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Emerging therapies for the treatment of skeletal muscle wasting in chronic obstructive pulmonary disease

Samantha L. Passey [a], Michelle J. Hansen [b], Steven Bozinovski [a,b], Christine F. McDonald [c,d], Anne E. Holland [e], Ross Vlahos [a,b,*]

[a] School of Health and Biomedical Sciences, RMIT University, Melbourne, Australia
[b] Lung Health Research Centre, Department of Pharmacology and Therapeutics, The University of Melbourne, Melbourne, Australia
[c] Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Australia
[d] Department of Medicine, University of Melbourne, Institute for Breathing and Sleep, Heidelberg, Melbourne, Australia
[e] Department of Physiotherapy, La Trobe University and Alfred Health, Melbourne, Australia

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease that constitutes a major global health burden. A significant proportion of patients experience skeletal muscle wasting and loss of strength as a comorbidity of their COPD, a condition that severely impacts on their quality of life and survival. At present, the lung pathology is considered to be largely irreversible; however, the inherent adaptability of muscle tissue offers therapeutic opportunities to tackle muscle wasting and potentially reverse or delay the progression of this aspect of the disease, to improve patients' quality of life. Muscle wasting in COPD is complex, with contributions from a number of factors including inflammatory cytokines, oxidative stress, growth and anabolic hormones, nutritional status, and physical activity. In this review, we discuss current and emerging therapeutic approaches to treat muscle wasting in COPD, including a number of pharmacological therapies that are in development for muscle atrophy in other pathological states that could be of relevance for treating muscle wasting in COPD patients.

1. Introduction—Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease caused by excessive inflammation leading to irreversible damage to the airways and lung tissue. Symptoms include cough and shortness of breath, relating to underlying small airways disease with or without chronic bronchitis, and emphysema (an enlargement of the airspaces caused by destruction of the alveoli). COPD is a major global health burden and is currently the 3rd leading cause of death worldwide (Lozano et al., 2012). A major cause of COPD is cigarette smoking; however, COPD may also occur in non-smokers. Other important risk factors for COPD include inhalation of noxious substances such as particulate matter in wood smoke, air pollution or dust (Salvi & Barnes, 2009), asthma, and genetic factors. The severity of airflow limitation in COPD is graded based on spirometric measurements of lung function according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, with the mildest airflow limitation classed as GOLD 1, progressing to the most severe airflow limitation at GOLD 4 (GOLD, 2016). COPD is increasingly being recognized as a systemic disease, and additional metrics such as body mass index (BMI), degree of shortness of breath (dyspnea), and physical capacity (6-minute walk distance, 6MWD) are also predictive of patient outcomes (Celli et al., 2015).

The pulmonary pathology of COPD arises due to remodeling and narrowing of the airways, and damage to the lung parenchyma that leads to alveolar damage and emphysema (Barnes, 2014). Development and progression of the disease is driven by chronic inflammation and oxidative stress within the lungs, initiated in response to inhalation of noxious substances. Inflammation is perpetuated by immune cells such as neutrophils and macrophages recruited to the lungs as part of the inflammatory response. Once the process is initiated, the disease progresses due to persistent inflammation and the production of

Abbreviations: COPD, Chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWD, 6-minute walk distance; AECOPD, Acute exacerbations of COPD; FFMI, Fat-free mass index; BMI, Body mass index; IGF-1, Insulin-like growth factor 1; mTOR, Mammalian target of rapamycin; MuRF-1, Muscle ring finger 1; TNF, Tumor necrosis factor; IL, Interleukin; NFκB, Nuclear factor kappa B; MAPK, Mitogen-activated protein kinase; SAA, Serum amyloid A; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; SOD, Superoxide dismutase; Gpx, Glutathione peroxidase; NAC, n-acetyl cysteine; Nox, NADPH oxidase; TGF, Transforming growth factor; ActRIIB, Activin receptor IIB; SARM, Selective androgen receptor modulator; NMES, Neuromuscular electrical stimulation.

* Corresponding author at: School of Health and Biomedical Sciences, RMIT University, Bundoora, VIC 3083, Australia. Tel.: +61 3 9925 7362; fax: +61 3 9925 6539.
E-mail address: ross.vlahos@rmit.edu.au (R. Vlahos).

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oxidants from endogenous cellular sources, even in the absence of external stimuli such as cigarette smoke.

In addition to chronic inflammation and oxidative stress in stable COPD, patients are also more susceptible to respiratory infections, which are the predominant cause of acute exacerbations of COPD (AECOPD). During an exacerbation, patients experience a worsening of their symptoms, including increased sputum production and dyspnea, necessitating a change to their regular medication and often requiring hospitalization for additional treatment. Acute exacerbations can accelerate the decline in lung function in COPD patients, through the generation of persistent inflammation within the lungs (Wedzicha et al., 2014).

The pathology of COPD extends beyond the lung environment, giving rise to systemic effects and the development of a number of comorbidities including skeletal muscle wasting, cardiovascular disease, and osteoporosis (Barnes & Celli, 2009).

2. Skeletal muscle wasting in chronic obstructive pulmonary disease

Skeletal muscle wasting and dysfunction is experienced by up to 40% of COPD patients (Schols et al., 2005; Sergi et al., 2006; Vestbo et al., 2006) and loss of muscle mass is commonly assessed by measuring the patients' fat-free mass index (FFMI). Some studies have shown that the incidence of patients with a low FFMI increases with disease severity, reaching 50% in patients with GOLD stage 4 COPD (Vestbo et al., 2006), reflecting an association between muscle mass and the severity of the lung pathology. Muscle dysfunction is, however, observed across the full spectrum of COPD severities—an important observation suggesting that muscle is affected from an early stage in the progression of COPD and could be effectively targeted therapeutically before it becomes a debilitating condition.

COPD develops slowly but inexorably with most COPD patients being diagnosed at age 45 or older. While it is normal for people to experience a decline in muscle mass with increasing age, COPD patients in one study experienced a decline in muscle mass of up to 4.3% per year (Hopkinson et al., 2007), approximately double the rate of decline associated with ageing (Frontera et al., 2000). The clinical impact of muscle wasting in COPD patients is significant, resulting in not only reduction in quality of life, independence, and exercise capacity, but also overall survival. Patients with severe COPD who have reduced mid-thigh cross-sectional area (less than 70cm^2) have an approximately 4 times higher odds ratio for mortality than similar patients with a similar degree of airflow limitation but with preserved muscle size (Marquis et al., 2002). Low FFMI and reduced quadriceps strength have been identified as predictors of COPD mortality, independent of lung function decline (Schols et al., 2005; Swallow et al., 2007), highlighting the importance of muscle mass and function in the overall pathology of COPD.

Concomitant with a reduction in muscle mass is a loss of strength in the limb muscles. Interestingly, it appears that the lower limbs are more susceptible to wasting than the upper limb muscles (Caron et al., 2009), a feature that is similar to the pattern of wasting seen in disuse. While this suggests that disuse plays a significant role in wasting in COPD, it is likely that other mechanisms also contribute and therapies could be combined with exercise training to yield overall improvements in muscle strength and function.

The maximum voluntary contraction of the quadriceps muscles is reduced by as much as 40% in COPD patients (Bernard et al., 1998; Plant et al., 2010; Seymour et al., 2010). Some studies have demonstrated an increase in the prevalence of quadriceps weakness with increasing COPD severity (Kharbanda et al., 2015) and a positive correlation between mid-thigh cross-sectional area and severity of airflow limitation (Bernard et al., 1998), indicating a link between the severity of the lung pathology and the extent of muscle impairment. However, significant muscle weakness has also been detected in patients with mild COPD (GOLD stages 1–2) or mild dyspnea (Seymour et al., 2010) and even in smokers without COPD compared to healthy controls (Seymour et al., 2010; Kok et al., 2012), suggesting that skeletal muscle dysfunction may occur at an early stage even prior to the onset of respiratory symptoms.

In addition to loss of muscle mass and strength, phenotypic changes also occur in the muscle of COPD patients. A shift in the fiber types has been observed, with an increase in the proportion of fast glycolytic Type II fibers and a reduction in slow, oxidative Type I fibers (Jobin et al., 1998; Whittom et al., 1998; Debigare et al., 2003; Gosker et al., 2007; Vogiatzis et al., 2011).

Skeletal muscle mass is adversely affected both during and following an acute exacerbation; quadriceps strength declines in hospitalized patients during an AECOPD and only partially recovers even up to 90 days following an exacerbation in the absence of interventions such as pulmonary rehabilitation (Spruit et al., 2003). More frequent exacerbations are associated with a more rapid decline in strength (Ansari et al., 2012), further suggesting a link between AECOPD and muscle health.

