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REVIEW PAPER

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Membrane lipids under norm and pathology

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ABSTRACT

Introduction. Lipid is an essential component of the cell and its organelles membrane. The uniqueness and selectivity of lipids to specific functions and asymmetry of lipid distribution in the organelle's membrane give the cell ability of being highly qualified and specified.

Aim. The paper provides a comprehensive review of membrane lipids in different tissues and organelles of the cell in norm and disease.

Material and methods. The paper analyzed the present literature data on membrane lipids behavior in physiology and pathology.

Analysis of the literature. The major structural and functional lipids of the cell membrane are phosphatidylcholine > phosphatidylethanolamine. The absence/deficiency or augmentation of a specific type of lipid results in serious defects and usually life-threatening with a permanent disability. The observations discussed here suggest, the lipid peroxidation severity depends on the membrane lipid composition of the cell. Some tissue cells can handle lipoperoxidation and protect themselves from the peroxidation damaging products better, while other cells cannot compensate. Therefore, some organs are highly sensitive to peroxidation and irreversible changes occur rapidly.

Conclusion. To sum up, the understanding of lipid's role in norm and disease is clinically crucial to evaluate a novel therapeutic target to treat many metabolic disorders such as metabolic syndrome and some lysosomal storage disorders via targeting specific new signaling pathways, lipid molecules, and enzymes.

Keywords. cholesterol, lipid distress syndrome, membrane lipids, peroxidation, phosphatidylcholine, plasmenylethanolamine

The list of abbreviations:

AD - Alzheimer disease, Akt - protein kinase B, Chl - cholesterol, Co-Q - coenzyme-Q, COX - cyclooxygenase, Hsp70 - heat shock protein 70, IMM - inner mitochondrial membrane, INM - inner nuclear membrane, LOX - lipoxygenase, LT - leukotrienes, MAM - Mitochondria associated Membrane, MDA (MA)- malonyldialdehyde (Malondialdehyde), NE - Nuclear Envelope, OMM - outer mitochondrial membrane, ONM - outer nuclear membrane, PA - phosphatidic acid, PC (PtdCho) - phosphatidylcholine, PE (PtdEtn)- phosphatidylethanolamine, PhA_2 - phospholipase A2, PG - Phosphatidylglycerol, PlsC - plasmenylcholines, PE (PlsEtn)- plasmenylethanolamine, PrP - prion

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protein, PS (PtdSer) - phosphatidylserine, PSD - phosphatidylserine decarboxylase, PUFA - polyunsaturated fatty acid, SL - sphingolipid, SM - sphingomyelin, VSMC - Vascular smooth muscle cells, ARE- antioxidant response element, NFE2- nuclear factor erythroid 2, Nrf2- nuclear related factor 2, GPX4- Glutathione peroxidase 4, ER- endoplasmic reticulum

Introduction

In 1855, at the age of 34, Rudolf Virchow stated his popular aphorism "the whole pathology is the cell pathology".[1] For many years it was believed, all diseases begin on the cell level until recently when well developed the molecular biology field and the appearance of high-resolution images. In fact, the pathological process digs deeper inside the organelles of the cell that can be considered as complete structural and functional units that combined and give rise to this magical machinery unit called a cell. Usually, membrane lipids build in double layers to have more efficacy in their function. Since lipids constitute 40% of the cell and its organelles membrane with their irreplaceable functions, this yielded the importance of studying the lipids structure, function, and their role in norm and pathology.[2] The membrane lipids are the primary units of normal cell physiology and anatomy. The membrane lipids are extremely important because they condition the proper environment for the cellular processes. Physiologically, the membrane lipids function differently from each and are unevenly distributed in different cell compartments according to their task including receptor, signaling pathway as a first and second messenger, protection against prions, regulate permeability and membrane surface charge, and ion supply to the cell. Disturbance to such crucial and complex units in the cell with no doubt results in serious defects (ex. Gaucher disease and Tay-Sachs disease). Lipids consist of oxygen, carbon, and hydrogen; some may have phosphate and nitrogen. In humans, there is approximately a thousand major lipid including phospholipids, triacylglycerols (TAG), and sterols, besides the minor lipids.[3] The organelles lipid bilayer membrane contains variable admixtures of lipid depending on the task assigned to it. For instance, in the mitochondrion, the lipids comprise up to 25% of the inner mitochondrial membrane (IMM).[3] While the endoplasmic reticulum (ER) has the same lipid structure of the outer nuclear membrane (ONM), but in less cholesterol (Chl) concentration due to different functions.[4–6] The lysosome, peroxisome form a single phospholipid layer, and Golgi apparatus membrane lipid consists of phosphatidylserine (PS), sterols, and sphingolipids.[7] (Table 1) The major lipids of outer plasma membrane leaflet are phosphatidylcholine (PC), sphingolipids (SL), and cholesterol while in the cytosolic surface phosphatidylserine and phosphatidylethanolamine (PE). To sum up, the understanding of lipid's role in norm and disease is clinically crucial to evaluate a novel therapeutic target to treat many metabolic disorders such as metabolic syndrome and some lysosomal storage disorders via targeting specific new signaling pathways, lipid molecules, and enzymes. The lipidated proteins contribute to the appearance of a wide range of diseases since lipids build a critical percentage of the cell. The presence of lipids in such an amount determines the function and health of cells therefore revealed the importance of studying the composition and metabolism of membrane lipids in norm and disease besides lipid homeostasis disorders has become an urgent problem in recent decades.

Aim

The study aimed to analyze the literature data on the problem of homeostasis of membrane lipids in various intracellular structures of body tissues in the norm and pathology in addition to the function of each in the pathogenesis of diseases. The review comprehensively will discuss the major membrane lipid types, lipid biosynthesis and degradation, protein lipidation and lipid rafts, and lipid peroxidation.

Material and methods

The paper analyzed the present literature data on membrane lipids behavior in norm and pathology.

