

# The role of CD36 in cardiovascular disease

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## Abstract

CD36, also known as the 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 is regulated by post-translational modifications, including phosphorylation, ubiquitination, glycosylation, and palmitoylation. CD36 is decreased in pathological cardiac hypertrophy caused by ischaemia–reperfusion and pressure overload, and increased in diabetic cardiomyopathy and atherosclerosis. Deficiency of CD36 alleviates diabetic cardiomyopathy and atherosclerosis, while overexpression of CD36 eliminates ischaemia–reperfusion damage, together suggesting that CD36 is closely associated with the progression of cardiovascular diseases and may be a new therapeutic target. This review summarizes the regulation and post-translational modifications of CD36 and evaluates its role in cardiovascular diseases and its potential as a therapeutic target.

## Keywords

CD36 • Post-translational modification • Diabetic cardiomyopathy • Ischaemia–reperfusion • Cardiac hypertrophy

## 1. Introduction

CD36 [also known as fatty acid translocase (FAT), glycoprotein IIIb (GPIIIb), or glycoprotein IV], is a member of the class B2 scavenger receptor family, which includes low-density lipoprotein (LDL), high-density lipoprotein (HDL)-bound scavenger receptor B1, and HDL-bound scavenger receptor B3.<sup>1–3</sup> The ligands of CD36 are mainly divided into lipid and protein molecules. The former includes oxidized LDL particles,<sup>4</sup> long-chain fatty acids (LCFA),<sup>5</sup> phospholipids,<sup>6</sup> and others, and the latter includes thrombospondin,<sup>7</sup> advanced glycation end products (AGEs),<sup>8,9</sup> advanced oxidation protein products (AOPPs),<sup>10,11</sup> S100 family proteins (S100-A8, S100-A9, S100-A12),<sup>12–14</sup> growth hormone-releasing peptide,<sup>15</sup> cell-derived microparticles,<sup>16</sup> and amyloid proteins.<sup>17</sup>

CD36 is expressed in various tissues, including endothelial cells,<sup>18</sup> cardiac muscle cells,<sup>19</sup> renal tubular epithelial cells,<sup>20</sup> liver cells,<sup>21</sup> adipocytes,<sup>22</sup> platelets,<sup>23</sup> and macrophages,<sup>24</sup> and is involved in many pathophysiological processes, including immune regulation<sup>25</sup> and metabolic regulation.<sup>26</sup> For example, CD36 on the cytomembrane of endothelial cells optimizes fatty acid uptake in tissues.<sup>18</sup> It also facilitates the uptake of AOPPs in renal tubular epithelial cells, which leads to

lipotoxicity and renal tubule interstitial fibrosis in diabetic nephropathy.<sup>10</sup> In liver cells CD36 is involved in fatty acid metabolism,<sup>27</sup> while on platelets it is related to platelet activation.<sup>28</sup> In myocardial tissue, CD36 mediates the uptake of long-chain fatty acids.<sup>29</sup> Fatty acids provide over 70% of the adenosine triphosphate (ATP) for myocardial tissue and most of the fatty acids enter the cells through protein-mediated diffusion. Importantly, 70% of this intake is mediated by CD36,<sup>29</sup> therefore, CD36 plays an essential role in myocardial lipid metabolism.

The synthesis and translocation of CD36 are affected by many stimuli.<sup>30</sup> Short-term stimulation of insulin promotes the translocation of CD36 from the endosome to the cell membrane,<sup>31</sup> while long-term stimulation induces protein synthesis.<sup>32</sup> Hyperglycaemia and hyperlipidaemia also facilitate the translocation of CD36 to the cell membrane.<sup>33</sup> It has been proven that impaired synthesis and abnormal distribution of CD36 shorten myocardial energy supply,<sup>34</sup> resulting in the impairment of myocardial contractile function.<sup>35</sup> Pressure overload decreases the level of one of the controllers of CD36 synthesis, nuclear receptor peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ),<sup>36</sup> resulting in insufficient myocardial fatty acid uptake and the accumulation of toxic lipids, ultimately leading to heart failure. However, downregulating CD36 in

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diabetic cardiomyopathy reduces toxic lipids<sup>37</sup> and improves the contractile function of the heart. Therefore, the influence of CD36 on the myocardium may not be consistent and largely depends on the pathological background.

In this review, we summarize gene polymorphism and post-translational modification of CD36 and focus on its role in cardiovascular diseases, particularly ischaemia/reperfusion, diabetic cardiomyopathy, pathological cardiac hypertrophy, physiological cardiac hypertrophy, and atherosclerosis. We also provide some suggestions for basic and clinical research on CD36, to emphasize the significance of CD36 in the cardiovascular system and shed light on its potential as a therapeutic target.

## 2. Cd36 gene polymorphism

The human CD36 gene is located on 7q21.11, which has 36 kb and consists of 19 exons with multiple upstream regulatory promoters.<sup>38</sup> Single nucleotide polymorphisms (SNPs) of CD36 are relatively common and have been shown to be closely related to several cardiovascular diseases.

The rs1761663 of the CD36 gene has independent effects on body mass index and left ventricular mass.<sup>39</sup> A study conducted among young adult populations in Australia showed that the rs1527479 and rs1984112 of CD36 are related to exercise, heart rate, and lipid oxidation.<sup>40</sup> In the Chinese Han population, the AG genotype of rs1761667 is associated with an increased risk of coronary heart disease (odds ratio 2.337, 95% confidence interval 1.336–4.087;  $P = 0.003$ ), and the plasma oxLDL level of patients with the AG genotype was significantly higher than that of patients with the GG and AA genotypes.<sup>41</sup> For rs1049673, rs7755, and rs321159 sites, patients with premature coronary heart disease have a family genetic predisposition at high LDL-C levels with GA, AA, and TT genotypes.<sup>42</sup> Four common CD36 SNPs were found (rs1049673, rs7755, rs3211956, and rs3173798) to be significantly associated with extreme lipid profiles in the male Han population in northern China, but no significance was identified in the female population.<sup>43</sup> In addition, rs3211938, which affects susceptibility to malaria, has been shown to resist metabolic syndrome, increase high-density lipoprotein cholesterol, and reduce triglycerides.<sup>44</sup> These genetic studies suggest that CD36 gene polymorphism plays a predictive role in distinguishing cardiac disease risk factors. Therefore, early prevention might be carried out for susceptible people, using CD36 genotyping.

## 3. Cd36 protein

Human CD36 has a total length of 472 amino acids and a predicted molecular weight of 53 kd,<sup>45</sup> although due to glycosylation, the actual molecular weight is 88 kd.<sup>46</sup> CD36 contains two phosphorylation sites and four palmitoylation sites, which are distributed at the terminals of NH<sub>2</sub> and COOH. Two ubiquitination sites are also found at the COOH terminus.

Knowledge of the crystal structure of CD36 remains unclear, but insight into the potential mechanism of FA transport by CD36 can be derived from the recently reported crystal structure of the CD36 family member, lysosomal integral membrane protein-2 (LIMP-2).<sup>47</sup> LIMP-2 is a helical bundle where  $\beta$ -glucocerebrosidase binds, and where ligands are most likely to bind to CD36. The crystal structure also shows the existence of a large cavity that serves as a tunnel through which cholesterol (esters) are delivered from the bound lipoprotein to the outer leaflet of the plasma membrane. CD36 is a double transmembrane protein that

cannot form a channel by itself to allow for fatty acids to transfer through to the inside.<sup>48</sup> Interestingly, the outer ring of CD36 contains a large hydrophobic cavity, which provides a docking site for fatty acids and other hydrophobic ligands,<sup>49</sup> facilitating the attraction of hydrophobic ligands to the cell surface, thus promoting the transportation of fatty acids into the cell.

