Fat for life: new stories on old grease

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Due to the alarming epidemic in the modern world of obesity, dyslipidemia, and the parallel increasing prevalence of the related metabolic and cardiovascular diseases such as type 2 diabetes and atherosclerosis, the neutral lipids triglycerides and cholesteryl esters have a notorious reputation. The excessive accumulation of triglycerides reflects energy surplus, which ultimately causes the excessive adiposity that leads to obesity; in addition, the deposition of cholesteryl esters in the artery walls is an inevitable step for the fatty plaque formation hastening the development of atherosclerosis. Prevention and treatment of neutral lipid-related metabolic and cardiovascular diseases are major challenges for modern medicine.

For many years, neutral lipids had been misperceived as “boring grease”. The primary reason is that these lipids are extremely hydrophobic. As a result, the biochemical studies regarding the synthesis and degradation of neutral lipids as well as the elucidation of their metabolic function were largely at the descriptive level. Enzymes involved in the metabolic flux of these lipids are often either intrinsic membrane proteins or favor an extremely hydrophobic environment, which has historically been difficult to isolate through traditional protein purification techniques. Fortunately, in the last two decades, powered with the revolution and the elegant combined use of methodologies in biochemistry, molecular biology, bioinformatics, cell biology, and forward and reverse genetics, we have witnessed an impressive transformation of the neutral lipid field. Today, many steps, if not all, of the neutral lipid metabolic pathways have been revealed in molecular detail. In addition, along with the improved analytic tools, the previously underappreciated complexity of neutral lipids has also started to be revealed. Cases have been identified that establish the relationship between specific species of neutral lipids and specific disease states. The purpose of this review series is to highlight such progress. Because of the richness of the science and the expansion of the field, nine excellent reviews have been divided into four separate parts, each of which will be published in this Journal over the next four consecutive issues.

Part I: Pathways for De Novo Triglyceride Synthesis and Assimilation of Exogenous Dietary Fat

In eukaryotes, triglycerides are synthesized through two major pathways, the glycerol phosphate pathway and the monoacylglycerol pathway. The glycerol phosphate pathway is believed to be present in the majority of cells and responsible for the de novo synthesis of triglycerides. In contrast, the monoacylglycerol pathway is known to play a major role in the small intestine for the absorption of exogenous dietary fat. The review by Drs. Takeuchi and Reue (7) details the complexity of the biochemistry and genetics of the glycerol phosphate pathway. The first committed step for this pathway is the acylation of glycerol-3-phosphate by glycerol phosphate acyltransferase (GPAT). A second fatty acid moiety is subsequently transferred to lysophosphatidic acid by acylglycerol-phosphate acyltransferase (AGPAT) to produce phosphatidate, which in turn is converted to diacylglycerol through the action of phosphatidate phosphatase (PAP). PAP enzyme activity is conferred by the lipin protein family. Diacylglycerol can either be further acylated by diacylglycerol acyltransferase (DGAT) to synthesize triglyceride or be used in phospholipid synthesis through the Kennedy pathway. In this review, the authors focus on three protein families: GPAT, AGPAT, and PAP enzymes.

In the second review, Drs. Iqbal and Hussain (3) discuss the recent progress in the dietary fat absorption pathway. The major species of dietary fat is triglyceride. The remaining portion is comprised of a wide array of polar and nonpolar lipids, such as phospholipids, sterols, and many minor lipids including fat-soluble vitamins. The complicated process of dietary fat digestion and absorption can be divided into four sequential steps: the emulsification and hydrolysis of dietary fat in the lumen of the intestine, the uptake of hydrolyzed products by enterocytes, the resynthesis and packaging of fat into lipoproteins in the enterocytes, and last, the secretion of lipoproteins into circulation. In this context, the authors update the current knowledge pertaining to intestinal lipid absorption.

Part II: Membrane Enzymes Crucial for the Synthesis of Triglycerides and Cholesteryl Esters

