Obesity, Metabolic Syndrome, and Airway Disease: A Bioenergetic Problem?

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KEYWORDS

• Mitochondria • Asthma • Bioenergetics • Reactive oxygen species
• Metabolic syndrome • Arginine • Statin • Metformin

KEY POINTS

- Mitochondrial dysfunction increases severity or risk of asthma.
- Caloric excesses and reduced physical activity lead to insulin resistance, obesity, and the metabolic syndrome through abnormal mitochondrial bioenergetics.
- Caloric restriction and aerobic exercise promote mitochondrial biogenesis and improve bioenergetics. Metformin treatment recapitulates some of the effects of caloric restriction.
- Mitochondrial-targeted antioxidants like coenzyme Q10 and MitoQ may be beneficial in severe asthma.

INTRODUCTION

Asthma and obesity are twin epidemics in the developed world that are becoming increasingly prevalent globally.[1–3] Not only are obese people at increased risk of asthma, but also asthma in obese individuals does not respond as well to conventional anti-inflammatory therapy, suggesting novel pathogenic mechanisms that contribute to both asthma and obesity—two seemingly disparate diseases.[4] Such mechanisms likely relate to processes that contribute to induction or maintenance of obesity or to consequences of obesity itself.[5,6] Mitochondrial dysfunction is one such process. Here we review our current understanding of how dietary and lifestyle factors lead to changes in mitochondrial metabolism and cellular bioenergetics, inducing various components of the cardiometabolic syndrome as well as airway disease. We provide

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Immunol Allergy Clin N Am 34 (2014) 785–796
http://dx.doi.org/10.1016/j.iac.2014.07.004 immunology.theclinics.com
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an overview of potential mitochondria-targeted therapies and discuss the emerging use of mesenchymal stem cells as mitochondrial donors in alleviating disease.[7]

BACKGROUND

Optimal cellular bioenergetic function is the key to health.[8] It is, therefore, not surprising that bioenergetic dysfunction is seen in multiple diseases.[9–13] Normally, energy demand of most cells is met through efficient oxidative phosphorylation reactions that occur in mitochondria.[8] A substantial reserve exists in terms of mitochondrial capacity and optimal concentrations of metabolic substrates such as glucose, permitting a matching of bioenergetic supply to demand. Conversely, inadequate numbers of mitochondria, degradation of mitochondrial function, or dysregulated substrate transport are all associated with a bioenergetic failure that can occur in disease. What is less clear is whether mitochondrial dysfunction is a trigger for or a consequence of disease. Recently, there is increasing recognition that bioenergetic failure is not just an outcome of disease, (ie, driven by earlier or more upstream mechanisms) but rather a common pathogenesis thread that links a wide range of comorbidities that occur in multifactorial diseases such as obesity, metabolic syndrome, and asthma.[9,14–16] In this review, we focus on our current understanding of bioenergetic changes in obesity, insulin resistance, and asthma, highlighting a functional basis for the intertwined epidemiology. A brief overview of normal mitochondrial metabolism follows, to provide context for disease-associated changes described subsequently.

PHYSIOLOGY

Cellular bioenergetics takes place largely within the mitochondria, which are semiautonomous organelles thought to have originated from endosymbiotic relationships between ancient eukaryotic cells and proteobacteria.[8,9] Mitochondria release energy from substrates processed through the tricarboxylic acid cycle and electron transport chain (ETC), such that carbon-hydrogen bonds are oxidized to carbon dioxide and water; the liberated energy is captured in the high-energy phosphate bond of adenosine-triphosphate (ATP). The interconversion of chemical energy is by nature an inefficient process, and tight coupling between the reactions is necessary to minimize leakage. During the necessary oxygen-dependent ATP production in the ETC, there is some electron leak, leading to the generation of reactive oxygen species (ROS) as a natural byproduct. ROS, such as superoxide and hydrogen peroxide, are highly reactive molecules that are mutagenic. Although low levels of mitochondrial ROS (mtROS) can serve physiologic functions, such as signaling, excessive levels from more leaky mitochondria can be detrimental by damaging mitochondrial DNA (mtDNA) and critical oxidative phosphorylation proteins and oxidizing the lipid membrane. Not only can they cause damage within the mitochondria, thereby setting up a spiraling decline of mitochondrial function, but can adversely impact other organelles, eventually triggering apoptosis.[8,17,18] Multiple counterregulatory mechanisms are therefore in place to monitor mitochondrial quality, degrade or disrupt poorly functioning mitochondria, maintain mitochondrial networks, and form new mitochondria as demand increases.

