

Fatty acid translocase: a culprit of lipid metabolism dysfunction in disease

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Abstract

Dysregulation of lipid deposition into and mobilization from white adipose tissue (WAT) underlies various diseases. Long-chain fatty acids (LCFA) and cholesterol trafficking in and out of adipocytes is a process relying on transporters shuttling lipids from the plasma membrane (PM) to lipid droplets (LD). CD36 is the fatty acid translocase (FAT) that transports LCFA and cholesterol across the PM. Interactions of CD36 with proteins PHB1, ANX2, and CAV1 mediate intercellular lipid transport between adipocytes, hematopoietic, epithelial, and endothelial cells. Intracellularly, the FAT complex has been found to regulate LCFA trafficking between the PM and LD. This process is regulated by CD36 glycosylation and S-acylation, as well as by post-translational modifications of PHB1 and ANX2, which determine both protein–protein interactions and the cellular localization of the complex. Changes in extracellular and intracellular LCFA levels have been found to induce the post-translational modifications and the function of the FAT complex in lipid uptake and mobilization. The role of the CD36/PHB1/ANX2 complex may span beyond lipid trafficking. The requirement of PHB1 for mitochondrial oxidative metabolism in brown adipocytes has been revealed. Cancer cells which take advantage of lipids mobilized by adipocytes and oxidized in leukocytes are indirectly affected by the function of FAT complex in other tissues. The direct importance of CD36 interaction with PHB1/and ANX2 in cancer cells remains to be established. This review highlights the multifaceted roles of the FAT complex in systemic lipid trafficking and discuss it as a potential target in metabolic disease and cancer.

Keywords: fatty acid translocase, lipid metabolism

1. The role of CD36 in health and disease

Changes in lipid metabolism underlie the progression of all diseases ^[1]. Fatty acids (FA), cholesterol, their derivatives, and other lipids are used as a source of energy, cell structure components, and signaling molecules. White adipocytes are the rheostat of FA, contained as triglycerides in the lipid droplets (LD), as well as of cholesterol. White adipose tissue (WAT) can store or release lipids, which affects metabolism and the immune system systemically ^[2,3]. In contrast, brown adipose tissue (BAT) and beige adipocytes in WAT serve as energy sink by catabolizing lipids through adaptive thermogenesis ^[4]. Adipocyte dysfunction and imbalance between lipid storage and mobilization aggravates chronic cardiovascular, inflammatory, and malignant conditions ^[5]. Adipocyte hypertrophy, a hallmark of obesity, leads to WAT inflammation, dyslipidemia, and systemic lipotoxicity resulting in type-2 diabetes ^[6,7]. Conversely, excessive WAT lipolysis and lipid mobilization is associated with cachexia and cancer progression ^[8–10]. The transport of lipids across the PM is an active process controlling cell metabolism. A key mediator of lipid transport is the scavenger receptor cluster of differentiation 36 (CD36), also known as fatty acid translocase (FAT). This protein, along with co-factors such as Src family kinases and G protein–coupled receptors (GPCRs), facilitates the intracellular and extracellular trafficking of long-chain

fatty acids (LCFA), cholesterol, oxidized low-density lipoprotein (OxLDL), and extracellular matrix proteins ^[11–15]. The interaction of CD36 with Src kinases and GPCRs allows for detection of specific lipids and the downstream activation of unique signaling pathways. For instance, CD36 binding of oleic acid activates mammalian target of rapamycin (mTOR) and extracellular signal-regulated kinase (ERK)1/2 pathways and is associated with tumor cell progression and metastasis ^[16,17]. Moreover, CD36 interaction with GPR120 and GPR40 in taste buds is implicated in the perception of dietary lipids and may play a role in obesity-associated diseases ^[18].

Ample evidence indicates the importance of CD36 in AT. CD36 inhibition attenuates the effect of lipolysis induction ^[19] and reduces hypertrophy of visceral WAT in mice fed high-fat diet ^[20,21]. Based on this notion, CD36 has been investigated as a therapeutic target. However, these pursuits have been complicated because CD36 is expressed by various cell types including hematopoietic ^[22], and epithelial and endothelial cells ^[23,24] in which it plays diverse roles. In models of atherosclerosis, suppression of CD36 transcription ^[25,26], function ^[27], or increased CD36 degradation ^[28] were associated with a reduction in foam cell formation and reduced uptake of oxidized lipids by macrophages. Consistent with a pathogenic role of CD36, its inhibition attenuated hepatic steatosis/fibrosis ^[29,30] and myosteatosis ^[31]. However, global deletion of CD36 results in dyslipidemia, subclinical inflammation ^[32], and an increased risk of atherosclerosis ^[33]. Moreover, expression of CD36 was found to be an important regulator of proper muscle satellite cell differentiation and myofiber regeneration ^[34]. Expression of CD36 is also important for suppressing neuroinflammation in demyelinating disorders ^[35]. Collectively, these findings suggest that targeting the CD36 pathway requires cell type-specific strategies, and systemic inhibition of CD36 may have undesirable off-target effects.