Membrane lipid synthesis and conditioning

Every synthesis process begins from the nucleus by stimulating a specific sequence of DNA, which then passes through the central dogma and gives rise to proteins that can serve and do their great duty. However, for the lipids, it is somehow different, since they are taken directly from the food that you intake as a chylomicron which contains TAG, then breaks down into free fatty acid and glycerol (therefore, the researcher believes that obesity is not hereditary, it's just a metabolic disorder, may be explained by the disturbance in the regulation mechanisms of lipid synthesis). Besides, some of the fatty acids are synthesized from Acetyl Co-A and NADPH.[8] What is interesting that the cell uses only 5% of its genome to synthesis all these various types of lipids.[9] Scramblase; present on the cytosolic surface of the ER while the flippases and floppases are present in the cytosolic surface; responsible for picking up the phospholipids and flipping them to the opposite side to balance the absolute number of phospholipids. There are up to 200 different types of phospholipid molecules depending on the need of this particular cell.[10]After the inflows of the food to the cells then they break down by specific enzymes to form free fatty acids and phosphate. Then the fatty acid will bind with the phosphate group through specific enzymes present on the outer surface (cytoplasmic leaflet) of ER, so they will add phospholipids

only to the outer surface of the ER (It's not known how the phosphoglycerolipids across the ER bilayer).[11] Thus, lead to augment the density of the cytosolic leaflet and its bending. This tension and change in physical properties in the membrane are detected by scramblases. Then, scramblases will randomly pick up non-selective phospholipids and flip them to the opposite side (luminal side) to sure the number of phospholipids on both sides is the same. Once the membrane has been made in the ER, it is sent through the cytoskeletal that connects with the Golgi apparatus (lipid trafficking/modifications).

The Golgi apparatus does not synthesis a new phospholipid membrane; it only modifies the lipid according to the necessity in different types of cells. Two basic rules in Golgy work; different locations (nucleus, lysosomes, peroxisome, ER, plasma membrane) within the cells have different needs, therefore they have different chemistry. Asymmetry of the inner and the outer surface working structure of the membrane (leaflet). It is responsible for conditioning the phospholipid bilayer, giving its specificity and selectivity even in the different parts of the same organelle or membrane. The question is how Golgi does that, and how does it know the destination to which it should send.[10,16]

Flippases and floppases present on the cytosolic surface of the Golgi apparatus too, they are specific for every phospholipid molecule (because there different shapes and active site differences). Flippases flip specific phospholipid molecules (maybe all these specific phospholipid molecules or just a percentage) from the outer surface to the inner surface (cytofacial), more exactly the PS and PE. Floppases work oppositely by flipping another specific phospholipids molecules from the cytosolic surface (PC, SL, and Chl) to the outer surface to correct the asymmetry of deposition of the phospholipids which has done by the scramblases. All these processes are against gradient therefore they use ATP. The flip-flop process occurs less than once a month for any individual molecule.[14] On the interior surface of Golgi present specific enzymes that can add sugar groups to the inner surface phosphate heads, later through a specific orientation, these sugar groups will found only on the outer membrane to form glycolipids. Therefore, the Golgi can modify the chemistry of phospholipids directly or indirectly to condition it to the location where it is needed to do its job.[10]

When the lipids have synthesized in the ER, they are sent to their final destination (plasma membrane, nucleus membrane, ER membrane, lysosome membrane, peroxisome membrane, and to the Golgi complex structure membranes) through an elusive non-clear mechanism, suspected to be by one of these pathways; the serum albumin, lipoproteins, vesicle transport, lipid transfer proteins (LTPs), lipid lateral diffusion through membranes, free diffusion through the cytosol, membrane to membrane contact, lipid flip-flop.[3,17–19] Glycerophospholipids undergo base-exchange, methylation, and decarboxylation reactions for interconversion. These reactions and activities of phospholipases A_2, C, and D are involved in the turnover, compositional maintenance, and rearrangements of glycerophospholipids in the membrane.[20]

Membrane lipid degradation

The etiological clues that damage the lipid layer structure of different organelles of the cell are: free radicals; reactive nitrogen species, reactive oxygen species, star-

Table 1. Lipid composition of subcellular fractions of rat and human liver cells, a membrane of human RBC, neuron, and myelin. Data from.[3,12–15] N.D. indicates not detected and blank indicates not analyzeľd. (OMM; outer mitochondrial membrane, IMM; inner mitochondrial membrane, NE; nuclear envelope, ER; endoplasmic reticulum)

	Rat liver cell (mol % of total phospholipids)														
	Mitochondrial Membrane			Endoplasmic reticulum Membrane	Lysosome Membrane	Golgi Membrane	Plasma membrane	NE	Human RBC Membrane	Neurons	Myelin	Mammalian Liver cell	Human ER	Human mitochondria (IMM and OMM)	Lysosome membrane
	Total	OMM	IMM												
PC	44	54	40	48-60	48	51	40	44	20	48	11	45-55	48	38	23
PE	35	29	34	19-23	13-17	21	24	17	18	21	17	15-25	19	29	13
PI	5	13	5	8-10	6	12	8	6	3	7	1	10-15	8	3	6
PS	2	2	3	2-4	0-3	6	9	4	7	5	9	5-10	4	0	-
Cardiolipin	14	<1	18	1	1-5	1	1	1	-	0	-	2-5	-	14	5
Phosphatidic acid	<1	1	-	1	1	<1	1	-	-	-	-	1-2	-	-	-
SM		1		3-5	23-24	8	17	3	18	4	8	5-10	5	0	23
	mol % of total lipids														
Chl	3	N.D.	N.D.	6	14	8	50	10	20	11	28	10-20	6	3	14
Glycolipid		Trace		Trace	-	0	-	Trace	3	3	20	-	Trace	Trace	-
Others		21		10	16	43	-	11	11	1	6	-	10	13	16

