Hypoxia and muscle maintenance regulation: implications for chronic respiratory disease

Citation for published version (APA):

de Theije, C., Costes, F., Langen, R. C., Pison, C., & Gosker, H. R. (2011). Hypoxia and muscle maintenance regulation: implications for chronic respiratory disease. *Current Opinion in Clinical Nutrition and Metabolic Care*, 14(6), 548-553. <https://doi.org/10.1097/MCO.0b013e32834b6e79>

Document status and date:

Published: 01/11/2011

DOI:

[10.1097/MCO.0b013e32834b6e79](https://doi.org/10.1097/MCO.0b013e32834b6e79)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Hypoxia and muscle maintenance regulation: implications for chronic respiratory disease

Chiel de Theije^a, Frédéric Costes^{b,c}, Ramon C. Langen^d, Christophe Pison^{e,f,g,h} and Harry R. Gosker^d

^aNutrim School for Nutrition, Toxicology and Metabolism, Department of Anatomy and Embryology, Maastricht University Medical Centre+, Maastricht, The Netherlands, ^bService de Physiologie Clinique et de l'Exercice, Hôpital Nord, CHU Saint-Etienne, ^cLaboratoire Physiologie de l'Exercice, EA4338 Université Jean Monnet, Saint-Etienne, France, ^dNutrim School for Nutrition, Toxicology and Metabolism, Department of Anatomy and Embryology, Maastricht University Medical Centre+, Maastricht, The Netherlands, ^eClinique de Pneumologie, CHU Grenoble, ^fUniversité Joseph Fourier, ^gInsermU1055, Grenoble and ^hEuropean Institute for Systems Biology & Medicine, Lyon, France

Correspondence to H.R. Gosker, Department of Respiratory Medicine, Maastricht University Medical Centre+, PO Box 616, 6200 MD Maastricht, The Netherlands
Tel: +31 43 3884247;
e-mail: h.gosker@maastrichtuniversity.nl

Current Opinion in Clinical Nutrition and Metabolic Care 2011, 14:548–553

Purpose of review

Muscle wasting and impaired muscle oxidative metabolism are common extrapulmonary features of chronic respiratory failure (CRF) that significantly increase disease burden. This review aims to address the question whether hypoxia, an obvious consequence of this disease, actually plays a causal role in these muscle impairments.

Recent findings

In experimental models, a causal role for hypoxia in muscle atrophy and metabolic impairments has clearly been shown. Although the hypoxia-inducible factors and nuclear factor kappa B are putative mediators of these hypoxia-induced alterations, their true involvement remains to be proven. Molecular signatures of disrupted regulation of muscle mass and oxidative metabolism observed in these experimental models also have been shown in muscles of patients suffering from CRF, suggestive of but not conclusive for a causal role of hypoxia. Therapies, including but not restricted to those aimed at alleviating hypoxia, have been shown to partially but not completely restore muscle mass and oxidative capacity in CRF patients, which may imply an additive effect of nutritional modulation of substrate metabolism.

Summary

Although hypoxia clearly affects skeletal muscle maintenance, it remains to be confirmed whether and by which underlying molecular mechanisms hypoxia is causally involved in CRF-related muscle atrophy and impaired oxidative capacity.

Keywords

atrophy, chronic respiratory failure, hypoxia, metabolism, skeletal muscle

Curr Opin Clin Nutr Metab Care 14:548–553
© 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins
1363-1950

Introduction

Muscle wasting is a common but often under-recognized extrapulmonary feature of chronic respiratory failure (CRF) that significantly increases disease burden. Loss of muscle mass can largely be attributed to muscle fibre atrophy, particularly of type II fibres [1,2]. In addition to the loss of muscle mass, peripheral muscles of patients with chronic obstructive pulmonary disease (COPD) often are characterized by a so-called loss of oxidative phenotype (OXPHEN); a shift from slow oxidative type I fibres towards fast glycolytic type II fibres, reduced oxidative enzyme capacities and mitochondrial impairments; for reviews, see [3,4]. In addition to increased fatigability, loss of muscle OXPHEN may contribute to elevated energy requirements (as oxidative energy metabolism is more efficient than glycolytic energy metabolism) and to enhanced oxidative stress, thereby augmenting the onset or progression of muscle wasting [5]. Hypoxemia, either chronic or intermittent, is an

obvious feature of respiratory failure, but surprisingly its potential impact on muscle maintenance in CRF patients is rather unexplored.

