Dealing with Stress: Defective Metabolic Adaptation in Chronic Obstructive Pulmonary Disease Pathogenesis

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Abstract

The mitochondrion is the main site of energy production and a hub of key signaling pathways. It is also central in stress-adaptive response due to its dynamic morphology and ability to interact with other organelles. In response to stress, mitochondria fuse into networks to increase bioenergetic efficiency and protect against oxidative damage. Mitochondrial damage triggers segregation of damaged mitochondria from the mitochondrial network through fission and their proteolytic degradation by mitophagy. Post-translational modifications of the mitochondrial proteome and nuclear cross-talk lead to reprogramming of metabolic gene expression to maintain energy production and redox balance. Chronic obstructive pulmonary disease (COPD) is caused by chronic exposure to oxidative stress arising from inhaled irritants, such as cigarette smoke. Impaired mitochondrial structure and function, due to oxidative stress–induced damage, may play a key role in causing COPD. Deregulated metabolic adaptation may contribute to the development and persistence of mitochondrial dysfunction in COPD. We discuss the evidence for deregulated metabolic adaptation and highlight important areas for investigation that will allow the identification of molecular targets for protecting the COPD lung from the effects of dysfunctional mitochondria.

Keywords: mitochondrial dynamics; metabolic reprogramming; oxidative stress; metabolic adaptation

Chronic exposure to inhaled irritants, such as cigarette smoke (CS) and biomass fuels, and the resulting oxidative stress are major triggers of chronic obstructive pulmonary disease (COPD) inflammation and the associated pathology, which includes emphysema, chronic bronchitis, and small airways remodeling (1). Accelerated cellular aging and senescence are important in the development of emphysema, fibrosis, and inflammation, whereas airway smooth muscle (ASM) thickening contributes to small airways remodeling (1, 2). There is evidence of impaired mitochondrial function in the lungs of patients with COPD, possibly caused by chronic exposure to oxidative stress (3–8). Defective metabolic adaptation in COPD may lead to the development and persistence of mitochondrial dysfunction. We review what is known of the potential mechanisms of adaptation to mitochondrial dysfunction and how these may be deregulated in COPD, while highlighting the areas that require further investigation.

Mitochondria Are Hubs of Energy Production, Biosynthesis, and Redox Regulation

Mitochondria likely originated from α-proteobacteria that were engulfed by primitive eukaryotes, establishing a symbiotic relationship (9). Their bacterial ancestry is reflected by their structure, which is comprised of an outer and an inner membrane, enclosing the matrix and intermembrane space, and a small circular genome. Mitochondrial DNA (mtDNA) encodes for 13 proteins involved primarily in mitochondrial respiration. During evolution, a considerable proportion of the bacterial genome was transferred to the eukaryotic nucleus. Thus, the majority of mitochondrial proteins are encoded by the nuclear genome (10). Because mitochondria cannot be created de novo, mitochondrial biogenesis involves the growth and division of pre-existing mitochondria. Mitochondria divide by the process of fission, and subsequently fuse
Mitochondrial biogenesis is induced in response to changes in energy demand and environmental cues, by the key transcription factor, peroxisome proliferator–activated receptor γ coactivators (PGCs) 1α and β (12).

Mitochondria provide most of the cell’s energy requirements in the form of ATP through oxidation of glucose, fatty acids, and amino acids. Lung mitochondria primarily use glucose as a substrate; however, they also oxidize fatty acids, glutamine, and lactate (13, 14).

Glucose is taken up by the cells via glucose transporters, and is phosphorylated by hexokinase to glucose-6-phosphate, which enters the glycolytic pathway in the cytoplasm, leading to the production of pyruvate. Most pyruvate is transported through the mitochondrial inner membrane to the mitochondrial matrix, where it is decarboxylated into acetyl-coenzyme A (CoA) by pyruvate dehydrogenase (PDH), whereas a small proportion of it is converted to lactate in the cytoplasm. PDH is negatively regulated by PDH kinase, which acts as a gatekeeper, controlling the flow of pyruvate into the mitochondrion. Fatty acids are taken up by the cells via plasma membrane transporters or they are synthesized de novo. Fatty acids are activated by acetyl-CoA in the cytoplasm and associate with carnitine molecules, forming acylcarnitines that are transported into the mitochondrion, where fatty acid oxidation (FAO) occurs, producing acetyl-CoA (Figure 1) (15).