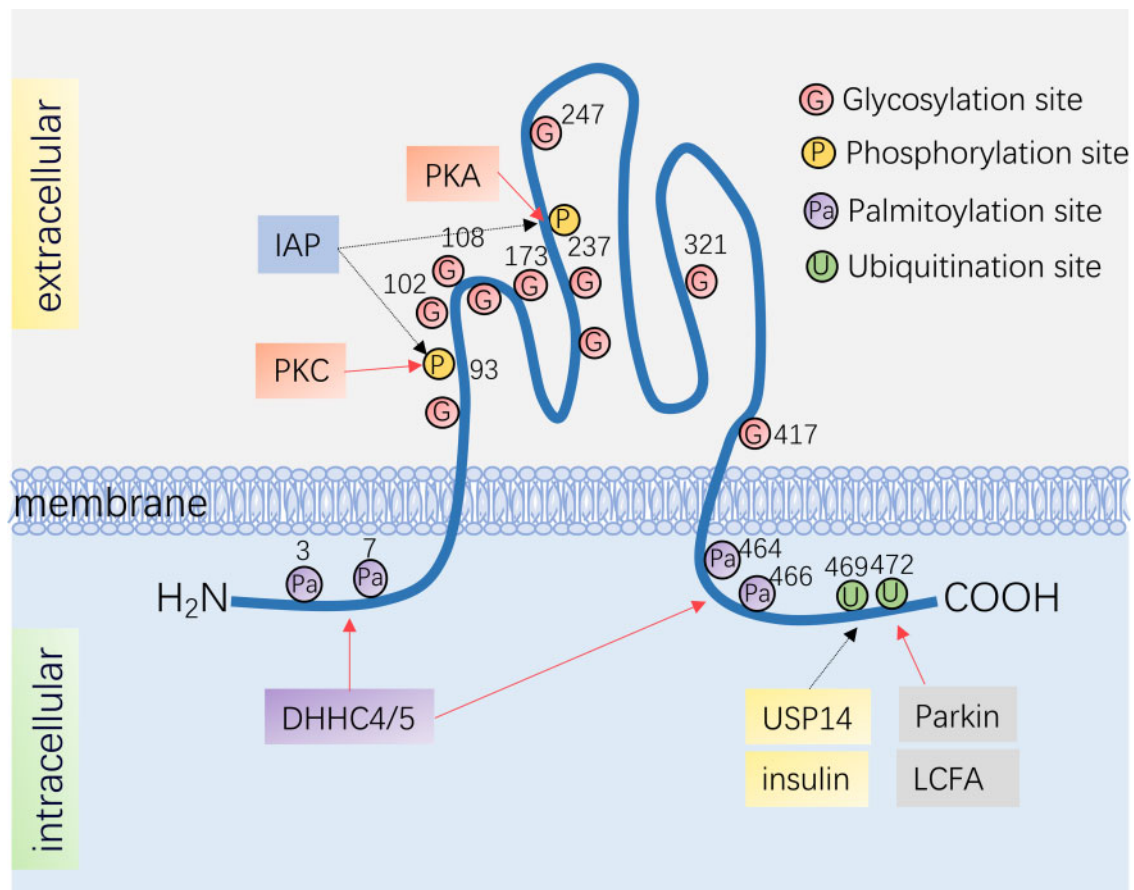
### 3.1 Cd36 signalling

CD36 is a membrane protein that is synthesized in the polyribosome and then transferred to the endoplasmic reticulum and Golgi apparatus for further processing, and then finally transported by the endosome to the cytomembrane.<sup>50</sup> Under the stimulation of insulin<sup>51</sup> or contraction,<sup>31</sup> it moves to the lipid rafts of the cell membrane to facilitate LCFA uptake, which may be associated with the activation of PI3K-Akt and adenosine monophosphate (AMP) kinase (AMPK). CD36 is not only located in plasma membranes and endosomes but is also distributed on mitochondria,<sup>52</sup> although its specific function on mitochondria remains unclear.

The transfer of CD36 from the endosome to the cell membrane surface is mainly regulated by insulin and contraction stimulation,<sup>53</sup> which induces CD36 translocation through different signalling pathways, but finally converges into Rab GTPase proteins AS160 and Rab 8a, accelerating CD36 translocation with the (guanosine triphosphate) GTP/ (guanosine diphosphate) GDP cycle.<sup>54</sup>

PI3K in the insulin signalling pathway has been shown to be critical for CD36 translocation, supported by the fact that specific inhibitors of PI3K (Wortmannin and LY-294002) can eliminate CD36 translocation and downregulate LCFA uptake induced by insulin.<sup>55</sup> In addition, among the two downstream effectors of PI3K, PKC-zeta also participates in insulin-induced CD36 translocation, and the other downstream effector, Akt, is involved in the regulation of FOXO1 activity that acts on the CD36 promoter region to regulate CD36 transcription.<sup>56</sup> It is worth mentioning that insulin signalling also promotes the translocation of GLUT4. Under the stimulation of insulin, CD36 and GLUT4 are simultaneously transferred to the sarcolemma, resulting in increased fatty acid and glucose uptake. This is contradictory to the Randle cycle phenomenon, which states that a competitive inhibition exists between free fatty acid (FFA) oxidation and glucose utilization.<sup>53</sup> Further exploration of the time response of GLUT4 and CD36 to different insulin concentrations, and knowledge of the distinction between the vesicle transport pathway and subcellular trafficking will help in understanding this contradictory phenomenon.<sup>57</sup> Recent studies have found that specific family members of vesicle-associated membrane proteins (VAMPs) mediate the intracellular transport of either CD36 or GLUT4. Specifically, VAMP4 translocates CD36 between the mother endosomal compartment and a hypothetical endosomal CD36-specific intermediate compartment,<sup>58</sup> while VAMP5 and VAMP7 mediate GLUT4 homing to intracellular compartments.<sup>58,59</sup> In particular, the distinct subcellular trafficking of CD36 and GLUT4 has been discussed in detail in a recent review.<sup>57</sup>

Similar to insulin, contraction stimulation promotes the translocation of GLUT4 and CD36 simultaneously.<sup>60</sup> Importantly, contraction stimulation is in an AMPK-dependent manner.<sup>61</sup> It has been confirmed that both 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and oligomycin can induce CD36 translocation by activating AMPK to promote LCFA uptake. Along with various negative feedback mechanisms, AMPK activation-induced CD36 translocation regulates AMPK activity in turn; CD36 forms a protein complex with the AMPK kinase LKB1 and the Src kinase Fyn,<sup>62</sup> and this complex promotes Fyn phosphorylation of LKB1 and its nuclear sequestration, hindering LKB1 activation of AMPK. This



**Figure 1** Post-translational modifications of CD36. There are two ubiquitination sites on the N-terminus of CD36: Lys472 and Lys469. CD36 ubiquitination levels decrease upon insulin stimulation while increase with the presence of LCFA; Parkin is CD36's E3 ubiquitin ligase, which monoubiquitinates CD36 and enhances its stability, while USP14 mediates CD36 deubiquitylation. There are four palmitoylation sites at the C-terminus and the N-terminus of CD36, Cys3, Cys7, Cys464, Cys466, and DHHC4/5 are palmitoyl transferases that promote palmitoylation of CD36; CD36 also has two phosphorylation sites, Thr93 and Ser237, which are phosphorylated by PKC, PKA, and dephosphorylated by IAP, respectively. The large extracellular loop has 10 observed N-linked glycosylation sites. DHHC, Asp-His-His-Cys; IAP, intestinal alkaline phosphatase; LCFA, long-chain fatty acid; PKA, protein kinase A; PKC, protein kinase C; USP14, ubiquitin specific peptidase 14.

feedback mechanism facilitates the cells to respond appropriately to the outside fatty acid and balance the fatty acid oxidation and uptake.

## 3.2 Cd36 post-translational modifications

The synthesis, distribution, and function of CD36 are largely affected by its post-transcriptional modification, including ubiquitination, glycosylation, phosphorylation, and palmitoylation. It is worth noting that although there are many acetylation sites on CD36, further research is required to reveal their effect.

