The role of CD36 in cardiovascular diseases

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Abstract

CD36, also known as scavenger receptor B2, is a multifunctional receptor widely expressed in various organs. CD36 plays a crucial role in the uptake of long-chain fatty acids, the main metabolic substrate in myocardial tissue. The maturation and transportation of CD36 was regulated by the post-translational modifications including phosphorylation, ubiquitination, glycosylation, and palmitoylation. CD36 is decreased in pathological cardiac hypertrophy caused by ischemia-reperfusion and pressure overload, while increased in diabetic cardiomyopathy. Deficiency of CD36 alleviate diabetic cardiomyopathy, while overexpression of CD36 eliminates the damage of ischemia-reperfusion, suggesting that CD36 is closely associated with the progression of cardiovascular diseases. and it is expected to be a new therapeutic target. This review summarizes the regulation and post-translational modifications of CD36, and evaluates its role in main cardiovascular diseases and its potential as a therapeutic target.

Abbreviations

AMPK	AMP kinase	
DAGL	diacylglycerol lipase	diacylglycerol lipase
DHHC	Asp–His–His–Cys	Asp–His–His–Cys
FGF21	fibroblast growth factor 21	fibroblast growth factor 21
FOXO1	forkhead box O1	forkhead box O1
GPAT	glycerol-3-phosphate acyltransferase	glycerol-3-phosphate acyltransferase
HCM	hereditary hypertrophic cardiomyopathy	hereditary hypertrophic cardiomyopathy
HDL	high density lipoprotein	high density lipoprotein
HSL	hormone-sensitive lipase	hormone-sensitive lipase
IAP	Intestinal alkaline phosphatase	Intestinal alkaline phosphatase
LCFA	long-chain fatty acid	long-chain fatty acid
LDL	low density lipoprotein	low density lipoprotein
MHC	myosin heavy chain	myosin heavy chain
PGC1α	peroxisome proliferator-activated receptor γ coactivator-1α	peroxisome proliferator-activated receptor γ coac
PKA	protein kinase A	protein kinase A
PPARα	peroxisome proliferator-activated receptor α	peroxisome proliferator-activated receptor α
PPARγ	peroxisome proliferator-activated receptor-γ	peroxisome proliferator-activated receptor-γ
ROS	reactive oxygen species	reactive oxygen species
SCD1	stearoyl-CoA desaturase 1	stearoyl-CoA desaturase 1
SCD2	stearoyl-CoA desaturase 2	stearoyl-CoA desaturase 2
SREBP-1c	sterol-responsive element-binding protein-1c	sterol-responsive element-binding protein-1c
TAC	transverse aortic constriction	transverse aortic constriction

1 Introduction

CD36 is a member of the class B2 scavenger receptor family, including low density lipoprotein (LDL), high density lipoprotein (HDL)-bound scavenger receptor B1, and HDL-bound scavenger receptor scavenger receptor B3(Luiken et al., 2016). The ligands of CD36 are mainly divided into lipid ligands and protein ligands. The former includes oxidized LDL particles(Jay et al., 2015), long-chain fatty acids (LCFA)(Liu et al., 2018a), phospholipids(Lee et al., 2015), etc., and the latter includes collagen(Lee et al., 2019), thrombospondin(Simantov et al., 2005). In addition, apoptotic cells also serve as ligands for CD36(Albert et al., 1998).

CD36 is expressed in various tissues, including endothelial cells(Son et al., 2018), cardiac muscle cells(Yu et al., 2020), renal tubular epithelial cells(Hou et al., 2015), liver cells(Couturier et al., 2019), adipocytes(Ladanyi et al., 2018), platelets(Yang et al., 2018), macrophage(Frank et al., 2019), et al., and involved in many pathophysiological processes, including immune regulation(Wang and Li, 2019), metabolic regulation(Glatz and Luiken, 2017) et al. In myocardial tissue, CD36 mainly mediates the uptake of long-chain fatty acids(Kim and Dyck, 2016). Fatty acids provide over 70% of the ATP for myocardial tissue and most of the fatty acids enter the cells through protein-mediated diffusion. Importantly, 70% of total fatty acid intake is mediated by CD36(Kim and Dyck, 2016). Therefore, CD36 is indispensable in cardiovascular system.

The synthesis and translocation of CD36 are affected by many stimuli. Short-term stimulation of insulin promotes the translocation of CD36 from the endosome to the cell membrane(Luiken et al., 2002), while long-term stimulation induces its protein synthesis(Cheng et al., 2011). Hyperglycemia and hyperlipidemia also facilitate the translocation of CD36 to the cell membrane(Angin et al., 2012). It has been proved that impaired synthesis and abnormal distribution of CD36 shorten myocardial energy supply(Sung et al., 2017), resulting in the impairment of myocardial contractile function(Abumrad and Goldberg, 2016). Pressure overload decreases a controller of CD36 synthesis, nuclear receptor peroxisome proliferator-activated receptor α (PPARα)(Dobrzyn et al., 2013), resulting in insufficient myocardial fatty acid uptake and the accumulation of toxic lipids, and ultimately leading to heart failure. However, down-regulating CD36 in diabetic cardiomyopathy reduces the toxic lipids(Xu et al., 2019), and improves the contractile function of the heart. Therefore, the influence of CD36 on myocardium may not be consistent and largely depend on the pathological background.

In this review, we summarize regulation and post translational modification of CD36, and focus on its role in the cardiovascular diseases, especially in ischemia/reperfusion, diabetic cardiomyopathy, pathological cardiac hypertrophy, and physiological cardiac hypertrophy. we also provide some suggestions for basic and clinical research of CD36, aiming to emphasize the significance of CD36 in the cardiovascular system and shed light on its therapeutic target.

2 CD36 Protein

Human CD36 has a total length of 472 amino acids and a predicted molecular weight of 53 kd(Abumrad et al., 1993). Due to glycosylation, the actual molecular weight is 88 kd(Greenwalt et al., 1992). CD36 contains two phosphorylation sites and four palmitoylation sites, which are distributed at the terminals of NH2 and COOH, respectively. And two ubiquitination sites are also at the COOH terminal.

CD36 is a membrane protein that is synthesized in the polyribosome, then transfers to the endoplasmic reticulum and Golgi apparatus for further processing, finally transported by endosome to the cytomembrane(Glatz et al., 2016). Under the stimulation of insulin(Samovski et al., 2018) or contraction(Luiken et al., 2002), it moves to the lipid rafts of the cell membrane to facilitate LCFA uptake, which may be associated with activation of PI3K-Akt and AMP kinase (AMPK). CD36 not only locates in plasma membranes and endosomes, but also distributes on mitochondrial(Monaco et al., 2015), but its specific function on mitochondrial remains unclear. CD36 is a double transmembrane protein which can't form a channel that allows for fatty acids transferring from outside to the inside(Pepino et al., 2014). Interestingly, the outer ring of CD36 contains a large hydrophobic cavity, which provides a docking site for fatty acids and other hydrophobic ligands(Gomez-Diaz et al., 2016), facilitating the proximity of hydrophobic ligands to the cell surface, thus

promoting the transportation of fatty acids into the cell.

3 CD36 post translational modifications

The synthesis, distribution and activation of CD36 are largely affected by its post-translational, including ubiquitination, glycosylation, phosphorylation and palmitoylation. However, it is worth noticing that though there are many acetylation sites on CD36, no research reveals the effect of its acetylation.

3.1 CD36 ubiquitination

Protein ubiquitination is the coupling of protein and ubiquitin, mediated by ubiquitin ligase (E3)(Popovic et al., 2014). CD36 is the target of E3 ligase Parkin(Abumrad and Moore, 2011) (Figure 1). Differing from the degradation effect of ubiquitination, monoubiquitylation of CD36 by Parkin enhances its stability and increase its plasma membrane level. In the presence of parkin(Kim et al., 2011), LCFA-induces polyubiquitination and degradation of CD36 is significantly down-regulated, probably because one of the ubiquitination sites (Lys469 and Lys472) of LCFA is also the target of Parkin. A recent study confirmed that USP14 is a deubiquitinating enzyme that mediates CD36 deubiquitylation on macrophages, USP14 cleaves ubiquitin chains from ubiquitinated CD36 proteins, thus avoiding the fate of CD36 being transported into the proteasome for degradation(Zhang et al., 2020)(Figure 1). However, whether Parkin and USP14 respectively act as E3 ligase and deubiquitinating enzyme in cardiomyocytes remains unclear.