Acetyl-CoA, from glucose or fatty acid oxidation, enters the tricarboxylic acid (TCA) cycle, a series of enzymatic reactions in the mitochondrial matrix giving rise to the electron carriers reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH₂), which donate electrons to the electron transport chain (ETC) in the inner membrane. The ETC is comprised of four electron-carrier protein complexes (I–IV), which, through a series of redox reactions, transfer electrons to oxygen. During this process, termed oxidative phosphorylation (OXPHOS), complexes I, III, and IV pump protons into the intermembrane space, creating a mitochondrial membrane potential (ΔΨm). ΔΨm drives the influx of protons back into the mitochondrial matrix via a proton channel coupled to the F₅F₁ ATP synthase (complex V), which facilitates the phosphorylation of ADP to ATP (16). In situations of increased energy demand, such as in proliferating cells, glutamine is also used as a mitochondrial respiration fuel by undergoing glutaminolysis into glutamate, which enters the TCA cycle (Figure 1) (17, 18).

Leakage of electrons during OXPHOS, particularly at complexes I and III, leads to partial reduction of oxygen to produce reactive oxygen species (ROS). ROS have also been shown to be produced as a result of PDH activity, the TCA cycle, and FAO (19, 20). Mitochondrial ROS are maintained at low levels through the action of antioxidants, such as Mn superoxide dismutase and glutathione. Mitochondrial ROS at low levels are involved in the propagation of homeostatic mechanisms, but, at high levels, lead to damage of proteins, lipids, and nucleic acids, and thus cause disease (Figure 1) (16, 19).

Cellular bioenergetic, biosynthetic, and redox processes are highly coordinated to produce energy, while maintaining adequate levels of macromolecules required for biosynthesis and maintenance of redox balance. Citrate from the TCA cycle enters de novo fatty acid synthesis through its conversion to acetyl-CoA by ATP-citrate lyase in the cytoplasm, to replenish fatty acid levels (21). The glycolytic pathway, via glucose-6-phosphate, branches off into the anabolic pentose phosphate pathway (PPP), which produces ribose-5-phosphate, a precursor of nucleotide biosynthesis, and reduced nicotinamide adenine dinucleotide phosphate (NADPH), which is required for fatty acid biosynthesis and antioxidant protection (22). Glutaminolysis also provides nitrogen for nucleotide and protein synthesis, and glutamate, which is a precursor for glutathione synthesis (Figure 1) (17).

Mitochondrial Dysfunction in COPD

There is mounting evidence supporting the presence of mitochondrial dysfunction in the lungs of patients with COPD and its role in the development or progression of the disease (23). Morphologic abnormalities consistent with mitochondrial damage, such as elongated and swollen mitochondria, with poorly defined cristae were reported in bronchial epithelial cells of patients with COPD (4, 5). Impaired mitochondrial function reflected by loss of ΔΨm, increased mitochondrial ROS, and reduced mitochondrial respiration was also reported in ASM cells (ASMCs) and endobronchial biopsies of patients with COPD (8). Mitochondrial damage is possibly caused by oxidative stress as a result of chronic exposure to CS. This is supported by studies showing impaired mitochondrial function in CS- and ozone-induced mouse models of COPD (3, 7, 8). A recent study has provided evidence for increased expression of the iron-responsive element-binding protein 2, a key protein involved in iron homeostasis, that could lead to mitochondrial iron overload and dysfunction in COPD (8, 24). Impaired mitochondrial function has been shown to mediate lung cell apoptosis and senescence and the development of lung inflammation and emphysema, indicating a role in disease pathology (3, 4, 6–8, 25). The effects of mitochondrial dysfunction in disease may be mediated by excessive mitochondrial ROS (3, 4, 6–8) and release of mitochondrial components from damaged cells, such as mtDNA and cardiolipin, which act as danger-associated molecular patterns to induce inflammatory responses (26–28).

The dynamic nature of the mitochondria and their ability to move and communicate with other organelles enables them to adapt to oxidative stress, changes in energy and nutrient levels, and even damage. Loss of these adaptive responses, due to chronic exposure to high levels of oxidative stress or due to inherent defects, may lead to prolonged mitochondrial dysfunction in COPD.

