Skeletal muscle dysfunction in COPD: clinical and laboratory observations

William D.-C. MAN*, Paul KEMP*, John MOXHAM† and Michael I. POLKEY*
*London Respiratory Muscle Group, Royal Brompton & Harefield NHS Trust, Sydney Street, London SW3 6NP, U.K., and
†Respiratory Muscle Laboratory, King's College London School of Medicine, King's College Hospital, Bessemer Road, London SE5 9PJ, U.K.

A B S T R A C T

COPD (chronic obstructive pulmonary disease), although primarily a disease of the lungs, exhibits secondary systemic manifestations. The skeletal muscles are of particular interest because their function (or dysfunction) not only influences the symptoms that limit exercise, but may contribute directly to poor exercise performance. Furthermore, skeletal muscle weakness is of great clinical importance in COPD as it is recognized to contribute independently to poor health status, increased healthcare utilization and even mortality. The present review describes the current knowledge of the structural and functional abnormalities of skeletal muscles in COPD and the possible aetiological factors. Increasing knowledge of the molecular pathways of muscle wasting will lead to the development of new therapeutic agents and strategies to combat COPD muscle dysfunction.

INTRODUCTION

COPD (chronic obstructive pulmonary disease) is a global health problem and is predicted to be the third most common cause of death worldwide by 2020 [1]. Furthermore, the WHO (World Health Organization) predicts COPD to rank fifth as a worldwide burden of disease and chronic disability by 2020 [2]. Despite maximal medical therapy with inhaled bronchodilators and steroids, COPD patients often have distressing symptoms, poor health status and present frequently to primary care and hospital physicians.

Recently, it has been increasingly recognized that COPD, although primarily a disease of the lungs, exhibits secondary systemic manifestations. Broadly speaking, those may be grouped into those conditions that are likely to be epiphenomena, for example ischaemic heart disease, or non-specific for COPD, such as depression. Other conditions may be more truly considered secondary, since a pathophysiological mechanism can be postulated. Into this group we would include cachexia and loss of fat-free mass (because, in part, of increased work of breathing), osteoporosis (because of immobility), autonomic dysfunction (through hypoxia) and skeletal muscle dysfunction. Particular interest has focused on the respiratory and peripheral skeletal muscles because their function (or dysfunction) not only influences the symptoms that limit

exercise, but may contribute directly to poor exercise performance [3]. Furthermore, skeletal muscle weakness is recognized to contribute, independently of lung function parameters, to poor health status [4], increased healthcare utilization [5] and even mortality [6]. The muscles therefore represent a potential site to improve patients' level of function and quality of life, in contrast with the largely irreversible impairment of the lungs. Over the past decade or more, clinical and laboratory studies have identified significant dysfunction and histological abnormalities of the skeletal muscles (particularly the quadriceps) [7], and the aetiology of these changes remains a focus of research interest. Over the same period, much has been learnt regarding the molecular basis of muscle wasting in animal models, but whether these mechanisms are relevant in COPD remains speculative.

The present review summarizes some of the clinical and laboratory observations concerning muscle abnormalities in COPD and the existing debate regarding aetiological mechanisms, with reference to recent findings from animal models of muscle wasting.

MUSCLE DISEASE IN COPD: CLINICAL OBSERVATIONS

Several clinical observations implicate extra-thoracic factors as significant contributors towards morbidity, and even mortality, in COPD patients. It is well established that indices of lung disease severity, such as the FEV_1 (forced expiratory volume in 1 s), are imperfect predictors of mortality when compared with composite indices [8]; indeed once FEV_1 is less than 50% predicted, it yields no prognostic value for death in COPD [6]. Despite correction of lung function by double lung transplantation, peak exercise remains only approx. 50% of predicted workload for age and gender, whether studied 3 months or 1–2 years after surgery [9] (Figure 1). Furthermore, pulmonary rehabilitation is effective in improving health-related quality of life and exercise performance in COPD patients, but does not improve lung function [10].

What extra-thoracic factors might be relevant? It has long been observed that a proportion of severe COPD patients develop a 'cachexic' state with significant weight and muscle-mass loss. Schols et al. [11] demonstrated that up to 45% of stable COPD patients eligible for pulmonary rehabilitation were either underweight or had a depletion in fat-free mass (mainly muscle mass). Although there are no results regarding the direct measurement of muscle mass of individual muscles, radiological techniques have demonstrated significant reductions in mid-thigh [12] and calf muscle [13] CSA (cross-sectional area) in COPD patients compared with matched controls.

The suspicion that muscle abnormalities in the lower limbs may be contributing towards morbidity has been corroborated by detailed study of patients' self-reported
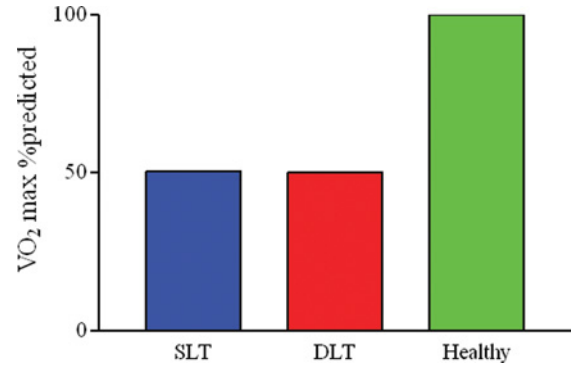
Figure 1   Exercise capacity remains impaired in COPD patients despite normalization of lung function following lung transplantation

SLT, single lung transplant; DLT, double lung transplant. This Figure was drawn with data taken from [9].
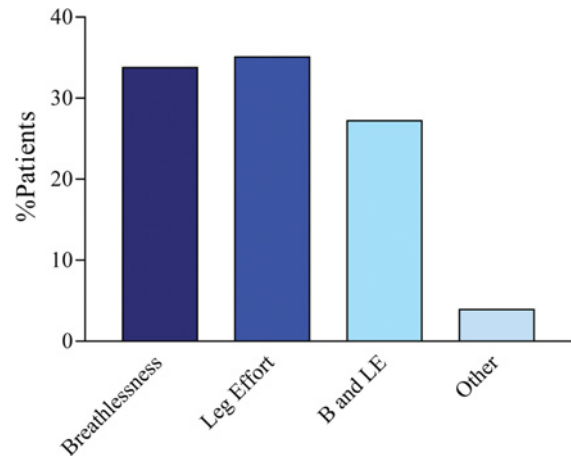
Figure 2   Symptoms limiting cycling exercise in a cohort of COPD patients

Leg effort was the limiting symptom in two-thirds of patients. B and LE, breathlessness and leg effort equally. This Figure was drawn with data taken from [15].

symptoms. Although exertional breathlessness is a commonly cited symptom, Killian et al. [14] have demonstrated that a surprisingly large proportion of patients also experience symptoms of leg effort, implying that lower limb dysfunction may contribute to reduced exercise capacity. We extended these observations by measuring the limiting symptoms reported by a cohort of COPD patients at the end of exhaustive incremental and endurance walking and cycling exercise [15]. Breathlessness alone was the predominant limiting symptom following walking exercise, but up to 25% placed leg fatigue as an equal or more important cause of exercise limitation. The sensation of leg fatigue became an even more important limiting symptom following cycling exercise, with only 30% citing breathlessness as the principal cause of exercise limitation [15] (Figure 2).
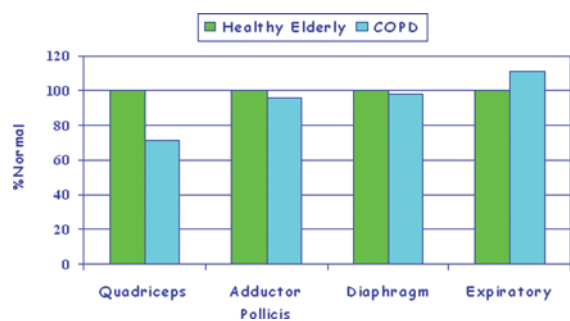
Figure 3 Skeletal muscle weakness is localized to the locomotor muscles, such as the quadriceps

This Figure was drawn with data taken from [16,17].

Table 1 Quadriceps muscle abnormalities in COPD

Abnormality	
Clinical	Reduced strength
	Increased fatigability
	Reduced endurance
	Reduced mid-thigh CSA
Structural	Reduced fibre type I proportion and increased fibre type IIx proportion
	Reduced fibre CSA
	Reduced capillary contacts to fibre CSA
Metabolic	Reduced oxidative enzyme capacity, and increased glycolytic enzyme activity (?)
	Increased intracellular acidosis
	Increased lactic acid
	Reduced PCr/P_i ratio

Several physiological studies of the lower limbs have demonstrated peripheral muscle weakness, particularly of the quadriceps, in COPD patients. This has been confirmed with both volitional and non-volitional tests of quadriceps strength [12,16,17]. Compared with age-matched controls, quadriceps strength is reduced by approx. 20–30 %, although these differences disappear when quadriceps strength is normalized to the mid-thigh CSA [12]. The majority of studies have also demonstrated a reduction in quadriceps endurance [18–21] and an increase in quadriceps fatigability for equivalent workloads [22]. These abnormalities appear to be particularly localized to the quadriceps. Despite the presence of a 30 % reduction in quadriceps strength, we have demonstrated that the strength of the diaphragm, adductor pollicis and abdominal muscles are relatively preserved in COPD patients compared with age-matched healthy controls [16,17,23] (Figure 3). Furthermore, in comparison with the quadriceps, the diaphragm is relatively fatigue-resistant to exhaustive exercise and maximum voluntary ventilation in COPD patients [24,25]; indeed, we have shown recently [26], from single-fibre contraction studies, that fibres from the diaphragm of COPD patients are metabolically more efficient than those from control subjects. One study has also shown normal endurance of the elbow flexors [27], but others have suggested reduced adductor pollicis endurance [28].

