wjpls, 2023, Vol. 9, Issue 9, 03-15 *Reiew Article* ISSN 2454-2229

World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

THE INTERPLAY OF COMPLEMENTS AND THEIR REGULATORS IN THE HUMAN BODY

Rao Muhammad Abid Khan[1]*, Kulsoom[2], Ramsha Mukhtar[3], Muhammad Faisal[2], Muhammad Yaseen[4], Muhammad Shaheen Iqbal[5]

[1]Sindh Institute of Urology and Transplantation (SIUT), Sindh Institute of Medical Sciences (SIMS), Karachi 74200, Pakistan.
[2]Department of Microbiology, University of Karachi, Karachi 75270.
[3]Alamgir Welfare Trust International, Karachi, Pakistan.
[4]Riaz Ahmed Misri Memorial Hospital.
[5]FBRC PCSIR Complex Lahore.

***Corresponding Author: Rao Muhammad Abid Khan**
Sindh Institute of Urology and Transplantation (SIUT), Sindh Institute of Medical Sciences (SIMS), Karachi 74200, Pakistan.

Article Received on 05/07/2023 **Article Revised on 25/07/2023** **Article Accepted on 15/08/2023**

ABSTRACT
An infection can be seen as a battle between the invading pathogens and the host. Human body is equipped with natural defenses to fight off these invading pathogens. Complement system is an evolutionary conserved arm of innate immunity to handle this tug of war by several means including labeling of bacteria with opsonins, facilitating phagocytosis through chemoattractants, bacterial lysis through pore formation and production of antibodies by switching innate to adaptive immunity. However, by no means it is explicitly fool proof. Non-specific nature, over activation, polymorphism, genetic mutations, and alteration in self-cells (i.e. cancer) may result in unwanted complement-mediated damage to self-body. On the other hand, deficiencies in complement proteins result in high risk of getting frequent infections. Furthermore, complements are essential in maintaining homeostasis by coordinating inflammation, eliminating and recycling cellular debris, and maintaining apoptosis. Vigilant regulation of complement is essential to avoid self-harm to host body. One of the strategy for regulation is most of the complement proteins are synthesized as inactive precursors and each act as a triggered protease which successively cleaves other proteins in a cascade. Another manoeuvre is the group of charismatic proteins called regulators of complement activation (RCA). A number of soluble-circulating and membrane-bound RCA have been delineated so far in the literature. In this review, we describe the three complement pathways and interplay of complements and their soluble-circulating and membrane-bound regulators in the human body.

KEY WORDS: Complements, innate immunity, opsonin, phagocytosis, regulators, serine proteases.

BACKGROUND
Complement system is an evolutionary conserved arm of innate immunity, essential for combatting billions of microorganisms by interacting with adaptive immune system in the human host.[1] Peoples with complement deficiencies are at high risk of getting frequent infections.[2, 3] Complements are set of more than fifty membrane-bound and fluid-phase proteins most of which are synthesized in liver and circulate in blood as an inactive precursors. Each protein act as a triggered protease which successively cleaves other proteins in a cascade resulting in formation of effector molecules, opsonins and membrane attach complex (MAC) which facilitates phagocytosis and pore formation on the target cell.[4] Non-pathogenic microbes are normally recognized and destroyed by complement system, all successful pathogens including bacteria, spirochetes viruses, fungus and protozoa have evolved gambits to escape this host manoeuvre.[5] The Regulators of Complement Activation (RCA) are a fascinating group of proteins that prevent the host from self-destruction and link the innate and acquired immunity.[6]

COMPLEMENT SYSTEM
Depending on the distinct stimuli for activation of initiation protein, complement system is organized in three pathways: the classical (CP), lectin (LP) and alternative (AP) pathways. The CP is triggered by interaction between C1q and pre-bound immunoglobulin G or M class or specific pathogen associated molecular patterns (PAMPs). The four subclasses of human IgG are known to differ in activating complements and subclass IgG1 and IgG3 have been reported to activate complements effectively whereas IgG4 can not activate

complements.[7] The LP is initiated by pattern recognition of bacterial associated saccharide by Mannose binding lectin (MBL) or ficolins (ficolin-1, 2 or 3) or collectins. The AP is constitutively auto-activated through spontaneous hydrolysis of thioester bond in the C3 molecule[8] **Figure 01.**

