Lipidomics

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Lipid analysis provides additional insight into the pathogenesis of ischemia/reperfusion (I/R) disorders and reveals new targets for drug action. The profile of changes in the composition of fatty acids in the cell, as well as the time course of these changes, indicate both the mechanism of damage and new therapeutic possibilities.

ischemia/reperfusion lipidomics kidney liver

1. Lipidomics

The determination of the lipidome profile is often called lipidomics. The lipidome represents all the small molecules metabolomes with a mass lower than 1500 in the system [1]. Lipids are involved in many biological processes in organisms due to their hydrophobic part, such as building biological membranes, keeping energy for further consumption, and playing an essential role in cell signaling. Production and lipids concentrations must be strictly controlled because any lipid metabolism dysregulation can lead to disease [2]. Hence, nowadays, the analysis of the lipid profile is a rapidly developing field.

Based on their hydrophobic moiety, lipids are divided into eight categories: fatty acids (FAs), prenols, sterols, glycerophospholipids, glycerolipids, sphingolipids, polyketides, and saccharolipids (Table 1) [3].

Table 1. Lipid classification based on Lipid Maps Structure Database.

Lipid Categories	
01. Fatty Acyls [FA]	**04. Sphingolipids [SP]**
[FA01] Fatty Acids and Conjugates	[SP01] Sphingoid bases
[FA02] Octadecanoids	[SP02] Ceramides
[FA03] Eicosanoids	[SP03] Phosphosphingolipids
[FA04] Docosanoids	[SP04] Phosphonosphingolipids
[FA05] Fatty alcohols	[SP05] Neutral glycosphingolipids
[FA06] Fatty aldehydes	[SP06] Acidic glycosphingolipids
[FA07] Fatty esters	[SP07] Basic glycosphingolipids
[FA08] Fatty amides	[SP08] Amphoteric glycosphingolipids
[FA09] Fatty nitriles	[SP09] Arsenosphingolipids
[FA10] Fatty ethers	[SP00] Other Sphingolipids
[FA11] Hydrocarbons	**05. Sterol Lipids [ST]**
[FA12] Oxygenated hydrocarbons	[ST01] Sterols
[FA13] Fatty acyl glycosides	[ST02] Steroids
[FA00] Other Fatty Acyls	[ST03] Secosteroids
02. Glycerolipids [GL]	[ST04] Bile acids and derivatives

Lipid Categories	
[GL01] Monoradylglycerols	[ST05] Steroid conjugates
[GL02] Diradylglycerols	[ST00] Other Sterol lipids
[GL03] Triradylglycerols	**06. Prenol Lipids [PR]**
[GL04] Glycosylmonoradylglycerols	[PR01] Isoprenoids
[GL05] Glycosyldiradylglycerols	[PR02] Quinones and hydroquinones
[GL00] Other Glycerolipids	[PR03] Polyprenols
03. Glycerophospholipids [GP]	[PR04] Hopanoids
[GP01] Glycerophosphocholines	[PR00] Other Prenol lipids
[GP02] Glycerophosphoethanolamines	**07. Saccharolipids [SL]**
[GP03] Glycerophosphoserines	[SL01] Acylaminosugars
[GP04] Glycerophosphoglycerols	[SL02] Acylaminosugar glycans
[GP05] Glycerophosphoglycerophosphates	[SL03] Acyltrehaloses
[GP06] Glycerophosphoinositols	[SL04] Acyltrehalose glycans
[GP07] Glycerophosphoinositol monophosphates	[SL05] Other acyl sugars
[GP08] Glycerophosphoinositol bisphosphates	[SL00] Other Saccharolipids
[GP09] Glycerophosphoinositol trisphosphates	**08. Polyketides [PK]**
[GP10] Glycerophosphates	[PK01] Linear polyketides
[GP11] Glyceropyrophosphates	[PK02] Halogenated acetogenins
[GP12] Glycerophosphoglycerophosphoglycerols	[PK03] Annonaceae acetogenins
[GP13] CDP-Glycerols	[PK04] Macrolides and lactone polyketides
[GP14] Glycosylglycerophospholipids	[PK05] Ansamycins and related polyketides
[GP15] Glycerophosphoinositolglycans	[PK06] Polyenes
[GP16] Glycerophosphonocholines	[PK07] Linear tetracyclines
[GP17] Glycerophosphonoethanolamines	[PK08] Angucyclines
[GP18] Di-glycerol tetraether phospholipids	[PK09] Polyether antibiotics
[GP19] Glycerol-nonitol tetraether phospholipids	[PK10] Aflatoxins and related substances
[GP20] Oxidized glycerophospholipids	[PK11] Cytochalasins
[GP00] Other Glycerophospholipids	[PK12] Flavonoids
	[PK13] Aromatic polyketides
	[PK14] Non-ribosomal peptide/polyketide hybrids
	[PK15] Phenolic lipids
	[PK00] Other Polyketides

