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Review Article

The membrane complement regulatory protein CD59 and its association with rheumatoid arthritis and systemic lupus erythematosus

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ABSTRACT

The complement cascade consisting of about 50 soluble and cell surface proteins is activated in autoimmune inflammatory disorders. This contributes to the pathological manifestations in these diseases. In normal health, the soluble and membrane complement regulatory proteins protect the host against complement-mediated self-tissue injury by controlling the extent of complement activation within the desired limits for the host's benefit. CD59 is a membrane complement regulatory protein that inhibits the formation of the terminal complement complex or membrane attack complex (C5b6789n) which is generated on complement activation by any of the three pathways, namely, the classical, alternative, and the mannose-binding lectin pathway. Animal experiments and human studies have suggested importance of membrane complement proteins including CD59 in the pathophysiology of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Here is a brief review on CD59 and its distribution, structure, functions, and association with RA and SLE starting with a brief introduction on the complement system, its activation, the biological functions, and relations of membrane complement regulatory proteins, especially CD59, with RA and SLE.

1. Introduction

The complement system represents about fifty cell surface and soluble proteins consisting of zymogens, receptors, and regulators. The zymogens get activated by three different pathways, namely, the classical pathway, the alternative pathway, and the mannose-binding lectin pathway triggered by different molecular patterns (Fig. 1 a). To name a few, immune complexes, altered self-molecules, and microbial mannose surfaces trigger the classical, alternative, and lectin pathways, respectively. The activation takes place in a step-wise cascade manner flowing down from the 1st complement component C1 (qrs) to the terminal complement component C9 via the activation of C2, C4, C3 and C5 ending in a nonenzymatic assembly of C6–C9 with active fragment from C5. On activation, the conversion of inactive zymogens to biologically active peptides occurs by the cleavage of the parent protein, the primary fragments named as 'a' and 'b' such as C3a, C3b, C4a, C4b, C5a, and C5b. The classical pathway commences with the activation of C1, alternative pathway with the activation of C3, and the lectin pathway with the activation of C2 and C4.

Each of the active peptides has effecter functions expedited by their interactions with the specific cell surface receptors. C3a and C5a are endowed with strong chemotactic and anaphylactic properties, whereas C3b and C4b are opsonins. In addition, C5b gets assembled with C6-9 to form a terminal complement complex C5b-6-7-8-9(n) also known as the membrane attack complex (MAC).

Abbreviations: MAC, Membrane attack complex; CRPs, Complement regulatory proteins; TCC, Terminal complement complex; DAF, decay-accelerating factor; MCP, Membrane cofactor protein; fH, Factor H; SLE, Systemic lupus erythematosus; RA, Rheumatoid arthritis; OA, Osteoarthritis; HRF-2, Homologous Restriction factor-2; GPI, glycosylphosphatidylinositol; LPS, Lipopolysaccharide; RTX, Rituximab; AA, Aplastic anemia; PNH, Paroxysmal nocturnal hemoglobinuria; AIMF, Autoimmune myelofibrosis; PBMC, Peripheral Blood Mononuclear Cells.