C1 complex is composed of C1q, C1r and C1s. C1q binding to its ligand results in auto-activation of accompanying serine protease C1r which subsequently stimulates adjoining C1s. C1s cleaves C4 into C4a (whose function is poorly understood) and C4b. The exposed thioester domain of C4b permits binding of C2 and now C1s dissociates the smaller C2b while larger C2a remains attached to the C4b and generates CP C3 convertase (C4bC2a).[8]

Like C1q, the LP initiators: MBL, ficolins and collectins are also accompanied by proteases, termed as MBL-associated serine proteases (MASPs). Following interactions of LP initiators with microbial associated saccharides, MASPs become activated and MASP-2 specifically cuts C4 into C4a and C4b, while both MASP-1 and MASP-2 cleaves C2 into C2a and C2b. C2a attaches to C4b generating a C3 convertase identical to the CP.[8]

AP is the consequence of spontaneous hydrolysis of the C3 complement into conformational active form, C3(H2O). Formation of biologically active conformation can be boosted via synthetic and biotic influences. Factor B (FB) binds to the exposed thioester domain of C3(H2O) and becomes preferential substrate for Factor D (FD). FD disassociates Ba while Bb remains attached to C3(H2O), making the fluid-phase C3 convertase, C3(H2O)Bb. Fluid-phase C3 convertase cleaves C3 into two proteolytic fragments C3a and C3b. While C3a is an important inflammatory mediator, C3b covalently binds to exposed hydroxyl groups on microbial surfaces. Any bound C3b on one hand interacts with FB (a pro-enzyme), and on other hand further augments the C3b deposition by the CP and LP through positive feedback loop. FD detaches the Ba while Bb remains attached to C3b; forming AP C3 convertase, C3bBb.[9] The AP is unique in sense it is activated by its own product C3b and C3b also amplifies the triggered CP and LP.[10] The C3 convertase of AP is unstable and has short half-life **Figure 01.**

Factor P (Properdin) is 53-kDa protein that occurs in blood at a specific ratio (26:54:20) of dimers, trimers, and tetramers respectively. Properdin binds to C3 convertase (C3bBb) and C5 convertase (C3bBbC3b) and stabilize the enzyme C3 convertase (C3bBb) 5-10 fold from rapid inactivation by forming a lattice of properdin.[11, 12] Furthermore, properdin can itself bind to microbial surfaces and offer a platform for the in situ assembly and activity of the AP C3 convertase, thus acting as a positive regulator.[13] Properdin contains numerous identical subunits, each carrying a distinct ligand-binding site and its maximum stabilizing activity depends on binding multiple ligands at a time.[10] Individuals with inherent deficiency of properdin are more susceptible to lethal Neisseria infections and recombinant properdin (P_n) was shown more promising over native and was protective against *N. menigitidis* and *S. pneumoniae* infections.[9]