Molecular sensors of hypoxia

Probably, the most important regulators of cellular responses to hypoxia belong to the hypoxia inducible factor (HIF) family of transcription factors [6]. These factors are heterodimeric proteins composed of a HIF α (HIF1–3 α , of which HIF1 α is best described) and a HIF β subunit. The HIF α gene is continuously expressed, but under normoxic conditions, the protein is rapidly hydroxylated by specific prolyl hydroxylases (PHDs), enabling binding of the E3 ligase von Hippel-Lindau (VHL) leading to degradation by the ubiquitin proteasome pathway. As oxygen levels drop, so does the rate of hydroxylation, thereby allowing for the build-up of transcriptionally active HIF proteins, driving the expression of its target genes that are mainly involved in

glycolytic metabolism and angiogenesis [6]. Evidence is accumulating that the above mentioned PHDs can also modulate nuclear factor kappa B (NF- κ B) signalling [7[•],8], indicative of hypoxia-signalling independent of HIF1 α . NF- κ B is a family of proteins involved in innate immunity, inflammation and apoptosis. Its upstream regulation involves formation of an I κ B kinase complex, which through its kinase activity ultimately results in NF- κ B transcriptional activity [9]. Interestingly, evidence for crosstalk between HIF1 α and NF- κ B is also emerging [7[•],8]: although HIF1 α is primarily post transcriptionally regulated, NF- κ B has been reported to up-regulate HIF1 α gene expression and *vice versa* it has been shown that HIF activates NF- κ B signalling as well. Given these facts, a primary regulatory role of the HIF and NF- κ B signalling pathways, orchestrated by the PHDs, seems, therefore, credible in hypoxia-induced alterations in muscle maintenance.

Hypoxia and maintenance of muscle mass

It is quite evident that hypoxia leads to muscle atrophy. Observational studies in humans showed that long-term exposure to high altitude resulted in loss of limb muscle mass, which has been described as an adaptive mechanism to improve muscle oxygenation by a relatively increased capillarization [10,11]. Muscle atrophy also occurs in animals exposed to experimental hypoxia [12[•],13[•]]. The balance between protein synthesis and degradation is an important determinant of the maintenance of skeletal muscle mass. Although most experimental work on hypoxia-induced protein turnover has thus far focused on regulation of protein synthesis by hypoxia, effects on ubiquitin (Ub) 26S-proteasome-mediated protein degradation, as well as autophagy also have been described (see Fig. 1 for a schematic overview). As most of this work has been performed in nonmuscular cell types and tissues, extrapolation of these results to skeletal muscle protein turnover must be done with care.

Control of transcription can influence the rate of protein synthesis and can be regulated by transcription factors. HIFs are recognized as a key modulator of the transcriptional response during hypoxic stress and are involved in many adaptive responses including protein synthesis [14[•]]. The rate of mRNA translation is mainly controlled during the initiation phase by eukaryotic translation initiation factors (eIFs). eIF2 α is permissive to mRNA translation in the nonphosphorylated state, but blocks the initiation of protein synthesis once it becomes phosphorylated by one of the four stress kinases which are, among others, activated by hypoxia [15], oxidative and endoplasmic reticulum stress [16]. Another eIF, eIF4E, is inhibited when bound by eIF4E-binding protein 1 (4EBP1). Phosphorylation of 4EBP1 by the mammalian target of rapamycin (mTOR) results in dissociation of

Key points

- Maintenance of muscle mass and metabolism is clearly affected by hypoxia.
- The molecular mechanisms through which chronic hypoxia affects muscle maintenance are poorly understood.
- A causal role for hypoxia in muscle atrophy and impaired oxidative phenotype (OXPHEN) in chronic respiratory failure is feasible, though remains to be confirmed.
- Despite these uncertainties, therapies aimed at alleviating hypoxemia or multimodal rehabilitation strategies including nutritional modulation can, at least partially, restore muscle mass and OXPHEN in chronic respiratory failure.

eIF4E from 4EBP1 and the formation of the translation-initiation complex [17]. mTOR also activates ribosomal protein S6 kinase beta-1 (P70S6K1), which in turn, phosphorylates the ribosomal protein S6 (S6) and, thus, stimulates translation. Hypoxia reduces phosphorylation of mTOR and its downstream effectors 4EBP1 and P70S6, and, thus, inhibits protein synthesis [18]. mTOR phosphorylation itself is controlled by the tuberous sclerosis protein 1 and 2 (TSC1/TSC2) complex, which

Figure 1 Schematic overview of potential direct or indirect hypoxia signals with respect to the control of muscle protein turnover

