Trans-Endothelial Fatty Acid Transport and Cardiac Metabolism/Contractile

Subjects: Endocrinology & Metabolism

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The heart is a metabolic omnivore that combusts a considerable amount of energy substrates, mainly long-chain fatty acids (FAs) and others such as glucose, lactate, ketone bodies, and amino acids. There is emerging evidence that muscle-type continuous capillaries comprise the rate-limiting barrier that regulates FA uptake into cardiomyocytes. The transport of FAs across the capillary endothelium is composed of three major steps—the lipolysis of triglyceride on the luminal side of the endothelium, FA uptake by the plasma membrane, and intracellular FA transport by cytosolic proteins. In the heart, impaired trans-endothelial FA (TEFA) transport causes reduced FA uptake, with a compensatory increase in glucose use. In most cases, mice with reduced FA uptake exhibit preserved cardiac function under unstressed conditions. When the workload is increased, however, the total energy supply relative to its demand (estimated with pool size in the tricarboxylic acid (TCA) cycle) is significantly diminished, resulting in contractile dysfunction. The supplementation of alternative fuels, such as medium-chain FAs and ketone bodies, at least partially restores contractile dysfunction, indicating that energy insufficiency due to reduced FA supply is the predominant cause of cardiac dysfunction.

cardiac metabolism fatty acid capillary endothelium trans-endothelial fatty acid transport contractile function

1. Mechanisms of FA Uptake by the Heart

1.1. Source of Long-Chain Fatty Acids

As shown in **Figure 1**, FAs are supplied to the heart as either free FAs (FFAs) bound to albumin or as FAs released from the TG contained in TG-rich lipoproteins (TGRLPs): chylomicrons (CM) that are synthesized in the intestine from exogenous dietary fat and very low-density lipoproteins (VLDL) that are synthesized by the liver from endogenous lipids [1][2][3][4][5]. FFAs bound to albumin originate from adipose tissue lipolysis, with some derived from “spillover” through the action of lipoprotein lipase (LPL). Both circulating FFAs and TGRLPs significantly contribute to the overall FA supply to cardiomyocytes.

