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Adding Insult to Injury: Does COVID-19 Promote Acute Respiratory Distress Syndrome by Inhibiting Surfactant?

Pulmonary surfactant, which is composed of phospholipids, SP-A to SP-D (surfactant proteins A to D), and other proteins, prevents alveolar collapse by reducing surface tension at the alveolar surface (1). The importance of pulmonary surfactant is demonstrated by the observation that premature infants who lack surfactant often die of respiratory distress syndrome (RDS) (2). In 1968, Rüfer wrote, "the reason for disturbed breathing mechanics in the respiratory distress syndrome seems to be a lack of surfactant rather than inhibition of surfactant" on the basis of the observation that exogenous surfactant reduces atelectasis *ex vivo* in lungs from neonates who died of RDS (3). Rüfer's statement remained true for more than 50 years, and surfactant replacement has saved the lives of thousands of infants (4).

Enter the coronavirus disease (COVID-19) pandemic, which has killed nearly 6.5 million people worldwide (5). About one-third of patients hospitalized for COVID-19 develop acute RDS (ARDS) (6), and postmortem analyses of lungs from these patients show diffuse alveolar damage similar to that seen in patients who develop ARDS from other causes (7). Although our understanding of COVID-19 pathophysiology is incomplete, there appear to be both shared and distinct pathophysiologic mechanisms between COVID-19 and other viral causes of ARDS, such as influenza (8). One potentially unique property of COVID-19 is its tendency to induce self-reactive antibodies to immunomodulatory and other proteins (9–11). Although multiple studies have documented the presence of self-reactive IgG antibodies in patients with COVID-19, whether self-reactive IgA antibodies are also generated by COVID-19 is less clear.

In this issue of the *Journal*, Sinnberg and colleagues (pp. 38–49) provide evidence that IgA antibodies targeting SP-B/C may contribute to COVID-19–induced lung injury (12). The authors purified IgA-bound proteins in BAL fluid (BALF) from 18 hospitalized patients with severe COVID-19 (defined by need for supplemental oxygen) and 18 control subjects without COVID-19 and characterized these proteins using liquid chromatography–tandem mass spectrometry. They found that the percentage of samples with IgA-bound SP-B was higher in patients with COVID-19 than in those without COVID-19 (50% vs. 17%), and mean concentrations of bound SP-B were about 10-fold higher in COVID-19 BALF.

These intriguing results raised two questions: *1*) whether patients with COVID-19 have autoantibodies to other surfactant proteins and *2*) whether formation of these antibodies is specific to COVID-19 or a more general phenomenon in response to respiratory infection. To answer the first question, the authors used lentiviral transduction to express individual surfactant proteins in two epithelial cell lines (HEK293 and A549) and quantified IgA signal after incubating these cells with plasma from patients with COVID-19. The results indicated that patients with COVID-19 harbor IgA antibodies reactive to SP-B and SP-C but not SP-A or SP-B. To answer the second question, the authors performed IgA and SP-B/C immunostaining in lung sections from two patients who died of influenza and three patients who died of melanoma. No IgA signal was observed within alveoli or lung parenchyma in patients with influenza or melanoma, suggesting anti–SP-B/C IgA antibodies are specific to COVID-19.

The authors then addressed whether anti–SP-B/C IgA antibodies are associated with COVID-19 severity. They measured concentrations of anti–SP-B/C IgA in plasma from 77 patients hospitalized with severe COVID-19 (defined by the need for supplemental oxygen), 12 patients hospitalized with mild COVID-19, and 12 healthy control subjects. They noted higher concentrations of anti–SP-B/C IgA antibodies in plasma from individuals with severe disease compared with those with mild disease or control subjects. This effect was observed using both recombinant SP-B/C and poractant alfa, a mixture of porcine surfactant that is clinically used to treat RDS in premature infants. Similar results were seen in an independent cohort of 60 patients with severe COVID-19 relative to 30 patients with bacterial pneumonia and 10 healthy control subjects.

Why would COVID-19 pneumonia, but not influenza or bacterial pneumonia, induce formation of anti–SP-B/C IgA antibodies? One intriguing possibility is that there are shared peptide motifs between surfactant proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (13). To test this hypothesis, the authors preincubated plasma from patients with COVID-19 with an excess of SARS-CoV-2 lysate and found that this resulted in a significant, albeit modest, reduction in binding to SP-B/C. This finding suggests that molecular mimicry between the SARS-CoV-2 proteins and SP-B/C at least partially explains why anti–SP-B/C antibodies form in patients with COVID-19.

Finally, to test the functional relevance of anti–SP-B/C IgA antibodies, the authors used an *in vitro* assay to measure the surface tension of poractant alfa after addition of plasma from patients with severe or mild COVID-19 or uninfected control subjects. As expected, plasma from patients with severe COVID-19 reduced the surface tension of poractant alfa, presumably through cross-reactivity of human anti–SP-B/C IgA antibodies with porcine SP-B/C.

Although the study by Sinnberg and colleagues (12) has numerous strengths, there are some important limitations that deserve mention. First, identification of anti–SP-B/C IgA antibodies in BALF was based on a limited number of samples from a single institution, and determination of the specificity of anti–SP-B/C antibodies to COVID-19 was based on only a handful of patients. Second, the cross-sectional design of the study meant that the appearance of anti–SP-B/C antibodies could not be correlated with clinical endpoints in individual patients. Third, because

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immunosuppression was nearly ubiquitous in patients with severe disease but rare in patients with mild disease, the authors cannot exclude the possibility that immunosuppression confounded their results, although this would likely bias the results toward the null hypothesis. Fourth, the authors did not report viral titers, so we are left wondering whether the increased frequency of anti–SP-B/C IgA antibodies in patients with severe COVID-19 pneumonia is associated with higher viral titers. Finally, although the authors detected dimeric IgA in alveoli by immunostaining, quantification of monomeric versus dimeric IgA was not performed, and these two forms of IgA can have very different biologic effects.

Despite these limitations, the authors should be congratulated on an interesting study that should spur additional investigations at the bench and the bedside. At the bench, several additional autoantibodies identified in the authors' initial screen merit follow-up investigation, particularly uteroglobin (also known as Scgb1a1 [secretoglobin family 1A member 1]), which dampens inflammatory responses in response to viral infection *in vivo* (14). Follow-up studies investigating the IgA autoantibody response to multiple SARS-CoV-2 variants might improve our understanding of the peptide motifs driving autoantibody formation and explain differing degrees of lung pathogenicity among variants. At the bedside, future studies might examine whether response to corticosteroids differs on the basis of IgA autoantibody titers, allowing more targeted patient selection. Finally, development of chronic symptoms after COVID-19 (e.g., "long COVID-19") is an emerging public health issue. IgA autoantibodies have been described in patients with autoimmune disease (15), providing a rationale for examination of IgA autoantibodies in patients with long COVID-19. ■

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