Review of: "[Review] Structural and Functional Roles of Non-bilayer Lipid Phase in Mitochondria"

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Article under scrutiny: [Review] Structural and Functional Roles of Non-bilayer Lipid Phase in Mitochondria.

Report

I have gone through the article carefully. The monolayer structure of mitochondria is certainly an issue, which needs a deeper probe by a programmed teamwork involving biochemical, genetic, and ultra-structure researchers putting their heads together to resolve the problems associated with mitochondrial structure and function.

There are several issues associated with the mitochondrial functions in the cells.

Resting somatic cells and the totipotent stem cells have limited role for mitochondrial respiration/ ATP production. Mitochondrial function is activated only in metabolically activated tissues or growing embryos. The bioenergetic theories created the erroneous concept that ATP production is the sole function, and carbohydrates are the source of ATP production to maintain metabolically active cells. Developments over the past thirty years clearly demonstrated that stress factors (be it starvation, nutrient stress, mechanical, replicative or pathogenic stress) activates cell transformation, remodels metabolism to counter stress. Several ignored reports of 19^{th} and 20^{th} century as well as recent studies suggest that phosphate (Pi), sodium (Na^+) and fructose trigger the metabolic remodelling, and the lactate cycles activate the regenerative oxidative metabolism. The primary role of ATP is phosphate transfers between the organic metabolites within a cell. Once the intracellular phosphate transfers are optimised, ATP is exported into microenvironments through exosomes. Membrane bound Ectonucleoside Triphosphate Diphosphohydrolases (ENTPDs) hydrolyze the ATP in the microenvironment, liberated Pi activates the cross talk between the epithelial, mesenchymal , immune, inflammatory, and myeloid cells in tissue remodelling. Nutrient limitation (calorie restriction) maintains a healthy recycling of metabolites and metabolic homeostasis.

Resting somatic cells and totipotent embryonic cells have least metabolic activity. One carbon metabolic pathway (serine -folate biosynthetic pathway) is kept inactive in somatic and embryonic cells. Parkin ubiquitinates the enzyme PHGDH, the sole regulatory enzyme of the pathway. During the nutrient recycling, and the cell turn over PTEN induced kinase (PINK1) destabilizes the Parkin, to activate nucleotide synthesis and the RNA synthesis for biogenic programmes associated with the nutrient recycling and tissue remodelling. Cell cycle is restricted before the restriction point of the G1 phase to facilitate the RNA synthesis. Developing embryos and carcinogenic cells require activation of ATP synthesis, mitochondrial respiration, and progression of cell cycle to increase the cell number and organogenesis. High fat and high protein diets dysregulate the metabolic remodelling, homeostatic mechanisms and symmorphosis resulting in pathological disorders. Vector mediated infections and familial genetic disorders are the primary cause of Pathological disorders, which require a separate analysis.

Coming to the structure and function of mitochondria, the central issue discussed in the paper: The authors suggest that non-bilayer lipid filled vacuoles and cardiolipin promotes ATP synthesis and mitochondrial function. VDAC functions and Cardiolipin functions are sperate. Both are involved in monolayer globular structure formation.

The authors are completely silent on VDAC . ATP production as well as mitochondrial structure are two highly distorted issues promoted by Warburg and the protagonists of bioenergetic theories.

Benda coined the term Mitochondria (From Greek word: *Mitos,* meaning the thread; *Chondros,* meaning the granules for the presence of granular and filamentous structures coexisting in the cells (Ernster and Schatz (1981) Mitochondria: A Historical Review (PMID: 7033239)). The double membrane structure of mitochondria is a figment of artistic imagination created by Palade. A careful examination of the electron micrographs published by Palade give the impression that the watery layer surrounding the lipid enriched mitochondrial membrane separating globular structures from the rest of the filamentous units and endoplasmic structures could be mistaken as the double layer. Even the globular structures are divided between cristae absent and cristae enriched structures. Palade added a schematic figure to cristae containing globular structures to justify the double membrane structure of the mitochondria. Palade used the parenchyma cells and metabolically active proximal convoluted tubules in his micrographs. Several other reports especially those from the embryonic structures give a mixture of filamentous and vacuolar structures. See sample figures:

According to the present models, mitochondrial double membranes contain an outer membrane protein VDAC1 and inner membrane cardiolipin. Several reports suggest that lipid laden mitochondrial globule formation inhibit the cardiolipin synthesis and promotes fatty liver disease (see the latest article In Nature Communication (PMID: 36765117) and nearly 100 similar articles).

Cardiolipin synthesis requires the phospholipids, phosphatidylcholine (PC) and phosphatidyl-ethanolamine (PE) synthesized in One-Carbon metabolic pathway (Known as Kennedy pathway) (PMID: 28411170). The relative ratios of PC to PE define the structure of outer and inner membranes, PE in coordination with pyrimidine CTP and cardiolipin maintains the stability outer membrane.PE has diverse cellular functions, and serves as the precursor for phosphatidylcholine biosynthesis, and as a substrate for important posttranslational modifications, influencing membrane

topology, and promoting cell and organelle membrane fusion, oxidative phosphorylation, mitochondrial biogenesis, and autophagy (PMID: 26811286).

Present models also project Pyruvate entry into mitochondria activates oxidative metabolism and ATP synthesis in respiratory chain. Pyruvate metabolism in mitochondria is partitioned between pyruvate carboxylation, and pyruvate glutamine amino acid amino transferase (GPT2) by two mitochondrial carrier proteins MPC2 and MPC1 respectively (discovered in 2012). While pyruvate carboxylation is activated independent of functional respiratory chain, pyruvate metabolism requires functional respiratory chain. The pathway activates cytoplasmic aspartate synthesis, and citrate metabolising ATP citrate lyase (ACLY) dependent palmitoyl-CoA biosynthesis required for the elongation and unsaturation of fatty acids by stearoyl-CoA desaturase (SCD), which are activated by Peroxisome proliferator-activated receptor gamma (PPARγ). Unsaturated fatty acids are required for the biosynthesis of cardiolipin and for proliferation of cells. While calorie restriction promotes cardiolipin biosynthesis (PMID: 28213011), high fat diets and high protein diets inhibit cardiolipin synthesis and promote obesity and carcinogenesis (PMID: 32245049) .

VDAC maintains the membrane potential (Δψm) for ATP synthesis. Haemoglobin degradation by Haemoxygenases differently regulate the cell metabolism under anaerobic and aerobic metabolism. Hemoxygenase 1 (HO1) activates the Iron mediated ROS production and cytotoxicity, cytosolic NADPH oxidase, xanthine oxidase and P450 enzymes, which can lead to ferroptosis in the absence nutrient insufficiency. Mitochondrial respiratory chain assembly requires several fatty acid metabolites, and transport proteins like carnitine palmitoyl transferase, which are synthesized in peroxisomes. Fatty acid synthesis activates Hemoxygenase 2 (HO2) promotes cardiolipin monolayered globular mitochondria, glycine decarboxylase system dependent respiratory chain assembly and cell differentiation and/or senescence. Recent reports also suggest that VDAC down regulation activates cardiolipin biosynthesis. Besides, Cardiolipin biosynthesis requires both the pyrimidine CTP and unsaturated fatty acids in the cytoplasm. Cardiolipin monolayered Cristae containing globular structures activate GTP synthesis mTORC1 activation to reconstruct the cell membranes and plasma membranes lost during cell transformation to EMT.

I regret that for the reasons given above, I am not in a position to recommend the publication of the paper; it does not add to any meaningful scientific output and may contribute to further confusions.