MDPI

Review

Mitochondrial Dysfunction and Nanocarrier-Based Treatments in Chronic Obstructive Pulmonary Disease (COPD)

Kiyoshi Sato * and **Hiroyoshi Kawakami** *

Department of Applied Chemistry for Environment, Tokyo Metropolitan University, 1-1 Minami-Osawa, Hachioji 192-0397, Japan
* Correspondence: sato-kiyoshi@tmu.ac.jp (K.S.); kawakami-hiroyoshi@tmu.ac.jp (H.K.)

Abstract: Mitochondrial dysfunction significantly contributes to the pathogenesis and progression of chronic obstructive pulmonary disease (COPD). To treat mitochondrial dysfunction in COPD, novel drug delivery systems (DDS) are needed. In this review, we provide a brief overview of the current understanding of the factors in COPD and highlight the trends in novel nanocarriers/nanoparticles for targeting mitochondrial dysfunction. These drug-encapsulated nanoparticles are still in the early stages of clinical application but represent the most promising system for COPD therapy.

Keywords: chronic obstructive pulmonary disease; mitochondrial dysfunction; nanoparticles; drug carriers

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common lung disease and a general term for progressive diseases of the respiratory system that comprise chronic bronchitis and emphysema. COPD is characterized by chronic inflammation, progressive airway constriction, and alveolar destruction, resulting in symptoms such as persistent cough, shortness of breath, and increased mucus production [1]. The symptoms of this incurable lung disease are thought to be mainly caused by inflammation of bronchial/airway epithelial cells, impaired lung fibroblasts, and alveolar destruction [2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recently proposed a new definition of COPD as a "heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, expectoration, exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction" [2]. While cigarette smoking is the primary cause of COPD, prolonged exposure to harmful environmental pollutants, including dust, fumes, chemicals, air pollution (such as PM2.5 and toxic gases), and indoor smoke from coal or biomass fuels can also contribute to the onset of the disease [1]. The World Health Organization reported over 320 million COPD patients in 2020, and the disease is also attributed to over 3 million annual deaths, the third leading cause of death globally [3].

Despite the worldwide prevalence of COPD, the molecular processes underlying the disease still remain elusive [4]. Therefore, current treatment methods for COPD are limited to symptomatic therapy. Since COPD is progressive, the treatment approach depends on severity. Bronchodilators (β2 agonists, anticholinergics, and theophylline) are commonly used for stable COPD patients. For more severe cases, combination therapy of long-acting β2 agonists (LABA) or long-acting muscarinic antagonists (LAMA) with inhaled corticosteroids (ICS) is the standard treatment for COPD. Triple therapy (LABA/LAMA/ICS) might also be considered an option for certain patients. These medications are generally administrated by inhalation [5].

Mitochondria are known as "the powerhouse of the cell" because of their main role in the energy production of ATP synthesis via oxidative phosphorylation. But mitochondria

are not just the powerhouse of the cell. In addition to energy production, mitochondria execute many other crucial functions such as regulation of cellular metabolism, nucleotide-synthesizing, calcium-buffering, and control of cell cycle and cell death [6]. The decline or dysregulation of these functions of mitochondria is leading to the overproduction of ROS, loss of ATP and metabolite production, disruption of calcium homeostasis, and senescence induction [6]. The accumulation of dysfunctional mitochondria in cells is associated with metabolic disorders [7,8], signal transduction abnormalities [9], inflammation [10], and mal-function not only at the cellular level but also in tissues, organs, and the entire organism. In recent years, the relationship between mitochondrial dysfunction and many diseases, such as cancer, diabetes, and neurodegenerative diseases, has been well-recognized [6,11,12]. Although the exact mechanisms are still being studied, recent studies suggest that mito-chondrial dysfunction contributes to the development and progression of COPD [13,14]. Oxidative stress, inflammation, apoptosis, cellular senescence, skeletal muscle dysfunction, and autophagy/mitophagy dysfunction might be related to both mitochondrial dysfunc-tion and COPD (Table 1). These connections are being explored, but the relationship is complex and not fully understood [15]. Researchers continue to investigate the molecular pathways and mechanisms underlying this relationship in order to better understand how mitochondrial dysfunction contributes to COPD pathogenesis (Figure 1).

Table 1. Potential relationship between mitochondrial dysfunction and COPD.

Biological Events	Relation to Mitochondrial Dysfunction and COPD	References
Oxidative Stress	Mitochondrial ROS are natural byproducts of cellular respiration. However, stress-induced mitochondrial dysfunction causes excessive ROS production, contributing to inflammatory immune responses and alternation of functions in lung and airway epithelial cells, leading to the development of COPD.	[16–18]
Inflammation	Airway inflammation caused by altered immunity is associated with the pathogenesis and progression of COPD. Inflammatory responses affect mitochondrial function, and dysfunctional mitochondria, in turn, release molecules to promote inflammation, creating a negative feedback loop.	[19]
Apoptosis	Oxidative stress-induced abnormal apoptosis of alveolar epithelial cells and decrease in VEGF result in the emphysema observed in COPD. Activated CD8+ cells further induce apoptosis of alveolar cells. Reduction in neutrophil apoptosis leads to chronic inflammation and tissue injury. Increased apoptosis of T-cells contributes to the high frequency of infections in COPD patients.	[20,21]
Cellular Senescence	Excessive ROS accelerate cellular senescence and aberrant cytokine secretion. Senescent cells propagate inflammation, and the accumulation of senescent cells in COPD patients contributes to the difficulty of tissue repair and further secretion of multiple inflammatory proteins and cytokines.	[22,23]
Skeletal Muscle Dysfunction	Dysfunctional mitochondria in skeletal cells decrease ATP production, potentially contributing to the weakness of muscle contractility and endurance often experienced by COPD patients. Skeletal muscle dysfunction further exacerbates the symptoms of COPD.	[24,25]
Autophagy	Dysregulated autophagy in COPD contributes to an inappropriate immune response, exaggerated inflammation, and exacerbated proteostasis imbalance. Autophagy in airway smooth muscle cells influences airway remodeling and bronchial hyperresponsiveness.	[26–29]
Mitophagy	Mitophagy removes damaged mitochondria from the cell and suppresses oxidative stress. The accumulation of dysfunctional mitochondria due to impaired mitophagy in COPD leads to excessive ROS generation, resulting in further oxidative stress and cellular damage.	[28,29]
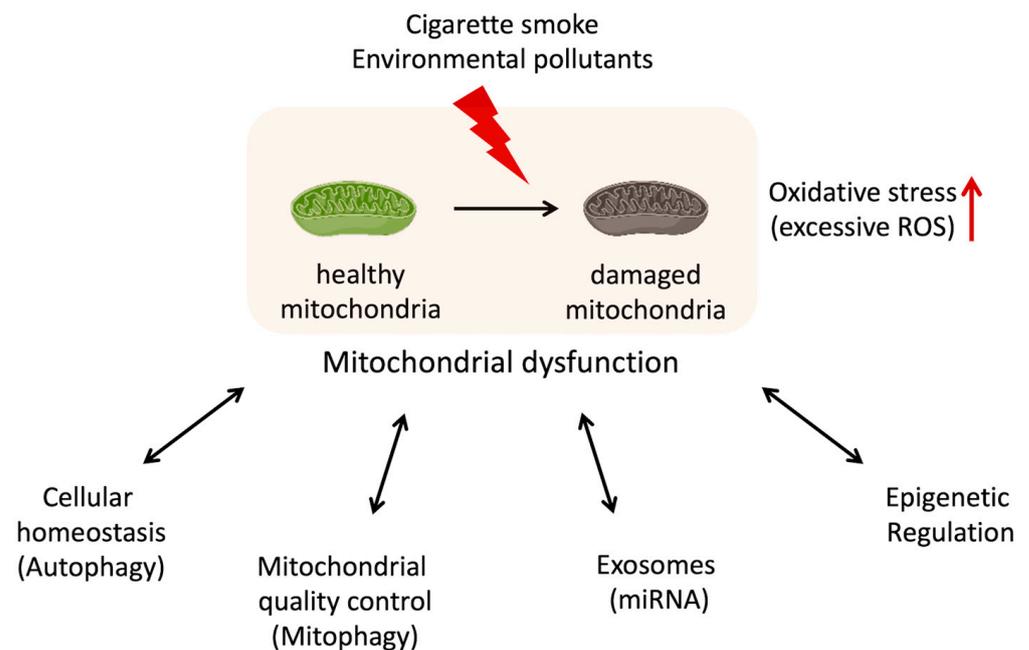
Figure 1. Potential relationship between mitochondrial dysfunction and dysregulation in the cellular function with COPD.

