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EC PULMONOLOGY AND RESPIRATORY MEDICINE

Review Article

The Role of Mitochondrial Imbalance in Pulmonary Diseases

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Received: February 07, 2019; **Published:** March 20, 2019

Abstract

A role for mitochondrial imbalance of reliance on anaerobic glycolysis in cancer metabolism was first discovered by Otto Warburg in 1924, at a time that mitochondria were not known. The tricarboxylic acid cycle (TCA) was described by his student, Hans Krebs. But the role of this organelle in oxidative phosphorylation was not understood despite an enormous contribution by Chance until the Nobel Prize (1978) discovery of oxidative phosphorylation by Peter Mitchell. The electron transport chain (ETC) consists of a sequence of electron transport carriers, complexes I - IV arranged with the spontaneous flow of electrons, each step forward having greater electron affinity, generating a proton gradient (H+) across the inner mitochondrial membrane (IMM) and coupled with synthesis of adenosine triphosphate (ATP) with the oxidation of reduced nicotinic adenine dehydrogenase (NADH). It was only more recently discovered that the mitochondria have a larger role than creating oxidative energy with the modulation of oxidation-reduction process, homeostatic sensing, monitors and modulators of oxidation-reduction, quality control, and signaling mechanisms that are described here. While these organelles have a different distribution among organs based on functional needs, such as heart, brain, and skeletal or smooth muscle, this discussion is specifically limited to the important relationship to the lung and pulmonary diseases.

Keywords: *Inner Mitochondrial Membrane (IMM); Adenosine Triphosphate (ATP); Nicotinic Adenine Dehydrogenase (NADH)*

Abbreviations

AcCoA: Acetyl Coenzyme A; UPRam: Activated Mistargeted UPR; (ATF4): Activating Transcription Factor 4; ALI: Acute Lung Injury; ARDS: Acute Respiratory Distress Syndrome; ATP: Adenine Triphosphate; BMR: Basal Metabolic Rate; Ca^{+2}: Calcium; COPD: Chronic Obstructive Pulmonary Disease; C/EBP: Homologous Protein CHOP; IMM: Cristae; CFTR: Cystic Fibrosis Transmembrane Regulator; CytC: Cytochrome c; DAMPS: Damage Associated Molecular Patterns; DCA: Dichloroacetate; Dsb: Disulfide Bond; dy: Electrochemical Potential; ER: Endoplasmic Reticulum; EMT: Epithelial to Mesenchymal Transition; ECM: Extracellular Matrix; MAPK: Extracellular Signal Related Kinase; FAD: Flavin Adenine Dinucleotide; HOI: Haem Oxygenase-1; IPF: Idiopathic Pulmonary Fibrosis; ILD: Inflammatory Lung Disease; IMS: Intermembrane Space; IL: Interleukin; mTOR: Mammalian Target of Rapamycin; MnSOD: Manganese Superoxide Dismutase; MICOS: Mitochondrial Contact Site and Cristae Organizing System; mtDNA: Mitochondrial DNA; Mfn2: Mitochondrial Fusion Protein; Dym: Mitochondrial Membrane Potential; MPP: Mitochondrial Processing Peptidase; Mrp: Mitochondrial Ribosomal Protein; UPRmt: Mitochondrial Unfolded Protein Response; MAPK: Mitogen-activated Protein Kinases; NAC: N-acetylcysteine; NOX: NADP-oxidase; NAD^+, NADH: Nicotinic Acid Dinucleotide; $NADP^+$, NADPH: Nicotinic Acid Dinucleotide Diphosphate; nDNA: Nuclear DNA; OXPHOS: Oxidative Phosphorylation; PDK: Pyruvate Dehydrogenase Kinase; PAM: Presequence Translocase Associated Motor; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; rRNA: Ribosomal RNA; SAM: Sorting and Assembly Machinery; H_2O_2: Superoxide Anions; O^-_2: Superoxide Anion Radicals; SOD: Superoxide Dismutase; SIRS: Systemic Inflammatory Response Syndrome; TGF: Transforming Growth Factor; tRNA: Transfer RNA; TIM: Translocase of Inner membrane; TOM: Translocase of Outer Membrane; TTR: Transthyretin; TCA: Tricarboxylic Acid Cycle; UPR: Unfolded Protein Response; VILI: Ventilator Induced Lung Injury; ADAC: Voltage Dependent Ion Channel