### 3.2.1 Cd36 ubiquitination

Protein ubiquitination is the coupling of protein and ubiquitin, mediated by a ubiquitin ligase (E3).<sup>63</sup> CD36 is the target of the E3 ligase, Parkin<sup>64</sup> (Figure 1). Differing from the degradation effect of ubiquitination, the monoubiquitylation of CD36 by Parkin enhances its stability and increases its plasma membrane level. In the presence of Parkin,<sup>65</sup> LCFA-induced polyubiquitination and degradation of CD36 is significantly down-regulated, likely because one of the ubiquitination sites 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<sup>66</sup> (Figure 1). However, whether Parkin and USP14 act as E3 ligases and deubiquitinating enzymes in cardiomyocytes remains unclear.

LCFA, a ligand of CD36, significantly enhances the ubiquitination of CD36<sup>67</sup> and promotes its degradation after long-term interaction<sup>68</sup> (Figure 1). This is a negative factor for the cellular uptake of fatty acids. Recent studies have shown that ubiquitinated CD36 in myocytes stabilizes the structure of insulin receptor substrate 1<sup>69</sup> and thus maintains insulin signalling. Given that insulin reduces its ubiquitination<sup>68</sup> (Figure 1), CD36 may be involved in the self-regulation of the insulin signalling pathway. Moreover, CD36 ubiquitination in macrophages inhibits the formation of atherosclerosis by decreasing fatty acid uptake.<sup>70</sup> However, the role of ubiquitinated CD36 in the heart has not yet been elucidated.

### 3.2.2 Cd36 glycosylation

The glycosylation of CD36 is N-linked at asparagine residues (Asn) mediated by glycosyltransferase.<sup>71,72</sup> There are 10 glycosylation modification sites of CD36 in humans, located in the extracellular segment of CD36.<sup>73</sup>

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.<sup>74</sup> It affects the folding of CD36, thus influencing its correct translocation to the cell membrane. It has been proven that carboxyl-terminal sites Asn247, Asn321, and Asn417 are indispensable for CD36 trafficking.<sup>71</sup> Mutations in Asn108 and Asn173 sites result in the abnormal distribution of CD36 on the COS m6 cell membrane.<sup>73</sup> Mutations in Asn 102 of CD36 have been found in spontaneously hypertensive rats (SHRs).<sup>75</sup> Since Asn102 is located in the fatty acid-binding pocket, mutations at this glycosylation site may have a greater potential to affect fatty acid docking in the CD36 pocket, thereby affecting fatty acid transport. CD36 protein levels in SHR are significantly down-regulated and fatty acid intake is reduced, which may be related to the glycosylation mutation of Asn102. However, the role of Asn102 in SHRs has not yet been confirmed experimentally. Further research is required to clarify the role of Asn102 and other glycosylation sites in cardiovascular diseases.

### 3.2.3 Cd36 phosphorylation

CD36 has two phosphorylation sites, Thr92 and Ser237, phosphorylated by protein kinase C (PKC)<sup>76</sup> and protein kinase A (PKA),<sup>77</sup> respectively (Figure 1). CD36 in small intestinal epithelial cells is dephosphorylated by intestinal alkaline phosphatase (IAP)<sup>78</sup> (Figure 1). In platelets, phosphorylation of Thr92 mediates the binding of CD36 and thrombospondin.<sup>79</sup> 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.<sup>80</sup> CD36 phosphorylated at Ser237 downregulates the fatty acid uptake rate of platelets and enterocytes.<sup>78,81</sup> However, *in vivo* studies are insufficient to validate the *in vitro* findings of CD36 phosphorylation.

### 3.2.4 Cd36 palmitoylation

Most members of the DHHC (Asp–His–His–Cys) family of proteins have palmitoyl transferase activity, and these members are confirmed to include the main palmitoyl acyl transferases (PATs).<sup>82</sup> DHHC4/5 have been shown to be the PATs of CD36 in adipocytes (Figure 1). The absence of either DHHC4 or DHHC5 prevents palmitoylation and the insertion of CD36 on the adipose membrane, thereby destroying the CD36-dependent fatty acid uptake.<sup>83</sup> Selenoprotein K (SelK),<sup>84</sup> which is neither a PAT nor a palmitoyl-protein thioesterase (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: Cys3, Cys7, Cys464, and Cys466 (Figure 1). Palmitoylation is strengthened by insulin stimulation. Combined mutations of these four palmitoylation sites hinder CD36 translocation to the cell membrane for fatty acid uptake, even in the presence of insulin and AMPK.<sup>85</sup> With the inhibition of CD36 palmitoylation by ceruloplasmin,<sup>86</sup> a palmitoylation-specific inhibitor, the processing of CD36 at the endoplasmic reticulum and transport through the secretory pathway extends from 90 min to 4 h 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.<sup>27</sup> The decrease in CD36 palmitoylation downregulates the uptake of fatty acids and helps to balance the fatty acid metabolism in the liver cells, thus eliminating liver steatosis and fibrosis.<sup>27</sup> However, no research has revealed the effects of the palmitoylation of CD36 in the cardiovascular system.

