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Structural and Functional Changes of Peripheral Muscles in Copd Patients

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Abstract

Purpose of Review—The purpose of this review is to identify new advances in our understanding of skeletal muscle dysfunction in patients with COPD.

Recent findings—Recent studies have confirmed the relevance of muscle dysfunction as an independent prognosis factor in COPD. Animal studies have shed light on the molecular mechanisms governing skeletal muscle hypertrophy/atrophy. Recent evidence in patients with COPD highlighted the contribution of protein breakdown and mitochondrial dysfunction as pathogenic mechanisms leading to muscle dysfunction in these patients.

Summary—Chronic Obstructive Pulmonary Disease (COPD) is a debilitating disease impacting negatively on health status and the functional capacity of patients. COPD goes beyond the lungs and incurs significant systemic effects among which muscle dysfunction/wasting is one of the most important. Muscle dysfunction is a prominent contributor to exercise limitation, healthcare utilization and an independent predictor of morbidity and mortality. Gaining more insight into the molecular mechanisms leading to muscle dysfunction/wasting is key for the development of new and tailored therapeutic strategies to tackle skeletal muscle dysfunction/wasting in COPD patients.

Keywords

COPD; systemic effects; muscle dysfunction; muscle wasting

Introduction

Chronic Obstructive Pulmonary Disease (COPD) affects approximately 280 million people worldwide(1-3), is the fourth leading cause of death, claiming 2.75 million lives annually(4). COPD is a debilitating disease impacting negatively on health status and limiting the functional capacity of patients.

The largely irreversible nature of the airway obstruction defines the disease. Nevertheless, the degree of airway obstruction measured as the forced expiratory volume in the first

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second (FEV₁) correlates poorly with the severity of symptoms, health-related quality of life (HRQoL) and survival.

Exercise intolerance is one of the main complains of COPD patients and it has been classically attributed to respiratory system constrains. However, more than 15 years ago, Killian et al(5) demonstrated that, as well as age matched controls, a large proportion of COPD patients experience leg fatigue during exercise, implying that lower limb dysfunction may contribute to reduced exercise capacity. Years later other investigators confirmed leg fatigue as an objective contributor to exercise intolerance in COPD patients(6;7)* independent of the degree of airway obstruction(8). A true dissociation between airway obstruction and exercise tolerance can be defined. Lung function deterioration after lung volume reduction surgery (LVRS) occurs faster than deterioration in exercise capacity(9). Although improved after double lung transplant, exercise tolerance does not reach normal predicted values(10;11). Exercise training improves exercise tolerance without improving lung function(12). Moreover, pulmonary rehabilitation further improves exercise tolerance following lung transplantation(13)*. All this evidence suggests that, besides lung function, peripheral and circulatory factors are critical in limiting exercise capacity.

COPD is a preventable and treatable disease that goes beyond the lungs and incurs significant systemic effects with an impact on morbidity and mortality(14). Different phenotypes of the disease can be defined, particularly associated with systemic consequences of the disease. Moreover, multidimensional grading systems that take into account not only lung function, but also parameters reflecting the patient's perception and the systemic impact of the disease, show a greater ability to predict important outcomes such as mortality, compared to lung function assessment alone(15;16)*.

Among the systemic effects of the disease, peripheral muscle dysfunction is one of the most important and is a prominent contributor to exercise limitation(8), healthcare utilization(17) and an independent predictor of morbidity and mortality(18).

From a physiological point of view, muscle function can be defined as the ability to produce force (muscle strength), and sustain a muscle contraction for a time (muscle endurance). The latter is inversely related to muscle fatigue. Peripheral muscle dysfunction, particularly leg muscle dysfunction, has been largely demonstrated in COPD patients. Peripheral muscle strength(19-21), endurance(22-25), and fatigability(6;26) are impaired in COPD (Figure 1).

Peripheral muscles patho-physiological findings

Muscle dysfunction is characterised by two related phenomena: a) malfunctioning of the muscle; and, b) net loss of muscle mass, which occurs in a subgroup of patients(18).

