohisa Yamashita; Marenao Tanaka; Hideaki Yoshida; et al.Kazuaki ShimamotoTetsuji Miura Elevation of Fatty Acid-Binding Protein 4 Is Predisposed by Family History of Hypertension and Contributes to Blood Pressure Elevation. *American Journal of Hypertension* **2012**, *25*, 1124-1130, 10.1038/ajh.2012.88.

82. Aneta Mankowska-Cyl; Magdalena Krintus; Pawel Rajewski; Grazyna Sypniewska; A-FABP and its association with atherogenic risk profile and insulin resistance in young overweight and obese women. *Biomarkers in Medicine* **2013**, *7*, 723-730, 10.2217/bmm.13.61.

83. G. Tuncman; Ebru Erbay; X. Hom; I. De Vivo; H. Campos; E. B. Rimm; G. S. Hotamisligil; A genetic variant at the fatty acid-binding protein aP2 locus reduces the risk for hypertriglyceridemia, type 2 diabetes, and cardiovascular disease. *Proceedings of the National Academy of Sciences* **2006**, *103*, 6970-6975, 10.1073/pnas.0602178103.

84. Kazuhisa Maeda; Haiming Cao; Keita Kono; Cem Z. Gorgun; Masato Furuhashi; Kadir T. Uysal; Qiong Cao; Genichi Atsumi; Harry Malone; Bala Krishnan; et al.Yasuhiko MinokoshiBarbara B. KahnRex A. ParkerGökhan S. Hotamisligil Adipocyte/macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes. *Cell Metabolism* **2005**, *1*, 107-119, 10.1016/j.cmet.2004.12.008.

85. K. Teoman Uysal; Ludger Scheja; Sarah M. Wiesbrock; Susan Bonner-Weir; Gökhan S. Hotamisligil; Improved Glucose and Lipid Metabolism in Genetically Obese Mice Lacking aP2. *Endocrinology* **2000**, *141*, 3388-3396, 10.1210/en.141.9.3388.

86. Giacomo Ruotolo; Barbara V. Howard; Dyslipidemia of the metabolic syndrome. *Current Cardiology Reports* **2002**, *4*, 494-500, 10.1007/s11886-002-0113-6.

87. Børge G. Nordestgaard; Triglyceride-Rich Lipoproteins and Atherosclerotic Cardiovascular Disease. *Circulation Research* **2016**, *118*, 547-563, 10.1161/circresaha.115.306249.

88. Henry N. Ginsberg; Insulin resistance and cardiovascular disease. *Journal of Clinical Investigation* **2000**, *106*, 453-458, 10.1172/jci10762.

89. Tsutomu Hirano; Pathophysiology of Diabetic Dyslipidemia. *Journal of Atherosclerosis and Thrombosis* **2018**, *25*, 771-782, 10.5551/jat.rv17023.

90. G F Lewis; K D Uffelman; L W Szeto; B Weller; G Steiner; Interaction between free fatty acids and insulin in the acute control of very low density lipoprotein production in humans.. *Journal of Clinical Investigation* **1995**, *95*, 158-166, 10.1172/jci117633.

91. Jean E. Schaffer; Lipotoxicity: when tissues overeat. *Current Opinion in Lipidology* **2003**, *14*, 281-287, 10.1097/00041433-200306000-00008.

92. Thomas Unger; Claudio Borghi; Fadi Charchar; Nadia A. Khan; Neil R. Poulter; Dorairaj Prabhakaran; Agustin Ramirez; Markus Schlaich; George S. Stergiou; Maciej Tomaszewski; et al.Richard D. WainfordBryan WilliamsAletta Schutte 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension* **2020**, *75*, 1334-1357, 10.1161/hypertensionaha.120.15026.

93. Hidekatsu Yanai; Yoshiharu Tomono; Kumie Ito; Nobuyuki Furutani; Hiroshi Yoshida; Norio Tada; The underlying mechanisms for development of hypertension in the metabolic syndrome. *Nutrition Journal* **2008**, *7*, 10-10, 10.1186/1475-2891-7-10.

94. Hideki Katagiri; Tetsuya Yamada; Yoshitomo Oka; Adiposity and Cardiovascular Disorders. *Circulation Research* **2007**, *101*, 27-39, 10.1161/circresaha.107.151621.

