Mitochondrial phospholipids: role in mitochondrial function

Edgard M. Mejia · Grant M. Hatch

Abstract Mitochondria are essential components of eukaryotic cells and are involved in a diverse set of cellular processes that include ATP production, cellular signalling, apoptosis and cell growth. These organelles are thought to have originated from a symbiotic relationship between prokaryotic cells in an effort to provide a bioenergetic jump and thus, the greater complexity observed in eukaryotes (Lane and Martin 2010). Mitochondrial processes are required not only for the maintenance of cellular homeostasis, but also allow cell to cell and tissue to tissue communication (Nunnari and Suomalainen 2012). Mitochondrial phospholipids are important components of this system. Phospholipids make up the characteristic outer and inner membranes that give mitochondria their shape. In addition, these membranes house sterols, sphingolipids and a wide variety of proteins. It is the phospholipids that also give rise to other characteristic mitochondrial structures such as cristae (formed from the invaginations of the inner mitochondrial membrane), the matrix (area within cristae) and the intermembrane space (IMS) which separates the outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM). Phospholipids are the building blocks that make up these structures. However, the phospholipid composition of the OMM and IMM is unique in each membrane. Mitochondria are able to synthesize some of the phospholipids it requires, but the majority of cellular lipid biosynthesis takes place in the endoplasmic reticulum (ER) in conjunction with the Golgi apparatus (Fagone and Jackowski 2009). In this review, we will focus on the role that mitochondrial phospholipids play in specific cellular functions and discuss their biosynthesis, metabolism and transport as well as the differences between the OMM and IMM phospholipid composition. Finally, we will focus on the human diseases that result from disturbances to mitochondrial phospholipids and the current research being performed to help us gain a better understanding of their function.

Keywords Phospholipid · Mitochondria · Cardiolipin · Phosphatidylcholine · Phosphatidylethanolamine · Metabolism · Phosphatidylinositol · Phosphatidylserine · Phosphatidic acid · phosphatidylglycerol

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The outer mitochondrial membrane (OMM)

The OMM is comprised of a phospholipid bilayer that houses vital components such as metabolic enzymes and transport proteins. Other components mediate specific actions including cellular apoptosis, bi-directional lipid trafficking and endoplasmic reticulum (ER) to mitochondria tethering (as will be discussed later on). The OMM contains a variety of lipids. The major components of this bilayer include phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylinositol (PI) (de Kroon et al. 1997). Other phospholipids found in the OMM include phosphatidylserine (PS), phosphatidylglycerol (PG), cardiolipin (CL), phosphatidic acid (PA), lysophospholipids, sterols and sphingomyelin. It has been reported that in the mammalian OMM, the most prominent of these lipids are PC (~54 % of total), PE (~29 %) and PI (~14 %) (Daum and Vance 1997). The remaining lipids comprise approximately 3 % of the total OMM composition. This

phospholipid composition remains relatively similar between different species (mammals, plants and yeast). Regardless of the abundance of individual lipids, each lipid plays an important role in the functions of the OMM.

The inner mitochondrial membrane (IMM)

In comparison to the OMM, the IMM is structurally more complex. The IMM has a larger surface area compared to the OMM and this is due to the in-foldings (cristae) that form the mitochondrial matrix. The ratio of phospholipids to proteins is also lower in the IMM compared to the OMM in all cell types (Daum and Vance 1997). This is indicative of the roles and functions of the IMM. One of the main functions of the IMM is the housing of proteins that make up the electron transport chain (ETC) which ultimately produces ATP. The ability to take up ADP and produce ATP is made possible in the mitochondria by the adenine nucleotide transporter, a very prominent protein in the IMM (Klingenberg 2008). Other functions include lipid and protein trafficking, regulation of cellular metabolism and transient storage of calcium necessary for signal transduction. The lipid composition of the IMM varies from that of the OMM. PC and PE are still the most abundant phospholipids in the IMM, comprising about 75 % of total lipids. However, the concentration of PE is slightly higher in the IMM compared to the OMM, while the opposite is true for PI (Daum and Vance 1997). One of the biggest differences between OMM and IMM lipid composition is the greater concentration of CL that is found in the IMM. Here, CL makes up about 15–20 % of the total phospholipid mass (Daum and Vance 1997). This enrichment of CL in the IMM can be found in all eukaryotic organisms. The reasons for this difference will be discussed later on in this review.

Phosphatidylcholine (PC)

PC is comprised of a hydrophilic choline head group attached at the stereospecific numbering (sn)-3 position of a glycerol-3-phosphate molecule which contains saturated and/or *cis*-unsaturated fatty acyl groups at the sn-1 and sn-2 positions (van Meer et al. 2008). The 1,2-diacyl-sn-glycerol (DAG) portion of the molecule forms a hydrophobic tail (van Meer et al. 2008). The nature of its fatty acyl groups allows PC to remain fluid at room temperature and thus promotes membrane fluidity. PC has a tubular/cylindrical shape and it organizes itself in a planar bilayer in which the tails of different PC molecules face each other while the polar head groups face the aqueous environment. In eukaryotes, PC is required to maintain the structural integrity of cellular membranes. It is also a major component of bile, lung surfactant and lipoproteins (reviewed in (Cole et al. 2012)). Despite its large abundance in

mitochondrial membranes, PC is actually imported into mitochondria from other cellular sites.