Skeletal muscle atrophy

Muscle mass loss is present in 18 to 36% of these patients(27;28) and is responsibly for weight loss(28) evident in 17 to 35% of COPD patients depending on the studied population(27-31). Indeed, muscle wasting is present in 6 to 21% of patients with normal weight(27-29). Moreover, muscle loss relates to muscle strength(19;32;33) and exercise tolerance(28;34-36) independent of the degree of airway obstruction(36). Hence, muscle wasting is a better predictor of health related quality of life(37) and survival(38;39) than body weight.

Net loss of muscle mass is responsible for the diminished muscle strength(40)* in these patients by a decrease in functional units available for muscle contraction.

Interestingly, when corrected by muscle mass, the differences in muscle strength between COPD patients and healthy controls vanishes(19;41). This shows that a reduced muscle mass relates to an impairment in muscle strength, but it does not account for abnormal muscle endurance(41)* which seems to be related to alterations in skeletal muscle bioenergetics. Moreover, muscle weakness can be present in early stages of the disease(42;43)* and has also been related to ACE(44) and Vitamin D(45)* genotype in these patients.

A number of patho-physiological findings responsibly for the malfunction of the muscle have been described in the peripheral muscles of patients with COPD. Most of these findings come from studies on thigh muscle biopsies from patients with COPD (Figure 1) and are described below:

Fibre type re-distribution

Peripheral skeletal muscle of patients with COPD present an increment of type II (less oxidative) fibre proportion to the detriment of type I (more oxidative) fibres(46-53). This increment of type II fibres is characterized by a rise of the number of type IIx fibres(47;49;54;55). The presence of hybrid fibres (I/IIa y IIa/IIx) has also been described, suggesting that the transformation from one fibre type to another could constitute a mechanism leading to the re-distribution of fibres seen in COPD(55).

Type IIx and hybrid fibres IIa/IIx present the highest level of atrophy(54). Since disuse-related atrophy affects mainly type I fibres(56), the prevalence of type IIx atrophy may suggest other causes of atrophy in COPD. Moreover, this kind of fibre type re-distribution has been described in association with hypoxia(57) and energy imbalance conditions such as anorexia(58).

Alteration in muscle bioenergetics

Several studies have demonstrated a deficit in peripheral muscle oxidative capacity in COPD patients(51;59;60) which correlates with exercise tolerance(61). Furthermore, an early lactate release during exercise has been described in these patients(62-64). This phenomenon is explained by lactate production by leg muscles and not by the respiratory muscles(65) and contributes to explain, at least in part, the exercise intolerance of COPD patients(62). The early lactate release described during exercise in COPD patients can be explained by different phenomena such as the impaired O₂ delivery to the muscle, the recruitment of fibre type II, with a predominant lactate metabolism, or the diminished oxidative capacity of the muscle cell.

Alteration of the O₂delivery/O₂utilization relationship is associated with a lower efficiency of the muscle in these patients. Also, the relationship phosphate/phospho creatine during sub-maximal exercise is increased in the skeletal muscle of COPD patients(60). Moreover, these patients have a higher leg VO₂ at comparable sub-maximal exercise loads in comparison with healthy controls(53;60), which might be explained by the higher percentage of fibre type II. There is convincing evidence that the energetic cost is elevated in the peripheral muscle of these patients(66). An increment of cytochrome oxidase activity has been described, which may contribute to the incremented VO₂ described for iso-load(67).

Interestingly, it has recently been shown that skeletal muscle of patients with COPD exhibit lower Na/K ATPase activity compared to healthy controls. This may have major effects on membrane excitability and fatigability(68)*.

Alteration in muscle capillarization

Electro(69) and optic(50) microscopy studies have shown that there is a reduced capillary density in peripheral muscles of patients with COPD. Moreover, the number of contacts between capillaries and fibres is also reduced(47;50). However, one study(53) did not show these abnormalities in the muscle capillarization, but interestingly, a large proportion of the patients included in this study had followed a pulmonary rehabilitation program. Pulmonary rehabilitation has been associated with an increase in the number of capillary-fibre contacts in patients with COPD(47). This alteration in the micro vascular bed may have an impact on the tissue oxygenation particularly in those patients presenting with continuous or intermittent hypoxemia or in situations of increased skeletal muscle oxygen demand such as during exercise.