Lower limb muscle dysfunction in COPD is clinically significant. Among patients with advanced disease, quadriceps strength is a predictor of mortality [6], as are radiological indices of muscle bulk [29]. Quadriceps weakness is also associated with reduced walking distance [3], reduced $\dot{V}O_{2max}$ (maximal oxygen consumption) [30] and increased health resource utilization [5]. When objectively monitored, patients with quadriceps weakness have reduced activity throughout the day [31]. Although skeletal muscle weakness is a feature of cachexia, quadriceps weakness in COPD is not simply an epiphenomenon; indeed, weakness is prevalent in a ratio of approx. 2:1 compared with the loss of fat-free mass [32,33], indicating that it must precede cachexia.

MUSCLE DISEASE IN COPD: LABORATORY OBSERVATIONS

The majority of evidence for skeletal muscle structural abnormalities in COPD has come from investigations at the cellular level, particularly of the quadriceps muscle, which is readily accessible for biopsy and a primary muscle of locomotion. Previous findings are summarized in Table 1. Most have reported a reduced proportion of type I fibres in the vastus lateralis muscle of severe COPD patients compared with control subjects [34–37], often accompanied by an increase in the proportion of type IIx fibres [36]. This has been corroborated by studies demonstrating a significantly greater proportion of MHC (myosin heavy chain) type II isoforms in the vastus lateralis of COPD patients than in healthy subjects [38,39]. This change represents a reversal of the normal trend towards type I fibres as an individual ages. In addition to changes in fibre-type proportion, several investigators have reported atrophy of type I, IIa and IIx fibres [36,40], and a reduced number of capillary contacts for all muscle fibre types [36,41].

Analysis of the metabolic enzyme profiles of muscle biopsy samples from COPD subjects have consistently demonstrated lower oxidative enzyme activity in the vastus lateralis muscles compared with age-matched healthy controls [42,43], but conflicting evidence exists concerning glycolytic enzyme activity. Jakobsson et al. [42] demonstrated an increase in the activity of phosphofructokinase and a trend towards increased lactate dehydrogenase in the quadriceps muscles of COPD patients. In comparison, Maltais et al. [43] found no difference in glycolytic enzyme activity between patients and healthy controls [43]. Our laboratory has recently demonstrated that non-volitional quadriceps endurance capacity correlates significantly with the proportion of type I

fibres and with the oxidative/glycolytic enzyme activity ratio [44].

A reduced oxidative capacity and a shift towards glycolytic metabolism has important negative implications on exercise performance. Several studies have demonstrated a rapid rise in blood lactate levels during exercise [43,45], which in turn is responsible for a fall in muscle pH and a systemic acidosis [46]. Femoral venous blood lactate levels are neither correlated with oxygen delivery to the lower limbs nor with lower limb blood flow [43,45], providing support for a biochemical abnormality, rather than a delivery problem, in COPD. Studies utilizing ^{31}P-MRS (magnetic resonance spectroscopy) have allowed the *in vivo* assessment of tissue energy metabolism. The ratio of PCr (phosphocreatine) to P_i is closely related to that of ATP to ADP and, hence, is a useful marker of muscle energy status. The PCr/P_i ratio is significantly lower [47] during exercise in COPD patients, with faster PCr depletion [48], and post-exercise recovery is slower in patients compared with healthy controls. Gosker et al. [49] have also demonstrated significantly reduced levels of UCP-3 (uncoupling protein-3) (implicated in the regulation of energy metabolism) in vastus lateralis muscle biopsies of COPD patients [49].

In comparison with the quadriceps, other muscles of COPD patients have been less studied. As discussed above, the diaphragm and other non-locomotor muscles do not appear to have the weakness or fatigability of the quadriceps. This is corroborated by investigations at a cellular level. For example, the reduction in type I fibre proportion found in the quadriceps is not observed in the biceps [50]. Similarly, Gea et al. [51] demonstrated a preserved or even increased oxidative enzyme capacity in the deltoid muscle in severe COPD subjects. It is also interesting to note that the structural adaptations of the diaphragm of COPD patients is diametrically opposite to those seen in the quadriceps, with an increase in type I fibre proportion, reduced type IIx proportion [52] and an increase in oxidative capacity [53]. A similar fast-to-slow fibre-type transformation also occurs in the parasternal intercostal muscles in severe COPD [54].

The recognition that skeletal muscle dysfunction is particularly localized to the lower limbs has led to the simple hypothesis of a downward disease spiral, which is shown in Figure 4. Dyspnoea, and the associated sedentary lifestyle in COPD patients, leads to inactivity and muscle deconditioning, particularly of the locomotor muscles. The resulting lower limb muscle dysfunction leads to excessive lactic acid as a by-product of anaerobic metabolism which, when buffered, produces carbon dioxide and, hence, a metabolic stimulus to increase ventilation and exacerbate breathlessness. This hypothesis is dependent on the assumption that disuse atrophy is the major aetiological factor for skeletal muscle dysfunction. Although this is undoubtedly so in a significant proportion of patients, it remains unknown whether other local
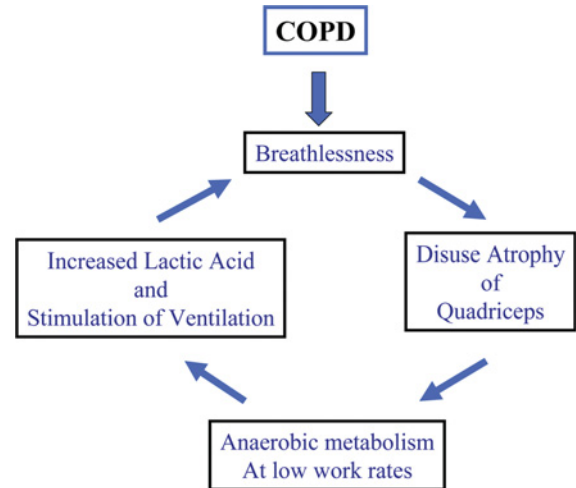
**Figure 4   Downward disease spiral in COPD**

or systemic factors augment the effects of disuse or even become the main driving stimuli in certain patients.

AETIOLOGY OF SKELETAL MUSCLE DYSFUNCTION IN COPD

Despite the clinical relevance and growing interest in the area, the aetiology of the skeletal muscle abnormalities described in COPD remains unknown. Most investigators believe that the aetiology is multi-factorial, but the relative importance of systemic or local factors remains an active research area. Factors considered potentially relevant to skeletal muscle dysfunction include hypoxia, hypercapnia, drugs, such as corticosteroids, nutritional depletion, anabolic/catabolic hormone imbalance, systemic or local inflammation, oxidative stress, genetic susceptibility and reduced daily activity (Figure 5).

Hypoxia

Chronic or intermittent hypoxia is commonly found in COPD, and may have a detrimental effect on skeletal muscle function. In healthy humans exposed to high-altitude hypoxia over weeks and months, functional, morphological and metabolic changes occur in skeletal muscle that bear similarities to those observed in COPD patients. Strength and endurance are reduced [55,56] as well as muscle fibre CSA [57]. Howald et al. [58] showed the activity of enzymes involved in the Krebs cycle, fatty acid oxidation and the respiratory chain are reduced, whereas the activity of glycolytic enzymes is enhanced. Rats exposed to intermittent hypoxia for 5 days have reduced levels of PCr and Krebs cycle substrates, but increased levels of glycolytic enzymes [59]. As discussed above, concentrations of ATP, glycogen and PCr are lower in COPD patients with
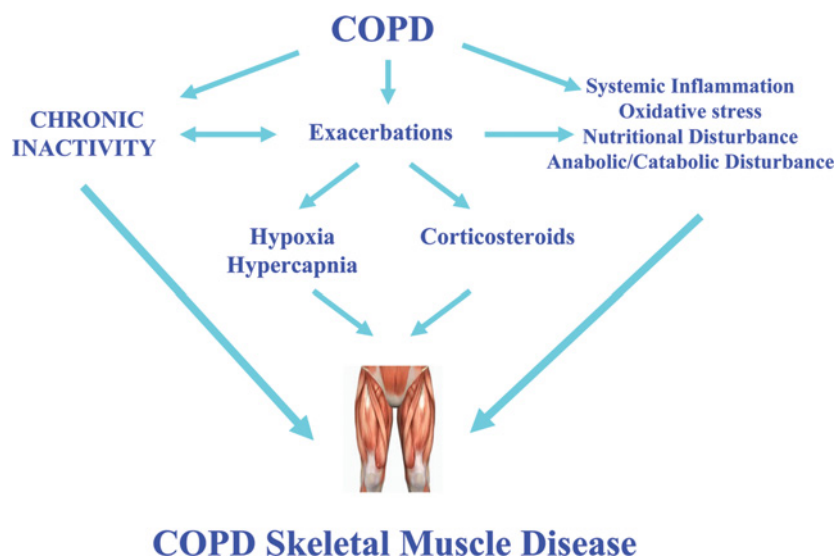
Figure 5   Proposed aetiology of COPD muscle dysfunction

chronic respiratory failure compared with patients without respiratory failure [34]. In hypoxic patients, the proportion of type I fibres in peripheral muscles was significantly smaller than in non-hypoxic patients [37]. It is interesting to note that the reductions in skeletal muscle contractility observed in hypoxic COPD patients are partly ameliorated with supplementary oxygen [28]. Furthermore, aerobic metabolism is also improved with the addition of oxygen [60]. Hypoxia may contribute to muscle wasting in COPD by a variety of mechanisms, including reduced anabolic hormone levels [61], increased levels of pro-inflammatory cytokines [62] and by the generation of ROS (reactive oxygen species) that contribute to oxidative stress [63]. However, it should be noted that several studies have documented significant skeletal muscle dysfunction, morphological changes and metabolic derangements in moderate-to-severe COPD patients without chronic or intermittent hypoxia.

