

Review

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Review

Cellular and Molecular Biology of Mitochondria in Chronic Obstructive Pulmonary Disease

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a continually advancing respiratory disorder, characterized by enduring airflow limitation along with long-lasting inflammation in the airways. An expanding pool of evidence is emphasizing how mitochondrial dysfunction directly impacts the development and progression of COPD. This comprehensive review delves deeper into the intricate cellular and molecular biology of mitochondria within the framework of COPD, spotlighting significant alterations in structure and function that accompany mitochondrial dysfunction. In this narrative, we delve into the observed changes in mitochondrial shape, behavior, and respiratory chain complex alterations seen in individuals afflicted with COPD. The discussion includes implications on cellular signaling pathways and how this affects the natural process of programmed cellular death (apoptosis) and cellular aging, particularly in reference to COPD. Additionally, we consolidate ongoing therapeutic strategies, honing in on the management of COPD through a focus on mitochondrial dysfunction. Prominent among these strategies is the potential role of antioxidants and mitochondrial biogenesis inducers, which are emerging as promising fields of intervention. Furthermore, we embark on an overview of the possible use of mitochondrial biomarkers as innovative tools in diagnosing COPD, evaluating disease progression, and monitoring the efficacy of COPD treatments. As we unravel the rather complex interplay between mitochondrial biology and COPD, this review highlights the critical importance of formulating treatments that target mitochondrial dysfunction. The ultimate goal of these strategic interventions is to slow down the rate of COPD progression and significantly improve patient outcomes. Lastly, though our understanding of the nexus between COPD and mitochondrial dysfunction has significantly enhanced, ample scope remains for further investigation. Improved insights into the mechanisms of mitochondrial dysfunction, discovered biomarkers, and targeted therapies could encompass a revolutionary step towards comprehensive disease management. The future of COPD treatment seems to lean towards a combination of strategies, prioritizing not only the management of symptoms but also focused on preserving and restoring lung function, improving physical capacity, and enhancing quality of life for COPD patients.

Keywords: chronic obstructive pulmonary disease; cellular and molecular biology of mitochondria; antioxidants and mitochondrial biogenesis; mitochondrial biomarkers

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a relentlessly progressing global health issue, marked by persistent airflow obstruction and long-lasting respiratory symptoms [1,2]. Observations show that the prevalence of COPD is escalating worldwide, posing a substantial load on healthcare infrastructures and significantly affecting patients' quality of life [3,4]. Though COPD has conventional links to cigarette smoking, it also intertwines a complex mix of genetic susceptibilities, environmental factors, and intricate molecular mechanisms that contribute to its pathogenesis [5,6].

Recent findings spotlight the relevance of mitochondrial dysfunction in perpetuating COPD development and propelling disease evolution[7,8].

Aptly called the cell's powerhouses, mitochondria are integral to several cellular processes, including metabolism, energy synthesis, and signal transduction[9,10]. Besides these core functions, current research emphasizes the fundamental role mitochondria play in maintaining cellular equilibrium and managing stress responses[11,12]. Emerging research pinpoints mitochondrial dysfunction as a characteristic attribute in the narrative of COPD pathology, implicated in diverse cellular operations such as inflammation, oxidative stress-induced damage, and apoptosis - the programmed cell death [13,14].

Recognizing the nuances of cell biology, specifically the function and mechanisms of mitochondria in COPD, is crucial to deciphering the disease's convoluted progression and identifying plausible therapeutic strategies and targets[15,16]. This review strives to provide a holistic depiction of the current understanding of mitochondrial dysfunction's role in COPD, with a focus on structural alterations in mitochondria, the associated cellular repercussions, and potential therapeutic strategies aimed at promoting mitochondrial health restoration[17,18].

The aim is to untangle the complex relationship between mitochondrial biology and COPD, fostering a comprehensive understanding from which innovative therapeutic interventions and improved COPD management strategies can be developed[19,20]. Emphasizing the role of mitochondria in COPD underscores the potential of exploring mitochondria-targeted therapeutics and redox-based interventions as paths for enhancing patient outcomes and halting disease progression.

Lastly, future investigative efforts should concentrate on the prominent interactions between inflammation, oxidative stress, genetic predispositions, and environmental influences, which could instigate revolutionary transformations in COPD management and therapeutic approaches. A deeper understanding of mitochondrial dysfunction's role in COPD could fuel the advancement of personalized medicine strategies aimed at tackling the disruption of cellular homeostasis. This could move the focus away from merely symptomatic treatment and towards specific disease modification, thereby offering hope for efficacious management of this chronic and debilitating condition

2. Mitochondrial Dysfunction in COPD

Long anchored in the realm of pulmonary ailments, Chronic Obstructive Pulmonary Disease (COPD) - marked by chronic inflammation, excessive oxidative stress, and compromised lung function - is increasingly being recognized as a systemic disease with implications profound enough to affect the body beyond the confines of the respiratory system[21,22]. Integral to this narrative are the mitochondria, the dynamic entities within cells that orchestrate energy production, thereby ensuring cellular homeostasis. Their role in the pathogenesis of COPD is becoming increasingly significant.

2.1. Oxidative Stress and Mitochondrial Dysfunction

The association between COPD and oxidative stress is perhaps most evident in the excessive presence and continual production of reactive oxygen species (ROS) within the body, reflecting an imbalanced state it endures[23]. Located at the epicenter of this disturbance are the mitochondria, primarily responsible for producing ROS within the cells. In response to the exaggerated ROS, mitochondria find themselves under siege, accruing oxidative damage that leads to impaired functionality. Apart from the damage, the excessive ROS, characteristic of COPD, exacerbates mitochondrial disruption, specifically assaulting the electron transport chain (ETC) that is vital for energy production. Furthermore, it compromises the structural and functional integrity of the mitochondrial DNA (mtDNA), which translates into mitochondrial inefficiencies and deformities[24,25].

2.2. Inflammation and Mitochondrial Dysfunction

A defining feature of COPD is chronic inflammation, fueled by the activation of cellular immunity mechanisms and the release of pro-inflammatory mediators[26]. Mitochondria navigate a complex role vis-a-vis inflammation; they are recipients of inflammatory signaling and also active contributors to propagating such signals. In the COPD environment, inflammatory cytokines rend the fabric of mitochondrial functionality, triggering an overdrive in ROS production, leading to exacerbated mitochondrial damage. At the same time, mitochondrial dysfunction can trigger an avalanche of inflammatory pathways, reinforcing a vicious cycle of inflammation, tissue damage, and disease progression[18].

