The International Journal of Biochemistry & Cell Biology xxx (2013) xxx–xxx

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Review

Triggers and mechanisms of skeletal muscle wasting in chronic obstructive pulmonary disease☆

R.C.J. Langen*, H.R. Gosker, A.H.V. Remels, A.M.W.J. Schols

NUTRIM School for Nutrition, Toxicology & Metabolism, Department of Respiratory Medicine, Maastricht University Medical Center+, Maastricht, The Netherlands

ARTICLE INFO

Article history:
Available online xxx

Keywords:
Muscle atrophy
Protein synthesis
Proteolysis
Myogenesis

ABSTRACT

Skeletal muscle wasting contributes to impaired exercise capacity, reduced health-related quality of life and is an independent determinant of mortality in chronic obstructive pulmonary disease. An imbalance between protein synthesis and myogenesis on the one hand, and muscle proteolysis and apoptosis on the other hand, has been proposed to underlie muscle wasting in this disease. In this review, the current understanding of the state and regulation of these processes governing muscle mass in this condition is presented. In addition, a conceptual mode of action of disease-related determinants of muscle wasting including disuse, hypoxemia, malnutrition, inflammation and glucocorticoids is provided by overlaying the available associative clinical data with causal evidence, mostly derived from experimental models. Significant progression has been made in understanding and managing muscle wasting in chronic obstructive pulmonary disease. Further examination of the time course of muscle wasting and specific disease phenotypes, as well as the application of systems biology and omics approaches in future research will allow the development of tailored strategies to prevent or reverse muscle wasting in chronic obstructive pulmonary disease.

This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

Contents

Abbreviations: 4E-BP1, 4E-binding protein-1; AA, amino acid; ALS, autophagy-lysosomal system; AMPK, adenosine monophosphate-activated protein kinase; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ERK, extracellular signal regulated kinase; FFM, fat-free mass; FOXO, forkhead box O; GC, glucocorticoid; GR, glucocorticoid receptor; GRE, GR DNA binding element; GSK3β, glycogen synthase kinase 3β; HIF1α, hypoxia inducible factor 1α; HPA axis, hypothalamic-pituitary-adrenal axis; IGF-1, insulin-like growth factor-1; IL, interleukin; IRS-1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; MAFbx, muscle atrophy F-box; MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; MuRF1, muscle RING finger protein; Nedd4, neural precursor cell expressed developmentally down-regulated protein 4; NF-κB, nuclear Factor kappa-light-chain-enhancer of activated B cells; P70S6K, p70S6-kinase; PARP, poly ADP ribose polymerase; PI-3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; REDD1, regulated in development and DNA damage responses-1; REE, resting energy expenditure; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-alpha; TSC2, tuberous suppressor complex 2; TWEAK, tumor necrosis factor-like weak inducer of apoptosis; Ub, ubiquitin; UPS, ubiquitin 26S-proteasome system.

☆ This article is part of a Directed Issue entitled: Molecular basis of muscle wasting.

* Corresponding author at: NUTRIM School for Nutrition, Toxicology & Metabolism, Department of Respiratory Medicine, Maastricht University Medical Center+, P.O. Box 5800, NL-6202 AZ Maastricht, The Netherlands. Tel.: +31 43 3884247; fax: +31 43 3875051.
E-mail addresses: r.langen@maastrichtuniversity.nl, a.schols@maastrichtuniversity.nl (R.C.J. Langen).

1357-2725/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.biocel.2013.06.015

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a lung disorder with progressive airflow obstruction resulting from inflammation and remodeling of the airways which often includes development of emphysema. Dominant symptoms are dyspnea and impaired exercise capacity adversely affecting health-related quality of life. COPD is characterized by episodes of acute worsening of symptoms referred to as exacerbations, which negatively affect disease progression (Tanabe et al., 2011) and survival (Soler-Cataluna et al., 2005). Although the lung is the primary diseased organ, COPD is increasingly acknowledged as a systemic disease due to its clinically significant extra-pulmonary consequences (Barnes and Celli, 2009). Systemic degenerative manifestations in COPD include osteoporosis (Romme et al., 2012) and muscle wasting. The prevalence of muscle atrophy is relatively high in COPD: 20–40% depending on definition and disease stage (Engelen et al., 1994; Schols et al., 1993). Moreover, as body composition is not routinely assessed, the prevalence of muscle atrophy most likely is underestimated as selective depletion of fat-free mass (FFM) despite relative preservation of fat mass is seen in a substantial proportion of patients with normal body weight (Engelen et al., 1999). Importantly, muscle wasting not only contributes to diminished muscle function, reduced exercise capacity and decreased health status (Baarends et al., 1997a; Mostert et al., 2000), but is also a determinant of mortality in COPD independent of airflow obstruction (Schols et al., 2005; Vestbo et al., 2006). In addition to muscle mass depletion, a shift in muscle fiber composition from type I to type II, accompanied by a decrease in oxidative capacity culminates in reduced muscle endurance. This not only contributes to reduced exercise capacity (Gosker et al., 2002; Maltais et al., 2000), but may also accelerate muscle wasting in COPD (Remels et al., 2012) since type II fibers are generally more susceptible to atrophy stimuli (*as reviewed elsewhere in this issue*). Muscle atrophy in COPD has been demonstrated by decreases in FFM at whole body level, but also specifically at the level of the extremities (Bernard et al., 1998). In addition, muscle atrophy is apparent as a decrease in the size of individual muscle fibers, and this muscle fiber atrophy in COPD seems selective for type II fibers in peripheral muscle (Caron et al., 2009; Gosker et al., 2002).

