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Letter to the Editor Reply Regarding Endothelial cell-activating antibodies in COVID-19

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We appreciate the letter by Palmer-Toy DE, et al. regarding our manuscript by Shi H, et al. We agree with Palmer-Toy and colleagues that VWF is an important mediator of thromboinflammation. VWF released from Weibel-Palade bodies and platelet alpha granules following activation of endothelial cells and platelets, respectively, leads to a cascade of heterotypic cellular interactions in support of a procoagulant and proinflammatory milieu (1). Correlations between (i) increases in the circulating pool of VWF and (ii) severity or mortality of COVID illness have been reported by many teams (2-7), including Palmer-Toy and colleagues. Recent reports from our group and others demonstrating the ability of polyclonal COVID antibody fractions to activate neutrophils and platelets, as well as to suppress physiologic antiviral responses, led us to focus on autoantibodies in this exploration of endothelial dysfunction in COVID. In our study, it is important to note that purified IgG fractions from COVID serum—especially from patients with elevated circulating antiphospholipid antibodies—recapitulated the activation of endothelial cells by intact COVID serum, suggesting that the circulating antibody milieu in COVID bears a foudroyant capacity to transform the endothelial surface and facilitate leukocyte adhesion. The specific targets of these antibodies and whether they ligate receptors or recognize antigens at the endothelial surface remains unknown and is worthy of investigation. Additional mechanisms of endothelial activation in COVID include denudation of the protective glycocalyx, mobilization of Weibel-Palade bodies, sex-specific steroid effects, and others. Acknowledging the relevance of understanding the kinetics by which the endothelium acquires a thromboinflammatory phenotype, this is likely superseded by the need to define the upstream stimuli that trigger the shift away from a quiescent state. Although we did not examine platelet-endothelial interactions in our study, these have been described in COVID and are, at least in part, attributable to the actions of VWF. There is reasonable plausibility that polyclonal COVID IgG pools enriched in antiphospholipid antibodies can facilitate platelet-endothelial interaction through VWF string formation as has been seen in prior studies of antiphospholipid antibodies. We certainly support the intent of Palmer-Toy and colleagues to promote the exploration of endothelial and hematopoietic cell interactions in pursuit of understanding the mechanisms that differentiate normal physiologic responses from their maladaptive counterparts that result in tissue injury.

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