95. Gareth Beevers; Gregory Y H Lip; Eoin O'Brien; ABC of hypertension: The pathophysiology of hypertension. *BMJ* **2001**, *322*, 912-916, 10.1136/bmj.322.7291.912.

96. Leonardo A. Sechi; Mechanisms of insulin resistance in rat models of hypertension and their relationships with salt sensitivity. *Journal of Hypertension* **1999**, *17*, 1229-1237, 10.1097/00004872-199917090-00001.

97. Pasquale Strazzullo; Antonio Barbato; Ferruccio Galletti; Gianvincenzo Barba; Alfonso Siani; Roberto Iacone; Lanfranco D'Elia; Ornella Russo; Marco Versiero; Eduardo Farinaro; et al.Francesco P Cappuccio Abnormalities of renal sodium handling in the metabolic syndrome. Results of the Olivetti Heart Study. *Journal of Hypertension* **2006**, *24*, 1633-1639, 10.1097/01.hjh.0000239300.48130.07.

98. Guido Grassi; Renin–angiotensin–sympathetic crosstalks in hypertension: reappraising the relevance of peripheral interactions. *Journal of Hypertension* **2001**, *19*, 1713-1716, 10.1097/00004872-200110000-00003.

99. Guido Grassi; Gino Seravalle; Bianca M. Cattaneo; Giovanni B. Bolla; Antonio Lanfranchi; Manuela Colombo; Cristina Giannattasio; Amelia Brunani; Francesco Cavagnini; Giuseppe Mancia; et al. Sympathetic Activation in Obese Normotensive Subjects. *Hypertension* **1995**, *25*, 560-563, 10.1161/01.hyp.25.4.560.

100. Gemma Aragonès; Paula Saavedra; Mercedes Heras; Anna Cabré; Josefa Girona; Lluís Masana; Fatty acid-binding protein 4 impairs the insulin-dependent nitric oxide pathway in vascular endothelial cells. *Cardiovascular Diabetology* **2012**, *11*, 72-72, 10.1186/1475-2840-11-72.

101. Tatsuya Iso; Hiroaki Sunaga; Hiroki Matsui; Shu Kasama; Naomi Oshima; Hikari Haruyama; Nozomi Furukawa; Kiyomi Nakajima; Tetsuo Machida; Masami Murakami; et al.Tomoyuki YokoyamaMasahiko Kurabayashi Serum levels of fatty acid binding protein 4 and fat metabolic markers in relation to catecholamines following exercise. *Clinical Biochemistry* **2017**, *50*, 896-902, 10.1016/j.clinbiochem.2017.05.021.

102. Stephen Kaptoge; Lisa Pennells; Dirk De Bacquer; Marie Therese Cooney; Maryam Kavousi; Gretchen Stevens; Leanne Margaret Riley; Stefan Savin; Taskeen Khan; Servet Altay; et al.Philippe AmouyelGerd AssmannSteven BellYoav Ben-ShlomoLisa BerkmanJoline W BeulensCecilia BjörkelundMichael BlahaDan G BlazerThomas BoltonRuth Bonita BeagleholeHermann BrennerEric BrunnerEdoardo CasigliaParinya ChamnanYeun-Hyang ChoiRajiv ChowdrySean CoadyCarlos J CrespoMary CushmanGilles R DagenaisRalph B D'agostino SrMakoto DaimonKarina DavidsonGunnar EngströmIan FordJohn GallacherRon T GansevoortThomas Andrew GazianoSimona GiampaoliGreg GranditsSameline GrimsgaardDiederick E GrobbeeVilmundur GudnasonQi GuoHanna TolonenSteve HumphriesHiroyasu IsoJ Wouter JukemaJussi KauhanenAndre Pascal KengneDavood KhaliliWolfgang KoenigDaan KromhoutHarlan KrumholzTai Hing LamGail LaughlinAlejandro Marín IbañezTom W MeadeKarel G M MoonsPaul J NietertToshiharu NinomiyaBørge G NordestgaardChristopher O'DonnellLuigi PalmieriAnushka PatelPablo PerelJackie F PriceRui ProvidênciaPaul M RidkerBeatriz RodriguezAnnika RosengrenRonan RousselMasaru SakuraiVeikko SalomaaShinichi SatoBen SchöttkerNawar SharaJonathan E ShawHee-Choon ShinLeon A SimonsEleni SofianopoulouJohan SundströmHenry VölzkeRobert B WallaceNicholas J WarehamPeter WilleitDavid WoodAngela WoodDong ZhaoMark WoodwardGoodarz DanaeiGregory RothShanthi MendisOyere OnumaCherian VargheseMajid EzzatiIan GrahamRod JacksonJohn DaneshEmanuele Di Angelantonio World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *The Lancet Global Health* **2019**, *7*, e1332-e1345, 10.1016/s2214-109x(19)30318-3.

