Multi-author Review
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Introduction

There is increasing recognition that lipids not only serve important roles as membrane constituents and in energy supply and fuel storage, but also that specific lipids function in regulating a wide variety of cellular processes, including gene expression. The most notable example is that long-chain fatty acids and some oxygenated derivatives can bind and thereby activate nuclear receptor proteins, in particular the so-called peroxisome proliferator activated receptors (PPARs), which in turn influence the expression of specific genes like those involved in lipid metabolism. In this way, fatty acids act as signaling molecules regulating the cellular routes and capacity for lipid utilization.

Another and related development is the disclosure that the level of lipid storage, for instance in adipose tissue, can be sensed by specific constituents. The corollary is that lipid droplets can no longer be viewed as inert intracellular deposits but rather appear dynamic structures able to communicate with other intracellular compartments.

Taken together, a dynamic interplay among lipids, proteins, and membranes is of central importance for the proper physiological regulation of cellular functions. This multi-author review highlights examples of new developments in this emerging field, both with regard to the sensing of lipids and the role of lipids as signaling molecules.

Sensing of lipids

The regulation of lipid intake is incompletely understood. Only recently has it become clear that lipolysis of dietary fat starts already in the oral cavity and is important for the oro-sensory detection of fat [1]. These studies suggest that long-chain fatty acids may be operant in the mechanism, which explains why rodents show a spontaneous preference for dietary lipids. In following up of this notion, Laugerette and co-workers [2] recently discovered that the membrane protein CD36 functions as an oral sensor for long-chain fatty acids in mice and rats. They showed that taste cells express CD36, which interacts with unsaturated long-chain fatty acids, and that this results in a preference for lipid-rich foods. Interestingly, this lipid-CD36 interaction also elicits enhanced pancreatobiliary excretions (bile acid flux and pancreatic juice protein content), indicating interorgan signaling to prepare for the digestion of increased dietary fat [2]. CD36 was already known as an endogenous receptor for various lipid species, including long-chain fatty acids and oxidized low-density lipoproteins [3]. Interestingly, CD36 is also a selective and non-redundant sensor of microbial diacylglycerols that signal via the toll-like receptor 2 [4].

A major question is whether the body is capable of sensing the amount of lipid stored in adipose cells. In this issue, Dugail and Hajduch review the emerging evidence for the existence of such a mechanism. In the last decade it was well established that lipid droplets in adipose cells contain a large variety of associated proteins, including enzymes involved in lipid synthesis and proteins that function in vesicular trafficking. In

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addition, the lipid droplet surface is covered with a phospholipid monolayer containing free cholesterol. The discovery that adipose tissue excretes hormonal factors (cytokines) such as leptin, and that leptin production is linearly correlated to the adipose cell size and lipid loads [5], has led to the suggestion that lipid droplets might actively communicate with other intracellular compartments, thereby regulating the production of leptin and other factors. Dugail and Hajduch propose that during the process of lipid loading, cholesterol is being redistributed in the adipose cell, which redistribution could be sensed by cholesterol sensors in the endoplasmic reticulum. That would lead to activation of sterol responsive element binding protein (SREBP), which in turn would regulate the expression of several proteins. In this concept cholesterol might function as a lipid mediator and second messenger for the intracellular regulation of cell metabolism.

Lipids as signaling molecules

Lipids of both dietary and endogenous origin act as signaling molecules that are implicated in the regulation of whole-body lipid and carbohydrate metabolism. Grimaldi reviews our current understanding of the molecular mechanisms involved in lipid signaling, especially the interaction of fatty acids and fatty acid derivatives with their nuclear receptors, i.e., the so-called peroxisome proliferator-activated receptors (PPARs). Three types of PPARs have been described, PPARα, PPARβ/δ, and PPARγ, with each type showing a characteristic pattern of tissue distribution. While these receptors bind a diversity of fatty acids and fatty acid derivatives, both natural and synthetic compounds have been identified that are selective agonists for the PPAR isotypes. Upon ligand binding PPARs heterodimerize with the retinoid X receptor, whereafter the complex binds to a specific DNA responsive element which is found in a large number of genes encoding proteins functioning in aspects of lipid and carbohydrate metabolism. As a result, PPARs are implicated in several biological processes, such as the regulation of energy metabolism, inflammatory response, and in development.