vation, ischemia, toxins, high intracellular Ca^{+2} level, some types of snake venom, etc.[21] The process of degradation of the membrane lipid may be enzymatically derived (physiologically) or non-enzymatically (pathologically) such as free radicals results of lipid membrane peroxidation.[22] The chain of damage by free radicals continues if the protecting antioxidant defense system cannot eliminate the free radicals. In compensated state degradation done by the phospholipase group of enzymes PhA_2, the most important one is the Ca^{+2} independent PhA_2 enzyme. When they do so this results in the formation of arachidonic acid, then enzymatically transferred into eicosanoids (leukotrienes, prostacyclins, and prostaglandins). Three main pathways for eicosanoids formation, firstly by cyclooxygenase (COX) enzyme synthesis prostaglandins (PG_s), thromboxane A2 (TXA_2), and prostaglandins I 2 (PGI_2) then via some reactions the PG_s reduces into PGG_2 and PGH_2, these are unstable molecules and short-lived.[23] Their synthesis depends on the expression of specific PG-synthesizing enzymes.[23,24] For instance, the TxA_2 is synthesized in platelets and macrophages, whereas PGI_2 is the dominant COX product of macrovascular endothelial cells.[24,25] Secondly, the lipoxygenase (LOX) enzymes such as 12-lipoxygenase and of particular importance 5-lipoxygenase which responsible for the synthesis of leukotrienes (LT) that contribute to the host defense and immediate-type hypersensitivity reactions.[25,26] Finally, through the cytochrome P450 enzymes can catalyze the arachidonic acid and result in the formation of hydroxy or epoxy derivatives of arachidonic acid as their major products.[27] In addition to the enzymatical pathway, there is a non-enzymatically pathway due to the effect of free radicals, lipid peroxidation, and lipids stress syndrome that can lead to the formation of PG-like compounds called isoprostanes.[28,29]

Protein lipidation and lipid rafts

After lipids uptake by lipophagy, it is stored intracellularly in the form of lipid droplets. Lipidation of protein is a term used to describe a protein conjugated with membrane lipids that physiologically attributes to membrane trafficking, control localization, organelle specificity, and intracellular signaling pathways.[30] In contrast, lipidation contributes to the development of various pathological disorders such as cancer progression and some neurodegenerative prion diseases, particularly via Rab25 gene mutation results in breast and ovarian cancers development, while mutation to palmitoylation of c-Src proto-oncogene tyrosine-protein kinase leads to prostate cancer. Besides, GPI-anchored disorders were found to be correlated with paroxysmal nocturnal hemoglobinuria (PNH).[31–33] The lipid rafts are glycolipoprotein lipid microdomains that range from 10–200 nm in size, present on the plasma membrane; consisting of glycosphingolipids, cholesterol, and protein receptors. The lipid rafts participate in various signaling transduction such as EGF, IgE, T- and B-cell antigen receptor signaling. Also, they serve as a platform for virus entry into the cells.[34]

Membrane lipid alteration under peroxidation

Peroxidation is a broad process that encompasses destroying membrane lipids, membrane proteins, enzymes, receptors, and even the ion channels, therefore in the clinical setting can find elevation in the hydrophobic and hydrophilic products of peroxidation.[35,36] Lipid peroxidation (LP) begins with initiation through the propagation and eliminates with termination.[37–39] LP starts after the abstraction of a hydrogen atom from a methylene group of polyunsaturated fatty acid (PUFA) that results in the formation of unstable carbon-centered free radicals, peroxyl radicals, alkoxyl radicals, and lipid hydroperoxide derived from unsaturated fatty acids; phospholipids; glycolipids; cholesterol esters, and cholesterol itself.[37,40] The later degradation to hydrocarbons, alcohols, ethers, epoxides, F2-isoprostane, and aldehydes.[41] Malondialdehyde (MDA) and the 4-hydroxy-2-nonenal (4-HNE) are the main functioning products of lipid peroxidation that can provoke apoptosis in addition to the inhibition of the gene expression process.[42–44] The aldehydes can cause damage to a far distance from their origin due to their relative long-lived, that promote aldehydes binding to the macromolecules and cause further damage by lipid peroxidation. The endogenous origins of the reactive oxygen species are the mitochondria, ER, plasma membrane, peroxisomes.[45] Melatonin and albumin show to have free radical scavenger and antioxidant effects.[46–48] PhA_2 serves as a secondary antioxidant via the elimination of the products of peroxidized fatty acid and forming a new one. If it is not completely replaced by a new fatty acid, it can act as a detergent and destroy the membrane. Other mechanisms of defense are glutathione peroxidase, particularly the phosphohydrolipid glutathione peroxidase that scavenge the hydroperoxides.[49] GPX4 is the only known enzyme that efficiently reduces lipid-hydroperoxides within biological membranes.[40] The few previous decades findings concluded that nuclear-related factor 2 (Nrf2) induces the detoxification and elimination of exogenous and endogenous chemicals through enhancing drug-metabolized enzyme by antioxidant and electrophiles, while this requires antioxidant response element (ARE) that parallel nuclear factor erythroid 2 (NFE2)-binding motive, culminating in enhancing anti-oxidative stress response.[50] In various tissues and different types of inflammation, the lipid peroxidation effects are variable depends on cell membrane lipid type (hepatocytes, nephrons, lung cells, intestine cells, etc.). The natural detoxification organs of lipid peroxidation products are the lung, liver,

