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Review Article

PERSPECTIVES OF COMPLEMENT SYSTEM AND ITS CONTROL IN INFLAMMATION: A REVIEW

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Abstract: The Complement system provides a rapid and efficient means to protect the host from foreign organisms. Complement is considered an important mediator of inflammation and actively regulate the immune response. Also , an uncontrolled activation of complement is prevented by a number of regulatory complement proteins either circulating in the plasma or expressed on the cell surface i.e being membrane bound. Erythrocyte CR1 bind potentially pathogenic, complement fixing immune complexes. The most important observations behind the concept is that erythrocyte CR1 is physiologically relavant for the handling of immune complexes, (IC) in immune complex diseases viz. Systemic lupus erythromatosus (SLE) and Rhematoid arthritis. The potential role of complement in the control of malignant cells has been well emphasiged. In cancer patients complement activation with subsequent deposition of complement components on tumor tissue have been demonstrated. However in general , complement resistance of tumor cells limits the potential of anti- tumor antibodies. Development of potent inhibitors of various repair mechanisms pertaining to complement resistance, will lead to better sensitization of tumor cells leading to its killing by antibody and complement.

Key words: Complement regulatory proteins, Inflammation .

The Complement system provides a rapid and efficient means to protect the host from invasive micro-organisms. Due to its diverse biological activities, complement is the major mediator of inflammation , a natural response to the host tissue to any injury [1,2]. Evidences are available to show that complement significantly contributes to the regulation of immune response. Furthermore, the effector functions arising from complement activation carry the potential for harming the host by directly or indirectly mediating inflammatory tissue destruction. Inappropriate or excessive activation of

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Dr. P. D. Gupta — An Incredible and Evergreen Scientist. My Scientific Journey with Dr. P.D. Gupta started form 1975 at the All India Institute of Medical Sciences, New Delhi and continuing till date. During all these years, we had worked together on various aspects of Biochemistry, Cell Biology and Immunology and published papers on all the above said areas. Working together in science, also made us close family friends which we cherish. Wishing PD all the best on his 81st birth day and wish him a long life with happy, healthy and scientifically productive years ahead.

the complement system can lead to harmful, potentially life-threatening consequences due to severe inflammatory destruction. Genetic complement deficiencies or complement depletion have been found to be beneficial in reducing tissue injury of severe complement dependent inflammation. Considerable clinical and experimental evidence along with the work done in our laboratory implicate the role of complement and complement receptors (complement receptor-1; MCP; DAF and CD-59) in the pathogenesis of various inflammatory diseases viz. immune-complex and autoimmune disorders as also organ failure as consequence to sepsis, multiple trauma and burns [3,4]. Recently considerable advances have been made towards the utility of the measurements of the complement and complement receptors for the diagnosis and assessment of disease severity and response to therapy as well as of prognostic value in early recognition of patients at risk to develop multiple organ failure after trauma or with graft rejection following renal transplantation (Fig. 1).

The work progress during recent years on complement system and its receptors along-with complement derived breakdown products (C3a; C3d; C5a) or protein-protein complexes provide a comprehensive insight into the activation state of the system and have led to provide strategies towards a novel therapeutic control and approach of complement system for many inflammatory diseases. We have found in our laboratory, that the value of Complement receptor-1/Erythrocyte(CR1/E) in patients with SLE (Systematic Lupus Erythematosus) was significantly lower than their consanguineous relatives and healthy subjects. CR1/E was found to be stable in consecutive samples in control. Our results suggest that low levels of CR1 on erythrocytes in SLE patients are acquired during the course of the disease. In patients, the numbers varied between low and high during the course of the treatment. With the increasing acceptance of the importance of complement in severe inflammation, more and more interest has been shown in recent years by the investigators towards diagnostic, prognostic and follow-up studies pertaining to inflammatory disorders. It is further believed that therapeutic inhibition of complement include utilization of soluble complement inhibitors (C1-inhibitor; recombinant soluble complement receptor-1; administration of blocking antibodies for key components of complement cascade viz. C3 and C5) or even neutralizing the effect of anaphylatoxins (C5a and C3a) generated during the pathways of complement activation [5,6].