1.1. Lipid Transport Across Cell Membranes

In particular, there is an increased accumulation of free FAs in certain types of tissue damage with subsequent cell death (“lipotoxicity”), which is why incorporation of FAs into the TG pool serves as a vital cell-protective mechanism [4]. The FAs have a vital function in physiology, being directly synthesized in the cytosol (in situ), released from intracellular metabolic processes (e.g., hydrolysis of triglycerides, TGs, and phosphatidylcholine, PC), or obtained from extracellular sources through CD36-mediated uptake [5]. The enzymes involved in TG synthesis, such as acyl-coenzyme A:diacylglycerol acyltransferases (DGATs), are present in various tissues, for example, kidneys and liver [6][7].

Besides the internalization of lipoprotein particles (LDL, chylomicron remnants, and IDL) by endocytosis in the presence of LDL receptors and their degradation in lysosomes, various other proteins participate in the transmembrane transport of lipids. Such transport may play a significant role in the pathogenesis of IR injury.

CD36 (fatty acid translocase), a member of the class B2 scavenger receptor family of cell surface proteins, is found on blood cells (platelets, erythrocytes, monocytes), adipocytes, hepatocytes, as well as cells of the myocardium, spleen, and renal tubule epithelium. Ligands for CD36 are proteins and lipids, and the latter includes oxidized LDL particles, long-chain fatty acids, phospholipids, and others. CD36s are involved in fatty acid metabolism, atherosclerosis, and other processes. Their role in long-chain fatty acid uptake is particularly important. In the liver, CD36s are directly linked to fatty acid metabolism, and in the kidneys, they are involved in the uptake of advanced oxidation protein products and the development of lipototoxicity. In the heart, more than 70% of ATP is formed from fatty acids, and CD36 mediates 70% of the intake of fatty acids into the cardiac cells [8]. The number of CD36s on the cell membrane of cardiomyocytes decreases in ischemia and remains low during reperfusion. Reducing the number of CD36s in ischemia reduces the transport of long-chain fatty acids into cells and their breakdown in mitochondria. Simultaneously, the number and activity of GLUT4 transporters for glucose and anaerobic glucose metabolism to pyruvate increases. Pyruvate is further metabolized in the mitochondria to form ATP. Simultaneously, the cytoplasm's pH decreases due to proton accumulation, which interferes with the transport of CD36 from the endosome back to the cell membrane. The reduced number of CD36 in the cell membrane prevents the lipotoxic accumulation of fatty acids in the fat chains and enables the survival of cells in ischemia. During reperfusion, under aerobic conditions, anaerobic glycolysis and proton accumulation decrease. However, protons accumulated during ischemia further interfere with the transport of CD36 back to the cell membrane. Simultaneously, the production of ATP by aerobic oxidation of long-chain fatty acids in mitochondria increases now, and the metabolism of pyruvate, as a product of glycolysis, declines.