The last two decades have yielded some insight in the impairments of the processes governing muscle mass, *i.e.* protein- and myonuclear turnover, and identified putative triggers of muscle wasting in COPD. The current knowledge on the processes that govern muscle mass in relation to muscle wasting in COPD is mostly derived from (immuno)histochemical and biochemical analyses of patient muscle biopsies, and described in the first part of this review. A number of factors that may result in muscle atrophy have been implicated as potential triggers of muscle wasting in COPD. These include disuse, hypoxemia, malnutrition, inflammation, and glucocorticoids. In the second part of this review, the associative evidence between these putative triggers and muscle wasting in COPD, as well as the data derived from experimental models supporting a causal contribution of these factors to muscle wasting will be presented.

2. Regulation of muscle mass maintenance in COPD: a matter of balance

Muscle mass is determined by the net balance of muscle protein synthesis and protein breakdown with at least a supportive role of the balance between myonuclear loss and -accretion determined by apoptosis of myofiber nuclei and recruitment of myonuclei from muscle progenitor cells including satellite cells.

2.1. Muscle protein turnover in COPD

It is currently unclear whether reduced muscle protein synthesis, increased proteolysis or both are responsible for muscle atrophy in COPD. Increased protein turnover on the whole body level has been reported in COPD (Engelen et al., 2000a; Kao et al., 2011). This could reflect activation of muscle protein synthesis as a compensatory adaptation to increased muscle proteolysis in an attempt to maintain muscle mass. However, when assessing whole body protein turnover, the contribution of different compartments has to be considered. For instance, pulmonary remodeling, myelopoiesis, and hepatic production of acute phase response proteins, are all energy-demanding processes involving increased protein synthesis, which may rely on amino acids (AA) provided by increased muscle proteolysis (Pereira et al., 2005). To illustrate this, when stratified for the presence of emphysema, which is characterized by active pulmonary remodeling, muscle leucine concentrations were decreased in emphysematous compared to non-emphysematous COPD patients (Engelen et al., 2000b).

2.1.1. Muscle proteolysis regulation in COPD

Whereas the studies in which muscle protein synthesis was measured are limited in COPD (Morrison et al., 1988), none exist on direct detection of muscle protein degradation rates. This is likely the consequence of technical challenges imposed by measuring muscle proteolysis; surrogate indices however have been reported in COPD. Whole body myofibrillar protein degradation was found to be increased in underweight patients compared to controls and normal-weight patients (Rutten et al., 2006). Additional indirect evidence for increased muscle proteolysis rate was shown in emphysematous and underweight COPD patients based on increased circulatory levels of 3-methylhistidine, which is a product of myofibrillar protein breakdown (Ubhi et al., 2011). Although our knowledge of muscle protein degradation and synthesis derived from direct muscle protein turnover measurements are limited in COPD, some insights can be distilled from studies in which the regulatory cues and pathways of these processes were investigated in muscle biopsies.

Several proteolytic systems in skeletal muscle appear to be involved in the degradation of myofibrillar proteins. The ubiquitin (Ub) 26S-proteasome system (UPS) is considered a rate-limiting proteolytic system involved in muscle atrophy. Protein degradation by the UPS relies on selective conjugation of Ub molecules to substrate protein by E3 Ub-ligases. These poly-Ub chains are subsequently recognized and degraded by the 26S-proteasome. Increased levels of Ub conjugation have been demonstrated in

Please cite this article in press as: Langen RCJ, et al. Triggers and mechanisms of skeletal muscle wasting in chronic obstructive pulmonary disease. Int J Biochem Cell Biol (2013), http://dx.doi.org/10.1016/j.biocel.2013.06.015