Weight loss and weakness have long been observed in patients with COPD, but it is only in recent decades that we have begun to understand at the molecular level the processes contributing to wasting. To date, therapeutic options to restore muscle mass have been limited. In 2006, we reviewed the development of therapies for muscle wasting in COPD (Hansen et al., 2006). Here we provide an update on the current state of therapy targeting COPD-associated muscle dysfunction, discussing some of the mechanisms of muscle wasting as well as the advancement of therapeutic options in the last decade. We also discuss emerging therapies in development and clinical trials to treat muscle wasting in other conditions such as cancer cachexia and sarcopenia that share some similarities with the wasting observed in COPD, as these may be of relevance for the treatment of COPD patients to restore muscle mass and function.

3. Pathways regulating skeletal muscle mass

Broadly speaking, overall muscle mass is regulated by the balance between protein synthesis and protein degradation, with additional contributions from regenerative processes and satellite cells. In cases of atrophy in response to disuse, immobilization, or pathological conditions such as cancer cachexia, the balance shifts toward an increase in protein degradation and a decrease in protein synthesis. The overall aim in developing therapeutic approaches to tackle muscle wasting is to push the balance in the opposite direction, increasing protein synthesis and decreasing protein breakdown to lead to an overall increase in muscle mass.

The mechanisms and signaling pathways regulating muscle anabolic and catabolic processes are complex (Fig. 1). These intracellular pathways are controlled by a wide range of extracellular factors including inflammatory mediators, oxidative stress, circulating hormones, nutritional and exercise factors. In addition, chronic use of anti-inflammatory corticosteroids such as prednisolone is known to cause muscle weakness and atrophy, through their effects on various signaling pathways regulating muscle mass (Decramer et al., 1994).

The major pathway leading to muscle growth (hypertrophy) is through the insulin-like growth factor (IGF-1)/Akt/mTOR pathway, which promotes protein synthesis through stimulation of protein translation via activation of positive regulators of translation (p70S6 kinase) and inhibition of the negative regulator 4E-BP1 (Glass, 2003). Akt signaling also inhibits the FoxO transcription factors, leading to inhibition of the ubiquitin proteasome pathway and decreasing muscle proteolysis (Stitt et al., 2004). Muscle mass can also be increased through regenerative pathways following the activation of the muscle-resident stem cells, called satellite cells (Charge & Rudnicki, 2004).

Opposing the hypertrophy pathway are mechanisms that lead to atrophy. Muscle atrophy is largely driven by increased proteolytic breakdown of muscle proteins via the ubiquitin–proteasome system. Proteins are targeted for degradation by the proteasome by the covalent attachment of multiple ubiquitin molecules by ubiquitin-ligase proteins. A

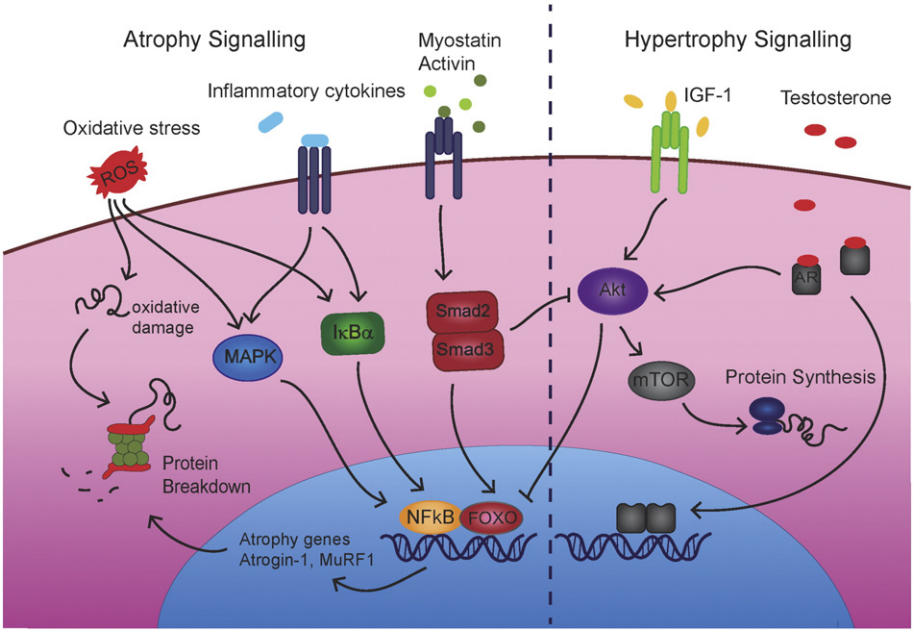

Fig. 1. Overview of signaling pathways regulating atrophy and hypertrophy of skeletal muscle. ROS, reactive oxygen species; MAPK, mitogen-activated protein kinase; NFκB, nuclear factor kappa B; FoxO, forkhead box; IGF-1, insulin-like growth factor 1; Akt, protein kinase B; mTOR, mammalian target of rapamycin; AR, androgen receptor.

number of muscle-specific ubiquitin ligases are expressed in skeletal muscle, including atrogin-1/Fbxo32 and muscle ring finger 1 (MuRF-1/Trim63), and expression of these proteins is often elevated in conditions of muscle atrophy (Bodine et al., 2001; Gomes et al., 2001; Bodine & Baehr, 2014; Yuan et al., 2015), reflecting the central role of the proteasome in regulating protein catabolism in atrophic states. An additional pathway of protein breakdown is the autophagy pathway that is responsible for degradation of organelles and other cellular constituents through the lysosomal degradation process (Hussain & Sandri, 2013).

Alterations in many of these pathways have been characterized in the muscle of COPD patients and are associated with loss of muscle mass in these patients. Increased expression of atrogenes – genes that encode proteins involved in muscle atrophy pathways – has been measured in COPD. The muscle-specific E3 ligases atrogin-1 and MuRF-1 are upregulated in COPD muscles (Doucet et al., 2007; Plant et al., 2010), suggesting an upregulation of the Ub-proteasome system and increased proteolysis. Indeed, increased muscle protein breakdown occurs in cachectic COPD patients compared to COPD patients with normal FFM and healthy controls (Rutten et al., 2006). There is little information on the contribution of the autophagy pathway to muscle protein breakdown; however, Plant et al. detected no change in the levels of autophagy proteins beclin-1 and LC3, suggesting that autophagy was not upregulated in the muscle from COPD patients in that cohort (Plant et al., 2010).

While reduced IGF-1 expression has been observed in some COPD patients (Plant et al., 2010), consistent with a decrease in protein synthesis, others have reported upregulated phosphorylated Akt and other components of the Akt/mTOR pathway in muscle from COPD patients (Doucet et al., 2007). It has been suggested that in the presence of strong atrophy signaling, the Akt pathway, may be upregulated in an effort to normalize muscle mass (Doucet et al., 2007); however, the mechanisms underlying these findings are yet to be fully explored.

Satellite cells in the muscle of COPD patients show evidence of senescence (Theriault et al., 2012), and COPD patients exhibit reduced muscle regenerative capacity (Theriault et al., 2014). Isolated satellite cells from COPD patients show reduced myotube diameter and increased atrophy signaling and oxidative stress in vitro (Pomies et al., 2015), suggesting an inherent alteration in the satellite cells themselves could be contributing to the reduced regenerative ability in COPD patients. The exact role of satellite cells and their ability to contribute to muscle regeneration in COPD is not yet fully understood and further investigation into this area is needed.

4. Inflammation

The link between inflammation and skeletal muscle health is well established. A number of inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-6, are known to induce muscle atrophy in animal models and healthy human volunteers (Goodman, 1991, 1994; Haddad et al., 2005; Bach et al., 2013; Zhou et al., 2016). Pro-inflammatory mediators including TNF-α, IL-6 and C-reactive protein (CRP) are elevated in COPD patients (Yende et al., 2006; Vogiatzis et al., 2007) and are associated with reduced muscle function. Elevated IL-6 levels have been associated with reduced lung function and increased muscle wasting in COPD patients compared to healthy elderly controls (Yende et al., 2006).

TNF-α is a key cytokine in the regulation of muscle mass signaling via a number of pathways to reduce muscle protein content and satellite cell differentiation. Through activation of the transcription factor NF-κB, TNF-α induces expression of MuRF-1 and increases activity of the ubiquitin–proteasome pathway leading to muscle protein degradation (Llovera et al., 1997). TNF-α-induced activation of the p38 mitogen-activated protein kinase (MAPK) pathway stimulates expression of atrogin-1 (Li et al., 2005), and this is proposed to be through the transcription factor FoxO4 (Moylan et al., 2008). In addition, TNF-α reduces muscle regeneration via inhibition of the myogenic regulatory factor MyoD (Guttridge et al., 2000; Langen et al., 2001). Given the established effects of TNF-α in muscle atrophy, and the association between elevated TNF-α levels and reduced muscle strength in COPD, targeting this cytokine therapeutically is an attractive prospect. This notion is supported by evidence from mouse cancer models, where inhibiting TNF-α signaling through administration of a soluble TNF-α receptor resulted in both increased bodyweight and increased appetite in tumor-bearing mice (Torelli et al., 1999).

Despite the important role of TNF-α in mediating muscle wasting and encouraging preclinical data supporting the use of anti-TNF-α agents for muscle wasting, the results of clinical trials for both muscle wasting in a range of conditions and the lung pathology of COPD have been somewhat disappointing (See Table 1). Treatment with the anti-

Table 1
Pharmaceutical therapies targeting chronic inflammation and oxidative stress for treatment of muscle wasting.