The anatomic structure of the lung

The lung has three lobes on the right and two on the left. There are the trachea, the branching bronchi, and the lower and terminal bronchioles. The bronchi are lined by columnar epithelium that have mucus secreting glands. The air exchange occurs in the terminal respiratory alveoli that have Type 1 epithelial cells (8%) and the alveoli lined by Type 2 epithelial cells (92%) [1]. The alveoli consist of epithelium on the outside that surrounds a capillary on the inside. Gas exchange occurs across the alveolar wall, oxygen in inspiration and carbon dioxide on expiration. The Type 1 cells are flat and have few mitochondria, and the Type 2 cells are somewhat cuboidal, and are rich with mitochondria. The epithelial cells have a cleft between them [2]. The alveolar macrophage has lysosomes, a rich endoplasmic reticulum (ER) and Golgi. The macrophage is derived from bone marrow by way of blood macrophage. Inhaled toxins, including cigarette smoke, have a negative effect on macrophage viability and activity. The macrophages are the primary phagocytes of the innate immune system, and they clear the air spaces of infectious, toxic, or allergic particles, and they also function as regulators of innate alveolar defenses against respiratory infection. Biological energy conversion in mitochondria occurs in the inner membrane cristae by the respiratory chain and mitochondrial ATP synthase. Mitochondria have transferred 99% of their genes to the nucleus. In the cell, mitochondria form a tubular network that changes by division and fusion.

Mitochondria in cellular function

The mitochondrial function has an important role in normal function and in pathology as well. This bean shaped organelle has a role in a dynamic network that fuses, divides, and is involved in a functions that are central to cell life, death, and differentiation [3]. More specifically, they have a role in calcium handling, apoptosis, heme turnover, inflammation, and oxygen and nutrient sensing, and they have a critical role in monitoring oxidation-reduction processes, cell proliferation, mitochondrial biogenesis, mitophagy, inflammasome activation, cell proliferation, and prevention of fibrosis [4]. Mitochondrial biogenesis and mitophagy is the means by which cells replace dysfunction mitochondria that involves mitochondrial fusion and fission. Damaged type 2 alveolar epithelial cells (AEC) are removed by mitophagy regulated by PINK1, BNIP, Parkin, and ATG5/12. These cells undergo membrane remodeling through cycles of fusion and division [4]. Mitochondrial damage associated molecular patterns (mtDAMPS) act as second messengers and act in activating the induction of inflammatory cascades.

They activate pathogen recognition receptors (PRRs) in initiating the inflammatory cascade. Mitochondrial reactive oxidant system (ROS) is regulated by the electron transport chain (ETC) to generate a one electron reduction of molecular oxygen to superoxide anion (O^{2-}).

How do proteins enter the mitochondrion? They do this by way of translocators in the inner and outer membranes and this lies especially with a protein called Tim22 stabilized by a disulfide bond [5]. Only 13 polypeptides are coded by mtDNA. The cytosolically synthesized proteins encoded by nuclear DNA (nDNA) are imported into the mitochondria by cytosolic chaperones, which protect the precursors from aggregating by protecting their hydrophobic regions. The stability of the TIM23 depends on the translocase of the inner membrane Tim23 [6]. There are two pathways into the intermembrane space (IMS) - the stop-transfer pathway, and the second is the intermembrane space (IMS) import pathway, which introduces disulfide bonds to preproteins that fold and are retained in the IMS. Only certain subunits of TOM and SAM complexes of different eukaryotes are conserved (TOM22, Tom40, and SAM50) [7]. The balance between the production and removal of reactive oxygen species (ROS) and reactive nitrogen species (RNS) is critical and maintenance of a balance directly influences the environment in which these processes take place [8]. This balance involves activation of transcription factors, protein proofreading and protein biogenesis. The import of many intermembrane space proteins depends on cysteine residues and the oxidoreductase Mia40, which interacts with a mitochondrial protein Mrp10 that renders import intermediates accessible to Mia40 [9]. Components of the Mitochondrial Disulfide Relay are Mia40, that has two disulfide bonds, and Erv1, a flavin adenine dinucleotide (FAD) [10]. The CPC motif has to be in an oxidized state. The substrate binds to the hydrophobic groove in the loop-helix domain of Mia40. The CXXC motif in the shuttle domain of Erv1 forms an intermediate disulfide with Mia40 (11). Electrons are shuttled via the FAD domain to a cytochrome C (Cyt c). Erv1 stabilizes the four-helix bundle of the FAD domain. The mitochondrial disulfide relay resembles the disulfide bond (Dsb) system of bacterial periplasm 2 billion years ago.