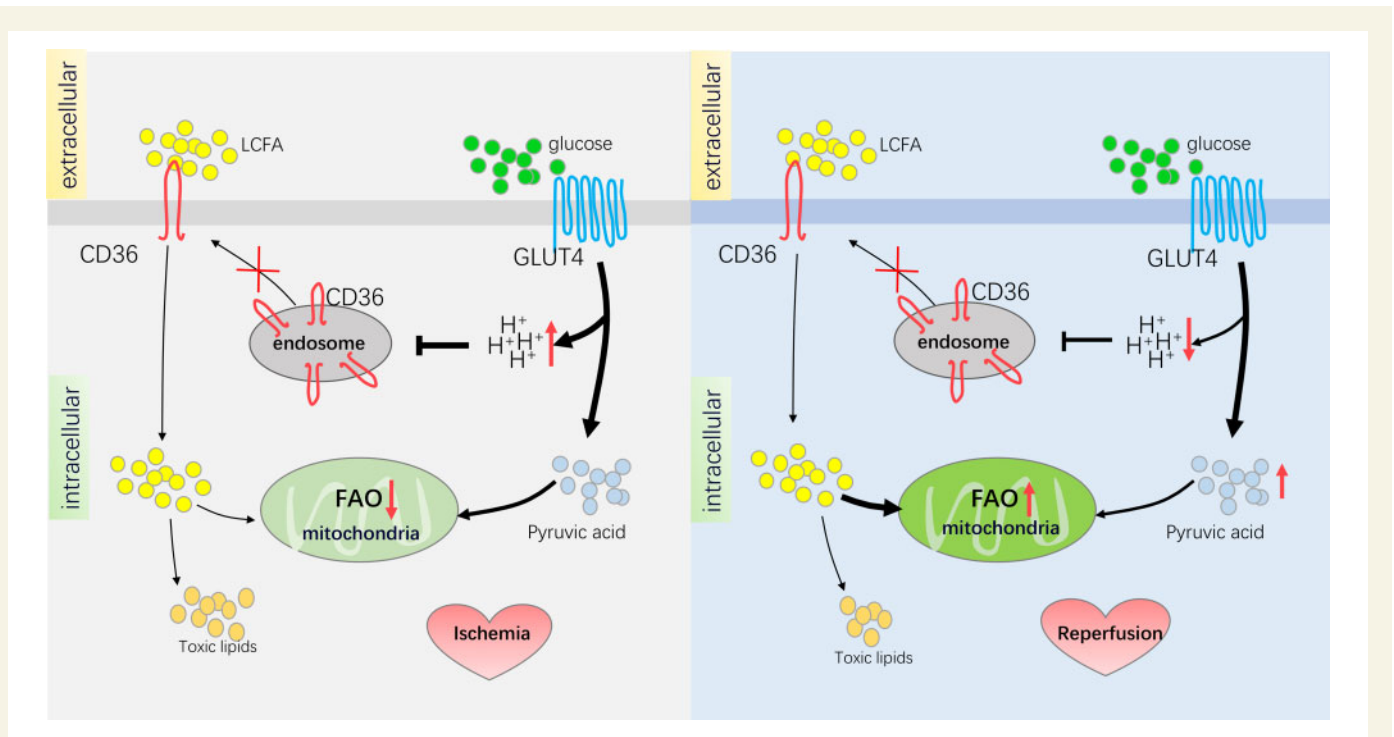
## 4. Cd36 and cardiovascular diseases

### 4.1 Cd36 and ischaemia/reperfusion

Ischaemia/reperfusion is characterized by the abrupt interruption, followed by the subsequent restoration, of blood flow.<sup>87</sup> The cut-off of oxygen and nutrition results in various metabolic changes,<sup>88</sup> including alterations in lipid metabolism. The change of CD36 in ischaemia/reperfusion has been shown by using (3) H-labelled metabolic substrates to measure the metabolic changes in Wistar rat hearts at different stages during ischaemia/reperfusion.<sup>89</sup> During ischaemia, CD36 of the sarcolemma is down-regulated by 32%, and the fatty acid oxidation rate decreases by 95%. In the reperfusion stage, CD36 levels remained low, but the fatty acid oxidation rate returned to the pre-ischaemic state.<sup>89</sup> The increased pH of the endosome may contribute to the low level of CD36 throughout the whole ischaemia/reperfusion period.<sup>90</sup> The 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 ischaemia, myocardial glycolysis increased by 86% and lactic acid level increased by seven-fold<sup>89</sup> (Figure 2), leading to a low pH state and subsequently suppressed CD36 translocation. When shifting to the reperfusion phase, the lactic acid in cardiomyocytes could not be effectively eliminated in a short period; the cells may still be at a low pH, and CD36 translocation is still suppressed (Figure 2).

At the same oxygen consumption level, glucose provides more energy than lipids, so it is the preferred choice for maintaining myocardial function.<sup>91,92</sup> The reduction of CD36 is beneficial to the conversion of the metabolic substrates from fatty acids to glucose during hypoxia. The consistently low level of CD36 may help cardiomyocytes to maintain energy balance (Figure 2). Moreover, the rate of fatty acid oxidation in cardiomyocytes in ischaemia is reduced to 5% of basal states,<sup>89</sup> and a relatively low CD36 prevents the accumulation of triglycerides in the cytosol by reducing the absorption of fatty acids (Figure 2). High concentrations of fatty acids in cardiomyocytes reduce the recovery of ischaemic heart function during the reperfusion stage by triggering insulin resistance and cardiomyocyte apoptosis.<sup>93–95</sup> Therefore, the reduction of CD36 during ischaemia benefits the heart by avoiding the excessive accumulation of triglycerides, and a CD36 decrease during ischaemia is a favourable adaptation for cardiomyocytes to survive.

The left ventricle undergoes a wound healing response after myocardial infarction,<sup>96</sup> including a strong infiltration of macrophages that promote the removal of dead cells and the renewal of extracellular matrix.<sup>97</sup> Contrary to the effects of a decrease in CD36, which is beneficial to the energy production and survival of cardiomyocytes, the reduction of CD36 in macrophages has been proven to be detrimental to the repair stage after myocardial infarction. The lack of CD36 leads to a reduction in the phagocytic receptor (myeloid-epithelial-reproductive-tyrosine kinase, Mertk) and nuclear receptor (nuclear receptor subfamily 4, group A, member 1, Nr4a1),<sup>98</sup> which affects the phagocytic function of cardiac macrophages, and exacerbates heart rupture caused by myocardial ischaemia.<sup>99</sup> CD36 blockers inhibit phagocytosis of macrophages and restrain cardiac remodelling after myocardial infarction.<sup>99</sup> In addition,



**Figure 2** Effects of CD36 in ischaemic/reperfusion. During the ischaemic phase, the distribution of CD36 on the cell membrane decreases, leading to a decline in LCFA uptake and LCFA entering the mitochondria for aerobic oxidation, while GLUT4 increases on the cell membrane, which results in the uptake of more glucose. Because of ischaemia and hypoxia, the anaerobic glycolysis process is enhanced, and produces a large quantity of protons, thus resulting in a low cytoplasmic pH. Hydron 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 in CD36 prevents the accumulation of toxic lipids and indirectly promotes the aerobic oxidation of glucose, which is beneficial to the survival of myocardial cells during the ischaemic 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 the large number of protons accumulated in the ischaemic 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 accumulation of triglycerides in the ischaemic phase, which is essential for energy production. During this process, the low level of CD36 helps reduce the accumulation of toxic lipids, and the aerobic oxidation of LCFAs provides most of the energy for the myocardium.

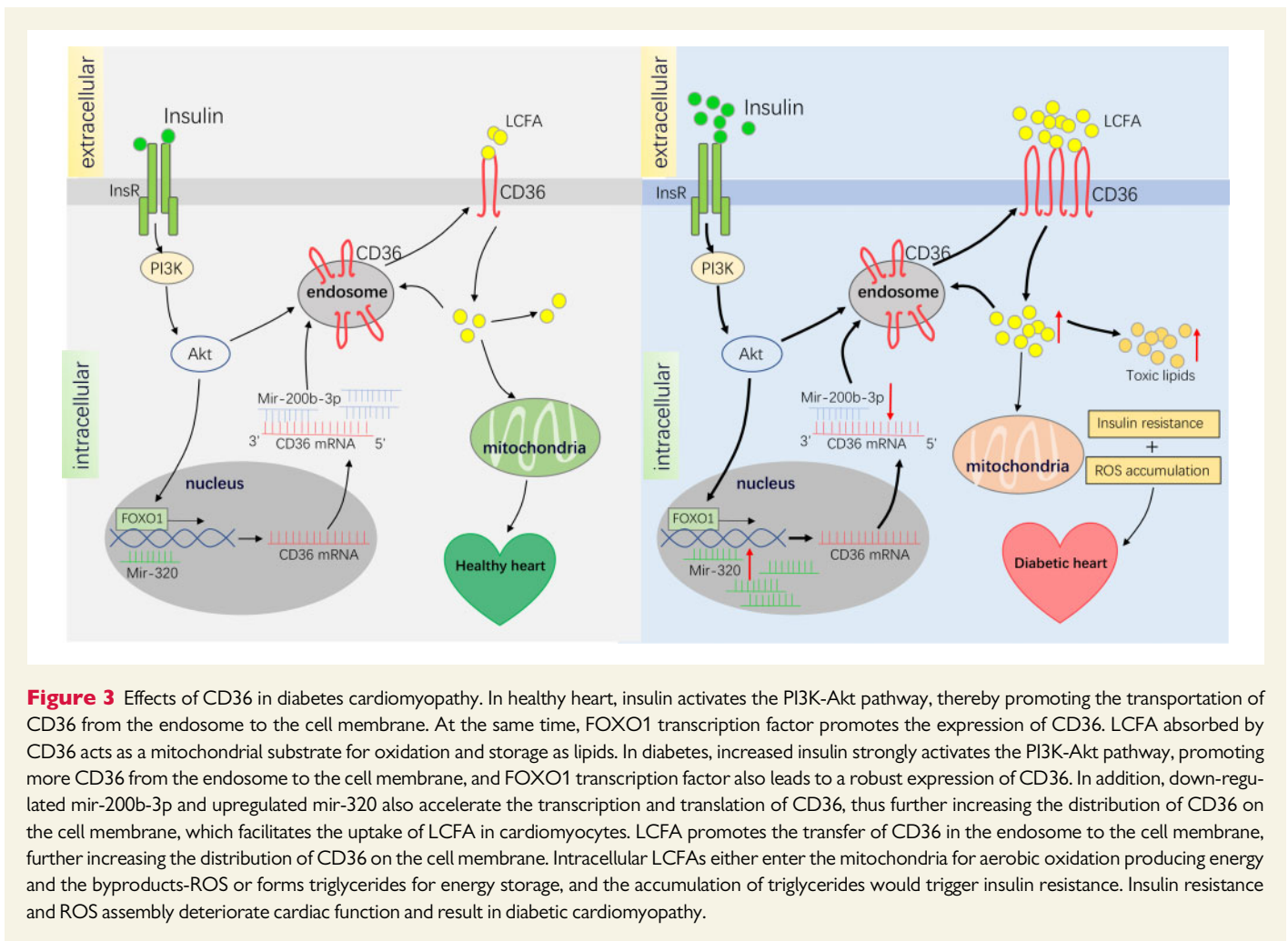
platelet factor 4 (PF4) reduces the phagocytic function of macrophages and leads to higher mortality from myocardial infarction, which is also attributed to CD36 signalling down-regulation.<sup>100</sup> Therefore, the decrease of CD36 or its dysfunction in macrophages deteriorates myocardial infarction. Although CD36 is more abundantly expressed in endothelial cells than in cardiomyocytes,<sup>101</sup> the role of endothelial CD36 in ischaemic cardiomyopathy remains unclear.