2.3. Altered Mitochondrial Morphology and Dynamics

Nuanced findings from ultrastructural examinations reveal profound alterations in the morphology and dynamism of mitochondria within individuals afflicted with COPD[16]. Manifestations range from mitochondrial fragmentation and elongation to disruptions in the critical process of mitochondrial biogenesis, implying a disrupted equilibrium of mitochondrial fission and fusion. These disturbances, no less than a pervasive disorder of mitochondrial dynamics, lead to dyshomeostasis of cellular function, impacting ATP production, calcium balance, and mitochondria turnover - all of which are integral to maintaining cell health[27].

2.4. Impaired Mitochondrial Respiratory Function

The deleterious effect of COPD extends to compromising mitochondrial respiratory function, leading to an inefficiency in energy production[28,29]. Evidence supports a reduction in the activity of respiratory chain complexes, particularly complex I and IV, within COPD patients. This compromised mitochondrial respiration has significant repercussions; notably, it is associated with muscle weakness, exercise intolerance, and an array of systemic manifestations that are characteristic of COPD[30,31].

2.5. Mitochondrial DNA Damage and Mutations

Given its proximity to ROS production epicenters within the mitochondria, mtDNA is particularly susceptible to oxidative damage[32]. Studies reveal an alarming increase in damage and mutations to mtDNA within COPD patients. These modifications have a fallout that jeopardizes mitochondrial protein synthesis and respiratory functionality. Furthermore, such mtDNA related aberrations find relations with systemic COPD manifestations like skeletal muscle dysfunction and cardiovascular comorbidities, expanding the impact of the disease[33–35].

Gaining a comprehensive understanding of the complex interplays between mitochondrial dysfunction and COPD is pivotal for the progression of targeted therapeutic strategies aiming to restore mitochondrial health and limit disease progression[36,37]. This potential shift from symptomatic management to cellular normalization could broaden the spectrum of viable coping strategies for COPD like never before. Tackling oxidative stress, limiting inflammation, and rejuvenating the functionality of mitochondria collectively offers a pathway to transform and redefine the COPD treatment narrative. This potential leap forward holds promise for significantly improving patient outcomes while finding ways to halt disease progression.

3. Structural and Functional Changes in Mitochondria:

The mitochondria - highly dynamic organelles responsible for cellular energy production - undergo significant structural and functional alterations in the milieu of Chronic Obstructive Pulmonary Disease (COPD)[1,38]. These perturbations have far-reaching implications on cellular function, positioning them at the heart of COPD pathogenesis.

3.1. Altered Mitochondrial Morphology

In-depth ultrastructural analyses have revealed dramatic changes in mitochondrial shapes and sizes in patients afflicted with COPD[28]. This includes mitochondrial fragmentation, swelling, and compromise in the integrity of cristae - internal compartments vital to mitochondrial function. This disruption in mitochondrial morphology is closely associated with compromised mitochondrial function and a disturbance in cellular equilibrium. While the exact mechanisms fueling these morphological alterations in mitochondria remain a subject of ongoing research, probable culprits include oxidative stress, inflammation, and irregularities in mitochondrial dynamics[39].

3.2. Impaired Mitochondrial Dynamics

Mitochondrial dynamics encompass the fundamental processes of fission and fusion, which are crucial for maintaining mitochondrial homeostasis. Within the sphere of COPD, irregularities in these dynamics fuel mitochondrial fragmentation and impair quality-control mechanisms leading to a decline in ATP production, disturbed calcium balance, and increased susceptibility to apoptosis - programmed cell death[40]. This points towards the possibility of manipulating mitochondrial dynamics as a new avenue for therapeutic intervention.

3.3. Mitochondrial Respiratory Chain Dysfunction

The mitochondrial respiratory chain, composed of five enzymatic complexes, underpins oxidative phosphorylation and ATP synthesis - the cell's primary energy production machinery. Disturbances in the function of this respiratory chain have been reported in COPD, characterised by reduced activity levels of complex I and IV[6,41]. This dysfunction leads to decreased ATP production and increased reactivity of oxygen species (ROS), contributing to cellular inflammation and damage that are defining features of COPD.

3.4. Disrupted Mitochondrial Biogenesis

Mitochondrial biogenesis - the process responsible for the creation of new mitochondria - is governed by an interconnected network of nuclear and mitochondrial factors[42]. In the narrative of COPD, this biogenesis process is disrupted, negatively impacting mitochondrial turnover and function. This disruption is further amplified by a reduced expression of regulators like the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). As a therapeutic approach, reinstating this mitochondrial biogenesis could enhance mitochondrial function and curb the progression of COPD[43].

3.5. Mitochondrial Quality Control Mechanisms

Mitochondrial quality control mechanisms, including mitophagy - the selective destruction of mitochondria by autophagy - and the mitochondrial unfolded protein response (UPR_{mt}), are critical for ensuring mitochondrial integrity and preserving function[44]. In individuals with COPD, these quality control mechanisms face setbacks, leading to an accumulation of damaged mitochondria and subsequent mitochondrial dysfunction. Therefore, therapeutic strategies aiming at enhancing these quality control mechanisms could potentially preserve mitochondrial function, decelerating COPD progression[45].

Having a comprehensive understanding of the structural and functional changes the mitochondria undergo within the context of COPD is essential for identifying new potential therapeutic targets. This understanding can clear a path for the development of interventions focused on restoring mitochondrial health and stalling the progression of COPD.

4. Implications of Mitochondrial Dysfunction in COPD

Considered pivotal to the onset and growth of Chronic Obstructive Pulmonary Disease (COPD), mitochondrial dysfunction's influence ripple through multiple cellular and systemic avenues. This

cornerstone role underscores the importance of a detailed comprehension of the havoc wrought by mitochondrial dysfunctions on COPD's cellular machinery and systemic reactions, which could lead to potential therapeutic breakthroughs[46,47].

