We Know More Than We Can Tell About Diabetes and Vascular Disease: The 2016 Edwin Bierman Award Lecture

Clay F. Semenkovich

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Diabetes is a disorder of abnormal lipid metabolism, a notion strongly supported by the work of Edwin Bierman, for whom this eponymous lecture is named. This abnormal lipid environment continues to be associated with devastating vascular complications in diabetes despite current therapies, suggesting that our understanding of the pathophysiology of blood vessel disease in diabetes is limited. In this review, potential new insights into the nature of diabetic vasculopathy will be discussed. Recent observations suggest that while the concept of distinct macrovascular and microvascular complications of diabetes has been useful, vascular diseases in diabetes may be more interrelated than previously appreciated. Moreover, the intermediary metabolic pathway of de novo lipogenesis, which synthesizes lipids from simple precursors, is robustly sensitive to insulin and may contribute to these complications. De novo lipogenesis requires fatty acid synthase, and recent studies of this enzyme suggest that endogenously produced lipids are channeled to specific intracellular sites to affect physiology. These findings raise the possibility that novel approaches to treating diabetes and its complications could be based on altering the intracellular lipid milieu.

As a scientist who also provides medical care for people with diabetes, I am honored to deliver the Edwin Bierman Award lecture. Dr. Bierman was an eminent physician-scientist, and it is likely that he would have agreed with the statement that nothing drives the search for novel mechanisms that might lead to new therapies like managing a patient with the chronic complications of diabetes.

PROGRESS IN VASCULAR COMPLICATIONS

Dr. Bierman helped define the role of abnormal lipid metabolism in the pathogenesis of vascular disease, the most common cause of death in people with diabetes. Since the time of his contributions, authentic progress has been made to decrease the incidence of diabetes-related complications involving both macrovascular and microvascular disease (1). Relative risks for acute myocardial infarction, stroke, amputations, and end-stage renal disease associated with diabetes decreased between 1990 and 2010. How this happened is probably multifactorial, including the use of statins and inhibitors of the renin-angiotensin system, more options for glucose lowering, and less tobacco use. Despite this progress in relative risk, the overall burden of vascular complications continues to increase for at least two reasons. First, despite currently available therapies, people with diabetes remain much more likely that those...
without diabetes to have heart attacks, strokes, limb loss, and renal failure (1). And second, the incidence of both type 1 and type 2 diabetes has increased (2,3).

The considerable residual risk of complications despite modern treatment often prompts clinicians to rely on tacit knowledge that is not easily explained. The title of this lecture, “We Know More Than We Can Tell About Diabetes and Vascular Disease,” paraphrases a concept known as Polanyi’s Paradox for diabetes care. Michael Polanyi (1891–1976) was an accomplished physical chemist who subsequently became a social scientist and philosopher, developing the premise that human tacit knowledge is critical for the scientific process (4). His paradox deals with the idea that certain tasks require intuitive knowledge that is experiential and cultural and that is distinct from detailed technical knowledge. For example, driving a car requires more than knowing how an engine interacts with a transmission to transmit force to wheels. Likewise, anticipating hypoglycemic events and altering treatment in the context of complicated medical regimens and psychosocial conditions requires more than knowing how insulin suppresses gluconeogenesis and promotes glucose disposal. Tacit knowledge is not evidence-based medicine but is almost certainly required for designing clinical trials that produce robust results destined to alter practice patterns. And in the absence of relevant trial data for an individual patient, skilled providers use tacit knowledge to care for people with diabetes.

