**Characterization of Unique Pathological Features of COVID-Associated Coagulopathy: Studies with AC70 hACE2 Transgenic Mice Highly Permissive to SARS-CoV-2 Infection**

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COVID-associated coagulopathy seemly plays a key role in post-acute sequelae of SARS-CoV-2 infection. However, the underlying pathophysiological mechanisms are poorly understood, largely due to the lack of suitable animal models that recapitulate key clinical and pathological symptoms. Here, we fully characterized AC70 line of human ACE2 transgenic (AC70 hACE2 Tg) mice for SARS-CoV-2 infection. We noted that this model is highly permissive to SARS-CoV-2 with values of 50% lethal dose and infectious dose as ~ 3 and ~ 0.5 TCID50 of SARS-CoV-2, respectively. Mice infected with 105 TCID50 of SARS-CoV-2 rapidly succumbed to infection with 100% mortality within 5 days. Lung and brain were the prime tissues harboring high viral titers, accompanied by histopathology. However, viral RNA and many inflammatory mediators could be readily detectable in other organs, suggesting the nature of a systemic infection. Lethal challenge of AC70 hACE2 Tg mice caused acute onset of leukopenia, lymphopenia, along with an increased neutrophil-to-lymphocyte ratio. Importantly, infected animals recapitulated key features of COVID-19-associated coagulopathy, including significantly elevated levels of D-dimer, t-PA, PAI-1, and circulating NETs, along with activated platelet/endothelium marker. Immunohistochemical staining with anti-PF4 antibody revealed profound platelet aggregates especially within blocked veins of the lungs. ANXA2 is known to interact with S100A10 to form heterotetrametric complexes, serving as coreceptors for t-PA to regulate membrane fibrinolysis. Thus, our results revealing elevated IgG type anti-ANXA2 antibody production, downregulated de novo ANXA2/S100A10 synthesis, and reduced AnxA2/S100A10 association in infected mice support an important role of this protein in the pathogenesis of acute COVID-19. In summary, we showed that acute SARS-CoV-2 infection of AC70 hACE2 Tg mice triggered a hypercoagulable state coexisting with ill-regulated fibrinolysis, accompanied by dysregulation of ANXA2 system, which might serve as druggable targets for development of antithrombotic and/or anti-fibrinolytic agents to attenuate pathogenesis of COVID-19.