Mitochondrial lipid transport at a glance

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Journal of Cell Science 126, 5317–5323

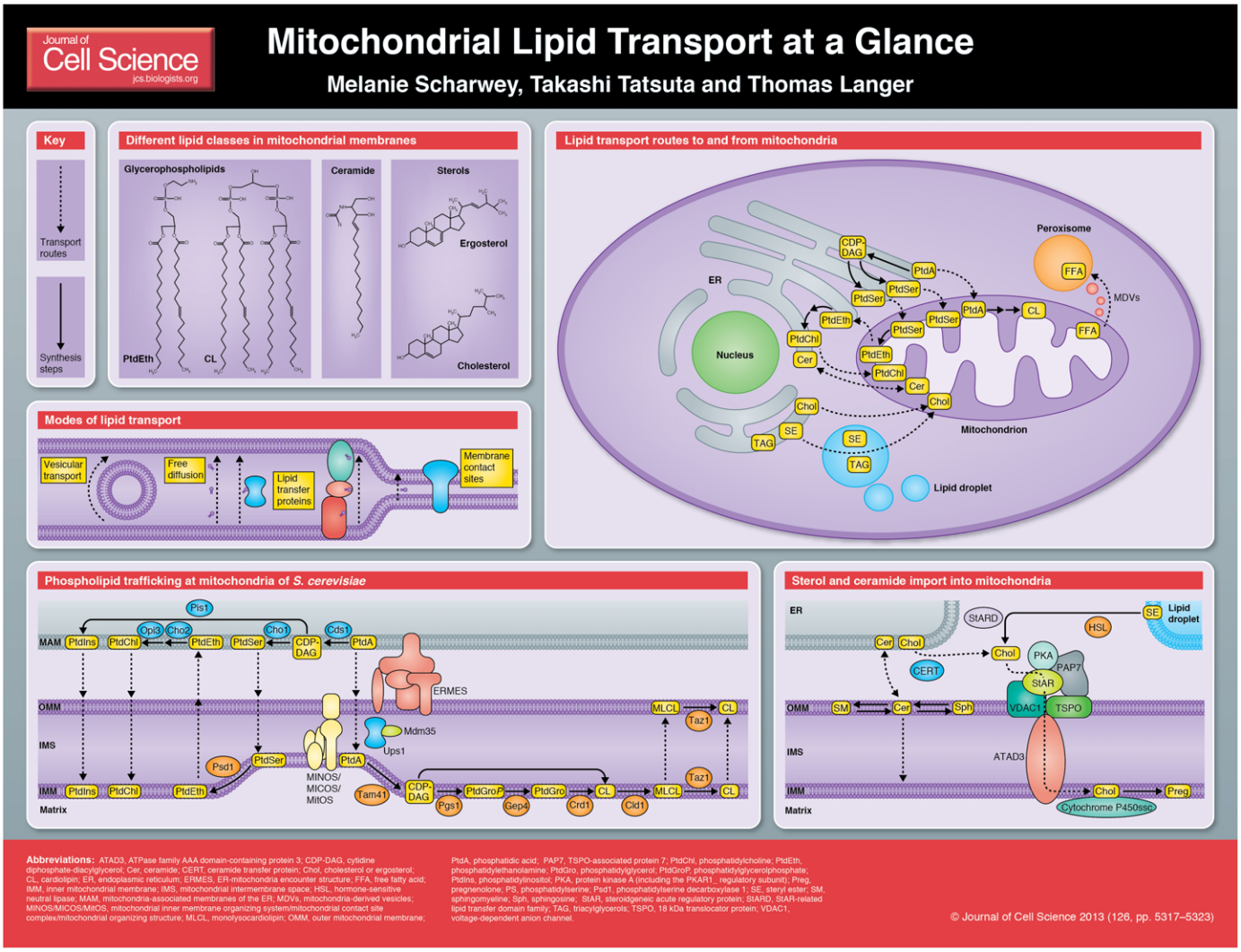
doi: 10.1242/jcs.134130

Summary

Lipids are the building blocks of cellular membranes and are synthesized at distinct parts of the cell. A precise control of lipid synthesis and distribution is crucial for cell function and survival. The endoplasmic reticulum (ER) is the major lipid-synthesizing organelle. However, a subset of lipids is synthesized within mitochondria, and this aspect has become a focus of recent lipid research. Mitochondria form a dynamic membrane network that is reshaped by fusion and fission events. Their functionality therefore depends on a continuous lipid supply from the ER and the distribution of lipids between both mitochondrial membranes. The mechanisms of mitochondrial lipid trafficking are only now emerging and appear to involve membrane contact sites and lipid transfer proteins. In this Cell Science at a Glance article, we will discuss recent discoveries in the field of mitochondrial lipid trafficking that build on long-standing observations and shed new light on the shuttling of membrane lipids between mitochondria and other organelles.

Introduction

The lipid metabolism and the maintenance of membrane homeostasis require an extensive exchange of lipids and metabolic intermediates between cellular membranes. Most of the phospholipids, sterols, sphingolipids and neutral lipids are synthesized within the endoplasmic reticulum (ER) and redistributed to other cellular membranes. Mitochondrial integrity depends on lipid uptake from the ER, but mitochondria also contribute to the cellular synthesis of phosphatidylethanolamine (PtdEth), which is released from mitochondria to the ER.



(See poster insert)

As the site of catabolic degradation of fatty acids (β-oxidation) and, to some degree, of fatty acid synthesis (Wanders et al., 2010), mitochondria have a central role in lipid metabolism and communicate with other cellular compartments, such as lipid droplets or peroxisomes. Lipid droplets are derived from the ER and serve as storage for sterols