

Mitochondrial Function in Allergic Disease

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Abstract

Purpose of the Review The connections between allergy, asthma and metabolic syndrome are becoming increasingly clear. Recent research suggests a unifying mitochondrial link between the diverse phenotypes of these interlinked morbidities. The scope of this review is to highlight cellular mechanisms, epidemiology and environmental allergens influencing mitochondrial function and its importance in allergy and asthma. We briefly also consider the potential of mitochondria-targeted therapies in prevention and cure.

Recent Findings Recent research has shown allergy, asthma and metabolic syndrome to be linked to mitochondrial dysfunction. Environmental pollutants and allergens are observed to cause mitochondrial dysfunction, primarily by inducing oxidative stress and ROS production. Malfunctioning mitochondria change the bioenergetics of the cell and its metabolic profile to favour systemic inflammation, which drives all three types of morbidities.

Summary Given the existing experimental evidence, approaches targeting mitochondria (e.g. antioxidant therapy and mitochondrial replacement) are being conducted in relevant disease models—with some progressing towards clinical trials, making mitochondrial function the focus of translational

therapy research in asthma, allergy and linked metabolic syndrome.

Keywords Asthma · Metabolic syndrome · Allergy · Mitochondrial dysfunction · Systemic inflammation · Air pollution · Mitochondrial transfer therapy

Abbreviations

<i>AIM2</i>	Absent in melanoma 2
<i>BAL</i>	Bronchoalveolar lavage
<i>Drp1</i>	Dynamin 1 like protein
<i>ETC</i>	Electron transport chain
<i>IFN</i>	Interferon Gamma
<i>IgE</i>	Immunoglobulin E
<i>IL</i>	Interleukin
<i>KDa</i>	Kilodalton
<i>NLRP3</i>	Nod Like receptor family pyrin domain containing 3
<i>Opa1</i>	Optic Atrophy 1
<i>PGC</i>	Peroxisome proliferator-activated receptor gamma
<i>Iα</i>	coactivator 1 alpha
<i>ROS</i>	Reactive oxygen species
<i>TET</i>	Ten-eleven translocation
<i>TFAM</i>	Transcription Factor A Mitochondrial
<i>Th2</i>	T helper cells type 2
<i>TNFα</i>	Tumour Necrosis Factor Alpha

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Introduction

Asthma and allergies have been on a rapid rise in the recent past. This rise has been observed in an age-, culture- and geography-independent manner, suggesting greater influence of environmental factors over genetic components [1]. Asthma has also become linked with comorbidities like

obesity, cardiovascular abnormality and symptoms classified as the ‘metabolic syndrome’ [2–4]. It is being increasingly found that metabolic syndrome (MetS) and asthma are interlinked by systemic inflammation and share common mechanisms, such that factors potentiating one increases the propensity for the other.

Interestingly, the incidence of MetS and asthma shows a bias in socioeconomic strata, with the affluent classes generally bearing greater risk [5]. Therefore, sedentary lifestyle habits along with unrestricted access to food have been considered central [6•]; as has the ‘hygiene hypothesis’ which puts forth limited exposure to pathogens during early developmental stages, as the cause of reduced immune tolerance [7]. The loss of tolerance promotes Th2-type inflammatory responses that have been observed to drive allergies; asthma; airway hyperresponsiveness and, more recently, MetS [8]. Another factor seems to be the concomitant increase in the levels and persistence of air pollutants, also directly impacted by anthropogenic activities [9•]. A central hypothesis connecting pollution, microbial triggers, inflammatory predisposition, allergies, asthma and metabolic disease is beginning to emerge, with mitochondria as the nexus. This review examines how mitochondria critically modulate immune response and cites recent studies connecting mitochondrial dysfunction and allergic diseases, particularly asthma, additionally bringing out the connection with metabolic disorders as would be expected in a mitochondria-centric pathology. We also take this opportunity to bring out the important causal role of air pollution, acting via mitochondrial dysfunction. The potential of mitochondria-targeted therapies as the new age approach in prevention and cure is touched upon.

Mitochondria and MitoDAMPs: Environmental Stress Sensors and Immunity Modulators

The endosymbiotic evolution and prokaryotic characteristics of the mitochondria uniquely enable them to serve as sensors of environmental threats/stress to the cell. Being semiautonomous and regulating their machinery via an independently replicating and transcribing DNA, the mitochondria code for unique constituents making up their structure. For example, mitochondrial DNA (mtDNA) and n-formyl peptides are very akin to their prokaryotic counterparts in having unmethylated CpG motifs and n-formyl methionine respectively [10, 11]. Further, Cardiolipin, a phospholipid present in the inner mitochondrial membrane, is distinct from eukaryotic membrane lipid composition [12]. Consequently, by the simple mechanism of the necrosis of stressed cells in an organ, the released mitochondrial constituents act as effective extracellular ‘damage-associated molecular patterns (DAMPs)’ and trigger immune response by associating with receptors reserved for intercepting pathogen-associated molecular patterns

(PAMPs) [13, 14]. Upon binding, the Toll-like receptors (TLRs) and Nod-like receptors (NLRs) trigger signalling cascades that modulate immune responses, depending on the type of cells getting activated [15, 16]. As detailed below, most experimental evidence points towards a proinflammatory effect of mitoDAMPs on the immune system, achieving distant organ effects and causing tissue damage.

Interestingly, intracellular release of DAMPs into the cytosol also elicits signalling responsive to environmental stress and insults. The mitochondria house the electron transport chain and Krebs cycle activity, giving their matrix a high concentration of metabolic enzymes like aconitase, metabolites like citrate, ATP and succinate, redox proteins, electron donors/acceptors and free radical species—as compared to the cytosol and other organelles. Therefore, mitochondrial damage/dysfunction can modulate the concentration and activity of these entities, enabling a switch in metabolism—primarily between carbohydrate and fat [6•]. Thus, as a response to environmental factors, the mitochondria can elicit a switch in metabolism and/or mount proinflammatory immune response.

ATP Extracellular ATP is demonstrated to be perhaps the most direct and damaging of mtDAMPs with autocrine and paracrine effects in the cellular milieu. The BAL fluids of patients with respiratory diseases and smoking habits show high levels of ATP [17, 18].

