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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, King-Wah Chiu is a Distinguished Professor at the Cheng Shui University in Kaohsiung, Taiwan, Republic of China. Having received his Bachelor's degree from China Medical University College of Medicine in 1985, he rose to Chief in the Gastroenterology Division of the Kaohsiung Chang Gung Memorial Hospital Affiliated to Chang Gung University of College of Medicine in 2002. Dr. Chiu is a recognized expert in hepato-gastroenterology, having practiced for 30 years, and the pioneer of transplant hepatology in the field of liver transplantation, practicing in Kaohsiung Chang Gung Memorial Hospital since 1998. His ongoing research interests involve the application of molecular biology in transplant hepatology, particularly to study the effects of integrative basic medicine on and management of living-donor liver transplantation establishment. (L-Editor: Filipodia)

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MINIREVIEWS

Lipidome is lipids regulator in gastrointestinal tract and it is a life collar in COVID-19: A review

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Abstract

The term lipidome is mentioned to the total amount of the lipids inside the biological cells. The lipid enters the human gastrointestinal tract through external source and internal source. The absorption pathway of lipids in the gastrointestinal tract has many ways; the 1st way, the lipid molecules are digested in the lumen before go through the enterocytes, digested products are re-esterified into complex lipid molecules. The 2nd way, the intracellular lipids are accumulated into lipoproteins (chylomicrons) which transport lipids throughout the whole body. The lipids are re-synthesis again inside the human body where the gastrointestinal lipids are: (1) Transferred into the endoplasmic reticulum; (2) Collected as lipoproteins such as chylomicrons; or (3) Stored as lipid droplets in the cytosol. The lipids play an important role in many stages of the viral replication cycle. The specific lipid change occurs during viral infection in advanced viral replication cycle. There are 47 lipids within 11 lipid classes were significantly disturbed after viral infection. The virus connects with blood-borne lipoproteins and apolipoprotein E to change viral infectivity. The viral interest is cholesterol- and lipid raft-dependent molecules. In conclusion, lipidome is important in gastrointestinal fat absorption and coronavirus disease 2019 (COVID-19) infection so lipidome is basic in gut metabolism and in COVID-19 infection success.

Key Words: Lipidome; Gastrointestinal tract; Fat metabolism; COVID-19; Viral infection; Future therapy

Core Tip: The lipidome is mentioned to the total amount of the lipids inside the biological cells. The lipid enters the human gastrointestinal tract through external

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source and internal source. The tissue distribution of lipid is completely different among different species. The lipids play an important role in many stages of the viral replication cycle. The specific lipid change occurs during viral infection. The virus connects with blood-borne lipoproteins and apolipoprotein E. The viral interest is cholesterol- and lipid raft-dependent molecules. This review focuses on the important of lipidome in both gastrointestinal fat absorption and coronavirus disease 2019 infection.

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INTRODUCTION

The term lipidome or lipidomic is mentioned to the total amount of the lipids inside the biological cells. There are 4 principal constituents occurs inside the biological cells or organs and these 4 constituents are lipids, proteins, sugars and nucleic acids. Lipids are the most important compounds in the living organisms, where they build blocks for cellular membranes, energy storage, and signaling molecules. The technique used in lipidome is generally mass spectrometry (MS)[1]. Lipid metabolism plays an important role in the regulation of cellular homeostasis. Lipid compositions are often used to evaluate lipid metabolism though the application of lipodome[2]. The lipidome or lipidomic is one of the omics science applies in modern biology[3]. There are a tight correlation between lipidomic, metabolomics, genomic and proteomic especially in protective and therapeutic studies[4-6]. Figure 1 explores different types of omics. The lipidome technique applies either by MS or by bioinformatics or ordinary lab-based methods[7,8]. The repeated doses of the drug to micro-tissues lead to collect lipid molecules for 5 time points (2, 4, 7, 9, and 11 d) and hepatotoxic effect occurs[9]. The absorption pathway of lipids in the gastrointestinal tract has many ways; the 1st way, the lipid molecules are digested in the lumen before go through the enterocytes (inside the enterocytes), digested products are re-esterified into complex lipid molecules. The 2nd way, the intracellular lipids are accumulated into lipoproteins (chylomicrons) which transport lipids throughout the whole body[10]. The chylomicrons carrying most of lipids which secreted into the intercellular space, then into the lamina propria, then the lipids enter into the lacteals, and then into the lymphatic system. Thus, the gastrointestinal lymphatic system has a principal role in the absorption of lipids[11-13]. The gastrointestinal lipid metabolism is important to supply of energy (in the form of lipids) to the different organs in the body where the defects in the process of lipid absorption can lead to severe pathological diseases.

Coronavirus disease 2019 (COVID-19) is the last coronavirus outbreak. Coronavirus is derived its name from Latin corona word. Corona virus is first discovered in 1930, while first diagnostic in 1940 in animal models. The first human case of coronavirus is reported in China in 2003 but the COVID-19 was discovered in 2019. This is 3rd serious coronavirus outbreak during the last 20 years, after severe acute respiratory syndrome-related coronavirus (SARS-CoV) in 2002-2003 and Middle East respiratory syndrome-related coronavirus (MERS-CoV) in 2012[14]. There are 7 coronaviruses induce human infections (4 of which, cause cold symptoms in humans while the other 3 coronaviruses called SARS-CoV, MERS-CoV, and COVID-19) cause severe respiratory illness[15]. The coronavirus RNA genome size = 27-34 kilo-bases and this size is the largest RNA genome size. The life cycle of coronavirus is summarized into 3 successive steps: (1) Viral entry; (2) Viral replication; and (3) Viral release. The transmission of COVID-19 in human is occurred though a specific connection process between viral protein and host cell receptor. There are 4 types of coronavirus: (1) *Alphacoronavirus*; (2) *Betacoronavirus*; (3) *Gammacoronavirus*; and (4) *Deltacoronavirus*. Table 1 reveals different genus of coronaviruses. *Betacoronavirus* is the dangerous one because it contains Human coronavirus *e.g.*,., COVID-19, MERS, and severe acute respiratory syndrome-related coronavirus-2 (SARS-CoV-2, SARS-CoV-2). In COVID-19 cases, the attention of blood safety is recommended where coronaviruses have globally arisen especially in endemic areas[16].

