Racial Differences in Circulating csRAGE and Alternatively Spliced esRAGE in Healthy Adolescents: Relation with Aortic Stiffness

[1]Ericka Tank, [1]Lauren Wegman-Points, [3]Mohana Pajaniappan, [3]Katherine Darracott, [1,2]Gary L. Pierce

[1]Department of Health and Human Physiology and [2]Fraternal Order of Eagles Diabetes Research Center, University of Iowa, Iowa City, IA, USA; [3]Georgia Prevention Institute, Department of Pediatrics, Georgia Health Science University, Augusta, GA, USA

Background: Binding of ligands to the receptor for advanced glycation end products (RAGE) triggers pro-inflammatory/oxidant signaling in the vascular wall. Increased circulating soluble forms of RAGE (sRAGE) are associated with decreased vascular risk and may be protective by acting as a decoy to prevent ligand binding to full-length RAGE. Sheddases, such as matrix metalloproteinase-9 (MMP 9) proteolytically cleave cell surface receptors including RAGE, forming cleaved soluble RAGE (csRAGE). However, sRAGE also includes endogenous secretory RAGE (esRAGE), an isoform of RAGE without receptor function derived from alternative splicing of RAGE pre-mRNA. sRAGE is lower in African-American (AA) compared with Caucasian adults and is hypothesized to contribute to elevated arterial stiffening and vascular risk in AAs. Indeed, we have previously demonstrated that sRAGE (1567±68.9 vs. 955±101.1 pg/mL, $p<0.001$) but not MMP9 is higher in Caucasian compared with AA adolescents and associated with lower carotid-femoral pulse wave velocity (CFPWV) (5.3±0.2 vs. 5.9±0.2 m/sec, $p<0.05$).

Objectives: We hypothesized that increased sRAGE in Caucasian versus AA adolescents is from increased circulating esRAGE through alternative splicing of RAGE pre-mRNA.

Methods and Results: Circulating esRAGE (ELISA) was significantly higher (369±24.8 vs. 242±26.5 pg/mL, $P<0.01$) in Caucasian (n=24, age 16.5±0.3 yrs; BMI 22.9±0.8 kg/m^2) vs. AA (n=15, age 16.8±0.3 yrs; BMI 24.5±1.0 kg/m^2) adolescents ($P>0.05$). esRAGE was correlated with sRAGE ($r=0.708$, $P<0.001$), but esRAGE:sRAGE ratio did not differ between race (0.24±0.01 vs. 0.33±0.09, $p>0.05$). Preliminary data in pooled Caucasian (n=3) human umbilical vein endothelial cells (HUVECs) demonstrates greater esRAGE mRNA (qRT-PCR) than AA HUVECs, but similar full-length RAGE mRNA.

Conclusion: These preliminary data suggest that higher sRAGE in Caucasian compared with AA adolescents is likely not from higher esRAGE but a combination of cleavage from non-MMP9 sheddases and alternative splicing of RAGE.