Archivum Immunologiae et Therapiae Experimentalis, 2000, **48,** 367–372
PL ISSN 0004-069X

Review

Complement Regulatory Proteins and Autoimmunity

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Abstract. To discriminate self from non-self is an essential issue in the immune system. Autologous cells are protected against complement-mediated cell injury by the self-recognition mechanism using complement regulatory proteins composed of complement receptor type 1 (CR1, CD35), membrane cofactor protein (MCP, CD46), decay accelerating factor (DAF, CD55) and homologous restriction factor (protectin, CD59). Recently, the up-regulation of these molecules has been widely shown in inflammatory tissues and organs affected by autoimmune diseases, and *in vitro* assays have revealed that immune complexes or several cytokines, including interferonγ, tumor necrosis factorα, interleukin1β and transforming growth factorβ, can up-regulate these molecules. In contrast, it has been found that expression of these complement regulatory proteins is markedly decreased on autologous cells undergoing apoptosis. These findings suggest that complement regulatory proteins have dual roles at inflammatory sites: enhancement of cellular resistance to complement attack and acceleration of the clearance of cells injurious to the organism due to complement-mediated mechanisms. To assist the former function, a therapeutic approach using recombinant soluble complement regulatory proteins may provide a promising strategy for the treatment of autoimmune diseases.

Key words: membrane cofactor protein (CD46); decay accelerating factor (CD55); homologous restriction factor (CD59); complement receptor type 1 (CD35).

New approaches to the treatment of autoimmune diseases are being actively sought. In this review, I outline one such promising approach that has been suggested by recent advances in the study of basic immunology. In the course of the evolution of the immune system, discrimination of self from infectious and other non-self was very important[1, 19]. The alternative complement pathway is a primitive and non-adoptive immune response system which distinguishes self from non-self immediately and attacks non-self through the formation of the membrane attack complex (MAC) [1, 19]. At the first step of the alternative pathway, C3 is deposited on the surface of non-self followed by activation of a subsequent complement cascade and MAC perforates the target cells[37]. In addition, released C3a and C5a, which are products cleaved by C3 and C5 convertases (C3bBb), dilate capillaries and increase vascular permeability to assemble neutrophils in the inflammatory site[37]. On the other hand, normal human cells are resistant to complement-mediated lysis by mechanisms using a special self-recognition system. This system is composed of specific membrane-bound proteins such as decay accelerating factor (DAF, CD55)[34], membrane cofactor protein (MCP, CD46)[7, 45] and homologous restriction factor (protectin, CD59)[9]. Complement receptor type 1 (CR1, CD35)[18] is also involved in the regulation of C3 fragment deposition. Neoplastic cells are also protected from autologous

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complement-mediated cell injury by these complement regulatory proteins[4, 5, 44]. In contrast, the absence of these molecules on tumor cells makes them susceptible to complement attack[4, 5, 44].

Complement Regulatory Proteins

The inhibitory points of the complement activation cascade are different in each protein (Table 1). CD46 and CD55 block C3b deposition on the autologous cell surface[7, 34, 45]. CD46 acts as a cofactor for the factor I-mediated cleavage of the activated complement components C3b and C4b[7, 45]. CD55 accelerates the dissociation of C3bBb and limits amplification of the complement cascade[34]. CD59 influences the later step of the alternative pathway, where CD59 interferes with C9 incorporation into C3b-8 complex[9]. CD55 and CD59 are glycosylphosphatidylinositol (GPI)-anchored proteins, the absence of which is pathogenetically essential and clinically important in paroxysmal nocturnal hemoglobinuria (PNH)[20].

Soluble Forms of Complement Regulatory Proteins

Although complement regulatory proteins are membrane-bound proteins and usually act on autologous cell surfaces, soluble forms of each molecule are detected in serum, saliva, tear, urine and other body fluids[17, 26, 29, 39, 43]. The serum levels of these soluble molecules, however, are not sufficient to control complement attack on the affected organs[23]. So the measurement of soluble complement regulatory proteins is useful merely to estimate local inflammation with complement involvement. Moreover, some neoplasms are also known to influence serum levels of these soluble complement regulatory proteins by shedding these molecules from their surfaces[4].

