Review

CellPress

Lipid metabolites as metabolic messengers in inter-organ communication

Sihao Liu*, Ryan K. Alexander, and Chih-Hao Lee

Department of Genetics and Complex Diseases, Division of Biological Sciences, Harvard School of Public Health, Boston, MA 02115, USA

Metabolic homeostasis is achieved through coordinated regulation across several tissues. Studies using mouse genetic models have shown that perturbation of specific pathways of lipid metabolism in metabolically active tissues impacts systemic metabolic homeostasis. The use of metabolomic technologies combined with genetic models has helped to identify several potential lipid mediators that serve as metabolic messengers to communicate energy status and modulate substrate utilization among tissues. When provided exogenously, these lipid metabolites exhibit biological effects on glucose and lipid metabolism, indicating a therapeutic potential for treating metabolic diseases. In this review we summarize recent advances in inter-organ communication through novel mechanisms, with a focus on lipid mediators synthesized *de novo* or derived from dietary sources, and discuss challenges and future directions.

Metabolic flexibility in energy metabolism

Obesity is a growing health issue that is associated with a collection of metabolic disorders such as dyslipidemia, insulin resistance, and cardiovascular diseases. The underlying mechanism for how the obese state is causative to metabolic diseases is multifaceted and has been reviewed extensively [1–4]. Significant effort has focused on the pathological effect of obesity-induced ectopic fat deposition, or lipotoxicity, characterized by the accumulation of lipid intermediates in non-adipose tissue [3,4]. This leads to cellular dysfunction and diminished efficiency and flexibility in energy metabolism, thereby establishing a metabolic vicious cycle.

Metabolic flexibility can be described as the capacity of the body to switch between carbohydrates and lipids as the predominant source of energy substrates [5]. After a meal, elevated blood glucose level triggers insulin release by pancreatic β cells. The anabolic action of insulin promotes glucose uptake and utilization by insulin-sensitive tissues while suppressing fatty acid release from white adipose tissue. Surplus glucose is converted to fat via *de novo* lipogenesis in the liver and is exported to white adipose tissue for long-term storage. Conversely, a decline in blood glucose levels during the fasted state dampens insulin secretion and enhances the action of counter-regulatory hormones that facilitate fatty acid release from adipose tissue to be used as a major energy source [6].

Although it is indisputable that insulin is a key regulator of substrate switching, as seen in the fasting/feeding cycle, metabolic flexibility appears to be applicable to a broader range of physiology. As discussed in detail below, after a period of caloric restriction, food intake leads to a transient upregulation of adipose tissue lipogenesis and suppression of hepatic lipogenesis [7]. By contrast, endurance exercise not only enhances fatty acid burning in muscle but also in adipose tissue and the liver [8]. How these metabolic states are achieved is under active investigation. Nevertheless, cumulative evidence suggests the existence of additional metabolic signals that serve as messengers among metabolically active tissues to orchestrate coordinated control of energy metabolism. The seminal work by Randle *et al*. (Box 1), which demonstrated altered glucose uptake in isolated rat muscle upon fatty acid perfusion in the absence of insulin, suggests that fatty acids or their derivatives could be potential regulators of metabolic flexibility [9].

We describe here recent discoveries of novel mechanisms mediated by lipid metabolites that are capable of modulating metabolic flexibility and other key metabolic pathways. They are proposed to serve as long-range hormones but can act in a paracrine manner to integrate metabolic processes between tissues or cells. The therapeutic potential of these lipid mediators and the challenges in studying their functions in physiological contexts will also be discussed.

Lipogenic pathways and systemic metabolic homeostasis

Whereas animals can usually acquire a sufficient amount of fatty acids through dietary sources [10], mouse genetic models have suggested an essential role for the *de novo* lipogenic pathway. Whole-body knockout of either acetyl-CoA carboxylase 1 (Acc1, or Acaca) or fatty acid synthase (Fasn), two rate-limiting enzymes of *de novo* lipogenesis (Figure 1), is embryonic lethal [11,12]. By contrast, essential

Corresponding author: Lee, C.-H. (clee@hsph.harvard.edu).

Keywords: lipid metabolites; lipogenesis; Tregs; PPARs; metabolic flexibility; BAIBA.

Current address: Gene Expression Laboratory, The Salk Institute for Biological Studies, La Jolla, CA 92037, USA

1043-2760/

 http://dx.doi.org/10.1016/j.tem.2014.05.002

Box 1. *De novo* lipogenesis, lipotoxicity, and the Randle hypothesis

Fatty acids, a major component of dietary macronutrients, are normally stored in the form of triacylglyerols which provide energy substrates for cellular metabolism. With the exception of a few essential fatty acids, such as linoleic acid, the human body can synthesize fatty acids *de novo* from carbohydrates. Products of *de novo* lipogenesis are building blocks for complex lipids such as triglycerides and phospholipids. The breakdown intermediates of these lipids accumulate in obesity to generate several classes of lipid metabolites implicated in mediating lipotoxicity. Randle and colleagues proposed a glucose–fatty acid cycle hypothesis in which fat oxidation in the mitochondria generates metabolic signals that block glucose usage through inhibition of glycolytic enzymes [9]. This basic concept of lipotoxicity has been expanded and several underlying mechanisms have been proposed [3]. For example, fatty acids have been shown to activate c-Jun N-terminal kinases, which suppress insulin signaling through inhibitory phosphorylation of insulin receptor substrates 1/2. The metabolites of fatty acids, including diacylglycerol, ceramides, and acyl-carnitines, have all been suggested to decrease insulin sensitivity via different signaling pathways [3,4].

fatty acids are required for normal physiology by virtue of being precursors of signaling molecules such as eicosanoids [4], as will be discussed later.