Here, we provide a current overview of how mitochondrial dysfunctions impinge on COPD. Additionally, this review highlights a nanoparticle-based drug delivery system (DDS) for COPD therapy.

2. Mitochondrial Dysfunction in COPD

2.1. Oxidative Stress/Reactive Oxygen Species (ROS)

Oxidative stress has been recognized as a major risk factor for COPD pathogenesis and a target for COPD treatments. Exogenous ROS, such as cigarette smoke or harmful stimuli, and endogenous ROS from activated inflammatory cells or dysfunctional mitochondria may affect signaling pathways and antioxidant defenses, leading to damage and death of epithelial cells in the airway and lung, which may contribute to the development and progression of COPD [16].

Currently, there is accumulating evidence of mitochondrial dysfunction and over-production of mitochondrial ROS in the lung/pulmonary epithelial cells of COPD patients [17,18,30]. Cigarette smoke contains 10^{15}–10^{17} ROS/puff [31], responsible for mitochondrial DNA (mtDNA) damage and mitochondrial ROS generation. Oxidative stress-induced mitochondrial ROS activate the immune response in lung tissue, resulting in the production of inflammatory cytokines and secretion of pro-inflammatory interleukins [19]. Long-term cigarette smoke exposure leads to changes in mitochondrial structure and function in bronchial epithelial cells [32], resulting in extensive apoptosis [20,21] and cellular senescence [22,23].

Mitochondrial ROS and dysfunction of mitochondria contribute to the reduction in skeletal muscle strength and exercise endurance in COPD patients [24]. Skeletal muscle cells in COPD patients are characterized by increased mitochondrial ROS, decreased mitochondrial biogenesis and ATP production, and impaired mitochondrial respiratory chain complexes, possibly associated with mitochondrial apoptosis [25].

2.2. Autophagy and Mitophagy

Autophagy and mitophagy are cellular processes for maintaining cellular health and functions and preventing the accumulation of dysfunctional cellular components. Autophagy

degrades damaged or abnormal cellular components to maintain cellular homeostasis. Mitophagy is a specific form of autophagy that selectivity removes impaired mitochondria.

Accumulating evidence has demonstrated the activation of autophagy in the lung tissue of human COPD patients and model mice [26]. For example, cigarette smoke extract-exposed mice lung tissues showed a remarkable elevation of the LC3-II/LC3-I ratio [33]. Autophagy activation protects the lung by decreasing cellular senescence [27]. However, autophagy exerts both protective and destructive effects in COPD [28,29]. Activated autophagy increases inflammatory cytokines such as TNF-α, IL-6, and IL-8, leading to aggravating pathological processes of COPD and affecting prognosis [33]. Therefore, whether autophagy activation protects the lung or aggravates COPD needs further elucidation.

Mitophagy is generally thought to control the quality of mitochondria by eliminating dysfunctional mitochondria [34]. However, in COPD patients, cigarette smoke extract impairs Parkin-dependent mitophagy by the accumulation of cytoplasmic p53, which inhibits Parkin recruitment to damaged mitochondria [35]. Impaired mitophagy and accumulation of dysfunctional mitochondria affect the activity of epithelial cells in the lung and promote COPD. In addition, cigarette smoke exposure-induced mitophagy regulates RIP1/RIP3 kinase-depended necroptosis, a programmed cell death in necrosis. In the lungs of COPD patients, the expression of mitophagy-associated molecule PINK1 and necroptosis-associated molecule RIP3 is enhanced compared to that of healthy individuals, suggesting that mitophagy is associated with necroptosis induction involved in the pathogenesis of COPD [36].

Understanding these mechanisms could potentially lead to the development of targeted therapies to restore or enhance autophagy and mitophagy processes. However, further research is needed to fully elucidate the precise roles and interactions of autophagy/mitophagy in COPD.

3. Mitochondrial Transfer

Transfer of healthy mitochondria can restore damaged cells and maintain tissue homeostasis. For example, intercellular mitochondrial transfer from mesenchymal stem cells (MSCs) to lung structural cells reduces mitochondrial damage due to oxidative stress [37]. Therefore, intercellular mitochondrial transfer and artificial mitochondrial transfer have been expected for novel therapeutic approaches for COPD [38,39].

Agrawal et al. demonstrated that levels of mitochondrial Rho-GTPase (Miro1) in MSCs regulate intercellular mitochondrial transfer. Mitochondrial dysfunction in bronchial epithelial cells treated with a pro-inflammatory supernatant of IL-13-induced macrophages was reversed by the donation of mitochondria from Miro1-overexpressed MSCs. This result suggests that amplification of mitochondrial transfer may increase the efficacy of MSCs to repair cell functions of damaged cells in COPD [40].

A recent report demonstrates that airway smooth muscle cells (ASMCs) also exchange mitochondria by extracellular vesicles (EVs) under the stress of cigarette smoke. The authors also found autophagy-related proteins in the EVs, suggesting that the transferred damaged mitochondria were delivered for outsourced degradation referred to as "transmitophagy" owing to regulation bioenergetics and cellular function in airways. The results are particularly intriguing since they suggest novel homeostatic mechanisms in lung stromal cells and a new potential treatment modality for COPD [41].

4. Relationship between Epigenetic Dysregulation and Mitochondrial Dysfunction

Epigenetics refers to the regulation of gene expression without any alterations in DNA sequence but rather by changes to DNA methylation (methylation of cytosines in the promotor region of genes) or histone modification (acetylation or methylation of lysine in histone tails). These epigenetic modifications influence how genes turn-on or turn-off, thereby affecting the activity of specific genes and corresponding proteins [42].

