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COMPLEX LIPIDS

An overview of inborn errors of complex lipid biosynthesis and remodelling

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Abstract In a review published in 2012, we delineated 14 inborn errors of metabolism (IEM) related to defects in biosynthesis of complex lipids, particularly phospholipids and sphingolipids (Lamari et al 2013). Given the numerous roles played by these molecules in membrane integrity, cell structure and function, this group of diseases is rapidly expanding as predicted. Almost 40 new diseases related to genetic defects in enzymes involved in the biosynthesis and remodelling of phospholipids, sphingolipids and complex fatty acids are now reported. While the clinical phenotype associated with these defects is currently difficult to outline, with only a few patients identified to date, it appears that all organs and systems may be affected — central and peripheral nervous system, eye, muscle, skin, bone, liver, immune system, etc. This chapter presents an introductive overview of this new group of IEM. More broadly, this special issue provides an update on other IEM involving complex lipids, namely dolichol and isoprenoids, glycolipids and congenital disorders of glycosylation, very long chain fatty acids and plasmalogens. Likewise, more than 100 IEM may actually lead to primary or secondary defects of complex lipids synthesis and remodelling. Because of the implication of several cellular compartments, this new group of disorders affecting the synthesis and remodelling of complex molecules challenges our current classification of IEM still largely based on cellular organelles—i.e. mitochondrial, lysosomal, peroxisomal disorders. While most of these new disorders have been identified by next generation sequencing, we wish to emphasize the promising role of lipidomics in deciphering their pathophysiology and identifying therapeutic targets.

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Introduction

Lipids are composed of over a thousand different types of species defined as hydrophobic or amphipathic small molecules with high solubility in organic solvents. They have been broadly subdivided into simple and complex lipids, simple lipids being fatty acids (FA), sterols and acylglycerols and complex lipids being glycerophospholipids, ether phospholipids and sphingolipids (Fahy et al 2005). In addition to serving as structural components and building blocks of cell membranes and myelin, lipids are involved in membrane protein anchoring, mitochondrial cristae formation and organelle fusion and fission processes. Lipids are a reservoir of cellular energy and have been increasingly recognized as a source of lipid mediators involved in communication and signalling within and between cells. The involvement of lipids in human pathology such as the metabolic syndrome and atherosclerosis is widely studied whereas their involvement

in inherited errors of metabolism (IEM) is just emerging. The metabolism of these molecules involves all intracellular organelles and their interfaces. Their biosynthesis takes place in the endoplasmic reticulum (ER), the Golgi, mitochondria and peroxisomes while their remodelling occurs in cell and organelle membranes; ultimately, their catabolism takes place mostly in lysosomes (complex lipids) and mitochondria and peroxisomes (FA) (Table 1). Conventionally, and unlike IEM related to energy metabolism, amino acids metabolism and glycosaminoglycans, IEM related to defects in lipid metabolism have been classified according to organelles. Thus, defects in sphingolipids catabolism are classified as lysosomal diseases, defects in plasmalogens biosynthesis and very long chain FA (VLCFA) catabolism as peroxisomal diseases, and defects in cardiolipin, lipoic acid and coenzyme Q biosynthesis as mitochondrial diseases. Following this historical classification, it became difficult to classify the increasing number of newly discovered IEM in which many intracellular organelles are involved. Here, we illustrate the refinement of these disorders in a new category of IEM notwithstanding that the delineation between synthesis and catabolism of such lipid membranes can sometimes be debated due to frequent membranes remodelling.

Complex lipid structure

The fatty acyl structure represents the major lipid building block of complex lipids and therefore is one of the most fundamental categories of biological lipids (Fig. 1a, b). The fatty acyl group from FA and conjugates is characterized by a repeating series of methylene bridges that impart hydrophobic character to this category of lipids. The longest chain of branched-chain FA defines the chain length of these compounds. The large structural variability of these molecules originates from the chain length of FA as well as the degree of their unsaturation and hydroxylation (Fahy et al 2005). Glycerolipids essentially encompass all glycerol-containing lipids and include glycerophospholipids (phosphatidyl-choline, −ethanolamine, −serine and -inositol) and glycerolipids (mono, di and triacylglycerol), both groups resulting from the link between FA and a glycerol backbone through ester bounds. Phospholipids consist of a glycerol molecule, two FA and a phosphate group that is modified by an alcohol (Fig. 1c). The phosphate group represents the negatively-charged polar head, which is hydrophilic, while the FA chains represent the uncharged, nonpolar tails that are hydrophobic. These two components give to this class of lipids its amphipathic character. Triacylglycerols are different from glycerophospholipids because they have a third ester bound acyl chain instead of the phosphate group, making them completely hydrophobic (Fig. 1b) (Coleman and Lee 2004). Ether phospholipids, including plasmalogens, constitute a special class of phospholipids characterized by the presence of an ether bond at the sn-1 position of the glycerol backbone rather than an ester bond (Fig. 1e) (Brites et al 2004). Three major classes of plasmalogens have been identified: choline, ethanolamine and serine plasmalogens. Ethanolamine plasmalogen is prevalent in myelin while choline plasmalogen is abundant in cardiac tissue. Furthermore, sphingolipids are a complex family of compounds that share a common structural feature, a sphingoid base backbone that is synthesized de novo from serine and a long chain fatty acyl-CoA. The sphingoid bases are acylated with a FA forming ceramide which can carry a hydrophilic head group, especially phosphorylcholine in the case of sphingomyelin, carbohydrate residues in the case of sphingolipids and a phosphate moiety in the case of ceramide-1-phosphate (Fig. 1f) (Merrill and Sandhoff 2002; Platt 2014) .

Role of complex lipids

In mammalian cells, lipids are the second major components of cellular mass, water being the first. Cells are spatially defined by their plasma membranes in which lipids are the fundamental components; they constitute about 40 % of the dry mass of the brain. In addition to serving as structural components and providing energy storage, lipids have been increasingly shown to be involved in communication and signalling within and between cells.

Energy homeostasis and storage

Glycerolipids account for a high proportion of total lipids in plasma and comprise triacylglycerols (TAGs), diacylglycerols (DAGs), and ether-linked glycerolipids. The synthesis and storage of glycerolipids has a central role in the maintenance of energy homeostasis since TAGs are the most calorie-dense form of energy storage. The liver is a central organ in the regulation of triglycerides metabolism; it participates in triglyceride synthesis, export, uptake and oxidation. Therefore, hepatocytes can shift from intensive FA synthesis — in fed state — to rapid FA breakdown — during starvation. Hepatosteatosis, considered as the fundamental cause of hepatic injuries, inflammation and fibrosis, is often found in individuals with defect in TAG metabolism, as observed in individuals with CGI-58 (ABHD5), PNPLA2 (ATGL) and *GPD1* mutations (Reilich et al 2011; Aguilera-Méndez et al 2013; Wu and Mitchell this issue). Moreover, a lack of adipose tissue, either complete or partial, is the hallmark of disorders known as lipodystrophies, such as AGAPT2 deficiency (Agarwal et al 2002; Wu and Mitchell, Garcia Cazorla this issue). Interestingly, transient neonatal cholestatic jaundice and/or liver failure followed by neurodegenerative symptoms is a frequent finding in several IEM affecting

Table 1 Non-exhaustive overview of over 100 inherited errors of metabolism linked to primary and secondary defects of complex lipids biosynthesis and remodelling. The table reports the pathway, the corresponding gene defect, the human disease, together with the subcellular localization of the protein and the main affected organs/systems. All disorders but those indicated AD or X-linked in the table have an autosomal recessive inheritance

