Prokaryotic and Mitochondrial Lipids: A Survey of Evolutionary Origins

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Abstract

Mitochondria and bacteria share a myriad of properties since it is believed that the powerhouses of the eukaryotic cell have evolved from a prokaryotic origin. Ribosomal RNA sequences, DNA architecture and metabolism are strikingly similar in these two entities. Proteins and nucleic acids have been a hallmark for comparison between mitochondria and prokaryotes. In this chapter, similarities (and differences) between mitochondrial and prokaryotic membranes are addressed with a focus on structure-function relationship of different lipid classes. In order to be suitable for the theme of the book, a special emphasis is reserved to the effects of bioactive sphingolipids, mainly ceramide, on mitochondrial membranes and their roles in initiating programmed cell death.

Keywords

Membrane lipids · Sphingolipids · Mitochondria · Prokaryotes · Evolution

Abbreviations

BCFA	branched-chain fatty acids
Cer	ceramide
CL	cardiolipin
DAG	diacyl glycerol
DES	DHCer desaturase
DHCer	dihydroceramide
DMPE	dimethyl-PE
ER	endoplasmic reticulum
GDGT	glycerol dibiphytanyl glycerol tetraether
HIF-1α	hypoxia inducible factor
LPS	lipopolysaccharide
MAM	mitochondria-associated membranes
MDOs	membrane-derived oligosaccharides
MICOS	mitochondrial contact site and cristae organizing system
MIM	mitochondria inner membrane
MMPE	monomethyl-PE
MOM	Mitochondrial outer membrane
MOMP	MOM permeabilization
mtDNA	mitochondrial DNA
MUFA	monounsaturated fatty acids
PE	phosphatidylethanolamine
PG	phosphatidylglycerol
PI	phosphatidylinositol
PLs	phospholipids
PUFA	polyunsaturated fatty acids
SLs	sphingolipids
SPT	serine palmitoyltransferase

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2.1 Introduction

Life is a complex phenomenon. Starting from very simple prokaryotic organisms, life has evolved to be more complicated and advanced (Lane 2011). The exact evolutionary origins of eukaryotic cells remain elusive despite mounting evidence that links organelles, particularly mitochondria and chloroplasts, to a prokaryotic origin (Allen 2015; Ku et al. 2015; Muller et al. 2012; Stefano et al. 2015). The links between prokaryotic cells and mitochondria have been postulated as endosymbiotic (Douglas 2014; Lopez-Garcia et al. 2017); a proto-eukaryotic cell engulfing a bacterium which found a safe haven to procreate and thrive while giving the newly-formed cell ample energy in the form of ATP from oxidative phosphorylation (Pittis and Gabaldon 2016). This view was recently modified to what is known as the "*inside out origin*" hypothesis (Baum and Baum 2014) that postulates that membranes were made to cover the prokaryotic cell and make a new cell. Whether each hypothesis is acceptable and correct is beyond the scope of this chapter. The common theme between both theories is the membrane.

Membranes are made of lipids and proteins that are in a continuous dynamic motion. Lipids are enigmatic molecules in cells (Fujimoto and Parton 2011), as they serve a multitude of functions in cellular architecture and physiology. Lipids are characterized by their hydrophobicity. Yet many amphipathic lipids are absolutely essential for the cell, as membranes are made from them. Many lipids were considered to be merely structural with no actual biological role in the cell. This view has changed considerably in the past three decades as more lipids have been proven to be "bioactive" (Bazan et al. 1997; Chiurchiu et al. 2018; Dahinden et al. 1990; Hannun and Obeid 2018; Ioan-Facsinay and Kloppenburg 2018; Mene et al. 1989). Indeed, lipids do have a very important structural role in cells; nevertheless one cannot only categorize their biological functions as such. Lipids have been implicated as signaling molecules in a variety of cellular functions: from regulation of receptor proteins (Coskun et al. 2011) to cell division (Negishi et al. 2016), senescence (Hannun 1996), apoptosis (Abou-Ghali and Stiban 2015; Mathias et al. 1998; Mulkidjanian et al. 2018; Praharaj et al. 2018), mobilization of stem cells (Klyachkin et al. 2014; Nagareddy et al. 2014), and ageing (Das 2018), among a plethora of other important cellular functions (Balla 2013; Magtanong et al. 2016).

Both prokaryotes and mitochondria share similar membranes and compartments. Both mitochondria and bacteria may secrete outer membrane vesicles into the surrounding environments, and this was postulated to be the evolutionary origin of the eukaryotic endomembrane system (Gould et al. 2016). Interactions between lipids forming the plasma membrane in bacteria and eukaryotes have been revealed indicating the evolutionary origins of the eukaryotic cell from bacterial lipids. Both mitochondrial and chloroplast membrane lipids share significant similarities with bacterial membrane lipids (Bansal and Mittal 2015). It is not farfetched to envisage that lipids did move throughout evolution from a type of cell to another, as movement of lipids in the cell from one organelle to another have been implicated in a variety of lipid metabolic routes (Petrungaro and Kornmann 2018; Vance 2014, 2018) and functions (Stiban et al. 2008a). In this chapter, a comparison between lipid content in prokaryotes and mitochondria will be undertaken trying to underline the evolutionary relationships between prokaryotic and eukaryotic cells. Roles of different lipids in mitochondria and prokaryotes will also be addressed to identify possible converging physiological mechanisms within the tree of life.

2.2 Bacterial and Mitochondrial Membranes

The ability of mitochondria to generate ATP for the cell is strictly correlated with their structure (Mannella et al. 2001). Mitochondrial cristae localize proton gradients, concentrate metabolite, and prevent the release of signaling molecules (as in apoptosis) (Munoz-Gomez et al. 2017). The mitochondrial contact site and cristae organizing system (MICOS) is a multi protein complex in

charge of creating both cristae junctions and cristae contact sites at the mitochondrial envelope by combining the functions of its six different subunits. The similarity between the intracytoplasmic membranes of photosynthetic bacteria and cristae was the basis for the homology hypothesis proposed by Stewart and Mattox that suggested that cristae were derived from purple non-sulfur bacteria and had a pre-endosymbiotic origin (Stewart and Mattox 1984). Mic60 is the central and largest protein in MICOS, and together with Mic10, constitutes the core of the complex (John et al. 2005). The major components of MICOS are conserved amongst animal and fungi, Mic60 and Mic10 are consistently identified outside these groups, and a homolog of Mic60 has been isolated in α-proteobacteria confirming the endosymbiotic origin of cristae (Munoz-Gomez et al. 2015).

Photosynthetic bacteria also show an interesting lipid composition. The purple bacterium *Rhodobacter sphaeroides* membrane contains betaine lipid and a glycolipid, while the membrane of the green sulfur bacterium *Chlorobium limicola* contains sphingolipids (Benning 1998).

2.3 Bacterial Lipids

Like all cells, prokaryotic cells are bounded by membranes. Prokaryotic cell membranes carry out the usual function as selective barriers for the exchange of material between the cytoplasm and the environment. In addition, they are the location of proteins involved in communication (receptors) and interaction with other cells and the environment, and, in many cases, also carry out the role of being the site of cellular metabolism (Dowhan and Bogdanov 2002; Huffer et al. 2011). According to the chemiosmotic theory, the production of ATP during respiration and photosynthesis requires the presence of a membrane to generate the gradient of protons necessary for the proton motive force that drives ATP synthesis through the action of ATP synthase (Lane 2017). As the vast majority of prokaryotic cells do not contain internal membranes or organelles that can be dedicated to these functions, cellular respiration and photosynthesis take place on the prokaryotic plasma membrane. It is worth noting that in some cases a number of rare and uncommon organelles have been described in prokaryotic cells (Murat et al. 2010). In particular, the chromatophores of purple photosynthetic bacteria and the thylakoid membranes of cyanobacteria can be considered compartmentalized structures with defined functions (Liu 2016; Noble et al. 2017). The only phylum presenting extensive compartmentalization of the cytoplasmic space is, however, *Planctomycetes* (Fuerst and Sagulenko 2013; Lindsay et al. 2001). In this phylum it is possible to observe the separation of the chromosome through a double lipid-bilayer membrane to form a nuclear body reminiscent of the eukaryotic nucleus (Liu 2016; Murat et al. 2010).

Bacteria and archaea are both prokaryotic cells and they share the characteristic of not having a defined nucleus or a system of internal membranes. These two types of cells belong to two separate domains and there are substantial differences between them. While bacterial membranes are composed mainly of a phospholipid bilayer, archaeal membranes present more variability and unique characteristics (Jain et al. 2014). One major difference between the lipids of archaea and bacteria is the absence of ester bonds between glycerol and fatty acids: Archaea fats contain exclusively ether bonds. Moreover, phospholipids (PLs) are not the only major component of membranes, and a unique type of tetraether monolayer can be found in some archaeal cells, most commonly in those that are adapted to living in extreme environments (Albers et al. 2000; Siliakus et al. 2017).