4.1. Cellular Signaling Pathways

At the cellular level, mitochondria command a central role by acting as signaling hubs associated with various critical processes like apoptosis, inflammation, and oxidative stress[48]. The emission of cellular distress signals from ailing mitochondria, including pro-apoptotic factors and reactive oxygen species (ROS), instigates apoptotic signaling cascades. This process accelerates tissue damage specific to COPD. Additionally, aberrations in mitochondrial task fulfillment disrupt intracellular signaling networks, inciting abnormal immune responses and fostering chronic inflammation emblematic of COPD[49].

4.2. Oxidative Stress and Inflammation

Acknowledged as the progenitors of heightened oxidative stress and inflammation seen in COPD, dysfunctional mitochondria indirectly instigate various disease aspects[50]. Inherent to ailing mitochondria is an unbalanced overproduction of ROS, creating an oxidative onslaught on various cellular entities. This domino effect feeds into causing inflammation by lighting up pro-inflammatory signaling routes, and mobilizing immune cells towards the lungs. The inflammation then further vaunts mitochondrial distress, setting off a cycle of disease potentiation.

4.3. Cellular Senescence and Tissue Remodeling

Mitochondrial dysfunction acts as a catalyst encouraging cellular senescence and tissue remodeling - potent COPD characteristics[51]. Excessively accumulated damaged mitochondria steer the cell towards senescence, ultimately stifling growth and impeding tissue repair mechanisms. Senescent cells, armed with pro-inflammatory cytokines and matrix metalloproteinases, contribute to COPD-induced tissue destruction and airway remodeling. Consequently, senescence hastened by mitochondrial malfunction may likely worsen lung function decline, increase COPD exacerbation susceptibility, and heighten overlying disease severity.

4.4. Metabolic Reprogramming and Muscle Dysfunction

Mitochondrial dysfunction swings the pendulum towards metabolic rearrangements, resulting in muscle dysfunction central to COPD[33]. Unhealthy mitochondria curb oxidative phosphorylation efficiency, thus causing a deficit in ATP supply and negatively impacting skeletal muscle strength and patient exercise tolerance. The metabolic reprogramming characterized by a glycolytic tilt and an overdependence on anaerobic metabolism may compound muscle wasting and functional impairments in COPD[52]. This implies that interventions aiming to rejuvenate mitochondrial health could aid in preserving muscle mass, enhancing exercise capacity, and improving overall patient wellness.

4.5. Exacerbation Susceptibility and Disease Progression

Evidence substantiates an intrinsic connection between mitochondrial dysfunction and an increased risk of exacerbations, including accelerated disease progression in COPD[53,54]. Dysfunctional mitochondria compromise the body's cellular fortitude against external stressors, thereby heightening tissue damage during COPD exacerbations. Apart from exacerbation susceptibility, mitochondrial dysfunction also correlates with a rapid deterioration in lung function and accelerated COPD progression. Consequently, therapeutic blueprints looking to reinstate mitochondrial function might be crucial for minimizing COPD exacerbation risks and slowing down disease progression.

Indeed, understanding the comprehensive implications of mitochondrial dysfunction is vital to the landscape of COPD, serving as the building blocks for potential treatment breakthroughs. This

comprehension could contribute to ushering in an era of effective interventions aiming to hinder disease progression and optimize clinical outcomes - perhaps a fresh dawn of hope for reversible cellular damage marked in COPD patients.

5. Therapeutic Targeting of Mitochondria in COPD

Mounting evidence points toward mitochondrial dysfunction as a crucial component in the pathology of Chronic Obstructive Pulmonary Disease (COPD), making it a potential bullseye for therapeutic strategies[55]. Current investigations delve into a variety of therapeutic approaches intending to rejuvenate mitochondrial function and stall disease progression. These strategic lines of defense mainly focus on portfolio aspects such as abatement of oxidative stress, amplification of mitochondrial biogenesis, and fortification of mitochondrial quality control mechanisms.

5.1. Antioxidant Therapy

Non-specific antioxidants have conventionally been deployed as a primary measure to curtail COPD's oxidative stress, acting as neutralizing agents against ROS[56]. These include thiol-group compounds like N-acetylcysteine (NAC) and carbocysteine alongside dietary antioxidants like vitamins C and E. Encouraging results have been observed in animal models, indicating beneficial effects of antioxidant therapies[57,58]. Real-world evidence gathered from clinical trials involving COPD patients, however, remain inconclusive. Despite small-scale trials suggesting NAC as potentially capable of reducing exacerbation frequency[59], larger studies have not corroborated such findings[60]. Furthermore, hyper-dosing non-targeted antioxidants could paradoxically inflict harm due to potential interference with physiological processes. Ambiguity around dosage guidelines and lack of specificity collectively restricts their usage in clinical practice.

5.2. Mitochondrial Biogenesis Inducers

Pioneering a new potential COPD therapeutic avenue are mitochondrial biogenesis inducers, especially PGC-1 α activators[61]. The fundamental role of PGC-1 α in supervising mitochondrial biogenesis and function amplifies the potential efficacy of therapeutic intervention across this axis. Experimental results from in-vivo models exhibiting improved mitochondrial function and curbed inflammation through pharmacological activation of PGC-1 α inspire optimism in this field [62]. Currently, large-scale clinical trials probing the effectiveness of PGC-1 α activators are underway. While still in exploratory stages, these studies may well pave the way for innovative, mitochondria-focused therapies.

5.3. Mitochondrial Quality Control Enhancers

Investigative interests lean towards enhancing mitochondrial quality control mechanisms as a tangible COPD combat strategy [63]. This typically involves encouraging the process of mitophagy, specifically targeting and eliminating damaged mitochondria. This approach could assist in purging dysfunctional mitochondria while maintaining cellular homeostasis within COPD afflicted environments. In addition, sparking the mitochondrial unfolded protein response (UPR^{mt}) might promote mitochondrial proteostasis, enhancing the mitochondrial functional response amid cellular stress. Ongoing preclinical research on the efficacy of mitophagy inducers and UPR^{mt} activators in COPD is quite promising. It shapes a thrilling landscape filled with future therapeutic potentials awaiting their due acknowledgment in the field of COPD treatment.