Metabolic pathways	N	Gene	Human disease	Subcellular localization	Main organ /system involvement
Phospholipids	2				
Phosphatidylcholine		*CHKB*	Congenital muscular dystrophy	Cyto	Muscle, CNS, bone
		PCYT1A	Spondylometaphyseal dysplasia/cone-rod dystrophy.	Cyto, membrane	Bone, eye, Dys
Phosphatidylserine		*PTDSS1*	Lenz-Majewski syndrome (AD)	Memb, ER	Bone, CNS, skin, Dys
Cardiolipin	3	*AGK*	Sengers syndrome	MIT	Muscle, heart, eye
		SERAC1	MEGD(H)EL syndrome	IMM (MAM), ER	Liver, deafness, CNS
		TAZ	Barth syndrome (X-linked)	MIT	Muscle, heart, HEM
Membranes lipids remodelling	6	*PLA2G6*	INAD/NBIA	Membrane	CNS, Eye
		DDHD1-2	SPG28/SPG54	ER, Cyt, Golgi	CNS, PNS
		PNPLA6	SPG39, Boucher-Neuhauser, Gordon Holmes syndromes	ER	CNS, PNS, eye, End
		CYP2U1	SPG49	ER	CNS, PNS
		ABHD12	PHARC syndrome	Membranes	CNS, PNS, eye
Phosphoinositides biosynthesis and remodelling	16	*PIK3CD*	Immunodeficiency	Cyt	Immune system
		PIK3R1	Autosomal recessive agammaglobulinemia; SHORT syndrome	Cyt, membrane	Immune system, Dys
		PIK3R2	Megalencephaly-polymicrogeria-polydactyly-hydrocephalus syndrome	Cyt	Dys, CNS
		PIK3R5	Ataxia-oculomotor apraxia	Cyt, membrane, Nucl	CNS
		PIKFYVE	Corneal fleck dystrophy	Membrane	Eye
		PIP5K1C	Lethal congenital contractural syndrome	Membrane, Cyt, Nucl	CNS
		PLCB1	Epileptic encephalopathy, early infantile	Cyt, Nucl	CNS
		PLCB2	Platelet PLC beta-2 deficiency	Cyt	Blood
		PLCB4	Auriculo-condylar syndrome	Cyt, Nucl	Dys
		PLCD1	Nonsyndromic congenital nail disorder	Membrane, Cyt,	Dys
		PLCE1	Nephrotic syndrome type 3	Membrane, Cyt, Golgi	Kidney
		PLCG2	Autoinflammation, antibody deficiency and immune dysregulation syndrome; Familial cold auto inflammatory syndrome	Cyt, membrane	Immune system
		FIG 4	Yunis-Varon syndrome	Golgi	Bone, Dys
		INPP5E	Mental retardation, truncal obesity, retinal dystrophy, and micropenis	Golgi	CNS, End, eye
		INPPL1	Opsismodysplasia	Cyt, membrane	Bone, Dys
		OCRL	Dent disease 2	Cyt, Golgi,	Kidney
Coenzyme A	2				
Pantothenate kinase CoA synthase		*PKAN2*	NBIA	MIT, Cyt	CNS, NBIA, eye
		COASY	NBIA	MIT	CNS, NBIA
Sphingolipids	8				
Biosynthesis		*SPTLC1-2*	Hereditary sensory autonomic neuropathies (AD)	ER	PNS, CNS, eEye
		ST3GAL5	Amish infantile epilepsy syndrome	Golgi	PNS, CNS, skin, Dys

Table 1 (continued)

Metabolic pathways	N	Gene	Human disease	Subcellular localization	Main organ /system involvement
		CERKL	Retinitis pigmentosa-26	Cyt, ER, Golgi, Nucl	Eye
		CERS1	Myoclonic epilepsy and cognitive decline	ER	CNS
		CERS2	Progressive myoclonic epilepsy (AD)	ER	CNS
		CERS3	Autosomal recessive congenital ichthyosis	Nucl	Skin, eye
		B4GALNT1	SPG26	Membrane, Golgi	CNS, PNS
		FA2H	NBIA	ER	CNS
Catabolism/recycling	>10	Lysosomal enzymes	Sphingolipidosis	Lysosomes	"Storage disorders "
Plasmalogens	2	*GNPAT*	Chondrodysplasia Punctata, type 2	Peroxisome	Dys, bone, eye, CNS
Enzyme defects		*AGPS*	Rhizomelic Chondrodysplasia Punctata, type 3	Peroxisome	Dys, bone, eye, CNS
Biogenesis defects	>10	*PEX 7*	Rhizomelic Chondrodysplasia Punctata, type 1	Peroxisome	Dys, bone, eye, CNS
		Many other PEX	Peroxisomal biogenesis defects	Peroxisome	Multi systemic
Isoprenoids	>30				
Cholesterol	8	*DHCR7*	Smith-Lemli-Opitz syndrome	ER	Dys, multisystemic
		DHCR24	Desmosterolosis	ER, Golgi	Dys, bone, CNS
		MVK	Mevalonic aciduria	Cyt	Multi systemic,immune
		EBP	Conradi Hunermann syndrome (X-linked)	ER	Dys, bone, skin
		NSDHL	CHILD syndrome, CK syndrome (X-linked)	ER	Dys, bone
		MSMO1	Syndromic late onset ichthyosis	ER	Skin, eye, CNS
		LBR	Greenberg Dysplasia (HEM skeletal dysplasia)	Membrane, Nucl	Dys, bone
		SC5D	Lathosterolosis	ER	Dys, multisystemic
Ubiquinone	8	*CoQ 2-4-6-9*	Fatal infantile multiorgan disease	MIT	Kidney, muscle, CNS, multisystemic
		PDSS1,*PDSS2*, *ADCK3*, *ADCK4*	All 8 gene mutations result in Coenzyme Q 10 deficiency .Patients may benefit from high dose oral supplementation with CoQ 10.		
Dolichol	7	*DHDDS*	DDHDS CDG	Cyto, ER	Skin, bone, eye
		SRD5A3	CDG1q	Cyto, ER	Dys, CNS, eye, heart, liver, skin
		DOLK	CDG1m	Cyto, ER	CNS, skin, bone, muscle, heart
		MPDU1	CDG1f	Membrane	CNS, muscle, skin, eye, bone
		DPM1/*DPM2*/*DPM3*	CDG1e/DPM2CDG/CDG1o	Cyto,ER	Muscle, CNS, eye, heart
Glycosylphosphatidylinositol	>10	*PIGA*	Paroxysmal nocturnal hemoglobinuria, somatic	ER	Dys, HEM, thrombosis,CNS
(GPI) anchor		*PIGL*	CHIME syndrome (PIGL CDG)	ER	Skin, Dys, CNS, eye, heart
(Glycolipids)		*PIGM*	Glycosylphosphatidylinositol deficiency	ER	Dys, CNS, thrombosis
		PIGN	Multiple congenital anomalies-hypotonia-seizures syndrome 1	ER	Dys, CNS
		PIGV/*PIGO*	Hyperphosphatasia with mental retardation syndrome1/ 2	ER	Dys, CNS, hyperphosphatasia
		PIGT	Paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome)	ER	Hematology thrombosis
		PGAP	Multiple congenital anomalies	ER	Dys, CNS
Triacylglycerol	8	*ABHD5*	Chanarin Dorfman syndrome	Lipid droplet, Cyt	Liver, skin, muscle
		AGPAT2	Berardinelli–Seip syndrome	ER	Skin, end, CNS

Table 1 (continued)

Metabolic pathways	N	Gene	Human disease	Subcellular localization	Main organ /system involvement
		LPIN1	Recurrent rhabdomyolysis and myoglobinuria	Nucl, ER, Cyt	Muscle, immune
		LPIN2	Majeed syndrome	Nucl, ER, Cyt	Immune, skin, bone
		DGAT1	Congenital diarrhea disorder	Membrane	Gastrointestinal
		PNPLA1	Autosomal recessive congenital ichthyosis (ARCI10)	Cyt	Skin
		PNPLA2	Neutral lipid storage disease with myopathy	Lipid droplet, membrane	Muscle, liver
		DGKE	Atypical hemolytic uremic syndrome	Cyto, membrane	Kidney,hematology
Fatty acids synthesis/recycling	7				
Acetyl-CoA carboxylase		*ACACA*, *ACACB*	Multiple carboxylase deficiencies (Biotinidase, HCS defects)	Cyto, MIT, ER	Skin, multi systemic
Elongases		*ELOVL 4–1*	Congenital ichthyosis and neurological symptoms.	ER	CNS, skin
		ELOV 5	Spinocerebellar ataxia and erythrokeratodermia.(AD) Stargardt (AD) Spinocerebellar ataxia (SCA 38) AD	ER	CNS, skin, eye CNS
		PTPLA	Congenital myopathy	ER	Muscle
Lipoic acid synthase		*LIAS*	Early-onset lactic acidosis and encephalopathy	MIT	CNS, PNS,
Racemase		*AMACR*	Adult onset sensorimotor neuropathy	Peroxisome	CNS, PNS, muscle, eye
Fatty alcohol dehydrogenase		*ALDH3A2*	Sjogren-Larsson syndrome	Membrane	CNS, PNS, skin, eye
Phytanyl-CoA hydroxylase		*PHYH*	Refsum disease	Peroxysome	PNS, CNS, eye, skin, bone
Leukotriens	4	*LTC4S*	Fatal developmental syndrome	Membrane, ER, Nucl	CNS, PNS, eye, skin
		ALOXE3	Autosomal recessive congenital ichthyosis	Cyto	Skin
		ALOX12B	Autosomal recessive congenital ichthyosis	Cyto	Skin
		FLJ39501	Autosomal recessive congenital ichthyosis	ER, membrane	Skin
Miscellaneous: secondary consequences on lipid synthesis					
Citrate carrier		*SLC25A1*	DL-hydroxyglutaric aciduria, neurological symptoms	MIT	CNS
Glycolytic enzymes		*TPI*	Hemolytic anemia and severe neurological deterioration	Cyto	Hem. CNS, muscle
		PGK1	Hemolytic anemia, myopathy	Cyto	Hem. CNS, muscle
		GPD1	Transient hyper TG, hepatomegaly, fibrosis	Cyto	Liver
Serine synthesis enzymes		*PHGDH*	Neu-Laxova syndrome, microcephaly, ichthyosis, epilepsy,	Cyto	CNS, PNS, skin, Dys
		PSAT1	Growth and mental retardation, microcephaly, epilepsy, hypertonia	Cyto	CNS, PNS, skin
		PSPH	Growth and mental retardation, microcephaly, epilepsy, hypertonia	Cyto	CNS, PNS, skin