All three pathways converge in the formation of two types of C3 convertases i.e. AP C3 convertase (C3bBb) and CP/LP C3 convertase (C4b2a). Despite the evolutionary different ancestors, both C3 convertases have identical function and act on same substrate. C3 convertase acts as a serine protease and cleave the core complement component C3 into two proteolytic fragments C3a and C3b.[14] C3 is an evolutionary conserved, 186 kDa mammalian protein, mostly synthesized in the liver and belongs to α-macroglobulin family. This large (1400-1800 amino acids) molecules is central to the three pathways and it has been the focus of intensive studies due to its functional versatility. C3 gene is located in chromosome 19 and several allelic variants exist, of which the C3F and C3S are the most common.[15] C3 is comprised of two chains; α (111 kDa) and β (75 kDa) connected together by many disulfide bonds and noncovalent forces. The C3 convertase of either the CP(C4b2a) or the AP(C3bBb) cleaves between residues 77(Arg) and 78 (Ser) of the α-chain and release C3a (9 kDa, an anaphylatoxin) and C3b (177 kDa, an opsonin). C3b is composed of α–chain (102 kDa) and β–chain (75 kDa) and binds covalently to the hydroxyl or amino groups present on cell surfaces, immune complexes or complex carbohydrates through its thiolester group.[16] Activity of thiolester group involves the Glu 990 and Cys 988, both of which are situated in the C3d fragment. Each C3 convertase additionally binds to the C3b fragment and forms two types of C5 convertases i.e. C3bBbC3b and C4b2bC3b which subsequently cleaves C5. C5 is structurally similar to C3 and also belongs to the α-macroglobulin family. C5 is cleaved into 10.4 kDa C5a (an anaphylatoxin) and a large integral membrane attack complex (MAC) component; C5b. C5b cleaves downstream C6, C7, C8 and C9 in a cascade. C5b-7 permits interaction and C5b-8 promotes insertion into the lipid bilayer of target cell. Finally, the annexation of several C9 molecules results in the construction of a tubular MAC pore on the target surface which results in cell lysis[17, 18] **Figure 01.** The complement system thus either labels the pathogens to be destroyed by phagocytes or execute MAC mediate lysis. Comparatively, gram-positive bacteria are more resistant to MAC mediated lysis due to their thick peptidoglycan outer layer.[19]

