Serum sIL-6Ra Predicts Impairments in Cutaneous Nitric Oxide-Dependent Vasodilation in Humans.

1Kutz, J., 2Cannon, J., 1Kenney, W.L., FACSM, 1Alexander-Holowatz, L., FACSM. 1The Pennsylvania State University, University Park, PA, 2School of Allied Health Sciences, Medical College of Georgia, Augusta, GA.

jlk5268@psu.edu, jcannon@georgiahealth.edu, w7k@psu.edu, lma191@psu.edu

Purpose: Interleukin-6 (IL-6) contributes to atherosclerotic plaque development and plaque destabilization by promoting inflammation. Soluble IL-6 receptors (sIL-6R) are capable of stimulating a variety of cellular responses through trans-signaling including activation of inflammatory processes inducing endothelial dysfunction in the vasculature. The aim of the present study was to determine if sIL-6Ra was related to impairments in nitric oxide (NO)-dependent cutaneous vasodilation in humans across a broad range of serum low-density lipoprotein (LDL) concentrations.

Methods: In 19 men and women, with a broad range of serum LDL concentrations (LDL: 75-233 mg/dl), skin blood flow (SkBF) was measured by laser-Doppler flowmetry during a standardized local heating protocol (42°C) to induce eNOS-dependent vasodilation. After full expression of SkBF during sustained local heating, NO-dependent vasodilation was quantified by perfusion of the NOS inhibitor L-NAME. All data were normalized as a percentage of maximum cutaneous vascular conductance (%CVC$_{max}$ = laser-Doppler flux/ mean arterial pressure: 28mM sodium nitroprusside). Serum samples were analyzed for the inflammatory cytokines IL-6, sIL-6Ra and TNFα using a customized cytometric bead assay. Results: NO-dependent vasodilation ranged from 22 to 82 %CVC$_{max}$ and sIL-6Ra values were measured from 13.8 to 31.6 ng/ml. NO-dependent vasodilation was negatively related to sIL-6Ra (R$^2$ = 0.368, p= 0.006) and to serum LDL concentrations (R$^2$ = 0.328, p= 0.01). IL-6 and TNFα were not related to NO-dependent vasodilation. Stepwise regression revealed that sIL-6Ra was the best predictor of NO-dependent vasodilation. Conclusion: Both sIL-6Ra and low-density lipoproteins are independently associated with impairments in cutaneous microvascular function. Research funded by NIH Grant HL-089302-05.