The fatty acid transport proteins (FATPs) are part of the family of the solute carrier 27 (Slc27) proteins which also have an essential place in the transport of exogenous fatty acids [9][10]. It should be emphasized that FATPs play the role of a gateway in such transport, regardless of whether they are located on the cell membrane or intracellularly, at the junction of the membranes with the endoplasmic reticulum. Therefore, some representatives of this group of transport proteins, such as FATP-1, -2, and -4, are suitable targets for drug action. By the way, six members of this group of proteins, FATP1–6, have been identified in mammals, and some of them are very long chain acyl CoA synthetases.

The family of fatty acid-binding proteins (FABP) has 12 members ("lipid-binding chaperones") and plays a role in the intracellular transport of fatty acids, eicosanoids, retinoids, and other lipophilic compounds, their trafficking, and signaling [11][12]. Their presence in the liver, intestine, peripheral nervous system, skeletal and heart muscle, adipocytes, skin, and brain has been confirmed. Besides the transport of fat, FABPs are involved in vasculogenesis, cell differentiation, and pathogenesis of various metabolic disorders [13]. Their role in transporting lipid compounds to PPAR receptors may be associated with brain IR injury [13]. Additionally, pharmacological inhibition of FABP4 may protect the kidneys from rhabdomyolysis-induced acute kidney injury (AKI) [14]. Namely, BMS309403, a selective inhibitor of FABP4, reduced glycerol-induced renal tubule damage, alleviated endoplasmic reticulum stress in the murine model of this AKI, decreased serum creatinine levels, and expressed proinflammatory cytokine expression. Further, the FABP4 gene induces hepatocyte hypoxia, which sensitizes liver cells in a hepatic IR injury model [15].

Efferocytosis can also be a vital process in transporting lipid substances and mitigating IR injury consequences [16]. This is a specific process that participates in removing apoptotic cells (AC), reducing the possibility of further secondary necrosis and inflammation development. It differs from classical phagocytosis. It takes place through several phases: AC finding, their binding, internalization, and degradation. Efferocytosis reduces inflammation by increasing the production of anti-inflammatory cytokines and reducing the synthesis of proinflammatory molecules. For example, sterols that reach efferocytes stimulate PPAR-gamma, PPAR-delta, and liver X receptor-α, leading to further stimulation of the release of anti-inflammatory IL10 and TGF-beta and differentiation of T cells that suppress inflammation. Such a defense mechanism removes the excess cholesterol that occurs during phagocytosis of apoptotic cells and can be cytotoxic to efferocytes. In other words, AC-derived cholesterol can be esterified under the influence of acyl-CoA cholesterol acyltransferase to cholesterol esters deposited as neutral fat droplets or subject to efflux. AC-derived fatty acids can be broken down by oxidation in mitochondria and further increase the expression of anti-inflammatory IL-10 via sirtuin-1. Finally, binding of phosphatidylserine (PS) of AC membrane to efferocytes leads to upregulation of glucose transporter 1 (GLUT1) and its incorporation into the cell membrane.

The process of FAs oxidation occurs in mitochondria and peroxisomes [17]. FAs can pass through the membrane of mitochondria or peroxisomes only via the carnitine cycle. First, the binding of acyl-CoA to carnitine is catalyzed by carnitine palmitoyl-transferase 1, and the product, long-chain acyl-carnitine (LCAC), subsequently passes through the membranes of mitochondria and peroxisomes via carnitine-acyl-carnitine translocase. Then, free carnitine is regenerated within mitochondria under the influence of carnitine palmitoyl-transferase 2, while the end product, acyl-CoA, undergoes beta-oxidation within mitochondria and peroxisomes in the presence of FAD and NAD. Very-long-chain FAs are metabolized in peroxisomes. Essential regulators of cell lipid metabolism are AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-α (PPARα) receptors. AMPKs are well-known energy sensors. On the other hand, PPARs form heterodimers with retinoid X receptors (RXR) and serve as ligand-activated transcription factors that play significant roles in the metabolism of lipids and inflammation.

