Role of the fatty acid-binding protein 4 in heart failure and cardiovascular disease

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Abstract

Obesity and ectopic fat accumulation in non-adipose tissues are major contributors to heart failure (HF) and cardiovascular disease (CVD). Adipocytes act as endocrine organs by releasing a large number of bioactive molecules into the bloodstream, which participate in a communication network between white adipose tissue and other organs, including the heart. Among these molecules, fatty acid-binding protein 4 (FABP4) has recently been shown to increase cardiometabolic risk. Both clinical and experimental evidence have identified FABP4 as a relevant player in atherosclerosis and coronary artery disease, and it has been directly related to cardiac alterations such as left ventricular hypertrophy (LVH) and both systolic and diastolic cardiac dysfunction. The available interventional studies preclude the establishment of a direct causal role of this molecule in CVD and HF and propose FABP4 as a biomarker rather than as an aetiological factor. However, several experimental reports have suggested that FABP4 may act as a direct contributor to cardiac metabolism and physiopathology, and the pharmacological targeting of FABP4 may restore some of the metabolic alterations that are conducive to CVD and HF. Here, we review the current knowledge regarding FABP4 in the context of HF and CVD as well as the molecular basis by which this protein participates in the regulation of cardiac function.

Key Words
- heart failure
- cardiovascular disease
- adipokines
- FABP4

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Introduction

Heart failure (HF) is one of the most important health problems around the world (for a review, see Hunt *et al.* 2009). The prevalence of HF is especially ominous in developed societies. Between the EU and the United States, there are more than 20 million people afflicted with this pathology (Mosterd & Hoes 2007, Mozaffarian *et al.* 2015). It is estimated that HF is currently the leading cause of hospitalisation in people over the age of 65 years (Forman *et al.* 2009), and approximately 108 billion dollars are spent each year on health costs associated with this pathology (Stewart *et al.* 2002, Neumann *et al.* 2009, Cook *et al.* 2014). Despite advances in the treatment of HF and the amount of money invested to combating this pathology, the number of deaths as a consequence of HF is steadily increasing. It is predicted that up to 30% of HF patients will die within 1 year following hospitalisation,

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and half will die within 5 years of their initial diagnosis (Loehr *et al*. 2008, Writing Group *et al*. 2010).

Increasing evidence has highlighted the role of metabolic diseases as important risk factors for HF. In particular, obesity has been proposed as one of the main contributors to the onset and progression of HF (Lavie *et al*. 2009). Despite the obesity-related comorbidities that may explain part of this association, a direct relationship between the risk of HF and adipokines has also been proposed (Baldasseroni *et al*. 2012, Djousse *et al*. 2013, Liu *et al*. 2013). Among these adipokines, fatty acid-binding protein 4 (FABP4) has recently been linked to cardiovascular and metabolic diseases. Additionally, FABP4 is highly expressed in macrophages, contributing to the development of atherosclerosis and cardiovascular disease (CVD). Here, we will review the current knowledge of FABP4 in HF and CVD as well as the molecular basis by which this protein participates in the regulation of cardiac function.

Obesity as a risk factor for heart failure

Among the risk factors for HF, we identified the so-called metabolic syndrome, which encompasses multiple metabolic disorders, including high blood pressure, dyslipidaemia, insulin resistance and obesity (Wang *et al*. 2010). Specifically, both overweight and obesity have been closely related to HF and other CVDs (Lavie *et al*. 2009). Recently, several studies have demonstrated a positive correlation between obesity/overweight and the risk of developing HF. A 5–7% increase in the incidence of HF per unit of increased body mass index (BMI) (Go *et al*. 2014) was found in a seminal study from the Framingham Heart Study (Kenchaiah *et al*. 2009). Interestingly, a graded increase in the risk of HF was found across all BMI categories. Similar data were obtained from a Finnish study, showing a greater risk of HF in overweight and obese subjects than that in normal-weight participants (Hu *et al*. 2010). However, while some authors attribute these correlations to the downstream development of metabolic risk factors such as inflammation, insulin resistance or type 2 diabetes mellitus (Ingelsson *et al*. 2005, Bahrami *et al*. 2008, Voulgari *et al*. 2011), the data from other studies report that obesity directly correlates with the risk of HF, independent of other metabolic risk factors (Morkedal *et al*. 2014). Paradoxically, once HF has been established, obesity confers survival benefits (Oreopoulos *et al*. 2008, Shah *et al*. 2014). Despite the exploration of the role of confounding factors, the underlying mechanism that explains this finding remains unclear. Interestingly, this paradox is not evident in obese patients with diabetes (Zamora *et al*. 2016).