Metabolic Adaptation to Stress and Mitochondrial Dysfunction

Mitochondria not only act as sensors, but are also regulators of metabolic activity. Changes in energy status are signaled by changes in intermediates, such as the ratios of oxidized to reduced NAD (NAD⁺/NADH) and AMP/ATP, and acetyl-CoA levels (29). These signals are detected by molecular sensors, such as hormones, transcription factors, and kinases, that act to restore metabolic and cellular homeostasis (30). Acute responses to stress, mitochondrial dysfunction, or altered nutrient supply involve changes in mitochondrial morphology, movement and quality control, and post-translational modifications of mitochondrial proteins. Furthermore, retrograde signaling between the mitochondrion and nucleus triggers transcriptional changes that lead to more lasting metabolic changes, termed “metabolic reprogramming” (30, 31).
Figure 1. Central role of mitochondria in energy production, biosynthesis, and redox regulation. Mitochondria integrate energy metabolism, biosynthesis, and redox balance. (1) Glucose is phosphorylated by hexokinase (HK) to glucose-6-phosphate (Glucose-6-P), which undergoes glycolysis in the cytoplasm to produce pyruvate. Under normal, aerobic conditions, most of the pyruvate that enters is converted to acetyl-coenzyme A (CoA) by the pyruvate dehydrogenase (PDH) complex in the mitochondrial matrix, whereas a small proportion of it is converted to lactate by lactate dehydrogenase (LDH). Glycolytic intermediates also feed into biosynthetic pathways. Glucose-6-phosphate is redirected into the pentose phosphate pathway to produce the nucleotide precursor, ribose-5-phosphate, and reduced nicotinamide adenine dinucleotide phosphate (NADPH) required for the maintenance of reduced glutathione (GSH) levels. (2) Fatty acids are transported into the mitochondrion after their conjugation to carnitine by carnitine palmitoyltransferase 1 (CPT1), to undergo fatty acid oxidation, leading to acetyl-CoA production. (3) Acetyl-CoA combines with oxaloacetate (OAA) to form citrate, which enters the tricarboxylic acid (TCA) cycle in the mitochondrial matrix, generating electron carriers, nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH). Citrate produced by the TCA cycle is converted, by ATP-citrate lyase (ACL), to cytoplasmic acetyl-CoA, which is required for fatty acid synthesis. (4) Cells with increased energy demands, such as rapidly proliferating cells, use glutamine for energy production. Glutamine is converted to glutamate by glutaminolysis through the action of glutaminase (GLS). Glutamate acts as a precursor for glutathione synthesis, but can also be converted, by glutamate dehydrogenase (GLDH), into α-ketoglutarate, which feeds into the TCA cycle. Glutamine also provides nitrogen for amino acid and nucleotide synthesis. (5) Electrons (e−) are transferred from NADH and FADH2 to molecular oxygen (O2) through redox reactions facilitated by a series of electron carrier protein complexes (I–IV) located in the inner mitochondrial membrane (IMM), a process termed “oxidative phosphorylation” (OXPHOS). The energy released by the electron flow drives the movement of protons into the intermembrane space (IMS) creating a membrane potential (∆Ψm). ∆Ψm drives the influx of protons back into the mitochondrial matrix via the ATP synthase complex (complex V), which phosphorylates ADP to ATP. Electron leakage during OXPHOS leads to univalent reduction of oxygen to form superoxide anion (O2•−). O2•− is converted to the less reactive oxidant, hydrogen peroxide (H2O2), which is eliminated through the action of catalase and GSH. (6) In response to oxidative stress and/or mitochondrial...
Mitochondrial Morphology, Movement, and Quality Control

Mitochondria have a very dynamic morphology, and can be found segregated or linked together into linear or branched networks as a result of continuous cycles of fission and fusion, mediated by multidomain dynamin-related GTPases (30). Mitochondrial fission and fusion are pivotal in the ability of cells to survive under conditions of stress (32).