LCFA, a ligand of CD36, significantly enhances the ubiquitination of CD36(Tran et al., 2011) and promotes its degradation after a long-term interaction(Smith et al., 2008) (Figure 1). This is a negative feedback for the cellular uptake of fatty acids. Recent studies have shown that ubiquitinated CD36 in myocytes stabilizes the structure of insulin receptor substrates 1(Sun et al., 2018), and thus maintains insulin signaling. Giving that insulin reduces the ubiquitination of it(Smith et al., 2008) (Figure 1), CD36 may be involved in self-regulation of insulin signaling pathway. Moreover, CD36 ubiquitination in macrophages inhibits the formation of atherosclerosis by decreasing fatty acids uptake(Srikanthan et al., 2014). But the role of ubiquitinated CD36 in heart have not yet been elucidated.

3.2 CD36 glycosylation

The glycosylation of CD36 is N-linked at asparagine residues (Asn) mediated by glycosyltransferase(Hoosdally et al., 2009; McDonald et al., 2018). There are 10 glycosylation modification sites of CD36 in human, located in the extracellular segment of CD36(Vinals et al., 2003).

Apart from increasing the molecular weight of CD36, glycosylation could also stabilize the tertiary folding of polypeptides and is therefore essential for forming the spatial structure of CD36(Mitra et al., 2006). And it affects the folding of CD36 theoretically thus influences the correct translocation of it to the cell membrane. It has been proved that carboxyl-terminal sites Asn247, Asn321, and Asn417 are indispensable for CD36 trafficking(Hoosdally et al., 2009). And mutations in Asn108 and Asn173 sites result in the abnormal distribution of CD36 on the COS m6 cells membrane(Vinals et al., 2003). Mutations in Asn 102 of CD36 has been found in spontaneously hypertensive rats (SHR)(Lauzier et al., 2011). Since Asn102 is located in the fatty acid binding pocket, mutations at this glycosylation site may have a greater possibility to affect fatty acid docking in the CD36 pocket then affect fatty acid transport. CD36 protein levels in SHR are significantly downregulated and fatty acid intake is reduced, which may be related to the glycosylation mutation of Asn102. However, the role of Asn102 in SHR has not yet been confirmed by experiments. Further researches are required to clarify the role of Asn102 and other glycosylation sites in cardiovascular diseases.

3.3 CD36 phosphorylation

CD36 has two phosphorylation sites, Thr92 and Ser237, phosphorylated by PKC(Chu and Silverstein, 2012) and PKA(Hatmi et al., 1996), respectively(Figure 1). CD36 in small intestinal epithelial cells is also dephosphorylated by intestinal alkaline phosphatase (IAP)(Lynes et al., 2011) (Figure 1). In platelets, phosphorylation of Thr92 mediated the binding of CD36 and thrombospondin(Asch et al., 1993). Phosphorylation of

CD36 at Thr92 is also necessary for the adhesion of plasmodium falciparum-infected erythrocytes to human dermal microvascular endothelial cells under flow condition(Ho et al., 2005). CD36 phosphorylated at Ser237 downregulates the fatty acid uptake rate of platelets and enterocytes(Guthmann et al., 2002; Lynes et al., 2011).

3.4 CD36 palmitoylation

Most members of the DHHC(Asp–His–His–Cys)family of proteins have palmitoyl transferase activity, and are confirmed to be the main PATs(De and Sadhukhan, 2018). DHHC4/5 has been proved to be the palmitoylase of CD36 in adipocytes (Figure 1). The absence of either DHHC4 or DHHC5 prevents the palmitoylation and the insertion of CD36 on the adipose membrane, thereby destroying the CD36-dependent fatty acid uptake(Wang et al., 2019). Besides, SelK(Meiler et al., 2013), which belongs to neither PATs nor PPT, is also required for palmitoylation of CD36 in macrophages, suggesting that other proteins may also be involved in the palmitoylation of CD36.

CD36 has four palmitoylation sites Cys 3, Cys7, Cys464, and Cys466 (Figure 1). And the palmitoylation is strengthened by insulin stimulation. Combined mutations of these four palmitoylation sites hinders CD36 translocate to the cell membrane for fatty acid uptake even in the presence of insulin and AMPK(van Oort et al., 2014). With the inhibition of CD36 palmitoylation by ceruloplasmin(Thorne et al., 2010), a kind of palmitoylation specific inhibitor, the processing of CD36 at the endoplasmic reticulum and transport through the secretory pathway extends from 90 minutes to 4 hours in melanoma cells, indicating that palmitoylation is essential for the transport and translocation of CD36.

Increased palmitoylation of CD36 is found in liver steatosis and fibrosis(Zhao et al., 2018) .The decrease of CD36 palmitoylation down-regulates the uptake of fatty acids and helps to balance the fatty acid metabolism in the liver cells, thus eliminates the liver steatosis and fibrosis(Zhao et al., 2018). However, no research has revealed the effects of the palmitoylation of CD36 in cardiovascular system.

4 CD36 and cardiovascular diseases

4.1 CD36 and ischemia/reperfusion

Ischemia/reperfusion is characterized by the abruptly interruption of blood flow and subsequent restoration of blood flow(Lejay et al., 2016). The cutoff of oxygen and nutrition results in various metabolic changes(Lesnefsky et al., 2017), including lipid metabolism alterations. The change of CD36 in ischemia/reperfusion has been shown by using (3) H-labeled metabolic substrates to measure the metabolic changes of Wistar rat heart at different stages during ischemia/reperfusion(Heather et al., 2013). During ischemia, the CD36 of the sarcolemma is downregulated by 32%, and the fatty acid oxidation rate decreases by 95%. In the reperfusion stage, CD36 level remains low, but the fatty acid oxidation rate returned to the pre-ischemic state(Heather et al., 2013). The increased pH of the endosome may contribute to the low level of CD36 throughout the whole ischemia/reperfusion period(Steinbusch et al., 2010). Translocation of CD36 to the sarcolemma is significantly enhanced when the pH of the endosome is high, while a decrease in pH inhibits this translocation. During ischemia, myocardial glycolysis increases by 86% and lactic acid level increases by 7 folds(Heather et al., 2013) (Figure 2), which lead to a low pH state and subsequently suppresses the CD36 translocation. When shifting to the reperfusion phase, the lactic acid in cardiomyocytes could not be effectively eliminated in a short period of time, the cells may still be at a low pH status and CD36 translocation is still suppressed (Figure 2).

With same oxygen consumption, glucose provides more energy than lipid, so it is preferred to maintenance myocardial function(Fukushima et al., 2015; Umbarawan et al., 2018b). The reduction of CD36 is beneficial to the conversion of metabolic substrates from fatty acids to glucose during hypoxia. Thus the constantly low level of CD36 may help cardiomyocytes to maintain energy balance (Figure 2). What's more, the rate of fatty acid oxidation in cardiomyocytes in ischemia is reduced to 5% of basal states(Heather et al., 2013). A relatively low CD36 avoids the accumulation of triglycerides in cytosol by reducing the absorption of fatty acids (Figure 2). High concentrations of fatty acids in the cardiomyocytes could reduce the recovery

of ischemic heart function during the reperfusion stage by triggering insulin resistance and cardiomyocytes apoptosis(Adrian et al., 2017; Jelenik et al., 2018; Liu et al., 2018b). Therefore, the reduction of CD36 during ischemia benefits to the heart by avoiding excessive accumulation of triglycerides, and CD36 decreasing during ischemia is a favorable adaptation for cardiomyocytes to survive.

Focusing on inhibiting CD36 function, therapeutic strategies for ischemia-reperfusion have been developed. Mansor LS et al corrected post-hypoxia/reoxygenation cardiac metabolic disorders by injecting a CD36 inhibitor sulfo-N-succinimide oleate into the heart of type 2 diabetic male Wistar rats 4 minutes before hypoxia(Mansor et al., 2017). Pre-injection of selective CD36 ligand EP 80317 and azeptide CP-3(iv) in mice significantly reduced myocardial infarct size(Bessi et al., 2012; Huynh et al., 2018). Exenatide, a small molecule drug that generally regulates glucose metabolism, has also been shown to improve cardiac function after cardiac ischemia-reperfusion injury by inhibiting the translocation of CD36(Zheng et al., 2017).

