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Review

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Autophagy in skeletal muscle dysfunction of chronic obstructive pulmonary disease: implications, mechanisms, and perspectives

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Abstract: Skeletal muscle dysfunction is a common extrapulmonary comorbidity of chronic obstructive pulmonary disease (COPD) and is associated with decreased quality-of-life and survival in patients. The autophagy lysosome pathway is one of the proteolytic systems that significantly affect skeletal muscle structure and function. Intriguingly, both promoting and inhibiting autophagy have been observed to improve COPD skeletal muscle dysfunction, yet the mechanism is unclear. This paper first reviewed the effects of macroautophagy and mitophagy on the structure and function of skeletal muscle in COPD, and then explored the mechanism of autophagy mediating the dysfunction of skeletal muscle in COPD. The results showed that macroautophagy- and mitophagy-related proteins were significantly increased in COPD skeletal muscle. Promoting macroautophagy in COPD improves myogenesis and replication capacity of muscle satellite cells, while inhibiting macroautophagy in COPD myotubes increases their diameters. Mitophagy helps to maintain mitochondrial homeostasis by removing impaired mitochondria in COPD. Autophagy is a promising target for improving COPD skeletal muscle dysfunction, and further research should be conducted to elucidate the specific mechanisms by which autophagy mediates COPD skeletal muscle dysfunction, with the aim of enhancing our understanding in this field.

Key words: Autophagy; Skeletal muscle dysfunction; Chronic obstructive pulmonary disease; Mitochondria; Muscle satellite cell

1 Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous pulmonary condition characterized by chronic pulmonary symptoms, such as dyspnea and cough, resulting from airway and/or alveolar abnormality (Global Initiatives for Chronic Obstructive Lung Disease, 2023). In 2019, COPD ranked as the third leading cause of death worldwide (World Health Organization, 2019). Given the aging population and the increasing number of smokers, the prevalence of COPD is expected to rise (Christenson et al., 2022). Skeletal muscle dysfunction is a common extrapulmonary comorbidity of COPD, with an incidence of approximately 20%–40% (Vermeeren et al., 2006; Vestbo et al., 2006; Maltais et al., 2014; Benz et al., 2019), which is manifested by changes in skeletal muscle structure, function, and metabolism (Jaitovich and Barreiro, 2018). Skeletal muscle dysfunction, which leads to decreased respiratory function and exercise capacity, is detrimental to quality-of-life and is associated with a high risk of mortality in COPD (Fermont et al., 2019). Moreover, skeletal muscle dysfunction is the independent predictor of cachexia, admission rate, and survival rate in COPD patients (Swallow et al., 2007; Maltais et al., 2014). Therefore, it is imperative to address and prevent skeletal muscle dysfunction in COPD.

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The main molecular mechanisms of skeletal muscle dysfunction in COPD remain unknown. Skeletal muscle dysfunction in COPD can be attributed to various factors such as decreased physical activity, oxidative stress, inflammation, hypoxia, anabolic and catabolic imbalance, muscle recovery dysfunction, and autophagy (Hussain and Sandri, 2013; Maltais et al., 2014; Jaitovich and Barreiro, 2018). As one of the proteolysis systems, the autophagy–lysosome pathway may play an important role in COPD skeletal muscle dysfunction (Hussain and Sandri, 2013; Gouzi et al., 2018; Balnis et al., 2022; Ito et al., 2022). Autophagy sustains cellular homeostasis by eliminating long-lived proteins and impaired organelles (Wang et al., 2018). Its role in the skeletal muscle dysfunction of neurodegenerative disease and aging has been proven (García-Prat et al., 2016). In the context of COPD, in vivo and in vitro studies have demonstrated that levels of autophagy-related protein, such as microtubule-associated protein light chain 3 BII (LC3BII)/LC3BI, B-cell lymphoma 2 (BCL2)-interacting protein 1 (Beclin1), and sequestosome 1 (p62/SQSTM1) in COPD skeletal muscle, are significantly elevated (Hussain and Sandri, 2013; Mano et al., 2022) and are negatively related to the 6-min walking distance (Gouzi et al., 2018). Knockout of PARKIN, a crucial E3 ubiquitin ligase in mitophagy, made COPD mice exhibit reduced gastrocnemius muscle cross-sectional area (CSA) and grip strength (Ito et al., 2022). The diameter of cultured myotubes from COPD patients was significantly increased after the application of autophagy inhibitor 3-methyladenine (3-MA) (Gouzi et al., 2018). However, it has also been found that the systematic application of spermidine (autophagy inducer) can significantly alleviate the proliferation disorder of muscle satellite cells caused by autophagy deficiency (Balnis et al., 2022). Existing evidence has proved that autophagy-related proteins are significantly altered in COPD skeletal muscle, and the regulation of autophagy can significantly improve the structure and function of COPD skeletal muscle. However, the results are inconsistent. In order to further clarify the role of autophagy in COPD skeletal muscle dysfunction and the mechanisms, this paper reviewed recent studies on skeletal muscle autophagy in COPD to identify new targets for the treatment of COPD skeletal muscle dysfunction.

