Expression of complement regulatory proteins CD55, CD59, CD35, and CD46 in rheumatoid arthritis

Amanda Kirchner Piccoli[1], Ana Paula Alegretti[2], Laiana Schneider[3], Priscila Schmidt Lora[4], Ricardo Machado Xavier[5]

ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease associated with polyarticular inflammatory synovitis affecting mainly peripheral joints. It affects approximately 1% of the world population, being two to three times more prevalent in women. Rheumatoid arthritis has a complex and multifactorial pathogenesis. The synovium of the affected joints is infiltrated by T and B lymphocytes, macrophages, and granulocytes. The rheumatoid synovium has proliferative characteristics, forming the pannus, which invades cartilage and bone, leading to normal architecture destruction and function loss. The decreased expression of complement regulatory proteins (CRP) seems to play an important role in RA activity, and is associated with worsening of the clinical symptoms. In several models of autoimmune diseases, the overactivation of the complement system (CS) is the cause of disease exacerbation. This article aimed at reviewing the main aspects related to CS regulation in RA in order to provide a better understanding of the potential role of this system in the pathophysiology and activity of the disease.

Keywords: rheumatoid arthritis, complement system proteins, complement activation.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects mainly diarthrodial joints and periarticular structures, and can acquire a systemic character. Rheumatoid arthritis affects approximately 1% of the world population, being two to three times more common in women.[1]

The etiology of RA has not been completely clarified. However, environmental and genetic factors have contributed to the development of the disease. In the early stages of RA, proliferation and edema of the synovial layer cells occur, with infiltration of B and T cells, macrophages, and granulocytes. The synovium thickens, and the joint becomes swollen and painful. With progression, synovial proliferation leads to the formation of pannus, a tissue that invades the articular cartilage and bone. Joint destruction is irreversible. Osteoclasts reabsorb bone, and there is release of proteolytic enzymes, such as metalloproteinases, aggrecanases, and cathepsins, responsible for the destruction of extracellular matrix constituents, including bone and cartilage proteoglycans.[2] Neovascularization of the synovial layer surrounding the joint and of the pannus is evident.[3] As a result, cartilage and bone lose their normal architecture

Received on 03/15/2011. Approved on 06/16/2011. Authors declare no conflicts of interest. Financial Support: FIPE-HCPA.
Hospital de Clínicas de Porto Alegre – HCPA.
1. M.Sc. candidate in Medical Sciences at the Universidade Federal do Rio Grande do Sul – UFRGS; Biomedicine Specialist of the Service of Clinical Pathology of the Hospital de Clínicas de Porto Alegre – HCPA
2. M.Sc. in Medical Sciences at the UFRGS; Biochemical Pharmacist of the Clinical Pathology Service of the HCPA
3. Undergraduate student of Biomedicine at the Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA; Trainee of the Clinical Pathology Service of the HCPA
4. M.Sc. in Medical Sciences at the UFRGS; Researcher of the Service of Rheumatology of the HCPA
5. PhD Professor, Department of Rheumatology of the HCPA/UFRGS; Professor of the Medical School of the UFRGS; Chief of the Rheumatology Service of the HCPA
Correspondence to: Ricardo Machado Xavier, PhD. Hospital de Clínicas de Porto Alegre. Serviço de Reumatologia. Rua Ramiro Barcelos, 2350, sala 645 – Santana. CEP: 90035-003. Porto Alegre, RS, Brasil. E-mail: rmaxavier@hcpa.ufrgs.br

and function, leading to joint deformation, instability, pain, and inflammation.[4]

Synovial hyperplasia is a striking characteristic of RA patients, with overgrown membranes and villous projections of the synovium. The presence of autoantibodies, such as rheumatoid factor (RF) and citrullinated peptide antibody in the serum, provides an autoimmune character to the disease. The systemic characteristic of RA is represented by the potential impairment of multiple organs, which can be associated with the presence of these autoantibodies; however, this mechanism has not been well elucidated.[1]

COMPLEMENT SYSTEM

The complement system (CS) is composed of receptors and regulators bound to the cell membrane and different plasma proteins that interact with cells and mediators of the immune system (Figure 1).[5] More than 30 proteins act synergically to provide host defense against cells, microorganisms, and tissues identified as abnormal by a specific antibody. Most proteins are synthetized in the liver; however, myeloid cells, fibroblasts, and epithelial and endothelial cells can produce them.[6]

Evidence in the literature suggests that CS has an important immunoregulatory function through its role in humoral immunity, T cell immune modulation, and regulation of the tolerance to its own nuclear antigens. Although recognized by its highly efficient role in the defense against pathogens, such as bacteria, and cells infected by virus and parasites, the CS has also gained the attention of researchers due to its potential to damage cells of its own organism, because it is a complex system composed of several effector and receptor molecules involved in multiple immune responses.[7]