kidney. Interestingly, some researchers go further and make it organ-specific, referred to as organ lipid distress syndrome. For instance, in the lung, higher PhA2 activity and lower lipid peroxidation and oppositely in the liver.[36] The primary indicators of detoxification impairment of peroxidation products are elevation in conjugated dienes, peracids, epoxides, plasma malondialdehyde (MDA), mono-keto/mono-hydroxy(epoxy) ratio, and high activity of PhA2.[36,51,52] Moreover, a decrease in the cell protector antioxidant defense system level such as superoxide dismutase, Catalase in the peroxisome, myeloperoxidase, thioredoxin peroxidase, glutathione peroxidase, urate oxidase, heat shock protein, haptoglobin, ceruloplasmin, transferrin, bilirubin, vitamin E and C, etc.[36,53] Researchers have shown, under the uncompensated lipid peroxidation, the higher the cell content of lipid the more and intensive endotoxemia and damage to the organism, since the damaged membranes lipids become a source of toxins.[36] More importantly in the clinical setting, urine and plasma isoprostane levels have proven to be reliable markers of lipid peroxidation and oxidant stress in vivo.[28,29] The stable lipid peroxidation biomarkers help to measure the level of systematic or tissue-specific oxidative stress.[53] For example, elevated levels of urinary isoprostanes were detected in women with android obesity and in individuals with alcohol-induced liver injury.[54,55] Both conditions are associated with increased oxidant stress and inflammation, as determined by other independent markers. Generally, when present lipid distress syndrome thus leads to elevate destroying of TAG, monoacylglycerol (MG), and diacylglycerol (DG), at the same time increase in the free fatty acid (FFA) level and variable effects on the cholesterol, sphingolipid (SL), and Chl-ester in the cell. The oxidative agent increases the availability of PE in the outer leaflet of the plasma membrane.[56] For eliminating lipid peroxidation and or its products, some studies in vitro have shown that the reduced form of Co-Q (Co-QH_2) can be described as an antioxidant.[57] Co-QH_2 is affecting the initiation process and inhibit the synthesis of lipid peroxyl radicals. Therefore, the researchers suppose it has more efficacy than quenching these radicals by tocopherol.[58,59] In the few previous years, Vlasova in vivo showed that ethoxidol has a similar modification on mild lipid peroxidation products via enhancing the self-antioxidant defense system in a mechanism still not clear, expected to be by inhibiting the formation of free radicals products through its capacity to donate electron and protection the membrane lipid to not be peroxidized.[36] Due to the role which is played by the balance between the saturated and unsaturated fatty acids in the ER lipid membrane, we may control lipid peroxidation through some medication that can minimize and inhibit the lipid peroxidation on the ER level. [60]

The major types of the membrane lipid

Phospholipids are the major structural and functional units of the membrane lipid in the plasma membrane, where they account for 60-75% of total lipids.[16,61] Phospholipids attribute to cell growth, proliferation, and cell permeability regulation depending on the fatty acid tail state. About 65% of the nuclear envelop lipids (NE) are phospholipids.[62] Therefore, disruption of the phospholipid composition is associated with a huge number of diseases.

Plasmalogens comprise about 18% of the total phospholipids mass in humans.[63] Containing two head groups; plasmenylcholines and plasmenylethalomines. About 30-40% of human heart choline glycerophospholipids are plasmalogens.[3] Plasmalogen phospholip-

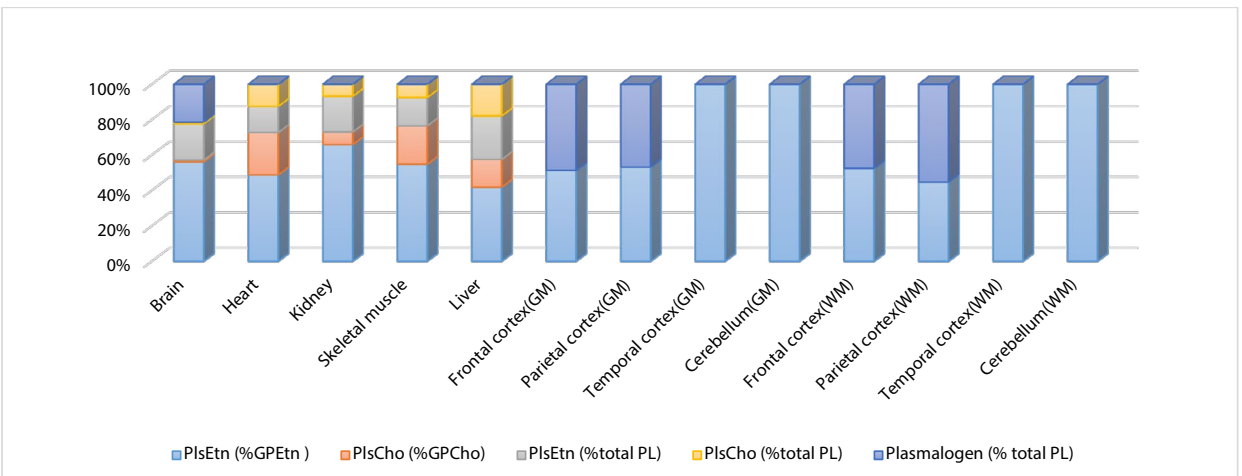

Fig. 1. Plasmalogen content in different human tissue. Abbreviations: GM; gray matter, WM; white matter, GPEtn; glycerophosphoethanolamine, GPCho; glycerophosphocholine, PLsEtn; plasmenylethanolamine, PlsCho; plasmenylcholines. The zero-percent does not necessarily mean absent. Source from.[71–74]

ids are involved in HDL-mediated cholesterol efflux.[64] Plasmenylcholine (PlsC) is known as the necessary storage for arachidonic acid in the heart.[65,66] Myelin sheath of the brain neurons has a high concentration of plasmenylethalomines and polyunsaturated fatty acid (PUFA) (Fig. 1).[4] Researchers believe plasmalogen disruption has been linked to Alzheimer's disease, Down syndrome, molecular signaling abnormalities, and cancer.[67] Plasmalogens synthesized in the ER then transported to the plasma membrane, depends on cellular ATP level. Disturbance of plasmalogen homeostasis impairs cholessterol biosynthesis.[68] Plasmalogens represent a major source of arachidonic acid, an important second messenger; it is believed that plasmalogens have a crucial role in protecting against oxidative damage.[69,70]

Sphingolipids (SL) are majorly founded in the outer leaflet of the plasma membrane, and devoid in the mitochondrial membrane. SL makes up 10% of all lipids in mammalian cells.[16] There are more than 60 different types of sphingolipids that function as a structure of different biological membranes, signal transduction, and biological recognition of these molecules.[3,75–78] Sphingomyelin is one type of SL; present in the outer membrane of the lipid bilayer plasma membrane, mostly founded in the nerve myelin sheath of myelinated neurons, lenses, and outer leaflet of the mammalian cell membrane. New research approved the anti-oxidant effect of SM in the elimination of lipid peroxidation propagation via the formation of an H-bond network within membranes as a biophysical antioxidant.[11,52] The inhibition of sphingolipid synthesis in the neurocytes is correlated with α-synuclein formation. The researchers pointed out that sphingolipids may decline with age in the human brain in PD and possible deficits of SL.