Hypoxia-inducible factor 1 α (HIF1 α), BCL2/adenovirus E1B 19kDa protein-interacting protein 3 (BNIP3), microtubule-associated protein 1 light chain-3 (LC3), eukaryotic translation initiation factor 2 α (eIF2 α), DNA-damage-inducible transcript 4 protein (REDD1), tuberous sclerosis protein 2 (TSC2), mammalian target of rapamycin (mTOR), eIF4E-binding protein 1 (4EBP1), eukaryotic initiation factor 4E (eIF4E), ribosomal protein S6 kinase beta-1 (P70S6K1), ribosomal protein S6 (S6), AMP-activated protein kinase (AMPK), serine/threonine protein kinase AKT (AKT), Myostatin (MSTN), Forkhead box O (FOXO), nuclear factor kappa B (NF- κ B), muscle atrophy F-box (Atrogin-1), muscle-specific ring finger 1 (MuRF1).

is regulated by hypoxia-sensitive pathways, including AMP-activated protein kinase (AMPK) and DNA-damage-inducible transcript 4 protein (DDIT4/REDD1). AMPK stimulates TSC2, which in turn inactivates mTOR [19]. The degree of AMPK activation depends on the severity of the hypoxic conditions [20]. Increased REDD1 expression during hypoxia results from increased expression of the transcription factors ATF4 and C/EBP- β . Hypoxia-induced expression of ATF4 and C/EBP- β is a result of the development of endoplasmic reticulum stress and signalling via eIF2 α and does not seem to be dependent on HIF1 α [12^{*},20,21]. Subsequent REDD1 expression results in activation of TSC2, which subsequently inhibits mTOR in response to hypoxia [22].

AKT is a serine/threonine protein kinase and a key protein in the regulation of muscle mass, which controls protein synthesis via mTOR, but also regulates protein degradation. AKT activation by phosphoinositide 3-kinase (PI3K) is involved in the stimulation of myogenic differentiation by insulin growth factor-1 (IGF-1). During hypoxia, this myogenic response changes into a mitogenic response by redirection of IGF-1 signalling to mitogen-activated protein kinase (MAPK) instead of AKT activation. This finding implies that oxygen gradients may be of importance for myogenesis. It is currently unknown by which mechanisms hypoxia influences AKT phosphorylation, although HIF1 α may play a role [14^{*}].

Increased protein degradation in skeletal muscle results from increased lysosomal and/or proteasomal protein degradation. Autophagy can be initiated in response to nutritional depletion or hypoxia via activation of HIF1 α and/or endoplasmic reticulum stress via BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and microtubule-associated protein 1 light chain-3 (LC3) [23,24^{*}]. Autophagy, which captures organelles and proteins in autophagic vacuoles, relies on lysosomal protein degradation and is important in muscle maintenance [25]. Muscle protein degradation is also controlled by the ubiquitin-proteasome system (UPS). In this pathway, the E3 Ub-ligases, muscle-specific ring finger 1 (MuRF1) and muscle atrophy F-box (Atrogin-1/MAFbx), label muscle proteins with poly-ubiquitin (Ub) chains, resulting in their targeted degradation by the 26S-proteasome. The expression of both MuRF and Atrogin-1 are increased during hypoxia [26,27]. The expression of these atrogenes is regulated by inducible transcription factors like NF- κ B [28] and Forkhead box O (FOXO). FOXO1 is negatively controlled by AKT-mediated phosphorylation, which results in its nuclear export and subsequent suppression of the transcription of MuRF1 and Atrogin-1 resulting in decreased protein degradation [29,30]. However, the mechanisms by which hypoxia controls expression of these atrogenes are still unclear.

The regulation of AKT activity may be the key in regulating muscle mass during hypoxic conditions. Myostatin (MSTN) signalling is able to suppress AKT activation, which in turn decreases protein synthesis via mTOR and derepression of FOXO1-mediated atrogenes transcription [31,32]. MSTN expression is increased in muscle atrophy during hypoxic conditions in humans, rats and muscle cells [13^{*}]. Protein synthesis and degradation are regulated by complex mechanisms, which allow rapid adaptation to acute hypoxic stress. However, in response to sustained hypoxic stress, adaptive mechanisms may not be adequate in maintaining the balance in muscle protein turnover, which may culminate in muscle atrophy in chronic disease.