Classically bacteria are classified as either Gram-positive or Gram-negative according to their coloring after applying the Gram staining technique (Coico 2005). This classification reflects structural differences between the cell walls of the two major types. The Gram-positive bacterial cell wall presents a plasma membrane and a thick peptidoglycan layer that can range between 20 and 80 nm in thickness; on the other hand, the Gram-negative cell wall consists of a plasma membrane, a thin (1.5–10 nm) peptidoglycan layer and an outer membrane

which is in direct contact with the environment (Mai-Prochnow et al. 2016). The outer membrane contains lipids that are exclusive to the Gram-negatives such as Lipid A and lipopolysaccharide (LPS). Another major group of Bacteria, the Mycobacteria, has a cell wall that does not fit into the Gram-positive or negative characterization and contains mycolic acid (Jankute et al. 2015).

For many years it was thought that bacterial lipids were limited in kind and metabolism. In addition to the well known and understood lipids of *Escherichia coli*, it is now evident that bacterial membrane composition is not only variable within species, but also depends on environmental conditions to which cells are exposed (Sohlenkamp and Geiger 2016).

E. coli has been regarded as the model organism for the study of the Gram-negative proteobacteria and much is known about lipid metabolism and membrane composition of this organism. The predominant lipid in *E. coli* membranes is phosphatidylethanolamine (PE) which constitutes about 75% of membrane lipids composition. In addition about 20% of the membrane is composed of phosphatidylglycerol (PG) and cardiolipin (CL) (Sohlenkamp and Geiger 2016). When compared with other bacteria it is now accepted that many variations in lipid composition exist. In many cases the variations are limited to modifications of PE like monomethyl-PE (MMPE) or dimethyl-PE (DMPE) (Sohlenkamp and Geiger 2016).

Moreover, the Gram-positive and Gram-negative bacteria membrane contains several enzymes including aminoacyl-phosphatidylglycerol synthases that can add amino acids to the polar heads of PG within the membrane using aminoacetylated tRNA as donor molecules (Roy et al. 2009). In some cases the amino acid modification changes the overall negative charge of the phosphate head to a positive charge with implications regarding the ability to resist antimicrobial peptides. Lysine (LysPG), alanine (AlaPG) or arginine (ArgPG) have been described (Sohlenkamp and Geiger 2016). In *Listeria monocytogenes* (a foodborne Gram-positive gastrointestinal pathogen) concentrations of LysPG are correlated to osmotic stress, growth temperature, and growth phase (Dare et al. 2014). These findings suggest a physiological role for these modifications beyond conferring antimicrobial peptide resistance. Modifications of the lipid composition and overall membrane charge have the potential of affecting the activity of membrane-associated proteins (Roy 2009; Roy et al. 2009). In *Staphylococcus aureus* LysPG may act as regulator of the cell cycle by controlling the number of replication origins per cell (Ichihashi et al. 2003).

Some bacteria are able to synthesize phosphatidylinositol (PI) which, in some cases can be modified with mannose residues and fatty acid residues to form acyl-phosphatidylinositol mannosides that can be further metabolized to form lipomannan and lipoarabinomannan. PI is an essential lipid at least in *Mycobacterium tuberculosis* (Jackson et al. 2000). In addition, bacteria produce lipids that lack phosphorus such as ornithine lipids (OL) and sulfoquinovosyl diacylglycerol (Sohlenkamp and Geiger 2016). An extensive analysis of bacterial lipids composition and metabolism can be found in the 2016 review by Sohlenkamp and Geiger (2016). Table 2.1 summarizes the findings of several research groups on the lipid composition of prokaryotic cells.

2.3.1 Environmental Factors

It is generally accepted that environmental conditions can influence lipid composition of membranes and that the concentration of PLs can also vary in response to growth phase; environmental factors such as pH, osmolarity, salinity, and the presence of organic solvents can have an impact on the relative amount of PLs found in the membrane (T. Y. Lin and Weibel 2016). In particular, CL seems to be strictly regulated according to the phase of growth and can increase by 200% as cells enter the stationary phase compared to cells in the logarithmic phase. CL content is regulated by the activity of CL synthase (Cls) with a feedback regulation mechanism during cellular growth in the absence of stress (T. Y. Lin and Weibel 2016).

Table 2.1 Plasma lipid composition in representative prokaryotic cells

Type of prokaryotic cell	Predominant lipid(s)	Reference
Gram-positive		
S. aureus	PG, CL, LPG, GPL	Sohlenkamp and Geiger (2016)
B. subtilis	PG, CL, PE, LPG, GL, GPL	Sohlenkamp and Geiger (2016)
L. monocytogenes	PG, CL, LPG, LCL, PI	Sohlenkamp and Geiger (2016)
Nocardia sp.	CL, PE, PI, PIM, OL, SQD, HOP	Sohlenkamp and Geiger (2016)
Gram-negative		
E. coli	PG, CL, PE	Sohlenkamp and Geiger (2016)
P. aeruginosa	PG, CL, PE, PC, OL, APG	Sohlenkamp and Geiger (2016)
R. tropici	PG, CL, PE, MMPE, DMPE, PC, OL, S2, P1, P2, DGTS, LPG	Sohlenkamp and Geiger (2016)
Mycobacteria		
M. tuberculosis	PG, CL, PE, PI, PIM, OL	Sohlenkamp and Geiger (2016)
M. leprae	PDIM, PGL, LAM	Kaur and Kaur (2017)
Archaea		
Halobacteriales	Archaeol, Extended archaeol	Villanueva et al. (2014)
Thermoplasmatales	GDGT-0, GDGT-1–4 GDGT-5–8	Villanueva et al. (2014)
Thermoproteales	GDGT-0, GDGT-1–4 GDGT-5–8	Villanueva et al. (2014)

Abbreviations used: *PG* phosphatidylglycerol, *CL* cardiolipin, *PE* phosphatidylethanolamine, *GPL* glycophospholipid, *LPG* lysyl-phosphatidylglycerol, *OL* ornithine lipid, *PI* phosphatidylinositol, *GL* glycolipid, *LCL* lysyl-cardiolipin, *APG* alanyl-phosphatidylglycerol, *MMPE* monomethyl PE, *DMPE* dimethyl PE, *S2* OL hydroxylated in ornithine headgroup, *P1* OL hydroxylated in the 2-position of the ester-bound fatty acid, *P2* OL hydroxylated in ornithine headgroup and in 2-position of ester-bound fatty acid, *DGTS* diacylglyceryl-N,N,N-trimethylhomoserine, *PIM* phosphatidylinositol mannoside, *SQD* sulfolipid sulfoquinovosyl diacylglycerol, *HOP* hopanoid, *PDIM* phthiocerol dimycocerosat, *LAM* lipoarabinomannan, *PGL* Phenolic glycolipid, GDGT glycerol dibiphytanyl glycerol tetraether (with 0 to 8 0–8 cyclopentane moieties)

Lipid metabolism and membrane lipids relative composition can change in bacteria in response to rapid changes in the environment. A molecular thermosensor of *Bacillus subtilis* can induce the expression of a PL acyl desaturase that inserts a *cis* double bond in pre-existing PLs as a response to decreased temperatures (Aguilar et al. 2001), thus preserving membrane fluidity. Response to acid stress in *E. coli* results in the transformation of pre-existing unsaturated fatty acids to cyclopropane fatty acids. This change is observed also as a physiological change during the growth phase. This modification starts at the beginning of stationary phase and is carried out until all the unsaturated fatty acids are modified. Such change is irreversible and if the cell re-enters a logarithmic growth phase the content of cyclopropane fatty acids needs to be diluted by *de novo* synthesis of *cis*-unsaturated fatty acids (Y. M. Zhang and Rock 2008).

Bacteria that have adapted to living in environments in which the majority of organisms would die (extreme environments), have permanent modifications of their membrane lipids and in some cases, require the presence of unique lipids. These lipids can vary from long polyunsaturated fatty acids (PUFAs) to tetraester or tetraether lipids. The following sections describe adaptations to such environmental conditions.

2.3.1.1 Pressure

Extreme barophilic bacteria (bacteria that require pressures of at least 50 MPa for growth and that are able to grow well at 100 MPa) have been shown to synthesize long PUFAs C22:6 (DHA) and C20:5 (EPA) as a mechanism to adapt to the low temperature and high hydrostatic pressure of deep sea environments (Fang et al. 2000). PUFAs could reduce the transition temperature and maintain membrane fluidity under low temperature and high pressure conditions (DeLong and Yayanos 1985; Fang et al. 2000). The bacterial origin of long PUFAs under high pressure conditions suggests that bacteria can be an important

source of C 20:5 and C22:6 to deep sea sediments.