and fatty acids in form of triacylglycerols (TAGs) and steryl esters, and peroxisomes are involved in lipid decomposition through β-oxidation. Inter-organellar lipid transport from and to mitochondria is therefore of pivotal importance. Similarly, mitochondrial activities depend on lipid exchange between the inner mitochondrial membrane (IMM) and outer mitochondrial membrane (OMM). Here, we will summarize the current knowledge on the transport of various lipids from other organelles to mitochondria, as well as transport within mitochondria, and discuss emerging mechanisms.

Inter-organellar lipid transport to and from mitochondria

Transport of phospholipids between the ER and mitochondria

Lipid and metabolite trafficking between ER and mitochondria has been extensively studied in the past (Dennis and Kennedy, 1972; Jelsema and Morré, 1978; Bell et al., 1981) and has led to the discovery that lipid transport between both organelles occurs at membrane contact sites (Vance, 1990; Achleitner et al., 1999) (Box 1). One of the main phospholipids in the cellular membranes, PtdEth, is mostly synthesized in the ER in mammalian cells and transported to mitochondria. However, the majority of PtdEth in cell membranes of *Saccharomyces cerevisiae* is generated upon decarboxylation of phosphatidylserine (PtdSer) by phosphatidylserine decarboxylase (Psd1 in yeast) in the IMM (Zinser et al., 1991) (see poster). PtdSer synthesis occurs at ER–mitochondria contact sites, but how PtdSer is transported to Psd1 and how PtdEth, the product of decarboxylation by Psd1, is redistributed between cellular membranes is still unclear. Two proteins have been implicated in the regulation of PtdSer transport to the mitochondria in yeast, namely the F-box protein Met30 and the transcriptional activator Met4 (Kaiser et al., 2000; Schumacher et al., 2002). Inactivation of Met4 by ubiquitylation enhances PtdSer transfer to mitochondria, whereas activation of Met4 decreases PtdSer transport. The export of PtdEth, by contrast, is an energy-demanding process in *S. cerevisiae* and was found to be reduced upon ATP depletion *in vivo* (Daum et al., 1986; Achleitner et al., 1995).