Hypoxia and maintenance of muscle metabolism

Literature is rather inconsistent regarding the long-term response of muscle metabolic profile to hypoxia and the underlying molecular mechanisms remain unclear. The adaptations of muscle in humans exposed to high altitude have been extensively studied and the overall consensus is that muscle adapts to high altitude hypoxia by a decrease in oxidative capacity, whereas combined with exercise training, muscle OXPHEN may even improve [6,33,34]. In addition, numerous experiments have been conducted in which rodents were exposed to chronic hypoxia and in some of these studies, a relative loss of muscle OXPHEN was indeed found, but not in others. Although yet to be confirmed, it is possible that these discrepancies were caused by differences in age as only the younger animals seemed to exhibit loss of muscle OXPHEN [35]. By using an in-vitro model in which cultured muscle cells were exposed to low oxygen levels, the mere effect of hypoxia could be studied, which revealed a hypoxia-induced downregulation of the expression of mitochondrial proteins [36]. The exact mechanisms underlying hypoxia-induced loss of muscle OXPHEN also remain largely unclear. There are a few indications that point towards involvement of HIF1 α , which as mentioned earlier, indisputably is an important enhancer of glycolytic metabolism, thus 'away from' oxidative metabolism. Muscles of patients with Chuvash polycythemia, a disease with a genetic abnormality resulting in an impaired HIF1 α degradation resulting in elevated HIF1 α levels at normal oxygen tensions, exhibited early and accelerated phosphocreatine depletion accompanied by increased acidosis and lactate accumulation during exercise, indicative of impaired muscle OXPHEN [37]. Furthermore, higher mitochondrial enzyme activities have been observed in muscles of mice lacking HIF1 α [38]. Another potential way of adjusting mitochondrial capacity to hypoxia is mitochondrial autophagy, which also requires HIF1 α [39]. In rats, HIF1 α expression levels were found to be highest in the

fast-twitch type II glycolytic muscles [40]. This study furthermore showed elevated HIF1 α levels in muscles electrically stimulated with a high frequency (inducing fast fibre type-specific genes) and reduced HIF1 α levels after low frequency stimulation (inducing slow fibre type-specific genes), stressing the role of HIF1 α in muscle OXPHEN regulation even independent of hypoxia. It is, however, unclear whether these results can be extrapolated to humans, as HIF1 α protein expression was found not to be highest in glycolytic muscles but rather in oxidative muscles [41]. The peroxisome proliferator-activated receptors (PPARs) and in particular their co-activator PGC1 α are key regulators of OXPHEN in the pre-existing and developing muscle [42^{••},43]. In-vitro studies showed that hypoxia can certainly impair components of the PPAR pathway at transcriptional and post-transcriptional level in cultured muscle cells [39], feasibly leading to loss of muscle OXPHEN. Controversially, PGC1 α has been shown to induce the expression of typical HIF1 α target genes [especially those involved in angiogenesis, like vascular endothelial growth factor (VEGF)] at physiological oxygen levels [44]. A plausible explanation for this apparent paradox might simply be the fact that PGC1 α -driven mitochondrial biogenesis leads to an increased oxygen demand, which is not (yet) matched by the oxygen supply and hence intracellular hypoxia occurs triggering HIF1 α -dependent gene expression [45]. Alternatively, as NF- κ B also has been implicated in hypoxia-signalling, it can be speculated that NF- κ B also mediates hypoxia-induced loss of muscle OXPHEN. Remels *et al.* [46] have recently shown that NF- κ B activation indeed impairs muscle OXPHEN, although it remains to be established whether this also occurs under hypoxia. Recapitulated, there are clear indications that hypoxia can impair muscle OXPHEN, but it remains to be clarified under what specific conditions and through what mechanisms this really occurs.

Implications for chronic respiratory disease

Having discussed the (potential) mechanisms through which hypoxia may impair muscle maintenance, what indications do we actually have that hypoxia is involved in muscle pathology in respiratory disease? The first probably came from Jakobsson *et al.* [47] who reported low percentages of type I fibres that were associated with low arterial oxygen pressures in COPD. Impaired muscle OXPHEN in COPD has been a consistent finding since then, but strong evidence for the involvement of hypoxia is lacking simply because this has not been further studied in groups of patients with severe hypoxemia (PaO₂ <7.3 kPa). In patients with restrictive lung disease and mild hypoxemia related to scoliosis, Swallow *et al.* [48[•]] showed that impaired muscle function was associated with a decreased proportion of type I fibres and increased oxidative stress. Pulmonary arterial hyperten-

