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Review

Fatty Acid Metabolism in Endothelial Cell

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Abstract: The endothelium is a monolayer of cells lining the inner of blood and lymphatic vessels. Endothelial cells (ECs) release subtracts that prevent platelet and leukocyte adhesion and aggregation and modulate blood flow, which is essential for the normal function of the vascular system. ECs play indispensable roles in angiogenesis, homeostasis, stimulus or immune response under normal physiological conditions and its dysfunction is closely associated with pathologies such as cancer, diabetes, and pulmonary hypertension. Abnormal EC metabolism, especially fatty acid dysfunctional metabolism, contributes to the leading causes of pulmonary diseases. Expanding the knowledge of ECs' dysfunctional metabolism in disease could pave a new way for new therapeutic approaches. In this review, we focus on discussing the latest advances in EC fatty acid metabolism in health and disease, with emphasis on its roles in the pathology of pulmonary hypertension (PH).

Keywords: endothelium; vascular biology; lipid; metabolism

1. Role of Endothelial cell in angiogenesis, homeostasis, stimulus/immune response

ECs lining the inner blood and lymphatic vessels are essential for the vascular system[1, 2]. In adults, ECs remain quiescent for years but still retain the capacity to switch rapidly from quiescent cells to activated sprout cells to initiate new vessel formation(angiogenesis) under certain conditions such as inflammation or injury[3, 4]. This tightly regulated process starts with the migratory tip cells and is followed by proliferating stalk cells until new vessel sprouts are created. The quiescent phalanx cells stimulated by angiogenic signals like vascular endothelial growth factor (VEGF), then proceed to line the established vessels to form the matured blood vessels[5].

Given that ECs occupy an important location between circulating blood and tissues, which enables ECs quick response to the changes in the environment via releasing a host of biologically active substances including relaxing factors [PGI2, EDRF(NO), and EDHF] and contracting factors (arachidonic acid metabolites, endothelin-1 and angiotensin II)[6]. These endothelium-derived factors are maintained in a balance to control blood flow and pressure and maintain the antithrombotic and anticoagulant balance in the bloodstream, which is extremely important for homeostasis[6, 7].

Under hormonal and chemical signal stimulation, ECs produce mediators such as nitric oxide synthase (NOS) and phospholipase A2 to modulate the responses of numerous cells, including vascular smooth muscle, platelets, and leukocytes[8, 9]. For instance, nitric oxide (NO) synthesized from endothelial NOS (eNOS), directly regulate the blood vessel dilation by stimulating soluble guanylyl cyclase, leading to an increase in cyclic guanosine monophosphate (cGMP) and subsequent relaxation of vascular smooth muscle, plays essential roles in maintaining vascular homeostasis[8, 10, 11].

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ECs act as a natural barrier inside blood vessels, are the first to recognize microbial components in the circulation, which indicates that ECs' recognition and response may be essential to early innate immune system activation. In addition, ECs express several innate immune receptors including the toll-like receptor (TLR), NOD-like receptors (NLR), and chemokine receptors[12]. For instance, in response to microbial stimulation, ECs could secrete pro-inflammatory cytokine interleukin-8 (IL-8) via NOD1-dependent signaling[13]. Moreover, ECs stimulated with Muramyl dipeptide could increase IL-6 secretion, which is required for CD4+ T helper cell-17 (Th17) polarization[14].

2. Endothelial Cell Metabolism

EC metabolism is confined to glucose, fatty acids (FAs) and amino acids (AAs), the three major substrates for energy and biomass production in ECs, which have been extensively studied and summarized [15-17]. The following sections will discuss ATP sources in ECs' metabolic routine including proliferation, migration, and differentiation.

3. Glucose and Amino Acid Metabolism

Glycolysis is the main energy resource in cultured ECs, with higher rates of glycolysis and glucose consumption, which is also presented in many types of cancer cells[18]. ECs prefer to utilize glycolysis instead of oxidative metabolism, that is because the ECs need to maintain reactive oxygen species (ROS) levels in control[19] and enhance the diffusion of oxygen to perivascular cells[19, 20]. Additional reasons are glycolysis produces faster kinetic ATP under pro-angiogenic signals during angiogenesis [18], which is essential for ECs' rapid proliferation and migration[18, 21]. In addition to glucose-derived carbons, ECs also utilize glutamine to sustain proliferation and vascular expansion[22, 23]. Glutamine, the most abundant circulating nonessential amino acid (NEAA) can supply 30% of the tricarboxylic acid (TCA) carbons, comparable to glycolysis and fatty acid oxidation (FAO)-derived carbon[24, 25]. Depletion of either glutamine or arginine makes ECs vulnerable to ROS-induced damage during proliferation and migration, which is due to the endothelial eNOS dysfunction [23, 26].

4. Fatty acids (FAs) Metabolism

However, lipid uptake and metabolism are central to the function of organs such as heart, skeletal muscle, and adipose tissue, which differ from that of many other cell types[15]. This process requires passive diffusion from the blood or transport of FA into the cell for FAO[27]. ECs metabolize FAs to acetyl-coenzyme A (acetyl-CoA) to sustain the TCA cycle, which facilitates deoxy nucleotide triphosphate (dNTP) synthesis for EC proliferation[25, 28]. Endothelial-specific deficiency or silencing of carnitine palmitoyl transferase 1-A (CPT1A), the rate-limiting enzyme in FAO, causes vascular sprouting defects in vivo and in vitro owing to a reduction in proliferation, but not migration[29]. Furthermore, during lymphatic EC (LEC) differentiation, LECs upregulate CPT1A to support their proliferation, but also to promote their differentiation through acetyl-CoA production[30].

5. Fatty acid uptake and transport protein

Lipid uptake and metabolism are central to the function of organs such as heart, skeletal muscle, and adipose tissue, especial brown adipose tissue (BAT)[31]. These organs rely on FAs as their main source for energy production and therefore require an efficient supply system of FAs[25]. Uptake and activation of FA, like long-chain FAs (LCFAs) is integral to many cellular processes, including membrane synthesis, intracellular signal transduction, energy metabolism, posttranslational modifications, and transcriptional regulation of metabolic genes[32].

In mammals, lipids circulate in the blood as nonesterified free fatty acids (NEFAs), including medium-chain (with 6–12 carbons) and short-chain FAs (with 6 carbons), but

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mostly (≈90%) as esterified FA, including (LCFAs; FAs with 12–20 carbons). The LCFAs are transported in the bloodstream in the form of triglyceride (TG)-rich lipoproteins, phospholipids, and cholesteryl esters in lipoproteins[33], while uptake LCFAs requires transfer from the circulation across the EC barrier, a process coordinated by several membrane proteins including fatty acid translocase (FAT)/CD36[34-36], fatty acid binding proteins (FABPs)[37-42], long-chain fatty acylcoenzyme A (CoA) synthetase (ACSL)[43], and fatty acid transport proteins (FATPs)[44-46]. The major fatty acid transporter includes CD36, FABPs and FATPs, which will be summarized in the following sections.

6. CD36

CD36, also named fatty acid translocase (FAT), is the best characterized FA transporter that belongs to the CD36 class B scavenger receptor family including SR-B1, a lipoprotein binding receptor and the LIMP2 (lysosomal integral membrane protein 2)[47]. CD36 shares similar expression pattern as Fatp1 and Fatp4 by platelets, monocytes, ECs, and parenchymal cells in WAT, BAT, heart muscle, and skeletal muscle[48, 49]. Besides its important biological roles in binding LCFAs and facilitating their uptake into cells [35, 36, 50, 51], it also recognizes lipoproteins, bacterial lipids, and nonlipid ligands (eg,thrombospondin-1)[49, 52].