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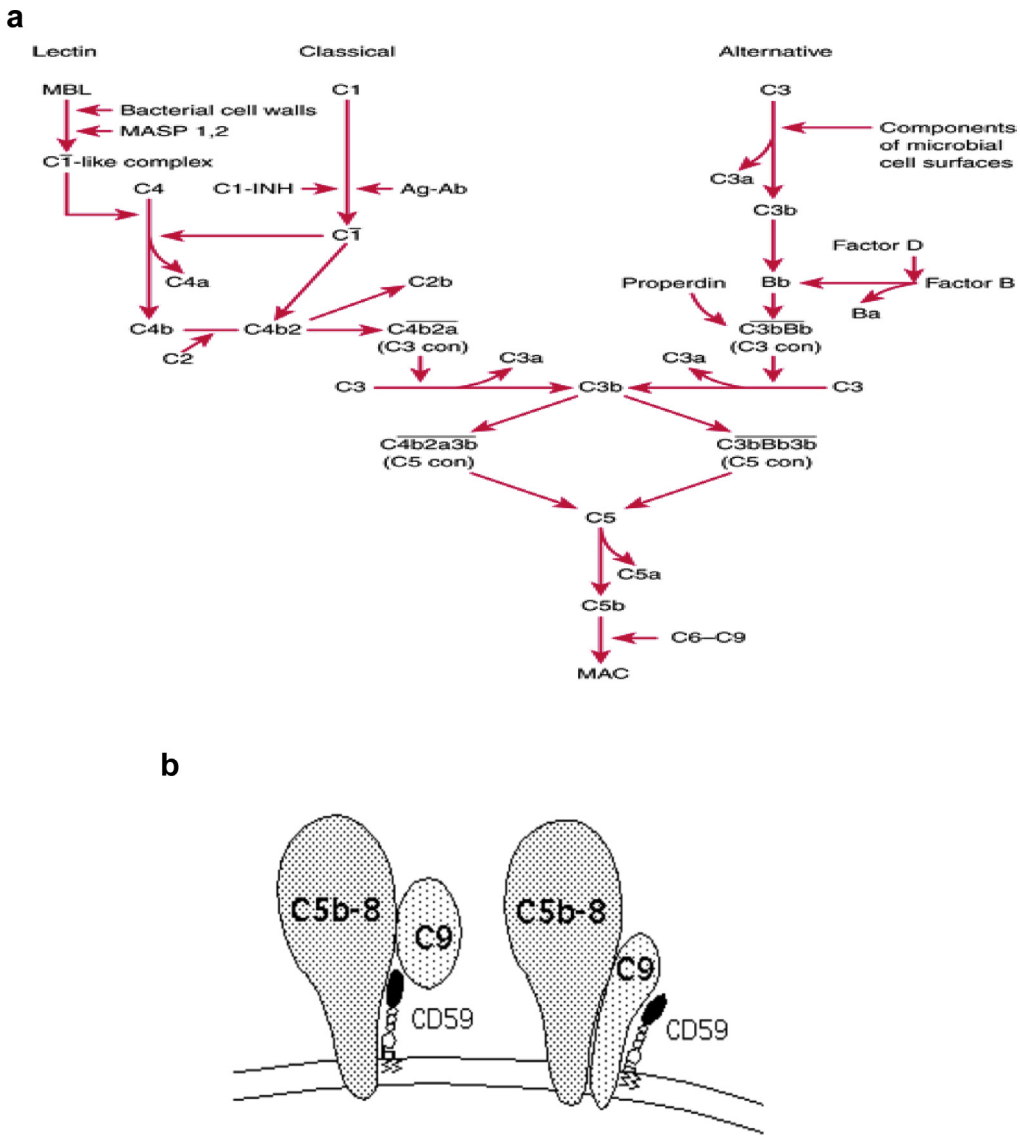

Fig. 1. (a) The complement cascade and activation pathways.[1] (b) Inhibition of MAC assembly by CD59.[20] MAC, membrane attack complex.

MAC forms a pore in the microbial membranes on which it got assembled after the cascade activation.

The system is the first line of defense against invading pathogens, but activation, if goes unabated, leads to severe inflammatory reactions and self-tissue injury because of the bystander or targeted effects of the MAC and the inflammatory peptides.

In normal health, the self-injury by complement activation remains insignificant because of the very stringent control effected by soluble and cell surface membrane complement regulatory proteins.

In autoimmune inflammatory disorders, exaggerated activation of the complement cascade had been evidenced.

Studies are in progress to determine the role of complement regulatory proteins in these diseases and also to explore their potential as disease markers and therapeutic targets.

A set of complement regulatory proteins such as complement receptor 1 (CR1 or CD35), factor H (fH), decay-accelerating factor (DAF or CD55), membrane cofactor protein (MCP or CD46), and protectin (CD59) have been shown to be associated with the pathogenesis of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[1]

Here is a brief review on the membrane complement regulatory protein CD59 and its association with the systemic autoimmune disorders RA and SLE.