sion is also an important cause of chronic hypoxemia and skeletal muscle abnormalities have indeed been reported in these patients as well, including decreased type I fibre proportions and slightly reduced oxidative enzymes [49]. As discussed above, the PPARs/PGC1 α are key OXPHEN regulators that may be under negative control of hypoxia. Reduced expression levels of these regulators have indeed been shown in muscles of patients with COPD [50]. Regarding muscle atrophy, there are some indications that in muscles of COPD patients, markers of the ubiquitin proteasome pathway, including the atrogenes MuRF1 and Atrogin-1, are increased [51,52]. Moreover, COPD exacerbations are frequently associated with augmented hypoxemia and fascinatingly, it has recently been shown that the gene expression of these atrogenes was upregulated, whereas OXPHEN expression was downregulated, in patients experiencing an exacerbation as compared to stable COPD patients [53[•]]. Finally, increased expression levels of MSTN have been reported for COPD patients characterized by hypoxemia [13[•]]. It is tempting to attribute all these findings to hypoxemia, but a definitive conclusion is impossible. To add to the ambiguity, the involvement of the putative hypoxia sensors HIF and NF- κ B in COPD-related muscle pathology also remains distinct: muscle HIF gene expression tended to be increased in COPD, whereas the expression of the E3 ligase VHL, which targets HIF α for degradation, was also increased [54[•]]. Increased muscle NF- κ B activation has indeed been reported in COPD patients with low body weight [55], although unaltered muscle NF- κ B activation has recently been observed in patients with muscle atrophy [52]. The influence of chronic hypoxemia was more specifically studied by Favier *et al.* [12[•]] who reported a downregulation of the anabolic AKT/mTOR pathway and a tendency towards an upregulation of its putative inhibitor REDD1 in hypoxemic *versus* normoxemic patients with COPD.

In addition to the above mentioned direct effects of hypoxia on muscle maintenance, indirect mechanisms may also be involved in COPD. Loss of appetite and subsequent cachexia is common in advanced COPD and elevated circulating levels of leptin, a hormone that indeed attenuates appetite and is induced by hypoxia through HIF1 α , have been reported for cachectic COPD patients with more severe hypoxemia [56] and for COPD patients suffering from an acute exacerbation [57]. Intriguingly, a correlation between the degree of hypoxemia and circulating tumor necrosis factor (TNF- α) in patients with COPD was observed as well [58], supportive of the occurrence of hypoxia-induced systemic inflammation [59], which in turn may contribute to muscle pathology as well.

Additional arguments in favour of a role of hypoxia in impaired muscle maintenance come from interventions

aimed at alleviating hypoxemia. Jakobsson and Jorfeldt [60] found signs of improved muscle oxidative metabolism after long-term oxygen therapy (LTOT). Lung volume reduction surgery (LVRS) represents a functional treatment for emphysema, which improves respiratory mechanics and reduces dyspnea. Mineo *et al.* [61] showed improvements in muscle mass that were maintained for at least 5 years following LVRS and were associated with improved outcomes. Interestingly, they also reported a decrease in plasmatic inflammatory markers, such as TNF- α , IL-6 and IL-8, 1 year after surgery [62^{••}], pointing towards the pre-existence of hypoxia-induced systemic inflammation. After lung transplantation, thus despite correction of hypoxemia, only partial restoration of muscle OXPHEN has been reported, suggesting a long-lasting signature of chronic hypoxia that could partially be reversed by rehabilitation [63–65]. Indeed, also therapies not (directly) aimed at alleviating hypoxemia may prove beneficial, as for example recently shown by improved muscle mass and performance in patients with CRF and cachexia after multimodal nutritional rehabilitation [66].

Conclusion

In experimental models, hypoxia evidently leads to skeletal muscle atrophy and renders muscles less dependent on oxidative energy metabolism. With respect to the latter, it is, however, still questionable whether hypoxia actually induces loss of muscle OXPHEN or merely increases anaerobic capacity. Loss of muscle mass and OXPHEN are evident in CRF and have been associated with hypoxemia and although therapies aimed at alleviating hypoxemia have in fact been shown to partially restore muscle mass and OXPHEN, a causal role for hypoxia in the muscle impairments in CRF remains to be verified. Moreover, alternative therapies, including nutritional modulation, offer perspectives on improvement of muscle maintenance in CRF.

Acknowledgements

Conflicts of interest

C.d.T., R.L. and H.G. participate within the framework of the Dutch Top Institute Pharma project T1–201. Top Institute Pharma approved the article and had no role in the study design or in the interpretation of the data. For the remaining authors, none were declared.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 649–650).