103. Johan Frostegård; Immunity, atherosclerosis and cardiovascular disease. *BMC Medicine* **2013**, *11*, 1-117, 10.1186/1741-7015-11-117.

104. Maximilian von Eynatten; Lutz P. Breitling; Marcel Roos; Marcus Baumann; Dietrich Rothenbacher; Hermann Brenner; Circulating Adipocyte Fatty Acid-Binding Protein Levels and Cardiovascular Morbidity and Mortality in Patients With Coronary Heart Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2012**, *32*, 2327-2335, 10.1161/atvbaha.112.248609.

105. Masato Furuhashi; Shutaro Ishimura; Hideki Ota; Manabu Hayashi; Takahiro Nishitani; Marenao Tanaka; Hideaki Yoshida; Kazuaki Shimamoto; Gökhan S. Hotamisligil; Tetsuji Miura; et al. Serum

Fatty Acid-Binding Protein 4 Is a Predictor of Cardiovascular Events in End-Stage Renal Disease. *PLOS ONE* **2011**, *6*, e27356, 10.1371/journal.pone.0027356.

106. Joseph Yeboah; John R. Crouse; Fang-Chi Hsu; Gregory L. Burke; David M. Herrington; Brachial Flow-Mediated Dilation Predicts Incident Cardiovascular Events in Older Adults. *Circulation* **2007**, *115*, 2390-2397, 10.1161/circulationaha.106.678276.

107. S. Yusuf; S. Hawken; S. Ounpuu; Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *ACC Current Journal Review* **2004**, *13*, 15-16, 10.1016/j.accreview.2004.11.072.

108. Barbara Messner; David Bernhard; Smoking and Cardiovascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2014**, *34*, 509-515, 10.1161/atvbaha.113.300156.

109. Ángeles C. Ochoa-Martínez; Tania Ruíz-Vera; Lucia G. Pruneda-Álvarez; Ana K. González-Palomo; Claudia I. Almendarez-Reyna; Francisco J. Pérez-Vázquez; Iván N. Pérez-Maldonado; Serum adipocyte-fatty acid binding protein (FABP4) levels in women from Mexico exposed to polycyclic aromatic hydrocarbons (PAHs). *Environmental Science and Pollution Research* **2016**, *24*, 1862-1870, 10.1007/s11356-016-7971-8.

110. D.C.Y. Yeung; A. Xu; C.W.S. Cheung; N.M.S. Wat; M.H. Yau; C.H.Y. Fong; M.T. Chau; K.S.L. Lam; Serum Adipocyte Fatty Acid-Binding Protein Levels Were Independently Associated With Carotid Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology* **2007**, *27*, 1796-1802, 10.1161/atvbaha.107.146274.

111. Yaping Hao; Xiaojing Ma; Yuqi Luo; Yun Shen; Jianxin Dou; Xiaoping Pan; Yuqian Bao; Weiping Jia; Serum Adipocyte Fatty Acid Binding Protein Levels Are Positively Associated With Subclinical Atherosclerosis in Chinese Pre- and Postmenopausal Women With Normal Glucose Tolerance. *The Journal of Clinical Endocrinology & Metabolism* **2014**, *99*, 4321-4327, 10.1210/jc.2014-1832.

112. H. E. Agardh; Lasse Folkersen; J. Ekstrand; D. Marcus; J. Swedenborg; Ulf Hedin; A. Gabrielsen; G. Paulsson-Berne; Expression of fatty acid-binding protein 4/aP2 is correlated with plaque instability in carotid atherosclerosis. *Journal of Internal Medicine* **2010**, *269*, 200-210, 10.1111/j.1365-2796.2010.02304.x.