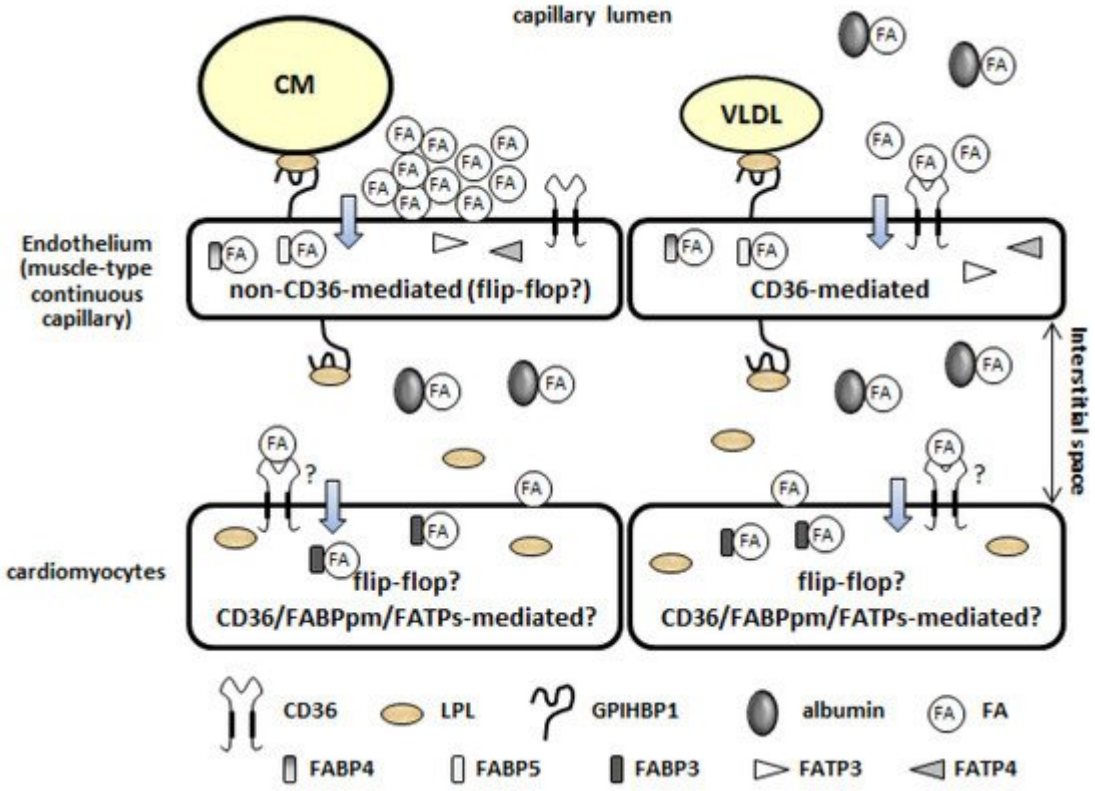

Figure 1. Mechanisms of fatty acid uptake by the heart. (1) Lipolysis of TG contained in TGRLPs on the luminal side of the capillary endothelium; (2) FA uptake by the plasma membrane of the capillary endothelium; (3) intracellular FA transport through the capillary endothelium; (4) FA uptake by cardiomyocytes.

1.2. Lipolysis of TG Contained in TG-Rich Lipoproteins on the Luminal Side of the Capillary Endothelium

LPL is an essential enzyme that hydrolyses the TG contained in TGRLPs [1][2][3][4]. Importantly, LPL is predominantly produced in cardiomyocytes and is transferred to the luminal side of the endothelium, where the enzyme functions (**Figure 1**). GPIHBP1, a glycosylphosphatidylinositol-anchored protein 1 expressed in the capillary endothelium, is the principal binding site for LPL on the endothelium (**Figure 1**). GPIHBP1 binds to LPL from interstitial spaces and shuttles it across the endothelium to the capillary lumen. On the luminal side, its ability to bind to both LPL and TGRLPs allows it to serve as a platform for TG lipolysis [2][6]. The VLDL receptor, expressed in the capillary endothelium, functions as a peripheral receptor for TGRLPs and facilitates the hydrolysis of TG in concert with LPL [3][7][8].

1.3. Fatty Acid Uptake by the Plasma Membrane of the Capillary Endothelium (Non-CD36-Mediated and CD36-Mediated Pathways)

There are two distinct pathways of FA uptake by the capillary endothelium [9][10]—a high-capacity non-saturable pathway (**Figure 1**, upper left) and a low-capacity saturable pathway (**Figure 1**, upper right). The non-saturable pathway operates at high ratios of FAs. CM-derived TG-FAs (high local release of FA) enter through a non-CD36-mediated route (low affinity, high capacity, and non-saturable, presumably via the flip-flop mechanism) [10]. The

saturable pathway has kinetics that are consistent with protein facilitation, with a high affinity for long-chain FAs (Km of approximately 10 nM). CD36, also known as fatty acid translocase (FAT), is a high-affinity receptor for long-chain FAs (Km of 5–10 nM) and is suitable for the low levels of FFAs. Importantly, in the heart, CD36 is more abundant in the capillary endothelium compared to cardiomyocytes [11][12]. It is likely that VLDL-derived TG-FAs (low local release of FAs) and albumin-bound FFAs enter the cell through a CD36-mediated channel (high affinity, low capacity, and saturable).

1.4. Intracellular Fatty Acid Transport through the Capillary Endothelium

Following FA uptake via the plasma membrane, intracellular FA transport is performed by cytosolic proteins. Fatty acid-binding proteins 4 and 5 (FABP4/5), abundantly expressed in the capillary endothelium in the heart, are potential candidates for transport (**Figure 1**) [13][14][15]. Cytoplasmic FABPs (FABP1–FABP9) are a family of 14–15 kDa proteins that bind to long-chain FAs with high affinity. Among them, FABP4/5 have a redundant function in the capillary endothelium. As lipid chaperones, FABP4/5 appear to facilitate the intracellular FA transport to the abluminal side of the capillary endothelium. Fatty acid transport proteins 3 and 4 (FATP3/4), which are induced in the capillary endothelium in response to an increase in vascular endothelial growth factor-B (VEGF-B) secreted from cardiomyocytes, are other candidates for intracellular FA transport (**Figure 1**) [16].