2. CD59 (protectin/membrane inhibitor of reactive lysis/HRF-20/MACIF)

CD59 is a membrane-bound regulator of the C cascade.[2] In humans, CD59 is broadly expressed in the cell surface of different tissues except erythrocytes. A soluble truncated form of CD59 is present in plasma and other body fluids.[3]

2.1. Structure of CD59

CD59 is an 18- to 20-kDa molecular-weight glycosylphosphatidylinositol (GPI)–anchored glycoprotein. The protein consists of 103 amino acid residues, with the first 25 amino acids constituting the signal sequence and the final 26 amino acids forming the GPI anchor. It has a single N-glycosylation site (N18 in human CD59) and several potential *O*-glycosylation sites. This structure is characterized as a single cysteine-rich domain, having a

hydrophobic core with three loops and a small fourth loop, which is helical.[4] The helical loop is made of two antiparallel beta sheets, and the other three loops are three antiparallel beta sheets, which form the core. Connecting each of these loops are five disulphide-bonded cysteine pairs.

The soluble CD59 derived from urine does not possess an intact GPI anchor, is unable to insert into cells, and is consequently a poor MAC inhibitor. In contrast, soluble CD59 from amniotic fluid, seminal plasma, and cerebrospinal fluid retains its GPI anchor, can incorporate into cell membranes, and is an efficient MAC inhibitor.[5]

Human CD59 is closely related to mouse Ly6 antigen.[6] The human gene gives rise to more than 4 different mRNA molecules, which are generated by alternative polyadenylation.[7]

The gene for CD59 is localized on region p14-p13 of the short arm of chromosome 11.[8] The CD59 gene consists of 4 exons. The first exon is untranslated, the second encodes the hydrophobic leader sequence of the protein, the third exon encodes the N-terminal portion of the mature protein, and the fourth exon encodes the remainder of the mature protein including the GPI anchor attachment in the plasma membrane.

2.2. Expression of CD59

CD59 is widely expressed in human cells and tissues. It is present on all circulating cells[9], endothelial cells[10], in most epithelial cells[11] and spermatozoa.[12] The average number of CD59 molecules on human erythrocytes is 25,000–50,000 per cell.[9,13] The protein is expressed also on the Schwann cell sheath of peripheral nerve fibers, neurons, microglia, oligodendrocytes, astrocytes, ependymal cells, and certain epithelial cells such as acinar cells of the salivary gland, bronchial epithelium, renal tubules, and squamous epithelium.[10,14,15] Soluble CD59 is present in cell-free seminal plasma at a concentration of at least 20 μg/ml. Soluble CD59 is also found in saliva, tears, sweat, concentrated cerebrospinal fluid, amniotic fluid, seminal fluid, and breast milk.

3. Biological functions of CD59

3.1. CD59 as a regulator of complement activation

By binding to the C5b-8 complex, CD59 limits C9 input and prevents formation of the polymeric C9 complex, thus preventing unfolding and polymerization of the final C9 pore.[16,17] The details of this process are not well understood. The activity of CD59 had been suggested to be species-restricted because of its apparent ability to inhibit human MAC primarily and MAC from other species to a lesser degree.[18,19] The function of CD59 is to inhibit final steps of MAC assembly on cell membranes by activated terminal complement proteins C5b to C9 and to protect the cell from complement-mediated cell lysis (Fig. 1b).[20]

3.2. CD59 and T-cell signaling

CD59 works in the innate immune system but had also been implicated in the adaptive immune system.[17] CD59 can influence the proliferation capacity of T cells and their ability to produce cytokines, which can influence how T cells respond to a given antigen entering the bloodstream. It has been reported that direct interaction between CD59 on a T cell and a specific receptor on an antigen-presenting cell (APC) transmitted an inhibitory signal to the T cell or the APC. This inhibitory signal resulted in down-modulation of APC activity and consequently T-cell activity. It was also reported that CD59 on the T cells could reduce the strength of the positive signal transduction pathway delivered through the T-cell receptor (TCR).[17] A study on human $CD4^+$ T cells demonstrated upregulation of CD59 on activated $CD4^+$ T cells which served to downmodulate their activity in response to polyclonal and Ag-specific stimulation.[21] Thus, CD59 is suggested to have a regulatory effect on T cells. In addition, CD59 is endowed with several pleotropic functions.