Drug name	Mode of action	Application	Results	Reference
Anti-cytokine				
Etanercept (Enbrel)	Anti-TNFα fusion protein	Cancer cachexia	No improvement in bodyweight	Jatoi et al., 2007
Infliximab (Remicade)	Anti-TNFα monoclonal antibody	Cancer cachexia	No improvement in bodyweight, increased fatigue and reduced quality of life	Jatoi et al., 2010
ALD518 (Alder Biopharmaceuticals)	Anti-IL-6	Cancer cachexia	Reduction in patients losing >5% bodyweight Reduced fatigue	Bayliss et al., 2011
Tocilizumab	IL-6 receptor antibody	Cancer cachexia	Improved bodyweight and appetite (case study)	Ando et al., 2013
MABp1 (Xilonix, Xbiotech)	Anti-IL-1α antibody	Cancer cachexia	Increased lean body mass, reduced fat mass. Reduced fatigue and increased quality of life scores	Hong et al., 2014
Dietary antioxidants				
Vits C & E, α-lipoic acid	ROS scavenger	COPD	No improvement in muscle time to exhaustion	Rossman et al., 2013
Resveratrol	Numerous: ROS scavenger, increases antioxidant enzyme activity	COPD	*In progress*	NCT02245932
Thiols				
NAC	Cysteine donor/ROS scavenger	COPD	Improved endurance but no effect on fatigue or dyspnea	Koechlin et al., 2004

TNF-α agent etanercept in cancer patients showed no significant improvement in bodyweight compared to those treated with the placebo (Jatoi et al., 2007). Similar results were seen in a later trial where patients were treated with the anti-TNF-α monoclonal antibody infliximab, and patients reported increased fatigue and an overall reduction in quality of life following infliximab treatment (Jatoi et al., 2010). In this study, no patients reached the primary endpoint of 10% or greater weight gain, and the trial was terminated early due to the lack of efficacy (Jatoi et al., 2010). It is worthwhile noting that while cancer cachexia and the wasting associated with COPD may be initiated by differing pathological conditions, the underlying molecular changes and mechanisms have been shown to be similar. For example, similar alterations in levels of oxidative stress and systemic inflammation, signaling pathways and muscle architecture have been observed in the muscles of patients with both lung cancer and COPD (Puig-Vilanova et al., 2015). Therapies targeting cachexia in cancer may prove to be of value to treat muscle wasting in COPD.

There has been considerable interest in targeting TNF-α in COPD as preclinical studies using TNF knockout mice display a marked reduction in lung inflammation and emphysema in experimental cigarette smoke models (Churg et al., 2004). However, a clinical study using anti-TNF therapy (Infliximab) failed to improve outcomes for COPD patients including symptom score, lung function, exercise capacity, dyspnea score, health status, and rate of acute exacerbations (Rennard et al., 2007). Anti-TNF-α therapies have been similarly ineffective at reducing local and systemic inflammation in COPD patients (Loza et al., 2012) and to date have not resulted in any overall clinical benefit in terms of the lung pathology (van der Vaart et al., 2005; Rennard et al., 2007). The reasons for this are unclear; however, there are important features that contribute to the differential response to blocking the function of TNF-α in preclinical experimental models versus human clinical trials. It is well established that the cigarette smoke exposure mouse model represents a mild stage of COPD where there is modest airspace enlargement and airway remodeling. In these models, therapies are either applied prophylactically to prevent development of disease or the gene of interest is knocked out prior to exposure. This is in contrast to the clinical scenario, where anti-TNF trials have been performed on COPD patients with severe or very severe COPD.

Hence, therapies would need to reverse established disease pathology including muscle wasting in order for the patient to obtain benefit from the treatment. An alternative approach would be to perform clinical trials on early-stage or mild COPD patients and determine whether anti-TNF-α therapy prevents or slows progression of disease as seen in experimental models; however, such an approach is cost prohibitive at this stage and chronic administration of TNF-α blockers have been linked to an increase risk of clinically diagnosed pneumonia and lung malignancies (Rennard et al., 2007). It is increasingly recognized that therapies will continue to fail in large COPD trials that include a broad spectrum of clinical and molecular phenotypes, which fall within a defined group based on lung function. Novel therapies targeted toward improving muscle function in advanced COPD patients should first be assessed for their ability to reverse established or severe disease in novel preclinical models. A better approach would be to prevent progression of disease and muscle wasting, where preclinical models can be informative; however, the application of long-term trials in early-stage disease remains a challenging prospect for industry. Another important limitation of targeting TNF-α is the multifactorial and multicytokine nature of COPD and skeletal muscle wasting; it is likely that the inhibition of a single cytokine is not sufficient to overcome the complex wasting pathways and disease pathology and lead to detectable clinical improvement.

While not currently used for treatment of muscle wasting in COPD, anti-IL-6 therapies have shown promise in the treatment of cancer cachexia. The humanized anti-IL-6 monoclonal antibody ALD518 has a high affinity for binding IL-6, and clinical trials in non-small-cell lung cancer have yielded some positive results, including a significant reduction in the proportion of patients losing more than 5% lean body mass as well as improvements in overall scores of fatigue (Bayliss et al., 2011). Tocilizumab, an IL-6 receptor antibody, has been reported to improve cachexia in two patients (Ando et al., 2013) and also in a mouse cachexia model (Ando et al., 2014), but has yet to be tested on a larger scale in human studies.

Similarly to other cytokines, signaling through the IL-1 receptor stimulates muscle atrophy via upregulation of atrogene expression and inhibition of IGF-1 signaling (Benbassat et al., 1999; Li et al., 2009). Both IL-1β, and more recently, IL-1α, have been shown to be elevated in the lungs of COPD patients compared to never smokers (Botelho et al., 2011; Pauwels et al., 2011), suggesting a role for these cytokines in the pathology of COPD. Initial clinical trials of MABp1, a monoclonal anti-IL-1α antibody, demonstrated an increase in lean body mass in 70% of MABp1-treated cancer patients, along with improvements in fatigue and general quality of life scores (Hong et al., 2014). Although the trial was small with only 30 patients being assessed for body mass by dual energy X-ray absorptiometry (DEXA) scan, it is of interest that the patients who experienced a gain in lean body mass also saw a reduction in fat mass, suggesting a role for IL-1α in regulation of metabolism and body composition. Such an effect could be of benefit in COPD patients, where body composition is often altered such that patients display increased abdominal adiposity while simultaneously losing muscle mass in their limbs (Schols et al., 2005).

During an exacerbation, inflammation is elevated above the levels seen in stable COPD patients. In addition, the acute phase protein

Serum Amyloid A (SAA) rises dramatically, up to 1000-fold, and SAA has been identified as a biomarker for the severity of the exacerbation (Bozinovski et al., 2008). We have recently shown that SAA has direct effects on muscle cells, inducing both the expression of pro-inflammatory cytokines and an atrophy response (Passey et al., 2016). These findings suggest that acute phase proteins elevated in COPD or during an exacerbation could be contributing to the decline in muscle function observed during and following an exacerbation. The regulation of SAA in the circulation is complex, and SAA is known to interact with a number of cell surface receptors. As yet there are no therapeutics targeting SAA-mediated inflammation in the clinic; however, approaches aimed at promoting the resolution of inflammation through the administration of mediators that oppose the actions of SAA could hold promise (Bozinovski et al., 2014).

5. Oxidative stress

Oxidative stress is emerging as an important contributor to both the lung and systemic pathologies of COPD. Recent detailed reviews describe the mechanisms by which oxidative stress contributes to COPD pathology in the lung (Rahman & Kinnula, 2012) and to the development of systemic comorbidities (Bernardo et al., 2015), and readers are directed to these extensive reviews for more detailed information on this topic. Oxidative stress and damage occurs when there is an imbalance between the levels of oxidants and antioxidants, leading to an excess of highly reactive oxygen species (ROS) including superoxide, hydroxyl radicals and hydrogen peroxide, and reactive nitrogen species (RNS) such as nitric oxide and peroxynitrite (Bernardo et al., 2015). This imbalance can arise due to reduced antioxidant defenses or increased oxidant production.

In the context of COPD, there is a high oxidant burden within the lungs arising both as a result of the oxidants found within cigarette smoke and also due to endogenous oxidants produced by leukocytes recruited to the lung as part of the inflammatory response (Rahman & Kinnula, 2012). Oxidative stress is also acutely elevated following exercise in COPD patients (Van Helvoort et al., 2006; Fisher-Wellman et al., 2009; Mercken et al., 2009). In healthy populations, such acute increases act as a stimulus for increased antioxidant defenses, resulting in a lower overall oxidative stress over time. These responses appear to be partially blunted in COPD patients with low muscle mass (Fisher-Wellman et al., 2009).