2.3.1.2 Temperature

Hyperthermophilic bacteria also need the synthesis of special lipids to support growth at high temperatures. The bacterium *Thermotoga maritima* grows at temperatures as high as 90 °C and contains a novel glycerol ether lipid containing 15,16-dimethyltriacontanedioic acid (Damste et al. 2007). It is interesting to note that at high temperatures bacteria show the presence of ether bonding which is usually considered an exclusive of archaeal lipids. In fact, it has been postulated that above 80 °C membranes that are composed exclusively of ester lipids are not stable, and that ether bonds are essential for hyperthermophilic growth (Siliakus et al. 2017).

Often extremophiles that grow at high temperatures present a monolayer rather than bilayer membrane (Siliakus et al. 2017); the tetraester and tetraether lipids found in bacteria adapted to life at high temperatures are similar to the tetraether lipids found in archaea and they are believed to be the result of a tail-to-tail condensation between fatty acids that originally belonged to bilayers (Fitz and Arigoni 1992). Tetraester lipids are found in *Thermoanaerobacter ethanolicus* (T_{max} = 78 °C) amongst others, while diether fatty acids are found in *Aquifex pyrophilus* (T_{max} = 95 °C) and *Thermodesulfobacterium commune* (T_{max} = 85 °C) (Siliakus et al. 2017).

Membrane proteins depend on their surrounding lipids to maintain correct folding and functionality (Findlay and Booth 2006). Considering the broad variation in membrane lipids and the relative stability of membrane proteins it is interesting to note that even profound variations as the ones seen in hyperthermophiles allow for protein based membrane physiological processes to be maintained. In the archeaon *Archaeoglobus fulgidus* the modifications to the membrane as adaptation to high temperatures are considerable and the membrane of this organism is mainly composed of ether-linked diglycerides of either conventional (diether) or cyclical tetraether architecture (Lai et al. 2008); comparison between the ammonium transporter Amt-1 of this archaeon with the one of *E .coli* shows remarkable similarity at the structural level. The same can be said for an aquaporin protein which shares 30% sequence similarity with aquaporin AqpZ of *E. coli* but presents very similar three dimensional structure (Sanders and Mittendorf 2011). When comparing crystal structures rather than amino acid or nucleotide sequences, in the hyperthermophilic bacterium *Thermus thermophilus* HB27, the three dimensional shape of a beta-barrel outer membrane protein TtoA, shows no obvious structural differences from mesophilic beta-barrel outer membrane proteins (Sanders and Mittendorf 2011) indicating once more that the modified surrounding lipids still retain the ability to allow correct folding and functionality of membrane proteins.

Archaea are mostly better adapted at living in high temperature environments compared to bacteria. The highest recorded maximum temperature for growth in bacteria is 100 °C for *Geothermobacterium ferrireducens* (Kashefi et al. 2002); the record for archaea is 122 °C in *Methanopyrus kandleri* when subjected to hydrostatic pressure of 40 MPa (Takai et al. 2008). It is therefore interesting to explore the reasons behind this difference and what it is that makes archaea that much better at maintaining their membrane in the liquid crystalline phase at temperatures significantly higher than the temperature of boiling water. Rather than assigning specific single lipids an intrinsic ability to resist high temperatures and therefore confer hypothermophilic characteristics to the organism, it has been proposed that archaeal lipids (isoprenoid ether lipids) in the context of the membrane provide the cell with a membrane that is in a low permeability liquid crystalline state throughout the possible growth temperature range (0–100 °C) and therefore allow these cells to grow and divide at all possible range of temperature without having to regulate lipid composition or concentration (Koga 2012).

Similarly psychrophiles (bacteria that grow at low temperatures, in some cases below the temperature at which water freezes) need to modify their membrane to adapt, and the modifications that are commonly observed are membranes with unsaturated fatty acids, short

chain fatty acids, branched-chain fatty acids (BCFAs), carotenoids, and glycolipids (Siliakus et al. 2017). The most prevalent modification found in the psychrophiles is the presence of monounsaturated fatty acids (MUFAs) that result from the activity of desaturases. In some Gram-positive (e.g. *B. subtilis*) as well as in some Gram-negative bacteria, the iso configuration of BCFAs (iso-BCFA) is modified to anteiso-BCFAs. The anteiso position of methyl groups in the latter causes greater fluidity of the membrane (Siliakus et al. 2017).

2.3.1.3 Hypersalinity

Halophiles and extreme halophiles grow at concentrations of salt that would kill the majority of microorganisms. The general principle that solute concentrations in the cytoplasm should be at least isoosmotic with the environment applies to these cells, but, like other microorganisms, the ability to increase cytoplasmic solute concentration to reach hypertonicity when compared to the environment, is the preferred option (Gunde-Cimerman et al. 2018). To maintain high osmotic pressure, prokaryotic cells can follow a number of strategies such as accumulation of inorganic salts (mainly KCl), or synthesis of organic compounds (compatible solutes) including polyols, sugars, amino acids, and betaines among others (Gunde-Cimerman et al. 2018).

Soil microorganisms are often facing dramatic changes in osmolarity due to fluctuations of water in soil during different seasons. The soil bacterium *B. subtilis* can tolerate changes in osmotic pressure by synthesizing the compatible solute glycine betaine. The precursor for glycine betaine is choline, which must be obtained from exogenous sources (Nau-Wagner et al. 2012; Wood et al. 2001). OpuB and OpuC are two high affinity choline transporters that are regulated by osmosis. In addition to synthesis of glycine betaine *B. subtilis* membranes contain multiple transport systems that have overlapping substrate specificity which can take up these osmoprotectants (Wood et al. 2001).

Salinibacter ruber on the other hand, is an extreme halophilic bacterium that grows optimally at salt concentrations between 200 and 300 g/L and requires a minimum concentration of salt of 150 g/L for growth. This bacterium prefers the salt-in option to the synthesis of compatible solutes and uses KCl for osmotic stabilization. The energy required for the pumps that move ions across the membrane is provided by the proton motive force generated by a bacteriorhodopsin-like retinal pigment that uses the energy provided by light to pump H^+ ions across the membrane (Oren 2013). CL is present in high concentrations (20%) in what might be an adaptation to high salt concentrations. In addition to increased concentrations of CL *Salinibacter* contains unusual sulfonolipids named acylhalocapnines (Baronio et al. 2010; Oren 2013).

In general, it is safe to say that the lipid composition of halophilic bacteria is not the most important factor for establishing adaptation. In *E. coli* (a normosmotic bacterium) stabilization of the cell against changes in osmolarity appears to be a function of membrane-derived oligosaccharides (MDOs) that changes the osmolarity of the periplasm (Kennedy 1982). The lipid byproduct of MDO synthesis is diacylglycerol (DAG) which could be involved in a signaling pathway analogous to that of PI in eukaryotes that, in turn, could regulate the response to changes in osmolarity by transcription of the genes encoding other cell wall proteins, including OsmB, OsmC, OsmE, and OsmY. Both OsmB and OsmE are believed to be lipoproteins. These proteins may be involved in osmoregulatory cell wall remodeling as structural elements and/or as enzymes (Wood 1999).

2.3.1.4 pH

Prokaryotic cells have also evolved mechanisms that allow them to grow in environments with pH values above or below neutrality. Some cells can simply tolerate and acclimatize to changes in pH. In other cases, conditions of low or high pH values are required for growth (Lund et al. 2014; X. Zhang et al. 2017). It is worth mentioning that prokaryotes often use proton gradients as a source of energy and protons are pumped across the cell membrane either as part of respiratory metabolism or using light in photosynthetic metabolism.

A bacterium that gained notoriety for growing in the low pH environment of the stomach is *Helicobacter pylori*. This bacterium is well adapted to the low acidity of the stomach through the secretion of urease enzyme that produces large amounts of ammonia, which is then protonated to create ammonium, thus creating a neutral bacterial microniche (Goodwin et al. 1986; Abadi 2017). Another important strategy that allows this bacterium to establish itself in the mucosa of the stomach is its helical shape that allows it to penetrate the mucous layers covering the stomach (Abadi 2017). However, so far there are no reports linking specific lipids to the ability of this bacterium to adapt to the stomach low pH.