3.3. Functions of CD59

Alternative roles of CD59 interacting with different proposed ligands are depicted in Fig. 2.[22]

1. The complement regulator CD59 has a major protective role against autolysis of cells and tissues by the complement system.
2. CD59 localized in lipid raft as glycosylphosphatidylinositol (GPI)-anchored protein helps in maintaining the stability of lipid raft in various cell types.
3. CD59 as another ligand for CD2 induces signal transduction pathway in T-cell activation.
4. It is also involved in endocytosis of CD59-C9 complex by signaling the cells.
5. CD59 mediates the attenuation of angiogenesis by preventing the lysis of newly grown blood vessels by complement cascade.
6. CD59 through complement-independent role transduces the lipopolysaccharide (LPS) signal into the nucleus via **Nuclear Factor kappa**-light-chain-enhancer of activated **B** cells (NF-KB) activation, inducing the release of proinflammatory and prothrombotic cytokines and growth factors.
7. The complement regulatory protein CD59 is strongly expressed in human pancreatic islet cells and involved in regulating the secretion of insulin by interacting with the exocytotic proteins Vesicle Associated Membrane Protein 2 (VAMP2) and syntaxin.

4. CD59 and its role in RA

4.1. Rheumatoid Arthritis

RA is a complex autoimmune and progressive inflammatory disease that involves the joints and leads to their destruction.[23] RA affects 0.5–1.0% of the adult population worldwide. Females are two to three times more likely than males to develop the disease. The highest prevalence rates had been observed in Native American populations such as Pima Indians and Chippewa Indians. In contrast, lowest prevalence rates had been reported from African and Asian countries. In the adult Indian population, prevalence of 0.75% had been observed.[24]

Similar to any other autoimmune disorder, RA is a disease of immune dysregulation precipitated by complex interactions of genetic, environmental, and immunological factors. All the cellular and humoral components of the innate and adaptive immunity appear to play a role in the pathophysiology of RA. Presence of autoreactive antibodies, especially those against the Fc portion of immunoglobulin G (IgG), and citrullinated proteins had frequently been observed in patients with RA. The immune complexes are formed which contribute significantly to the pathogenesis of RA by virtue of their interactions with cellular and humoral components of the immune system.[25]

4.2. CD59 and RA

Several studies on animal models and on human subjects with RA had been carried out to elucidate the relationship of CD59 with the pathophysiology of RA.

A recent study investigated the lytic activity of terminal complement complex (TCC) on bone tissues and in a CD59 knockout mouse mice. The reduced bone mineralization with increased