Some pathological conditions that are present in obese patients may be involved in the elevated risk of HF. Both visceral obesity and ectopic fat accumulation in non-adipose tissues, including the heart, have been related to cardiac structure abnormalities and increased cardiometabolic risk (Britton & Fox 2011). Cardiac steatosis has been found in subjects with dilated cardiomyopathy (Graner *et al*. 2014), and pericardial fat accumulation is independently correlated with left ventricular (LV) mass and is inversely correlated with LV mid-wall stress abnormalities in morbidly obese patients (Graner *et al*. 2014). As an endocrine organ, adipose tissue produces and secretes a wide range of bioactive factors known as adipokines, which take part in the network of communication between adipose tissue and peripheral organs, including the heart (Kershaw & Flier 2004). The most studied adipokines are adiponectin, leptin, resistin, plasminogen activator inhibitor-1 (PAI-1) and tumour necrosis factor α (TNFα); however, increasing evidence has proposed fatty acid-binding protein 4 (FABP4) as a new emerging adipokine involved in the development of metabolic disease and CVD. Apart from adipocytes, FABP4 is also highly expressed in macrophages and dendritic cells (Makowski *et al*. 2001, Rolph *et al*. 2006), further contributing to inflammation-related alterations, such as metabolic syndrome and CVD.

Fatty acid-binding protein 4

FABP4, also known as adipocyte FABP (A-FABP) or adipocyte P2 (aP2), belongs to a family of intracellular lipid chaperones that is expressed in active lipid metabolic tissues. Similar to other members of the FABP family, FABP4 is able to reversibly bind to hydrophobic ligands such as saturated and unsaturated long-chain fatty acids (FA), eicosanoids and other lipids (Coe & Bernlohr 1998, Zimmerman & Veerkamp 2002), thus taking part in the regulation of lipid trafficking and responses at the cellular level (Furuhashi & Hotamisligil 2008, Furuhashi *et al*. 2011). Specifically, FABPs have been proposed to actively facilitate the transport of FA to specific organelles in the cell, including mitochondria, peroxisomes, the nucleus and the endoplasmic reticulum. Therefore, FABPs take part in lipid oxidation, lipid-mediated transcriptional regulation and the signalling, trafficking and synthesis of membranes (Furuhashi & Hotamisligil 2008). In addition,

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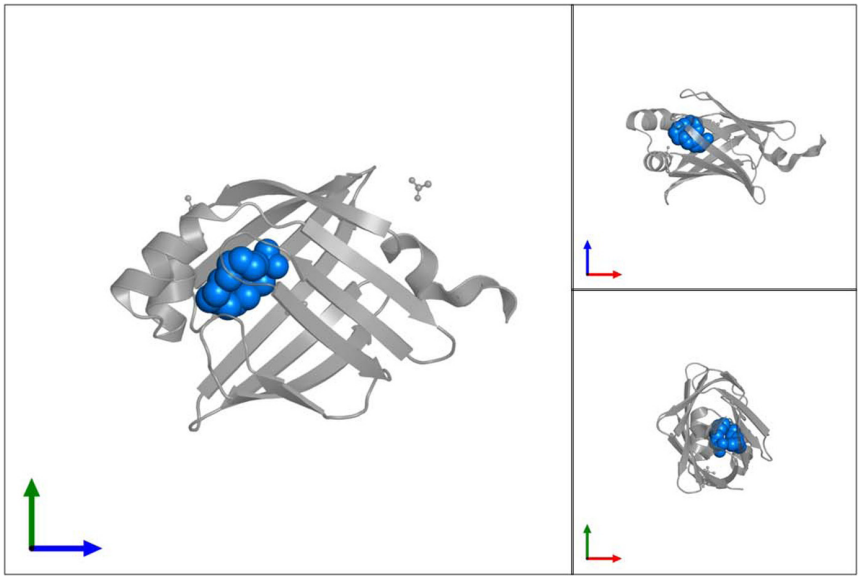