There is an increased concentration of hydrogen peroxide (H_2O_2) in exhaled breath condensate of COPD patients and this is further elevated during AECOPD (Dekhuijzen et al., 1996; Nowak et al., 1996). Increased levels of the oxidation product malondialdehyde (MDA) are present in both the sputum and plasma of COPD patients (Zeng et al., 2013), and increased lipid peroxidation and protein carbonylation has also been measured in plasma from COPD patients compared to healthy controls (Santos et al., 2004; Nadeem et al., 2005), indicating an increase in systemic oxidative stress in COPD. The level of local lung oxidative stress correlates with systemic (plasma) levels of oxidative stress (Zeng et al., 2013), lending support to the 'spillover' hypothesis that oxidants and inflammation within the lungs can extend into the systemic circulation leading to the development of systemic comorbidities of COPD.

Antioxidant defenses including superoxide dismutase (SOD), glutathione peroxidase (Gpx) and glutathione levels have been found to be decreased in COPD and AECOPD patients compared to smokers and healthy controls (Nadeem et al., 2005; Zeng et al., 2013), further indicating that an imbalance in antioxidant/oxidant status exists in patients with COPD.

In addition to oxidative damage in the lungs and plasma, total protein carbonylation is elevated in the vastus lateralis muscle of COPD patients compared to healthy controls (Barreiro et al., 2008), and levels of protein carbonylation correlate inversely with quadriceps strength (Barreiro et al., 2010). MDA-protein adducts and tyrosine nitration is also increased in muscle from COPD patients, and in cigarette smoke-exposed rodent models (Barreiro et al., 2010). A number of abundant proteins with important functions in glycolysis, energy production and muscle contraction show increased levels of carbonylation in both COPD patients and in cigarette smoke-exposed guinea pigs compared to controls (Barreiro et al., 2010). Interestingly, oxidative changes have also been detected in muscle from non-COPD smokers and in animal models before the onset of overt lung pathology (Barreiro et al., 2010), indicating that cigarette smoke itself can exert an oxidative burden on muscle that could contribute to the development of muscle dysfunction at early stages of COPD development.

The function of skeletal muscle is regulated in part by endogenous ROS and RNS, which are involved in processes such as contractile function, glucose uptake, and regenerative processes (Espinosa et al., 2016). ROS and RNS production increases during muscle contraction, and hence muscle has a high level of endogenous antioxidant defenses to prevent excess oxidative damage from free radicals generated during exercise and daily movement. Endogenous antioxidant defenses are often upregulated in the muscle of COPD patients (Gosker et al., 2005; Barreiro et al., 2009; Rodriguez et al., 2012) and the clinical benefit of antioxidant therapies to ameliorate muscle dysfunction in COPD is not yet clear. However, the elevated levels of oxidative damage observed in the muscle of COPD patients and the link between oxidative stress and muscle strength suggest that in the context of COPD, the levels of oxidative stress overwhelm the endogenous defenses. Thus, therapy aimed at reducing oxidative stress in muscle could be of benefit for improving the muscle pathology in COPD.

Therapeutic strategies to target oxidative stress include the use of scavenging molecules to 'mop up' excess oxidants and also the administration of molecules that mimic or increase the activity of endogenous antioxidant proteins such as SOD and Gpx.

5.1. Dietary antioxidants

Many antioxidant compounds are naturally occurring and can be obtained from dietary sources or through dietary supplementation, including vitamins E and C, carotenes, and resveratrol. Clinical trials of dietary antioxidants have yielded mixed results. Oral administration of vitamins E and C has been shown to be effective in reducing markers of oxidative stress but does not improve measures of fatigue in healthy people (Bentley et al., 2015) or COPD patients (Rossman et al., 2013). A recently completed trial (see ClinicalTrials.gov identifier: NCT01942889) investigated the effect of combined antioxidant (vitamins C and E, selenomethionine, and zinc gluconate) with pulmonary rehabilitation therapy to determine if dietary antioxidants could enhance the physiological effects of exercise training; however, the results are not yet published.

Reseveratrol, a polyphenol found most commonly in red wine, was able to reduce some markers of oxidative stress in mouse models of sarcopenia and disuse atrophy (Jackson et al., 2010, 2011). Resveratrol treatment was not able to attenuate sarcopenia in ageing mice (Jackson et al., 2011); however, it did reduce disuse atrophy in a hindlimb suspension model (Jackson et al., 2010) and has recently shown some promising effects in preventing cancer cachexia in the mouse C26 colon cancer cachexia model (Shadfar et al., 2011). Currently, there are no published data on the effect of resveratrol on muscle mass in COPD; however, a trial is currently underway (see ClinicalTrials.gov identifier: NCT02245932) investigating the effects of resveratrol in COPD patients and includes muscle volume and body composition as secondary outcomes, so further information on resveratrol as a therapeutic option for muscle wasting in COPD may be available in coming years.

5.2. Strategies to increase glutathione levels

Glutathione is the most abundant non-protein thiol in muscle cells and is a strong determinant of the intracellular redox status (Schafer &

Buettner, 2001). N-acetyl cysteine (NAC) is a small molecule derivative of the amino acid cysteine and acts as a strong reducing agent (Rahman & Kinnula, 2012) that can act directly with ROS and RNS as well as supporting glutathione synthesis through acting as a cysteine donor. Initial results of trials in the use of NAC were mixed (Rahman & Kinnula, 2012); however, high doses of NAC have been shown to be effective in reducing mucus hypersecretion and the frequency of acute exacerbations of COPD, and NAC treatment is now included in the American College of Chest Physicians and the Canadian Thoracic Society guidelines for preventing acute exacerbations of COPD (Criner et al., 2015). It is also included in the recent COPD-X guidelines in Australia and New Zealand (Abramson et al., 2015).

Increasing levels of glutathione through the administration of glutathione itself or NAC and other thiol donors improves measures of muscle fatigue and reduces oxidative stress both in animal models and in humans (Lands et al., 1999; Ferreira & Reid, 2008), including in COPD patients (Koechlin et al., 2004).

Recently, a novel glutathione precursor, named FT061452 or F1, has shown some efficacy in reducing muscle loss in ageing mice (Sinha-Hikim et al., 2013). Treatment with F1 resulted in reduced lipid peroxidation, improved GSH/GSSG ratio, reduced IL-6, and increased phosphorylation of Akt suggesting increased protein synthesis signaling through the Akt/mTOR pathway (Sinha-Hikim et al., 2013). Data on this formulation are only available from preclinical animal models at this time, and to date, no clinical studies have been conducted.

5.3. Nox inhibitors

Preclinical studies using antioxidants in cigarette smoke-exposed mouse models have shown that the nox2 inhibitor apocynin is effective in reducing lung inflammation in influenza A-infected smoke-exposed mice (Vlahos et al., 2011; Oostwoud et al., 2016). Apocynin reduces the levels of hydrogen peroxide and nitric oxide in exhaled breath condensate of asthmatic patients (Stefanska et al., 2012), suggesting therapeutic potential for apocynin in the treatment of lung pathology in COPD patients. Daily administration of apocynin in a mouse model of chronic cigarette smoke exposure (8 weeks) resulted in improvements in both lung inflammation and muscle mass (Vlahos, R. unpublished observations), offering promise that the therapeutic targeting of oxidative enzymes could be a useful therapy for COPD and muscle wasting. Whether these findings will translate into clinical benefit in COPD patients warrants further investigation.

5.4. Antioxidant enzyme mimetics

Drugs that mimic the effect of endogenous antioxidant enzymes have been developed with the aim of raising the levels of antioxidant defenses and reducing oxidant burden. SOD mimetics can be classified into three major classes—macrocyclic ligands, manganese metalloporphyrins, and 'salens' (manganese-based SOD mimetics) (Rahman & Kinnula, 2012). While SOD mimetics have shown some promise in animal models of lung inflammation (Rahman & Kinnula, 2012), they have not yet been clinically tested for efficacy in COPD or muscle wasting contexts.

Glutathione peroxidases are selenium-dependent antioxidant enzymes that catalyze the breakdown of reactive hydrogen peroxide to water and oxygen (Vlahos & Bozinovski, 2013). Levels of systemic Gpx have been shown to be depleted in COPD patients (Santos et al., 2004; Vibhuti et al., 2007). The Gpx mimetic ebselen reduces lung inflammation in response to cigarette smoke (Duong et al., 2010) and influenza infection (Yatmaz et al., 2013; Oostwoud et al., 2016) in mouse models, suggesting that increasing the levels of Gpx activity could be a potential therapeutic for COPD. The effects of Gpx mimetics on skeletal muscle are not well characterized, particularly in the context of COPD. To the best of our knowledge, no clinical trials have yet been reported for the use of ebselen to treat muscle wasting in COPD, cancer cachexia, or sarcopenia.