Recent findings add further levels of complexity to PPAR-mediated regulation of gene transcription. Thus, several co-activators and co-repressors have been identified that interact in a selective manner with the PPAR isotypes. In addition, as reviewed by Wolfrum, the intracellular transport system that transfers fatty acids from the plasma membrane to the nucleus has been found to affect the activity of PPARs by regulating ligand availability. This intracellular ligand transport is facilitated by cytoplasmic fatty acid binding proteins (FABPs) of which nine distinct types exist [6]. The fine interplay among these various ligands, proteins, and interaction partners in the distinct tissues will determine the metabolic activity of that tissue, especially in terms of lipid uptake, storage, and utilization. Due to this complexity, the mechanisms involved are only beginning to be understood. However, on the basis of detailed studies in adipose tissue it has been suggested that PPARβ/δ and PPARγ function in modulating the number of adipose cells and the amount of stored triacylglycerols to adapt the total adipose tissue storage capacity to the level of fatty acid supply [7]. These new insights clearly illustrate the central role of PPARs in whole body lipid metabolism. Very recently, evidence has been obtained for a role of PPARs in the brain. It was found that a physiological elevation in circulating lipids can be sensed within the hypothalamus, a brain region that is involved in eating behaviour [8].

Analogous to the action of fatty acids as regulators of gene transcription through activation of PPARs, it was found that fatty acids also activate specific nuclear receptors to regulate the expression of specific genes and modulate metabolic pathways. As outlined in the review by Scotti and co-workers, the molecular mechanism involved in bile acid regulation of gene transcription appears similar to that of fatty acids and PPARs. Bile acids will bind to the bile acid receptor, farnesoid X receptor, which is expressed in different tissues, especially those involved in the entero-hepatic circulation. After heterodimerization with the retinoid X receptor, the complex will bind to bile acid responsive elements that are found in a variety of genes. In this way, bile acids up- or downregulate the expression of a number of genes, not only those involved in bile acid homeostasis but, interestingly, also those involved in lipid and glucose metabolism. For instance, bile acids affect the expression of SREBP-1c which, in turn, controls the rate of fatty acid synthesis and thus affects hepatic triacylglycerol production and secretion. In addition, a membrane bile acid receptor has been discovered which acts as a G-protein-coupled receptor and may be part of a bile acid signaling pathway that plays a role among others in the fine-tuning of energy homeostasis [9].

Factors affecting lipid signaling

The involvement of lipids in signaling processes implies that factors determining lipid availability will also influence lipid signaling. An example of this was already mentioned above, namely that cytoplasmic FABP facilitates the delivery of fatty acids for PPAR

activation. Similarly, the plasma membrane contains specialized micro/nano domains, the so-called lipid rafts, which act as platforms regulating the induction of signaling pathways [10]. These new developments are reviewed by Hullin-Matsuda and Kobayashi, who describe plasma membrane domains enriched in sphingolipids and cholesterol that are capable of recruiting or excluding specific lipids or proteins. The current concept is that by keeping receptors, enzymes, and other signaling components in a restricted domain, lipid rafts induce a more rapid and efficient coupling. Essential for their role in signal transduction is that membrane domains are dynamic structures in which lipids and proteins can move with different kinetics. In this way, lipid rafts provide regulation by lateral compartmentalization.

Conclusions and future prospects

Lipid signaling and lipid-dependent gene expression already have become areas of much interest, while new insights into the sensing of lipids is an emerging topic. These developments clearly establish the importance of lipids beyond their functions as structural components and in the provision and efficient storage of energy. The examples described in this multi-author review show that fatty acids, fatty acid derivatives, and bile acids regulate a wide range of cellular functions by acting through various signaling cascades. Therefore, lipid signaling should be regarded as an integrated part of whole-body homeostasis.

Abnormalities in lipid-mediated signaling may lead to cellular malfunctioning and to disease states. Such abnormalities may be caused by changes in any of the components that are involved, i.e., availability of the signaling molecule, the receptor, or the presence of inhibiting or activating cofactors. On the other hand, excess lipids are commonly associated with disease, especially related to excess lipid intake associated with a western life style. Cholesterol accumulating in the vessel wall is central in the etiology of atherosclerosis and the development of coronary artery disease. Obesity, which is the result of enhanced lipid storage in the body, develops in many cases into non-insulin-dependent diabetes mellitus (type-2 diabetes). Such disease conditions affect whole-body lipid metabolism and may also influence signaling cascades involving lipids.

Although the fine interplay between lipid signaling, lipid storage, and whole-body lipid metabolism is only beginning to be understood, the new insights obtained so far on the molecular mechanisms involved have already opened new perspectives for the therapy of disease. In particular, the occurrence of specific types of nuclear receptors that show high ligand selectivity makes these receptors useful targets for pharmacological therapy. For instance, PPARγ agonists are commonly applied in diabetes therapy [11], while FXR agonists are considered as a therapeutic target for bile acid and lipid disorders [12]. Taken together, lipid sensing and lipid sensors can be expected to remain an area of intense scientific research in the coming years.

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