Although reducing the content of CD36 has contradictory effects on macrophages and cardiomyocytes, current treatments for ischaemia–reperfusion still focus on inhibiting the function of CD36. The likely reason is that there are significantly more cardiomyocytes than macrophages in myocardial tissue,<sup>102</sup> and the improvement of cardiomyocyte function by inhibiting CD36 may exceed the harm caused by macrophages. For example, Mansor *et al.* corrected post-hypoxia/reoxygenation cardiac metabolic disorders by injecting sulfo-*N*-succinimide oleate (a CD36-specific inhibitor that results in an arrest of the FFA transport<sup>103</sup>) into the hearts of type 2 diabetic male Wistar rats 4 min before hypoxia.<sup>104</sup> Pre-injection of selective CD36 ligand EP 80317 (a synthetic hexapeptide growth hormone-releasing peptide family analogue that is devoid of somatotroph activity<sup>105</sup>) and azapeptide CP-3(iv) in mice significantly reduced the myocardial infarct size.<sup>106,107</sup> Exenatide, a small-molecule drug

that regulates glucose metabolism, has also been shown to improve cardiac function after cardiac ischaemia–reperfusion injury by inhibiting the translocation of CD36.<sup>108</sup>

Drug studies provide 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 but improves functional recovery after ischaemia/reperfusion.<sup>109</sup> The decrease in fatty acid oxidation rate caused by the decrease in CD36 lays the foundation for increasing the rate of glucose oxidation. It has been shown that this recovery is due to the lower hydrogen ion concentration resulting from the uncoupling of glycolysis from glucose oxidation produced before and after ischaemia.<sup>109</sup> However, CD36 systemic knockout mice still suffer from severe ischaemia–reperfusion injury;<sup>110</sup> presumably, this relates to the general reduction of CD36. Not restricted to the heart, systemic metabolic changes occur in a vast number 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 on ischaemia/reperfusion in spontaneously hypertensive rats have challenged the protective effect of a decline in



**Figure 3** Effects of CD36 in diabetes cardiomyopathy. In healthy heart, insulin activates the PI3K-Akt pathway, thereby promoting the transportation of CD36 from the endosome to the cell membrane. At the same time, FOXO1 transcription factor promotes the expression of CD36. LCFA absorbed by CD36 acts as a mitochondrial substrate for oxidation and storage as lipids. In diabetes, increased insulin strongly activates the PI3K-Akt pathway, promoting more CD36 from the endosome to the cell membrane, and FOXO1 transcription factor also leads to a robust expression of CD36. In addition, 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 in 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 LCFAs either enter the mitochondria for aerobic oxidation producing energy and the byproducts-ROS or forms triglycerides for energy storage, and the accumulation of triglycerides would trigger insulin resistance. Insulin resistance and ROS assembly deteriorate cardiac function and result in diabetic cardiomyopathy.

CD36. Instead of the inhibition of CD36, the overexpression of CD36 in SHRs reduced the infarct size, but the underlying mechanism has not been clarified. Given that the model already has a pathological factor of hypertension, it is possible that the overexpression of CD36 reduces the myocardial injury risk brought by hypertension and indirectly protects the infarcted myocardium caused by ischaemia/reperfusion.<sup>111</sup>

#### 4.2 Cd36 and diabetic cardiomyopathy

The typical characteristics of diabetic cardiomyopathy are altered lipid metabolism and impaired insulin signalling pathways.<sup>112–114</sup> Without any pathological stimulus, CD36 on the cardiac sarcolemma is significantly increased in obese Zucker rats,<sup>115</sup> db./db. mice,<sup>116</sup> and high-fat-fed rats.<sup>117</sup> The up-regulation of CD36 has also been confirmed in the cardiomyocytes of patients with diabetic cardiomyopathy.<sup>118</sup>

The increase in CD36 expression in the sarcolemma in diabetic cardiomyopathy may be attributed to hyperinsulinaemia, hyperglycaemia, and hyperlipidaemia. Prior to insulin resistance, CD36 translocates from endosomes to the myometrium because of the alkalization of endosomes, which is caused by lipid-related inhibition of the proton pumping activity of vacuolar-type H<sup>+</sup>-ATPase (v-ATPase).<sup>30,119</sup> In the early stages of diabetes, insulin is at high levels.<sup>120</sup> Luiken et al. found that insulin stimulation in isolated myocardial rat cells resulted in a 1.5-fold increase in CD36 on the sarcolemma and a 62% decrease in intracellular CD36, suggesting that insulin could effectively promote the translocation of

CD36<sup>31</sup> (Figure 3). Chronic insulin stimulation also induces CD36 mRNA translation by activating the transcription factor forkhead box O1 (FOXO1), which further facilitates CD36 protein synthesis<sup>121</sup> (Figure 3). In the late stage of diabetes, the insulin level has decreased significantly, and the cardiomyocytes are resistant to insulin, but CD36 has been permanently transferred to the myometrium during the early stage.<sup>117</sup> The decline of insulin does not change the fact that a large number of fatty acids have already been taken into cardiomyocytes. Similar to chronic insulin stimulation, high glucose stimulation increases CD36 mRNA translation,<sup>122</sup> followed by increased CD36 expression, and membrane translocation of CD36 by palmitic acid stimulation.<sup>33</sup> In the advanced stage of diabetes, hyperglycaemia and hypertriglyceridaemia may occur, thus further promoting CD36 expression and increasing its membrane distribution.<sup>123</sup> In addition to external factors such as insulin, glucose, and lipids, the latest research suggests 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 mice with diabetic cardiomyopathy and promotes CD36 expression by directly acting on its nuclear transcription<sup>124</sup> (Figure 3). In contrast, miR-200b-3p is remarkably reduced in diabetic cardiomyopathy, which is an effective inhibitor of CD36 (Figure 3).

CD36 increases during diabetic cardiomyopathy, which in turn worsens heart function.<sup>125</sup> The increased distribution of CD36 on the myometrium results in the intake of a large amount of fatty acids. Fatty acids

in the cytoplasm could activate peroxisome proliferator-activated receptors (PPAR),<sup>26</sup> thereby inducing the up-regulation of enzymes necessary for mitochondrial  $\beta$ -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, 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<sup>126</sup> and trigger myocardial contractile dysfunction.<sup>121</sup> At the same time, high levels of  $\beta$ -oxidation of fatty acids produce a large amount of reactive oxygen species (ROS),<sup>127</sup> which can also induce inflammation<sup>128</sup> and insulin resistance<sup>129,130</sup> which aggravates myocardial contractile dysfunction (Figure 3). Lipids could directly lead to contractile dysfunction by promoting myocardial cell apoptosis.<sup>131</sup> 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.

A fatty acid–glucose balance is essential for maintaining normal cardiac function. The heart operates optimally when it uses a mixture of energy-providing substrates, especially in terms of fatty acids and glucose.<sup>132</sup> The preferential use of a single type of substrate impairs the flexibility of metabolism, limits auxiliary metabolic pathways, and affects the correct post-translational modification of putative proteins (particularly the transcriptional factors, such as PGC-1 $\alpha$  and PPAR $\alpha$ ),<sup>133</sup> thereby impairing heart function.<sup>134,135</sup> In diabetic cardiomyopathy, the metabolic substrate of the myocardium shifts to fatty acids. Cardiomyocytes are insufficiently equipped to store large amounts of lipids with accumulated acylglycerols and ceramides, causing cellular damage by lipotoxicity and insulin resistance.<sup>136</sup> Meanwhile, weakened glucose metabolism leads to an insufficient substrate supply of the pentose phosphate pathway and hexosamine biosynthetic pathway, resulting in impaired auxiliary metabolism.<sup>137</sup> Therefore, inhibiting myocardial fatty acid metabolism helps to reduce lipotoxicity and maintain the fatty acid–glucose balance, thereby improving diabetic cardiomyopathy.