5.5. Nrf2 activators

The expression of many antioxidant enzymes, including Gpx, is regulated by signaling through the transcription factor Nrf2 (Rahman & Kinnula, 2012). Disruption of Nrf2 in skeletal muscle impacts on muscle cell differentiation and regeneration and increasing the activity of Nrf2 by administration of sulforaphane has shown some efficacy in mouse muscular dystrophy models (Sun et al., 2015, 2016). However, there are no published data on the expression and activity of Nrf2 in the muscles of COPD patients, and further investigation is warranted to fully characterize the antioxidant defenses and redox balance at the molecular level in muscle from COPD patients and preclinical COPD models.

There are currently few therapeutic options to target oxidative stress in muscle wasting (Table 2), and the full effect of reducing the oxidant burden in COPD is not completely understood. Given the evidence of elevated oxidative burden and oxidative damage in lungs, systemic circulation and muscles of COPD and the known effects of oxidative damage on tissue function, further investigation into the area is important. (See Table 1.)

6. Inhibition of myostatin

The transforming growth factor (TGF)-β family member myostatin has been identified as a key negative regulator of muscle mass (McPherron et al., 1997), acting via both upregulation of atrophy genes and inhibition of Akt signaling to promote proteolysis and reduce protein synthesis. Deletion or mutation of the myostatin protein results in dramatically increased muscle growth in mice (McPherron et al., 1997), cattle (Grobet et al., 1997; McPherron & Lee, 1997), and humans (Schuelke et al., 2004). Myostatin is also known to have other effects on muscle physiology, including regulating muscle ROS production (Sriram et al., 2011) and also fiber type (Girgenrath et al., 2005).

Myostatin signals through the activin receptor type IIB (ActRIIB), a receptor that is shared with other TGF-β family member proteins activin and GDF11, which leads to phosphorylation of the transcription factors Smad2/3. Signaling through the Smads 2/3 pathway regulates muscle balance through inhibition of Akt and consequent activation of FOXO transcription factors leading to upregulated expression of atrogenes, and through direct effects of Smad on gene expression. In addition, it is becoming increasingly recognized that the Smad pathway has extensive cross-talk with other signaling pathways such as the mitogen-activated protein kinase pathway, inducing other cellular effects that regulate muscle atrophy and hypertrophy.

Consistent with its role in regulating muscle mass, myostatin expression is elevated in the vastus lateralis muscle from COPD patients compared to healthy controls (Man et al., 2010; Plant et al., 2010). Circulating myostatin protein is also elevated in serum from COPD patients and correlates with reduced muscle mass in male COPD patients (Ju & Chen, 2012).

A number of molecules targeting the myostatin/ActRIIB pathway have been, or are currently being, tested for efficacy in muscle wasting, in both COPD and other cachectic conditions (Table 3). Given the dramatic effects on muscle mass arising from myostatin deletion or loss of function, inhibition of myostatin itself using neutralizing antibodies is an obvious therapeutic approach. This notion is supported by a number of in vivo studies that have used antibodies directed against myostatin to treat muscle wasting in mouse models of cancer, disuse atrophy, sarcopenia, and glucocorticoid-induced wasting (Siriett et al., 2007; Murphy et al., 2010, 2011; Latres et al., 2015; Smith et al., 2015).

Preclinical studies using the monoclonal antimyostatin antibody LSN2478185 in naïve mice demonstrated an increase in muscle mass (Smith et al., 2015). Testing of the humanized derivative of this antibody, LY2495655, in the mouse C26 tumor model and the PC3 tumor model also demonstrated increased muscle mass and improvements in grip strength compared to the isotype control antibody (Smith et al., 2015). Interestingly, these antibodies also caused an increase in

Table 2
Therapeutic agents targeting myostatin and anabolic pathways to improve muscle wasting in COPD.

Drug name	Mode of action	Application	Results	Reference
Myostatin pathway inhibitors				
Bimigrumab (BYM338)	Activin II Receptor Antagonist	Sarcopenia (NCT01669174)	*In progress*	NCT01669174
		COPD (NCT01601600)	*In progress*	NCT01601600
LY2495655	Myostatin monoclonal antibody	sarcopenia/frailty, hip replacement	Improved muscle mass, reduced fat mass, some improvement in physical performance	Becker et al., 2015; Woodhouse et al., 2016
		Pancreatic cancer cachexia	*In progress*	NCT01505530
REGN-1033 (Regeneron)	Myostatin monoclonal antibody	Healthy volunteers (NCT01910220)	*In progress*	NCT01910220
		Sarcopenia (NCT01963598)		NCT01963598
AMG-745 (Amgen)	Peptibody (Fc-fusion protein)	Cancer	Increased muscle mass, reduced fat mass, no improvement in physical performance	Padhi et al., 2014
Androgen receptor modulators				
Enobosarm/Ostarine	SARM	Ageing/sarcopenia	Increased lean body mass, decreased fat mass,i mproved physical function (12 stair climb)	Dalton et al., 2011
		Cancer cachexia	Increased lean body mass, reduced fat mass Improved 12 stair climb and power, no improvement in 6MWD or hand grip strength	Dobs et al., 2013
Ghrelin/GH/IGF-axis				
Ghrelin	Stimulates GH secretion, orexigenic	COPD	Increase bodyweight and lean body mass Increased muscle strength and 6MWD	Miki et al., 2012; Nagaya et al., 2005
Anamorelin	Ghrelin receptor agonist	Cancer cachexia	Increased lean body mass	Garcia et al., 2015
		Cancer cachexia (non-small-cell lung cancer)	Increased lean body mass. No increase in handgrip strength	Temel et al., 2016
		Cancer cachexia (non-small-cell lung cancer)	Increased lean body mass, QOL and KPS scores. Increased IGF-1 levels No change in handgrip strength	Takayama et al., 2016
SUN11031	Synthetic Ghrelin	COPD	Increased bodyweight and lean body mass, increased serum IGF-1, no overall improvement in 6MWD or handgrip strength, although some improvement in subset of severe COPD patients.	Levinson & Gertner, 2012

muscle mass even in the context of caloric restriction, a finding that may be of importance in the treatment of muscle wasting in patients with reduced appetite and calorie intake as is often the case in COPD.

The humanized antimyostatin antibody LY2495655 (Landogrozumab) has since progressed to clinical trials and has demonstrated some promising, if modest, effects on muscle size in humans. In elderly patients with a history of falls, LY2495655 treatment resulted in a 2.5% increase in appendicular lean body mass after 24 weeks and showed a corresponding increase in total lean body mass and a reduction in fat mass (Becker et al., 2015). Treatment with LY2495655 also resulted in general increases in physical performance in tests of fast gait speed, stair climbing, and chair rising, although improvements in hand grip strength were not significant and no improvement was seen in isometric leg extension. Clinical trials for the use of LY2495655 to treat muscle atrophy in patients undergoing a total hip arthroplasty have revealed some efficacy in increasing muscle mass at 105 and 315 mg; however,

Table 3
Studies investigating the efficacy of neuromuscular electrical stimulation for treating muscle wasting in COPD.

Study population	Training protocol	Effects of NMES	Reference
After AECOPD (hospitalized)	35 Hz, 1 h per day, 5 days/week for 6 weeks. Both legs, hamstrings and quads.	Increased MVC and 6MWD, reduced muscle protein carbonylation (and reduced myosin heavy chain carbonylation); fiber type shift (increased Type I, decreased Type IIx).	Abdellaoui et al., 2011
During AECOPD	50 Hz, 30 min, 1× per day for 14 days. One leg only, quads and vastus medialis.	Increased quadriceps MVC in NMES treated leg (untreated leg decreased MVC)	Giavedoni et al., 2012
COPD	50 Hz, 30 min daily for 6 weeks. Both legs, quads only.	Increased 6MWD and MVC in NMES group vs placebo. Increased quad CSA.	Maddocks et al., 2016
COPD (moderate to severe, FEV_1 < 50% predicted)	50 Hz, 30 min per day, 5 days per week for 6 weeks. Both legs.	Increased quad strength (peak torque)and endurance (decreased fatigue). Reduced dyspnea.	Neder et al., 2002
COPD (severe to very severe, FEV_1 < 35% predicted)	HF-NMES (75 Hz) or LF-NMES (15 Hz), 18 min 2× per day, 5 days per week for 8 weeks.	Increased quad peak torque after HF-NMES but not LF-NMES. Increased endurance (total work) in HF-NMES and LF-NMES, but greater increase with HF-NMES. Reduced dyspnea.	Sillen et al., 2014
COPD (moderate to severe FEV_1 < 40% predicted)	50 Hz, 60 min, 2× per day, 5 days per week for 8 weeks. Both legs, quads.	Increased FEV_1 and exercise tolerance, reduced dyspnea. Increased 6 MWD. Increased fat-free mass, muscle mass and thigh CSA. Reduced TNFα and increase β-endorphin levels.	Vieira et al., 2014
COPD (severe)	50 Hz, 35 min quads, 25 min calves, 5× per week for 6 weeks. Both legs.	Increased mid-thigh and calf muscle CSA, improved strength and 6MWD (apart from 6 non-responder patients). Downregulation of catabolic protein atrogin-1, increase in anabolic pathway protein p70S6K.	Vivodtzev et al., 2012
COPD (moderate to severe, FEV_1 < 60% predicted, except 1 patient)	50 Hz, up to 1 h/eg, 5× per week for 6 weeks. Both legs, quads.	No significant effect of NMES on leg muscle mass, peak torque and 6MWD. Significant increase in Type II fiber CSA and a decrease in Type I fiber CSA—no changes in relative proportion of fiber types.	Dal Corso et al., 2007

Abbreviations: MVC, maximal voluntary contraction; 6MWD, 6 minute walk distance; CSA, cross-sectional area; HF-NMES, high-frequency NMES; LF-NMES, low-frequency NMES.

the threshold of the primary objective of the trial was not reached (Woodhouse et al., 2016). The antibody has also been tested for use in cancer cachexia in patients with pancreatic cancer (see ClinicalTrials.gov identifier: NCT01505530), although results are not yet available on the outcome of this trial.