Increased ATP levels correlated with decreased lung function, increased neutrophil infiltration of the lung and tissue injury [18]. Fungal spore extracts are shown to increase the extracellular levels of ATP, leading to the establishment of IL-33-mediated Th2 inflammation [19]. Extracellular ATP performs certain physiological functions, and its efflux concentration is determined by ecto-ATP/ADPases [20]. However, damaged cells can also secrete ATP [21, 22], where it leads to activation of inflammatory cells, which further secrete ATP, leading to a loop of autocrine and paracrine effects that potentiate inflammation [17, 23].

mtDNA Upon release and extracellular localisation, mtDNA interacts with TLR 9 receptors (recognising unmethylated CpGs) on neutrophils, monocytes, macrophages and vascular endothelial cells [14, 24], leading to organ infiltration by promoting chemotaxis, increasing proinflammatory cytokine production and upregulating surface adhesion molecules through the MyD88 pathway [25]. Intracellularly, mtDNA is shown to activate the NLRP3- and AIM2-dependent inflammasome [26, 27]. These findings assume importance in the face of environmental pollutants that cause mitochondrial stress, induction of ROS, promote mitochondrial membrane transition pores or affect mitochondrial biogenesis, wherein a cluster of cells facing environmental insults can not only remotely trigger proinflammatory action and tissue injury but can also

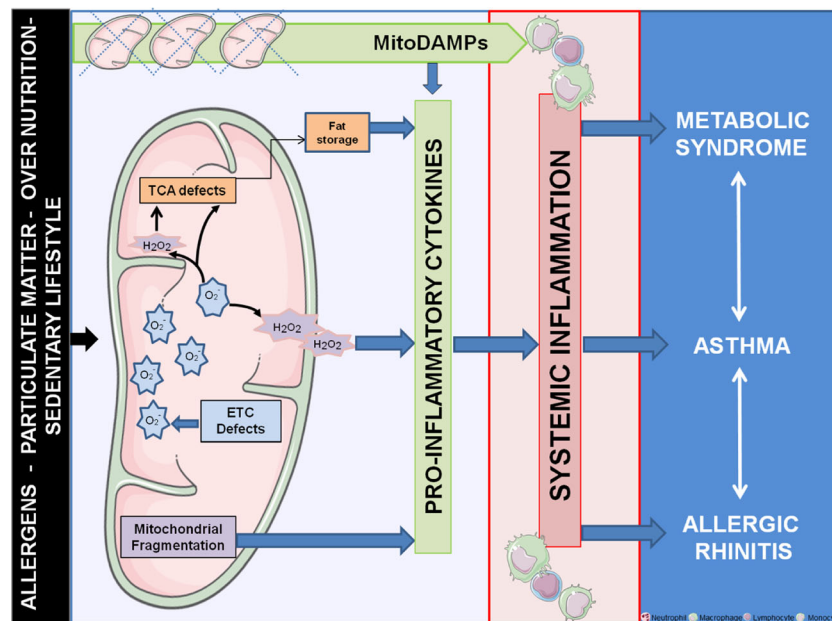


Fig. 1 A schematic overview of the convergence of environmental influences on mitochondrial dysfunction linking and potentiating metabolic syndrome, asthma and allergic rhinitis. Common allergens, airborne particulate matter, over nutrition and sedentary lifestyle cause mitochondrial dysfunction via ETC stress and oxidative damage. Resulting ROS production causes TCA defects, increased fat storage, mitochondrial fission or fragmentation and production of MitoDAMPs.

These outcomes can individually or collectively elicit proinflammatory cytokine upregulation and systemic inflammation that drive the changes in allergic rhinitis, metabolic syndrome and asthma establishing their bidirectional coexistence. *ETC* electron transport chain, *ROS* reactive oxygen species, O_2^- superoxide, H_2O_2 hydrogen peroxide, *TCA* tricarboxylic acid cycle

activate inflammatory pathways in the immune cells themselves, thereby exacerbating proinflammatory action at the organ site.

Succinate Extracellular succinate rises when the integrity of cytochrome B and C1 of the electron transport chain is compromised, either by inhibitors or by metabolic reprogramming [28]. Within the cell, succinate causes increased Ca^{2+} mobilization, promoting migration in immune cells [29]. Succinate has been shown to synergise with TLR agonists, leading to a proinflammatory $TNF\alpha$ and $IFN\gamma$ cascade [30].

Cardiolipin Cardiolipin, present in the mitochondrial inner membrane, is required for the protection and optimal functioning of the mitochondrial ETC [12]. Therefore, any deregulation in cardiolipin level potentiates mitochondrial dysfunction. It has been observed that cardiolipin is released into extracellular space following acute lung infections and injury, increasing the alveolar surfactant levels beyond the average 1–2% [31, 32]. External cardiolipin can be internalised via PAMP receptors, and within the cell, it promotes proinflammatory cytokine production by directly binding to NLRP3 [33]. It has also been observed to suppress anti-inflammatory signalling by inhibiting the production of IL-10 [34]. Therefore, cardiolipin release can lead to a persistent inflammatory

environment, conducive for the development of allergies, asthma and MetS.

N-Formyl Peptides N-formyl peptides (NFPs) derived from mitochondrial proteins are recognised by the formyl peptide receptors 1–3 present on immune cells and endothelial cells, leading to their activation [35]. High levels of ROS are generated in target cells upon binding of NFPs [36]. Further, these peptides have been shown to synergise with mtDNA to elicit the production of IL-8, which serves as a chemoattractant [14, 37].

Reactive Oxygen Species (ROS): The flux of high-energy electrons through the mitochondrial ETC, predisposes them to generate ROS, which is minimised by the high concentrations of antioxidants that neutralises ROS formed by leaks from the ETC. Mitochondria do release ROS in a controlled fashion during health, which seems to be necessary for optimal functioning [6•]. During stress or mitochondrial damage, mitochondrial ROS can increase manifold, setting into motion a cascade of signalling events that promote inflammation and lead to a switch in mitochondrial metabolism, as discussed elsewhere [6•, 13]. The critical role of mtROS in cellular fate and the tendency of damaged mitochondria to leak ROS are managed by a highly conserved program of mitochondrial dynamics and mitophagy, where damaged mitochondria that are releasing excessive ROS are selectively eliminated.

Disturbances in mitochondrial dynamics or mitophagy can thus lead to abnormal release of mtROS and consequent inflammation.

Mitochondrial Dysfunction and Allergy

As discussed in the preceding section, mitochondria are critical regulators of the immune response. Mitochondrial dysfunction and elevated ROS have been noted in a variety of allergic diseases including atopy, atopic dermatitis, allergic rhinitis and asthma [38•, 39–42]. Here, we will focus on allergic rhinitis and asthma, which are better studied in this context. Importantly, the connection between asthma and mitochondria transcends the allergic inflammatory pathways and is part of a broader metabolic phenotype. Whether the same is true for all allergies or allergic rhinitis is less clear, since the associations with obesity are much weaker [43].

Allergic rhinitis is an inflammatory condition of the upper respiratory tract, including the nasal passages, while asthma involves lower respiratory tract inflammation. Approximately 38% of patients with allergic rhinitis have or will develop concomitant asthma [44]. However, the two can be distinct and subtypes of asthma, especially those associated with obesity or metabolic dysfunction, may not exhibit allergic features. Global metabolic changes have been associated with both allergic rhinitis and asthma, despite their limited anatomical clinical presentation.