Drug studies provided strong evidence that inhibiting the function of CD36 contributes to the recovery of heart function, but the most direct evidence comes from heart CD36-knockout (cCD36KO) mice. Inducible cardiomyocyte-specific CD36 ablation does not alter cardiac morphology, while improves functional recovery after ischemia/reperfusion(Nagendran et al., 2013). The decrease in fatty acid oxidation rate caused by the decrease of CD36 lays the foundation for increasing the rate of glucose oxidation. And it was proved that this recovery is due to the lower hydrogen ion concentration resulting from the uncoupling of glycolysis from glucose oxidation produced before and after ischemia(Nagendran et al., 2013). However, CD36 systemic knockout mice still suffered from severe ischemia-reperfusion injury(Cera et al., 2010). Presumably, it is the general reduction of CD36 that matters. Not restricted in the heart, systemic metabolic changes occur in a vast of tissues in the systemic knockout mice, and due to various potential adaptive adjustments from the embryonic stage, these mice may be significantly different from heart-specific knockout mice.

However, some studies about spontaneously hypertensive rats on ischemia/reperfusion have challenged the protective effect of CD36 decline. Instead of the inhibition of CD36, the overexpression of CD36 in SHR rats reduced the infarct size, and the underlying mechanism has not been clarified. Giving that the model already has the pathological factor of hypertension, it is possible that the overexpression of CD36 reduce the myocardial injury risk brought by hypertension and indirectly protect the infarcted myocardium caused by ischemia/reperfusion(Neckar et al., 2012).

4.2 CD36 and diabetic cardiomyopathy

The typical characteristic of diabetic cardiomyopathy is the altered lipid metabolism and impaired insulin signaling pathways(Jia et al., 2016; Carpentier, 2018; Joubert et al., 2019). In the basic conditions, CD36 on the cardiac sarcolemma is significantly increased in obese Zuker rats(Coort et al., 2004), db/db mice(Carley and Severson, 2008) and high-fat-fed rats(Ouwens et al., 2007). The upregulation of CD36 has also been confirmed in cardiomyocytes of patients with diabetic cardiomyopathy(Garcia-Rua et al., 2012).

The increase of CD36 on the sarcolemma in diabetic cardiomyopathy may be attributed to hyperinsulinemia, hyperglycemia, and hyperlipidemia. In the early stages of diabetes, insulin is at high levels(Paolillo et al., 2019), Luiken JJ et al. found that insulin stimulation in isolated rat myocardial cells resulted in a 1.5-fold increase in CD36 on the sarcolemma and a 62% decrease in intracellular CD36, which suggested that insulin could effectively promote the translocation of CD36(Luiken et al., 2002) (Figure 3). Besides, chronic insulin stimulation also induces CD36 mRNA translation by activating the transcription factor forkhead box O1 (FOXO1), which further facilitates CD36 protein synthesis(Chistiakov et al., 2017) (Figure 3). In the late stage of diabetes, although the insulin level has decreased significantly, and the cardiomyocytes are not sensitive to insulin at this time due to insulin resistance, but CD36 has been already permanently transferred to the myometrium during the early stage(Ouwens et al., 2007). As a result, the decline of insulin doesn't change the facts that fatty acids have been taken into the cardiomyocytes in quantity. Similar to chronic insulin stimulation, high glucose stimulation could increase CD36 mRNA translation(Griffin et al., 2001), followed by increased CD36 expression, and palmitic acid stimulation could induce membrane translocation of CD36(Angin et al., 2012). In the advanced stage of diabetes, hyperglycemia and hypertriglyceridemia may

occur, thus further promote CD36 expression and increase its membrane distribution(Alonso et al., 2018). In addition to external factors such as insulin, glucose and lipids, the latest researches suggest that the increase in CD36 in diabetic cardiomyopathy is also associated with the regulation of microRNA. MiR-320 which acts as a small activating RNA in the nucleus is highly expressed in diabetic cardiomyopathy mice, and promotes CD36's expression by directly acting on its nuclear transcription(Li et al., 2019) (Figure 3). In contrast, miR-200b-3p is remarkably reduced in diabetes cardiomyopathy, which is an effective inhibitor of CD36 (Figure 3).

CD36 increases in diabetic cardiomyopathy, which in turn worsens heart function(Luiken, 2009). The increased distribution of CD36 on the myometrium result in the intake of a large amount of fatty acids. Fatty acids in the cytoplasm could activate peroxisome proliferator-activated receptors (PPAR)(Glatz and Luiken, 2017), thereby inducing the up-regulation of enzymes necessary for mitochondrial β-oxidation, leading to a significant increase in fatty acid oxidation rates. However, the rate of fatty acid uptake and storage is higher than the rate of oxidation, thus resulting in the accumulation of lipids in the cell (Figure 3). Excessive lipid intermediates, including diacylglycerol and ceramide, have been shown to induce insulin resistance(Petersen and Shulman, 2017), triggers myocardial contractile dysfunction(Chistiakov et al., 2017). At the same time, high levels of β-oxidation of fatty acids produce a large amount of reactive oxygen species (ROS)(Cortassa et al., 2017), which can also induce inflammation(Agita and Alsagaff, 2017) and insulin resistance(Di Meo et al., 2017; Sung et al., 2019) to aggravate myocardial contractile dysfunction (Figure 3). Besides. lipids could directly lead to contractile dysfunction by promoting myocardial cell apoptosis(Zhou et al., 2018). Therefore, inhibiting the uptake of long-chain fatty acids by targeting CD36 is the preferred strategy to reduce cardiac insulin resistance and ultimately prevent diabetic heart failure.

Several studies have proved that reducing the distribution of CD36 on the sarcolemma and thereby inhibiting the uptake of LCFA do help to improve the heart function of diabetic cardiomyopathy(Angin et al., 2012). For example, myosin heavy chain (MHC) -PPARα overexpressed mice shows severe cardiomyocyte lipid accumulation and cardiac dysfunction(Yang et al., 2007). However, due to the lack of CD36, the offspring produced by crossing MHC-PPARα mice with CD36-deficient mice (MHC-PPARα/CD36-/- mice) improves triglycerides accumulation and cardiac dysfunction under basic conditions and in a high-fat diet. Glucagon-like peptide-1 could eliminate the lipo-toxicity of diabetic cardiomyopathy by stimulating protein kinase A (PKA) inhibition of PPARα -CD36 pathway(Wu et al., 2018). Exogenous H_2S protects diabetic hearts by inhibiting the translocation of CD36(Yu et al., 2020). N-Acetylcysteine also restored Sevo-postC cardioprotection in diabetes by reducing Foxo1 and CD36(Lin et al., 2016). Fibroblast growth factor 21(FGF21) deletion aggravates cardiac lipid accumulation by up-regulating cardiac Nrf2-driven CD36 expression(Yan et al., 2015). Thus FGF21 is a potential agent to reduce lipid accumulation and ameliorates diabetic cardiomyopathy by down-regulating the expression of CD36.

4.3 CD36 and cardiac hypertrophy

4.3.1 CD36 in hereditary hypertrophic cardiomyopathy

Hereditary hypertrophic cardiomyopathy (HCM) is a disease with cardiac hypertrophy as the main pathological manifestation, and it is caused by a dominant mutation in the gene encoding cardiac sarcomeric protein(Sequeira et al., 2019). A survey about the CD36 and hereditary hypertrophic cardiomyopathy patients shows that 37.9% of HCM patients with asymmetric ventricular septal hypertrophy had a loss of CD36 protein(Tanaka et al., 1997), which is accompanied by defective myocardial long-chain fatty acid intake, suggesting that the reduced CD36 may play a role in the pathogenesis of hereditary hypertrophy. The relationship of CD36 translocation and left ventricular contractile dysfunction is verified in HCM mice(Tanaka et al., 1997; Magida and Leinwand, 2014). Owing to the decrease of CD36 translocation to the plasm membrane, ATP and triglyceride in the myocardium dramatically decrease. Although the mechanism of how CD36 decreases in hereditary hypertrophic cardiomyopathy remains to be investigated, increasing CD36 and improving fatty acid intake may provide a new solution for the treatment of hereditary hypertrophic cardiomyopathy.

4.3.2 CD36 in pathological/ physiological cardiac hypertrophy

Differing from hereditary hypertrophic cardiomyopathy generated by genetic mutations, secondary cardiac hypertrophy is mostly caused by external stress including pressure overload or physical exercise. And it is naturally divided into physiological cardiac hypertrophy and pathological cardiac hypertrophy according to different stimulus factors and outcomes. Changes in CD36 in two different types of hypertrophy hearts were first demonstrated in 2013(Dobrzyn et al., 2013). Exercise training significantly increases the expression of CD36 in the heart, but pressure overload reduces the expression of CD36(Iemitsu et al., 2003). The decrease in CD36 in pathological cardiac hypertrophy and the upregulation in physiological cardiac hypertrophy may be related to PPARα and peroxisome proliferator-activated receptor γ coactivator-1α (PGC1α). Physical exercise increases the expression of PPARα(Santos et al., 2016; Broderick et al., 2018) and PGC1α (Tao et al., 2015; Deloux et al., 2017)in the heart, while cardiac pressure overload reduces both of them(Oka et al., 2015; Karam et al., 2017) (Figure 4). The promoter region of CD36 contains PPARα response elements(van der Meer et al., 2010). And it has been shown that nuclear receptor PPARα and nuclear receptor peroxisome proliferator-activated receptor-γ (PPARγ) regulate CD36 expression in macrophages and cardiac microvascular endothelial cells(Madonna et al., 2011; He et al., 2019).

