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CLUSTERIN INHIBITION BY AL AMYLOIDOSIS LIGHT CHAIN PROTEINS AND HUMAN MICROVASCULAR PROTECTION BY CLUSTERIN/APOLIPOPROTEIN A1 COMPLEX

ACC Moderated Poster Contributions
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AL amyloidosis light chain proteins (LC) induce endothelial dysfunction (ED) and apoptotic injury. Recently, clusterin (CLU), a chaperone apolipoprotein involved in amyloid removal and cell survival, was shown to be abnormally produced in AL. We hypothesized that LC inhibit CLU production in human aortic endothelial cells (HAEC) and cotreatment of clusterin-apolipoprotein AI (CLU-ApoA1) protects against LC ED.

Methods: HAECs were treated with LC (20 µg/mLx24 hrs) and CLU (Western blotting) and mRNA (PCR) were measured. Ex-vivo human abdominal adipose arterioles from 22 subjects without AL were cannulated and dilator response to acetylcholine and papaverine were measured at baseline and post-1 hour of LC±purified CLU (300 ng/ml)-ApoA1 (1 µg/ml). Arteriole NO was measured using DAF-2 fluorescence.

Results: LC reduced precursor+secreted CLU protein (Fig. A) while causing 2.45±0.3-fold reduction ($p<0.001$) in CLU transcription in HAEC. Arteriole dilator response to acetylcholine/papaverine was impaired post-LC but restored by CLU-ApoA1 (Fig. B). LC reduced arteriole NO at 30 minutes vs. vehicle (0.99±0.2 vs. 1.38±0.01x baseline, $p<0.05$) but cotreatment with CLU/ApoA1 restored NO (1.39±0.2x).

Conclusions: LC reduce clusterin in HAEC and induce endothelial and non-endothelial dysfunction in human adipose arterioles. CLU-ApoA1 restores microvascular function likely through enhanced NO production. This is a novel pathway of injury and presents a potential new therapeutic target in AL.