RELATIONSHIPS BETWEEN VASCULAR DISEASES IN DIABETES

Tacit knowledge implies that some of the distinctions between macrovascular (larger vessel disease leading to heart attacks, strokes, and limb loss) and microvascular (smaller vessel disease leading to retinopathy, nephropathy, and neuropathy) disease are artificial. Recent studies support this concept. In a very large (more than 49,000 subjects) population-based cohort of people with type 2 diabetes, the cumulative burden of microvascular disease was associated with major adverse cardiovascular events (MACE) (5). This study also reported a dose-response relationship between the number of microvascular disease states and MACE hazard ratio as well as death from cardiovascular disease. Although these data are based on static measures of disease, other work suggests that dynamic changes in a microvascular target tissue may predict macrovascular events. In a discovery cohort as well as a replication cohort of individuals with type 2 diabetes representing a broad spectrum of ethnicity, subtle decrements in renal function over time were associated with a greater risk of MACE (6). These findings, generated in patients free of chronic kidney disease based on prevailing concepts of this disorder, suggest that changes in the renal vasculature mirror progression of macrovascular disease.

Table 1—Vascular conundrums in diabetes

| Conundrum                                                                 | Implication                                                                 |
|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Atherosclerotic lesions are generally similar in type 1 and type 2 diabetes. |                                                                 |
| Lowering blood pressure may improve vascular complications driven by hyperglycemia. |                                                                 |
| Statins that decrease the risk of coronary vascular events and stroke increase the risk of diabetes. |                                                                 |
| Statins do not improve lower-extremity peripheral vascular disease. |                                                                 |
| Statins are not beneficial in end-stage renal disease. |                                                                 |
| Triglycerides predict vascular disease but are not major components of atherosclerotic lesions. |                                                                 |

There is also evidence that specific vascular complications in diabetes may be interactive, i.e., the pathophysiology of one complication may modulate progression of another. We recently reported retinal microvascular disease in the setting of high-fat diet–induced obesity in mice without the administration of streptozotocin, a potential neurotoxin. Over the course of a year, mice with insulin resistance and glucose intolerance developed vascular lesions characteristic of diabetic retinopathy, but this was preceded by electoretinographic defects, suggesting that vascular disease in the eye may be modulated by neuropathy (7). Serial studies of humans with diabetes also suggest that neurodegeneration in the retina precedes classic findings of retinopathy (8). Hyperglycemia was present in both studies (7,8), clinical diabetic retinopathy is rarely observed in the absence of hyperglycemia, and glycemic control is important for the treatment and prevention of diabetic retinopathy, which may be driven in part by abnormalities in retinal nerve function.

CONUNDRUMS IN DIABETIC VASCULAR DISEASE

In addition to the possibility that various vascular complications may be more interrelated than appreciated, other unexplained vascular conundrums (Table 1) offer opportunities to develop new paradigms for treatment. Despite striking differences in pathophysiology, type 1 and type 2 diabetes are associated with generally similar types of atherosclerotic lesions. Glycemia contributes to most diabetic vascular complications, but lowering blood pressure using drugs with divergent mechanisms of action decreases some of these complications, suggesting that events beyond hyperglycemia impact blood vessel disease. Statin drugs decrease macrovascular events in people with diabetes but also increase the risk of diabetes, especially in the setting of metabolic syndrome. Statin drugs have transformed the landscape of coronary disease and stroke, but they are not effective for lower-extremity peripheral vascular disease. Curiously, they are also not effective for coronary disease in people with end-stage renal disease. Circulating triglycerides predict macrovascular disease and specific genetic variants responsible for this effect have been identified (9,10), but triglycerides are not major components of vascular lesions. These conundrums are in part the product of studying clinical end points from the perspective of circulating biomarkers. Biomarkers may be associated with vascular
disease as in the case of HDL particles, which are strongly inversely related to disease in multiple populations. But this association does not ensure a direct role in disease, as for HDL, since elevating levels of HDL independent of assessing its function by administering niacin or cholesteryl ester transfer protein inhibitors does not improve vascular event rates (11,12). Polanyi’s tacit knowledge suggests that intracellular lipid metabolism contributes to vascular disease in diabetes. De novo lipogenesis, the production of fats from simple precursors, is altered in diabetes, and this process requires fatty acid synthase (FAS).