Hypercapnia

As with hypoxia, hypercapnia is frequently observed in COPD patients with acute or chronic respiratory failure. Acute hypercapnia leads to intracellular acidosis that has marked effects upon muscle cell metabolism, including decreases in ATP, PCr and adenosine nucleotides [64,65]. Furthermore, acute hypercapnia in healthy humans reduces limb muscle and diaphragm contractility [66,67]. Findings from animal studies are conflicting; decreases in PCr and ATP/ADP ratios have been reported in rat muscles exposed to high carbon dioxide levels [68], whereas no differences were found in phosphate metabolite activity between hypercapnic and normocapnic rat diaphragms [69]. Clinical results are lacking, presumably because hypercapnia often co-exists with confounding

factors such as hypoxia and hyperinflation; further studies are required to document systematically the metabolic effects of gas exchange abnormalities on skeletal muscle function.

Corticosteroids

Steroid myopathy is well documented in both animal and human studies. As COPD patients may be treated with corticosteroids either as 'short-burst' therapy for acute exacerbations or as long-term low-dose 'maintenance' therapy, the possibility that corticosteroid treatment might make a significant contribution to the development of skeletal muscle dysfunction has been postulated. Patients treated with high-dose corticosteroids (average, 61 mg of prednisolone daily) for non-respiratory diseases develop a decrease in respiratory muscle strength and endurance, which resolves as the dose of steroids is reduced [70]. Diaphragm weakness has also been shown following the administration of high-dose methyl prednisolone to treat episodes of acute rejection following lung transplantation [71]. Conversely patients with Cushings syndrome sufficient to cause quadriceps weakness do not have diaphragm weakness [72]. However, investigators have differed over whether clinically relevant doses of corticosteroids have a significant role in the development of skeletal muscle dysfunction. Decramer et al. [73] have demonstrated a significant relationship between skeletal muscle weakness and the average daily dose of steroids received over the preceding 6 months (mostly as short-burst therapy during acute exacerbations) [73]. In COPD patients with a clinical diagnosis of steroid-induced myopathy, as compared with control COPD patients matched for age, gender and FEV_1, there is diffuse fibre atrophy of the quadriceps, predominantly affecting

fast-twitch fibres, and severe peripheral muscle weakness [74]. However, interpretation of these studies is difficult as the effects of steroid treatment cannot be clearly distinguished from the inflammation and immobility associated with frequent infective exacerbations for which the steroids had been administered. Our laboratory was not able to show any change in respiratory or quadriceps muscle strength in stable COPD outpatients following an oral steroid trial (a 2 week course of 30 mg of prednisolone daily) [75]. This suggests that, in the absence of other exacerbation factors that affect muscle function (such as inflammation or reduced mobility), isolated short-term treatment with steroids is unlikely to cause significant peripheral muscle abnormalities. Although the benefits of 'maintenance' systemic corticosteroid therapy remain unproven, a small proportion of COPD patients are treated with chronic low-dose steroids. This may arguably have more significant effects upon skeletal muscle than short-burst therapy. Bernard et al. [12] observed that their cohort of COPD patients on long-term low doses of corticosteroids had significantly reduced quadriceps strength and mid-thigh CSA compared with naïve patients, although the groups were not matched for other confounding factors.

Nutritional depletion

Much interest has focused on nutritional depletion in COPD, particularly with the recognition that even patients with normal body weight may have reduced fat-free mass [11]. Nutritional depletion is associated with reduced upper and lower limb muscle force [76], a loss of force at higher stimulation frequencies, slowing of muscle relaxation rate and a reduction in muscle endurance [77]. Studies have shown that it is the specific loss of fat-free mass that is related to impaired skeletal muscle strength [12], and that muscle mass is a much better predictor of survival in COPD patients than body weight [29]. It is not fully understood what causes a loss of fat-free mass, but it cannot be simply explained by insufficient calorific intake. A meta-analysis has reviewed the available studies on therapeutic dietary supplementation in COPD [78]. The pooled effects suggested that the impact of nutritional support alone on anthropometric variables was minor at best, and generally did not achieve clinical importance or statistical significance. Benefit is more likely to be obtained in selected patients, particularly those who are also undergoing pulmonary rehabilitation when energy requirements are increased, but this is yet to be proven.

Anabolic/catabolic hormone imbalance

The close relationship between muscle dysfunction and muscle wasting has prompted investigations into the balance between anabolic and catabolic hormones in COPD. Reduced levels of anabolic hormones, such as testosterone and IGF-1 (insulin-like growth factor-1), have been observed in COPD patients [79–81]; however, whether an imbalance in favour of a catabolic milieu is responsible for muscle disease in COPD remains contentious. Studies to date have not been able to establish a true cause–effect relationship. However, in contrast with nutritional intervention, most trials of pharmacological anabolic stimuli to promote protein synthesis (including testosterone, growth hormone and IGF-1) have documented modest, but significant, improvements in muscle mass and strength following intervention [82–84]. The effect on exercise capacity is less certain [82,85] and not presently judged sufficiently worthwhile to support these therapies entering mainstream clinical practice. Furthermore, given the ubiquitous nature of anabolic hormone receptors, there are difficulties in ensuring a localized effect on muscle, and unwanted side effects (such as glucose intolerance and salt/water retention) are not uncommon.

Systemic inflammation

Increasingly, given the inflammatory response that occurs in the lungs, systemic inflammation has been postulated as a major aetiological factor in the skeletal muscle dysfunction commonly seen in COPD. As with several other chronic diseases, COPD is characterized by low-grade systemic inflammation [86–88]. TNF-α (tumour necrosis factor-α) levels are elevated in patients who fail to gain weight during a rehabilitation and re-feeding programme [89], whereas increased blood levels of IL-6 (interleukin-6), IL-8, TNF-α and CRP (C-reactive protein) in COPD patients have been associated with increased resting energy expenditure [86,88], giving support to the concept that pro-inflammatory cytokines play a role in COPD-associated cachexia. Elevated IL-6 levels are also associated with radiological evidence of quadriceps wasting in COPD [79] and with reduced lean body mass [87]. Evidence suggests that the systemic inflammation associated with acute exacerbations may also be relevant. Spruit et al. [90] demonstrated a significant inverse relationship between IL-8 levels and quadriceps strength in patients admitted with an exacerbation of COPD. However, whether pro-inflammatory cytokines alone can induce skeletal muscle dysfunction remains debatable. *In vitro* studies have shown that the levels required to induce cachexia are far higher than the plasma concentrations observed in patients [91,92]. Furthermore, the relative preservation of some muscles, such as the diaphragm [23], is also difficult to explain if a systemic inflammatory aetiology is proposed. There is also debate as to whether local inflammation is relevant. In a recent study [93], our group conducted a cross-sectional study that measured cytokine levels in quadriceps specimens taken from severe COPD patients and healthy age-matched controls. Compared with controls, there were significantly lower levels of TNF-α, TNFRII (TNF-α receptor II) and VEGF (vascular endothelial growth factor), and similar protein levels of IL-6, IFN-γ (interferon-γ) and TGF-β (transforming growth

factor-β) [93]. Hence we were unable to demonstrate the presence of a pro-inflammatory environment within the quadriceps muscles of clinically and weight-stable patients with severe COPD. This has been corroborated by other investigators [81].

Oxidative stress

Oxidative stress has also been postulated as a potential mechanism for muscle dysfunction in COPD [94]. Free radicals (such as the superoxide anion and NO), when inadequately scavenged by antioxidants, can cause oxidative damage to lipids and proteins, significantly altering the activity of the mitochondrial respiratory chain complex. Increased levels of oxidative stress have been particularly observed during acute exacerbations [95] and during exercise [96], but also documented in stable COPD patients [93]. Treatment with N-acetylcysteine, an antioxidant, has been shown to reduce exercise-induced oxidative stress and improve quadriceps endurance [97]. However, conflicting evidence exists with regards to antioxidant levels in COPD patients, with some investigators showing reduced skeletal muscle antioxidant capacity at rest [96,98], whereas others have not demonstrated any significant differences between COPD patients and healthy controls [99]. Given that exercise training is one of the few therapies shown to reverse muscle abnormalities, it is slightly contrary that both low-intensity and strenuous exercise induces systemic oxidative stress in COPD patients [63,96]. Whether oxidative stress directly induces muscle dysfunction in COPD or whether it is part of a damage-repair phenomenon remains speculative.

Genetic susceptibility

Quadriceps strength is typically reduced by approx. 30% in moderate-to-severe COPD patients compared with age- and gender-matched healthy subjects. However, considerable overlap exists between patients and healthy controls, suggesting that some patients may be particularly susceptible to developing muscle dysfunction. Studies into genetic susceptibility in COPD remains in its infancy [100], but interesting findings have already been observed. Twin studies of healthy humans have demonstrated significant genetic influences on muscle mass and strength [101,102]. For example, a polymorphism of the human *ACE* (angiotensin-converting enzyme) gene has been identified in which the absence [D (deletion) allele] rather than the presence [I (insertion) allele] of a 287 bp fragment is associated with higher circulating and tissue ACE activity and, consequently, higher AngII (angiotensin II) and lower bradykinin levels [103]. Local AngII is necessary both for angiogenesis [104] and for optimal muscle trophic response to loading [105], and may therefore be necessary for skeletal muscle growth. AngII has been shown to increases muscle strength in rat hindlimb preparations [106]. Our laboratory has shown that, in a cohort of 103 COPD patients, those with
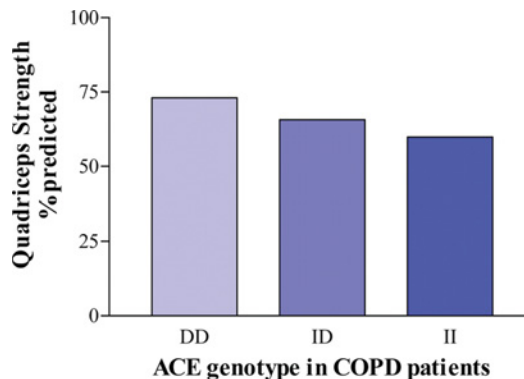

Figure 6 ACE genotype and influence on quadriceps strength
This Figure was drawn with data taken from [107].

the I/I polymorphism of the *ACE* gene had reduced quadriceps strength compared with those with the D/D polymorphism [107] (Figure 6). More recently, our group has also shown that polymorphisms of the vitamin D receptor are associated with quadriceps strength. For example, those homozygous for the C allele of the *Fok*I polymorphism had comparatively reduced quadriceps strength, whereas the b allele of the *Bsm*I polymorphism was associated with comparatively improved quadriceps strength [108]. Interestingly in neither of these studies was the same relationship observed in healthy controls, suggesting an interaction between gene and environment.