Ceramides are a key structural component of the stratum corneum of the epidermis serves as a skin barrier where they account for 50% of total lipid. Ceramides are a class of potential degradation products of sulfatides with some other molecules that are vital for the normal brain and the whole nervous system development. Ceramide Alteration is believed to be responsible for atopic dermatitis development. Their elevation in the white matter is expected to be responsible for dementia even the very mild dementia and AD.[79–82] Ceramides have a significant and key role in signal transduction in apoptosis, cell differentiation and maturation, regulatory function in the cell cycle, and cell stress.[83,84] Studies have shown that elevation of ceramide level can stimulate apoptosis in purposeless cell growth, and vice versa, the attenuation of ceramide content results in limiting the apoptosis process. For instance, in the endothelial cells and fibroblasts, ceramides regulate differentiation, maturation, and cell cycle arrest.[84–86] Ceramide synthesis inhibition prevents insulin resistance obesity, impairing the fatty acid oxidation, liver steatosis, and regulatory role in the inflammation.[43] Research has shown, ceramide can serve as a second messenger and inhibition for vascular smooth muscle cells (VSMC) division.[87–89] The ceramides are biosynthesized in the ER then transferred to the Golgi apparatus to be converted into complex sphingolipids then packed to their last destination. While GluCer and LacCer are the most common neutral glycosphingolipids in higher organisms. Elevation in their level is used as a marker of Gaucher disease (a rare lysosomal storage disorder).[90,91]

Phosphatidylglycerol is a minor lipid that comprises 1–2 mol% of phospholipids in a mammalian cell, but it has an important role and more abundant (10 mol%) in the lung surfactant. This indicates their significant role in protecting the alveoli from collapse and keep them open during expiration.[12,92] Also, researchers have demonstrated that under acute respiratory distress syndrome (ARDS) develop a depletion of phosphatidylglycerol (PG) and phosphatidylcholine (69 % from surfactant patient's fluid) via the PLA2G2A protein, which is strongly correlated to the high secretory phospholipase A2 (sPhA2) activity besides to extra alterations (elevation) in PI and SM levels in the surfactant fluid due to alteration their synthesis pathway or decreases consumption. Moreover, a novel study revealed the anti-inflammatory role of the PG in pulmonary tissue, in particular, viral infections and skin inflammatory diseases by inhibiting the DAMP. PG synthesized by head group exchange of phosphatidylcholine enriched phospholipid, using the enzyme phospholipase D. The presence of PG in the mitochondria and 20 mol% of CL in the IMM, with a high ratio of phosphatidylcholine (PC)/phosphatidylethanolamine (PE), assures its origin from bacteria.[93–96]

Phosphatidylcholine (PC) is one of the major components of the mammalian cell membrane (80%) and lipoproteins phospholipid, most of it in the outer leaflet (80%), while it accounts for 40-50% of total phosphoglycerolipids and is keenly involved in cell signaling.[9,11,97–99] About 40 mol% of the lipids in eukaryotic cells are phosphatidylcholines.[100] Choline, pyrimidine, and PUFAs are the regulatory precursors for PC synthesis. PC in the brain stimulate novel synapses formation, neurotransmitter formation and releasing, and cognition state of the individual, while thus can be of use in curing of AD. PC plays a key role in the alveoli surfactant, by forming its largest portion about 70-80% of its total lipid (90% lipid and 5-10% protein). PC forming approximately 40% of total lipids in the disks of the outer segment of the rods (light receptors, transfer electromagnetic to electrochemical signals, and has

rhodopsin and phospholipid in ratio 1:70).[101] Scientists have reported that PC microbial catabolite products; choline, trimethylamine oxide, and betaine elevate the atherosclerosis formation risk in mice, while its oral administration is used to improve ulcerative colitis.[102,103] PtdCho is primarily synthesized in the ER via repeated methylation of ethanolamine glycerophospholipids by S-adenosylmethionine (S-AdoMet), in addition to a minor pathway that seems to be similar to PtdEtn and PtdSer glycerophosphatides in the nucleus.[104] The rapid progress now being made in the area of chromatin organization as related to such factors as transcription regulation, RNA splicing, and nuclear transport mechanisms will simplify the role of lipid signaling in these processes.[5,105–107] PC is the major ER membrane bilayer phospholipid. Since the ER responsible for protein folding, therefore whatever discrepancy between its demand and supply for PC results in attenuation of its capacity for protein folding that culminates in unfolded protein response (UPR).[108–110] PC is required to facilitate the translocation of protein chain across the ER membrane due to its fluidity like property, moreover, its deficiency in the ER results in promoting calcium transport.[60]