As mentioned before, when myocardial cells are facing a crisis of ischemia and hypoxia, metabolism is remodeled. As for hypoxic pathological cardiac hypertrophy(Tham et al., 2015), early and timely reduction of the distribution of CD36 on the cell membrane helps to eliminate the injury brought by subsequent large intake of fatty acids. The reduction of CD36 not only promotes the substrate transition of fatty acids to glucose(Umbarawan et al., 2018b), but also eliminates the accumulation of toxic lipid intermediates. However, the reduction of CD36 may ultimately shorten the energy supply in the chronic stage of pathological cardiac hypertrophy. Glucose uptake and glucose oxidation increase in the early stage to sustain the energy generation, but it eventually decreased in the late stage(Iemitsu et al., 2003). And, glycolysis and energy generated from other substrates (lactic acid, branched-chain amino acids and ketone bodies) couldn't compensate for the reduction of fatty acid oxidation and glucose oxidation, putting the heart in an insufficient cardiac energy state (Figure 4). Besides, Although the reduction of CD36 leads to a remarkable decline in the overall intake of fatty acids, studies have proved that fat synthesis-related enzymes , including sterol-responsive element-binding protein-1c (SREBP -1c), stearoyl-CoA desaturase 1 (SCD1), stearoyl-CoA desaturase 2 (SCD2) and Glycerol-3-phosphate acyltransferase (GPAT) et al., are not down-regulated in pathological cardiac hypertrophic cardiomyocytes (Figure 4). But, the activity and content of hormone-sensitive lipase (HSL) and diacylglycerol lipase (DAGL) that break down fat decrease, resulting in a 31% increase in triglycerides and a 200% increase in diacylglycerol in myocardial cells(Tanaka et al., 1997) (Figure 4). insulin resistance caused by accumulated toxic lipids further exacerbates the lack of energy supply in the heart. Therefore, CD36 down-regulation is beneficial for the adaptive pathological cardiac hypertrophy, while is detrimental for maladaptive pathological cardiac hypertrophy.

Recent studies on CD36 cardiac-specific knockout mice and systemic knockout mice have demonstrated the role of CD36 in pathological cardiac hypertrophy. CD36 cardiac-specific knockout mice rapidly transferred from compensatory cardiac hypertrophy to heart failure due to the imbalance of energy. Comparatively, CD36 systemic knockout mice show pronounced myocardial interstitial fibrosis, cardiac enlargement and contractile dysfunction than wild-type mice after transverse aortic constriction (TAC) surgery(Nakatani et al., 2019). The myocardium of CD36KO-TAC leads to insufficient energy supply, not only due to the decrease of CD36, but also because of the increase of de novo amino acid synthesis from glucose, which further reduces the size of the high-energy phosphate pool(Umbarawan et al., 2018a). But, whether overexpression of CD36 relieves the energy deficiency in the pathological cardiac hypertrophy and in turn saves the failing heart caused by cardiac pressure overload needs further investigation. And it is certain that increasing the supply of fatty acids in myocardial cells to expand high-energy phosphate pool is beneficial for hypertrophic myocardium. Because even in the case of a decrease in medium-chain acetyl-CoA dehydrogenase, providing medium-chain fatty acids for cardiomyocytes lacking CD36 and bypassing long-chain fatty acids can still relieve cardiac pressure overload-induced heart failure(Sung et al., 2017).

5 Conclusion

Cardiovascular diseases have been seriously endangering the physical and mental health of the elderly people(Zhou et al., 2019), and now they are particularly prominent with the aging epidemic. Cardiac lipid metabolism remodeling plays a key role in cardiovascular system diseases including ischemia-reperfusion, diabetic cardiomyopathy, and cardiac hypertrophy(D'Souza et al., 2016). CD36 is an indispensable molecule in lipid metabolism(Kim and Dyck, 2016). Changes in its synthesis, localization, and function directly affect the energy supply and metabolism of the heart. And studies on CD36 in different diseases suggest that CD36 may be a potential target for treatment. Therefore, the transcriptional activation, post-translational modification and localization changes of CD36 may provide new directions for the treatment of cardiovascular diseases.

Post-translational modifications of CD36 have been studied for nearly 30 years(Asch et al., 1993). The post-translational modifications including phosphorylation, ubiquitination, palmitoylation and glycosylation, accurately regulate the maturation, transport and positioning of CD36(Luiken et al., 2016). Researches in vitro have revealed the impacts of post-translational modification of CD36 in cellular fatty acid uptake in adipocytes(Wang et al., 2019) and muscle cells(Sun et al., 2018), etc. But few demonstrates its importance in cardiovascular system. Whether these modifications of CD36 alter the cellular uptake of fatty acids in myocardium and further influence the cardiac function still remains to be elucidated, and which enzymes mediate these modifications in cardiomyocytes and whether these enzymes are supposed to be the new therapeutic target also need further investigations.

Because fatty acids may also cause excessive lipid accumulation while providing energy(Park et al., 2007; Evans and Hauton, 2016), whether the increase in fatty acids uptake caused by CD36 is good or bad are not consistent under different pathological conditions. In addition to being modulated by CD36, fatty acids in cells are also affected by the rate of mitochondrial aerobic oxidation and the rate of triglyceride synthesis and decomposition(Bjorkegren et al., 2001; Heier and Haemmerle, 2016). Therefore, to evaluate the role of CD36 on the myocardial lipid metabolism, the corresponding mitochondrial aerobic oxidation and triglyceride synthesis also need to be taken into consideration. Since it is not uncommon that more than two pathological factors are combined at the same time, such as diabetics suffering hypertension(Neckar et al., 2012) or myocardial infarction(Cheng et al., 2015), the impact of CD36 on myocardial lipid metabolism and cardiac function is definitely more complicated in that case. So, further researches also need to investigate these situations.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org
the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018),
and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017).

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Conflict of interest

The authors confirm that there are no conflicts of interest.

Author contributions

HY Shu drafted the manuscript; YZ Peng, N Zhou, WJ Hang, JL Nie critically revised the entire manuscript; and all authors approved the entire submitted and final version.

References

Abumrad, N.A., el-Maghrabi, M.R., Amri, E.Z., Lopez, E., and Grimaldi, P.A. (1993). Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced

during preadipocyte differentiation. Homology with human CD36. J. Biol. Chem. 268: 17665–17668.

Abumrad, N.A., and Goldberg, I.J. (2016). CD36 actions in the heart: Lipids, calcium, inflammation, repair and more? Biochim. Biophys. Acta 1861: 1442–1449.

Abumrad, N.A., and Moore, D.J. (2011). Parkin reinvents itself to regulate fatty acid metabolism by tagging CD36. J. Clin. Invest. 121: 3389–3392.

Adrian, L., Lenski, M., Tödter, K., Heeren, J., Böhm, M., and Laufs, U. (2017). AMPK Prevents Palmitic Acid-Induced Apoptosis and Lipid Accumulation in Cardiomyocytes. Lipids 52: 737–750.

Agita, A., and Alsagaff, M.T. (2017). Inflammation, Immunity, and Hypertension. Acta Med. Indones. 49: 158–165.

Albert, M.L., Pearce, S.F., Francisco, L.M., Sauter, B., Roy, P., Silverstein, R.L., et al. (1998). Immature dendritic cells phagocytose apoptotic cells via alphavbeta5 and CD36, and cross-present antigens to cytotoxic T lymphocytes. J. Exp. Med. 188: 1359–1368.

Alonso, N., Moliner, P., and Mauricio, D. (2018). Pathogenesis, Clinical Features and Treatment of Diabetic Cardiomyopathy. Adv. Exp. Med. Biol. 1067: 197–217.

Angin, Y., Steinbusch, L.K.M., Simons, P.J., Greulich, S., Hoebers, N.T.H., Douma, K., et al. (2012). CD36 inhibition prevents lipid accumulation and contractile dysfunction in rat cardiomyocytes. Biochem. J. 448: 43–53.