Mitochondrial dysfunction

Prolonged stress results in dysfunctional mitochondria leading to cell death if the stress persists beyond recovery. Mitochondria generate NADH and ATP through the TCA cycle and OXPHOS. Mitochondria pump protons from the matrix into the IMS increasing the negative charges, a process that increases the mitochondrial membrane potential (dym) [10]. Superoxide anions (O^{-2}), H_2O_2 and hydroxyl radicals produced are reactive oxygen species (ROS), and these including NADPH oxidases target the mitochondria. The mitochondria maintain their homeostasis by (1) dym (2) mitophagy (3) making acetyl CoA and (4) ROS generation. Oxidative damage by ROS results in generation of defective ETC subunits, which further leads to a disparity between prooxidants and antioxidants termed oxidative stress. Mitophagy responds to the disparity by regulating mitochondria quantity and separating damaged mitochondria to balance the redox state of the cell.

What is the clinical implication of mitophagy? Mitochondria are damaged in the clinical procedure of resuscitation of premature infants because of mechanical ventilation and hyperoxia. Chronic obstructive pulmonary disease (COPD) is characterized by increased ROS production, decreased antioxidant capacity, impaired OXPHOS and reduced number of mitochondria [11]. This is of particular interest with respect to skeletal muscle weakness. Mitochondria DNA (mtDNA) instability occurs in lung cancer and an increase in mtDNA copy number is associated with cancer risk. An increase in ROS by mitochondria in inflammatory cells is thought to occur in epithelial apoptosis in asthma. The increased mucus production in cystic fibrosis (CF) is related to a genetic mutation in the coding of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR).

Failure to eliminate the toxic ROS and RNS is detrimental to cells. This leads to nonfunctional OXPHOS enzymes with an adverse impact on cellular homeostasis. The mitochondria act as a metabolic hub the interconnects anabolic and catabolic processes, such as OXPHOS, the TCA cycle, b-oxidation of fatty acids, and steroidogenesis [12]. Mitochondria-ER junctions aid in lipid synthesis, calcium buffering and signaling, intracellular trafficking and mitochondrial biogenesis. The fusion protein (Mfn2) harnesses the endoplasmic reticulum (ER) to the mitochondrion by controlling mitochondrial uptake of calcium (Ca^{+}) the ER. The mitochondria ROS act as signal transducers that trigger the release of proinflammatory cytokines and as modulators of transcription factors. These mediators have roles in asthma, asthma, COPD and fibrosis [13]. The airways and lung parenchyma are sensitive to allergens, toxic pollutants and microorganisms that induce cellular stress and induce signaling, and drive enhanced Ca^{2+}, contractility, cell proliferation and functional change in the lung. Cystic fibrosis and COPD have already been described. Expression of Mnf2 has a role in lung cancer, and Mnf2 decrease may be accompanied by an increase in Drp1, and Dnp1 decrease with Mfn2 overexpression results in apoptosis. Lung cancer may also be associated with tumor suppressor genes Ras, Myc and p53 inducing uncontrolled production of ROS.