6. Therapeutic Implications and Future Directions

Recognizing the pivotal role of mitochondrial dysfunction in Chronic Obstructive Pulmonary Disease paves the way for complementing current treatment strategies with novel, mitochondria-targeted therapeutic interventions. The objective of these innovative therapies is to alleviate disease symptoms and impede disease progression [64]. Mitochondria – the powerhouses of the cell – are central to cellular energy production, regulation of oxidative stress, and numerous cellular signaling

pathways. Thus, their potential as a therapeutic target in managing COPD cannot be overemphasized.

Advancements in biomedical research have led to the formulation of mitochondria-targeted antioxidants (MTAs), specifically designed to penetrate the lipid bilayer of the mitochondria. This offers a direct, targeted approach to neutralize Reactive Oxygen Species (ROS), the harmful byproducts of cellular metabolism, directly at their source [64]. These MTAs have trumped conventional, non-targeted antioxidants in preclinical studies by reducing apoptosis - a form of programmed cell death - and protecting against mitochondrial DNA (mtDNA) damage. This has brought MTAs to the forefront as promising therapeutic agents for COPD. As it stands, two clinical trials are examining the impact of a specific MTA, MitoQ, on COPD patients [65,66]. One of the substantial challenges in these trials relates to the determination of the most effective drug dosage and the establishment of consistent treatment protocols. This underscores the importance of standardizing these elements for the effective use of MitoQ in clinical practice and future COPD management.

Another potential therapeutic intervention in COPD entails modulating the dynamics of mitochondria, using specific compounds such as Dynamin-related protein 1 (Drp1) inhibitors and PTEN-induced kinase 1 (PINK1) activators. By influencing fundamental processes like mitochondrial fusion and fission, these compounds have the potential to restore the interconnectivity of the mitochondrial network, optimize the production of cellular energy – bioenergetics – and boost the survival of cells in COPD-affected lung tissues [39,67].

Moreover, enhancing mitophagy, the process of selectively removing damaged mitochondria, is emerging as an intriguing strategy to maintain mitochondrial health and prevent the buildup of dysfunctional organelles in COPD [68]. Compounds that stimulate mitophagy, such as rapamycin and urolithin A, may help eradicate damaged mitochondria, thereby reducing oxidative stress and mitigating cellular dysfunction – critical components of COPD pathogenesis.

A glimmer of hope for the future lies in the identification of novel mitochondrial biomarkers that could serve as unique, diagnostic indicators of mitochondrial dysfunction in COPD patients. These biomarkers could prove useful in early disease detection, and in observing responses to treatment over time, all while offering predictions of disease outcomes [69]. This could pave the way for personalized medicine approaches tailored to the individual needs of COPD patients.

Lastly, the complex interplay between mitochondria and other cellular pathways implicated in COPD pathogenesis deserves exploration. This includes pathways such as inflammation, autophagy – the cell's recycling process, and cellular senescence – ageing at the cellular level. Dissecting the intricate dynamics between mitochondrial dysfunction and these pathways could shed light on new therapeutic targets. Furthermore, it could offer fresh perspectives for developing innovative treatment strategies aimed at improving COPD management and patient outcomes [70].

6.1. Reactive Oxygen Species (ROS) and Oxidative Stress Markers

Mitochondrial dysfunction in Chronic Obstructive Pulmonary Disease (COPD) is linked with elevated levels of reactive oxygen species (ROS) and oxidative stress markers such as malondialdehyde (MDA) and 8-hydroxy-2'-deoxyguanosine (8-OHdG)[71]. The increase in ROS production by impaired mitochondria leads to oxidative damage to essential cellular components, further exacerbating inflammation and tissue damage characteristic of COPD. By measuring ROS and oxidative stress markers, researchers and clinicians may gain valuable insights into the severity of mitochondrial dysfunction and its relationship with disease severity in COPD [72]. Therefore, these variables could play an instrumental role in assessing, diagnosing, and monitoring the disease.

6.2. Mitochondrial DNA (mtDNA) Damage and Mutations

Mitochondrial DNA (mtDNA) damage and mutations are key indicators of mitochondrial dysfunction, and their detection can serve as potential biomarkers in COPD diagnosis and prognosis. It has been observed that oxidative stress and inflammation in COPD can cause significant mtDNA damage, resulting in impaired mitochondrial function and contribution to COPD progression.

Regular monitoring and quantification of mtDNA damage and mutations provide a unique glimpse into the extent of mitochondrial dysfunction and its impact on COPD pathogenesis [73,74]. This not only illuminates the molecular underpinnings of the disease but also enables the design of personalized therapeutic interventions based on the severity of mtDNA damage or mutations in individual patients.

6.3. Mitochondrial Respiratory Chain Enzyme Activity:

Evaluation of mitochondrial respiratory chain enzyme activity, particularly within complexes I, III, and IV, could prove to be a useful biomarker for indicating mitochondrial dysfunction in COPD. Any inhibition or reduction in the enzyme activity of these complexes indicates an impairment in mitochondrial respiration, leading to consequent deficits in ATP production and an upsurge in ROS generation—both crucial elements in COPD development and progression. The measurement of mitochondrial enzyme activity can provide an innovative diagnostic tool, offering possibilities to identify individuals suffering from mitochondrial dysfunction and to predict disease progression in COPD [75,76]. With such measurements, healthcare professionals can map the trajectory of the disease and adjust their treatment strategies accordingly, potentially leading to more effective management of COPD and improved patient outcomes.

7. Conclusion

The comprehensive study of cellular and molecular processes that influence mitochondria in the context of Chronic Obstructive Pulmonary Disease (COPD) highlights the critical role mitochondrial dysfunction plays both in disease onset and progression. Key scientific insights reveal that mitochondrial dysfunction plays a fundamental role in promoting oxidative stress, inflammation, cellular aging, and tissue remodeling in COPD [77]. Changes related to mitochondrial structure and functionality, including modifications in their morphology, behavior, and energy production processes, could act as potential aggravators, amplifying disease severity and susceptibility to exacerbations.

Focusing therapeutics on addressing mitochondrial dysfunction exhibits tremendous potential in COPD treatment. Intervention strategies aimed at limiting oxidative stress, promoting the formation of new mitochondria, and initiating mechanisms to promote better mitochondrial quality control present possible pathways to decelerate disease progression and improve clinical outcomes in COPD patients [78]. By uncovering ways to restore mitochondrial health, therapeutic avenues are opened which could potentially ease inflammation, safeguard lung function and enhance exercise tolerance in individuals with COPD.