Autoimmunity and Complement System

In autoimmune disease, the targeted tissue is destroyed mainly by autoreactive T cells or immune complex-mediated tissue damage. It is widely accepted that the complement system is also involved in the uncontrolled self-toxic immune system in autoimmune diseases[13, 14, 42]. Immune complexes formed in the blood or directly on the affected tissues induce activation of the complement system[15]. As a reflection of *in vivo* complement activation, decreased serum complement levels form a distinct feature of active systemic lupus erythematosus (SLE). Hence, a better understanding of complement regulatory proteins in active and inactive SLE or other autoimmune diseases may provide new insights into the role of complement system abnormalities in autoimmunity.

Regulation of Complement Regulatory Proteins in Inflammatory Tissues

The amounts of these complement regulatory proteins on cell surfaces are influenced by a variety of inflammatory situations and regulated by many chemical mediators. *In vitro* assays using cultured tumor cell lines or normal cultured human keratinocytes revealed that interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and transforming growth factor β (TGF-β) can up-regulate these molecules, with the type of protein up-regulated differing according to the individual cell type[3, 36, 41]. MASON et al.[27] showed that the amount of CD55 expression on cultured human endothelial cells was increased by TNF-α and IFN-γ, but this was not true of CD46 or CD59. SHIBATA et al.[46] demonstrated that immune complex formation and complement activation *in vitro* significantly increased CD55 expression on the mesangial cells. Phorbol-12--myristate-13 acetate (PMA) and calcium ionophore were also shown to induce up-regulation of CD59 on a cultured human endothelial cell line[30]. In lupus nephritis, increased expression of CD59[48] and CD46[12] has

Table 1. Function of complement regulatory proteins

CD no.	Other name(s)	Function
CD35	Complement receptor 1 (CR1)	Complement inhibitor of classical and alternative pathway
CD46	Membrane cofactor protein (MCP)	Cofactor for factor I-mediated cleavage of the C3b and C4b
CD55	Decay-accelerating factor (DAF)	Acceleration of the dissociation of C3 and C5 convertases
CD59	Homologous restriction factor (HRF-20), protectin	Inhibition of membrane attack complex

been reported on glomerular endothelial cells and mesangial cells, where C3b/C3c deposition occurs. Circulating sCD46 was also increased in active SLE and decreased with control of the disease activity[23]. Similarly, up-regulated expression of CD46, CD55 and CD59 was detected on the acinar and ductal epithelial cells in Sjögren's syndrome (SS) and high concentrations of soluble CD55 and CD59 have been shown in saliva from SS patients[8]. In inflammatory joints of rheumatoid arthritis (RA) patients, these three molecules are strongly stained on the chondrocyte surfaces and their up-regulation is observed if cultured chondrocytes are stimulated with IL-1[10]. It was also shown that the neutrophils in the synovial fluid (SF) from patients with RA possessed an increased amount of CD55 as compared to those in peripheral blood[21]. In these diseases, although complement regulatory proteins are originally localized at normal tissues[2, 16, 35, 38], the up-regulation of these molecules at affected organs may imply a common protective response against unexpected attack by the complement system. These observations suggest that, in the self-destructive processes of autoimmune disease, each cell of the affected organ resists complement attack through up-regulation of cell surface-bound complement regulatory proteins.