1.5. Fatty Acid Uptake by Cardiomyocytes

Following TEFA transport (lipolysis, FA uptake by the plasma membrane, and intracellular FA transport), FAs are bound by albumin (300 μM) in the interstitial space of the heart (**Figure 1**) [5][17]. Circulating albumin is internalized by fluid-phase uptake by the capillary endothelium and transferred to the interstitial space by transcytosis [18][19]. The trans-sarcolemmal uptake of FA by cardiomyocytes may be facilitated by membrane-associated proteins. Similar to the capillary endothelium, the main membrane-associated protein might be CD36 in cardiomyocytes (**Figure 1**), although the expression of CD36 in cardiomyocytes is much lower than that in the capillary endothelium [11][12][20].

2. Molecular Mechanisms Underlying the Induction of Genes Associated with Trans-Endothelial Fatty Acid Transport

Recent studies have revealed that the expression of genes associated with TEFA transport is regulated by several ligands, receptors, and transcription factors (**Table 1**) [21][22][23][24]. It is likely that these systems can be roughly divided into two groups according to their target genes. One includes the peroxisome proliferator-activated receptor γ (PPARγ), mesodermal homeobox-2/transcription factor 15 (Meox2/Tcf15), Notch signaling, and the apelin/apelin receptor (APLNR), and it mainly controls the expression of CD36, FABPs, and GPIHBP1. The other is a group that includes the VEGF-B/VEGF receptor (VEGFR), angiopoietin-like 2 (ANGPTL2), and 3-hydroxyisobutyrate (3-HIB), and it regulates the expression/function of FATP3/4 (**Table 1**). Although impairments of the systems influence both local and systemic metabolism, cardiac metabolism seems to only be affected by PPARγ, Meox2/Tcf15, Notch signaling, and VEGF-B/VEGFR (**Table 1**) [21][22][23][24]. The trans-endothelial transport of other substrates and

molecules (e.g., lipoproteins, lipoprotein lipase, glucose, and insulin) and endothelium-derived metabolic regulators (e.g., nitric oxide, extracellular matrix proteins, hormones, growth factors, and enzymes) is described elsewhere [21][22][24].

Table 1. FA handling genes regulated by the indicated system in capillary endothelium.

Ligand	Receptor/Transcription Factor	Target Genes										Target Tissues Influenced by the System	Reference
		PPARγ	CD36	FABP4	FABP5	LPL	GPIHBP1	ANGPTL4	LIPG	FATP3	FATP4		
	PPARγ		○	○			○					heart, skeletal muscle, adipose tissue	[25][26][27]
	Meox2/Tcf15	○	○	○	○	○	○					heart	[28]
Dll4	Notch1/N1-ICD/Rbp-jκ	independent	○	○	○			●	○			heart, skeletal muscle	[29][30]
Apelin	APLNR/phosphorylation of FOXO1			●								skeletal muscle	[31]
VEGF-B	VEGFR/NPR1									○	○	heart, BAT, skeletal muscle	[16]
ANGPTL2	integrin α5β1		○							○		subcutaneous adipose tissue	[32]
3-HIB										○*	○*	skeletal muscle	[33]

○ induced; ● suppressed; ○* post-translational effect?

2.1. Peroxisome Proliferator-Activated Receptor γ

Cardiac metabolism is transcriptionally regulated by the three members of the PPAR family (PPARα, β/δ, and γ) of ligand-activated transcription factors [34][35][36]. PPARs do not act on a single target but rather orchestrate several pathways whereby nutrients regulate their own metabolism. The expression of PPARs is high in cardiomyocytes and regulate FA metabolism, such as FA uptake and FA oxidation. PPARγ and its target genes are abundantly expressed in the capillary endothelium in the heart and facilitate FA uptake through the endothelial layer.

