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Review

Mitochondrial membrane lipid remodeling in pathophysiology: A new target for diet and therapeutic interventions

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ABSTRACT

Mitochondria are arbiters in the fragile balance between cell life and death. These organelles present an intricate membrane system, with a peculiar lipid composition and displaying transverse as well as lateral asymmetry. Some lipids are synthesized inside mitochondria, while others have to be imported or acquired in the form of precursors. Here, we review different processes, including external interventions (e.g., diet) and a range of biological events (apoptosis, disease and aging), which may result in alterations of mitochondrial membrane lipid content. Cardiolipin, the mitochondria lipid trademark, whose biosynthetic pathway is highly regulated, will deserve special attention in this review. The modulation of mitochondrial membrane lipid composition, especially by diet, as a therapeutic strategy for the treatment of some pathologies will be also addressed.

Contents

Abbreviations: AIF, apoptosis-inducing factor; ATP, adenosine triphosphate; BTHS, Barth syndrome; CL, cardiolipin; cyt *c*, cytochrome *c*; DNA, deoxyribonucleic acid; DOX, doxorubicin; ER, endoplasmic reticulum; GD3, ganglioside GD3; IMM, inner mitochondrial membrane; iPLA2γ, calcium-independent phospholipase A2γ; MAM, mitochondria-associated membrane; MLCL, monolysocardiolipin; MPT, mitochondrial permeability transition; mtDNA, mitochondrial DNA; OMM, outer mitochondrial membrane; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PI, phosphatidylinositol; PG, phosphatidylglycerol; PS, phosphatidylserine; PTP, mitochondrial permeability transition pore; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; Smac/DIABLO, second mitochondria-derived activator of caspases/direct IAP binding protein with low Pi; UCP, uncoupling protein.

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1. Mitochondria: evolution, physiology and the role of their membrane lipids

Mitochondria are membrane-enclosed cellular structures, which are classically defined as energy-producing organelles, although their influence extends to many other cell functions. In the classic, although controversial at the time, endosymbiotic theory proposed by Lynn Margulis in the late sixties [1], an amitochondriate anaerobic eukaryote engulfed an oxygen consuming proteobacterium. In one of those chance events that most likely allowed for the expansion of life on Earth, the engulfed bacterium was not destroyed, but rather lived in symbiosis with its host. The emergent biological system became equipped with skills to adapt to different types of environment, especially oxygen-rich niches. In fact, this new aerobic organism, an ancestor of eukaryotic cells, earned the advantage of using a wider variety of substrates to generate even higher amounts of energy, which provided it with a replicative superiority in relation to competition [2]. By its turn, the proteobacterium gained a better protection from the harshness of the environment and a steady flux of substrates. Over millions of years, the proteobacterium evolved into what we now recognize as the mitochondrion. Further evolution steps resulted in a remodeling of mitochondria to suit the needs of fungi, animals or plants. Thus, despite being mostly similar to their mammalian counterparts, plant mitochondria have interesting differentiating features [3], including inner membrane alternative oxidases (AOX) [4] and type II NAD(P)H dehydrogenases [5], which result in high metabolic plasticity and make plants endowed with a remarkable potential for adaptation. Interestingly, taking into account the widespread taxonomic distribution of AOX, which is also present in prokaryotes and, among eukaryotes, in fungi, plants and animals, it has been proposed that the proteobacterial ancestor from which mitochondria evolved were provided with AOX and this had been lost over evolutionary time by vertebrates and arthropods [6].