Early studies in yeast have indicated that mitochondrial phospholipid import is likely to be protein dependent (Achleitner et al., 1999). Consistently, electron tomography has revealed that ER and mitochondria are adjoined by protein tethers of 10–25 nm (Csordás et al., 2006). In recent years, several protein complexes have been discovered that bridge ER and mitochondria, but their role in lipid trafficking between both organelles either remains unaddressed or is still under debate (Kornmann et al., 2009; Grimm, 2012; Nguyen et al., 2012; Rowland and Voeltz, 2012; Voss et al., 2012; Kornmann, 2013). Using a synthetic biology approach in yeast, a protein complex termed ER mitochondria encounter structure (ERMES) has been identified and was proposed to be involved in lipid transport (Kornmann et al., 2009; Kornmann, 2013). ERMES consists of four structural components (Mmm1, Mdm34, Mdm12 and Mdm10) and a regulatory subunit (Gem1) (Boldogh et al., 2003; Kornmann et al., 2009; Stroud et al., 2011; Kornmann, 2013) (see poster). It localizes to contact sites between the ER and mitochondria that initiate the fission of mitochondrial membranes and are emerging as central hubs for membrane trafficking (Friedman et al., 2011; Bernard and Klionsky, 2013; Hamasaki et al., 2013). Mmm1, Mdm12 and Mdm34 possess a synaptotagmin-like, mitochondrial and PH (SMP) domain, which is common to a group of conserved eukaryotic proteins (Lee and Hong, 2006; Kopec et al., 2010). The domain harbors an elongated hydrophobic groove to which different lipids can bind, and it was therefore named the tubular-lipid-binding (TULIP) domain. However, whether or not this domain plays a direct role in lipid transport remains to be established. ERMES subunits are conserved in fungi and organisms that harbor hydrogenosomes, but there appear to be no homologous proteins in metazoans (Wideman et al., 2013). However, several protein complexes have been identified that bridge ER and mitochondria in metazoans and that might fulfill a similar tethering function. These include protein complexes between the inositol trisphosphate ($InsP_3$) receptor in the ER membrane and the voltage-dependent anion channel 1 (VDAC1) in the OMM, mediated by the chaperone GRP75 (Szabadkai et al., 2006), homomeric complexes between the dynamin-related GTPase mitofusin 2, which has been found to localize to both ER and the mitochondrial outer membrane (de Brito and Scorrano, 2008), and protein complexes between the scaffold protein BAP31 (also known as BCAP31) in the ER and FIS1 in the OMM (Iwasawa et al., 2011).

Box 1. MAMs as sites of communication between the ER and mitochondria

Parts of the ER membrane co-purify with mitochondria using standard subcellular fractionation procedures and are therefore termed mitochondria-associated membranes (MAMs). MAMs have been identified as the sites of lipid exchange between mitochondria and ER and are emerging as central hubs for the communication between both organelles (Vance, 1990; Achleitner et al., 1999). Many lipid-metabolizing enzymes have been localized to MAMs, such as fatty acid CoA ligase 4 (FACL4) (Lewin et al., 2001; Lewin et al., 2002), phosphatidylserine synthase 1 and 2 (PSS1 and PSS2) (Rusiñol et al., 1994; Stone and Vance, 2000), phosphatidylethanolamine methyltransferase 2 (PEMT2) (Cui et al., 1993) and acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT1, also known as SOAT1) (Rusiñol et al., 1994), as well as acyl-CoA:diacylglycerol acyltransferase 2 (DGAT2) (Stone et al., 2009). Moreover, a specific glycosphingolipid-enriched microdomain has been described as being associated with MAMs (Hayashi and Su, 2003; Browman et al., 2006). MAMs thus appear to represent distinct membrane domains that are characterized by a defined protein and lipid composition. With the identification of tethering complexes between ER and mitochondria, the function of MAMs has been linked to an increasing number of processes affecting mitochondrial function, including Ca^{2+} signaling, mitochondrial dynamics, mtDNA inheritance and the formation of autophagosomes (Friedman et al., 2011; Hamasaki et al., 2013; Kornmann, 2013; Murley et al., 2013).