Mitochondrial function is also coupled to bioenergetic demand.[19] ATP, the energy currency, is exported out of mitochondria and circulated within the cell, where energy can be released by controlled hydrolysis of the phosphate bonds, forming diphosphates and monophosphates (adenosine monophosphate [AMP]). Cellular energy reserve and nutrient status is monitored through well-orchestrated machinery, including AMP-sensitive protein kinase and NAD^+-dependent deacetylase SIRT1, which regulates glucose uptake, autophagy, and mitochondrial biogenesis.[19,20]

Further, the mitochondrion is intimately coupled to overall cellular physiology via the mitochondria-associated endoplasmic reticulum membrane, which regulates lipid and sterol metabolism and calcium signaling. As a result, mitochondria exhibit plasticity (ie, rapid alteration of their numbers and characteristics in response to metabolic fluctuations for meeting cellular needs).[19,21,22] Diet, exercise, insulin, and drugs strongly shape this plastic behavior and consequently mitochondrial health.

Fig. 1 illustrates the central role of mitochondria in energy metabolism. High mitochondrial reserve, low baseline ROS production, low burden of mtDNA damage, balanced cellular demand and nutrient supply, and high levels of endogenous ROS scavengers characterize health. It is notable that the inverse occurs during natural aging, obesity, and inflammatory disease (Fig. 2).

PATHOPHYSIOLOGY

Mitochondrial Dysfunction and Metabolic Syndrome

Caloric excess and reduced physical activity are increasingly prevalent aspects of the modern lifestyle. Surplus nutrient supply overloads mitochondria,[23] leading to overproduction of ROS and accumulation of incompletely oxidized substrates. Damage from these ROS can reduce mitochondrial integrity, triggering their clearance, and can also activate stress pathways that reduce insulin sensitivity and thereby limit nutrient uptake.[24,25] Chronic nutrient oversupply leads to oxidative stress, mitochondrial loss, and reduced maximal oxygen consumption. This is exacerbated by physical inactivity, as adaptive mechanisms for increasing mitochondrial activity or mitochondrial biogenesis are strongly related to aerobic exercise.[20] Together, this appears to be the foundation of insulin resistance, and numerous studies in humans and animal models have confirmed that insulin resistance is associated with reduced mitochondrial mass or oxidative function in insulin-sensitive tissues. This sets off a vicious