Legend: *N* number of disorders described in the pathway, *INAD* infantile neuroaxonal dystrophy, *Dys* dysmorphic syndrome and/or malformations, *HEM* hematology, *MS* multisystemic, *End*, endocrinology, *Cyto* cytoplasm, *Nucl* nuclei, *ER* endoplasmic reticulum, *MIT* mitochondria, *MAM* mitochondrial associated membrane, *IMM* internal mitochondrial membrane, *GPI* glycosyl phosphatidic inositol, *AD* autosomal dominant

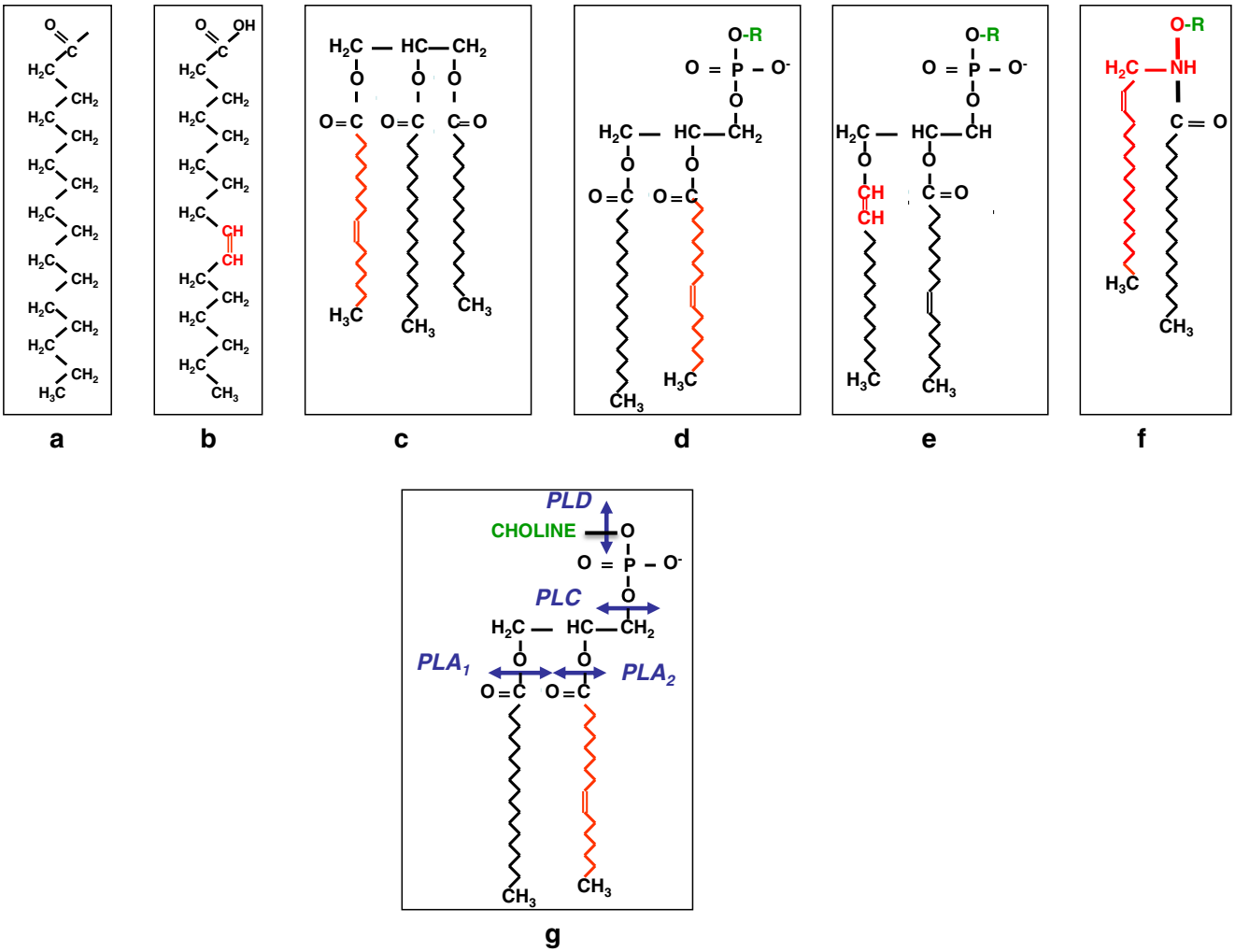

Fig. 1 Schematic structure of complex lipids: saturated (**a**) and unsaturated (**b**) fatty acids are the building blocks of complex lipids. Triglycerides (**c**) are composed of three fatty acid chains linked by ester bounds to a glycerol. Phosphatidic acid (R=H) (**d**) results from two fatty acids linked by ester bounds to a glycerol backbone at the sn-1 and sn-2 position, the third hydroxyl at the sn-3 is esterified by a phosphate group. Radical substitution (R- in green) by an organic base (Choline, ethanolamine, serine) or an alcohol (inositol), lead to the formation of the main families of glycerophospholipids (phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinositol). Ether phospholipids (plasmalogens) (**e**) are phospholipids characterized by the presence of an ether bond at the sn-1 rather than an ester bond. Sphingolipids (**f**) results from a condensation of serine with fatty acid forming the sphingoid base that can be N-acylated by fatty acid forming ceramide. The substitution of the hydroxyl (green) by an hydrophilic head group, lead to the formation of sphingomyelin, galactosylsphingolipids and glycosylsphingolipids. Phospholipids remodelling by phospholipases (**g**): phospholipases are composed of four large families of enzymes, which hydrolyze phospholipids specifically at different positions. Phospholipase A1 (PLA1), A2 (PLA2), C (PLC) and D (PLD)

phospholipids, cholesterol or FA metabolism (Garcia Cazorla this issue).

Membrane shape and structure

Glycerophospholipids, sphingolipids, plasmalogens and sterols function as major components of semi-permeable biological membranes. Their dynamics directly affects cellular processes by controlling cell and organelle membrane fluidity and permeability. The curvature of biological membranes is related to the type of lipids, especially phospholipids (PL). Phosphatidylcholine, phosphatidylserine and phosphatidylinositol are known as cylindrical bilayer forming PL, whereas phosphatidylethanolamine and cardiolipin are conical non bilayer forming PL (Garwisch 2012). This feature plays an important role in the formation of mitochondrial cristae and in organelle fission and fusion processes (Mayr this issue). Post-translational modifications by lipids, mainly glycosylphosphatidylinositol (GPI), serve to anchor proteins and glycans to membrane surfaces, thereby affecting and regulating their function including lipid raft partitioning, signal transduction and targeting to the apical membrane (Margot et al 2008). At least 26 genes are involved in the biosynthesis and modification of the GPI anchors. Recently, mutations in a