Looking ahead, research should endeavor to unpack the complex mechanisms underlying mitochondrial dysfunction in COPD. Investigative inquiries into the interplay between mitochondrial dysfunction and other disease processes, such as inflammation, cellular aging, and metabolic shifts, will be central to the creation of targeted therapies [78]. Additionally, the detection of new biomarkers indicative of mitochondrial dysfunction and understanding their clinical implications may enable early diagnosis, inform prognosis, and monitor disease management in patients with COPD [79].

Bridging the gap between promising early-stage research findings and application in a clinical setting will necessitate concerted efforts in translational research. This requires the collaborative engagement of basic scientists, clinical experts, and pharmaceutical developers to translate preclinical interventions into robust, clinically effective therapies for COPD [80]. Further advancements in tailored therapeutic platforms, such as targeted drug delivery systems and gene editing technologies, could provide a springboard for precision medicine approaches in COPD management [81].

In conclusion, the therapeutic targeting of mitochondrial dysfunction bears great promise for slowing down COPD progression and improving clinical outcomes. Future research initiatives focused on elucidating the complexities of mitochondrial function within COPD pathophysiology and effectively translating preclinical discoveries into clinical practice hold the key to evolving treatment strategies and the overall management of this disabling respiratory disease.

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Table 1. Biomarkers of Mitochondrial Dysfunction in COPD.

Biomarker	Clinical Implications
Reactive Oxygen Species (ROS)	Indicator of oxidative stress and disease severity
Mitochondrial DNA (mtDNA) Damage	Impairment of mitochondrial function
Mitochondrial Respiratory Chain Enzyme Activity	Biomarker of mitochondrial dysfunction and disease progression indicator
Mitochondrial Biogenesis and Dynamics Markers	Insight into mitochondrial health and disease severity
Circulating Mitochondrial Components	Non-invasive biomarkers for assessing mitochondrial dysfunction and monitoring disease progression

Table 2. Therapeutic Targets for Mitochondrial Dysfunction in COPD.

Therapeutic Approach	Mechanism of Action
Antioxidant Therapy	Reduction of oxidative stress through neutralizing ROS
Mitochondrial Biogenesis Inducers	Activation of PGC-1 α to promote mitochondrial function
Mitochondrial Quality Control Enhancers	Enhancement of mitophagy and activation of UPRmt
Modulators of Mitochondrial Dynamics	Regulation of mitochondrial fusion and fission processes

References

1. Decramer, M.; Janssens, W.; Miravittles, M., Chronic obstructive pulmonary disease. *Lancet* **2012**, 379, (9823), 1341-51.

2. MacLeod, M.; Papi, A.; Contoli, M.; Beghé, B.; Celli, B. R.; Wedzicha, J. A.; Fabbri, L. M., Chronic obstructive pulmonary disease exacerbation fundamentals: Diagnosis, treatment, prevention and disease impact. *Respirology* **2021**, 26, (6), 532-551.

3. Fletcher, M. J.; Upton, J.; Taylor-Fishwick, J.; Buist, S. A.; Jenkins, C.; Hutton, J.; Barnes, N.; Van Der Molen, T.; Walsh, J. W.; Jones, P.; Walker, S., COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. *BMC Public Health* **2011**, 11, 612.

