

# Membrane complement regulatory protein CD59 in systemic lupus erythematosus and rheumatoid arthritis

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## Abstract

**Background:** Complement proteins constitute a proinflammatory system of the innate immunity which bridges with the adaptive immunity. It comprises of a group of serum zymogens, complement regulatory proteins (Cregs) and receptors. Most of the Cregs, namely CD59, CR1, DAF and MCP are membrane bound. Their soluble forms circulate in the body fluids. Activation of the zymogens through three distinct but interconnected pathways generate functionally important peptides. Most of the effects are produced by the interaction of the active peptides with their cell surface receptors. Uncontrolled activation of the system due to the overburdening triggers and deficient regulatory mechanisms leads to self-tissue injury in autoimmune and inflammatory disorders. Modulation of the Cregs has been evidenced in systemic rheumatoid disorders.

**Objective:** This review is an attempt to collate the literature culminated and insight gained regarding the association of CD59, a membrane Creg with the pathophysiology of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and its potential as a biomarker and therapeutic target for these two diseases.

**Methodology:** This review enfoldes the information obtained from the original primary research papers, citations and review articles including our own laboratory findings and publications with key search from the PUBMED. Although CD59 has been implicated in several diseases, here our search remained focused only to SLE and RA.

**Results:** Evidences suggest disease related modulation and protective role of CD59 in SLE and RA. The bulk of information came from the animal studies.

**Conclusions:** An intimate relation of CD59 with the pathophysiology of SLE and RA is envisaged. CD59 appears to hold promise as a biomarker and therapeutic target for these two autoimmune disorders. More studies on human subjects along with supportive evidences from the animal models are needed. Modulation of CD59 expression by cytokines opens up a new avenue in the context.

**Keywords:** CD59, Complement, Creg, SLE, RA, Pathophysiology

## Introduction

Complement system is a proinflammatory system that bridges between the innate and adaptive immunity. It comprises of about 50 humoral and cellular components consisting of a group of serum zymogens, complement regulatory proteins and complement receptors. Most of the Cregs are membrane bound. The effector functions of the system are initiated by the activation of the zymogens through three distinct but interconnected pathways by defined molecular patterns [1].

The system is a double-edged sword. On one hand, it serves as the first line of defense against invading pathogens and clears the undesired body elements including the immune complexes and senescing proteins, debris and apoptotic cells [2], on the other hand, its effector mechanisms, if massive and un-controlled, may cause severe inflammatory reactions and cellular injury serving as the key mediator of the immune inflammatory disorders [3].

Over the years, a large body of research has been carried out to gain insight into the molecular mechanisms underlying the pathophysiology of autoimmune diseases and association of the complement proteins with the same. In this context, the work on the complement regulatory proteins (Cregs), however, has gained momentum only in the recent years.

Following this quick introduction, the article commences with a brief account of the complement system, the complement regulatory proteins, the relevant details on CD59, ending with its relations with the pathophysiology of SLE, RA, its potential as a biomarker and, as a therapeutic target for these two diseases.

### **The complement system**

The components of the system are the humoral complement cascade proteins, the membrane bound and soluble complement regulatory proteins and membrane complement receptors.

### **The complement cascade and its activation**

The classical proteins of the complement cascade are C1 to C9. Further, Factor B, factor P, D, and later, mannan binding lectin (MBL) and MBL associated serum proteases 1(MASP1) and 2 (MASP2) were added to the system [4].

Complement is activated through the classical, MBL, or the alternative pathway. Whatever may be the activation pathway, the common strategy is the initiation of the cascade activation by distinct molecular triggers, formation of C3 and C5 convertases which lead to the proteolytic cleavage of these components to generate biologically active peptides, which further assemble to form the C5b, C6-C9(n) the membrane attack complex (MAC) also known as the terminal complement complex (TCC). The classical pathway begins with the activation of C1, alternative pathway with the activation of C3 and the lectin pathway starts with the activation of C2, C4.