CD36 plays an important role in facilitating FA import into cells and is involved in a variety of cell signaling processes including Notch signaling [53-58], but the biological role of CD36 in the endothelium is still not fully understood. In EC, CD36 plays role in FA delivery via optimizing radiolabeled long-chain FAs into the heart, skeletal muscle, and brown adipose tissue [59]and mediating albumin transcytosis[60]. ECs utilize FAs in a CD36-dependent manner to promote their migration and invasion for new vessel formation following vascular injury [61]. In addition, extracellular vesicles (EV) inhibit angiogenic microvascular endothelial cell (MVEC) functions also via CD36-dependent Signaling Pathway[62]. It has also been reported that EC-specific knockout of CD36 in mice had increased glucose clearance compared with controls when fed with multiple diets and Female EC CD36/LDLR-deficient mice have reduced atherosclerosis[63]. Moreover, CD36 silencing in cultured LECs could suppress cell respiration, via reducing VEGF-C-mediated VEGFR2/AKT phosphorylation and destabilizing VE-cadherin junctions, which highlights a new mechanism for the etiology of visceral obesity and insulin resistance[64]. Beside the important role of CD36 in FA uptake and FAO in ECs[65], CD36-dependent FA uptake is also required for Megakaryocyte (MK) maturation and proplatelet formation[66], differentiation and activation of Tumor-Associated Macrophages[67], metastasis and resistance in cancer[56, 68], regulation of inflammation in non-alcoholic steatohepatitis(NASH)[69]. A summary of additional functions of CD36 can be found in the cited review[70].

It was reported that CD36 can be upregulated by the transcription factor peroxisome-proliferator activated receptor gamma (PPARγ)[71-73] and is strongly induced by cold exposure in the BAT and, together with LPL, mediated increased cellular TG accumulation to sustain thermogenesis[74]. In additional, DHHC4 and DHHC5 could palmitoylated CD36 for its plasma membrane localization and FA uptake activity, deficiency in DHHC4 or DHHC5 leads to decreased FA uptake and increased susceptibility to cold[57].

7. The FABPs

The FABPs are a family consist by at least 13 members that act as intracellular FA handling proteins[75]. They exhibit unique patterns of tissue expression[76], with a direct positive correlation to the lipid metabolizing capacity of the tissue. FABPs actively facilitate the transport of FAs to specific organelles in the cell for lipid oxidation in the mitochondrion or peroxisome, transcriptional regulation in the nucleus, signaling, trafficking

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and membrane synthesis in the endoplasmic reticulum (ER), and regulation of enzyme activity and storage as lipid droplets in the cytoplasm[77].

Among the FABPs, FABP4 ,also known as A-FABP and aP2, is predominantly expressed in microvascular ECs in several physiological and pathological tissues[40, 78-80], playing a pro-angiogenic role by promoting EC proliferation, survival, and migration[40, 79, 81]. In additional, Fabp4 is also expressed in adipocytes, macrophages, cardiac and renal capillaries and veins in both humans and mice[40, 78]. Fabp5, also known as E-FABP and mal1[82-84], is expressed in the endothelium of placenta, heart, skeletal muscle, small intestine, lung, and renal medulla, in the epidermis of lung, as well as by tissue cells of several organs such as heart, skeletal muscle, and lung[38, 39]. In contrast to the cytosolic FABPs, the PM-associated FABP ($FABP_{PM}$) belongs to a separate family of FA handling proteins[42], which is larger (~40 kDa) than the small cytosolic FABPs. FABPPM is associated with biological membranes found both in mitochondria and on the extracellular side of cardiomyocytes, myocytes, hepatocytes, adipocytes, and ECs[41, 42]. More information about the classification and expression pattern of FABPs is summarized in other reviews [85, 86].

In contrast to CD36/FAT, FABPs as a cytosolic non-enzymatic protein can directly bind free LCFA[87], which overcome the insolubility of LCFA in aqueous phase and facilitating the delivery of LCFA to different intracellular sites for oxidation. In addition to binding LCFAs, FABPs bind eicosanoids and other compounds including prostaglandin E1 (PGE1)[76, 88]. Beyond FABPs' essential role for metabolic homeostasis and different lipid-mediated biological processes in various tissues[88-90], FABPs are also involved in CVDs, abnormal lipid signaling, high lipid storage, trafficking, and signaling capacity of macrophages and adipocytes[76, 89]. FABPs' expression and function are tightly regulated by various molecules including angiogenic regulator Notch[58], VEGF[40], mTORC1[79] and PPARγ [91-94].

FABPs can bind a variety of hydrophobic ligands, such as LCFAs, eicosanoids, leukotrienes and prostaglandins[95, 96]. Among all the FABPs, FABP4 and FABP5 are notedly studied, they share 55 % amino acid sequence homology and have a primarily microvascular expression pattern in both microvascular and large blood vessel ECs[39, 97]. FABP4 deficient mice exhibit marked protection against insulin resistance, atherosclerosis, fatty liver disease, and asthma, which indicates FABP4 playing an important role in regulation of glucose and lipid homeostasis as well as inflammation[89, 95, 98-102]. Moreover, FABP4 plays pro-angiogenic role in ECs by modulating stem cell factor/c-kit pathway, which can be inhibited by mTORC1 inhibitor Rapamycin[79]. Consistent with these studies, FABP4 specific inhibitor, BMS309403, exhibits therapeutic potential in treatment with EC dysfunction associated diseases including atherosclerosis and diabetes [103-105].

Similarly, FABP5 also plays an essential role in FA uptake in the heart and skeletal muscle ECs[97], regulation of inflammatory, metabolic responses and angiogenesis [89, 106-108]. Consistent with these findings, it was reported that mice with combined deficiency of FABP4 and FABP5 exhibited greater protection against diet-induced obesity, insulin resistance, and atherosclerosis than mice deficient for either of them[99, 109]. In addition, during the process of FA transport, FABP4 and FABP5 are both induced by PPARγ [110] and they can in turn regulate PPARγ signaling [111-113]. However, Notch signaling regulated FABP4 expression during triacylglycerol hydrolysis and LCFA transport was not interrupted by inhibition of PPARγ [58].

8. FATPs

FATPs, also known as SLC27 or SLC27A, belong to a six members family of transmembrane spanning proteins, which allow and enhance the uptake of LCFA) into cells[34, 114-116]. Individual FATPs expression pattern has been analyzed by specific primers for each FATP in murine heart, muscle, BAT, WAT, liver, and kidney[117]. In details, Fatp1 is mainly expressed by tissue cells in muscle, WAT, and BAT[48]. Fatp2 is expressed in

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the kidney and liver, whereas Fatp5 is exclusively detected in the liver[48, 118, 119]. Fatp3 is the only FATP member that is expressed specifically in the vasculature, at least in muscular tissues[44, 48, 120]. Fatp4 has a similar expression pattern as FATP1, but is also expressed in the skin, intestine and in endothelium, while Fatp6 is strictly expressed in the heart[44, 121-124]. In general, the FATPs are predominately localized to the PM, Golgi network, and the endoplasmic reticulum (ER)[125-127]. However, under insulin stimulation, FATP1 and FATP4 will be transported to the PM of adipocytes and myocytes[128-130].