Although excessive lipid synthesis is causative to metabolic diseases such as hepatic steatosis [13], *de novo* lipogenesis is not always associated with pathology. In the liver, *de novo* lipogenesis promotes the sequestration of detrimental lipid species in lipid droplets, thereby limiting hepatic lipotoxicity [14]. The insulin-sensitizing effect of the thiazolidinedione class of drugs, high-affinity ligands for the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ), is in part mediated by the lipogenic effect of PPARγ activation in adipose tissue (Box 2) [15]. Although these localized beneficial activities of *de novo* lipogenesis are well documented, studies base on mouse genetic models seem to suggest that the effects of *de novo* lipogenic programs extend beyond the tissue boundary.

Forced glucose uptake by adipose tissue through fat-specific overexpression of the glucose transporter Glut4 (Slc2a4) activates the transcription factor carbohydrate response element binding protein β (ChREBP-β, also termed Mlxipl), a protein that, in a glucose-dependent manner, increases the transcription of lipogenic genes in adipose tissue. This leads to an improvement not only in the metabolic profile of adipose tissue but also in peripheral insulin-stimulated glucose uptake [16]. Conversely, adipose tissue-specific deletion of Glut4 impairs insulin sensitivity in both muscle and liver [17]. Further, mice with a double knockout of fatty acid binding proteins Fabp4 and Fabp5 exhibit altered cellular and systemic lipid transport and composition, with enhanced adipose tissue lipogenesis and protection from diet-induced obesity [18]. Activation of *de novo* lipogenesis in the liver also promotes metabolic changes in other tissues. For example, hepatic overexpression of glucokinase or 6-phosphofructo-2-kinase, which drives glucose flux for hepatic lipogenesis, concomitantly promotes muscle fatty acid oxidation [19]. In addition, liver-specific knockout of stearic-CoA desaturase 1 (Scd1), an enzyme that catalyzes a rate-limiting step in the synthesis of unsaturated fatty acids, protects mice from high-carbohydrate diet-induced metabolic disorders as a consequence of suppressed hepatic lipid accumulation and gluconeogenesis and reduced adipose tissue weight [20].

Box 2. PPARs and lipid metabolism

PPARs belong to the nuclear receptor superfamily. They are transcription factors whose activities can be modulated by dietary lipids, notably fatty acids. The three PPARs, PPARα, PPARβ/δ and PPARγ, show distinct tissue distributions and regulate various aspects of lipid metabolism [71]. The best-described functions for these receptors include the adipogenic and insulin-sensitizing effects of PPARγ and regulation of fatty acid catabolism/mitochondrial oxidative metabolism by PPARα and PPARδ in liver and muscle, respectively. In the liver, PPARα and PPARδ exhibit opposing activities in the control of diurnal lipid metabolism. PPARα is upregulated in the fasted state to regulate fat catabolism. By contrast, PPARδ is most active in the fed state and controls the transcription of lipogenic genes.

These early studies provide clues for a link between the lipogenic program and systemic metabolic responses, although how tissue crosstalk in these genetic models is mediated is mostly unclear. The common feature of perturbed *de novo* lipogenesis underlying these mice models points to an unexpected role for lipogenic pathways in the maintenance of systemic metabolic homeostasis. It also raises the possibility that blood-borne factors, likely lipid metabolites, can serve as signaling molecules for inter-organ communication to achieve coordinated energy substrate utilization. In fact, metabolic improvements, including reduced hepatic lipogenesis and enhanced insulin actions in muscle in Fabp4/5 double-knockout mice, were shown to be induced by a lipogenic product originated from adipose tissue (discussed below) [21]. In the following section we discuss recent studies that identify bioactive lipids synthesized *de novo* or derived from dietary fats implicated in such communication.

Lipid metabolites as signaling molecules mediating tissue crosstalk

Liver

Despite ample genetic evidence implicating the hepatic lipogenic pathway in metabolic homeostasis, few lipid mediators have been identified. A notable observation came from hepatic Fasn knockout mice. These mice developed hypoglycemia and fatty liver under a fat-free diet, phenotypes that resemble nuclear receptor PPARα deficiency in the liver. Furthermore, these metabolic defects can be rescued with a synthetic PPARα agonist, suggesting that Fasn is required for the production of endogenous PPARα ligands under fat-free conditions [22]. In a follow-up study, mass spectrometry profiling of liver extracts from wild type or Fasn knockout mice was performed to screen for lipids bound by PPARα [23]. Specifically, phosphocholine PC(16:0/18:1) was identified as a putative PPARα ligand (Figure 1). In fact, PC(16:0/18:1) infusion through the portal vein increased fatty acid oxidation in a PPARα-dependent manner. However, it is interesting to note that, in mice, Fasn and lipogenesis are most active in the dark (feeding) cycle, whereas PPARα is known to control fat catabolism in the light cycle. Thus, further investigation is needed with regard to the role of PC(16:0/18:1) as a PPARα ligand in physiologic feeding/fasting cycles.