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Editorial

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Supplement Factor in Covid-19 Remedial and Vaccines

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As there is no pre-existing immunity to the novel causative agent, SARS-CoV-2, the COVID-19 pandemic is a significant global concern, and serious illnesses also have a poor prognosis. Major initiatives are underway to develop preventive steps, including vaccines and passive immunization therapies using purified immunoglobulins and recombinant monoclonal antibodies. These strategies largely focus on the virus spike (S) protein (see Glossary), which interacts via the receptor-binding domain with host angiotensin-converting enzyme 2 (ACE2) to facilitate cellular entry and viral replication. This method is intended to elicit neutralizing antibodies, although we know that neutralizing antibodies are not always adequate for other pathogens to confer a high degree of protective efficacy and may require additional immune mechanisms.

This can involve activation of the complement system by antibody-mediated drugs, which may contribute to different immunological outcomes against target pathogens. While several recent studies have involved extreme disease complement behavior, we hypothesis instead that complement can also contribute to SARS-CoV-2 protective immunity, which is a research field that has been largely understudied. The potential role of complement in innate immune responses and adaptive immune responses is explored here, as well as how complementation can be targeted or exploited for the production of SARS-CoV-2 therapeutics and vaccines.

The human complement is an ordered system of >30 serum proteins, many of which have protease activity that enables one complement protein to activate another in a sequential cascade. Three different pathways can trigger this process. An adaptive immune response triggered by interactions between complement protein C1q and antibodies bound to antigens is the classical pathway (IgM, IgG1, and IgG3 have the greatest activity). As an innate reaction triggered by natural IgM or preformed autoantibodies, the classical pathway may also occur. The remaining two pathways are innate responses that activate in an antibody-independent manner quickly against pathogens. Both include the mannose-binding lectin (MBL) pathway through which MBL binds directly to the sugar molecules expressed on the surfaces of the pathogen and the alternative pathway through spontaneous C3 activation on the target cells. Via the mannose-binding lectin (not shown) or alternative pathway, the latter triggered by spontaneous C3 activation, innate complement activation occurs rapidly against target pathogens.

Potential pathways for the activation of the innate complement against SARS-CoV-2 may include: I deposition of C3b that can interact with C3b receptors (CR1, CR3, and CRIg) on phagocytes for virus clearance and degradation; and (ii) deposition of C5b and development of a membrane attack complex (MAC) that produces a membrane pore leading to virus lysis. The activation of the adaptive complement depends on the acquisition of antibodies specific to the antigen, which takes time to create. Potential adaptive complement activation mechanisms against SARS-CoV-2 may include: I C1q binding to antigen-specific antibodies that can significantly boost antibody-mediated virus neutralization, likely due to a larger antibody-C1q complex that blocks receptor-ligand interactions more effectively, or through C1q stabilization or improvement in the binding of antibodies with low affinity or Since the antibody threshold required for neutralization could be reduced by C1q; C3b deposition and phagocytosis; and C5b deposition, MAC formation and lysis. Initiation through all three pathways leads to activation of C3 protein and subsequent activation of C5.

This includes protein cleavage into the subunits of activated C3a and C5a, which play a major role in proinflammatory responses and immune cell recruitment. The C3b cleavage product may bind to pathogens and mark them on immune cells for uptake and degradation (phagocytosis) via C3b receptors. The C5b fragment, which forms part of the membrane attack complex (MAC) that reaches the target cell membrane, causing pore formation and lysis, may also mediate pathogen clearance. However, as observed for Schwann cells and oligodendrocytes, sub lytic amounts of MAC on the surface of nucleated cells may instead play a role in activation and proliferation, The enhancement of antibody neutralization activity resulting from C1q binding to antibodies, even in the absence of other complement proteins, is another important function of the complement.

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