Phosphatidylinositol (PI) is a major inner leaflet of plasma membrane phospholipid that comprises 10 %.[100] Usually found in brain tissue where it accounts for 10% of total phospholipids, while 98 % of the total in the liver and about 92 % in the brain are PI. PI is mostly founded in the INM and IMM where they are expected to be responsible for maintaining Ca^{2+} homeostasis in the nucleoplasm.[111] There are two important roles played by the plasma membrane PI when phosphorylated, first, they are the site for binding other enzymes, secondly, serve as a substrate for phospholipase C. When PI has been broken down this gives inositol triphosphate and diacylglycerol each of which important for further signaling events. Anderson and his colleagues have shown, a homozygous mutation in LPIAT1$^{-/-}$ (gene coding for variable PI species) reduces the PtdIns and PtdInsP2 content in the brain and liver approximately 26–44%, also PC and PE levels by 47% and 55% respectively, and non-compensable elevation in the less abundant PI species; lyso-PtdIns by 300% and 525% respectively, confirming reacylation disorder.[112] After hydrolyzing PI into DAG and inositol triphosphate, they serve as a second messenger in signal transduction, gene expression, hormone signaling transduction and metabolism, ion channels, pumps, transporters, control both endocytic and exocytic processes, and vesical traffic.[8,113–120] While these events can initiate parallel metabolic cascades that can mobilize intracellular calcium stores, activate protein kinase C, and release arachidonic acid. PI comprises 7-15 % of total phospholipids in the mitochondria where it is synthesized in small quantities. PI biosynthesized in the ER from phosphatidic acid via the intermediate cytidine diphosphate-diacylglycerol (CDP-DAG) derived by the rate-limiting enzyme CDP-diacylglycerol synthase (Fig. 2).[12] Its synthesis rate is regulated by the relative concentrations of the precursors and products. The phosphatidylinositol cycle proteins are responsible for transferring lipids between the ER and plasma membrane in both directions through membrane-associated family (PITPNM or nir2). The dysregulation of PI metabolism and signaling is a factor in many diseases, including cancer. Mutation in the phosphatidylinositol glycan class A (PIGA) gene results in Paroxysmal Nocturnal Hemoglobinuria.[121] The PI widely present in the ER much of it in the cytoplasmic surface, its deficiency results in ER stress that ends with unfolded (misfolded) protein response (UPR) in addition to extra metabolic disorders. While the external supply of PI precursor (myoinositol) could be beneficial for ER by enhancing its function and response to ER stress, insulin resistance (still ambiguous but thought to be through improving the putative inositol-containing mediators signaling pathway), and non-alcoholic liver steatosis. Alongside PI shown benignant effects on the weak spermatogenesis, polycystic ovary syndrome, gestational diabetes, metabolic syndrome, and retinopathy of prematurity.[122]

Phosphatidylserine (PS) is one of the essential components of membrane phospholipids where it accounts for 3-5 mol% of total phospholipids in the mammalian cell and approximately 2-15% of total phosphoglycolipids in the plasma membrane mostly in the inner leaflet (80%).[8,123] PS is most abundant in the brain tissue where it comprises 15% of total lipid.[101] More than 36% of the PS in the gray matter consists of docosahexaenoyl acyl chain, it is believed they responsible for normal brain and visual system functioning and development.[124] PS contributes to the activation of the synaptotagmin, dynamin-1, Annexin V, protein kinase C that regulates PS synthesis by phosphorylation (in vivo), and protein kinase B (Akt).[125–128] PS exposure to the cell surface has a significant role in platelet aggregation as well as in the elimination of apoptotic cells by the macrophages.[129–133] On the contrary, PS exposure to the inner leaflet results in plasma membrane bending and endosome formation.[134] The intracellular function of PS had not been discovered until recently, its ability to target proteins to phagosomes, and enhancing ion channel synthesis in the plasma membrane by binding to the heat shock protein (Hsp70) as well as caveolae formation in the plasma membrane through the signaling events.[135–137] PS comprises 13% of the total phospholipids of the disks of the outer segment of the rods.[99] Study by Zachowski on the erythrocyte membrane indicates that > 96% of PS resides on the inner leaflet of the bilayer lipid membrane.[138] PS lowest concentration in the mitochondria

particularly in the IMM.[139] PS biosynthesized by calcium-dependent base-exchange reactions in the ER where there is liberation for one polar head group choline or ethanolamine from the pre-existing phospholipid by the enzymes PS synthase-1 and PS synthase-2 in the mitochondria-associated membrane (MAM).[140,141] Through direct ER/MAM contact sites PS is transferred to mitochondria for decarboxylation and PE synthesis by phosphatidylserine decarboxylase (PSD).[142] PS is obligatorily required for cell viability, and its synthesis is regulated by PS cellular level. PS synthase-1 mRNA is highly activated in the brain, liver, and kidney.[143] While PS synthase-2 mRNA is expressed in the nurse cells of the testis and less in the liver and the brain.[144–146] Disruption to PS synthase-1 impairs the PS synthesis in 95% and appears to be responsible for Lenz-Majewsky syndrome development.[11,147] The elevation of osteoclast PS level showed to enhance bone formation with no change in the resorption rate.[148–150] Studies have shown that in the first stages of cytotoxic T-cell apoptosis increases the PS as well as PE level on the outer leaflet of the plasma membrane. Other findings indicated that tumor vasculature endothelial cells and cells under irradiation have elevated PE level on the outer leaflet plasma membrane too.[151–153]

