2017 George Lyman Duff Memorial Lecture

Fat in the Blood, Fat in the Artery, Fat in the Heart: Triglyceride in Physiology and Disease

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Abstract—Cholesterol is not the only lipid that causes heart disease. Triglyceride supplies the heart and skeletal muscles with highly efficient fuel and allows for the storage of excess calories in adipose tissue. Failure to transport, acquire, and use triglyceride leads to energy deficiency and even death. However, overabundance of triglyceride can damage and impair tissues. Circulating lipoprotein-associated triglycerides are lipolyzed by lipoprotein lipase (LpL) and hepatic triglyceride lipase. We inhibited these enzymes and showed that LpL inhibition reduces high-density lipoprotein cholesterol by >50%, and hepatic triglyceride lipase inhibition shifts low-density lipoprotein to larger, more buoyant particles. Genetic variations that reduce LpL activity correlate with increased cardiovascular risk. In contrast, macrophage LpL deficiency reduces macrophage function and atherosclerosis. Therefore, muscle and macrophage LpL have opposite effects on atherosclerosis. With models of atherosclerosis regression that we used to study diabetes mellitus, we are now examining whether triglyceride-rich lipoproteins or their hydrolysis by LpL affect the biology of established plaques. Following our focus on triglyceride metabolism led us to show that heart-specific LpL hydrolysis of triglyceride allows optimal supply of fatty acids to the heart. In contrast, cardiomyocyte LpL overexpression and excess lipid uptake cause lipotoxic heart failure. We are now studying whether interrupting pathways for lipid uptake might prevent or treat some forms of heart failure.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2018;38: 700-706. DOI: 10.1161/ATVBAHA.117.309666.)**

Key Words: atherosclerosis ■ fatty acids ■ heart failure ■ lipoprotein lipase ■ triglycerides

Since my time as a fellow in Virgil Brown's laboratory, I have looked forward to the annual George Lyman Duff Memorial Lecture at the American Heart Association Scientific Sessions. I have attended several dozen of these talks beginning in the early 1980s. As atherosclerosis research has advanced, it remains true to 2 axioms: (1) things are always more complicated than they seem, and (2) the dogma is always wrong or at least incomplete. Now that the low-density lipoprotein (LDL) hypothesis has been proven by human clinical trials, atherosclerosis research is focusing on how inflammation and other lipoproteins impact atherosclerosis and why LDL alone does not always define cardiovascular disease (CVD) risk.

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Our understanding of the inter-relationship between lipoproteins and CVD risk has shifted in the past decade. High-density lipoprotein (HDL) and its biology have been the focus of several Duff Lectures. Today, we realize that the exact function of this circulating lipoprotein still has many mysteries to unmask; its relationship to atherosclerosis is uncertain. In contrast, the past decade has seen renewed interest in a possible role of triglyceride as a marker for CVD risk. This interest has been driven by genetics as well as re-evaluation of older epidemiological data. Triglyceride-rich lipoprotein reduction may be an approach to decreasing residual risk in patients with CVD. Others in this series have pioneered these ideas. In his 1978 lecture, Zilversmit[1] discussed the possible role of postprandial lipemia and the creation of atherogenic remnant particles via lipoprotein lipase (LpL) actions as a potential CVD risk. His hypothesis was supported by several studies of postprandial lipemia; increased lipemia is associated with greater risk and is often reflected in low circulating levels of HDL cholesterol (HDL-c). More recently, in 2011, Young discussed his discovery of a new endothelial cell LpL-binding protein, required for removal of circulating triglyceride-rich lipoproteins.[2] In this year's lecture, I will try to provide an overview that links triglyceride-rich lipoprotein metabolism to both atherosclerosis and heart failure.

Fat in the Blood

Triglyceride and its component fatty acids (FAs) are the central molecules in lipoprotein metabolism, major mediators of insulin actions,[3,4] primary sources of energy for heart function, and a major cause of heart dysfunction. Incorporation of triglycerides into circulating lipoproteins allows for the efficient

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movement of calories from the gut and liver to peripheral organs. The triglyceride-rich lipoproteins have a common metabolic step requiring LpL to convert the triglyceride into nonesterified FAs, the source of energetic and storage lipids. This common lipolysis step produces remnant lipoproteins from chylomicrons and very-low-density lipoprotein (VLDL).