2 Overview of COPD skeletal muscle dysfunction and autophagy

2.1 Overview of COPD skeletal muscle dysfunction

COPD skeletal muscle dysfunction is characterized by structural, functional, and metabolic alterations (Jaitovich and Barreiro, 2018). Structural changes include a decrease in CSA, muscle mass, and myogenesis protein, as well as an increase in muscle degradation proteins. Studies have shown a significant decrease in mid-thigh CSA in COPD patients (Bernard et al., 1998; Roig et al., 2011), regardless of the severity of the disease stages (Shrikrishna et al., 2012). Furthermore, even when compared to age- and fat-free-mass-matched healthy controls, COPD showed a 25% decrease in rectus femoris CSA (Seymour et al., 2009). In terms of muscle protein turnover, stable COPD patients have lower levels of muscle-specific atrophy F-box protein in the quadriceps muscle (Lemire et al., 2012; Natanek et al., 2013). Additionally, pectoralis CSA has been found to be significantly related to forced expiratory volume in one second to forced vital capacity ratio (Tashiro et al., 2021), and decreased pectoralis CSA has been associated with increased all-cause mortality, independent of body mass index and primary muscle mass (Mason et al., 2022). Functional changes in COPD muscle include decreased muscle strength and endurance. A meta-analysis of 728 COPD patients and 440 healthy controls demonstrated a significant decrease in quadriceps endurance in COPD patients compared with controls (Evans et al., 2015). Decreases in knee extension absolute strength (Roig et al., 2011), rectus lateralis muscle isometric strength per CSA, maximal voluntary capacity (MVC), and endurance have also been observed in COPD patients (Debigaré et al., 2003; Faucher et al., 2004). In addition, COPD patients exhibited decreased strength and endurance in digital flexors and biceps muscles (Faucher et al., 2004; Franssen et al., 2005). Furthermore, a 2-year study involving 162 moderate-to-severe COPD patients found that only quadriceps MVC and age were predictors of mortality (Swallow et al., 2007), which was supported by another 4-year study (Spositon et al., 2022). Metabolic changes in COPD patients mainly involve alterations in muscular fiber types, with a decreased proportion of slow muscle fibers. Decreased size, oxidative capacity, and mitochondrial density of type I fibers were observed in the

quadriceps of COPD patients (Mathur et al., 2014). Additionally, there was a decrease in the proportion of type I muscle fibers and an increase in type IIB and type IIX muscle fibers in the peripheral muscles of COPD patients (Debigaré et al., 2003; Torres et al., 2011). These changes are accompanied by a decrease in oxidase (citrate synthase and 3-hydroxyacyl-CoA dehydrogenase) activity and oxidative capacity, as well as an increase in the glycolytic enzyme phosphofructokinase in COPD's quadriceps muscles (Jakobsson et al., 1995; Mador and Bozkanat, 2001). In conclusion, COPD patients exhibit significant abnormalities in skeletal muscle, which are correlated with clinical function and exacerbation outcomes.

2.2 Overview of autophagy

Autophagy, as one of the proteolysis systems of organisms, plays a crucial role in maintaining cellular homeostasis by removing long-lived proteins and damaged organelles (Wang et al., 2018). Various pro-atrophic stimuli, such as starvation, muscle denervation, hypoxia, oxidative stress, organelle damage, and the accumulation of mutant proteins, can induce autophagy (Gouzi et al., 2018). In skeletal muscle dysfunction in COPD, the primary types of autophagy studied are macroautophagy and mitophagy. Macroautophagy degrades cellular components by enclosing them in autophagosomes, which then fuse with lysosomes to form autophagolysosomes (Mizushima et al., 2008). The initiation of macroautophagy is regulated by Unc-51-like autophagy-activating kinase 1 (ULK1), which is inactivated by the mammalian target of rapamycin (mTOR) (Singh et al., 2017). On the other hand, adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) inhibits mTOR, thereby activating ULK1 and forkhead box O3 (FOXO3) to promote macroautophagy (Bujak et al., 2015). Following initiation, the autophagic nucleation process is induced by the class III phosphatidylinositol 3-kinase (PI3K III) complex, consisting of Beclin1, vesicle sorting protein 34 (VSP34), and VSP15. This complex recruits autophagy-related (ATG) proteins and lipids in the cytoplasm to synthesize a large number of bilayer membrane structures. These membrane structures continue to elongate and eventually encapsulate intracellular material, forming an autophagosome structure under the action of ATG12-ATG5 and ATG8/LC3 conjugation systems (Suzuki et al., 2013). The formation of LC3BII, a marker of autophagosome formation, is positively correlated with the number of autophagosomes (Mizushima and Yoshimori, 2007). Subsequently, the autophagosome, along with numerous autophagy-related proteins (ATG5-ATG12-ATG16-like 1 complex), transports ubiquitination-labeled cellular waste to the lysosome and merges with it to form the autophagolysosome. Within the autophagolysosome, the waste is digested and degraded into small molecules such as amino acids, nucleic acids, and fatty acids, which are then recycled back into the cytoplasm (Suzuki et al., 2013; Wang et al., 2018). In this process, p62, which links ubiquitinated substrates with LC3B, is integrated into the autophagolysosome and degraded (Jeong et al., 2019).

