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ROLE OF COMPLEMENT PATHWAY IN COVID-19 INFECTION & POTENTIAL TREATMENTSTRATEGIES

Dr. Rachana Acharya*

Asst. Professor Ramniranjan Jhunjhunwala College.

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***Corresponding Author**
Dr. Rachana Acharya
Asst. Professor Ramniranjan Jhunjhunwala College.

ABSTRACT

Structure and mode of infection of Sars Cov 2 virus which is the causative agent of the ongoing pandemic is being elaborately studied. Every possible information regarding the mechanism of infection and the factors affecting the severity of the infection is crucial in understanding and deciding the combat strategies to prevent the infection from becoming severe and fatal. In this article the role played by complement components in increasing the severity of the COVID-19 infection and the strategies therin to prevent the suspected outcomes have been elucidated. Complement components adversely affect the host due to the unique mechanism of the Sars Cov2 virus entry into the cell. Better understanding of this mechanism can be useful in deciding the strategies for preventing such severe reactions and thus proposing several novel treatment options.

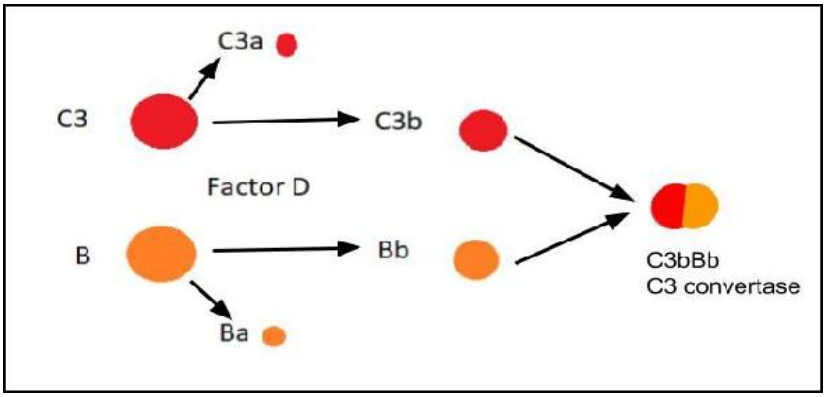
INTRODUCTION

Whenever any foreign pathogen such as bacteria or virus enters our body and tries to establish itself, our body starts to react to this with two strategies - one being non-specific and immediate called the “Innate immune response” and the other being more specific but delayed called the “Acquired immune response”.

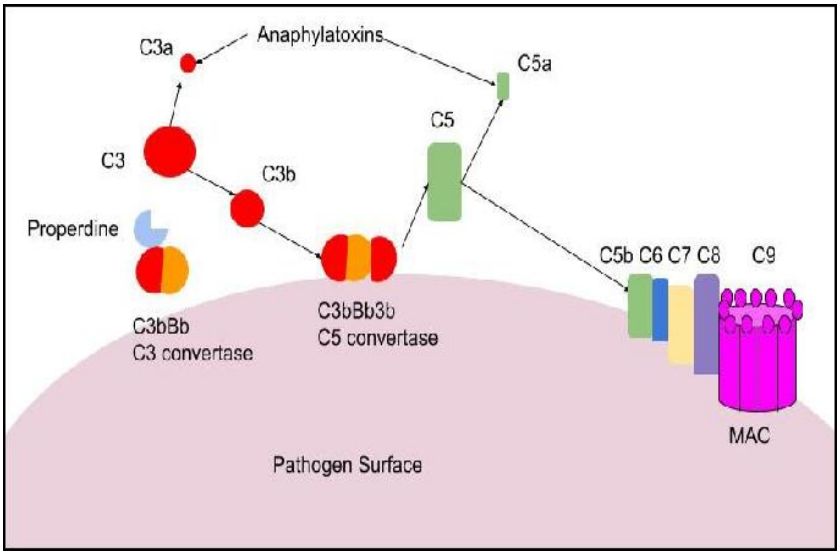
Innate immune response involves firstly, ingestion of the pathogens by our white blood cells (called “phagocytosis”). Secondly it involves the activation of the Complement System which when triggered destroys the pathogen. Activation of the complement system brings about sequential activation of a cascade of proteins ultimately leading to formation of pores in the membrane that is being attacked called the membrane attack complex (MAC).