113. Jani Saksi; Petra Ijäs; Mikko I. Mäyränpää; Krista Nuotio; Pia M. Isoviita; Jarno Tuimala; Erno Lehtonen-Smeds; Markku Kaste; Antti Jula; Juha Sinisalo; et al.Markku S. NieminenMarja-Liisa LokkiMarkus PerolaAki S. HavulinnaVeikko SalomaaJohannes KettunenMatti JauhiainenPetri T. KovanenPerttu J. Lindsberg Low-Expression Variant of Fatty Acid–Binding Protein 4 Favors Reduced Manifestations of Atherosclerotic Disease and Increased Plaque Stability. *Circulation: Cardiovascular Genetics* **2014**, *7*, 588-598, 10.1161/circgenetics.113.000499.

114. Yang Xiao; Xiaoyu Xiao; Aimin Xu; Xiaoyan Chen; Weili Tang; Zhiguang Zhou; Circulating adipocyte fatty acid-binding protein levels predict the development of subclinical atherosclerosis in

type 2 diabetes. *Journal of Diabetes and its Complications* **2018**, *32*, 1100-1104, 10.1016/j.jdiacomp.2018.09.001.

115. Michael S. Rolph; Timothy R. Young; Bennett Shum; Cem Z. Gorgun; Carsten Schmitz-Peiffer; Ian A. Ramshaw; Gökhan S. Hotamisligil; Charles Mackay; Regulation of Dendritic Cell Function and T Cell Priming by the Fatty Acid-Binding Protein aP2. *The Journal of Immunology* **2006**, *177*, 7794-7801, 10.4049/jimmunol.177.11.7794.

116. Josefa Girona; Roser Rosales; Núria Plana; Paula Saavedra; Lluís Masana; Joan-Carles Vallvé; FABP4 Induces Vascular Smooth Muscle Cell Proliferation and Migration through a MAPK-Dependent Pathway. *PLOS ONE* **2013**, *8*, e81914, 10.1371/journal.pone.0081914.

117. Yuchang Fu; Nanlan Luo; Maria F Lopes-Virella; W.Timothy Garvey; The adipocyte lipid binding protein (ALBP/aP2) gene facilitates foam cell formation in human THP-1 macrophages. *Atherosclerosis* **2002**, *165*, 259-269, 10.1016/s0021-9150(02)00305-2.

118. Jeffrey B. Boord; Kazuhisa Maeda; Liza Makowski; Vladimir R. Babaev; Sergio Fazio; MacRae F. Linton; Gökhan S. Hotamisligil; Combined Adipocyte-Macrophage Fatty Acid–Binding Protein Deficiency Improves Metabolism, Atherosclerosis, and Survival in Apolipoprotein E–Deficient Mice. *Circulation* **2004**, *110*, 1492-1498, 10.1161/01.cir.0000141735.13202.b6.

119. Matthew Layne; Anand Patel; Yen-Hsu Chen; Vivienne Rebel; Irvith M. Carvajal; Andrea Pellacani; Bonna Ith; Dezheng Zhao; Barbara Schreiber; Shaw-Fang Yet; et al.Mu-En LeeJudith StorchMark A. Perrella Role of macrophage-expressed adipocyte fatty acid binding protein in the development of accelerated atherosclerosis in hypercholesterolemic mice. *The FASEB Journal* **2001**, *15*, 1-19, 10.1096/fj.01-0374fje.

120. Kaylee A. Steen; Hongliang Xu; David A. Bernlohr; FABP4/aP2 Regulates Macrophage Redox Signaling and Inflammasome Activation via Control of UCP2. *Molecular and Cellular Biology* **2017**, *37*, e00282-16, 10.1128/mcb.00282-16.

121. Sverre Holm; Thor Ueland; Tuva B. Dahl; Annika E. Michelsen; Mona Skjelland; David Russell; Ståle H. Nymo; Kirsten Krohg-Sørensen; Ole Petter Clausen; Dan Atar; et al.James L. JanuzziPäl AukrustJesper Khedri JensenBente Halvorsen Fatty Acid Binding Protein 4 Is Associated with Carotid Atherosclerosis and Outcome in Patients with Acute Ischemic Stroke. *PLOS ONE* **2011**, *6*, e28785, 10.1371/journal.pone.0028785.