Acidophiles (cells that require relatively low pH values for growth) alter the expression of certain membrane proteins (proton pumps) to maintain a cytoplasmic neutral pH, which results in reversal of their membrane potential. In addition to this strategy, changes in the membrane lipids can be put into place to modify membrane permeability (Siliakus et al. 2017). In a study of acid resistance in pathogenic *E. coli* O157:H7 growth at low pH induced an increase in palmitic acid (C16:0) and a decrease in *cis*-vaccenic acid (C18:1 Δ^{11}) indicating a preference to saturated rather than unsaturated fatty acids in response to acidic environment (Yuk and Marshall 2004). This adaptation allows *E. coli* to establish itself in the digestive tract where it can cause serious diseases such as diarrhea, hemorrhagic colitis, and hemolytic-uremic syndrome in humans (Nguyen and Sperandio 2012). Changes in membrane lipids composition in response to acidic stress seems to be variable in nature. *Streptococcus mutans* (one of the major causes of caries and the major component of plaque in the oral cavity) increases the proportion of MUFAs in the plasma membrane together with a shift to longer carbon chains in the membrane fatty acids, in response to growth in acidic pH (Baker et al. 2017). CL also seems to play a critical role in the ability of *S. mutans* to respond to acid stress and deletion of Cls produces a more acid-sensitive strain with lower percentage of unsaturated fatty acids (Baker et al. 2017).

Enterococcus faecalis (a commensal human bacterium) has the ability to obtain exogenous fatty acids from external sources like bile and serum. The incorporation in the plasma membrane of oleic acid (C18:1 Δ^{9}) and linoleic acid (C18:2 $\Delta^{9,12}$) could confer resistance to stress (Saito et al. 2014). It is worth mentioning that even though this bacterium has been considered for a long time a harmless commensal member of the intestinal microbiome, it is quickly becoming a serious concern for human disease as well (Fisher and Phillips 2009). A further adaptation example is the one of *Listeria monocytogenes* which adapts to acidity stress by increasing anteiso- and decreasing iso-BCFAs (Siliakus et al. 2017).

Extreme acidophilic bacteria (bacteria that tolerate pH lower than 2.5) of which *Alicyclobacillus* (*Bacillus*) *acidocaldarius* is an example, show a more consistent pattern of lipid membrane adaptations. MUFAs and saturated fatty acids, high levels of iso- and anteiso-BCFAs, uncommon β-hydroxy, ω-hydroxy, and cyclopropane fatty acids are standard modifications in these bacteria. A widespread presence of iso-diabolic acid lipids was also detected in species of the phylum *Acidobacteria*. So far, no bacteria have been isolated that grow at pH lower than 1, while there are examples of archaea with optimum pH of 0.7 (Siliakus et al. 2017). The archaeon *Picrophilus torridus* showed enrichment of glycerol dibiphytanyl glycerol tetraether (GDGT) with 4, 5, and 6 cyclopentyl rings and depletion of GDGT with 1, 2, and 3 cyclopentyl rings in cells undergoing pH or thermal stress relative to those grown under optimal conditions suggesting that GDGT composition may be a physiological response to acidic and temperature stress (Feyhl-Buska et al. 2016).

Organic acids, generally considered weak acids, play an important role in food microbiology as preservatives and are found in fruits and vegetables where they play a protective role against bacterial contamination and spoilage. However, it is possible for bacteria to become accustomed to the presence of these acids and to acquire tolerance and the ability to grow in their presence (Hirshfield et al. 2003; H. Yu et al. 2010). Both *E. coli* and *Salmonella enterica* show the ability to grow in acidic media if they are pre-exposed to mildly acidic conditions. This

phenomenon is referred to as the Acid Tolerance Response and it results in new protein synthesis as well as modifications of the membrane similar to the ones described above (Baik et al. 1996; Hirshfield et al. 2003). In particular, an increase in cyclopropane fatty acids with an accumulation of C17 and C19 odd-chain fatty acids can be observed after habituation to acidic conditions (Hirshfield et al. 2003).

On the other hand, alkaliphiles present bis-monoacylglycerophosphate lipids and CL in high concentrations. Their membranes can also contain large amounts of both iso- and anteiso-BCFAs; and it is often possible to identify the presence of MUFAs. Characteristically these cells present squalene, tetrahydrosqualenes and other polyisoprenes (Siliakus et al. 2017).

2.3.2 The Gram-Negative Outer Membrane

Gram-negative outer membrane is a bilayer consisting of PLs (innermost layer) and LPS forming the outermost layer (Beveridge 1999). The Lipid A moiety of LPS forms the hydrophobic core; Lipid A is bound through 2-keto-deoxyoctanoate to a core polysaccharide (Ladner-Keay et al. 2016). The outer polysaccharide is known as O antigen and consists of up to 25 repeating units of 3–5 sugars. The combination of Lipid A and the polysaccharides confers the molecule amphipathic properties. While lipid A is required for growth, the O antigen and core sugars are not but afford the bacteria protection from antibiotics and complement-mediated lysis (Bos et al. 2007; Raetz et al. 2007). Lipid A is a unique and distinctive phosphoglycolipid. It contains glucosamine residues, which are present as β(1 → 6)-linked dimers. The disaccharide contains α-glycosidic and non-glycosidic phosphoryl groups in the 1 and 4′ positions, and (*R*)-3-hydroxy fatty acids at positions O-2, O-3, O-2′ and O-3′ in ester and amide linkages, of which two are usually further acylated at their 3-hydroxyl group. Changes in growth conditions and environmental stresses can induce a response that results in the modification of Lipid A (Raetz et al. 2007).

Cationic antimicrobial peptides can induce the modification of lipid A either by acylation or addition of an aminoarabinose moiety to increase resistance in *Salmonella typhimurium* (Bader et al. 2005; Otto 2009). Hexa acylated *E. coli* Lipid A with side chains of 12–14 carbons in length induces a robust immune response in humans, while a change to the length of the attached fatty acids can reduce the immune response considerably. Lipid A chains with only four or five acyl chains confer the bacteria the ability to hide from the immune system increasing their virulence and pathogenicity (Miller et al. 2005).

H. pylori is a Gram-negative bacterium that colonizes the gastric mucosa of humans, can cause recurrent gastroduodenal inflammatory disease, and is the primary cause of chronic gastritis and peptic ulcers in humans (Blaser 1993). *H. pylori* persists in the gastric mucosa thanks to modifications to its LPS that allow it to minimize host defenses. In particular, *H. pylori* presents tetracylated Lipid A with 16-carbon and 18-carbon fatty acids that is poorly recognized by Toll-Like Receptors, rendering the innate immunity response much weaker than required to remove the pathogen (Miller et al. 2005). The O side chain of some *H. pylori* strains have been shown to mimic $Lewis^X$ and $Lewis^Y$ blood groups antigen giving the bacteria the ability to camouflage further diminishing the immune response (Moran et al. 1997). Interestingly key enzymes in Lipid A biosynthesis were found to be targeted to mitochondria in the plant *Arabidopsis thaliana* although the structure of the final Lipid A molecule remains undetermined (C. Li et al. 2011).

In the case of *Pseudomonas aeruginosa* colonization of patients with cystic fibrosis, a fixed mutation induces highly modified Lipid A with aminoarabinose and fatty acids side chains (Maldonado et al. 2016; Miller et al. 2005). Besides having a role in pathogenicity and virulence, modifications of LPS have also been linked to the ability of extremophiles to adapt to extreme environmental conditions. A novel type of Lipid A that contains D-galacturonic acid instead of phosphate residues has been isolated from *Aquifex pyrophilus*, a hyperthermophile that

grows at temperatures as high as 95 °C (Plotz et al. 2000).

2.3.3 Common, and Uncommon, Lipids in Bacteria

2.3.3.1 Hopanoids and Sterols

Membranes fluidity is highly influenced by the ratio of saturated to unsaturated fatty acids, and the molecular order of membrane lipids influences functionality (Pinto et al. 2014; Stiban et al. 2008b). Besides PLs and their variants, sterols also play a fundamental role in maintaining this order, and in eukaryotes, they are also involved in intra- and intercellular signaling (Desmond and Gribaldo 2009). Bacteria contain hopanoids which provide a similar structure and function in this domain.

Both steroids and hopanoids derive from the universal precursor isopentyl diphosphate that is metabolized to squalene and its cyclization products. For the synthesis of sterols the metabolism of squalene is very demanding in oxygen and up to 11 molecules of oxygen are required for the synthesis of one molecule of cholesterol (Summons et al. 2006). Bacterial squalene-hopene cyclases, on the other hand, produce hopanoids without a requirement for molecular oxygen. It has been proposed that hopanoids are the ancestor molecules of sterols and that the pathway of sterol biosynthesis appeared after the emergence of oxygenation of the atmosphere and oceans (Summons et al. 2006). Hopanoids are one of the most common lipids in sedimentary rocks and can be used to predict the presence of microbial ancient life (Ourisson and Albrecht 1992), which provides a solid foundation that hopanoids are molecular predecessors of sterols. The function of hopanoids as molecular stabilizers of membrane *in vivo* has been shown in the Gram-negative bacterium *Methylobacterium extorquens*, a plant associated hopanoid producer. In this bacterium, hopanoids have been shown to interact in a preferential way with glycolipids of the outer membrane to produce highly ordered membrane domains (Saenz et al. 2015). Stress like high temperatures, low pH, high osmotic pressures, and antibiotic or detergent treatments have an influence on the relative amounts of hopanoids in the bacterial membrane; the 2-methyl-hopanoids seem to be the modification of preference for pH stress. High temperature adaptations seem to require hopanoids with elongated side chains (Poalla et al. 1984). The cyanobacterium *Nostoc punctiforme* forms spore-like structures called akinetes under low light or phosphate starvation, allowing it to survive cold and desiccation. These spores, like the spores of *Streptomyces coelicolor*, have an increased concentration of hopanoids (Belin et al. 2018).