Phosphatidylethanolamine (PE) compromises about 20-40 % of total phospholipids, while it accounts for 15-25% of total phospholipids in the mammalian cell.[11,100,154] PE distributed asymmetrically between the inner and outer leaflet plasma membrane (approximately 80% in the inner leaflet).[8,97,123] For instance, 5% out of the total phospholipids in the outer leaflet of the human RBC plasma membrane are PE.[155] Diacyl, alkylacyl, and alkenylacyl are the three main PE subgroups. Alkenylacyl accounts for 0.8% of the hepatocytes, while in the brain plasmenyl PE comprises 70% of total ethanolamine phospholipids, particularly 30% of neurocyte plasma membrane from total phospholipids and 90% from the ethanolamine phospholipids.[67,70] Researchers believe that the senile attenuation in PE level in the brain responsible for PD development via the formation of α-synuclein foci (unfolded or misfolded protein) in the Lewy bodies of the damaged dopaminergic neurons of pars compacta.[156–160] PE is required in the cytokinesis for disassembly of the contractile ring, also to evoke membrane curvature and fusion.[161,162] PE makes about 45% of total phospholipids in the nervous tissue such as the white matter of the brain and spinal cord. PE functions as an endogenous cofactor that by itself can facilitate prion propagation using PrP molecules from multiple animal species and without the assistance of any proteins or nucleic acids.[139,163] PE present in the inner mitochondrial membrane (IMM) in the highest concentration (40% of total phospholipid) than any other intracellular organelles lipid membrane. Moreover, sometimes there is a possibility to develop antiPhosphatidylethanolamine autoantibodies result in phospholipid syndrome.[164] PE accounts for 40% of the total phospholipid in the disks of the outer segment of the rods.[99] PE biosynthesized by four different pathways, one in the mitochondria (PSD pathway contributes in 5%) and the others in the ER (CDP-ethanolamine pathway contributes to 50% of rat hepatocytes PE synthesis, base-exchange pathway contribute to synthesis 8-9% of PE in the rat hepatocytes, and through the acylation of lyso-PE).[165–168] Most likely, it depends on the type of the cell to determine which pathway to use, for instance, fibroblast produces 80% of its PE through the PSD pathway.[169] The de novo pathway is regulated by the NF-Y transcription factor, protein kinase c-mediated phosphorylation.[170,171] PE, phosphatidic acid (PA), phosphatidylglycerol (PG), cardiolipin (CL), and CDP-DAG can be synthesized in the mitochondria as an auxiliary pathway.[172,173] The disruption or decrease of PE synthesis in the mitochondria results in impairment of the mitochondrial respiration activity of proteins of ETC and even mitochondrial morphological alterations and its fragmentation, this endorses the hypothesis that mitochondrial PE synthesized inside of the mitochondria. The mitochondrial malfunction is thought to be correlated with the development of serious defects such as neurodegeneration progression, cardiovascular dysfunction (due to its cardioprotective role against ischemia/reperfusion injury through activating STAT-3 transcription factor).[174–176] Besides, it has been shown that elevation in the PE ratio to the PC in the mitochondria could have opposite effects by stimulating mitochondrial respiration activity of ETC proteins and energy liberation. The PSD-derived PE plays an important role in the autophagy process through binding to LC3 protein and autophagosome formation, therefore PE deficiency leads to impairment autophagy and processing of GPI-Aps.[165,177–179] In addition to its role in the mitochondria, PE has a significant structural and functional role in the ER membrane shows that the misbalance between the PE/PC ratio of 1.3 in the ER membrane can activate the UPR.[60,180,181] And this would explain how the neurodegeneration progress under low PE level in the dopaminergic neuron and how choline could rescue the low content of PE in vitro. PE also contributes to the cannabinoid receptors synthesis in the brain.[182] Recent studies have shown that ferroptosis can oxidize the PE and forming cytotoxic species, which can be prevented by decreasing the content of long polyunsaturated ω^6 fatty acids with no need for Glutathione peroxidase 4 (GPX4). PE of the ER has been associated with the arachidonic acid and adrenic acid (AdA) oxidation in ferroptosis results in oxidized PE hydroperoxides species formation that kill cells.[60,183] Moreover, PE-AA-OOH molecule has been shown to promote ferroptosis,

while vitamin E inhibits oxidation through lipoxygenase (LOX) enzyme, which is considered an effective tool for ferroptosis prevention. It remains to be seen whether a link exists between ferroptosis and pathophysiological events, such as in ischemic-reperfusion injury or neurodegenerative disease. [184,185] PE is a key regulator of membrane fluidity in eukaryotic cells and helps pre-osteoclast fusion to form osteoclasts.[186,187]

Cardiolipin (CL) binding of PG molecules to a PA molecule forms a CL that comprises 20% of total lipids.[21] Tetra-linoleyl-CL (TLCL) is the most abundant species of CL, accounts for 80–85% of total CLs, and is associated as a precursor of signaling molecules. CL is symmetrically founded with all four FA molecules enriched in the inner leaflet of the IMM mostly of the cardiomyocytes, liver, and muscles.[8,133] CL forming the CO-Q also referred to as the third complex in the IMM, which involved in ETC as an electron carrier, extra-mitochondrial electron transport, endogenously synthesized lipid-soluble antioxidant, regulation mitochondrial permeability transition pores, and activation of mitochondrial uncoupling proteins, etc.[57] Also, it contributes to the intrinsic apoptosis, therefore CL responsible for mitochondrial stability and dynamics. The translocation of CL from IMM to the OMM is a sign of cell execution and completion of apoptosis.[133,188] CL interacts with respiratory chain complexes and substrate carrier proteins that are involved in the organization of the element of ETC into a higher assembly. Many enzymes of the respiratory chain are activated by CL and its lack results in serious defects. CL insufficiency is suspected to be responsible for the development of Barth syndrome, probably due to impaired remodeling of its fatty acids.[189] CL expression on the cytoplasmic surface of the mitochondria is a positive signal for autophagy and PhA2 activity to eliminate the damaged mitochondria through the microtubule-associated protein 1 light chain 3 (LC3). CL biosynthesized from PG and cytidine diphosphate diacylglycerol (CDP-DAG) in the inner leaflet of IMM besides some reactions occur in the ER.[190–192]

Phosphatidic acid (PA) is an intermediate in glycerolipid synthesis and cell signaling.[98,193] Studies have shown that the lacking form of PA for one fatty acid moiety (Lyso-PA) is highly involved as a signaling molecule, which contributes to the proliferation, migration, and survival of cells. Lyso-PA belongs to lysophospholipids (LPLs), where they normally provoke cell survival, ply mitogenic/antimitiogenic control of the cell cycle, affect cell motility and shape, control cell specialization, regulate Ca^{+2} homeostasis, lipid second messenger, and regulate the immunological response.[117,118,194] LPLs are shown to be correlated with tumor invasion, angiogenesis, neointima development, heart ventricles development, resistance in radiation and chemotherapies, facial dysmorphism, nociception, and suckling behavior. The PA founded in little quantities in the mitochondria as a minor lipid serves as a precursor of CDP-diacylglycerol for synthesis PI and PG in mitochondria.[12,195] Finally, Lysobisphosphatidic acid (LBPA) is specific for lysosomal membrane and secondary endosomes, where it appears to play an important role in controlling the formation of multivesicular bodies.

