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Commentary

Targeting innate immunity by blocking CD14: Novel approach to control inflammation and organ dysfunction in COVID-19 illness

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ABSTRACT

The SARS-CoV-2 pandemic has produced an unprecedented rush to develop new therapies, ranging from immunizations and antivirals to host-directed therapies to dampen potentially deleterious host inflammatory responses. With a sense of urgency, many groups have proposed repurposing approved drugs for other indications that might be deployed rapidly to control the viral infection or improve host responses. However, many of these therapies are based on drug availability rather than on a rational understanding of important steps in pathogenesis, particularly in the lungs, that lead to critical illness and life-threatening acute respiratory failure. Here we propose that the viral infection initially triggers a profound activation of innate immunity in the lungs that generates a self-perpetuating cytokine storm affecting the entire body. Inhibiting key proximal points in innate immunity pathways is feasible and offers a science-based approach to improving outcomes in moderate to severe COVID-19 illness.

The SARS-CoV-2 virus causes severe respiratory failure due in large part to viral tropism for the ACE2 protein on the surface of alveolar epithelial and vascular endothelial cells, facilitated by the TMPRSS2 tissue protease. As a consequence, the gas exchange parenchyma of the lungs is severely affected, leading to the pathological picture of diffuse alveolar damage with severe ventilation/perfusion mismatching and life-threatening hypoxemia. The overall case-fatality rate is approximately 7% worldwide and most deaths occur in people over 65 years old (https://coronavirus.jhu.edu/). The rapid spread of the virus with mounting deaths and widespread disruption of the world economy has produced an unprecedented avalanche of proposals for treatment of all stages of disease. Attempts to develop vaccines and antivirals in an effort to limit viral entry and replication in the lungs make sense, but many of the proposals to control deleterious host responses to the virus by targeting individual cytokines or pathways represent "Hail Mary" approaches based on drugs that are available and might be repurposed, instead of being based on careful consideration of plausible steps in pathophysiology. Here we propose the hypothesis that targeting the most proximal steps in innate immunity offers the best hope for controlling the host response to SARS-CoV-2 and improving outcomes.

Clinical and pathological studies show that severe COVID-19 pneumonia shares features with the adult respiratory distress syndrome (ARDS) including a cytokine "storm" in the systemic circulation and pathological features of diffuse alveolar damage in those who die. A likely pathophysiologic sequence involves initial viral infection of alveolar epithelial, endothelial and microvascular endothelial cells via the ACE2 receptor, causing direct cell lysis and additional destruction of virally infected cells by innate immune cells that recognize viral epitopes on the cell surface. Aside from viral moieties like single and double-stranded RNA that belong to the class of pathogen-associated molecular patterns (PAMPs), infected host cells also release damaged proteins, oxidized mitochondrial DNA, HMGB1 and other intracellular molecules called damage-associated molecular patterns (DAMPs) that are recognized as danger signals by a series of pattern recognition receptors (PRR) on macrophages, dendritic cells and other innate immune cells [1]. This proximal recognition step leads to rapid activation of intracellular signaling pathways that produce a self-amplifying downstream network of proinflammatory cytokines, including IL-1β, TNFα, IL-8, IL-6, GM-CSF, Type I interferons and others that recruit activated leukocytes into the lungs and increase microvascular permeability. The profound innate inflammatory response in the lungs produces a strongly oxidative and procoagulant environment that is perpetuated by oxidized phospholipids and other products in the airspaces and impairs gas exchange by alveolar flooding. This pathophysiological process can be fatal unless it is followed by a reparative phase with restoration of normal gas exchange. The key role of innate immunity in SARS-CoV-2 infection is shown by RNA profiling of bronchoalveolar lavage cells and is

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supported by the discovery that bats have a defect in inflammasome activation, which allows the virus to persist without triggering destructive inflammation[2,3]. This initial sequence suggests that the most appropriate therapeutic approach, aside from preventive vaccination, would be to combine an effective antiviral therapy with a treatment to dampen host innate immune responses without adversely impairing antimicrobial host defenses in the lungs and elsewhere. A common failing of proposed drugs for COVID-19 is that most target more distal points in this pathophysiologic sequence, such as single pro-inflammatory cytokines that have not been proven to control the redundant network of innate immunity pathways.

Recognition of PAMPs and DAMPs by PRRs on host cells is the most proximal event in the triggering and amplification of innate immune responses. PRRs are found on all cells involved in innate immune responses, including blood-derived monocytes, lung macrophages and dendritic cells and are exemplified by the Toll-like receptors (TLR) and key accessory proteins that recognize PAMPs and DAMPs. The magnitude of PRR-induced inflammatory responses is greatly enhanced by accessory proteins such as CD14, a protein found in both membrane and soluble forms (mCD14 and sCD14) that serves as a PRR and facilitates activation of TLR2, TLR3 and TLR4 by bacterial, viral and host-derived products [4]. Importantly, sCD14 can present ligands to cells that normally lack CD14, such as endothelial and epithelial cells, resulting in cytokine production and expansion of proinflammatory responses [5]. Lung lavage fluids of patients with ARDS contain high concentrations of sCD14, which is strongly related to neutrophil and protein concentrations, two hallmarks of acute lung injury [6]. In COVID-19, the plasma concentration of sCD14 increases markedly with severity of illness [7]. The potential therapeutic relevance of CD14 is shown by antibody mediated inhibition of CD14, which has been protective in primates, pigs and rabbits and has blocked cytokine and procoagulant responses to lipopolysaccharide infusion in normal volunteers and patients with sepsis [8]. In a pilot study of 13 patients with ARDS (7 treated, 6 controls), we found that blocking CD14 with a specific monoclonal antibody (IC14) produced trends for reductions in neutrophil concentrations in bronchoalveolar lavage (BAL) fluid and cytokine concentrations in BAL fluid and plasma (Implicit Bioscience Ltd., data on file for IND12209).

CD14 is a relevant target in RNA viral infections like SARS-CoV2, as mononuclear cells from mice lacking CD14 do not generate inflammatory responses to influenza A virus and CD14 recognizes oxidized phospholipids that generate inflammation in the lungs of patients with ARDS due to SARS-CoV1 [9,10]. Mouse experiments showing the involvement of CD14 in inflammasome activation during the coincident recognition of microbial ligands and oxidized endogenous phospholipids and the finding that bats have defective inflammasome activation support a central role for inflammasome activation in the host response to SARS-CoV2 [3,10]. Thus, CD14 emerges as an important initial point in host recognition of viral and host-derived products in the lungs. Targeting CD14 provides an opportunity to inhibit multiple inflammatory responses at a very proximal point in the host response to SARS-CoV-2 and is a rational and feasible therapeutic approach to dampen deleterious host responses in seriously ill patients. An inhibitory monoclonal antibody against CD14 has been used in more than 165 human subjects without increasing secondary bacterial infections (Implicit Bioscience, Ltd, IND149641). Combining an effective antiviral therapy with a host response modifier that is appropriately targeted at a proximal point in the innate immunity cascade is a science-based approach to therapy for patients who are seriously ill with SARS-CoV-2 infection.

Declaration of Competing Interest

The authors declare no conflict of interests.

Authors' contributions

Thomas R. Martin conceived the idea, wrote the first draft and edited the manuscript. Mark M. Wurfel, Ivan Zanoni, and Richard Ulevitch contributed scientific content and edited the manuscript.

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