Nevertheless, the generally made assumption that bacteria do not produce sterols is somehow misguided. Even though the presence of sterols in bacteria seems to be relatively limited, sterols have been reported in bacterial membranes as early as 1976 in *Methylococcus capsulatus* (Bouvier et al. 1976).

M. capsulatus produces modified lanosterol products and the presence of similar sterols has been demonstrated in other aerobic methanotrophs of the *Methylococcales* order within the γ-proteobacteria. In addition, sterol biosynthesis has also been observed in a few myxobacteria of the δ-proteobacteria and the planctomycete *Gemmata obscuriglobus* (Wei et al. 2016). A bioinformatics-based research on the presence of oxidosqualene cyclase, a key enzyme in the biosynthesis of sterols, predicts its presence in 34 bacterial genomes from 5 phyla and in 176 metagenomes, indicating that the presence of sterols in bacteria might be much more widespread than previously predicted (Wei et al. 2016).

2.3.3.2 Sphingolipids and Lipid Rafts

Sphingolipids (SLs) are structural components of the membrane and play significant roles in eukaryotic cell signaling (Hannun 1996; Hannun et al. 1993). They are acylated derivatives of the amino alcohol sphingosine (Hannun et al. 1993; Olsen 2001; Stiban et al. 2008b). SLs are present in bacterial membranes and their role and

characterization is still poorly understood. SLs occurrence seems to be more common in anaerobes (LaBach and White 1969), even though their presence is not restricted to this group of bacteria (A. S. B. Olsen and Faergeman 2017; Olsen 2001). The Gram-negative genus *Sphingomonas* contains glycosphingolipids rather than LPS in its outer membrane (Kawasaki et al. 1994). The genus *Bacteroides* show heterogeneity in the composition of SLs and contains ceramides (Cer), Cer phosphoethanolamines, glucosyl sphinganine and Cer phosphoinositols (I. J. Olsen 2001). The list of bacteria containing SLs is growing and not restricted to the phylum *Bacteroidetes* (Kato et al. 1995; Miyagawa et al. 1979; Nichols et al. 2004).

In eukaryotic cells lipid rafts are defined as membrane regions with rich content of sterols and SLs that play specific roles including adhesion, migration, and membrane transport (Stiban et al. 2008b). In bacteria, the presence of functional membrane microdomains was unexpectedly discovered in *B. subtilis* while studying the ability of this bacterium to form biofilms (Lopez et al. 2009). These membrane regions are particularly compact and contain high concentrations of hopanoids which make protein movement more difficult and result in the trapping of proteins with specific functions. These proteins are normally defined as cargo proteins. There is convincing evidence that the lipids are associated with bacterial flotillins in strong similarity with the structure of lipid rafts in eukaryotic cells (Bramkamp and Lopez 2015). In *B. subtilis* lipid rafts have been associated with signaling that can result in cell division and cell differentiation (Bramkamp and Lopez 2015) similar to the roles of lipid rafts in eukaryotes.

Some bacteria have the SL biosynthetic machinery, yet others that do not synthesize SLs may scavenge these lipids from the host to increase their virulence (An et al. 2011). In the case of *Chlamidya trachomatis* (the causal agent of trachoma) the acquisition of SLs from the host prevents fusion of the endosome of macrophages with the lysosome protecting the bacterium from the lytic activity of hydrolytic enzymes (van Ooij et al. 2000). *Mycobacterium tuberculosis* also uses host SLs to influence the level of Ca^{2+} in the cytoplasm to control the maturation of the endosome (Heung et al. 2006).

2.3.3.3 Ladderanes

Planctomycetes are a relatively recent discovery in microbiology (Kuenen 2008). Even though the presence of a microbe able to oxidize ammonia under anaerobic conditions was predicted as early as 1977 (Broda 1977), the actual isolation of this group of organisms took place in the nineties (Kuenen 2008). This group of bacteria is quite unique from several perspectives:

Recent revisions of the tree of life based on ribosomal RNA sequences place the *Planctomycetales* deep at the base of the tree as the first branching bacterial group (Brochier and Philippe 2002) even though it has been argued that *Planctomycetes* belong to a super phylum that includes the *Verrucomicrobia* and the *Chlamydia* (Wagner and Horn 2006).

The cell wall lacks peptidoglycan, a defining component of bacterial cell walls. It appears to be more similar to the cell wall of archaea rather than bacterial cells (Fuerst 2005). Despite the absence of peptidoglycan, recent sequencing of the genome of *Kuenenia stuttgartiensis* revealed the presence of a gene cluster for proteins involved in peptidoglycan synthesis even though they might not be active (Kartal et al. 2013).

Possibly the most interesting feature unique to these bacteria is the lipid composition of the anammoxosome compartment. This organelle is dedicated to the metabolism of ammonia that generates highly toxic intermediates such as hydrazine (N_2H_4) and hydroxylamine (NH_2OH) (Sinninghe Damste et al. 2005). The anammoxosome membrane consists mostly of the highly unusual lipids known as ladderanes. Ladderanes contain one or both of two different ring systems: either three cyclobutane moieties and one cyclobutane moiety substituted with an octyl chain, or five linearly concatenated cyclobutane rings substituted with a heptyl chain. In both systems the rings are fused by *cis*-ring junctions which gives the structure an overall staircase-like arrangement (van Niftrik and Jetten

2012). This is a unique set of lipids that is not seen anywhere else to our knowledge.

2.4 Lipids in Mitochondria

In contrast to most prokaryotes, eukaryotic cells contain internal membranes, including the energy-producing cellular powerhouses, the mitochondria. The uniqueness of mitochondria in cellular physiology is a result of the complex roles they perform in cells. Mitochondria are implicated in cell survival and cell death, among other vital cellular processes (Birbes et al. 2002). They contain two independent genetic systems, as most of their components are synthesized outside and imported into mitochondria (Sickmann et al. 2003). Mitochondrial DNA (mtDNA) is responsible for the synthesis of very specific subset of proteins and RNA molecules in the organelle (Stiban et al. 2016). The roles that mtDNA (which is mostly maternally inherited) play in mitochondrial physiology are well documented and several diseases have been identified due to aberrant mitochondrial genetics (El-Hattab et al. 2017; Stiban et al. 2014, 2016; Viscomi and Zeviani 2017). mtDNA is located in the matrix which is shielded by the cristae of the mitochondrial inner membrane (MIM). Mitochondria are surrounded by two membranes, which are structurally and functionally very different. While the mitochondrial outer membrane (MOM) is permeable to solutes under 5 kDa in size (Mannella 1992; Vander Heiden et al. 2000), the MIM is mostly impermeable (Carbonera and Azzone 1988). The protein:lipid ratio of the MIM is the largest of all cellular membranes (Schenkel and Bakovic 2014), thus supporting the impermeability of the membrane. The MOM is in close proximity of other organelles, particularly the endoplasmic reticulum (ER) and this proximity is necessary for several important processes in the cell (such as PL translocation across membranes and apoptosis induction) (Ardail et al. 1990; Daum and Vance 1997; Fiorini et al. 2019; Stiban et al. 2008a; Vance 2014).

The lipids in mitochondrial membranes have been studied extensively (for excellent reviews (Horvath and Daum 2013; Schenkel and Bakovic 2014)), mainly focusing on the unique mitochondrial PL, CL, which are also prevalent in bacteria (see previous). CL is located primarily in the MIM and is essential for respiration (Chabi et al. 2018), protein clustering and cell death (Mulkidjanian et al. 2018). Yet, other lipid components of mitochondria have been identified as key regulators of cell function and homeostasis. Traffic across and within mitochondrial membranes remains a hot topic in cellular biochemistry, as it is an important aspect in energy metabolism and also cell death. Transport of fatty acids into the matrix via the carnitine-acylcarnitine shuttle initiates β-oxidation (Rubio-Gozalbo et al. 2004), while transport of pro-apoptotic proteins from the intermembrane space into the cytosol initiates apoptosis (Matassa et al. 2001). Hence, the lipid (and protein) composition of mitochondrial membranes is of paramount significance.