The complement cascade (CC) can be divided into four major phases: early complement activation; C3-convertase activation and amplification; C5-convertase activation; and formation of the membrane attack complex (MAC). Once activated, the CC generates effector molecules that interact with cell receptors indiscriminately. However, progression of the cascade is regulated by multiple regulatory and inhibitory molecules at all levels of the cascade.[7]

Early complement activation

Complement is activated through three different pathways. The alternative pathway is spontaneously and constantly activated on cell membrane, plasma, and other fluids. The classical pathway is triggered by an antibody bound to the target antigen. The lectin pathway begins when mannose-binding lectin, a soluble component of the organism, binds to carbohydrates present on the surface of the target microorganism. In 2006, Huber-Lang et al.[8] reported an additional complement activation pathway, independent of the C3 action, and mediated by the action of thrombin on C5 convertase. Other complement

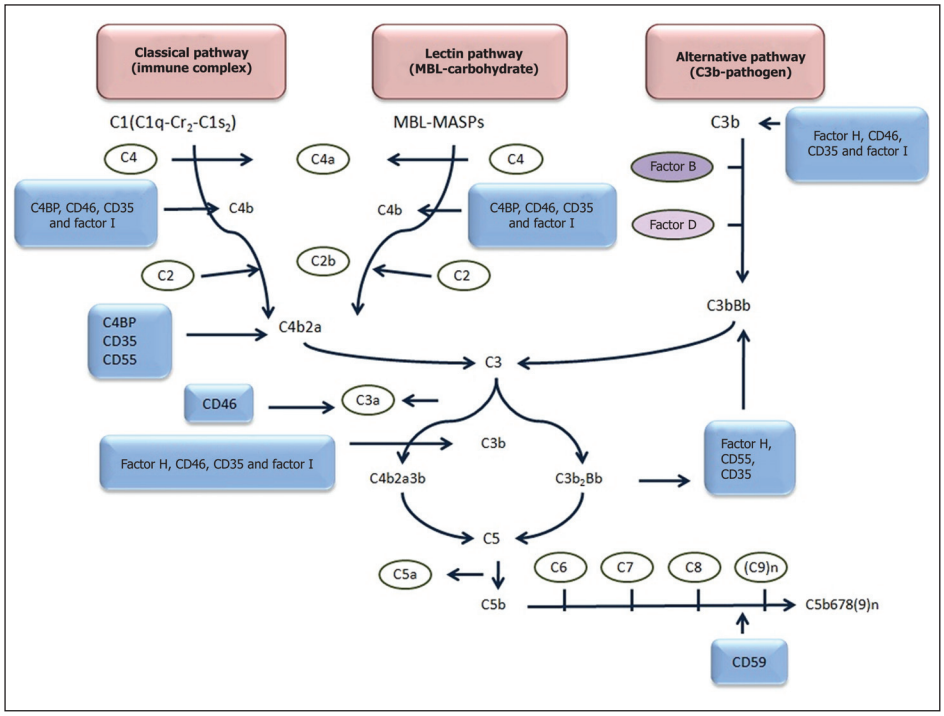

Figure 1
Complement can be activated through the classical, lectin, and alternative pathways. The C1 component is composed of C1q, C1r, and C1s, and recognizes the immune complex bound to cell membrane; mannose-binding lectin (MBL) recognizes certain carbohydrates on the membrane of some specific pathogens; and C3b recognizes carbohydrates present on the membrane of pathogens. All activation pathways originate the formation of C3 and C5 convertases, which generate anaphylatoxins C3a and C5a, opsonin C3b, and the membrane attack complex (MAC). C3b also amplifies the alternative pathway. Figure adapted from Kemper.[5]

Table 1
Major inhibitory functions of complement regulatory proteins CD55/CD59

Protein	Complement regulatory function
CD55	Inhibits C3 and C5 cleavage by inhibiting the formation of new C3 and C5 convertases, in addition to accelerating the degradation of these pre-formed enzymes.
CD59	Interferes directly with the structuration of MAC through its physical incorporation in the complex being formed, preventing C9 units from binding to the C5b-8 complex.
CD46	Binds to the opsonins C3b and C4b, acting as a cofactor in their proteolytic degradation by the serine protease factor I.
CD35	Interacts with C3b and C4b to promote neutrophil-mediated phagocytosis. Acts as a cofactor to inactivate C3b and C4b to iC3b and iC4b through factor I.

activation pathways occur through proteases, such as plasmin, plasma calycrein, and elastase, which cleave and activate C3.[9] The activation of each of these pathways results in the first enzyme of the cascade, C3 convertase.