Figure 1
Three-dimensional structure of human FABP4 complexed with palmitic acid. The 10-stranded anti-parallel β-barrel structure of FABP4 is shown. The bound palmitic acid in the pocket of the β-barrel structure is shown. The images were rendered from the PDB file 2HNX, which contains the crystal structure of human FABP4. A full colour version of this figure is available at http://dx.doi.org/10.1530/JOE-17-0031.

FABPs also take part in the regulation of the enzymatic activity and storage of lipid droplets in the cytoplasm (Furuhashi & Hotamisligil 2008), the conversion of FA to eicosanoids and the stabilisation of leukotrienes (Ek *et al.* 1997, Zimmer *et al.* 2004). Apart from FABP4, the FABP family is composed of eight other isoforms in mammals based on tissue distribution, including the liver (FABP1), intestines (FABP2), heart (FABP3), epidermis (FABP5), ileum (FABP6), brain (FABP7), myelin (FABP8) and testis (FABP9). Despite the wide range of sequence identity between the different members of the FABP family (15–70%) (Chmurzynska 2006), all members share similar three-dimensional structures, including two orthogonal 5-stranded β-sheets and a 10-stranded anti-parallel β-barrel structure (Chmurzynska 2006, Marr *et al.* 2006, Furuhashi & Hotamisligil 2008) (Fig. 1).

Specifically, the human FABP4 gene encodes a polypeptide of 132 amino acids in length with a molecular mass of 14.6 kDa (GenBank accession number NM_024406). FABP4 expression is strongly induced during adipocyte differentiation (Bernlohr *et al.* 1985*a*), which has led to proposals of this molecule as an adipocyte differentiation marker (Bernlohr *et al.* 1985*b*, Smith *et al.* 1988, Yang *et al.* 1989). Similar to adipocytes, FABP4 expression is also induced during differentiation from monocytes to macrophages, and its expression in these cells is regulated by a wide range of proinflammatory stimuli (Pelton *et al.* 1999, Fu *et al.* 2000, Makowski *et al.* 2001, Fu *et al.* 2002, Kazemi *et al.* 2005, Wang *et al.* 2011). In macrophages, FABP4 increases the accumulation of cholesterol ester and induces foam cell formation as well as inflammatory responses through the activation of the IKK-NF-κB and JNK-AP-1 pathways (Makowski *et al.* 2005, Hui *et al.* 2010). FABP4 expression is controlled at the transcriptional level by CEBP (CCAAT/enhancer-binding protein) (Christy *et al.* 1989) and PPARγ (peroxisome proliferator-activated receptor γ) (Kletzien *et al.* 1992, Cabre *et al.* 2007). Additionally, cAMP (cyclic adenosine monophosphate) further controls FABP4 expression by relieving a negative regulatory element in the FABP4 promoter (Yang *et al.* 1989). As mentioned previously, FABP4 acts as a lipid-binding chaperone for long-chain non-esterified fatty acids (NEFA) (Coe & Bernlohr 1998), which are transported via the interior water-filled binding cavity formed by the β-barrel (LaLonde *et al.* 1994) (Fig. 1). In addition, FABP4 enhances the hydrolytic activity of hormone-sensitive lipase (HSL) by a molecular mechanism involving specific protein–protein interactions (Shen *et al.* 2001). Furthermore, FABP4 regulates PPARγ activity by taking part in delivering specific PPARγ agonists, including thiazolidinedione and linoleic acid, from the cytosol to the nucleus (Adida & Spener 2006, Gillilan *et al.* 2007). Interestingly, the FABP4 nuclear localisation signal is only found in the three-dimensional structure of the protein when bound to PPARγ agonists (Ayers *et al.* 2007, Gillilan *et al.* 2007); meanwhile, the binding of other FABP4 ligands that are not PPARγ activators, including oleate or stearate, does not result in a stable nuclear localisation signal (Gillilan *et al.* 2007).