The classical pathway is initiated by antibodies produced during the humoral response, by natural antibodies, either aggregated or in the form of immune complexes and, by other molecules like C-reactive protein or serum amyloid protein that are generated as a result of an inflammatory reaction. The activation of the pathway takes place in a step wise cascade manner flowing down from the 1<sup>st</sup> complement component C1 (qrs) to the terminal complement component C9 via the activation of C2, C4, C3, C5 ending in non- enzymatic assembly of C6-C9(n) with active fragment of C5, the C5b. On activation, the conversion of inactive zymogens to biologically active peptides occur by the cleavage of the parent protein, the primary fragments named as 'a' and 'b' like C3a, C3b, C4a, C4b, C5a, C5b.

The Mannose binding lectin pathway commences with binding of the complex MBL and mannan-binding lectin-associated proteases 1 and 2 (MASP1 and MASP2), respectively, to a bacterial cell wall. MASP2, a protein similar to C1s, leads to the formation of the C3 convertase C4b2a.

The alternative pathway is initiated by the spontaneous hydrolysis of C3 with the formation of C3(H<sub>2</sub>O). This forms a complex with factor B, followed by the cleavage of factor B within this complex by factor D. Subsequently, the C3(H<sub>2</sub>O) Bb complex is formed which activates more of C3 to C3b forming C3bBb. The C3bBb complex cleaves C3 to C3b and C3a. C3b gets deposited on the surface of the pathogens or other adherent surfaces and binds more of factor B, Once deposited on the surface of cells or pathogens, and this binding

gradually amplifies the activation cascade. The binding of properdin stabilizes the C3bBb complex, the C3 convertase of the alternative pathway. C3 convertases generated through various pathways cleave C3 to C3a and C3b. C3b leads to the formation of the C5 convertase which cleaves C5 to C5a and C5b.

After the formation of C5b, the steps are all identical. The effector peptides and the membrane attack complex generated by these three different pathways are the same irrespective of the pathway involved C3b further gets proteolyzed to produce biologically active peptides C3c and C3d.

### **Effector functions of the biologically active complement peptides**

The effector functions of the biologically active complement peptides include inflammation and anaphylaxis by C3a and C5a; immune adherence and opsonization followed by facilitation of phagocytosis and immune complex clearance by C3b, C4b, and ultimate lysis of the cell membrane of the microbes by the formation of C5-C9(n), the membrane attack complex (MAC). Complement C3d is important in the induction of the B-cell responses and C3b contributes to immune regulation and immune complex clearance. It is also suggested that these fragments contribute to immune tolerance and immunological memory. While the membrane attack complex directly gets inserted onto the cell membrane, rest of the functions of the effector peptides are mediated by the complement receptors, namely, CR1, CR2, CR3, CR4 and C3a, C5a and C3d receptors distributed either ubiquitously or in a cell specific manner predominantly on the blood cells [4].

Complement regulatory proteins are listed (Table 1). They protect the host against complement mediated tissue damage. Membrane-bound complement regulatory proteins are expressed on the cells of the hematopoietic system and protect the host cells against the complement mediated lyses. The balance between acceleration and inhibition of complement activation is critical to determine whether complement activation leads to the host defense, or, to the tissue injury of the host organs [5].