Alternate Complement Pathway

The complement pathway that gets activated immediately upon entry of the pathogen in our body, and which is a part of innate immune response, is called the Alternate Complement Pathway. The first reaction in this Alternate complement pathway is the formation of a complex C3bBb. This is formed due to the action of a serum protein Factor D on 2 serum proteins C3 and B.

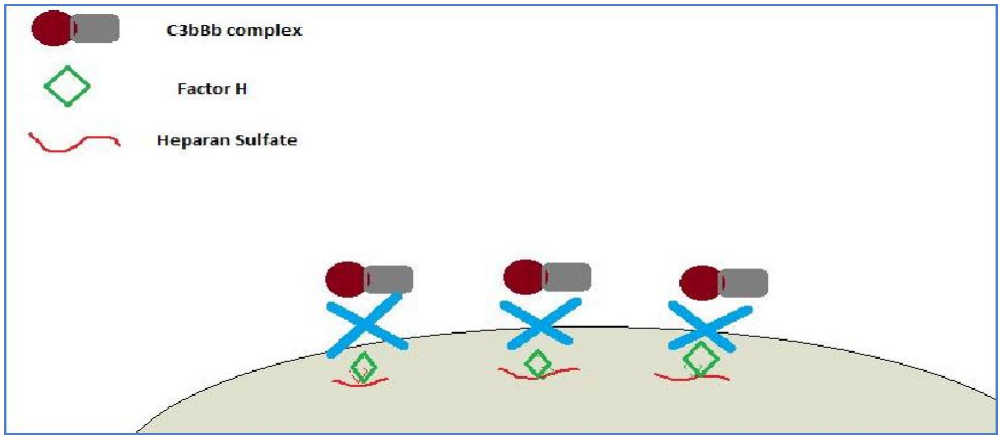


C3bBb then settles on the surface of the pathogen and is stabilized by another serum protein called Properdine. The stabilized C3bBb complex triggersa cascade of events as shown in the figure, finally leading to formation of the membrane attackcomplex (MAC), that forms pores on the surface ofthe pathogen leading to the destruction of the pathogen.[2]



The pathway once triggered leads to a huge amount of destruction of cells, causing inflammation and a lot of liquid accumulation. Inflammation inturn may activate a large number of immune cells and trigger production of a variety of cytokines, which again leads to

excessive inflammation. This phenomenon is called 'cytokine storm' since it invariably harms the host more than the invading pathogen. The complement pathway being so destructive in nature is highly regulated. Our body produces various inhibitors of the complement cascade in order to prevent unnecessary or excessive activation that may eventually lead to destruction of our own cells.