Mitophagy is a selective autophagic response that specifically targets damaged mitochondria (Klionsky et al., 2021). The two well-studied mitophagy pathways in mammalian cells are ubiquitination-dependent and receptor-mediated mitophagy. Mitochondrial injury leads to decreased mitochondrial membrane potential, resulting in increased stability of phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) on the outer mitochondrial membrane. PINK1 then recruits the E3 ubiquitin ligase PARKIN to the outer mitochondrial membrane. Self-phosphorylation of PINK1 activates PARKIN, which polyubiquitinates mitochondrial proteins. These ubiquitinated proteins bind to the structural domains of autophagy receptors (p62, calcium-binding and coiled-coil domain-containing protein 2 (CALCOCO2), and optineurin) and form autophagosomes. The autophagosome subsequently fuses with lysosomes, leading to mitochondrial degradation (Lazarou et al., 2015; Fivenson et al., 2017; Su et al., 2023). Receptor-mediated mitophagy occurs through the interaction between LC3B interaction area on the receptor proteins and LC3B or γ-aminobutyric acid (GABA) receptor-associated protein on autophagic vesicles. FUN14 domain-containing protein 1 (FUNDC1) and BCL2/adenovirus E1B-interacting protein 3 (BNIP3), which have the LC3B interaction area, act as mitophagy receptor proteins in the mitochondrial outer membrane (Chen et al., 2016). The homolog of BNIP3, BNIP3-like (BNIP3L or NIX), can mediate mitophagy through the GABA receptor-associated protein (Romanello and Sandri, 2016; Su et al., 2023). Additionally, BNIP3 can activate macroautophagy by inhibiting mTOR or competitively binding with BCL2 to release Beclin1 (Bellot et al., 2009; Lin et al., 2014).

3 Role of autophagy in COPD skeletal muscle dysfunction

3.1 Role of macroautophagy dysregulation in COPD skeletal muscle dysfunction

Macroautophagy-related changes in COPD skeletal muscle are related to structural alterations, such as CSA and muscle mass. Studies have indicated that LC3BII, Beclin1, and p62 proteins and autophagosome numbers increase in the vastus lateralis of COPD, with more prominent changes in COPD sarcopenia (Guo et al., 2013; Hussain and Sandri, 2013; Kneppers et al., 2017). Furthermore, LC3B lipidation has found to be negatively correlated with COPD thigh CSA (Guo et al., 2013). The activation levels of FOXO, which induce the expression of autophagic proteins (e.g., LC3B, GABA receptor-associated protein, BNIP3, and BNIP3L), are negatively correlated with COPD body mass index ($r=-0.96$) (Puig-Vilanova et al., 2015). This seems to indicate that the level of macroautophagy is significantly elevated in COPD skeletal muscle and is significantly negatively correlated with skeletal muscle structure. It is consistent that autophagy flux in the myoblasts of COPD is increased (Gouzi et al., 2018). An in vitro study that applied autophagy inhibitor 3-MA to cultured COPD myotubes found a significant increase in the diameter of myotubes (Gouzi et al., 2018). Therefore, inhibiting skeletal muscle autophagy in COPD led to an improvement in skeletal muscle structure. An interesting finding is that oxidative stress may affect COPD skeletal muscle structure through decreased autophagy. In fact, the administration of ascorbic acid on COPD myotubes decreased the LC3B lipidation ratio and p62 level, along with a significant increase in myotube CSA (Gouzi et al., 2018).

The dysregulation of macroautophagy has been implicated in the muscle function alteration in COPD. In the vastus lateralis muscle of COPD patients, the levels of phospho-AMPK (p-AMPK) and total AMPK are significantly increased (Guo et al., 2013). This increase can activate ULK, leading to autophagy promotion through phosphorylation at Ser317 and Ser777 (Kim et al., 2011). COPD patients with muscle wasting have significantly decreased levels of p-ULK1 (Ser757, inhibitory)/ULK1 in the vastus lateralis muscle compared to those without muscle wasting (Kneppers et al., 2017). Animal models of COPD further support the dysregulation of macroautophagy, with increased protein level of ULK1 in the quadriceps muscle (Mao et al., 2020) and decreased level of p-ULK1 (Ser757)/ULK1 in the gastrocnemius muscle (Ceelen et al., 2017). The elevation of AMPK and ULK1 may contribute to the deterioration of muscle function in skeletal muscle. Although direct evidence supporting these findings in COPD is lacking, similar changes have been observed in other disease models. For instance, Laker et al. (2017) demonstrated the necessary role of AMPKα in the activation of autophagy after endurance exercise. The deletion of ULK1 hindered the improvement of glucose tolerance after exercise. In COPD skeletal muscle, discrepant findings have been reported. Gouzi et al. (2018) found that the use of autophagy inhibitors improved COPD muscle fiber diameter, while Balnis et al. (2022) found a decrease in autophagosome formation rate in COPD satellite cells and a decrease in myogenesis, which is significantly alleviated by the systemic administration of spermidine (an autophagy inducer). These differences may arise from the different functions of muscle fibers and satellite cells. Muscle fibers generate force and movement, while satellite cells are responsible for regenerating and repairing damaged muscle. Therefore, they may have distinct needs and responses to autophagy regulation. Similarly, previous studies have demonstrated that both activation and inhibition of autophagy can improve lipid metabolism and glucose uptake in obese mice (He et al., 2012; Kim et al., 2013).