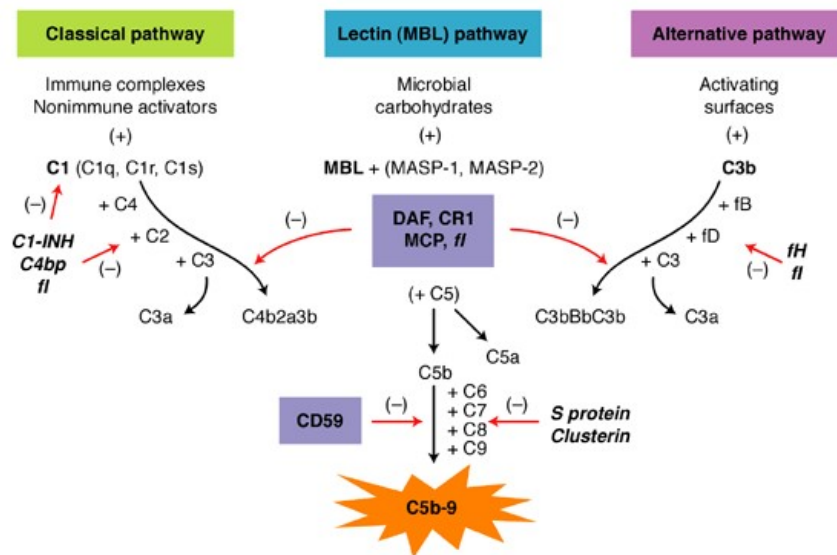
A large number of complement regulatory proteins are known of which, CR1, DAF, MCP, and CD59 are membrane bound. Soluble form of these membrane bound complement regulatory proteins are also known [6]. These Cregs control the complement activation at the specific steps of the complement cascade ( Figure1).

### **CD59 (Protectin/ Membrane inhibitor of Reactive Lysis [MIRL]/ Homologous Restriction Factor-20 [HRF-20]/ Mac Inhibitory Factor [MACIF] CD59 glycoprotein, MAC-inhibitory protein [MAC-IP])**

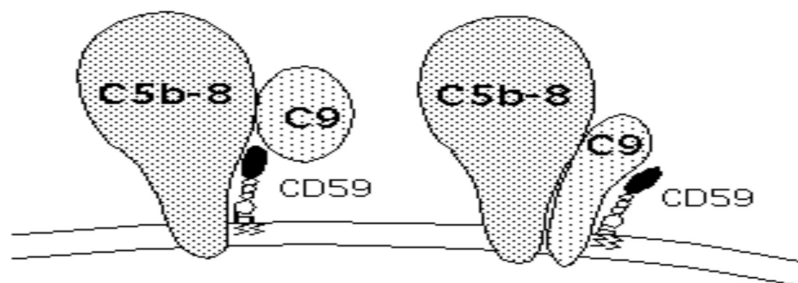
Cluster of differentiation 59 (CD59) is an 18-21 KD, GPI-anchored glycoprotein (GPIAP). It belongs to the leukocyte antigen 6 (Ly6) family of proteins. It has a high homology to the mouse protein, Ly6 [7]. CD59 attaches to the host cells via its glycosphosphatidyl inositol (GPI) anchor. When complement activation leads to the deposition of C5b678 on the host cells, CD59 is the only complement regulator that can prevent C9 from polymerizing and forming the complement membrane attack complex and also the channel formation to dig through the membrane [8,9] (Figure 2).

Thus, it is the most crucial regulator of the complement cascade that prevents direct tissue injury because of the complement

<b>Table 1:</b> Regulators of complement activation, their location and functions as the regulator of the complement cascade.		
<b>Regulator</b>	<b>Location</b>	<b>Function</b>
C1 INH	Plasma	Dissociates activated C1
C4 binding protein (C4BP)	Plasma	Dissociates classical C3 convertase, Cofactor for Factor I
Properdin	Plasma	Stabilizes C3bBb3b
Factor H	Plasma	Dissociates alternative C3 convertase, Cofactor for Factor I
Factor I	Plasma	Degrades C4b and C3b
Serum proteases	Plasma	Inactivate anaphylatoxins
S protein (vitronectin)	Plasma	Block membrane binding of soluble C567
CR1	Membrane	Dissociates C3 convertase, Cofactor for Factor I
Decay Accelerating Factor (DAF, CD55)	Membrane	Dissociates C3 and C5 convertases, Cofactor for Factor I
Membrane Cofactor Protein (MCP, CD46)	Membrane	Cofactor for Factor I
Homologous restriction Factor (HRF, C8BP, MIP)	Membrane	Inhibits MAC formation
MIRL (protectin, CD59)	Membrane	Inhibits MAC formation



**Figure 1:** Regulation of the complement cascade. The figure depicts the Cregs and their sites of action in inhibiting the complement cascade. CD59 inhibits the assembling of C5-C9 as soon as they start assembling at the membrane surface, thereby preventing the formation of the membrane attack complex and controlling their injurious effects on cells and tissues.



