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ABSTRACT
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# Abstract 154: Crossroads Of Immunity And Coagulation: Protease Activity Of Complement Component C1s Inhibits Protein C Activation In Covid-19

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**Abstract**

**Introduction:** There is an abundance of crosstalk between innate immunity and coagulation in thrombo-inflammatory diseases such as COVID-19. Several potential procoagulant effects of complement activation have been described, but whether complement proteases affect antithrombotic pathways in is not known. **Aims:** We tested the hypothesis that complement component 1 (C1) impairs the protein C antithrombotic pathway.

**Methods:** Plasma levels of the C1 complex were measured in plasma collected from healthy individuals and COVID-19 patients hospitalized early in the COVID-19 pandemic (NCT04360824). Activation of protein C by recombinant thrombomodulin was measured in a two-stage assay. In the first stage, protein C, thrombin, and thrombomodulin were incubated to generate activated protein C. The reaction mix was incubated with either healthy or COVID-19 plasma in the presence or absence of C1 inhibitor (which binds to C1 to inhibit its activity) or sutimlimab (a specific C1s inhibitor). During the second stage, protein C activation was measured using spectrophotometry with the chromogenic substrate S-2366.

**Results:** In the inflammatory condition COVID-19, plasma levels of the C1 complex were increased compared to healthy controls ($p$ = 0.004). Generation of activated protein C by recombinant thrombomodulin was decreased in the presence of COVID-19 plasma ($p$ = 0.001), whereas the addition of healthy plasma had no significant effect ($p$ = 0.469). Addition of C1 inhibitor or sutimlimab normalized protein C activation in the presence of COVID-19 plasma ($p$ = 0.022 and 0.039, respectively). Addition of recombinant C1s protease, but not C1r protease or C1q, impaired the generation of activated protein C in a dose dependent fashion.

**Conclusions:** We have uncovered a novel role of the protease C1s in regulating the generation of anticoagulant activated protein C. These findings suggest that the classical pathway of complement activation may impair anticoagulant responses in COVID-19.