Several studies have suggested a connection between epigenetic changes and the development and progression of COPD. For example, cigarette smoke and air pollution

can induce epigenetic changes [43,44]. Liu et al. reported that chronic exposure of cigarette smoke condensate to human small airway epithelial cells and bronchial epithelial cells induces histone alterations (increasing of H3K27Me3 and decreasing of H4K16Ac and H4K20Me3) together with a reduction in DNA methyltransferase-1 (DNMT1) and an increase in DNMT3b expression, resulting in hypomethylation of repetitive DNA sequences (D4Z4, NBL2, and LINE-1) and hypermethylation of tumor suppressor genes such as RASSF1A and RAR-β [45]. These changes can alter the expression/silencing of the target genes, increasing the risk of developing COPD. The DNA methylation patterns of human lung fibroblasts of different COPD stages were recently analyzed [46]. The high-resolution multi-omic analysis demonstrated that significant changes, particularly in genome regulatory regions, occur at an early stage. They identified that the regions contain binding sites for transcription factors TCF21 and FOSL2/FRA2 as novel regulators of the key fibroblast processes in COPD [46].

In patients with COPD, the epigenome of lung cells has significantly altered and regulated changes in cellular programming. The suppression and prevention of the development of COPD are aided by the dysregulation of histone deacetylase (HDAC) activity caused by certain variables and miRNAs. Additionally, COPD treatments are suggested that target HDAC2 and miRNA. However, it is still unknown which epigenetic alterations directly affect lung fibroblasts or how these changes activate aberrant signaling pathways inducing fibroblast dysfunction [44].

Epigenetic modifications can also influence mitochondrial metabolism and biogenesis. For example, changes in mitochondrial DNA can influence the regulation of genes encoding proteins involved in oxidative phosphorylation. The increased production of ROS from damaged mitochondria can lead to DNA damage and modify epigenetic marks [47]. Conversely, these epigenetic changes can affect gene expression and contribute to the development of COPD. In summary, epigenetic dysregulation and mitochondrial dysfunction are intricately linked processes that can influence each other bidirectionally.

Understanding the intricate relationship between epigenetics and mitochondrial dysfunction in COPD could provide insights into disease mechanisms and the discovery of novel biomarkers or potential therapeutic targets. In addition, epigenetic modifications are reversible in some cases, which raises the possibility of developing interventions to mitigate the symptoms of COPD or slow progression by targeting these epigenetic changes [48,49]. However, further research is needed to fully elucidate the specific epigenetic mechanisms underlying COPD and their potential clinical applications.

5. Nanocarrier-Based Treatments for COPD

Oxidative stress is an effective target for COPD treatment, but conventional antioxidants face obstructions such as airway immune response, mucous hypersecretion, inflammation, and low bioavailability, necessitating an efficient DDS [50].

The most successful drug delivery platform for COPD currently under development is nanoparticles used as carriers (Figure 2) because nanoparticles provide various advantages [51–54]. For instance, the use of nanoparticles allows for better penetration into alveolar epithelial tissue than conventional treatments, minimizes drug dosage by attachment of targeting function, and can transport poorly soluble drugs, leading to enhanced treatment efficacy together with reducing toxicity [55]. Nanoparticle-based drug carriers can also be modified to effectively deliver drugs to target organelles such as mitochondria [56]. However, current challenges in nanoparticle-based respiratory disease treatment are airway defense, mucus hypersecretion, and severe inflammation. Surface modification and size control of nanoparticles are important to enhance biodistribution [57,58].
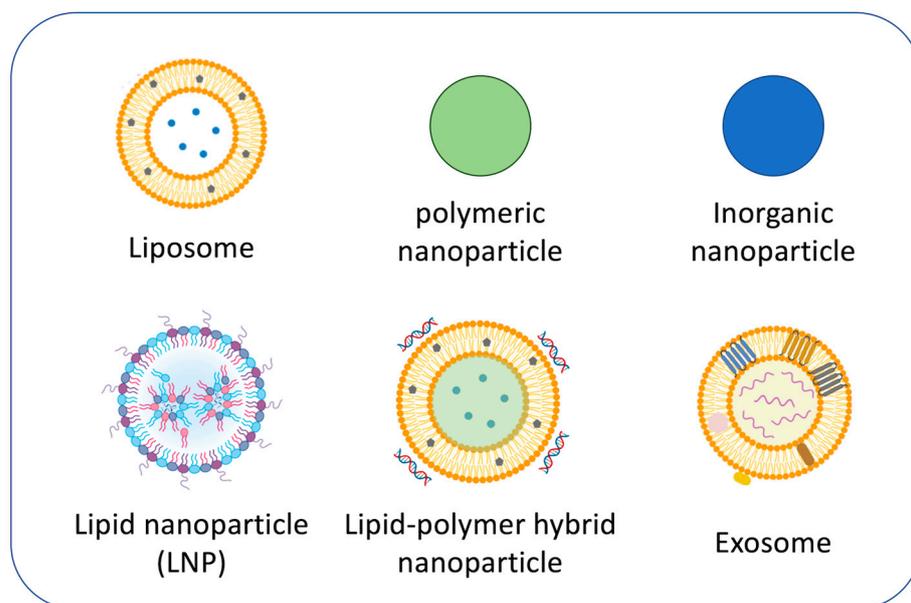
Figure 2. Representative nanoparticles for COPD treatments.

5.1. Liposomes

Liposomes are a promising platform for nanoparticle-based DDS and the most common type of FDA/EMA-approved nanoparticles. Liposomes can transport both hydrophilic and hydrophobic/lipophilic drugs, making them suitable for combination therapy in COPD. In addition, liposomes often modify their surface to enhance the delivery of encapsulated drugs [59–61]. For example, curcumin-loaded liposomes coated with chitosan or hyaluronic acid were prepared to improve the antioxidant effect [62]. Both examples of polymer-coated liposomes greatly improved the stability, biocompatibility, and antioxidant ability of curcumin to protect A549 cells from mitochondrial oxidative stress. In particular, hyaluronic acid-coated liposomes showed enhancement of proliferation and metabolic activity [62].

A major challenge in transferring liposome-based treatments from research to clinical stages exists in the administration method of liposomes. Although inhaled therapy is a fundamental key in COPD treatments, inhalation of liposomes has limitations due to the instability of liposomes during dehydration, storage, and nebulization, leading to leakage of drugs. To be effective, liposomes must maintain their physical properties at pre-/post-inhalation, necessitating approaches for increased stability. Currently, a number of nebulizable liposome formulations have entered clinical trials [63].

5.2. Polymeric Nanoparticles

Biodegradable polymer-based nanoparticles have great potential as DDS and various polymeric nanoparticles have been reported for COPD treatments.

PLA nanoparticles are FDA-approved carriers and have been applied as drug carriers for the treatment of COPD. Buhecha et al. prepared poly(lactic acid) nanoparticles (PLA NPs) co-encapsulated theophylline (hydrophilic bronchodilator) and budesonide (lipophilic corticosteroid) by a double emulsification solvent diffusion method for combination therapy of COPD [64]. The PLA NPs showed sustained release of the two drugs into a 1:1 mixture of simulated lung fluid and MeOH, which is expected to extend the dose intervals and reduce the incidence of side effects.