Reduced daily physical activity

The preferential involvement of some muscle groups suggests that local muscle factors must be involved in the development of skeletal muscle dysfunction. Perhaps the most obvious local factor is inactivity, as it is reasonable to assume that patients with pulmonary and functional impairment are more sedentary than their healthy counterparts. Previous studies using activity monitors, which can objectively quantify activity, provide evidence for reduced daily activity in COPD patients [31,109–112], as well as localized reduced lower limb activity [111]. The clinical importance of inactivity has been emphasized by prospective studies showing that moderate-to-high levels of regular physical activity are associated with reduced lung function decline and COPD risk among smokers [113]. Furthermore, regular physical activity improves the course of COPD with respect to hospitalizations [114,115] and all-cause and respiratory mortality [114] in large population-based samples. Several lines of evidence support the contribution of inactivity towards skeletal muscle dysfunction in COPD. First, studies have consistently demonstrated preferential lower limb muscle weakness with a relative preservation of the upper limbs [12] and the diaphragm [23,116]. This is in line with the notion that inactivity leads to subsequent muscle
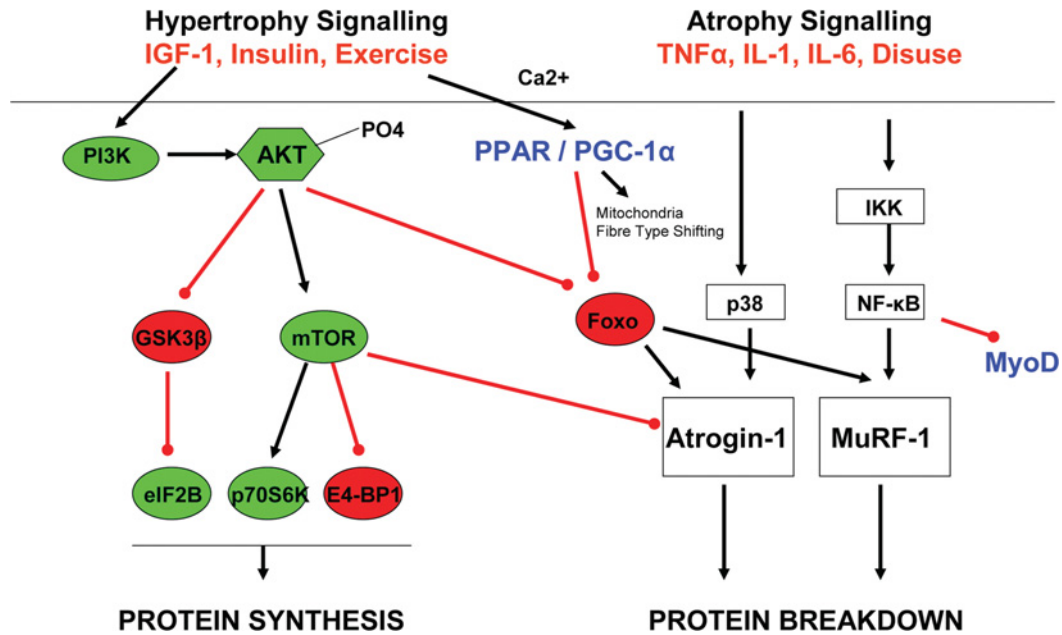
Figure 7   Muscle atrophy and hypertrophy pathways
See main text for abbreviations. eIF2B, eukaryotic initiation factor 2B.

deconditioning with the greatest effect upon muscles that are least used (i.e. the lower limbs). Secondly, consistent with the observations on muscle strength, the metabolic and morphological characteristics of the quadriceps muscle differ from other muscles in COPD. The deltoid and diaphragm muscles show an increase in oxidative capacity [51,53], and there is a fast-to-slow fibre type transformation (i.e. an increase in type I fibres) in the diaphragm of severe COPD patients [52]. Thirdly, many of the skeletal muscle abnormalities found in the quadriceps of COPD patients are mirrored in otherwise healthy patients with deconditioning, reduced activity or prolonged bed rest [117]. Similarly, despite different systemic aetiologies, the skeletal muscle abnormalities found in COPD patients are extremely similar to those found in chronic heart failure and chronic renal failure patients [117]. Other local factors, as yet unidentified, may also be involved in initiating muscle dysfunction. Maltais et al. [39] have demonstrated modifications in the MHC profile in the vastus lateralis of COPD patients compared with healthy subjects despite only modest differences in physical fitness. Furthermore, studies on emphysematous hamsters have shown reduced oxidative capacity of their hindlimb muscles despite the absence of a reduction in their level of activity compared with control animals [118].

Further studies are required to elucidate the relative importance of systemic and local factors in the aetiology of skeletal muscle dysfunction in COPD patients. A reasonable integrative hypothesis is that systemic factors (e.g. cytokines and growth factors), although not markedly elevated, may synergize with local factors (e.g.

inactivity, ROS and acidosis) to produce an imbalance between anabolism and catabolism (Figure 5). It must also be remembered that COPD is a diagnostic label encompassing a group of diseases with subtle phenotypic differences, and there is increasing evidence that genetic susceptibility is relevant. It is possible that the relative importance of aetiological factors vary depending on both the phenotypic characterization of the patient (for example, systemic inflammation may be more influential in patients with general cachexia).

MUSCLE-WASTING MECHANISMS: ANIMAL MODELS

In recent years, considerable progress in skeletal muscle biology has led to a deeper understanding of muscle-wasting mechanisms, and the carefully regulated processes of protein synthesis and protein breakdown. Several animal models of hypertrophy and atrophy have identified that the PI3K (phosphoinositide 3-kinase)/Akt/mTOR (mammalian target of rapamycin) pathway is up-regulated during hypertrophy and down-regulated during muscle atrophy [119] (Figure 7). Anabolic hormones, such as IGF-1, stimulate the PI3K/Akt pathway, resulting in downstream activation of targets required for protein synthesis [120]. Akt, when in its phosphorylated active form, stimulates mTOR, which can promote protein synthesis by the activation of p70^{S6K} (70 kDa ribosomal S6 protein kinase) [120] and by the inhibition of 4E-BP1 (eukaryotic initiation factor 4E binding protein-1)/PHAS-I [121]. Independently of

the p70^{S6K} and 4E-BP1 pathways, phosphorylated Akt can also stimulate protein synthesis by the inhibition of GSK-3β (glycogen synthase kinase-3β) [122], a repressor of protein synthesis [123].

Several animal models of atrophy have established the involvement of the ubiquitin–proteasome pathway [124]. This pathway is up-regulated by a variety of factors that are relevant to muscle dysfunction in COPD, including muscle inactivity, pro-inflammatory cytokines and glucocorticosteroids. Proteasomes are large multi-subunit complexes, localized in the nucleus and cytosol, that selectively degrade intracellular proteins. A protein marked for degradation is covalently attached to multiple molecules of ubiquitin by a multi-enzymatic system consisting of E1 (ubiquitin-activating), E2 (ubiquitin-conjugating) and E3 (ubiquitin-ligating) enzymes. Ubiquitinated protein is then escorted to the 26S proteasome, where it undergoes final degradation and the ubiquitin is released and recycled. Differential expression screening studies have identified two genes whose expression is increased significantly in multiple animal models of skeletal muscle atrophy. These two genes MuRF-1 (muscle ring finger-1; *TRIM63*) and MAFbx (muscle atrophy F-box; *FBXO32*) [125], which is also known as atrogin-1 [126], encode E3 ubiquitin ligases [125]. Apart from stimulating muscle hypertrophy pathways, activated Akt is also able to block muscle protein breakdown by down-regulating MuRF-1 and atrogin-1 expression. This action is mediated by the inactivation of the FoxO (forkhead box O) class of transcription factors [127]. However, it remains speculative as to whether Akt alone is able to completely block atrophy pathways, as experiments involving IGF-1 have only been partially successfully in inhibiting muscle atrophy [128].

As described above, several pro-inflammatory cytokines have been shown to produce muscle wasting, notably TNF-α. NF-κB (nuclear factor κB) activation has been shown to be required for the cytokine-induced loss of muscle proteins. Furthermore, as NF-κB is also activated by disuse [129], it has been postulated that this pathway is a central trigger of muscle atrophy mechanisms [130]. NF-κB is controlled by the IKK [IκB (inhibitor of NF-κB) kinase] complex. Transgenic mice in which the NF-κB pathway was activated [MIKK (muscle-specific expression of IKK)] had an up-regulation of MuRF-1, but not atrogin-1 [130], suggesting a second parallel pathway that up-regulates atrogin-1.

Studies to determine whether these hypertrophy and atrophy pathways are relevant in the aetiology of muscle dysfunction in COPD remains in its infancy. Doucet et al. [131] have demonstrated significantly increased mRNA levels of MuRF-1 and atrogin-1, and FoxO-1 protein content in the quadriceps muscles of COPD patients, suggesting an up-regulation of muscle atrophy pathways. However, these were not related to measures of quadriceps function, and no difference was found between patients with and without clinical muscle atrophy [131]. Rather unexpectedly, the authors also found an increase in phosphorylated Akt, suggesting that the transcriptional regulation of MuRF-1 and atrogin-1 via FoxO1 occurs independently of Akt. Furthermore, increases in phosphorylation status of three muscle hypertrophy protein signals (p70^{S6K}, GSK-3β and 4E-BP1) were observed in COPD patients with low muscle mass when compared with those with preserved muscle mass. This could be the result of a feedback loop resulting in a failed attempt to compensate for muscle atrophy or, alternatively, a defective hypertrophy and muscle regeneration response may be present in COPD patients.