Transport of proteins into the mitochondrion

A majority of proteins in the mitochondrion are formed in the cytoplasm and there is a mechanism to transport precursor proteins across the OM. This mechanism is by an outer membrane transport called the TOM. The TOM complexes are located in subdomains of the OM close to openings in the IM called cristae junctions [13]. The precursor proteins with a-helical structure are directed to the insertase of the MIM, and b-barrel precursors are directed to the sorting and assembly machinery (SAM) by small Tim chaperone proteins. Tim23 is associated with cleavable N-terminal proteins, and cysteine-rich proteins are directed to the IMS by the intermembrane mitochondrial assembly (MIA) pathway. TIM23 is associated with the protein-associated matrix (PAM) that transfers proteins in an ATP-dependent manner. The preproteins that enter the IMS are recognized and cleaved by the mitochondrial processing peptidase (MPP). Membrane insertion via TIM22 and TIM23 requires the electrochemical across the IM. Translocases are essential for mitochondrial function. The unfolded protein response related to the mitochondria is mtUPR, and the increase of mistargeted proteins in the cytosol triggers the unfolded protein response is termed the activating the mistargeting of proteins (UPRam). Mutations in the genes that provide quality control in mitophagy are Parkin1 and cytosolic E3 ubiquitin ligase Parkin, which are related to early onset Parkinson's disease.

The unfolded protein response in chronic obstructive pulmonary disease

The lung tissue undergoes accumulates nonfunctional and cytotoxic, misfolded proteins in COPD, that may lead to apoptosis, inflammation, and autophagy [14]. The UPR is involved in processes that decrease protein synthesis, while at the same time enhancing protein degradation. The UPR lung has the capacity to eliminate damaged protein present in the tissue by the activity of ER chaperones that are

in the UPR, and protein folding occurs when there is an imbalance of ER capacity and the folding capacity because of a related ER stress. The secretion of mucus is enhanced in asthma, cystic fibrosis, and COPD.

Apoptosis, inflammation of lung cells, and autophagy have a role in the process of lung destruction and remodeling in COPD. Pulmonary hypertension occurs secondary to COPD [15]. This is because respiratory muscle fatigue and alveolar hypoventilation resulting in hypoxia, respiratory acidosis, and pulmonary vasoconstriction with severe respiratory failure. COPD is characterized by progressive airflow limitation with loss of lung function [15]. Patients with COPD have weight loss associated with skeletal muscle loss in the course of the disease [16]. Weight loss occurs in a third of disabled patients with COPD [17]. The basal metabolic rate (BMR) is elevated by 10 - 20% in up to 40% of these patients.

Cigarette smoke, diesel exhaust, or allergens induce ER stress and dysregulate the ER homeostasis [18].

IRE1 binds to unfolded proteins in the peptide binding groove in IRE1 luminal domain, and activation ofIRE1 and PERK causes them to dimerize and phosphorylate. IRE1 is the oldest UPR branch.

COPD is the third largest cause of death in the world, and has a relationship to stroke. COPD-related systemic inflammation and oxidative stress contribute to its morbidity and mortality. Oxidative stress may affect the structure and function of mitochondria as a result of the action PTEN-kinase 1/Parkin and p62 in mitophagy in which Akt ubiquitin ligase is a mediator associated with cigarette smoke. In addition, inflammatory cells are induced by cigarette smoke in the ER stress response through activating transcription factor-4 (ATF4) mediated induction of C/EBP homologous protein (CHOP) in primary small airways [19].

Allergic asthma is characterized by accumulation of T-helper 2 type lymphocytes, mast cells, eosinophils, and by airway remodeling with thickening of the basement membrane [20]. This is stimulated by inhaled allergens, concomitantly with bacterial or viral infection, or air pollution. Idiopathic pulmonary fibrosis (IPF) is the most common and devastating form of interstitial lung diseases or idiopathic interstitial pneumonias causing progressive fibrosis. Pulmonary artery hypertension (PAH) is a disease of the lung vasculature caused by excess proliferation of vascular smooth muscle (VSM) due to elevated blood pressure in the pulmonary arteries. Cystic Fibrosis is the most common inherited autosomal recessive disorder. In culture pulmonary artery smooth muscle cells with UPR induction produced IL-6 and CCL-2/MCP-1 and stimulated macrophage migration [20].