Mitochondrial bioenergetics depends largely on the physiology of the inner mitochondrial membrane (IMM), which hosts the redox complexes of the respiratory system and phosphorylation apparatus that performs the highly efficient energy-generating process known as oxidative phosphorylation. In this process, the energy made available from the oxidation of nutrients is used to drive ATP synthesis. Electrons from specific substrates, funneled to nicotinamide nucleotides (NAD^+ or $NADP^+$) or flavin nucleotides (FMN or FAD), enter the mitochondrial electron transport chain, through which they are transferred to oxygen [7]. As electrons flow through a sequence of membrane-bound protein and non-protein carriers, protons are pumped from the mitochondrial matrix to the intermembrane space. Therefore, according to the chemiosmotic theory introduced by Peter Mitchell [8], the free energy of substrate oxidation is conserved as a transmembrane proton electrochemical potential (Δp), part of which composed by the electric component ($\Delta\Psi$) which is used to drive ATP synthesis by the ATP synthase complex, through a rotational catalysis mechanism [9]. Mitochondrial oxidative phosphorylation accounts for about 90% of cellular oxygen consumption and provides more than 80% of the energy demands for cellular life metabolism [10]. However, besides cellular energy production, mitochondrial have other functions in the cell, including the modulation of calcium signaling, regulation of cell death, the maintenance of cellular redox balance and the housing of important biosynthetic pathways [11]. Therefore, it is fair to say that mitochondria function as gatekeepers of cell life and cell death. In the latter case, mitochondria have been associated with both apoptotic and necrotic cell death [11], discussed in detail in the next section.

Mitochondrial membrane lipids are involved in a number of processes as diverse as protein biogenesis, energy production, membrane fusion and apoptosis [12]. Moreover, spatially defined lipid distribution (Fig. 1A) may also affect mitochondrial processes as fusion and fission or the topology of proteins in the membrane plane [12]. In the particular case of energy production, evidence that membrane lipids modulate mitochondrial respiration has been generated by dietary manipulations of the lipid content in mitochondrial membranes. These approaches have shown that dietary interventions that are able to influence mitochondrial membrane lipid composition, hence modifying its physical properties [13–20], alter respiration [20–29] as well as other mitochondrial processes involving generation of reactive oxygen species (ROS) [30] and Ca^{2+}-induced MPT [20,31]. The role of membrane lipids in mitochondria function is best exemplified by cardiolipin (CL), the signature phospholipid of those organelles. CL has been linked to a number of important mitochondrial processes, including oxidative phosphorylation [32], apoptosis [33] and the assembly and function of mitochondrial membrane proteins [34].

The phospholipid composition of mitochondrial membranes is thought to be under genetic control, and varies markedly between different tissues and organs within an individual animal, representing a specific feature of each membrane [35].

Under physiologic conditions, phospholipid composition of mitochondria relies on the conjugated expression and activity of a number of proteins involved in lipid synthesis and interconversion. Mitochondrial regulation of phospholipid levels is not fully understood, but it depends on the action of mitochondrial proteins, as reported for CL and PE [36]. On the other hand, studies on genetic manipulation of mitochondria membrane lipid content [37–39] point to the need to maintain a "physiologic" lipid composition of mitochondria membranes. We envision that environmental factors, including diet, can impact on the genetic control of lipid synthesis, remodeling and incorporation in membranes, thus inducing alterations in membrane lipid composition. Despite diet-induced changes in the expression/genetic regulation of mitochondrial proteins have been reported [40,41], the mechanisms involved in the regulation of mitochondrial lipid content and their susceptibility to the interference of external stressors at the level of gene/protein expression were not yet fully clarified. An alternative way for external interventions to alter mitochondrial membrane lipid composition may be related with the supply of different lipid precursors, which may be in excess or not available for lipid synthesis.

In the following sections, we will address issues regarding the modulation of mitochondrial membrane lipid composition in the context of apoptosis, cancer or other diseases and aging (Section 2), as well as the possibility to explore diet-induced alterations in mitochondrial membrane lipids as a strategy for therapeutic purposes (Section 3).

2. Remodeling of mitochondrial membrane lipids in pathophysiology: an early event or a consequence?

A great deal of data has been accumulated regarding alterations of cell and organellar lipids in health and disease conditions. An

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