Several studies have shown that reducing the distribution of CD36 on the sarcolemma, thereby inhibiting the uptake of LCFAs, helps to improve the heart function of diabetic cardiomyopathy.<sup>33</sup> For example, mice overexpressing myosin heavy chain (MHC)-PPAR $\alpha$  show severe cardiomyocyte lipid accumulation and cardiac dysfunction.<sup>138</sup> However, due to the lack of CD36, the offspring produced by crossing MHC-PPAR $\alpha$  mice with CD36-deficient mice (MHC-PPAR $\alpha$ /CD36 $^{-/-}$  mice) had decreased triglyceride accumulation and cardiac dysfunction under basic conditions and on a high-fat diet. Glucagon-like peptide-1 could eliminate the lipotoxicity of diabetic cardiomyopathy by stimulating protein kinase A (PKA) inhibition of the CD36 pathway.<sup>139</sup> Exogenous H<sub>2</sub>S protects diabetic hearts by inhibiting the translocation of CD36.<sup>19</sup> N-Acetylcysteine also restored Sevo-postC cardioprotection in diabetes by reducing Foxo1 and CD36.<sup>140</sup> Fibroblast growth factor 21 (FGF21) deletion aggravates cardiac lipid accumulation by upregulating cardiac Nrf2-driven CD36 expression,<sup>141</sup> therefore, FGF21 is a potential agent for the reduction of lipid accumulation as it ameliorates diabetic cardiomyopathy by downregulating the expression of CD36.

## 4.3 Cd36 and cardiac hypertrophy

### 4.3.1 Cd36 in hereditary hypertrophic cardiomyopathy

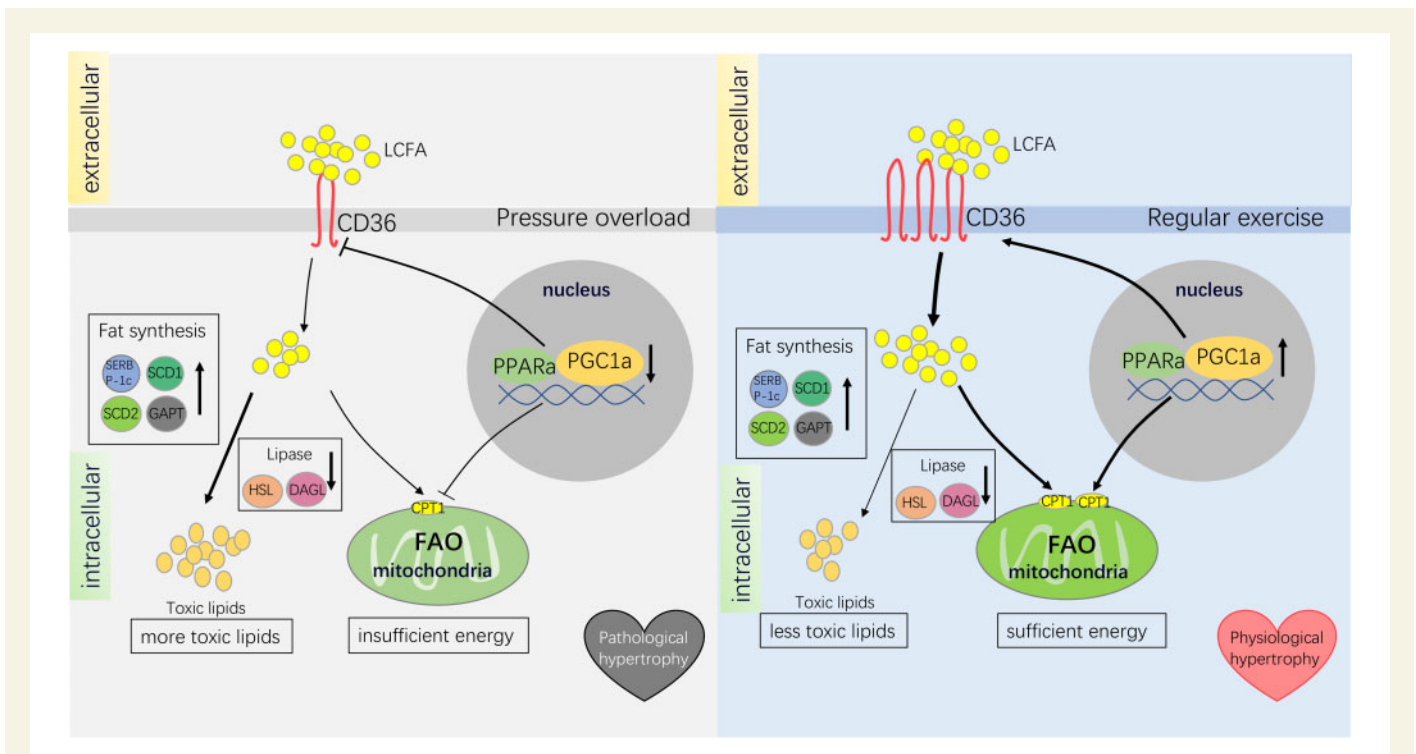
Hereditary hypertrophic cardiomyopathy (HCM) is a disease whose main pathological manifestation is cardiac hypertrophy, and it is caused by a dominant mutation in the gene encoding the cardiac sarcomeric protein.<sup>142</sup> A survey of CD36 and hereditary hypertrophic

cardiomyopathy patients showed that 37.9% of HCM patients with asymmetric ventricular septal hypertrophy had a loss of CD36 protein,<sup>143</sup> 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 between CD36 translocation and left ventricular contractile dysfunction has been verified in HCM mice.<sup>143,144</sup> Owing to the decrease in CD36 translocation to the plasma membrane, ATP and triglycerides in the myocardium dramatically decline. Although the mechanism by which 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 mainly caused by external stress, including pressure overload or physical exercise. 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 hypertrophic hearts were first demonstrated in 2013.<sup>36</sup> Exercise training significantly increased the expression of CD36 in the heart, but pressure overload reduced the expression of CD36.<sup>145</sup> The decrease in CD36 in pathological cardiac hypertrophy and the up-regulation in physiological cardiac hypertrophy may be related to PPAR $\alpha$  and peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  (PGC1 $\alpha$ ). Physical exercise increases the expression of PPAR $\alpha$ <sup>146,147</sup> and PGC1 $\alpha$ <sup>148,149</sup> in the heart, while cardiac pressure overload reduces them<sup>150,151</sup> (Figure 4). The promoter region of CD36 contains PPAR $\alpha$  response elements.<sup>152</sup> It has been shown that the nuclear receptor PPAR $\alpha$  and nuclear receptor peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) regulate CD36 expression in macrophages and cardiac microvascular endothelial cells.<sup>153,154</sup>

As mentioned before, when myocardial cells are facing a crisis of ischaemia and hypoxia, metabolism is remodelled. As for hypoxic pathological cardiac hypertrophy,<sup>155</sup> early and timely reduction of the distribution of CD36 on the cell membrane helps to eliminate the injury caused by a subsequent large intake of fatty acids. The reduction of CD36 not only promotes the substrate transition of fatty acids to glucose<sup>92</sup> 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.<sup>145</sup> Although the glycolytic pathway of glucose is enhanced in maladaptive pathological cardiac hypertrophy due to the inhibition of fatty acid metabolism, by elevated phosphofructokinase and lactate dehydrogenase levels,<sup>145</sup> glycolysis and energy generated from other substrates (lactic acid, branched-chain amino acids, and ketone bodies) could not compensate for the reduction of fatty acid oxidation, putting the heart in an insufficient cardiac energy state (Figure 4). Although the reduction of CD36 leads to a remarkable decline in the overall intake of fatty acids, studies have shown 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), are not down-regulated in pathological cardiac hypertrophic cardiomyocytes (Figure 4). However, the activity and content of hormone-sensitive lipase (HSL) and diacylglycerol lipase (DAGL) that break down fat both decrease, resulting in a 31% increase in triglycerides and a 200% increase in diacylglycerol in myocardial