A recent report indicates that allergic rhinitis causes systemic metabolic changes in peripheral blood mononuclear cells (PBMCs). In a study of 11 patients with history of grass pollen allergy, a primary sensitisation dose of pollen through nasal spray was given, followed by a secondary challenge after 4 weeks. The PBMCs were then isolated and the maximal respiratory rate of the ETC was determined by high-resolution respirometry. It was found that the maximal respiratory rate was lowered by 50% in subjects receiving the secondary pollen challenge, as compared to the placebo, 6 h after sensitisation. The respiration rate was however restored 24 h after the challenge. The authors point to previous studies that report the acute phase of the nasal immune response to last 3–24 h after challenge, with the 6 h time point marking the peak of immune response activity [45•]. This is one of the first links between pollen allergy and systemic inflammation that involve mitochondrial dysfunction. House dust mite allergen (HDM) was previously known to cause inflammation in airway epithelial cells, via the endoplasmic reticulum stress response. Using human bronchial epithelial cells and HDM treatment, a study reports increased contacts of stressed endoplasmic reticulum with the mitochondria, leading to the assembly of DRP1 (mitochondrial fission protein) at points of contact, resulting in mitochondrial fragmentation. Production

of the proinflammatory cytokines IL-8 and IL-1 β , were events downstream to mitochondrial fragmentation [46].

In experimental models, it has been shown that the allergic response to ragweed allergen is enhanced in mice that have pre-existing defects in the mitochondrial ETC [38•]. Such mice had greater IgE response with increased airway remodelling and hyperresponsiveness. The mechanistic connections between allergens and mitochondrial dysfunction may take one or more of many parallel paths [47]. Pollens and other natural allergens are a complex mixture of proteases, antigens, lipids and oxidases. Proteases can not only damage cell junctions, increasing allergen penetration to dendritic cells, but also induce protease-activated receptor (PAR) signalling in epithelial cells [47]. Increased release of ROS by oxidases or mitochondria forms an important second hit, during this cascade, which is critical for sustained immune response. Release of proinflammatory mtDAMPs via cell injury, immune cell activation or even via exogenous modulators such as air pollution influences this process, as discussed previously.

Mitochondrial Dysfunction in Asthma and Connection to Metabolic Syndrome

Mechanistic aspects of the link between mitochondrial dysfunction and asthma are well reported by others and us. Importantly, bizarre dysfunctional mitochondria are a histological feature of airway epithelium from asthma patients; pre-existing mitochondrial dysfunction leads to a stronger asthma phenotype in experimental models (as discussed above) and mitochondrial-targeted therapies show efficacy in models of asthma. The association appears fundamental and beyond the allergic process. Epidemiologic data strongly connects MetS, which is strongly associated with systemic mitochondrial dysfunction at a molecular level, with asthma [2]. While asthma-like changes in lungs can occur independent of any allergy [48], there is also a synergistic convergence between allergic inflammation and metabolic stress, at the level of mitochondria. In particular, arginine metabolism seems to be tightly interconnected between allergic and metabolic processes, in the context of mitochondrial function. Asymmetric dimethyl arginine (ADMA), an endogenous uncoupler of nitric oxide synthase, has been associated strongly with MetS as well as asthma, especially obese-asthma. IL-4, the prototypical allergic cytokine, modulates ADMA metabolism such that ADMA synthesis is increased and degradation decreased. Synergistic action of IL-4 and ADMA potently induces reduction in mitochondrial numbers and increase in mtROS via the cellular hypoxic response and consequent downregulation of TFAM and PGC 1 α [41]. Such changes in mitochondrial function are already well known in insulin resistance, diabetes and MetS.

It is to be noted that aberrations in a mitochondrial bioenergetic within a normal cell can be easily buffered by the presence of high mitochondrial number. It is therefore interesting and significant that existing literature cumulatively indicates reduction in mitochondrial biogenesis and the persistence of stressed mitochondria within the cell, leading to defects due to oxidative stress and propagation of asthma/MetS. While environmental stressors such as allergens, cigarette smoke or air pollutants are important modulators of mitochondrial function in allergy or asthma, at least some of the risk appears to be inherited. Mitochondrial haplogroup U and polymorphisms in mitochondrially encoded genes have been associated with increased IgE or asthma, as reported previously [49].

Air-Borne Particulate Matter as a Trigger of Mitochondrial Dysfunction and Implications for Metabolic and Allergic Diseases

Air pollution, especially exposure to airborne particulate matter (PM), has been linked to multiple diseases including allergies [50], asthma and cardiometabolic syndromes. There are several pathways, which connect airborne PM exposure to mitochondrial dysfunction, potentially culminating in increased risk for these disorders. Given the increasing global threat of air pollution and the likely consequences to human health, we discuss the mechanisms in greater detail.

The Effect of PM on Mitochondrial Dynamics

In a study assessing the impact of fine particulate matter below 2.5 μm in diameter (PM 2.5), PM2.5-exposed rat lung injury was found to be associated with mitochondrial fusion-fission dysfunction, ROS generation, mitochondrial lipid peroxidation and cellular homeostasis imbalance, leading to disruption of mitochondrial dynamics [51•]. Mitochondrial fission and fusion are crucial for the maintenance of metabolic efficiency and mitochondrial quality control. Under conditions of cytosolic stress, which often results in oxidative damage to the mitochondrial membrane through lipid peroxidation or the oxidation of mitochondrial proteins, smaller, damaged mitochondria fuse together to preserve metabolic efficiency. These larger hypertrophied mitochondria are characteristic of high cytosolic stress and oxidative damage. Mitochondrial fission serves as a mechanism for removal of damaged components of the organelle through autophagy. PM 2.5 influences the expression of dynamin-related proteins such as Opa1 in mammals, required for inner membrane fusion, and Drp1 in mammals that assemble on the mitochondrial surface to mediate mitochondrial fission [52, 53]. Since increased rates of mitochondrial fission and fusion are part of the conserved mitochondrial response to stress, PM 2.5-mediated disruption of

mitochondrial dynamics is expected to accelerate irreversible mitochondrial dysfunction.

PM-Mediated Damage to Mitochondrial DNA

That mitochondrial DNA is susceptible to oxidative damage due to oxidative stress has been well documented. Located in the mitochondrial matrix, near the inner mitochondrial membrane where both ATP and free radicals are produced, it is prone to mutations in the absence of DNA repair mechanisms and the protection offered by histone molecules. The mitochondrial genome encodes 37 genes that are mostly related to the electron transport chain and plays a pivotal role in the synthesis of mitochondrial proteins, and its preservation would have a direct effect on the overall efficiency of oxidative phosphorylation. Mutations in mtDNA therefore result in a loss of encoded respiratory chain subunits and an overall reduction in the efficiency of ATP synthesis, the earliest indicators of metabolic dysfunction [54]. Evidence of PM-associated increase in mitochondrial oxidative DNA damage during pregnancy in both mothers and their newborns was observed in a study assessing the effect of particulate air pollution exposure in early life with 9-OHdG levels as a biomarker for oxidative stress [55•]. Effects of air pollution on mtDNA damage, including copy number variation, 8-hydroxy-2'-deoxyguanosine (8-OHdG) formation and heteroplasmy in 'complex' mitochondrial diseases, have been reported in human and animal studies [56].