Idiopathic pulmonary fibrosis (IPF)

Cyclic stretch from ventilation with high tidal volumes increased the activation of the NF-kb signaling pathway and promoted ventilation-induced superoxide production [21]. Trials of antioxidant treatments have been inconsistent [22]. Positive correlations were found with heme-oxygenase 1 (HO-1) by alveolar macrophages in IPF [23]. There were positive correlations between the score of HO-1 and the release of IL-12 and IL-8 by macrophages in IPF and sarcoidosis. There is an imbalance of oxidant-antioxidant imbalance [22,23] leading to oxidative stress that involves epithelial cells, fibroblasts and inflammatory cells that leads to fibrosis with the development of profibrotic cell phenotypes [24]. Tissue repair is an orchestrated process involving recruitment, proliferation, differentiation, deactivation, and activation of cell types. Senescence results in diminished capacity to carry out tissue repair and is a hallmark of aging [25]. When tissue repair is not controlled, fibrosis may occur with attendant loss of organ function. Inflammation occurs due to sustained mesenchymal activation with excessive accumulation of extracellular mesenchymal matrix (ECM). This is related to redox imbalance/oxidative stress with mesenchymal activation and impaired epithelial regeneration.

Endothelial stress

Unfolded proteins accumulate within mitochondria by a response known as the mtUPR. The mtUPR reestablishes protein homeostasis by a inducing mitochondrial chaperone and protease genes [27]. The activation of signaling cascades to restore a favorable folding environment occurs in response to ER luminal conditions or altered chaperone capacity [28]. This is referred to as ER stress, which results

in the UPR. Approximately 30% of newly synthesized proteins are rapidly degraded, and this is due to compromised ability to produce properly folded proteins, resulting in accumulation of unfolded and misfolded proteins [29]. The UPR consists of three signaling systems initiated by localized stress sensors: IRE1, PERK, and ATF6. When the UPR is disturbed or inadequate to deal with stress conditions, cellular apoptosis ensues.

The activation of IRE1 by ER stress is expected of receptor kinase proteins [30]. The IRE catalyzes the splicing of the HAC1 mRNA. The PERK kinase is activated and phosphorylates elF2a, which attenuates translation of the ATF4, blocking the expression of APR target genes. IRE1 dimerization is activated and causes ARE1 -mediated splicing of XBP1 mRNA. The translation of spliced XBP1 mRNA leads to upregulation of target genes. ATF6 activation translocates to the Golgi, is processed to release a transcription factor that translates to the nucleus and binds to UPR target genes. GADD34 protein dephosphorylates elF2a restoring global protein synthesis. Apoptosis related Bax and Bak proteins interact directly with the cytosolic domain of IRE1 in response to ER stress and are required for normal IRE1 signaling, and are involved in stress-related apoptosis. In addition, ER stress with apoptosis mediated by mitochondrial mechanisms involves the Bcl-2 family of proteins. Bcl-2, Bax and Bak associate with both the mitochondria and the ER. The Bcl-2 family of proteins are involved with mediating stress-induced apoptosis. Ca^{2+} is released from the ER to the cytoplasm and ER Ca^{2+} stores are depleted. Another pathway involves mitochondrial uptake of cytosolic Ca^{2+} with depolarization of the MIM and CytC release, which causes the assembly of the apoptosome. Phosphorylated Bcl2 also enhances Ca^{2+} efflux from the ER and increases Ca^{2+} uptake by the mitochondria. mTOR regulates the balance between mitochondrial and nonmitochondrial sources of ATP generation, and inhibition of mTOR shifts glucose metabolism away from mitochondrial respiration. This results in accumulation of lactic acid [31,32]. The role of the mtUPR in maintaining or reestablishing protein homeostasis within mitochondria is by transcriptionally inducing mitochondrial molecular chaperone and protease genes [33]. Mitochondrial ER stress signals to the mitochondria by CHOP and JNK influencing the regulation of Bcl-2 proteins.