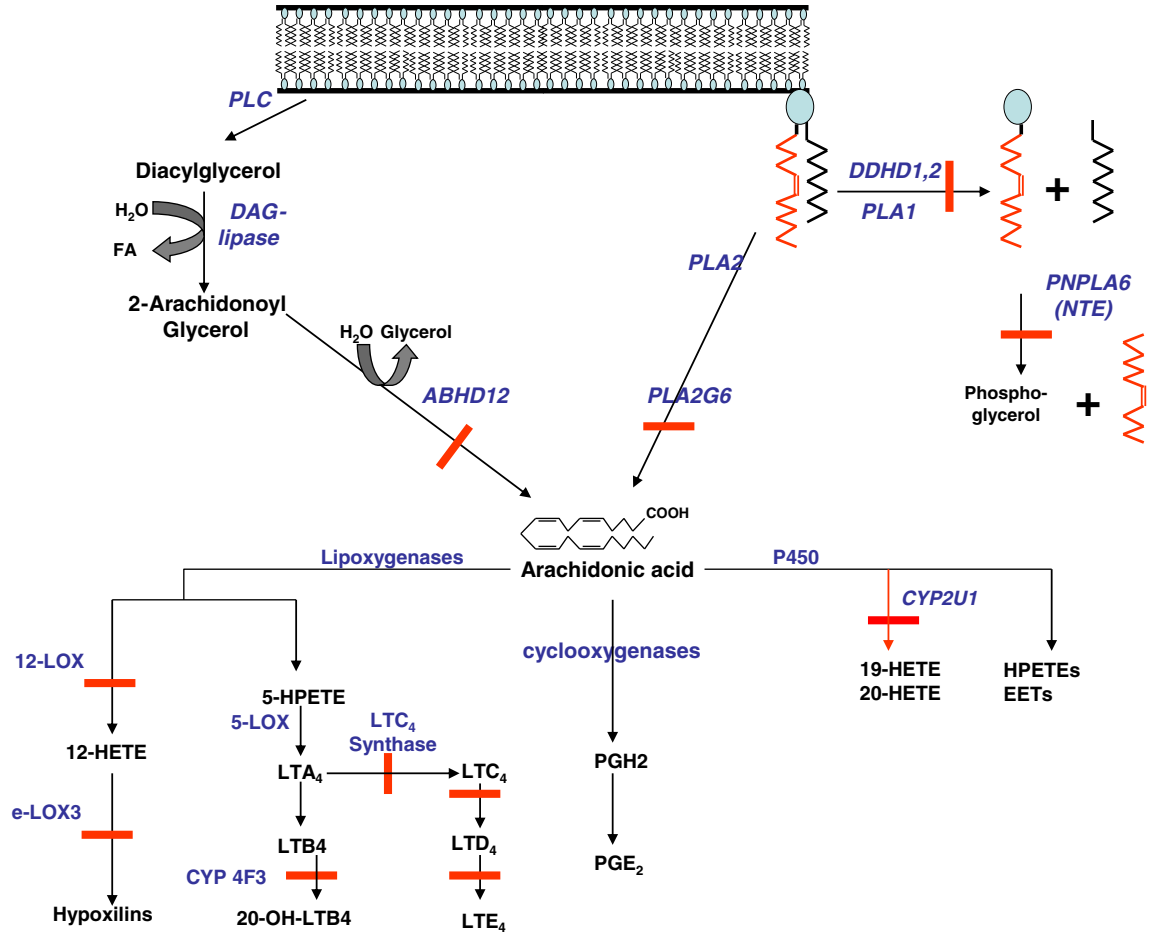

Fig. 2 Phospholipid remodelling and a simplified biosynthesis pathway of eicosanoids: Membrane phospholipids are subjected to the action of phospholipases and continually released to renew membranes and to releases bioactive lipids for cell signalling. A growing number of IEM concerning this pathway have been recently discovered. Released arachidonic acid from phospholipids by phospholipases A2, can be metabolized by three different pathways (cycloxygenases, lipoxygenases and cytochrome P450), leading to the formation of leukotrienes (LTs), prostaglandins (PGs), hydroxyeicosatetraenoic acid (HETE) and hydroxypentatetraenoic acid (HPETE). Red bars indicate inherited metabolic blocks described so far. Phospholipase C (*PLC*), phospholipase A (*PLA*), patatin-like containing protein-6 (*PNPLA6*), cytochrome P450 2U1 (*CYP2U1*), /-hydrolase containing domain-12 (*ABHD12*)

number of these genes (Table 1) have been described as causing IEM (Murakami et al 2014), (Freeze and Lefeber this issue). Besides their structural function, PL and sphingolipids are involved in membrane trafficking, signal transduction and autophagy-mediated protein degradation. Sphingolipids, including cerebrosides, sulfatides, globosides and gangliosides, are particularly abundant in the myelin sheath of neuronal cells (Kolter 2011; Levade this issue). Plasmalogens are also a constituent of cell membranes where they seem to play a role as radical scavengers and in proper assembly and function of multispan transmembrane transport proteins and ion channels (Wallner and Scmitz 2011; Brites in this issue). One particular plasmalogen (choline plasmalogen), also called platelet activating factor (PAF), has been identified as a powerful biological mediator of hypersensitivity, acute inflammatory reactions and anaphylactic shock.

Epidermal water barrier and visual cycle

A hydrophobic extracellular lipid matrix in the stratum corneum composed primarily of ceramides, cholesterol and free FA provides a barrier against the movement of water and electrolytes. Genetic defects in lipid metabolism and transporters have been associated with ichthyosis, either non syndromic autosomal recessive congenital ichthyosis (ARCI): ALOX3, ALOX12B, CYP4F22, LIPN, PNPLA1, CERS3, deficiencies (Jobard et al 2002; Lefèvre et al 2006; Akiyama 2010; Israeli et al 2011; Grall et al 2012), or syndromic, i.e. numerous neuro-cutaneous syndromes (see Garcia Cazorla this issue). This highlights the role of FA, ceramides and phospholipids in skin integrity (Feingold 2009; Oji et al 2010; Israeli et al 2011). Similarly, the lipid phase of the photoreceptor outer segment membrane is essential to the

photon capturing and signalling functions of rhodopsin. The rearrangement of PL in the bilayer accompanies the formation of the active intermediates of rhodopsin following photon absorption. Furthermore, evidence for the formation of a condensation product between the photolyzed chromophore all-trans-retinal and phosphatidylethanolamine indicates that PL may also participate in the motion of retinoids in the membrane (Sparrow et al 2010). Isolated or syndromic retinitis pigmentosa and cataracts are frequent findings in disorders affecting complex lipids and FA synthesis and remodelling (ELOVL4, ABHD12, PCYT1A, PLA2G6 deficiencies) (Garcia Cazorla this issue). The transport of lipids across biological membranes is critical in the metabolism of complex lipids. This process is typically carried out by a variety of integral membrane proteins such as ATP binding cassette (ABC) transporters. Mutations in the retinal PL transporter (ABCA4) are a major cause of macular degeneration (Molday et al 2009), whereas mutations in *ABCA12* highly expressed in keratinocyte are a cause of a non syndromic ARCI-4A (Lefèvre et al 2003).

Bone formation and calcification

The recent discovery of mutations in genes encoding enzymes involved in PL biosynthesis and remodelling highlighted the crucial role of PL in bone formation and resorption. PL were identified as major players in the crystal formation process. Indeed, it became clear that phosphatidylserine (PS), together with proteins of the annexin family, was among the most important molecules in binding calcium ions (Merolli and Santin 2009). PS plays an important role in bone mineralization by its anionic character and, thus, its high affinity for calcium. Moreover, PS enhances osteogenic differentiation via ERK signal pathways (Xu et al 2013). About 20 inborn errors affecting the synthesis or remodelling of phosphatidylcholine and PS, phosphatidylinositol, plasmalogens or cholesterol present with major bone and cartilage involvement. Besides the already well known defects of cholesterol and plasmalogen biosynthesis, original entities affecting PL metabolism have recently been described: (i) Lenz-Majewski syndrome caused by a gain of function mutation in the gene encoding phosphatidylserine synthase 1 (PTDSS1), which impairs the negative feedback regulation of the enzyme by its reaction product PS (Sousa et al 2014); (ii) spondylometaphyseal dysplasia with cone-rod dystrophy caused by mutations in the gene encoding phosphatidylcholine cytidylyl transferase (PCCT1A), a key enzyme in phosphatidylcholine biosynthesis (Yamamoto et al 2014); (iii) Yunis-Varon syndrome presenting with cleidocranial dysplasia and skeletal abnormalities, recently linked to mutations in Fig. 4 that encodes a phosphoinositide phosphatase required for the regulation of phosphatidylinositol 3,5-biphosphate (PI(3,5)P2) (Campeau et al 2013; Oikawa et al 2013); and (iv) opsismodysplasia, a severe chondrodysplasia caused by defects in inositol-1,4,5-trisphosphate 5-phosphatase INPPL1 (Huber et al 2013; Below et al 2013) (see Garcia Cazorla and Wortmann this issue).