Overall, the expression levels of macroautophagy-related proteins are significantly increased in COPD skeletal muscle, and they are negatively correlated with muscle function and structure. Yet, the role of autophagy in different muscle cells in COPD skeletal muscle function is inconsistent.

3.2 Improvement of COPD skeletal muscle dysfunction through mitophagy acceleration

Promoting mitophagy increases COPD myotube CSA and myosin heavy chain (MHC) and decreases E3 ubiquitination ligase. *BNIP3* messenger RNA (mRNA) in the vastus lateralis of COPD patients increases significantly (Guo et al., 2013). In COPD animal models, BNIP3 proteins increase in the soleus and tibialis anterior muscle and *BNIP3* mRNAs increase in gastrocnemius (Ceelen et al., 2017; Balnis et al., 2022; Mano et al., 2022). In vivo, cigarette smoke exposure

decreases the MHC of gastrocnemius muscle in PARKIN$^{-/-}$ mice compared with wild-type controls (Ito et al., 2022). Additionally, cigarette smoke extract-treated C2C12 cells with PARKIN small interfering RNA (siRNA) showed myotube atrophy, and PARKIN overexpression further confirmed these results. These findings suggest that the increase in mitophagy-related proteins may be a protective response, as mitophagy helps to remove impaired mitochondria and prevent their accumulation. Impaired mitochondria can lead to increased mitochondrial permeability transition pore opening, the activation of the inner membrane anion channel, and the leakage of more reactive oxygen species (ROS) (Zorov et al., 2014). Mitochondria-derived ROS are known to contribute to oxidative damage and skeletal muscle dysfunction in COPD skeletal muscle (Puente-Maestu et al., 2009, 2012). Promoting mitophagy can accelerate the removal of mitochondria-derived ROS, thus alleviating skeletal muscle dysfunction (Ito et al., 2022). The accumulation of damaged mitochondria and increased 4-hydroxynonenal (4-HNE) was observed in PARKIN$^{-/-}$ mice, while the administration of mitochondrial antioxidant significantly improved the decreased MHC and diameter in cigarette smoke extract-treated C2C12 myotubes (Ito et al., 2022). Additionally, astaxanthin was shown to decrease 4-HNE, BNIP3, and atrophy F-box proteins in soleus, leading to increased muscle mass, type I muscle fiber ratio, and CSA of types I and IIA muscle fibers (Mano et al., 2022).

Mitophagy dysfunction has been linked to skeletal muscle strength and overall exercise capacity in COPD, with BNIP3 proteins in quadriceps being negatively correlated with the percentage of the 6-min walking distance to predicted value ($r=-0.736$) (Gouzi et al., 2018), and PARKIN$^{-/-}$ COPD mice exhibit a weaker grip strength compared to wild-type COPD mice (Ito et al., 2022). These findings support the role of mitophagy in COPD skeletal muscle structure, and suggest that it plays a protective role in removing impaired mitochondria.

According to the above studies, the level of macroautophagy-related proteins is significantly increased in COPD skeletal muscle, and the effect of regulating macroautophagy may be cell type-dependent. Insufficient mitophagy can lead to structural and functional dysfunction of skeletal muscle in COPD. For a detailed summary of the relevant literature, please refer to Table 1.

4 Mechanisms of autophagy leading to COPD skeletal muscle dysfunction

4.1 Role of macroautophagy in muscle satellite cell function in COPD

Muscle stem cells (MuSCs) are skeletal muscle resident stem cells located below the basal lamina of myofibers, which are quiescent in the general state and can proliferate and differentiate into myofibers in response to stimuli such as muscle injury (Henrot et al., 2023). MuSCs play essential roles in myoblast nuclear turnover and muscle regeneration. Autophagy regulates the maintenance of the quiescence, activation, proliferation, and differentiation of MuSCs (Chen et al., 2022). Quiescent MuSCs maintain the renewal of organelles and proteins through autophagy. Autophagy is induced during the activation and proliferation of MuSCs after injury, which may result from high energy demand. Autophagy is activated again during muscle differentiation (Chen et al., 2022).

The dysfunction of MuSCs in COPD has been investigated. In COPD patients, MuSCs have delayed activation, reduced myosin heavy chain expression during myotube formation, and decreased myotube diameter when cultured in vitro (Thériault et al., 2014; Pomiès et al., 2015). The reduced proliferative capacity of MuSCs can also be detected in COPD (Balnis et al., 2022). Recent studies have revealed significant changes in autophagy levels in COPD MuSCs. Balnis et al. (2022) found dysregulated autophagy in COPD MuSCs by RNA sequencing (RNAseq) analysis and western blot validation. Bafilomycin (autophagy inhibitor) utilization further reduced the autophagosome turnover efficiency of MuSCs. The whole-body application of spermidine, a natural inducer of autophagy (3 mmol/L drinking water for four weeks), significantly increased the proliferation rate and myogenesis of MuSCs after injury. The study suggests that reduced autophagy in COPD MuSCs may contribute to muscle regenerative dysfunction. One study found that spermidine could not preserve the proliferative ability of MuSCs in ATG7 (essential for canonical macroautophagy) knockout mice, suggesting that autophagy mediates the pro-proliferative ability of spermidine on MuSCs (García-Prat et al., 2016). Mechanistically, Zhang et al. (2018) found that, after the spermidine treatment of MuSCs, the affinity of mothers against decapentaplegic homolog 3 (Smad3) for the promoters of the myogenic