Table 1 Different genus of coronaviruses

Coronaviruses	Genus	Type species	Species
Coronaviruses	Alphacoronavirus	Alphacoronavirus 1	Alphacoronavirus 1
			Human coronavirus 229E
			Human coronavirus NL63
			Miniopterus bat coronavirus 1
			Miniopterus bat coronavirus HKU8
			Porcine epidemic diarrhea virus
			Rhinolophus bat coronavirus HKU2
			Scotophilus bat coronavirus 512
	Betacoronavirus	Murine coronavirus	Betacoronavirus 1 (Bovine , Human coronavirus OC43)
			Hedgehog coronavirus 1
			Human coronavirus HKU1
			MERS-CoV
			Murine coronavirus
			Pipistrellus bat coronavirus HKU5
			Rousettus bat coronavirus HKU9
			SARS-CoV, SARS-CoV-2
			Tylonycteris bat coronavirus HKU4
	Gammacoronavirus	Avian coronavirus	Avian coronavirus
			Beluga whale coronavirus SW1
	Deltacoronavirus	Bulbul coronavirus	Bulbul coronavirus HKU11
			Porcine coronavirus HKU15

MERS-CoV: Middle East respiratory syndrome-related coronavirus; SARS-CoV: Severe acute respiratory syndrome-related coronavirus.

The aim of this review is to provide a link between the lipid important in both gastrointestinal fat absorption and COVID-19 infection success. So, this review deals with lipidome in gastrointestinal metabolism and in COVID-19 infection success.

GASTROINTESTINAL UPTAKE OF LIPIDS

The lipid enters the human gastrointestinal tract through 2 sources; external source such as dietary food and internal source such as enterocytes emerge from the gastrointestinal mucosa and from liver bile[17]. The dietary lipids include non-polar lipids, triacylglycerols, cholesterol esters, and polar phospholipids. The liver bile lipids are dissolved in bile acid (include cholesterols and phospholipids). In the gut, the external lipids in diet are hydrolysis by gut lipase to diacylglycerols and fatty acids. The gastrointestinal lipids such as high density lipoproteins, very low density lipoprotein excretion, cytosolic lipid drops and fatty acid oxidation are also included in gastrointestinal lipids[18]. The lipids, as well as, proteins and mucins adhere to plastic particles such as polyvinyl chloride, polyethylene, polyethylene terephthalate polypropylene, and polystyrene. The human gastrointestinal tract do not decays these particles[19]. The high lipid containing-diet for 1 d declined the number of small intestinal intraepithelial lymphocytes and lamina propria lymphocytes. The effect of high lipid containing-diet on the intestinal immune system was independent of the gut microbes. The oral intake of free fatty acids declined the number of small intestinal intraepithelial lymphocytes and lamina propria lymphocytes. So, free fatty acids damaged the intestines and intestinal lipotoxicity occurred as in the case of colorectal cancer or food allergy[20]. The deficiency of fatty acid lead to tissue-resident memory T (Trm) cells death. The gastric adenocarcinoma cells pushed Trm cells for lipid uptake

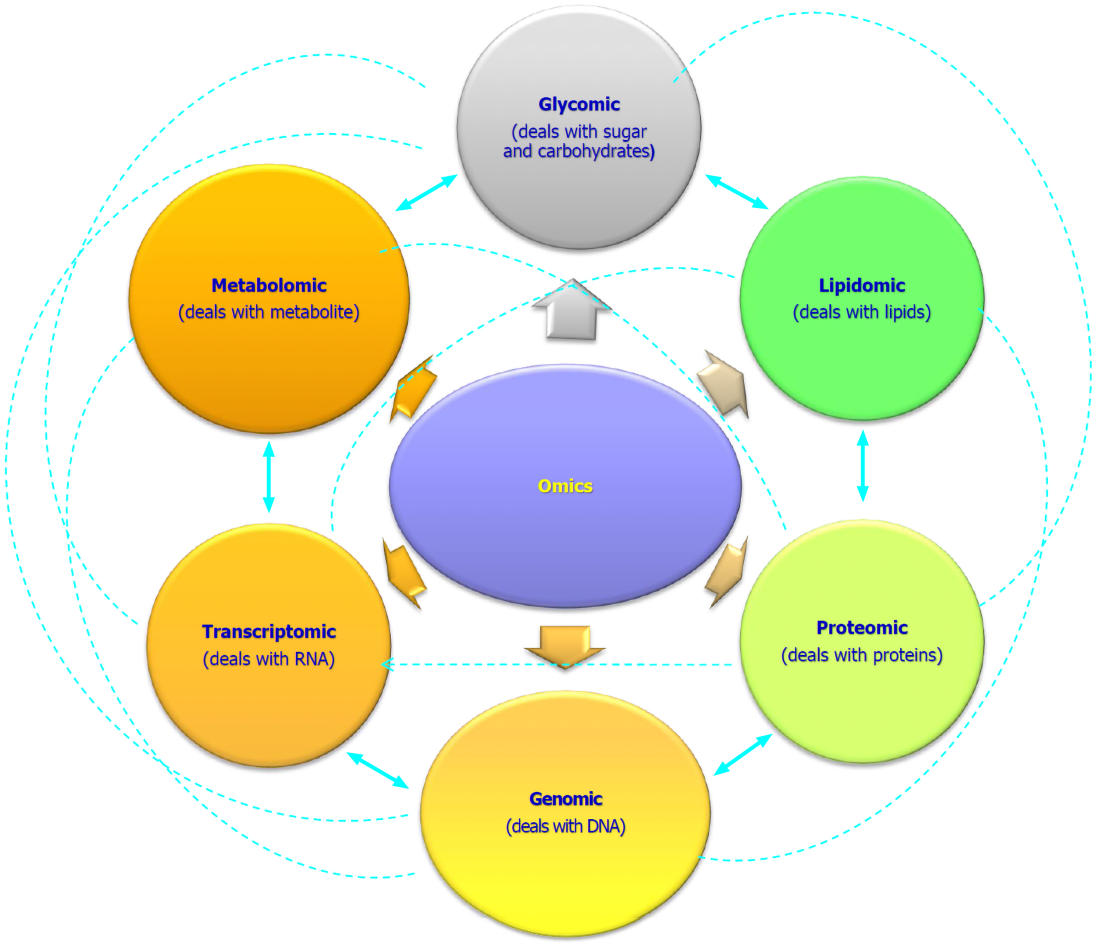

Figure 1 Different types of omics.

and caused Trm cell death[21]. The cancer-associated fibroblasts, through lipidomic technique, accumulate more fatty acids and phospholipids in colorectal cancer cells that plays a principal role in colorectal cancer progress. The fatty acids synthase enzyme, which increased fatty acids synthesis, is considerably increased in cancer-associated fibroblasts[22]. The lipidomics technique in dextran sulfate sodium-induced intestinal barrier dysfunction inhibited the transport and uptake of most of bee pollen lipids such as glycerophospholipids, sphingomyelins, and glycosylsphingolipids. The administration with bee pollen lipids controlled glycerophospholipid and sphingolipid metabolisms that correlated with gastrointestinal permeability barriers and improving gastrointestinal oxidative stress[23]. The gastrointestinal-fatty acid binding protein connected with high-fat diet, leads to changes in gut motility and morphology which caused thinner phenotype occurring at the human whole body. So, gastrointestinal-fatty acid binding protein is incorporated in dietary lipid sensing and signaling which effecting gastrointestinal motility, intestinal configuration, and nutrient absorption and consequently effecting total energy metabolism[24].