Cell signalling

Complex lipids serve as a source of bioactive lipids, important for cell signalling and communication. The first lipids discovered as participating in cell signalling were DAG and inositol-1,4,5-triphosphate involved in the regulation of various cellular processes. Phosphorylation of the inositol ring of phosphatidylinositol by specific kinases leads to the formation of all phosphoinositides (PIPn) species (PI3P, PI4P, PI5P, PI(4,5)P2). PIPn control the regulation of ion channels, actin-cytoskeleton dynamics, vesicular transport, endocytosis, exocytosis and signal transduction pathways. Upon stimulation by growth factors, PI-specific isoforms of phospholipase C (PI-PLC) cleave PI(4,5)P2 in the plasma membranes into inositol-1,4,5-triphosphate (IP3) and DAG. IP3 is a water soluble signalling molecule which can activate Ca2+ channels and release Ca2+ from the ER. DAG itself is a potent lipid secondary messenger that can activate different DAG-binding proteins (Carsasco et al 2007). More recently, phosphatidylinositol-3-phosphate has been reported to regulate sorting and processing of amyloid precursor protein (APP) through the endosomal system (Morel et al 2013). A number of inherited disorders affecting the phosphatidylinositol phosphate synthesis, metabolism or transport have been described. They may involve either a specific organ/ system or present with multiorgan failure (Balla 2013). It should be noted that a number of mutations in these pathways are accompanied by immune dysfunctions (Table 1). This group of disorders is not extensively presented in this issue.

Other glycerophospholipids such as phosphatidic and lysophosphatidic acids monoacylglycerol and 2-arachidonoyl glycerol — ligands for cannabinoïd receptors — also serve as a key intermediates in cell signalling (Quehenberger et al 2010). Hydrolysis of membrane PL by phospholipases (mainly phospholipase A2) is crucial for releasing lipid signalling molecules such as arachidonic acid (Fig. 2). Several IEM in this pathway have been reported in humans. Arachidonic acid is the precursor of eicosanoids, giving rise to mainly pro-inflammatory molecules, including prostaglandins, thromboxanes, leukotrienes and hydroxyeicosatetraenoic acid derivatives. Another group of bioactive lipids is formed by sphingolipids such as sphingosine, which exerts a pleitropic effect on protein kinases, regulating the actin cytoskeleton, endocytosis, cell cycle and apoptosis (Hannun and Obeid 2008). Ceramide mediates many cell-stress responses, including the regulation of apoptosis, whereas sphingosine-1 phosphate has a crucial role in cell survival, migration and inflammation.

Protein palmitoylation/depalmitoylation

Lipids, and particularly palmitic acid, are involved in protein trafficking and function by post translational modification of proteins, called palmitoylation. Palmitoylation is part of a group of lipid modifications — collectively termed lipidation — that include the common N-myristoyl and isoprenyl modifications (Salaun et al 2010; Resh 2012). Such lipidation events occur in all eukaryotes and can be reversible (S-palmitoylation) or irreversible (N-palmitoylation). S-palmitoylation is dynamically regulated by two opposing types of enzymes which add — palmitoyl acyltransferases, PAT — or remove — acyl protein thioesterases — palmitate from proteins. To date, eight palmitoylation related genes have been reported to be associated with human disease including (i) Alzheimer disease — the major amyloid precursor protein APP cleaving enzyme BACE1 is palmitoylated at four sites; (ii) Goltz syndrome — caused by mutations in the Porcupine (*Porcn*) gene, a member of the MBOAT family; of note, many members of the MBOAT family are lysophospholipid acyltransferases; and (iii) neuronal ceroid lipofuscinosis type 1 due to palmitoyl protein thioesterase 1 deficiency (Hornemann this issue). There is no human disease of myristoylation known so far, but in case of prenylation, mutations in the X-chromosomal CHM gene, encoding REP1, a subunit of a 2-subunit RAB geranylgeranyl transferase, are known to cause choroideremia. (Esposito et al 2011)

IEM related to complex lipid biosynthesis

There is a close relationship between energy metabolism and complex lipids biosynthesis. Disorders of complex lipids biosynthesis may result from a primary defect in biosynthetic pathways but can also be related to defects in energy metabolism pathways (Fig. 3).

Inborn errors of glucose metabolism affecting complex lipids biosynthesis (Fig. 3)

At the high energy fed state, mitochondrial citrate is exported to the cytosol, by the dicarboxylic acid transporter SLC25A1, where it is split by citrate lyase back to acetyl-CoA and oxaloacetate. Mutations in the gene *SLC25A1*, lead to a devastating neurologic disorder with D-L-hydroxyglutaric aciduria and significant alterations on cholesterol synthesis (Nota et al 2013; Mühlhausen et al 2014). High cytoplasmic citrate reduces the metabolic flux of glycolysis by inhibiting the phosphofructokinase and redirecting metabolites to the pentose-phosphate pathway (PPP) producing NADPH and glyceraldehyde 3-phosphate (GA3P), both molecules being indispensable for complex lipids synthesis. GA3P is further metabolized to dihydroxyacetone phosphate (DHAP) and glycerol 3-phosphate through triose phosphate isomerase (TPI) and glycerol 3-phosphate dehydrogenase (GPD), respectively. Mutations in the gene *GPD1* result in a severe liver dysfunction with liver steatosis and fibrosis associated with a paradoxical transient infantile hypertriglyceridemia (Basel-Vanagaite et al 2012; Joshi et al 2014; Mitchell in this issue). Citrate also activates acetyl-CoA carboxylase (ACC) for malonyl-CoA synthesis. The synthesis of malonyl-CoA is the first committed step of FA synthesis and the enzyme that catalyzes this reaction, ACC, is the major site of regulation of FA synthesis. Defective FA synthesis has been suspected in multiple carboxylase deficiency linked to biotinidase defects (Munnich et al 1980). DHAP is the primer of plasmalogen synthesis, which starts in peroxisomes with the acylation of DHAP with long chain acyl CoAs. Subsequently, the acyl chain from acyl-DHAP is exchanged with a long chain alcohol. Metabolic blocks along these steps lead to chondrodysplasia punctata type 1, 2 and 3 (Fig. 4) (Brites et al 2004). In cells in which there is a low biosynthetic capacity for the synthesis of alcohol-derived lipids, the fatty alcohols and fatty aldehydes are reduced back to FA by a microsomal fatty aldehyde dehydrogenase, which is part of the alcohol: NAD-oxidoreductase complex that is deficient in Sjögren-Larsson syndrome (Willemsen et al 2001; Brites this issue). In the glycolytic pathway, GA3P can be metabolized by glyceraldehyde 3-phosphate dehydrogenase (GA3PDH) to 1,3-biphosphoglycerate and 3-phosphoglycerate by phosphoglycerate kinase (PGK). Interestingly both GA3PDH and PGK deficits present with severe neurological findings that could be at least partly explained by secondary disruption of lipid metabolism in the nervous system (Chiarelli et al 2012; Shaheen et al 2014). 3-phosphoglycerate is the primer of serine *de novo* synthesis that encompasses three sequential enzymatic steps, which deficiencies are responsible for severe neurologic dysfunction (van der Crabben et al 2013; Shaheen et al 2014). Sphingolipids synthesis starts with the condensation of L-serine and palmitoyl-CoA by L-serine palmitoyl transferase (SPTLC). Gain of function mutations in *SPTLC 1* and *2* cause the autosomal dominant hereditary sensory autonomic neuropathy type I (HSAN I) (Dawkins et al 2001; Bejaoui et al 2001; Levade this issue). Furthermore, the synthesis of isoprenoids (cholesterol, ubiquinone, dolichol) starts in the cytoplasm from acetyl CoA to HMG-CoA formation. HMG-CoA is further reduced by NADPH to mevalonate by the highly regulated HMG-CoA reductase. Mevalonate is the starter molecule of isoprenoids. To date, there are about 30 diseases related to defects in cholesterol, dolichol, coenzyme Q and related pathways (Lefeber, Freeze and Salviati this issue).