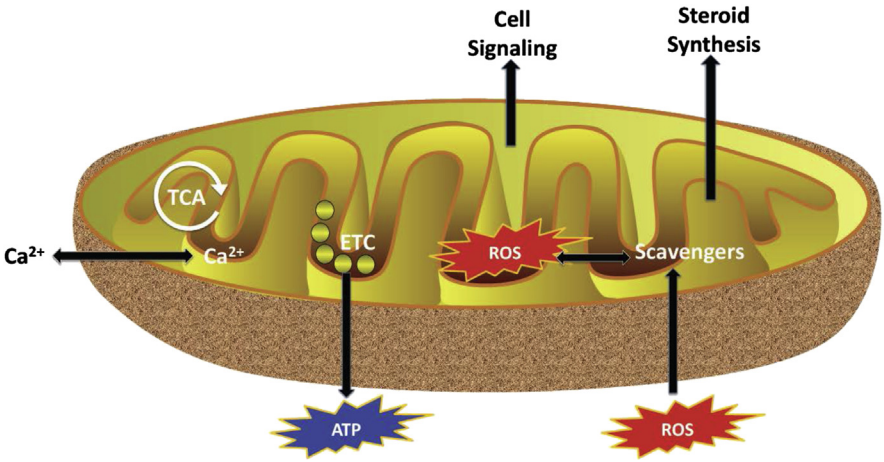

Fig. 1. Mitochondrial function in health. Mitochondria are the powerhouses of cells. The tricarboxylic/citric acid cycle (TCA) and ETC work in conjunction with glycolysis and fatty acid oxidation to extract the energy stored in carbon-hydrogen bonds and store it in ATP, which is the energy currency of the cell. ROS are generated during flow of electrons across ETC, which are scavenged by local antioxidants. A low level of ROS is important in cell signaling, and, other than ATP production, mitochondria also participate in calcium regulation and steroid synthesis.

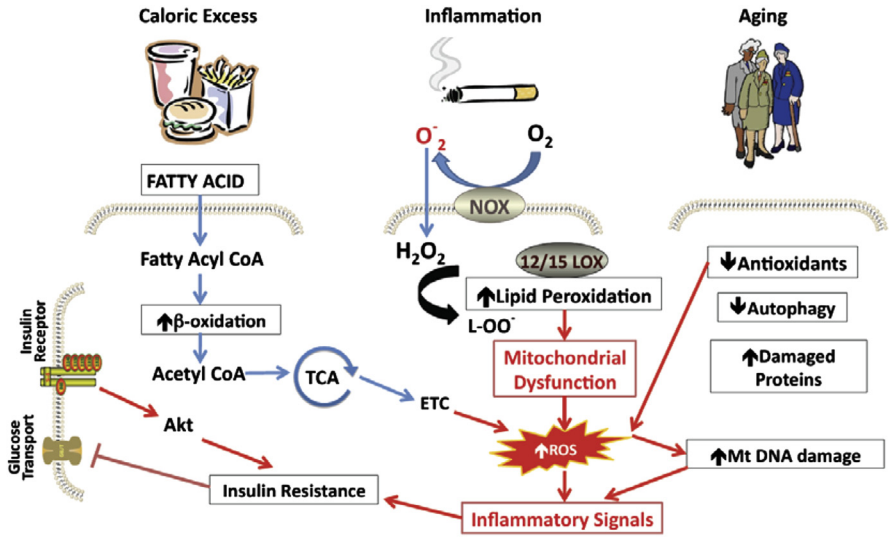

Fig. 2. Mitochondrial dysfunction is a common point of convergence during normal aging or pathologic stress. Activation of NADPH oxidase (NOX) or 12/15 lipoxygenase (LOX) is an important trigger for lipid peroxidation during inflammatory states. Increased ROS generation caused by nutrient excess or accumulation of damage with age can lead to similar endpoints.

feed-forward loop, as insulin action is important in maintaining mitochondrial metabolism and biogenesis. Because fatty acid oxidation for energy can only happen in mitochondria, fats are not adequately metabolized, leading to intracellular accumulation and increased circulating lipids. Hyperinsulinemia is the primary compensatory response to insulin resistance in the principal glucose, utilizing organs such as liver and skeletal muscle, creating β cell stress and eventually secretory deficiency. Together this forms the basis for the triad of obesity, dyslipidemia, and hyperglycemia, namely the metabolic syndrome.

Metabolic syndrome, especially obesity, represents a strong risk factor for asthma.[3,6] Hyperinsulinemia seems to be an independent risk factor in some studies, and we have previously reviewed how hyperinsulinemia may lead to changes in the lung characteristic of asthma via growth factor–like effects and increased PI3/Akt signaling.[26] Recently, a vagally mediated bronchoconstrictor effect of hyperinsulinemia has also been described.[27] These associations form the basis of exploring whether and how mitochondrial mechanisms important in metabolic syndrome can also contribute to asthma.