GASTROINTESTINAL UPTAKE OF FATTY ACIDS

Fatty acids are uptake by the gastrointestinal tract through 2 ways; the 1st way, fatty acids transfer from the intestinal membrane from higher concentration to lower concentration inside the cell while the 2nd way occurs from the cell to the lumen when the fatty acids concentration inside the cell is higher than lumen fatty acids concentration. The gastrointestinal bile acids are essential for the conservation of their enterohepatic flow. Most of the bile acids are absorbed by gastrointestinal tract *via* certain carrier proteins. These proteins are up-regulate in the distal ileum. The bile acids uptake by gastrointestinal cells reduces the stimulation of cytosolic and membrane receptors (farnesoid X receptor and guanine nucleotide-binding proteins-coupled bile acid receptor 1). These receptors effect on hepatic synthesis of bile acids,

glucose, and lipid metabolism. The increase in bile acid absorption leads to the pathophysiology of liver and metabolic disorders such as fatty liver diseases and type 2 diabetes mellitus[25]. Short-chain fatty acids *e.g.*,. butyrates are bacterial metabolites formed in the gastrointestinal tract and these fatty acids are benefit for host cells. These short-chain fatty acids are stimulators of gastrointestinal cellular gene expression. The propionate and butyrate exert higher efficacy for controlling cell differentiation and gene expression[26]. The tumor necrosis factor-α (TNF-α) is an inflammatory agent associated with gastrointestinal inflammation while omega-3 polyunsaturated fatty acids exert anti-inflammatory activities and stop TNF-α inhibition of sugar uptake by gastrointestinal tract in the human colon cancer cell line (Caco-2). In Caco-2 cancer cells, TNF-α reduces glutamine uptake which counteracts by pro-resolving lipid mediators. So, pro-resolving lipid mediators are favorable biomolecules to restore intestinal nutrients transport during intestinal inflammation[27]. The long-chain fatty acids uptake is an essential physiological process that controls cellular energy homeostasis. The 5' adenosine monophosphate-activated protein kinase accelerates the gastrointestinal long-chain fatty acids uptake by up-regulating human protein is encoded by the CD36 gene (CD36 protein) and stimulating its membrane translocation in the same time[28]. The metabolite of intestinal microbes (TMAVA) level increased in plasma from subjects with liver steatosis compared with controls. The TMAVA declined synthesis of carnitine. The TMAVA changed fecal microbiomes and declined cold tolerance. The TMAVA decreased plasma and liver levels of carnitine and acyl-carnitine. The hepatocytes possessed lower liver fatty acid oxidation. The high fat diet stimulated liver steatosis which declined by carnitine administration. The decrease levels of carnitine and fatty acid oxidation leads to the increase of uptake and liver accumulation of free fatty acids[29]. The colorectal cancer is correlated with the change of fatty acids level in serum and tumor tissues. The colorectal cancer tissues had higher levels of polyunsaturated fatty acids than normal large intestinal mucosa. The change in tumor and serum polyunsaturated fatty acids level is due to the uptake of these fatty acids by cancer cells. The polyunsaturated fatty acids are essential for formation of cell membrane phospholipids during rapid multiplying of cancer cells[30]. The fatty acid system possessed a memory. The memory of the fatty acid system consists of small intestine enterocytes [CD36, scavenger receptor class B type 1, long-chain fatty acid transport protein 4 (FATP4), fatty acid-binding protein 1 (FABP1), FABP2] and hepatocytes. In these cells, the short-term memory fatty acids are found. These short-term fatty acids consist of cytoplasmic lipid droplet cycles. The short-term memory of enterocytes and hepatocytes are united together to form long-term fatty acids memory. These long-term fatty acids memory are found in the adipocyte and in cellular membranes. The formation of fatty acids memory depend on sensing environmental material, encoding, consolidation, long-term storage, retrieval, re-encoding, re-consolidation, and renewed long-term storage[31]. The gastrointestinal microbiome controls many homeostatic processes in the healthy host such as immune function and gut barrier protection. Loss of normal gastrointestinal microbial configuration and function correlated with diseases such as clostridioides difficile infection, asthma, and epilepsy. The change of gastrointestinal microbiome stimulate sepsis by many processes such as: (1) Stimulates pathogenic intestinal bacteria; (2) Instructs the immune system for inflammatory response; and (3) Decreases section of beneficial microbial products such as short-chain fatty acids[32]. 2 meal/d against 12 meal/d declined peri-renal fat weight and serum triglyceride and liposaccharide levels in high fat diet-fed pigs. The decline of meal frequncy down-regulated mRNA expression of lipoprotein lipase, CD36 molecule, interleukin 1 beta, tumor necrosis factor alpha, toll-like receptor 4, myeloid differentiation factor 88, and nuclear factor kappa beta 1 as well as protein expression of myeloid differentiation primary response 88 (MYD88) in perirenal fat of high fat diet-fed pigs. So, the 2 meal/d against the 12 meal/d enhanced high fat diet-induced fat deposition and inflammatory response by decreasing fatty acid uptake[33].

GASTROINTESTINAL UPTAKE OF CHOLESTEROL

The aryl hydrocarbon receptor (AHR) modifies hepatic expression of cholesterol synthesis. Niemann-Pick C1-like intracellular cholesterol transporter (NPC1L1) facilitates the intestinal absorption of dietary cholesterol. The transcription of NPC1L1 involved in the cholesterol synthesis pathway is controlled by sterol-regulatory element-binding protein-2. So, the AHR possessed a role in the homeostatic regulation of cholesterol synthesis and absorption which referred to the application of this