**FAS AND INTRACELLULAR LIPID METABOLISM**

FAS is large, consisting of two identical ~270 kD subunits that contain multiple distinct catalytic activities necessary for the synthesis of fatty acids. After being primed with acetyl-CoA, the enzyme successively adds two carbon fragments to an acyl chain in the form of malonyl-CoA (with the loss of carbon dioxide at each addition) to yield a long-chain fatty acid that is cleaved from the enzyme by a thioesterase activity in FAS. FAS produces mostly palmitate (16:0) (as well as smaller amounts of myristate [14:0] and stearate [18:0]), which requires eight moles of ATP. De novo lipogenesis is stimulated by insulin signaling, in part through transcriptional events. The FAS message is strongly increased by insulin, and SREBP-1c is involved in this induction, although other transcription factors also stimulate FAS expression.

FAS expression is decreased in many tissues of diabetes models, and its tissue-specific inactivation in mice has revealed phenotypes relevant to the complications of diabetes. Mice with liver-specific inactivation of FAS develop fatty liver, hypoglycemia, and enhanced insulin sensitivity (13). Liver FAS knockout animals phenocopy mice with genetic deficiency of the nuclear receptor PPARα (14); their metabolic abnormalities are rescued by administration of pharmacological activators of PPARα, such as fibrates; and subsequent studies of these liver-specific mice identified a specific phosphatidylcholine species as one of the endogenous ligands of PPARα (15). Knockout of FAS in the hypothalamus (16,17) decreases body weight through bioenergetic effects that include altered food intake and physical activity, a phenotype that is rescued by central nervous system infusion of a PPARα agonist. Knockout of FAS in macrophages results in PPARα-associated changes in genes involved in atherosclerosis (18) and protects mice from experimental atherosclerosis. Collectively, these findings suggest that FAS is involved in channeling phospholipids to modulate PPARα activity in a manner that could impact vascular disease in diabetes.

Consistent with the idea that macrovascular and microvascular complications may be more related than appreciated, the PPARα agonist fenofibrate appears to decrease the risk of both cardiovascular events (in selected subgroups) and retinopathy in diabetes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial did not demonstrate cardiovascular benefit for the addition of fenofibrate to a statin (19), but long-term follow-up of the participants in this study suggests that fenofibrate is beneficial in a subgroup of people with diabetes, triglycerides >204 mg/dL, and HDL cholesterol <34 mg/dL (20), consistent with subset analyses from other fibrate trials. Fenofibrate, which can rescue some cellular effects induced by FAS deficiency, decreased diabetic retinopathy progression in the ACCORD trial (21). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, another fibrate trial, showed that fenofibrate did not reduce the coronary event primary outcome (22) but did demonstrate decreased need for laser treatment of diabetic retinopathy (23), an effect independent of circulating lipids. The underlying mechanism is unknown, and it is possible that benefits of fenofibrate in the eye are due to effects on circulating lipids not generally measured in clinical trials, such as phospholipids, or related to potential antioxidant actions of this drug. However, one plausible interpretation of these results is that intracellular lipid metabolism, perhaps driven by insulin effects on FAS, can impact vascular disease in diabetes.

In normal mice, the induction of hind limb ischemia results in an angiogenic response that preserves blood flow to the extremity. In mice with FAS deficiency in endothelial cells, this response is impaired and causes limb loss, an effect associated with deficient palmitoylation of endothelial nitric oxide synthase (eNOS) (24). Palmitoylation of cysteine residues is required for normal localization of eNOS to the plasma membrane, where it carries out several functions relevant to vascular health. As FAS is insulin responsive in human vascular endothelial cells and eNOS palmitoylation is decreased in animal models of insulin deficiency and insulin resistance (24), it is plausible that effects on endothelial FAS could be involved in peripheral vascular disease and the risk for amputation in people with diabetes. Although FAS is necessary for endothelial integrity, it also appears to maintain epithelial integrity in the gut. When intestinal FAS is inactivated using an inducible Cre, mice develop systemic inflammation due to disruption of the mucous barrier that limits the access of the microbiota to the vasculature (25). This effect is associated with deficient palmitoylation and secretion of mucin 2, a critical component of the gel-like mucinous barrier in the gut. As FAS deficiency in the intestine characterizes mouse models of diabetes (25) and colonic lymph drains to pancreatic lymph nodes (26), it is possible that deficient FAS in the gut could be responsible for the observation that subclinical endotoxemia in humans appears to promote the development of diabetes independent of BMI, glucose, and metabolic syndrome (27).

