commentary

Fight fat with DGAT[1]

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The triglyceride synthesis pathway is active in virtually every cell type. Conversion of fatty acids into triglycerides (TGs) serves two main purposes. First, it allows for storage of fuel in a very energy dense form and second, it neutralizes free fatty acids and other lipotoxic derivates. Synthesis of TGs is governed by the glycerol phosphate and the monoacylglycerol pathway (1). Most cells use the glycerol phosphate pathway, whereas the monoacylglycerol pathway is utilized specifically by adipocytes, enterocytes, and hepatocytes (2). The final reaction step of both pathways, which involves the joining of fatty acyl-CoA and diacylglycerol (DAG) to form a TG, is catalyzed by the acyl-CoA:diacylglycerol acyltransferase enzymes DGAT1 and DGAT2. Whereas DGAT2 is primarily expressed in liver and adipose tissue (3), DGAT1 is expressed ubiquitously, including in skeletal muscle, heart, and intestine (4).

Loss- and gain-of-function studies have revealed that the role of DGAT1 is diverse and, in addition to regulating cellular TG storage levels, affects the development of obesity, insulin resistance, and fatty acid-induced inflammation (5, 6). DGAT1 overexpression leads to increased cellular TG storage in white adipose tissue, skeletal muscle, and liver in a tissue-specific manner and thereby limits the amounts of intracellular DAG and free fatty acids. Because elevated levels of DAG and free fatty acids are lipotoxic and lead to reduced cell survival and enhanced inflammation, elevated DGAT1 activity may prevent these lipotoxic alterations by converting DAG and fatty acids into relatively inert TG pools. Consistent with this notion, overexpression of DGAT1 in adipose tissue promotes obesity in animals fed a high-fat diet (HFD) (6), yet protects against HFD-induced steatosis and adipose tissue inflammation and improves insulin sensitivity.

Paradoxically, deletion of DGAT1 also confers metabolic benefits in the form of prevention of HFD-induced obesity and enhanced insulin sensitivity (7). Surprisingly, the absence of DGAT1 did not lead to elevated levels of DAG or acyl-CoA in muscle, liver, and adipose tissue upon high-fat diet feeding (8). Considering its enzymatic function, DGAT1 deficiency is expected to cause accumulation of DAG, ceramide and fatty acids in tissues and thereby enhance lipotoxicity.

In this issue of the *Journal of Lipid Research*, Liu et al. (9) examine the impact of acute and chronic loss of DGAT1-activity in cardiac muscle and provide insight into the molecular pathways governed by DGAT1. In line with the effect of DGAT1 deletion in other tissues (8), loss of DGAT1, either by genetic or chemical modulation, failed to raise levels of DAG and ceramide in cardiac muscle. Additionally, absence of DGAT1 did not lead to changes in cardiac function. In order to identify molecular pathways that may protect against formation of lipotoxic intermediates in DGAT1$^{-/-}$ mice, the authors analyzed expression levels of several genes related to lipid metabolism. Strikingly, mRNA levels of PPARα, PPARδ, and PPARγ, as well as their downstream target genes involved in lipid uptake and oxidation were markedly reduced in hearts of DGAT1$^{-/-}$ mice and in wild-type mice treated with a DGAT1-inhibitor. Simultaneously, cardiac expression levels of glucose transporters GLUT1 and GLUT4 were upregulated in the absence of DGAT1. The changes at mRNA level were corroborated by a reduction in fatty acid oxidation and an increase in glucose uptake in cardiac cells in vivo and in vitro.

The results indicate that DGAT1-deficiency changes substrate utilization in heart. The authors suggest that these effects are mediated through transcriptional downregulation of PPARs and their target genes. By suppressing genes involved in lipid uptake and oxidation and inducing glucose transport via GLUT1 and GLUT4, DGAT1 deficiency protects against lipotoxicity. Interestingly, the effects on gene expression, fatty acid oxidation, and glucose uptake were reproduced in vitro, suggesting that the alterations inflicted by DGAT1 deficiency do not require cross-talk with other tissues or result from developmental adaptations in vivo.

Overall, the study by Liu et al. (9) yields crucial insight into the molecular mechanism that explains the lack of buildup of lipotoxic intermediates in the absence of DGAT1. The most thought-provoking aspect of the paper is the finding that DGAT1-deficiency causes downregulation of PPARα, PPARδ, and PPARγ, which carry out diverse functions (10), as well as a number of their target genes. The results raise the question of how much each of the

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different PPAR-isotypes contribute to the observed phenotype and to what extent the lack of lipotoxicity in DGAT1-deficient hearts is purely mediated by downregulation of PPAR-dependent genes.

Even more importantly, what mechanism may account for the observed downregulation of all three PPAR-isoforms in (cardio)myocytes in vivo and in vitro? Interestingly, effects seen in DGAT1-deficient hearts mimic the effects of sepsis or lipopolysaccharide (LPS)-induced inflammation on fatty acid uptake and oxidation in heart (11). Although studies on the transcriptional regulation of PPAR expression are limited, it has been shown that inflammation elicited by LPS treatment decreases PPARα and PPARδ expression in heart (12). Moreover, LPS treatment downregulated PPAR target genes in heart including Cd36, Lpl, and Cpt1b. It could be envisioned that the absence of DGAT1 triggers activation of inflammatory pathways that, in turn, negatively impacts PPAR expression levels. This possibility can easily be explored by studying the effect of DGAT1 siRNA mediated knockdown on inflammatory signaling pathways and gene expression using tools such as transcriptomics.

The authors themselves speculate that DGAT1 deficiency may affect a pathway needed for uptake of lipids into the cells and movement of endogenous PPAR agonists to the nucleus. Alternatively, formation of endogenous agonists could be reduced upon inhibition of DGAT1.

As a final note, the effect of DGAT1 deficiency on specific PPAR target genes involved in fatty acid oxidation was different in liver, which indicates that the pathway leading to PPAR suppression is nonfunctional in hepatocytes.

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