receptor in the treatment of hyperlipidosis-associated metabolic diseases[34]. The decrease of gastrointestinal microbiota diminished albuminuria and tubulointerstitial damage. The serum acetate level was declined in antibiotics-treated diabetic rats and associated with the cholesterol level in the kidney. The acetate increased cholesterol increase in human kidney-2 (HK-2) cells which was induced by higher expression of proteins that reducing cholesterol synthesis and uptake. So, the acetate formed from gastrointestinal microbiota facilitated the imbalance of cholesterol homeostasis and consequently gastrointestinal microbiota reprogramming helping in diabetic nephropathy prevention and therapy[35]. Higher secretion of bile salts into the canalicular lumen increases bile formation and promotes biliary cholesterol and phospholipid output. Disturbing hepatic bile salt uptake was found to limit bile salt flux *via* the liver and consequently decrease biliary lipid excretion. Higher lysosomal discharge into bile increased biliary lipid secretion. The higher bile salts exposed to canalicular membrane leads to more cholesterol and phospholipid molecules to be excreted per bile salt. The increase of biliary lipid secretion is independent on variations in bile salt output, biliary bile salt hydrophobicity, or cholesterol and phospholipid transporters activities. Consequently, increase exposure of the canalicular membrane to bile salts associated with increased biliary cholesterol secretion and this process controls biliary cholesterol and phospholipid secretion[36]. The low-density lipoprotein, high-density lipoprotein and cholesterol levels in the blood become low in Plasmodium falciparum parasites infections in humans. These parasites import cholesterol from the surrounding environment. So, cholesterol import by Plasmodium falciparum includes hepatocytes and cholesterol uptake by the parasites[37]. Lipid structure of liposome alters the cell response for permeability, transport, and uptake in small intestine. The surface statuses of cholesterol-containing liposomes were smooth but they did not affect their transport and uptake through Caco-2 cell and microfold cells monolayers[38]. The sterols occur in the blood circulation either from cholesterol synthesis or gastrointestinal uptake. They are esterified or oxygenated. The cholesterol, cholesterol precursors, plant sterols and oxysterols accumulated in carotid artery plates. The circulating sterols were not reflected sterols levels. The normal cholesterol level occurs when plant sterol (but not oxysterol level) connected between plasma and plates. The oxysterols were lower in plates. Both cholesterol and plant sterols were lower esterified in plates than in plasma. The cholesterol, cholesterol precursors, plant sterols, and oxysterols were increased in symptomatic compared to asymptomatic patients[39]. The brown fat stimulation increases the uptake of cholesterol by the liver and so lowers plasma cholesterol and protects against atherosclerosis occurs. The hepatic cholesterol is converted into bile acids which secreted into the intestine. The bile acids seizure prevents the higher level of plasma bile acids which induced by brown fat activation. This process improves cholesterol metabolism and declines atherosclerosis occurs. Consequently, the collection of both brown fat activation and bile acids seizure is a favorable new therapeutic strategy to decline hyperlipidaemia and cardiovascular diseases[40]. The human Caco-2 cell line is well known *in vitro* model of the gastrointestinal epithelial barrier. The intestine is a major border in cholesterol uptaking and represents a non-biliary way for cholesterol excretion. The Caco-2 cells are a valuable model for investigating cholesterol homeostasis such as cholesterol uptake and efflux[41]. The Caco-2 cells signify the structure and functional properties of small intestinal cells. It is able of expressing brush borders, tight junctions, intestinal efflux and uptake and this control infusion of drugs and food extracts from intestinal lumen to blood circulation. The functional foods and their constituents had anti-proliferative and anti-cancer effects through apoptosis, cell cycle halt and decrease of all signal paths include in Caco-2 cell lines. The transportation, bioavailability, metabolism, mechanisms of actions, cellular paths created by food stuffs in Caco-2 cell lines are affected by their molecular weight, structures and physicochemical properties[42]. The cholesterol homeostasis is controlled by external factors such as diet and internal factors such as certain receptors, enzymes and transcription factors. The receptor 36 (CD36) is a membrane receptor takes place in fatty acid uptake, lipid metabolism, atherothrombosis and inflammation. The CD36 is vital molecule for cholesterol homeostasis in many processes such as absorption/reabsorption, synthesis, and transport of cholesterol and bile acids. The amount of fatty acids and fatty acid structure in the diet affects the CD36 Level and CD36 facilitated cholesterol metabolism in the liver, intestine and macrophages. The CD36 facilitated cholesterol and lipoprotein homeostasis counteracted by dietary saturated fatty acids and *trans*-fatty acids in the diet[43].

UPTAKE OF LYSOPHOSPHOLIPIDS

The bee venom caused skin inflammation which includes erythema, blisters, edemas, pain, and itching. The bee venom has an inhibitory effect on toll-like receptors. The toll-like receptors caused by secretory phospholipase A2. This secretory phospholipase A2 facilitates the hydrolysis of membrane phospholipids into lysophospholipids and free fatty acids[44]. The metabolic analysis in human cancers increased uptake of lysophospholipids and lipid storage, associated with increased fatty acid oxidation that maintains both adenosine triphosphate (ATP) levels and reactive oxygen species (ROS)-detoxifying reduced form of nicotinamide adenine dinucleotide phosphate (NADPH)[45]. The glycerol phosphate process creates higher than 90% of the hepatic triacylglycerol. The lysophosphatidic acid (an intermediate in this process) is created by glycerol-3-phosphate acyltransferase domain containing 3. The glycerophosphodiester phosphodiesterase creates lysophosphatidic acid from lysophospholipids. In human, liver glycerophosphodiester phosphodiesterase overexpression caused increased both lysophosphatidic acid and fatty acids uptake. The liver steatosis patients have increased glycerol-3-phosphate acyltransferase domain containing 3 mRNA levels compared with normal one. Consequently, the glycerol-3-phosphate acyltransferase domain containing 3 overexpression have a vital role in liver triacylglycerol increase and controls liver steatosis[46]. The microalga (Chlorella vulgaris) when exposed to the flame retardant triphenyl phosphate increase the synthesis of membrane lipids but decrease of lysoglycerolipids, fatty acids, and glyceryl-glucoside. On the other side, the microalga Scenedesmus obliquus when exposed to the flame retardant triphenyl phosphate increase lipolysis process such as accumulation of fatty acids, lysophospholipids, and glycerol phosphate[47]. The breathing of sphingosine increased the levels of sphingosine in the luminal membrane of bronchi and the trachea. The breathing of sphingosine without any side effects even with high doses[48]. The lysophosphatidic acid (LPA) is a bioactive lipid mediator which is incorporated in development, physiology, and pathological processes of the cardiovascular system. The LPA created both inside the cells and in the biological fluids. Most of the LPA is created by the secreted lysophospholipase D, autotaxin, *via* its binding to various β integrins or heparin sulfate on cell surface and hydrolyzing many lysophospholipids. The LPA possessed many effects on many blood cells and vascular cells that associated in the development of cardiovascular diseases such as atherosclerosis and aortic valve sclerosis. The LPA caused diversity of monocytes into macrophages and arouses oxidized low-density lipoproteins uptake by macrophages to form foam cells during atherosclerosis[49]. The docosahexaenoic acid-associated lysophosphatidyl choline declined triacylglycerol level due to the increase of carnitine palmitoyltransferase 2 and acyl-CoA oxidase levels and the decrease of acetyl-CoA carboxylase and glucose-6-phosphate dehydrogenase levels in the liver. So, the docosahexaenoic acid-associated lysophosphatidylcholine rich oil has hypolipidemic effect[50].

