

SARS-CoV-2 hijacks host cellular proteins to expand tropism and subvert antiviral innate immune responses

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Abstract text

Text: The innate immune system acts as a first line defense against enveloped viruses, including SARS-CoV-2. Within the humoral arm of innate immunity, the complement system activated on viral surfaces is responsible for the clearance of opsonized viral particles. This is done either through their direct lysis or their phagocytosis by innate immune cells attracted to the site of infection by complement-generated anaphylatoxins. The cellular innate immune arm, represented foremost by monocytes and macrophages, is additionally able to recognize viruses via pattern recognition receptors, leading to production of inflammatory mediators to fully establish the immune response. Many viruses have evolved strategies to overcome these innate defense mechanisms, but the immune evasive strategies of SARS-CoV-2 are still incompletely understood. Here we show that SARS-CoV-2 incorporates a number of host cellular proteins into its virions during egress from infected cells. We characterize these host-derived proteins by biochemical, immunological and functional assays and reveal that: (1) virion-incorporated regulators of complement activation prevent the terminal complement pathway and virolysis of complement-opsonized SARS-CoV-2 virions; (2) host-derived cyclophilins mediate the non-classical infection of ACE-2-negative cells by SARS-CoV-2 through binding to their cognate receptor CD147 (Basigin); (3) human blood monocytes, infected via the cyclophilin-CD147 axis, engage endosomal single-stranded RNA-sensing Toll-like receptors to produce proinflammatory cytokines TNF, IL-1 β and IL-6, comprising the core hyperinflammatory signature observed in severe COVID-19. In conclusion, our results reveal a central role of hijacked host cellular proteins in immune escape mechanisms of SARS-CoV-2 to prevent destruction by humoral innate immunity, to broaden its tropism and trigger hyperinflammation, and provide novel insights into the immunopathology of COVID-19.

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Conflict of Interest statement

Do you have any conflict of interest to declare?: No

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