1.2. The Role of Fatty Acids in Metabolic Pathways

The essential FAs play a critical role in metabolism, where the key point is the ratio of the polyunsaturated n3 and 6 [18]. Recent research highlights the importance of mono- and polyunsaturated FAs. For example, arachidonic acid (AA) is involved in metabolic pathways as an “ancestor” of the numerous lipid mediators, for example, eicosanoids [19]. The importance of concentration of AA (C20:4n-6), dihomo-γ-linolenic acid (DGLA; C20:3n-6), eicosapentaenoic acid (EPA; C20:5n-3), and docosahexaenoic acid (DHA; C22:6n-3) in the liver reperfusion was emphasized by Kirac et al. They analyzed liver tissue specimens and observed that the ratio of AA/DHA was significantly increased while AA/EPA remained the same [20]. The neuroprotective role of free fatty acids, such as AA and docosahexaenoic acid (DHA; 22:6), in brain I/R injury in rats was the main reason for their rapid accumulation, as shown by Adibhtala et al. [21]. In the same study, the authors concluded that increasing the concentration of ceramide inhibits mitochondrial electron transport, which leads to cell apoptosis. Montero-Bullón et al. showed that I/R and starvation increase the concentration of saturated fatty acids such as C16:0, C18:0, and polyunsaturated C20:4 and C22:6, while C18:2 decreases [19]. Further, the influence of the phospholipid profile on the acute myocardial infarction was analyzed. They observed the increase of the phospholipids bearing FAs, such

as phosphatidylcholine and phosphatidylethanolamine compounds PC(18:0–22:6), PE(16:0–22:6), and PE(18:0–22:6). That conclusion was additionally confirmed in the study of Zheng et al., which pointed out the importance of PC and lysophosphatidylcholine (LPC) in brain ischemia [22]. The principal component analysis of this study emphasized the role of the monotonic relationship between the levels of PC(16:0/16:0) and LPC(16:0) and their increment in concentration. De la Monte et al. investigated the white matter cerebral lipid profile in I/R in sheep. They characterized alterations in cerebral white matter lipid profiles in an established foetal sheep model [23]. They observed that changes in CL, PC, phosphatidylinositol monomannoside, sphingomyelin, sulfatide, and ambiguous or unidentified lipids occur mainly after 48 h of I/R (I/R-48) and normalized or suppressed at I/R-72. ROS also increase the levels of oxidative phosphatidylcholines (OxPCs) in the I/R injury in the heart [24]. OxPCs may trigger apoptosis through phosphorylation of p38 mitogen-activated protein kinase (p38MAPK).

In the serum of patients who underwent myocardial infarction, 16 fatty acids were isolated as biomarkers that enable early monitoring and have diagnostic value [25]. After acute cardiac ischemia, serum levels of these fatty acids increase, indicating inhibition of their beta-oxidation (it is the dominant source of ATP in the myocardium under normal conditions). Then, during reperfusion, fatty acids are taken into the myocardium, and their beta-oxidation intensifies. The accumulation of fatty acids in the heart muscle leads to its damage with inhibition of contractility and the appearance of dysrhythmias, as well as increased oxygen consumption without a simultaneous increase in myocardial work.

1.3. Lipids as Signaling Molecules

Particular attention should be paid to lipid signaling. It is known that lipids target proteins by modulating the most important processes in the cell. At the same time, they are not deposited but are synthesized de novo, easily passing through the membranes.