All FATPs have been shown to enhance cellular LCFA uptake[44-46], by interacting with the FA in the plasma membrane, trapping the FA through its activation or interacting with membrane transporters providing vectorial transfer of FA to mitochondrial[31], but its nature function in ECs is still need further interpretation. It was reported that knockdown of CD36 and FATP3, but not of FATP4, can attenuate Angiopoeitin2 (Angpt2) stimulated FA uptake process in ECs, which indicates further investigation in animal models with targeted EC deletion of FATP3 and FATP4, and their functional protein interactions is needed[31]. It reported that EC FATP4 can use mitochondrial ATP to activate FA and influence EC FA uptake and oxidation[131]. VEGF-B has been demonstrated to regulate the uptake and trans-endothelial transport of LCFAs via FATP3 and FATP4 within the endothelium[44], which is also required for 3-hydroxyisobutyrate (3HIB)-induced FA uptake[132]. Given that FABPs' role in facilitating FAs accumulation, this family proteins have strong association with cardiometabolic disease including atherosclerosis and CVD[133, 134].

Fatp4 knockout mice are embryonically/neonatally lethal, which is attributed to defects either in embryonic FA absorption or to a disrupted epidermal barrier with aberrant lipid content[124, 135]. Somatic FATP4 mutation has been found in patients with ichthyosis prematurity syndrome, which is related with premature birth, respiratory symptoms, and swollen skin with severe caseosa-like scaling[136-138]. Overexpression of FATP1 in suprabasal keratinocytes restores the neonatal lethality and rescues the skin phenotype in Fatp4 mutants, which indicates FATP1 and FATP4 sharing common substrate preferences, enzymatic activities, and biological functions[139]. As expected, FATB4 is required for incorporation of saturated ultralong-chain fatty acids into epidermal ceramides and monoacylglycerols and its mutation causing FA accumulation[139].

FATP5, like the other members of the FATP family, can enhance the FA uptake[34] and activate LCFAs and very long-chain fatty acids by catalyzing the covalent attachment of coenzyme A (CoA)[140]. Furthermore, FATP5 is also involved in the reactivation of C24 bile acids to their CoA derivatives[141, 142]. Consistently, in FATP5 knockout mice model, it shows that FATP5 is a liver-specific protein required for efficient hepatic LCFA uptake and hepatic lipid homeostasis[143]. In addition to its major role in lipid metabolism, FATP5 is also involved in tumorigenesis and metastasis in different cancers including lung cancer, esophageal squamous cell carcinoma (ESCC), hepatocellular carcinoma (HCC) and Colorectal Carcinoma (CRC).

9. Endothelial fatty acid storage and lipolysis

Lipid droplets as the central regulators of FA uptake and metabolism[148], are cytosolic fat storage organelles present in most eukaryotic cells including ECs[149]. Lipid droplets are dynamically synthesized and broken down in response to cellular needs and environmental signals[150], which is tightly balanced by LD biogenesis and Lipolysis. Synthesis of neutral lipids is the first step of lipid droplet biogenesis, where activated FAs were esterified by diacylglycerol acyltransferases (DGAT1 and DGAT2) to diacylglycerol or by acylCoA:cholesterol Oacyltransferases (ACAT1 and ACAT2) to sterol, respectively[151]. Lipolysis relies on the direct activation of LD-associated lipases, such as adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL) and monoglyceride lipase (MGL)[152-155]. Under basal conditions, perilipin limits access of cellular HSL and

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ATGL to the core of TG within LDs, thereby preventing uncontrolled TG hydrolysis and limiting release of free FAs and glycerol[156].

Lipid metabolism in ECs is derived primarily from the role of LPL on the surface of capillary ECs, where LPL hydrolyzes very low-density lipoproteins (VLDL) and chylomicrons to generate FFA [54] for energy utilization in skeletal and cardiac muscle or re-esterified into TG in liver[157]. In ECs, ATGL elucidates same significance in lipid storage by initiating TG hydrolysis as in adipose tissue[158], while DGAT1 is primarily responsible for TG synthesis[155]. ATGL knockout mice were suffered from severe micro- and macrovascular endothelial dysfunction, which can be partially rescued in by chronically treated with a PPARα agonist[159]. In human aortic endothelial cells (HAEC), silencing ATGL decreased efficiency of stimulus-induced arachidonic acid (AA) release and prostacyclin secretion[160], and increased incidence of atherosclerosis[161].

Lipid droplets exhibit their ability to buffer excess lipids, thereby providing immediate protection from lipotoxicity, and to release them later, gradually and according to cellular needs[149], which is particularly important for ECs exposed to rapidly changing conditions of stress[162, 163].

10. Endothelial cell derived FAO in health

Mitochondria are the main site of ATP production in many cell types, like ECs, myocytes and adipocytes [164]. For example, cardiomyocytes primarily burn FAs to supply ATP, however, in ECs, mitochondria are more than an energy powerhouse [25, 30, 164-168]. FAO-derived carbons sustain the TCA cycle to produce the precursors aspartate and glutamate from its intermediates oxaloacetate (OAA) and a-ketoglutarate (a-KG) for dNTP synthesis during the proliferation of stalk cells[25]. Silencing CPT1A, a rate-controlling enzyme of FAO that imports FAs into the mitochondria, perturbs EC sprouting in vitro due to a decrease in the dNTP pool[25]. Moreover, lymphatic ECs proliferation during lymphatic development also rely on FAO to produce dNTPs, which is same in vascular ECs[30, 169].

Under glucose deprivation condition, ECs will increase their FAO flux in an adenosine monophosphate activated protein kinase (AMPK)–dependent manner to generate more ATPs[170]. Recent reports also reveal that FAO has a broad role in cell fate control including ECs and immune cells[171]. Silencing CPT2 in mouse model could cause augmented embryonic endothelial-to-mesenchymal transition (EndoMT), required for normal cardiac development, which is evidenced by thickened cardiac valves increased permeability in these mice[172].

11. Fatty acid metabolism in Pulmonary Hypertension

Given multiple molecules and their complex regulation network involved in FA metabolism in ECs, any abnormality in these regulations will lead to a pathological state and even develop into diseases like PH and cancer. Here, we will only discuss the abnormal EC-driven FA oxidation in pulmonary hypertension. Additional diseases involving FA metabolism, including cancer, can be found in other reviews[16, 17, 173].

Pulmonary arterial hypertension (PAH) is characterized by an increase in pulmonary vascular resistance, resulting in elevated resting pulmonary artery pressure and right ventricular failure[174]. Besides other cell types that are known to be involved in PAH pathogenesis (e.g. smooth muscle cells, fibroblasts and leukocytes), recent studies have demonstrated that EC share a crucial role in the initiation and progression of PAH[175]. Indeed, silencing Prolyl-4 Hydroxylase 2(PHD2) or bone morphogenetic protein receptor 2(BMPR2) induced EC hyperproliferation contributes to loss of small pulmonary arterioles and vascular occlusion. Plexiform lesions in severe PAH represent an extreme type of disordered angiogenesis[176, 177].

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To data, increasing evidence indicates that FA metabolism dysfunction is closely associated with pathogenesis of pulmonary hypertension[179-182]. In both heritable pulmonary arterial hypertension (HPAH) and right ventricular hypertrophy mouse model, FA metabolic genes are abnormally changed due to FA oxidation deficiency caused lipid disposition[179, 180]. In addition, circulating levels of FABP-4, FGF-21, and adiponectin were significantly elevated in human PH lungs and experimental PH rat lungs[183]. Indeed, increased pulmonary arterial pressures are associated with increases in the ratio of FDG/FTHA uptake in the RV, which reflects a shift towards increased FA oxidation and glycolysis associated with RV failure in PAH[184]. Alternatively, in the SU5416/hypoxia (SuHx) rat model, oral treatment with the PPARγ agonist pioglitazone completely reverses severe PAH and vascular remodeling and prevents RV failure, which also relies on suppressing Cpt1b and Fabp4 FAO[185]. However, the role of EC FA metabolism is largely unexplored and under intensive investigation.