Table 1 Studies on skeletal muscle autophagy changes in chronic obstructive pulmonary disease (COPD) in the past five years

Study	Group	Changes in major autophagy parameters	Changes in muscle dysfunction parameters
Leermakers et al., 2018	EG: mild-to-severe COPD; CG: healthy controls	Protein: BNIP3L↑, FUNDC1↓, PARKIN↑, LC3BI↑, LC3BII/LC3BI↓, p62→ in VL; mRNA: *PARKIN2*↑, *OPTN*↑	mRNA: *Myh7*↓
Gouzi et al., 2018	EG: muscle cells from VL of moderate-to-severe COPD; CG: muscle cells from VL of sedentary healthy subjects	Myoblast: protein: LC3↑, LC3BII/LC3BI↑, p62↑; mRNA: *SQSTM1*↑, *BNIP3*↑; autophagic flux↑; Myotube: protein: LC3↑, p62↑; mRNA: *p62*↑, *BNIP3*↑; autophagic flux→	
	EG: VL cells of COPD treated with 3-MA; CG: VL cells of COPD control	Myotube protein: p62↓, BNIP3↓	Myotube diameter↑
	EG: COPD VL myotube treated with ascorbic acid; CG: COPD VL myotube control	Myotube protein: p62↓, BNIP3↓, LC3BII/LC3BI↓	Myotube diameter↑
Leermakers et al., 2020	EG: male mice+lipopolysaccharide; CG: male mice+saline	Protein: BNIP3↑, BNIP3L-II↑, FUNDC1↓, PARKIN2↑, LC3BII↑ in GN after injection for 96 h; mRNA: *BNIP3L*↑, *BNIP3*↑, *Map1lc3b*↑, *Gabarapl1*↑, *p62*↑ in GN after injection for 48 h	GN weight/body weight↓
Mao et al., 2020	EG: rats+CSE+*Klebsiella pneumonia* suspension+saline; CG: rats+saline	Protein: LC3BII/LC3BI↑, ULK1↑, PINK↑, PARKIN↑, AMPKα↓, p-AMPKα↓; mRNA: *Map1lc3b*↑, *Ulk1*↑, *Pink1*↑, *Parkin*↑, *Prkaa2*↓ in quadriceps	
	L6+CSE; L6 control	Protein: ULK1↑, PINK↑, PARKIN↑, AMPKα↓, p-AMPKα↓, mTOR↓; mRNA: *Prkaa2*↓, *Ulk1*↑, *Pink1*↑, *Parkin*↑, *Mtor*↓ in quadriceps	
Balnis et al., 2022	EG: *IL13*^{TG} COPD mice; CG: WT mice	mRNA: *Ulk1*↑, *Beclin1*↑, *Bnip3*↑, *Map1lc3b*↑, *Sqstm1*↑, *Atg7*↑, *Atg3*↑ in TA	Grip strength↓, EDL maximum absolute-isolated contraction↓, EDL CSA↓, GN muscle mass↓, TA muscle mass↓
	EG: *IL13*^{TG} COPD mice with acute TA injury; CG: WT mice with acute TA injury		CSA on Day 14 after injury↓
	EG: TA satellite cells from *IL13*^{TG} or *MMP1*^{TG} COPD mice; CG: TA satellite cells from WT mice	mRNA: *Beclin1*↑	Cell proliferation↓, cell counts→; mRNA: *Myod*↓, *Myf5*↓, *Myh3*↓
	Group 1: bafilomycin-treated GFP-LC3+*IL13*^{TG} mice; Group 2: GFP-LC3+*IL13*^{TG} mice; CG: GFP-LC3+WT mice	Protein: LC3↑ (Group 2 compared with CG; Group 2 compared with Group 1) in muscle satellite cells	
	EG: GFP-LC3+*IL13*^{TG} mice; CG: GFP-LC3+WT mice	Protein: LC3↑	

To be continued

Table 1 (continued)