Pathogenic mechanisms of Muscle dysfunction

Despite the relevance of skeletal muscle dysfunction in COPD, the pathogenic mechanisms of this phenomenon remain unclear. Several potential mechanisms have been related to peripheral muscle dysfunction/wasting in patients with COPD: a) protein synthesis/breakdown balance, b) nutritional abnormalities, c) muscle disuse, d) systemic corticosteroids, e) tissue hypoxia and hypercapnia, f) alterations in muscle remodelling, g) inflammation, h) oxidative/nitrosative stress; and, i) mitochondrial abnormalities. (Figure 1)

Protein synthesis/breakdown balance

Skeletal muscle mass is maintained by a delicate balance between protein synthesis and protein breakdown and experiences hypertrophy and atrophy in response to altered functional demands by adjusting either side of this equilibrium. Several studies showed an abnormal protein turnover in patients with COPD(70-72).

The signalling pathways that govern muscle hypertrophy and/or atrophy have yet to be fully defined. However, several key actors have been identified so far (Figure 2). Akt (protein kinase B), an intracellular serine/threonine protein kinase, is a central regulator of involved in the regulation of both hypertrophy and atrophy signalling pathways(73;74). Akt is activated by insulin like growth factor-1 (IGF-1) through the phosphorylation of Akt by phosphoinositide 3-kinase (PI3k) and, by inactivation of the forkhead box class O (FoxO) of transcription factors, is able to block muscle protein breakdown by down regulation of the muscle-specific E3-ligases atrogin-1 and muscle-specific RING finger protein 1 (MuRF1). Phosphorylated AKT also stimulates a variety of hypertrophic pathways, including mammalian target of rapamycin (mTOR) and glycogen synthase kinase-3beta (GSK3 β). mTOR can promote protein synthesis through the activation of 70-kD ribosomal S6 protein kinase (p70^{S6K}) and by the inhibition of eukaryotic translation initiation factor 4E binding protein-1 (4E-BP1).

Several studies have focused on the balance between catabolic and anabolic hormones in COPD(75-78). Ubiquitin-mediated protein degradation seems to have a role in skeletal muscle protein breakdown in COPD patients. Doucet et al(79) showed increased levels of atrogin-1 and MuRF1 mRNA, and of phosphorylated AKT and 4E-BP1 and FoxO-1 proteins in skeletal muscle of patients with COPD with muscle atrophy compared with healthy control subjects, whereas atrogin-1, p70S6K, GSK3 β , and FoxO-3 protein levels were similar. Patients with COPD with muscle atrophy showed an increased expression of p70S6K, GSK3 β , and 4EBP1 compared with patients with COPD with preserved muscle mass. They conclude that the increase in the expression of the ligases may occur via FoxO-1 while the over expression of the muscle hypertrophic signalling pathways could represent an attempt to restore muscle mass.

Plant et al(80)* showed increased levels of atrogin-1 and Nedd4, two ligases regulating ubiquitin-mediated protein degradation, in the muscle of COPD patients compared to healthy controls. They did not find differences in the level of phosphorylation of Akt, GSK3 β or p70^{S6K}.

Nutritional depletion

Muscle wasting is the main mechanism leading to weight loss observed in patients with COPD(28). It is important to differentiate “malnutrition” from “cachexia” being the first one associated with a diminished calorie intake and a reduced basal metabolism with a good response to nutritional support and a relatively preserved muscle mass. The latter better reflects the situation of some COPD patients. A third condition, sarcopenia, has also been described in patients with COPD and consist of a the loss of muscle mass without an overall loss of weight(28;29;81).

In contrast to acute exacerbations of COPD (ECOPD), a reduction in calorie intake does not seem to be relevant in stable patients(82). However, basal metabolism is increase in patients with COPD(83), particularly in those with weight loss(84). Traditionally this increment was explained by the increased oxygen utilization by the respiratory muscles(85). Nevertheless, the increased oxygen uptake for an established workload(53;60) and the increased energy expenditure during activities of daily living(86;87) may contribute to the increase in the energy consumption.

The increase in the energy expenditure together with an unmatched calorie intake may contribute to explain the waste of muscle mass in the cachectic COPD patients(83).