12. Therapeutic opportunities

So far, many candidates that can regulate FA uptake or FAO have been applied in laboratory and clinical trials. Recent studies have demonstrated the beneficial therapeutic effect of CPT1 inhibition by etomoxir (ETO) in pathological ocular angiogenesis[25]. Indeed, ETO reduced tumor growth in an FAO-dependent tumor model, though it remains to be determined if this is also due to tumor angiogenesis inhibition[186]. In addition, the c agonist pioglitazone that could reverse PH and prevent right heart failure via FAO, could also be a potential therapeutic candidate[185]. Moreover, FAO inhibitor Oxfenicine promoted de-remodeling of pulmonary arteries in SuHx rats by increasing mitochondrial mass and decreasing the density of perivascular macrophage infiltration and attenuated endothelin-1 induced vasoconstriction, which indicates FAO inhibition may be beneficial in human PAH[187].

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Reference

1. Potente, M., H. Gerhardt, and P. Carmeliet, *Basic and therapeutic aspects of angiogenesis.* Cell, 2011. **146**(6): p. 873-87.
2. Eelen, G., et al., *Basic and Therapeutic Aspects of Angiogenesis Updated.* Circ Res, 2020. **127**(2): p. 310-329.
3. Takubo, N., et al., *Cohesive and anisotropic vascular endothelial cell motility driving angiogenic morphogenesis.* Sci Rep, 2019. **9**(1): p. 9304.
4. Boas, S.E. and R.M. Merks, *Tip cell overtaking occurs as a side effect of sprouting in computational models of angiogenesis.* BMC Syst Biol, 2015. **9**: p. 86.
5. Jakobsson, L., et al., *Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting.* Nat Cell Biol, 2010. **12**(10): p. 943-53.
6. Jaffe, E.A., *Cell biology of endothelial cells.* Hum Pathol, 1987. **18**(3): p. 234-9.
7. Lai, W.K. and M.Y. Kan, *Homocysteine-Induced Endothelial Dysfunction.* Ann Nutr Metab, 2015. **67**(1): p. 1-12.
8. Steinberg, H.O., et al., *Free fatty acid elevation impairs insulin-mediated vasodilation and nitric oxide production.* Diabetes, 2000. **49**(7): p. 1231-8.
9. Leo, F., et al., *Red Blood Cell and Endothelial eNOS Independently Regulate Circulating Nitric Oxide Metabolites and Blood Pressure.* Circulation, 2021. **144**(11): p. 870-889.
10. Pircher, A., et al., *Endothelial cell metabolism: A novel player in atherosclerosis? Basic principles and therapeutic opportunities.* Atherosclerosis, 2016. **253**: p. 247-257.
11. Förstermann, U. and W.C. Sessa, *Nitric oxide synthases: regulation and function.* Eur Heart J, 2012. **33**(7): p. 829-37, 837a-837d.
12. Sokolova, M., et al., *Palmitate promotes inflammatory responses and cellular senescence in cardiac fibroblasts.* Biochim Biophys Acta Mol Cell Biol Lipids, 2017. **1862**(2): p. 234-245.

13. Opitz, B., et al., *Nod1-mediated endothelial cell activation by Chlamydophila pneumoniae.* Circ Res, 2005. **96**(3): p. 319-26.
14. Kim, Y.S., et al., *Vascular endothelial growth factor is a key mediator in the development of T cell priming and its polarization to type 1 and type 17 T helper cells in the airways.* J Immunol, 2009. **183**(8): p. 5113-20.
15. Li, X., A. Kumar, and P. Carmeliet, *Metabolic Pathways Fueling the Endothelial Cell Drive.* Annu Rev Physiol, 2019. **81**: p. 483-503.
16. Rohlenova, K., et al., *Endothelial Cell Metabolism in Health and Disease.* Trends Cell Biol, 2018. **28**(3): p. 224-236.
17. Eelen, G., et al., *Endothelial cell metabolism in normal and diseased vasculature.* Circ Res, 2015. **116**(7): p. 1231-44.
18. De Bock, K., et al., *Role of PFKFB3-driven glycolysis in vessel sprouting.* Cell, 2013. **154**(3): p. 651-63.
19. De Bock, K., M. Georgiadou, and P. Carmeliet, *Role of endothelial cell metabolism in vessel sprouting.* Cell Metab, 2013. **18**(5): p. 634-47.
20. Helmlinger, G., et al., *Formation of endothelial cell networks.* Nature, 2000. **405**(6783): p. 139-41.
21. Yu, P., et al., *FGF-dependent metabolic control of vascular development.* Nature, 2017. **545**(7653): p. 224-228.
22. Kim, B., et al., *Glutamine fuels proliferation but not migration of endothelial cells.* Embo j, 2017. **36**(16): p. 2321-2333.
23. Huang, H., et al., *Role of glutamine and interlinked asparagine metabolism in vessel formation.* Embo j, 2017. **36**(16): p. 2334-2352.
24. Mayers, J.R. and M.G. Vander Heiden, *Famine versus feast: understanding the metabolism of tumors in vivo.* Trends Biochem Sci, 2015. **40**(3): p. 130-40.
25. Schoors, S., et al., *Fatty acid carbon is essential for dNTP synthesis in endothelial cells.* Nature, 2015. **520**(7546): p. 192-197.
26. DeBerardinis, R.J. and T. Cheng, *Q's next: the diverse functions of glutamine in metabolism, cell biology and cancer.* Oncogene, 2010. **29**(3): p. 313-24.
27. Hülsmann, W.C. and M.L. Dubelaar, *Aspects of fatty acid metabolism in vascular endothelial cells.* Biochimie, 1988. **70**(5): p. 681-6.
28. Schoors, S., et al., *Corrigendum: Fatty acid carbon is essential for dNTP synthesis in endothelial cells.* Nature, 2015. **526**(7571): p. 144.
29. Schoors, S., et al., *Partial and transient reduction of glycolysis by PFKFB3 blockade reduces pathological angiogenesis.* Cell Metab, 2014. **19**(1): p. 37-48.
30. Wong, B.W., et al., *The role of fatty acid β-oxidation in lymphangiogenesis.* Nature, 2017. **542**(7639): p. 49-54.
31. Abumrad, N.A., et al., *Endothelial Cell Receptors in Tissue Lipid Uptake and Metabolism.* Circ Res, 2021. **128**(3): p. 433-450.
32. Kazantzis, M. and A. Stahl, *Fatty acid transport proteins, implications in physiology and disease.* Biochim Biophys Acta, 2012. **1821**(5): p. 852-7.
33. Dallinga-Thie, G.M., et al., *The metabolism of triglyceride-rich lipoproteins revisited: new players, new insight.* Atherosclerosis, 2010. **211**(1): p. 1-8.
34. Hirsch, D., A. Stahl, and H.F. Lodish, *A family of fatty acid transporters conserved from mycobacterium to man.* Proc Natl Acad Sci U S A, 1998. **95**(15): p. 8625-9.
35. Martin, C., et al., *CD36 as a lipid sensor.* Physiol Behav, 2011. **105**(1): p. 36-42.
36. Podrez, E.A., et al., *Macrophage scavenger receptor CD36 is the major receptor for LDL modified by monocyte-generated reactive nitrogen species.* J Clin Invest, 2000. **105**(8): p. 1095-108.
37. Huang, H., et al., *Liver fatty acid-binding protein targets fatty acids to the nucleus. Real time confocal and multiphoton fluorescence imaging in living cells.* J Biol Chem, 2002. **277**(32): p. 29139-51.
38. Smathers, R.L. and D.R. Petersen, *The human fatty acid-binding protein family: evolutionary divergences and functions.* Hum Genomics, 2011. **5**(3): p. 170-91.
39. Masouyé, I., et al., *Endothelial cells of the human microvasculature express epidermal fatty acid-binding protein.* Circ Res, 1997. **81**(3): p. 297-303.
40. Elmasri, H., et al., *Fatty acid binding protein 4 is a target of VEGF and a regulator of cell proliferation in endothelial cells.* Faseb j, 2009. **23**(11): p. 3865-73.
41. Antohe, F., et al., *Heart microvessels and aortic endothelial cells express the 15 kDa heart-type fatty acid-binding proteins.* Eur J Cell Biol, 1998. **76**(2): p. 102-9.
42. Glatz, J.F., J.J. Luiken, and A. Bonen, *Membrane fatty acid transporters as regulators of lipid metabolism: implications for metabolic disease.* Physiol Rev, 2010. **90**(1): p. 367-417.
43. Digel, M., et al., *Acyl-CoA synthetases: fatty acid uptake and metabolic channeling.* Mol Cell Biochem, 2009. **326**(1-2): p. 23-8.
44. Hagberg, C.E., et al., *Vascular endothelial growth factor B controls endothelial fatty acid uptake.* Nature, 2010. **464**(7290): p. 917-21.
45. Milger, K., et al., *Cellular uptake of fatty acids driven by the ER-localized acyl-CoA synthetase FATP4.* J Cell Sci, 2006. **119**(Pt 22): p. 4678-88.
46. DiRusso, C.C., et al., *Comparative biochemical studies of the murine fatty acid transport proteins (FATP) expressed in yeast.* J Biol Chem, 2005. **280**(17): p. 16829-37.
47. Canton, J., D. Neculai, and S. Grinstein, *Scavenger receptors in homeostasis and immunity.* Nat Rev Immunol, 2013. **13**(9): p. 621-34.
48. Sandoval, A., et al., *Fatty acid transport and activation and the expression patterns of genes involved in fatty acid trafficking.* Arch Biochem Biophys, 2008. **477**(2): p. 363-71.
49. Silverstein, R.L. and M. Febbraio, *CD36, a scavenger receptor involved in immunity, metabolism, angiogenesis, and behavior.* Sci Signal, 2009. **2**(72): p. re3.
50. Asch, A.S., et al., *Isolation of the thrombospondin membrane receptor.* J Clin Invest, 1987. **79**(4): p. 1054-61.
51. Hoebe, K., et al., *CD36 is a sensor of diacylglycerides.* Nature, 2005. **433**(7025): p. 523-7.