Study	Group	Changes in major autophagy parameters	Changes in muscle dysfunction parameters
Ito et al., 2022	C2C12 were divided into: control group (CG) and CSE group (CSE+WT)	CSE+WT compared with CG: protein: PARKIN↓; mRNA: *PARKIN*↓	CSE+WT compared with CG: protein of MHC↓, average myotube diameters↓, MuRF1↑
	PARKIN siRNA+CSE; PARKIN siRNA; Control siRNA+CSE; Control siRNA;	CSE+PARKIN siRNA compared with Control siRNA+CSE: protein: p62↑, PINK1↑	CSE+PARKIN siRNA compared with Control siRNA+CSE: MHC→, average myotube diameters↓, MuRF1↑;
	PARKIN ov+CSE; PARKIN ov; Vector+CSE; Vector		CSE+PARKIN ov compared with Vector+CSE: MHC↑, myotube diameter↑
	Female WT C57BL/6J mice+CSE; Female WT C57BL/6J mice control; Female PARKIN KO mice+CSE; Female PARKIN KO mice control	WT+CSE compared with WT: protein: PARKIN↓, p62→, PINK1→ in GN; PARKIN KO+CSE compared with WT+CSE: protein: PARKIN↓, p62↑, PINK1↑ in GN	WT+CSE compared with WT: grip force↓, GN muscle weight/length→, TA muscle weight/length→, EDL muscle weight/length→, soleus muscle weight/length↓, GN average muscle fiber diameter↓; PARKIN KO+CSE compared with WT+CSE: muscle weight/length↓, GN average muscle fiber diameter↓, MHC↓
	EG: COPD patients with sarcopenia; CG: patients with no COPD	Protein: PARKIN↓, PINK1↑, p62↑ in gluteus maximus muscle	MuRF1↑ in gluteus maximus muscle
Mano et al., 2022	Male C57BL/6J mice divided into: EG: PPE-treated; CG: saline-treated	Soleus protein: BNIP3↑	Weight of the soleus↓, % type I muscle↓, % type IIA↑, CSA↓; Protein: MuRF1↑, Atrogin1↑ in the soleus
	EG: PPE+astaxanthin-treated; CG: PPE-treated	Protein: BNIP3↓	Soleus weight↑, % type I fibers↑, type I CSA↑, type IIA CSA↑; Protein: Atrogin1↓, MuRF1→
	EG: PPE+p38 MAPK inhibitor-treated; CG: PPE-treated	Protein: BNIP3↓	Soleus weight↑, % type I fibers↑, type I CSA↑, type IIA CSA↑; Protein: MuRF1↓

↑: increased compared with CG unless noted; ↓: decreased compared with CG unless noted; →: has no changes compared with CG unless noted; Atrogin1: muscle atrophy F-box; AMPK/Prkaa2: adenosine 5'-monophosphate (AMP)-activated protein kinase; ATG: autophagy-related; Beclin1: B-cell lymphoma 2 (BCL2)-interacting protein 1; BCL2/adenovirus E1B-interacting protein 3; BCG: control group; BNIP3: CSA: cross-sectional aera; CSE: cigarette smoke extract; EDL: extensor digitorum longus; EG: experimental group; MHC: myosin heavy chain; FUNDC1: FUN14 domain-containing protein 1; GABARAPL1: γ-aminobutiric acid receptor-associated protein-like 1; GN: gastrocnemius muscle; Map1lc3b: microtubule-associated protein light chain 3; LC3: light chain 3; MAPK: mitogen-activated protein kinase; 3-MA: 3-methyladenine; mRNA: messenger RNA; mTOR: mammalian target of rapamycin; MuRF1: muscle ring finger protein l; Myf5: myogenic factor 5; Myh7: recombinant myosin heavy chain 7; MyoD1: myogenic differentiation 1; OPTN: optineurin; PINK: phosphatase and tensin homolog (PTEN)-induced kinase; ov: overexpression; PPE: porcine pancreatic elastase; p62/SQSTM1: sequestosome 1; siRNA: small interfering RNA; TA: tibialis anterior muscle; ULK1: Unc-51-like kinase 1; VL: vastus lateralis muscle; WT: wild-type.

factors (myogenic factor 5 (Myf5) and myogenic differentiation (MyoD)) was decreased, and the myogenic capacity was reduced. The above studies indicate that the activation of COPD autophagy can restore the regenerative capacity of MuSCs.

4.2 Role of mitophagy in mitochondrial homeostasis in COPD muscle

Mitochondria play a central role in cellular energy homeostasis, and regulate various processes such as

amino acid synthesis, lipid metabolism, and apoptotic signaling (Eldeeb et al., 2022). Autophagy helps decrease mitochondrial oxidative damage and maintain mitochondrial function. Inhibiting ATG7 in myoblasts leads to decreased mitochondrial membrane potential, mitochondria function-related proteins (peroxisome proliferative-activated receptor γ coactivator 1α (PGC-1α), mitochondrial dynamin-like GTPase, and dynamin-related protein 1 (DRP1)), and increased 4-HNE (Baechler et al., 2019).

In COPD, mitochondrial dysfunction in skeletal muscle is evident through reduced mitochondrial density, dysregulated respiratory function, and the increased production of mitochondrial ROS (Gifford et al., 2018). The main consequence of mitochondrial dysfunction is a decrease in muscle oxidative capacity, resulting in increased lactate production during low-intensity and endurance exercise (Puente-Maestu et al., 2013). The reduction in mitochondrial content in quadriceps muscle fibers results in decreased oxidative capacity, which is consistent with a reduction in type I muscle fibers (Puente-Maestu et al., 2013). Correcting skeletal muscle mitochondrial dysfunction significantly improves COPD skeletal muscle function, as seen by reduced atrophy and increased MHC levels after administering mitochondrial ROS-specific antioxidants to COPD myotubes (Ito et al., 2022). Overall, mitochondrial dysfunction mediates the dysfunction observed in COPD skeletal muscle.