Altogether, FABP4 is involved in the regulation of proteins that control both lipid metabolism and insulin sensitivity. Apart from its well-known role as a lipid chaperone in adipocytes, FABP4 has been detected in the bloodstream and is independently and strongly

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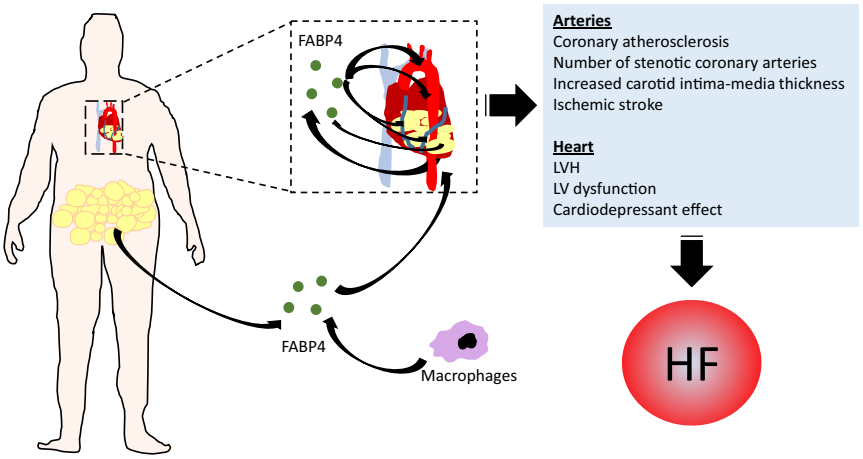

Figure 2
Endocrine and paracrine effects of FABP4 linked to obesity-induced HF and CVD. Both visceral and cardiac fat accumulation are important sources of FABP4, which is released into the bloodstream and targets several organs, including the heart. Additionally, macrophages and cardiomyocytes are relevant producers of FABP4. FABP4 is associated with coronary atherosclerosis, the number of stenotic coronary arteries, increased carotid intima-media thickness and ischaemic stroke. FABP4 exerts a cardiodepressant effect and has directly been linked to LVH and LV dysfunction. Thus, FABP4 directly contributes to CVD and HF development. A full colour version of this figure is available at http://dx.doi.org/10.1530/JOE-17-0031.

correlated with adiposity (Xu *et al*. 2006, Ishimura *et al*. 2013). Despite its lack of an N-terminal secretory signal sequence (Furuhashi & Hotamisligil 2008), FABP4 has been reported to be released from adipocytes through additional mechanisms (Coe *et al*. 1999, Scheja *et al*. 1999, Shen *et al*. 1999, Mita *et al*. 2015) and acts as an adipokine in several organs, including the heart (Fig. 2).