52. Pepino, M.Y., et al., *Structure-function of CD36 and importance of fatty acid signal transduction in fat metabolism.* Annu Rev Nutr, 2014. **34**: p. 281-303.
53. Bastie, C.C., et al., *CD36 in myocytes channels fatty acids to a lipase-accessible triglyceride pool that is related to cell lipid and insulin responsiveness.* Diabetes, 2004. **53**(9): p. 2209-16.
54. Goldberg, I.J., R.H. Eckel, and N.A. Abumrad, *Regulation of fatty acid uptake into tissues: lipoprotein lipase- and CD36-mediated pathways.* J Lipid Res, 2009. **50 Suppl**(Suppl): p. S86-90.
55. Hao, J.W., et al., *CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis.* Nat Commun, 2020. **11**(1): p. 4765.
56. Pan, J., et al., *CD36 mediates palmitate acid-induced metastasis of gastric cancer via AKT/GSK-3β/β-catenin pathway.* J Exp Clin Cancer Res, 2019. **38**(1): p. 52.
57. Wang, J., et al., *DHHC4 and DHHC5 Facilitate Fatty Acid Uptake by Palmitoylating and Targeting CD36 to the Plasma Membrane.* Cell Rep, 2019. **26**(1): p. 209-221.e5.
58. Jabs, M., et al., *Inhibition of Endothelial Notch Signaling Impairs Fatty Acid Transport and Leads to Metabolic and Vascular Remodeling of the Adult Heart.* Circulation, 2018. **137**(24): p. 2592-2608.
59. Son, N.H., et al., *Endothelial cell CD36 optimizes tissue fatty acid uptake.* J Clin Invest, 2018. **128**(10): p. 4329-4342.
60. Raheel, H., et al., *CD36 mediates albumin transcytosis by dermal but not lung microvascular endothelial cells: role in fatty acid delivery.* Am J Physiol Lung Cell Mol Physiol, 2019. **316**(5): p. L740-l750.
61. Bou Khzam, L., et al., *Endothelial cell CD36 deficiency prevents normal angiogenesis and vascular repair.* Am J Transl Res, 2020. **12**(12): p. 7737-7761.
62. Ramakrishnan, D.P., et al., *Extracellular Vesicles Activate a CD36-Dependent Signaling Pathway to Inhibit Microvascular Endothelial Cell Migration and Tube Formation.* Arterioscler Thromb Vasc Biol, 2016. **36**(3): p. 534-44.
63. Rekhi, U.R., et al., *Endothelial Cell CD36 Reduces Atherosclerosis and Controls Systemic Metabolism.* Front Cardiovasc Med, 2021. **8**: p. 768481.
64. Cifarelli, V., et al., *Visceral obesity and insulin resistance associate with CD36 deletion in lymphatic endothelial cells.* Nat Commun, 2021. **12**(1): p. 3350.
65. Yoshida, Y., et al., *Exercise- and training-induced upregulation of skeletal muscle fatty acid oxidation are not solely dependent on mitochondrial machinery and biogenesis.* J Physiol, 2013. **591**(18): p. 4415-26.
66. Valet, C., et al., *Adipocyte Fatty Acid Transfer Supports Megakaryocyte Maturation.* Cell Rep, 2020. **32**(1): p. 107875.
67. Su, P., et al., *Enhanced Lipid Accumulation and Metabolism Are Required for the Differentiation and Activation of Tumor-Associated Macrophages.* Cancer Res, 2020. **80**(7): p. 1438-1450.
68. Feng, W.W., et al., *CD36-Mediated Metabolic Rewiring of Breast Cancer Cells Promotes Resistance to HER2-Targeted Therapies.* Cell Rep, 2019. **29**(11): p. 3405-3420.e5.
69. Zhao, L., et al., *CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis.* J Hepatol, 2018. **69**(3): p. 705-717.
70. Chen, Y., et al., *CD36, a signaling receptor and fatty acid transporter that regulates immune cell metabolism and fate.* J Exp Med, 2022. **219**(6).
71. Rosen, E.D. and B.M. Spiegelman, *Peroxisome proliferator-activated receptor gamma ligands and atherosclerosis: ending the heartache.* J Clin Invest, 2000. **106**(5): p. 629-31.
72. Tontonoz, P., et al., *PPARgamma promotes monocyte/macrophage differentiation and uptake of oxidized LDL.* Cell, 1998. **93**(2): p. 241-52.
73. Maréchal, L., et al., *The CD36-PPARγ Pathway in Metabolic Disorders.* Int J Mol Sci, 2018. **19**(5).
74. Bartelt, A., et al., *Brown adipose tissue activity controls triglyceride clearance.* Nat Med, 2011. **17**(2): p. 200-5.
75. Storch, J. and L. McDermott, *Structural and functional analysis of fatty acid-binding proteins.* J Lipid Res, 2009. **50 Suppl**(Suppl): p. S126-31.
76. Dutta-Roy, A.K., *Cellular uptake of long-chain fatty acids: role of membrane-associated fatty-acid-binding/transport proteins.* Cell Mol Life Sci, 2000. **57**(10): p. 1360-72.
77. Furuhashi, M. and G.S. Hotamisligil, *Fatty acid-binding proteins: role in metabolic diseases and potential as drug targets.* Nat Rev Drug Discov, 2008. **7**(6): p. 489-503.
78. Lee, C.H., D.T.W. Lui, and K.S.L. Lam, *Adipocyte Fatty Acid-Binding Protein, Cardiovascular Diseases and Mortality.* Front Immunol, 2021. **12**: p. 589206.
79. Elmasri, H., et al., *Endothelial cell-fatty acid binding protein 4 promotes angiogenesis: role of stem cell factor/c-kit pathway.* Angiogenesis, 2012. **15**(3): p. 457-68.
80. Cataltepe, O., et al., *Fatty acid binding protein 4 is expressed in distinct endothelial and non-endothelial cell populations in glioblastoma.* Neuropathol Appl Neurobiol, 2012. **38**(5): p. 400-10.
81. Ghelfi, E., et al., *Fatty acid binding protein 4 regulates VEGF-induced airway angiogenesis and inflammation in a transgenic mouse model: implications for asthma.* Am J Pathol, 2013. **182**(4): p. 1425-33.
82. Owada, Y., T. Yoshimoto, and H. Kondo, *Spatio-temporally differential expression of genes for three members of fatty acid binding proteins in developing and mature rat brains.* J Chem Neuroanat, 1996. **12**(2): p. 113-22.
83. Mita, R., et al., *Brain fatty acid-binding protein and omega-3/omega-6 fatty acids: mechanistic insight into malignant glioma cell migration.* J Biol Chem, 2010. **285**(47): p. 37005-15.