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2. Formation of the PHB1/ANX2/CD36 complex and its importance in lipid trafficking and mitochondrial homeostasis

The complexity of FAT signaling and its functions has become even more apparent since the identification of post-translational modifications regulating CD36-induced lipid trafficking from the plasma membrane (PM) to the LD and vice versa. Glycosylation is one such modification, which is particularly pronounced in adipocytes^[36,37]. Another modification is S-acylation of CD36 by the palmitoyl acyltransferases DHHC4 or DHHC5. Palmitoylation induces CD36 translocation to the PM, which enables its binding of extracellular lipids and the subsequent internalization of the lipid-FAT complex via caveolin-1 (CAV1)-mediated endocytosis^[38]. Other proteins mediating this process are prohibitin-1 (PHB1) and annexin 2 (ANX2), which interact with CD36 at the surface of adipose endothelium and adipocytes^[39]. Dynamic S-acylation of PHB1 and ANX2 is important for the formation of the PHB1/ANX2/CD36 complex and its trafficking to and from the PM^[40]. Furthermore, lipolysis induction results in CD36 deacylation, internalization, and an apparent dissociation from PHB1 and ANX2 in the cytosol. Transient colocalization of CD36 and CAV1 at the LD during LCFA transport suggests that CD36 may play a role in lipid trafficking not only at the cell surface but also for transporting lipids from the PM to the LD. The detailed roles of PHB1 and ANX2 in regulating CD36-mediated lipid transport remain to be completely understood. Although the inhibition of either PHB1 or ANX2 leads to a phenotype akin to CD36 knockout and^[39,41], these proteins have other functions in addition to lipid transport. Both PHB1 and ANX2 are found in various cell organelles, in which they regulate distinct processes^[41–48]. A key function of PHB1 is to maintain mitochondrial biogenesis and function^[49–51]. Indeed, ablation of PHB1 in adipocytes results in decreased mitochondrial content and function, which accounts for the loss of BAT and thermogenesis^[52,53]. Interestingly, PHB1 does not possess a mitochondrial targeting domain, instead, phosphorylation of PHB1 at Thr258 by AKT is considered the mechanism promoting mitochondrial localization of PHB1^[54].

Since the discovery of the interaction of PHB1 with CD36 in adipocytes, and the critical role of PHB1 in mitochondrial respiration, it is logical to extrapolate this mechanism to non-adipogenic cells and postulate that the PHB1/ANX2/CD36/CAV1 interactome may act as a ubiquitous lipid-sensing pathway. One possibility is that lipid delivery to the mitochondrial membrane and stabilization of electron transport chain enzymes, mediated by these proteins, may increase mitochondrial oxidative phosphorylation and biogenesis, favoring FA oxidation for ATP generation. This concept could have critical implications in the context of tumor cell physiology. Tumor cells regularly endure hypoxia, changes in fuel source availability, and high levels of reactive oxygen species (ROS). These processes involve changes in mitochondrial function that are likely to engage PHB1 and hence relay back to the FAT complex.

As previously stated, CD36 has been shown to regulate mTOR signaling yet our understanding of the mechanism by which this occurs remains lacking. Interestingly, PHB1 plays a direct role in the regulation of mTOR signaling. Although a consensus suggests PHB1 increases protein translation via activation of mTOR signaling^[55,56], some studies report contradictory findings^[57]. Given its association with CD36 and status as a chaperone protein^[50], PHB1 may act as a rheostat for FA metabolism in cells, regulating the shuttling of CD36 between the PM and LD while also activating mTOR and stabilizing mitochondrial metabolism and ATP production. ANX2 binds calcium, actin, and lipids and is a crucial component for stabilizing and organizing lipid microdomains at the PM, which are important sites for endo- and exocytosis^[58–60]. Thus, ANX2 may have a role in

directing CD36 to specific sites at the PM for lipid trafficking. These implied roles for PHB1 and ANX2 in CD36-mediated FA transport warrant investigation to increase our understanding of these interactions.