The second section will contain reviews regarding two types of membrane-associated enzymes known to be critical for the synthesis of triglycerides and cholesteryl esters: membrane-bound acyltransferases, which are intimately involved with the formation of neutral lipids and stearoyl-CoA desaturases (SCDs), whose function is to introduce double bonds to saturated long-chain fatty acids but is also believed to have a profound impact on neutral lipid synthesis. Membrane-bound acyl-CoA:cholesterol acyltransferase (ACAT), acyl-CoA:diacylglycerol acyltransferase (DGAT), and acyl-CoA:monoacylglycerol acyltransferase (MGAT) are enzymes responsible for the synthesis of the neutral lipids cholesteryl ester, triglyceride, and diacylglycerols, respectively. Albeit discovered more than 40 years ago, the molecular elucidation of these enzymes began only about 15 years ago by the landmark molecular cloning of ACAT1. In mammals, two ACAT isoforms exist, ACAT1 and ACAT2, which are encoded by two different genes. ACATs play important roles in cellular cholesterol homeostasis in various tissues. In the first review, Drs. Chang, Li, Chang, and Urano (1) review the current knowledge on ACAT-related research in two areas: 1) ACAT genes and proteins and 2) ACAT enzymes as drug targets for atherosclerosis and for Alzheimer’s disease. In the second review, Drs. Shi and Cheng (6) cover the recent progress of molecular and...
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functional elucidation of mammalian DGAT and MGAT enzymes. The metabolic complexity of triglyceride synthesis is reflected by the presence of multiple isoforms of DGAT and MGAT enzymes. To date, two DGATs and three MGATs have been identified, which have distinct catalytic properties, subcellular localization, and tissue distribution and are believed to have multiple functions, such as intestinal fat absorption, lipoprotein assembly, adipose tissue formation, signal transduction, satiety, and lactation. Recent data from studies using knockout mice also indicate that selective inhibition of MGAT or DGAT enzymes may provide novel strategies for treating obesity and related metabolic diseases. The third review, by Drs. Turkish and Sturley (8), highlights the genetic dissections of neutral lipid function in a variety of model systems, including yeast, fly, worm, and mouse. This review provides a philosophical perspective about how and why neutral lipids exist as an important class of lipid for the organism. In addition to triglyceride and cholesteryl ester, two types of neutral lipids that are emphasized in other reviews, the authors also discuss acyl-CoA: wax alcohol acyltransferase (AWAT), another membrane-bound acyltransferase that is responsible for the synthesis of wax esters and which is believed to play an important role in maintaining skin integrity.

The last review in Part II, by Drs. Paton and Nambi (4), covers the topic of SCD. SCD is an enzyme that catalyzes the Δ⁹-cis desaturation of a wide range of long-chain fatty acyl-CoA substrates. Characterization of SCD1-deficient mice has revealed the essential role of de novo synthesized oleate in the formation of many neutral lipids, including cholesteryl esters, triglycerides, and wax esters. In addition, SCD1 deletion in mice also leads to a reduction of body weight, decreased adiposity, improved lipid profile, and increased insulin sensitivity, thereby establishing SCD1 as a putative pharmaceutical target for the treatment of diabetes and obesity.

Part III: Lipolytic Degradation of Neutral Lipids and Its Metabolic Implication

In contrast to the preceding two parts, which focus on the synthesis of neutral lipids, Part III deals with lipolytic degradation pathways for neutral lipids. Depending on the locale of the neutral lipids, they can be degraded either extracellularly, such as in the plasma, or intracellularly, such as within the adipocyte. In the first review in this section, Drs. Wang and Eckel (9) review the current state of knowledge regarding lipoprotein lipase (LPL), an extracellular lipase. Although many tissues synthesize this enzyme, LPL functions in the capillary endothelium. LPL is the primary enzyme responsible for the hydrolysis of the triglyceride core of chylomicrons and very-low-density lipoproteins. The resulting free fatty acids and monoacylglycerols are subsequently taken up by the local adjacent tissues for various functions. Unique to LPL, this lipase exerts critical functions in both the anabolic and catabolic phases of triglyceride metabolism and, hence, is divergently regulated by different metabolic cues in a tissue-specific manner. The mechanisms pertaining to the regulation and physiological implications for LPL have been revealed by various transgenic and knockout models that are systematically reviewed by the authors.

The review by Drs. Schweiger, Lass, Zimmermann, and Zechner (5) delves into a recently discovered aspect of the intracellular lipolytic pathway in adipose tissue. The discussion is focused on adipose triglyceride lipase (ATGL) and its regulator CGI-58/ABHD5. For many years, hormone-sensitive lipase (HSL) was thought to be the only significant lipase in white adipose tissue (WAT) responding to catabolic hormones. However, recent cloning and knockout data indicate that ATGL is an additional essential player for lipolysis in WAT. Interestingly, ATGL is activated by its partner CGI-58/ABHD5, an adiposome-associated protein. In their review, the authors present an extended discussion of recent data showing that mutations in ATGL gene and CGI-58/ABHD5 lead to various forms of neutral lipid storage disease (NLSD) in human patients, further indicating that the ATGL-mediated lipolytic system serves a pivotal role in neutral lipid metabolism.

Part IV: Analytic Examples of Complexity of Neutral Lipid Species

In the final part of this cluster of reviews on neutral lipids, Drs. Gross and Han (2) discuss the application of shotgun lipidomics, a novel mass spectrometry-based technology, in elucidating the previously underappreciated complexity of neutral lipids. The power of shotgun lipidomics lies in its high sensitivity and its exquisite discerning ability. The review first summarizes the basic principles of shotgun lipidomics. The discussion emphasizes the technical breakthroughs for the analysis of neutral lipids, which were previously difficult to analyze by mass spectrometry. In the second part, specific illustrative cases are discussed regarding the identification of subpopulations of lipids and their relationship to the disease or physiological states.

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