Role of complement system in the clearance of immune complex from circulation: The significance of the complement system in clearing immune complexes is visualized in patients with autoimmune disease – Systematic Lupus Erythematosus (SLE). Other individuals produce large quantities of immune complexes and suffer tissue damage as a result of complement mediated lysis and generation of Type II and Type III hypersensitivity reactions. Although complement plays a significant role in the development of tissue damage in SLE, paradoxically the deficiencies of C1, C2, C4 and CR1 predispose an individual to SLE. It seems the complement deficiencies interfere with effective stabilization and clearance of immune complexes and as a result, these complexes persist, leading to tissue damage in effect by the same system whose deficiency was to be blamed for such a happening. This is depicted in figure 2.

The attachment of soluble immune complexes with C3b is considered to facilitate their binding to CR1 on erythrocytes and erythrocytes in an individual , accounts for about 90% of CR1 in the blood [6]. This being the prime reason for erythrocytes to play a significant role in binding C3b-coated immune complexes and carrying these complexes to the liver and spleen. In these organs, the immune complexes are detached from the blood cells and phagocytosed, thereby preventing their depletion in tissues.

In SLE patients, deficiencies in C1, C2 and C4, each contribute to advanced levels of C3b on immune complex and thereby initializing their clearance. The lower levels of CR1 expressed on the erythrocytes of SLE patients may also interfere with the proper binding and clearance of immune complexes. Similar mechanism occurs in other autoimmune/ immunecomplex diseases such as rheumatoid arthritis [7].

Molecular mechanisms involved in complement system-based resistance of cancer cells: The potential role of complement in the control of malignant cells, has been well documented through several studies. Also documented in cancer patients, the complement activation with subsequent deposition of complement components on tumor tissues. Microbial vaccines have attempted to stimulate the

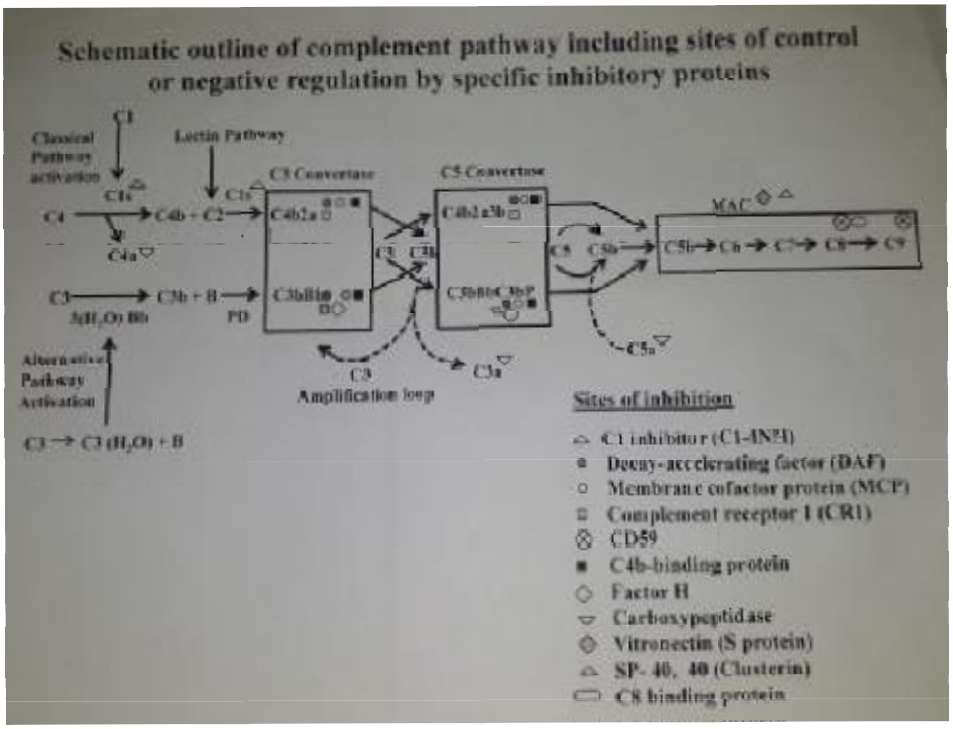
Schematic outline of complement pathway including sites of control or negative regulation by specific inhibitory proteins
Classical Pathway activation
Lectin Pathway
C3 Convertase
C5 Convertase
MAC
Alternative Pathway Activation
Amplification loop
Sites of inhibition
C1 inhibitor (C1-INH)
Decay-accelerating factor (DAF)
Membrane cofactor protein (MCP)
Complement receptor 1 (CR1)
CD59
C4b-binding protein
Factor H
Carboxypeptidase
Vitronectin (S protein)
SP-40, 40 (Clusterin)
C8 binding protein