C3 convertase and amplification

C3 convertase cleaves the central component of complement, C3, into C3a, an anaphylactic and antimicrobial peptide, and opsonin C3b. In the classical and lectin pathways, C3 convertase is formed by a fragment of C4b and C2a (C4b2a), while, in the alternative pathway, C3b and factor Bb are part of this enzyme (C3bBb).[9] Cleavage is followed by a reaction of amplification that generates additional C3 convertases, leading to the accumulation of more C3b close to where they are generated.[9] The C3b fragments cover microbial surfaces or cell debris undergoing apoptosis, and signal these particles for rapid phagocytosis. On the membrane surface of its own intact cells, under normal conditions, C3b accumulation is prevented by complement regulatory proteins (CRP), inhibiting progression of the cascade. Subsequently, C3b is inactivated and degraded. Its degradation products mediate other important effector functions.[7,9]

C5 convertase

If activation progresses, a new enzyme is generated, C5 convertase (C4b2a3b for the classical and lectin pathways, and C3bBbC3b for the alternative pathway). This enzyme cleaves C5, releasing the powerful anaphylactic peptide, C5a, and the fragment that induces the final phase, C5b.[7,9]

MAC formation

C5b recruits the components C6, C7, C8, and C9 for the target surface. The change in conformation of these soluble and hydrophilic proteins and their aggregation induce the formation of a complex, in which the functional unit is a pore inserted in the phospholipid bilayer that interferes with the property of membrane selective permeability, allowing the entrance of water, ions, and small molecules into the cytosol, leading to cell lysis.[10] Recent studies have reported additional functions to MAC, including the stimulating activity on T helper cells and platelet activation.[11,12]

In an acute inflammatory reaction, complement acts at all phases by activating pro-inflammatory mediators, producing anaphylactic peptides, cytolytic and antimicrobial components, recruiting cells, and inducing effector responses. Complement has other biological activities in the organism, such as opsonization and phagocytosis, solubilization and removal of immune complexes (IC) and apoptotic cells, and interface between innate and adaptive immunity. In addition, complement participates in angiogenesis, mobilization of hematopoietic progenitor cells, tissue regeneration, and lipid metabolism. These effects occur by binding the activation products with specific membrane receptors present in different cell types.[9]

Complement regulatory proteins CD55, CD59, CD46, and CD35

To prevent complement-mediated injury, normal cells have regulatory mechanisms constituted by proteins categorized into two major classes: soluble in biological fluids, such as properdin and factor H; and cell-membrane-anchored proteins, such as CD55 (or decay-accelerating factor – DAF), CD59 (or membrane inhibitor of reactive lysis – MIRL), CD46 (or membrane cofactor protein – MCP), and CD35 (or complement receptor type 1 – CR1) (Table 1).[13]

Regulatory cell-membrane-anchored proteins control the three complement activation pathways. Regulatory soluble proteins are more specific and control either the alternative or the classical or the lectin pathways, acting almost exclusively on C3 or C4. This review approaches exclusively the regulatory cell-membrane-anchored proteins.

The mechanism of action and the way these proteins attach to the cell membrane differ amongst themselves. CD55 prevents the cleavage of C3 and C5 by inhibiting the formation

of new C3 and C5 convertases, in addition to accelerating the decay of these pre-formed enzymes.[14] The protein CD59 interferes directly with the structuration of MAC through its physical incorporation in the forming complex, preventing C9 units from binding to the C5b-8 complex.[15] On the other hand, CD46 and CD35 act on the C3b and C4b inactivation. CD35 also participates in the IC processing and cleaning.[13]

The CD55 is a globular glycoprotein anchored to the membrane by glycosylphosphatidylinositol (GPI).[13] It is expressed in different cell types and found in the soluble form in tears, saliva, urine, synovial fluid, cerebrospinal fluid, and plasma.[16] In addition to its function of complement regulation, it acts as a negative modulator of the T cell response,[17] and seems to protect cells against the natural killer (NK)-mediated lysis.[18] In the epithelial mucosa, CD55 regulates the movement of neutrophils through epithelial layers.[19] It also acts as a ligand of intercellular adhesion, interacting with CD97 in leukocytes,[20] and as a receptor for certain virus and microorganisms.[21]

CD59 is also a globular glycoprotein anchored to the membrane by GPI. Because it plays a crucial role in preventing damage to its own cells by the inadequate accumulation of MAC, this protein is widely expressed in most tissues and all circulating cells, such as synovium, erythrocytes, and leukocytes. Its role in the complement regulation has been well defined. However, properties of cell signaling have been evidenced due to its location inside the lipid layers – central for immune synapse formation.[22] CD59 seems to be involved in T cell adhesion and activation,[23] neutrophil activation through tyrosine kinase,[24] and cell death induction.[25] In addition, Omidvar et al.,[26] assessing the significance of CD59 on target cells in modulation of cytotoxicity, have reported an increased susceptibility of CD59-expressing target cells to NK cell-mediated lysis.