Asch, A.S., Liu, I., Briccetti, F.M., Barnwell, J.W., Kwakye-Berko, F., Dokun, A., et al. (1993). Analysis of CD36 binding domains: ligand specificity controlled by dephosphorylation of an ectodomain. Science 262: 1436–1440.

Bessi, V.L., Labbe, S.M., Huynh, D.N., Menard, L., Jossart, C., Febbraio, M., et al. (2012). EP 80317, a selective CD36 ligand, shows cardioprotective effects against post-ischaemic myocardial damage in mice. Cardiovasc. Res. 96: 99–108.

Bjorkegren, J., Véniant, M., Kim, S.K., Withycombe, S.K., Wood, P.A., Hellerstein, M.K., et al. (2001). Lipoprotein secretion and triglyceride stores in the heart. J. Biol. Chem. 276: 38511–38517.

Broderick, T.L., Cusimano, F.A., Carlson, C., and Babu, J.R. (2018). Biosynthesis of the Essential Fatty Acid Oxidation Cofactor Carnitine Is Stimulated in Heart and Liver after a Single Bout of Exercise in Mice. J. Nutr. Metab. 2018: 2785090.

Carley, A.N., and Severson, D.L. (2008). What are the biochemical mechanisms responsible for enhanced fatty acid utilization by perfused hearts from type 2 diabetic db/db mice? Cardiovasc. Drugs Ther. 22: 83–89.

Carpentier, A.C. (2018). Abnormal Myocardial Dietary Fatty Acid Metabolism and Diabetic Cardiomyopathy. Can. J. Cardiol. 34: 605–614.

Cera, M., Salerno, A., Fragasso, G., Montanaro, C., Gardini, C., Marinosci, G., et al. (2010). Beneficial electrophysiological effects of trimetazidine in patients with postischemic chronic heart failure. J. Cardiovasc. Pharmacol. Ther. 15: 24–30.

Cheng, W., Wu, P., Du, Y., Wang, Y., Zhou, N., Ge, Y., et al. (2015). Puerarin improves cardiac function through regulation of energy metabolism in Streptozotocin-Nicotinamide induced diabetic mice after myocardial infarction. Biochem. Biophys. Res. Commun. 463: 1108–1114.

Cheng, Y., Liu, G., Pan, Q., Guo, S., and Yang, X. (2011). Elevated expression of liver X receptor alpha (LXRα) in myocardium of streptozotocin-induced diabetic rats. Inflammation 34: 698–706.

Chistiakov, D.A., Orekhov, A.N., and Bobryshev, Y. V (2017). The impact of FOXO-1 to cardiac pathology in diabetes mellitus and diabetes-related metabolic abnormalities. Int. J. Cardiol. 245: 236–244.

Chu, L.-Y., and Silverstein, R.L. (2012). CD36 ectodomain phosphorylation blocks thrombospondin-1 binding: structure-function relationships and regulation by protein kinase C. Arterioscler. Thromb. Vasc. Biol. 32: 760–767.

Coort, S.L.M., Hasselbaink, D.M., Koonen, D.P.Y., Willems, J., Coumans, W.A., Chabowski, A., et al. (2004). Enhanced sarcolemmal FAT/CD36 content and triacylglycerol storage in cardiac myocytes from obese zucker rats. Diabetes 53: 1655–1663.

Cortassa, S., Sollott, S.J., and Aon, M.A. (2017). Mitochondrial respiration and ROS emission during β-oxidation in the heart: An experimental-computational study. PLoS Comput. Biol. 13: e1005588.

Couturier, J., Nuotio-Antar, A.M., Agarwal, N., Wilkerson, G.K., Saha, P., Kulkarni, V., et al. (2019). Lymphocytes upregulate CD36 in adipose tissue and liver. Adipocyte 8: 154–163.

D'Souza, K., Nzirorera, C., and Kienesberger, P.C. (2016). Lipid metabolism and signaling in cardiac lipotoxicity. Biochim. Biophys. Acta 1861: 1513–1524.

De, I., and Sadhukhan, S. (2018). Emerging Roles of DHHC-mediated Protein S-palmitoylation in Physiological and Pathophysiological Context. Eur. J. Cell Biol. 97: 319–338.

Deloux, R., Vitiello, D., Mougenot, N., Noirez, P., Li, Z., Mericskay, M., et al. (2017). Voluntary Exercise Improves Cardiac Function and Prevents Cardiac Remodeling in a Mouse Model of Dilated Cardiomyopathy. Front. Physiol. 8: 899.

Dobrzyn, P., Pyrkowska, A., Duda, M.K., Bednarski, T., Maczewski, M., Langfort, J., et al. (2013). Expression of lipogenic genes is upregulated in the heart with exercise training-induced but not pressure overload-induced left ventricular hypertrophy. Am. J. Physiol. Endocrinol. Metab. 304: E1348-58.

Evans, R.D., and Hauton, D. (2016). The role of triacylglycerol in cardiac energy provision. Biochim. Biophys. Acta 1861: 1481–1491.

Frank, A.-C., Ebersberger, S., Fink, A.F., Lampe, S., Weigert, A., Schmid, T., et al. (2019). Apoptotic tumor cell-derived microRNA-375 uses CD36 to alter the tumor-associated macrophage phenotype. Nat. Commun. 10: 1135.

Fukushima, A., Milner, K., Gupta, A., and Lopaschuk, G.D. (2015). Myocardial Energy Substrate Metabolism in Heart Failure : from Pathways to Therapeutic Targets. Curr. Pharm. Des. 21: 3654–3664.

Garcia-Rua, V., Otero, M.F., Lear, P.V., Rodriguez-Penas, D., Feijoo-Bandin, S., Noguera-Moreno, T., et al. (2012). Increased expression of fatty-acid and calcium metabolism genes in failing human heart. PLoS One 7: e37505.

Glatz, J.F.C., and Luiken, J.J.F.P. (2017). From fat to FAT (CD36/SR-B2): Understanding the regulation of cellular fatty acid uptake. Biochimie 136: 21–26.

Glatz, J.F.C., Nabben, M., Heather, L.C., Bonen, A., and Luiken, J.J.F.P. (2016). Regulation of the subcellular trafficking of CD36, a major determinant of cardiac fatty acid utilization. Biochim. Biophys. Acta 1861: 1461–1471.

Gomez-Diaz, C., Bargeton, B., Abuin, L., Bukar, N., Reina, J.H., Bartoi, T., et al. (2016). A CD36 ectodomain mediates insect pheromone detection via a putative tunnelling mechanism. Nat. Commun. 7: 11866.

Greenwalt, D.E., Lipsky, R.H., Ockenhouse, C.F., Ikeda, H., Tandon, N.N., and Jamieson, G.A. (1992). Membrane glycoprotein CD36: a review of its roles in adherence, signal transduction, and transfusion medicine. Blood 80: 1105–1115.

Griffin, E., Re, A., Hamel, N., Fu, C., Bush, H., McCaffrey, T., et al. (2001). A link between diabetes and atherosclerosis: Glucose regulates expression of CD36 at the level of translation. Nat. Med. 7: 840–846.

Guthmann, F., Maehl, P., Preiss, J., Kolleck, I., and Rustow, B. (2002). Ectoprotein kinase-mediated phosphorylation of FAT/CD36 regulates palmitate uptake by human platelets. Cell. Mol. Life Sci. 59: 1999–2003.

Hatmi, M., Gavaret, J.M., Elalamy, I., Vargaftig, B.B., and Jacquemin, C. (1996). Evidence for cAMP-dependent platelet ectoprotein kinase activity that phosphorylates platelet glycoprotein IV (CD36). J. Biol. Chem. 271: 24776–24780.

He, C., Zhang, G., Ouyang, H., Zhang, P., Chen, Y., Wang, R., et al. (2019). Effects of β2/aβ2 on oxLDL-induced CD36 activation in THP-1 macrophages. Life Sci. 239: 117000.

Heather, L.C., Pates, K.M., Atherton, H.J., Cole, M.A., Ball, D.R., Evans, R.D., et al. (2013). Differential translocation of the fatty acid transporter, FAT/CD36, and the glucose transporter, GLUT4, coordinates changes in cardiac substrate metabolism during ischemia and reperfusion. Circ. Heart Fail. 6: 1058–1066.

Heier, C., and Haemmerle, G. (2016). Fat in the heart: The enzymatic machinery regulating cardiac triacylglycerol metabolism. Biochim. Biophys. Acta 1861: 1500–1512.

Ho, M., Hoang, H.L., Lee, K.M., Liu, N., MacRae, T., Montes, L., et al. (2005). Ectophosphorylation of CD36 regulates cytoadherence of Plasmodium falciparum to microvascular endothelium under flow conditions. Infect. Immun. 73: 8179–8187.