Neutrophils have emerged as a novel target in COPD treatments. Neutrophils usually help defend the lungs against the risk of infections, but migration and accumulation of activated neutrophils at inflammatory tissues lead to further damage to the lungs in COPD patients. However, drug delivery to neutrophils remains a significant challenge. Surface modification with specific ligands can improve targeting and enhance drug delivery. Vij et al. demonstrated that a PEGylated PLGA-nanoparticle conjugated with anti-NIMP-

R14 antibodies selectively delivered ibuprofen into neutrophils to inhibit neutrophilic inflammation in COPD model mice [65].

In recent years, the study of RNA-based COPD treatments has increased. Direct delivery of RNA is optimal for minimizing adverse reactions, but the elevation of RNA stability during delivery remains the next challenge to realize RNA therapies [66]. Mohamed et al. demonstrate the potential of polymeric nanoparticles as a miRNA delivery vehicle. They used a mixture of poly(glycerol adipate-co-ω-pentadecalactone) (PGA-co-PDL) and cationic lipid (DOTAP) for the carrier of miR-146a. The miRNA-loaded nanocomposite particles effectively delivered miR-146a into lung epithelial cells and reduced the expression of the target gene and the level of the IRAK1 protein [67]. Then, the authors applied the miR-146a/PGA-co-PDL nanoparticles for dry powder inhalation. L-leucine and mannitol were used as dispersion enhancers and protective excipients to formulate micro-sized composite particles by spray-drying [68].

5.3. Lipid-Polymer Hybrid Nanoparticles

Lipid-polymer nanoparticles are hybrid-type nanoparticles with a biodegradable polymer core and lipid shell. These lipid-enveloped polymeric nanoparticles have features of polymeric nanoparticles and liposomes.

Craparo et al. prepared alveolar macrophage-targeted lipid-polymer hybrid nanoparticles as a potential carrier for the delivery of Roflumilast, a PDE4 inhibitor, to treat COPD because the overexpression of PDE4 in alveolar macrophages implicated the inflammatory pathogen [69]. Roflumilast-loaded polymeric nanoparticles and liposomal vesicles of DPPC and DSPE-PEG2000-mannose phospholipids were combined by high-pressure homogenization. The obtained core-shell type lipid-polymer hybrid nanoparticles slowly released the drug which was taken up by macrophages via a mannose-mediated process through binding to mannose receptors overexpressed on the surface of alveolar macrophages in the lungs of COPD patients. The hybrid nanoparticles were successfully encapsulated in poly(vinyl alcohol)/leucine-based microparticles into an inhalable formulation by spray drying.

Excessive ROS production by mitochondrial dysfunction leads to a decrease in histone deacetylase 2 (HDAC2) that causes glucocorticoid resistance in COPD patients in an epigenetic manner [43,70]. To improve glucocorticoid resistance, Chikuma et al. prepared lipid-polymer hybrid nanoparticles composed of a Mn-porphyrin dimer (MnPD)-encapsulated PLGA core coated with a HDAC2-encoding plasmid DNA (pHDAC2)-bound cationic lipid (DOTAP) shell. Co-delivery of MnPD and pHDAC2 exhibited effective elimination of mitochondrial ROS and significant enhancement of HDAC2 expression with a decrease in IL-8 expression that indicates improvement of glucocorticoid resistance in COPD model cells [71].

5.4. Lipid Nanoparticles

Lipid nanoparticles (LNPs) are now widely used for nucleic acid delivery vehicles, which generally consist of four lipids: ionizable lipids necessary to form complexes with nucleic acids and promote endosomal escape, phospholipids for particle formation, cholesterol for stability and membrane fusion, and PEGylated lipids for improved circulation [72].

Recently, powdered LNPs compatible with dry powder inhaler devices have been investigated. Powdered LNPs prepared under proper manufacturing conditions not only recapitulate drug efficacy but also improve the stability of nanoparticles and encapsulated drugs. Zimmermann et al. tested the spray-drying process of siRNA-encapsulated LNP powders. The spray dried LNPs, prepared using 5% lactose solution, effectively penetrated into the artificial mucus layer and showed efficient gene silencing (>90% protein downregulation) in H1299 cells with good cellular compatibility. The spray dried LNPs also efficiently encapsulated up to 50% silenced GAPDH genes in ex vivo human lung tissues [73].

5.5. Inorganic Nanoparticles

Metallic nanoparticles such as Au and TiO_2 or inorganic materials such as calcium phosphate have been suggested as potential nanocarriers for COPD treatment [74,75].

Wang et al. fabricated mitochondria-targeting porous $Se@SiO_2$ antioxidant nanoparticles, which showed evaluated protective effects on airway epithelial cells and an acute lung injury model mouse through reducing mitochondrial ROS. Pretreatment with the $Se@SiO_2$ nanoparticles significantly increased the resistance to oxidative injury and suppressed LPS-induced gene expression changes (downregulation of mitochondrial fusion proteins such as OPA1 and MFN2) by maintaining mitochondrial dynamics, suggesting therapeutic potential for acute lung injury [76].

Although intercellular mitochondrial transfer protects the injured cells, it limits transfer efficiency and selectivity for therapeutic utilization. Huang et al. report a potential method of using iron oxide nanoparticles that induce the transfer of healthy mitochondria from hMSCs to damaged cells to repair mitochondrial dysfunctions by enhancement of connexin43-containing intercellular gap junctions through the JNK pathway. The nanoparticle-treated MSCs significantly reduced fibrosis progression in a pulmonary fibrosis model mouse without serious safety issues [77].

Li et al. successfully prepared drug-controlled-release chitosan/black phosphorus quantum dot nanoparticles (PEG@CS/BPQDs-AM NPs) by ion crosslinking and PEG modification [78]. The nanoparticles effectively penetrated into the pulmonary mucus barrier and adhered to mucosal epithelial cells. Then, BPQDs were rapidly degraded and released amikacin, an antibacterial drug for gram-negative bacilli lung infections intercurrent with COPD. At the same time, the protonated chitosan effectively avoided biofilm formation by the antibacterial effect. In vivo experiments in mice demonstrated a significant improvement of airway obstruction and inhibition effects on pseudomonas aeruginosa, leading to a significant reduction in the toxicity and side effects.

On the other hand, it has been noted that inorganic nanoparticles induce potential toxicity through the accumulation of ROS, mitochondrial damage, inflammation, apoptosis, DNA damage, cell cycle, and epigenetic regulation linked with mitochondrial dysfunction [79,80].

5.6. Exosomes

Exosomes and EVs are small vesicles released from various cells for transporting bioactive molecules and signaling molecules such as proteins and nucleic acids for intercellular communication. Recently, they have gained significant attention due to their roles in physiological and pathological processes, including their potential involvement in COPD [81,82]. Several studies reported increased secretion of endothelial cell-derived exosomes in COPD patients, suggesting that the exosomes are related to the exacerbation of COPD [83]. The promotion of COPD also affects the profile of miRNA in exosomes. For instance, cigarette smoke exposure alters exosomes released from bronchial epithelial cells and significantly increases miR-210. The exosomes are taken up by lung fibroblasts, and the delivered miR-210 downregulates autophagy and induces differentiation into myofibroblasts. Accumulation of this degeneration potentially leads to exacerbated airflow obstruction [84].