Membrane cofactor protein or CD46 is a transmembrane protein expressed in all cells, except for erythrocytes.[13] Its major function is to protect autologous cells from complement attack through C3 inactivation. It binds to opsonins C3b and C4b, acting as a cofactor in their proteolytic degradation through serine-protease factor I.[13] In addition to its role in innate immunity, CD46 also regulates the acquired immune response. The co-stimulation of $CD4^+$ T cells with CD46 induces the proliferation of these cells and differentiation to a specific class of regulatory T cells, called Tr1[27] and characterized by expressing interferon γ (IFNγ), interleukin 10 (IL10), and other molecules.[28]

Changes in surface molecules during apoptosis, due to CD46 and CD59 loss, allow cell death to occur due to complement activation and consequent opsonization by C3b and C4b, followed by phagocytosis.[7] CD46 is a receptor of a growing list of human pathogens, such as human herpes virus 6, measles virus, *Streptococcus pyogenes*, adenovirus, *Neisseria* sp.[29-31] The ubiquity of surface expression, regulatory activity, and cell signaling contribute to make CD46 the target of multiple pathogens.[32]

The formation and accumulation of IC is one of the immune mechanisms that occur in RA and other autoimmune diseases. In physiological conditions, these complexes can be removed from the bloodstream via complement receptors (CR), such as CD35. CD35 is a transmembrane single-chain glycoprotein[33] that interacts with C3b and C4b to promote neutrophil-mediated phagocytosis, and acts as a cofactor to inactivate C3b and C4b to iC3b and iC4b, via factor I.[34] It is expressed in different cell types, such as erythrocytes, and myeloid and lymphoid cells.[35] Its biological function varies according to the cell in which it is expressed.

In phagocytic cells, CD35 is involved in the adhesion and uptake of particles covered with C3b and C4b, while, in B lymphocytes and follicular dendritic cells, it promotes antigen localization and processing.[36] In humans, 90% of total CD35 is found in the erythrocytes, where it binds to microorganisms or C3b- or C4b-opsonized IC, processing and transporting them through phagocytes to the liver and spleen.[37] Microorganisms, such as *Leishmania*, mycobacteria and HIV, when covered with C3b, use CD35 to enter the host cell.[38] More recently, CD35 in *Plasmodium-falciparum*-non-infected erythrocytes has been identified as a receptor for the infected ones.[39]

The relevance of CRP in humans can be evidenced in studies on acquired hemolytic disease, paroxysmal nocturnal hemoglobinuria (PNH), in which acquired mutations in the hematopoietic stem cell originate a cell line with early block of the synthesis of GPI anchors, responsible for maintaining dozens of proteins with specific functions, such as CD55, CD59, and CD46, adhered to plasma membrane. Failure to synthesize a mature GPI molecule generates absence of all surface proteins normally anchored by it.[40]

Literature on the profile of the normal expression of these proteins in blood cells is scarce. In 2001, Oelschlaegel et al.[41] assessed, by use of flow cytometry (FC), samples of 52 healthy blood donors and obtained a reference value of 3% of CD55/CD59 deficiency in circulating erythrocytes and granulocytes. Christmas et al.[42] have reported changes in the expression levels of the regulatory proteins CD46, CD55 and CD59 in monocytes and subpopulations of lymphocytes after activation with phytohemagglutinin and lipopolysaccharides. Only monocytes showed a uniform increase in regulators after activation with phytohemagglutinin, and, except for CD46,

using lipopolysaccharides. These data reinforce the concept that the regulation of the expression of these regulatory proteins is neither coordinated nor uniform in different leukocyte subpopulations.[43]

The role of complement and the proteins CD55/CD59/CD46/CD35 in RA

In RA, complement activation occurs initially through the classical pathway due to the presence of autoantibodies, IC, and apoptotic cells in the joint. The involvement of the alternative pathway has been evidenced because of the presence of Bb fragments in the synovial fluid. This pathway can be activated by the immunoglobulin A (IgA)-type RF present in some patients with RA and/or type-II collagen, specific for cartilage, which is exposed as a result of proteolysis during the disease. High levels of complement activation products, such as MAC, release of anaphylatoxins C3a and C5a, and increased C3 and C4 consumption can be detected in the synovial fluid. Thus, the CS overactivation and the absence or reduction in the expression of CRP are factors that contribute to disease exacerbation.[1]

It is possible that, to control the excessive complement activation in the joint, the synovial tissue expresses CRP. Analyses of CRP expression in the rheumatoid synovium have revealed an increase in CD55[44] and a decrease in CD59 compared to non-inflamed synovium.[45] These findings suggest that CD59 can be the key to synovial membrane protection, and its lost could be associated with a higher susceptibility to damage by MAC.

