REVIEW ARTICLE

Epigenetics and muscle dysfunction in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease and a major leading cause of morbidity and mortality worldwide. In COPD, comorbidities, acute exacerbations, and systemic manifestations negatively influence disease severity and progression regardless of the respiratory condition. Skeletal muscle dysfunction, which is one of the commonest systemic manifestations in patients with COPD, has a tremendous impact on their exercise capacity and quality of life. Several pathophysiological and molecular underlying mechanisms including epigenetics (the process whereby gene expression is regulated by heritable mechanisms that do not affect DNA sequence) have been shown to participate in the etiology of COPD muscle dysfunction. The epigenetic modifications identified so far in cells include DNA methylation, histone acetylation and methylation, and noncoding RNAs such as microRNAs. Herein, we first review the role of epigenetic mechanisms in muscle development and adaptation to environmental factors in several models. Moreover, the epigenetic events reported so far to be potentially involved in muscle dysfunction and mass loss of patients with COPD are also discussed. Furthermore, the different expression profile of several muscle-enriched microRNAs in the diaphragm and vastus lateralis muscles of patients with COPD are also reviewed from results recently obtained in our group. The role of protein hyperacetylation in enhanced muscle protein catabolism of limb muscles is also discussed. Future research should focus on the full elucidation of the triggers of epigenetic mechanisms and their specific downstream biological pathways in COPD muscle dysfunction and wasting. (Translational Research 2014;■:1–12)

Abbreviations: ■■ = ■■■

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease and a major leading cause of morbidity and mortality worldwide.[1] COPD is characterized by persistent progressive airflow limitation together with an enhanced chronic inflammatory response to noxious particles or gases, usually inhaled cigarette smoke, in the airways and lungs of the patients. Most of these patients very often have concomitant diseases known as comorbidities, which significantly impair their quality of life. Acute exacerbations are also common in patients with COPD. They have a substantial impact on the patients' quality of life, especially because of the reported loss of muscle mass and bone mineral density after hospital discharge for COPD acute exacerbations.[1-3] Moreover, besides respiratory symptoms, the function of other organs such as bones, the cardiovascular system, and skeletal muscles may also be altered in COPD. Taken together, comorbidities, acute exacerbations, and systemic manifestations negatively influence disease severity and progression regardless of the respiratory condition in COPD.[1-3] Skeletal muscle dysfunction, which is one of the commonest systemic manifestations in patients with COPD, has a tremendous impact on their exercise capacity. Several cellular and molecular mechanisms have been shown to underlie the etiology of COPD muscle dysfunction. In the last few years, the role of epigenetics has also emerged as a relevant mechanism potentially involved in muscle mass maintenance and performance in several models including COPD.[4,5] Specifically, the present article encompasses several sections in which the following topics have been reviewed: skeletal muscle dysfunction in COPD, types of epigenetic mechanisms, epigenetic regulation of muscle development and adaptation, the presence of epigenetic events in muscles and blood in COPD, and the differential expression profile of epigenetic mechanisms in respiratory and limb muscles of COPD patients with different disease severity.

Skeletal muscle dysfunction in COPD. COPD is a highly prevalent condition that imposes a significant economic burden worldwide as a consequence of acute exacerbations and comorbidities. In patients with COPD, skeletal muscle dysfunction is a common systemic manifestation that affects both respiratory and limb muscles,[6] resulting in a significant impairment of their quality of life. Quadriceps muscle dysfunction appears in one-third of the patients, even at very early stages of the disease when severe airway obstruction has not yet developed.[7] Additionally, quadriceps weakness, defined as reduced muscle strength, and lower muscle mass as measured by mid-thigh cross-sectional area were also shown to be good predictors of COPD mortality.[8,9] Skeletal muscle dysfunction in patients with COPD is characterized by reduced muscle strength and endurance, probably because of the interaction of different systemic and local factors, which act through different biological mechanisms (Fig 1).

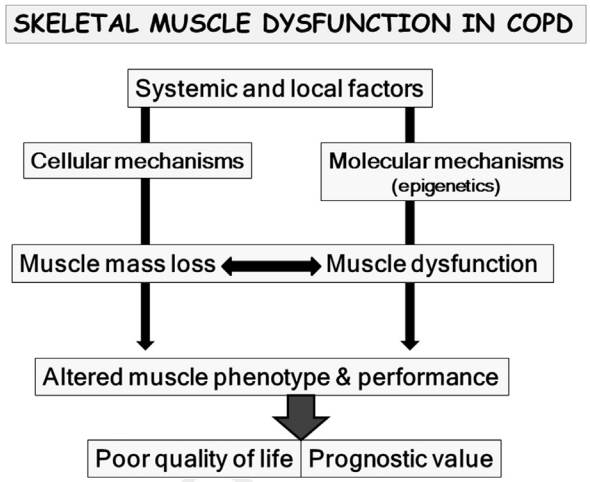

Fig 1. Schematic representation of skeletal muscle dysfunction in patients with COPD. Systemic and local factors through the action of biological (cellular and molecular) mechanisms including epigenetics underlie the etiology of muscle dysfunction and muscle mass loss in COPD. In this context, muscle phenotype and performance of the muscles will impair in the patients. Muscle mass and function loss, which negatively influence exercise tolerance and quality of life in the patients, are prognostic factors in COPD, because they predict survival. COPD, chronic obstructive pulmonary disease.

Skeletal muscle dysfunction in COPD is also highly dependent on the specific function of the muscle.[10] In this regard, in patients with severe COPD, the mechanical loads imposed by the respiratory system, which modify the resting length of the diaphragm, play a major role in their respiratory muscle dysfunction. Additionally, biological and structural factors are also involved in the pathophysiology of respiratory muscle dysfunction in patients with COPD, although to a lesser extent to their recognized effects on the lower limb muscles.[10,11] In general, lower limb muscles are more adversely affected than inspiratory muscles, probably because of disuse or deconditioning.[12] As the limb muscles do not have to contract at a specific length, biological and structural factors are the main players of peripheral muscle dysfunction in patients with COPD (Fig 1). For instance, the vastus lateralis muscle of patients with severe COPD consistently exhibits a slow-to-fast fiber-type switch.[10,13,14] Atrophy of fast-twitch fibers has also been reported in the peripheral muscles of patients with severe COPD with nutritional abnormalities and significant muscle wasting.[14]

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