From PurUUpurU to Cytokine Storm to Hyperviscosity, Thrombosis and Other Complications of Coronavirus Disease 2019

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Abstract

Background: Severe coronavirus disease 2019 (COVID-19) is associated with pathological elevations of tumor necrosis factor-alpha (TNF-a) and interleukin 6 (IL-6). These cause extreme elevations of the acute phase reactant fibrinogen and plasma viscosity. Severe COVID-19 is also associated with poorly understood complications including a high incidence of arterial and venous thrombosis despite prophylactic anticoagulation, silent hypoxemia, pulmonary microvascular thrombosis, excess neutrophil extracellular trap formation, encephalopathy, and cardiac dysfunction. Aims: To investigate the cause of this pathological inflammatory response, the authors determined the number of purine-uridine-uridine-purine-uridine (purUUpurU) motifs in the genomes of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other RNA viruses. This motif is the precursor to the oligonucleotide which is the minimal motif required to activate inflammation via toll-like receptor 8 (TLR8). A genome containing the same nucleotides in SARS-CoV-2 in random order was used as a control. Result: PurUUpurU occurred 2.8 times more often in the actual SARS-CoV-2 genome than the randomized genome. The number of purUUpurU motifs correlates with the severity of the acute illnesses caused by the RNA viruses examined, except for influenza A. Conclusion: Hyperactivation of TLR8 mediated inflammation by purUUpurU may cause pathological inflammation in COVID-19. Marked elevations of TNF-a, IL-6, and fibrinogen will cause erythrocyte aggregation and increase blood viscosity. This promotes thrombosis and decreases tissue perfusion. Therapeutic plasmapheresis reduces blood hyperviscosity and should be used in severe COVID-19. To date, use of this therapy has only been reported in COVID-19 associated thrombosis.

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