4. Gutiérrez Villegas, C.; Paz-Zulueta, M.; Herrero-Montes, M.; Parás-Bravo, P.; Madrazo Pérez, M., Cost analysis of chronic obstructive pulmonary disease (COPD): a systematic review. *Health Economics Review* **2021**, *11*, 1-12.
5. Bernardo, I.; Bozinovski, S.; Vlahos, R., Targeting oxidant-dependent mechanisms for the treatment of COPD and its comorbidities. *Pharmacology & therapeutics* **2015**, *155*, 60-79.
6. Antunes, M. A.; Lopes-Pacheco, M.; Rocco, P. R., Oxidative stress-derived mitochondrial dysfunction in chronic obstructive pulmonary disease: A concise review. *Oxidative Medicine and Cellular Longevity* **2021**, *2021*, 1-11.
7. Agusti, A.; Sobradillo, P.; Celli, B., Addressing the complexity of chronic obstructive pulmonary disease: from phenotypes and biomarkers to scale-free networks, systems biology, and P4 medicine. *American journal of respiratory and critical care medicine* **2011**, *183*, (9), 1129-1137.
8. Prakash, Y.; Pabelick, C. M.; Sieck, G. C., Mitochondrial dysfunction in airway disease. *Chest* **2017**, *152*, (3), 618-626.
9. van der Schee, M. P.; Paff, T.; Brinkman, P.; van Aalderen, W. M. C.; Haarman, E. G.; Sterk, P. J., Breathomics in lung disease. *Chest* **2015**, *147*, (1), 224-231.
10. Javadov, S.; Kozlov, A. V.; Camara, A. K., Mitochondria in health and diseases. In MDPI: 2020; Vol. 9, p 1177.
11. Rabe, K. F.; Fabbri, L. M.; Israel, E.; Kögler, H.; Riemann, K.; Schmidt, H.; Glaab, T.; Vogelmeier, C. F., Effect of ADRB2 polymorphisms on the efficacy of salmeterol and tiotropium in preventing COPD exacerbations: a prespecified substudy of the POET-COPD trial. *The Lancet Respiratory Medicine* **2014**, *2*, (1), 44-53.
12. Zhang, B.; Pan, C.; Feng, C.; Yan, C.; Yu, Y.; Chen, Z.; Guo, C.; Wang, X., Role of mitochondrial reactive oxygen species in homeostasis regulation. *Redox Report* **2022**, *27*, (1), 45-52.
13. Hikichi, M.; Mizumura, K.; Maruoka, S.; Gon, Y., Pathogenesis of chronic obstructive pulmonary disease (COPD) induced by cigarette smoke. *Journal of thoracic disease* **2019**, *11*, (Suppl 17), S2129.
14. Wang, X.; Wang, Z.; Tang, D., Aerobic exercise alleviates inflammation, oxidative stress, and apoptosis in mice with chronic obstructive pulmonary disease. *International journal of chronic obstructive pulmonary disease* **2021**, 1369-1379.
15. O'Donnell, D. E.; Flüge, T.; Gerken, F.; Hamilton, A.; Webb, K.; Aguilaniu, B.; Make, B.; Magnussen, H., Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* **2004**, *23*, (6), 832-40.
16. Caldeira, D. d. A. F.; Weiss, D. J.; Rocco, P. R. M.; Silva, P. L.; Cruz, F. F., Mitochondria in focus: from function to therapeutic strategies in chronic lung diseases. *Frontiers in Immunology* **2021**, *12*, 782074.
17. Barnes, P. J., Reduced histone deacetylase in COPD: clinical implications. *Chest* **2006**, *129*, (1), 151-5.
18. Zhou, W.-c.; Qu, J.; Xie, S.-y.; Sun, Y.; Yao, H.-w., Mitochondrial dysfunction in chronic respiratory diseases: implications for the pathogenesis and potential therapeutics. *Oxidative Medicine and Cellular Longevity* **2021**, *2021*.
19. Bodas, M.; Min, T.; Vij, N., Critical role of CFTR-dependent lipid rafts in cigarette smoke-induced lung epithelial injury. *Am J Physiol Lung Cell Mol Physiol* **2011**, *300*, (6), L811-20.
20. Chellappan, D. K.; Paudel, K. R.; Tan, N. W.; Cheong, K. S.; Khoo, S. S. Q.; Seow, S. M.; Chellian, J.; Candasamy, M.; Patel, V. K.; Arora, P., Targeting the mitochondria in chronic respiratory diseases. *Mitochondrion* **2022**, *67*, 15-37.
21. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2024 Report. . www.goldcopd.org (May 2),
22. Houben-Wilke, S.; Augustin, I. M.; Vercoulen, J. H.; van Ranst, D.; Bij de Vaate, E.; Wempe, J. B.; Spruit, M. A.; Wouters, E. F. M.; Franssen, F. M. E., COPD stands for complex obstructive pulmonary disease. *Eur Respir Rev* **2018**, *27*, (148).
23. Taniguchi, A.; Tsuge, M.; Miyahara, N.; Tsukahara, H., Reactive oxygen species and antioxidative defense in chronic obstructive pulmonary disease. *Antioxidants* **2021**, *10*, (10), 1537.
24. Rogers, L. K.; Cismowski, M. J., Oxidative stress in the lung—the essential paradox. *Current opinion in toxicology* **2018**, *7*, 37-43.
25. Mumby, S.; Adcock, I. M., Recent evidence from omic analysis for redox signalling and mitochondrial oxidative stress in COPD. *Journal of inflammation* **2022**, *19*, (1), 10.
26. Bu, T.; Wang, L. F.; Yin, Y. Q., How do innate immune cells contribute to airway remodeling in COPD progression? *International Journal of Chronic Obstructive Pulmonary Disease* **2020**, 107-116.
27. Chan, D. C., Mitochondrial dynamics and its involvement in disease. *Annual review of pathology: mechanisms of disease* **2020**, *15*, 235-259.
28. Aghapour, M.; Remels, A. H.; Pouwels, S. D.; Bruder, D.; Hiemstra, P. S.; Cloonan, S. M.; Heijink, I. H., Mitochondria: at the crossroads of regulating lung epithelial cell function in chronic obstructive pulmonary disease. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **2020**, *318*, (1), L149-L164.
29. Cloonan, S. M.; Kim, K.; Esteves, P.; Trian, T.; Barnes, P. J., Mitochondrial dysfunction in lung ageing and disease. *European Respiratory Review* **2020**, *29*, (157).