PM-Induced Changes in Mitochondrial Membrane Potential

While the inner membrane is impermeable to protons to maintain the necessary H^+ gradient, the inner membrane in unhealthy cells becomes permeable to solutes less than 1.5 kDa. This leads to permeability transition and significantly reduces the potential difference across the membrane, culminating in opening of the permeability transition pore complex [57•]. Diesel exhaust particles are strongly implicated in triggering the mitochondrial apoptotic pathway through increased ROS production and an overall disruption of mitochondrial function, via a sequence of events that commence with change in the mitochondrial membrane potential, followed by cytochrome c release and subsequent development of membrane asymmetry [58]. A study assessing the effect of cadmium on MRC 5 foetal lung fibroblasts found that cadmium-induced oxidative stress led to peroxidation of lipids, DNA damage and protein oxidation. Further, in mouse and rat liver cells, subcutaneous administration of cadmium led to cadmium intoxication for 4–8 h and caused sustained lipid peroxidation [59]. Lipid peroxidation is known to cross-link and polymerise membrane components resulting in modification of membrane lipids and altered membrane activity such as release of

mitochondrial calcium. The released Ca^{2+} can potentiate ROS formation, which in turn leads to production of oxidised lipids and cross-linked proteins, culminating in membrane permeability [60–63]. As cadmium is seen to induce a 12.5-fold increase of Ca^{2+} after 2 h of intoxication in osteosarcoma cells, cadmium intoxication may be involved in mitochondrial membrane transition via lipid peroxidation and calcium release [64].

PM 2.5-Mediated Ubiquitin-Proteasome System Inhibition

The ubiquitin proteasome system (UPS) is a mechanism to eliminate surplus or dysfunctional mitochondrial proteins, or whole damaged organelles that can negatively influence cellular homeostasis, and functions mainly by eliminating misfolded or damaged proteins. Damaged/misfolded proteins are selectively polyubiquitinated, recognised and then degraded by proteasomes. The initial impairment of the UPS implicated in the generation of ROS, occurs in the mitochondria through proteasome inhibition [64–66]. Proteasomal activity is normally seen to decline with age as a result of decreased expression and oxidative modification of proteasomal proteins [50]. Exposure to air pollution toxicants too has been found to result in decreased proteasomal activity, directly resulting in oxidative stress [67]. Damage to the proteasome is known to result in the accumulation of oxidatively damaged polyubiquitinated proteins, which further inhibit proteasome function either by exceeding its binding capacity or by poisoning its catalytic properties. These findings are consistent with an increase in the level of oxidative stress following the inhalation of diesel exhaust particles or secondary organic aerosols. It remains unclear, however, whether the role of UPS inhibition is pathological, homeostatic or merely a marker of exposure.

Mitochondrial Targeted Therapy in Allergy, Asthma and Metabolic Syndrome

It is being increasingly seen that the importance of the mitochondria lies beyond its canonical roles of ATP synthesis, apoptosis and stress signalling. A novel study reports the role of mitochondria in cytosolic protein homeostasis, wherein aggregated cytoplasmic proteins are imported into the mitochondria for degradation [68]. There are several reports that mitochondria can epigenetically regulate the nucleus both at the level of DNA and histones [69, 70]. While the exact cellular mechanism is not yet elucidated, the upregulation of TET proteins—the only known effectors of hydroxymethylation of cytosines in nuclear DNA—and the resulting epigenetic changes in the nuclear gene signature is documented under conditions of oxidative stress [71]. Similarly, ETC stress

induced in *C. elegans* upregulated *jmjd 1.2* and *jmjd 3.1* encoded lysine demethylases that act upon H3Kme2 and H3Kme3 modifications, leading to nuclear gene expression promoting longevity [69]. Therefore, a mitochondrial population which is intact and unharmed in all respects is critical to ensure a cell's healthy continual.

This understanding comes in the face of reports that show ambiguous results of antioxidant therapy. Intuitively, the administration of antioxidants in the case of MetS/asthma should have been effective, as these are mtROS disorders. However, administration of alpha tocopherol and vitamin C has not been successful [2, 72, 73]**. This is probably because the surge of mtROS is too high to be countered by antioxidants or that the oxidative damage sustained by mitochondria is too far gone to be helped by belated quenching of ROS. However, the mitochondrial antioxidant coenzyme Q10 and its derivative Mito Q are being looked upon as potential therapeutic molecules, after a study involving steroid-dependent asthma patients administered with a daily dose of coenzyme Q10, alpha tocopherol and vitamin C showed increased corticosteroid sensitivity [74]. It is important to note that untargeted quenching of ROS could achieve different results in different cells. While increased mtROS is harmful in airway smooth muscle cells and fibroblasts leading to mitochondrial dysfunction and asthma, fluctuating mtROS levels in homing immune cells, such as Tregs, promote fatty acid metabolism and consequent anti-inflammatory functions that should be left undisturbed [72]**. Therefore, cell type-specific ROS quenching is called for in this approach to therapy.

There are two emerging approaches with potential for therapy of metabolic disorders that are still in experimental stages. One of these is reduction of heteroplasmy or elimination of damaged mitochondria. MetS is characterised by SNPs in the mtDNA, which serve as points of difference from their normal counterpart and can be exploited. A proof of principle for this approach is obtained from experiments in heteroplasmic cybrids carrying G14459A LHON/dystonia mutation in the ND 6 gene. A mitoTALEN specific for this site was introduced into the cybrid population, leading to transient decrease of mutant mitochondria and repopulation with the wild type [75]. Similarly, NBZ/BalbC heteroplasmic mice were either injected or intravenously infused to specific organs, with vectors encoding the mitochondrially targeted Apal1 restriction enzyme, under tissue-specific promoters. This led to the successful elimination of the mitochondrial haplotype that contained the Apal1 site [76•, 77].

A simpler alternative is the transfer of mitochondria or healthy mitochondrial repopulation in stressed cells by 'donation' from surrounding cells. Studies indicate that mitochondrial exchange between cells might be a regular physiological phenomenon. Intercellular mitochondrial transfer occurs unidirectionally (mesenchymal stem cells (MSCs) → injured lung epithelia) and bidirectionally (fibroblast ↔ fibroblast,

MSCs $\leftrightarrow$ fibroblasts) in the cellular milieu [78–80]*. It is speculated that such transfers enhance the availability of functional mitochondria in cells, supplementing the relatively slower, multistage process of mitochondrial biogenesis [79]. Even cancer cells depend on functional mitochondria for growth potential. Indeed, T7 rho0s (cancerous T7 without mitochondrial DNA) show a time lag to tumour initiation in mice, forming observable tumours only after they have acquired mitochondria from the neighbouring untransformed cells [81]. Mitochondrial transfer occurs via vesicles or through extracellular membrane connections called tunnelling nanotubes (TNTs) that form a connecting tunnel between two communicating cells [82, 83]. TNTs have been shown to transport mitochondria between cells [84, 85]. The Rho GTPase Miro1 regulates transfer of mitochondria between MSCs and injured epithelial cells. Using a mouse model of allergic asthma, it was shown that the intratracheal administration of MSCs to injured airway epithelium led to the reversal of airway injury—by the repopulation of injured epithelial cells with healthy mitochondria donated by MSCs—and attenuation of allergic inflammation. This phenomenon was found to occur with higher efficiency in Miro1 overexpressing MSCs [86**].