GASTROINTESTINAL METABOLISM OF ABSORBED LIPIDS

The tissue distribution of lipid is completely different among different species. Tiger puffer possesses lipid storage in the liver. There are 29 lipid metabolism-associated genes. These genes are included in lipogenesis, fatty acid oxidation, biosynthesis and hydrolysis of glycerides, lipid transport, and lipid transcription control. The intestine possesses the high transcription of lipogenic genes while the liver and muscle possesses low lipid gene expression. The intestine also has the highest transcription genes of most apolipoproteins and lipid metabolism-associated transcription factors. The fatty acid oxidation occurs in the mitochondrial β-oxidation in the liver and intestine. The re-acylation of absorbed lipids occurs in the intestine. In conclusion, the intestine is the center of lipid metabolism while the liver is the pure storage organ for lipid[51]. The highly lipophilic food stuffs are occurred in higher concentrations in the medium-chain triglycerides than the long-chain triglycerides. The 30% of the lipophilic food stuffs in medium-chain triglycerides are crossed the Caco-2 cells and 50% of the lipophilic food stuffs in medium-chain triglycerides were metabolized. The 60% of the lipophilic food stuffs in long-chain triglycerides were crossed the Caco-2 cells and 10% of the lipophilic food stuffs in long-chain triglycerides were metabolized. The higher lipid droplets and chylomicrons were formed for the long-chain triglycerides referring to of the lipophilic food stuffs transported through lymph. Although the medium-chain triglycerides possesses the higher of the lipophilic food stuffs, the final amount

of the lipophilic food stuffs absorbed and transported to the lymph was lower to that of the long-chain triglycerides formulation[52]. Vitamin B_6 is found in the diet in many forms but only pyridoxal 5'-phosphate (PLP) can serve as an enzymes cofactor. The intestine absorbs nonphosphorylated B_6 vitamers, which are changed to the active PLP form. Many human processes dependent on PLP such as amino acid and neurotransmitter metabolism, folate metabolism, protein and polyamine synthesis, carbohydrate and lipid metabolism, mitochondrial function and erythropoiesis. There are many roles of PLP beside the role of PLP as a cofactor B_6 vitamers and these roles are antioxidants, altering expression and action of steroid hormone receptors, affecting immune function, and antagonist of adenosine-5'-triphosphate (ATP)[53]. The oxysterols are oxidized forms of cholesterol which created by enzymes or by reactive oxygen species or both. The cholesterol or oxysterols are absorbed and stored in lipoproteins by hepatic cells. Inside the liver, additional cholesterol is metabolized to form bile acids. The endoplasmic reticulum is the main place for bile acid synthesis process. The metabolized sterols from this process are stored in the other places and in the cell membrane. The changes in membrane oxysterol: Sterol ratio affects the cell membrane stucture. The oxysterols changes membrane flexibility and receptor location. The hydroxylase enzymes in the mitochondria expedite oxysterol formation by an acidic process. In lysosomes, the oxysterols are also detected. The biochemical and physiological properties of oxysterols are many and important. Oxysterol levels are associated in many diseases such as chronic inflammatory diseases (Alzheimer's disease, atherosclerosis, and bowel disease), cancer and many neurodegenerative diseases[54]. The lipins possess vital roles in adipogenesis, insulin sensitivity, and gene regulation/mutation in these genes induces lipodystrophy, myoglobinuria, and inflammatory disorders. The lipids (lipid 1, 2, and 3) serve as phosphatidic acid phosphatase enzymes (need for triacylglycerol synthesis). The alteration of fatty acids in diet into triglycerides has been done by lipid 2 and 3. These 2 Lipids phosphatidic acid phosphatase enzymes activities have an important role in phospholipid homeostasis and chylomicron accumulation in enterocytes[55].

THE FINAL FORMS OF GASTROINTESTINAL LIPIDS

The lipids are re-synthesis again inside the human body where the gastrointestinal lipids are: (1) Transferred into the endoplasmic reticulum; (2) Collected as lipoproteins such as chylomicrons; or (3) Stored as lipid droplets in the cytosol. Both chylomicrons and cytosolic lipid droplets possess similar structure. The decrease of the microbiota which produces acetyl-CoA from acetate leads to suppress the change of fructose into hepatic acetyl-CoA and fatty acids. So, the higher fructose consumption facilitates fructose absorption in the small intestine and citrate breakdown in hepatocytes through lipogenesis process. But, the lipogenic transcriptional program stimulates by fructose that is independent of acetyl-CoA metabolism. Consequently, 2 mechanisms regulate hepatic lipogenesis by fructose inside the hepatocytes and these 2 mechanisms are: (1) The expression of lipogenic genes; and (2) The generation of microbial acetate feeds lipogenic pools of acetyl-CoA[56]. There are lower small intestine muscle mass, increase Bacteroidetes, decrease Firmicutes in the large intestine, and decrease of circulating short-chain fatty acids (SCFA) values in non-obese diabetic animals. These changes are correlated with increase body weight, hyperlipidemia, and severe insulin and glucose intolerance. Also, insulin resistance disturbances which related to energy metabolism such as decrease overall respiratory exchange rates but increase liver oxidative activity. There are changes related to gut and microbiota structure which accompanied with decrease of circulating SCFA that leads to metabolic disorders occurs[57]. Vitamin E includes 8 compounds; α-, β-, γ-, and delta-tocopherol and α-, β-, γ-, and delta-tocotrienol. α-tocopherol is found in the human diet. All the above forms of the vitamin E are absorbed in the small intestine, and then the liver metabolizes only α-tocopherol. The liver then removes and excretes the remaining vitamin E forms. Vitamin E deficiency is caused by a diet with low vitamin E or is caused by irregularities in dietary fat absorption or metabolism. Vitamin E is a lipid-soluble vitamin. Vitamin E reduces atherosclerosis and decrease rates of cardiac disease[58]. The different lipids during passage in gastrointestinal tract depend on lipid type and the microenvironment surrounding. The protein is the problem for pancreas lipase to catalyze lipid hydrolysis following gastric digestion. The higher free fatty acids secretion level and rate persistent in small intestine digestion in triacylglycerols (glycerol tripalmitate, glycerol tristearate, glycerol trioleate) in the order of glycerol tripalmitate > glycerol tristearate > glycerol trioleate, respectively[59]. The free fatty

acids secretion during 240 min in-vitro gastrointestinal digestion were measured, and the results proved that the release rate of short-chain saturated fatty acids were higher than the long-chain poly-unsaturated fatty acids. Also, the location of fatty acids inside triacylglycerols possesses an effect on the lipid hydrolysis process through pancreas lipase in gastrointestinal tract using in-vitro digestion model[60]. In the biological system, the gasotransmitters [nitric oxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO)] are molecules do neural purposes in the whole body. Also, the gasotransmitters are small and lipid molecules control the changes in lipids rates of production or consumption. Moreover, tissue levels of the gasotransmitters are controlled by the level of O_2 and reactive oxygen species[61]. The changes in intestinal barrier permeability cause severe gastrointestinal disturbances. The leaky gut syndrome is caused by intestinal hyperpermeability due to changes in the expression levels and functioning of tight junctions. The diseases linked to intestinal hyperpermeability are found in Western countries, where a diet possesses higher fats. The fructose is a key that incorporated in the control of the intestinal permeability and induced harmful effects (such as tight junction protein dysfunction). The short chain fatty acids (such as butyrate) cause decrease of intestinal permeability but long chain fatty acids (such as *n*-3 and *n*-6 polyunsaturated fatty acids) have unknown effects[62]. The transepithelial transport rates in the Caco-2 cell were as follows: Scoparone > hydroxycinnamic acid > rutin > quercetin. The main metabolism of hydroxycinnamic acid (quercetin, and scoparone) in transepithelial transport was found to be methylation. Also, triglyceride, low-density lipoprotein cholesterol, total cholesterol, aspartate aminotransferase, and alanine aminotransferase levels in human liver cancer cell line (HepG2 cells) were suppressed by 53.64%, 23.44%, 36.49%, 27.98%, and 77.42% compared to the oleic acid-induced group[63].