FABP4 as a cardiometabolic predictor for CVD

Apart from its well-known role as an adiposity biomarker (Xu *et al*. 2006, Ishimura *et al*. 2013), FABP4 has been associated with the following distinct components of metabolic syndrome based on a Third-Generation Framingham Heart Study cohort: BMI, triglycerides, total cholesterol, diastolic blood pressure, reduced HDL levels and impaired glomerular filtration rate (eGFR) (Kaess *et al*. 2012). Additionally, despite the lack of an association between FABP4 and prevalent diabetes (probably because of the low prevalence of diabetes in the studied cohort), this FA transporter was positively associated with insulin resistance and low-grade inflammation, which is consistent with the multifactorial pathogenesis of metabolic dysregulation. In addition, prospective studies have shown that FABP4 can predict the development of metabolic syndrome and type 2 diabetes (Tso *et al*. 2007, Xu *et al*. 2007). Since metabolic syndrome and insulin resistance are closely linked with CVD, a strong association between circulating FABP4 levels and this pathology has also been proposed (Yeung *et al*. 2007, Miyoshi *et al*. 2010, Xu *et al*. 2010, Bao *et al*. 2011, von Eynatten *et al*. 2012, Fuseya *et al*. 2014) (Fig. 2). Recently, FABP4 plasma levels have been associated with elevated CVD mortality in men with type 2 diabetes mellitus (Liu *et al*. 2016). Decreased FABP4 expression as a consequence of a genetic variant of the FABP4 promoter (T-87C) results in reduced serum triglycerides and a lower risk of CVD (Tuncman *et al*. 2006). In addition, FABP4 deficiency reduces aortic atherosclerotic lesions and increases the survival rate of apolipoprotein-E (ApoE)-deficient mice fed with a high-fat atherogenic diet (Makowski *et al*. 2001, Boord *et al*. 2004). The impact of FABP4 on atherosclerosis is mainly due to the role of this molecule in macrophages rather than that in adipocytes, as demonstrated by studies involving bone marrow transplantation (Makowski *et al*. 2001). Additionally, FABP4 from dendritic cells may further impact atherosclerosis, since it regulates inflammation and T-cell priming (Rolph *et al*. 2006). Moreover, the pharmacological inhibition of FABP4 also significantly protected against atherosclerotic plaque formation in the ApoE-deficient animal model of atherosclerosis, suggesting that the pharmacological inhibition of FABP4 might have beneficial effects against CVD (Furuhashi *et al*. 2007). In humans, FABP4 has been related to subclinical coronary atherosclerosis in type 2 diabetes mellitus subjects (Bagheri *et al*. 2010), and circulating FABP4 levels are also associated with increased carotid intima-media thickness, ischaemic stroke, coronary atherosclerotic burden and the number of stenotic coronary arteries (Yeung *et al*. 2007, Rhee *et al*. 2009, Miyoshi *et al*. 2010, Xu *et al*. 2010, Bao *et al*. 2011, Doi *et al*. 2011, Holm *et al*. 2011, Tso *et al*. 2011, Huang *et al*. 2013). Recently, FABP4 has been proposed as a prognostic biomarker in patients with acute coronary syndrome (Reiser *et al*. 2015). In addition, FABP4 is an important predictor of cardiovascular outcomes in patients with either coronary heart disease or acute ischaemic stroke (Holm *et al*. 2011, von Eynatten *et al*. 2012). Along with its potential role

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as a biomarker, a 12-year prospective study performed in a cohort without previous CVD revealed that FABP4 is a potential independent risk factor that predisposes individuals to CVD, showing the predictive value of FABP4 over the predictions based on traditional risk factors (Chow *et al*. 2013). FABP4 levels in atherosclerotic plaques have been further associated with an unstable plaque phenotype, which predicts the occurrence of an adverse cardiovascular event (Peeters *et al*. 2011, Lee *et al*. 2013). Specifically, unstable carotid plaques have been related to increased FABP4 expression in macrophages among samples from human endarterectomy (Agardh *et al*. 2011). Therefore, these findings support the role of FABP4 as a potential mediator of obesity/inflammation-related CVD. However, these studies precluded the establishment of a direct causal relationship between serum FABP4 and atherosclerosis.

FABP4, cardiac dysfunction and HF

FABP4 has been directly related to cardiac alterations (Fuseya *et al*. 2014) (Fig. 2). Specifically, FABP4 levels are associated with LVH as well as systolic and diastolic cardiac dysfunction (Balci *et al*. 2012, Engeli *et al*. 2013, Huang *et al*. 2013, Liu *et al*. 2013, Baessler *et al*. 2014), even in an apparently healthy population (Fuseya *et al*. 2014). A positive correlation between FABP4 and both LV dysfunction and myocardial perfusion abnormalities was found in patients with coronary artery disease (Huang *et al*. 2013). In addition, Engeli and coworkers found a modest but significant independent correlation between FABP4 serum concentrations and the LV mass in overweight and obese women (Engeli *et al*. 2013). Interestingly, longitudinal systolic and diastolic function was reduced in subjects with high serum FABP4 concentrations. The correlation between elevated serum FABP4 and the deterioration of LV function had previously been reported in non-obese patients who were hospitalised for acutely decompensated HF (Liu *et al*. 2013). However, others have failed to show an association between FABP4 and present (Balci *et al*. 2012) or future (Djousse *et al*. 2013) systolic dysfunction in subjects without prevalent cardiac disease (Liu *et al*. 2013). Altogether, these studies suggest only a marginal contribution of FABP4 to the development of early systolic dysfunction in obese humans.