Williams et al.[46] have assessed the role of CD59 in the protection of the articular tissue in a murine model of antigen-induced arthritis (AIA). These authors have shown that mice with CD59 deficiency had a higher deposition of MAC and articular damage compared to $CD59^{+}$ controls. To confirm whether disease exacerbation was due to absence of CD59 in the joint, these authors have reconstituted the CD59 expression using recombinant membrane-targeted CD59 (sCD59-APT542). An improvement was observed in the group treated with sCD59-APT542 compared to the group receiving recombinant untargeted CD59 (sCD59). This study has shown that MAC is one of the major effectors of articular damage in the AIA model.

Hoeck et al.,[47] assessing CD55 and/or D97 deletion, have identified that mice with CD55 deficiency showed a reduction in RA activity, different from what occurs in other diseases in which this deficiency seems to be an aggravating factor. CD55, present in fibroblast-like synoviocytes, binds to the adhesion-class heptahelical receptor CD97 present in the macrophages migrating to the joint, worsening inflammation. According to these authors, mice with a deficiency in CD55 or CD97, or those with an interaction blockage by use of an anti-CD97 antibody, have a reduction in the arthritis activity.

Assessments of rheumatoid joints have shown them to be a hypoxic environment associated with synovial cells proliferation and increased metabolic demand, combined with periodical occlusions of microvessels and cycles of hypoxia-reoxygenation. Kinderlerer et al.[48] have reported that statins have, in addition to anti-inflammatory effects on RA, cytoprotective effects and highlighted the improvement in the regulation of CRP expression and increase in CD59 expression in endothelial cells in hypoxic situations after the use of atorvastatin, thus preventing C3 and C9 deposition and cell lysis.

In RA, inflammation is not restricted to the joint, but occurs in a systemic form. In 1992, Gadd et al.[49] reported a significant increase in CD35 expression in peripheral blood (PB) monocytes of RA patients compared with controls. In contrast, the expression of CD35 in synovial fluid (SF) monocytes was significantly lower than that in PB monocytes. According to the authors, these data indicate a systemic change in the immune phenotype of monocytes from RA patients, thus allowing recruitment to the inflammation sites.

Torsteinsdóttir et al.,[50] assessing the activation of PB monocytes from RA patients, have identified, by use of FC, an elevated expression of CD35 in these cells compared to controls, which is in accordance with the findings of the studies by McCarthy et al.[51] and Gadd et al.[49] After four to six weeks of treatment with low doses of prednisolone, the expression normalized. According to the authors, the monocytes of RA patients showed signs of activation in peripheral circulation, related to adhesion and phagocytosis, and consequent synovial infiltration.

Synovial infiltration by leukocytes involves, in addition to mononuclear cells, neutrophils. Jones et al.,[52] aiming at assessing whether changes in the expression of certain proteins interfere with the migration of neutrophils to the joint, and with their subsequent activation and capacity to survive to complement attack, have assessed the expression of CD59, CD55, CD46, and CD35 in neutrophils o fPB and SF in RA patients and healthy individuals. The authors have identified a reduced expression of CD55, CD46, and CD35, but not a significant difference for CD59, in the PB neutrophils of RA patients compared with that of controls. The SF neutrophils expressed significantly more CD55 and CD35 compared with the PB neutrophils, and the expression of CD46 was lower and that of CD59 showed no difference between groups. According to the authors, the difference in expression of these molecules

leads to increased adhesion, resistance to complement, and higher capacity of the neutrophils to remove IC.

It is not clear if these changes contribute to the disease or are consequence of the chronic inflammatory state. However, data suggest that CRP can act systematically to suppress the disease activity associated with the uncontrolled complement activation in RA, similarly to that which occurs in other autoimmune diseases, as reviewed by Alegretti et al.[53]

The antibodies produced in autoimmune diseases bind to antigens of the cell surface or form IC after binding to circulating antigens. These ICs tend to deposit in organs, subsequently activating the CS, and causing damage to tissues. Despite the recognized effector action of complement on organ damage in autoimmune diseases, little is known about the mechanism of CRP in modulating the severity of that damage.[13]

Some studies in patients with systemic lupus erythematosus (SLE) have shown a reduction of these CRP and a possible association with the presence of cytopenia in these patients. Richaud-Patin et al.[54] have shown a reduction in the intensity of CD55 and CD59 expression in the membrane of erythrocytes of lupus patients with secondary autoimmune hemolytic anemia (AIHA). The same has been observed in the lymphocytes of patients with lymphopenia compared with those of controls.[55,56]