30. Leermakers, P.; Schols, A.; Kneppers, A.; Kelders, M.; De Theije, C.; Lainscak, M.; Gosker, H., Molecular signalling towards mitochondrial breakdown is enhanced in skeletal muscle of patients with chronic obstructive pulmonary disease (COPD). *Scientific reports* **2018**, 8, (1), 15007.
31. Haji, G.; Wiegman, C. H.; Michaeloudes, C.; Patel, M. S.; Curtis, K.; Bhavsar, P.; Polkey, M. I.; Adcock, I. M.; Chung, K. F.; consortium, C., Mitochondrial dysfunction in airways and quadriceps muscle of patients with chronic obstructive pulmonary disease. *Respiratory Research* **2020**, 21, 1-11.
32. Patergnani, S.; Bouhamida, E.; Leo, S.; Pinton, P.; Rimessi, A., Mitochondrial oxidative stress and “mito-inflammation”: actors in the diseases. *Biomedicines* **2021**, 9, (2), 216.
33. Wang, Y.; Li, P.; Cao, Y.; Liu, C.; Wang, J.; Wu, W., Skeletal Muscle Mitochondrial Dysfunction in Chronic Obstructive Pulmonary Disease: Underlying Mechanisms and Physical Therapy Perspectives. *Aging and Disease* **2023**, 14, (1), 33.
34. Sasaki, K.-i.; Fukumoto, Y., Sarcopenia as a comorbidity of cardiovascular disease. *Journal of cardiology* **2022**, 79, (5), 596-604.
35. Luan, Y.; Ren, K. D.; Luan, Y.; Chen, X.; Yang, Y., Mitochondrial Dynamics: Pathogenesis and Therapeutic Targets of Vascular Diseases. *Front Cardiovasc Med* **2021**, 8, 770574.
36. Chellappan, D. K.; Dharwal, V.; Paudel, K. R.; Jha, N. K.; MacLoughlin, R.; Oliver, B. G.; M Hansbro, P.; Dua, K., Mitochondrial dysfunctions associated with chronic respiratory diseases and their targeted therapies: an update. In *Future Science: 2021; Vol. 13*, pp 1249-1251.
37. Barnes, P. J., Oxidative stress-based therapeutics in COPD. *Redox biology* **2020**, 33, 101544.
38. Kang, M.-J.; Shadel, G. S., A mitochondrial perspective of chronic obstructive pulmonary disease pathogenesis. *Tuberculosis and Respiratory Diseases* **2016**, 79, (4), 207.
39. Pokharel, M. D.; Garcia-Flores, A.; Marciano, D.; Franco, M. C.; Fineman, J. R.; Aggarwal, S.; Wang, T.; Black, S. M., Mitochondrial network dynamics in pulmonary disease: Bridging the gap between inflammation, oxidative stress, and bioenergetics. *Redox Biology* **2024**, 103049.
40. Hara, H.; Kuwano, K.; Araya, J., Mitochondrial quality control in COPD and IPF. *Cells* **2018**, 7, (8), 86.
41. Karim, L.; Lin, C.-R.; Kosmider, B.; Criner, G.; Marchetti, N.; Bolla, S.; Bowler, R.; Bahmed, K., Mitochondrial ribosome dysfunction in human alveolar type II cells in emphysema. *Biomedicines* **2022**, 10, (7), 1497.
42. Rius-Pérez, S.; Torres-Cuevas, I.; Millán, I.; Ortega Á, L.; Pérez, S., PGC-1 α , Inflammation, and Oxidative Stress: An Integrative View in Metabolism. *Oxid Med Cell Longev* **2020**, 2020, 1452696.
43. Li, J.; Dai, A.; Hu, R.; Zhu, L.; Tan, S., Positive correlation between PPAR γ /PGC-1 α and gamma-GCS in lungs of rats and patients with chronic obstructive pulmonary disease. *Acta Biochim Biophys Sin (Shanghai)* **2010**, 42, (9), 603-14.
44. Bradley, K. L.; Stokes, C. A.; Marciniak, S. J.; Parker, L. C.; Condliffe, A. M., Role of unfolded proteins in lung disease. *Thorax* **2021**, 76, (1), 92-99.
45. Barabutis, N., Unfolded protein response in lung health and disease. *Frontiers in Medicine* **2020**, 7, 344.
46. Wiegman, C. H.; Michaeloudes, C.; Haji, G.; Narang, P.; Clarke, C. J.; Russell, K. E.; Bao, W.; Pavlidis, S.; Barnes, P. J.; Kanerva, J., Oxidative stress-induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease. *Journal of Allergy and Clinical Immunology* **2015**, 136, (3), 769-780.
47. Sharma, G.; Banerjee, R.; Srivastava, S., Molecular Mechanisms and the Interplay of Important Chronic Obstructive Pulmonary Disease Biomarkers Reveals Novel Therapeutic Targets. *ACS omega* **2023**, 8, (49), 46376-46389.
48. Sinha, K.; Das, J.; Pal, P. B.; Sil, P. C., Oxidative stress: the mitochondria-dependent and mitochondria-independent pathways of apoptosis. *Archives of toxicology* **2013**, 87, 1157-1180.
49. Dela Cruz, C. S.; Kang, M. J., Mitochondrial dysfunction and damage associated molecular patterns (DAMPs) in chronic inflammatory diseases. *Mitochondrion* **2018**, 41, 37-44.
50. Wiegman, C. H.; Michaeloudes, C.; Haji, G.; Narang, P.; Clarke, C. J.; Russell, K. E.; Bao, W.; Pavlidis, S.; Barnes, P. J.; Kanerva, J.; Bittner, A.; Rao, N.; Murphy, M. P.; Kirkham, P. A.; Chung, K. F.; Adcock, I. M., Oxidative stress-induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol* **2015**, 136, (3), 769-80.
51. Birch, J.; Barnes, P. J.; Passos, J. F., Mitochondria, telomeres and cell senescence: implications for lung ageing and disease. *Pharmacology & therapeutics* **2018**, 183, 34-49.
52. Layec, G.; Haseler, L. J.; Hoff, J.; Richardson, R. S., Evidence that a higher ATP cost of muscular contraction contributes to the lower mechanical efficiency associated with COPD: preliminary findings. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology* **2011**, 300, (5), R1142-R1147.
53. Hoffmann, R.; Jonker, M.; Brandenburg, S.; De Bruin, H.; Ten Hacken, N.; Van Oosterhout, A.; Heijink, I., Mitochondrial dysfunction increases pro-inflammatory cytokine production and impairs repair and corticosteroid responsiveness in lung epithelium. *Scientific reports* **2019**, 9, (1), 15047.