84. Beech, D.J., et al., *TRPC channel lipid specificity and mechanisms of lipid regulation.* Cell Calcium, 2009. **45**(6): p. 583-8.
85. Li, B., et al., *SnapShot: FABP Functions.* Cell, 2020. **182**(4): p. 1066-1066.e1.
86. Mallick, R., S. Basak, and A.K. Duttaroy, *Fatty acids and evolving roles of their proteins in neurological, cardiovascular disorders and cancers.* Prog Lipid Res, 2021. **83**: p. 101116.
87. Siegenthaler, G., et al., *Purification and characterization of the human epidermal fatty acid-binding protein: localization during epidermal cell differentiation in vivo and in vitro.* Biochem J, 1994. **302 (Pt 2)**(Pt 2): p. 363-71.
88. Dutta-Roy, A.K., N. Gopalswamy, and D.V. Trulzsch, *Prostaglandin E1 binds to Z protein of rat liver.* Eur J Biochem, 1987. **162**(3): p. 615-9.
89. Furuhashi, M., et al., *Adipocyte/macrophage fatty acid-binding proteins contribute to metabolic deterioration through actions in both macrophages and adipocytes in mice.* J Clin Invest, 2008. **118**(7): p. 2640-50.
90. Duttaroy, A.K., *Transport of fatty acids across the human placenta: a review.* Prog Lipid Res, 2009. **48**(1): p. 52-61.
91. Melki, S.A. and N.A. Abumrad, *Expression of the adipocyte fatty acid-binding protein in streptozotocin-diabetes: effects of insulin deficiency and supplementation.* J Lipid Res, 1993. **34**(9): p. 1527-34.
92. Cook, J.S., et al., *Expression of the differentiation-induced gene for fatty acid-binding protein is activated by glucocorticoid and cAMP.* Proc Natl Acad Sci U S A, 1988. **85**(9): p. 2949-53.
93. Amri, E.Z., et al., *Regulation of adipose cell differentiation. I. Fatty acids are inducers of the aP2 gene expression.* J Lipid Res, 1991. **32**(9): p. 1449-56.
94. Nakamura, M.T., B.E. Yudell, and J.J. Loor, *Regulation of energy metabolism by long-chain fatty acids.* Prog Lipid Res, 2014. **53**: p. 124-44.
95. Makowski, L. and G.S. Hotamisligil, *The role of fatty acid binding proteins in metabolic syndrome and atherosclerosis.* Curr Opin Lipidol, 2005. **16**(5): p. 543-8.
96. Haunerland, N.H. and F. Spener, *Fatty acid-binding proteins--insights from genetic manipulations.* Prog Lipid Res, 2004. **43**(4): p. 328-49.
97. Iso, T., et al., *Capillary endothelial fatty acid binding proteins 4 and 5 play a critical role in fatty acid uptake in heart and skeletal muscle.* Arterioscler Thromb Vasc Biol, 2013. **33**(11): p. 2549-57.
98. Hotamisligil, G.S., et al., *Uncoupling of obesity from insulin resistance through a targeted mutation in aP2, the adipocyte fatty acid binding protein.* Science, 1996. **274**(5291): p. 1377-9.
99. Maeda, K., et al., *Adipocyte/macrophage fatty acid binding proteins control integrated metabolic responses in obesity and diabetes.* Cell Metab, 2005. **1**(2): p. 107-19.
100. Scheja, L., et al., *Altered insulin secretion associated with reduced lipolytic efficiency in aP2-/- mice.* Diabetes, 1999. **48**(10): p. 1987-94.
101. Shum, B.O., et al., *The adipocyte fatty acid-binding protein aP2 is required in allergic airway inflammation.* J Clin Invest, 2006. **116**(8): p. 2183-2192.
102. Reynolds, J.M., et al., *Deficiency of fatty acid-binding proteins in mice confers protection from development of experimental autoimmune encephalomyelitis.* J Immunol, 2007. **179**(1): p. 313-21.
103. Furuhashi, M., et al., *Treatment of diabetes and atherosclerosis by inhibiting fatty-acid-binding protein aP2.* Nature, 2007. **447**(7147): p. 959-65.
104. Lee, M.Y., et al., *Chronic administration of BMS309403 improves endothelial function in apolipoprotein E-deficient mice and in cultured human endothelial cells.* Br J Pharmacol, 2011. **162**(7): p. 1564-76.
105. Chan, C.K., et al., *A-FABP and oxidative stress underlie the impairment of endothelium-dependent relaxations to serotonin and the intima-medial thickening in the porcine coronary artery with regenerated endothelium.* ACS Chem Neurosci, 2013. **4**(1): p. 122-9.
106. Furuhashi, M., et al., *Lipid chaperones and metabolic inflammation.* Int J Inflam, 2011. **2011**: p. 642612.
107. Yu, C.W., et al., *Dual role of fatty acid-binding protein 5 on endothelial cell fate: a potential link between lipid metabolism and angiogenic responses.* Angiogenesis, 2016. **19**(1): p. 95-106.
108. Ku, C.Y., et al., *Liver fatty acid-binding protein (L-FABP) promotes cellular angiogenesis and migration in hepatocellular carcinoma.* Oncotarget, 2016. **7**(14): p. 18229-46.
109. Boord, J.B., et al., *Combined adipocyte-macrophage fatty acid-binding protein deficiency improves metabolism, atherosclerosis, and survival in apolipoprotein E-deficient mice.* Circulation, 2004. **110**(11): p. 1492-8.
110. Kanda, T., et al., *PPARgamma in the endothelium regulates metabolic responses to high-fat diet in mice.* J Clin Invest, 2009. **119**(1): p. 110-24.
111. Schug, T.T., et al., *Overcoming retinoic acid-resistance of mammary carcinomas by diverting retinoic acid from PPARbeta/delta to RAR.* Proc Natl Acad Sci U S A, 2008. **105**(21): p. 7546-51.
112. Schug, T.T., et al., *Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors.* Cell, 2007. **129**(4): p. 723-33.
113. Makowski, L., et al., *The fatty acid-binding protein, aP2, coordinates macrophage cholesterol trafficking and inflammatory activity. Macrophage expression of aP2 impacts peroxisome proliferator-activated receptor gamma and IkappaB kinase activities.* J Biol Chem, 2005. **280**(13): p. 12888-95.
114. Houten, S.M. and R.J. Wanders, *A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation.* J Inherit Metab Dis, 2010. **33**(5): p. 469-77.