REGN1033 is a fully humanized, antimyostatin monoclonal antibody developed by Regeneron, that shows high specificity for binding myostatin and no detectable binding of either GDF11 or activin (Latres et al., 2015). In vitro reporter gene assays confirmed that the antibody specifically blocks Smad phosphorylation and activation following myostatin treatment but not after treatment with activin, further confirming the specificity of the antibody against myostatin alone. In naïve mice, REGN1033 caused a significant 19–25% increase in the weight of the gasctrocnemius following 28 days of treatment, with a similar magnitude effect in the tibialis anterior. The increased muscle size was accompanied by an increase in the isometric force production of the tibialis anterior, with maximal tetanic force increasing by 16.7%, indicating that muscle functional performance is also improved following treatment. In models of disuse atrophy and glucocorticoid-induced atrophy, REGN1033 prevented loss of both muscle mass and function.

Following these promising preclinical results, REGN1033 is now in clinical testing. Initial clinical trials have been completed for safety and bioeffect (see ClinicalTrials.gov identifier: NCT01910220) and more recently for safety and efficacy in patients with sarcopenia (see ClinicalTrials.gov identifier: NCT01963598).

A slightly different approach to inhibition of myostatin has been developed in the form of AMG-745, a peptibody against myostatin. Peptibodies are fusion proteins consisting of an active peptide fused to the Fc portion of an antibody and offer a number of advantages over individual peptides and antibodies as therapeutic agents, including improved longevity in vivo (Shimamoto et al., 2012). AMG-745 contains a fusion protein with a human Fc at the N-terminus, and a C-terminal bioactive peptide that neutralizes myostatin activity (Padhi et al., 2014). Initial clinical trials have shown results similar to those seen with monoclonal antibodies; in patients receiving androgen deprivation therapy for prostate cancer, AMG-745 treatment resulted in a 2.2% increase in lean body mass compared to placebo, and an overall decrease in fat mass of around 2.5% at 1 month follow up after a 28 day treatment protocol (Padhi et al., 2014). Similar to the findings with LY2495655, no improvement in leg strength was seen following AMG-745 treatment, suggesting either that a greater level of myostatin inhibition is needed or that inhibiting myostatin alone is not sufficient to translate into functional improvement.

In addition to myostatin, other TGF-β family members such as activin also exert effects on muscle mass via ActRIIB suggesting a certain level of redundancy within this pathway that requires important consideration for the development of therapeutics targeting myostatin and its signaling pathway.

An alternative strategy to inhibiting or neutralizing myostatin itself is to develop receptor antagonists that prevent myostatin from binding to ActRIIB and initiating downstream signaling. This strategy has worked well in cell culture and mouse models, where the ActRIIB antibody Bimagrumab (BYM338) effectively prevented the atrophic effects of myostatin and activin on cultured myotubes and caused muscle hypertrophy in mice (Lach-Trifilieff et al., 2014). Bimagrumab also inhibited the muscle wasting in response to glucocorticoid treatment in mice, a finding that may be of particular interest in the context of COPD where many patients are treated with glucocorticoids that are known to negatively impact on muscle mass and health. Interestingly, Bimagrumab also increased muscle mass in a mouse carrying a loss of function mutation in the myostatin gene, suggesting additional ligands such as activin play important roles in the regulation of muscle mass. ActRIIB blockade with Bimagrumab was around twice as effective as treatment with the myostatin-specific inhibitor propeptide D76A, further emphasizing the overlap in function between different TGF-β family members. This indicates that blockade at the point of receptor signaling is likely a more effective strategy than targeting ActRIIB ligands individually.

Together these findings provide ample support for further testing into possible clinical uses of Bimagrumab in muscle wasting conditions. Indeed clinical trials have recently been completed to test the efficacy of Bimagrumab in both sarcopenia (see ClinicalTrials.gov identifier: NCT01669174) and muscle wasting in COPD patients (see ClinicalTrials.gov identifier: NCT01601600), results have not yet been made available.

7. Anabolic therapies

Body composition in COPD patients is complex, and loss of muscle mass can occur with or without accompanying changes in fat mass, resulting in a population of patients with underlying muscle dysfunction but varying levels of underweight or obesity (Schols et al., 2005; Steuten et al., 2006). While higher body weight is generally associated with a better prognosis for COPD patients, excess body fat and obesity are associated with additional health risks. Anabolic therapies are aimed at increasing muscle mass through stimulation of protein synthesis and reduction of protein breakdown, while preferably avoiding excess fat gain, so promoting a favorable body composition to improve overall health.

7.1. Insulin-like growth factor-1

IGF-1 appears to be an attractive therapeutic target due to its positive effects on muscle hypertrophy; however, previous trials administering recombinant human IGF-1 have yielded mixed results in human patients with a range of muscle conditions including sarcopenia and cancer cachexia (Philippou & Barton, 2014). The biology of IGF-1 is complex—there are several isoforms of the protein and the protein is subject to post-translational processing—and several issues make therapeutic administration of IGF-1 problematic. The IGF-1 receptor is ubiquitously expressed and IGF-1 is a potent growth factor affecting cell proliferation and survival in many tissues, therefore IGF-1 administration could represent an increased cancer risk; a concern that has limited the doses and timeframes of IGF-1 administration in clinical trials to date (Philippou & Barton, 2014).

Therapeutic methods aimed at increasing the local expression of IGF-1 within the muscle tissue may be more effective in promoting muscle hypertrophy and may help to avoid unwanted systemic effects. Gene transfer or virus-mediated expression of IGF-1 within muscle tissue has been shown to be effective in increasing IGF-1 and promoting muscle repair and growth in animal models (Barton-Davis et al., 1998; Schertzer & Lynch, 2006) but has yet to be transferred to human studies. Although there are currently some trials investigating the use of IGF-1 in the treatment of muscular dystrophy, at present, to the best of our knowledge, no trials are in progress for the use of IGF-1 to treat muscle wasting in COPD.

A number of other anabolic hormones have been tested for efficacy in COPD patients, including testosterone, ghrelin, and growth hormone analogues and offer promise for future therapeutic use.

7.2. Testosterone

Perhaps the most widely known anabolic compound is the anabolic hormone testosterone, which has potent anabolic activity in muscle cells along with a lipolytic effect resulting in increased muscle mass and reduced fat mass (Dubois et al., 2012). Testosterone signals both through the androgen receptor and also via crosstalk with a number of intracellular signaling pathways to regulate protein synthesis and satellite cell differentiation, leading to an increase in muscle mass (Dubois et al., 2012).

Testosterone administration is known to increase the size of muscle fibers in a similar manner to that seen with resistance training. Testosterone itself must be administered by injection, or through the skin

via a gel or patch; however, a number of testosterone analogues have been developed that can be taken orally. Testosterone analogues have shown some promising results in COPD, with patients in a number of clinical studies showing increases in muscle mass following treatment (Schols et al., 1995; Creutzberg et al., 2003; Casaburi et al., 2004). To date, however, these changes have not consistently translated into other measurable patient-centered outcomes such as exercise capacity and lung function (Velema et al., 2012; Pan et al., 2014b).

Testosterone exerts both anabolic and androgenic effects, and the administration of testosterone and its analogues is associated with a number of side effects, including increased risk of cardiovascular events and dermatological disorders (Basaria et al., 2010), that have limited its uptake in clinical practice. In recent years, a new class of molecules known as selective androgen receptor modulators (SARMs) have been developed that interact with the androgen receptor and can mimic some of the effects of testosterone while avoiding some of the side effects (Mohler et al., 2009). These molecules offer some promise for the therapeutic treatment of muscle wasting in COPD and have recently been tested in clinical trials (See Table 2).

The nonsteroidal SARM Enobosarm (GTx-024) is reported to increase muscle mass and bone density in animal models and in healthy human males (Dalton et al., 2011). In elderly men and postmenopausal women, Enobosarm at 3 mg per day for 86 days caused a significant 1.3 kg increase in lean body mass, which was accompanied by a significant decrease in fat mass (Dalton et al., 2011). This increase also appeared to translate into improved function, with patients showing a decrease in the time to climb 12 stairs and an increase in stair climb power (Dalton et al., 2011). A more recent trial investigating the efficacy of Enobosarm in cancer patients also demonstrated a significant improvement in lean body mass and reduced fat mass (Dobs et al., 2013). No significant improvement was seen in 6-minute walk test or hand grip strength; however, Enobosarm-treated patients showed a decrease in stair climb time and increased stair climb power compared to placebo-treated patients, suggesting some improvement in muscle function following Enobosarm treatment (Dobs et al., 2013).