Differences in lipid composition between mitochondria from various organs are minimal. Cardiac mitochondria, for instance, contains plasmalogens which are ether lipids involved in membrane fusion and transmembrane protein functions. Lipid composition between the MOM and MIM varies greatly (Fig. 2.1). Generally, mitochondrial membranes show a characteristic abundance of CL, particularly in the MIM. Whereas the MOM is smooth, the MIM is convoluted with cristae that increase the surface area to accommodate higher respiration rates. This entails the MIM to be more flexible and accommodating for protein complexes to reside and function properly. Additionally, compared to other membranes, SL content is lower, as is the ratio of sterols, with the MIM being devoid of sterols. Protein:lipid ratio is higher than other membranes. Eighty percent of mitochondrial PL consists of PC and PE. PE, which is the abundant lipid in *E.* coli (see above), together with the presence of CL hint of a potential bacterial evolutionary origin of the MIM. Comparing the lipids in the membranes of

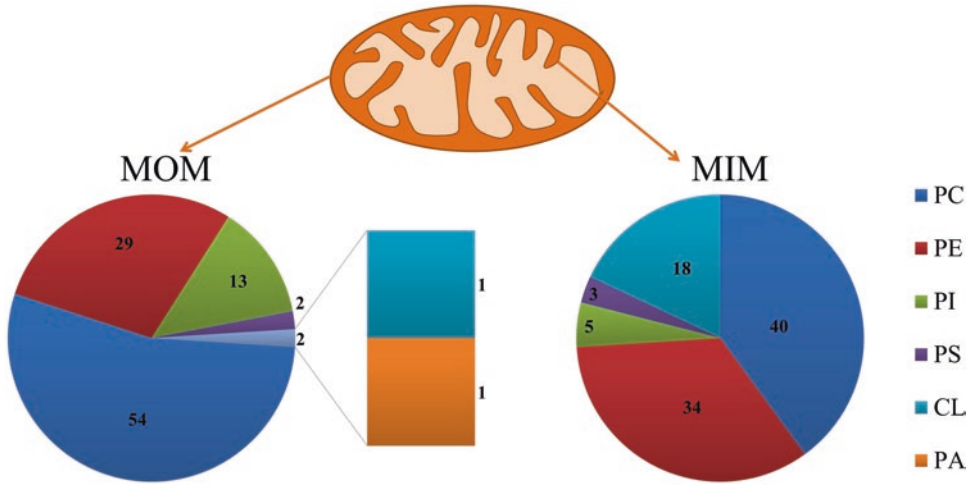

Fig. 2.1 Differences in MOM and MIM lipid composition. The data are obtained from (Daum and Vance 1997; Horvath and Daum 2013) and the numbers represent the percentage of total phospholipids in rat liver mitochondria. Abbreviations used: *PC* phosphatidylcholine, *PE* phosphatidylethanolamine, *PI* phosphatidylinositol, *PS* phosphatidylserine, *CL* cardiolipin, *PA* phosphatidic acid

Table 2.2 Comparison between lipid content of MIM from rat liver and bacterial membranes

	MIM[c]	Gram negative *E. coli* plasma membrane[a,b]	Gram negative *E. coli* outer membrane[a,b]	Gram positive *B. subtilis*[a,b]
Lipid	% total PL			
PC	44	0	0	0
PE	34	60	61	13
PI	5	0	0	0
PS	1	0	0	0
CL	14	20	1	4
PA	<1	NA	NA	NA
SM	1	0	0	0
Sterols	0.003 mg/mg protein	0	0	0

[a]Data from: (Sohlenkamp and Geiger 2016)
[b]Data from: (Warschawski et al. 2011)
[c]Data from: (Daum and Vance 1997)

different bacteria and the MOM, the similarity is evident (Table 2.2).

Like their bacterial counterparts, mitochondrial lipids play important roles in cellular homeostasis. Mitochondria are organelles that are very dynamic in structure. A plethora of proteins aid the double membranes to fuse with other mitochondria, or one mitochondrion to split by fission. In addition to proteins, fusion and fission of mitochondria are mediated by key membrane lipids (mainly, CL, PE, DAG and phosphatidic acid (PA)) (reviewed in (Frohman 2015)). In short, CL is required for the function of the GTPase Opa1 that induces mitochondrial fusion (DeVay et al. 2009). CL was shown to be important for the recruitment and dimerization of Opa1, which is a key event for its GTPase activity, and hence, fusion of the membrane (Ban et al. 2010). Interaction between the negatively charged CL head group with the positively charged lysine residues in Mgm1 (yeast homolog of Opa1) was necessary for the activity of the protein (Rujiviphat et al. 2009). Similarly, PE stimulates mitochondrial fusion as yeast lacking the decar-

boxylase that produces PE have shown to present fragmented mitochondria (Chan and McQuibban 2012). On the other hand, CL was also implicated in mitochondrial fission, via similar mechanisms. Recruitment by CL of Drp1, a key GTPase involved in fission, was required for the activity of the protein and for fission to occur (Macdonald et al. 2014; Nakamura et al. 2011; Ugarte-Uribe et al. 2014). Similar conclusions were made about CL interaction with other fission-inducing proteins such as alpha-synuclein (Guardia-Laguarta et al. 2014).

Interestingly, both PE and CL are implicated in the respiratory function of mitochondria oppositely. Whereas CL was shown to induce respiratory complex III and IV oligomerization and stability, and enhanced complex IV activity, PE favored the destabilization of the supercomplexes (Bottinger et al. 2012). Ubiquinone is another lipid directly involved in respiration by moving electrons from complexes I or II to complex III. Ubiquinone is present in both prokaryotic cells and mitochondria further indicating possible evolutionary connections (Degli Esposti 2017).

Unlike bacteria, which are free-living organisms, mitochondrial lipids are rarely affected by environmental conditions, obviously. The endosymbiotic nature of mitochondria within the eukaryotic cell obliterates the direct effects of the environment on mitochondria as the eukaryotic cell bears them instead. Additionally, eukaryotes seldom thrive in extreme conditions (except perhaps some species in deep oceans or hydrothermal vents), like many bacterial species. Hence, the effect of extreme environments on mitochondrial lipid composition is not established compared to that in prokaryotes.

2.4.1 Mitochondrial Cholesterol and Other Sterols

Cholesterol import into mitochondria, its metabolism and its egress seems to play vital roles in mitochondrial physiology (F. Li et al. 2015). Similar to bacteria and other eukaryotic membranes, cholesterol and other sterols modulate the fluidity of the membranes and impart structural and functional restrictions to membranes. As sterols are mostly planar with small hydrophilic head groups, fluidity is mediated differentially at different temperatures. Overall, cholesterol in eukaryotic membranes is distributed primarily to plasma membranes, Golgi, and ER (Table 2.2).

Compared to other subcellular organelles, however, mitochondria have significantly lower cholesterol levels in both membranes (Horvath and Daum 2013). Cholesterol is important for the function of mitochondria; it is needed for membrane biogenesis and maintenance and for the synthesis of other sterols (Martin et al. 2016). The low abundance of cholesterol in mitochondria implies that even small changes in cholesterol concentrations can influence mitochondrial physiology greatly. The levels of mitochondrial cholesterol are regulated by the transfer of cholesterol from the ER to MOM (possibly via mitochondria-associated membranes (MAM)), and transfer from the MOM to the MIM, and its metabolism in the matrix. Modulation of mitochondrial cholesterol content has been implicated in several pathological conditions. Higher mitochondrial cholesterol levels have been described in human hepatocellular carcinoma (Montero et al. 2008). Interestingly, knockout mice for a cholesterol-transferring protein (CAV1) have been shown to accumulate cholesterol in mitochondria leading to respiratory chain dysfunctions and susceptibility to apoptosis and predisposing mice to steatohepatitis and neurodegeneration (Bosch et al. 2011). Conversely, lowering cholesterol level in mitochondria following exercise, helped mitochondria to be resistant to calcium-induced swelling, therefore increasing mitochondrial health (Ziolkowski et al. 2013). In A549, THP-1 and U937 cultured cells, (human lung epithelial adenocarcinoma, monocytic leukemia, and histiocytic lymphoma, respectively) however, initiation of apoptosis by the steroid saponin Rh2 is exacerbated by removal of cholesterol from mitochondrial membranes (Verstraeten et al. 2018). Increase of mitochondrial PL and reduction of cholesterol have been shown to be directly correlated with the preventative effects of S-allyl cysteine sulfoxide on the onset of myocardial infarction in Wistar rats

(Sangeetha and Darlin Quine 2009). In Alzheimer's disease, cholesterol accumulation in mitochondria as a result of amyloid beta-induced ER stress cause neurotoxicity. Protection against mitochondrial cholesterol loading ameliorated these effects (Barbero-Camps et al. 2014). Thus higher or lower mitochondrial cholesterol levels may serve several complex roles in different body systems under differing conditions.

