Molecular Enzymology and Drug Targets

Extended Abstract
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Metabolomics has been increasingly recognized as an enabling technique with the potential to identify key metabolomic features in an attempt to understand the pathophysiology and differentiate different stages of Coronary Heart Disease (CHD). We performed comprehensive metabolomic analysis in human plasma from 28 human subjects with Stable Angina (SA), Myocardial Infarction (MI), and Healthy Control (HC). Subsequent analysis demonstrated a uniquely altered metabolic profile in these CHD: a total of 18, 37 and 36 differential metabolites were identified to distinguish SA from HC, MI from SA, and MI from HC groups respectively. Among these metabolites, glycerophospholipid (GPL) metabolism emerged as the most significantly disturbed pathway. We used a targeted metabolomic approach to systematically analyse GPL, oxidized phospholipid (oxPL), and downstream metabolites derived from polyunsaturated fatty acids (PUFAs), such as arachidonic acid and linoleic acid. Surprisingly, lipids associated with lipid peroxidation (LPO) pathways including oxidized PL and isoprostanes, isomers of prostaglandins, were significantly elevated in plasma of MI patients comparing to HC and SA, consistent with the notion that oxidative stress-induced LPO is a prominent feature in CHD. Optical coherence tomography (OCT) has been considered as the ideal tool for the evaluation of atherosclerotic plaques. Circulating trimethylamine-N-oxide (TMAO), which is a metabolite of the dietary lipid phosphatidylcholine by gut microbiota, has recently been linked to elevated CHD risk. A total of 26 patients with CAD were recruited to assess coronary plaque using OCT and measure plasma TMAO level. According to plaque rupture status, patients were divided into plaque rupture group (n=12) and non-plaque rupture group (n=14). Plasma TMAO level was significantly higher in patients with plaque rupture than in those with non-plaque rupture (8.6±4.8 μmol/L vs. 4.2±2.4 μmol/L, p=0.011). In conclusion, circulating TMAO level may reflect coronary plaque vulnerability and progression. Lipid metabolism is the synthesis and degradation of lipids in cells, involving the breakdown or storage of fats for energy and the synthesis of structural and functional lipids, such as those involved in the construction of cell membranes. In animals, these fats are obtained from food or are synthesized by the liver. Lipogenesis is the process of synthesizing these fats.The majority of lipids found in the human body from ingesting food are triglycerides and cholesterol. Other types of lipids found in the body are fatty acids and membrane lipids. Lipid metabolism is often considered as the digestion and absorption process of dietary fat; however, there are two sources of fats that organisms can use to obtain energy: from consumed dietary fats and from stored fat. Vertebrates (including humans) use both sources of fat to produce energy for organs such as the heart to function. Since lipids are hydrophobic molecules, they need to be solubilized before their metabolism can begin. Lipid metabolism often begins with hydrolysis which occurs with the help of various enzymes in the digestive system. Lipid metabolism also occurs in plants, though the processes differ in some ways when compared to animals. The second step after the hydrolysis is the absorption of the fatty acids into the epithelial cells of the intestinal wall. In the epithelial cells, fatty acids are packaged and transported to the rest of the body. Digestion is the first step to lipid metabolism, and it is the process of breaking the triglycerides down into smaller monoglyceride units with the help of lipase enzymes. Digestion of fats begin in the mouth through chemical digestion by lingual lipase. Ingested cholesterol is not broken down by the lipases and stays intact until it enters the epithelium cells of small intestine. Lipids then continue to the stomach where chemical digestion continues by gastric lipase and mechanical digestion begins (peristalsis). The majority of lipid digestion and absorption, however, occurs once the fats reach the small intestines. The second step in lipid metabolism is absorption of fats. Short chain fatty acids can be absorbed in the stomach. While most absorption of fats occurs only in the small intestines. Once the triglycerides are broken down into individual fatty acids and glycerols, along with cholesterol, they will aggregate into structures called micelles. Fatty acids and monoglycerides leave the micelles and diffuse across the membrane to enter the intestinal epithelial cells. Due to the hydrophobic nature of membrane lipids, triglycerides and cholesterols, they require special transport proteins known as lipoproteins. The amphipathic structure of lipoproteins allows the tryglycerols and cholesterol to be transported through the blood. Chylomicrons are one sub-group of lipoproteins which carry the digested lipids from small intestine to the rest of the body. Triacylglycerols, lipid membrane and cholesterol can be synthesized by the organisms through various pathways. There are two major classes of membrane lipids: glycerophospholipids and sphingolipids. Although many different membrane lipids are synthesized in our body, pathways share the same pattern. The first step is synthesizing the backbone (sphingosine or glycerol), the second step is the addition of fatty acids to the backbone to make phosphatidic acid. Phosphatidic acid is further modified with the attachment of different hydrophilic head groups to the backbone. The phosphatidic acid is also a precursor for triglyceride biosynthesis. Phosphatidic acid phosphotasecatalyzes the conversion of phosphatidic acid to diacylglyceride, which will be converted to triacylglyceride by acyltransferase. Tryglyceride biosynthesis occurs in the cytosol. The precursor for fatty acids is acetyl-CoA and it occurs in the cytosol of the cell. The overall net reaction, using palmitate (16:0) as a model substrate is: 8 Acetyl-coA + 7 ATP + 14 NADPH + 6H+ □ palmitate + 14 NADP+ + 6H2O + 7ADP + 7Pi. Lipid metabolism disorders (including inborn errors of lipid metabolism) are illnesses where trouble occurs in breaking down or synthesizing fats (or fat-like substances). Lipid metabolism disorders

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are associated with an increase in the concentrations of plasma lipids in the blood such as LDL cholesterol, VLDL, and triglycerides which most commonly lead to cardiovascular diseases.

Biography

LeminZheng has completed his PhD in 2005 from Cleveland Clinic/ Cleveland State University in Clinical/BioanalyticalChem- istry. Currently, he is the Lab Director and Professor in Institute of Cardiovascular Sciences, Peking University (China), Key Laboratory of Molecular Cardiovascular Science of Ministry of Education. His main field of research is lipoprotein, lipids, vas- cular function and bio-material. He has published more than 60 papers in reputed journals, such as the Journal of Clinical Investigation, Clin. Cancer Res. Advanced Functional Materials, Nanoscale, ACS APPL MATER INTERFACES, Free Radical Biol- ogy and Medicine, JAHA, International Journal of Cardiology, BBA-Molecular and Cell Biology of Lipids, JBC, Nature Structural & Molecular Biology, ATVB, Int. J Cancer, CardiovascDiabetol, Journal of Translational Medicine, AJP, etc. He has more than 1600 SCI citations. He has served as an Editorial Board Member of Cardiovascular &Hematological Disorders - Drug Targets, and Lipid & Cardiovascular Research. He has a US patent.

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