In adipose tissue, another site where FAS is strongly induced by insulin, FAS knockout promotes the formation of beige fat and decreases insulin resistance (28). Beiging is associated with the loss of an interaction of alkyl ether lipids with the nuclear receptor PPARγ. Adipose knockout of the terminal peroxisomal enzyme required for ether lipid synthesis, PexRAP (peroxisomal reductase activating
PPARγ), causes the same phenotype as FAS adipose knockout mice (28), suggesting FAS and PexRAP share a lipogenic pathway contributing to insulin resistance in diabetes. Insulin resistance and diabetes commonly contribute to heart failure. FAS expression is increased the hearts of humans with end-stage cardiomyopathy as well as mouse models of heart failure (29), an unexpected finding as energy depletion characterizes heart failure and FAS requires abundant ATP to synthesize lipids. Mice with FAS deficiency in the heart die soon after the experimental stress of transaortic constriction and die prematurely with age, both likely due to abnormal calcium handling (29).

**COMPLEX EFFECTS OF ALTERING DE NOVO LIPOGENESIS**

Given the striking effects of FAS modulation on diabetes phenotypes mediated by the mechanisms shown in Fig. 1, it is not surprising that several companies have pursued pharmacological inhibition of FAS. Platensimycin, a reversible small molecule inhibitor of FAS, improves insulin resistance in mouse models of diabetes (30) and nonhuman primates (31), but this compound is no longer being developed for human applications. A summary of the tissue-specific effects of FAS inhibition is presented in Table 2. FAS inhibition in liver, macrophages, hypothalamus, and adipose tissue would be beneficial through decreased hepatic glucose production, less atherosclerosis, less adiposity caused by decreased appetite and increased physical activity, and less adiposity due to beiging of white fat. But FAS inhibition in skeletal muscle, heart, endothelium, and intestine would be detrimental because of weakness despite improved glucose control, arrhythmias caused by aberrant calcium handling, hypertension and defective angiogenesis due to endothelial dysfunction, and endotoxemia due to loss of the normal gut barrier. As FAS is ubiquitous, its inhibition would be problematic unless specific sites were targeted. Notably, FAS is increased in many cancers and an FAS inhibitor, TVB-2640, is in clinical trials for the treatment of advanced stage solid malignancies (NCT02223247).

Palmitate is the dominant direct product of the FAS reaction, but the effects of FAS deficiency in mice are not rescued by addition of exogenous palmitate. Cells can distinguish between endogenous palmitate from FAS and exogenous palmitate from other sources. FAS-derived fatty acids appear to be channeled to specific sites, and these lipid channeling pathways and their targets could be modified to alter the course of vascular disease in diabetes. Translational studies of skeletal muscle provide support for this strategy.

In skeletal muscle, high-fat feeding and insulin resistance in normal mice are associated with an increase in FAS message, protein, and enzyme activity (32), effects opposite to those in most other tissues. This unexpected induction represents a stress response in the setting of high-fat feeding to specifically remodel the sarcoplasmic reticulum (SR) membrane to preserve muscle contractile function. Chow-fed mice with skeletal muscle–specific inactivation of FAS are phenotypically normal in terms of metabolic variables and muscle strength. However, when these mice are fed a high-fat diet, they are protected from obesity-associated insulin resistance but become weak without changes in expression of PPARα-dependent genes or palmitoylation. Instead, the muscle findings are due to a reduction in the activity of sarco/endoplasmic reticulum calcium ATPase (SERCA), which normally sequesters calcium from the ER/SR

![Figure 1](https://example.com/figure1.png)