Mitochondria and cancer

Cholesterol metabolism is disturbed in cancer cells and mitochondrial cholesterol loading may contribute to the Warburg concept of aerobic glycolysis having a role in apoptosis of proliferating cells, but protecting them from mitochondria [34]. The mtDNA codes for 7 NADH dehydrogenase subunits for complex I, a cytochrome b for complex III, 3 cytochrome oxidase (COX) subunits for complex IV, and 2 ATPases (ATPase6/8) for complex V. Complex II is encoded by nDNA [35]. The overall biogenesis of mitochondria is synchronized with cell proliferation. However, the nDNA unlike the mtDNA is protected by histones. The mtDNA has little repair capacity. The mitochondria constantly produce superoxide radicals. The mitochondria possess genomes for 13 of 87 proteins need for OXPHOS.

In all organisms with mitochondria, the mitochondrial contact site and cristae organizing system (MICOS), an assembly of one soluble and 5 membrane proteins is anchored to the outer membrane by the cristae. The ATP synthase anchored in the cristae uses the EC gradient across the IMM to produce ATP. Linear arrays of ATP synthase complexes are found in the curved regions along the cristae ridges. The proton gradient across the cristae membrane is created by three large membrane protein complexes of the respiratory chain: complex I (NADH/ubiquinone oxidase, II (cytochrome c reductase and IV (cytochrome c oxidase). Proton pumps of the ETC assemble into supercomplexes called respirasomes. During aging fission overpowers fusion and the mitochondrial network disassembles.

Tumor suppressor p53 regulates mitochondrial respiration [36]. In apoptosis tumor suppressor p53 directly regulates mitochondrial function through an assembly protein encoded by the gene Synthesis of Cytochrome c Oxidase 2 (SCO2) in both mice and human cancers. Decreased aerobic respiration of p53 deficient cells was rescued by reintroducing SCO2 at physiological levels. The maintenance of similar proliferation rates in both p53 -/- and SCO2 +/- cells with an increase in glycolysis suggested coordinate regulation of both aerobic and anaerobic pathways. Expression of TIGAR decreased glycolytic activity and also decreased ROS generation and apoptosis. Glutathione production was accompanied by a decrease ROS generation and apoptosis.

Human cancers have high mitochondrial membrane potential (HJm) [37]. Dichloroacetate (DCA) inhibits mitochondrial pyruvate dehydrogenase, inhibits mitochondrial pyruvate dehydrogenase kinase, shifting metabolism from glycolysis to glucose oxidation. DCA reverses the metabolic electrical remodeling to glucose oxidation. DCA induces apoptosis, decreases proliferation, and inhibits tumor growth. Genetic mutability and all hallmarks of cancer, including the Warburg effect, can be linked impaired respiration and energy metabolism [38]. Mitochondria control cell viability by regulating programmed death, Ca^{2+} levels, and trafficking of metabolites. Mutations of isocitrate dehydrogenases (ICD1 and ICD2) are associated with cancer, and also succinate dehydrogenase (SDH). MtDNA mutations are most often associated with cancer initiation and progression are associated with Complex I, known as NADH: ubiquinone oxidoreductase. Cancer cells employ aerobic glycolysis (Warburg effect) by increasing glycolysis while impairing TCA cycle and OXPHOS.

Cancer cells with dysfunctional mitochondria, such as mtDNA-deficient q0 cells and blocked ETC were highly sensitive to glucose deprivation [39]. There may be a link between mitochondria and the ER during the UPR under glucose deprivations and through modulating the UPR for cell survival. Deregulation of mitochondrial plays a key role in tumor initiation and during tumor progression.

Mitochondrial dysfunction might enable cancer cells to adapt to the tumor environment.