Muscle repair and regeneration are dependent on myogenic satellite cells [132]. These are usually quiescent but can be activated, leading to rapid proliferation following muscle injury. This process is controlled by a number of growth- and myogenic-regulatory factors. One such regulatory factor, for example, is MyoD, which has an essential role in cell differentiation [133]. TNF-α has been shown to inhibit MyoD expression and suppress muscle hypertrophy via activation of NF-κB [134]. Another regulatory factor of myogenic satellite cells is myostatin (also known as growth differentiation factor 8), a member of the TGF-β superfamily. Myostatin inhibits satellite cell differentiation by suppressing MyoD and other myogenic regulatory factors [135]. Interestingly, certain cattle breeds (Belgian Blue and Piedmontese), which are famed for their muscle bulk, have mutations in the myostatin gene produced through breeding [136]. Similarly, a German boy, noted for his significantly increased muscle strength compared with his peers, was diagnosed with mutations of the myostatin-producing gene [137]. Myostatin protein levels both in serum and muscle are also significantly increased in muscle-wasting conditions, such as HIV infection [138]. Although MyoD has been shown to be up-regulated following rehabilitative exercise [139], it remains speculative as to whether myogenic regulatory factors, such as myostatin and MyoD, are relevant in the pathogenesis of muscle disease in COPD.

Aside from muscle atrophy, a fibre-type switch from type I to type II fibres is observed in the quadriceps muscles of COPD patients, resulting in decreased oxidative capacity [36]. It is not known whether these processes occur independently or whether there is a unifying pathway. Animal studies have revealed putative mechanisms involving the PPARs (peroxisome-proliferator-activated receptors), as well as PGC-1α (PPAR-γ coactivator-1α), a strong co-activator of PPAR transcriptional activity. These have been shown to be key regulators of mitochondrial biogenesis [140] and of skeletal muscle oxidative capacity [141], as well as being essential in mediating a fibre-type shift towards endurance properties (i.e. type II to I) [142,143]. Furthermore, transgenic mice expressing increased PGC-1α in skeletal muscle

appear to be protected against muscle wasting mediated via the FoxO3/atrogin-1 and MuRF-1 pathways [144], and PPAR-δ agonists have been shown to synergize with exercise training to improve running endurance in sedentary mice [145]. PPAR-α and PPAR-δ activity is suppressed by factors relevant to COPD, such as hypoxia [146] and systemic inflammation [147]. In humans, reduced PPAR activity has been observed in other chronic conditions, including spinal cord injury, chronic heart failure and diabetes. Interestingly, recent studies on a small cohort demonstrated that PPAR-δ protein and PGC-1α mRNA levels were significantly lower in COPD patients than in age-matched controls [148], and that PPAR-α mRNA was significantly lower in the cachectic compared with non-cachectic COPD patients [148].

CONCLUSIONS

The last decade has seen a widespread recognition of the clinical importance of skeletal muscle dysfunction, particularly of the peripheral locomotor muscles, in COPD. Parallel with this has been increasing knowledge of the molecular mechanisms of muscle wasting. In the next decade, it is anticipated that new agents will be developed to combat muscle-wasting mechanisms. Although direct interventions targeting skeletal muscle structure and function are of great interest, it must be remembered that only one practical therapeutic intervention currently exists that reverses some of the skeletal muscle abnormalities observed in COPD, namely exercise training as pulmonary rehabilitation. The effects of pulmonary rehabilitation on quadriceps muscle in COPD are described in a related review appearing in *Clinical Science* [149].

FUNDING

REFERENCES

1 Lopez, A. D. and Murray, C. C. (1998) The global burden of disease, 1990–2020. Nat. Med. **4**, 1241–1243
2 Murray, C. J. and Lopez, A. D. (1996) Evidence-based health policy: lessons from the Global Burden of Disease Study. Science **274**, 740–743
3 Gosselink, R., Troosters, T. and Decramer, M. (1996) Peripheral muscle weakness contributes to exercise limitation in COPD. Am. J. Respir. Crit. Care Med. **153**, 976–980
4 Simpson, K., Killian, K., McCartney, N., Stubbing, D. G. and Jones, N. L. (1992) Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax **47**, 70–75
5 Decramer, M., Gosselink, R., Troosters, T., Verschueren, M. and Evers, G. (1997) Muscle weakness is related to utilization of health care resources in COPD patients. Eur. Respir. J. **10**, 417–423
6 Swallow, E. B., Reyes, D., Hopkinson, N. S., Man, W. D., Porcher, R., Cetti, E. J., Moore, A. J., Moxham, J. and Polkey, M. I. (2007) Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. Thorax **62**, 115–120
7 American Thoracic Society, European Respiratory Society (1999) Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. Am. J. Respir. Crit. Care Med. **159**, S1–S40
8 Celli, B. R., Cote, C. G., Marin, J. M., Casanova, C., Montes de Oca, M., Mendez, R. A., Pinto Plata, V. and Cabral, H. J. (2004) The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N. Engl. J. Med. **350**, 1005–1012
9 Williams, T. J., Patterson, G. A., McClean, P. A., Zamel, N. and Maurer, J. R. (1992) Maximal exercise testing in single and double lung transplant recipients. Am. Rev. Respir. Dis. **145**, 101–105
10 Griffiths, T. L., Burr, M. L., Campbell, I. A., Lewis-Jenkins, V., Mullins, J., Shiels, K., Turner-Lawlor, P. J., Payne, N., Newcombe, R. G., Ionescu, A. A. et al. (2000) Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet **355**, 362–368
11 Schols, A. M., Soeters, P. B., Dingemans, A. M., Mostert, R., Frantzen, P. J. and Wouters, E. F. (1993) Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am. Rev. Respir. Dis. **147**, 1151–1156
12 Bernard, S., LeBlanc, P., Whittom, F., Carrier, G., Jobin, J., Belleau, R. and Maltais, F. (1998) Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **158**, 629–634
13 Wuyam, B., Payen, J. F., Levy, P., Bensaidane, H., Reutenauer, H., Le Bas, J. F. and Benabid, A. L. (1992) Metabolism and aerobic capacity of skeletal muscle in chronic respiratory failure related to chronic obstructive pulmonary disease. Eur. Respir. J. **5**, 157–162
14 Killian, K. J., Leblanc, P., Martin, D. H., Summers, E., Jones, N. L. and Campbell, E. J. (1992) Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am. Rev. Respir. Dis. **146**, 935–940
15 Man, W. D., Soliman, M. G., Gearing, J., Radford, S. G., Rafferty, G. F., Gray, B. J., Polkey, M. I. and Moxham, J. (2003) Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **168**, 562–567
16 Man, W. D., Soliman, M. G., Nikoletou, D., Harris, M. L., Rafferty, G. F., Mustfa, N., Polkey, M. I. and Moxham, J. (2003) Non-volitional assessment of skeletal muscle strength in patients with chronic obstructive pulmonary disease. Thorax **58**, 665–669
17 Man, W. D., Hopkinson, N. S., Harraf, F., Nikoletou, D., Polkey, M. I. and Moxham, J. (2005) Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease. Thorax **60**, 718–722
18 Serres, I., Gautier, V., Varray, A. and Prefaut, C. (1998) Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. Chest **113**, 900–905
19 Van't Hul, A., Harlaar, J., Gosselink, R., Hollander, P., Postmus, P. and Kwakkel, G. (2004) Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease. Muscle Nerve **29**, 267–274
20 Allaire, J., Maltais, F., Doyon, J. F., Noel, M., LeBlanc, P., Carrier, G., Simard, C. and Jobin, J. (2004) Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. Thorax **59**, 673–678
21 Swallow, E. B., Dayer, M. J., Moore, A. J., Hopkinson, N. S., Moxham, J. and Polkey, M. I. (2005) Non-volitional assessment of quadriceps endurance by rapid rate magnetic stimulation. American Thoracic Society 2005 International Conference, 20–25 May 2005, San Diego, CA, U.S.A., A498

22 Mador, M. J., Deniz, O., Aggarwal, A. and Kufel, T. J. (2003) Quadriceps fatigability after single muscle exercise in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **168**, 102–108

23 Polkey, M. I., Kyroussis, D., Hamnegard, C. H., Mills, G. H., Green, M. and Moxham, J. (1996) Diaphragm strength in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **154**, 1310–1317

24 Polkey, M. I., Kyroussis, D., Keilty, S. E., Hamnegard, C. H., Mills, G. H., Green, M. and Moxham, J. (1995) Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. Am. J. Respir. Crit. Care Med. **152**, 959–964

25 Polkey, M. I., Kyroussis, D., Hamnegard, C. H., Mills, G. H., Hughes, P. D., Green, M. and Moxham, J. (1997) Diaphragm performance during maximal voluntary ventilation in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **155**, 642–648

26 Stubbings, A. K., Moore, A. J., Dusmet, M., Goldstraw, P., West, T. G., Polkey, M. I. and Ferenczi, M. A. (2008) Physiological properties of human diaphragm muscle fibres and the effect of chronic obstructive pulmonary disease. J. Physiol. **586**, 2637–2650

27 Newell, S. Z., McKenzie, D. K. and Gandevia, S. C. (1989) Inspiratory and skeletal muscle strength and endurance and diaphragmatic activation in patients with chronic airflow limitation. Thorax **44**, 903–912

28 Zattara-Hartmann, M. C., Badier, M., Guillot, C., Tomei, C. and Jammes, Y. (1995) Maximal force and endurance to fatigue of respiratory and skeletal muscles in chronic hypoxemic patients: the effects of oxygen breathing. Muscle Nerve **18**, 495–502