Cholesterol (Chl) is a non-polar sterol lipid and a major membrane component; range from 0.1% to 40% depending on the cell species and which subcellular compartment is under consideration.[16] Chl serves as a precursor for all steroid hormones. Approximately 20% of human erythrocyte weight is cholesterol.[100] While trace amount of Chl in IMM present.[3] In the NE can be founded only in the ONM and ganglioside (GM1) founded in the INM of neuronal cells. Chl is embedded in both cell membrane phospholipid bilayer structure, between phospholipids and phospholipid bilayers.[100,196] Cholesterol constitutes about 50% of the total lipid. About 10% (3 that of ER) of the NE lipids are cholesterol; lesser amounts of other neutral lipids (Chl-ester, diacylglycerol (DG), and triacylglycerol (TAG)). Generally, sterols are minor lipid components in the mitochondrial membrane.[3,12,62,197] Cholesterol supports and helps to stabilize the cell membrane and imitates as a fluidity buffer by regulating the permeability during high and low temperature and prevent leakage of small water-soluble molecules.[2,197] Chl organizes clusters of transmembrane proteins into lipid rafts (segregated, ordered domains within the cellular membranes formed by SM and cholesterol 50 mol %) and as a molecular "glue" that holds together membrane lipid rafts.[3,115] Elevation in cholesterol leads to serious pathological consequences such as atherosclerosis. Chl is unevenly disrupted in the ER, Golgi, and endosomes. In spite, Chl synthesized in the ER through the mevalonate pathway but it alternatively has low Chl content (<5 mol %). Cholesterol depletion inactivates Akt and strengthens membrane–cytoskeleton adhesion to be more rigid, while cholesterol incorporation activates Akt.[198] In 1985 the laureates Brown and Goldstein won a Nobel Prize for their discovery "receptor-mediated endocytosis" of the LDL cholesterol which contributes to the building lipids of the cell membrane, that later appeared to play a key pathological role in the familial hypercholesterolemia (FH) development via a mutation of LDL receptors that leads to high LDL plasma level and atherosclerosis formation.[199] Extra investigations should be done to role-out the influence of changes in cellular cholesterol levels and cholesterol distribution among cellular membranes on cell signaling. Chl- ester is not a highly significant structural part of the cell membrane, but it constitutes a huge portion of

the adrenal glands, and they concentrate inside the fatty lesions of atherosclerotic plaques.[200]

Triacylglycerol (TAG) has three free fatty acid chains and a glycerol group. These are the main fuel depot. FFA accounts for 15% of total lipid in the NE.[62] Studies In vitro show, Pcyt2 gene mutation causes TAG and DG accumulation in the hepatocytes, indicating the impairment of DG utilization into PE that leads to fatty liver development.[201,202] In the few past years, scientists indicated that whatever disturbance in the ER membrane saturated FA and/or cholesterol culminates in UPR directly (through the misbalance) or indirectly (due to UPR).[203–207] The PUFA is a precursor in stimulating PC synthesis.

Glycolipids are one of the three major lipids of the plasma membrane and loosely founded in the mitochondrial membrane, comprise of carbohydrate and lipid with sphingosine backbone.[12,14] Glycosphingolipids build about 5-10% of lipids in the outer surface of the plasma membranes. Besides, glycolipids have an important role in intercellular communication and protect in the harsh environment on the surface of the epithelial cells. Alteration to glycolipid was shown to be related to CNS pathologies. Glycolipids are thought to be responsible for the cell recognition process in the cell-cell adhesion process. Gangliosides are the most complicated glycolipids founded in the plasma membrane of the neurocytes, due to their charge gangliosides are believed to be responsible for control membrane potential especially the Ca^{+2} at the membrane surface.[14,208]

Prenol – few data suggested that prenol is an important simple isoprenoid that functions as an antioxidant and precursor of vitamin A.[209] When sugar groups bind directly to the membrane lipid this complex is known as a saccharolipid, which serves as a major structural component of the outer leaflet of the plasma membrane.[61] Polyketides are synthesized by classic enzymes as well as iterative and multimodular enzymes with semiautonomous active sites that share mechanistic features with the fatty acid synthases, including the involvement of specialized acyl carrier proteins; commonly used polyketides or polyketide derivatives as antimicrobial, antiparasitic, and anticancer agents such as erythromycins, tetracyclines, nystatins, avermectins, and antitumor epothilones. Besides some polyketides are potent toxins.[210,211]

Conclusion

Thus, an analysis of the literature data showed that the lipid composition of membrane structures depends on the type and function of organelles and the cell as a whole, as well as the type of tissue. The uniqueness and selectivity of lipids to specific functions and asymmetry of lipid distribution in the organelle's membrane gives power to the cell to be highly qualified and specified. The major structural and functional lipids in the cell membrane are Phosphatidylcholine (PC) > Phosphatidylethanolamine (PE). The absence/deficiency or augmentation of a specific type of lipid results in serious defects usually life-threatening with a permanent disability. The apparent indicator under lipid peroxidation is the dramatic elevation of peroxidation products that smash the membrane lipids, particularly when the protecting antioxidant defense system is impaired and cannot compensate to eliminate the highly reactive species. Further study of lipid homeostasis of cell membranes will reveal new intracellular signaling pathways, functions of lipid molecules, expanding knowledge about their role in normal and pathological cells. To sum up, the understanding of lipid's role in norm and disease is clinically crucial to evaluate a novel therapeutic target to treat many metabolic disorders such as metabolic syndrome and some lysosomal storage disorders via targeting specific new signaling pathways, lipid molecules, and enzymes.

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