Muscle disuse

Dyspnoea associated with exercise is the main complaint of patients with COPD and contributes to the sedentary habit of these patients. Activities of daily living are reduced in COPD(88-92)*. Changes in the work load of the muscles have a dramatic effect in the muscle size and metabolic capacity of the fibres(93-96). Skeletal muscle plasticity is remarkable. The fact that exercise training contributes to improved muscle function in patients with COPD, reinforces the role of muscle disuse in occurrence of skeletal muscle dysfunction in these patients(60;97;98). Moreover, several of the skeletal muscle abnormalities found in COPD patients are similar to other populations of deconditioned patients(99).

Systemic corticosteroids

Corticosteroids associated myopathy is the most common pharmacological adverse event in the muscle associated with COPD. It has been described as an acute and chronic steroid myopathy, being the first rare condition not described in patients with COPD. The chronic corticosteroid myopathy constitutes the classical condition associated to the chronic use of systemic corticosteroids. It is characterized for diffuse muscle atrophy with a prominent effect on fibre type IIx(100). There is a close relationship between the duration and doses of the treatment and the functional and structural changes(101). The use of systemic corticosteroids for relatively short periods of time does not seems to have a deleterious effect on the muscle(102), while long-term use of corticosteroids, even in low doses had significant effects in muscle strength and bulk(19).

Tissue hypoxia and hypercapnia

A chronic or intermittent alteration in arterial blood gas composition is a common feature in COPD. The deleterious effect of tissue hypoxia on the muscle is supported by several publications on healthy humans exposed to high altitude hypobaric hypoxia and animal

models. Tissue hypoxia limits the production of energy and affects the protein synthesis(103) leading to muscle loss(104;105), increases in glycolytic enzyme activity and a fall in oxidative enzymes activity(106;107). Hypoxia inhibits mitochondrial protein synthesis(108) and muscle protein synthesis reducing myosin contents(109;110) and oxidative capacity(51). Hypoxic patients have a lower proportion of type I fibres(55). Hypoxemia can also trigger other of the mentioned pathogenic mechanisms related to muscle dysfunction such as increase the levels of cytokines(111), oxidative stress(112), or reduction of anabolic hormones(113). Hypoxemia has been related to mitochondrial uncoupling and early lactate release during exercise in COPD patients (114). Hypercapnia increments the intracellular acidosis in the skeletal muscle(115) which inhibit the activity of oxidative enzymes(116) and accelerate protein degradation(117). Elevated levels of CO₂ reduce the deposits of Pcr and ATP(118) in experimental models and COPD patients(119).

Alterations in muscle remodelling

Adult skeletal muscle fibres are terminally differentiated, their nuclei are post mitotic and are thus not able to replicate. Muscle injury repairs and growth (hypertrophy and hyperplasia) are accomplished by satellite cells. Satellite cells, the stem cells of adult skeletal muscle first described by Mauro in 1961(120), reside beneath the basal lamina closely juxtaposed to the muscle fibres. Satellite cells constitute around 30 % of the total population of skeletal muscle cells in newborn and 5 % in adult life. Although mitotically quiescent, they are activated and re-enter the cell cycle in response to different stimulus like stress induced by weight-bearing exercise and, trauma including injury. In recent years, the importance of satellite cells has been emphasised by the discovery that their proliferation is evoked not only by acute muscle injury but also by muscle overuse and increased muscle tension. Myogenic regulatory factors (MRFs) are part of a super family of basic helix-loop-helix (bHLH) transcription factors involved in the satellite cell differentiation process(121)*. The primary MRFs, MyoD and Myf-5, appear to be required for *myogenic determination*, whereas the secondary MRFs, myogenin and MRF4, are required downstream of MyoD and Myf-5 as *differentiation factors* (Figure 3)(122). Several animal models and cell culture studies have helped to progress the understanding of muscle repair mechanisms. Few studies assessed the molecular aspects of muscle remodelling in COPD. Plant et al(80) showed no differences in skeletal muscle expression of Myf5, MyoD or myogenin. Crul et al showed no differences in MyoD in stable COPD patients. However, patients undergoing an ECOPD present with reduced levels of MyoD compared to healthy controls(78). Vogiatzis et al(123) showed that exercise training increased the expression of MyoD in peripheral muscle of patients with COPD. Lewis et al(124) showed an increment in IGF-I protein with exercise training and a combination of exercise training and testosterone together with an increment in myogenin mRNA expression. More studies in this field are needed to clarify whether abnormalities in muscle differentiation may play a role in the muscle dysfunction/wasting occurring in these patients.