The changes in mitophagy status are significantly correlated with mitochondrial function in COPD skeletal muscle. The PARKIN$^{-/-}$ COPD mice also exhibited increased translocase of the outer membrane 20, 4-HNE, and damaged mitochondrial accumulation. Meanwhile, MHC in the gastrocnemius and average CSA decrease significantly (Ito et al., 2022). Impaired mitophagy, swollen mitochondrial cristae, and increased mitochondrial membrane disruption were observed in CSE-induced C2C12 myotubes after PARKIN siRNA transduction, accompanied with increased MuRF1 and decreased myotube (Ito et al., 2022). Although the role of receptor protein-mediated mitochondrial autophagy in COPD skeletal muscle function has not been investigated, studies have shown a significant increase in BNIP3 protein levels in COPD skeletal muscle (Guo et al., 2013; Balnis et al., 2022; Mano et al., 2022). BNIP3 is known to decrease oxidative phosphorylation, increase mitochondrial protease activity, and potentially promote mitochondrial homeostasis (Rikka et al., 2011). Furthermore, FUNDC1 in COPD skeletal muscle decreases. These studies may elucidate that FUNDC1 and BNIP3 are regulated by different mechanisms, although both of them mediate receptor-dependent mitophagy. Overall, the available evidence suggests that mitochondrial autophagy may preserve skeletal muscle function in COPD by clearing damaged mitochondrial ROS and maintaining mitochondrial integrity.

The mechanism of autophagy leading to COPD skeletal muscle dysfunction is depicted in Fig. 1.

5 Conclusions

In COPD skeletal muscle, the levels of autophagy-related proteins are significantly increased. Mitophagy may help maintain COPD skeletal muscle homeostasis, whereas macroautophagy has opposite regulatory effects in myotubes and muscle satellite cells. Mechanistically, macroautophagy can regulate the myogenesis and regenerative capacity of satellite cells, whereas mitophagy helps restore mitochondrial homeostasis in skeletal muscle cells. Studying the effect and mechanism of autophagy on COPD skeletal muscle dysfunction is helpful for obtaining a new perspective on this issue and providing a theoretical basis for its clinical treatment.

6 Perspectives

This is an updated review on the role of autophagy in COPD skeletal muscle dysfunction. Numerous studies have been published in the ten years since the last review (Hussain and Sandri, 2013). Unfortunately, there are few articles (Gouzi et al., 2018; Balnis et al., 2022; Ito et al., 2022) on regulating the level of autophagy and observing the changes of skeletal muscle structure and function in COPD. Moreover, the results from these few articles are inconsistent. Based on the current research, there are several limitations and areas for improvement that need to be addressed in future studies. Firstly, most studies have only examined the expression of autophagy-related molecular markers at the protein and mRNA levels, without dynamically monitoring autophagic flux. Consequently, these