A major site of PC biosynthesis is the endoplasmic reticulum (ER) where PC can be produced via two different pathways in mammals. PC is primarily synthesised via the cytidine diphosphate (CDP) choline-pathway (also known as the Kennedy pathway) in all nucleated cells (Kennedy and Weiss 1956). This pathway requires the dietary in-take of choline which is then followed by three enzymatic steps leading to the production of PC (Cole et al. 2012). In the first step choline is converted to phosphocholine catalyzed by choline kinase. Phosphocholine is then converted to CDP-choline in a reaction requiring CTP catalyzed by CTP:phosphocholine cytidylyltransferase. Finally, CDP-Choline is converted to PC in a reaction catalyzed by CDP-choline:1,2-DAG cholinephosphotransferase. PC may also be synthesised endogenously with the use of PE as a substrate. This pathway utilizes sequential methylation of PE with a specific enzyme known as phosphatidylethanolamine N-methyltransferase (PEMT) to produce PC. PEMT is a 22.3 kDa protein encoded by the *PEMT* gene which produces two isoforms. PEMT1 is localised to the ER, while PEMT2 is found in the mitochondria-associated ER membrane (MAM) (Vance 2013; Horvath and Daum 2013). In mammalian cells, this pathway appears to be specific to hepatocytes, accounting for approximately 30 % of total PC biosynthesis in the liver (Sundler and Akesson 1975). This methylation pathway appears to be carried out when dietary choline levels are diminished. Altering the expression of PEMTs may have a major influence on certain biological functions. For example, over-expression of pemt2 in rat hepatoma cells resulted in the inhibition of cell proliferation and the induction of apoptosis (Li et al. 2009). Upon inspection of the fatty acid composition of PC in pemt2 over-expressed cells, it was observed that the acyl composition of PC was predominantly enriched with oleic acid. The PC synthesised by PEMT2 was also mainly localized to the mitochondria where it increased membrane fluidity and the release of cytochrome c into the cytosol, which resulted in the activation of caspase-9 and capase-3. This resulted in the observed apoptosis induction in pemt2 over-expressed cells.

Once PC is synthesized, the next step involves transporting it to the outer and inner mitochondrial membranes. It was originally believed that phospholipids were transported between the ER and mitochondria via vesicular transport. It is now believed that contact sites between the MAM and mitochondria appear to be responsible for the majority of lipid transport between these two organelles. Specific proteins such as ER-mitochondria encounter structures (ERMES) have been shown to tether the ER (MAM) and mitochondria in yeast (Kornmann et al. 2009; Kornmann 2013). The PC content of ERMES-diminished mitochondria was decreased due to the reduction in PS conversion to PC (via PE) (Kornmann et al.

2009; Tamura et al. 2012). These studies demonstrate the importance of contact sites for lipid biosynthesis and transport between the ER and mitochondria. PC may also be transported into mitochondria with the help of an intracellular protein structure called PC transfer protein (PC-TP), also known as steroidogenic acute regulatory (StAR)-related lipid transfer domain protein 2 (STARD2) (van Golde et al. 1980; Wirtz 1991). PC-TP is highly enriched in liver and macrophages. To date, no PC-TP dysfunction has been reported in humans. However, studies in *Pctp* $^{-/-}$ mice have demonstrated that PC-TP can potentially modulate the development of atherosclerosis (Wang et al. 2006) as well as alter the sensitivity of the liver to insulin, reducing glucose and free fatty acid levels (Scapa et al. 2008).

Once in the mitochondria, PC performs its intended function that mainly includes serving as a structural component of the OMM and IMM, but it may also interact with various proteins (Fig. 1). Knowledge of PC-specific interactions with mitochondrial proteins is limited. In yeast, Gut2p is an

enzyme required for proper utilization of glycerol as a carbon source (Janssen et al. 2002). (Janssen et al. 2002) demonstrated that glycerol-phosphate dehydrogenase (Gut2p) is a peripheral membrane protein bound to the IMM via hydrophobic interactions to PC. These authors suggested that Gut2p interaction with PC may be required for PC import into yeast mitochondria or that it may be a necessary relationship that allows Gut2p to carry out its activities. PC is also reported to be an important substrate for the formation of other mitochondrial lipids, most notably the mitochondrial specific phospholipid CL. Upon its *de novo* synthesis, CL is quickly remodelled by tafazzin, a transacylase enzyme that transfers acyl groups from PC or PE to a monolysocardiolipin (MLCL) molecule to produce mature CL (Hatch 2004). From the previous descriptions, it can be seen that PC plays a very important role in mitochondria, which is why it is not surprising that any disturbances to this phospholipid result in serious disorders in humans. A recent report examined the potential genetic cause of congenital muscular dystrophy cases observed in 15
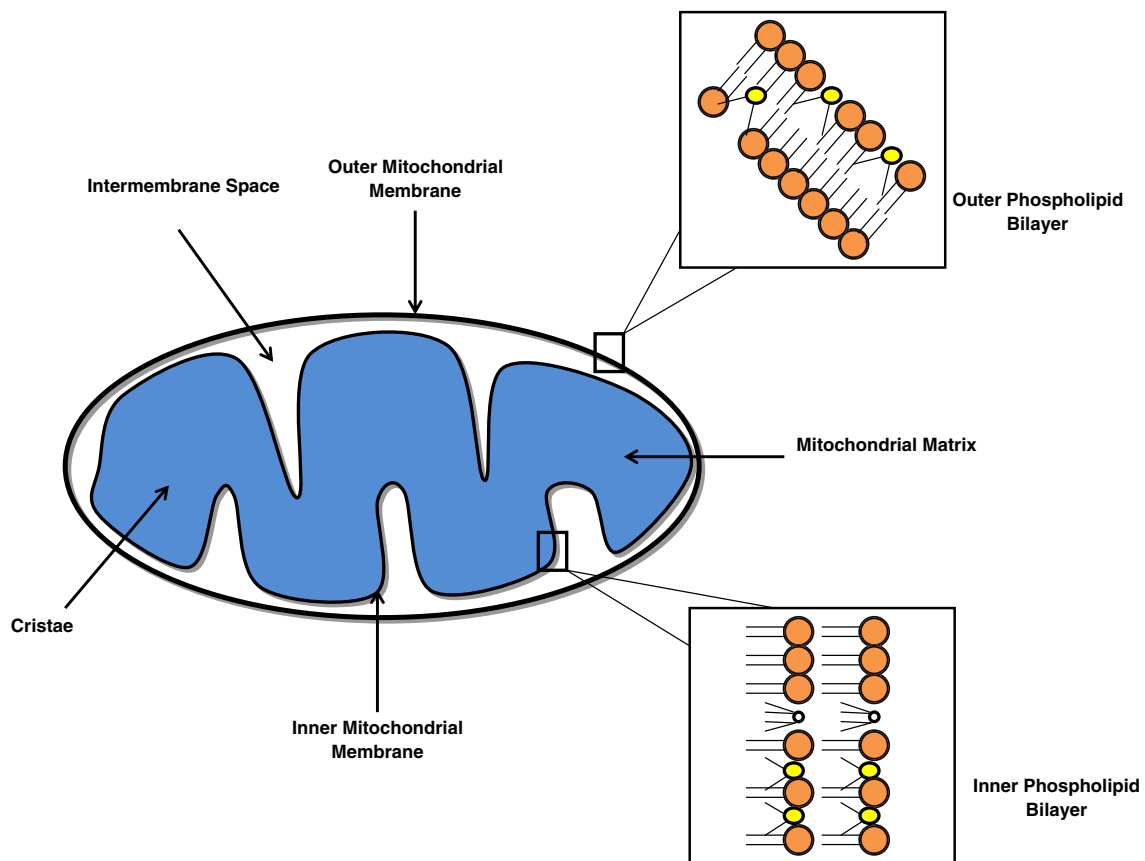

