



Editorial

Epigenetics and Susceptibility to Muscle Wasting in COPD[☆]



Epigenética y propensión a la atrofia muscular en la EPOC

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Loss of muscle mass is a common co-morbidity in COPD patients; it impacts their quality of life and is associated with increased mortality. Consequently, understanding the mechanisms that drive muscle atrophy associated with COPD is important in order to develop therapies to improve the length and quality of patient life.

Muscle mass is maintained by balancing the processes that synthesise new muscle growth (protein synthesis and satellite cell activation and recruitment [regeneration]) with those that breakdown muscle (proteolysis, autophagy and apoptosis). Excessive proteolysis or reduced regeneration have been suggested to cause muscle loss in COPD, and both are likely to contribute. For example, myofibrillar breakdown has been shown to be greater in cachectic patients compared with non-cachectic patients.¹ Similarly, 2 studies show decreased centralised nuclei in the muscle of patients with a low fat free mass index (FFMI) indicating reduced muscle regeneration compared to those with a normal FFMI.^{2,3} However, understanding the relative importance of these mechanisms is complicated, because loss of muscle mass is only loosely associated with lung disease severity, and FFMI can be low in some patients with mild disease, but normal in others with severe lung impairment. Understanding the factors that lead to this variation will help to clarify the processes that contribute to muscle wasting in COPD and identify the patients most at risk.

Epigenetics (processes that affect gene expression and thereby phenotype without changing genotype) have been suggested to be an important link between the environment and disease susceptibility, as exemplified by the foetal origins of adult disease hypothesis.⁴ Epigenetic mechanisms include microRNAs (miRNAs) that promote mRNA degradation and/or inhibit translation, as well as DNA methylation and histone acetylation, which regulate transcription (reviewed in [5]). These mechanisms have significant cross-talk, whereby miRNAs regulate the expression of histone-modifying proteins or DNA methylases, and miRNA

expression is regulated by histone modification and DNA methylation.

Interestingly, poor foetal growth is a risk factor for sarcopenia.⁶ Babies born small for their gestational age are more likely to become sarcopenic than those with normal birth weight. It is, therefore, conceivable that disease-associated epigenetic differences that are either inherited or established during development or in response to the environment can contribute to susceptibility for muscle loss.

Two environmental factors that contribute to muscle phenotype in COPD are physical inactivity and smoking. Numerous studies have shown changes in the expression of miRNAs associated with muscle development in response to exercise (reviewed in [7]) and smoking history is associated with miR-1 expression, a microRNA that contributes to muscle regeneration. Furthermore, the effects of both smoking and exercise modify DNA methylation, and these changes also contribute to muscle development. For example, demethylation of the MyoD promoter leads to expression of this myogenic transcription factor and initiation of the myogenic differentiation programme. Moreover, polymorphisms leading to hypomethylation of DNA are more prevalent in elite athletes.

Epigenetic Studies in COPD

The most widely studied miRNA in the skeletal muscle of COPD patients is miR-1, an miRNA that is highly enriched in skeletal muscle and targets the histone deacetylase HDAC4. Interestingly, findings regarding the relative expression of both miR-1 and HDAC4 in the muscle of COPD patients differ widely, but their relationship has been shown to be reciprocal. We showed reduced miR-1 expression in COPD patients compared to controls and increased HDAC4 protein,⁸ whereas Puig-Vilanova et al. showed increased miR-1 and reduced HDAC4 accompanied by increased histone acetylation in the patients.⁹ Such opposing results are difficult to explain, but may arise from differences in patient population or controls, or from methodological considerations. For example, in our study the controls were predominantly never-smokers, whereas in Puig-Vilanova et al. they were predominantly current and ex-smokers. Another potential variable is biopsy timing relative to any activity, as miR-1 has been shown to be elevated by acute activity.⁷ This response to activity may make the long-term

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consequences of inter-individual variations in miR-1 difficult to identify.