**Figure 4** Effects of CD36 in pathological and physiological cardiac hypertrophy. Under pressure overload, intranuclear PPAR $\alpha$  and PGC1 $\alpha$  are down-regulated 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, 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 PPAR $\alpha$  and PGC1 $\alpha$  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 the mitochondrial outer membrane, more LCFA undergoes aerobic oxidation in mitochondria. The increase in PPAR $\alpha$  and PGC1 $\alpha$  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, and the activity of HSL and DAGL that break down fat are both upregulated, thereby avoiding excessive accumulation of toxic lipids. Sufficient energy and less toxic lipids maintain the proper cardiac function of physiological cardiac hypertrophy. CPT1, carnitine palmitoyl transferase 1; DAGL, diacylglycerol lipase; GPAT, glycerol-3-phosphate acyltransferase; HSL, hormone-sensitive lipase; SCD1, stearoyl-CoA desaturase 1; SCD2, stearoyl-CoA desaturase 2; SREBP-1c, sterol-responsive element-binding protein-1c.

cells<sup>143</sup> (Figure 4). Insulin resistance caused by accumulated toxic lipids further exacerbates the lack of energy supply in the heart. In addition, pressure overload-induced cardiac hypertrophy leads to an excessive metabolic shift from fatty acid to glucose.<sup>156</sup> As mentioned before, the aberrant preference to one substrate would cripple the metabolic flexibility and cardiac contractility.<sup>134,135,157</sup> Fatty acid metabolism needs to be strengthened in order to restore the balance of fatty acid and glucose and improve cardiac metabolism. In other words, heart function will worsen if CD36 is excessively down-regulated.

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 an imbalance of energy. Comparatively, CD36 systemic knockout mice, when compared to wild-type mice, show pronounced myocardial interstitial fibrosis, cardiac enlargement, and contractile dysfunction after transverse aortic constriction (TAC) surgery.<sup>158</sup> 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.<sup>159</sup> However, whether overexpression of CD36 relieves the energy deficiency in pathological cardiac hypertrophy, and thereby stops the heart failure caused by cardiac pressure overload needs further investigation. It is certain that increasing the supply of fatty acids in myocardial cells to expand the high-energy phosphate pool is beneficial for hypertrophic myocardium. 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.<sup>34</sup>

#### 4.4 Cd36 and atherosclerosis

Atherosclerosis is a progressive chronic inflammation of the arterial wall, manifested by the accumulation of foam cells, retention of macrophages in plaques, and thrombosis.<sup>160</sup> CD36 expression in macrophages is significantly increased in human carotid atherosclerotic tissue, particularly in advanced atherosclerosis.<sup>161</sup> In diet-induced mouse atherosclerosis models and *in vitro* atherosclerosis models, CD36 on macrophages was also remarkably elevated.<sup>162,163</sup>



The main cause of foam cell generation is the excessive influx of modified low-density lipoproteins (LDL), and the accumulation of cholesterol esters in intimal macrophages. As an important scavenger receptor in macrophages, CD36 plays a critical role in cellular oxLDL accumulation and foam cell formation. Macrophages bind with and internalize oxLDL via CD36 due to their high-affinity CD36-oxLDL.<sup>23</sup> Along with the internalization of the CD36-oxLDL assembly, oxLDL enters the cell and accumulates, to transfer the macrophages into the foam cells. OxLDL also provides putative oxidized lipids as ligands for the transcription factor PPAR- $\gamma$ , which is the main transcription factor of CD36, thereby activating CD36 gene expression to further increase the uptake of oxLDL.<sup>164</sup> The uptake of oxLDL by CD36 triggers a chain reaction and creates a cycle, putting CD36 in the centre of foam cell formation.

Many pathogenic factors that lead to atherosclerosis are involved in the regulation of CD36. Smoking and hyperglycaemia are risk factors for atherosclerosis;<sup>122,165</sup> nicotine promotes the expression of CD36 in macrophages in a PPAR- $\gamma$  dependent manner, and hyperglycaemia results in high CD36 mRNA translation efficiency, which increases the expression of CD36. Premature atherosclerotic cardiovascular disease is a common destructive complication of systemic lupus erythematosus (SLE), which may be related to elevated CD36 expression, for reasons currently unknown.<sup>166</sup> IL-34, a cytokine associated with various inflammations and autoimmune diseases, also increases the expression of CD36 via the p38 MAPK signalling pathway to promote the formation of foam cells, and thus is a potential biomarker of atherosclerosis.<sup>167</sup> CCN3 (Cyr61, CTGF, Nov) is an important regulator of vascular homeostasis.<sup>168</sup> The lack of CCN3 leads to the increased formation of foam cells, which is attributed to the increased expression of CD36, possibly due to the elevated level of CCN1 protein. Thrombin also promotes the formation of atherosclerosis by regulating protein kinase C $\theta$  dependent activating transcription factor 2-mediated CD36 expression.<sup>169</sup> Retinol binding protein 4 (RBP4), an adipokine that plays a decisive role in glucose metabolism and insulin sensitivity, has recently been shown to promote atherosclerosis by upregulating CD36 expression. The method is dependent on the Jun N-terminal kinase signal transducer and activator of transcription 1, and activation of CD36-mediated cholesterol uptake to facilitate the formation of foam cells.<sup>170</sup>

In addition to the formation of foam cells, CD36 is also involved in the inflammatory response of macrophages. For example, targeting CD36 inhibits the NLRP3 inflammasome, resulting in a decrease in serum IL-1 $\beta$  in atherosclerotic mice.<sup>171</sup> CD36-related uptake of oxLDL induces the specific expression profile of macrophage oxidative stress markers (5-epi-5-F2t-IsoP, 15-E1t-IsoP, 8-F3t-IsoP, and 15-keto-15-F2t-IsoP) and inflammation markers (PGDM, 17-trans-PGF3 $\alpha$ , and 11 $\beta$ -PGF2 $\alpha$ ).<sup>172</sup> Even relatively low concentrations of oxLDL can induce a durable atherogenic macrophage phenotype through epigenetic histone modification.<sup>173</sup> In addition, CD36 was recently found to drive the chronic inflammatory response of macrophages by reprogramming mitochondrial metabolism.<sup>174</sup>

Generally, the acute inflammatory response gradually subsides, as the infiltrating immune cells gradually migrate to the draining lymph nodes.<sup>175</sup> However, inflammation in atherosclerosis does not spontaneously subside. Macrophages, with a pro-inflammatory phenotype, are trapped in the atherosclerotic plaque, causing a continuous inflammatory response.<sup>176,177</sup> The oxLDL/CD36 interaction is essential for the retention of macrophages in plaques. The migration chemokines, CCL19 and CCL21, largely decrease in macrophages after oxLDL stimulation,<sup>178</sup> with persistent expression of CD146 that promotes macrophage retention in plaques.<sup>178</sup> Importantly, the migration of CD36 null macrophages

is not inhibited by oxLDL, compared with wild-type macrophages, underscoring the importance of CD36 signalling in macrophage retention.<sup>179</sup> Two mechanisms may explain oxLDL/CD36 signal-related macrophage retention. Firstly, oxLDL-mediated CD36 signal transduction results in the continuous activation of focal adhesion kinase and the inactivation of Src homology 2 containing phosphotyrosine phosphatase, which leads to disorders of cytoskeleton assembly and disassembly,<sup>179</sup> and the loss of macrophage activity. Secondly, oxLDL can also induce the loss of macrophage polarity by activating the Vav/Rac pathway and inactivating the non-muscle myosin II.<sup>176</sup> In addition to oxLDL stimulation, CD36 also mediates the inhibitory effect of advanced glycation end product [N $\epsilon$ -carboxymethyllysine (CML)] on the retention of macrophages.<sup>180</sup> CD36 is activated by CML and triggers the production of nicotinamide adenine dinucleotide phosphate oxidase (NOX)-derived ROS, which then promotes F-actin polymerization to inhibit the migration of macrophages and accelerate the development of atherosclerosis in diabetic patients.