Two enzymes contribute most of the lipolytic activity in postheparin human blood, regulating triglyceride removal, LDL size distribution, and HDL levels. Surprisingly, inhibitory antibodies to these enzymes tend to be species specific. Catabolism of chylomicrons requires LpL, and defects because of mutations in LpL or in the proteins required for its activation (apolipoprotein C-II), intracellular assembly (LMF-1 [lipase maturation factor-1]), and endothelial-binding (glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1) lead to marked hypertriglyceridemia and occasionally pancreatitis. Using monoclonal antibodies to LpL, we found that almost all LDL apolipoprotein B (apoB) in the cynomolgus monkey was derived from VLDL.[5,6] Subsequently, using genetically modified mice, we found that hepatic LpL production created fatty liver and allowed ketone body production needed to prevent the hypoglycemia that led to neonatal death of LpL-deficient mice.[6]

In human blood, hepatic triglyceride lipase (HTGL), also referred to as hepatic lipase, accounts for ≈40% to ≈60% of the postheparin lipolytic activity when assayed using artificial substrates and physiological ionic strength solutions. HTGL is a major regulator of HDL. Unlike its cousin endothelial lipase, HTGL is a triglyceride lipase as well as a phospholipase. Using polyclonal antibodies made in a goat and infused into monkeys, we[7] and others helped define the physiological function of HTGL (Figure 1). HTGL inhibition increased the plasma levels of small VLDL and converted LDL to a more buoyant density. Small dense LDL levels decreased. These data, along with those in rats and studies in humans with HTGL deficiency, implicated HTGL as the final step of clearance of chylomicron remnants and conversion of VLDL remnants to LDL. Increased circulating concentrations of chylomicron remnants are characteristic of humans with HTGL deficiency and Western diet–fed rabbits that have low HTGL activity. HTGL knockdown increased HDL size but, unlike in studies in some rodents, did not markedly alter HDL-c levels in the monkey. In contrast, LpL inhibition had major effects on monkey HDL levels.

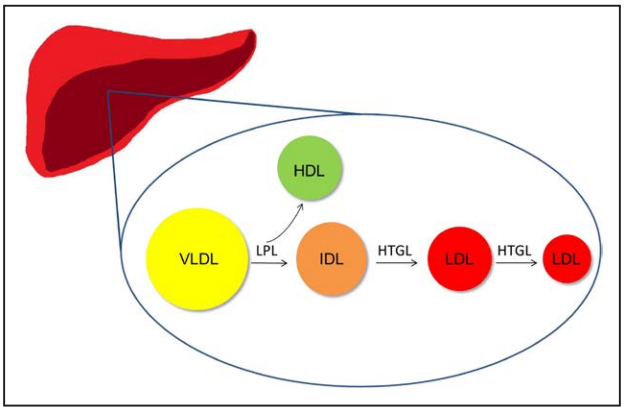

Figure 1. Lipases and generation of low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Heparin injection into humans releases both lipoprotein lipase (LpL) and hepatic triglyceride lipase (HTGL) into the circulation. Using selective immune-inhibition, we showed that LpL deletion markedly reduces HDL levels while HTGL deletion increased circulating levels of small very-low-density lipoprotein (VLDL) and larger, more buoyant LDL. IDL indicates intermediate-density lipoprotein. Figure derived from Goldberg et al.[8]

Hydrolysis of triglyceride-rich lipoproteins regulates both the production and catabolism of HDL. In addition to severe hypertriglyceridemia, patients with LpL deficiency have low levels of circulating HDL-c. This reduction in HDL-c was also seen in monkeys with acute LpL inhibition.[9] Part of this HDL reduction is because of the actions of cholesteryl ester transfer protein. However, an induced global LpL deficiency in mice who also have cholesteryl ester transfer protein deficiency led to a >50% reduction in HDL-c.[10] Studies by Havel et al,[11] performed >50 years ago, showed that components of triglyceride-rich lipoproteins are transferred to and incorporated into HDL during lipolysis. So, lipolysis contributes to HDL creation. Smaller HDL that likely have not received protein and lipids transferred from triglyceride-rich lipoproteins are more rapidly cleared from the circulation.[12,13] When we created triglyceride-enriched HDL to mimic HDL that were rapidly cleared in hypertriglyceridemic humans, HTGL actions reduced the size of these particles and increased their clearance by perfused kidneys.