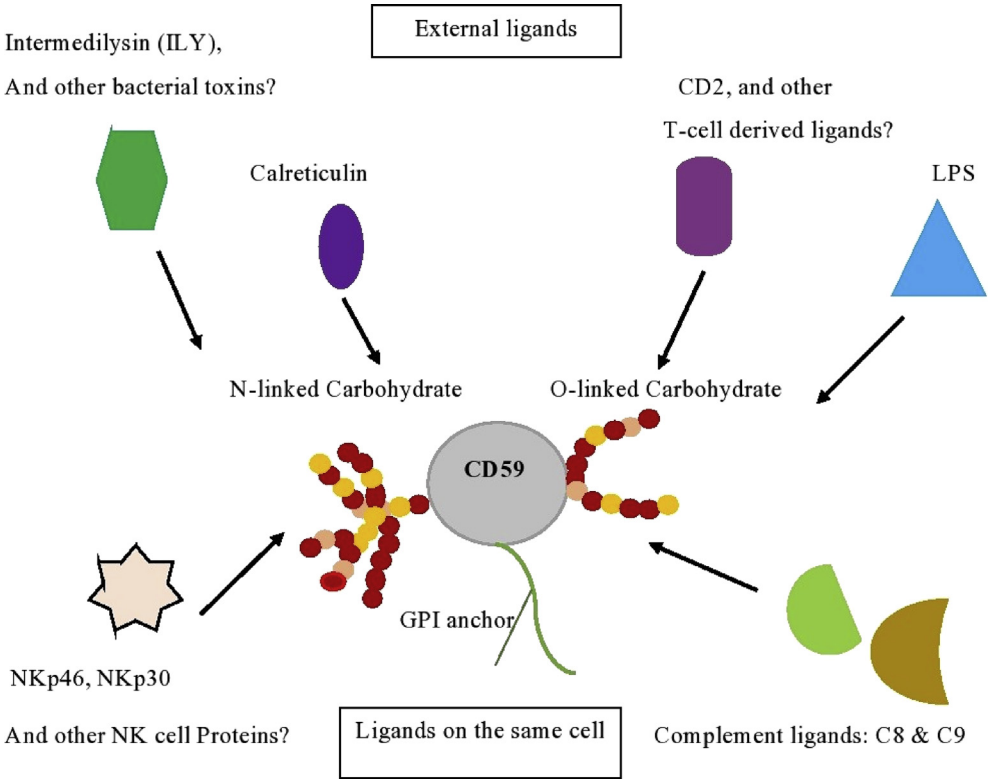

Fig. 2. Different functions of CD59 shown by different ligands.[22] LPS, lipopolysaccharide; GPI, glycosylphosphatidylinositol.

osteoclastic activity was observed in the knockout mice. This strengthened the role of CD59 as a negative regulator of TCC.[26] Furthermore, the experimental and clinical studies indicated that TCC promotes the development and severity of osteoarthritis (OA) and RA.[27] In a study with C5-deficient mice, wherein the TCC assembly got hampered, fracture healing was affected.[28]

In a rat collagen induced arthritis (CIA) model, the membrane complement regulators CD59 and Crry (a rodent functional homolog of human MCP and DAF), were blocked using F(ab')2 fragments of monoclonal antibodies against these two proteins injected intraarticularly which further increased inflammation.[29,30] In adjuvant arthritis (AIA) mice model, arthritis worsened in CD59a-deficient mice (a form of mouse CD59 that is widely distributed in tissues). The effects of this deficiency were reversed by intraarticular administration of membrane-targeted soluble CD59 (sCD59-APT542).[31] In synovial cells, the reduced tissue and synovial fluid levels of the MAC inhibitory clusterin, vitronectin, and CD59 were reported.[32] CD59 expression appears to be significantly reduced on the synovial lining, stromal cells, and endothelial cells (EC). In CD59 knockout mice, the TCC plays a predominant role in development of more severe OA than wild-type control mice.[33]

Several studies have demonstrated increased plasma and synovial fluid levels of TCC in patients with RA,[34,35] indicating the potential role of C-mediated tissue injury in the disease process. Because CD59 is a very important surface molecule protecting the autologous cells from MAC-mediated lysis, it is likely that it plays an important role in the modulation of the complement-mediated injury in RA.

Konttinen et al[36] analyzed the expression of CD59 in rheumatoid synovium and observed markedly reduced expression of CD59, compared with that in the noninflamed tissue.

A single report had suggested decline in CD59 surface expression on T cells in patients with RA,[37] whereas few reported no change on neutrophils and B cells.[37,38] Jones [38] observed no difference in CD59 surface expression on synovial fluid neutrophils compared with the peripheral blood neutrophils of patients with RA.

Reduced expression of erythrocytes CD59 (E-CD59) had been documented in RA.[37,39,40] The decline had been suggested as the consequence of the disease process. Spontaneous vesiculation of CD59 on incubation with C5b-9 was suggested as the reason for acquired loss of E-CD59 in RA.[39]