122. Xiang-Lei Huang; Association of Serum Levels of Adipocyte Fatty Acid-Binding Protein and High-Sensitivity C Reactive Protein with Severity of Acute Ischemic Stroke. *Cell Biochemistry and Biophysics* **2014**, *72*, 359-361, 10.1007/s12013-014-0464-9.

123. Maurizio Acampa; Daniele Romano; Pietro Enea Lazzerini; Sara Leonini; Francesca Guideri; Rossana Tassi; Tommaso Casseri; Sandra Bracco; Giuseppe Martini; Increased Arterial Stiffness is Associated with Poor Collaterals in Acute Ischemic Stroke from Large Vessel Occlusion. *Current Neurovascular Research* **2018**, *15*, 34-38, 10.2174/1567202615666180326100347.

124. A. W. K. Tso; T. K. Y. Lam; A. Xu; K. H. Yiu; H. F. Tse; L. S. W. Li; L. S. C. Law; B. M. Y. Cheung; R. T. F. Cheung; K. S. L. Lam; et al. Serum adipocyte fatty acid-binding protein associated with ischemic stroke and early death. *Neurology* **2011**, *76*, 1968-1975, 10.1212/wnl.0b013e31821e54b3.

125. Yi Yang; Gary A. Rosenberg; Matrix metalloproteinases as therapeutic targets for stroke. *Brain Research* **2015**, *1623*, 30-38, 10.1016/j.brainres.2015.04.024.

126. Mustafa Mücahit Balci; Uğur Arslan; Hikmet Firat; Ibrahim Kocaoğlu; Mustafa Gökhan Vural; Kevser Gülcihan Balci; Orhan Maden; Oğuz Alp Gürbüz; Sadik Ardiç; Ekrem Yeter; et al. Serum Levels of Adipocyte Fatty Acid–Binding Protein Are Independently Associated With Left Ventricular Mass and Myocardial Performance Index in Obstructive Sleep Apnea Syndrome. *Journal of Investigative Medicine* **2012**, *60*, 1020-1026, 10.2310/jim.0b013e31826868f2.

127. Stefan Engeli; Wolfgang Utz; Sven Haufe; Valéria Lamounier-Zepter; Martin Pofahl; Julius Traber; Jürgen Janke; Friedrich C Luft; Michael Boschmann; Jeanette Schulz-Menger; et al.Jens Jordan Fatty acid binding protein 4 predicts left ventricular mass and longitudinal function in overweight and obese women. *Heart* **2013**, *99*, 944-948, 10.1136/heartjnl-2013-303735.

128. Véronique L. Roger; Epidemiology of Heart Failure. *Circulation Research* **2013**, *113*, 646-659, 10.1161/circresaha.113.300268.

129. Chi-Lun Huang; Yen-Wen Wu; Chih-Cheng Wu; Lin Lin; Yu-Chin Wu; Pei-Ying Hsu; Yuh-Shiun Jong; Wei-Shiung Yang; Association between serum adipocyte fatty-acid binding protein concentrations, left ventricular function and myocardial perfusion abnormalities in patients with coronary artery disease. *Cardiovascular Diabetology* **2013**, *12*, 105-105, 10.1186/1475-2840-12-105.

130. W. H. Wilson Tang; Gary S. Francis; David A. Morrow; L. Kristin Newby; Christopher P. Cannon; Robert L. Jesse; Alan B. Storrow; Robert H. Christenson; Fred S. Apple; Jan Ravkilde; et al.Alan H. B. WuCommittee Members National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Clinical Utilization of Cardiac Biomarker Testing in Heart Failure. *Circulation* **2007**, *116*, e99-109, 10.1161/circulationaha.107.185267.

131. A Baessler; V Lamounier-Zepter; S Fenk; C Strack; Claas Lahmann; Thomas Loew; G Schmitz; M Blüher; S R Bornstein; M Fischer; et al. Adipocyte fatty acid-binding protein levels are associated with left ventricular diastolic dysfunction in morbidly obese subjects. *Nutrition & Diabetes* **2014**, *4*, e106-e106, 10.1038/nutd.2014.3.