115. Schaffer, J.E. and H.F. Lodish, *Expression cloning and characterization of a novel adipocyte long chain fatty acid transport protein.* Cell, 1994. **79**(3): p. 427-36.
116. Digel, M., et al., *FATP4 contributes as an enzyme to the basal and insulin-mediated fatty acid uptake of C_2C_{12} muscle cells.* Am J Physiol Endocrinol Metab, 2011. **301**(5): p. E785-96.
117. Hagberg, C., et al., *Endothelial fatty acid transport: role of vascular endothelial growth factor B.* Physiology (Bethesda), 2013. **28**(2): p. 125-34.
118. Gimeno, R.E., *Fatty acid transport proteins.* Curr Opin Lipidol, 2007. **18**(3): p. 271-6.
119. Johnson, A.C., A. Stahl, and R.A. Zager, *Triglyceride accumulation in injured renal tubular cells: alterations in both synthetic and catabolic pathways.* Kidney Int, 2005. **67**(6): p. 2196-209.
120. Pei, Z., et al., *Mouse very long-chain Acyl-CoA synthetase 3/fatty acid transport protein 3 catalyzes fatty acid activation but not fatty acid transport in MA-10 cells.* J Biol Chem, 2004. **279**(52): p. 54454-62.
121. Gimeno, R.E., et al., *Characterization of a heart-specific fatty acid transport protein.* J Biol Chem, 2003. **278**(18): p. 16039-44.
122. Doege, H. and A. Stahl, *Protein-mediated fatty acid uptake: novel insights from in vivo models.* Physiology (Bethesda), 2006. **21**: p. 259-68.
123. Gimeno, R.E., et al., *Targeted deletion of fatty acid transport protein-4 results in early embryonic lethality.* J Biol Chem, 2003. **278**(49): p. 49512-6.
124. Herrmann, T., et al., *Mice with targeted disruption of the fatty acid transport protein 4 (Fatp 4, Slc27a4) gene show features of lethal restrictive dermopathy.* J Cell Biol, 2003. **161**(6): p. 1105-15.
125. Mootha, V.K., et al., *Integrated analysis of protein composition, tissue diversity, and gene regulation in mouse mitochondria.* Cell, 2003. **115**(5): p. 629-40.
126. García-Martínez, C., et al., *Impact on fatty acid metabolism and differential localization of FATP1 and FAT/CD36 proteins delivered in cultured human muscle cells.* Am J Physiol Cell Physiol, 2005. **288**(6): p. C1264-72.
127. Davies, B.S., et al., *GPIHBP1 is responsible for the entry of lipoprotein lipase into capillaries.* Cell Metab, 2010. **12**(1): p. 42-52.
128. Wu, Q., et al., *FATP1 is an insulin-sensitive fatty acid transporter involved in diet-induced obesity.* Mol Cell Biol, 2006. **26**(9): p. 3455-67.
129. Stahl, A., et al., *Insulin causes fatty acid transport protein translocation and enhanced fatty acid uptake in adipocytes.* Dev Cell, 2002. **2**(4): p. 477-88.
130. Jain, S.S., et al., *Additive effects of insulin and muscle contraction on fatty acid transport and fatty acid transporters, FAT/CD36, FABPpm, FATP1, 4 and 6.* FEBS Lett, 2009. **583**(13): p. 2294-300.
131. Ibrahim, A., et al., *Local Mitochondrial ATP Production Regulates Endothelial Fatty Acid Uptake and Transport.* Cell Metab, 2020. **32**(2): p. 309-319.e7.
132. Jang, C., et al., *A branched-chain amino acid metabolite drives vascular fatty acid transport and causes insulin resistance.* Nat Med, 2016. **22**(4): p. 421-6.
133. Miller, M., et al., *Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association.* Circulation, 2011. **123**(20): p. 2292-333.
134. Ginsberg, H.N., *Lipoprotein physiology in nondiabetic and diabetic states. Relationship to atherogenesis.* Diabetes Care, 1991. **14**(9): p. 839-55.
135. Yamamoto, H., et al., *Skin permeability barrier formation by the ichthyosis-causative gene FATP4 through formation of the barrier lipid ω-O-acylceramide.* Proc Natl Acad Sci U S A, 2020. **117**(6): p. 2914-2922.
136. Bygum, A., P. Westermark, and F. Brandrup, *Ichthyosis prematurity syndrome: a well-defined congenital ichthyosis subtype.* J Am Acad Dermatol, 2008. **59**(5 Suppl): p. S71-4.
137. Klar, J., et al., *Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome.* Am J Hum Genet, 2009. **85**(2): p. 248-53.
138. Sobol, M., N. Dahl, and J. Klar, *FATP4 missense and nonsense mutations cause similar features in Ichthyosis Prematurity Syndrome.* BMC Res Notes, 2011. **4**: p. 90.
139. Lin, M.H. and J.H. Miner, *Fatty acid transport protein 1 can compensate for fatty acid transport protein 4 in the developing mouse epidermis.* J Invest Dermatol, 2015. **135**(2): p. 462-470.
140. Steinberg, S.J., et al., *Role of very-long-chain acyl-coenzyme A synthetase in X-linked adrenoleukodystrophy.* Ann Neurol, 1999. **46**(3): p. 409-12.
141. Mihalik, S.J., et al., *Participation of two members of the very long-chain acyl-CoA synthetase family in bile acid synthesis and recycling.* J Biol Chem, 2002. **277**(27): p. 24771-9.
142. Steinberg, S.J., et al., *The human liver-specific homolog of very long-chain acyl-CoA synthetase is cholate:CoA ligase.* J Biol Chem, 2000. **275**(21): p. 15605-8.
143. Doege, H., et al., *Targeted deletion of FATP5 reveals multiple functions in liver metabolism: alterations in hepatic lipid homeostasis.* Gastroenterology, 2006. **130**(4): p. 1245-58.
144. Geng, Q.S., et al., *Over-Expression and Prognostic Significance of FATP5, as a New Biomarker, in Colorectal Carcinoma.* Front Mol Biosci, 2021. **8**: p. 770624.
145. Wang, M.D., et al., *Fatty acid transport protein-5 (FATP5) deficiency enhances hepatocellular carcinoma progression and metastasis by reprogramming cellular energy metabolism and regulating the AMPK-mTOR signaling pathway.* Oncogenesis, 2021. **10**(11): p. 74.