The attraction of mitochondrial transfer therapy lies in its relative simplicity and inherent specificity. In our experiments, we find that the donor MSCs shrink or disappear completely after airway rehabilitation, possibly on account of robust donation of mitochondria to injured cells (unpublished). Further, TNT formation between MSCs and the injured epithelial cells is vastly more abundant compared to that of MSCs and other cells in the milieu, conferring specificity to the intervention.

Conclusions

Allergens and air pollutants cause mitochondrial dysfunction and mtROS-mediated systemic inflammation, which is crucial in the pathogenesis of allergy, asthma and MetS, individually. Research is increasingly providing evidence that inflammation during any one of these conditions can drive the pathogenesis of another, establishing a bidirectional cause-and-effect relationship, as illustrated in Fig. 1. With increased persistence of air pollutants and allergies, a common effective therapy for the comorbidities is needed. This now seems possible by targeting dysfunctional mitochondria in these disorders. While mitochondrial antioxidant coenzymes Q10 and Mito Q are an effort in that direction and have entered clinical trials, mitochondrial transfer therapy is potentially promising in skewing the cellular heteroplasmy in favour of healthy mitochondrial numbers and has met with success in many experimental animal models. Mitochondrial targeted therapy, therefore, merits greater research focus in mtROS-linked disorders.

Repair, reprogramming and replacement are the three axes around which clinical interventions could be designed [87**].

Compliance with Ethical Standards

Conflict of Interest Drs. Iyer, Mishra, and Agrawal declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Strachan DP. The role of environmental factors in asthma. *Br Med Bull.* 2000;56(4):865–82.
2. Agrawal A, Mabalirajan U, Ahmad T, Ghosh B. Emerging interface between metabolic syndrome and asthma. *Am J Respir Cell Mol Biol.* 2011;44(3):270–5. doi:10.1165/rcmb.2010-0141TR.
3. Kent BD, Lane SJ. Twin epidemics: asthma and obesity. *Int Arch Allergy Immunol.* 2012;157(3):213–4. doi:10.1159/000329874.
4. Perez MK, Piedimonte G. Metabolic asthma: is there a link between obesity, diabetes, and asthma? *Immunol Allergy Clin N Am.* 2014;34(4):777–84. doi:10.1016/j.iac.2014.07.002.
5. Tedeschi A, Airaghi L. Is affluence a risk factor for bronchial asthma and type 1 diabetes? *Pediatr Allergy Immunol.* 2006;17(7):533–7. doi:10.1111/j.1399-3038.2006.00445.x.
6. James AM, Collins Y, Logan A, Murphy MP. Mitochondrial oxidative stress and the metabolic syndrome. *Trends Endocrinol Metab.* 2012;23(9):429–34. doi:10.1016/j.tem.2012.06.008. **A detailed review on the biochemical mechanisms linking mitochondrial ROS, mitochondrial dysfunction, systemic inflammation and metabolic syndrome**
7. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med.* 2002;347(12):911–20. doi:10.1056/NEJMra020100.
8. Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis". *Thorax.* 2000;55(Suppl 1):S2–10.
9. Beggs PJ, Bambrick HJ. Is the global rise of asthma an early impact of anthropogenic climate change? *Environ Health Perspect.* 2005;113(8):915–9. **New insight into increased persistence of environmental allergens due to climate changes**
10. Hong EE, Okitsu CY, Smith AD, Hsieh CL. Regionally specific and genome-wide analyses conclusively demonstrate the absence of CpG methylation in human mitochondrial DNA. *Mol Cell Biol.* 2013;33(14):2683–90. doi:10.1128/MCB.00220-13.
11. Smith AE, Marcker KA. N-formylmethionyl transfer RNA in mitochondria from yeast and rat liver. *J Mol Biol.* 1968;38(2):241–3.
12. Daum G. Lipids of mitochondria. *Biochim Biophys Acta.* 1985;822(1):1–42.
13. Arnoult D, Soares F, Tattoli I, Girardin SE. Mitochondria in innate immunity. *EMBO Rep.* 2011;12(9):901–10. doi:10.1038/embor.2011.157.
14. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, et al. Circulating mitochondrial DAMPs cause inflammatory responses