29 Marquis, K., Debigare, R., Lacasse, Y., LeBlanc, P., Jobin, J., Carrier, G. and Maltais, F. (2002) Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **166**, 809–813

30 Hamilton, A. L., Killian, K. J., Summers, E. and Jones, N. L. (1995) Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am. J. Respir. Crit. Care Med. **152**, 2021–2031

31 Pitta, F., Troosters, T., Spruit, M. A., Probst, V. S., Decramer, M. and Gosselink, R. (2005) Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **171**, 972–977

32 Franssen, F. M., Broekhuizen, R., Janssen, P. P., Wouters, E. F. and Schols, A. M. (2005) Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. Med. Sci. Sports Exercise **37**, 2–9

33 Hopkinson, N. S., Tennant, R. C., Dayer, M. J., Swallow, E. B., Hansel, T. T., Moxham, J. and Polkey, M. I. (2007) A prospective study of decline in fat free mass and skeletal muscle strength in chronic obstructive pulmonary disease. Respir. Res. **8**, 25

34 Jakobsson, P., Jorfeldt, L. and Brundin, A. (1990) Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. Eur. Respir. J. **3**, 192–196

35 Hildebrand, I. L., Sylven, C., Esbjornsson, M., Hellstrom, K. and Jansson, E. (1991) Does chronic hypoxaemia induce transformations of fibre types? Acta Physiol. Scand. **141**, 435–439

36 Whittom, F., Jobin, J., Simard, P. M., Leblanc, P., Simard, C., Bernard, S., Belleau, R. and Maltais, F. (1998) Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. Med. Sci. Sports Exercise **30**, 1467–1474

37 Gosker, H. R., van Mameren, H., van Dijk, P. J., Engelen, M. P., van der Vusse, G. J., Wouters, E. F. and Schols, A. M. (2002) Skeletal muscle fibre-type shifting and metabolic profile in patients with chronic obstructive pulmonary disease. Eur. Respir. J. **19**, 617–625

38 Satta, A., Migliori, G. B., Spanevello, A., Neri, M., Bottinelli, R., Canepari, M., Pellegrino, M. A. and Reggiani, C. (1997) Fibre types in skeletal muscles of chronic obstructive pulmonary disease patients related to respiratory function and exercise tolerance. Eur. Respir. J. **10**, 2853–2860

39 Maltais, F., Sullivan, M. J., LeBlanc, P., Duscha, B. D., Schachat, F. H., Simard, C., Blank, J. M. and Jobin, J. (1999) Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD. Eur. Respir. J. **13**, 850–854

40 Gosker, H. R., Engelen, M. P., van Mameren, H., van Dijk, P. J., van der Vusse, G. J., Wouters, E. F. and Schols, A. M. (2002) Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. Am. J. Clin. Nutr. **76**, 113–119

41 Jobin, J., Maltais, F., Doyon, J. F., LeBlanc, P., Simard, P. M., Simard, A. A. and Simard, C. (1998) Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle. J Cardiopulm. Rehabil. **18**, 432–437

42 Jakobsson, P., Jorfeldt, L. and Henriksson, J. (1995) Metabolic enzyme activity in the quadriceps femoris muscle in patients with severe chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **151**, 374–377

43 Maltais, F., Simard, A. A., Simard, C., Jobin, J., Desgagnes, P. and LeBlanc, P. (1996) Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am. J. Respir. Crit. Care Med. **153**, 288–293

44 Swallow, E. B., Gosker, H. R., Ward, K. A., Moore, A. J., Dayer, M. J., Hopkinson, N. S., Schols, A. M., Moxham, J. and Polkey, M. I. (2007) A novel technique for nonvolitional assessment of quadriceps muscle endurance in humans. J. Appl. Physiol. **103**, 739–746

45 Sala, E., Roca, J., Marrades, R. M., Alonso, J., Gonzalez De Suso, J. M., Moreno, A., Barbera, J. A., Nadal, J., de Jover, L., Rodriguez-Roisin, R. and Wagner, P. D. (1999) Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **159**, 1726–1734

46 Polkey, M. I., Hawkins, P., Kyroussis, D., Ellum, S. G., Sherwood, R. and Moxham, J. (2000) Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD. Thorax **55**, 547–549

47 Kutsuzawa, T., Shioya, S., Kurita, D., Haida, M., Ohta, Y. and Yamabayashi, H. (1995) Muscle energy metabolism and nutritional status in patients with chronic obstructive pulmonary disease. A 31P magnetic resonance study. Am. J. Respir. Crit. Care Med. **152**, 647–652

48 Thompson, C. H., Davies, R. J., Kemp, G. J., Taylor, D. J., Radda, G. K. and Rajagopalan, B. (1993) Skeletal muscle metabolism during exercise and recovery in patients with respiratory failure. Thorax **48**, 486–490

49 Gosker, H. R., Schrauwen, P., Hesselink, M. K., Schaart, G., van der Vusse, G. J., Wouters, E. F. and Schols, A. M. (2003) Uncoupling protein-3 content is decreased in peripheral skeletal muscle of patients with COPD. Eur. Respir. J. **22**, 88–93

50 Sato, Y., Asoh, T., Honda, Y., Fujimatsu, Y., Higuchi, I. and Oizumi, K. (1997) Morphologic and histochemical evaluation of muscle in patients with chronic pulmonary emphysema manifesting generalized emaciation. Eur. Neurol. **37**, 116–121

51 Gea, J. G., Pasto, M., Carmona, M. A., Orozco-Levi, M., Palomeque, J. and Broquetas, J. (2001) Metabolic characteristics of the deltoid muscle in patients with chronic obstructive pulmonary disease. Eur. Respir. J. **17**, 939–945

52 Levine, S., Kaiser, L., Leferovich, J. and Tikunov, B. (1997) Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. N. Engl. J. Med. **337**, 1799–1806

53 Levine, S., Gregory, C., Nguyen, T., Shrager, J., Kaiser, L., Rubinstein, N. and Dudley, G. (2002) Bioenergetic adaptation of individual human diaphragmatic myofibers to severe COPD J. Appl. Physiol. **92**, 1205–1213

54   Levine, S., Nguyen, T., Friscia, M., Zhu, J., Szeto, W., Kucharczuk, J. C., Tikunov, B. A., Rubinstein, N. A., Kaiser, L. R. and Shrager, J. B. (2006) Parasternal intercostal muscle remodeling in severe chronic obstructive pulmonary disease. J. Appl. Physiol. **101**, 1297–1302

55   Caquelard, F., Burnet, H., Tagliarini, F., Cauchy, E., Richalet, J. P. and Jammes, Y. (2000) Effects of prolonged hypobaric hypoxia on human skeletal muscle function and electromyographic events. Clin. Sci. **98**, 329–337

56   Badier, M., Guillot, C., Lagier-Tessonnier, F. and Jammes, Y. (1994) EMG changes in respiratory and skeletal muscles during isometric contraction under normoxic, hypoxemic, or ischemic conditions. Muscle Nerve **17**, 500–508

57   Hoppeler, H., Kleinert, E., Schlegel, C., Claassen, H., Howald, H., Kayar, S. R. and Cerretelli, P. (1990) Morphological adaptations of human skeletal muscle to chronic hypoxia. Int. J. Sports Med. **11**, (Suppl. 1), S3–S9

58   Howald, H., Pette, D., Simoneau, J. A., Uber, A., Hoppeler, H. and Cerretelli, P. (1990) Effect of chronic hypoxia on muscle enzyme activities. Int. J. Sports Med. **11**, (Suppl. 1), S10–S14

59   Pastoris, O., Dossena, M., Foppa, P., Arnaboldi, R., Gorini, A., Villa, R. F. and Benzi, G. (1995) Modifications by chronic intermittent hypoxia and drug treatment on skeletal muscle metabolism. Neurochem. Res. **20**, 143–150

60   Payen, J. F., Wuyam, B., Levy, P., Reutenauer, H., Stieglitz, P., Paramelle, B. and Le Bas, J. F. (1993) Muscular metabolism during oxygen supplementation in patients with chronic hypoxemia. Am. Rev. Respir. Dis. **147**, 592–598

61   Semple, P. D., Beastall, G. H., Watson, W. S. and Hume, R. (1980) Serum testosterone depression associated with hypoxia in respiratory failure. Clin. Sci. **58**, 105–106

62   Takabatake, N., Nakamura, H., Abe, S., Inoue, S., Hino, T., Saito, H., Yuki, H., Kato, S. and Tomoike, H. (2000) The relationship between chronic hypoxemia and activation of the tumor necrosis factor-α system in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **161**, 1179–1184

63   Heunks, L. M., Vina, J., van Herwaarden, C. L., Folgering, H. T., Gimeno, A. and Dekhuijzen, P. N. (1999) Xanthine oxidase is involved in exercise-induced oxidative stress in chronic obstructive pulmonary disease. Am. J. Physiol. **277**, R1697–R1704

64   Gertz, I., Hedenstierna, G., Hellers, G. and Wahren, J. (1977) Muscle metabolism in patients with chronic obstructive lung disease and acute respiratory failure. Clin. Sci. Mol. Med. **52**, 396–403

65   Pouw, E. M., Schols, A. M., van der Vusse, G. J. and Wouters, E. F. (1998) Elevated inosine monophosphate levels in resting muscle of patients with stable chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **157**, 453–457

66   Vianna, L. G., Koulouris, N., Lanigan, C. and Moxham, J. (1990) Effect of acute hypercapnia on limb muscle contractility in humans. J. Appl. Physiol. **69**, 1486–1493

67   Juan, G., Calverley, P., Talamo, C., Schnader, J. and Roussos, C. (1984) Effect of carbon dioxide on diaphragmatic function in human beings. N. Engl. J. Med. **310**, 874–879

68   Sahlin, K., Edstrom, L. and Sjoholm, H. (1983) Fatigue and phosphocreatine depletion during carbon dioxide-induced acidosis in rat muscle. Am. J. Physiol. **245**, C15–C20