**Figure 1**—De novo lipogenesis driven by the insulin-responsive enzyme FAS channels lipids to specific intracellular sites relevant to the vascular complications of diabetes. Depending on the tissue being targeted, inactivating FAS can impact inflammation, insulin sensitivity, atherosclerosis, vascular function, muscle function, and intestinal barrier function, among other effects. ER, endoplasmic reticulum.
cytoplasm. Elevated cytosolic calcium promotes glucose uptake but decreases muscle contraction. The decrease in SERCA activity is caused by altered phospholipid composition of the SR, specifically an increase in the ratio of phosphatidylcholine (PC) to phosphatidylethanolamine (PE) species (32) due mostly to decreased abundance of PE. Decreased PE in model membranes is known to impair SERCA activity (33), and our findings of an increased PC-to-PE ratio leading to decreased calcium uptake confirms the work of others studying endoplasmic reticulum (the homolog of SR in nonmuscle tissue) stress in liver (34).

FAS channels lipids to phospholipid synthesis mediated by the Kennedy pathway (35). The terminal enzyme in this pathway is choline/ethanolamine phosphotransferase 1 (CEPT1), and as seen with FAS, high-fat feeding to normal mice induces CEPT1 (36). Mice with skeletal muscle–specific inactivation of CEPT1 have the same phenotype as mice with FAS deficiency in muscle: normal strength and glucose metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance with high-fat feeding at the expense of muscle metabolism with chow feeding, protection from insulin resistance 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lipogenesis, suggesting that FAS-mediated membrane effects may have broad relevance to inflammation biology. Consistent with this concept, a newly discovered protein named FAMIN forms a complex with FAS at the peroxisome to promote de novo lipogenesis and modulate risk for juvenile rheumatoid arthritis, leprosy, and Crohn disease (49). Collectively, multiple lines of evidence support the notion that pathways involving FAS and directing newly synthesized lipids to specific intracellular sites could be targeted to treat the vascular complications of diabetes, perhaps by repurposing drugs that modulate phospholipid metabolism.

A PRACTICAL APPROACH TO VASCULAR DISEASE IN DIABETES

Although our evolving understanding of the potential role of FAS in diabetes complications may lead to new therapies, many patients are not deriving maximal benefit from currently available therapies. In more than 2,000 adults with diabetes but no cardiovascular disease followed for 11 years, achieving blood pressure, LDL cholesterol, and HbA1c goals was associated with substantially lower risk of heart disease (50). Unfortunately, only about 7% of patients reached these relatively modest targets for blood pressure (130/80 mmHg), LDL cholesterol (100 mg/dL), and HbA1c (7% [53 mmol/mol]).

So how should we manage a typical patient with type 2 diabetes at risk for vascular disease? One approach is presented in Table 3. Appropriate glycemic control should be achieved using metformin often in combination with either a sodium–glucose cotransporter 2 inhibitor (51) or GLP-1 receptor agonist (52) shown to provide mortality benefits. Context-specific counseling should be provided about diet, exercise, and smoking cessation, and blood pressure should be controlled, which usually requires more than one agent. In the absence of a contraindication, every person with diabetes should be treated with a high-intensity statin. Fenofibrate can be considered in certain clinical situations, especially in males with elevated triglycerides and low HDL cholesterol who have suffered cardiovascular events in the setting of statin therapy, as it may decrease cardiovascular event rates and prevent progression of retinopathy. PCSK9 inhibitors, despite their cost, might be shown to be beneficial and could be especially useful in statin-intolerant patients.

An aphorism attributed to both Hippocrates and William Osler holds that it is more important to know what sort of patient has a disease than what sort of disease a patient has. Knowing what sort of patient has diabetes requires intuitive skills represented by Polanyi's statement that "we know more than we can tell." FAS-mediated intracellular lipid flux channels lipids to specific sites. Most scientists focus on altering the function of proteins to affect end points, but protein function is frequently dependent on the lipid environment. The intracellular phospholipid environment could be amenable to modifications appropriate for treating vascular disease in diabetes. But it may take knowing more than we can tell to convince our patients that doing the hard work of diabetes care using currently available therapies often prevents serious complications.