Mitochondrial fusion is induced in the initial stages of cellular stress. The membrane-anchored proteins, mitofusin (Mfn)-1 and -2, facilitate the fusion of the outer membranes, whereas optic atrophy (Opa) 1 mediates the fusion of the inner membranes and controls cristae formation, leading to the formation of networks of elongated mitochondria (33). This leads to complementation between mitochondria through sharing of mtDNA, lipids, and proteins, limiting detrimental mutations and mitochondrial damage. Moreover, fusion maintains OXPHOS efficiency through the formation of ETC super complexes, preventing the proteolytic degradation of mitochondria and facilitating interactions between mitochondria and endoplasmic reticulum (ER) (11). Mitochondrion–ER interactions are important stress response mechanisms in that they allow the movement of Ca^{2+} that triggers mitochondrial biogenesis as well as transport of essential mitochondrial lipids, such as cardiolipin (34, 35). The proteolytic processing of Opa1 is pivotal in the regulation of mitochondrial dynamics. Under normal conditions, processing by the mitochondrial quality control proteases, ATPas es associated with diverse cellular activities proteins, maintains Opa1 in long transmembrane and short, soluble isoforms (36, 37). Under conditions of stress, stomatin-like protein 2, a prohibitin-related scaffolding protein expressed in the mitochondrial inner membrane, maintains Opa1 in the long conformation, promoting mitochondrial hyperfusion (32). Acute exposure to oxidative stress can induce mitochondrial hyperfusion, which possibly acts as a first line of defense against ROS by minimizing cellular damage and increasing metabolic efficiency (38, 39). Thus, mitochondrial hyperfusion has been linked to increased survival and apoptosis resistance (32).

Mitochondrial fission is induced by more prolonged stress and mitochondrial dysfunction. Fission is mediated by the cytosolic dynamin, Drp1, recruited to the fission sites by mitochondrial dynamics factors 49 and 51 or mitochondrial fission factor 1 (33). The fission sites are determined by sites where ER tubules interact with mitochondria in a process termed "ER-associated mitochondrial division" (40). Drp1 forms spiral structures around the mitochondrion, which constricts to split the inner and outer membranes (41). Segregation of mitochondria is required not only for cell division, but also for degradation of damaged mitochondria and induction of apoptosis (11, 30, 33). Loss of ΔΨm leads to Opal1 cleavage into small and inactive isoforms by the metalloprotease, overlapping activity with m-ATPas es associated with diverse cellular activities protease 1 (Oma1), halting fusion and allowing the defective mitochondrion to be segregated from the network through fission to allow its efficient removal (36). Defective mitochondria are removed by autophagic degradation, a process termed "mitophagy." Mitophagy is activated by prolonged reduction in ΔΨm which triggers the recruitment of the serine/threonine kinase, phosphatase and tensin homolog–induced putative kinase 1 (PINK1), from the intermembrane space to the surface of the mitochondria, where it recruits the E3 ubiquitin ligase, Parkin. Parkin ubiquititates outer membrane proteins, including Mfn-1 and Mfn-2, leading to inhibition of mitochondrial fusion and initiating the formation of autophagosomes, which are degraded by fusing with lysosomes (36, 42, 43). Another aspect of the dynamic nature of mitochondria is their ability to move across the cell, along microtubules, to interact with other organelles. This process is facilitated by the outer membrane–localized guanosine triphosphatases (GTPas), mitochondrial Rho GTPase 1 and mitochondrial Rho GTPase 2, which interact with the kinesin and dynein motor proteins via adaptor proteins to transport mitochondria toward the cell membrane or the nucleus (44). Perinuclear clustering of mitochondria plays a key role in hypoxia-inducible factor (HIF)-1α–mediated gene activation, and thus to adaptive responses to hypoxia (45). Acute exposure of alveolar epithelial cells to nontoxic concentrations of CS extract induces elongation and fusion of mitochondria, which appears to be protective, as these cells show increased oxygen consumption and ΔΨm and low mitochondrial ROS levels, suggesting increased mitochondrial respiration efficiency (46). Prolonged exposure (6 mo) of bronchial epithelial cells to CS extract, however, leads to swollen mitochondria with poorly defined cristae, which show both branching and fragmentation. Intriguingly, all these structural changes, apart from fragmentation, persisted after withdrawal of CS extract, indicating that mitochondrial hyperfusion may be a maladaptive mechanism triggered by chronic CS exposure (5). Importantly, a similar morphology, which is characteristic of aging mitochondria (47), was also observed in bronchial epithelial cells of ex-smoking patients with COPD (5). Prohibitin 1, an inner-membrane scaffolding protein that is important in the proteolytic processing of Opal1, was found to be reduced in COPD lungs, suggesting a possible mechanism underlying the impaired morphology and cristae formation (48). A different study in bronchial epithelial cells from patients with COPD reported swollen and cristae-depleted mitochondria, which, however, showed a fragmented morphology (4). The discrepancy in the morphology reported by these studies may be due to differences in cell culturing conditions. Studies of mitochondrial morphology in lung tissue from patients with COPD would therefore be of value.

