C5a neutralization is protective in severe pneumonia

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Video Abstract

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Abstract

Even with antibiotics, severe pneumonia can lead to sepsis and death. Researchers in Germany have now identified a promising new therapy that may improve outcomes. Reporting in the journal Anesthesiology, the scientists indicate that targeting C5a, a component of the body's complement system, may be a novel adjunctive therapy for severe pneumonia. One reason why patients don't fare well with Streptococcus pneumoniae is that their highly activated immune system can damage tissue as it tries to clear the pathogen from the body. An important part of the body's first-line immune defense is the complement system, plasma proteins that patrol the body and coordinate with immune cells to kill invading bacteria. For example, when complement protein C5 is cleaved into C5a and C5b, C5b goes on to poke holes in bacteria. The smaller C5a is pro-inflammatory, attracting and activating neutrophils and making blood vessel walls more permeable to immune cells. Too much neutrophil activation can lead to tissue injury; and excessive vessel wall permeability may lead to lung injury. The team hypothesized that C5a concentrations would be increased in pneumonia and that neutralizing C5a might protect against lung injury and pulmonary sepsis. To find out, the team first tested the blood concentration of C5a in a group of nearly 400 patients with community-acquired pneumonia. Compared with healthy volunteers, these patients had 1.4 times more C5a in their blood. Accordingly, the group found elevated C5a in mice infected with Streptococcus pneumoniae. Next, the group tested the effects of complement C5a neutralization using an L-configured RNA aptamer called NOX-D19. The aptamer specifically binds to C5a, neutralizing its biological functions like an antibody. Due to its chirality, NOX-D19 is resistant to nucleases and thus highly biostable. In mice infected with Streptococcus, aptamer treatment reduced pulmonary permeability and disease severity. C5a neutralization also protected mice from injury of other organs, namely the liver, a complication frequently observed when the pneumonia develops into sepsis. The authors applied a second lung injury model combining pneumonia with mechanical ventilation, a significant contributor to lung injury in patients with respiratory failure. In this model, NOX-D19 treatment also reduced the "leakiness" of pulmonary blood vessels, the main mechanism of Acute Respiratory Distress Syndrome. Thus, protecting the barrier function of lung tissue is a reasonable add-on therapy for severe pneumonia. Exactly how C5a neutralization by NOX-D19 serves a protective function remains elusive. But these experiments suggest that neutralizing C5a could be an effective way to limit acute respiratory failure and sepsis-related liver injury in pneumonia. Further studies are warranted to decipher the exact mode of action as well as the potential to reduce mortality in severe pneumonia by L-RNA aptamer-mediated C5a neutralization.