Table 3—One approach to decrease vascular risk in type 2 diabetes

| Glycemic control, such as metformin with SGLT2 inhibitor or GLP-1 receptor agonist |
| Exercise, diet, and smoking cessation counseling |
| Blood pressure control, often with more than one agent |
| High-intensity statin, as tolerated |
| Fenofibrate, especially in males with elevated triglycerides and low HDL cholesterol |
| Consideration of PCSK9 inhibition based on clinical circumstance |

SGLT2, sodium–glucose cotransporter 2.
12. Schwartz GG, Olsson AG, Alt M, et al.; dAl-OCTIMUS Investigators. Effects of dalceprapib in patients with a recent acute coronary syndrome. N Engl J Med 2012; 367:2089–2099

13. Chakravarthy MV, Pan Z, Zhu Y, et al. “New” hepatic fat activates PPARα to maintain glucose, lipid, and cholesterol homeostasis. Cell Metab 2005;1: 309–322

14. Guerre-Millo M, Rouault C, Poulain P, et al. PPAR-alpha-null mice are protected from high-fat diet-induced insulin resistance. Diabetes 2001;50:2809–2814

15. Chakravarthy MV, Lodhi UJ, Yin L, et al. Identification of a physiologically relevant endogenous ligand for PPARα in liver. Cell 2009;138:476–488

16. Chakravarthy MV, Zhu Y, López M, et al. Brain fatty acid synthase activates PPARα to maintain energy homeostasis. J Clin Invest 2007;117:2539–2552

17. Chakravarthy MV, Zhu Y, Yin L, et al. Inactivation of hypothalamic FAS protects mice from diet-induced obesity and inflammation. J Lipid Res 2009;50:630–640

18. Schneider JG, Yang Z, Chakravarthy MV, et al. Macrophage fatty-acid synthase deficiency decreases diet-induced atherosclerosis. J Biol Chem 2010;285:23398–23409

19. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574

20. Elam MB, Ginsberg HN, Lovato LC, et al.; ACCORDION Study Investigators. Association of fenofibrate therapy with long-term cardiovascular risk in statin-treated patients with type 2 diabetes. JAMA Cardiol 2017;2:370–380

21. Chew EY, Ambrosius WT, Davis MD, et al.; ACCORD Study Group; ACCORD Eye Study Group. Effects of medical therapies on retinopathy progression in type 2 diabetes. N Engl J Med 2010;363:233–244

22. Keech A, Simes RJ, Barter P, et al.; FIELD Study Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849–1851

23. Keech A, Mitchell P, Summanen PA, et al.; FIELD Study Investigators. Effect of fenofibrate on the need for laser treatment for diabetic retinopathy (FIELD study): a randomised controlled trial. Lancet 2007;370:1687–1697

24. Wei X, Schneider JG, Shenouda SM, et al. De novo lipogenesis maintains vascular homeostasis through endothelial nitric-oxide synthase (eNOS) palmitoylation. J Biol Chem 2011;286:2933–2945

25. Wei X, Yang Z, Rey FE, et al. Fatty acid synthase modulates intestinal barrier function through palmitoylation of mucin 2. Cell Host Microbe 2012;11:140–152

26. Carter PB, Collins FM. The route of enteric infection in normal mice. J Exp Med 1974;139:1189–1203

27. Pussinsson PJ, Havalina AS, Lehto M, Sundvall J, Salomaa V. Endotoxemia is associated with an increased risk of incident diabetes. Diabetes Care 2011;34:392–397

28. Lodhi UJ, Yin L, Jensen-Urstad AM, et al. Inhibiting adipose tissue lipogenesis reprograms thermogenesis and PPARγ activation to decrease diet-induced obesity. Cell Metab 2012;16:189–201