Imprinted miRNAs have also been implicated in muscle atrophy in COPD patients, and could be better markers of susceptibility to muscle wasting.² Imprinted genes are expressed from either the maternal or paternal chromosome, with the other chromosome being silenced by DNA methylation. Paternally expressed genes are normally associated with promoting growth (e.g. IGF-2), whereas maternally expressed genes are associated with limiting growth (e.g. IGF2R). Our recent study found that paternally expressed miRNAs from a cluster on chromosome 19 (C19MC) were reduced in male patients with a low FFMI, whereas the maternally imprinted miR-675 was increased in these patients. As C19MC miRNAs promote stem cell pluripotency and miR-675 inhibits myoblast proliferation and promotes differentiation, the balance between these miRNAs may show the regeneration capacity of the individual. Consistent with the role of DNA methylation in this process, expression of H19, the lncRNA that encodes miR-675, was inversely associated with FFMI and methylation of the imprinting control region (ICR) that regulates the H19 locus. Methylation of the H19 ICR was also greater in weak patients compared to those with retained strength. These imprinted miRNAs did not associate with either FFMI or strength in normal healthy elderly individuals, and this suggests that regenerative capacity can become limited in the presence of disease, and that this capacity is determined by epigenetics to a measurable extent.

The data, therefore, suggest that muscle wasting occurs in response to disease-related stress, perhaps as an evolved response to use muscle protein as a source of amino acids for the damaged organ or inflammatory system. However, the extent of wasting

depends not only on the severity of the stress, but also on the ability of the individual to respond by regenerating tissue. This latter response is in part dependent on the epigenetic make-up of the individual, although identification of the pathways involved and the contribution of epigenetic variation to the stress response itself require further investigation. The data suggest that COPD patients who were born small for their gestational age will be more susceptible to muscle wasting.

References

1. Rutten EP, Franssen FM, Engelen MP, Wouters EF, Deutz NE, Schols AM. Greater whole-body myofibrillar protein breakdown in cachectic patients with chronic obstructive pulmonary disease. *Am J Clin Nutr.* 2006;83:829–34.
2. Lewis A, Lee JY, Donaldson AV, Nataneek SA, Vaidyanathan S, Man WD, et al. Increased expression of H19/miR-675 is associated with a low fat free mass index in patients with COPD. *J Cachexia Sarcopenia Muscle.* 2016;7:330–44.
3. Theriault ME, Pare ME, Maltais F, Debigare R. Satellite cells senescence in limb muscle of severe patients with COPD. *PLoS One.* 2012;7:e39124.
4. Fernandez-Twinn DS, Constanca M, Ozanne SE. Intergenerational epigenetic inheritance in models of developmental programming of adult disease. *Semin Cell Dev Biol.* 2015;43:85–95.
5. Barreiro E, Sznajder JI. Epigenetic regulation of muscle phenotype and adaptation: a potential role in COPD muscle dysfunction. *J Appl Physiol.* 1985;2013;114:1263–72.
6. Sayer AA, Syddall HE, Gilbody HJ, Dennison EM, Cooper C. Does sarcopenia originate in early life? Findings from the Hertfordshire cohort study. *J Gerontol A Biol Sci Med Sci.* 2004;59:M930–4.
7. Zacharewicz E, Lamon S, Russell AP. MicroRNAs in skeletal muscle and their regulation with exercise, ageing, and disease. *Front Physiol.* 2013;4:266.
8. Lewis A, Riddoch-Contreras J, Nataneek SA, Donaldson A, Man WD, Moxham J, et al. Downregulation of the serum response factor/miR-1 axis in the quadriceps of patients with COPD. *Thorax.* 2012;67:26–34.
9. Puig-Vilanova E, Martinez-Llorens J, Ausin P, Roca J, Gea J, Barreiro E. Quadriceps muscle weakness and atrophy are associated with a differential epigenetic profile in advanced COPD. *Clin Sci (Lond).* 2015;128:905–21.