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EDITORIAL

SKELETAL MUSCLE DYSFUNCTION IN COPD: NOVELTIES IN THE LAST DECADE

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Skeletal muscle dysfunction, characterized by impaired strength and/or endurance properties of muscles, is a relevant systemic manifestation in patients with chronic cardiac and respiratory conditions such as chronic obstructive pulmonary disease (COPD). Muscle dysfunction negatively affects exercise capacity in the patients, thus diminishing their quality of life. Furthermore, muscle dysfunction and wasting of the lower limbs has been shown to predict disease morbidity and mortality regardless of the airway obstruction[1-3]. Several factors and biological mechanisms are involved in the multifactorial etiology of muscle dysfunction in COPD[4]. Interestingly, while both respiratory and peripheral muscles are disturbed in the patients, the latter are usually more severely affected and have been the matter of abundant research in the last two decades. Besides, current evidence has also shown that several cellular and molecular events are differentially expressed in the respiratory and limb muscles of patients with COPD. The current editorial aims to provide an overview of the most relevant biological mechanisms that have been shown so far to participate in the pathophysiology of the lower limb muscle dysfunction in patients with COPD.

In the last two decades several advances have been developed in the identification of the biological mechanisms that underlie muscle dysfunction in COPD. Elucidation of the most relevant contributing mechanisms in this condition will help design therapeutic strategies that will alleviate muscle mass loss and dysfunction in patients with COPD. A rise in oxidative stress as measured by protein oxidation levels has been repeatedly demonstrated in the limb muscles of patients with COPD[4]. Moreover, oxidative stress markers were also shown to inversely correlate with clinical parameters such as exercise capacity, body composition, and quadriceps strength among patients with COPD[5]. These results suggest that oxidative events may hamper muscle function through the induction of alterations of key cellular processes involved in muscle contraction. Indeed, the content of several specific muscle proteins such as creatine kinase and myosin heavy chain was reduced in the vastus lateralis of patients with severe COPD and muscle wasting, while a rise in their levels of oxidation was detected in the same proteins[5-7]. Systemic levels of oxidative stress have also been demonstrated in patients with COPD[7-8].

Several markers of the ubiquitin-proteasome system were consistently upregulated in the lower limb muscles of COPD patients[4,6,7]. Moreover, the number of autophagosomes and the expression of other autophagy markers were also increased in the vastus lateralis of patients with severe COPD and muscle mass loss[4,7,9]. Importantly, several redox signaling cellular pathways such as nuclear factor (NF)-κB and forkhead box (FoxO)1 and FoxO3 are likely to mediate the loss of muscle mass in patients with severe COPD and cachexia[6,7]. Increased levels of terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL)-positive nuclei were also seen in the vastus lateralis of severe COPD patients with normal body composition, whereas levels of ultrastructural apoptosis were low and did not differ in the muscles of the patients from those detected in the healthy controls[4,10].

Epigenetic control of cells, defined as the process whereby gene expression is regulated by heritable mechanisms that do not affect DNA sequence, has recently emerged as a potential biological mechanism that may regulate muscle function and mass in COPD. The epigenetic modifications identified so far in cells are the following: 1) DNA methylation, 2) histone acetylation, 3) histone methylation, and 4) non-coding RNAs such as microRNAs. The epigenetic events modify gene transcription in different ways. For instance, DNA methylation at the 5 position of cytosine specifically reduces gene expression. Acetylation is a transient, enzymatically controlled biochemical process, and the commonest posttranslational modification of histones. Acetylation, a process mediated by histone acetyltransferases (HTA), results in a rather open chromatin structure that is transcriptionally active, while deacetylation through the action of histone deacetylases (HDAC) blocks transcription. Additionally, methylation of histones may activate or repress gene transcription depending on the proteins recruited to the chromatin.

Evaluation of the expression of microRNAs has recently gained much attention in the study of the etiology of respiratory diseases. MicroRNAs, encoded by eukaryotic nuclear DNA, are non-coding single-stranded RNA molecules (18-24 nucleotides) that function in the post-transcriptional regulation of gene expression. Interestingly, they exert their action via base-pairing with complementary sequences in mRNA molecules that result in gene silencing via translational repression or target degradation. MicroRNAs may have different mRNA targets and a given mRNA may also be targeted by multiple microRNAs. MicroRNAs regulate many physiological cellular processes and may play a significant role in the pathogenesis of several lung diseases including lung cancer and COPD.

Recently, several investigations have focused on the analyses of epigenetic modifications in the muscles of COPD patients. As such, in patients with mild COPD, miR-1 expression was increased and positively correlated with the airway obstruction and quadriceps force[11]. Importantly, the expression of miR-1, miR-206, and miR-27a, levels of lysine-acetylated proteins and histones, and acetylated histone 3 were increased in the quadriceps of COPD patients, especially in those with muscle weakness and wasting, while expression of HDAC3, HDAC4, and sirtuin-1 were reduced[12]. In other experiments, levels of miR-1 levels were lower, while those of HDAC4 were greater in the vastus lateralis of COPD patients with preserved body composition[13]. Furthermore, levels of the transcription factor Yin Yang (YY)1, which modifies histones, inversely correlated with the size of slow- and fast-twitch fibers in the limb muscles of COPD patients with normal body composition[14]. Interestingly, systemic levels of muscle-specific microRNAs were also upregulated in patients with severe COPD and normal body composition[15]. In summary, several epigenetic events that are differentially expressed in the limb muscles of COPD patients with and without muscle mass loss may counterbalance the underlying mechanisms that deteriorate their muscle mass and function.

Future research is still required in order to identify additional mechanisms that may also underlie the etiology of skeletal muscle dysfunction in patients with COPD. We are in the need to identify new cellular and molecular mechanisms that can be specifically targeted using pharmacological strategies and/or exercise training modalities to prevent skeletal muscle from undergoing further functional deterioration and wasting.

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