Hoosdally, S.J., Andress, E.J., Wooding, C., Martin, C.A., and Linton, K.J. (2009). The Human Scavenger Receptor CD36: glycosylation status and its role in trafficking and function. J. Biol. Chem. 284: 16277–16288.

Hou, Y., Wu, M., Wei, J., Ren, Y., Du, C., Wu, H., et al. (2015). CD36 is involved in high glucose-induced epithelial to mesenchymal transition in renal tubular epithelial cells. Biochem. Biophys. Res. Commun. 468: 281–286.

Huynh, D.N., Bessi, V.L., Menard, L., Piquereau, J., Proulx, C., Febbraio, M., et al. (2018). Adiponectin has a pivotal role in the cardioprotective effect of CP-3(iv), a selective CD36 azapeptide ligand, after transient coronary artery occlusion in mice. FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol. 32: 807–818.

Iemitsu, M., Miyauchi, T., Maeda, S., Sakai, S., Fujii, N., Miyazaki, H., et al. (2003). Cardiac hypertrophy by hypertension and exercise training exhibits different gene expression of enzymes in energy metabolism. Hypertens. Res. 26: 829–837.

Jay, A.G., Chen, A.N., Paz, M.A., Hung, J.P., and Hamilton, J.A. (2015). CD36 binds oxidized low density lipoprotein (LDL) in a mechanism dependent upon fatty acid binding. J. Biol. Chem. 290: 4590–4603.

Jelenik, T., Flogel, U., Alvarez-Hernandez, E., Scheiber, D., Zweck, E., Ding, Z., et al. (2018). Insulin Resistance and Vulnerability to Cardiac Ischemia. Diabetes 67: 2695–2702.

Jia, G., DeMarco, V.G., and Sowers, J.R. (2016). Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nat. Rev. Endocrinol. 12: 144–153.

Joubert, M., Manrique, A., Cariou, B., and Prieur, X. (2019). Diabetes-related cardiomyopathy: The sweet story of glucose overload from epidemiology to cellular pathways. Diabetes Metab. 45: 238–247.

Karam, C.N., Warren, C.M., Henze, M., Banke, N.H., Lewandowski, E.D., and Solaro, R.J. (2017). Peroxisome proliferator-activated receptor-α expression induces alterations in cardiac myofilaments in a pressure-overload model of hypertrophy. Am. J. Physiol. Heart Circ. Physiol. 312: H681–H690.

Kim, K.-Y., Stevens, M. V, Akter, M.H., Rusk, S.E., Huang, R.J., Cohen, A., et al. (2011). Parkin is a lipid-responsive regulator of fat uptake in mice and mutant human cells. J. Clin. Invest. 121: 3701–3712.

Kim, T.T., and Dyck, J.R.B. (2016). The role of CD36 in the regulation of myocardial lipid metabolism. Biochim. Biophys. Acta 1861: 1450–1460.

Ladanyi, A., Mukherjee, A., Kenny, H.A., Johnson, A., Mitra, A.K., Sundaresan, S., et al. (2018). Adipocyte-induced CD36 expression drives ovarian cancer progression and metastasis. Oncogene 37: 2285–2301.

Lauzier, B., Merlen, C., Vaillant, F., McDuff, J., Bouchard, B., Beguin, P.C., et al. (2011). Post-translational modifications, a key process in CD36 function: lessons from the spontaneously hypertensive rat heart. J. Mol. Cell. Cardiol. 51: 99–108.

Lee, B.-C., Lin, K.-H., Hu, C.-Y., and Lo, S.-C. (2019). Thromboelastography characterized CD36 null subjects as slow clot formation and indicative of hypocoagulability. Thromb. Res. 178: 79–84.

Lee, S., Eguchi, A., Sakamoto, K., Matsumura, S., Tsuzuki, S., Inoue, K., et al. (2015). A role of CD36 in the perception of an oxidised phospholipid species in mice. Biomed. Res. 36: 303–311.

Lejay, A., Fang, F., John, R., Van, J.A.D., Barr, M., Thaveau, F., et al. (2016). Ischemia reperfusion injury, ischemic conditioning and diabetes mellitus. J. Mol. Cell. Cardiol. 91: 11–22.

Lesnefsky, E.J., Chen, Q., Tandler, B., and Hoppel, C.L. (2017). Mitochondrial Dysfunction and Myocardial Ischemia-Reperfusion: Implications for Novel Therapies. Annu. Rev. Pharmacol. Toxicol. 57: 535–565.

Li, H., Fan, J., Zhao, Y., Zhang, X., Dai, B., Zhan, J., et al. (2019). Nuclear miR-320 Mediates Diabetes-Induced Cardiac Dysfunction by Activating Transcription of Fatty Acid Metabolic Genes to Cause Lipotoxicity in the Heart. Circ. Res. 125: 1106–1120.

Lin, J., Wang, T., Li, Y., Wang, M., Li, H., Irwin, M.G., et al. (2016). N-Acetylcysteine Restores Sevoflurane Postconditioning Cardioprotection against Myocardial Ischemia-Reperfusion Injury in Diabetic Rats. J. Diabetes Res. 2016: 9213034.

Liu, J., Yang, P., Zuo, G., He, S., Tan, W., Zhang, X., et al. (2018a). Long-chain fatty acid activates hepatocytes through CD36 mediated oxidative stress. Lipids Health Dis. 17: 153.

Liu, Y., Neumann, D., Glatz, J.F.C., and Luiken, J.J.F.P. (2018b). Molecular mechanism of lipid-induced cardiac insulin resistance and contractile dysfunction. Prostaglandins. Leukot. Essent. Fatty Acids 136: 131–141.

Luiken, J.J.F.P. (2009). Sarcolemmal fatty acid uptake vs. mitochondrial beta-oxidation as target to regress cardiac insulin resistance. Appl. Physiol. Nutr. Metab. = Physiol. Appl. Nutr. Metab. 34: 473–480.

Luiken, J.J.F.P., Chanda, D., Nabben, M., Neumann, D., and Glatz, J.F.C. (2016). Post-translational modifications of CD36 (SR-B2): Implications for regulation of myocellular fatty acid uptake. Biochim. Biophys. Acta 1862: 2253–2258.

Luiken, J.J.F.P., Koonen, D.P.Y., Willems, J., Zorzano, A., Becker, C., Fischer, Y., et al. (2002). Insulin stimulates long-chain fatty acid utilization by rat cardiac myocytes through cellular redistribution of FAT/CD36. Diabetes 51: 3113–3119.

Lynes, M., Narisawa, S., Millan, J.L., and Widmaier, E.P. (2011). Interactions between CD36 and global intestinal alkaline phosphatase in mouse small intestine and effects of high-fat diet. Am. J. Physiol. Regul. Integr. Comp. Physiol. 301: R1738-47.

Madonna, R., Salerni, S., Schiavone, D., Glatz, J.F., Geng, Y.-J., and Caterina, R. De (2011). Omega-3 fatty acids attenuate constitutive and insulin-induced CD36 expression through a suppression of PPAR α/γ activity in microvascular endothelial cells. Thromb. Haemost. 106: 500–510.

Magida, J.A., and Leinwand, L.A. (2014). Metabolic crosstalk between the heart and liver impacts familial hypertrophic cardiomyopathy. EMBO Mol. Med. 6: 482–495.

Mansor, L.S., Sousa Fialho, M. da L., Yea, G., Coumans, W.A., West, J.A., Kerr, M., et al. (2017). Inhibition of sarcolemmal FAT/CD36 by sulfo-N-succinimidyl oleate rapidly corrects metabolism and restores function

in the diabetic heart following hypoxia/reoxygenation. Cardiovasc. Res. 113: 737–748.

McDonald, A.G., Tipton, K.F., and Davey, G.P. (2018). A mechanism for bistability in glycosylation. PLoS Comput. Biol. 14: e1006348.

Meer, D.L.M. van der, Degenhardt, T., Väisänen, S., Groot, P.J. de, Heinäniemi, M., Vries, S.C. de, et al. (2010). Profiling of promoter occupancy by PPARalpha in human hepatoma cells via ChIP-chip analysis. Nucleic Acids Res. 38: 2839–2850.

Meiler, S., Baumer, Y., Huang, Z., Hoffmann, F.W., Fredericks, G.J., Rose, A.H., et al. (2013). Selenoprotein K is required for palmitoylation of CD36 in macrophages: implications in foam cell formation and atherogenesis. J. Leukoc. Biol. 93: 771–780.