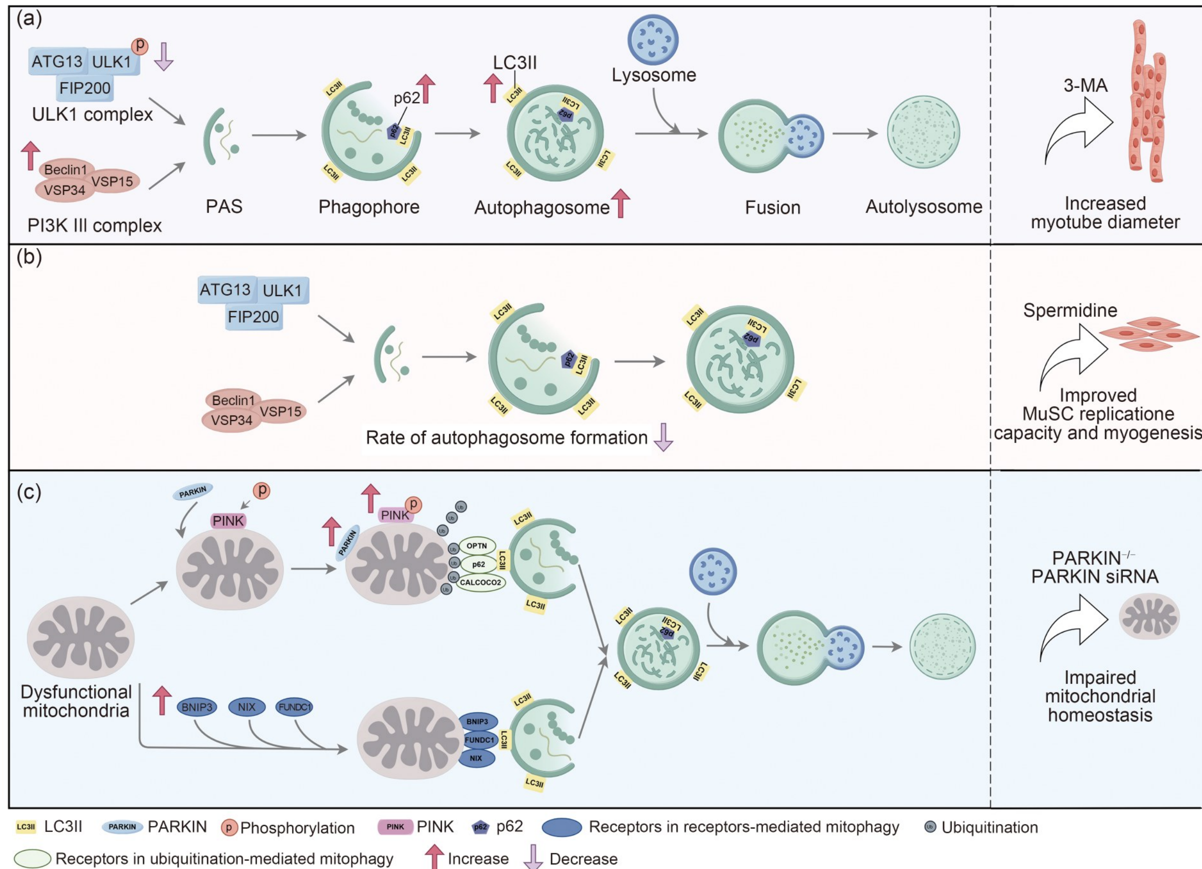

Fig. 1 Mechanism of autophagy leading to COPD skeletal muscle dysfunction. (a) Autophagy-related proteins were significantly increased in the myotubes and myoblasts of COPD skeletal muscle. The use of 3-MA (autophagy inhibitor) in COPD myotubes led to an increase in myotube diameter. (b) However, in MuSCs in COPD, the rate of autophagosome formation decreased, and spermidine (autophagy inducer) increased the diameter of MuSCs. (c) Mitophagy-related proteins were increased, and PARKIN underexpression may promote muscle dysfunction through exacerbating mitochondrial homeostasis. ATG: autophagy-related; Beclin1: B-cell lymphoma 2 (BCL2)-interacting protein 1; BNIP3: BCL2/adenovirus E1B-interacting protein 3; CALCOCO2: calcium-binding and coiled-coil domain-containing protein 2; COPD: chronic obstructive pulmonary disease; FIP200: 200 kD FAK family kinase-interacting protein; FUNDC1: FUN14 domain-containing protein 1; LC3II: light chain 3 II; 3-MA: 3-methyladenine; MuSC: muscle satellite cell; NIX: BNIP3-like; OPTN: optineurin; PINK: phosphatase and tensin homolog (PTEN)-induced kinase; PAS: pre-autophagosomal structure; PI3K III: class III phosphatidylinositol 3-kinase; siRNA: small interfering RNA; ULK1: Unc-51 like autophagy activating kinase 1; VSP: vesicle sorting protein. The figure is generated by Figdraw (figdraw.com).

studies are not sufficient to effectively reflect the true changes in autophagy, requiring a more cautious interpretation of the findings. To address this limitation, the use of green fluorescent protein (GFP)-LC3 mice can allow for the dynamic observation of changes in autophagy in COPD muscle cells after drug treatment (Balnis et al., 2022). Furthermore, changes in autophagy can be inferred by observing changes in autophagy-related protein expression and using autophagy modulators such as bafilomycin or 3-MA to measure autophagic flux. These dynamic detection methods can better reflect the true state of the disease. Additionally, in exploring changes in autophagy, further validation of changes in different stages of autophagy, such as initiation, nucleation, elongation, maturation, fusion, and degradation, is needed to achieve the precise regulation of autophagy. Secondly, the detection of autophagy levels in COPD skeletal muscle may be influenced by various factors, such as disease stage, muscle fiber type, and muscle cell differentiation status. Many studies have demonstrated that autophagy plays different roles at different stages of disease and physiological processes (Fiacco et al., 2016). It is crucial to understand whether there is differential regulation of

autophagy in COPD skeletal muscle at different disease stages for the precise regulation of autophagy to improve COPD skeletal muscle function. For instance, Leermakers et al. (2020) found that the protein levels of BNIP3 and BNIP3L-II in the gastrocnemius muscle of mice reached a peak at 48 h after the induction of a pneumonia model, while BNIP3L reached its lowest abundance at 72 h. In soleus, there was no significant difference in the protein or mRNA level of BNIP3L. Consistently, chronic ATG7 knockout mice showed only increased glycolytic muscle apoptosis protein and protein hydrolytic enzyme activity, with decreased strength and twitch kinetics (Paré et al., 2017). Furthermore, different types of muscle fibers have different responses to changes in autophagy, highlighting the need for the further exploration of the differential regulation of autophagy in different fiber types of COPD. Additionally, autophagy plays different roles in different statuses of muscle satellite cells, yet there is no research on the role of autophagy in different stages of muscle satellite cells in COPD. Furthermore, autophagy is a promising target for the targeted therapy of COPD skeletal muscle dysfunction. The systemic application of autophagy activators has shown improvement in COPD skeletal muscle dysfunction in rodent models. However, it is important to consider the potential impact of systemic autophagy intervention on autophagy in other organs that could affect COPD skeletal muscle. Moreover, due to the multiple biological effects of autophagy modulators, the interpretation of experimental results is limited. To overcome these limitations, the development of skeletal muscle-specific autophagy regulators and precise autophagy modulation drugs would help to further elucidate the role and specific mechanisms of autophagy in skeletal muscle dysfunction in COPD patients.

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Author contributions

Weibing WU and Xiaodan LIU performed the conceptualization and design; Xiaoyu HAN performed the drafting; Xiaoyu HAN, Peijun LI, and Meiling JIANG performed the analysis and interpretation; Yuanyuan CAO, Yingqi WANG, Linhong JIANG, Peijun LI, Meiling JIANG, Xiaoyu HAN, and Weibing WU contributed to the critical revision. All authors have read and agreed the final manuscript.

Compliance with ethics guidelines

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