**Figure 2:** Inhibition of MAC assembly by CD59. CD59 anchored on the cell membrane by its GPI portion, intervenes in the formation of the C5-9 assembly and polymerization of C9 and inhibits the formation of the membrane attack complex.

activation in the normal health. CD59 also facilitates endocytosis of the CD59-CD9 complex and may signal the cell to perform active measures such as antigen presentation, immune tolerance, down regulation of the MAC and T-cell activation [10,11].

Mechanisms underlying the CD59-mediated transduction of signals into the cells, remain unclear as CD59 does not span the membrane. However, the recent studies suggest that the lipid rafts act as platforms for the associations of signaling molecules [12]. Therefore, the function of CD59 in signal transduction is dependent on its localization to the lipid rafts.

It is hypothesized that the phosphatidyl inositol (PI) moiety of the GPI may participate in signal transduction via a palmitate group that is located at the second position of the PI (PI- 2nd). Linker for activation of T-cells (LAT) was first observed in 1990. In the year 1998; it was purified from activated Jurkat cells and named LAT based on its properties [13].

CD59 is widely expressed in the majority of tissues, including the heart, liver, kidneys, and the circulating cells, such as leukocytes and red blood cells [14].

The Soluble CD59 is present in cell-free seminal plasma at a concentration of at least 20µg/ml. It is also found in saliva, tears, sweat, concentrated cerebro-spinal fluid, amniotic fluid, seminal fluid and breast milk. CD59 from amniotic fluid, seminal plasma and cerebrospinal fluid retains its GPI anchor, can incorporate into cell membranes and, is an efficient MAC inhibitor whereas that found in urine is devoid of its GPI anchor [15].

#### **CD59 and disease association**

Altered expression of CD59 in the immune- inflammatory diseases and cancers facilitated the understanding on the pathophysiology of these diseases and formed the basis of envisaging and exploring the diagnostic and therapeutic potential of this protein. Reduced expression of CD59 or the GPI anchor had been found associated with the severity of poor prognosis of the diseases like PNH, Alzheimer's, advanced macular degeneration and few other diseases [16]. Over expression of CD59 had been observed in a variety of cancers. This might make cancer cells protected against complement mediated lyses [17]. Following is an update on the association of CD59 with SLE and RA.

#### **Association of CD59 with SLE and RA**

Recent studies with gene knockout mice have suggested that membrane-bound complement regulatory proteins may critically determine the sensitivity of host tissues to complement mediated injury in autoimmune and inflammatory disorders [18]. A good number of studies suggest close association of CD59 with cancer and, that it can serve as a biomarker and therapeutic target. This review however is focused entirely to the importance of CD59 in SLE and RA.

#### **CD59 and SLE**

SLE is a multi-systemic disorder and may have cutaneous, musculoskeletal, renal, cardiopulmonary, neurological, hematological or gastrointestinal manifestations. Clinically, SLE is difficult to diagnose and manage because of its heterogeneous presentation and unpredictable course that consists of periods of remission and exacerbation (flares).

Although most flares are caused by reversible inflammatory processes, over the time, they can lead to irreversible organ damage that greatly affects the morbidity and mortality of the patients with SLE. The disease has multi-factorial etiology. It predominantly affects women in their childbearing age (female: male ratio is 9:1)[19].