Does HDL functionality, rather than HDL levels, explain the clinical observations that patients with several genetic diseases associated with extremely low HDL-c do not have marked CVD risk? A recent effort to resuscitate HDL as an important modulator of atherosclerosis emanates from the observations of Rohatgi et al[14] who have related the ability of HDL to accept effluxed macrophage cholesterol to atherosclerosis risk. The importance of HDL function is illustrated by the observation that patients with lecithin cholesterol acyl transferase deficiency with 1/10 normal HDL-c have relatively preserved HDL function.[15] Similarly, our recent studies (unpublished) show that triglyceride enrichment of HDL and loss of cholesterol does not alter HDL function. We do not yet know how the lipids and proteins that transfer to HDL during lipolysis or HTGL digestion alter HDL composition and function.

Fat in the Artery

Which circulating lipid causes atherosclerosis? This was a common question on rounds when I was a medical student, and was the reaction to a paper by Goldstein et al[16] on lipoprotein abnormalities in patients with CVD. This paper found that patients with CVD commonly had hypertriglyceridemia. Despite decades of study, we still debate the relationship between triglyceride and CVD. This is because epidemiology has been confounded by the inverse relationship between HDL and triglyceride; clinical trials of triglyceride reduction primarily treated subjects without hypertriglyceridemia while histological studies focused on plaque content of cholesterol often to the exclusion of other lipids. Moreover, while hypercholesterolemia causes atherosclerosis in mice (albeit with levels of cholesterol rarely seen in humans), even marked hypertriglyceridemia caused minimal lesion.[17] Nevertheless, recent genetic analyses have resurrected the triglyceride/atherosclerosis hypothesis.[18]

The relationship between triglyceride levels and vascular disease could either be because of deposition of triglyceride-rich lipoproteins or their remnants within the artery (the Zilversmit Hypothesis) or to vascular toxicity from lipolysis products[19] (Figure 2). This latter hypothesis is supported by our studies showing that perfusion with VLDL and LpL led to greater leakiness of the arterial wall and more LDL deposition within the artery.[20] In support of the triglyceride-rich lipoprotein atherosclerosis hypothesis, VanderLaan et al[21] reported that the extent of atherosclerosis in *Ldlr*$^{-/-}$ mice correlated with VLDL concentrations. We[22,23] and others[23] also implicated arterial wall LpL, and specifically LpL produced by arterial macrophages, as an atherogenic molecule. Such an effect is supported by in vitro experiments showing that in the presence of triglyceride-rich lipoproteins, LpL increased macrophage triglyceride and cholesteryl ester content.[24–26] In addition, LpL actions will increase macrophage phagocytosis under low glucose conditions,[27] perhaps an environment similar to that in the arterial wall. Such local effects of LpL seem to conflict with the beneficial effects on atherosclerosis associated with changes in lipoprotein levels.

For >50 years, deposition of cholesterol within the artery has been thought to initiate atherosclerosis.[28] However, what causes apoB lipoproteins to stick to matrix molecules is unclear. The most heavily charged region of apoB is the region of the molecule that codes for the LDL receptor-binding region. However, apoB48 that does not contain this region is equally atherogenic[29] and equally capable of binding to heparin,[29,30] an interaction that is thought to mimic binding to matrix proteoglycans. From studies to isolate LpL, we realized that LpL was a much more avid heparin-binding protein than LDL. Moreover, both in vitro and ex vivo studies using isolated arteries demonstrated that LpL could form a bridge to anchor LDL or VLDL to the subendothelial cell matrix or to the arterial wall.[20] Others[23] also found that LpL associated with some lesions. Furthermore, altering proteoglycan sulfation affected atherosclerosis and likely the ability of LpL to form a bridge that anchors LDL to the matrix.

Despite decades of investigation, an atherosclerosis model to assess how triglyceride or triglyceride lipolysis affects vascular biology is missing. This failure, along with a lack of definitive clinical trial data, has led to continued uncertainty in both clinical medicine and vascular biology. Perhaps, a different approach to CVD biology is required. One option is that the failure to show the effects of triglyceride on atherosclerosis is because of the overwhelming toxicity of high circulating levels of apoB-containing lipoproteins that swamp out any triglyceride-rich lipoprotein-mediated vascular effects. Moreover, the focus on lipids and atherogenesis limits our ability to understand CVD. Recently, more attention has been directed to how arteries repair after medication-induced reduction of cholesterol. Like for the effects of triglyceride on atherogenesis, studies of the vascular effects of diabetes mellitus had been confounded by the presence of high levels of circulating cholesterol, which likely masked many effects on the arteries and created conditions that were unlike those in most humans with CVD.