Inflammation

COPD is recognized as an inflammatory disease(14). Whether or not originating in the lungs, evidence of systemic inflammation in COPD has been previously shown in several studies(29;125-127). Elevated pro-inflammatory cytokines(128)* have been associated with reduced lean mass(29), muscle wasting(77), and increased rest energy expenditure(127;129). Moreover, patients who fail to gain weight in response to nutritional support present high circulating levels of TNF α (130).

The presence of local inflammation in the skeletal muscle of patients with COPD is still a controversial issue. Some studies have shown increased levels of TNF α expression in the peripheral muscle of COPD patients(131;132). Other investigators could not reproduce these

findings(78;133)*. Cell culture models showed that pro-inflammatory cytokines such as TNF α induced protein breakdown and interfere with muscle differentiation process through the activation of NF κ B via increased production of mitochondrial ROS(134-136). Whether this can be extrapolated to COPD patients remains to be elucidated. Interestingly, Agusti et al demonstrated an increased in NF κ B-DNA binding activity in the peripheral muscle of COPD patients compared to healthy controls(137).

Oxidative/Nitrosative stress

An imbalance between oxidants and antioxidant capacity of the cells can lead to oxidative damage of protein, lipids and nucleic acids, a process known as oxidative stress. Several studies have shown increased levels of systemic(133;138-144) and local oxidative/nitrosative stress(144-148)*.

Oxidative stress can alter muscle contractility(149) potentially affecting muscle strength and contribute to muscle fatigue. The administration of antioxidants improve exercise tolerance in COPD patients(150), showing a direct effect of ROS on exercise capacity in these patients.

Oxidative stress can also contribute to accelerate protein breakdown(151-154) as a potential mechanism leading to muscle wasting(145;155). It is worthwhile to mention levels of uncoupling protein 3 in the skeletal muscle (UCP3) are reduced(156), particularly in the subgroup of patients with low BMI(114) and in the more oxidative fibres(157). UCP3 is a protein that may protect mitochondria against lipotoxicity preventing fatty acid from ROS-induced oxidative damage in cases where fatty acid influx exceeds the capacity to oxidise them(97). Moreover, UCP3 levels correlates with fat free mass (FFM) index in skeletal muscle of COPD patients(114) and may account for a reduced ability to prevent fatty acids oxidation favouring lipid peroxidation, particularly at mitochondria level.

Mitochondrial abnormalities

When compared with healthy controls, mitochondrial density is reduced in the skeletal muscle of patients with COPD(158). One study has shown that the acceptor control ratio (ACR), an index of mitochondrial complexes coupling in *ex vivo* mitochondria, is reduced in patients with COPD and low body mass index (BMI) compared with COPD patients with normal BMI and healthy controls(114). Moreover, the levels of ACR correlated significantly with PaO₂ and with early lactate release during exercise in this population of patients(114). Interestingly, Picard et al showed a reduced mitochondrial oxygen uptake in COPD patients, however, when normalized by mitochondrial density this difference vanished(159)*. Puente-Maestu et al also showed reduced mitochondrial oxygen uptake in COPD patients with normal BMI with a reduced acceptor control ratio(160)*. These authors also showed a higher cytochrome c release in *ex vivo* mitochondria stimulated with H₂O₂(161)*. Release of cytochrome c constitutes an early event in the signalling of apoptosis. Agusti et al showed increased skeletal muscle apoptosis in patients with COPD and low BMI compared with COPD with normal BMI and healthy controls(162).

Peroxisome-proliferator-activated receptors (PPARs) and PPAR- γ co-activator 1 α (PGC-1 α) have been shown to be key regulators of skeletal muscle oxidative capacity(163), mitochondrial biogenesis(164) and fibre-type shifting towards more oxidative fibre(165;166). Remels et al showed reduced PPAR δ protein levels and PGC1 α mRNA expression in the skeletal muscle of patients with COPD(167). Moreover, cachectic COPD patients showed lower levels of PPAR α mRNA expression compared to non-cachectic patients(167).