- 1 Eliason G, Abdel-Halim S, Arvidsson B, *et al.* Physical performance and muscular characteristics in different stages of COPD. *Scand J Med Sci Sports* 2008; 19:865–870.
- 2 Gosker HR, Engelen MPKJ, van Mameren H, *et al.* Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr* 2002; 76:113–119.
- 3 Gosker HR, Zeegers MP, Wouters EF, Schols AM. Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax* 2007; 62:944–949.
- 4 Rabinovich RA, Vilaro J. Structural and functional changes of peripheral muscles in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med* 2010; 16:123–133.
- 5 Schols AM, Gosker HR. The pathophysiology of cachexia in chronic obstructive pulmonary disease. *Curr Opin Support Palliat Care* 2009; 3:282–287.
- 6 Lundby C, Calbet JA, Robach P. The response of human skeletal muscle tissue to hypoxia. *Cell Mol Life Sci* 2009; 66:3615–3623.
- 7 Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med* 2011; 364:656–665.
- An excellent review on the cross-talk between hypoxia and inflammation, both hallmarks of CRF, on the cellular and whole-body level.
- 8 Taylor CT, Cummins EP. The role of NF-kappaB in hypoxia-induced gene expression. *Ann N Y Acad Sci* 2009; 1177:178–184.
- 9 Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. *Cell* 2008; 132:344–362.
- 10 Boyer SJ, Blume FD. Weight loss and changes in body composition at high altitude. *J Appl Physiol* 1984; 57:1580–1585.
- 11 Hoppeler H, Kleinert E, Schlegel C, *et al.* Morphological adaptations of human skeletal muscle to chronic hypoxia. *Int J Sports Med* 1990; 11:S3–S9.
- 12 Favier FB, Costes F, Defour A, *et al.* Downregulation of Akt/mammalian target of rapamycin pathway in skeletal muscle is associated with increased REDD1 expression in response to chronic hypoxia. *Am J Physiol Regul Integr Comp Physiol* 2010; 298:R1659–R1666.
- An elegant translational study in which the effect of hypoxia was studied in an experimental animal model as well as in hypoxemic versus nonhypoxemic COPD patients.
- 13 Hayot M, Rodriguez J, Vernus B, *et al.* Myostatin up-regulation is associated with the skeletal muscle response to hypoxic stimuli. *Mol Cell Endocrinol* 2011; 332:38–47.
- A translational study showing that hypoxia induces the atrophy factor MSTN in an experimental model, but also that the expression of this factor is indeed increased in muscles of humans suffering from a chronic respiratory disease.
- 14 Ren H, Accili D, Duan C. Hypoxia converts the myogenic action of insulin-like growth factors into mitogenic action by differentially regulating multiple signaling pathways. *Proc Natl Acad Sci U S A* 2010; 107:5857–5862.
- An in-vitro study demonstrating how myoblasts adapt to oxygen availability by promoting mitogenic or myogenic action of growth factors.
- 15 Koritzinsky M, Rouschop KM, van den Beucken T, *et al.* Phosphorylation of eIF2alpha is required for mRNA translation inhibition and survival during moderate hypoxia. *Radiother Oncol* 2007; 83:353–361.
- 16 Koumenis C, Naczki C, Koritzinsky M, *et al.* Regulation of protein synthesis by hypoxia via activation of the endoplasmic reticulum kinase PERK and phosphorylation of the translation initiation factor eIF2. *Mol Cell Biol* 2002; 22:7405–7416.
- 17 Ma XM, Blenis J. Molecular mechanisms of mTOR-mediated translational control. *Nat Rev Mol Cell Biol* 2009; 10:307–318.
- 18 Arsham AM, Howell JJ, Simon MC. A novel hypoxia-inducible factor-independent hypoxic response regulating mammalian target of rapamycin and its targets. *J Biol Chem* 2003; 278:29655–29660.
- 19 Inoki K, Zhu T, Guan K-L. TSC2 mediates cellular energy response to control cell growth and survival. *Cell* 2003; 115:577–590.
- 20 Liu L, Cash TP, Jones RG, *et al.* Hypoxia-induced energy stress regulates mRNA translation and cell growth. *Mol Cell* 2006; 21:521–531.
- 21 Jin H-O, Seo S-K, Woo S-H, *et al.* Activating transcription factor 4 and CCAAT/enhancer-binding protein-beta negatively regulate the mammalian target of rapamycin via Redd1 expression in response to oxidative and endoplasmic reticulum stress. *Free Rad Biol Med* 2009; 46:1158–1167.
- 22 DeYoung MP, Horak P, Sofer A, *et al.* Hypoxia regulates TSC1/2-mTOR signaling and tumor suppression through REDD1-mediated 14-3-3 shuttling. *Genes Dev* 2008; 22:239–251.
- 23 Bellot G, Garcia-Medina R, Gounon P, *et al.* Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. *Mol Cell Biol* 2009; 29:2570–2581.
- 24 Rouschop KMA, Beucken TVD, Dubois L, *et al.* The unfolded protein response protects human tumor cells during hypoxia through regulation of the autophagy genes MAP1LC3B and ATG5. *Cancer* 2010; 120:127–141.
- An extensive in-vitro study showing the role of the unfolded protein response in regulating autophagy during hypoxia.