69   Fitzgerald, R. S., Howell, S. and Jacobus, W. E. (1988) 31P-NMR study of resting *in vitro* rat diaphragm exposed to hypercapnia. J. Appl. Physiol. **65**, 2270–2277

70   Weiner, P., Azgad, Y. and Weiner, M. (1993) The effect of corticosteroids on inspiratory muscle performance in humans. Chest **104**, 1788–1791

71   Nava, S., Fracchia, C., Callegari, G., Ambrosino, N., Barbarito, N. and Felicetti, G. (2002) Weakness of respiratory and skeletal muscles after a short course of steroids in patients with acute lung rejection. Eur. Respir. J. **20**, 497–499

72   Mills, G. H., Kyroussis, D., Jenkins, P., Hamnegard, C. H., Polkey, M. I., Wass, J., Besser, G. M., Moxham, J. and Green, M. (1999) Respiratory muscle strength in Cushing's syndrome. Am. J. Respir. Crit. Care Med. **160**, 1762–1765

73   Decramer, M., Lacquet, L. M., Fagard, R. and Rogiers, P. (1994) Corticosteroids contribute to muscle weakness in chronic airflow obstruction. Am. J. Respir. Crit. Care Med. **150**, 11–16

74   Decramer, M., de Bock, V. and Dom, R. (1996) Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **153**, 1958–1964

75   Hopkinson, N. S., Man, W. D., Dayer, M. J., Ross, E. T., Nickol, A. H., Hart, N., Moxham, J. and Polkey, M. I. (2004) Acute effect of oral steroids on muscle function in chronic obstructive pulmonary disease. Eur. Respir. J. **24**, 137–142

76   Engelen, M. P., Schols, A. M., Baken, W. C., Wesseling, G. J. and Wouters, E. F. (1994) Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur. Respir. J. **7**, 1793–1797

77   Lopes, J., Russell, D. M., Whitwell, J. and Jeejeebhoy, K. N. (1982) Skeletal muscle function in malnutrition. Am. J. Clin. Nutr. **36**, 602–610

78   Ferreira, I. M., Brooks, D., Lacasse, Y. and Goldstein, R. S. (2000) Nutritional supplementation in stable chronic obstructive pulmonary disease. Cochrane Database Syst. Rev., CD000998, doi:10.1002/14651858.CD000998.pub2

79   Debigare, R., Marquis, K., Cote, C. H., Tremblay, R. R., Michaud, A., LeBlanc, P. and Maltais, F. (2003) Catabolic/anabolic balance and muscle wasting in patients with COPD. Chest **124**, 83–89

80   Kamischke, A., Kemper, D. E., Castel, M. A., Luthke, M., Rolf, C., Behre, H. M., Magnussen, H. and Nieschlag, E. (1998) Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur. Respir. J. **11**, 41–45

81   Crul, T., Spruit, M. A., Gayan-Ramirez, G., Quarck, R., Gosselink, R., Troosters, T., Pitta, F. and Decramer, M. (2007) Markers of inflammation and disuse in vastus lateralis of chronic obstructive pulmonary disease patients. Eur. J. Clin. Invest. **37**, 897–904

82   Burdet, L., de Muralt, B., Schutz, Y., Pichard, C. and Fitting, J. W. (1997) Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am. J. Respir. Crit. Care Med. **156**, 1800–1806

83   Schols, A. M., Soeters, P. B., Mostert, R., Pluymers, R. J. and Wouters, E. F. (1995) Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am. J. Respir. Crit. Care Med. **152**, 1268–1274

84   Casaburi, R., Bhasin, S., Cosentino, L., Porszasz, J., Somfay, A., Lewis, M. I., Fournier, M. and Storer, T. W. (2004) Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **170**, 870–878

85   Creutzberg, E. C., Wouters, E. F., Mostert, R., Pluymers, R. J. and Schols, A. M. (2003) A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest **124**, 1733–1742

86   Di Francia, M., Barbier, D., Mege, J. L. and Orehek, J. (1994) Tumor necrosis factor-α levels and weight loss in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **150**, 1453–1455

87   Eid, A. A., Ionescu, A. A., Nixon, L. S., Lewis-Jenkins, V., Matthews, S. B., Griffiths, T. L. and Shale, D. J. (2001) Inflammatory response and body composition in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **164**, 1414–1418

88   Schols, A. M., Buurman, W. A., Staal van den Brekel, A. J., Dentener, M. A. and Wouters, E. F. (1996) Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. Thorax **51**, 819–824

89   Creutzberg, E. C., Schols, A. M., Weling-Scheepers, C. A., Buurman, W. A. and Wouters, E. F. (2000) Characterization of nonresponse to high caloric oral nutritional therapy in depleted patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **161**, 745–752

90   Spruit, M. A., Gosselink, R., Troosters, T., Kasran, A., Gayan-Ramirez, G., Bogaerts, P., Bouillon, R. and Decramer, M. (2003) Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. Thorax **58**, 752–756

91   Langen, R. C., Schols, A. M., Kelders, M. C., Wouters, E. F. and Janssen-Heininger, Y. M. (2001) Inflammatory cytokines inhibit myogenic differentiation through activation of nuclear factor-κB. FASEB J. **15**, 1169–1180

92   Li, Y. P., Schwartz, R. J., Waddell, I. D., Holloway, B. R. and Reid, M. B. (1998) Skeletal muscle myocytes undergo protein loss and reactive oxygen-mediated NF-κB activation in response to tumor necrosis factor α. FASEB J. **12**, 871–880

93   Barreiro, E., Schols, A. M., Polkey, M. I., Galdiz, J. B., Gosker, H. R., Swallow, E. B., Coronell, C. and Gea, J. (2008) Cytokine profile in quadriceps muscles of patients with severe COPD. Thorax **63**, 100–107

94   Couillard, A. and Prefaut, C. (2005) From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. Eur. Respir. J. **26**, 703–719

95   Rahman, I., Skwarska, E. and MacNee, W. (1997) Attenuation of oxidant/antioxidant imbalance during treatment of exacerbations of chronic obstructive pulmonary disease. Thorax **52**, 565–568

96   Couillard, A., Maltais, F., Saey, D., Debigare, R., Michaud, A., Koechlin, C., LeBlanc, P. and Prefaut, C. (2003) Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **167**, 1664–1669

97   Koechlin, C., Couillard, A., Simar, D., Cristol, J. P., Bellet, H., Hayot, M. and Prefaut, C. (2004) Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? Am. J. Respir. Crit. Care Med. **169**, 1022–1027

98   Engelen, M. P., Schols, A. M., Does, J. D., Deutz, N. E. and Wouters, E. F. (2000) Altered glutamate metabolism is associated with reduced muscle glutathione levels in patients with emphysema. Am. J. Respir. Crit. Care Med. **161**, 98–103

99   Rabinovich, R. A., Ardite, E., Troosters, T., Carbo, N., Alonso, J., Gonzalez de Suso, J. M., Vilaro, J., Barbera, J. A., Polo, M. F., Argiles, J. M. et al. (2001) Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease Am. J. Respir. Crit. Care Med. **164**, 1114–1118

100   Debigare, R., Maltais, F., Cote, C. H., Michaud, A., Caron, M. A., Mofarrahi, M., Leblanc, P. and Hussain, S. N. (2008) Profiling of mRNA expression in quadriceps of patients with COPD and muscle wasting. COPD **5**, 75–84

101   Arden, N. K. and Spector, T. D. (1997) Genetic influences on muscle strength, lean body mass, and bone mineral density: a twin study. J. Bone Miner. Res. **12**, 2076–2081

102   Carmelli, D., Kelly-Hayes, M., Wolf, P. A., Swan, G. E., Jack, L. M., Reed, T. and Guralnik, J. M. (2000) The contribution of genetic influences to measures of lower-extremity function in older male twins. J. Gerontol. A Biol. Sci. Med. Sci. **55**, B49–B53

103   Brown, N. J., Blais, Jr, C., Gandhi, S. K. and Adam, A. (1998) ACE insertion/deletion genotype affects bradykinin metabolism. J. Cardiovasc. Pharmacol. **32**, 373–377

104   Amaral, S. L., Papanek, P. E. and Greene, A. S. (2001) Angiotensin II and VEGF are involved in angiogenesis induced by short-term exercise training. Am. J. Physiol. Heart Circ. Physiol. **281**, H1163–H1169

105   Gordon, S. E., Davis, B. S., Carlson, C. J. and Booth, F. W. (2001) ANG II is required for optimal overload-induced skeletal muscle hypertrophy. Am. J. Physiol. Endocrinol. Metab. **280**, E150–E159

106   Rattigan, S., Dora, K. A., Tong, A. C. and Clark, M. G. (1996) Perfused skeletal muscle contraction and metabolism improved by angiotensin II-mediated vasoconstriction. Am. J. Physiol. **271**, E96–E103

107   Hopkinson, N. S., Nickol, A. H., Payne, J., Hawe, E., Man, W. D., Moxham, J., Montgomery, H. and Polkey, M. I. (2004) Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **170**, 395–399

108   Hopkinson, N. S., Li, K. W., Kehoe, A., Humphries, S. E., Roughton, M., Moxham, J., Montgomery, H. and Polkey, M. I. (2008) Vitamin D receptor genotypes influence quadriceps strength in chronic obstructive pulmonary disease. Am. J. Clin. Nutr. **87**, 385–390

109   Singh, S. and Morgan, M. D. (2001) Activity monitors can detect brisk walking in patients with chronic obstructive pulmonary disease. J. Cardiopulm. Rehabil. **21**, 143–148

110   Schonhofer, B., Ardes, P., Geibel, M., Kohler, D. and Jones, P. W. (1997) Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. Eur. Respir. J. **10**, 2814–2819

111   Walker, P. P., Burnett, A., Flavahan, P. W. and Calverley, P. M. (2008) Lower limb activity and its determinants in COPD. Thorax **63**, 683–689