The Fisher laboratory has pioneered models to assess regression with genetic reduction in liver lipoprotein production and transplantation into nonhypercholesterolemic mice.[31] Using these techniques, we showed that regression was impaired in diabetes mellitus[32] and that this impairment corrected with glucose reduction that also decreased circulating white blood cell numbers.[33] These striking differences seen in regression between normal and type 1 diabetic mice contrast with the limited differences in atherosclerosis progression

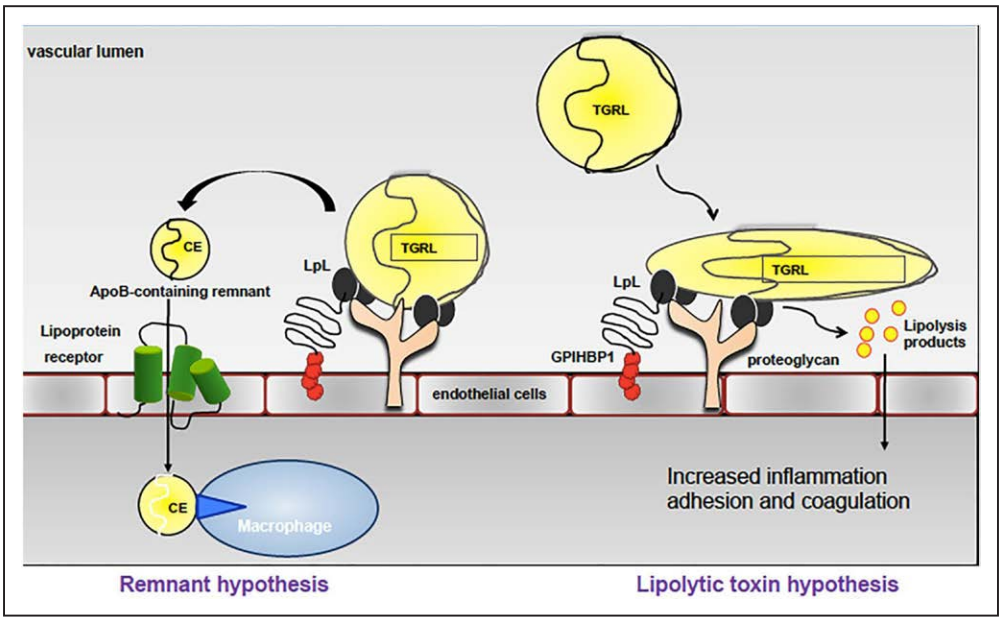

Figure 2. Triglyceride (TG)-rich lipoproteins and atherogenesis.TG-rich lipoproteins might increase atherosclerosis by their conversion into remnants that enter the artery wall and become a source of cholesterol and likely other toxic lipids. Alternatively, local lipolysis of fatty acids produces compounds such as lysolecithin that might damage the endothelium or cause activation of arterial macrophages. ApoB indicates apolipoprotein B; CE, cholesterol ester; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein 1; LpL, lipoprotein lipase; and TGRL, triglyceride-rich lipoprotein. Reproduced from Goldberg et al[19] with permission. Copyright © 2011, American Heart Association, Inc.

that occur in the setting of hypercholesterolemia,[34] unless the toxic effects of hyperglycemia are amplified for example by expression of the alternative glucose metabolic enzyme aldose reductase.[35,36] Perhaps, we require similar approaches to illustrate the presumably toxic effects of hypertriglyceridemia or lipolysis products.

Fat in the Heart

What is the role of triglyceride and lipolysis in heart function? Studies from the Zechner laboratory showed that physiological expression levels of LpL only in cardiomyocytes is sufficient to maintain normal plasma triglyceride levels.[37] By creating mice with tissue-specific LpL knockout in cardiomyocytes, we showed that the heart was a major modulator of plasma triglyceride because these mice were hypertriglyceridemic.[38] FA oxidation provides the primary source of energy for the heart. By showing that heart LpL deficiency reduced PPAR (peroxisomal proliferator-activated receptor)-activated genes and increased glucose use in mice and humans[39] despite normal heart uptake of circulating FAs, we demonstrated that triglyceride-rich lipoproteins were the primary source of heart energetic lipids. Moreover, heart LpL-deficient mice developed heart failure with aging and were unable to normally respond to increased afterload.[40] This defect was corrected by greater uptake of glucose.[41] At least in the mouse, the heart is a major site of triglyceride lipolysis, and this process is required for optimal heart response to aging and nonischemic stress.