Mitochondrial cholesterol has also been implicated in redox signaling mediated by hypoxia inducible factor (HIF-1α). Cholesterol was shown to induce HIF-1α activation under normoxic conditions in the liver (Anavi et al. 2014). HIF-1α, which is a nuclear transcription factor induced under low oxygen, promoted transcription of several proteins in mitochondria including some electron transport chain proteins such as complex IV (Hwang et al. 2015). Both mitochondrial lipids and proteins, therefore, are modulated by hypoxic conditions that affect mitochondrial health, with cholesterol an important factor in such adaptability.

2.4.2 Mitochondrial Sphingolipids

The concentration of Ceramides (Cer) and other SLs in mitochondrial membranes are minimal, but once imported, detrimental effects to the mitochondria and the cell ensue (Hannun and Obeid 2008). Cer is the parent SL consisting of sphingosine backbone *N*-acylated with a variety of fatty acyl-CoAs. Sphingosine is an amino alcohol long chain base synthesized from condensation and reduction of the amino acid serine, and palmitoyl-CoA (Jenkins et al. 2002). The head group of Cer consists of a hydroxyl functional group (Fig. 2.2). Cer is a highly bioactive lipid; it is involved in a variety of cellular processes, particularly programmed cell death, or apoptosis (Bartke and Hannun 2009). While being a minority of mitochondrial lipids, Cer accumulation in mitochondria leads to permeabilization of the MOM (Siskind et al. 2006), mitochondrial dysfunction (J. Yu et al. 2007) and cell death. Cer biogenesis is highly compartmentalized in eukaryotic cells (Hernandez-Corbacho et al. 2017). Cer lies in the center of all SL metabolism (Fig. 2.3). The majority of Cer is produced in the ER by the *de novo* synthesis pathway (Reynolds et al. 2004), or in the plasma membrane via the sphingomyelin hydrolysis pathway (Mathias et al. 1998). Alternatively, the salvage pathway of Cer biogenesis involves the recycling of complex SLs into Cer again in the ER (Becker et al. 2005).

In the *de novo* pathway, serine palmitoyltransferase (SPT) condenses serine with palmitoyl-CoA using the pyridoxal 5′-phosphate cofactor to form ketosphinganine, which is subsequently reduced by a reductase and NADPH to sphinganine (which is also named dihydrosphingosine). A family of 6 mammalian Cer synthases (CerS) acylates the amino group of sphinganine with different length of fatty acyl-CoAs forming dihydroceramides (DHCer) (Stiban et al. 2010). Cer is later produced by oxidation and desaturation of the 4–5 bond in DHCer using molecular oxygen and the enzyme DHCer desaturase (DES). The compartmentalization of Cer metabolism ensures that Cer is produced in certain places where it can have specific functions. In MCF-7 cells, it was shown that generation of Cer directly in mitochondria, but not in other cellular locations, induced apoptosis (Birbes et al. 2001). Hence, mitochondria are organelles that are affected severely by Cer, yet not all Cer biosynthetic machinery was found there. Interestingly some enzymes (such as CerS) were located in MAM and mitochondria (Bionda et al. 2004), yet others (such as DES) were only located in MAM but not

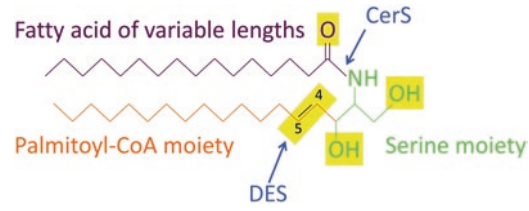

Fig. 2.2 The structure of C_{16}-Cer. The functional groups and key groups for the biological activity of Cer are highlighted in yellow. Bonds added by important *de novo* synthetic enzymes, CerS and DES, are indicated by blue arrows. Serine moiety is indicated in green and palmitoyl-CoA in orange. CerS *N*-acylate sphinganine with a fatty acids of variable chain lengths (purple)

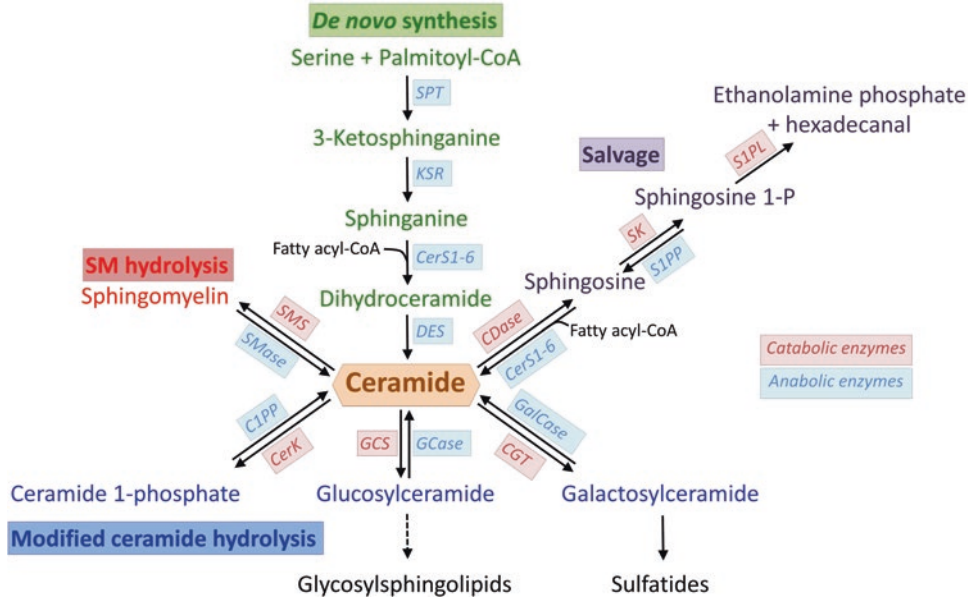

Fig. 2.3 Centrality of Cer in SL metabolism (adjusted from (Abou-Ghali and Stiban 2015)). Four different metabolic pathways can lead to Cer production in cells. The *de novo* pathway (green) employs four enzymes to produce Cer from the amino acid serine and palmitoyl-CoA. In the salvage (or recycling) pathway (purple), sphingosine, which is a direct metabolite of Cer, can be acylated back to Cer by CerS. S1PL breaks down sphingosine 1-phosphate and thus is the exit point of SL metabolism. The hydrolysis of complex SL (e.g. SM (red) and glycosphingolipids (blue)) represents the final pathways of Cer generation. Anabolic enzymes are in blue boxes whereas catabolic enzymes are in red boxes. Enzyme abbreviations used are as follows: *SPT* Serine palmitoyltransferase, *KSR* 3-ketosphinganine reductase, *CerS1-6* ceramide synthase, *DES* dihydroceramide desaturase, *CDase* ceramidase, *SK* sphingosine kinase, *S1PL* sphongosine 1-phosphate lyase, *S1PP* sphingosine 1-phosphate phosphatases, *SMase* sphingomyelinases, *SMS* sphingomyelin synthase, *GCS* glucosylceramide synthase, *GCase* glucosylceramidase, *CGT* ceramide galactosyltransferase, *GalCase* galactosylceramidase, *CerK* ceramide kinase, *C1PP* ceramide 1-phosphate phosphatase

mitochondria (Stiban et al. 2008a). Nevertheless, other enzymes in SL metabolism were also found in mitochondria (e.g., CDases (El Bawab et al. 2000) and nSMase (Wu et al. 2010)). Irrespective to whether the whole machinery of Cer generation exists in mitochondria, Cer generation in (or transport to) this organelle is sufficient to induce MOM permeabilization, cytochrome *c* release and the onset of apoptosis (Birbes et al. 2002). Ionizing radiation-induced apoptosis in *C. elegans* was abolished in cells lacking functional CerS. This was later corrected by the exogenous addition of Cer signifying the role of Cer in mitochondria inducing apoptosis (Deng et al. 2008).

2.5 Programmed Cell Death

Programmed cell death, or apoptosis, is a characteristic of cells that allows unneeded and/or damaged cells to be removed without causing an inflammatory response in the surrounding tissue. In eukaryotic cells, mitochondria are at the center of intrinsic apoptosis. Interestingly, prokaryotes,

despite being single-celled, can undergo apoptosis to benefit the community.

