COVID-19 and PM Exposure: Identifying and Mitigating the Synergistic Deleterious Effects

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RATIONALE Coronavirus Disease-2019(COVID-19), caused by the severe acute respiratory syndrome coronavirus-2(SARS-CoV-2), causes multi-organ failure and death. Metabolic syndrome(MetSyn) characteristics are also risks for COVID-19. The Receptor for Advanced Glycation End-Products(RAGE) is a MetSyn mediator. SARS-CoV via its Spike protein binds ACE2 as its 1°-receptor, and may activate TLR2. Particulate matter(PM) similarly activates an innate immune response, partially via the RAGE receptor, and increases ACE2 expression. Excessive hyaluronan(HA) levels are found in lungs of COVID-19 patients. Reducing HA synthesis and stabilizing the HA shield surrounding cells may be therapeutic. A HA-binding peptide, P15-1, is anti-inflammatory and reduces HA. HA and its binding proteins may provide a link explaining synergistic ACE2 and RAGE signaling, reducing interaction of receptors with their ligands and ultimately inflammation-related changes in peripheral blood mononuclear cells(PBMCs), the severity of which correlate with patient outcome after SARS-CoV-2 exposure. Our focus is to develop novel therapeutic strategies for SARS-CoV-2 inflammation. To begin to explore our HYPOTHESIS that COVID-19 Spike protein and PM co-exposure synergistically induces an inflammatory phenotype and that phenotype can be mitigated by stabilizing the pericellular HA matrix and by inhibiting RAGE. METHODS. We performed in vitro exposure of PBMCs isolated from 9/11 World Trade Center(WTC) 1st-Responders to i. Media alone(MA); ii. WTC PM; iii. SARS-CoV-2 Spike RBD(C19); iv. C19 and PM; v. C19 and P15-1; vi. C19, PM and P15-1 vii. C19, PM and RAGE inhibitor($RAGE_{Inh}$) FPS-ZM1; viii. LPS(positive control). Total mRNA levels for Cox-2, IL-1β, IL-6 and MMP-13 24 hours after exposure were analyzed by real time PCR. Comparisons by Student’s t- and Mann-Whitney U-tests. Correlations by Spearman’s. Significance $p<0.05$. RESULTS COX-2, IL-1β, IL-6 and MMP-13 mRNA levels were significantly increased 24-hrs after the administration of PM and C19. Co-exposure to PM and C19 yielded a synergistic increase in the mRNA of IL-β, Figure 1B. P15-1 and RAGE inhibition significantly reduced mRNA levels of inflammatory markers in primary PBMCs exposed to C19, WTC PM, or a combination of the two, Figure 1. CONCLUSIONS Our work focuses on mitigating the COVID-19 inflammatory phenotype by stabilizing the pericellular HA matrix and by inhibiting RAGE. Preliminary data presented in this abstract will be further explored using PBMCs and cell lines in a multidisciplinary approach.

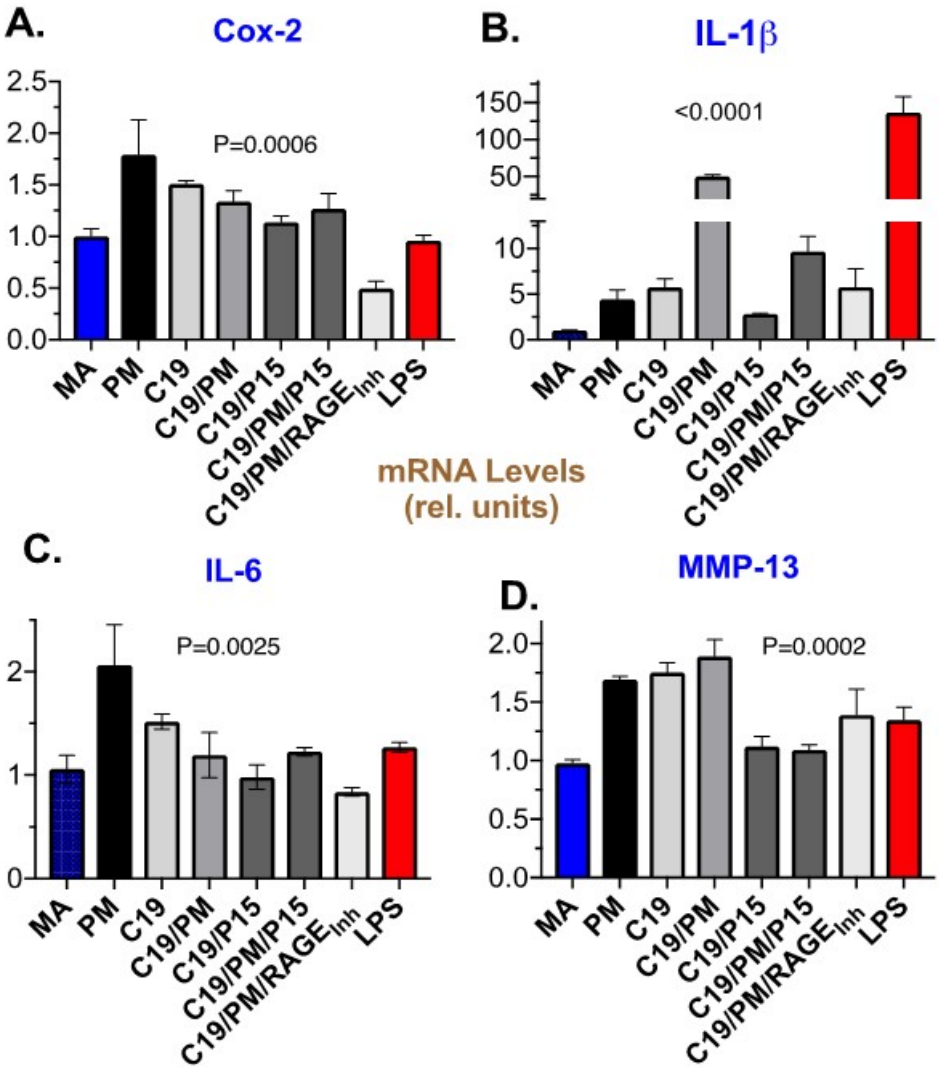

Figure 1: A. COX-2 B.IL-1b C.IL-6 D. MMP-13. All Mean (SD), presented P values are by one-way-ANOVA. Cells plated at $1x10^6$ cells/mL; p15=4.25ug; C19=250ug; RAGE=500uM; PM=100ug

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