Fig. 1 The outer mitochondrial membrane (OMM) and inner mitochondrial membrane (IMM) contain structural phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE) and cardiolipin (CL). Phospholipid abundance varies between the OMM and IMM. PC and PE make up the majority of phospholipids, and PE and CL are more abundant in the IMM compared to the OMM. The tubular formation of PC allows for the formation of planar bilayers in both the OMM and IMM. Non-bilayer forming phospholipids such as PE and CL have a smaller hydrophilic head group compared to their hydrophobic acyl groups, thus favouring hexagonal phase formations. This introduces tension into mitochondrial membranes which allows the incorporation of proteins and can also contribute to the negative curvature of the membrane thereby facilitating specific mitochondrial functions such as fusion and/or fission. [Orange=PC, yellow=PE, white=CL]

individuals (Mitsuhashi et al. 2011). These patients not only suffered from muscular dystrophies, but also mental retardation and microcephaly without structural brain abnormalities (Mitsuhashi et al. 2011). Muscle biopsies from three individuals revealed undetectable choline kinase beta (CHKB) activity, enlarged mitochondria at the periphery of the muscle fibers and over all reduced PC content. These phenotypes were a result of mutations on the *CHKB* gene responsible for PC synthesis in the CDP choline pathway described above (Cole et al. 2012; Aoyama et al. 2004). Thus, PC plays an important role in mitochondrial structure, lipid to protein interactions and phospholipid biosynthesis and disturbance of mitochondrial PC may have severe effects on human health.

Phosphatidylethanolamine (PE)

As mentioned previously, PE is the second most abundant phospholipid in mitochondrial membranes, comprising about 30 % of the total phospholipid mass, and is the most abundant non-bilayer forming phospholipid in mitochondria (Daum and Vance 1997). Its molecular structure consists of a glycerol-3-phosphate backbone that contains a hydrophilic ethanolamine head group attached at the sn-3 position. The small size of this head group (relative to the rest of the molecule) gives PE a conical shape (Osman et al. 2011). At the sn-1 and sn-2 positions of its glycerol backbone are saturated and/or *cis*-unsaturated fatty acyl groups. Biosynthesis of PE in mammalian cells occurs via four different pathways, one of which includes mitochondria producing a significant portion of cellular PE. Similar to PC, one of the major pathways of PE synthesis is the Kennedy Pathway (or CDP-ethanolamine pathway) (Kennedy and Weiss 1956). The first step involves the phosphorylation of ethanolamine (acquired through dietary means) by ethanolamine kinase (EK) (Vance and Tasseva 2013). Next, CTP:phosphoethanolamine cytidylyltransferase converts phosphoethanolamine to CDP-ethanolamine. This is followed by a reaction between CDP-ethanolamine and DAG catalyzed by the ER enzyme CDP-ethanolamine:1,2-DAG ethanolaminephosphotransferase (Vance and Tasseva 2013). This is the major pathway responsible for the majority of the PE required by cells. Mitochondria, which also require PE for proper function, can make their own PE from PS. This requires the transport of PS into the IMM where a decarboxylation reaction takes place that ultimately produces PE. PS, which is largely synthesised by the ER, is transported into mitochondria through transient contact sites that exist between the MAM and the OMM (Shiao et al. 1995). The mitochondrial enzyme PS decarboxylase (PSD) catalyses the conversion of PS to PE (Schuiki and Daum 2009). There are two other pathways that are minor contributors to the cellular content of PE in mammalian cells. One pathway involves the acylation of lyso-PE in the MAM using an acyl-CoA dependent enzyme known as lyso-PE acyltransferase (LPEAT) to produce PE (Riekhof et al. 2007). Another pathway involves the exchange of the serine base forming the head group in PS for an ethanolamine base to produce PE (Vance and Tasseva 2013). The contribution of these two pathways to the overall PE pool in mammalian cells is believed to minor (Vance and Tasseva 2013; Sundler et al. 1974). For the purposes of this review, we will focus on the mitochondrial production of PE.

The characteristic conical molecular structure of PE (Fig. 1) is critical for the vital role it plays in mitochondria. In vivo, PE forms a large part of the lipid bilayer that makes up both the OMM and IMM (van Meer et al. 2008). However, due to its structure, PE has a tendency to organize itself into hexagonal phases. The force of maintaining PE in a bilayer structure introduces tension into mitochondrial membranes and potentially allows PE to play a role in membrane fusion and protein movement across membranes (den van Brink-Van Der Laan et al. 2004). The IMM is rich in proteins and membrane curvatures (due to the formation of cristae). This could be one of the reasons why PE is found in greater quantities in the IMM compared to the OMM. This is not to say that PE does not play a key role in the OMM. Recent studies conducted in yeast have demonstrated that the presence of PE is necessary for the proper functioning of the outer membrane translocase (TOM) and its ability to transport β-barrel proteins into mitochondria (Becker et al. 2013). β-barrel proteins are important components of the OMM which are required for the formation of various protein structures. A study conducted in a clonal Normal Rat Kidney cell line, focussed on gaining a better understanding of the origins of autophagosomes, demonstrated the importance of PE in autophagy (Hailey et al. 2010). Autophagy is a process that involves the engulfment of cytosolic components by structures called autophagosomes which then transport their contents to lysosomes for catabolism. This process may take place in times of starvation to ensure the maintenance of energy levels necessary for proper cellular function. The OMM may be the source of starvation-induced autophagosome biogenesis (Hailey et al. 2010), and (Nebauer et al. 2007) demonstrate that PE is needed for the proper function of these structures.