IEM related to FA biosynthesis and remodelling (Fig. 3)

Long chain FA (LCFA) and VLCFA, composed of different chain structure and saturation, are required for the

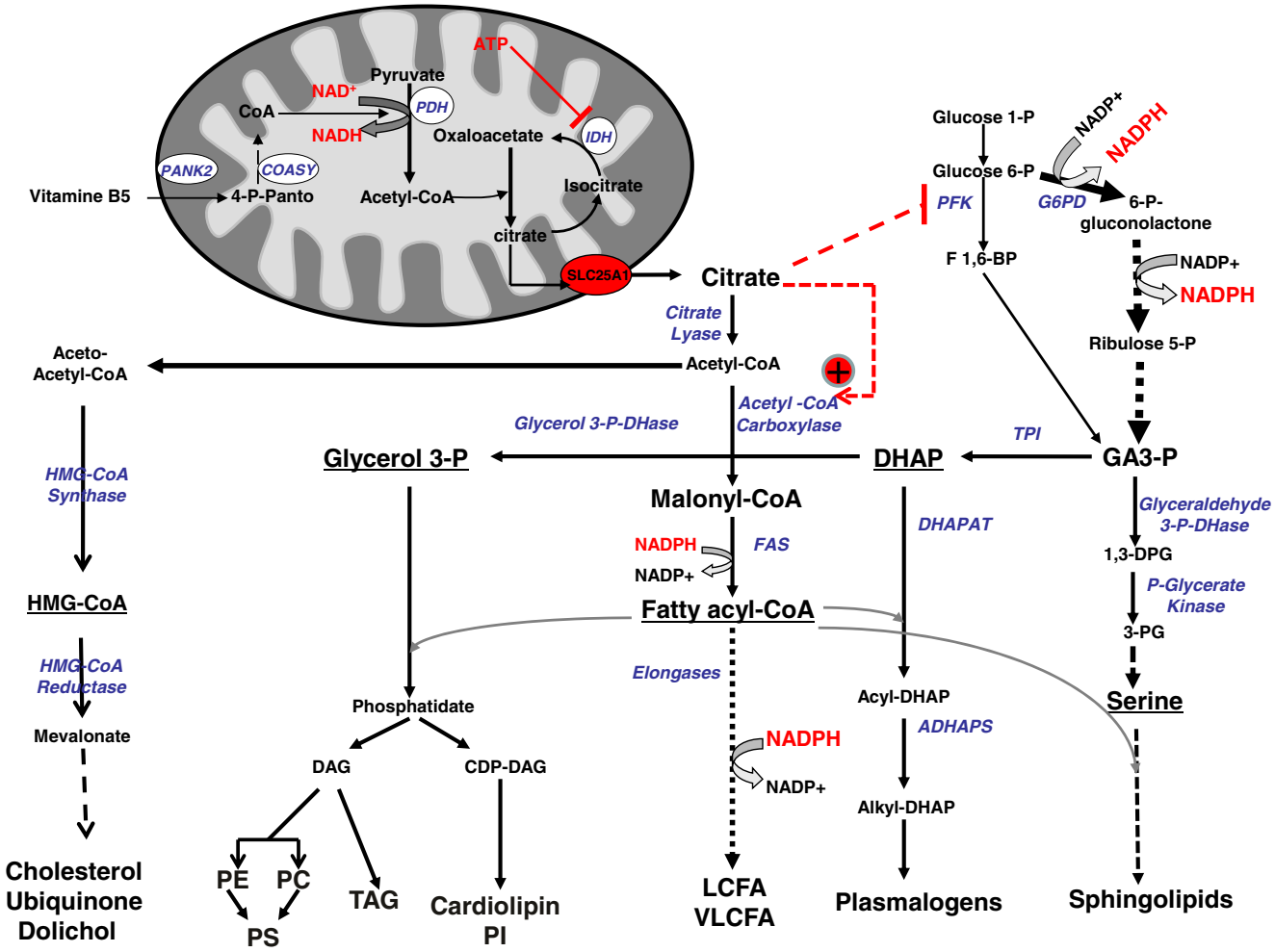

Fig. 3 Overview of de novo complex lipids biosynthesis and its relation to glucose metabolism. In the fed state, basic compounds required for complex lipids biosynthesis (Acetyl CoA, NADPH, glycerol, dihydroxyacetonephosphate and serine) are provided by glucose metabolism. The biosynthetic pathways take place in different cell compartments and organelles (cytosol, endoplasmic reticulum, mitochondria, mitochondria-associated membranes, peroxysome and Golgi). 4-phospho-pantothenate (4-P-Panto), CoA (coenzyme A), CoA-synthase (*COASY*), pantothenate kinase 2 (*PANK2*), phosphofructokinase (*PFK*), tTriose phosphate isomerase (*TPI*), Glyceraldehyde 3 phosphate, 1,3-diphosphoglycerate (1,3-DPG), 3-phosphoglycerate (3-PG), Fatty acid synthase (*FAS*), dihydroxyacetone phosphate (DHAP), DHAP acyltransferase (*DHAPAT*), alkyl-DHAP synthase (*ADHAPS*), diacylglycerol (DAG), citydyldiphosphate-DAG (CDP-DAG), glycerophospholipids (GPL), triacylglycerol (TAG), long chain fatty acid (LCFA), very long chain fatty acid (VLCFA)

biosynthesis of PL, plasmalogens and sphingolipids, as well as the remodelling of their acyl chains. The biosynthesis of FA consisting of up to 16 carbons (palmitic acid) in length is performed in the cytoplasm by different FA synthases (FAS) and is initiated by the elongation of a primer (acetyl or propionyl) with two carbons from malonyl-CoA (Riezman 2007). FA synthesis and elongation by FAS and elongases, respectively, are done by the repetition of the following reaction sequence: condensation, reduction, dehydration and reduction using NADPH as a reductant, which is provided by the PPP. A distinct FAS II is responsible for mitochondrial FA synthesis, which mostly leads to the synthesis of lipoic acid. Lipoic acid is an essential cofactor for mitochondrial alpha decarboxylation reactions and the glycine cleavage system (Hiltunen et al 2010). Defects in lipoic acid synthesis result in multiple mitochondrial dysfunctions and are associated with devastating neurological conditions (Mayr et al 2011; Soreze et al 2013). A significant amount of the FA produced by FAS I, as well as those taken up from the diet, are further elongated into long chain FA containing 18 carbons, or more, thus forming LCFA and VLFCA. The formation of VLCFA occurs in the ER by membrane bound enzymes called elongases using the same four enzymatic steps previously described for FAS (Jakobsson et al 2006). The third step of VLCFA biosynthesis is catalyzed by the enzyme 3-hydroxyacyl-CoA dehydratase, where mutated gene *HADC1* has been reported in individuals with a congenital myopathy (Muhammad et al 2013). Autosomal dominant mutations in the gene *ELOVL4* encoding elongase-4 have been associated with a juvenile form of macular degeneration known as Stargardt disease type 3