Preclinical studies suggest that MSC-based cell therapy is a novel treatment modality for COPD due to its differentiation potential into alveolar epithelial cells and immunomodulatory properties [85]. Although the MSC-mediated effects are the paracrine action of their exosomes, most of the study of COPD treatments using MSC-derived exosomes is still limited to animal models [86].

Maremanda et al. investigated the combination treatment of MSCs and MSC-derived exosomes in cigarette smoke-exposed COPD model mice. Although cigarette smoke exposure led to a significant increase in mitochondrial fission protein DRP1 and damage-associated molecular pattern mediators S100A4/AB, HMGB1, RAGE, and AGE, the combination treatment increased the expression of mitochondrial fusion genes (*mfn1*, *mfn2*,

and *opa1*) and mitochondrial transport/mitophagy facilitating genes (*rhot1*), indicating the protection effects against lung inflammation caused by mitochondrial dysfunction [87].

While the role of exosomes and EVs in COPD is an active area of research, our understanding of their precise contributions to the disease is still evolving. Further studies are needed to elucidate the influence of COPD progression and to explore their therapeutic targets. In addition, the heterogeneity of exosomes might limit the extensive application in COPD patients [86].

6. Concluding Remarks

In this concise review, we have overviewed current knowledge and efforts about treatments for COPD focused on mitochondrial dysfunction and nanoparticle-based therapy. As tackled against the intricate and multi-faceted connections between mitochondrial dysfunction and COPD, nanoparticle-based DDS offers a promising avenue to enhance therapeutic efficacy. Alongside exploring advanced drug delivery methods, further efforts to elucidate the molecular pathways linking mitochondrial dysfunction and COPD are crucial for developing more efficient targeted therapeutic strategies. By leveraging knowledge and drug-delivery systems, we can enhance the precision and effectiveness of COPD therapies, potentially improving the quality of life for patients with COPD.

References

1. Safiri, S.; Carson-Chahhoud, K.; Noori, M.; Nejadghaderi, S.A.; Sullman, M.J.M.; Ahmadian Heris, J.; Ansarin, K.; Mansournia, M.A.; Collins, G.S.; Kolahi, A.A.; et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: Results from the Global Burden of Disease Study 2019. *BMJ* **2022**, *378*, e069679. [CrossRef] [PubMed]
2. Agustí, A.; Celli, B.R.; Criner, G.J.; Halpin, D.; Anzueto, A.; Barnes, P.; Bourbeau, J.; Han, M.K.; Martinez, F.J.; Montes de Oca, M.; et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Am. J. Respir. Crit. Care Med.* **2023**, *207*, 819–837. [CrossRef] [PubMed]
3. Fact Sheets of COPD, World Health Organization. Available online: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) (accessed on 31 July 2023).
4. Wang, C.; Zhou, J.; Wang, J.; Li, S.; Fukunaga, A.; Ydoi, J.; Tian, H. Progress in the mechanism and targeted drug therapy for COPD. *Signal Transduct. Target.* **2020**, *5*, 248. [CrossRef]
5. Fabbri, L.M.; Roversi, S.; Beghé, B. Triple therapy for symptomatic patients with COPD. *Lancet* **2017**, *389*, 1864–1865. [CrossRef]
6. Nunnari, J.; Suomalainen, A. Mitochondria: In sickness and in health. *Cell* **2012**, *148*, 1145–1159. [CrossRef] [PubMed]
7. Bhatti, J.S.; Bhatti, G.K.; Reddy, P.H. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A step towards mitochondria based therapeutic strategies. *Biochim. Biophys. Acta Mol. Basis Dis.* **2017**, *1863*, 1066–1077. [CrossRef]
8. Moos, W.H.; Faller, D.V.; Glavas, I.P.; Harpp, D.N.; Kamperi, N.; Kanara, I.; Kodukula, K.; Mavrakis, A.N.; Pernokas, J.; Pernokas, M.; et al. Pathogenic mitochondrial dysfunction and metabolic abnormalities. *Biochem. Pharmacol.* **2021**, *193*, 114809. [CrossRef]
9. Chandel, N.S. Mitochondria as signaling organelles. *BMC Biol.* **2014**, *12*, 34. [CrossRef]
10. Marchi, S.; Guilbaud, E.; Tait, S.W.G.; Yamazaki, T.; Galluzzi, L. Mitochondrial control of inflammation. *Nat. Rev. Immunol.* **2023**, *23*, 159–173. [CrossRef]

11. Zhunina, O.A.; Yabbarov, N.G.; Grechko, A.V.; Starodubova, A.V.; Ivanova, E.; Nikiforov, N.G.; Orekhov, A.N. The Role of Mitochondrial Dysfunction in Vascular Disease, Tumorigenesis, and Diabetes. *Front. Mol. Biosci.* **2021**, *8*, 671908. [CrossRef]

12. Norat, P.; Soldozy, S.; Sokolowski, J.D.; Gorick, C.M.; Kumar, J.S.; Chae, Y.; Yağmurlu, K.; Prada, F.; Walker, M.; Levitt, M.R.; et al. Mitochondrial dysfunction in neurological disorders: Exploring mitochondrial transplantation. *NPJ Regen. Med.* **2020**, *5*, 22. [CrossRef]

13. Lerner, C.A.; Sundar, I.K.; Rahman, I. Mitochondrial redox system, dynamics, and dysfunction in lung inflammaging and COPD. *Int. J. Biochem. Cell Biol.* **2016**, *81 Pt B*, 294–306. [CrossRef]

14. Fang, T.; Wang, M.; Xiao, H.; Wei, X. Mitochondrial dysfunction and chronic lung disease. *Cell Biol. Toxicol.* **2019**, *35*, 493–502. [CrossRef]

15. 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.; et al. Targeting the mitochondria in chronic respiratory diseases. *Mitochondrion* **2022**, *67*, 15–37. [CrossRef]

16. Boukhenouna, S.; Wilson, M.A.; Bahmed, K.; Kosmider, B. Reactive Oxygen Species in Chronic Obstructive Pulmonary Disease. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 5730395. [CrossRef] [PubMed]

17. Antunes, M.A.; Lopes-Pacheco, M.; Rocco, P.R.M. Oxidative Stress-Derived Mitochondrial Dysfunction in Chronic Obstructive Pulmonary Disease: A Concise Review. *Oxidative Med. Cell. Longev.* **2021**, *2021*, 6644002. [CrossRef] [PubMed]

18. Mumby, S.; Adcock, I.M. Recent evidence from omic analysis for redox signalling and mitochondrial oxidative stress in COPD. *J. Inflamm.* **2022**, *19*, 10. [CrossRef] [PubMed]

19. Brightling, C.; Greening, N. Airway inflammation in COPD: Progress to precision medicine. *Eur. Respir. J.* **2019**, *54*, 1900651. [CrossRef] [PubMed]

20. Plataki, M.; Tzortzaki, E.; Rytila, P.; Demosthenes, M.; Koutsopoulos, A.; Siafakas, N.M. Apoptotic mechanisms in the pathogenesis of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2006**, *1*, 161–171. [CrossRef] [PubMed]