In the IMM, PE is a crucial component necessary for the maintenance of mitochondrial morphology. (Steenbergen et al. 2005) showed that mice lacking PSD (encoded by *Pisd*) activity exhibit fragmented and misshapen mitochondria. The CDP-ethanolamine pathway (as well as other mechanisms for the production of PE) did not compensate for the loss of PSD and ultimately lead to embryonic lethality. A moderate (<30 %) decrease in mitochondrial PE (mtPE) via a reduction in mtPE synthesis, mediated by reduced PSD, resulted in aberrant mitochondrial morphology in Chinese Hamster Ovary (CHO) cells (Tasseva et al. 2013). Another study has shown that loss of cardiolipin (CL) in combination with the loss of

mitochondrial PE is lethal in yeast (Gohil et al. 2005). However, loss of cytosolic PE in combination with the loss of CL did not result in lethality. Recent studies have examined the CL and PE relation on mitochondrial morphology. Conditional mutants for CL synthase (crd1Δ) and PSD1 (psd1Δ) constructed in *S. cerevisiae* resulted in the formation of highly fragmented mitochondria (Joshi et al. 2012). The reduction in CL present in the crd1Δ mutant did not result in altered mitochondrial morphology, while a reduction in PE observed in the psd1Δ cells exhibited some mitochondrial fragmentation. These results indicate that PE may play a compensatory role in mitochondria in the event that other non-bilayer forming lipids such as CL are reduced. A reduction in CL is a clinical manifestation observed in patients with Barth Syndrome (BTHS) and PE compensation could explain the wide range of phenotypes observed in these patients. This topic will be discussed further in a later section of this review.

Mitochondrial fusion and fission are important processes that must be considered when examining the role of phospholipids in mitochondrial function. Fusion involves the merging of two mitochondria into one, while fission involves division of one mitochondria into two. These two processes control the organelle's number, size, length and shape and are necessary for the development, adaptation and over all function of the organism (Detmer and Chan 2007). Decreased CL synthesis in *S. cerevisiae* crd1Δ conditional mutants resulted in mixing of mitochondrial content indicating that fusion took place (Joshi et al. 2012). In contrast, a decrease in PE synthesis in *S. cerevisiae* psd1Δ conditional mutants resulted in decreased but not complete elimination of fusion. The combination of decreased CL and PE synthesis in crd1Δ/psd1Δ conditional double mutants resulted in the complete blockage of mitochondrial fusion. These results demonstrate that PE plays a vital role in the regulation of mitochondrial fusion and has overlapping functions with CL.

PE has been shown to play a vital role in oxidative phosphorylation, a process that is required for mitochondrial ATP production. In CHO cells where PSD activity was silenced, decrease in mtPE not only adversely affected mitochondrial morphology, but resulted in a decrease in respiratory capacity and ATP production (Tasseva et al. 2013). These observations could be related to a potential function of PE in the IMM. (Bottinger et al. 2012) used a strain of *S. cerevisiae* lacking Psd1 and Psd2 to illustrate the effects of diminished PE levels on protein import into mitochondria. They showed that the import of subunit β of the F_1/F_0-ATP synthase (responsible for producing ATP) was strongly reduced in cells lacking both Psd1 and Psd2. Since the import of this subunit is highly dependent on a higher mitochondrial membrane potential ($\Delta\psi$) (Martin et al. 1991), a decrease in this potential, as observed in these mutants, would adversely affect import of the subunit β. This implies that the $\Delta\psi$ is highly dependent on the presence of PE in the IMM. Thus, PE plays a vital role in many essential mitochondrial functions.

Phosphatidylserine (PS)

PS, like the previously discussed phospholipids, has a molecular structure that is composed of a DAG backbone containing a phosphate group at the sn-3 position. The phosphate group is esterified to L-serine (van Meer et al. 2008). In mammalian and plant mitochondria, PS is found in relatively small quantities compared to other phospholipids (~1.0 % of total phospholipids) (Daum and Vance 1997). Slightly higher levels are found in the mitochondria of *S. cerevisiae* (~3 % of total mitochondrial phospholipids), and even higher levels of PS (~34 % of the total phospholipids) are found in its plasma membrane (Zinser et al. 1991). Why PS is enriched in the plasma membrane of *S. cerevisiae* is unknown.

In mammalian cells, PS synthesis takes place in the MAM via calcium-dependent base-exchange reactions that remove either choline or ethanolamine from PC or PE, respectively, and replace the polar head group with L-serine (Vance and Tasseva 2013). These reactions are catalyzed by PS synthase-1 (PSS1) and PS synthase-2 (PSS2) in mammals. PSS1 performs the base exchange on PC while PSS2 exchanges the base on PE to form PS (Vance 2008). In prokaryotes and *S. cerevisiae*, only one PSS enzyme exists which uses CDP-DAG and L-serine to create PS (Vance and Tasseva 2013). PS is transported from the MAM to mitochondrial membranes via transient membrane contact between the MAM and the OMM (Shiao et al. 1995; Wu and Voelker 2001; Simbeni et al. 1991; Vance 1991). Once PS enters the mitochondria, it appears that its main function is to serve as substrate for the production of PE, as PS is rapidly decarboxylated in the mitochondria by PS decarboxylase (PSD) to produce mitochondrial PE (Voelker 1989; Vance 1990). This might explain why PS is found in such low quantities in mitochondrial membranes, particularly the IMM where PSD is localized. Yeast contain two PSD enzymes, one in the mitochondria (Psd1) (Trotter et al. 1993; Leventis and Grinstein 2010) and one in the Golgi/vacuole (Psd2) (Leventis and Grinstein 2010; Trotter and Voelker 1995; Trotter et al. 1995). Mammals on the other hand contain only one PSD enzyme in mitochondria (Leventis and Grinstein 2010). To date, no human diseases are associated with dysfunctional PS in mitochondria.