One group of the essential lipid signaling molecules are ceramides (“lipid hub”). Ceramides are a family of lipid molecules consisting of sphingosine backbone and fatty acid residues. The fatty acids in ceramide, saturated or mono-unsaturated, have 14 to 26 C chains in length. Ceramides are widely present in the cell membrane, forming sphingomyelin with phosphocholine. Due to their structural characteristics, they could be found in particular cell membrane regions called rafts. Besides the structural role, they also participate in different processes such as cell differentiation and apoptosis. Ceramides are part of the lipotoxicity cascade, whose intracellular concentration increases due to various processes, such as increased synthesis from palmitoyl-CoA and serine, recycling of complex sphingolipids, dephosphorylation of ceramide-1-phosphate, or increased degradation/hydrolysis of sphingomyelin. The latter process may occur in the different phases of the IR injury. For example, early activation of neutral sphingomyelinases in the IR-injured cardiomyocytes in the presence of FAN protein (factor associated with neutral sphingomyelinases, FAN) gives rise to the increased release of ceramide and subsequent apoptosis. Further increase in the ceramide levels in cardiomyocytes occurs during reperfusion due to decreased ceramidase activity [26]. The concentration of ceramide increases in renal IR injury as well [27]. Additionally, ceramide may induce apoptosis of renal tubular cells [28]. A balance between sphingosine-1 phosphate and ceramide (anti- and pro-apoptotic signal, respectively) is essential for such a process. Ceramide stimulates pro-apoptotic Bcl-2 proteins

and increases the mitochondrial outer membrane's permeability, with further formation of reactive oxygen species, cytochrome C release, and activation of effector caspases.

In addition to the other lipid signaling molecules, such as sphingolipid second messengers, second messengers from phosphatidylinositol, or activators of G-protein coupled- and nuclear receptors, exosomes that transmit lipid signals between cells should be mentioned, both in physiological and pathological conditions (for example, ischemia-reperfusion injury, cancer, and heart failure). Exosomes, microvesicles, and apoptotic bodies belong to extracellular vesicles that transmit various signals between cells [29]. The former is released by fusion with the cell membrane and contain lipids in their membrane and intravesical milieu. For example, ceramide, cholesterol, or sphingomyelin are enriched in exosomes relative to the cells from which they originate. Exosome has been investigated during the previous decade, both for diagnostic (biomarkers) and therapeutic purposes. Further research should focus on the role of exosomes in organ crosstalk, which occurs during I/R injury.

2. Lipid Metabolism in I/R Injury

Lipids are among the major targets of ROS in oxidative stress [30]. Both free radicals and non-radical ROS (for example, superoxide anion, hydroxyl radical, and hydrogen peroxide, respectively) impair various cell molecules in oxidative stress. Along with ROS, reactive nitrogen species, RNS (e.g., peroxynitrite and nitrogen dioxide) may also affect cellular molecules in reperfusion-related oxidative stress. Activated macrophages and neutrophils release both ROS and RNS. The main intracellular sources of ROS are mitochondria and peroxisomes. Namely, mitochondrial complexes I and III release superoxide anions, which are converted to hydrogen peroxide by superoxide dismutase, and subsequently to highly toxic hydroxyl free radical in the presence of ferrous iron (the Fenton reaction).

There is ample evidence of adverse accumulation of FAs in renal I/R injury, which ultimately may give rise to lipotoxicity [5][24]. The term "lipotoxicity" refers to the condition with an unwanted accumulation of lipids in non-adipose tissues that are incapable of metabolizing them. The full mechanism of lipotoxicity remains to be clarified, but certain steps have already been explained. For example, during ischemia and reperfusion, there is decreased FA beta-oxidation and increased phospholipid hydrolysis, fatty acid uptake, and lipid synthesis. The latter could serve as an early buffer mechanism against fatty acid overload. The accumulation of non-toxic cholesterol and TGs and FAs, as well as diacylglycerol and ceramide (downstream metabolites of unsuccessful esterification or breakdown of complex lipids), was detected in renal I/R injury [31][32]. Of note, even subtle changes in lipid content, structure, function, or location in the cell may significantly impact cell homeostasis [33].

