Molecular mechanisms mediating development of pulmonary cachexia in COPD

av

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Abstract


Cigarette smoking (CS) represents the main causative agent underlying development and progress of COPD. Recently, involvement of CS in the pathogenesis of COPD-associated muscle abnormalities is becoming increasingly evident. Nevertheless, involved triggers and underlying mechanisms remain largely unknown. This study was conceived in order to examine effects of cigarette smoke exposure on skeletal muscle morphology, vascular supply and function. For this purpose, we have specifically designed murine COPD/emphysema model and gastrocnemius muscle was examined, while in-vitro experiments were conducted using murine C2C12 skeletal muscle myocytes.

In addition to the mild emphysematous changes present in the lungs of CS-exposed mice, our results demonstrated evident signs of muscle atrophy reflected by decreased fiber cross-sectional area, profound fiber size variation and reduced body mass. Furthermore, we have observed impairment in terminal myogenesis and lower number of myonuclei in skeletal muscles of CS-exposed animals despite evident activation of muscle repair process. Additionally, our results demonstrate capillary rarefaction in skeletal muscles of CS-exposed animals which was associated with deregulation of hypoxia-angiogenesis signaling, reduced levels of angiogenic factors such as HIF1-α and VEGF and enhanced expression of VHL and its partner proteins PHD2 and Ube2D1. The results of our in-vitro experiments demonstrated that VHL and its ubiquitination machinery can be synergistically regulated by TNF and hypoxia consequentially impairing angiogenic potential of skeletal muscle myocytes. Finally, we have shown that CS elicits chronic ER stress in murine skeletal muscles which is associated with activation of ERAD and apoptotic pathways as mirrored by elevated expression of Usp19, caspase 12 and caspase 3 in skeletal muscles of CS-exposed animals. Moreover, molecular and morphological alterations in CS-exposed mice resulted in impairment of muscle function as reflected by their impaired exercise capacity.

Taken together, from our results it is evident that cigarette smoke exposure elicits set of morphological, vascular and functional changes highly resembling those observed in COPD. Additionally, CS induces wide range of molecular alterations and signaling pathway deregulations suggesting profound effects of cigarette smoke exposure on skeletal muscle cell homeostasis.

Keywords: COPD, cachexia, atrophy, cigarette smoke, myogenesis, angiogenesis

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