Phosphatidylinositol (PI)

PI is described as both a structural and signaling lipid in eukaryotic membranes (van Meer et al. 2008), yet its specific role in mitochondrial membranes is poorly understood. PI is

composed of a DAG backbone containing a phosphate group at the sn-3 position. The head group esterified to the phosphate is a hexahydroxycyclohexane (or inositol) ring. While the inositol molecule exists in various isoforms in nature, the predominant form in mammalian cells is *myo*-D-inositol (Tolias and Cantley 1999). PI is reported to make up ~5 % and ~13 % of the total phospholipids in the IMM and OMM, respectively, in mammalian cells (Daum and Vance 1997). The larger presence of PI in the OMM compared to the IMM is consistent in other organisms (i.e., plants and yeast) (Daum and Vance 1997), and could be indicative of the role PI plays in mitochondria. In eukaryotic plasma membranes, where it is the third most abundant phospholipid after PC and PE, PI plays a major role as a precursor to the synthesis of phosphoinositides. Phosphoinositides are involved in processes such as vesicle trafficking, actin rearrangement and calcium regulation (Tolias and Cantley 1999). These signalling molecules are produced by phosphorylation of the inositol ring by various kinases and phosphatases in eukaryotic cells. PI also serves as a precursor for the synthesis of glycerophosphatidylinositol (GPI)-anchored proteins and inositol-containing sphingolipids (Tolias and Cantley 1999; Nikawa and Yamashita 1997). However, these are processes that take place in the plasma membrane. Similar reactions may be taking place in the OMM where PI could allow for mitochondria to communicate with other cellular components. PI is enriched in arachidonic acid (AA) and is one of the main sources of AA released via PLA$_2$ for prostaglandin production (Tanaka et al. 2003; Lee et al. 2012). The biological significance of the AA enrichment of PI was investigated by (Lee et al. 2012). Mice deficient in lysophosphatidylinositol acyltransferase 1 (LPIAT1), which incorporates AA into PI, exhibited reduced AA content in PI, and this was accompanied by cerebral cortex and hippocampal atrophy and lethality within a month (Lee et al. 2012). These results suggested that AA integration into PI may be necessary for normal brain development.

In mammalian cells, PI is synthesised in the ER by PI synthase (PIS) using CDP-DAG and inositol as substrates (Paulus and Kennedy 1960; Antonsson 1997). Transfer proteins then traffic PI from the ER to the plasma membrane. Recently, (Kim et al. 2011) challenged this view by presenting new data describing a mobile PIS-containing membrane compartment that generates a PI signalling pool at the plasma membrane. In *S. cerevisiae*, PI synthase (Pis1) is reported to be localized to the MAM (Gaigg et al. 1995). In addition, this study showed that, similar to other phospholipids, PI may be delivered to mitochondria via transient contact sites between the MAM and the OMM. Further studies are required to gain a better understanding of PI synthesis and trafficking within the cell.

Not only are PI and phosphoinositides present in mitochondria, but also the various kinases, phosphatases and phospholipases responsible for their synthesis (Daum and Vance 1997; Schon 2007). Yet the specific function of these phospholipids in mitochondria is not well known. (Rosivatz and Woscholski 2011) has suggested that phosphatidylinositol-4,5-bisphosphate (PI(4, 5)P$_2$) may be involved in mitochondrial fission and mitophagy. They showed that not only is PI(4, 5)P$_2$ present in the OMM but loss or masking of PI(4, 5)P$_2$ lead to mitochondrial fragmentation eventually resulting in autophagy. This study indicated that PI(4, 5)P$_2$ may only be functional or present in the OMM, not the IMM.

Phosphatidylglycerol (PG)

PG is an anionic phospholipid containing an L-glycerol molecule esterified to phosphate at the sn-3 position of phosphatidic acid with saturated and/or unsaturated acyl chains at the sn-1 and sn-2 positions. Similar to PC, PG serves as an essential component of pulmonary surfactant (Hallman and Gluck 1976). PG is the second most abundant phospholipid in lung surfactant, comprising 7–15 % of the total lipids, while PC comprises approximately 80 % (Agassandian and Mallampalli 2013). Not only is PG an important structural component of pulmonary surfactant, but it may be involved in regulating the innate immune response in the lungs. PG was shown to suppress pathogen-induced eicosanoid production in human and mouse macrophages resulting from *M. pneumoniae* infection (Kandasamy et al. 2011).

Mitochondrial levels of PG in various organisms are consistently low, <1 % of total phospholipids in mammalian cells (Hostetler 1982). This is widely believed to be due to the fact that in mitochondria the main role of PG is to act as a precursor in the CL biosynthetic pathway. Thus, most PG produced in mitochondria is quickly metabolized to form nascent CL. Mitochondrial PG is synthesized by the cytidine-5′-diphosphate-1,2-diacyl-sn-glycerol pathway and the enzymes are localized on the matrix side of the IMM (Osman et al. 2011; Hatch 1994). (Tamura et al. 2013) recently identified an IMM protein, Tam41, which converts PA into CDP-DAG. This enzyme was originally described as a maintenance protein for the Tim23 complex (Tamura et al. 2006). CDP-DAG is then converted to phosphatidylglycerolphosphate (PGP) by PGP synthase. PGP is then dephosphorylated to form PG, a process that was previously described as being catalysed by an unknown phosphatase. However, (Zhang et al. 2011b) identified this enzyme as protein tyrosine phosphatase mitochondrion 1 (PTPMT1). PTPMT1 is reported to be localized exclusively in the IMM with expression in various organisms including animals, plants and bacteria (Zhang et al. 2011a). This pathway is highly conserved between mammals and yeast. From this point, PG goes on to produce CL (discussed later in this review).

Despite the fact that most of the PG produced by mitochondria is used as a substrate for CL, studies have shown that its function may be more diverse. (Su and Dowhan 2006) generated *S. cerevisiae PGS1* (which encodes for PGP synthase) mutants (pgs1Δ) which gave rise to cells that were deficient in both PG and CL. These pgs1Δ cells expressed dysfunction in the translation of both mitochondrial and nuclear encoded subunits of cytochrome c oxidase (complex IV). In these pgs1Δ yeast cells, *trans* factors acting on *cis*-elements were responsible for inhibition of COX4 mRNA translation in the nucleus. Deletion of most of the 5′ UTR, which is believed to be responsible for the production of these *cis*-elements, restored reporter function and thus, COX4 expression. Thus, a cross-talk mechanism may exist between the nucleus and mitochondria that is mediated by levels of both CL and PG. Even though a direct link between PG and/or CL levels and complex IV function was never established, future research may uncover the potential mechanism of lipid-mediated nucleus to mitochondria cross-talk.