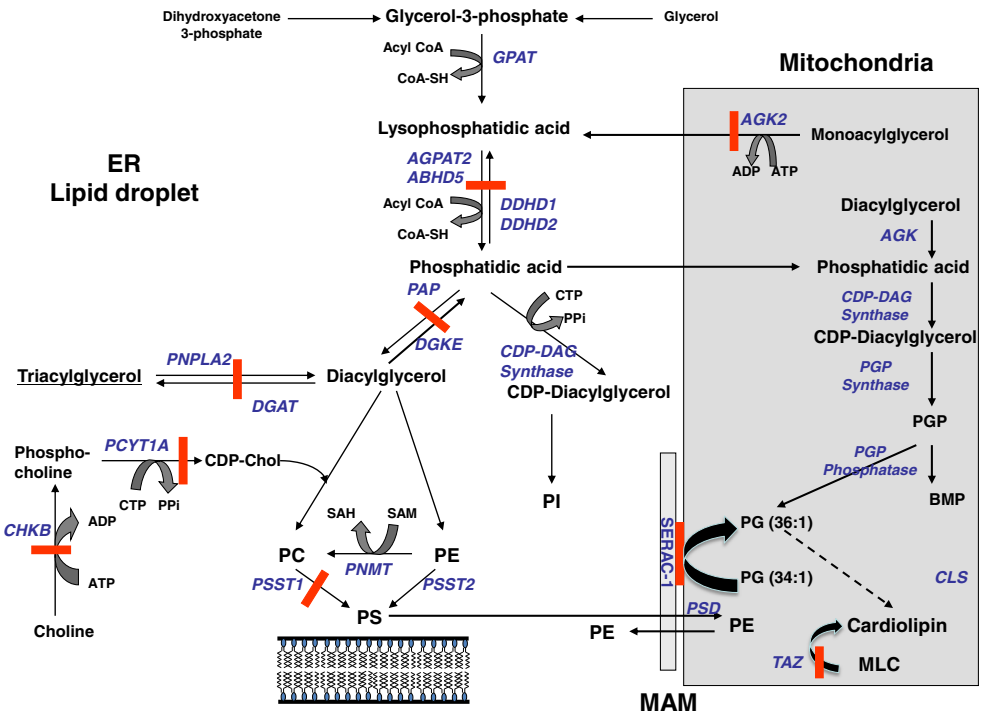

Fig. 4 De novo biosynthesis of glycerophospholipids: phospholipids biosynthesis takes place mainly in endoplasmic reticulum but also in lipid droplet, mitochondria and mitochondria-associated membranes (MAM). For more explanations on cardiolipin synthesis and remodelling see Wortmann this issue. Glycerol-3-phosphate acyl transferase (*GPAT*), acylglycerol phosphate acyl transferase (*AGPAT*), /-hydrolase containing domain-5 (*ABHD5*), DDHD domain containing protein-1 and 2 (*DDHD1*, *2*), phosphatidic acid phosphatase (*PAP*), acylglycerol kinase (*AGK*), diacylglycerol kinase (*DGKE*), patatin-like containing domanain-2 (*PNPLA2*), dDiacylglycerol acyl transferase (*DGAT*), choline kinase (*CHK*) choline cytidylyl transferase (*PCCT*), Phosphatidylserine synthase (*PSST*), cardiolipin synthase (*CLS*), phosphatidylglycerol (PG), phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), phosphatidylinositol (PI), bis(monoacylglycero)phosphate (BMP)

leading to early childhood blindness (Zhang et al 2001). Very recently, heterozygote mutations in *ELOVL4* have been reported in a large family with autosomal dominant spinocerebellar ataxia and erythrokeratodermia (Cadieux-Dion et al 2014). Homozygous mutations in the same gene have also been reported in patients with congenital ichthyosis, spastic paraplegia and intellectual disability resembling Sjögren-Larsson syndrome (Aldahmesh et al 2011; Mir et al 2014; Aubourg in this issue). Of note, *ELOVL5* heterozygote mutations have just been identified in three unrelated families with autosomal dominant spinocerebellar ataxia (SCA38) (Di Gregorio et al 2014).

NADPH and coenzyme A are essential cofactors for the synthesis of FA. Indeed, *de novo* synthesis of a FA such as palmitic acid requires the input of eight molecules of acetyl CoA and 14 molecules of NADPH. NADPH is mainly produced by the PPP and coenzyme A is produced from pantothenic acid (vitamin B5) after several steps that include pantothenate kinase 2 (PANK2) and the bifunctional enzyme CoA synthase (COASY). Mutations in *PANK2* and *COASY* are responsible for a form of neurodegeneration with brain iron accumulation (NBIA) (Zhou et al 2001; Gregory and Hayflick 2005; Dusi et al 2014; Tiranti this issue). To our knowledge, the potential consequences of PPP defects on lipid synthesis have not been investigated in patients. Beside FA, fatty alcohols provide substrates for the synthesis of wax esters and ether glycerolipids; they are metabolized through the fatty alcohol cycle (Rizzo 2014) (not shown on Fig. 3). Fatty aldehyde dehydrogenase (FALDH) is also involved in the conversion of the dietary phytol into phytanic acid. Phytanic acid is a branched-chain FA that cannot be beta-oxidized due to the presence of the first methyl group at the 3-position. Instead, phytanic acid undergoes alpha-oxidation to produce pristanic acid. Phytanoyl-CoA 2-hydroxylase deficiency causes Refsum disease (Wanders et al 2011). Since only the stereoisomer with a 2-methyl group in S-configuration can be degraded by beta-oxidation, 2R-pristanic acid needs to be racemized prior to its degradation by an alpha-Methyl-CoA racemase (AMACR). Mutations in *AMACR* lead to a severe neuropathy (Verhoeven and Jakobs 2001; Ferdinandusse et al 2000) as well as relapsing forms of encephalomyopathy and rhabdomyolysis (Thompson et al 2008; Kapina et al 2010) suggesting a likely link with energy metabolism (see Aubourg and Garcia Cazorla in this issue)

Defects in triacylglycerol biosynthesis pathway (Fig. 4)

The de novo synthesis of glycerolipids occurs in the ER and to a lesser extent in the mitochondria (Fig. 4). The synthesis pathway starts by reducing DHAP to glycerol phosphate with NADH as the reductant, a step catalyzed by NAD+dependent glycerol phosphate dehydrogenase. Two consecutive acylations lead to lysophosphatidic (LPA) and phosphatidic acid (PA) synthesis. PA is further dephosphorylated to DAG, an important metabolic crossing point leading to TAG and PL synthesis. DAG is produced from phosphatidate in the reaction catalyzed by PA phosphatase (PAP) also named Lipin (Csaki et al 2013). Lipin exists in several isoforms. Lipin 1 encoded by *LPIN-1* is highly expressed in muscle and its mutations lead to recurrent rhabdomyolysis in childhood (Zeharia et al 2009; Michot et al 2010, 2012; Wu and Mitchell in this issue). Expression of Lipin-2 is ubiquitous and mutations in *LPIN-2* cause Majeed syndrome (Ferguson et al 2005; Garcia Cazorla this issue). DAG can also be converted to PA by diacylglycerol kinase and mutations in the gene *DGKE* encoding a diacylglycerol kinase have been recently reported as a cause of an early onset form of atypical haemolytic uremic syndrome type 1 (Lemaire et al 2013; Wortmann this issue). IEM linked to the metabolism of cytoplasmic triglycerides are discussed in greater detail in the chapter by Wu and Mitchell in this issue.

IEM linked to de novo phospholipids biosynthetic pathway (Fig. 4)

Phosphatidic acid plays a central role in lipid biosynthetic pathways. In addition to its conversion to DAG, the precursor of TAG and glycerophospholipids, PA can also lead to CDP-DAG, which serves as a precursor for the mitochondrial synthesis of non bilayer PL such as phosphatidylethanolamine (PE), phosphatidylglycerol (PG) and cardiolipin (CL: diphosphatidylglycerol). Conversely, acyl glycerol kinase (AGK) catalyzes the phosphorylation of DAG and, with a lower affinity, monoacylglycerol. *AGK* mutations cause Sengers syndrome (Mayr et al 2012). Cardiolipin is a unique phospholipid with a dimeric structure containing four acyl chains and two phosphatidyl moieties linked to glycerol. Its biosynthesis starts from phosphatidylglycerophosphate to generate PG. The final biosynthesic step of CL is catalyzed by cardiolipin synthase. Subsequent to its biosynthesis, CL acquires a new set of FA. CL remodelling depends on tafazzin, a phospholipid–lysophospholipid transacylase encoded by *TAZ*, and on SERAC1 which facilitates the remodelling of PG through the synthesis of bis(monoacylglycerol)phosphate. Mutations in *TAZ* and *SERAC1* cause Barth and MEGDEL syndromes, respectively (Ichida et al 2001; Barth et al 2004; Wortmann et al 2012; Sarig et al 2013). Both are disorders of PL remodelling (Wortmann in this issue).

As for PG and CL, phosphatidylinositol (PI) is formed biosynthetically from the precursor CDP-DAG by reacting with inositol. PI is catalyzed by the enzyme CDP-diacylglycerol inositol phosphatidyltransferase (phosphatidylinositol synthase). The inositol rings undergo phosphorylation at multiple positions by specific kinases and hydrolysis by phospholipases C producing seven unique species known as phosphoinositides (not shown in Fig. 4). Many disorders affecting the synthesis, remodelling and transport of these molecules have been already described (Table 1).