COVID-19 AND LIPIDOME

The COVID-19 pandemic presents a global threat to global public health. The plasma lipidome is analyzed in mild, moderate, and severe COVID-19 patients and healthy subjects. Plasma lipidome of COVID-19 contains monosialodihexosyl ganglioside (GM3)-enriched exosomes, with sphingomyelins (SMs) and GM3s, and decrease diacylglycerols (DAGs). The COVID-19 patients with increase disease severity have an increase in GM3s. So, GM3-enriched exosomes participate in pathological cases of COVID-19 and presents the higher source on the plasma lipidome to COVID-19[64]. There is a change in lipid metabolism especially short and medium chain saturated fatty acids, acyl-carnitines, and sphingolipids in COVID-19 patients. But, there are no changes in hematological parameters (red blood cells, hematocrit, and mean corpuscular hemoglobin concentration, with slight increase in mean corpuscular volume) is observed[65,66]. MS-related methods such as lipidomics has been applied in COVID-19 disease outbreaks. Ultra-high-pressure liquid chromatographies with high-resolution mass spectrometry (UHPLC-HRMS)-based lipidomics are used to identify infectious pathogens and biomarkers related in COVID-19. Polymerase chain reaction-mass spectrometry (PCR-MS) is a new technology to determine known pathogens from the clinical specimens. Also, miniaturized MS provides an application with fast, high sensitive and easy way to analyze for COVID-19. Consequently, MS-related methods are an easy and sensitive way in studying corona outbreaks such as COVID-19[67]. MS-related, lipidomics method provides a suitable way of virus-induced changes to the host after infection and can lead to the determination of new therapeutic agents for preventing disease spreading. The omics study with MERS-CoV is used lipid extraction to develop a single sample in lipids determination in COVID-19 infection[68]. The lipidomic changes such as structural-lipids, the eicosanoids, and docosanoids lipid mediators (LMs) are important for the diagnosis of COVID-19 disease severity. The progression from moderate to severe disease is accompanied with loss of specific immune regulatory LMs and increased pro-inflammatory cytokines[69,70]. COVID-19 exerts higher effect on the metabolism. The lipidomic analysis showed pathogenic redistribution of the lipoprotein particle size and composition to increase the atherosclerotic danger. The metabolomic analysis showed abnormal high levels of ketone bodies such as acetoacetic acid, 3-hydroxybutyric acid, and acetone. Also, higher increase of 2-hydroxybutyric acid (an indication of hepatic glutathione synthesis and oxidative stress marker). So, SARS-CoV-2 infection caused liver damage correlated with dyslipidemia and oxidative stress[71]. The viral infection is depended on the lipid metabolism of the infected cells. From a lipidomics view, there are many mechanisms connecting to viral infection such as viral entry, the disorder of host cell

lipid metabolism, and the role related to different lipids in the infection efficiency. So, lipids play an important role in COVID-10 infection success especially the role of cholesterol in the success of viral infection[72]. Figure 2 exhibits lipidome and COVID-19 in gastrointestinal tract.

LIPIDOME VIEW IN VIRAL REPLICATION CYCLES

COVID-19 is a virus and this virus is dependent on its lipid cover which possesses high capability to detergent. The lipids play an important role in many stages of the virus replication cycle. The definite lipid change occurs during viral infection in higher viral replication cycle. There are 47 lipids within 11 lipid classes were significantly disturbed after viral infection. There are 4 polyunsaturated fatty acids (PUFAs): (1) Arachidonic acid (AA); (2) Docosahexaenoic acid (DHA); (3) Docosapentaenoic acid (DPA); and (4) Eicosapentaenoic acid (EPA) were upregulated during viral infection. The 3 of these 4 fatty acids (PUFAs; AA, DHA, and EPA) declined viral replication. Consequently, enteroviruses modify the host lipid pathways for higher virus replication. Higher exogenous lipids prevent effective viral replication. The control of the host lipid profile is a host-targeting antiviral strategy for enterovirus infection[73]. In hepatitis C virus (HCV) infection, the HCV reproduction depends on many lipid metabolic processes during viral life cycle. The HCV induces cells' lipidomic profile changes by controlling many key pathways of lipid synthesis, remodeling and utilization. So, the lipids play a significant role in HCV RNA replication, meeting and entrance. In viral process, there are many changes in the cell fatty acid content and variations of the membrane lipid composition during replication of the virus. In viral process, the lipids represent lipid provider during replication and as an essential hub for HCV meeting. The lipoproteins play an important role in HCV maturation and entrance[74]. There is an increase in the levels of many phosphatidylethanolamine (PE) lipids in the serum of Zika virus patients, most of them plasmenyl-phosphatidylethanolamine (pPE) (or plasmalogens) correlated with polyunsaturated fatty acids. The plasmalogens correlated with polyunsaturated fatty acids are abundant in neural membranes of the brain and these represent 20% of total phospholipids in humans. The biosynthesis of plasmalogens is necessary for efficient peroxisomes, which are important sites for Zika virus replication[75]. A stable benzoic derivative of retinoic acid (AM580) and retonic acid receptor-αagonist has greater effective in disturbing the life cycle of many viruses such as MERS-coronavirus and influenza A virus. The sterol regulatory element binding protein (SREBP) connect with AM580 and exerts antiviral effect. Consequently, lipidome technique plays a major role in human viral infections where SREBP is an effective agent in the antiviral strategies development[76]. The glycerophospholipids and fatty acids increased in human coronavirus 229E-infected cells and the linoleic acid (LA) to AA metabolism was disturbed in HCoV-229E infection by using high performance liquid chromatography-associated with lipidome technique. Supplementation with LA or AA in HCoV-229E-infected cells depressed HCoV-229E virus replication. The inhibition of LA and AA on virus replication can be seen in MERS-CoV. So, the host lipid metabolic processes correlated with human-coronavirus proliferation. Consequently, the control of lipid metabolism is the main goal for coronavirus infections[77]. The cell lipidome technique shows an increase in phospholipase A2 (PLA2) activity to produce lyso-phosphatidylcholine (lyso-PChol). The PLA2 enzyme family is activated in West Nile virus strain Kunjin virus-infected cells and produces lyso-PChol lipid molecules that need for viral reproduction. The production of lyso-PChol is increased by inhibition of PLA2 in West Nile virus strain Kunjin virus reproduction and production of infectious virus is occurred. The lyso-PChol related to the formation of the West Nile virus strain Kunjin virus replication complex (RC). Consequently, lipid homeostasis enables the researchers to understand flaviviruses replication[78]. The HCV-infected cells contain higher amounts of phosphatidylcholines and triglycerides with longer fatty acyl chains and increased use of C18 fatty acids especially oleic acid. So, decrease of fatty acid elongases and desaturases reduces HCV reproduction. There is an increase in the levels of polyunsaturated fatty acids (PUFAs) in HCV infection. The decrease of the PUFA synthesis path damaged viral reproduction, indicating that higher PUFAs are needed for viral replication. Consequently, the control of the host cell lipid metabolism is needed and caused by HCV to increase viral replication[79].