CD36 is a glycoprotein with a high expression level in platelets and is closely related to the formation of the prethrombotic phenotype in the high-fat state. Accumulating evidence has shown that there is a high correlation between the platelet activation response to oxLDL and the expression level of CD36.<sup>181</sup> CD36 null subjects have slow thrombosis, while elevated platelet CD36 expression may increase the risk of thromboembolism.<sup>182,183</sup> Animal experiments showed that the deletion of the CD36 gene protects mice from the increased platelet reactivity associated with hyperlipidaemia and the accompanying thrombotic phenotype.<sup>184</sup> OxLDL-mediated CD36 signal transduction can activate platelets in a variety of ways. Firstly, after CD36 is activated, it recruits Src family kinases Fyn and Lyn, and further promotes the activation of non-receptor tyrosine kinases Syk and (c-Jun-N-terminal kinase) JNK, leading to the exposure of P-selectin and activated integrin, thereby enhancing thrombosis.<sup>185</sup> Secondly, oxLDL stimulates the continuous generation of NOX2-derived ROS through the CD36-PKC pathway and promotes platelet hyperfunction by regulating cGMP signal transduction.<sup>28</sup> Thirdly, in response to the signal of oxLDL/CD36, the activated protein kinase ERK5 promotes the exposure of procoagulant phosphatidylserine (P $\text{Ser}$ ) on the platelet surface,<sup>186</sup> thereby causing platelet activation and aggregation.<sup>23</sup> Meanwhile, CD36 also activates platelets through the interaction with endothelial cell-derived microparticles oxPL, which makes platelets more sensitive to low concentrations of agonists.<sup>16,187</sup> Lastly, advanced glycosylation products (AGEs) in diabetic patients also serve as ligands to bind to platelet CD36, leading to platelet hyperreactivity and inducing a prethrombotic phenotype.<sup>8</sup>

In view of the important role of CD36 in promoting atherosclerosis, anti-atherosclerotic drugs mainly focus on reducing the expression of CD36. Traditional Chinese medicine, including salivianolic acid B (a hydrophilic component derived from the herbal *Salvia miltiorrhiza*),<sup>188</sup> andrographolide (the biologically active component of *Andrographis paniculata*),<sup>189</sup> and scopolamine (plant flavonoids),<sup>162</sup> all suppress the development of atherosclerosis by lowering the expression of CD36. Tamoxifen, an anti-breast cancer drug, has also been confirmed to inhibit the expression of CD36 by inhibiting the PPAR- $\gamma$  signalling pathway, thereby combating atherosclerosis.<sup>190</sup> The apoA-I mimetic peptide D4F can also reduce the formation of macrophage-derived foam cells by inhibiting the expression of CD36.<sup>191</sup> The new members of the calcitonin gene-related peptide family intermedin and C1q/tumour necrosis factor-related protein 13 (CTRP13) inhibit the formation of macrophage foam cells and reduce atherosclerosis plaques by promoting the degradation of CD36 mRNA and promoting autophagolysosomal-dependent

CD36 degradation, respectively.<sup>192</sup> Vasostatin-1 is a chromogranin A (CgA)-derived peptide (76 amino acids) that can inhibit vasoconstriction and angiogenesis. Its inhibitory effect on atherosclerosis is also associated with the down-regulation of CD36. Currently, researchers are studying the nanoparticles targeting CD36 specifically to enhance efficacy and reduce side effects.<sup>193</sup>

## 5. Conclusion and perspective

Cardiovascular diseases have been seriously endangering the physical and mental health of older adults,<sup>194</sup> and they are particularly prominent with the current increase in the aging population. Cardiac lipid metabolism remodelling plays a key role in cardiovascular system diseases such as ischaemia–reperfusion, diabetic cardiomyopathy, and cardiac hypertrophy.<sup>195</sup> CD36 is a vital molecule in lipid metabolism.<sup>29</sup> Changes in its synthesis, localization, and function directly affect the energy supply and metabolism of the heart. Studies on CD36 in different diseases suggest that CD36 may be potentially useful for treatment. Therefore, 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.<sup>79</sup> Post-translational modifications, including phosphorylation, ubiquitination, palmitoylation, and glycosylation, accurately regulate the maturation, transport, and positioning of CD36.<sup>1</sup> *In vitro* research has revealed the impact of post-translational modification of CD36 on cellular fatty acid uptake in adipocytes<sup>83</sup> and muscle cells.<sup>69</sup> However, few studies have demonstrated its importance in cardiovascular systems. Whether these modifications of CD36 alter the cellular uptake of fatty acids in the myocardium and further influence cardiac function still remains to be elucidated. Determining which enzymes mediate these modifications in cardiomyocytes and whether these enzymes are useful as new therapeutic targets, requires further investigation.

Fatty acids may also cause excessive lipid accumulation while providing energy.<sup>196,197</sup> The increase in fatty acid uptake caused by CD36 can be beneficial or harmful under different pathological conditions. Fatty acids in cells are modulated by CD36 and are also affected by the rates of mitochondrial aerobic oxidation, and triglyceride synthesis and decomposition.<sup>198,199</sup> Therefore, to evaluate the role of CD36 in myocardial lipid metabolism, the corresponding mitochondrial aerobic oxidation and triglyceride synthesis also needs to be taken into consideration. Since it is not uncommon that more than two pathological factors are combined at the same time, such as hypertension<sup>111</sup> and myocardial infarction<sup>200</sup> in diabetes, the impact of CD36 on myocardial lipid metabolism and cardiac function is definitely more complicated when that occurs. Therefore, further research is needed to investigate these situations.

The function of CD36 in regulating lipid metabolism in cardiomyocytes is not limited to lipid uptake. CD36 in mitochondria increases in parallel with the up-regulation of FA oxidation, and recent studies have shown that CD36 mediates a mitochondrial metabolic switch from oxidative phosphorylation to superoxide production in response to its ligand, oxidized LDL.<sup>201,202</sup> Moreover, mitochondrial-specific inhibition of superoxide inhibited oxidized LDL-induced nuclear factor- $\kappa$ B (NF- $\kappa$ B) activation and inflammatory cytokine generation.<sup>174</sup> In addition, CD36 also forms complexes with certain metabolic molecules and participates in the energy regulation process through direct interactions. For example, CD36 regulates the activity of AMPK by forming a molecular

complex with Lyn and LKB1 and inhibits the activation of LKB1,<sup>62</sup> which is a known AMPK<sup>202</sup> agonist. Further study on the function of CD36 beyond myocardial lipid uptake will help to provide a more comprehensive understanding of myocardial lipid metabolism dysfunction and related cardiovascular complications.

In response to insulin and contraction stimulation, both CD36 and GLUT4 translocate to the sarcolemma to increase fatty acid and glucose uptake, respectively, which is contradictory to the Randle cycle phenomenon.<sup>203,204</sup> How to specifically regulate CD36, without affecting the recycling of subcellular GLUT4, is also an area that remains to be determined. Previous studies have focused on the related proteins in the GLUT4 and CD36 vesicle transport pathways. For example, VAMP4 mainly mediates vesicle transport of CD36, while VAMP5 and VAMP7 are involved in GLUT4 vesicle transport.<sup>58</sup> These studies on the subcellular transport of CD36 and GLUT4 help explain and distinguish the different energy regulation patterns made by cardiomyocytes in the face of different signal stimuli.

In the cardiovascular system, CD36 is not only expressed on the surface of cardiomyocytes but also exists in other cells, such as endothelial cells.<sup>176</sup> Although a large number of studies have reported that the CD36 of endothelial cells is critically involved in the progression of vascular diseases such as atherosclerosis,<sup>205,206</sup> little research has been performed to explore its effect on diabetic cardiomyopathy, hypertrophic cardiomyopathy, and other diseases. Therefore, an in-depth study of the effects of CD36 on myocardial metabolism in other types of cells is also an important issue. In addition, in view of the universality of CD36 expression, drugs developed for targeting CD36 should specify cell populations and CD36 sites to limit side effects, avoid the potential for off-target effects, and improve their efficacy.

## Data accessibility

Most of the 207 references are accessible in pubmed.

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