Interventions directed to improve peripheral muscle dysfunction

Without any doubt, exercise training is the most successful strategy to treat muscle dysfunction/wasting in patients with COPD(168;169). Exercise training improves exercise tolerance(170;171)* through improving muscle strength, endurance and reducing fatigue(168;169). Exercise training improves body weight through improving FFM(172), skeletal muscle oxidative capacity and fibre type distribution(60;97;173); and is clearly recommended for COPD patients with exercise intolerance independent of the degree of severity of airway obstruction(174).

Nutritional support has proven not to be effective in improving weight in patients with COPD as a group(175). However, it is worthwhile mentioning that the absence of response to nutritional support has been associated with higher levels of markers of systemic inflammation(130). When subgroups of COPD patients have been analyzed, it has been shown that nutritional support improves survival in those patients that gain more than 2 kg of weight(176) or 1 Kg.m⁻² of BMI(177). In contrast to nutritional support, most trials of pharmacological anabolic replacement have documented significant improvements in muscle mass and strength(178-180). However, the absence of an impact of increased muscle mass on physiological effects such as exercise tolerance(178-182) and the fact that the use of anabolic replacement is not exempt from adverse reactions such as benign prostatic hyperplasia, prostate cancer, erythrocytosis and oedema (183), do not encourage the use of this therapy.

Conclusion

The systemic nature of COPD is recognized. Different phenotypes of the disease can be defined, and are particularly associated with systemic consequences of the disease. Peripheral muscle dysfunction/wasting, one of the most important systemic effects, relates to several patho-physiological findings caused by multiple pathogenic mechanisms. Recent studies in COPD highlighted the role of the ubiquitine proteasome system in the skeletal muscle protein breakdown in COPD patients. A malfunctioning of the mitochondria has also recently been identified in these patients. Exercise training constitutes the most successful strategy orientated to reverse peripheral muscle dysfunction/wasting.

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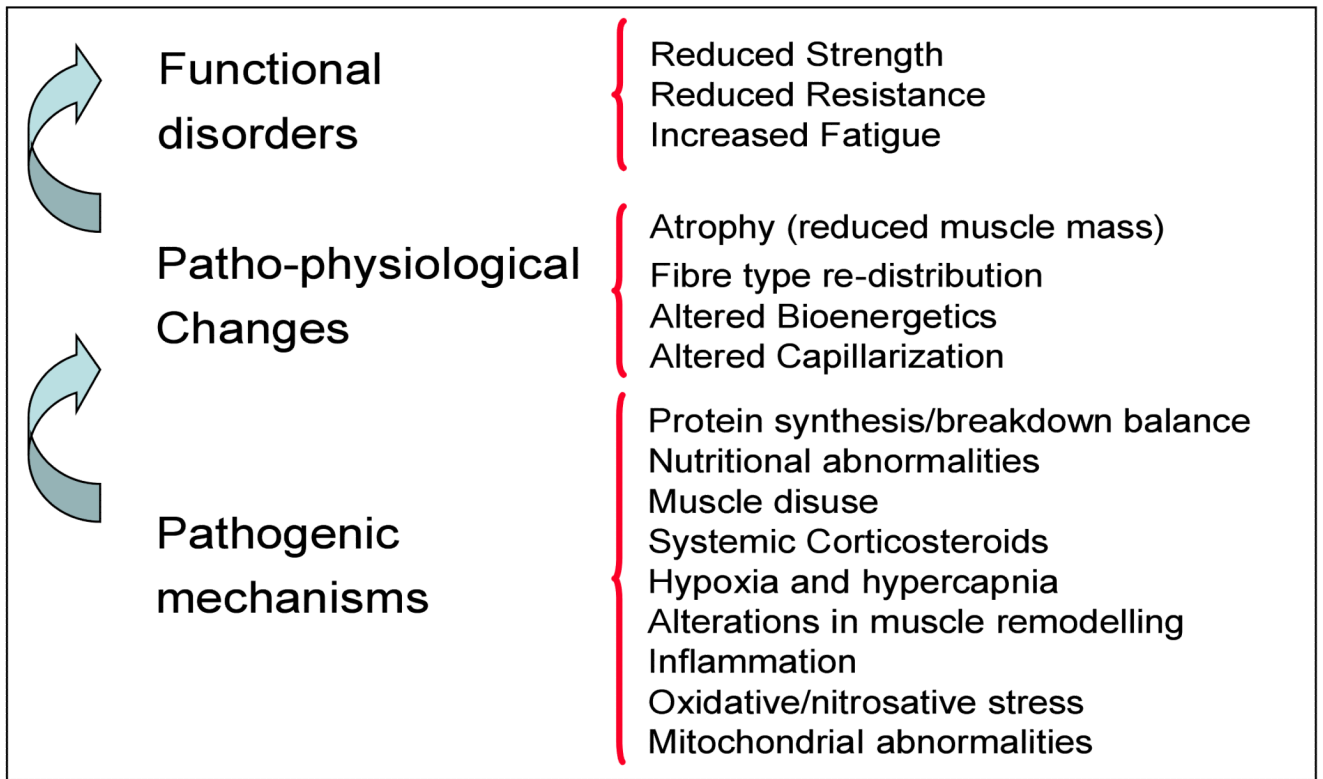