146. Liu, K.T., et al., *Regulatory mechanism of fatty acid-CoA metabolic enzymes under endoplasmic reticulum stress in lung cancer.* Oncol Rep, 2018. **40**(5): p. 2674-2682.
147. Guo, J.C., et al., *Protein-coding genes combined with long non-coding RNAs predict prognosis in esophageal squamous cell carcinoma patients as a novel clinical multi-dimensional signature.* Mol Biosyst, 2016. **12**(11): p. 3467-3477.
148. Wilfling, F., et al., *Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from the ER to lipid droplets.* Dev Cell, 2013. **24**(4): p. 384-99.
149. Jarc, E. and T. Petan, *Lipid Droplets and the Management of Cellular Stress.* Yale J Biol Med, 2019. **92**(3): p. 435-452.
150. Herker, E. and M. Ott, *Unique ties between hepatitis C virus replication and intracellular lipids.* Trends Endocrinol Metab, 2011. **22**(6): p. 241-8.
151. Olzmann, J.A. and P. Carvalho, *Dynamics and functions of lipid droplets.* Nat Rev Mol Cell Biol, 2019. **20**(3): p. 137-155.
152. Lizaso, A., K.T. Tan, and Y.H. Lee, *β-adrenergic receptor-stimulated lipolysis requires the RAB7-mediated autolysosomal lipid degradation.* Autophagy, 2013. **9**(8): p. 1228-43.
153. Schroeder, B., et al., *The small GTPase Rab7 as a central regulator of hepatocellular lipophagy.* Hepatology, 2015. **61**(6): p. 1896-907.
154. Kaushik, S. and A.M. Cuervo, *Degradation of lipid droplet-associated proteins by chaperone-mediated autophagy facilitates lipolysis.* Nat Cell Biol, 2015. **17**(6): p. 759-70.
155. Kuo, A., M.Y. Lee, and W.C. Sessa, *Lipid Droplet Biogenesis and Function in the Endothelium.* Circ Res, 2017. **120**(8): p. 1289-1297.
156. Paul, A., L. Chan, and P.E. Bickel, *The PAT family of lipid droplet proteins in heart and vascular cells.* Curr Hypertens Rep, 2008. **10**(6): p. 461-6.
157. Young, S.G. and R. Zechner, *Biochemistry and pathophysiology of intravascular and intracellular lipolysis.* Genes Dev, 2013. **27**(5): p. 459-84.
158. Zimmermann, R., et al., *Fat mobilization in adipose tissue is promoted by adipose triglyceride lipase.* Science, 2004. **306**(5700): p. 1383-6.
159. Schrammel, A., et al., *Endothelial dysfunction in adipose triglyceride lipase deficiency.* Biochim Biophys Acta, 2014. **1841**(6): p. 906-17.
160. Riederer, M., et al., *Reduced expression of adipose triglyceride lipase decreases arachidonic acid release and prostacyclin secretion in human aortic endothelial cells.* Arch Physiol Biochem, 2017. **123**(4): p. 249-253.
161. Jocken, J.W., et al., *Adipose triglyceride lipase and hormone-sensitive lipase protein expression is decreased in the obese insulin-resistant state.* J Clin Endocrinol Metab, 2007. **92**(6): p. 2292-9.
162. Bosch, M., et al., *Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense.* Science, 2020. **370**(6514).
163. Thiam, A.R. and M. Beller, *The why, when and how of lipid droplet diversity.* J Cell Sci, 2017. **130**(2): p. 315-324.
164. Vander Heiden, M.G., L.C. Cantley, and C.B. Thompson, *Understanding the Warburg effect: the metabolic requirements of cell proliferation.* Science, 2009. **324**(5930): p. 1029-33.
165. Kalucka, J., et al., *Quiescent Endothelial Cells Upregulate Fatty Acid β-Oxidation for Vasculoprotection via Redox Homeostasis.* Cell Metab, 2018. **28**(6): p. 881-894.e13.
166. Saddik, M. and G.D. Lopaschuk, *Myocardial triglyceride turnover and contribution to energy substrate utilization in isolated working rat hearts.* J Biol Chem, 1991. **266**(13): p. 8162-70.
167. Lopaschuk, G.D. and J.R. Ussher, *Evolving Concepts of Myocardial Energy Metabolism: More Than Just Fats and Carbohydrates.* Circ Res, 2016. **119**(11): p. 1173-1176.
168. Neely, J.R. and H.E. Morgan, *Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle.* Annu Rev Physiol, 1974. **36**: p. 413-59.
169. Zecchin, A., et al., *Live imaging reveals a conserved role of fatty acid β-oxidation in early lymphatic development in zebrafish.* Biochem Biophys Res Commun, 2018. **503**(1): p. 26-31.
170. Dagher, Z., et al., *Acute regulation of fatty acid oxidation and amp-activated protein kinase in human umbilical vein endothelial cells.* Circ Res, 2001. **88**(12): p. 1276-82.
171. Xiong, J., *Fatty Acid Oxidation in Cell Fate Determination.* Trends Biochem Sci, 2018. **43**(11): p. 854-857.
172. Xiong, J., et al., *A Metabolic Basis for Endothelial-to-Mesenchymal Transition.* Mol Cell, 2018. **69**(4): p. 689-698.e7.
173. Eelen, G., et al., *Endothelial Cell Metabolism.* Physiol Rev, 2018. **98**(1): p. 3-58.
174. Thenappan, T., et al., *Pulmonary arterial hypertension: pathogenesis and clinical management.* Bmj, 2018. **360**: p. j5492.
175. Evans, C.E., et al., *Endothelial cells in the pathogenesis of pulmonary arterial hypertension.* Eur Respir J, 2021. **58**(3).
176. Dai, Z., et al., *Prolyl-4 Hydroxylase 2 (PHD2) Deficiency in Endothelial Cells and Hematopoietic Cells Induces Obliterative Vascular Remodeling and Severe Pulmonary Arterial Hypertension in Mice and Humans Through Hypoxia-Inducible Factor-2α.* Circulation, 2016. **133**(24): p. 2447-58.
177. Diebold, I., et al., *BMPR2 preserves mitochondrial function and DNA during reoxygenation to promote endothelial cell survival and reverse pulmonary hypertension.* Cell Metab, 2015. **21**(4): p. 596-608.
178. Liu, B., et al., *Endothelial PHD2 deficiency induces nitrative stress via suppression of caveolin-1 in pulmonary hypertension.* Eur Respir J, 2022.
179. Gomez-Arroyo, J., et al., *Metabolic gene remodeling and mitochondrial dysfunction in failing right ventricular hypertrophy secondary to pulmonary arterial hypertension.* Circ Heart Fail, 2013. **6**(1): p. 136-44.

180. Hemnes, A.R., et al., *Evidence for right ventricular lipotoxicity in heritable pulmonary arterial hypertension.* Am J Respir Crit Care Med, 2014. **189**(3): p. 325-34.
181. Singh, N., et al., *Inhibition of fatty acid synthase is protective in pulmonary hypertension.* Br J Pharmacol, 2016. **173**(12): p. 2030-45.
182. Sutendra, G., et al., *Fatty acid oxidation and malonyl-CoA decarboxylase in the vascular remodeling of pulmonary hypertension.* Sci Transl Med, 2010. **2**(44): p. 44ra58.
183. Papathanasiou, A.E., et al., *Adipokines and Metabolic Regulators in Human and Experimental Pulmonary Arterial Hypertension.* Int J Mol Sci, 2021. **22**(3).
184. Ohira, H., et al., *Shifts in myocardial fatty acid and glucose metabolism in pulmonary arterial hypertension: a potential mechanism for a maladaptive right ventricular response.* Eur Heart J Cardiovasc Imaging, 2016. **17**(12): p. 1424-1431.
185. Legchenko, E., et al., *PPARγ agonist pioglitazone reverses pulmonary hypertension and prevents right heart failure via fatty acid oxidation.* Sci Transl Med, 2018. **10**(438).
186. Qu, Q., et al., *Fatty acid oxidation and carnitine palmitoyltransferase I: emerging therapeutic targets in cancer.* Cell Death Dis, 2016. **7**(5): p. e2226.
187. Lee, M.H., et al., *Contribution of Fatty Acid Oxidation to the Pathogenesis of Pulmonary Hypertension.* Am J Physiol Lung Cell Mol Physiol, 2022.