In the cascade of events described previously, the key initiator is mitochondrial dysfunction caused by caloric excesses and physical inactivity. So far, there is no clear evidence that this finding is related to mitochondrial genome variations, although some mtDNA polymorphisms are associated with metabolic syndrome components.[28] Although the ratio of mitochondrial DNA to nuclear DNA is markedly reduced in metabolic syndrome, it is not associated with any major genomic deletions and most likely simply represents increased damage, accelerated clearance, and, importantly, reduced mitochondrial biogenesis.[29,30] The resultant mitochondrial dysfunction, especially in key insulin-sensitive tissues like liver and muscle, potentiates hyperinsulinemia and obesity, which increase asthma risk through several pathways as discussed in this special issue and elsewhere.[3,5,6] Restricting calories and maintaining physically active

lifestyles protect against such mitochondrial dysfunction, lead to weight loss, and are shown to improve asthma.[4] However, beyond this indirect link among metabolic syndrome, mitochondrial dysfunction, and asthma that is mediated by obesity and insulin resistance, there is also a much more direct link within the lung.

Mitochondrial Dysfunction and Asthma

As far back as 1985, it had been described that human bronchial epithelial cells of asthmatics showed swollen mitochondria.[31] Mabalirajan and colleagues[32,33] dissected this further in experimental mouse models of allergic airway inflammation and found this to be an integral part of the asthma phenotype. Key inflammatory cytokines associated with asthma such as interleukin-4 and inaterleukin-13 are found to induce mitochondrial dysfunction via upregulation of the oxidized linoleic acid metabolite, 13-S-HODE.[33–35] Also, allergic airway inflammation is associated with increase in asymmetric dimethyl arginine (ADMA), an endogenous methyl-arginine that uncouples nitric oxide synthase, leading to ROS formation and mitochondrial dysfunction.[36,37] Interestingly, ADMA is also increased in obesity because of increased protein turnover.[6] A causal role for mitochondrial dysfunction was further suggested by studies in mice with a genetic deficiency of mitochondrial ubiquinol-cytochrome C-reductase core II protein in the airway epithelium.[38] These mice, which have airway mitochondrial dysfunction, exhibited much greater inflammation and airway remodeling than normal mice during allergen sensitization and challenge.[38] In other work, treatment of mice with low-dose inhaled rotenone, an ETC blocker, led to features of airway remodeling and hyperresponsiveness.[7] Importantly, both mice treated with rotenone and those with allergic airway inflammation, show marked attenuation of asthmatic features if mitochondrial function is restored (see later discussion).

Currently, there is limited human evidence for a causal role of mitochondrial dysfunction in asthma. However, human genetic studies of asthma are suggestive of a mitochondrial component.[39] Although there are no consistent reports of mitochondrial mutations in asthma, vertical transmission from mothers has been reported along with some genetic associations.[40–42] Mutations in genes encoding mitochondrial tRNAs and the ATP synthase mitochondrial F1 complex assembly factor 1 gene have been associated with childhood asthma. This evidence together with experimental observations, suggest a direct role of mitochondrial dysfunction in asthma pathogenesis. What is less clear is which aspects of mitochondrial function or dysfunction contribute to human asthma phenotype, particularly along the spectrum of mild through severe asthma. It also remains unclear whether mitochondria contribute to the sensitivity or resistance of asthmatic airways to existing therapies such as corticosteroids. It is well known that mitochondria have a complex morphology because of highly regulated fission and fusion and normally form an intricate tubuloreticular branched network.[14,43] It is now also apparent that this structure has multiple and far-reaching implications, including protecting mitochondrial stability, respiratory functions, cell fate determination, and adaptation to cellular stress. Mitochondrial fragmentation and other morphologic changes occur during allergic asthma, cigarette smoke exposure, or diet-induced obesity.[14,44] These issues are not fully reversed by anti-inflammatory therapy and may contribute to progressive disease.