132. Luc Djoussé; Traci M. Bartz; Joachim H. Ix; Jinesh Kochar; Jorge R. Kizer; John S. Gottdiener; Russell P. Tracy; Dariush Mozaffarian; David S. Siscovick; Kenneth J. Mukamal; et al.Susan J. Zieman Fatty acid-binding protein 4 and incident heart failure: the Cardiovascular Health Study. *European Journal of Heart Failure* **2013**, *15*, 394-399, 10.1093/eurjhf/hfs196.

133. Mingya Liu; Mi Zhou; Yuqian Bao; Zhiyong Xu; Huating Li; Hao Zhang; Wei Zhu; Jialiang Zhang; Aimin Xu; Meng Wei; et al.Weiping Jia Circulating adipocyte fatty acid-binding protein levels are independently associated with heart failure. *Clinical Science* **2012**, *124*, 115-122, 10.1042/cs20120004.

134. Valéria Lamounier-Zepter; Christiane Look; Julio Alvarez; Torsten Christ; Ursula Ravens; Wolf-Hagen Schunck; Monika Ehrhart-Bornstein; Stefan R. Bornstein; Ingo Morano; Adipocyte Fatty Acid–Binding Protein Suppresses Cardiomyocyte Contraction. *Circulation Research* **2009**, *105*, 326-334, 10.1161/circresaha.109.200501.

135. V Lamounier-Zepter; C Look; W-H Schunck; I Schlottmann; C Woischwill; S R Bornstein; A Xu; I Morano; Interaction of epoxyeicosatrienoic acids and adipocyte fatty acid-binding protein in the modulation of cardiomyocyte contractility. *International Journal of Obesity* **2014**, *39*, 755-761, 10.1038/ijo.2014.193.

136. Ricardo Rodríguez-Calvo; Josefa Girona; Josep M. Alegret; Alba Bosquet; Daiana Ibarretxe; Luis Masana; Role of the fatty acid-binding protein 4 in heart failure and cardiovascular disease. *Journal of Endocrinology* **2017**, *233*, R173-R184, 10.1530/joe-17-0031.

137. Mi Zhou; Yuqian Bao; Haobo Li; Yong Pan; Lingling Shu; Zhengyuan Xia; Donghai Wu; Karen S.L. Lam; Paul M. Vanhoutte; Aimin Xu; et al.Weiping JiaRuby L.-C. Hoo Deficiency of adipocyte fatty-acid-binding protein alleviates myocardial ischaemia/reperfusion injury and diabetes-induced cardiac dysfunction. *Clinical Science* **2015**, *129*, 547-559, 10.1042/cs20150073.

138. Valéria Lamounier-Zepter; Christiane Look; Julio Alvarez; Torsten Christ; Ursula Ravens; Wolf-Hagen Schunck; Monika Ehrhart-Bornstein; Stefan R. Bornstein; Ingo Morano; Adipocyte Fatty Acid–Binding Protein Suppresses Cardiomyocyte Contraction. *Circulation Research* **2009**, *105*, 326-334, 10.1161/circresaha.109.200501.

139. V Lamounier-Zepter; C Look; W-H Schunck; I Schlottmann; C Woischwill; S R Bornstein; A Xu; I Morano; Interaction of epoxyeicosatrienoic acids and adipocyte fatty acid-binding protein in the modulation of cardiomyocyte contractility. *International Journal of Obesity* **2014**, *39*, 755-761, 10.1038/ijo.2014.193.

140. Ricardo Rodríguez-Calvo; Josefa Girona; Josep M. Alegret; Alba Bosquet; Daiana Ibarretxe; Luis Masana; Role of the fatty acid-binding protein 4 in heart failure and cardiovascular disease. *Journal of Endocrinology* **2017**, *233*, R173-R184, 10.1530/joe-17-0031.

141. Mi Zhou; Yuqian Bao; Haobo Li; Yong Pan; Lingling Shu; Zhengyuan Xia; Donghai Wu; Karen S.L. Lam; Paul M. Vanhoutte; Aimin Xu; et al.Weiping JiaRuby L.-C. Hoo Deficiency of adipocyte fatty-acid-binding protein alleviates myocardial ischaemia/reperfusion injury and diabetes-induced cardiac dysfunction. *Clinical Science* **2015**, *129*, 547-559, 10.1042/cs20150073.