54. Lerner, C. A.; Sundar, I. K.; Rahman, I., Mitochondrial redox system, dynamics, and dysfunction in lung inflammaging and COPD. *The international journal of biochemistry & cell biology* **2016**, 81, 294-306.
55. Fairley, L. H.; Das, S.; Dharwal, V.; Amorim, N.; Hegarty, K. J.; Wadhwa, R.; Mounika, G.; Hansbro, P. M., Mitochondria-Targeted Antioxidants as a Therapeutic Strategy for Chronic Obstructive Pulmonary Disease. *Antioxidants (Basel)* **2023**, 12, (4).
56. Kirkham, P. A.; Barnes, P. J., Oxidative stress in COPD. *Chest* **2013**, 144, (1), 266-273.
57. Dekhuijzen, P. N.; van Beurden, W. J., The role for N-acetylcysteine in the management of COPD. *Int J Chron Obstruct Pulmon Dis* **2006**, 1, (2), 99-106.
58. Jomova, K.; Raptova, R.; Alomar, S. Y.; Alwasel, S. H.; Nepovimova, E.; Kuca, K.; Valko, M., Reactive oxygen species, toxicity, oxidative stress, and antioxidants: Chronic diseases and aging. *Archives of toxicology* **2023**, 97, (10), 2499-2574.
59. Ansari, S. F.; Memon, M.; Brohi, N.; Tahir, A.; Ansari, S.; Siddiqui, A., N-acetylcysteine in the management of acute exacerbation of chronic obstructive pulmonary disease. *Cureus* **2019**, 11, (11).
60. Huang, C.; Kuo, S.; Lin, L.; Yang, Y., The efficacy of N-acetylcysteine in chronic obstructive pulmonary disease patients: a meta-analysis. *Therapeutic Advances in Respiratory Disease* **2023**, 17, 17534666231158563.
61. Li, J.; Dai, A.; Hu, R.; Zhu, L.; Tan, S., Positive correlation between PPAR γ /PGC-1 α and γ -GCS in lungs of rats and patients with chronic obstructive pulmonary disease. *Acta Biochim Biophys Sin* **2010**, 42, (9), 603-614.
62. Barnes, P. J., Targeting cellular senescence as a new approach to chronic obstructive pulmonary disease therapy. *Current Opinion in Pharmacology* **2021**, 56, 68-73.
63. Suárez-Rivero, J. M.; Pastor-Maldonado, C. J.; Povea-Cabello, S.; Álvarez-Córdoba, M.; Villalón-García, I.; Talaverón-Rey, M.; Suárez-Carrillo, A.; Munuera-Cabeza, M.; Reche-López, D.; Cillerós-Holgado, P., UPRmt activation improves pathological alterations in cellular models of mitochondrial diseases. *Orphanet journal of rare diseases* **2022**, 17, (1), 204.
64. Fairley, L. H.; Das, S.; Dharwal, V.; Amorim, N.; Hegarty, K. J.; Wadhwa, R.; Mounika, G.; Hansbro, P. M., Mitochondria-targeted antioxidants as a therapeutic strategy for chronic obstructive pulmonary disease. *Antioxidants* **2023**, 12, (4), 973.
65. Rodríguez-Miguel, P., Mitochondrial Derived Reactive Oxygen Species on Cardiovascular Health in Chronic Obstructive Pulmonary Disease (COPD). In Virginia Commonwealth University: 2024.
66. Richardson, R., : Vascular Function in Health and Disease. In George E Wahlen VA Medical Center: 2023.
67. Wang, Z.; White, A.; Wang, X.; Ko, J.; Choudhary, G.; Lange, T.; Rounds, S.; Lu, Q., Mitochondrial Fission Mediated Cigarette Smoke-induced Pulmonary Endothelial Injury. *Am J Respir Cell Mol Biol* **2020**, 63, (5), 637-651.
68. Monsel, A.; Zhu, Y. G.; Gennai, S.; Hao, Q.; Liu, J.; Lee, J. W., Cell-based therapy for acute organ injury: preclinical evidence and ongoing clinical trials using mesenchymal stem cells. *Anesthesiology* **2014**, 121, (5), 1099-121.
69. Houssaini, A.; Abid, S.; Mouraret, N.; Wan, F.; Rideau, D.; Saker, M.; Marcos, E.; Tissot, C. M.; Dubois-Randé, J. L.; Amsellem, V.; Adnot, S., Rapamycin reverses pulmonary artery smooth muscle cell proliferation in pulmonary hypertension. *Am J Respir Cell Mol Biol* **2013**, 48, (5), 568-77.
70. Ghebre, M. A.; Pang, P. H.; Diver, S.; Desai, D.; Bafadhel, M.; Haldar, K.; Kebabdzé, T.; Cohen, S.; Newbold, P.; Rapley, L.; Woods, J.; Rugman, P.; Pavord, I. D.; Johnston, S. L.; Barer, M.; May, R. D.; Brightling, C. E., Biological exacerbation clusters demonstrate asthma and chronic obstructive pulmonary disease overlap with distinct mediator and microbiome profiles. *J Allergy Clin Immunol* **2018**, 141, (6), 2027-2036.e12.
71. Li, F.; Xu, M.; Wang, M.; Wang, L.; Wang, H.; Zhang, H.; Chen, Y.; Gong, J.; Zhang, J.; Adcock, I. M., Roles of mitochondrial ROS and NLRP3 inflammasome in multiple ozone-induced lung inflammation and emphysema. *Respiratory research* **2018**, 19, 1-12.
72. Burton, G. J.; Jauniaux, E., Oxidative stress. *Best Pract Res Clin Obstet Gynaecol* **2011**, 25, (3), 287-99.
73. Aravamudan, B.; Kiel, A.; Freeman, M.; Delmotte, P.; Thompson, M.; Vassallo, R.; Sieck, G. C.; Pabelick, C. M.; Prakash, Y., Cigarette smoke-induced mitochondrial fragmentation and dysfunction in human airway smooth muscle. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **2014**, 306, (9), L840-L854.
74. Scarpulla, R. C., Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network. *Biochim Biophys Acta* **2011**, 1813, (7), 1269-78.
75. Barrientos, A.; Fontanesi, F.; Díaz, F., Evaluation of the mitochondrial respiratory chain and oxidative phosphorylation system using polarography and spectrophotometric enzyme assays. *Curr Protoc Hum Genet* **2009**, Chapter 19, Unit19.3.
76. Carvalho, V. F.; Barreto, E.; Victoni, T.; Lagente, V., The Role of Oxidative Imbalance on Pulmonary Diseases. In Hindawi: 2022; Vol. 2022.
77. Sharma, A.; Ahmad, S.; Ahmad, T.; Ali, S.; Syed, M. A., Mitochondrial dynamics and mitophagy in lung disorders. *Life sciences* **2021**, 284, 119876.

78. Hoffmann, R. F.; Zarrintan, S.; Brandenburg, S. M.; Kol, A.; de Bruin, H. G.; Jafari, S.; Dijk, F.; Kalicharan, D.; Kelders, M.; Gosker, H. R.; Ten Hacken, N. H.; van der Want, J. J.; van Oosterhout, A. J.; Heijink, I. H., Prolonged cigarette smoke exposure alters mitochondrial structure and function in airway epithelial cells. *Respir Res* **2013**, *14*, (1), 97.
79. Sato, K.; Kawakami, H., Mitochondrial Dysfunction and Nanocarrier-Based Treatments in Chronic Obstructive Pulmonary Disease (COPD). *Oxygen* **2023**, *3*, (4), 394-406.
80. Guarnier, L. P.; Moro, L. G.; Lívero, F.; de Faria, C. A.; Azevedo, M. F.; Roma, B. P.; Albuquerque, E. R.; Malagutti-Ferreira, M. J.; Rodrigues, A. G. D.; da Silva, A. A.; Sekiya, E. J.; Ribeiro-Paes, J. T., Regenerative and translational medicine in COPD: hype and hope. *Eur Respir Rev* **2023**, *32*, (169).
81. Bolger, G. B., Therapeutic Targets and Precision Medicine in COPD: Inflammation, Ion Channels, Both, or Neither? *Int J Mol Sci* **2023**, *24*, (24).

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