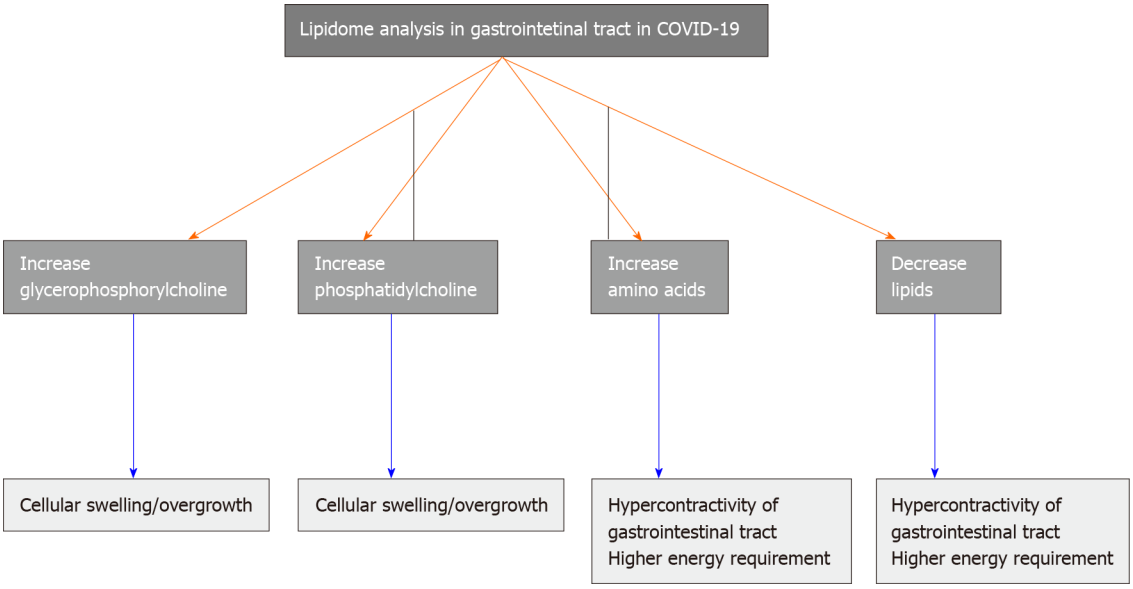

Figure 2 Lipidome and COVID-19 in gastrointestinal tract.

THE ROLE OF LIPIDOME DURING THE HOST-VIRAL INTERACTIONS

In the recent century, researches using genetic, cell biological, and biochemical techniques has led to huge increase in molecular and biological insight into interaction of virus with their hosts. Cell biological studies depend on microscope as a principal technique, of basic microbiology methods so these researches added more data to host-viral interactions. On the other hand, the biomedical researches, the main focus was on the determination of genes and proteins necessary for activity. Based on these findings there is now increased consciousness that lipids (both of host and of virus) play vital roles in regulating infection stability, entry into host cells, as well as, replication and persistence of the virus. There is a connection between the host protein disulfide isomerase (PDI) with dengue virus protein and role of lipid raft in viral infection. The PDI correlates with dengue virus nonstructural protein 1 (NS1) inside the biological cell as well as on the surface in the lipid raft molecule. Disturbance of this relation between PDI and NS1 is important in treatment strategy to stop dengue virus infection[80]. The virus connects with blood-borne lipoproteins and apolipoprotein E (apoE) to change viral infectivity. Viral interest is cholesterol- and lipid raft-dependent (24-dehydrocholesterol reductase, 3-hydroxy-3-methylglutaryl-CoA reductase, fibrin degradation products, raft-linking protein, Sterol regulatory element-binding transcription factor 1). The virus is gone to the nucleus through the dynein and kinesin motors. Amyloid precursor protein has a role nucleus invention by the virus. The viral protein removes mitochondrial DNA as in Alzheimer's disease case. The virus connects with the host transcription factors transcription factor CP2 and POU domain, class 2, transcription factor 1 that control many other genes. Viral inactivity is controlled by interleukin 6 (IL6) and IL1β. Viral avoidance occurs by inhibition of the antigen processor human gene that encodes the protein antigen peptide transporter 2, the production of an Fc immunoglobulin receptor mimic and inhibition of the viral-activated kinase eukaryotic interferon-inducible factor 2 alpha kinase[81]. The role of lipidome during the host-viral interactions includes 2 main categories: (1) cell and chemical biology in the viral-host interaction; and (2) lipid profiling in the viral-host interaction.

Cell and chemical biology in the viral-host interaction

There is an important host factor (CPSF6) connects with nuclear protein (NP1). The CPSF6 increases the nuclear production of NP1 in the same time CPSF6 possesses an important role in progress of capsid mRNAs inside the nucleus. The connection between viral NP1 and host CPSF6 gives the scientist the mechanism enables viral protein increases the viral gene expression and replication as well as antiviral drug discovery[82]. The virus infection causes spreading of the distraction of transcription termination (DoTT) of RNA polymerase II (RNAPII) in host genes. The herpes simplex virus-1 (HSV-1) immediate early protein (ICP27) causes widespread DoTT through connection with essential mRNA 3' processing factor (CPSF). The ICP27 stimulates