Another study examined the crystalline structure of bovine complex IV and showed that 13 phospholipids were closely associated with this complex (Shinzawa-Itoh et al. 2007). Of these 13 lipids, 4 were PG molecules. Only *cis*-vaccenate derivatives of PG interacted with the hydrophobic grooves of subunit III near the O_2 transfer pathway of complex IV. The results of this study suggest that PG may play a role in the O_2 transfer mechanism of complex IV. Interaction of PG with other complexes of the electron transport chain has not been reported to date, and considering the relatively small quantities of PG in mitochondria, the above observation of PG interaction with complex IV indicate a potentially specialized role of PG in the IMM.

Phosphatidic acid (PA)

PA, or 1, 2-diacyl-*sn*-glycero-3-phosphate, is structurally the simplest (diacyl) glycerophospolipid. It is an anionic phospholipid consisting of a phosphate head group as well as the signature glycerol backbone with two acyl chains, one at the sn-1 position and the other at sn-2 (Kooijman et al. 2005). Like PE, PA is a non-bilayer forming lipid (Osman et al. 2011). PA comprises only a small portion of the lipid composition of mitochondrial membranes in mammals and yeast (~1–2 % in each) (Daum and Vance 1997). Despite its relatively low abundance, PA is known to play important roles in the mitochondria as a precursor for the synthesis of various lipids.

PA is produced in the cell via a number of different pathways. The major pathway (present in prokaryotes, plants, yeast and mammals) begins with the acylation of glycerol-3-phosphate (G3P) at the sn-1 position using G3P acyltransferase (GPAT) (Athenstaedt and Daum 1999). This is followed by an acylation of the product, 1-acyl-sn-glycerol-3-phosphate (also known as lysophosphatidic acid or LPA), at the sn-2 position by 1-acyl-sn-glycerol-3-phosphate acyltransferase (AGPAT) which produces PA . In mammals, four GPAT isoforms have been identified, with GPAT1 and GPAT2 residing in the mitochondria (Gimeno and Cao 2008). On the other hand, GPAT3 and GPAT4 reside predominantly in microsomal fractions. In yeast however, no GPATs have been identified in mitochondria to date (Pagac et al. 2012). AGPAT exists in multiple isoforms in mammals (six in humans and five in mice) and are localized to either the ER or mitochondrial membranes (Lu et al. 2005), while yeast is reported to express this enzyme on the luminal side of the ER (Pagac et al. 2011). Another pathway for *de novo* biosynthesis of PA (present only in mammals and yeast) involves the acylation of dihydroxyacetone phosphate (DHAP) via DHAP acyltransferase to produce the intermediate 1-acyl-DHAP (Athenstaedt and Daum 1999). This intermediate is then converted to LPA in an NADPH-dependent reaction catalysed by 1-acyl-DHAP reductase (Athenstaedt and Daum 1999). From this point the pathways converge and LPA is converted to PA as described above. The enzyme DHAP acyltransferase is present in both the ER and mitochondria of mammalian and yeast cells, while 1-acyl-DHAP reductase appears to be present only in the ER of these organisms. This could be indicative of a rescue mechanism employed in these organisms to maintain PA levels.

PA may also be synthesized via a third mechanism that involves the phosphorylation of DAG. DAG kinases (DAGKs) are enzymes that are responsible for metabolising DAG and thus terminating its signalling functions. This DAG metabolism ultimately results in the production of PA (Cai et al. 2009). Ten DAGKs have been identified in mammals (Cai et al. 2009). Finally, phospholipase D (PLD) hydrolysis of phospholipids (for example, PC) may produce PA with the resulting release of a free head group (in this case, choline) (Cockcroft 2001). To date, two mammalian isoforms (PLD1 and PLD2) have been identified and these have become therapeutic targets for the treatment of various conditions including Alzheimer′s disease and stroke (Oliveira and Di Paolo 2010; Stegner et al. 2013). In addition, another PLD, mitochondrial PLD (MitoPLD), is localized to the OMM. This enzyme uses CL as a substrate, hydrolysing it and ultimately producing PA (Choi et al. 2006). Thus, PA may be generated through at least five enzymatic pathways where it then can go on to perform various cellular processes. For this review, we will focus on the function of PA in mitochondria as well as recent advances made in understanding new potential roles in this organelle.

PA is required for the synthesis of glycerophospholipids and triacylglycerols (Athenstaedt and Daum 1999). In mitochondria, it acts as a precursor for the synthesis of PG, CDP-DAG and CL (Hostetler 1982; Hostetler and van den Bosch 1972). However, other mitochondrial functions of PA have

recently been described in a number of studies. It has been postulated that PA plays an important role in mitochondrial fusion and fission, however, the mechanism of action is not fully understood. One proposed mechanism is that due to its small head-group and negative charge, PA can contribute (in part) to the negative curvature of mitochondrial membranes, thus facilitating mitochondrial fusion and fission (Yang and Frohman 2012). However, the relatively small quantities of PA found in the mitochondria suggest that microdomains of PA must be present in order to facilitate fusion and fission. Overexpression of MitoPLD in NIH3T3 cells increased PA levels and resulted in increased mitochondrial aggregation (Choi et al. 2006). In contrast, inhibition of MitoPLD resulted in mitochondrial fragmentation. To confirm that MitoPLD was involved in mitochondrial fusion, mitochondrial fusion assays were performed and revealed that cells deficient in MitoPLD (or expressing an inactive form of the enzyme) had significantly decreased levels of fusion. Mitochondrial PA has been linked to the progression of early spermatogenesis. Although mice lacking MitoPLD were viable (Huang et al. 2011) they exhibited consistent phenotypes including meiotic arrest, DNA damage and male infertility. The authors if this study proposed that mitochondrial-surface PA recruits the phosphatase Lipin-1 which converts PA into DAG, which then promotes mitochondrial fission (Huang et al. 2011). Ultimately, this study illustrated that MitoPLD is required for the production of piRNA during gametogenesis. This specialized RNA, which prevents transposon mobilization that causes genomic damage, is produced by an organelle known as the nuage, which is transiently associated to mitochondria during spermatogenesis (Eddy 1975). In summary, these studies provide some insight into the diversity of the functions of PA in mitochondria, where it was previously believed to have single role.

