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EDITORIAL COMMENT

In the Age of COVID

Genomic Changes Over the Lifespan Help Explain Severe SARS-CoV-2 Disease*

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Angiotensin-converting enzyme 2 (ACE2), a metalloprotease functioning in vasoactive peptide cleavage, was characterized as the entry receptor for the first severe acute respiratory syndrome-coronavirus-2 (SARS-CoV) in 2003. It has since been implicated in the entry of the causative agent of the current pandemic, SARS-CoV-2. Along with ACE2, the serine protease TMPRSS2 was found to be needed for viral entry into host cells. With that elucidated, potentially effective therapeutic approaches for viral entry inhibition could be investigated.

Because additional receptor interactions have been implicated in host cell invasion by previous coronaviruses, other receptors have been investigated for their potential role in SARS-CoV-2 infection. Basigin (CD147) is one of the putative receptors being investigated. This receptor has some positive evidence for its role in this infection (1), even though some may disagree (2). This lack of consensus notwithstanding, a clinical trial is in place using an anti-CD147 antibody, meplazumab, with some promising results (3). Previous studies have also implicated peptidylprolyl isomerase A (PPIA) and peptidylprolyl isomerase B (PPIB) in SARS-CoV infections (4), creating interest in exploration of their role in SARS-CoV-2 infections.

Increasing age is a significant comorbidity for severe COVID-19 outcomes, including adverse thrombotic events. The study by Ahmetaj-Shala et al. (5) in this issue of *JACC: Basic to Translational Science* addresses this question by carefully piecing together data from a wide variety of sources. Specifically, the investigators accessed gene expression data from close to 1,000 individuals to come to their conclusions, making their results more robust and applicable to the clinical picture of COVID than previous efforts.

Ahmetaj-Shala et al. (5) compiled data from a large number of individuals from the Genotype-Tissue Expression project, which seeks to provide expression data to the widest possible array of scientists for study. Combining data from up to 779 separate people per sample type, the investigators analyzed tissue expression in both the cardiac tissues, such as aorta, coronary artery, whole blood, and heart, as well as the kidney, lung, colon, and spleen. Genes of interest include 9 of those implicated in SARS-CoV-2 disease such as *ACE2*, *TMPRSS2*, *BSG*, *PPIA*, and *PPIB*.

The potential entry gene *BSG* was found to be in higher abundance in cardiorenal tissues than in the lung, though it was well-expressed in all tissues examined. This is in contrast to *ACE2*, which was found to be expressed at low levels in lung, but higher levels in cardiorenal tissues (kidney, heart, and blood vessels) across the individuals examined. Genes responsible for processing viral spike protein or ACE2 to allow for viral entry, *ADAM17* and *FURIN*, were found to be high in lung tissue. Taken together, this could explain the higher levels of viral replication in

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lung tissue for SARS-CoV-2, even if the receptor itself is not highly expressed.

TMPRSS2 was expressed highly in the lung, with good expression also seen in the colon and kidney, but with low levels in cardiovascular tissues. This indicates that *TMPRSS2* may not be playing a large role in damage seen in the vascular and cardiac tissues during infection. *BSG*, *PPIA*, and *PPIB* were all found to be expressed more highly in vessels, potentially implicating them in vascular damage in lieu of TMPRSS2 availability in those regions.

Next, Ahmetaj-Shala et al. (5) investigated the expression of these genes in immune cells (peripheral blood mononuclear cells [PBMCs]) and endothelial cells, with respiratory tissues broken into regions. *BSG* shows a pattern of high expression in endothelial cells and PBMCs, with lower levels in airway epithelial cells. *ACE2* shows a somewhat reversed pattern, with higher levels in nasal epithelium and lower in bronchial cells, endothelial cells, and PBMCs. *ADAM17* is highly expressed in PBMCs, with *FURIN* being expressed well in respiratory epithelium but very high in endothelial cells and high in PBMCs. *PPIA* and *PPIB* are expressed very high in endothelial cells relative to their expression in the other cell types. This suggests a mechanism by which SARS-CoV-2 could infect non-respiratory tissues if non-ACE2/TMPRSS2 pathways play a role.

Next, the investigators explored how these genes changed with respect to age in these individuals. Individuals were categorized as under 40 years of age or 40 years of age and above. *ACE2* expression decreased linearly with age in arterial tissue and was decreased in colon and blood, but was not differentially expressed in heart or kidney. This adds to a prior study that found decreased expression of *ACE2* in the airways of children, indicating a bell curve of expression over a lifetime (6). *ACE* was also reduced in the nasal epithelium in the over 40 years of age category. By contrast, *BSG* expression increased with age in endothelial cells. Males also had an increased expression of *BSG*, *PPIA*, and *PPIB* in endothelial cells, and higher levels of ACE2 and TMPRSS2 in the coronary artery. This may help explain the higher mortality seen in male patients.

The BSG/PPIA(B) pathway, and its differential expression, if it does play a role in SARS-CoV-2 infection, provides a potential mechanism by which infection affects cardiovascular function, rather than this infection being one confined solely to the airways. This study highlights that the typical ACE2/TMPRSS2 receptor expression does not positively correlate to increased risk of severe COVID-19 disease. More work must be done to elucidate the likely multitude of reasons why this is not the case, though *BSG* may be a part of that puzzle.

Future studies should also examine the effect that active, as well as prior, infection has on expression levels of genes of interest. SARS-CoV infection down-regulates *ACE2* expression during infection, leading to speculation that this occurs in SARS-CoV-2 infection as well, which should be confirmed experimentally. Likewise, the potential for the expression of other genes of interest to follow this down-regulated trend, and whether it occurs differentially in the severely ill versus mild/asymptomatic cases, should also be investigated. Knowledge of these expression changes provides another tool for development of therapeutics, as well as prognostics, for the fight against this pandemic.

In all, the work of Ahmetaj-Shala et al. (5) shines a light on the mechanistic reasons for differential tissue infection by SARS-CoV-2, moves forward our understanding of why males and people of increasing age are affected more severely by this pandemic, and paves the way for future therapeutic and prognostic insights into COVID-19.

AUTHOR DISCLOSURES

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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