Figure 1. Peripheral muscle dysfunction in COPD. Skeletal muscle functional disorders and its relationship with the responsible patho-physiological changes and pathogenic mechanisms leading to muscle dysfunction/wasting in COPD patients.

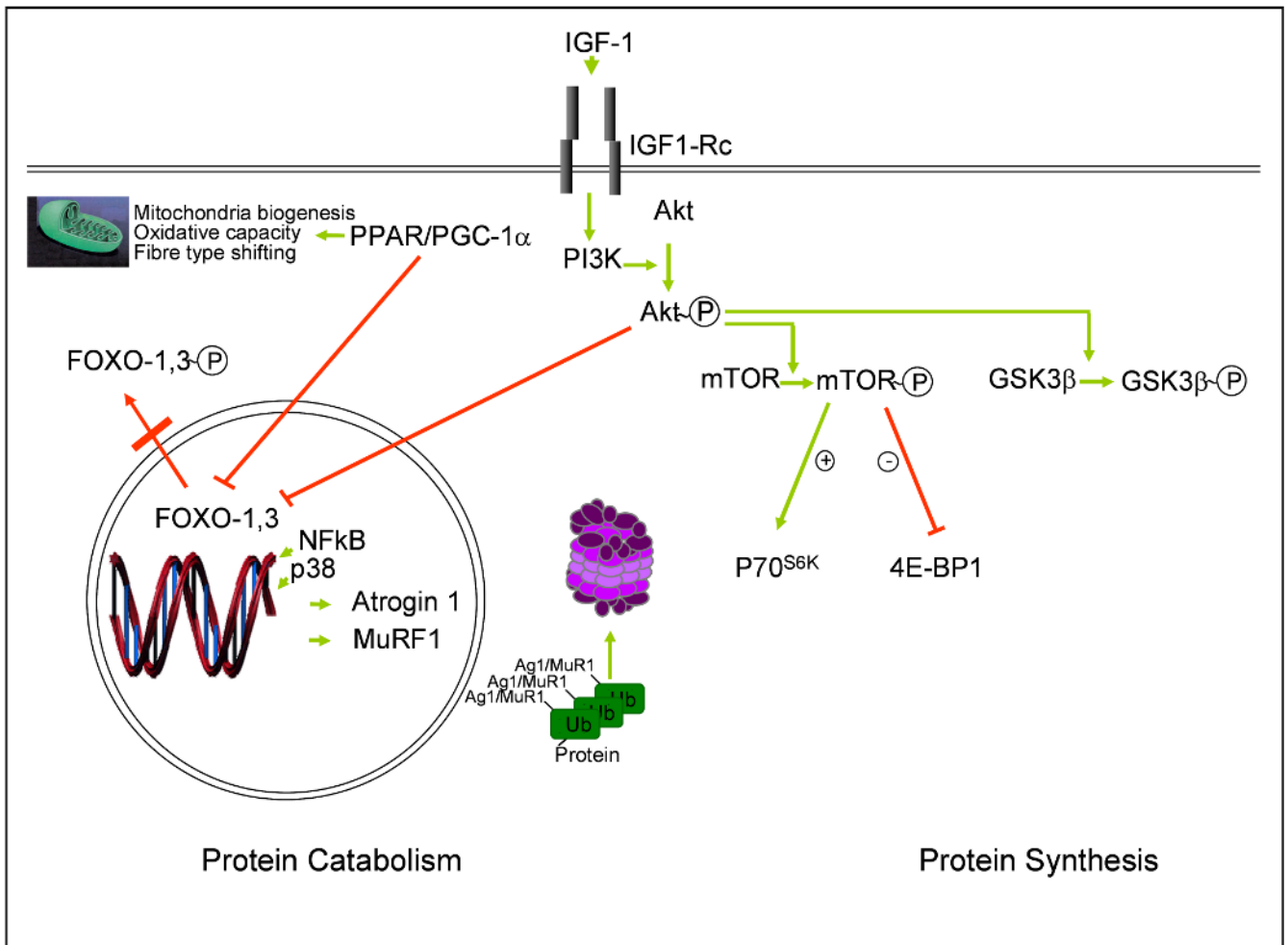


Figure 2. Signalling pathways that govern muscle hypertrophy and/or atrophy. Complexity of pathways governing skeletal muscle hypertrophy and atrophy. See main text for explanation and abbreviations.