Mitochondrial Dysfunction and Chronic Obstructive Pulmonary Disease

Cigarette smoking and second-hand exposure increase the risk or severity of asthma and chronic obstructive pulmonary disease (COPD). Short-term as well as longer exposure to cigarette smoke are found to induce mitochondrial dysfunction.[45,46] This is accompanied by increased mitochondrial network fragmentation and ROS

generation, which can be perpetuated by cell signaling pathways such as ERK, PI3/Akt, PKC and transcriptional regulation by NFκB and Nrf2.[14] This finding represents an important intersection between asthma and COPD, as airway smooth muscle (ASM) cells from asthmatics show such fragmentation and ROS generation at baseline, which is further enhanced by cigarette smoke.[14] Oxidative stress is well known as an important part of asthma and COPD pathogenesis, and there is well-known mitochondrial pathology in skeletal muscle of COPD patients.[9,47] It seems likely, therefore, that cigarette smoke–induced mitochondrial dysfunction potentiates oxidative stress in the lung, contributing to cell senescence and apoptosis. These issues represent a form of accelerated aging of the lung, which has been recently implicated in the genesis of COPD.[48–50]

TREATMENT

Currently, there is no specific approved therapy for mitochondrial dysfunction or separate treatment guidelines for obese patients with asthma. There is, however, increasing recognition that such obese-asthma is clinically different and may not respond fully to convention anti-inflammatory therapy (see review by Sherry Farzan elsewhere in this issue). The accompanying review by Nijra Lugogo in this issue, describes the role of weight loss in the management of asthma and evaluates the evidence for bariatric surgery in obese-asthma. Here we briefly focus on therapies that are associated with improvement in mitochondrial function that are shown to have potential benefit in metabolic syndrome and asthma (Fig. 3).

Lifestyle modification and weight loss should be first-line recommendations in obese-asthma, because they have general health benefits. Exercise and caloric restriction are found to enhance natural antioxidant scavengers, reduce mtROS, promote mitochondrial biogenesis, and slow aging.[20,51,52] However, it is also possible

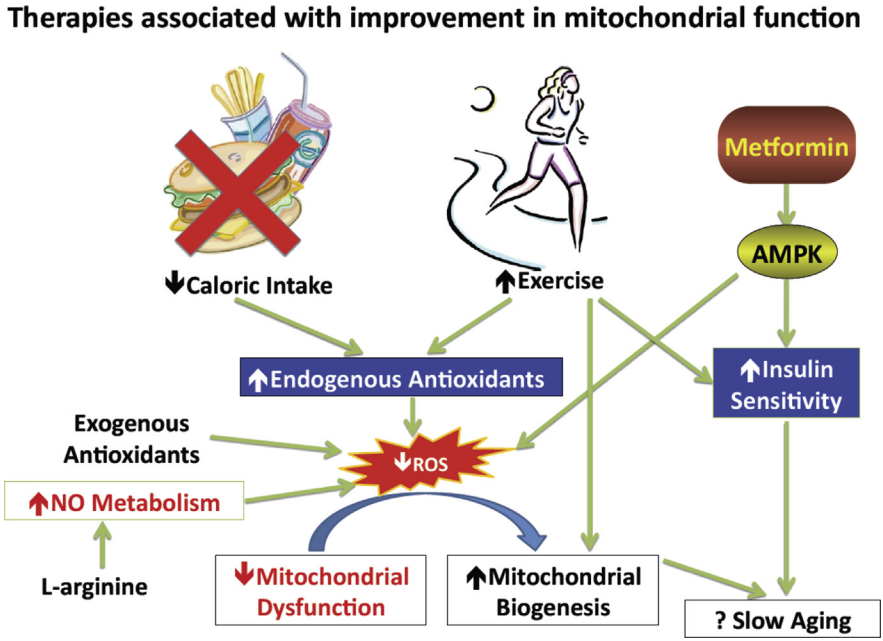

Fig. 3. Reversing bioenergetic failure in obesity and asthma.

that caloric restriction may not be acceptable to the patient, and exercise capacity may be impaired by the combination of asthma and obesity. Accordingly, although diet and lifestyle changes can have substantial beneficial effects in the context of asthma, more directed therapies are needed.