Transport of sphingolipids from the ER to mitochondria

Mitochondrial membranes also contain low amounts of sphingolipids, including ceramides (Zambrano et al., 1975; Zinser and Daum, 1995), which have been implicated in development and aging (Cutler and Mattson, 2001; Kujjo et al., 2013), as well as in apoptotic and non-apoptotic cell death pathways (Perez et al., 2005; Chipuk et al., 2012; Kujjo and Perez, 2012; Perera et al., 2012; Sentelle et al., 2012). Most ceramides appear to be generated by ceramide synthases that are localized to the ER membrane (Yu et al., 2007; Hannun and Obeid, 2008). Thus, ceramides appear to be transported from the ER to mitochondria, but it remains to be elucidated how the transport occurs. Notably, mitochondria have also been proposed to possess ceramide synthase and ceramidase activities (Bionda et al., 2004; Yu et al., 2007), suggesting that they might control ceramide levels by *de novo* synthesis. Regardless, increasing evidence suggests that mitochondrial membrane ceramides have a crucial role in maintaining mitochondrial integrity. For instance, mice lacking ceramide synthase 2 show reduced activities of respiratory complex IV, which is associated with increased oxidative stress (Zigdon et al., 2013). Similarly, mutant mice lacking the ceramide transfer protein (CERT), which functions in the transfer of ceramide from the ER to the Golgi, show a compromised mitochondrial structure and function (Wang et al., 2009). Furthermore, CERT mutant embryos accumulate ceramide in the ER, but also mislocalize ceramide to the mitochondria, with deleterious effects for the organelle (Wang et al., 2009).

Cholesterol transport to mitochondria

Cholesterol either is synthesized *de novo* in the ER or can be mobilized by the hydrolysis of steryl esters by lipases such as hormone-sensitive neutral lipase (HSL) in lipid droplets before it is transported to mitochondria (see poster). The cholesterol content of mitochondrial membranes is generally low in higher eukaryotes, whereas the yeast IMM contains significant amounts of the sterol ergosterol, which needs to be imported into the organelle (Daum, 1985; Zinser and Daum, 1995; de Kroon et al., 1997). Similarly, mammalian cells that produce steroid hormones contain high levels of cholesterol. Cholesterol is mobilized from steryl esters in these cells, before being imported into mitochondria and converted by cytochrome P450scc into pregnenolone, which serves as a precursor lipid for the synthesis of all steroid hormones (Miller and Bose, 2011).

Cholesterol in its free form is nearly insoluble in water (Haberland and Reynolds, 1973) and therefore needs to be transported by cholesterol-binding proteins (Mesmin and Maxfield, 2009). The steroidogenic acute regulatory protein (StAR) controls the supply of cholesterol to mitochondria in steroidogenic cells, and thereby steroidogenesis. StAR is the first described member of a protein family that contains the StAR-related lipid transfer (START) domain (Ponting and Aravind, 1999). Fifteen START domain (StarD) proteins have now been demonstrated to have a role in the intracellular transfer of lipids in mammals (Soccio and Breslow, 2003). StarD4, StarD5 and StarD6 are closely related to StAR (Soccio et al., 2002) and might be involved in intracellular cholesterol traffic from lipid droplets and the ER to the OMM, whereas StarD7 has been implicated to facilitate phosphatidylcholine (PtdChl) transport to mitochondria (Horibata and Sugimoto, 2010).

StAR has a hydrophobic pocket that binds a single molecule of cholesterol (Tsujishita and Hurley, 2000) and it has been found that it can transport cholesterol between membranes *in vitro* (Christensen et al., 2001; Tuckey et al., 2002). StAR releases cholesterol to the OMM, and this lipid is subsequently imported into mitochondria for degradation (Granot et al., 2007). How the release of cholesterol from StAR is regulated and how cholesterol reaches cytochrome P450scc in the IMM is only poorly understood. StAR function depends on a multi-protein complex at the mitochondrial surface that spans both membranes and contains the 18 kDa translocator protein TSPO, VDAC1, TSPO-associated protein 7 (PAP7, also known as ACBD3), protein kinase A regulatory subunit 1α (PKAR1α), and the IMM protein ATAD3 (Li and Rousseau, 2012; Rone et al., 2012; Miller, 2013). This multi-protein complex is thought to shuttle cholesterol directly to cytochrome P450scc for the synthesis of pregnenolone (Rone et al., 2012; Miller, 2013).

