Official Journal of the Asian Pacific Society of Respirology
Respirology

EDITORIAL

Gateway to the lungs: Viral entry receptors and susceptibility to COVID-19

Key words: angiotensin-converting enzyme 2, ACE2, coronavirus disease, COVID-19, SARS-CoV-2, viral infection.

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2 is a rapidly spreading infectious syndrome that causes a spectrum of clinical manifestations. Advanced age and male gender are now well recognized to be major risk factors for COVID-19 mortality.[1] Whether certain chronic respiratory comorbidities such as asthma also predispose to altered risk remain controversial. Initial reports suggested that the prevalence of asthmatic subjects in hospitalized COVID-19 cases was not increased compared to the general population[2,3] with no clear evidence of increased severity or mortality observed in a meta-analysis of published studies[4] However, larger epidemiological studies within the large OPENSAFELY and ISARIC cohorts report the converse finding that asthma is associated with increased risk of severe disease.[5,6]

The mechanisms that govern differential risk of COVID-19 severity are poorly understood; a greater understanding of these mechanisms could identify novel therapeutic targets and drive development of more effective therapies to reduce mortality. SARS-CoV-2 utilizes the viral entry receptor angiotensin-converting enzyme 2 (ACE2), with priming of the serine protease transmembrane serine protease 2 (TMPRSS2) to gain entry into the respiratory tract. A range of other putative receptors and proteases have also been proposed and one plausible hypothesis is that altered expression of some of these factors within the respiratory tract may modify the risk of virus acquisition and consequent susceptibility to severe disease. Conducting translational science to interrogate these hypothesized mechanisms has been challenging due to difficulties in recruiting prospective participants with understandable reluctance to attend research settings for sampling during pandemic restrictions. As such, interrogation of existing biobanks of primary airway samples from healthy controls and subjects with potential risk factors provides an invaluable and pragmatic alternative approach.

In a recent publication in *Respirology*, Wark *et al.* evaluate the expression of selected factors postulated to play a role in SARS-CoV-2 infection in primary bronchial epithelial cells from 145 donors.[7] These include various proposed cell-binding sites for SARS-CoV-2 (ACE2, CD147, HSPA5 and GRP78) and other proteins thought to facilitate cell entry (TMPRSS2, CTL, furin, TMPRSS11A/D, ADAM-10, ADAM-17 and PI4KB). The authors study a relatively large number of subjects within two independent cohorts and the inclusion of a broad set of putative genes is commendable. Moreover, the authors importantly corroborate their mRNA findings at the protein level using immunohistochemical analyses in bronchial biopsies. Their findings indicate increased ACE2 expression with advanced age and male gender, associations that were significant even after multivariable analysis for a range of other putative risk factors. The association with age was, however, noted by the authors to be weak (Pearson's rho 0.2, $P = 0.02$). Given the magnitude of increased risk with advanced age,[1] a modest change in ACE2 expression seems unlikely to be the sole driver of increased susceptibility in this group, although it may be contributory.

In asthmatic subjects, the authors identify reduced bronchial expression of ACE2 and furin and increased ADAM-17 with no differences in the other genes assessed. This attenuation in ACE2 is consistent with some[8] but not all previous studies[9,10] and may be due to immune changes that affect ACE2 (e.g. negative regulation by interleukin (IL)-13[11]) or confounding variables such as the use of inhaled corticosteroid which, although not independently associated with altered ACE2 in the current study, has recently been shown to downregulate ACE2 when directly administered in human epithelial cells and animal models.[12] The authors hypothesize that increased expression of ADAM-17 may provide the mechanism for ACE2 downregulation, as ADAM-17 mediates ACE2 shedding from the cell surface. However, ADAM-17-mediated ACE2 cleavage facilitates SARS-Co-V infection[13] and ADAM-17 also cleaves pro-inflammatory mediators such as tumour necrosis factor (TNF),[14] which have been implicated in the hyperinflammatory response characteristic of severe COVID-19. It is also important to note that recent studies have convincingly described a novel truncated isoform of ACE2 (designated as dACE2), which is highly expressed in respiratory cells and is inducible by interferons and viruses,[15] and may also be differentially expressed in certain disease groups. The quantitative polymerase chain reaction (qPCR) assays employed in the current study will not discriminate this isoform from others and future studies should focus more closely on specific isoforms of functional importance.

Further work is also needed to delineate whether differential ACE2 expression and consequent risk may be ascribed to different asthma endotypes (e.g. type 2 high asthma, neutrophilic asthma and so on). ACE2 downregulation in asthma could theoretically be a protective factor by reducing viral entry but alternatively could predispose to severe disease as animal studies suggest that ACE2 functionally prevents the development of

doi: 10.1111/resp.14039

acute lung injury in sepsis models.[16] Studies following the original SARS outbreak found that SARS-CoV-1 binding leads to reduced ACE2 expression,[17] which may contribute to pathophysiology in more severe infection.

The study by Wark *et al*. furthers our understanding of the respiratory expression of viral entry receptors in clinical risk groups and stimulates a number of further questions to be addressed, as discussed above. Future studies are now needed to disentangle the complex roles played by ACE2 and other putative viral entry factors in governing the risk of SARS-CoV-2 infection in individuals at higher clinical risk of mortality from COVID-19.

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Disclosure statement: A.S. has received honoraria for speaking from Astra Zeneca.

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