Studies demonstrated that the increased plasma levels of sMAC are negatively correlated with CD59 expression levels in patients with arthritis during the active phase of the disease. The study implies that the TCC levels were enhanced in synovial fluids of patients with OA.[33] In a recent study, the increased levels of soluble CD59 in synovial fluid of patients with knees injuries and osteochondral fractures were reported.[41] In a cohort study of patients with RA with rituximab (RTX), the expression of complement regulatory proteins (CRPs) of CD55, CD59, CD35, and CD46 in peripheral B lymphocytes was analyzed. It was detected that the increased expression of CD46 and CD35 with no statistical significance may be associated with reduced complement-mediated lysis that can be one of the modes of action of RTX and also found that there was no correlation between expression of CD55 and CD59 in B cells of peripheral blood with the repopulation of B lymphocytes in peripheral blood of patients with RA after treatment with RTX.[42]

Piccoli et al[43] in a study determined the expression of complement regulatory proteins: CD59, CD55, CD46, and CD35 in all peripheral blood cells of patients with RA. A significantly increased expression of CD59 in RA cells was observed with no significant difference in the expression of CD55, CD46, and CD35 in all peripheral cells of patients with RA.

A more recent study on peripheral blood mononuclear cell (PBMC) CD59 surface protein and transcript in patients with RA found disease-related modulation of CD59. While median values for CD59 declined in patients with active disease, the prospective

studies showed increase in the levels of CD59 transcript in patients on remission, thus relating with the good prognosis. Patients with no improvement in the levels of CD59[44] deteriorated clinically. Studies are in progress to delineate the factors that regulate and modulate the expression of CD59 in RA.

Expression of CD59 on human vascular endothelial cells had been shown to be upregulated by interleukin (IL)-4 and tumor necrosis factor (TNF)-α and downregulated by IL-1β.[45] Gasque and Morgan[46] reported upregulation of CD59 expression after interferon (IFN)-γ treatment of human oligodendrocytes. The studies carried out by Anand et al.[44] showed that IL-18 downregulated the expression of CD59 in PBMCs in patients with RA.

The aggravation of disease in CD59 knockout animal models, deposition of MAC in the RA synovium, disease-associated downregulation of CD59 in patients with RA, and relations of CD59 with the prognosis of RA suggest a close association and protective role of CD59 with the pathophysiology of RA, its potential as a disease marker, and its upregulation as a therapeutic strategy.

5. CD59 (protectin) and its role in SLE

5.1. Systemic lupus erythematous (SLE)

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disorder with systemic presentation. It is characterized by multisystem involvement and autoantibodies directed primarily against nuclear antigens. The primary pathological findings in patients with SLE are those of inflammation, vasculitis, immune complex deposition, nephritis, and vasculopathy.[47]

SLE exhibits a striking preponderance in females, especially in their childbearing age, as compared with males (F: M, 9:1). The prevalence, disease severity of SLE, and response to treatment vary with ethnicity and geographical location. The prevalence of SLE for northern Indian population is about 3.2 per lakh in contrast to the population of developed countries that ranges from 14 to 60 per lakh.[48]

Immune dysregulation in SLE is multifaceted – loss of immune tolerance, increased antigenic load, excess T-cell help, defective B-cell suppression, aberrant cytokine profile, and so on. All these lead to B-cell hyperactivity and production of pathogenic autoantibodies. The production of abnormal antibodies such as anti–double-stranded DNA antibody (anti–dsDNA Ab) by B cells remains the hallmark of lupus erythematosus. Defective immune regulatory mechanisms and clearance of apoptotic cells and immune complexes are important contributors to the disease manifestations in SLE.[47] The pathophysiology of SLE however is not completely understood.

5.2. CD59 and SLE

Due to the fact that CD59 is of immense importance in protecting self-tissues against MAC-mediated auto injury, it had justifiably been envisaged to play a crucial role in the pathophysiology of SLE. The suppression of CD59 by monoclonal antibodies has shown a dose-dependent increase in MAC deposition and exacerbated tubulointerstitial injury in rats[49–51] Cultured glomerular epithelial, endothelial, and mesangial cells have been shown to exhibit increased susceptibility to C-mediated lysis in the presence of neutralizing antibodies in vitro.[52,53]

In a study on CD59a gene knockout mice, Turnberg et al.[54] demonstrated that mice lacking the mCD59a gene were more susceptible to accelerated nephrotoxic nephritis than matched controls. These mice developed greater glomerular cellularity early in the disease process and more severe glomerular thrombosis and proteinuria at later time points. The excess C9 deposition reflects the presence of a greater quantity of MAC and most likely represents the mechanism whereby the absence of CD59a caused greater tissue injury. It is also suggested that CD59 induces T-cell immune response via complement-independent mechanism inhibiting systemic autoimmunity.