Cardiolipin (CL)

CL is unique because unlike the previously discussed phospholipids, which are found in various parts of the cell, it is predominantly found in mitochondria. Another unique aspect is its dimeric molecular structure which is composed of three glycerol groups, two phosphate moieties and four acyl chains (Cheng and Hatch 1995). The acyl chain composition of CL plays a major role in its function and pathophysiology, which will be discussed later on. Like PE and PA, CL is a non-bilayer forming phospholipid due to its conical shape which favours hexagonal phase formation (den van Brink-Van Der Laan et al. 2004) (Fig. 1). CL comprises approximately 10–15 % of the total phospholipids in mitochondrial membranes of yeast and mammals, and it is predominantly found in the IMM with trace amounts in the OMM (Daum and Vance 1997; Hovius et al. 1993). Studies also indicate that CL is enriched in contact sites between the OMM and the IMM of yeast and mammals (Simbeni et al. 1991; Ardail et al. 1990).

The *de novo* biosynthesis of CL is a process that is highly conserved in eukaryotes. It takes place in the matrix side of the IMM (Schlame and Haldar 1993). In mammals, CL is synthesized via the cytidine-5′-diphosphate-1,2-diacylglycerol pathway (Hatch 1994). This pathway involves the utilization of precursors that include glycerol-3-phosphate, PA and PG (reviewed in (Mejia et al. 2013)). The steps from glycerol-3-phosphate to PG have been described in the above section for PG. Once PG is synthesized, it is quickly converted to nascent CL by the enzyme CL synthase (CLS). This enzyme, which is localized in the IMM (Hostetler et al. 1971), has been isolated and characterized in rat liver, yeast and Arabidopsis (reviewed in (Schlame 2008)). CLS is also present in the plasma membrane of bacteria where CL is a minor yet necessary component of the bilayer required for production of ATP (reviewed in (Schlame 2008)). CLS does not have a strict acyl chain specificity, as shown in studies conducted in various organisms (Hostetler et al. 1975; Nowicki et al. 2005; Houtkooper et al. 2006), yet the CL found in membranes contains specific acyl chains that play a major role in its function. This is perhaps why nascent CL undergoes a remodeling process that incorporates specific acyl groups onto CL prior to its membrane integration. Upon *de novo* biosynthesis, CL is hydrolysed to monolysocardiolipin (MLCL) by various phospholipases that include PLA_2 (Hostetler et al. 1978), calcium independent PLA_2 (Mancuso et al. 2007; Seleznev et al. 2006), and secretory PLA_2 (Muralikrishna Adibhatla and Hatcher 2006). MLCL can then be remodeled to contain specific acyl chains via one of three enzymes, including: tafazzin (Xu et al. 2006), monolysocardiolipin acyltransferase-1 (MLCL AT-1) (Taylor and Hatch 2009) and acyl-CoA:lysocardiolipin acyltransferase-1 (ALCAT-1) (Cao et al. 2004). Tafazzin is a transacylase that catalyzes both the forward and reverse transfer of acyl groups (predominantly linoleic acid) from PC and CL (Xu et al. 2006). Mutations in the *TAZ* gene (located on chromosome Xq28 (Bolhuis et al. 1991; Ades et al. 1993)) lead to a severe X-linked recessive condition called Barth Syndrome (BTHS). This disorder results in young male patients experiencing symptoms that can include cardyomyopathies, neutropenia and growth retardation (Barth et al. 1983). *TAZ* gene mutations result in decreased CL remodeling and therefore decreased CL mass and non-specific acyl chain content. BTHS is the only disease that is directly caused by the alteration of CL (Vreken et al. 2000). MLCL AT-1, unlike tafazzin, utilizes linoleoyl coenzyme A for the specific acylation of MLCL (Taylor and Hatch 2009). This enzyme (located in the IMM) is a splice variant of the larger trifunctional protein α-subunit, and (Taylor and Hatch 2009) have shown it has the ability to incorporate linoleic acid onto CL as well as elevate CL mass in BTHS lymphoblasts. Similarly, ALCAT-1 is reported to perform an acyl-CoA-

dependant reacylation of MLCL to produce CL (Cao et al. 2004). Studies indicate that this enzyme is located in the MAM (Li et al. 2010). Unlike MLCL AT-1, however, ALCAT-1 has been linked to pathological remodeling of CL that leads to its oxidative damage and ultimately mitochondrial dysfunction (Li et al. 2010). Therefore, further studies are still required to fully understand what role ALCAT-1 serves in CL and lipid remodeling.

The occurrence of BTHS demonstrates that CL (and its remodeling) is absolutely required for development and overall maintenance of health. This is not surprising considering the large body of evidence that has emerged demonstrating the various functions CL plays in the cell. Initially, like other phospholipids, the structural function of CL in mitochondria must be considered. Like PE, CL has a small polar head group and a bulky hydrophobic tail end that ultimately leads to hexagonal phase, non-bilayer formation. These features introduce tension into a lipid bilayer which help induce negative curvature; a feature that is important in the IMM for the highly folded cristae structure. This leads to the assumption that the presence of CL may be vital for cristae formation. (Acehan et al. 2007) demonstrated through microscopic tomography studies that mitochondria from lymphoblasts of BTHS patients exhibited a collapsed intracristae space. Mitochondrial cristae are not only highly folded structures, but they are also rich in membrane proteins. Proteins that form the electron transport chain (ETC) are located in the IMM and are responsible for the generation of ATP. Recently, studies have generated evidence demonstrating not only the existence of interactions between ETC proteins (i.e., supercomplexes), but also a functional significance associated with these interactions. This field of research has been expertly reviewed by (Vartak et al. 2013) who summarize past and recent advances that have lead to the understanding of the presence of mitochondrial respiratory supercomplexes (MRSCs). Research aimed at understanding the role of CL in BTHS has lead to the development of sophisticated studies looking at the interaction of CL and ETC complexes. For example, using neonatal mouse cardiomyocytes deficient in tafazzin, (Powers et al. 2013) demonstrated a reduction in respiratory reserve capacity which may be attributed to a decrease in complex III activity. The development of Blue Native Polyacrylamide Gel Electrophoresis (BN-PAGE) (Schagger and von Jagow 1991; Schagger and Pfeiffer 2000; Wittig et al. 2006) has been instrumental not only for the understanding of mitochondrial supercomplexes, but also their CL-dependent formation. Studies conducted in yeast were among the first to show the importance of CL for the stabilization and optimal function of supercomplexes (Zhang et al. 2002; Pfeiffer et al. 2003; Zhang et al. 2005). Recently, an induced pluripotent stem cell model of BTHS was used to study supercomplex formation and overall mitochondrial function (Dudek et al. 2013). The authors found that diminished CL levels in this BTHS model not only