Meo, S. Di, Iossa, S., and Venditti, P. (2017). Skeletal muscle insulin resistance: role of mitochondria and other ROS sources. J. Endocrinol. 233: R15–R42.

Mitra, N., Sinha, S., Ramya, T.N.C., and Surolia, A. (2006). N-linked oligosaccharides as outfitters for glycoprotein folding, form and function. Trends Biochem. Sci. 31: 156–163.

Monaco, C., Whitfield, J., Jain, S.S., Spriet, L.L., Bonen, A., and Holloway, G.P. (2015). Activation of AMPKα2 Is Not Required for Mitochondrial FAT/CD36 Accumulation during Exercise. PLoS One 10: e0126122.

Nagendran, J., Pulinilkunnil, T., Kienesberger, P.C., Sung, M.M., Fung, D., Febbraio, M., et al. (2013). Cardiomyocyte-specific ablation of CD36 improves post-ischemic functional recovery. J. Mol. Cell. Cardiol. 63: 180–188.

Nakatani, K., Masuda, D., Kobayashi, T., Sairyo, M., Zhu, Y., Okada, T., et al. (2019). Pressure Overload Impairs Cardiac Function in Long-Chain Fatty Acid Transporter CD36-Knockout Mice. Int. Heart J. 60: 159–167.

Neckar, J., Silhavy, J., Zidek, V., Landa, V., Mlejnek, P., Simakova, M., et al. (2012). CD36 overexpression predisposes to arrhythmias but reduces infarct size in spontaneously hypertensive rats: gene expression profile analysis. Physiol. Genomics 44: 173–182.

Oka, S., Zhai, P., Yamamoto, T., Ikeda, Y., Byun, J., Hsu, C.-P., et al. (2015). Peroxisome Proliferator Activated Receptor-α Association With Silent Information Regulator 1 Suppresses Cardiac Fatty Acid Metabolism in the Failing Heart. Circ. Heart Fail. 8: 1123–1132.

Oort, M.M. van, Drost, R., Janbetaen, L., Doorn, J.M. Van, Kerver, J., Horst, D.J. Van der, et al. (2014). Each of the four intracellular cysteines of CD36 is essential for insulin- or AMP-activated protein kinase-induced CD36 translocation. Arch. Physiol. Biochem. 120: 40–49.

Ouwens, D.M., Diamant, M., Fodor, M., Habets, D.D.J., Pelsers, M.M.A.L., Hasnaoui, M. El, et al. (2007). Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. Diabetologia 50: 1938–1948.

Paolillo, S., Marsico, F., Prastaro, M., Renga, F., Esposito, L., Martino, F. De, et al. (2019). Diabetic Cardiomyopathy: Definition, Diagnosis, and Therapeutic Implications. Heart Fail. Clin. 15: 341–347.

Park, T.-S., Yamashita, H., Blaner, W.S., and Goldberg, I.J. (2007). Lipids in the heart: a source of fuel and a source of toxins. Curr. Opin. Lipidol. 18: 277–282.

Pepino, M.Y., Kuda, O., Samovski, D., and Abumrad, N.A. (2014). Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism. Annu. Rev. Nutr. 34: 281–303.

Petersen, M.C., and Shulman, G.I. (2017). Roles of Diacylglycerols and Ceramides in Hepatic Insulin Resistance. Trends Pharmacol. Sci. 38: 649–665.

Popovic, D., Vucic, D., and Dikic, I. (2014). Ubiquitination in disease pathogenesis and treatment. Nat. Med. 20: 1242–1253.

Samovski, D., Dhule, P., Pietka, T., Jacome-Sosa, M., Penrose, E., Son, N.-H., et al. (2018). Regulation of Insulin Receptor Pathway and Glucose Metabolism by CD36 Signaling. Diabetes 67: 1272–1284.

Santos, M.H.H., Higuchi, M. de L., Tucci, P.J.F., Garavelo, S.M., Reis, M.M., Antonio, E.L., et al. (2016). Previous exercise training increases levels of PPAR-α in long-term post-myocardial infarction in rats, which is correlated with better inflammatory response. Clinics (Sao Paulo). 71: 163–168.

Sequeira, V., Bertero, E., and Maack, C. (2019). Energetic drain driving hypertrophic cardiomyopathy. FEBS Lett. 593: 1616–1626.

Simantov, R., Febbraio, M., and Silverstein, R.L. (2005). The antiangiogenic effect of thrombospondin-2 is mediated by CD36 and modulated by histidine-rich glycoprotein. Matrix Biol. 24: 27–34.

Smith, J., Su, X., El-Maghrabi, R., Stahl, P.D., and Abumrad, N.A. (2008). Opposite regulation of CD36 ubiquitination by fatty acids and insulin: effects on fatty acid uptake. J. Biol. Chem. 283: 13578–13585.

Son, N.-H., Basu, D., Samovski, D., Pietka, T.A., Peche, V.S., Willecke, F., et al. (2018). Endothelial cell CD36 optimizes tissue fatty acid uptake. J. Clin. Invest. 128: 4329–4342.

Srikanthan, S., Li, W., Silverstein, R.L., and McIntyre, T.M. (2014). Exosome poly-ubiquitin inhibits platelet activation, downregulates CD36 and inhibits pro-atherothombotic cellular functions. J. Thromb. Haemost. 12: 1906–1917.

Steinbusch, L.K.M., Wijnen, W., Schwenk, R.W., Coumans, W.A., Hoebers, N.T.H., Ouwens, D.M., et al. (2010). Differential regulation of cardiac glucose and fatty acid uptake by endosomal pH and actin filaments. Am. J. Physiol. Cell Physiol. 298: C1549-59.

Sun, S., Tan, P., Huang, X., Zhang, W., Kong, C., Ren, F., et al. (2018). Ubiquitinated CD36 sustains insulin-stimulated Akt activation by stabilizing insulin receptor substrate 1 in myotubes. J. Biol. Chem. 293: 2383–2394.

Sung, H.K., Song, E., Jahng, J.W.S., Pantopoulos, K., and Sweeney, G. (2019). Iron induces insulin resistance in cardiomyocytes via regulation of oxidative stress. Sci. Rep. 9: 4668.

Sung, M.M., Byrne, N.J., Kim, T.T., Levasseur, J., Masson, G., Boisvenue, J.J., et al. (2017). Cardiomyocyte-specific ablation of CD36 accelerates the progression from compensated cardiac hypertrophy to heart failure. Am. J. Physiol. Heart Circ. Physiol. 312: H552–H560.

Tanaka, T., Sohmiya, K., and Kawamura, K. (1997). Is CD36 deficiency an etiology of hereditary hypertrophic cardiomyopathy? J. Mol. Cell. Cardiol. 29: 121–127.

Tao, L., Bei, Y., Lin, S., Zhang, H., Zhou, Y., Jiang, J., et al. (2015). Exercise Training Protects Against Acute Myocardial Infarction via Improving Myocardial Energy Metabolism and Mitochondrial Biogenesis. Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol. 37: 162–175.

Tham, Y.K., Bernardo, B.C., Ooi, J.Y.Y., Weeks, K.L., and McMullen, J.R. (2015). Pathophysiology of cardiac hypertrophy and heart failure: signaling pathways and novel therapeutic targets. Arch. Toxicol. 89: 1401–1438.

Thorne, R.F., Ralston, K.J., Bock, C.E. de, Mhaidat, N.M., Zhang, X.D., Boyd, A.W., et al. (2010). Palmitoylation of CD36/FAT regulates the rate of its post-transcriptional processing in the endoplasmic reticulum. Biochim. Biophys. Acta 1803: 1298–1307.

Tran, T.T.T., Poirier, H., Clement, L., Nassir, F., Pelsers, M.M.A.L., Petit, V., et al. (2011). Luminal lipid regulates CD36 levels and downstream signaling to stimulate chylomicron synthesis. J. Biol. Chem. 286: 25201–25210.

Umbarawan, Y., Syamsunarno, M.R.A.A., Koitabashi, N., Obinata, H., Yamaguchi, A., Hanaoka, H., et al. (2018a). Myocardial fatty acid uptake through CD36 is indispensable for sufficient bioenergetic metabolism to prevent progression of pressure overload-induced heart failure. Sci. Rep. 8: 12035.

Umbarawan, Y., Syamsunarno, M.R.A.A., Koitabashi, N., Yamaguchi, A., Hanaoka, H., Hishiki, T., et al. (2018b). Glucose is preferentially utilized for biomass synthesis in pressure-overloaded hearts: evidence from fatty acid-binding protein-4 and -5 knockout mice. Cardiovasc. Res. 114: 1132–1144.