ROS produced in oxidative stress cause the release of lipid radicals from membrane TGs and PCs. The chain reaction begins with the separation of hydrogen from lipids, which gives rise to the lipid radical release and their subsequent oxidation into lipid peroxy-radicals (LOO-) [33]. These radicals are rapidly oxidized with lipid peroxidation of acyl chains. The reaction spreads in a chain with a further restructuring of membrane PCs and trapping of lipid radicals. Peroxidized acyl chains are further cleaved (Hock cleavage) to α-, β-polyunsaturated lipid aldehydes, leaving shortened acyl chains of parent TFs and PCs, which disrupt membrane structure and alter its

permeability. Polyunsaturated lipid aldehydes are highly cytotoxic and can modify cellular proteins and nucleic acids, which may lead to mitochondrial dysfunction, the unfolded protein response (UPR), endoplasmic reticulum (ER)-stress, and apoptosis. The type of lipid aldehydes depends on the local milieu, i.e., the species n3 and n6 polyunsaturated FA species that dominate in the tissue affected by oxidative stress. There are different aldehyde-containing oxidized lipid products such as malondialdehyde, acrolein, 4-hydroxyhexenal (HHE), and 4-hydroxynonenal (HNE) [34]. In the liver, HHE predominates among reactive lipid aldehydes. 4-HNE has a significant role in cell damage, having a genotoxic effect, and acting as a secondary free radical messenger. It modulates the level of transcription factors involved in cell protection, such as Nrf2, activating protein-1 (AP-1), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and peroxisome proliferator-activated receptors (PPAR). We would particularly emphasize the role of lipid hydroperoxides in cell damage because they are much more stable substances than reactive oxygen and nitrogen species.

Cardiolipin (Calcutta antigen) or 1,3-bis(sn-3′-phosphatidyl)-sn-glycerol) is an important component of the inner mitochondrial membrane that accounts for ~20% of its total lipid content. Cardiolipin serves as a stabilizer of mitochondrial cristae and is vital for the integrity of the respiratory chain. On the other hand, it is susceptible to lipid peroxidation and formation of HNE, which is an essential part of the intrinsic (mitochondrial) pathway of apoptosis. Peroxidation of cardiolipin by hydrogen peroxide triggers the release of cytochrome C and its transport to the outer mitochondrial membrane, which initiates apoptosis [35]. Further, oxidized cardiolipin itself migrates to the outer mitochondrial membrane, where it triggers the formation of mitochondrial voltage-dependent anion channel through the interaction with Bax, apoptosis regulator, and a member of Bcl2.

Reactive lipid aldehydes are very stable and easily diffuse inside and outside the cell. On the other hand, they easily react with proteins and nucleic acids. The reaction between lipid aldehydes and proteins is called protein carbonylation. It may cause either loss-of-function modification of certain proteins, for example, enzymes of glycolysis, or a change in protein function and their interactions. In addition, carbonylation may inhibit protein degradation and can be used as a biomarker of oxidative stress. In particular, such modification of proteins within the endoplasmic reticulum (ER) may trigger ER stress and the accumulation of unfolded proteins. Antioxidant enzymes such as glutathione S-transferase inactivate lipid peroxidation products and prevent protein carbonylation.

Lipid peroxidation is closely related to ferroptosis as a type of cell death distinct from apoptosis, necrosis, etc. [36]. Depletion of glutathione or inactivation of glutathione peroxidase 4 triggers ferroptosis. Neither caspase-3-induced cleavage of poly (ADP ribose) polymerase 1 nor the release of cytochrome c from mitochondria are detected. Instead, it is characterized by an excessive peroxidation of polyunsaturated fatty acids, including membrane PCs. Ferroptosis plays a key role in hepatic and renal I/R injury. Surprisingly, Shimada et al. [37] reported that statin-mediated inhibition of HMG-CoA reductase actually facilitates ferroptosis, which is in contrast to many studies showing protective effects of simvastatin in the acute renal I/R injury [38][39]. Such a discrepancy can be explained by the fact that the pleiotropic effects of a single dose of statins initiate other protective mechanisms compared to their lipid-lowering action.

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