21. Demedts, I.K.; Demoor, T.; Bracke, K.R.; Joos, G.F.; Brusselle, G.G. Role of apoptosis in the pathogenesis of COPD and pulmonary emphysema. *Respir. Res.* **2006**, *7*, 53. [CrossRef]

22. Rivas, M.; Gupta, G.; Costanzo, L.; Ahmed, H.; Wyman, A.E.; Geraghty, P. Senescence: Pathogenic Driver in Chronic Obstructive Pulmonary Disease. *Medicina* **2022**, *58*, 817. [CrossRef] [PubMed]

23. Araya, J.; Kuwano, K. Cellular senescence-an aging hallmark in chronic obstructive pulmonary disease pathogenesis. *Respir. Investig.* **2022**, *60*, 33–44. [CrossRef] [PubMed]

24. Wiegman, C.H.; Michaeloudes, C.; Haji, G.; Narang, P.; Clarke, C.J.; Russell, K.E.; Bao, W.; Pavlidis, S.; Barnes, P.J.; Kanerva, J.; et al. 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*, 769–780. [CrossRef] [PubMed]

25. Meyer, A.; Zoll, J.; Charles, A.L.; Charloux, A.; de Blay, F.; Diemunsch, P.; Sibilia, J.; Piquard, F.; Geny, B. Skeletal muscle mitochondrial dysfunction during chronic obstructive pulmonary disease: Central actor and therapeutic target. *Exp. Physiol.* **2013**, *98*, 1063–1078. [CrossRef]

26. Racanelli, A.C.; Kikkers, S.A.; Choi, A.M.K.; Cloonan, S.M. Autophagy and inflammation in chronic respiratory disease. *Autophagy* **2018**, *14*, 221–232. [CrossRef]

27. Kuwano, K.; Araya, J.; Hara, H.; Minagawa, S.; Takasaka, N.; Ito, S.; Kobayashi, K.; Nakayama, K. Cellular senescence and autophagy in the pathogenesis of chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). *Respir. Investig.* **2016**, *54*, 397–406. [CrossRef]

28. Albano, G.D.; Montalbano, A.M.; Gagliardo, R.; Profita, M. Autophagy/Mitophagy in Airway Diseases: Impact of Oxidative Stress on Epithelial Cells. *Biomolecules* **2023**, *13*, 1217. [CrossRef]

29. Jiang, S.; Sun, J.; Mohammadtursun, N.; Hu, Z.; Li, Q.; Zhao, Z.; Zhang, H.; Dong, J. Dual role of autophagy/mitophagy in chronic obstructive pulmonary disease. *Pulm. Pharmacol. Ther.* **2019**, *56*, 116–125. [CrossRef]

30. Manevski, M.; Muthumalage, T.; Devadoss, D.; Sundar, I.K.; Wang, Q.; Singh, K.P.; Unwalla, H.J.; Chand, H.S.; Rahman, I. Cellular stress responses and dysfunctional mitochondrial-cellular senescence, and therapeutics in chronic respiratory diseases. *Redox Biol.* **2020**, *33*, 101443. [CrossRef]

31. Church, D.F.; Pryor, W.A. Free-radical chemistry of cigarette smoke and its toxicological implications. *Environ. Health Perspect.* **1985**, *64*, 111–126. [CrossRef]

32. 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.; et al. Prolonged cigarette smoke exposure alters mitochondrial structure and function in airway epithelial cells. *Respir. Res.* **2013**, *14*, 97. [CrossRef] [PubMed]

33. Li, D.; Hu, J.; Wang, T.; Zhang, X.; Liu, L.; Wang, H.; Wu, Y.; Xu, D.; Wen, F. Silymarin attenuates cigarette smoke extract-induced inflammation via simultaneous inhibition of autophagy and ERK/p38 MAPK pathway in human bronchial epithelial cells. *Sci. Rep.* **2016**, *6*, 37751. [CrossRef] [PubMed]

34. Hara, H.; Araya, J.; Ito, S.; Kobayashi, K.; Takasaka, N.; Yoshii, Y.; Wakui, H.; Kojima, J.; Shimizu, K.; Numata, T.; et al. Mitochondrial fragmentation in cigarette smoke-induced bronchial epithelial cell senescence. *Am. J. Physiol. Lung Cell Mol. Physiol.* **2013**, *305*, L737–L746. [CrossRef] [PubMed]

35. Ahmad, T.; Sundar, I.K.; Lerner, C.A.; Gerloff, J.; Tormos, A.M.; Yao, H.; Rahman, I. Impaired mitophagy leads to cigarette smoke stress-induced cellular senescence: Implications for chronic obstructive pulmonary disease. *FASEB J.* **2015**, *29*, 2912–2929. [CrossRef]

36. Mizumura, K.; Cloonan, S.M.; Nakahira, K.; Bhashyam, A.R.; Cervo, M.; Kitada, T.; Glass, K.; Owen, C.A.; Mahmood, A.; Washko, G.R.; et al. Mitophagy-dependent necroptosis contributes to the pathogenesis of COPD. *J. Clin. Investig.* **2014**, *124*, 3987–4003. [CrossRef]

37. Murray, L.M.A.; Krasnodembskaya, A.D. Concise Review: Intercellular Communication via Organelle Transfer in the Biology and Therapeutic Applications of Stem Cells. *Stem Cells* **2019**, *37*, 14–25. [CrossRef] [PubMed]

38. Liu, D.; Gao, Y.; Liu, J.; Huang, Y.; Yin, J.; Feng, Y.; Shi, L.; Meloni, B.P.; Zhang, C.; Zheng, M.; et al. Intercellular mitochondrial transfer as a means of tissue revitalization. *Signal Transduct. Target. Ther.* **2021**, *6*, 65. [CrossRef]

39. Liu, Z.; Sun, Y.; Qi, Z.; Cao, L.; Ding, S. Mitochondrial transfer/transplantation: An emerging therapeutic approach for multiple diseases. *Cell Biosci.* **2022**, *12*, 66. [CrossRef]

40. Ahmad, T.; Mukherjee, S.; Pattnaik, B.; Kumar, M.; Singh, S.; Kumar, M.; Rehman, R.; Tiwari, B.K.; Jha, K.A.; Barhanpurkar, A.P.; et al. Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *EMBO J.* **2014**, *33*, 994–1010.