Like any other autoimmune disorder, SLE is an outcome of the multifaceted immune dysregulation. These may include; loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression and aberrant cytokine profiles. All these lead to B cell hyperactivity and the production of pathogenic auto antibodies. The presence of anti-double-stranded DNA antibody (anti-dsDNA Ab) remains the hallmark of lupus erythematosus. Defective immune regulatory mechanisms, clearance of apoptotic cells and immune complexes are important contributors to the disease manifestations in SLE. The pathophysiology of SLE however, is not completely understood. Complement proteins especially the reduced levels of C3, genetic or acquired, had been found associated with the pathophysiology of SLE [20].

The exact etiology of SLE remains elusive. Predisposing factors include; genetic factors (certain types of human leukocyte antigens, null complement alleles and a host of other susceptibility genes), environmental factors (e.g., sun exposure, some drugs such as sulfa antibiotics, viral infection, etc.) and hormonal factors. The disease shows a strong familial aggregation, with a much higher frequency among first-degree relatives of patients indicating a genetic basis. However, most cases of SLE are sporadic without identifiable genetic predisposing factors [21].

#### **CD 59**

Several studies have demonstrated increased serum levels of MAC in active SLE patients [22] indicating the potential role of complement mediated tissue injury in the disease process. Since CD59 is a very important surface molecule protecting the autologous cells from the MAC mediated lysis and self-tissue injury, it is likely that it plays an important role in the modulation of the complement mediated injury in SLE. Up regulation of CD59, when suppressed by different doses of monoclonal antibody, a dose dependent increase in MAC deposition and exacerbated tubulointerstitial injury in rats had been observed [23,24]. This, further elucidated the role of CD59 in the maintenance of normal integrity of kidney. Cultured glomerular epithelial, endothelial and mesangial cells have been shown to exhibit increased susceptibility to complement mediated lysis in the presence of neutralizing antibodies in vitro [25,26]. In a study on CD59a gene knockout mice, Turnberg and coworkers [27] demonstrated that mice lacking the mCD59a gene were more susceptible to accelerated nephrotoxic nephritis than matched controls. These mice developed higher glomerular cellularity, severe glomerular thrombosis and proteinuria at different time points. Higher levels of C9 deposition indicated a larger quantity of MAC. This apparently related to the absence of CD59 which caused greater tissue damage. Most of the studies on CD59 in autoimmunity relate to the expression of CD59 in the kidney of patients with renal diseases. Arora et al. [28] reported that in SLE patients with diffuse proliferative glomerulonephritis, expression of CD59 on the RBCs increased significantly. Another report stated that the levels of CD59 on the red cells of SLE patients with autoimmune hemolytic anemia were decreased [29]. Thus, the expression of CD59 on erythrocytes may vary with the varied manifestations of SLE.

Tamai et al. [29] were the first to report an up-regulation of CD59 in the glomerular cells of lupus nephritis patients. Few other reports also showed increased CD59 in the glomeruli of SLE patients [28]. Studies carried out by Biswas [30] found significant down regulation of CD59 in lymphocytes from the patients with SLE but not in the neutrophils and monocytes.

A serial study on 12 patients with alternating flare-remission pattern of the SLE showed a significant reduction in the expression of CD59 transcript in the patients during remission when compared to the CD59 levels during the first flare. Levels of CD59 transcripts increased significantly in the patients who suffered a second flare when compared to the remission state and that during the first flare [30]. Recently, in a case study, CD59 deficiency syndrome was found associated with serial clinical features of repeated acute inflammatory polyradiculoneuropathy, angioedema, paresthesia, myelitis, and finally malar rash and autoantibodies with final diagnosis of SLE [31].

Apart from its role as a regulator of MAC formation, CD59 enhances T cell proliferation and IL-2 secretion [32]. This function of CD59 in the alteration of cytokine profile and induction of T cell proliferation may have some significance in the pathogenesis of SLE.