The expression of PPARγ is induced in the capillary endothelium by fasting, leading to the induction of its target genes, such as CD36, FABP4, and GPIHBP1 [25][26][27]. Endothelial-specific PPARγ knockout mice exhibited hyperchylomicronemia after olive oil gavage and higher levels of circulating FFAs during fasting, results that are

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consistent with the defective function of GPIHBP1 (i.e., LPL) and CD36/FABP4/5, respectively[25][26]. Thus, endothelial FA uptake and transport involve both an LPL-mediated low-affinity, high-capacity, non-saturable pathway and a CD36-mediated high-affinity, low-capacity, saturable pathway, both of which are enhanced during fasting.

2.2. Mesodermal Homeobox-2/Transcription Factor 15

Meox2 is a homeobox gene that is expressed in the microvascular endothelium in the heart [28]. Meox2 forms a heterodimer with a basic helix–loop–helix Tcf15, which is highly expressed in the capillary endothelium. The Meox2/Tcf15 heterodimer drives the endothelial expression of genes associated with FA metabolism, including PPARγ, CD36, FABP4/5, LPL, and GPIHBP1, to facilitate FA uptake and transport across the capillary endothelium [28]. Importantly, the haplodeficiency of Meox2/Tcf15 in mice was found to cause reduced FA uptake with compensatory glucose use in the heart (**Table 2**), suggesting their robust effects on cardiac metabolism.

2.3. Notch Signaling

Notch signaling is not only a master regulator of angiogenesis but also a regulator of TEFA transport. The inhibition of endothelial Notch signaling in the adult heart leads to reduced FA transport, resulting in heart failure and hypertrophy [29][30]. The activation of Notch signaling facilitates FA transport by inducing CD36, FABP4/5, and lipase G endothelial type (LIPG) and by suppressing angiopoietin-like 4 (ANGPTL4), a well-characterized inhibitor of LPL [29][30].

Table 2. Cardiac metabolism and performance in vivo in the indicated knockout mice under unstressed condition.

Target Genes	Deficient Site	Inducible Knockout	VLDL-TG Uptake	FA Uptake	Glucose Uptake	Glut1/4	Ketone in Serum	Contractile Performance In Vivo Estimated by Echocardiography	Reference
LPL (functions at luminal side of capillary)	cardiomyocyte		↓	↑	↑	↑		↓ aged	[37]
	cardiomyocyte	○						↓	[38]
CD36	whole			↓	↑	↑	↑	intact	[39][40][41][42]
	whole			↓	↑			prevention from age-induced cardiomyopathy	[42]
	endothelium			↓	↑	↑		not available	[11]
FABP4/5	whole			↓	↑	↑	↑	intact	[13][43]

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Target Genes	Deficient Site	Inducible Knockout	VLDL-TG Uptake	FA Uptake	Glucose Uptake	Glut1/4	Ketonein Serum	Contractile Performance In Vivo Estimated by Echocardiography	Reference
Meox2$^{+/-}$:Tcf15$^{+/-}$	endothelium: whole			↓	↑			↓ aged	[28]
Rbp-jκ (Notch signal)	endothelium	○		↓	↑	↓		↓↓	[29]
PPARγ	endothelium			→↓	→			intact (personal observation)	[25]
VEGF-B	whole			↓	↑	↑		not available	[16]
FABP3	whole			↓	↑	→	↑	not available	[44][45]
CD36	cardiomyocyte			→	→			not available	[11]
	cardiomyocyte	○		↓ (ex vivo)	↑ (ex vivo)			intact	[46][47]

○ inducible knockout; ↓ reduced; ↑ increased; → no change.

