



How SARS-CoV-2 viral fragments can mediate inflammatory, cardiovascular, and rheumatic pathologies



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Abstract

At present, we can recognize genomic features in coronaviruses that promote human infection. However, this is a necessary rather than a sufficient condition for pandemic coronaviruses, as 20-30% of common colds are caused by coronaviruses. In the present state of knowledge, it is unclear how SARS-CoV-2 infection in particular leads to the strong but ineffective inflammatory response that characterizes severe COVID-19. Proteolytic degradation of SARS-CoV-2 virions is one of the critical steps in host viral clearance, but the impact of viral peptide fragments from such processing at high viral loads is largely unknown. Using high-resolution mass spectrometry, we identify in tracheal aspirates of critical COVID-19 patients exposed SARS-CoV-2 peptide fragments with architectures cognate to host antimicrobial peptides (AMPs), which are critical components of the innate immune amplification machinery. To assess effects of AMP-like viral fragments on host cells, we use machine learning to map out all sequence motifs in the SARS-CoV-2 proteome that mimic host cationic antimicrobial peptides ('xenoAMPs'). Such xenoAMPs are strongly enriched in SARS-CoV-2 relative to low-pathogenicity coronaviruses. Moreover, xenoAMPs from SARS-CoV-2 but not low-pathogenicity homologs chaperone and organize dsRNA into nanocrystalline complexes with lattice constants commensurate with the steric size of Toll-like receptor TLR-3 and therefore capable of cooperative multivalent binding. Such complexes amplify cytokine secretion in diverse uninfected cell types in culture (epithelial cells, endothelial cells, monocytes, and macrophages). The induced transcriptome matches well with the global gene expression pattern in COVID-19, despite using <0.3% of the viral proteome. Delivery of these complexes to uninfected mice boosts plasma IL-6 and CXCL1 levels as observed in COVID-19 patients. We critically review the phenomenology of COVID-19, selective suppression of immune cell types (CD8+ T-cells, plasmacytoid dendritic cells), coagulation pathologies, cardiac inflammation, lupus-like and rheumatoid arthritis like syndromes, and relate them to SARS-CoV-2 viral fragments. Implications for vaccine design will be discussed.

Biography

Gerard C. L. Wong is a Professor in the Department of Bioengineering, Department of Chemistry, and the California NanoSystems Institute at UCLA. Wong received his BS and PhD at Caltech physics and Berkeley physics respectively. He joined the Materials Science & Engineering Dept and Physics Dept at the University of Illinois at Urbana-Champaign in 2000 and moved to UCLA in 2009. His research recognition includes: the Beckman Young Investigator Award, Alfred P Sloan Fellowship, and Sackler Distinguished Speaker. He is a Fellow of the American Physical Society (2011), a Fellow of the American Academy of Microbiology (2016), and a Fellow of the American Institute for Medical and Biological Engineering (2018). His current research interests include bacterial biofilm communities, innate immunity, and antibiotic design.