The biosynthesis of phosphatidylcholine (PC) and PS starts from DAG. Cytidyl triphosphate (CTP) rather than ATP is the activating nucleotide (Kennedy 1989). CTP synthase 1 deficiency in humans has recently revealed its central role in lymphocyte proliferation but potential consequences on lipid metabolism in patients' lymphocytes have not been investigated (Martin et al 2014). The biosynthesis of PC, the most abundant PL in cells, occurs *via* the CDP-choline pathway. Choline is an essential nutrient provided by the diet, its transport in and out of the cell occurs *via* specific transporters and is tightly regulated (Barwick et al 2012). Choline is first phosphorylated by choline kinase ATP:choline phosphotransferase. Choline kinase exists in three isoforms that are encoded by two separate genes *CHKA* and *CHKB* (Aoyama et al 2002). Mutations in *CHKB* encoding the subunit cause a congenital muscular dystrophy (Mitsuhashi et al 2011). Using cytidine-triphosphate (CTP), phosphocholine is converted into CDP-choline by phosphocholine cytidylyltransferase (PCCT), a rate-limiting step in the synthesis of PC (Vance 2002). PCCT is encoded by two genes *CCT* and *CCT*, and only the isoform contains a nuclear localization signal (Cornell and Northwood 2000). Mutations in the gene *PCYT1A* encoding CCT cause a spondylometaphyseal dysplasia with cone-rod dystrophy (Yamamoto et al 2014; Hoover-Fong et al 2014). The final step in the biosynthesis of PC via the Kennedy pathway is catalyzed by choline transferase in which phosphocholine is transferred from CDP choline to DAG. PC can also be synthesized from PE methylation by a reaction catalyzed by phosphatidylethanolamine N-methyltransferase (PEMT). In this reaction, three molecules of S-adenosylmethionine are used as methyl donors with their subsequent transformation to S-adenosylhomocysteine. The de novo biosynthesis of PE also occurs via the Kennedy pathway and follows the same steps with specific enzymes: ethanolamine kinase, phosphoethanolamine cytidylyltransferase and ethanolamine transferase (not shown in Fig. 4). In contrast to PC and PE, PS can not be synthetized de novo but is obtained from both PC and PE by a reaction catalyzed by phosphatidylserine synthase (PSS). Two isoforms of PSS have been identified, PSS1 converts PC to PS, whereas PSS2 converts PE to PS (Vance and Tasseva 2013). Gain of function mutations in the gene *PTDSS1*, which encodes PSS1, cause Lenz-Majewski syndrome (Sousa et al 2014; Wortmann in this issue).

IEM linked to phospholipid remodelling (Fig. 2)

Lipids in membranes can be hydrolyzed by a plethora of enzymes able to release simple lipids that are essential for the maintenance of membrane integrity, lipid signalling and energy homeostasis. These processes are ensured by a large group of lipid hydrolases, including diverse enzymes involved in the hydrolysis of ester and amide bonds of FA. This group includes TAG hydrolases (lipases), phospholipases, ceramidases as well as cholesterol ester and retinol ester hydrolases. The structure of PL is continually remodelled through the action of acyltransferases and phospholipases (Fig. 2). These enzymes are able to exchange a base from a given PL or to release, from membrane PL, bioactive lipids that are required for cell signalling. Phospholipase and lysophospholipases are enzymes able to hydrolyse PL or lysophospholipids into FA and another lipophilic compound. There are four major classes, named A, B, C and D that can be distinguished by the type of reaction that they catalyze: (i) phospholipase A1 cleaves the sn-1 acyl chain; (ii) phospholipase A2 releases the sn-2 acyl chain thereby producing arachidonic acid; (iii) phospholipase B, also known as lysophospholipase, releases both sn-1 and sn-2 acyl chains; (iv) phospholipase C releases the phosphate group releasing DAG and a phosphate-containing head group; and (v) phospholipase D also releases after the phosphate, producing phosphatidic acid and an alcohol (Fig. 1). The mammalian family of lipid hydrolases, designated as Patatin-like phospholipase domain containing protein (PNPLA), has attracted attention as its members were found to be associated with human diseases. The PNPLA family harbours the evolutionarily conserved consensus serine lipase motif Gly-X-Ser-X-Gly and exhibits nonspecific acyl-hydrolase activity. Several of these enzymes have been associated with human diseases affecting energy homeostasis, skin integrity and neuronal function (Kienesberger et al 2009). *PNPLA1* mutations lead to the congenital ichthyosis-10 (Grall et al 2012; Garcia Cazorla this issue). *PNPLA2* mutations cause neutral lipid storage disease (NLSD) with myopathy (Fig. 4) (Fischer et al 2007; Mitchell in this issue). Neuropathy target esterase (NTE) also called Patatin domain containing protein-6 (PNPLA6) is a phospholipase B that has been associated with a complex form of hereditary spastic paraplegia as well as cerebellar ataxia and hypogonadism (Rainier et al 2008; Synofzik et al 2014; Wortmann this issue). Phospholipase A2G6 is a patatin domain containing protein-8 (PNPLA8) that is able to hydrolyze phospholipids in sn-2 position releasing arachidonic acid. Mutations in the gene *PLA2G6* lead to a distinct form of NBIA (Gregory et al 2008; Paisán-Ruiz et al 2010; Yoshino et al 2010; Garcia Cazorla, Tiranti this issue). DDHD domain-containing protein 1 (DDHD1) and 2 (DDHD2) are two phospholipases A1 (PLA1). DDHD1 is reported as a phosphatidic acid-preferring PLA1 (PA-PLA1) but is also capable of generating arachidonic acid from lysophosphatidylinositol (LPI) (Inoue et al 2012; Baba et al 2014). PA-PLA1 seems to regulate mitochondrial dynamics via PA remodelling. DDHD2 is also an intracellular phosphalipase A1 able to cleave PA and other PL. Mutations in *DDHD1* and *DDHD2* cause hereditary spastic paraplegia 54 and 28, respectively (Tesson et al 2012; Schuurs-Hoeijmakers et al 2013; Wortmann this issue; Garcia Cazorla this issue). Arachidonic acid is converted to hydroxyeicosatetraenoic acids (19-HETE and 20-HETE) through a reaction catalyzed by a cytochrome P450 hydroxylase CYP2U1 (Fig. 2). Mutations in the gene *CYP2U1* cause another form of complex hereditary spastic paraplegia, SPG49 (Tesson et al 2012; Citterio et al 2014; Wortmann this issue). 2-arachidonoyl-glycerol (2-AG) together with N-arachidonoylethanolamide (anandamide) are molecules belonging to the group of endocannabinoid agonists that are involved in a variety of physiological processes including appetite, pain-sensation, mood, and memory. 2-AG is hydrolyzed into arachidonic acid and glycerol by the serine hydrolase /-hydrolase containing domain-12, ABHD12. Mutations in *ABHD12* cause PHARC syndrome (Fiskerstrand et al 2009; Nishiguchi et al 2014). Phosphoinositide kinases (PIK) have eight PI3K catalytic subunits that are divided into three classes based on similarities in structure and function (D'Souza and Epand 2014). Numerous IEM affecting genes encoding PIK or their regulatory proteins have been reported (Table 1). Deletions in *PLCG2* encoding phospholipase C cause an immune dysregulation presenting as cold urticaria, immunodeficiency and autoimmunity (Ombrello et al 2012). Other mutations in phospholipases C that are involved in phosphoinositides remodelling have been reported as causing IEM (Table 1).

Conclusion

Although the majority of IEM linked to the biosynthesis and remodelling of complex lipids have been discovered through genetic approaches, the biochemical analysis of lipids is nevertheless essential. The identification of lipid biomarkers is required not only for the diagnosis and monitoring of these diseases but also to evaluate the therapeutic responses to future drug development. Lipidomics could provide a very useful tool to evaluate the consequences of substrate reduction therapy on the lipids turnover actually used in sphingolipids catabolism defects (Schiffmann in this issue). The analysis of the lipid diversity has been neglected for a long time because the tools required to analyze molecules as diverse and complex as lipids were not available until recently. Through the development of mass spectrometric methods, it becomes increasingly possible to quantitatively analyse the different lipid

molecular species in biological samples using lipidomics (Quehenberger et al 2010; Vaz, Colsch in this issue). Moreover, there is significant evidence for the existence of numerous lipid species of low abundance, lipid transporters and receptors for which our knowledge is quite limited. The recent work on tetralinoleoyl-cardiolipin synthesis provides a nice example on how the elucidation of the structure of a minor lipid paved the way to the identification of a critical biosynthetic pathway (Garwisch 2012). Furthermore, lipidomics could also help elucidate the intriguing mechanism(s) of dominant (heterozygous mutation) *versus* recessive (homozygous or composite heterozygous mutations) inheritance observed for the same gene in a growing number of these disorders (Dawkins et al 2001; Bejaoui et al 2001; Zhang et al 2001; Michot et al 2012; Cadieux-Dion et al 2014; Sousa et al 2014).

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