The absence of CD59a was found to complicate the skin disease and lymphoproliferation, leading to systemic autoimmunity in MLR/lpr mice.[55]

Several studies have demonstrated increased serum levels of MAC (C5b-9) in patients with active SLE,[56,57] indicating the potential role of C-mediated tissue injury in the disease process.[58] Tamai et al. first reported an upregulation of CD59 in the glomerular cells of patients with lupus nephritis, which was followed by a few other reports of increased CD59 in the glomeruli of patients with SLE. Most of the studies on the role of CD59 in autoimmunity deal with the expression of CD59 in the kidney of patients with renal diseases.[59] Arora et al. reported an increased expression of CD59 on the red blood cells (RBCs) of patients with SLE with diffuse proliferative glomerulonephritis.[59] In a cohort study of patients of SLE, it was found that 75% of the patients frequently associated.[60] The pathological association of SLE with cytopenia was found to contribute to the bone marrow failure.[61] Bone marrow failure in SLE illustrates the further study on noninvasive biomarkers with potential use for diagnostics and therapy to make further progress in improving the clinical outcomes in autoimmune diseases.[62] Moreover, it has been reported that SLE is associated with myelodysplastic syndrome,[63] aplastic anemia (AA),[64] paroxysmal nocturnal hemoglobinuria (PNH),[65] autoimmune myelofibrosis (AIMF),[66] pure red cell aplasia,[67] and hemophagocytosis.[68] Reduced levels of CD59 along with DAF has been found to be associated with lymphopenia and neutropenia[69] in SLE. CD59 and CR1 expression on RBCs was significantly reduced in patients with SLE with anemia.[69]

Studies carried out by Das et al.[70] found significant downregulation of CD59 in lymphocytes from the patients with SLE but not in neutrophils and monocytes. In a prospective study involving 12 patients with alternating flare-remission pattern of the SLE, a significant reduction of CD59 expression at the transcript level was observed in the patients during remission when compared with the CD59 levels during the first flare. In addition, there was a significant increase in CD59 transcripts in the patients who suffered a second flare when compared with the remission state and that during the first flare.[70]

In another study, it has been reported that host CD59 expression is highly unregulated by the Varicella zoster virus (VZV) infection in human T cells and dorsal root ganglia (DRG) but not 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.[71] Studies are in progress to elucidate the molecules that might be modulating the levels of CD59 in SLE.

IFN-1 was shown to increase CD59 expression in human PBMCs ex vivo and in patients with SLE.[72]

Das et al.[73] also found IFN-γ to cause marked significant increase in CD59 transcripts in the neutrophils of patients with SLE. The same had been true for TNF-α.

To summarize, CD59 is suggested to have a protective role in SLE; its positive modulation during flares and downregulation during remission suggest a compensatory mechanism and disease-related modulation of CD59 in SLE. Transcript levels of CD59 in neutrophils may help assessing the disease prognosis, and its appropriate modulation may help designing an effective therapeutic strategy for SLE.

To conclude, CD59 is associated significantly with the pathophysiology of RA and SLE and holds promise as a disease marker and therapeutic target for these two diseases. The molecule gets

differently modulated in RA and SLE. Studies are in preliminary stage but have opened up a new avenue for elucidation of pathophysiology, disease marker, and treatment strategy not only for SLE and RA but also for diverse immune inflammatory disorders.

Conflict of interest

1) The authors did not receive any payment or services from a third party (government, commercial, private foundation, etc.) for any aspect of the submitted, and there is no conflict of interest of any kind.
2) There were no financial activities of any kind outside the submitted work, and there is no conflict of interest regarding the same.
3) There is no patent, none planned nor submitted broadly relevant to the work.
4) No other relationships/conditions/circumstances exist that could present a potential conflict of interest.

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