112   Pitta, F., Troosters, T., Probst, V. S., Spruit, M. A., Decramer, M. and Gosselink, R. (2006) Physical activity and hospitalization for exacerbation of COPD. Chest **129**, 536–544

113   Garcia-Aymerich, J., Lange, P., Benet, M., Schnohr, P. and Anto, J. M. (2007) Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: a population-based cohort study. Am. J. Respir. Crit. Care Med. **175**, 458–463

114   Garcia-Aymerich, J., Lange, P., Benet, M., Schnohr, P. and Anto, J. M. (2006) Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax **61**, 772–778

115   Garcia-Aymerich, J., Farrero, E., Felez, M. A., Izquierdo, J., Marrades, R. M. and Anto, J. M. (2003) Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax **58**, 100–105

116   Similowski, T., Yan, S., Gauthier, A. P., Macklem, P. T. and Bellemare, F. (1991) Contractile properties of the human diaphragm during chronic hyperinflation. N. Engl. J. Med. **325**, 917–923

117   Franssen, F. M., Wouters, E. F. and Schols, A. M. (2002) The contribution of starvation, deconditioning and ageing to the observed alterations in peripheral skeletal muscle in chronic organ diseases. Clin. Nutr. **21**, 1–14

118   Mattson, J. P. and Poole, D. C. (1998) Pulmonary emphysema decreases hamster skeletal muscle oxidative enzyme capacity. J. Appl. Physiol. **85**, 210–214

119   Bodine, S. C., Stitt, T. N., Gonzalez, M., Kline, W. O., Stover, G. L., Bauerlein, R., Zlotchenko, E., Scrimgeour, A., Lawrence, J. C., Glass, D. J. and Yancopoulos, G. D. (2001) Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy *in vivo*. Nat. Cell Biol. **3**, 1014–1019

120   Rommel, C., Bodine, S. C., Clarke, B. A., Rossman, R., Nunez, L., Stitt, T. N., Yancopoulos, G. D. and Glass, D. J. (2001) Mediation of IGF-1-induced skeletal myotube hypertrophy by PI$_3$K/Akt/mTOR and PI$_3$K/Akt/GSK3 pathways. Nat. Cell Biol. **3**, 1009–1013

121   Hara, K., Yonezawa, K., Kozlowski, M. T., Sugimoto, T., Andrabi, K., Weng, Q. P., Kasuga, M., Nishimoto, I. and Avruch, J. (1997) Regulation of eIF-4E BP1 phosphorylation by mTOR. J. Biol. Chem. **272**, 26457–26463

122   Cross, D. A., Alessi, D. R., Cohen, P., Andjelkovich, M. and Hemmings, B. A. (1995) Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature **378**, 785–789

123 Vyas, D. R., Spangenburg, E. E., Abraha, T. W., Childs, T. E. and Booth, F. W. (2002) GSK-3β negatively regulates skeletal myotube hypertrophy. Am. J. Physiol. Cell Physiol. **283**, C545–C551

124 Jagoe, R. T., Lecker, S. H., Gomes, M. and Goldberg, A. L. (2002) Patterns of gene expression in atrophying skeletal muscles: response to food deprivation. FASEB J. **16**, 1697–1712

125 Bodine, S. C., Latres, E., Baumhueter, S., Lai, V. K., Nunez, L., Clarke, B. A., Poueymirou, W. T., Panaro, F. J., Na, E., Dharmarajan, K. et al. (2001) Identification of ubiquitin ligases required for skeletal muscle atrophy. Science **294**, 1704–1708

126 Gomes, M. D., Lecker, S. H., Jagoe, R. T., Navon, A. and Goldberg, A. L. (2001) Atrogin-1, a muscle-specific F-box protein highly expressed during muscle atrophy. Proc. Natl. Acad. Sci. U.S.A. **98**, 14440–14445

127 Stitt, T. N., Drujan, D., Clarke, B. A., Panaro, F., Timofeyva, Y., Kline, W. O., Gonzalez, M., Yancopoulos, G. D. and Glass, D. J. (2004) The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. Mol. Cell **14**, 395–403

128 Criswell, D. S., Booth, F. W., DeMayo, F., Schwartz, R. J., Gordon, S. E. and Fiorotto, M. L. (1998) Overexpression of IGF-I in skeletal muscle of transgenic mice does not prevent unloading-induced atrophy. Am. J. Physiol. **275**, E373–E379

129 Hunter, R. B., Stevenson, E., Koncarevic, A., Mitchell-Felton, H., Essig, D. A. and Kandarian, S. C. (2002) Activation of an alternative NF-κB pathway in skeletal muscle during disuse atrophy. FASEB J. **16**, 529–538

130 Cai, D., Frantz, J. D., Tawa, Jr, N. E., Melendez, P. A., Oh, B. C., Lidov, H. G., Hasselgren, P. O., Frontera, W. R., Lee, J., Glass, D. J. and Shoelson, S. E. (2004) IKKβ/NF-κB activation causes severe muscle wasting in mice. Cell **119**, 285–298

131 Doucet, M., Russell, A. P., Leger, B., Debigare, R., Joanisse, D. R., Caron, M. A., LeBlanc, P. and Maltais, F. (2007) Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **176**, 261–269

132 Hawke, T. J. and Garry, D. J. (2001) Myogenic satellite cells: physiology to molecular biology. J. Appl. Physiol. **91**, 534–551

133 Megeney, L. A., Kablar, B., Garrett, K., Anderson, J. E. and Rudnicki, M. A. (1996) MyoD is required for myogenic stem cell function in adult skeletal muscle. Genes Dev **10**, 1173–1183

134 Langen, R. C., Van Der Velden, J. L., Schols, A. M., Kelders, M. C., Wouters, E. F. and Janssen-Heininger, Y. M. (2004) Tumor necrosis factor-α inhibits myogenic differentiation through MyoD protein destabilization. FASEB J. **18**, 227–237

135 Joulia, D., Bernardi, H., Garandel, V., Rabenoelina, F., Vernus, B. and Cabello, G. (2003) Mechanisms involved in the inhibition of myoblast proliferation and differentiation by myostatin. Exp. Cell Res. **286**, 263–275

136 Kambadur, R., Sharma, M., Smith, T. P. and Bass, J. J. (1997) Mutations in myostatin (GDF8) in double-muscled Belgian Blue and Piedmontese cattle. Genome Res. **7**, 910–916

137 Schuelke, M., Wagner, K. R., Stolz, L. E., Hubner, C., Riebel, T., Komen, W., Braun, T., Tobin, J. F. and Lee, S. J. (2004) Myostatin mutation associated with gross muscle hypertrophy in a child. N. Engl. J. Med. **350**, 2682–2688

138 Gonzalez-Cadavid, N. F., Taylor, W. E., Yarasheski, K., Sinha-Hikim, I., Ma, K., Ezzat, S., Shen, R., Lalani, R., Asa, S., Mamita, M. et al. (1998) Organization of the human myostatin gene and expression in healthy men and HIV-infected men with muscle wasting. Proc. Natl. Acad. Sci. U.S.A. **95**, 14938–14943

139 Vogiatzis, I., Stratakos, G., Simoes, D. C., Terzis, G., Georgiadou, O., Roussos, C. and Zakynthinos, S. (2007) Effects of rehabilitative exercise on peripheral muscle TNFα, IL-6, IGF-I and MyoD expression in patients with COPD. Thorax **62**, 950–956

140 Koves, T. R., Li, P., An, J., Akimoto, T., Slentz, D., Ilkayeva, O., Dohm, G. L., Yan, Z., Newgard, C. B. and Muoio, D. M. (2005) Peroxisome proliferator-activated receptor-γ co-activator 1α-mediated metabolic remodeling of skeletal myocytes mimics exercise training and reverses lipid-induced mitochondrial inefficiency. J. Biol. Chem. **280**, 33588–33598

141 Luquet, S., Lopez-Soriano, J., Holst, D., Fredenrich, A., Melki, J., Rassoulzadegan, M. and Grimaldi, P. A. (2003) Peroxisome proliferator-activated receptor δ controls muscle development and oxidative capability. FASEB J. **17**, 2299–2301

142 Puigserver, P. and Spiegelman, B. M. (2003) Peroxisome proliferator-activated receptor-γ coactivator 1 α (PGC-1 α): transcriptional coactivator and metabolic regulator. Endocr. Rev. **24**, 78–90

143 Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., Michael, L. F., Puigserver, P., Isotani, E., Olson, E. N. et al. (2002) Transcriptional co-activator PGC-1 α drives the formation of slow-twitch muscle fibres. Nature **418**, 797–801

144 Sandri, M., Lin, J., Handschin, C., Yang, W., Arany, Z. P., Lecker, S. H., Goldberg, A. L. and Spiegelman, B. M. (2006) PGC-1α protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc. Natl. Acad. Sci. U.S.A. **103**, 16260–16265

145 Narkar, V. A., Downes, M., Yu, R. T., Embler, E., Wang, Y. X., Banayo, E., Mihaylova, M. M., Nelson, M. C., Zou, Y., Juguilon, H. et al. (2008) AMPK and PPARδ agonists are exercise mimetics. Cell **134**, 405–415

146 Narravula, S. and Colgan, S. P. (2001) Hypoxia-inducible factor 1-mediated inhibition of peroxisome proliferator-activated receptor α expression during hypoxia. J. Immunol. **166**, 7543–7548

147 Beier, K., Volkl, A. and Fahimi, H. D. (1997) TNF-α downregulates the peroxisome proliferator activated receptor-α and the mRNAs encoding peroxisomal proteins in rat liver. FEBS Lett. **412**, 385–387

148 Remels, A. H., Schrauwen, P., Broekhuizen, R., Willems, J., Kersten, S., Gosker, H. R. and Schols, A. M. (2007) Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. Eur. Respir. J. **30**, 245–252

149 Man, W. D.-C., Kemp, P., Moxham, J. and Polkey, M. I. (2009) Exercise and muscle dysfunction in COPD: implications for pulmonary rehabilitation. Clin. Sci. **117**, 281–291