3. CD36 and cancer

The importance of lipid metabolism in cancer has been realized in recent years^[61–63]. Progression of carcinomas to epithelial-to-mesenchymal (EMT), chemotherapy resistance, and metastasis is linked with increased LCFA uptake by tumors^[64,65]. Recent studies of our group demonstrated the role of adipocyte and endothelial CD36 in LCFA mobilization from WAT and their bioavailability for cancer cells^[40,63]. However, CD36 is also expressed by cancer cells, in which its glycosylation is relatively low, and the function is debated^[40]. Increased expression of CD36 in tumor epithelium is associated with poor prognosis of various GI carcinomas as well as of ovarian cancer, glioblastoma, oral squamous cell carcinoma, and melanoma^[66]. Interestingly, it is low CD36 expression that marks a poor prognosis for kidney renal clear cell carcinoma and pancreatic adenocarcinoma^[67]. Conflicting results have been published for breast cancer^[68,69]. Despite this controversy, there appears to be a clear link of high CD36 expression, particularly in combination with CAV1 expression, and metastasis^[70]. Pharmacological intervention results are consistent with cell surface CD36 being an important promoter of cancer aggressiveness^[71]. Studies have identified CD36 expression as a driver of EMT in cervical^[72], ovarian^[73], colon^[74], breast^[75], hepatocellular carcinoma^[76], and pancreatic^[77] cancers.

CD36 expression in the tumor microenvironment is also a key component of tumor progression. It has been reported that CD36-mediated uptake of oxidized lipids by leukocytes undermines anti-tumor immune response^[66,78,79]. Increased CD36-mediated uptake of oxidized lipids by killer T-cells causes them to become dysfunctional and switch from a cytotoxic to immunosuppressive role^[79]. Studies investigating tumor-associated macrophages (TAMs) show that blocking CD36-mediated uptake of oxidized lipids by TAMs significantly reduces tumor progression by reducing pro-tumor cytokines produced from TAMs^[80]. Interestingly, in breast cancer down-regulation of CD36 expression in cancer-associated fibroblasts is linked with reduced tumor cell proliferation^[81]. The CD36-interacting proteins have been individually implicated in promoting cancer progression. Elevated PHB1 is associated with increased metastasis in lung^[82] and prostate^[83] cancers, while both PHB1 and ANX2 have been implicated in breast cancer metastasis^[84,85]. A possible role of the PHB1/ANX2/CD36/CAV1 interactome in cancer progression remains to be determined and put into the context of what is known about other proteins, such as FATP1, which also regulate FA transport in cancer cells^[86].

4. Targeting CD36 as a novel therapy for metabolic and metastatic disease

Despite the paucity of the FAT complex functions, its directed targeting may still pose an attractive approach for treating metabolic diseases and warrants further investigation. Clinical studies targeting CD36 signaling in cancer are underway^[66]. Those that have been completed have largely failed due to off-target and adverse side effects, suggesting a refined approach is needed to increase the accuracy of inhibiting CD36 in target tissues^[87,88]. Our group has used homing peptides to direct experimental therapies to specific cell types^[89–93]. In brief, this approach utilizes combinatorial phage-displayed peptide libraries to identify peptide sequences for homing affinity to target cells^[94]. After screening, candidate peptides are validated for

receptor-blocking properties. For example, a peptide mimicking the PHB1-binding site in ANX2 has been shown to block FA transport [39]. Potentially, receptor-homing peptides could be used to deliver molecules neutralizing CD36 complex transport function and signaling specifically in WAT, hepatocytes, or other cells for the treatment of obesity, hepatosteatosis, type-2 diabetes, and metastatic disease. Furthermore, specific targeting of CD36 in cancer cells using phage-display may be an approach to interfere with tumor lipid metabolism, hence making chemotherapy more effective. However, the notion that the loss of PHB1 in adipocytes and in endothelial cells has opposite effects on metabolism [95] reiterates the point that targeting molecules in the FAT complex may need to be directed to specific cell types in order to be beneficial.

Increased interest in the relevance of lipid trafficking in disease will undoubtedly advance our understanding of metabolic and malignant disease. However, several aspects of what role the PHB1/ANX2/CD36 complex plays requires further investigation. For instance, CD36 has been shown to bind various ligands resulting in differential activation of downstream pathways, especially regarding Src family kinases and GPCRs. Detailed mechanisms showing how different classes of lipids binding the PHB1/ANX2/CD36 complex alters its interaction with secondary messengers, including any conformational changes, post-translational modification sites, and protein-protein interactions needs to be elucidated. Furthermore, the premise that this complex may act as a lipid-sensing pathway affecting intracellular lipid trafficking and metabolism in multiple cell types is intriguing. Detailed analyses of the functions of PHB1 and ANX2 after dissociation from the complex, especially if novel roles are identified for their involvement in lipid metabolism, protein synthesis, and mitochondrial function, would be important advances for linking lipids with chemoresistance and cancer progression. Future studies will establish and build on the relative importance of the FAT complex proteins in cells of WAT and BAT vs other benign and malignant tissues.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

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