#### **CD59 and RA**

RA is a complex immune-mediated disease affecting 0.5%-1.0% of the adult population world-wide with two to three times more female than male patients [33,34]. It is the most common systemic autoimmune disease characterized by the presence of various autoantibodies in serum and synovial fluid [35]. The disease can start at any age, although the mean age at the onset is 40 to 60 years [36,37]. The etiology of RA has been elusive. However, a growing body of evidence suggests that it results from a combination of genetic, environmental and immunological factors [38,39]. Studies had reported correlation of complement split products (C3d, C4d, C3b, C3bi, C3c, C4b/c) and circulating immune complex (CIC) levels with the RA disease activity [40-42]. However, plasma levels of complement activation products are rarely used as an inflammation marker in RA since analysis of complement activation in patients is hampered by *in vitro* artifacts. RA can be serologically characterized by the presence of auto antibodies such as Rheumatoid Factor (RF) or anti-citrullinated protein antibodies (ACPA), which are present in about two third of individuals with the disease. C1q-C4 complexes had been described that hold promise as potential biomarker for disease activity in RA [43].

**CD59:** There are studies to suggest that CD59 has an important role in the pathogenesis of RA.

However, most of the data indicating a possible role of CD59 in the pathogenesis of RA came from the animal studies. In a study on CD59a gene knockout mice, Williams et al. [44] demonstrated that mice lacking the CD59a gene had exacerbated joint pathology. These mice developed significantly greater joint swelling, as well as increased scores in multiple histological parameters of damage. Synovial deposits of MAC were present in the arthritic joints of CD59a deficient mice.

Prevention of MAC assembly is, therefore, considered important for protection from tissue injury and here CD59 is envisaged to play a very significant role.

When rat knee joints were injected with a monoclonal antibody that specifically blocked the activity of CD59, joint swelling, thickening of the synovial tissues, infiltration of inflammatory cells into the synovium and deposition of membrane attack complex (MAC on the synovial surface occurred [45].

Lack of CD59 in the synovial lining cells and relatively weak expression of CD59 in the stromal and endothelial cells in RA had earlier been observed [46]. A single study documented decreased expression of CD59 on T-cells in RA [47]. Studies on CR1, CR2 and CD59 deficient mice models further emphasized that these two complement regulatory proteins protect hosts from developing pathological manifestations of RA [48]. Mizuno et al. [49] demonstrated that when CD59 and Crry, a rodent functional homologue of human MCP and DAF were functionally blocked at 2 weeks after the induction of CIA in rats, swelling of the knee joints was markedly increased. Deposits of membrane attack complex were found in the synovium. Membrane-targeted recombinant rat CD59 (sCD59-APT542) administration at the time of disease induction markedly reduced pathology in CD59a knockout mice. The crucial role played by CR1 and CD59 in preventing tissue injury in RA further came from studies on animal models. Systemic inhibition of early complement activation and MAC by administration of recombinant soluble CR1 (sCR1) and membrane-targeted soluble recombinant form of rat CD59 (sCD59-APT542) respectively inhibited development and progression of joint disease in RA animal models.

While there is ample evidence from animal studies that implicates CD59 in RA, there are only few reports on the status of CD59 expression in humans. Several studies had reported increased levels of plasma and synovial fluid TCC in RA patients [49-52]. High levels of MAC deposits in the synovium had also been reported [53-55]. *In vitro* studies had shown that non-lethal amounts of MAC stimulate human synoviocytes to secrete prostaglandins, reactive oxygen metabolites and pro-inflammatory cytokines [56,57].