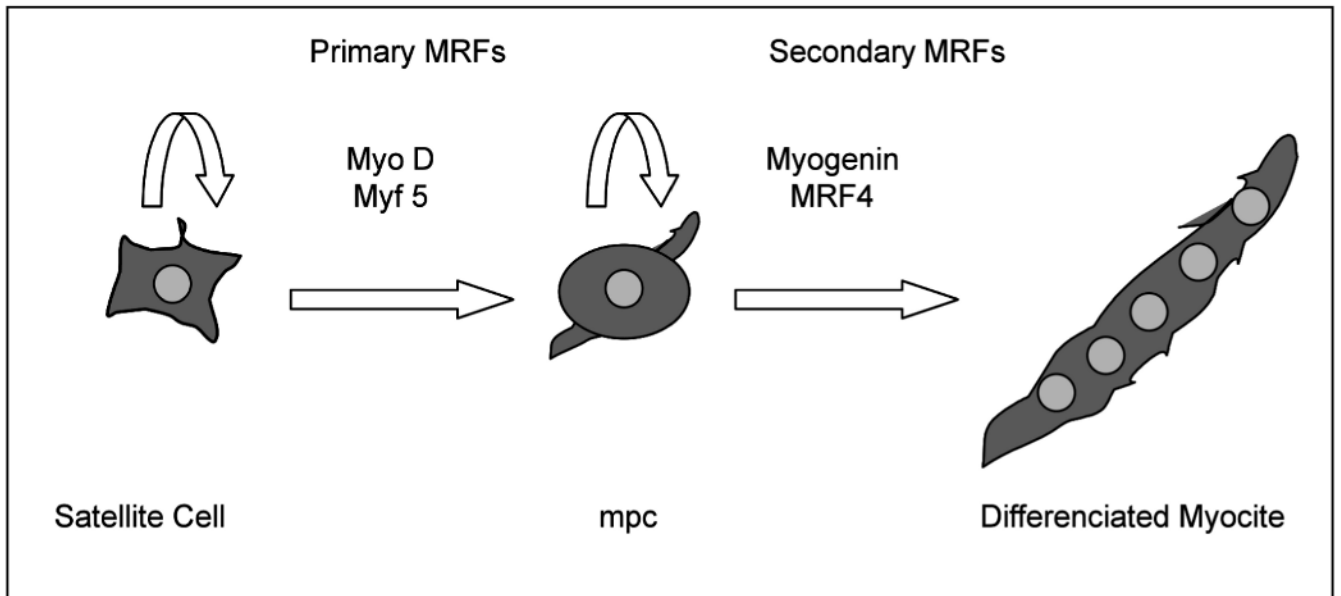


Figure 3.
Skeletal muscle differentiation regulatory factors
Satellite cells re-enter the cell cycle in response to acute muscle injury and muscle overuse and tension. Primary (MyoD and Myf5) and secondary (Myogenin and MRF4) myogenic regulatory factors (MRFs) are required for myogenic determination (myogenic precursor cell [mpc]) and differentiation (differentiated myocyte).