

## INSIGHTS

# COVID-19 stokes inflammasomes

Clare Bryant

The poor success rate of treating patients with aggressive sepsis in SARS-CoV-2 infections has highlighted again the challenges of managing systemic inflammatory conditions. In this issue of *JEM*, Rodrigues et al. (<https://doi.org/10.1084/jem.20202413>) discuss the role of inflammasome activation in COVID-19 disease severity, opening new possibilities for therapeutic management of sepsis syndromes.

In this issue of *JEM*, Rodrigues et al. (2020) show that activation of inflammasomes by SARS-CoV-2 infection is linked with COVID-19 disease severity in patients, potentially providing new therapeutic avenues for this intractable condition. Inflammasomes are macromolecular inflammatory signaling complexes that may be canonical (composed of a receptor, such as a nucleotide oligomerization domain leucine rich repeat receptor [NLR] or AIM-2 like receptor; an adaptor [ASC]; and an effector [caspase 1]) or noncanonical (composed of caspase 4 or 5 in humans or caspase 11 in mice; Broz and Dixit, 2016). Activation of canonical inflammasomes results in the processing of pro-IL-1 $\beta$  and pro-IL-18 to their bioactive forms along with cleavage of the cell death-inducing protein gasdermin D to release its pore-forming N-terminal (Shi et al., 2017). The NLRP3 inflammasome is triggered by a diverse array of stimuli, many of which would be released in response to the kind of cell damage that occurs during sepsis (Swanson et al., 2019). It is linked to many diseases including type II diabetes, Alzheimer's disease, and Parkinson's disease, with NLRP3 inhibitors currently being tested for a range of conditions in the clinic (Swanson et al., 2019). Noncanonical inflammasome activity induces gasdermin D-driven pyroptotic cell death, but also indirectly activates the NLRP3 inflammasome and is important in sepsis models (Broz and Dixit, 2016).

The challenges of treating the severe systemic inflammatory syndrome associated with COVID-19 in patients (Wang et al., 2020) have highlighted, yet again, the importance of sepsis and our very limited capacity for therapeutic intervention in this condition. Despite sepsis being a hugely important unmet medical need and the recent explosion of knowledge in inflammatory mechanistic biology, little progress has been made in new treatments for it. A number of studies, particularly those in rodents, have suggested that activation of the NLRP3 inflammasome is important in different sepsis models (Danielski et al., 2020), and there has been much speculation that NLRP3 would be linked to the pathogenesis of COVID-19. The Zamboni paper (Rodrigues et al., 2020) provides nice evidence to support this hypothesis (see figure) in SARS-CoV-2-infected patients; however, it also suggests a role for other inflammasomes in the pathogenesis of this disease. This suggests that inhibition of NLRP3 alone may have limited usefulness in COVID-19 sepsis, although its importance in other human septic syndromes remains to be determined. The involvement of more than one inflammasome in COVID-19 sepsis suggests approaches that inhibit multiple inflammasomes and/or a common effector mechanism may prove a useful adjunct to current therapeutic approaches.

Strategies for therapeutic targeting of the IL-1 $\beta$  and IL-18 cytokines processed by



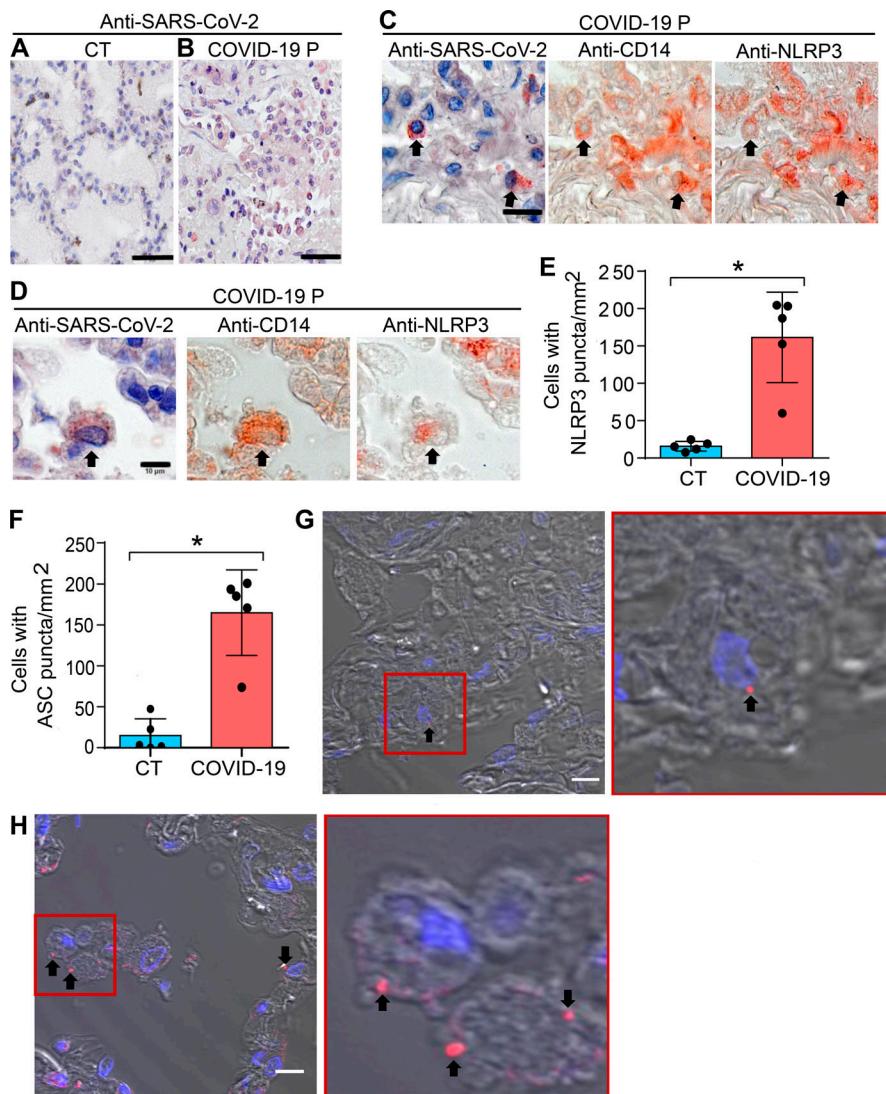
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inflammasomes are in the clinic and/or in late phase clinical trials (Mantovani et al., 2019; Mokry et al., 2019). Patients with autoinflammatory syndromes driven by gain of function mutations in NLRP3 respond well to treatments that neutralize IL-1 $\beta$  such as the IL-1 receptor antagonist anakinra or the neutralizing monoclonal anti-IL-1 $\beta$  antibody canakinumab (Mantovani et al., 2019). In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS), neutralization of IL-1 $\beta$  had beneficial effects in preventing atherosclerosis-associated cardiovascular events, arthritis, gout, and reduced lung cancer incidence, but an important side effect of the treatment was an increased infection susceptibility in patients (Mantovani et al., 2019). Even though there are elevated levels of IL-1 $\beta$  in sepsis, inhibition of the effects of this