Conclusions

The presentation that has been provided "The Role of Mitochondrial Imbalance in Pulmonary Diseases" argues that there is significant complexity to the function and malfunction of the lung architecture. However, the findings that have been displayed are very consistent with our growing knowledge of the pathophysiology of pulmonary function. The understanding is based on the primary function of the respiratory system, and resides in the interaction between the airways and the contact with an impure air, and the mechanism that pulmonary epithelium, mucous glands, muscularis, and vascular infiltrates are involved in the respiratory processes.

We started with the anatomy and physiology of the lungs. We proceeded to the handling of inhaled atmospheric content, and the generation of reactive oxygen and nitrogen species generated in the breathing of air. The lungs deliver O_2 to the circulation in return for CO_2 in repeated cycles and at a rate needed for transport to the tissues. Of course there is a difference in utilization between skeletal muscle a brain that is reflected in the mitochondrial content of the organ, and in the short spurts of energy generated in running and other sports.

Otto Warburg's studies in a controlled environment observed that cells that normally utilize oxygen rely on glycolysis, such as cancer cells. Mitochondria were not known at the time, and were called "grana". The aerobic metabolic pathway, referred to as citric acid cycle, was subsequently determined by Hans Krebs. Warburg's observation was analogous to observations of yeast in soil sixty years earlier. It was subsequently determined that there are three major pathways: anaerobic glycolysis, the aerobic citric acid cycle, and a pentose phosphate shunt (for nucleotides). The difference between the aerobic and anaerobic pathways lies in the generation of ATP. Warburg observed that cells that require oxygen in his controlled experiment rely on aerobic glycolysis.

The basis for aerobic glycolysis lies in the citric acid cycle within the mitochondrion. The mitochondria are bean shaped organelles within them at the inner membrane. There are inner and outer membranes and an intermembrane space. The inner membrane has cristae on which the protein complexes of respiration reside. The mitochondria are the key for ATP metabolism. The mitochondria generate energy, also generate free radicals, are important for apoptosis, increase oxidative stress, and cause ROS-mediated damage to DNA. The mitochondria have a small number of mtDNA, the remainder are in the nucleus (nDNA) protected by protein.

The mitochondria generate energy by oxidative phosphorylation embedded in the electron transport chain. NADH and $FADH_2$ are formed in glycolysis and energy is generated when electrons are transported from NADH/$FADH_2$ to a lower energy state with the energy coupled to generation of ATP, called oxidative phosphorylation, which accounts for 90% of ATP synthesized by the cell. There is still more to the mitochondria role in the cell than the TCA cycle, such as b-oxidation and amino acid oxidation. The components of the electron transport system are a sequential order of electron carriers, four membrane-bound multiprotein complexes called complex I, II, II and IV, of which I, III, and IV are proton pumps. Complex II is succinate dehydrogenase.

Lung diseases are among the most common illnesses when we consider allergens, cigarette smoke, and air pollutants. I discussed more fully the mechanism of idiopathic pulmonary fibrosis, asthma, chronic lung disease and lung cancer. Lung cancer is not uncommon, and it has a poor 5 year survival. It is perhaps a late diagnosis more often than not. This discussion relates an extensive regulatory role of the mitochondria in health and disease. Mitochondria are intricately involved in cell signaling. There is a range of lung diseases that are associated with mitochondrial dysfunction. The mitochondria fuse, divide, and are involved with an array of functions related to life, death, and differentiation. Mitophagy is the process by which cells quickly replace damaged mitochondria. Fusion requires GTPases at the outer membrane and fission requires DRP1 from the cytosol to interact with receptors. The mitochondria are involved with calcium handling, apoptosis, heme, inflammation, and oxidation-reduction, related to biogenesis, mitophagy, inflammasome activation, cell proliferation, and fibrosis.

During OXPHOS mitochondria at Complex I and Complex III produce superoxide anion radicals (O^{2-}) that are converted to hydroxyl, H_2O_2 and superoxide anions that are ROS. mtDNA is involved in lung cancer.

Excessive ROS in inflammatory cells are involved with epithelial cell apoptosis and asthma. ROS disrupt cellular homeostasis. The role of mitochondria in lung disease has been fully discussed.

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Volume 8 Issue 4 April 2019