CONCLUSION

Few studies about the profile of the expression of complement regulatory proteins CD55, CD46, CD35, and CD59 in RA patients are found in the literature, and some are controversial. The acquired deficiency or overexpression of these proteins in some autoimmune diseases seems to be associated with the disease activity. Most studies on RA have shown that CD35 is increased in PB monocytes, and only one study has reported a reduction in CD55, CD35, and CD46 in PB neutrophils. Aiming at explaining the changes in the expression of these molecules, the major hypotheses of these studies are related to their major action as inhibitors of the exacerbated complement activation, to their functions of immune regulation or cell adhesion, to stimulatory or inhibitory factors that regulate their expression, or even to the presence of specific enzymes that cleave the binding of these proteins in the cell membrane.

The pattern of CRP expression in RA patients has not been well established. Defining that pattern of expression is important to assess its potential meaning in the development of the inflammatory process or cytopenia in these patients, and also to optimize the use of cell depletion therapies involving CS activation, such as anti-CD20 therapies.

REFERENCES

REFERÊNCIAS

1. Okroj M, Heinegård D, Holmdahl R, Blom AM. Rheumatoid arthritis and the complement system. Ann Med 2007; 39(7):517-30.
2. Lark MW, Bayne EK, Flanagan J, Harper CF, Hoerrner LA, Hutchinson NI *et al*. Aggrecan degradation in human cartilage. Evidence for both matrix metalloproteinase and aggrecanase activity in normal, osteoarthritic, and rheumatoid joints. J Clin Invest 1997; 100(1):93-106.
3. Szekanecz Z, Gáspár L, Koch AE. Angiogenesis in rheumatoid arthritis. Front Biosci 2005; 10:1739-53.
4. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nat Rev Drug Discov 2003; 2(6):473-88.
5. Kemper C, Atkinson JP. T-cell regulation: with complement from innate immunity. Nat Rev Immunol 2007; 7(1):9-18.
6. Wagner E, Frank MM. Therapeutic potential of complement modulation. Nat Rev Drug Discov 2010; 9(1):43-56.
7. Zipfel PF, Skerka C. Complement regulators and inhibitory proteins. Nat Rev Immunol 2009; 9(10):729-40.
8. Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR *et al*. Generation of C5a in the absence of C3: a new complement activation pathway. Nat Med 2006; 12(6):682-7.
9. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol 2010; 11(9):785-97.
10. Morgan BP. Complement membrane attack on nucleated cells: resistance, recovery and non-lethal effects. Biochem J 1989; 264(1):1-14.
11. Bossi F, Fischetti F, Pellis V, Bulla R, Ferrero E, Mollnes TE *et al*. Platelet-activating factor and kinin-dependent vascular leakage as a novel functional activity of the soluble terminal complement complex. J Immunol 2004; 173(11):6921-7.
12. Bossi F, Rizzi L, Bulla R, Debeus A, Tripodo C, Picotti P *et al*. C7 is expressed on endothelial cells as a trap for the assembling terminal complement complex and may exert anti-inflammatory function. Blood 2009; 113(15):3640-8.

