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COMMENT

Rethinking sepsis after a two-year battle with COVID-19

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Sepsis is an overwhelming host reaction to infection that results in high morbidity and mortality. The term sepsis or septicemia originated in 1914, and the definition of sepsis has evolved over time due to the complications of the disease. Systemic inflammatory response syndrome (SIRS) and infection are characteristics of sepsis; however, in the absence of infection, SIRS does not lead to sepsis, and not all cases of sepsis manifest symptoms of systemic inflammation, especially in elderly individuals. The new 2016 definition of sepsis is life-threatening organ dysfunction due to a dysregulated host response to infection [1]. By this definition, severe COVID-19, a currently much-discussed worldwide topic, is a type of viral sepsis. Common signs of sepsis, such as fever or chills, difficulty in breathing, pain, and confusion, are usually experienced by people with severe COVID-19. Data obtained from hospitalized COVID-19 patients and autopsies have revealed features of sepsis, including the activation of the complement system, the activation of coagulation, immune cell reprogramming, eicosanoid storms, cytokine storms, immunosuppression with T-cell exhaustion, and massive widespread cell death in the host [2–6]. Organ dysfunction, which, in severe COVID-19, is the dysfunction of the respiratory system caused by lung damage similar to acute respiratory distress syndrome (ARDS) in sepsis, is most likely the leading cause of death in COVID-19 patients. Therefore, in the medical community, the idea that infection with SARS-CoV-2 can progress to sepsis has often been discussed. What we have learned from the studies of sepsis could be valuable for COVID-19 studies and vice versa.

Despite remarkable advances made in understanding the role of inflammatory responses in organ failure and individual death in sepsis patients, thousands of registered clinical trials worldwide have not led to new therapeutic treatments for this complicated disease in the past 40 years. In the research community, the failure of translational sepsis research is often ascribed to the fact that the preclinical hints are heavily dependent on mouse models that do not fully recapitulate human cases and that the diverse etiology of this disease is not taken into consideration when selecting patients for clinical trials. However, even with these lessons in mind, translational studies of COVID-19 have still moved forward difficultly in the past two years.

The COVID-19 pandemic has triggered rigorous efforts in finding therapeutics for this disease. The heterogeneity of etiology in patients in COVID-19 trials can be easily avoided as the pathogen and infection route are known and selecting age groups and eliminating patients with underlying diseases is feasible. Currently, antiviral and immunomodulatory agents are used almost equally in therapeutic trials of COVID-19 (https://www.clinicaltrials.gov/). Previous clinical studies of sepsis and current studies of COVID-19 have consistently shown that the inhibition of a given pathogen had an effect only if the inhibitor was applied in the early stages of the disease; thus, disordered immune reactions are the cause of deterioration, and the cure should rely on evidence-based therapeutics such as modulating immune responses [7, 8]. However, the immunomodulating strategies used in COVID-19 trials thus far have not appeared to be more advanced than those applied in the past sepsis trials, and as in cases of the treatment of sepsis patients, the treatment of COVID-19 patients with general immunosuppressive drugs, such as dexamethasone and other corticosteroids, has led to limited or no improvement in the outcomes [9]. Decades of disappointment in the translational research of sepsis continue today, and this seems to be the case with COVID-19 as well.

A major obstacle in developing efficient therapy for COVID-19 is the limited knowledge about the underlying mechanisms of the pathogenesis of SARS-CoV-2. Although unprecedented large amounts of data on gene expression at the subtype or single-cell level of the immune system during infection have been generated [10, 11], implications from these tremendous amounts of human data are limited, and people still cannot accurately distinguish between an appropriate and inappropriate immune response at a given time point during the progression of COVID-19. To expedite clinical development, animal models have to be used.

Golden hamsters, ferrets, and some nonhuman primates are susceptible to SARS-CoV-2 infection and have been used in studies [12]. Mice naturally cannot be infected by prototypical SARS-CoV-2 owing to the inability of ACE2 in mice to bind the spike protein. Nevertheless, attempts have been made to circumvent this obstacle. One attempt has been introducing human ACE2 into mice, and the other has been selecting and using SARS-CoV-2 variants that can bind mouse ACE2 [12]. Both approaches allow viral infection in mice, but the manifestations of SARS-CoV-2 infection vary in different mouse models, ranging from mild to lethal outcomes. A repertoire of genetically modified mouse strains is available for SARS-CoV-2 studies, with different strains suitable for different pathophysiological evaluations and purposes [12]. However, limitations of using mice in designing and evaluating therapeutic interventions exist and cannot be overcome, similar to what was encountered in translational sepsis research in recent decades.

Clear differences exist between mice and humans in response to septic insult. For instance, mice develop bradypnea and

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1318 bradycardia, whereas humans develop tachypnea and tachycardia. The concern of human relevance in using mouse models also applies to COVID-19 studies. Nonetheless, mice are still, unavoidably and essentially, the most feasible in vivo model. A guideline aiming to enhance the translational value of sepsis studies using animal models was therefore proposed [13]. Basically, this guideline suggests the incorporation of factors found in human patients, such as sex, underlying diseases, and route of infection, into the design of animal experiments to mimic different categories of human patients. Such a study design should have some value in improving preclinical studies of sepsis as well as of COVID-19.

People in the sepsis field emphasize the complexity and heterogeneity of this disease when talking about the failure to develop effective new treatment, but evidence reveals that we do not sufficiently understand sepsis. Strategies to inhibit inflammation or to augment inflammatory responses have been used in clinical trials for sepsis. However, when revisiting hundreds of studies that interfered with gene expression in different inflammatory pathways in septic mice, we found that none of these interferences could completely prevent septic mice from death. The limited benefits in mice may already imply that interfering with these molecules to treat sepsis patients would not work. More preclinical studies are needed to find the right/better therapeutic targets. We may have to return to reductionist approaches by limiting the number of variables and using simple models. Although this might distance the model from the real disease, it is undoubtedly required for mechanistic studies and translational research. Monomicrobial *Escherichia coli* infection is a simple mouse sepsis model. The lack of *Tlr4* or *Myd88* in mice is able to fully protect them from *E. coli*-induced septic death [14, 15]. The absence of caspase-1, caspase-11, caspase-8, and RIP3, the downstream effectors mediating cell death and tissue damage, also fully rescued the mice from septic death by *E. coli*. Molecules contributing to lethality are clear, but spatiotemporal regulation in vivo awaits further investigation. Similar studies using other simplified or complicated models, such as monomicrobial *Salmonella typhimurium* or *Staphylococcus aureus* infection models, polymicrobial infection models, and sepsis models induced by viruses, fungi, or parasites, will reveal different pathways leading to death in these types of sepsis. Only when sufficient information has been collected can evidence-based therapeutics be adequately evaluated with mechanistic insights and achieved with confidence.

At this point, we shall state that data obtained from laboratory experiments and bedside clinical studies are not all the same. Distinguishing between similarities and differences and making modifications/revisions/adaptations/improvements are truly important when designing experiments and clinical trials, but the major current problem is that we know too little about the underlying mechanisms of organ dysfunction which is the central issue in the pathogenesis of sepsis and COVID-19. Basic studies emphasizing the intrinsic molecular/cellular programs that participate in organ damage must be conducted more extensively.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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