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NLRP3 inflammasome activation in pulmonary tissue of COVID-19 patients. (A and B) Representative lung histological of controls (CT; A) or COVID-19 patients (P; B) stained with anti-SARS-CoV-2 antibody. (C and D) Multiplex immunohistochemistry staining with anti-SARS-CoV-2, anti-CD14, and anti-NLRP3 antibodies. (E and F) Quantification of NLRP3 (E) or ASC puncta (F) in pulmonary tissues of controls and COVID-19 patients. (G and H) Multiphoton microscopy of pulmonary tissues stained with anti-NLRP3 (G) or anti-ASC (H) antibodies showing inflammasome puncta. Please refer to Fig. 3 in the related article by Rodrigues et al. (2020) for a full explanation of the figure.

cytokine has yet to show beneficial effects in clinical trials for severe systemic inflammatory syndromes; although this is being tested in COVID-19 patients, any therapy which increases the susceptibility of patients to infection may well be problematic. IL-18 levels in sepsis are linked to disease severity and patient prognosis, but whether inhibition of this cytokine alone would be beneficial in septic patients has yet to be determined (Zhu et al., 2020). Inhibition of both IL-1 $\beta$  and IL-18 is effective at reducing sepsis in rodent models (Vanden Berghe et al., 2014), but this combination approach of neutralizing more

than one cytokine has yet to be explored extensively in patients because of the potential infection risks.

Inhibition of caspase activity, particularly caspase 1, 8, and 4/5/11, could simultaneously target many inflammasomes (Chauhan et al., 2020). Multiple caspase-driven cell death pathways are likely to be important in sepsis, including apoptosis, necroptosis, and pyroptosis. There is considerable cross talk between caspase-dependent cell death pathways (Kesavardhana et al., 2020) and redundancy either in cytokine-processing mechanisms or in cytokine-signaling pathways.

Small molecule and peptide inhibitors of caspases have been developed, and in animal sepsis models these inhibitors can be protective with or without accompanying cytokine blockade (Aziz et al., 2014). The complexities of caspase activity in inflammation and infection, particularly with the diverse genetic background of the human population, along with toxicity issues associated with these inhibitors means these drugs, have not made it to the clinic for treating sepsis (Aziz et al., 2014). Inhibition of gasdermin D activity as the common executioner protein for all inflammasomes could also provide a new avenue for treating sepsis associated with inflammasome activation (Orning et al., 2019). The repurposing of existing drugs, as well as the development of new molecules, to inhibit gasdermin D activity and hence block inflammation are the subject of intensive research at the moment (Lieberman et al., 2019).

Therapeutic strategies in sepsis require targeting the overactive cytokine response with immunomodulators while maintaining a sufficient inflammatory response for pathogen clearance. There is, unfortunately, a sad history of unsuccessful clinical trials in sepsis, including the failure of many cytokine neutralization strategies and inhibitors of Toll-like receptor 4. The reasons for this are many, including the multifactorial causes of sepsis (bacterial, viral, trauma), the complex network of interlinked induced immune responses, how these responses change during the course of systemic inflammation, the genetic background of the patient, and the point at which new interventions are tested, particularly toward the end of a life course. Application of machine learning to the analysis of the large datasets generated from different cohorts of septic patients (Giannini et al., 2019), for example, from those with COVID-19, should help to stratify different patient groups to select the most appropriate therapeutic strategies. Rodrigues et al. (2020) have linked inflammasome activity with COVID-19 disease severity, which potentially provides an important biomarker to assist in patient stratification. Taking out a single cytokine or signaling pathway is unlikely to be successful in treating sepsis because of functional redundancies and the potential for destabilizing the various immunological balances particularly between inflammation, immunosuppression, and anti-inflammatory pathways.

Inflammasome activation, particularly in the context of NLRP3, acts as a regulator of immune homeostasis, so whether inhibition of this pathway will prove a useful therapeutic approach in sepsis, particularly as part of combination therapy, remains to be seen.

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