Exogenous RAGE Inhibitor Attenuates Particulate Matter Induced Airway Hyperreactivity

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RATIONALE Metabolic Syndrome (MetSyn), is a cardiovascular disease risk. MetSyn phenotypic characteristics are predictors of World Trade Center-Lung Injury (WTC-LI) and airway hyperreactivity (AHR) in FDNY WTC-particulate matter (WTC-PM) exposed 1st responders. Our earlier studies show that after a single particulate matter (PM) exposure changes are seen after both 24-hours and many persist even after 1-Month. Specific remodeling included fibrotic changes (collagen deposition and increased expression of alpha-smooth muscle actin [α-SMA]), oxidative stress, advanced glycation end-product (AGE) receptor (AGER also known as RAGE) induction, distinct metabolite profiles and vascular changes. In contrast, Ager deficient (Ager$^{-/-}$) mice are protected from acute and chronic PM effects. Therefore, in light of these findings we investigated if pretreatment with receptor for AGE (RAGE) inhibitor recapitulated the phenotype seen in Ager$^{-/-}$. METHODS Murine Model. C57Bl/6 wild type (WT) mice (Jackson Lab, ME) (n=5/group) were pretreated with a single dose of FPS-ZM1 (Sigma), 1.5 mg/kg via intraperitoneal injection, a commercially available RAGE inhibitor, (dissolved in DMSO and further diluted with PBS) 1-hour before WTC-PM (100 µg) was oropharyngeally aspirated. Control treatment consisted of equal volumes of DMSO diluted with PBS. Methacholine challenge performed (Flexivent; Scireq). Histology. Lung sections (5 µm) were stained with Periodic Acid Schiff (PAS) (Abcam, MA) to evaluate mucous. Immunostaining also performed with primary antibodies for RAGE, α-SMA and DAPI (Santa Cruz Biotechnology, CA). RESULTS Our current study using FPS-ZM1, recapitulated the protective effects of Ager deficiency in regards to the development of AHR, 24-hours after WTC-PM exposure, Figure 1A. There was PAS-stained material (mucin) in the airway epithelial cells indicating mucus production. Interestingly, FPS-ZM1 inhibited mucus production after WTC-PM exposure, Figure 1B-E. RAGE and α-SMA, a marker of activated fibroblasts, collagen formation and impaired vascular contractility were reduced with FPS-ZM1, Figure 1H-I when compared to controls, Figure 1F-G. CONCLUSIONS. Our preliminary work shows that the commercially available RAGE inhibitor FPS-ZM1 is similarly protective of some of the deleterious effects of particulate matter inhalation. Specifically, airway hyperreactivity, mucus production and expression of pro-collagen markers are mitigated after pretreatment with FPS-ZM1. Future studies will focus on later time points and furthering our understanding of mechanisms related to RAGE inhibition.

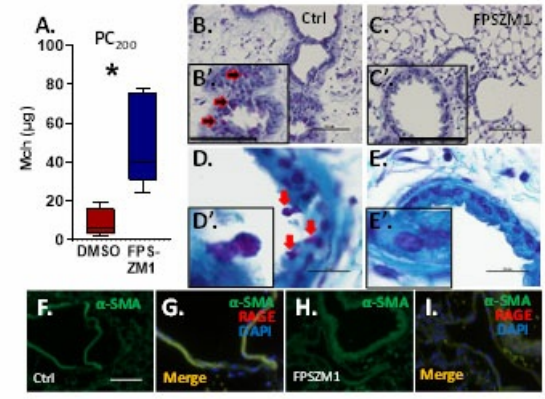

Figure 1. RAGE Inhibition Attenuates the Effects of PM Exposure. A. PC$_{200}$ *p<0.05. **Mucin PAS Staining B/D.** Ctrl (PM). **C/E.** PM+FPS-ZM1. **C'** Reduced PAS after FPS-ZM1 (**B'**) Numerous PAS stained cells (red outlined black arrows). **D-E.** PAS-stained (100x) **D'.** Magenta stained goblet cells releasing granules (red arrows). **E'.** Intact goblet cells. **F-G. Immunoexpression of α-SMA (green) & RAGE (red). F-G.** CTRL's and **H-I.** FPS-ZM1. **G/I.** α-SMA/RAGE/DAPI merge. Nuclei-DAPI (blue). Scale 500 µm.

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