13. Kim DD, Song WC. Membrane complement regulatory proteins. Clin Immunol 2006; 118(2-3):127-36.
14. Lublin DM, Atkinson JP. Decay-accelerating factor: biochemistry, molecular biology, and function. Annu Rev Immunol 1989; 7:35-58.
15. Farkas I, Baranyi L, Ishikawa Y, Okada N, Bohata C, Budai D *et al*. CD59 blocks not only the insertion of C9 into MAC but inhibits ion channel formation by homologous C5b-8 as well as C5b-9. J Physiol 2002; 539(Pt 2):537-45.
16. Medof ME, Walter EI, Rutgers JL, Knowles DM, Nussenzweig V. Identification of the complement decay-accelerating factor (DAF) on epithelium and glandular cells and in body fluids. J Exp Med 1987; 165(3):848-64.
17. Heeger PS, Lalli PN, Lin F, Valujskikh A, Liu J, Muqim N *et al*. Decay-accelerating factor modulates induction of T cell immunity. J Exp Med 2005; 201(10):1523-30.
18. Finberg RW, White W, Nicholson-Weller A. Decay-accelerating factor expression on either effector or target cells inhibits cytotoxicity by human natural killer cells. J Immunol 1992; 149(6):2055-60.
19. Lawrence DW, Bruyninckx WJ, Louis NA, Lublin DM, Stahl GL, Parkos CA *et al*. Antiadhesive role of apical decay-accelerating factor (CD55) in human neutrophil transmigration across mucosal epithelia. J Exp Med 2003; 198(7):999-1010.
20. Hamann J, Vogel B, van Schijndel GM, van Lier RA. The seven-span transmembrane receptor CD97 has a cellular ligand (CD55, DAF). J Exp Med 1996; 184(3):1185-9.
21. Pham T, Kaul A, Hart A, Goluszko P, Moulds J, Nowicki S *et al*. DRA-related X adhesins of gestational pyelonephritis-associated Escherichia coli recognize SCR-3 and SCR-4 domains of recombinant decay-accelerating factor. Infect Immun 1995; 63(5):1663-8.
22. Kimberley FC, Sivasankar B, Paul Morgan B. Alternative roles for CD59. Mol Immunol 2007; 44(1-3):73-81.
23. Deckert M, Kubar J, Bernard A. CD58 and CD59 molecules exhibit potentializing effects in T cell adhesion and activation. J Immunol 1992; 148(3):672-7.
24. van den Berg CW, Cinek T, Hallett MB, Horejsi V, Morgan BP. Exogenous glycosyl phosphatidylinositol-anchored CD59 associates with kinases in membrane clusters on U937 cells and becomes $Ca(2^{+})$-signaling competent. J Cell Biol 1995; 131(3):669-77.
25. Monleón I, Martínez-Lorenzo MJ, Anel A, Lasierra P, Larrad L, Piñeiro A *et al*. CD59 cross-linking induces secretion of APO2 ligand in overactivated human T cells. Eur J Immunol 2000; 30(4):1078-87.
26. Omidvar N, Wang EC, Brennan P, Longhi MP, Smith RA, Morgan BP. Expression of glycosylphosphatidylinositol-anchored CD59 on target cells enhances human NK cell-mediated cytotoxicity. J Immunol 2006; 176(5):2915-23.
27. Cardone J, Le Friec G, Vantourout P, Roberts A, Fuchs A, Jackson I *et al*. Complement regulator CD46 temporally regulates cytokine production by conventional and unconventional T cells. Nat Immunol 2010; 11(9):862-71.
28. Barchet W, Price JD, Cella M, Colonna M, MacMillan SK, Cobb JP *et al*. Complement-induced regulatory T cells suppress T-cell responses but allow for dendritic-cell maturation. Blood 2006; 107(4):1497-504.
29. Giannakis E, Jokiranta TS, Ormsby RJ, Duthy TG, Male DA, Christiansen D *et al*. Identification of the streptococcal M protein binding site on membrane cofactor protein (CD46). J Immunol 2002; 168(9):4585-92.
30. Källström H, Blackmer Gill D, Albiger B, Liszewski MK, Atkinson JP, Jonsson AB. Attachment of Neisseria gonorrhoeae to the cellular pilus receptor CD46: identification of domains important for bacterial adherence. Cell Microbiol 2001; 3(3):133-43.
31. Mori Y, Yang X, Akkapaiboon P, Okuno T, Yamanishi K. Human herpesvirus 6 variant A glycoprotein H-glycoprotein L-glycoprotein Q complex associates with human CD46. J Virol 2003; 77(8):4992-9.
32. Riley-Vargas RC, Gill DB, Kemper C, Liszewski MK, Atkinson JP. CD46: expanding beyond complement regulation. Trends Immunol 2004; 25(9):496-503.
33. Erdei A, Prechl J, Isaák A, Molnár E. Regulation of B-cell activation by complement receptors CD21 and CD35. Curr Pharm Des 2003; 9(23):1849-60.
34. Krych-Goldberg M, Atkinson JP. Structure-function relationships of complement receptor type 1. Immunol Rev 2001; 180:112-22.
35. Roozendaal R, Carroll MC. Complement receptors CD21 and CD35 in humoral immunity. Immunol Rev 2007; 219:157-66.
36. Krych-Goldberg M, Hauhart RE, Subramanian VB, Yurcisin BM, 2nd, Crimmins DL, Hourcade DE *et al*. Decay accelerating activity of complement receptor type 1 (CD35). Two active sites are required for dissociating C5 convertases. J Biol Chem 1999; 274(44):31160-8.
37. Pham BN, Kisserli A, Donvito B, Duret V, Reveil B, Tabary T *et al*. Analysis of complement receptor Type 1 expression on red blood cells in negative phenotypes of the Knops blood group system, according to CR1 gene allotype polymorphisms. Transfusion 2010; 50(7):1435-43.
38. Cooper NR. Complement evasion strategies of microorganisms. Immunol Today 1991; 12(9):327-31.
39. Krych-Goldberg M, Moulds JM, Atkinson JP. Human complement receptor type 1 (CR1) binds to a major malarial adhesin. Trends Mol Med 2002; 8(11):531-7.
40. Arruda MM, Rodrigues CA, Yamamoto M, Figueiredo MS. Paroxysmal nocturnal hemoglobinuria: from physiopathology to treatment. Rev Assoc Med Bras 2010; 56(2):214-21.
41. Oelschlaegel U, Besson I, Arnoulet C, Sainty D, Nowak R, Naumann R *et al*. A standardized flow cytometric method for screening paroxysmal nocturnal haemoglobinuria (PNH) measuring CD55 and CD59 expression on erythrocytes and granulocytes. Clin Lab Haematol 2001; 23(2):81-90.
42. Christmas SE, de la Mata Espinosa CT, Halliday D, Buxton CA, Cummerson JA, Johnson PM. Levels of expression of complement regulatory proteins CD46, CD55 and CD 59 on resting and activate human peripheral blood leucocytes. Immunology 2006; 119(4):522-8.
43. Moutabarrik A, Nakanishi I, Namiki M, Hara T, Matsumoto M, Ishibashi M *et al*. Cytokine-mediated regulation of the surface expression of complement regulatory proteins, CD46(MCP), CD55(DAF), and CD59 on human vascular endothelial cells. Lymphokine Cytokine Res 1993; 12(3):167-72.
44. Hamann J, Wishaupt JO, van Lier RA, Smeets TJ, Breedveld FC, Tak PP. Expression of the activation antigen CD97 and its ligand CD55 in rheumatoid synovial tissue. Arthritis Rheum 1999; 42(4):650-8.
45. Konttinen YT, Ceponis A, Meri S, Vuorikoski A, Kortekangas P, Sorsa T *et al*. Complement in acute and chronic arthritides: assessment of C3c, C9, and protectin (CD59) in synovial membrane. Ann Rheum Dis 1996; 55(12):888-94.