One approach toward chemically mimicking caloric restriction is to administer metformin, which via its actions on AMP-sensitive protein kinase, restores insulin sensitivity and promotes mitochondrial metabolism.[53] Metformin is already the treatment of choice for diabetes and is being considered for use in obese nondiabetics.[54] In mice with high-fat, diet-induced obesity, metformin attenuates allergen-induced eosinophilic inflammation.[55] Metformin-treated animals behaved similarly to lean controls, hastening the resolution of inflammation. Antiasthma effects of metformin were also noted in other allergen models of asthma[56] but not in genetically obese mice with intrinsic airway hyperresponsiveness or ozone-induced inflammation.[57] This finding suggests that the beneficial effects of metformin are through common metabolic processes between allergic asthma and dietary obesity, although these remain to be fully characterized.

Nitric oxide metabolism is impaired in obesity and metabolic syndrome because of increased methyl-arginines such as ADMA and reduced L-arginine bioavailability. These have also been strongly implicated in mitochondrial dysfunction and asthma. Previously we found that supplementation of L-arginine not only benefits cardiovascular aspects of the metabolic syndrome but also attenuates mitochondrial dysfunction and asthma features in experimental models.[36,58] Similar effects on nitric oxide metabolism and asthma were obtained by inhibition of L-arginine degradation by arginase[59] or by statin-mediated restoration of eNOS levels and degrading of ADMA.[60] Even metformin has important effects of nitric oxide metabolism, suggesting that this may be a critical common interface between obesity and asthma. These drugs are now in clinical trial for asthma, and the review elsewhere in this issue by Nicholas Kenyon, on novel therapeutic strategies for obese-asthma, provides more detail.

Exogenous antioxidants to scavenge ROS, inhibitors of 12/15 lipoxygenase (baicalein and esculetin) to reduce mitotoxicity, and sirtuin activators such as resveratrol to stimulate mitochondrial biogenesis, have all been found to attenuate experimental asthma.[43,61–64] Although these pathways are also implicated in obesity and metabolic syndrome, any benefits of these strategies in obese-asthma remain to be ascertained.

Mitochondria-targeted antioxidants are also of potential benefit. Coenzyme Q10 (CoQ10), also known as ubiquinone, is a component of the ETC and can, therefore, exist in both fully oxidized and reduced states, making it a powerful mitochondria-targeted antioxidant.[65] In a small study of 56 asthmatics, Gazdik and colleagues[66] reported reduction of CoQ10 in plasma and whole blood. In a subsequent open-label crossover study of 41 steroid-dependent asthma patients, they found that supplementation with a daily antioxidant cocktail, consisting of CoQ10 (120 mg) + 400 mg α-tocopherol + 250 mg vitamin C, was associated with a reduction in steroid usage.[67] Because glucocorticoids can induce mitochondrial dysfunction and are relatively ineffective in obese-asthma, this is potentially important. CoQ supplementation is also variably found to be beneficial in cardiac components of the metabolic syndrome.[68] However, supplementation with other exogenous antioxidants like α-tocopherol and vitamin C have not been successful, and there are conflicting reports including interference with mitochondrial signaling and biogenesis.[69] Thus, mitochondria-targeted antioxidants such as CoQ10 and its modified forms (MitoQ) merit further investigation in the treatment of obese-asthma.[70]

One limitation of any mitochondrial-targeted therapy in asthma is that mitochondrial numbers and dysfunction in different cell types may have different implications and

may even be a double-edged sword.[9,14,71] For example, ROS produced during fatty acid oxidation in mitochondria suppress the inflammatory Th17 lymphocyte polarization, and dominant fatty acid metabolism promotes formation of regulatory T cells that have important anti-inflammatory function.[71] Thus, normal mitochondrial ROS generation can be beneficial, and antioxidant therapy may not always be helpful. However, airway epithelial cells from allergically inflamed lungs show increased ROS, mitochondrial dysfunction, and a reduction in mitochondrial biogenesis.[7] The ASM shows increased mitochondrial fission, dysfunctional mitochondrial network formation, and increased ROS, although the biogenesis may be increased.[7,14] Together, these promote the aberrant fibrotic and hypercontractile pathology of asthma that is characterized by epithelial injury but ASM and fibroblast proliferation. An additional layer of cell-type specific targeting, either through delivery routes and carriers or through novel biologicals, may be required to specifically target mitochondrial function.