41. Frankenberg Garcia, J.; Rogers, A.V.; Mak, J.C.W.; Halayko, A.J.; Hui, C.K.M.; Xu, B.; Chung, K.F.; Rodriguez, T.; Michaeloudes, C.; Bhavsar, P.K. Mitochondrial Transfer Regulates Bioenergetics in Healthy and Chronic Obstructive Pulmonary Disease Airway Smooth Muscle. *Am. J. Respir. Cell Mol. Biol.* **2022**, *67*, 471–481. [CrossRef]

42. Schamberger, A.C.; Mise, N.; Meiners, S.; Eickelberg, O. Epigenetic mechanisms in COPD: Implications for pathogenesis and drug discovery. *Expert Opin. Drug Discov.* **2014**, *9*, 609–628. [CrossRef]

43. Zhang, L.; Valizadeh, H.; Alipourfard, I.; Bidares, R.; Aghebati-Maleki, L.; Ahmadi, M. Epigenetic Modifications and Therapy in Chronic Obstructive Pulmonary Disease (COPD): An Update Review. *COPD* **2020**, *17*, 333–342. [CrossRef]

44. Wu, D.D.; Song, J.; Bartel, S.; Krauss-Etschmann, S.; Rots, M.G.; Hylkema, M.N. The potential for targeted rewriting of epigenetic marks in COPD as a new therapeutic approach. *Pharmacol. Ther.* **2018**, *182*, 1–14. [CrossRef]

45. Liu, F.; Killian, J.K.; Yang, M.; Walker, R.L.; Hong, J.A.; Zhang, M.; Davis, S.; Zhang, Y.; Hussain, M.; Xi, S.; et al. Epigenomic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate. *Oncogene* **2010**, *29*, 3650–3664. [CrossRef] [PubMed]

46. Schwartz, U.; Llamazares Prada, M.; Pohl, S.T.; Richter, M.; Tamas, R.; Schuler, M.; Keller, C.; Mijosek, V.; Muley, T.; Schneider, M.A.; et al. High-resolution transcriptomic and epigenetic profiling identifies novel regulators of COPD. *EMBO J.* **2023**, *42*, e111272. [CrossRef] [PubMed]

47. Ambekar, T.; Pawar, J.; Rathod, R.; Patel, M.; Fernandes, V.; Kumar, R.; Singh, S.B.; Khatri, D.K. Mitochondrial quality control: Epigenetic signatures and therapeutic strategies. *Neurochem. Int.* **2021**, *148*, 105095. [CrossRef] [PubMed]

48. Mercado, N.; Ito, K.; Barnes, P.J. Accelerated ageing of the lung in COPD: New concepts. *Thorax* **2015**, *70*, 482–489. [CrossRef]

49. Zhang, X.Y.; Li, W.; Zhang, J.R.; Li, C.Y.; Zhang, J.; Lv, X.J. Roles of sirtuin family members in chronic obstructive pulmonary disease. *Respir. Res.* **2022**, *23*, 66. [CrossRef]

50. Xu, Y.; Liu, H.; Song, L. Novel drug delivery systems targeting oxidative stress in chronic obstructive pulmonary disease: A review. *J. Nanobiotechnol.* **2020**, *18*, 145. [CrossRef]

51. de Menezes, B.R.C.; Rodrigues, K.F.; Schatkoski, V.M.; Pereira, R.M.; Ribas, R.G.; Montanheiro, T.L.D.A.; Thim, G.P. Current advances in drug delivery of nanoparticles for respiratory disease treatment. *J. Mater. Chem. B* **2021**, *9*, 1745–1761. [CrossRef]

52. Virmani, T.; Kumar, G.; Virmani, R.; Sharma, A.; Pathak, K. Nanocarrier-based approaches to combat chronic obstructive pulmonary disease. *Nanomedicine* **2022**, *17*, 1833–1854. [CrossRef] [PubMed]

53. Liu, D.; Long, M.M.; Gao, L.L.; Chen, Y.J.; Li, F.; Shi, Y.; Gu, N. Nanomedicines Targeting Respiratory Injuries for Pulmonary Disease Management. *Adv. Funct. Mater.* **2022**, *32*, 2112258. [CrossRef]

54. Taghavizadeh Yazdi, M.E.; Qayoomian, M.; Beigoli, S.; Boskabady, M.H. Recent advances in nanoparticle applications in respiratory disorders: A review. *Front. Pharmacol.* **2023**, *14*, 1059343. [CrossRef] [PubMed]

55. Zhong, W.; Zhang, X.; Zeng, Y.; Lin, D.; Wu, J. Recent applications and strategies in nanotechnology for lung diseases. *Nano Res.* **2021**, *14*, 2067–2089. [CrossRef]

56. Pathak, R.K.; Kolishetti, N.; Dhar, S. Targeted nanoparticles in mitochondrial medicine. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2015**, *7*, 315–329. [CrossRef] [PubMed]

57. Ibarra-Sánchez, L.Á.; Gámez-Méndez, A.; Martínez-Ruiz, M.; Nájera-Martínez, E.F.; Morales-Flores, B.A.; Melchor-Martínez, E.M.; Sosa-Hernández, J.E.; Parra-Saldívar, R.; Iqbal, H.M.N. Nanostructures for drug delivery in respiratory diseases therapeutics: Revision of current trends and its comparative analysis. *J. Drug Deliv. Sci. Technol.* **2022**, *70*, 103219. [CrossRef]

58. Forest, V.; Pourchez, J. Nano-delivery to the lung—By inhalation or other routes and why nano when micro is largely sufficient? *Adv. Drug Deliv. Rev.* **2022**, *183*, 114173. [CrossRef]

59. Anselmo, A.C.; Mitragotri, S. Nanoparticles in the clinic: An update post COVID-19 vaccines. *Bioeng. Transl. Med.* **2021**, *6*, e10246. [CrossRef]

60. Anselmo, A.C.; Mitragotri, S. Nanoparticles in the clinic: An update. *Bioeng. Transl. Med.* **2019**, *4*, e10143. [CrossRef]

61. Fenton, O.S.; Olafson, K.N.; Pillai, P.S.; Mitchell, M.J.; Langer, R. Advances in Biomaterials for Drug Delivery. *Adv. Mater.* **2018**, *30*, 1705328. [CrossRef]