The hyperfused mitochondrial morphology is a key feature of cells undergoing senescence, and has been attributed to loss of Drp1 activity or fission...
factor 1 expression (49, 50). Induction of mitochondrial fragmentation by Opa1 knockdown protects HeLa cells from cellular senescence, indicating that fusion/fission imbalance is an important driver of senescence (51). Although studies in epithelial cells have reported changes in fusion/fission protein expression (5, 46) and localization in response to CS exposure (4), no differences have been reported in cells of COPD. Furthermore, the mechanisms linking deregulated mitochondrial morphology and function with cellular dysfunction in COPD are unclear.

The presence of elongated and dysfunctional mitochondria in close proximity to the nuclei of lung fibroblasts exposed to CS extract may provide an important link between mitochondrial dysfunction and cellular senescence (3). Prolonged perinuclear accumulation of damaged mitochondria, which could be a result of impaired mitochondrial mobility mechanisms (52) or prolonged exposure to hypoxic conditions (45), is likely to lead to direct ROS-induced DNA damage (3) or to induce epigenetic modifications in the nucleus (53), ultimately leading to the cellular senescence seen in COPD.

Mitochondrial dysfunction in COPD epithelium may be precipitated by deregulated quality control. Hyperfused mitochondria are spared from mitophagic degradation, possibly due to their large size (54). Indeed, elongated and fused mitochondria were associated with impaired mitophagy, due to suppressed mitochondrial translocation of Parkin-1 by p53, in the lungs of cigarette-exposed mice and of healthy smokers and patients with COPD. Impaired mitophagy was shown to contribute to the development of epithelial cell and fibroblast senescence and emphysema in CS-exposed mice (3). Reduced Parkin expression has also been linked to defective mitophagy in lung tissue from patients with COPD (6). In contrast, another study reported swollen, but increasingly fragmented, mitochondria associated with PINK1-dependent mitophagy in pulmonary epithelial cells exposed to CS extract. The same study reported increased Drp1 and PINK1 in COPD, and demonstrated a role of mitophagy amplifying the mitochondrial damage and contributing to necroptosis of lung epithelial cells and the development of emphysema in a CS-induced mouse model (7). The discrepancy in the findings regarding mitochondrial dynamics and quality in in vitro and in vivo model control may stem from differences in experimental conditions, such as the levels of CS used. A more in-depth study of mechanisms of mitochondrial morphology and mitophagy in cells and lung tissue from patients with COPD is required to understand how these mechanisms are deregulated in disease.

Mitochondrial dysfunction and ER stress are evident in the lungs in response to aging and CS exposure (55, 56). Under conditions of ER stress, ER–mitochondrial coupling is facilitated by Mfn-2 (57). ER stress was shown to contribute to mitochondrial fusion and impaired mitophagy, leading to mitochondrial dysfunction in alveolar epithelial type II cells from aged mice (55). The mechanisms underlying ER-mediated mitochondrial dysfunction are unclear; however, increased Ca\(^{2+}\) flux may play a role. These findings highlight the importance of investigating mitochondria–ER cross-talk as a possible mechanism of defective metabolic function in COPD.

