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Mechanisms of VCP/p97 and Proteasomal Pathway in COPD Pathogenesis

ABSTRACT

Cigarette smoking induces oxidative stress and unfolded protein response (UPR), and is the major risk factor for emphysema and COPD (chronic obstructive pulmonary disease) pathophysiology, although it is not clear why only few smokers develop COPD or why some non-smokers have COPD. We identified that protein levels of AAA (ATPase associated with diverse cellular activities) molecular chaperone and UPR modulator, p97/VCP (Valosin containing protein) and proteasomal subunits correlates with severity of COPD using lung tissues from patients with FEV1% predicted of >80 (mild), 50-80% (moderate) and <50% (severe).

The goal of this grant is to dissect the mechanisms of VCP-mediated protein processing and proteasomal pathways in COPD and emphysema. The primary hypothesis of this proposal is that VCP regulates UPR, proteasomal activity, and oxidative stress, and is a critical mediator of COPD pathogenesis. A secondary hypothesis is that selective interference of VCP's ERAD function or modulating proteasomal pathway will not only bypass protein-aggregation and uncontrolled UPR but also rescue the other components associated with the pathophysiology of COPD.

Specific Aim 1 will determine if VCP and proteasomal pathways play a key role in COPD disease pathogenesis. The correlation of VCP proteolytic subunit expression to proteolytic activities, apoptosis, and oxidative stress and inflammatory markers in control and COPD subjects will help us evaluate if VCP and proteasomal pathways have a critical UPR modifier function in COPD lung disease. We anticipate elucidating the role of VCP and proteasomal pathways in COPD disease pathogenesis. Specific Aim 2 will evaluate if other components of VCP protein-complex are critical for COPD disease pathogenesis. We aim to evaluate the physiological role of VCP associated ubiquitin ligases in COPD by correlating there expression and severity of lung disease to proteolytic activities, apoptosis and inflammatory markers (Aim 1). We anticipate identifying the mechanism(s) of VCP and proteasomal pathways in pathogenesis of chronic obstructive lung disease.