It is presently unclear whether cholesterol transport to mitochondria is facilitated by direct membrane contacts, either between ER and mitochondria or between lipid droplets and mitochondria. It has been reported that yeast cells lacking the ERMES complex have reduced ergosterol levels in mitochondria, pointing to a role of ER–mitochondria contacts for ergosterol exchange (Tan et al., 2013). Non-vesicular transport of cholesterol mediated by protein–protein interactions between lipid droplets and mitochondria has been observed in steroidogenic cells (Boström et al., 2007; Goodman, 2008; Murphy et al., 2009; Zehmer et al., 2009), but it remains unknown how contacts between lipid droplets and mitochondria are maintained. It has been proposed that soluble NSF attachment protein receptor (SNARE) proteins, such as SNAP23, tether both organelles and facilitate transport of cholesterol (Jägerström et al., 2009). In addition, perlipins, a family of conserved scaffolding proteins, have been suggested to have a role in the interaction between lipid droplets and mitochondria (Fong et al., 2002; Kimmel et al., 2010), because they are present in lipid droplets of steroidogenic cells (Londos et al., 1995). For example, perilipin 5 has been found to recruit mitochondria to lipid droplets under oxidative stress (Wang et al., 2011), demonstrating a physical and metabolic link between lipid droplets and mitochondria. Similarly, perilipin 3 also associates with mitochondria under stress conditions (Hocsak et al., 2010).

Lipid transport between mitochondria and peroxisomes

Mitochondria and peroxisomes are responsible for the degradation of fatty acids by β-oxidation and thus share common metabolic functions (Poirier et al., 2006; Wanders et al., 2010). Whereas peroxisomes are the only site of β-oxidation in yeast and plants, in mammalian cells, very long chain fatty acids are degraded in peroxisomes and medium chain fatty acids in mitochondria (Wanders et al., 2010), pointing to a flux of fatty acids between both organelles. In which form and how fatty acids are transported remains to be determined, but the recently discovered mitochondrial-derived vesicles (MDVs) (Neuspiel et al., 2008) offer an attractive possibility for transport. It has been speculated that these vesicles are involved in transport of proteins, metabolites and lipids to peroxisomes (Schumann and Subramani, 2008; Camões et al., 2009). These lipids might include cardiolipin, which has been

reported to be present at low levels in peroxisomal membranes (Wriessnegger et al., 2007). Notably, MDVs might also mediate lipid transfer from mitochondria to lysosomes, as they have been shown to deliver oxidized mitochondrial proteins to lysosomes for degradation (Soubannier et al., 2012).

Intra-mitochondrial transport of lipids

Mitochondria are surrounded by two membranes that differ significantly in their protein content and lipid composition. Membrane lipids that were synthesized in the ER and transported to the OMM must be redistributed within mitochondria. Moreover, phospholipids, such as PtdSer or phosphatidic acid (PtdA), which serve as precursor lipids for PtdEth- and cardiolipin-synthesizing enzymes in the IMM, must be transported from the OMM to the IMM and back (see poster). These lipid transport processes include transbilayer movements across both mitochondrial membranes, as well as lipid transfer across the intermembrane space (IMS). We are only beginning to understand the mechanisms of intra-mitochondrial lipid trafficking, but recent evidence suggests that lipid transfer proteins and contact sites between OMM and IMM have central roles, as discussed below.

