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Early View

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Peter AB Wark, Prabuddha S. Pathinayake, Mathew Suji Eapen, Sukhwinder Singh Sohal

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Asthma, COPD and SARS-CoV-2 infection (COVID-19): potential mechanistic insights

Peter AB Wark[1,2], Prabuddha S. Pathinayake[1], Mathew Suji Eapen[3], Sukhwinder Singh Sohal[3#]

[1]Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute and School of Medicine and Public Health, University of Newcastle, Newcastle, NSW, Australia.

[2]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, NSW, Australia.

[3]Respiratory Translational Research Group, Department of Laboratory Medicine, School of Health Sciences, College of Health and Medicine, University of Tasmania, Launceston, TAS, Australia.

#Corresponding author

Dr Sukhwinder Singh Sohal

Respiratory Translational Research Group

Department of Laboratory Medicine, School of Health Sciences,

College of Health and Medicine, University of Tasmania

Locked Bag – 1322, Newnham Drive

Launceston, Tasmania 7248, Australia

Telephone number: +61 3 6324 5434

Email: **sssohal@utas.edu.au**

We read with interest, the manuscripts (1, 2) and the accompanying editorial (3) describing the risk of severe disease and infection with SARS-CoV-2 and asthma, but are struck by the difference seen with risk of complications from asthma and COVID-19 compared to the experience during the 2009 influenza pandemic, where people with asthma were clearly at heightened risk, at least of hospitalisation (4). In contrast those who smoke or with COPD, appear at greater risk. Observational studies will never be able to provide evidence of cause and effect and a greater understanding of the mechanisms of susceptibility to infection with SARS-CoV-2 is also required. Hence, we would like to take this further and enhance discussion on potential mechanisms (figure 1).

SARS-CoV-2 shows a strong affinity towards the human angiotensin-converting enzyme 2 (ACE2) receptor through their densely glycosylated spike (S) protein, which forms the initiation step for the virus attachment and subsequent entry into the human cells (5). The virus binds to the ACE2 receptor and requires the transmembrane serine protease 2 (TMPRSS2) to cleave the viral spike protein in order to enter a cell (5). This step appears to be facilitated by endosomal proteases such as Cathepsin- L (CTL) and enhanced by the Furin protein, while ADAM- 17, may promote uptake of SARS- CoV-2 (6).

In asthma we found reduced expression of ACE2 in the lower airways of people with asthma, both in terms of protein and gene expression (7). We also found in asthma that Furin expression was lower and ADAM-17 expression elevated. This provides a potential mechanism by which chronic type 2 airway inflammation through the effect of IL- 13 on the airway epithelium could increase ADAM-17, resulting in shedding and downregulation ACE2 expression prior to infection. An important and unanswered question is whether different asthma phenotypes may harbour different risks or whether through control of type 2 airway inflammation, such as with the use of biologics that ACE2 expression is increased and any advantage seen in asthma is then lost. This may in part explain the increased risk seen in those with more severe asthma or using biologics.

In contrast to asthma tobacco smoking and, more recently, vaping possesses toxic irritants and may enhance the risk of developing more severe COVID-19. Our recently published study identified that both smokers and COPD patients had upregulated expression of ACE2 on small airway epithelium, type II pneumocytes, and alveolar macrophages (8). We further reported a

concomitant rise in endocytic vacuoles, including early and late endosomes EEA1, RAB7 and lysosomal associated membrane protein-1 (LAMP-1) in the same tissue areas where ACE2 was expressed (8). We also identified CTL's increased expression, an endo-lysosomal protease that facilitates viral S protein membrane fusion in a low pH environment, usually found during increased lysosomal activity. Such mechanisms could also be active in patients with asthma, but this requires further investigations. When we compared endobronchial biopsies from patients with COPD to asthmatics there was reduced ACE2 levels in the bronchial epithelium of patients with asthma (7). It is quite possible that low levels of ACE2 in asthmatics could be due to inhaled corticosteroid use and lack of smoking in these patients. The study by Izquierdo et al also suggested that inhaled corticosteroid may be associated with a protective effect against SARS-CoV-2 infection.

The role of lung inflammation is critical to the viral infection and cytokine release syndrome is a significant morbidity associated with COVID-19 patients. The increase in IL-6 has been particularly called into question. In our previous observations, the bronchoalveolar lavage from patients with COPD had increased levels of Th2/M2 cytokines such as IL-6, CCL22, IL-4, IL-13, and IL-10 while Th1/M1 cytokines IL-12 and IFN-γ were suppressed (9). Similar to asthma, as mentioned above, IL-13 levels also increase in COPD, but the literature do not report any protective effects of that on ACE2 levels, if that works through ADAM17. Although ADAM17 deficiency have been suggested to protect against emphysema (10). Compared to asthmatics, these observations indicate smokers and COPD patients are primed for SARS-CoV-2 infection with favourable infectious cytokine profile which may respond in different ways given the disease in question.