SUMMARY AND FUTURE DIRECTIONS

Both obesity and asthma share common metabolic derangements that intersect at the level of mitochondrial function. It is likely that the mitochondrial dysfunction of insulin resistance or obesity increases asthma incidence or severity. Conversely, asthma-associated mitochondrial dysfunction may lead to systemic metabolic changes that promote insulin resistance and obesity.[72] Several clinical trials are in progress for evaluation of metabolic drugs like metformin, statins, and L-arginine in asthma, and the results are awaited. Mitochondrial-targeted antioxidants like CoQ10 and MitoQ also show promise. Until recently there were no strategies for replenishing healthy mitochondria and restoring normal bioenergetics by exogenous donation. However, recent

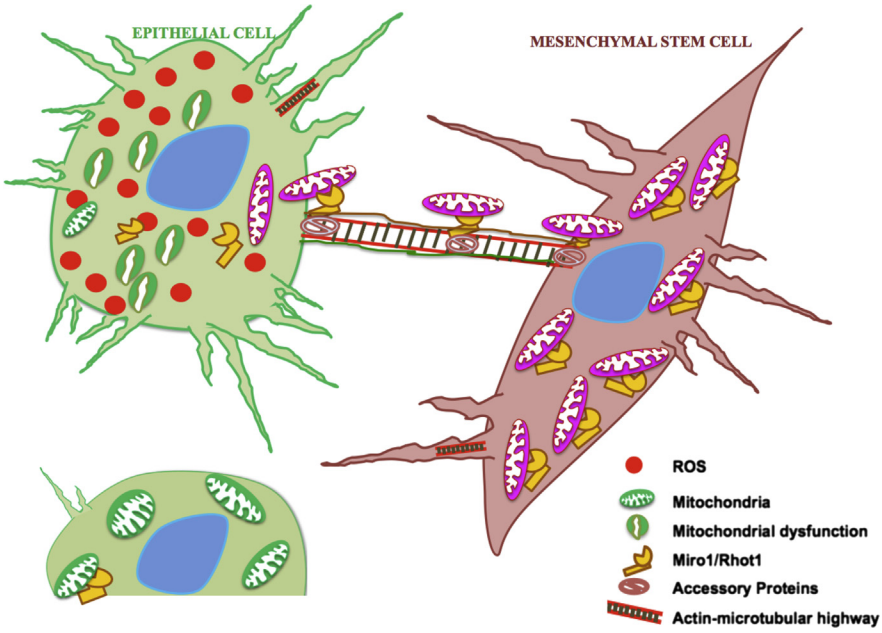

Fig. 4. Mesenchymal stem cells are potential mitochondrial donors that transfer healthy mitochondria via intercellular nanotubes to stressed epithelial cells. In experimental models, this has been associated with antiasthma effects.

work from Jahar Bhattacharya's laboratory[73] and the Agrawal lab[7] shows that exogenous mesenchymal stem cells (MSC) can donate mitochondria to lung epithelium, restoring bioenergetic function and attenuating inflammation and injury. This transfer seems to be regulated by Miro1, a GTPase, and MSC that overexpress Miro1 show amplification of mitochondrial donation as well as increased therapeutic efficacy in reversing experimental asthma.[7] This is being explored further in models of diet-induced obesity, metabolic syndrome, and asthma and represents an entirely new direction for the future (**Fig. 4**).

ACKNOWLEDGMENTS

This work was supported by the Lady Tata Memorial Trust (GAP63) and Council of Scientific and Industrial Research grant MLP5502 (A. Agrawal) and National Institutes of Health Grants HL088029 and HL056470 (Y.S. Prakash). The authors thank Shravani Mukherjee and Rohit Vashisht for their help.

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