- to injury. *Nature*. 2010;464(7285):104–7. doi:[10.1038/nature08780](https://doi.org/10.1038/nature08780).
15. Chen GY, Nunez G. Sterile inflammation: sensing and reacting to damage. *Nat Rev Immunol*. 2010;10(12):826–37. doi:[10.1038/nri2873](https://doi.org/10.1038/nri2873).
 16. Schwacha MG, Rani M, Zhang Q, Nunez-Cantu O, Cap AP. Mitochondrial damage-associated molecular patterns activate gamma delta T-cells. *Innate Immun*. 2014;20(3):261–8. doi:[10.1177/1753425913488969](https://doi.org/10.1177/1753425913488969).
 17. Idzko M, Hammad H, van Nimwegen M, Kool M, Willart MA, Muskens F, et al. Extracellular ATP triggers and maintains asthmatic airway inflammation by activating dendritic cells. *Nat Med*. 2007;13(8):913–9. doi:[10.1038/nm1617](https://doi.org/10.1038/nm1617).
 18. Lommatzsch M, Cicko S, Muller T, Lucattelli M, Bratke K, Stoll P, et al. Extracellular adenosine triphosphate and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2010;181(9):928–34. doi:[10.1164/rccm.200910-1506OC](https://doi.org/10.1164/rccm.200910-1506OC).
 19. Kouzaki H, Iijima K, Kobayashi T, O'Grady SM, Kita H. The danger signal, extracellular ATP, is a sensor for an airborne allergen and triggers IL-33 release and innate Th2-type responses. *J Immunol*. 2011;186(7):4375–87. doi:[10.4049/jimmunol.1003020](https://doi.org/10.4049/jimmunol.1003020).
 20. Lohman AW, Billaud M, Isakson BE. Mechanisms of ATP release and signalling in the blood vessel wall. *Cardiovasc Res*. 2012;95(3):269–80. doi:[10.1093/cvr/cvs187](https://doi.org/10.1093/cvr/cvs187).
 21. Grygorczyk R, Hanrahan JW. CFTR-independent ATP release from epithelial cells triggered by mechanical stimuli. *Am J Phys*. 1997;272(3 Pt 1):C1058–66.
 22. Hazama A, Shimizu T, Ando-Akatsuka Y, Hayashi S, Tanaka S, Maeno E, Okada Y. Swelling-induced, CFTR-independent ATP release from a human epithelial cell line: lack of correlation with volume-sensitive Cl^{-} channels. *J Gen Physiol*. 1999;114(4):525–33.
 23. Loomis WH, Namiki S, Ostrom RS, Insel PA, Junger WG. Hypertonic stress increases T cell interleukin-2 expression through a mechanism that involves ATP release, P2 receptor, and p38 MAPK activation. *J Biol Chem*. 2003;278(7):4590–6. doi:[10.1074/jbc.M207868200](https://doi.org/10.1074/jbc.M207868200).
 24. Collins LV, Hajizadeh S, Holme E, Jonsson IM, Tarkowski A. Endogenously oxidized mitochondrial DNA induces in vivo and in vitro inflammatory responses. *J Leukoc Biol*. 2004;75(6):995–1000. doi:[10.1189/jlb.0703328](https://doi.org/10.1189/jlb.0703328).
 25. Akira S, Takeda K. Toll-like receptor signalling. *Nat Rev Immunol*. 2004;4(7):499–511. doi:[10.1038/nri1391](https://doi.org/10.1038/nri1391).
 26. Nakahira K, Haspel JA, Rathinam VA, Lee SJ, Dolinay T, Lam HC, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat Immunol*. 2011;12(3):222–30. doi:[10.1038/ni.1980](https://doi.org/10.1038/ni.1980).
 27. Shimada K, Crother TR, Karlin J, Dagvadorj J, Chiba N, Chen S, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36(3):401–14. doi:[10.1016/j.immuni.2012.01.009](https://doi.org/10.1016/j.immuni.2012.01.009).
 28. Shaham O, Slate NG, Goldberger O, Xu Q, Ramanathan A, Souza AL, et al. A plasma signature of human mitochondrial disease revealed through metabolic profiling of spent media from cultured muscle cells. *Proc Natl Acad Sci U S A*. 2010;107(4):1571–5. doi:[10.1073/pnas.0906039107](https://doi.org/10.1073/pnas.0906039107).
 29. Rubic T, Lametschwandtner G, Jost S, Hinteregger S, Kund J, Carballido-Perrig N, et al. Triggering the succinate receptor GPR91 on dendritic cells enhances immunity. *Nat Immunol*. 2008;9(11):1261–9. doi:[10.1038/ni.1657](https://doi.org/10.1038/ni.1657).
 30. Tannahill GM, Curtis AM, Adamik J, Palsson-McDermott EM, McGettrick AF, Goel G, et al. Succinate is an inflammatory signal that induces IL-1 β through HIF-1 α . *Nature*. 2013;496(7444):238–42. doi:[10.1038/nature11986](https://doi.org/10.1038/nature11986).
 31. Ksenzenko SM, Davidson SB, Saba AA, Franko AP, Raafat AM, Diebel LN, Dulchavsky SA. Effect of triiodothyronine augmentation on rat lung surfactant phospholipids during sepsis. *J Appl Physiol*. 1997;82(6):2020–7.
 32. Liau DF, Barrett CR, Bell AL, Cernansky G, Ryan SF. Diposphatidylglycerol in experimental acute alveolar injury in the dog. *J Lipid Res*. 1984;25(7):678–83.
 33. Iyer SS, He Q, Janczy JR, Elliott EI, Zhong Z, Olivier AK, et al. Mitochondrial cardiolipin is required for Nlrp3 inflammasome activation. *Immunity*. 2013;39(2):311–23. doi:[10.1016/j.immuni.2013.08.001](https://doi.org/10.1016/j.immuni.2013.08.001).
 34. Chakraborty K, Raundhal M, Chen BB, Morse C, Tyurina YY, Khare A, et al. The mito-DAMP cardiolipin blocks IL-10 production causing persistent inflammation during bacterial pneumonia. *Nat Commun*. 2017;8:13944. doi:[10.1038/ncomms13944](https://doi.org/10.1038/ncomms13944).
 35. Boulay F, Tardif M, Brouchon L, Vignais P. The human N-formylpeptide receptor. Characterization of two cDNA isolates and evidence for a new subfamily of G-protein-coupled receptors. *Biochemistry*. 1990;29(50):11123–33.
 36. Panaro MA, Acquafredda A, Sisto M, Lisi S, Maffione AB, Mitolo V. Biological role of the N-formyl peptide receptors. *Immunopharmacol Immunotoxicol*. 2006;28(1):103–27. doi:[10.1080/08923970600625975](https://doi.org/10.1080/08923970600625975).
 37. Crouser ED, Shao G, Julian MW, Macre JE, Shadel GS, Tridandapani S, et al. Monocyte activation by necrotic cells is promoted by mitochondrial proteins and formyl peptide receptors. *Crit Care Med*. 2009;37(6):2000–9. doi:[10.1097/CCM.0b013e3181a001ae](https://doi.org/10.1097/CCM.0b013e3181a001ae).
 38. Aguilera-Aguirre L, Bacsí A, Saavedra-Molina A, Kurosky A, Sur S, Boldogh I. Mitochondrial dysfunction increases allergic airway inflammation. *J Immunol*. 2009;183(8):5379–87. doi:[10.4049/jimmunol.0900228](https://doi.org/10.4049/jimmunol.0900228). **The first experimental study to conclusively show that mitochondrial dysfunction promotes allergic inflammation**
 39. Kaminski MM, Sauer SW, Klemke CD, Suss D, Okun JG, Krammer PH, Gulow K. Mitochondrial reactive oxygen species control T cell activation by regulating IL-2 and IL-4 expression: mechanism of ciprofloxacin-mediated immunosuppression. *J Immunol*. 2010;184(9):4827–41. doi:[10.4049/jimmunol.0901662](https://doi.org/10.4049/jimmunol.0901662).
 40. Kim SR, Kim DI, Kim SH, Lee H, Lee KS, Cho SH, Lee YC. NLRP3 inflammasome activation by mitochondrial ROS in bronchial epithelial cells is required for allergic inflammation. *Cell Death Dis*. 2014;5:e1498. doi:[10.1038/cddis.2014.460](https://doi.org/10.1038/cddis.2014.460).
 41. Pattnaik B, Bodas M, Bhatraju NK, Ahmad T, Pant R, Guleria R, et al. IL-4 promotes asymmetric dimethylarginine accumulation, oxo-nitrate stress, and hypoxic response-induced mitochondrial loss in airway epithelial cells. *J Allergy Clin Immunol*. 2016;138(1):130–41 e9. doi:[10.1016/j.jaci.2015.11.036](https://doi.org/10.1016/j.jaci.2015.11.036).
 42. Reddy PH. Mitochondrial dysfunction and oxidative stress in asthma: implications for mitochondria-targeted antioxidant therapeutics. *Pharmaceuticals (Basel)*. 2011;4(3):429–56. doi:[10.3390/ph4030429](https://doi.org/10.3390/ph4030429).
 43. Raj D, Kabra SK, Lodha R. Childhood obesity and risk of allergy or asthma. *Immunol Allergy Clin N Am*. 2014;34(4):753–65. doi:[10.1016/j.iac.2014.07.001](https://doi.org/10.1016/j.iac.2014.07.001).
 44. Pedersen PA, Weeke ER. Asthma and allergic rhinitis in the same patients. *Allergy*. 1983;38(1):25–9.
 45. Qi S, Barnig C, Charles AL, Poirot A, Meyer A, Clere-Jehl R, et al. Effect of nasal allergen challenge in allergic rhinitis on mitochondrial function of peripheral blood mononuclear cells. *Ann Allergy Asthma Immunol*. 2017;118(3):367–9. doi:[10.1016/j.anaai.2016.11.026](https://doi.org/10.1016/j.anaai.2016.11.026). **First report linking allergic rhinitis with systemic inflammation**
 46. Cahoon JM VA. Endoplasmic reticulum—mitochondrial interactions in house dust mite induced inflammation: UVM College of Arts and Sciences College; 2015.