At this time, no trials are currently registered for the investigation of the effectiveness of SARMs in treating muscle wasting underlying COPD; however, this avenue offers promise, particularly in combination with other therapeutic approaches such as the combination of nutritional intervention and exercise training, which has been demonstrated to be an effective multimodal treatment approach in previous studies (Casaburi et al., 2004).

7.3. Ghrelin

Ghrelin is a peptide hormone of 28 amino acids that regulates growth hormone (GH) secretion from the anterior pituitary gland and has a number of effects with potential benefit for treating muscle wasting in COPD. Ghrelin is a potent orexigenic agent, stimulating appetite and feeding (Wren et al., 2001a, 2001b). Such effects could be beneficial in COPD patients who have reduced appetite and calorie intake. In addition, ghrelin can indirectly stimulate protein synthesis through stimulation of the GH-IGF-1 axis, promoting muscle anabolic processes. It also stimulates adiposity through inhibition of fat oxidation (Tschop et al., 2000), implying that caution may be needed in administering ghrelin to patients with higher fat mass.

Ghrelin levels appear to be higher in underweight patients with COPD compared to healthy controls (Itoh et al., 2004; Uzum et al., 2014) and normal weight COPD patients (Itoh et al., 2004), a phenomenon that has been observed in other cachectic states (Nagaya et al., 2001; Shimizu et al., 2003). Another study found reduced ghrelin levels in COPD patients (mean BMI of 18.5) compared to healthy controls (mean BMI 22) (Luo et al., 2005). The reason behind this discrepancy is unclear but may reflect differences in the COPD populations sampled (e.g., current smoking status, different inclusion criteria) and methodological differences in the isoforms of ghrelin measured in each study.

Clinical studies administering human ghrelin to COPD patients resulted in increased bodyweight and lean body mass and increases in both limb and respiratory muscle strength (Nagaya et al., 2005). Functional improvements have also been reported following ghrelin administration, with improved 6-minute walk distance reported in two studies (Nagaya et al., 2005; Miki et al., 2012). A recent study using the synthetic ghrelin peptide SUN11031 similarly resulted in increased bodyweight and lean body mass, accompanied by increased levels of IGF-1 (Levinson & Gertner, 2012). This study did not observe significant increases in 6-minute walk distance or handgrip strength in the overall trial population following SUN11031 treatment. However, in a *post-hoc* analysis of a subpopulation of patients with advanced muscle wasting at baseline then treated with the highest dose of SUN11031 had a significant increase in 6MWD and handgrip strength compared to placebo-treated patients.

The ghrelin receptor agonist anamorelin has not yet been tested in the context of COPD-associated muscle wasting. It has shown positive results on lean body mass in clinical studies in cancer cachexia; however, no increase in handgrip strength was observed despite increases in IGF-1 (Garcia et al., 2015; Takayama et al., 2016; Temel et al., 2016).

Despite evidence of increased bodyweight and lean body mass following treatment targeting the ghrelin pathway in cachectic patients with both COPD and other conditions, the translation of increased mass to improvements in strength and physical function has not been consistently demonstrated. Despite this, therapies targeting the ghrelin-GH pathway may still hold promise and, in combination with effective pulmonary rehabilitation programs, could result in beneficial increases in both muscle mass and function (See Table 2).

8. Physical inactivity and pulmonary rehabilitation

Numerous studies have shown that COPD patients are less physically active than healthy controls (Watz et al., 2009; Troosters et al., 2010; Vorrink et al., 2011; Watz et al., 2014), and physical inactivity is seen as a major contributor to the muscle wasting and loss of strength seen in COPD patients.

As with healthy people, physical activity and exercise have numerous health benefits in patients with COPD and exercise training through pulmonary rehabilitation programs is currently the gold standard for improving muscle strength and function (Spruit et al., 2013). Pulmonary rehabilitation incorporates a range of interventions including education, behavioral change, and exercise training with the aim of improving the physical and psychological condition of people with COPD (Spruit et al., 2013). The beneficial effects of exercise training in pulmonary rehabilitation are well established and a recent systematic review of 65 randomized controlled trials revealed that pulmonary rehabilitation leads to improvements in exercise capacity as well as in quality of life scores including symptoms of fatigue and dyspnea (McCarthy et al., 2015).

COPD patients often exhibit exercise intolerance due to a variety of factors including dyspnea, ventilatory limitation, fatigue, and peripheral muscle dysfunction (Spruit et al., 2013). Although exercise training in COPD patients is an effective therapeutic approach, the training modalities of pulmonary rehabilitation programs vary and there is still some debate about the most effective training protocols for the heterogeneous COPD population and a need to develop tailored training programs to accommodate differing patient abilities and needs.

Commonly used training modes include endurance/aerobic training and resistance/strength training, and protocols and training programs often differ even within individual training modalities. Endurance training, commonly through stationary cycling or walking activities, aims to condition the ambulatory muscles and improve cardiovascular fitness (Spruit et al., 2013). Factors such as duration, frequency, and intensity are important determinants of the physiological adaptations to exercise training. Although the optimal duration for a pulmonary rehabilitation is unclear, evidence of benefit in exercise capacity and quality of life is

demonstrable if participants attend a minimum of 12 sessions during a 2 or 3 day per week 6–12 week program (Bolton et al., 2013). In addition to the supervised exercise, patients are encouraged to continue exercising at home during the period of the program, following standard exercise prescription guidelines such as those of the American College of Sports Medicine, with exercise sessions of 20–60 min, 3–5 times per week at >60% of the patient's maximal work rate (Garber et al., 2011).

Endurance training leads to improved exercise capacity (Whittom et al., 1998; Troosters et al., 2000; Ortega et al., 2002; Vogiatzis et al., 2007, 2011). Additional increases in muscle cross-sectional area, IGF-1 expression, and a shift toward more oxidative type I fibers have also been reported (Vogiatzis et al., 2007, 2011).

Resistance or strength training involves lifting heavy weights for a prescribed number of repetitions, to build strength and increase muscle mass in individual muscles or muscle groups through upregulation of the mTOR signaling pathway (Terzis et al., 2008; Walker et al., 2011). Numerous randomized controlled trials have confirmed that resistance training protocols increase arm and leg strength, exercise capacity and muscle mass in COPD patients (O'Shea et al., 2009; Vonbank et al., 2012; Constantin et al., 2013). Similar changes in muscle size and isometric strength were observed in healthy controls and COPD patients after an 8 week resistance protocol, confirming that the muscles of COPD patients are still able to respond to strength training stimuli to the same extent as healthy controls, despite starting from a depleted baseline (Constantin et al., 2013).

While resistance training is well accepted as a method for improving strength, its effects on aerobic fitness and exercise endurance are less apparent. Resistance training results in some improvement in walking distance and cycling endurance compared to no exercise; however, it is much less effective than endurance/aerobic training at improving performance in these areas (O'Shea et al., 2009). It is likely that a combined training program including both resistance and endurance exercise modalities would be optimal to increase muscle mass, strength, and endurance in COPD patients, a hypothesis that has been supported by several studies (Ortega et al., 2002; Vonbank et al., 2012; Zambom-Ferraresi et al., 2015), and indeed most pulmonary rehabilitation programs include aspects of both endurance and resistance exercise to maximize gains from both modalities.

Despite the accepted benefits of exercise training for improving muscle mass and function in COPD patients, a number of therapeutic challenges still remain. Within the COPD population, there are 'non-responder' patients who do not show improvement with exercise interventions, largely due to the presence of more severe airflow limitation or comorbidities (Hill & Holland, 2014). It is estimated that around 50% of patients referred for pulmonary rehabilitation present with comorbidities that affect their ability to exercise, the most common of which are metabolic disorders (hypertension, diabetes, and dyslipidaemia) and heart diseases (chronic heart failure and coronary heart disease) (Crisafulli et al., 2008). Patients with comorbidities were still able to respond to exercise training and improve their physical capacity (Crisafulli et al., 2008); however, tailored and multimodal training programs are needed to accommodate the needs and abilities of different COPD patients, and a number of additional interventions have been proposed (Hill & Holland, 2014).

8.1. Interval training

Interval training involves performing short periods of intense exercise interspersed with periods of rest or lower intensity exercise. Although used for years in the training of athletes, interval training has emerged as an option for patient rehabilitation only recently. Interval training is generally well tolerated and offers some benefits for those patients who are unable to tolerate long periods of continuous aerobic exercise or are unable to achieve the target exercise intensity or duration to provide a sufficient training stimulus for improvement (Spruit et al., 2013). A number of trials have confirmed the efficacy of interval training methods in COPD if the same total work is performed as an endurance protocol (Puhan et al., 2006; Beauchamp et al., 2010; Zainuldin et al., 2011). Interval training is generally well tolerated and results in lower symptom scores than continuous endurance exercise protocols, despite similar overall work (Beauchamp et al., 2010).