mRNA 3' processing for viral and host transcription. So, ICP27 possesses an important role in HSV-1-causes viral infection while CPSF stimulates regulation of transcription end[83]. The RNA binding-deficient stores in nucleoprotein (NP) bodies and the nuclear RNA export factor 1 (NXF1) is necessary for viral protein expression but not for viral RNA synthesis. The NXF1 connects with viral mRNAs but not with viral RNAs. Consequently, the NXF1 promotes the export of viral mRNA:NXF1 complexes from inclusion bodies. This provides a basis for new therapeutic approaches for viruses[84]. The ribosomal proteins (RPs) contain 60S subunit control translation of specific mRNAs. The translation process of the RPs in this process controls in the catalyzing peptide bond formation. The ribosomal protein L13 (RPL13) is a regulator of viral translation and infection. Consequently, understanding this process gives rise to the effects for the translation of viral mRNA and thus for the development of viral prevention[85]. The influenza A viruses contain RNA genome include 8 segments. Each RNA segment correlated with the NP and viral RNA polymerase to and from a viral ribonucleoprotein (vRNP) molecule. The formation of viral mRNA is dependent on the host RNA transcription and for these processes to be occurred; the vRNPs must pass through the cell nuclear pore complex (NPC) to the nucleus. The influenza A virus NS2 protein, also called the nuclear export protein and this protein connects with the host cellular nucleoporins during the nuclear export of vRNPs. The human nucleoporin 214 (Nup214) is called NS2-binding protein and NS2 protein coonects with the amino terminal FG domain of the Nup214 protein. The influenza viral replication was decreased by the Nup214 protein. Consequently, the FG domains of nucleoporins have an important role in the connection of the influenza NS2 protein with host NPC for viral RNA (vRNA) spread[86]. The importin-α3 (one of the main nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transporters) is the expressed nuclear factor in the mammalian respiratory tract. Importin-α3 promoter effect is controlledby TNF-α-induced NF-κB. The increasing of TNF-α increasing pathogenic avian influenza A viruses (HPAIVs) in serious human cases protecting human polymerase signatures (PB2 627K, 701N) which downregulate importin-α3 mRNA expression in the lung cells. The decrease of Importin-α3 is returned by the mutating of the HPAIV polymerase into an avian-type signature (PB2 627E, 701D) which suppresses the high TNF-α levels. The decrease of importin-α3 decreased the NF-κB antiviral gene expression and increased influenza dangerous. Consequently, importin-α3 possesses a role in antiviral immunity in influenza and so importin-α3 in the lung help in the strategy to fight respiratory virus infections[87]. During rotavirus infection, the small interfering RNA (siRNA) facilitates genetic exhaustion of ATP5B or other ATP synthase molecules (ATP5A1 and ATP5O) decreases the production of viral new generations without modification of viral RNA amounts and translation. The ATP5B controls the late-stage rotavirus growth in intestinal cells. Consequently, the role of host proteins in rotavirus RNA identifies ATP5B as a novel pro-rotavirus RNA-binding protein that help scientists to understand virus growth and pathogenesis[88]. The host protein (hnRNP C1/C2) decreases viral RNA translation. The hnRNP C1/C2 connects with stem-loop V in the Internal Ribosome Entry Site' (IRES) and transfers binding protein where this protein controls of viral translation. The hnRNP C1/C2 causes changing of viral translation to replication. Consequently, the hnRNP C1/C2 controls of viral RNA translation to replication by a specific mechanism[89]. The connection of glycyl-tRNA synthetase (GARS) increases the environmental of the initiation area of the internal IRES in the mRNA binding site of the ribosome that increasing IRES effect at the step of initiation formation[90].

Lipid profiling in the viral-host interaction

The studies of viral lipids are not new trends. The main developments in analytical biochemistry have added new information to these studies. The liquid chromatography and MS are the most important techniques applied in the field of lipidome. These techniques allow detection, characterization, and quantification of huge molecules of lipids (although it is currently not possible to determine the full "lipidome" of a cell or tissue in one study). The major biochemical information of lipid lists (*e.g.*,. of mycobacteria) is now applied to investigate the details of lipid biosynthesis and lipid transporters. Potato is a natural host of Potato spindle tuber viroid (PSTVd) which causes arresting phenotype and alteration of leaves and tubers. The PSTVd virus replicates in the nucleus and moves in the plant. The host possesses defense, stress and sugar metabolism correlated genes which alters expression levels in infection and the hormone-related genes showed up- or down-regulation. Consequently, gibberellin and brassinosteroid paths possess an important role in tuber development upon PSTVd infection[91]. In dengue virus infection, there is an increase in mRNA, myeloid differentiation 2-related lipid recognition protein (ML) and Niemann

Pick-type C1 (NPC1) genes. These 3 genes translate lipid-binding proteins which play an important role in host-viral connection. The RNA interference (RNAi)-mediated gene stops the ML and NPC1 genes. In viral infection, ML and NPC1 increase viral infection by reducing the host immune ability. Consequently, the dengue virus effects the expression of these genes to stimulate viral infection of the mosquito host[92].

FUTURE THERAPY OF CORONAVIRUS

No vaccines or antiviral drug to prevent or treat human coronavirus infections is available. The coronavirus treatment is only caring. There are many antiviral agents used *e.g.*, viral proteases, polymerases and entry proteins. Coronavirus is capable to replicate in invitro study such as human lung cancer cell line (Calu-3 cells) and causes lower transcriptomic variations before 12 h after viral infection. As infection progress, coronavirus causes a significant dysregulation of the host transcriptome greater than SARS virus. Both viruses induced a similar stimulation of host receptors and the interleukin 17 paths but coronavirus inhibits the expression of many genes such as type I and II major histocompatibility complex genes. This viral effect identifies the ability of the host response to viral infection. There are 207 genes was inhibited following coronavirus infection, and was used to detect the antiviral secretions such as kinase inhibitors and glucocorticoids. Consequently, coronavirus and SARS virus possesses host gene expression reactions that effect on *in vivo* pathogenesis and therapeutic strategies[93]. In coronavirus infection, the whole blood cytokine investigations increased the cytokine expression in the viral cell infected case. The inflammatory gene expression increased after dysfunction of respiratory function, except the expression in the IL1 path. The investigations of CD4 and CD8 expression showed that the pro-inflammatory factors increased with T cell initiation that leads to prolong the disease or prolong the infection. Consequently, the pro-inflammatory factors such as IL1 and related pro-inflammatory paths analyzes and uses as therapeutic agents for COVID-19[94].

CONCLUSION

The term lipidome is mentioned to the total amount of the lipids inside the biological cells. The lipid enters the human gastrointestinal tract through external source and internal source. The lipids are re-synthesis again inside the human body where the gastrointestinal lipids are: (1) Transferred into the endoplasmic reticulum; (2) Collected as lipoproteins such as chylomicrons; or (3) Stored as lipid droplets in the cytosol. The tissue distribution of lipid is completely different among different species. Fatty acids are uptake by the gastrointestinal tract through 2 ways; the 1st way, fatty acids transfer from the intestinal membrane from higher concentration to lower concentration inside the cell while the 2nd way occurs from the cell to the lumen when the fatty acids concentration inside the cell is higher than lumen fatty acids concentration. The lipids play an important role in many stages of the viral replication cycle. There are 47 Lipids within 11 Lipid classes were significantly disturbed after viral infection. The virus connects with blood-borne lipoproteins and apolipoprotein E to change viral infectivity. The viral interest is cholesterol- and lipid raft-dependent molecules. The future therapy of coronavirus includes the investigations of CD4 and CD8 expression where these pro-inflammatory factors increased with T cell initiation that leads to prolong the infection.

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