- 25 Sandri M. Autophagy in skeletal muscle. *FEBS Lett* 2010; 584:1411–1416.
- 26 Cannata DJ, Ireland Z, Dickinson H, *et al.* Maternal creatine supplementation from mid-pregnancy protects the diaphragm of the newborn spiny mouse from intrapartum hypoxia-induced damage. *Pediatr Res* 2010; 68:393–398.
- 27 Razeghi P, Baskin KK, Sharma S, *et al.* Atrophy, hypertrophy, and hypoxemia induce transcriptional regulators of the ubiquitin proteasome system in the rat heart. *Biochem Biophys Res Commun* 2006; 342:361–364.
- 28 Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. *J Mol Med* 2008; 86:1113–1126.
- 29 Stitt TN, Drujan D, Clarke BA, *et al.* The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. *Mol Cell* 2004; 14:395–403.
- 30 Yoshida T, Semprun-Prieto L, Sukhanov S, Delafontaine P. IGF-1 prevents ANG II-induced skeletal muscle atrophy via Akt- and Foxo-dependent inhibition of the ubiquitin ligase atrogin-1 expression. *Am J Physiol Heart Circ Physiol* 2010; 298:H1565–H1570.
- 31 Sartori R, Milan G, Patron M, *et al.* Smad2 and 3 transcription factors control muscle mass in adulthood. *Am J Physiol Cell Physiol* 2009; 296:C1248–C1257.
- 32 Trendelenburg AU, Meyer A, Rohner D, *et al.* Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. *Am J Physiol Cell Physiol* 2009; 296:C1258–C1270.
- 33 Flueck M. Plasticity of the muscle proteome to exercise at altitude. *High Alt Med Biol* 2009; 10:183–193.
- 34 Murray AJ. Metabolic adaptation of skeletal muscle to high altitude hypoxia: how new technologies could resolve the controversies. *Genome Med* 2009; 1:117.
- 35 Gosker HR, Schols AM. Muscle metabolic modulation by chronic hypoxia. *J Proteome Res* 2007; 6:3400–3401.
- 36 Vijayasathya C, Damle S, Prabu SK, *et al.* Adaptive changes in the expression of nuclear and mitochondrial encoded subunits of cytochrome c oxidase and the catalytic activity during hypoxia. *Eur J Biochem* 2003; 270:871–879.
- 37 Formenti F, Constantin-Teodosiu D, Emmanuel Y, *et al.* Regulation of human metabolism by hypoxia-inducible factor. *Proc Natl Acad Sci U S A* 2010; 107:12722–12727.
- 38 Mason SD, Howlett RA, Kim MJ, *et al.* Loss of skeletal muscle HIF-1alpha results in altered exercise endurance. *PLoS Biol* 2004; 2:e288.
- 39 Regnault TR, Zhao L, Chiu JS, *et al.* Peroxisome proliferator-activated receptor -beta/delta, -gamma agonists and resveratrol modulate hypoxia induced changes in nuclear receptor activators of muscle oxidative metabolism. *PPAR Res* 2010; 2010:129173.
- 40 Lunde IG, Anton SL, Bruusgaard JC, *et al.* Hypoxia inducible factor 1(alpha) links fast-patterned muscle activity and fast muscle phenotype in rats. *J Physiol* 2011; 589:1443–1454.
- 41 Mounier R, Pedersen BK, Plomgaard P. Muscle-specific expression of hypoxia-inducible factor in human skeletal muscle. *Exp Physiol* 2010; 95:899–907.
- 42 Remels AH, Gosker HR, Schrauwen P, *et al.* Peroxisome proliferator-activated receptors: a therapeutic target in COPD? *Eur Respir J* 2008; 31:502–508. An outstanding translational study in COPD patients demonstrating how inflammation through the NF- κ B pathway impairs the oxidative phenotype.
- 43 Remels AH, Langen RC, Schrauwen P, *et al.* Regulation of mitochondrial biogenesis during myogenesis. *Mol Cell Endocrinol* 2010; 315:113–120.
- 44 Shoja J, Arany Z. Regulation of hypoxia-inducible genes by PGC-1 alpha. *Arterioscler Thromb Vasc Biol* 2010; 30:662–666.
- 45 O'Hagan KA, Cocchiiglia S, Zhdanov AV, *et al.* PGC-1alpha is coupled to HIF-1alpha-dependent gene expression by increasing mitochondrial oxygen consumption in skeletal muscle cells. *Proc Natl Acad Sci U S A* 2009; 106:2188–2193.
- 46 Remels AH, Gosker HR, Schrauwen P, *et al.* TNF-alpha impairs regulation of muscle oxidative phenotype: implications for cachexia? *FASEB J* 2010; 24:5052–5062.
- 47 Jakobsson P, Jorfeldt L, Brundin A. Skeletal muscle metabolites and fibre types in patients with advanced chronic obstructive pulmonary disease (COPD), with and without chronic respiratory failure. *Eur Respir J* 1990; 3:192–196.