47. Hosoki K, Boldogh I, Sur S. Innate responses to pollen allergens. *Curr Opin Allergy Clin Immunol*. 2015;15(1):79–88. doi:[10.1097/ACI.0000000000000136](https://doi.org/10.1097/ACI.0000000000000136).
48. Singh VP, Aggarwal R, Singh S, Banik A, Ahmad T, Patnaik BR, et al. Metabolic syndrome is associated with increased oxo-nitrative stress and asthma-like changes in lungs. *PLoS One*. 2015;10(6):e0129850. doi:[10.1371/journal.pone.0129850](https://doi.org/10.1371/journal.pone.0129850).
49. Raby BA, Klanderman B, Murphy A, Mazza S, Camargo Jr CA, Silverman EK, Weiss ST. A common mitochondrial haplogroup is associated with elevated total serum IgE levels. *J Allergy Clin Immunol*. 2007;120(2):351–8. doi:[10.1016/j.jaci.2007.05.029](https://doi.org/10.1016/j.jaci.2007.05.029).
50. Takizawa H. Impact of air pollution on allergic diseases. *Korean J Intern Med*. 2011;26(3):262–73. doi:[10.3904/kjim.2011.26.3.262](https://doi.org/10.3904/kjim.2011.26.3.262).
51. Ikeda YSS, Nagarajan N, Rubattu S, Volpe M, Frati G, Sadoshima J. New insights into the role of mitochondrial dynamics and autophagy during oxidative stress and aging in the heart. *Oxidative Med Cell Longev*. 2014;2014 doi:[10.1155/2014/210934](https://doi.org/10.1155/2014/210934). **Review on the associations between mitochondrial dynamics, mitophagy, oxidative stress and aging**
52. Li R, Kou X, Geng H, Xie J, Yang Z, Zhang Y, et al. Effect of ambient PM(2.5) on lung mitochondrial damage and fusion/fission gene expression in rats. *Chem Res Toxicol*. 2015;28(3):408–18. doi:[10.1021/tx5003723](https://doi.org/10.1021/tx5003723).
53. Westermann B. Bioenergetic role of mitochondrial fusion and fission. *Biochim Biophys Acta*. 2012;1817(10):1833–8. doi:[10.1016/j.bbabi.2012.02.033](https://doi.org/10.1016/j.bbabi.2012.02.033).
54. Wittkopp S, Staimer N, Tjoa T, Gillen D, Daher N, Shafer M, et al. Mitochondrial genetic background modifies the relationship between traffic-related air pollution exposure and systemic biomarkers of inflammation. *PLoS One*. 2013;8(5):e64444. doi:[10.1371/journal.pone.0064444](https://doi.org/10.1371/journal.pone.0064444).
55. Grevendonk L, Janssen BG, Vanpoucke C, Lefebvre W, Hoxha M, Bollati V, Nawrot TS. Mitochondrial oxidative DNA damage and exposure to particulate air pollution in mother-newborn pairs. *Environ Health*. 2016;15:10. doi:[10.1186/s12940-016-0095-2](https://doi.org/10.1186/s12940-016-0095-2). **Early life PM exposure is associated strongly with systemic oxidative stress and can be assessed via increased mitochondrial oxidative DNA damage during pregnancy in both mothers and their newborns**
56. Valavanidis A, Vlachogianni T, Fiotakis C. 8-hydroxy-2'-deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev*. 2009;27(2):120–39. doi:[10.1080/10590500902885684](https://doi.org/10.1080/10590500902885684).
57. Wang XB, Gao HY, Hou BL, Huang J, Xi RG, Wu LJ. Nanoparticle realgar powders induce apoptosis in U937 cells through caspase MAPK and mitochondrial pathways. *Arch Pharm Res*. 2007;30(5):653–8. **A study on the interaction between nanoparticle caspase, mitochondria and MAPK signal pathways to trigger apoptosis, model for PM 2.5 interaction postulated to be similar**
58. Gosens I, Post JA, de la Fonteyne LJ, Jansen EH, Geus JW, Cassee FR, de Jong WH. Impact of agglomeration state of nano- and sub-micron sized gold particles on pulmonary inflammation. *Part Fibre Toxicol*. 2010;7(1):37. doi:[10.1186/1743-8977-7-37](https://doi.org/10.1186/1743-8977-7-37).
59. Kamdar O, Le W, Zhang J, Ghio AJ, Rosen GD, Upadhyay D. Air pollution induces enhanced mitochondrial oxidative stress in cystic fibrosis airway epithelium. *FEBS Lett*. 2008;582(25–26):3601–6. doi:[10.1016/j.febslet.2008.09.030](https://doi.org/10.1016/j.febslet.2008.09.030).
60. Yang CF, Shen HM, Shen Y, Zhuang ZX, Ong CN. Cadmium-induced oxidative cellular damage in human fetal lung fibroblasts (MRC-5 cells). *Environ Health Perspect*. 1997;105(7):712–6.
61. Almeida AM, Bertoncini CR, Borecky J, Souza-Pinto NC, Vercesi AE. Mitochondrial DNA damage associated with lipid peroxidation of the mitochondrial membrane induced by Fe2+-citrate. *An Acad Bras Cienc*. 2006;78(3):505–14.
62. Cejas P, Casado E, Belda-Iniesta C, De Castro J, Espinosa E, Redondo A, et al. Implications of oxidative stress and cell membrane lipid peroxidation in human cancer (Spain). *Cancer Causes Control*. 2004;15(7):707–19. doi:[10.1023/B:CACO.0000036189.61607.52](https://doi.org/10.1023/B:CACO.0000036189.61607.52).
63. Madrigal JL, Olivenza R, Moro MA, Lizasoain I, Lorenzo P, Rodrigo J, Leza JC. Glutathione depletion, lipid peroxidation and mitochondrial dysfunction are induced by chronic stress in rat brain. *Neuropsychopharmacology*. 2001;24(4):420–9. doi:[10.1016/S0893-133X\(00\)00208-6](https://doi.org/10.1016/S0893-133X(00)00208-6).
64. Muller L. Consequences of cadmium toxicity in rat hepatocytes: mitochondrial dysfunction and lipid peroxidation. *Toxicology*. 1986;40(3):285–95.
65. Lippai MLP. The role of the selective adaptor p62 and ubiquitin-like proteins in autophagy. *Biomed Res Int*. 2014;2014:11. doi:[10.1155/2014/832704](https://doi.org/10.1155/2014/832704).
66. Taylor EB, Rutter J. Mitochondrial quality control by the ubiquitin-proteasome system. *Biochem Soc Trans*. 2011;39(5):1509–13. doi:[10.1042/BST0391509](https://doi.org/10.1042/BST0391509).
67. Kipen HM, Gandhi S, Rich DQ, Ohman-Strickland P, Laumbach R, Fan ZH, et al. Acute decreases in proteasome pathway activity after inhalation of fresh diesel exhaust or secondary organic aerosol. *Environ Health Perspect*. 2011;119(5):658–63. doi:[10.1289/ehp.1002784](https://doi.org/10.1289/ehp.1002784).
68. Ruan LZC, Jin E, Kucharavy A, Zhang Y, Wen Z, Florens L, Li R. Cytosolic proteostasis through importing of misfolded proteins into mitochondria. *Nature*. 2017; doi:[10.1038/nature21695](https://doi.org/10.1038/nature21695).
69. Merkwirth C, Jovaisaite V, Durieux J, Matilainen O, Jordan SD, Quiros PM, et al. Two conserved histone demethylases regulate mitochondrial stress-induced longevity. *Cell*. 2016;165(5):1209–23. doi:[10.1016/j.cell.2016.04.012](https://doi.org/10.1016/j.cell.2016.04.012).
70. Tian Y, Garcia G, Bian Q, Steffen KK, Joe L, Wolff S, et al. Mitochondrial stress induces chromatin reorganization to promote longevity and UPR(mt). *Cell*. 2016;165(5):1197–208. doi:[10.1016/j.cell.2016.04.011](https://doi.org/10.1016/j.cell.2016.04.011).
71. Coulter JB, O'Driscoll CM, Bressler JP. Hydroquinone increases 5-hydroxymethylcytosine formation through ten eleven translocation 1 (TET1) 5-methylcytosine dioxygenase. *J Biol Chem*. 2013;288(40):28792–800. doi:[10.1074/jbc.M113.491365](https://doi.org/10.1074/jbc.M113.491365).
72. Agrawal A, Prakash YS. Obesity, metabolic syndrome, and airway disease: a bioenergetic problem? *Immunol Allergy Clin N Am*. 2014;34(4):785–96. doi:[10.1016/j.jiac.2014.07.004](https://doi.org/10.1016/j.jiac.2014.07.004).
73. Gomez-Cabrera MC, Domenech E, Romagnoli M, Arduini A, Borrás C, Pallardo FV, et al. Oral administration of vitamin C decreases muscle mitochondrial biogenesis and hampers training-induced adaptations in endurance performance. *Am J Clin Nutr*. 2008;87(1):142–9.
74. Gvozdkova A, Kucharska J, Bartkovjakova M, Gazdikova K, Gazdik FE. Coenzyme Q10 supplementation reduces corticosteroids dosage in patients with bronchial asthma. *Biofactors*. 2005;25(1–4):235–40.
75. Jun AS, Trounce IA, Brown MD, Shoffner JM, Wallace DC. Use of trans-mitochondrial cybrids to assign a complex I defect to the mitochondrial DNA-encoded NADH dehydrogenase subunit 6 gene mutation at nucleotide pair 14459 that causes Leber hereditary optic neuropathy and dystonia. *Mol Cell Biol*. 1996;16(3):771–7.
76. Bacman SR, Williams SL, Garcia S, Moraes CT. Organ-specific shifts in mtDNA heteroplasmy following systemic delivery of a mitochondria-targeted restriction endonuclease. *Gene Ther*. 2010;17(6):713–20. doi:[10.1038/gt.2010.25](https://doi.org/10.1038/gt.2010.25). **In vivo study on manipulation of mitochondrial heteroplasmy through recombinant technology**
77. Bayona-Bafaluy MP, Blits B, Battersby BJ, Shoubridge EA, Moraes CT. Rapid directional shift of mitochondrial DNA heteroplasmy in animal tissues by a mitochondrially targeted