FABP4-related heart remodelling and cardiac dysfunction may directly contribute to the development of HF (Liu *et al*. 2013). Liu and coworkers provided the first clinical evidence demonstrating that serum FABP4 concentrations are significantly higher in patients with HF than those in non-HF subjects, and this association was significantly increased with the severity of HF (Liu *et al*. 2013). Interestingly, this association was further confirmed by others (Huang *et al*. 2013, Liu *et al*. 2013). In addition, FABP4 positively correlates with the serum levels of N-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP), a well-established and powerful marker of HF risk (Tang *et al*. 2007), and with all echocardiograph parameters, especially LV ejection fraction (LVEF) (Liu *et al*. 2013). Moreover, using logistic regression analysis, the authors proposed FABP4 as an independent risk factor for HF (Liu *et al*. 2013). These data were reported during the review process of a study performed by members of our team that demonstrates a strong correlation between FABP4 and NT-proBNP in HF patients (Cabre *et al*. 2013), thus confirming the data first reported by Liu and coworkers (Liu *et al*. 2013). Since NT-proBNP has been proposed as an indicator for HF follow-up therapy and prognosis (Olsson *et al*. 2007, Lainchbury *et al*. 2009), the parallel association of FABP4 and NT-proBNP supports the role of FABP4 as an HF biomarker (Cabre *et al*. 2013). Actually, an association between the FABP4 and NT-proBNP plasma levels was also found during treatment and follow-up, suggesting that an improvement in HF status was associated with a reduction in both the NT-proBNP and FABP4 concentrations (Cabre *et al*. 2013). Moreover, a large-scale prospective study reported that the FABP4 plasma levels predicted a higher risk of HF during a median follow-up period of 10.7 years (Djousse *et al*. 2013). However, while some authors support that FABP4 is directly associated with heart function (Liu *et al*. 2013), data from other studies suggest that circumstances other than myocardial function determine the association between FABP4 and HF markers (Cabre *et al*. 2013, Djousse *et al*. 2013). Thus, these contradictory data initially proposed FABP4 as a biomarker rather than as an aetiological agent in HF development. Nevertheless, additional reports have suggested that FABP4 may also promote heart dysfunction through its direct action on cardiomyocytes. Increased FABP4 expression has been reported in human epicardial adipose tissue from metabolic syndrome patients (Vural *et al*. 2008), suggesting a paracrine effect on cardiac cells. Additionally, a recent study by Furuhashi and coworkers showed that FABP4 that is locally produced by epicardial/perivascular fat and macrophages contributes to the development of coronary atherosclerosis (Furuhashi *et al*. 2016), highlighting the potential paracrine role of this adipokine. Interestingly, Lamounier-Zepter showed that

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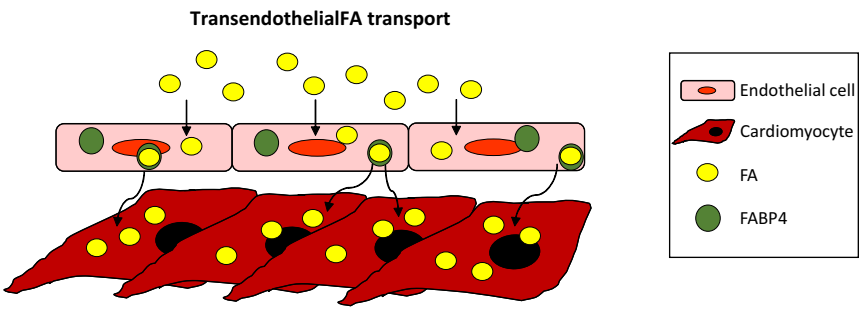

Figure 3
Cardiac transendothelial FA transport is regulated by FABP4. Endothelial cells are also an important source of FABP4, which increases transendothelial transport of FAs to the surrounding tissues including the heart. Given the sensitivity of cardiomyocytes in the use of FAs as an energy substrate, this may be one of the potential mechanisms by which FABP4 contributes to the dysregulation of cardiac metabolism and myocardial function. A full colour version of this figure is available at http://dx.doi.org/10.1530/JOE-17-0031.