- 48 Swallow EB, Barreiro E, Gosker H, *et al.* Quadriceps muscle strength in scoliosis. *Eur Respir J* 2009; 34:1429–1435. A comparative study showing that muscle abnormalities can be found in other respiratory diseases than COPD as well.
- 49 Mainguy V, Maltais F, Saey D, *et al.* Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. *Thorax* 2010; 65:113–117.
- 50 Remels AH, Schrauwen P, Broekhuizen R, *et al.* Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur Respir J* 2007; 30:245–252.
- 51 Doucet M, Russell AP, Leger B, *et al.* Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007; 176:261–269.
- 52 Plant PJ, Brooks D, Faughnan M, *et al.* Cellular markers of muscle atrophy in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 2010; 42:461–471.
- 53 Crul T, Testelmans D, Spruit MA, *et al.* Gene expression profiling in vastus lateralis muscle during an acute exacerbation of COPD. *Cell Physiol Biochem* 2010; 25:491–500. This study shows that impaired muscle maintenance is augmented during acute exacerbations in COPD, pointing towards the need to focus more on this active phase of the disease from a muscular perspective as well.
- 54 Jatta K, Eliason G, Portela-Gomes GM, *et al.* Overexpression of von Hippel-Lindau protein in skeletal muscles of patients with chronic obstructive pulmonary disease. *J Clin Pathol* 2009; 62:70–76. Although it seems to be a very obvious aspect to study, this is to our knowledge the first report on muscular HIF signalling in COPD.
- 55 Agusti A, Morla M, Saulea J, *et al.* NF-kappaB activation and iNOS upregulation in skeletal muscle of patients with COPD and low body weight. *Thorax* 2004; 59:483–487.
- 56 Takabatake N, Nakamura H, Minamihaba O, *et al.* A novel pathophysiologic phenomenon in cachectic patients with chronic obstructive pulmonary disease: the relationship between the circadian rhythm of circulating leptin and the very low-frequency component of heart rate variability. *Am J Respir Crit Care Med* 2001; 163:1314–1319.
- 57 Creutzberg EC, Wouters EF, Vanderhoven-Augustin IM, *et al.* Disturbances in leptin metabolism are related to energy imbalance during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162:1239–1245.
- 58 Takabatake N, Nakamura H, Abe S, *et al.* The relationship between chronic hypoxemia and activation of the tumor necrosis factor-alpha system in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 161:1179–1184.
- 59 Taylor CT. Interdependent roles for hypoxia inducible factor and nuclear factor-kappaB in hypoxic inflammation. *J Physiol* 2008; 586:4055–4059.
- 60 Jakobsson P, Jorfeldt L. Long-term oxygen therapy may improve skeletal muscle metabolism in advanced chronic obstructive pulmonary disease patients with chronic hypoxaemia. *Respir Med* 1995; 89:471–476.
- 61 Mineo D, Ambrogio V, Lauriola V, *et al.* Recovery of body composition improves long-term outcomes after lung volume reduction surgery for emphysema. *Eur Respir J* 2010; 36:408–416.
- 62 Mineo D, Ambrogio V, Cufari ME, *et al.* Variations of inflammatory mediators and alpha1-antitrypsin levels after lung volume reduction surgery for emphysema. *Am J Respir Crit Care Med* 2010; 181:806–814. This large prospective study confirms the association between the gain in muscle mass and the decrease in circulating cytokines secondary to improved respiratory mechanics.
- 63 Evans AB, Al Himyary AJ, Hrovat MI, *et al.* Abnormal skeletal muscle oxidative capacity after lung transplantation by ^{31}P -MRS. *Am J Respir Crit Care Med* 1997; 155:615–621.
- 64 Guerrero K, Wuyam B, Mezin P, *et al.* Functional coupling of adenine nucleotide translocase and mitochondrial creatine kinase is enhanced after exercise training in lung transplant skeletal muscle. *Am J Physiol Regul Integr Comp Physiol* 2005; 289:R1144–R1154.
- 65 Wang XN, Williams TJ, McKenna MJ, *et al.* Skeletal muscle oxidative capacity, fiber type, and metabolites after lung transplantation. *Am J Respir Crit Care Med* 1999; 160:57–63.
- 66 Pison CM, Cano NJ, Cherion C, *et al.* Multimodal nutritional rehabilitation improves clinical outcomes of malnourished patients with chronic respiratory failure: a randomised controlled trial. *Thorax* 2011. [Epub ahead of print]. <http://thorax.bmj.com/content/early/2011/06/23/thx.2010.154922>.