- restriction endonuclease. *Proc Natl Acad Sci U S A*. 2005;102(40):14392–7. doi:[10.1073/pnas.0502896102](https://doi.org/10.1073/pnas.0502896102).
78. Ahmad T, Aggarwal K, Pattnaik B, Mukherjee S, Sethi T, Tiwari BK, et al. Computational classification of mitochondrial shapes reflects stress and redox state. *Cell Death Dis*. 2013;4:e461. doi:[10.1038/cddis.2012.213](https://doi.org/10.1038/cddis.2012.213).
 79. Berridge MV, Dong L, Neuzil J. Mitochondrial DNA in tumor initiation, progression, and metastasis: role of horizontal mtDNA transfer. *Cancer Res*. 2015;75(16):3203–8. doi:[10.1158/0008-5472.CAN-15-0859](https://doi.org/10.1158/0008-5472.CAN-15-0859). **One of the early evidences for the physiological existence and importance of mitochondrial transfer between cells**
 80. Islam MN, Das SR, Emin MT, Wei M, Sun L, Westphalen K, et al. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med*. 2012;18(5):759–65. doi:[10.1038/nm.2736](https://doi.org/10.1038/nm.2736).
 81. Tan AS, Baty JW, Dong LF, Bezawork-Geleta A, Endaya B, Goodwin J, et al. Mitochondrial genome acquisition restores respiratory function and tumorigenic potential of cancer cells without mitochondrial DNA. *Cell Metab*. 2015;21(1):81–94. doi:[10.1016/j.cmet.2014.12.003](https://doi.org/10.1016/j.cmet.2014.12.003).
 82. Onfelt B, Nedvetzki S, Yanagi K, Davis DM. Cutting edge: membrane nanotubes connect immune cells. *J Immunol*. 2004;173(3):1511–3.
 83. Rustom A, Saffrich R, Markovic I, Walther P, Gerdes HH. Nanotubular highways for intercellular organelle transport. *Science*. 2004;303(5660):1007–10. doi:[10.1126/science.1093133](https://doi.org/10.1126/science.1093133).
 84. Abounit S, Zurzolo C. Wiring through tunneling nanotubes—from electrical signals to organelle transfer. *J Cell Sci*. 2012;125(Pt 5):1089–98. doi:[10.1242/jcs.083279](https://doi.org/10.1242/jcs.083279).
 85. Gerdes HH, Carvalho RN. Intercellular transfer mediated by tunneling nanotubes. *Curr Opin Cell Biol*. 2008;20(4):470–5. doi:[10.1016/j.ceb.2008.03.005](https://doi.org/10.1016/j.ceb.2008.03.005).
 86. Ahmad T, Mukherjee S, Pattnaik B, Kumar M, Singh S, Rehman R, et al. Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *EMBO J*. 2014;33(9):994–1010. doi:[10.1002/embj.201386030](https://doi.org/10.1002/embj.201386030). **First report providing mechanistic understanding of mitochondrial transfer through tunneling nanotubules and the critical role of mitochondria in allergic asthma models**
 87. Agrawal A, Mabalirajan U. Rejuvenating cellular respiration for optimizing respiratory function: targeting mitochondria. *Am J Physiol Lung Cell Mol Physiol*. 2016;310(2):L103–13. doi:[10.1152/ajplung.00320.2015](https://doi.org/10.1152/ajplung.00320.2015). **A perspective on the role of mitochondrial dysfunction in lung disease and a review of potential strategies to target mitochondria**