Lipid transfer across the IMS

The functional analysis of members of the Ups1 (yeast) or PRELI (mammalian) family of proteins and their role in cardiolipin synthesis (Box 2 and poster) has revealed direct insight into the mechanism of lipid transport across the IMS. Yeast cells that are deficient in the IMS protein Ups1 possess decreased levels of cardiolipin (Osman et al., 2009; Tamura et al., 2009) and accumulate PtdA (Connerth et al., 2012), suggesting that there is a role for Ups1 at early stages of cardiolipin synthesis. Ups1 is an intrinsically unstable protein and is stabilized upon the assembly with Mdm35 into hetero-dimeric complexes in the IMS (Potting et al., 2010). These complexes were found to act as lipid transfer proteins and to shuttle PtdA between liposomes *in vitro* (Connerth et al., 2012). Together with genetic interaction data, these findings strongly suggest that Ups1–Mdm35 complexes mediate PtdA transfer across the IMS in yeast (Connerth et al., 2012). This is consistent with a structural model of Ups1 that predicts a 'hot-dog-fold' structure similar to PITP, a phosphatidylinositol (PtdIns) and phosphatidylcholine (PtdCho) transfer protein (Connerth et al., 2012). Both Ups1 and Mdm35 are evolutionarily conserved. Their human homologues, PRELI and the p53-regulated protein TRIAP1, respectively, assemble in the IMS of human mitochondria (Potting et al., 2013). PRELI–TRIAP1 complexes exert PtdA transfer activity and are required for the accumulation of cardiolipin in mitochondrial membranes, thereby protecting cells against apoptosis (Potting et al., 2013).

Both complexes, Ups1–Mdm35 and PRELI–TRIAP1, transport PtdA with high selectivity (Connerth et al., 2012; Potting et al., 2013). It is therefore an attractive possibility that other members of the conserved family of Ups1/PRELI-like proteins (i.e. Ups2 and Ups3 in yeast, and PRELI2, SLMO1 and SLMO2 in mammals) form lipid transfer complexes with different specificities. In agreement with this hypothesis, Ups2 has been found to assemble with Mdm35 and to be required for the accumulation of PtdEth within mitochondria (Osman et al., 2009; Tamura et al., 2009). Similarly, Ups1/PRELI proteins might be involved in the redistribution of newly synthesized cardiolipin between mitochondrial membranes. However, although Ups1 binds to cardiolipin (Connerth et al., 2012), the ability to transport cardiolipin has not been demonstrated for any member of the Ups1 protein family. By contrast, a different factor, the human mitochondrial nucleoside diphosphate kinase Nm23-H4 (also known as NME4) has recently been proposed to be involved in cardiolipin shuttling from the IMM to the OMM (Schlattner et al., 2013).

The role of OMM–IMM contact sites in phospholipid transport

Lipid transfer across the IMS is likely to occur at contact sites between OMM and IMM, which might facilitate the transport of lipids through dedicated lipid transfer proteins. Contact sites between both mitochondrial membranes appear to form distinct membrane domains that are characterized by a defined protein and lipid composition. They are enriched in negatively charged phospholipids, such as cardiolipin, which has been proposed to recruit Ups1 to these sites (Connerth et al.,

Box 2. Cardiolipin – the signature phospholipid of mitochondria

Cardiolipin represents ~15% of total phospholipids in mitochondrial membranes and is predominantly present in the IMM, whereas the OMM contains only low amounts of cardiolipin (Daum, 1985; Zinser and Daum, 1995; de Kroon et al., 1997; Gebert et al., 2009). Cardiolipin is a dimeric phospholipid consisting of four acyl chains, and has a conical shape with a small hydrophilic head group and a relatively large hydrophobic domain (see poster). It shares these structural properties with PtdEth, a major constituent of all cellular membranes; when present at high local concentrations, both phospholipids can generate negative curvature stress in lipid bilayers. Cardiolipin is synthesized by an enzymatic cascade in the inner leaflet of the IMM from PtdA that is synthesized in the ER and transported to mitochondria (see poster). Lipid transfer proteins shuttle PtdA across the IMS (Connerth et al., 2012; Potting et al., 2013) allowing its stepwise conversion into cytidine diphosphate (CDP)-diacylglycerol (DAG), phosphatidylglycerolphosphate (PtdGro-*P*), phosphatidylglycerol (PtdGro) and finally into cardiolipin (Schlame, 2008; Osman et al., 2010; Osman et al., 2011; Tamura et al., 2013) (see poster). A cardiolipin-specific lipase (Cld1 in yeast) (Baile et al., 2013) and the acyltransferase tafazzin allow remodeling of cardiolipin acyl chains and generate mature cardiolipin (Claypool and Koehler, 2012; Schlame, 2013).