**Post-Translational Modification of Mitochondrial Proteins: Sirtuins**

A large proportion of mitochondrial proteins are acetylated, including TCA cycle enzymes and proteins involved in fatty acid, carbohydrate, amino acid, and nucleotide metabolism (58). Protein acetylation acts as a metabolic sensor, detecting acute changes in the cellular bioenergetic status and translating them into adaptive changes in mitochondrial function (31). Acetyl-CoA, produced from glucose or fatty acid oxidation, mediates mitochondrial protein acetylation, whereas, conversely, NAD\(^{+}\), accumulating in conditions of reduced energy, is required as a cofactor for the NAD\(^{+}\)-dependent lysine deacetylases, sirtuins. Sirtuins orchestrate stress responses, maintenance of metabolic homeostasis, and antiaging effects (59). Sirtuin (Sirt) 3 is the predominant deacetylase in the mitochondria, where it prevents hyperacetylation of ETC complexes I, II, and V, maintaining OXPHOS and ATP production (60–63). Under conditions of oxidative stress, Sirt3 triggers an adaptive response by driving mitochondrial fusion through deacetylation of Opal1 (64) and mtDNA repair by increasing the stability of the mtDNA repair enzyme, 8-oxoguanine-DNA glycosylase 1 (65). Sirt3 also enhances mitochondrial respiration under conditions of metabolic stress by promoting FAO through activation of long-chain acyl-CoA dehydrogenase (66) and glutaminolysis by glutamate dehydrogenase activation (67). Sirt3 also promotes mitochondrial redox balance by contributing to the regeneration of reduced glutathione by promoting NADPH production (68) and activation of Mn superoxide dismutase (69).

Reduced Sirt3 expression has been reported in the lungs of aged mice and in an elastase-induced mouse model of emphysema (70). Sirt3-deficient mice have been shown to demonstrate exaggerated bleomycin-dependent pulmonary fibrosis, inflammation, and mucus production (70–72). Moreover, transforming growth factor-β, a major driver of COPD pathology, inhibits Sirt3 expression in lung fibroblasts, leading to oxidative stress, mtDNA damage, and myofibroblast differentiation (70–72). Thus, defective mitochondrial sirtuin function and deregulated mitochondrial protein acetylation could be key contributors to poor metabolic adaptation to stress and susceptibility to premature aging and COPD, and merit further study.

**Metabolic Reprogramming**

The communication between the mitochondrion and nucleus allows the sensing and transmission of metabolic signals, in the form of altered metabolic intermediates, to reprogram metabolic gene expression and induce adaptive metabolic and redox changes.

The two key molecular sensors for metabolic adaptation are AMP-activated protein kinase (AMPK) and the sirtuin, Sirt1 (30). AMPK is activated by increased AMP:ATP ratio and increased ADP levels resulting from ATP depletion (73), and also by oxidative stress (74) and mitochondrial ROS due to mitochondrial dysfunction (75, 76). Activation of AMPK leads to inhibition of biosynthetic processes and activation of catabolic metabolism to increase energy production (29). AMPK increases mitochondrial biogenesis through PGC-1α activation (30). At the same time, it promotes production of acetyl-CoA required for mitochondrial respiration by activating FAO via PGC-1α activation, and glycolysis through phosphofructokinase-2 and hexokinase activation (74, 77). Inhibition of the
mechanistic target of rapamycin (mTOR) pathway by AMPK also ensures the availability of nutrients and respiration substrates by increasing mitophagy (78). Moreover, AMPK-dependent activation of the cytoprotective transcription factors, nuclear factor E2–related factor 2 and Forkhead box O3 (FoxO3), leads to increased antioxidant gene expression (79, 80), whereas induction of PPP activity provides NADPH required for redox balance (81). AMPK-mediated NAD⁺ levels activate Sir1, which induces PGC-1α and FoxO3 activity through deacetylation, to promote catabolic metabolism, ATP production, and antioxidant protection (82).

HIF-1 is another important molecular sensor that mediates adaptive metabolic changes in response to hypoxic conditions (83). Hypoxic cells show an HIF–1-dependent up-regulation of PDH kinase 1 that diverts pyruvate away from mitochondrial respiration and toward glycolysis (84). At the same time, increased expression of glucose transporters and glycolytic enzymes ensure a shift from OXPHOS to glycolysis and the PPP, maintaining ATP production and low ROS levels under hypoxic conditions (83, 85). This switch would lead to reduced flow of acetyl-CoA into the TCA cycle and fatty acid synthesis. Increased glutaminolysis, in response to HIF-1 activation, provides α-ketoglutarate for the TCA cycle and, consequently, citrate for fatty acid synthesis (85, 86).