Regulation of Complement Regulatory Proteins on Apoptotic Cell Surfaces

On the other hand, the involvement of the complement system in apoptotic cells has also been noted recently[28, 49]. In the course of apoptotic cell death of activated lymphocytes, these cells need first to be recognized as non-self with the apoptotic cells then cleared by phagocytes. The molecular mechanisms by which cells undergoing apoptosis are recognized and eliminated by phagocytes include thrombospondin (TSP) – TSP receptor (α v β3 integrin and CD36) interaction, phosphatidylserine (PS) – PS receptor interaction, CD14-mediated recognition and lectin-mediated recognition[11, 40]. In addition, reduced expression of these complement regulatory proteins has been reported on the surface of apoptotic cells[28]. TSUJI et al.[49] reported that the amount of CD46, CD55 and CD59 on apoptotic human umbilical vein endothelial cells (HUVEC) decreased in each case to about half of that on intact HUVEC. Reduced expression of CD46 and CD55 inducing attachment of C3b on the surface of apoptotic cells resulted in formation of iC3b, a ligand of the complement receptor type 3 (CR3) of phagocytes[28, 49]. In contrast, diminished CD59 implies susceptibility to complement-mediated cell lysis rather than apoptosis. However, sublytic MAC attack is thought to activate target cells in producing potential inflammatory mediators including oxidant products[32]. Although the detailed mechanism is unclear, target cell injury induced by sublytic MAC attack may be also involved in the process of apoptotic autologous cell clearance.

Epstein-Barr virus (EBV)-associated infectious mononucleosis (IM) is a well-analyzed acute viral infection, in which activation-induced cell death plays an important role in the clearance of activated $CD8^+$ T lymphocytes[51]. In this disease, decreased expression of CD59 was detected in an activated $CD8^+$ subpopulation of peripheral T lymphocytes, and these $CD59^{dim}CD8^+$ T cells were more susceptible to apoptosis than $CD59^{bright}CD8^+$ T cells[24]. Although whether decreased CD59 is involved in apoptotic lymphocyte clearance is unclear, this finding suggests that decreased expression of CD59 on $CD8^+$ T cells may discriminate the susceptibility of activated $CD8^+$ T cells to activation-induced cell death. A similar $CD59^{dim}CD8^+$ T cell subpopulation, more likely to undergo apoptosis when cultured *in vitro* without any growth factors, has been detected in a group of active SLE patients[50]. JONES and MORGAN[22] analyzed apoptotic polymorphonuclear leukocytes (PMN) and found a marked reduction in cell surface expression of CD59 and CD55, but not of CD46 on PMN. These findings suggest that decreased expression of complement regulatory proteins is a common feature of cells undergoing apoptosis and has an important role in the clearance of cells undergoing apoptosis.

Clinical Application of Complement Regulatory Proteins

To control complement-mediated autologous cell injury, soluble forms of complement regulatory proteins may provide useful therapeutic tools. An analysis of the function of recombinant soluble CD55 (rsCD55) revealed complement activation inhibiting activity in the fluid phase of this protein[31]. CHRISTIANSEN et al.[6] showed that rsCD35 was the most effective soluble complement regulatory protein at regulating both classical and alternative pathway activation and rsCD46 was as effective as rsCD35 in inhibiting the alternative pathway. Recombinant soluble CD59 is also useful in regulating complement attack[47] and has been applied to protect against hyperacute rejection in xenotransplantation[25]. Soluble CD59, however, is not as effective as other soluble complement regulatory proteins

(rsCD35, rsCD46 and rsCD55), especially in the presence of serum, because it needs to be positioned close to the site of MAC formation[25, 47, 52]. Hence, a specific antigen targeting antibody-CD59 fusion protein has been produced to supply soluble CD59 function at inflammatory sites[52]. Transfection of CD59 on cells also protects them from MAC attack and over-expression of complement regulatory proteins has shown therapeutic feasibility[33].

In summary, control of the activation of the complement system using recombinant soluble complement regulatory proteins is one promising strategy for the treatment of autoimmune diseases. If exaggerated complement reactions characteristic of these diseases can be selectively regulated using complement regulatory proteins without influencing the normal complement activation in inflammatory sites, then clinical application of these molecules in autoimmune diseases should become a clinical reality in the future. It is hoped that the information provided in this review will encourage further investigation of this field.

Acknowledgment. I thank Drs. H. Mabuchi, I. Koni, H. Muramoto and T. Seya for helpful advice, and Mr. J. S. Gelblum for a critical reading of the manuscript.

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Received in December 1999
Accepted in February 2000