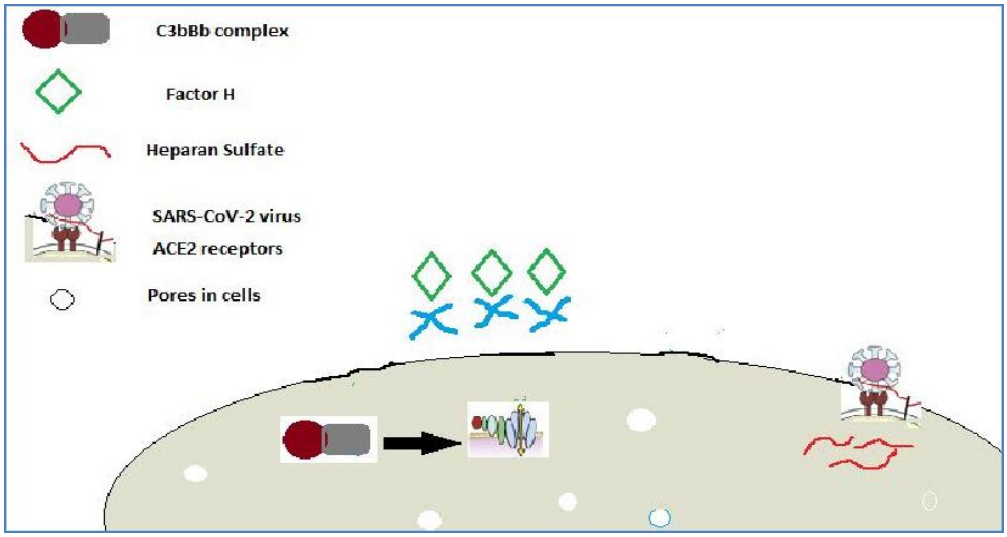
Self Defence

In order to protect the host cell membranes, meaning our own cells, from being attacked by the complement proteins, there exists a natural protective mechanism. In case the C3bBb complex settles on our own cells, a protein present in our serum called **Factor H** inactivates C3bBb complex and prevents the formation of membrane attack complex on our cells.

Factor H, which is a serum protein can inactivate the C3bBb complex only on the host cell surface but not on the pathogen surface because Factor H first bind to the host cell surface with the help of a molecule which is present on all human cell surfaces called the **Heparan sulfate**. Heparan sulfate is absent on foreign surfaces and hence Factor H cannot protect them and eventually the complement destroys the pathogen.

SARS CoV 2 Infection

In case of infection with SARS-CoV-2 virus which causes Covid-19, the virus attaches to the cells in the respiratory tract by binding to the ACE2 receptors on these cell surfaces. Recent research carried out at University of San Diego School of Medicine has discovered that SARS CoV-2 virus can attach to ACE2 receptors only in presence of heparan sulfate which is found on all host cell surfaces. The researchers found that the virus must bind both heparan sulfate and ACE2 receptors on the host cell surface to gain entry into the cell.



The entry of the SARS-CoV-2 virus into our body triggers the innate immune response leading to activation of the complement system and formation of C3bBb complex. Because the virus binds to heparan sulphate molecules on the host cell surface, it leads to local deficiency of these molecules on the host cells. In absence of heparan sulphate, Factor H cannot bind to the host cell surface. Thus there is no protective mechanism for inhibiting the C3bBb molecule from initiating complement cascade. The membrane attack complexes thus start forming on the host cell surface itself.

Effect of complement activation

1. Activation of complement cascade due to decreased Heparan phosphate concentration on host cell surface, leads to formation of pores on host cells and their lysis.[1]
2. This destruction of our own cells in the lungs and upper respiratory tract leads to massive inflammation.
3. Besides forming MAC, C5b6789 induces endothelial activation and dysfunction. Several proinflammatory molecules like C3a and C5a are released.[7]
4. Multi-organ failure and kidney damage are associated with complement over activation.[5]
5. C5a interacts with membrane C5aR on endothelial cells, inducing down regulation of thrombomodulin and activation of coagulation with secretion of P-selecting promoting platelet adhesion, aggregation and recruitment of white blood cells.[3]
6. Initiation of cytokine storm leads to increased vascular permeability and coagulation further leading to lung congestion and reduction in blood oxygen levels as seen in some patients, increasing the severity of the infection.

Novel Treatment Strategies based on these findings

1. Factor H can be administered to protect from the uncontrolled triggering of complement cascade. Research on Factor H production in recombinant moss is underway.
2. Modified heparin that can bind to the virus spike protein and prevent it from attachingto heparan sulfate on our cell surface, is being developed. Heparin is already an FDA approved drug.
3. Novel molecules which can inhibit Factor D thus preventing C3bBb formation are being developed.[8]
4. Treatment with a C5 inhibitor significantly attenuates respiratory inflammation and tissue damage.[4]
5. Suppression of C5 products could be achieved by the use of the approved drug, eculizumab, which inhibits C5, preventing its cleavage

The above strategies show promising potential for developing a successful medication for treatment of patients showing severe lung congestion, thus reducing morbidity.

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