A reduction in glycolytic flux in type II alveolar epithelial cells of mice exposed to CS for 4–8 weeks is accompanied by increased ETC complex protein activity and FAO (87). At the same time, induction of PPP activity provides NADPH for maintaining redox balance (87). These metabolic changes are reversed upon cessation of CS exposure (87, 88). A more recent study by Cloonan and colleagues (24) also demonstrates that CS-induced OXPHOS impairment in mice is accompanied by a shift toward glycolysis. Thus, CS-mediated stress triggers adaptive changes that allow increased mitochondrial efficiency and activation of alternative pathways to preserve energy and antioxidant levels, and thus cell survival. AMPK activation may facilitate these processes (89). Indeed, AMPK activation has been reported in human bronchial epithelial cells and macrophages, and mouse lungs after CS exposure, in a ROS-dependent manner (90, 91). Nonetheless, the involvement of AMPK in metabolic regulation was not investigated in those studies.

Metabolic analysis of basal cells from long-term smokers reveals reduced acetyl-CoA levels, reflecting defective glycolysis and/or FAO, and a deficit in succinate, NADH, and FADH₂, indicative of reduced TCA cycle activity (92). Moreover, in a model of elastase-induced emphysema, which simulates progressive disease, alveolar epithelial cell senescence and apoptosis were accompanied by a reduction in L-carnitine levels, possibly reflecting impaired FAO. L-carnitine supplementation reduced alveolar epithelial apoptosis and protected from emphysema development (93). This suggests that prolonged exposure to oxidative stress may lead to loss of metabolic flexibility in epithelial cells, rendering them unable to respond to the bioenergetic demands of stress, and thus leading to senescence, apoptosis, and impaired regenerative capacity in the COPD epithelium (94–96). This effect may be a result of deregulated nutrient sensing. Sir1 (97, 98) and FoxO3 (90, 99, 100) are reduced in the lungs of patients with COPD as a result of chronic exposure to CS, suggesting an impairment of the AMPK–Sir1–FoxO axis, with potentially detrimental effects on the ability of the cells to reprogram their metabolism and respond to stress. A number of studies have demonstrated a protective role for these pathways against the development of emphysema and inflammation in mouse models of COPD (76, 89, 97–99); however, their role in metabolic function in the lungs is still elusive. Conversely, prolonged activation of adaptive mechanisms could also drive pathogenic processes. CS-induced up-regulation of FAO, via a family with sequence similarity 13 member A (FAM13A)/Sir1–dependent pathway, was shown to promote lung epithelial cell apoptosis through increased ROS production (101). AMPK has been shown to promote inflammation through NF-κB activation in CS-exposed mice and human macrophages (89–91), and to induce cell senescence (102, 103).

On the other hand, extensive metabolic reprogramming resulting from overadaptation to hypoxia, exposure to inflammatory mediators, or disease-specific differences in metabolic regulation may also lead to aberrant cellular function. In cancer and pulmonary hypertension, a shift from OXPHOS to the use of glycolysis and glutaminolysis as energy sources leads to the production of intermediates for synthesis of lipids, amino acids, nucleotides, and antioxidants required for maintaining proliferation and survival (104, 105). We have demonstrated mitochondrial dysfunction and impaired OXPHOS in ASMCs from patients with COPD (8). Preliminary data in our laboratory suggest that COPD ASMCs do not show senescence, but, rather, increased proliferation in response to growth factors (unpublished data), suggesting that a similar maladaptive metabolic reprogramming may contribute to ASMC hyperplasia. Moreover, increased glycolysis in response to HIF-1 activation drives myofibroblast differentiation and contractility in lung fibrosis (106, 107). Recent studies have demonstrated an integral role of metabolic reprogramming in T cell activation (108) and macrophage phenotype switching (109). Metabolic reprogramming may, therefore, provide another level of regulation of airway inflammation and remodeling in COPD.

Concluding Remarks and Future Directions

Cells respond to stress and mitochondrial dysfunction through immediate changes in their morphology and localization, but also through post-translational modifications of nuclear and mitochondrial proteins and transcriptional changes leading to metabolic reprogramming. These responses are now recognized to be integrally linked and regulated in a coordinated manner (110, 111). Defective metabolic adaptation leads to increased susceptibility to mitochondrial damage in COPD, and may be associated with accelerated aging and disease pathogenesis. Detailed studies on the regulation of mitochondrial dynamics and movement, mitochondrial–ER cross-talk, as well as the mitochondrial proteome and metabolome in cells and lung tissue of COPD will allow us to gain a more complete picture of metabolic adaptation in COPD. This will allow the identification of molecular targets for protecting mitochondria in disease.

Author disclosures are available with the text of this article at www.atsjournals.org.
References