FABP4 induced a cardiodepressant effect in experimental models of isolated rat cardiomyocytes (Lamounier-Zepter *et al*. 2009, Lamounier-Zepter *et al*. 2015), thus showing the first evidence of a cause–effect relationship between FABP4 and cardiomyocyte physiology. Recently, it has been shown that FABP4 is also expressed in cardiomyocytes, and the overexpression of cardiac FABP4 exacerbates the cardiac hypertrophic response induced by pressure overload (Zhang *et al*. 2016). Conversely, FABP4 deficiency attenuates ischaemia-/reperfusion-induced myocardial injury and improves LV function in both non-diabetic and streptozotocin-induced diabetic mice (Zhou *et al*. 2015). Therefore, FABP4 secreted from epicardial fat tissue, subcutaneous and/or visceral adipose tissue or macrophages may influence heart dysfunction in a paracrine or endocrine manner. However, the underlying molecular mechanisms by which FABP4 regulates cardiomyocyte function are only just beginning to emerge.

FABP4 and the cardiac fuel supply

Given the role of FABP4 as an FA carrier, the effect of this protein on cardiomyocyte contraction and myocardial remodelling may be by regulating substrate uptake for energy production in cardiomyocytes. Interestingly, the energy requirements in a healthy heart are mainly met by FAs (70%) (Gray & Kim 2011) and, to a lesser extent, glucose (20%), with lactate and ketone bodies composing the remainder of the fuel sources for the heart (Huss & Kelly 2005, Lopaschuk *et al*. 2010). Substrate uptake from the circulation to cardiomyocytes is a process that is carefully regulated by capillary endothelial cells (ECs). Compared to sinusoidal ECs that have large fenestrations that allow for the passage of particles that include albumin and chylomicron remnants, FA transport in the capillary ECs from the heart involves proteins with a high affinity for FA in the capillary endothelial cytoplasm (van der Vusse *et al*. 2000, van der Vusse 2009). Thus, FABP4 may contribute to the dysregulation of cardiac metabolic disorders, leading to deficient contractile function and HF by regulating the transport of the external supply of substrates, such as FAs, to cardiomyocytes (Fig. 3). Actually, both FABP4 and FABP5 have been found to be expressed in capillary ECs in several tissues, including the heart (Masouye *et al*. 1997, Elmasri *et al*. 2009), suggesting that both molecules may have redundant roles in regulating transendothelial FA transport. Specifically, using FABP4/5 double-knockout mice (*Fabp4/5* DKO), Iso and coworkers showed that these molecules are essential for the regulation of substrate uptake into the heart. Although FA uptake was reduced in the *Fabp4/5* DKO compared with that in wild-type mice, glucose uptake was remarkably increased (Iso *et al*. 2013). Since FABP4 is transcriptionally regulated by PPARγ, this nuclear receptor may contribute to transendothelial FA transport by regulating FABP4 and other FA transporters in ECs (Kanda *et al*. 2009, Goto *et al*. 2013). PPARγ activation induced FA uptake into human cardiac microvessel ECs via the transcriptional regulation of both FABP4 and fatty acid translocase (FAT)/CD36 (Goto *et al*. 2013). Interestingly, knockdown of either FABP4 or CD36 partially inhibited the effect of PPARγ-induced FA uptake, suggesting that both PPARγ targets are involved in this process (Goto *et al*. 2013). Nevertheless, further research is required to fully clarify the role of FABP4 in regulating substrate uptake and its subsequent utilisation in the heart.