62. Manconi, M.; Manca, M.L.; Valenti, D.; Escribano, E.; Hillaireau, H.; Fadda, A.M.; Fattal, E. Chitosan and hyaluronan coated liposomes for pulmonary administration of curcumin. *Int. J. Pharm.* **2017**, *525*, 203–210. [CrossRef] [PubMed]
63. Elhissi, A. Liposomes for Pulmonary Drug Delivery: The Role of Formulation and Inhalation Device Design. *Curr. Pharm. Des.* **2017**, *23*, 362–372. [CrossRef] [PubMed]
64. Buhecha, M.D.; Lansley, A.B.; Somavarapu, S.; Pannala, A.S. Development and characterization of PLA nanoparticles for pulmonary drug delivery: Co-encapsulation of theophylline and budesonide, a hydrophilic and lipophilic drug. *J. Drug Deliv. Sci. Technol.* **2019**, *53*, 101128. [CrossRef]
65. Vij, N.; Min, T.; Bodas, M.; Gorde, A.; Roy, I. Neutrophil targeted nano-drug delivery system for chronic obstructive lung diseases. *Nanomedicine* **2016**, *12*, 2415–2427. [CrossRef]
66. Mei, D.; Tan, W.S.D.; Tay, Y.; Mukhopadhyay, A.; Wong, W.S.F. Therapeutic RNA Strategies for Chronic Obstructive Pulmonary Disease. *Trends Pharmacol. Sci.* **2020**, *41*, 475–486. [CrossRef]
67. Mohamed, A.; Kunda, N.K.; Ross, K.; Hutcheon, G.A.; Saleem, I.Y. Polymeric nanoparticles for the delivery of miRNA to treat Chronic Obstructive Pulmonary Disease (COPD). *Eur. J. Pharm. Biopharm.* **2019**, *136*, 1–8. [CrossRef]
68. Mohamed, A.; Pekoz, A.Y.; Ross, K.; Hutcheon, G.A.; Saleem, I.Y. Pulmonary delivery of Nanocomposite Microparticles (NCMPs) incorporating miR-146a for treatment of COPD. *Int. J. Pharm.* **2019**, *569*, 118524. [CrossRef]
69. Craparo, E.F.; Cabibbo, M.; Scialabba, C.; Giammona, G.; Cavallaro, G. Inhalable Formulation Based on Lipid-Polymer Hybrid Nanoparticles for the Macrophage Targeted Delivery of Roflumilast. *Biomacromolecules* **2022**, *23*, 3439–3451. [CrossRef]
70. Barnes, P.J.; Adcock, I.M. Glucocorticoid resistance in inflammatory diseases. *Lancet* **2009**, *373*, 1905–1917. [CrossRef]
71. Chikuma, K.; Arima, K.; Asaba, Y.; Kubota, R.; Asayama, S.; Sato, K.; Kawakami, H. The potential of lipid-polymer nanoparticles as epigenetic and ROS control approaches for COPD. *Free Radic. Res.* **2020**, *54*, 829–840. [CrossRef]
72. Mitchell, M.J.; Billingsley, M.M.; Haley, R.M.; Wechsler, M.E.; Peppas, N.A.; Langer, R. Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* **2021**, *20*, 101–124. [CrossRef] [PubMed]
73. Zimmermann, C.M.; Baldassi, D.; Chan, K.; Adams, N.B.P.; Neumann, A.; Porras-Gonzalez, D.L.; Wei, X.; Kneidinger, N.; Stoleriu, M.G.; Burgstaller, G.; et al. Spray drying siRNA-lipid nanoparticles for dry powder pulmonary delivery. *J. Control. Release* **2022**, *351*, 137–150. [CrossRef] [PubMed]
74. Geiser, M.; Quaile, O.; Wenk, A.; Wigge, C.; Eigeldinger-Berthou, S.; Hirn, S.; Schäffler, M.; Schleh, C.; Möller, W.; Mall, M.A.; et al. Cellular uptake and localization of inhaled gold nanoparticles in lungs of mice with chronic obstructive pulmonary disease. *Part. Fibre Toxicol.* **2013**, *10*, 19. [CrossRef] [PubMed]
75. Roulet, A.; Armand, L.; Dagouassat, M.; Rogerieux, F.; Simon-Deckers, A.; Belade, E.; Van Nhieu, J.T.; Lanone, S.; Pairon, J.C.; Lacroix, G.; et al. Intratracheally administered titanium dioxide or carbon black nanoparticles do not aggravate elastase-induced pulmonary emphysema in rats. *BMC Pulm. Med.* **2012**, *12*, 38. [CrossRef]
76. Wang, M.; Wang, K.; Deng, G.; Liu, X.; Wu, X.; Hu, H.; Zhang, Y.; Gao, W.; Li, Q. Mitochondria-Modulating Porous Se@SiO$_2$ Nanoparticles Provide Resistance to Oxidative Injury in Airway Epithelial Cells: Implications for Acute Lung Injury. *Int. J. Nanomedicine* **2020**, *15*, 2287–2302. [CrossRef]
77. Huang, T.; Zhang, T.; Jiang, X.; Li, A.; Su, Y.; Bian, Q.; Wu, H.; Lin, R.; Li, N.; Cao, H.; et al. Iron oxide nanoparticles augment the intercellular mitochondrial transfer-mediated therapy. *Sci. Adv.* **2021**, *7*, eabj0534. [CrossRef]
78. Li, Z.; Luo, G.; Hu, W.P.; Hua, J.L.; Geng, S.; Chu, P.K.; Zhang, J.; Wang, H.; Yu, X.F. Mediated Drug Release from Nanovehicles by Black Phosphorus Quantum Dots for Efficient Therapy of Chronic Obstructive Pulmonary Disease. *Angew. Chem. Int. Ed. Engl.* **2020**, *59*, 20568–20576. [CrossRef]
79. Lin, S.; Zhang, H.; Wang, C.; Su, X.L.; Song, Y.; Wu, P.; Yang, Z.; Wong, M.H.; Cai, Z.; Zheng, C. Metabolomics Reveal Nanoplastic-Induced Mitochondrial Damage in Human Liver and Lung Cells. *Environ. Sci. Technol.* **2022**, *56*, 12483–12493. [CrossRef]
80. Xuan, L.; Ju, Z.; Skonieczna, M.; Zhou, P.K.; Huang, R. Nanoparticles-induced potential toxicity on human health: Applications, toxicity mechanisms, and evaluation models. *MedComm* **2023**, *4*, e327. [CrossRef]
81. Gomez, N.; James, V.; Onion, D.; Fairclough, L.C. Extracellular vesicles and chronic obstructive pulmonary disease (COPD): A systematic review. *Respir. Res.* **2022**, *23*, 82. [CrossRef]
82. Wang, N.; Wang, Q.; Du, T.; Gabriel, A.N.A.; Wang, X.; Sun, L.; Li, X.; Xu, K.; Jiang, X.; Zhang, Y. The Potential Roles of Exosomes in Chronic Pulmonary Disease. *Front. Med.* **2021**, *7*, 618506. [CrossRef] [PubMed]
83. Hough, K.P.; Chanda, D.; Duncan, S.R.; Thannickal, V.J.; Deshane, J.S. Exosomes in immunoregulation of chronic lung diseases. *Allergy* **2017**, *72*, 534–544. [CrossRef] [PubMed]
84. Fujita, Y.; Araya, J.; Ito, S.; Kobayashi, K.; Kosaka, N.; Yoshioka, Y.; Kadota, T.; Hara, H.; Kuwano, K.; Ochiya, T. Suppression of autophagy by extracellular vesicles promotes myofibroblast differentiation in COPD pathogenesis. *J. Extracell. Vesicles* **2015**, *4*, 28388. [CrossRef] [PubMed]
85. Broekman, W.; Khedoe, P.P.S.J.; Schepers, K.; Roelofs, H.; Stolk, J.; Hiemstra, P.S. Mesenchymal stromal cells: A novel therapy for the treatment of chronic obstructive pulmonary disease? *Thorax* **2018**, *73*, 565–574. [CrossRef]

86. Rajabi, H.; Konyalilar, N.; Erkan, S.; Mortazavi, D.; Korkunc, S.K.; Kayalar, O.; Bayram, H.; Rahbarghazi, R. Emerging role of exosomes in the pathology of chronic obstructive pulmonary diseases; destructive and therapeutic properties. *Stem Cell Res. Ther.* **2022**, *13*, 144. [CrossRef]

87. Maremanda, K.P.; Sundar, I.K.; Rahman, I. Protective role of mesenchymal stem cells and mesenchymal stem cell-derived exosomes in cigarette smoke-induced mitochondrial dysfunction in mice. *Toxicol. Appl. Pharmacol.* **2019**, *385*, 114788. [CrossRef]