Long-term aspirin therapy as a predictor of decreased susceptibility to SARS-CoV-2 infection in aspirin-exacerbated respiratory disease

Aspirin-exacerbated respiratory disease (AERD) is characterized by the presence of asthma, chronic rhinosinusitis with nasal polyposis (CRwNP), and acute respiratory reactions induced by aspirin and other cyclooxygenase-1 inhibitors.

Aspirin desensitization followed by daily aspirin use is an effective treatment for aspirin-exacerbated respiratory disease (AERD). Aspirin-treated patients with AERD were observed not to contract severe acute respiratory syndrome coronavirus clade 2 (SARS-CoV-2) or develop coronavirus disease-19 (COVID19). There is pressing urgency to understand the pathogenesis of the SARS-CoV-2, which causes the disease COVID-19. SARS-CoV-2 spike (S) protein binds angiotensin-converting enzyme 2 (ACE2), and in concert with host proteases, principally transmembrane serine protease 2 (TMPRSS2), promotes cellular entry. *ACE2* and *TMPRSS2* were co-expressed at the epithelial sites of the lung and sputum cells, whereas CD147 (*BSG*) and CD26 (*DPP4*) were expressed both in epithelial and immune cells. Several human studies reported *ISG* upregulation in *ACE2*-expressing cells. Upregulation of *ACE2* in bronchial cells treated with either type I or type II interferon was also observed.

We aim to determine whether treatment with aspirin, which inhibits cyclooxygenase-1 enzyme, can serve as a predictor of decreased susceptibility to SARS-CoV-2 infection and COVID-19 in patients with AERD. We also attempt to assess genetic features that might predict or attenuate SARS-CoV-2 infection on high-dose aspirin therapy. We are going to evaluate the gene expression for interferons, known SARS-CoV-2 receptors, and other transcriptomes of the 96 genes in sputum and nasal cells as well as to assess the association between this expression and long-term high-dose aspirin therapy in patients with AERD.

We hypothesized that long-term high-dose aspirin therapy leads to decreased gene expression for the *ACE2* receptor and interferon-stimulated gene (*ISG*) in sputum and nasal cells in patients with AERD. Such effects were previously reported for inhaled corticosteroids (ICSs) in asthma. We speculated that aspirin causes even lower expression of *ACE2, TMPRSS2,* CD147 (*BSG*), and CD26 (*DPP4*) genes in sputum and nasal cells in AERD. Moreover, we assumed that aspirin might influence the expression of interferons α1 (*IFNA1*), β1 (*IFNB1),* γ (*IFNG),* as well as λ1 and λ2 (*IFNL1* and *IFNL2)*. Our preliminary research showed differences in sputum gene expression between healthy controls (n=13) and AERD patients (n=26) before aspirin desensitization followed by aspirin therapy.