29. Razani B, Zhang H, Schulze PC, et al. Fatty acid synthase modulates hematocrit responses to myocardial stress. J Biol Chem 2011;286:30849–30961

30. Wu M, Singh SB, Wang J, et al. Antiadipatic and antiatherosclerotic effects of the selective fatty acid synthase (FAS) inhibitor palmitosin in mouse models of diabetes. Proc Natl Acad Sci U S A 2011;108:5378–5383

31. Singh SB, Kang L, Navrocki AR, et al. The fatty acid synthase inhibitor palmitosin improves insulin resistance without reducing liver steatosis in mice and monkeys. PLoS One 2017;12:e0170721

32. Funai K, Song H, Yin L, et al. Muscle lipogenesis balances insulin sensitivity and strength through calcium signaling. J Clin Invest 2013;123:1229–1240

33. Gustavsson M, Traseth NJ, Velega G. Activating and deactivating roles of lipid bilayers on the 

34. Fu S, Yang L, Li P, et al. Aberrant lipid metabolism disrupts calcium homeostasis causing liver endoplasmic reticulum stress in obesity. Nature 2011;473:528–531

35. Henneberry AL, Wright MM, McMaster CR. The major sites of cellular phospholipid synthesis and molecular determinants of Fatty Acid and lipid head group specificity. Mol Biol Cell 2002;13:3148–3161

36. Funai K, Lodhi UJ, Spears LD, et al. Skeletal muscle phospholipid metabolism regulates insulin sensitivity and contractile function. Diabetes 2016;65:358–370

37. Newcom SA, Brozinick JT, Kiseljak-Vassiliades K, et al. Skeletal muscle phosphatidycholine and phosphatidylethanolamine are related to insulin sensitivity and respond to acute exercise in humans. J Appl Physiol (1985) 2016;120:1355–1363

38. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 2013;13:709–721

39. Slotte JP, Bierman EL. Depletion of plasma-membrane sphingomyelin rapidly alters the distribution of cholesterol between plasma membranes and intracellular cholesterol pools in cultured fibroblasts. Biochem J 1986;250:653–658

40. York AG, Williams KJ, Argus JP, et al. Limiting cholesterol biosynthetic flux spontaneously engages type I IFN signaling. Cell 2015;163:1716–1729

41. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444:860–867

42. Moore KJ, Sheedy FJ, Fisher EA. Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol 2013;13:709–721

43. Slote JP, Bierman EL. Depletion of plasma-membrane sphingomyelin rapidly alters the distribution of cholesterol between plasma membranes and intracellular cholesterol pools in cultured fibroblasts. Biochem J 1986;250:653–658

44. York AG, Williams KJ, Argus JP, et al. Limiting cholesterol biosynthetic flux spontaneously engages type I IFN signaling. Cell 2015;163:1716–1729

45. Zhou Y, Wong OJ, Cho KJ, et al. Membrane potential modulates plasma membrane phospholipid dynamics and K-ρ signaling. Science 2015;349:873–876

46. Everts B, Amiel E, Huang SC, et al. TLR-driven early glycolytic reprogramming via the kinases TBK1–IKKε supports the anabolic demands of dendritic cell activation. Nat Immunol 2014;15:323–332

47. Berod L, Friedrich C, Nandan A, et al. De novo fatty acid synthesis controls the fate between regulatory T and T helper 17 cells. Nat Med 2014;20:1327–1333

48. Moon JS, Lee S, Park MA, et al. UCP2-induced fatty acid synthase promotes NLRP3 inflammasome activation during sepsis. J Clin Invest 2015;125:665–680

49. Cader MZ, Boroviak K, Zhang Q, et al. C13orf31 (FAMIN) is a central regulator of NLRP3 in-ammation and metabolic disorders. Nat Immunol 2016;17:1046–1056

50. Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and car-diovascular disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care 2016;39:669–676

51. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

52. Masro SP, Daniels GH, Brown-Forand K, et al.; LEADER Steering Committee; LEADER Trial Investigators; Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–322