Cardiolipin affects the activity and stability of many membrane protein complexes, including respiratory chain complexes, ATP/ADP carrier proteins and import machineries, and it has important functions in the regulation of mitochondrial dynamics and the induction of apoptosis (Osman et al., 2011; Claypool and Koehler, 2012). Cardiolipin regulates the activity of dynamin-like GTPases that mediate the fusion and fission of mitochondrial membranes. Localized lipolysis of cardiolipin by a mitochondrial phospholipase D stimulates membrane fusion (Gao and Frohman, 2012). Moreover, cardiolipin retains the pro-apoptotic protein cytochrome *c* at the IMM and, upon induction of apoptosis, provides a platform for the oligomerization of BAX and BAK, leading to the permeabilization of the OMM. In agreement with the pleiotropic functions of cardiolipin, alterations in cardiolipin levels and cardiolipin acylation cause the cardiomyopathy present in Barth syndrome and are associated with aging (Osman et al., 2011; Claypool and Koehler, 2012).

2012). Proteomic studies and genetic interaction maps have led to the identification of a hetero-oligomeric protein complex at yeast mitochondrial contact sites that tethers IMM and OMM (termed either MINOS, MICOS or MitOS) (Harner et al., 2011; Hoppins et al., 2011; von der Malsburg et al., 2011; Alkhaja et al., 2012). Mitochondria lacking this complex contain elongated cristae and appear to lack cristae junctions (Harner et al., 2011; Hoppins et al., 2011; von der Malsburg et al., 2011). Genes encoding subunits of this complex (*AIM5*, *AIM13*, *FCJ1* and *AIM37*) show negative genetic interactions with the biosynthetic cardiolipin pathway, pointing to a role in lipid transfer and metabolism (Hoppins et al., 2011). It therefore will be of interest to examine the phospholipid composition of mitochondrial membranes in the absence of this tethering complex.

Transbilayer lipid transport

The complex metabolism of mitochondrial membrane lipids requires transbilayer movements of lipids at multiple steps. Phospholipids that are imported from the ER must travel across the OMM and, at least to some extent, the IMM to be metabolized. Similarly, phospholipids that are synthesized within mitochondria need to be redistributed between all leaflets of both mitochondrial membranes. How mitochondrial phospholipids are transported between the leaflets of mitochondrial membranes is not understood. Only one phospholipid scramblase, PLSCR3, is known to be localized to mitochondria (Liu et al., 2003). Phospholipid scramblases are thought to facilitate transbilayer movement of lipids in a Ca^{2+}-dependent manner without exhibiting specificity for certain lipids (Wiedmer et al., 2000; Sahu et al., 2007; Bevers and Williamson, 2010). PLSCR3 appears to modulate the sensitivity of cells towards TNFα-induced apoptosis by increasing the amount of cardiolipin at the mitochondrial surface (Van et al., 2007; Liu et al., 2008), but it remains to be elucidated how PLSCR3 affects the distribution of cardiolipin in mitochondrial membranes.

Perspectives

The recent identification of components involved in mitochondrial lipid trafficking holds the promise that mechanisms that determine the lipid composition of mitochondrial membranes can be unraveled. It would not come as a surprise if these studies led to an even more complex and dynamic view of mitochondrial membranes, including the identification of specific lipid transitions under defined physiological conditions. For example, lipid transport processes might be of importance to explain the increased mitochondrial ceramide levels upon induction of apoptosis, which is thought to facilitate permeabilization of the OMM. Regulated lipid transport might also contribute to local changes in the lipid composition of mitochondrial membranes. This view is supported by the genetic interaction of mitochondrial lipid transfer proteins in yeast with prohibitins, which are thought to serve as membrane scaffolds for both proteins and lipids in the IMM (Osman et al., 2009). It is therefore conceivable that localized lipid trafficking and membrane scaffold proteins, combined with a restricted localization of lipid-synthesizing enzymes, allow the establishment of an asymmetric lipid distribution within mitochondrial membranes, which is likely to be important for the regulation and maintenance of mitochondrial structure and function.

A high-resolution version of the poster is available for downloading in the online version of this article at jcs.biologists.org. Individual poster panels are available as JPEG files at http://jcs.biologists.org/lookup/suppl/doi:10.1242/jcs.134130/-/DC1.

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