Taking together we believe that patients with asthma are somewhat protected to SARS-CoV-2 infection, which may partly be due to decrease in ACE2 levels as we reported. This could be because of type 2 inflammation or a protective effect from low to medium dose inhaled or oral corticosteroid . At the same time asthmatics do seems to be slightly more at risk of developing COVID-19 as indicated by studies from Choi and Izquierdo but this may be confounded by factors of age and sex as shown in our asthma study (7). Compared to asthmatics, smokers and patients with COPD certainly have higher levels of ACE2. The underlying inflammatory cytokine profile in lung conditions is quite important to understand as that may dictate the

pathogenesis of disease or be protective. It will be highly beneficial and worth exploring mechanisms which allow such as patients with asthma to stay relatively protective against COVID-19 and how environmental factors, older age and other comorbidities further exaggerate such insidious infections. As rightly mentioned by Eger et al in the accompanying editorial that it is hard to draw any firm conclusions from both the studies as several factors may influence the reported incidences. Hence, understanding biological mechanisms behind such observations will have important public health benefits not only for COVID-19 but also for any future pandemics. COVID-19 is a dress rehearsal for the next pandemic and the one after.

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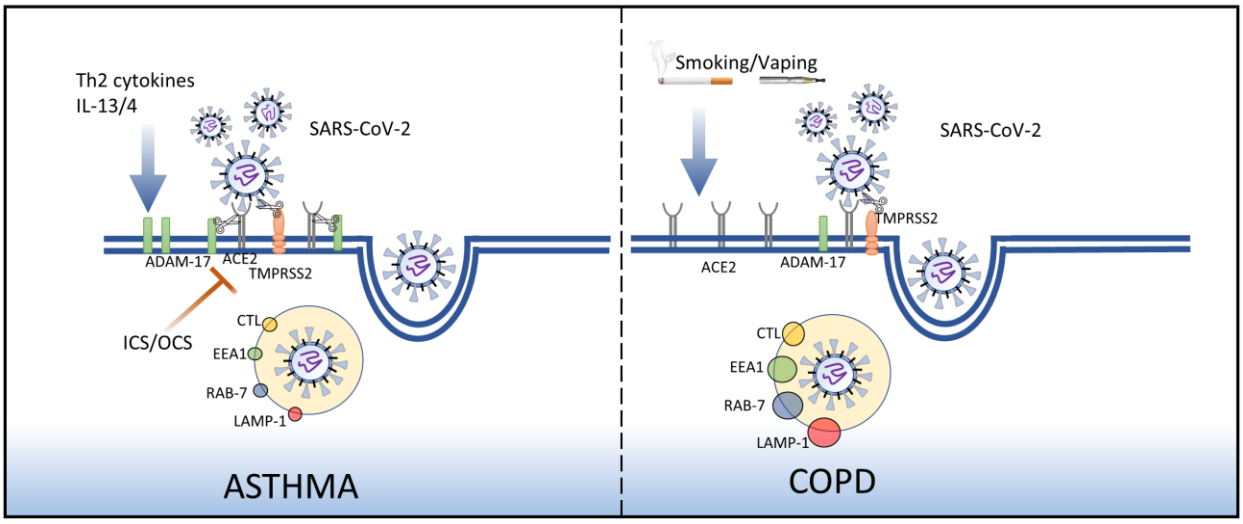
Figure 1: Cellular mechanisms of SARS-CoV-2 infection in Asthma and COPD. Smoking and vaping exposure upregulates ACE2 expression in airway epithelium while inhale corticosteroids (ICS) and oral corticosteroids (OCS) reduce ACE2 expression in asthma compared to COPD. Once SARS-CoV-2 binds to ACE2 receptor via spike protein, serine protease TMPRSS2 cleave viral spike protein facilitating viral uptake and internalization by endocytosis. Endosome and lysosome associated proteins EEA1, RAB7, LAMP1 and CTL that facilitate viral replication within the host cell are abundant in COPD epithelium. Th2 cytokines (IL-13) upregulate ADAM-17 expression in asthmatic epithelium resulting ACE2 shedding prior to infection.


Th2 cytokines
IL-13/4
SARS-CoV-2
ADAM-17
ACE2
TMPRSS2
ICS/OCS
CTL
EEA1
RAB-7
LAMP-1
ASTHMA
Smoking/Vaping
SARS-CoV-2
TMPRSS2
ACE2
ADAM-17
CTL
EEA1
RAB-7
LAMP-1
COPD