Vinals, M., Xu, S., Vasile, E., and Krieger, M. (2003). Identification of the N-linked glycosylation sites on the high density lipoprotein (HDL) receptor SR-BI and assessment of their effects on HDL binding and selective lipid uptake. J. Biol. Chem. 278: 5325–5332.

Wang, J., Hao, J.-W., Wang, X., Guo, H., Sun, H.-H., Lai, X.-Y., et al. (2019). DHHC4 and DHHC5 Facilitate Fatty Acid Uptake by Palmitoylating and Targeting CD36 to the Plasma Membrane. Cell Rep. 26: 209-221.e5.

Wang, J., and Li, Y. (2019). CD36 tango in cancer: signaling pathways and functions. Theranostics 9: 4893–4908.

Wu, L., Wang, K., Wang, W., Wen, Z., Wang, P., Liu, L., et al. (2018). Glucagon-like peptide-1 ameliorates cardiac lipotoxicity in diabetic cardiomyopathy via the PPARα pathway. Aging Cell 17: e12763.

Xu, L., Chen, W., Ma, M., Chen, A., Tang, C., Zhang, C., et al. (2019). Microarray profiling analysis identifies the mechanism of miR-200b-3p/mRNA-CD36 affecting diabetic cardiomyopathy via peroxisome proliferator activated receptor-gamma signaling pathway. J. Cell. Biochem. 120: 5193–5206.

Yan, X., Chen, J., Zhang, C., Zhou, S., Zhang, Z., Chen, J., et al. (2015). FGF21 deletion exacerbates diabetic cardiomyopathy by aggravating cardiac lipid accumulation. J. Cell. Mol. Med. 19: 1557–1568.

Yang, J., Sambandam, N., Han, X., Gross, R.W., Courtois, M., Kovacs, A., et al. (2007). CD36 deficiency rescues lipotoxic cardiomyopathy. Circ. Res. 100: 1208–1217.

Yang, M., Kholmukhamedov, A., Schulte, M.L., Cooley, B.C., Scoggins, N.O., Wood, J.P., et al. (2018). Platelet CD36 signaling through ERK5 promotes caspase-dependent procoagulant activity and fibrin deposition in vivo. Blood Adv. 2: 2848–2861.

Yu, M., Du, H., Wang, B., Chen, J., Lu, F., Peng, S., et al. (2020). Exogenous H2S Induces Hrd1 S-sulfhydration and Prevents CD36 Translocation via VAMP3 Ubiquitylation in Diabetic Hearts. Aging Dis. 11: 286–300.

Zhang, F., Xia, X., Chai, R., Xu, R., Xu, Q., Liu, M., et al. (2020). Inhibition of USP14 suppresses the formation of foam cell by promoting CD36 degradation. J. Cell. Mol. Med. 24: 3292–3302.

Zhao, L., Zhang, C., Luo, X., Wang, P., Zhou, W., Zhong, S., et al. (2018). CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis. J. Hepatol. 69: 705–717.

Zheng, A., Cao, L., Qin, S., Chen, Y., Li, Y., and Zhang, D. (2017). Exenatide Regulates Substrate Preferences Through the p38γ MAPK Pathway After Ischaemia/Reperfusion Injury in a Rat Heart. Heart. Lung Circ. 26: 404–412.

Zhou, M., Wang, H., Zeng, X., Yin, P., Zhu, J., Chen, W., et al. (2019). Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England) 394: 1145–1158.

Zhou, X., Chang, B., and Gu, Y. (2018). MicroRNA-21 abrogates palmitate-induced cardiomyocyte apoptosis through caspase-3/NF-ϰB signal pathways. Anatol. J. Cardiol. 20: 336–346.

Figure legends

Figure 1. Post-translational modifications of CD36.

There are two ubiquitination sites on the N-terminus of CD36, Lys472, Lys469. CD36 ubiquitination level decreases upon insulin stimulation while increases with the presence of LCFA; Parkin is CD36's E3 ubiquitin ligase, which monoubiquitinates CD36 and enhances its stability, while USP14 mediates CD36 deubiquitination; There are four palmitoylation sites at the C-terminus and the N-terminus of CD36, Cys3, Cys7,Cys464, Cys466, DHHC4/5 are palmitoyltransferases that promote palmitoylation of CD36; CD36 also has two phosphorylation sites, Thr93 and Ser237, which are phosphorylated by PKC and PKA, respectively. LCFA, long chain fatty acid; USP14, ubiquitin specific peptidase 14; DHHC, Asp-His-His-Cys; PKA, protein kinase A; PKC, protein kinase C; IAP, Intestinal alkaline phosphatase

Figure 2: Effects of CD36 in ischemic/reperfusion.

During the ischemic phase, the distribution of CD36 on the cell membrane decreases, leading to a decline of LCFA uptake and LCFA entering the mitochondria for aerobic oxidation, while GLUT4 increases on the cell membrane. Due to ischemia and hypoxia, the anaerobic glycolysis process is enhanced, and produces a large quantity of protons, thus resulting in a low cytoplasmic pH. Hydrion subsequently prevents the transport of CD36 from the endosome to the cell membrane, and further inhibits the distribution of CD36 on the cell membrane. The relatively increased pyruvate acid enters the mitochondria for aerobic oxidation to produce ATP. During this process, the decrease of CD36 prevents the accumulation of toxic lipid, and indirectly promotes the aerobic oxidation of glucose, which is beneficial to the survival of myocardial cells during the ischemic phase. During the reperfusion phase, the anaerobic glycolysis process of glucose decreased and the rate of proton production decreased. However, due to the low pH caused by a large number of protons accumulated in the ischemic phase, the membrane distribution of CD36 remains at a low level. At the same time, the rate of LCFA entering the mitochondria for aerobic oxidation is enhanced because of the triglyceride accumulate in ischemic phase, which is an essential supplementary for energy production. During this process, the low level of CD36 helps reduce the accumulation of toxic lipid, and the aerobic oxidation of LCFA provides most of the energy for the myocardium.

Figure 3: Effects of CD36 in diabetes cardiomyopathy.

In diabetes, increased insulin activates the PI3K-Akt pathway, thereby promoting the transportation of CD36 from the endosome to the cell membrane. FOXO transcription factor promotes the expression of CD36. Down-regulated mir-200b-3p and up-regulated mir-320 also accelerate the transcription and translation of CD36, thus further increasing the distribution of CD36 on the cell membrane, which facilitates the uptake of LCFA of the cardiomyocytes. LCFA promotes the transfer of CD36 in the endosome to the cell membrane, further increasing the distribution of CD36 on the cell membrane. Intracellular LCFA either enters the mitochondria for aerobic oxidation producing energy and the byproducts-ROS or forms triglyceride for energy storage, and the accumulation of triglyceride would trigger insulin resistance. Insulin resistance and ROS assembling deteriorate cardiac function and result in diabetic cardiomyopathy.

Figure 4: Effects of CD36 in pathological and physiological cardiac hypertrophy.

Under pressure overload, intranuclear PPARa and PGC1a are downregulated and lead to decreased CD36 expression and LCFA uptake by myocardial cells, resulting in an insufficient energy state. At the same time, the activity of HSL and DAGL that break down fat decreases, while fat synthesis-related enzymes, including SREBP-1c, SCD1, SCD2 and GPAT et al., are not down-regulated, leading to the accumulation of toxic lipids. Accumulated lipids and insufficient energy support both contribute to the development of pathological cardiac hypertrophy. During regular exercise, intranuclear PPARa and PGC1a increase and upregulate CD36 and fatty acid transfer rate-limiting enzyme CPT1, thus facilitating the uptake and utilization of LCFA. With the increase of CPT1 on mitochondrial outer membrane, more LCFA undergo aerobic oxidation in mitochondria. The increase of PPARa and PGC1a would also promote the transcription of mitochondrial oxidative phosphorylation-related proteins, which jointly improves the efficiency of fatty acid oxidation. Moreover, fat synthesis-related enzymes, including SREBP -1c, SCD1, SCD2 and GPAT et al and the activity of HSL and DAGL that break down fat are both up-regulated, thereby avoiding excessive

accumulation of toxic lipids. Sufficient energy and less toxic lipids maintain the proper cardiac function of physiological cardiac hypertrophy. SREBP-1c, sterol-responsive element-binding protein-1c; SCD1, stearoyl-CoA desaturase 1; SCD2, stearoyl-CoA desaturase 2; GPAT, Glycerol-3-phosphate acyltransferase; HSL, hormone-sensitive lipase; DAGL, diacylglycerol lipase