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

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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.

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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