8.2. Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) involves external electrical stimulation of isolated muscles via electrodes placed on the skin to evoke an action potential within the muscle and cause involuntary contraction (Maffiuletti, 2010). NMES offers a number of advantages for training of COPD patients; (1) the equipment used is portable and easy to use, allowing patients to use the equipment in a home setting for regular treatment; (2) NMES is generally well tolerated and has few side effects; (3) the exercise is passive, involving a low ventilatory load, which may be useful for patients who are not able to exercise due to respiratory symptoms; and (4) it can be used in bedbound or even unconscious subjects, making it potentially useful for maintaining muscle mass in hospitalized patients who cannot exercise (Spruit et al., 2013).

Trials in the use of NMES have reported consistent benefits in terms of improved muscle size and function, exercise endurance and capacity, improved lung function, and reduced dyspnea (Neder et al., 2002; Abdellaoui et al., 2011; Giavedoni et al., 2012; Vivodtzev et al., 2012; Sillen et al., 2014; Vieira et al., 2014; Maddocks et al., 2016)(see Table 3). In a direct comparison of high-frequency NMES with a resistance training protocol over 8 weeks, the increase in isokinetic quadriceps strength was similar in the two training groups, indicating that NMES can be as effective as traditional strength training (Sillen et al., 2014) and supporting the notion that it may be a particularly useful training modality to restore or maintain muscle mass in COPD patients who have difficulty exercising, for example, during hospitalization for an acute exacerbation (Zanotti et al., 2003; Vivodtzev et al., 2006).

In addition to improved muscle size and function, changes at the level of muscle architecture and biochemistry have been reported following NMES in COPD patients, including decreased expression of the atrophy-related gene atrogin-1 and increased phosphorylation (and hence activity) of P70S6K, a protein involved in the anabolic protein synthesis pathway (Vivodtzev et al., 2012). An increase in the proportion of Type I and Type IIa/x fibers has also been observed following NMES, suggesting a fast-to-slow shift in fiber type toward a more oxidative phenotype. Another study reported a decrease in Type I fibers, albeit in a population with less severe COPD and with variations in the stimulation protocol (Dal Corso et al., 2007). Other molecular changes reported include a reduction in markers of oxidative stress in the muscle of patients treated with NMES following acute exacerbation (Abdellaoui et al., 2011), and a reduction in serum TNF-α levels (Vieira et al., 2014), suggesting that NMES could affect levels of systemic oxidative stress and inflammation in addition to its direct effects on muscle strength and function.

While these observations are promising for the use of NMES to treat muscle wasting in COPD, they must be interpreted with caution due to the small size of many trials, the highly selected patients who were included and wide variation in treatment protocols used (Sillen et al., 2013; Pan et al., 2014a). Further investigation and large scale trials are needed to fully optimize treatment protocols and evaluate efficacy of NMES for the treatment of muscle wasting in COPD, and indeed a number of such trials are either recently completed or currently recruiting patients (see ClinicalTrials.gov identifiers: NCT02321163, NCT01799330, ISRCTN87439020, NCT02171377).

8.3. Muscle partitioning during exercise

Many COPD patients are not able to exercise at high intensity due to ventilatory constraints, which may limit the extent to which muscular

adaptations can be achieved through traditional endurance exercise training. An alternative method is to partition or limit the exercise to a smaller subset of muscle groups in order to reduce the ventilatory load on the patient and allow them to exercise that muscle group at higher intensity than they could if using larger muscle groups (Richardson et al., 1999).

An example of this is one-legged cycling, which has emerged as a potential training modality for COPD patients (Dolmage & Goldstein, 2006), and has been shown to improve peak muscle power and oxygen uptake while resulting in lower dyspnea than two-legged cycling at the same workload (Dolmage & Goldstein, 2008; Bjorgen et al., 2009). To date, only a few small trials have been conducted using this training modality in this area, and none have looked specifically at molecular or phenotypic changes in muscle tissue. The method is currently being expanded in a trial using single and double leg elastic band exercises (see ClinicalTrials.gov identifier: NCT02283580), that includes measurement of anabolic/catabolic signaling pathways, fiber types, and enzyme activities in the quadriceps muscles as secondary outcomes (Nyberg et al., 2015). Partitioning exercise approaches remain a very promising therapeutic alternative to traditional exercise training and could be readily translated into clinical practice (Evans et al., 2015).

8.4. Telehealth and community rehabilitation programs

Additional challenges in pulmonary rehabilitation include the problem of waning effects over the 12 months following completion of an exercise training program, and improving access to enable patients who have difficulty attending an outpatient rehabilitation program to participate in structured and supervised exercise training and improve their physical capabilities. It is estimated that up to 50% of patients who are referred for pulmonary rehabilitation will never attend, and dropout rates are estimated at 10–32% (Keating et al., 2011).

The relatively new and expanding field of telehealth offers opportunities for patients to participate in exercise programs in their own home or within the community while still under the remote supervision of trained medical staff and exercise therapists. Pilot studies using telehealth approaches have shown some promise. Recent studies have demonstrated improvements in 6MWD and dyspnea scores (Holland et al., 2013a; Wang et al., 2014; Zanaboni et al., 2016); however, patient numbers in each trial are still small. A meta-analysis conducted on 9 trials from 1996 to 2013 reported that telemedicine approaches did not improve physical exercise capacity or dyspnea but may have an effect on physical activity (Lundell et al., 2015); however, comparisons between trials were hampered by large variability in telehealth protocols and outcome measures.

Home- or community-based telerehabilitation programs have been shown to be well tolerated by participants, especially those living in remote areas for whom travelling to attend clinics is problematic (Burkow et al., 2015). The cost of delivering such programs is variable depending on the nature of the program and the equipment provided to participants but has been shown to be comparable or lower than the cost of attending an outpatient clinic (Burkow et al., 2015). Current and upcoming studies aimed at more directly comparing home-based programs with outpatient clinic rehabilitation will be valuable in addressing the direct and indirect costs associated with each mode of therapy (see ClinicalTrials.gov identifier: NCT01423227) (Holland et al., 2013b).

Some recent trials have further explored the use of modern technology for the delivery of home-base rehabilitation, with some exciting results. Interesting studies from Wang and colleagues involved a home-based walking program for COPD patients, which asked patients to walk in time to the speed of music played on their mobile phones (Liu et al., 2008; Wang et al., 2014). The tempo of the music was calculated to match a measured walking speed of 80% of maximal walking capacity based on exercise testing, allowing a fully personalized intervention to encourage patients to exercise at the required intensity. Patients using the music app showed clinically significant increases in walking distance in the Incremental Shuttle Walk Test (ISWT) of 49 and 58 m at 3 and 6 months, respectively, compared to baseline testing, which is above the minimum important difference of 47.5 m (Singh et al., 2008) and comparable to results typically seen following in-patient rehabilitation programs (Spruit et al., 2013). Strength was also improved after 6 months in patients using the music app, whereas control patients given the same walking program but not using the app showed a decline in walking distance over the same time period and no changes in strength (Wang et al., 2014). Measures of inflammation (CRP, IL-8, TNFα, and IL-6) all decreased in patients using the app compared to controls (Wang et al., 2014).

9. Concluding remarks

In the last few decades, as skeletal muscle wasting has become more recognized as a serious and prevalent comorbidity of COPD, our understanding of the molecular pathways leading to muscle wasting and the complex interplay between the lung and systemic pathologies of COPD has improved dramatically. As our knowledge of molecular mechanisms leading to muscle wasting increases, so promising new pharmacological targets are identified that could be targeted to reduce muscle wasting or delay disease progression.

Despite this, exercise training through pulmonary rehabilitation remains the cornerstone of COPD management with proven effectiveness in improving lean body mass, physical capability, and lung symptoms. Currently, there are no clinically proven licensed pharmacological therapies for muscle wasting in COPD. While exercise training is effective, many patients are limited in the amount and/or type of exercise they can do or are not able to access pulmonary rehabilitation services. There is a clinical need to develop effective pharmacological agents and therapeutic approaches to target muscle wasting processes in COPD, acting either alone or in conjunction with pulmonary rehabilitation programs.

The mechanisms of wasting in COPD are complex, including contributions from physical activity, systemic inflammation, lack of appetite, hormone signaling, and oxidative stress. It is likely that wasting may be worsened in patients for whom multiple factors are involved, for example, those who show elevated systemic inflammation, lack of appetite, and reduced physical activity. The signaling pathways leading to wasting may also interact with each other, working synergistically to increase atrophy. While it is unlikely that targeting a single aspect will be an effective approach to treating such a complex condition, it may be that even reducing the impact of a single factor could lead to clinically meaningful improvements in muscle mass and strength. However, the most promising outcome is likely to be achieved from combining therapeutic approaches to tackle multiple factors simultaneously.

Conflict of interest statement

The authors declare that there are no conflicts of interest

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