FABP4 as a potential therapeutic target for HF and CVD

Given that FABP4 has been proposed as a contributor for the development of metabolic-related CVD, pharmacological regulation of this molecule may be considered as a potential therapeutic approach for treating CVD and HF. Since individuals with decreased FABP4 expression show a reduced risk of CVD (Tuncman *et al*. 2006), strategies have been focused on inhibiting or reducing the circulating levels of FABP4. In a US Food and Drug Administration

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(FDA) screen for approved drug repurposing, several drugs were discovered as FABP4-binding molecules, including the broad-spectrum antibiotic levofloxacin as a high-affinity FABP4 inhibitor, among others (Wang *et al*. 2014). Additionally, several synthetic FABP4 inhibitors have been developed to date (Lehmann *et al*. 2004, Ringom *et al*. 2004, Sulsky *et al*. 2007, Furuhashi & Hotamisligil 2008, Barf *et al*. 2009, Hertzel *et al*. 2009, Lan *et al*. 2011, Liu *et al*. 2011, Xu *et al*. 2012, Chen *et al*. 2014). Among them, BMS309403, an active small molecule that impedes the binding of FAs to the FABP4 FA-binding cavity (Furuhashi *et al*. 2007, Sulsky *et al*. 2007, Furuhashi & Hotamisligil 2008), has been shown in several experimental models to protect against insulin resistance, diabetes mellitus, fatty liver disease and atherosclerosis (Furuhashi *et al*. 2007, Lee *et al*. 2011). Additionally, HTS01037, another FABP4 inhibitor, attenuated the proinflammatory profile in macrophages (Xu *et al*. 2015), showing the potential effect of FABP4 inhibitors on inflammation-related diseases. Other approaches have targeted circulating FABP4 using neutralising antibodies as well as improving insulin sensitivity and glucose homeostasis (Cao *et al*. 2013, Miao *et al*. 2015). Similar effects were found by directly targeting FABP4 expression with short-hairpin RNAs (shRNAs) in adipose tissue from obese diabetic mice (Won *et al*. 2014). Thus, although further studies are needed to determine the efficacy and safety of FABP4 inhibitors for clinical use, the experimental evidence strongly supports FABP4 inhibition as an emerging approach for the treatment of CVD-related metabolic diseases.

Conclusions

Recent studies have identified FABP4 as a novel adipokine that is involved in HF and CVD. FABP4 has been associated with several components of metabolic syndrome, atherosclerosis, insulin resistance and low-grade inflammation, and thus, it has been proposed as a cardiometabolic predictor for CVD. Additionally, FABP4 has been directly related to cardiac alterations, and it is directly related to well-established hallmarks for HF, such as NT-proBNP. Thus, it has been proposed as an independent predictor for HF. Experimental studies support that FABP4 directly contributes to altered cardiac function. However, the underlying molecular mechanisms involved in the FABP4-induced cardiac dysfunction are only just beginning to emerge. It has been proposed that FABP4 controls myocardial function by regulating the transendothelial fuel supply to cardiomyocytes. Nevertheless, the role of FABP4 has not been explored in insulin-resistant cardiomyocytes/hearts. It is currently unknown whether FABP4 may regulate cellular signalling in the absence of fatty acids in cardiac cells. In addition, it is not clear if this molecule can be internalised by cardiomyocytes and take part in the regulation of cellular responses, such as inflammation, lipid oxidation or lipid droplets storage, among other processes. Although further research is required to fully understand the role of FABP4 in cardiac regulation, the evidence reviewed here supports the claim that this molecule is a potential target for new therapeutic strategies against cardiac disturbances that lead to HF.

Despite evidence supporting that pharmacological inhibition of FABP4 confers protection towards several metabolic-related disturbances, different aspects should be addressed before considering FABP4 inhibition as a realistic option for the treatment of CVD and HF. First, FABP4 inhibitors have not been explored in experimental models of HF. Apart from the potential effects of the FABP4 inhibitors on preventing/improving HF, additional studies must be done to determine the safety of these drugs. Therefore, to fully exploit the potential of FABP4 inhibitors for the therapeutic intervention against CVD and HF, the pharmaceutical industry will have to employ new drug development strategies to guarantee the efficacy and safety of these molecules.

In summary, while FABP4 has been identified as a novel molecule related to HF and CVD, further research is warranted to fully understand the role of this molecule in the cellular responses underlying these processes. Additionally, there are still some concerns regarding the development of selective and safe FABP4 inhibitors. Although data from preclinical studies seem promising, the development of new drugs is required before FABP4 inhibition can be considered a realistic therapeutic approach for the clinical treatment of HF and CVD.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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