46. Williams AS, Mizuno M, Richards PJ, Holt DS, Morgan BP. Deletion of the gene encoding CD59a in mice increases disease severity in a murine model of rheumatoid arthritis. Arthritis Rheum 2004; 50(9):3035-44.
47. Hoek RM, de Launay D, Kop EN, Yilmaz-Elis AS, Lin F, Reedquist KA *et al*. Deletion of either CD55 or CD97 ameliorates arthritis in mouse models. Arthritis Rheum 2010; 62(4):1036-42.
48. Kinderlerer AR, Steinberg R, Johns M, Harten SK, Lidington EA, Haskard DO *et al*. Statin-induced expression of CD59 on vascular endothelium in hypoxia: a potential mechanism for the anti-inflammatory actions of statins in rheumatoid arthritis. Arthritis Res Ther 2006; 8(4):R130.
49. Gadd SJ, Felzmann T, Majdic O, Maurer D, Petera P, Chen WJ *et al*. Phenotypic analysis of functionally associated molecules on peripheral blood and synovial fluid monocytes from arthritis patients. Rheumatol Int 1992; 12(4):153-7.
50. Torsteinsdóttir I, Arvidson NG, Hällgren R, Håkansson L. Monocyte activation in rheumatoid arthritis (RA): increased integrin, FC gamma and complement receptor expression and the effect of glucocorticoids. Clin Exp Immunol 1999; 115(3):554-60.
51. McCarthy D, Taylor MJ, Bernhagen J, Perry JD, Hamblin AS. Leucocyte integrin and CR1 expression on peripheral blood leucocytes of patients with rheumatoid arthritis. Ann Rheum Dis 1992; 51(3):307-12.
52. Jones J, Laffafian I, Cooper AM, Williams BD, Morgan BP. Expression of complement regulatory molecules and other surface markers on neutrophils from synovial fluid and blood of patients with rheumatoid arthritis. Br J Rheumatol 1994; 33(8):707-12.
53. Alegretti AP, Mucenic T, Brenol JCT, Xavier RM. O papel das proteínas reguladoras do complemento CD55/CD59 em células de sangue periférico de pacientes com lúpus eritematoso sistêmico. Rev Bras Reumatol 2009; 49(3):276-87.
54. Richaud-Patin Y, Pérez-Romano B, Carrillo-Maravilla E, Rodriguez AB, Simon AJ, Cabiedes J *et al*. Deficiency of red cell bound CD55 and CD59 in patients with systemic lupus erythematosus. Immunol Lett 2003; 88(2):95-9.
55. Alegretti AP, Mucenic T, Merzoni J, Faulhaber GA, Silla LM, Xavier RM. Expression of CD55 and CD59 on peripheral blood cells from systemic lupus erythematosus (SLE) patients. Cell Immunol 2010; 265(2):127-32.
56. García-Valladares I, Atisha-Fregoso Y, Richaud-Patin Y, Jakez-Ocampo J, Soto-Vega E, Elías-López D *et al*. Diminished expression of complement regulatory proteins (CD55 and CD59) in lymphocytes from systemic lupus erythematosus patients with lymphopenia. Lupus 2006; 15(9):600-5.