Fig. 1

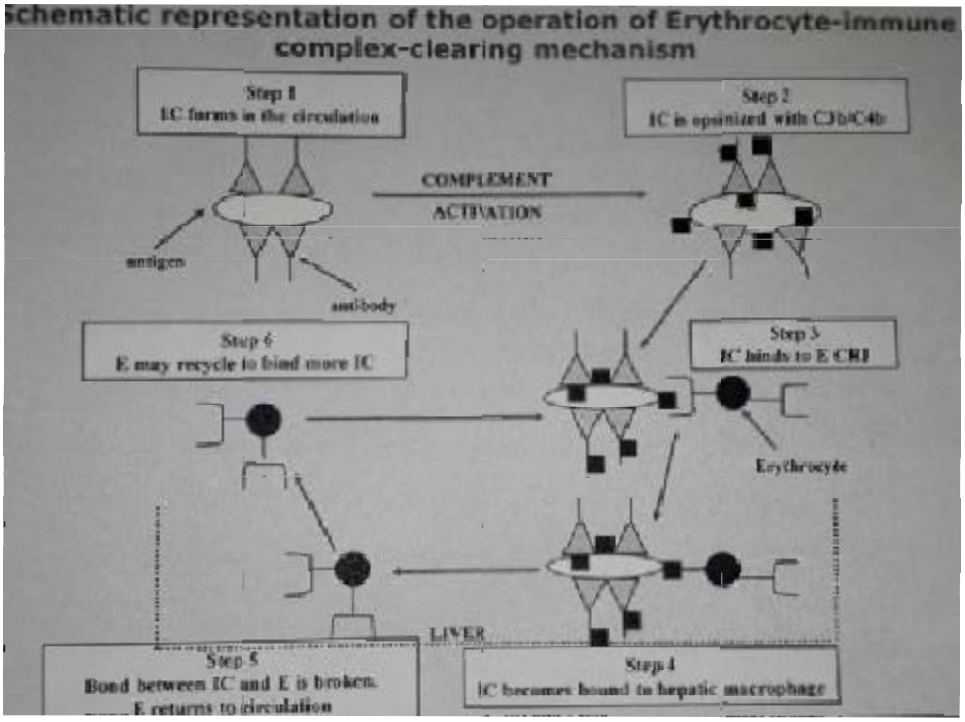
Schematic representation of the operation of Erythrocyte-immune complex-clearing mechanism
Step 1
IC forms in the circulation
Step 2
IC is opsinized with C3b/C4b
COMPLEMENT
ACTIVATION
antigen
anti-body
Step 6
E may recycle to bind more IC
Step 3
IC binds to E CR1
Erythrocyte
LIVER
Step 5
Bond between IC and E is broken.
E returns to circulation
Step 4
IC becomes bound to hepatic macrophage

Fig. 2

immune system with the hope to reverse the malignant process. Normal and malignant cells are protected from autologous complement attack by various cell-surface complement inhibitors viz. CR1 (Complement receptors Type I; CD35), DAF(Decay accelerating factor; CD55), MCP (Membrane co-factor protein; CD46) and CD59 (Protectin). These molecules regulate either the activation pathways of the complement cascade by affecting the generation of the C3 or interfere with the formation of membrane attack complex (CD59).

Membrane complement regulatory proteins (MCRP) are found on normal and malignant cells and their level of expression, even within the same tissues is very heterogenous. The expression of MCP, DAF and CD59 on several human tumor cells viz. lung and kidney cancer, colon adenocarcinoma, prostate cancer, breast cancer, neuroblastoma ovarian carcinoma have been demonstrated. Several observations have also indicated the MCRP are over expressed in malignant cells [8].

Selective targeting of complement on tumor cells by blocking MCRP with antibodies could serve as an adjuvant treatment in anti-tumor therapy. However, the challenging problem is the targeting of MCRP neutralizing mAb's selectively to the tumor by avoiding their binding to normal tissues. Bispecific antibodies which recognize tumor antigens as well as surface regulators such as CD59, have been shown to induce effective tumor cell killing with only a minimal effect on the surrounding cells. Our Studies pertaining to localization of Complement proteins through immunochemical approach could be helpful in providing tumor immunotherapy procedure [9,10].

In conclusion, it is quite apparent that Complement and Complement receptors along with their control mechanisms significantly affect inflammation thereby influencing the inflammatory diseases. Therapeutic management of these inflammatory diseases would also be required to be monitored through the complement proteins.

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