Szczepaniak et al[42] conjectured that obesity and heart accumulation of excess triglyceride is a major cause of heart failure. Several models including mice overexpressing LpL[43] and PPARγ made by us[43] and mice in which enzymes or transcription factors increased lipid uptake and trapping or decreased lipid oxidation (created by others) also led to heart failure and in some cases premature death (Figure 3; reviewed in Ref. [44]).

Triglycerides represent energy stored within lipid droplets and do not directly affect signaling pathways. In contrast, several intermediates in the triglyceride synthesis pathway or alternative pathways using FAs create potentially toxic signaling lipids. There are numbers of potentially harmful lipid species. We used the low-hanging fruit approach and asked whether genetic alterations that affect diacylglycerol or ceramide accumulation modulate toxicity in mice created by others or us. To reduce cardiomyocyte diacylglycerol concentrations, we overexpressed diacylglycerol acyl transferase-1, an enzyme that converts diacylglycerol to triglyceride. This transgene reduced diacylglycerol, improved 2 models of lipid-induced heart failure,[51,52] and improved response to ischemia.[53] The diacylglycerol acyl transferase-1 transgene also reduced heart levels of ceramides, presumably by redirecting some FAs, such as palmitic acid from ceramide to triglyceride synthesis. However, efforts to reduce ceramides in the heart using a tissue-specific deletion of serine palmitoyl transferase long chain base 2 led to reduced heart ceramide but also palmitate enrichment of phospholipids and toxicity associated with endoplasmic reticulum stress.[54] Not surprisingly, lipid metabolic pathways are interconnected. For this reason, efforts to define a single toxic species are likely to be unsuccessful.

How else can lipotoxicity be corrected? Duncan et al[55] corrected heart toxicity because of overexpression of PPARα by deletion of the FA transporter CD36 and, with us, deletion of heart LpL.[56] However, knowledge of exactly how these 2 proteins affect heart lipid uptake from VLDL and chylomicrons was lacking. By assessing triglyceride and cholesteryl ester or retinyl ester uptake into hearts, we observed that while LpL was essential for chylomicron triglyceride accumulation, CD36 did not seem to be required for chylomicron triglyceride uptake.[10] Although surprising at first, these results mimic cell culture[57] and in vivo[58] experiments showing that