2.5.1 Mitochondria and Apoptosis

Mitochondrial outer membrane permeabilization (MOMP) is a hallmark of the intrinsic apoptotic pathway (Stiban et al. 2006). Compromising the intactness of the MOM allows inter membrane space proteins (e.g. cytochrome *c*) to be released into the cytosol where they work in tandem with other cytosolic proteins to induce a cascade of events mediated by caspases to result in apoptosis (Birbes et al. 2002). MOMP is mediated by a variety of cellular components, from Bcl-2 family members (some of which are pro-, while others are anti-apoptotic) (Ganesan et al. 2010; Ganesan et al. 2012; S. H. Lin et al. 2011; Perera et al. 2012), to Cer (Abou-Ghali and Stiban 2015; Hannun 1996; Senkal et al. 2007) or combinations of Cer and Bax (Ganesan et al. 2010), to other possible channels (mitochondrial permeability transition pore) (Dhingra et al. 2019; Parks et al. 2019), or the mitochondria apoptosis channel (Pavlov et al. 2001). Regardless of the pathway of inter membrane space protein egress, MOM lipids play a crucial role in dictating when and how apoptosis is initiated. Stress-induced oxidized PLs induce apoptosis at the MOM by facilitating Bax translocation and oligomerization (Dingeldein et al. 2017). Oxidation of CL can trigger both pro-apoptotic (pore formation) and anti-apoptotic (membrane potential drop and reduction of reactive oxygen species production) reactions (Mulkidjanian et al. 2018). Membrane lipids and proteins, therefore, dictate key apoptotic functions in mitochondria.

Despite its low abundance, Cer is an important lipid for mitochondria. Cer levels increase in mitochondrial membranes prior to the initiation of apoptosis (Birbes et al. 2001; El Bawab et al. 2000; Zeidan et al. 2008). The ability of Cer to form barrel-stave channels in membranes was a key finding in the field of lipid biochemistry (Colombini 2013, 2017). Cer channels have been previously visualized by transmission electron microscopy in asolectin liposomes (Samanta et al. 2011) as well as liposomes derived from lysosomal membranes (Yamane et al. 2017). MOM permeabilization by Cer channel formation has been demonstrated in many studies (Shao et al. 2012; Siskind et al. 2002, 2005, 2006; Stiban et al. 2006; Stiban and Perera 2015). The ability of Cer to form channels in membranes is dependent on the lipid composition of the membrane (Perera et al. 2016). For instance, Cer is unable to permeabilize plasma membranes, as indicated by the lack of lysis of red blood cells in response to Cer treatment (Siskind et al. 2005). Within mitochondria, while the MOM is susceptible to Cer channel permeabilization, the MIM is very resistant to such channel formation activity (Siskind et al. 2002). Cer is produced in the ER and no channel forming activity was reported in that organelle to our knowledge (unpublished results). In lysosomes, the production of Cer was required to cause permeabilization and channel formation in liposomes derived from lysosomal membranes (Yamane et al. 2017). In all, the formation of Cer channels, and their regulation, is widely dependent on other lipids in the membrane. Thus the specificity of Cer action on the MOM and its role in permeabilization and apoptosis is lipid-specific. This deserves further studies on the lipid-lipid and protein-lipid interaction in mitochondria.

2.5.2 Bacterial Apoptosis

Even though it seems illogical for a unicellular organism to kill itself, bacteria do have a programmed cell death process that is activated when the cells are living in communities such as

biofilms (Bayles 2014). Multicellular biofilm communities consist of cells with differentiated structures that serve specialized functions resembling the relationships found in multicellular organisms.

The evolution of multicellular organisms is the result of selective pressures that gave multicellularity a selective advantage. Multicellular entities such as biofilms are provided with several advantages amongst which resistance to environmental stresses seems to be the most common. Living within a biofilm can protect cells from changes in temperature, pH, osmotic pressure, oxygen availability, desiccation, metals, and other compounds toxicity including antibiotics (Lyons and Kolter 2015). It is generally acknowledged that cells in a biofilm will have better access to nutrients as well, and there are some striking examples of how life in a multicellular entity provides considerable energy gains. One of such examples is found in deep sea sediments where filamentous bacteria of the *Desulfobulbaceae* family form multicellular cable-like structures that oxidize sulfur at one end and transport the harvested electrons to the other through internal, insulated wires to be used for oxygen reduction. The competitive advantage of such system is the ability of these cells to separate soluble electron acceptors and donors in space, enabling them to monopolize major energy sources (Pfeffer et al. 2012).

Bacteria populations that live as multicellular organisms use programmed cell death to sacrifice part of the colony to protect other cells (Allocati et al. 2015), a similar function to eukaryotic apoptosis. In biofilms, DNA released in the matrix by dying cells (extracellular DNA) is an important adhesion molecule for the establishment and maintenance of the biofilm (Conover et al. 2011) and is also a source of genes that can be picked up by other living cells in a horizontal gene transfer manner (Lewis 2000).

CidA and LgrA are bacterial proteins that were originally isolated from *Staphylococcus aureus*, but are widely conserved in bacteria (Ranjit et al. 2011). These proteins are holin-like molecules and it has been postulated that they work in an analogous manner to the Bcl-2 family proteins in eukaryotic cells (Rice and Bayles 2008). The CidA gene encodes a putative holin, with a positive effect on cell death, while LgrA encodes an anti-holin with inhibitory effect on the process (Ranjit et al. 2011). It is remarkable to note that, both Bcl-2-family proteins and holins cause depolarization of membranes (MOM and cytoplasmic membrane, respectively) and both are regulated by homologous proteins that oppose their function. MOM depolarization leads to the activation of caspases and cell death in eukaryotic cells, cytoplasmic membrane depolarization in bacteria leads to the activation of peptidoglycan hydrolases and bacterial cell death (Lewis 2000).

Experimental evidence in *E. coli* demonstrated that Bcl 2-family proteins are functional in these cells. Bax and Bak were found to polymerize on *E. coli* plasma membrane and induce cell death and lysis (Pang et al. 2011). Moreover, coexpression of Bax in *E. coli* with the anti-apoptotic protein Bcl-X_L resulted in the inhibition of cell death and lysis (Bayles 2014). These experiments clearly show that the function of these proteins is conserved between bacteria and eukaryotic cells and it is therefore possible to hypothesize that apoptotic proteins were transferred to the eukaryotic cell during the endosymbiosis process that resulted in the formation of mitochondria (Allocati et al. 2015; Bayles 2014). Interestingly, in *Arabidopsis thaliana* an LrgAB-like gene product, which is involved in the control of plant programmed cell death, is found in the chloroplast and when absent causes chlorosis and prematurely necrotic leaves, suggesting it has an anti-apoptotic role in plants (Yang et al. 2012).

2.6 Conclusions and Future Directions

While there may be many pieces of evidence implicating the evolutionary connections between mitochondria and prokaryotes, such as rRNA sequences, DNA structure, or ribosomes, the lipid content cannot be underestimated. Prominent MIM lipids such as CL and PE have been found only in prokaryotic cells and very rarely in other eukaryotic membranes. The enzymatic machinery that produces these lipids is also presented in these membranes, establishing further evidence of commonality in origin. Importantly, the relative low abundance of sterols and sphingolipids in mitochondria and prokaryotes indicate closeness of the membranes in ancestral trees. Whether the original protoeukaryotic cell "engulfed" a bacterium that eventually evaded degradation and remained as an integral component of the cell, or membranes were formed from a protonucleus to surround a prokaryotic cell remains to be elucidated. Regardless of the mechanism, it is evident that membrane lipids play central roles in mitochondrial and prokaryotic physiology and pathophysiology, roles that mitochondria may have inherited from their ancestors. It is worth noting that the lack of PC in bacteria and its high concentration in MIM represents a puzzle for evolutionary biologists. PC is made using proteins encoded in nuclear genes and imported into mitochondria to make the bulk of the PL membrane. It is of great importance to identify this discrepancy in the structure of the mitochondrial membrane compared to its ancestral prokaryotic membrane. In addition, there is now mounting evidence that programmed cell death is also a feature of prokaryotic cell death and it is possible to conceive of research in this field unveiling a universal mechanism underlying apoptosis. The holin-antiholin class of proteins were originally discovered in bacteriophages, where they modulate host cell lysis during lytic infection (van den Esker et al. 2017a). The transfer of genes from the phage to the bacterium through integration in the genome, could have resulted into a permanent feature of the bacterium. These bacteria delivered the genes to eukaryotes with the endosymbiotic event that created mitochondria and chloroplasts (van den Esker et al. 2017a). In some bacteria, like *B. subtilis*, the function of the holin-antiholin system seems to be essential in metabolism rather than cell death regulation (van den Esker et al. 2017b). Understanding the evolutionary origin of these proteins could shed light on the origin of apoptosis in eukaryotic cells and open new investigations on the potential of using these proteins for antimicrobial therapy in the age of antibiotic resistance.

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