resulted in altered supercomplex formation and decreased mitochondrial function, but also an increase in reactive oxygen species (ROS) production. Mammalian studies that have looked at the effect of CL on mitochondrial supercomplex formation are limited. However, the detrimental effects of the lack of supercomplex formation were recently demonstrated in bovine heart mitochondria. Treatment with dodecyl maltoside resulted in supercomplex dissociation and ultimately, an increase in ROS production (Maranzana et al. 2013). (McKenzie et al. 2006) found that the reduction in CL caused by the *TAZ* gene mutation resulted in the disturbance of complex I supercomplex assembly in BTHS lymphoblasts. Lack of supercomplex formation could be a major contributor to the development of the disease. BTHS is not the only human disease that may be affected by the interaction of CL with mitochondrial complexes and supercomplexes. Studies have already predicted a correlation between CL-supercomplex associations and disorders such as cancer (Gasparre et al. 2013), aging (Gomez and Hagen 2012), neurodegenerative diseases (Paradies et al. 2011) and heart failure (Rosca et al. 2008). As studies progress, we will gain a better understanding of the effects of CL on mitochondrial supercomplex formation and human disease.

CL is also reported to play an important role in mitochondrial-mediated apoptosis. Cells undergoing mitochondria-independent apoptosis are defined as type I cells, while cells that undergo mitochondria-dependent apoptosis are referred to as type II cells (Scaffidi et al. 1998). CL is required for the induction of apoptosis in type II cells (Gonzalvez et al. 2013). The mechanism by which CL affects apoptosis is not entirely clear, but some potential functions have been elucidated. For example, CL can target tBid to the OMM leading to binding and oligomerization of Bax which results in mitochondrial permeabilization (Lutter et al. 2000; Kuwana et al. 2002). CL may act as a platform that recruits caspase-8 to the OMM where it too undergoes oligomerization; a step required for the release of proapoptotic factors from the intermembrane space (Gonzalvez et al. 2008). Studies have demonstrated the inability of mitochondria from BTHS lymphoblasts to bind active caspase-8 thus blocking the signal transduction (Gonzalvez et al. 2013). Proapoptotic factors can include the release of cytochrome c (cyt c) from the IMM. In apoptosis, cyt c (once released from the IMM) interacts with the IP3 receptor on the ER triggering the release of calcium which in turn results in more cyt c release (Boehning et al. 2003). The increased levels of cyt c amplify the apoptotic signal which results in activation of other caspases which break down the cell. Interestingly, cyt c is reported to have an additional role acting as a peroxidase for CL (Kagan et al. 2005). CL may undergo oxidation by CL-bound cyt c prior to apoptosis which ultimately leads to the release of proapoptotic factors. Thus, these studies demonstrate the importance of CL in apoptosis. Under normal conditions, apoptosis occurs to

eliminate cells in a planned and organized fashion. Failure to do this can result in necrosis and could be a factor that influences various human diseases.

In addition to its role in mitochondrial structure, bioenergetics and apoptosis, CL has been linked to other cellular processes. For example, failure to produce CL biosynthesis precursors such as PG in yeast results in lack of mitochondrial function. (Ostrander et al. 2001) demonstrated that this is caused by a failure to translate a number of mitochondrial encoded genes (COX 1, COX2, COX3 and COB) as well as one nuclear encoded gene (COX4) which are necessary for proper IMM function. This demonstrates that CL may be involved in the translational control of ETC proteins. CL has also been shown to act as a mediator that facilitates the crosstalk between mitochondria and vacuoles (Chen et al. 2008). Failure to produce CL (via a disruption of the CRD1 gene in yeast) results in the formation of swollen vacuoles and loss of vacuolar acidification (Chen et al. 2008). The results of this study indicate that CL may be involved in signalling mechanisms by the mitochondria that control optimal vacuole function. CL is also required for mitochondrial protein import. For example, one study observed the effects of removing/reducing CL in yeast via CLS mutants (crd1Δ) and tafazzin mutants (tazΔ) coupled with the double deletion of genes encoding the TOM and SAM complex (Gebert et al. 2009). This resulted in the generation of growth defects and even lethality in some instances. Further investigation revealed that reduced CL levels lead to a dysfunction of the TOM complex assembly and function, indicating that CL is required for the function of OMM transport proteins. Another recent study examined a novel function of CL that involves its externalization from the IMM to the OMM as a signalling mechanism for mitophagy (Chu et al. 2013). Mitophagy is a cellular process required for the controlled removal of aberrant or damaged mitochondria and may prevent the triggering of cellular apoptosis or even necrosis (Kubli and Gustafsson 2012). Rotenone induced mitophagy resulted in the externalization of CL to the OMM in rat cortical neurons and in SH-SY5Y neuroblastoma cells. The autophagy protein microtubule-associated-protein-1 light chain 3 (LC3) was shown to bind to CL and the resulting interaction then signaled for the removal of mitochondria via autophagosomes. Decreasing CL levels through CLS knockdown, or preventing its externalization by phospholipid scramblase-3 knockdown, resulted in decreased mitophagy events. Thus, these results further demonstrate the importance of CL not only for mitochondrial function, but also for the well-being of the entire organism.

Conclusions

Phospholipids play a vital structural role in cellular and organelle membranes. They create the necessary boundaries between cellular components and also house a number of proteins that perform a wide variety of functions. Phospholipids express similar properties in different cellular locations, but as we have seen, they may also perform specialized functions in mitochondria. It is interesting to note that phospholipids do not behave as individual entities in mitochondria, but rather interact with each other often requiring the presence of other phospholipids for their function and even synthesis. The phospholipid profile of mitochondrial membranes is unique due to the presence of CL, a phospholipid found predominantly in the mitochondria. Even though the majority of phospholipids are produced outside the ER, mitochondria are capable of synthesizing some of their own (i.e., CL, PG, PE). Research conducted by many dedicated investigators has improved our understanding of mitochondrial phospholipids and their role in various human diseases. Continued research in this field will prove to be indispensable in helping us treat those who are suffering from mitochondrial disorders and other related diseases.

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