Previous studies had shown decreased expression of CD59 on erythrocytes [58-60]. Jones et al. [61] observed no difference in CD59 surface expression on synovial fluid neutrophils compared with the PBMCs of the RA patients. These results provide a link between the *in vivo* observations of MAC localization and inflammatory mediator production in rheumatoid synovium and firmly implicate the MAC in disease pathogenesis. In their retrospective study involving 114 controls and 110 patients with active RA, Anand D [62] found that the CD59 transcript in the isolated peripheral blood mononuclear cells (PBMCs) was significantly decreased in patients as compared to controls which correlated significantly and negatively with DAS28. Levels of CD59 transcript correlated significantly and negatively with the levels of C4 in patients. These observations suggested relationship of PBMC-CD59 with the RA pathology.

In a serial study involving 17 patients with active RA from the day 1 of their diagnosis, (the week 0) Anand D [62] also found that the levels of DAS28 declined significantly on the week 24 as compared to the week 0 and, week 12. No significant change in the levels of CD59 transcript on the week 24 as compared to the week 0 was observed. However, levels of CD59 transcript increased significantly on the week 24 as compared to the week 12. An analysis of the individual patients revealed that all the patients who improved at either on the week 12 or the week 24, showed an increase in the levels of CD59 transcript excepting three patients whose levels of CD59 transcript

remained unchanged. Patients who did not improve showed decline in the levels of CD59 excepting three patients whose levels of CD59 transcript remained unchanged [62].

Thus, this follow-up study revealed a relationship between the up-regulation of CD59 transcript with better prognosis and, vice versa.

### **Modulation of CD59 expression by cytokines in relation to SLE and rheumatoid arthritis**

Expression of CD59 on human vascular endothelial cells had been shown to be upregulated by interleukin-4 (IL-4) and tumor necrosis factor (TNF- $\alpha$ ) and downregulated by IL-1b [63]. Gasque and Morgan [64] reported upregulation of CD59 expression after interferon-gamma (IFN- $\gamma$ ) treatment of human oligo dendrocytes. IFN- $\gamma$  was shown to increase CD59 expression in human PBMCs *ex vivo* and in patients with SLE.

In another study, it has been reported that the host CD59 expression is highly unregulated by the Varicella zoster virus (VZV) infection in human T cells and dorsal root ganglia (DRG). The same however had not been observed in human skin xenografts in SCID-hu mice *in vivo*. The modulation of host CD59 might help VZV in evading the complement-mediated pathogenesis [65]. Studies are in progress to elucidate the molecules that might be modulating the levels of CD59 in SLE.

Das et al. [66] found IFN- $\gamma$  to cause marked significant increase in CD59 transcripts in the neutrophils of patients with SLE. The same had been true for the TNF- $\alpha$ . The studies carried out by Anand et al. [62] showed that IL-18 downregulated the expression of CD59 in PBMCs in patients with RA.

The modulation of CD59 by cytokines is being explored as a strategy to develop CD59 based therapeutics in several diseases especially cancer (Not discussed here).

### **Conclusions**

In brief, the studies suggest an association of CD59 with the pathophysiology of SLE. Expression of CD59 is related to the disease progression or remission. Up regulation of CD59 is related to good prognosis and vice versa. A protective role of CD59, is therefore envisaged. Studies also suggest that CD59 plays an important role in determining the course of both the diseases. This molecule, therefore, holds promise as a biomarker and therapeutic target for SLE and RA. A detailed study on the human subjects, therefore, is desired. There are studies to suggest modulation of CD59 by cytokines (Details not discussed) in different cell types in the normal health as well as in SLE.

The modulation of CD59 in the desirable dimension may emerge as a therapeutic strategy for both the diseases. A large-scale correlative study on the healthy human subjects and, in the patients with SLE and RA during the course of disease, would help evaluating the two way interlinks between CD59 and cytokines and, the significance of CD59 as a biomarker. Human studies however need to be supported and confirmed by the *ex vivo* and animal experimentations.

It is warranted that any cytokine therapy in these two diseases or otherwise, should take care of their synergistic or antagonist effect on the complement regulatory proteins. This review thus opens up a new horizon in the future management of RA and SLE.

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