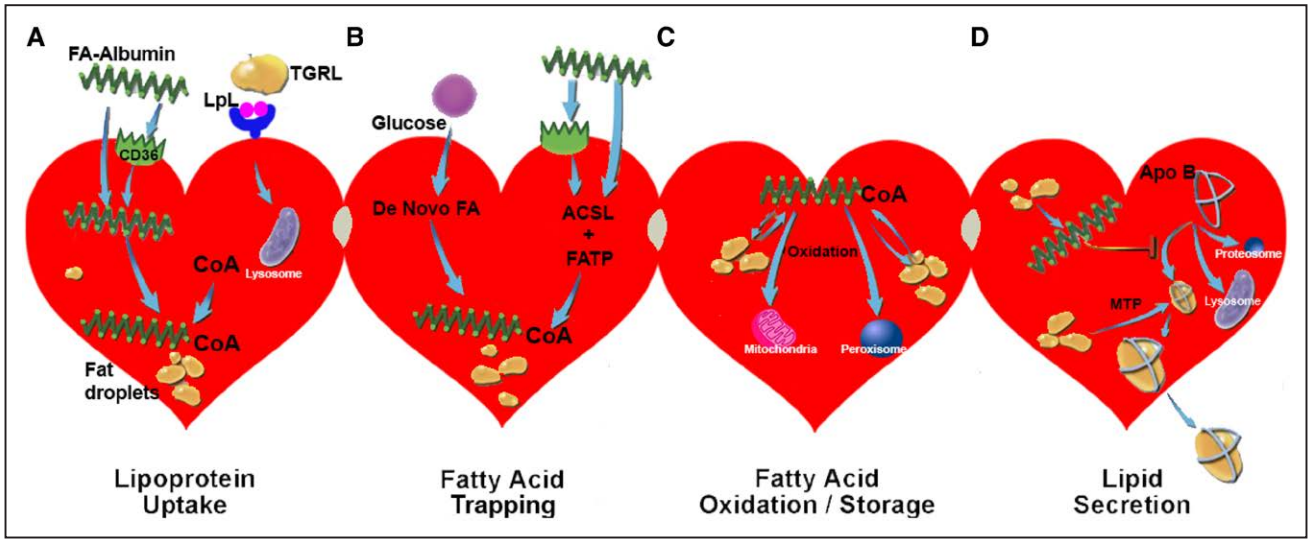

Figure 3. Generation of fatty hearts. Several models have established that excess lipid accumulation can lead to heart failure. **A**, Mice have been created that have greater uptake of circulating lipids; one of these models overexpresses an anchored form of lipoprotein lipase (LpL).[43] Overexpression of either PPARα[45] (peroxisomal proliferator-activated receptor) or PPARγ[46] also increase lipid uptake. **B**, Greater fatty acid (FA) trapping results from transgenic expression of ACSL1 (formerly known as acyl-coenzyme A synthetase, ACS)[47] and fatty acid transport protein (FATP)1.[48] **C**, Reduced FA oxidation, if uncoupled from lipid uptake, would also be expected to lead to greater lipid accumulation. **D**, The heart also has a limited ability to resecrete lipids because it expresses apolipoprotein B (apoB) and microsomal triglyceride transfer protein (MTP).[49,50] TGRL indicates triglyceride-rich lipoprotein.

CD36 contributed to nonesterified FA uptake at lower concentrations and that there seems to be a low affinity nonsaturable uptake of FAs.

Human tissues also have the fingerprint of lipid toxicity. Despite a reduction in stored triglyceride, probably reflecting the heart out of fuel, heart tissue from patients with end-stage heart failure have increased concentrations of ceramides and diacylglycerols.[59] This was associated with a marked decrease in mRNA for diacylglycerol acyl transferase-1. We reproduced this biology by creating mice with cardiomyocyte-specific deletion of diacylglycerol acyl transferase-1; these mice also had increased levels of ceramide and diacylglycerols and developed heart failure.[60] Excess lipid in the heart is thought to represent a toxicity associated with obesity or type 2 diabetes mellitus; others have suggested that it also reflects the changes in heart metabolism occurring when stress hormones drive-up circulating FA levels during failure.[61] In effect, heart failure causes lipotoxicity and leads to systemic insulin resistance, further impairing heart energetics.

As an approach to treatment, systemic deletion of either LpL or CD36 is not a viable option; one causes severe hypertriglyceridemia, and the other is associated with metabolic syndrome and insulin resistance.[62] This latter effect is also seen in mice on high-fat diets with global CD36 deficiency.[63] Insulin resistance in this model is surprising because reduced tissue FA uptake usually increases insulin sensitivity. The pathways involved in heart lipid metabolism and its effects on overall heart biology are under-researched. We have not characterized the cardiomyocyte lipid droplet with fasting and with lipid overload to the level of that in adipocytes or hepatocytes. FAs seem to be channeled differently to storage or oxidation; how does this occur and what regulates it? The accumulated lipids that cause toxicity are only partially known. How does the use of stored triglyceride affect the heart's ability to respond to ischemia or increased afterload? Finally, circulating nonesterified FAs and lipoprotein triglyceride-derived FAs must cross the endothelial cell barrier to reach myocytes and adipocytes. The cellular processes modulating lipid transfer to parenchymal cells are unclear. We expect that endothelial cells modulate lipid delivery and, in turn, tissue and organ metabolism.

Fat and the Future

As the central molecule in energy distribution, triglyceride modulates cellular metabolism. Triglyceride use has been associated with both inflammatory and reparative phenotypes in macrophages. Triglyceride accumulation in the proximal tubule is a fingerprint for renal failure.[64] Moreover, triglyceride hydrolysis creates ligands that activate PPARs and provide substrates and regulators of FA metabolism. In the blood, too little you starve, too much you suffocate. In the artery or along the arterial wall, lipolysis could be harmful, but this process will be limited if circulating triglyceride levels are low because of greater muscle lipolysis. In the heart, triglyceride lipolysis allows optimal function, protects against famine, and can either detoxify or father toxic lipids. Both for atherosclerosis and heart failure, studies of triglyceride metabolism still have answers to provide.

Disclosures

None.

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