SARS-CoV-2–triggered Immune Reaction: For COVID-19, Nothing Is as Old as Yesterday's Knowledge

In the initial phase of the pandemic, the coronavirus disease (COVID-19) caused by severe acute coronavirus 2 (SARS-CoV-2) was compared with other severe respiratory infections, such as influenza or the severe respiratory distress syndrome triggered by the SARS coronavirus 2002/2003. It is a characteristic of these diseases that they lead to an infection of the respiratory epithelium of the lower respiratory tract involving the alveolar cells. These cell populations become necrotic within a few hours or days. On the one hand, this is because of the virulence factors of the virus, and on the other hand, this is because of an excessive immune response driven by macrophages and granulocytes (1). As a consequence, this leads to a collapse of the alveolar/interstitial barrier. This resulting alveolar collapse leads to the hypoventilation of perfused areas of the lung, and thus to an intrapulmonary right-to-left shunt with hypoxemia. Because of the disturbance of the epithelial integrity, this then leads to an early invasion by mostly gram-positive pathogens and thus to secondary bacterial pneumonia.

However, COVID-19 caused by SARS-CoV-2 soon displayed other symptoms. The timeframe of 3–7 days between infection and initial symptoms is considerably longer than for influenza, and it takes a further 5–7 days until severe symptoms of respiratory failure develop. Although the virus affects the airway epithelial cells, for a long time the airway epithelium is not destroyed. Instead, probably dependent on the viral load, this leads to viremia, and the virus attacks practically all organ systems. As a result, findings from patients who died because of a viral infection of the capillaries of the pulmonary vasculature provide an explanation of why this resulted in a microthrombosis of the pulmonary circulation pathway (2). At the same time, a repair mechanism was set in motion to induce angiogenesis without these vessels being able to function (3). The hypoxemia of these patients with COVID-19 was thus primarily the result of a right-to-left shunt because of impaired perfusion with still preserved ventilation. The underlying endotheliitis/capillaritis was considered to be the result of a direct virus-induced inflammation.

In other organ systems too, like the heart or the kidney, evidence of the virus has also been proven. Cardiac complications described for COVID-19, such as left heart failure, arrhythmias, and acute kidney failure were also considered to be inflammatory damage directly induced by the virus (4, 5).

The paper on deceased patients by Dorward and colleagues (pp. 192–201) in this issue of the *Journal* (6) convinces with analyzing both virological and molecular biological findings to better understand the connection between virus identification and inflammation. Even though the number of patients examined is low, the results of this study are of great importance for the development of therapies. Surprisingly, the authors could in fact show that there is no direct connection between virus identification and inflammation. Although in some organ systems, such as the intestine, the kidney, or the heart, the virus but no inflammation was detectable, in the lung and the pulmonary vessels, excessive activation of macrophage/monocyte lineage cells was found. In addition, a pathological reticuloendothelial response could be demonstrated with a large number of reactive plasmocytes and iron-laden macrophages.

These results prove that the principal damage by SARS-CoV-2 is not caused by the virus itself but by the subsequent immune response triggered by the virus. This differs by specific organs and is mainly detected in the lung and as pulmonary vasculitis. Thus, it is understandable why antiviral therapies have practically no further effect on the second phase of COVID-19, although the virus is still detectable while an antiinflammatory therapy appears to be effective. The fact that the lung is the fundamental site of immune activation and tissue damage ought to be a good reason to consider inhalation therapy approaches for COVID-19 more widely in these discussions.

COVID-19 is a new disease. We are learning more and more each day about the pathogens and the disease, and we must adapt our therapeutic approaches to comply with the latest findings. ■

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