2.4. Apelin/Apelin Receptor/Forkhead Box O1

Apelin is a peptide identified as a ligand for the orphan G protein-coupled receptor APLNR [48]. Apelin/APLNR may be involved in maintaining endothelial APLNR-regulated tissue fatty acid uptake and is essential for apelin's glucose-lowering effects. Thus, endothelial APLNR enhances TEFA transport via the induction of FABP4, resulting in ectopic lipid deposition in muscle and impaired glucose utilization [31]. APLNR-mediated forkhead box O1 (FOXO1) phosphorylation inactivates its transcriptional activity on FABP4. Thus, Apelin/APLNR is a negative regulator of TEFA transport in skeletal muscle.

2.5. Angiopoietin-Like 2/Integrin α5β1

ANGPTL2 is secreted from adipose tissue [32]. ANGPTL2/integrin α5β1 signaling activates FA transport into subcutaneous adipose tissue via the induction of CD36 and FATP3 in the capillary endothelium, which suggests adipocyte–endothelial crosstalk.

2.6. 3-Hydroxyisobutyrate

3-HIB is a catabolic intermediate of a branched-chain amino acid valine and is secreted from skeletal muscle [33]. 3-HIB has been found to regulate TEFA transport in a paracrine fashion, probably via a post-translational effect on FATP3 and FATP4. Increased 3-HIB was found to promote lipid accumulation in muscle, leading to insulin resistance. This is the first reported evidence that metabolites can also modulate TEFA transport.

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3. Association between In Vivo Cardiac Metabolism and Contractile Function in Mice with Reduced Fatty Acid Uptake

3.1. Limitation of Experiments with Ex Vivo Perfused Hearts

Heart metabolism has long been studied, primarily in ex vivo perfused hearts. The major benefits of this approach include the ability to simultaneously monitor the oxidation of energy substrates (catabolism) and control hemodynamic parameters, which have provided invaluable assets in the metabolic research of the heart [49]. However, this approach has a weakness in addressing questions related to the metabolic disturbance of the heart in the context of oxygen supply and systemic response because isolated perfused hearts have a lower oxygen-carrying capacity, regional anoxia due to arteriole constriction, a lack of compensatory energy supply from blood, and a lack of neurohumoral feedback [50][51][52].

3.2. In Vivo Cardiac Metabolism and Contractile Function in Mice with Reduced Trans-Endothelial Fatty Acid Transport under Unstressed Conditions

Various phenotypic changes in metabolism have been reported in both humans and mice when FA catabolism is genetically disrupted. Defective FA oxidation at a mitochondrial level leads to severe impairments in local and systemic metabolism, including hypoketotic hypoglycemia, liver dysfunction, myopathy/rhabdomyolysis, arrhythmia, and cardiomyopathy, which frequently causes sudden infant death syndrome in humans [53][54]. In comparison, reduced FA uptake without defective machinery for mitochondrial FA oxidation results in a modest metabolic phenotype. In most cases, animals with this condition are born and normally develop, although they experience local and systemic alterations in their metabolism. **Table 2** summarizes the metabolic and cardiac phenotypes of mice with reduced FA uptake, mostly from those with impaired TEFA transport. **Table 2** also includes the phenotypes of whole CD36 KO mice, cardiomyocyte-specific CD36 KO mice, and whole FABP3 KO mice for comparison with impaired TEFA transport.

3.3. In Vivo Cardiac Metabolism in CD36 KO Mice under Unstressed Conditions

CD36 facilitates FA uptake in the heart, skeletal muscle, and adipose tissue. In the heart, CD36 is more abundant in the capillary endothelium compared to other cell types, including cardiomyocytes [11][12]. Endothelial-specific CD36 KO mice have shown reduced FA uptake with compensatory glucose use in the heart, which recapitulated the metabolic phenotype of whole CD36 KO mice (**Table 2**) [11][39][40][41]. In contrast, cardiomyocyte-specific CD36 KO mice were shown to exhibit no alteration in the uptake of FA and glucose, although lipid accumulation was reduced in the heart [11].

3.4. In Vivo Contractile Dysfunction in Mice with Reduced Trans-Endothelial Fatty Acid Transport under an Increased Afterload

Cardiac contraction is mostly preserved in mice with a genetic deletion of genes associated with FA uptake, as previously described. However, contractile function is significantly suppressed by an increased afterload in LPL KO

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