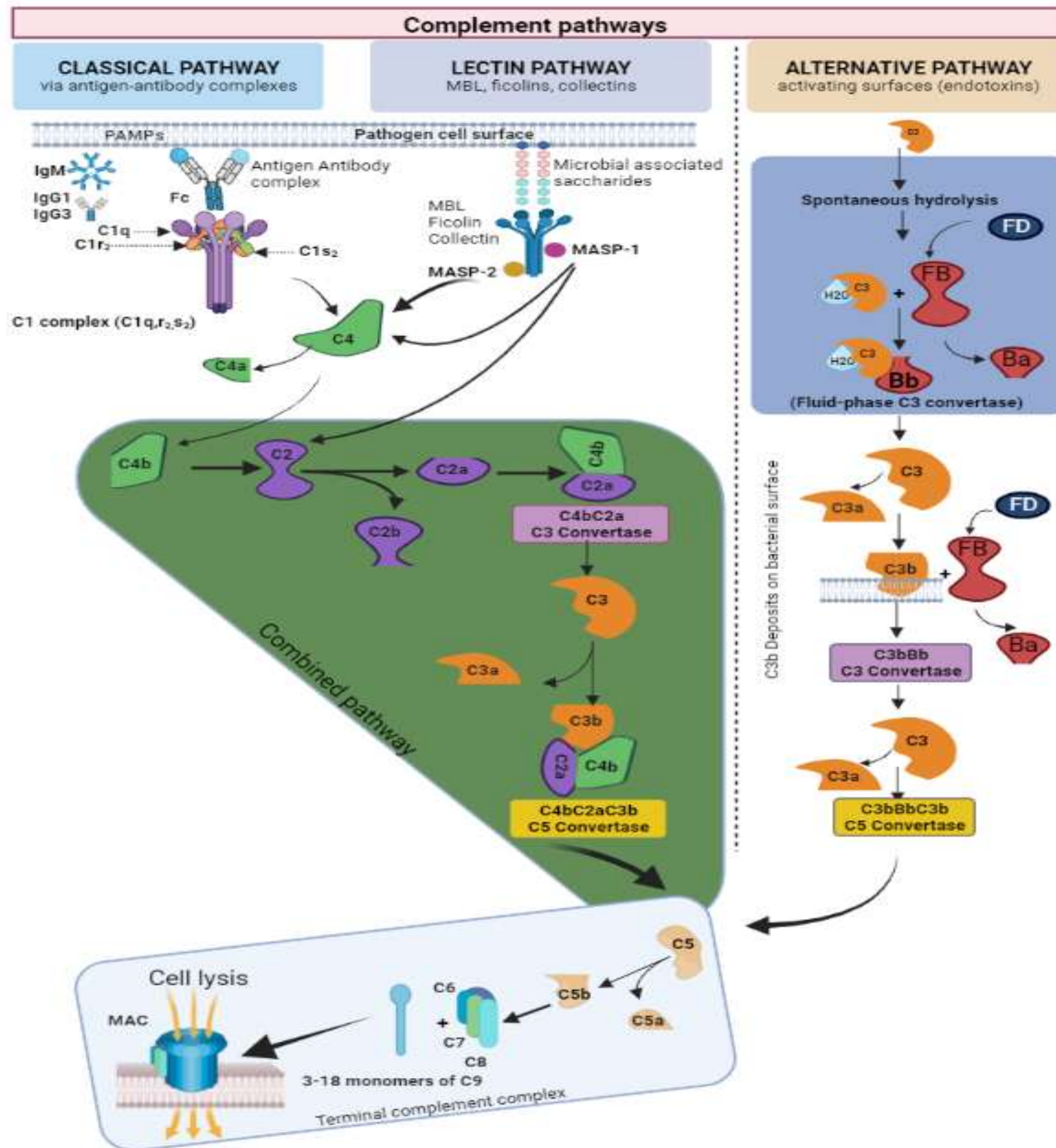

Figure 01: Shows the schematic representation of three complement pathways: Classical pathway, Lectin pathway and Alternative pathway. Green triangular box depicts combined pathway where both classical and lectin pathway get merge. Dark blue box depicts the formation of fluid-phase C3 convertase of alternative pathway. Light blue box shows the terminal complement complex where all three pathways merge.

REGULATORS OF COMPLEMENT ACTIVATION (RCA)

Uncontrolled and over activation of complements results in autoimmune disorders.[4] Vigilant regulation of complement is essential to avoid self-harm to host body. Complement control proteins (CCPs) or RCA are present in sufficient concentrations in the blood and on the surface of self-cells which prevent inadvertent targeting by the complement system. Two types of complement regulators: soluble-circulating [Factor H, C4b-binding protein (C4BP), factor I (FI), C1 inhibitor (C1-INH), factor B (FB), factor D (FD), Clusterin and vitronectin] and membrane-bound [CD35 (complement receptor 1; CR-1), CD21 (complement receptor 2; CR-2), CD46 (membrane cofactor protein; MCP), CD55 (decay accelerating factor; DAF) and CD59) inhibitors limit the damaging effects of complement on host cells.[20, 21] The genes for many of these regulators are located on chromosome 1q32. Complement regulators are collectively termed regulators of complement activation (RCA).[22]

Soluble-circulating Regulators of complement activation (sRCA)

Factor H:

FH is the 150 kDa, 1213 amino acids (a:a), single-chain glycoprotein, with functional domains extending over the entire length of the chain.[23] FH is the main soluble RCA

for the AP and amongst the most copious complement components (116 to 562 µg/ml) in human blood.[24] FH is chiefly synthesized in liver, however small amount is formed by fibroblasts, monocytes, platelets and endothelial cells.[25] Normal recognition of host cell glycan structures (polyanions, cell-surface markers) and C3b fragments is essential for FH function. Polymorphism or genetic mutations in host cells lead to inadequate recognition by FH resulting in unwanted complement-mediated damage to body.[24] Likewise, recognition of altered self-cells (i.e. cancer) or pathogens as self by FH can be misused as an immune evasion strategy.[24] FH mainly constrains the formation of C3 convertase (C3bBb) of AP either by deterring the binding of FB to C3b or by stimulating FI which breaks down C3b.[26] FH also promotes C3bBb dissociation (24). FH is comprised of 20 homologus short consensus repeat (SCR) domains, of each contain four highly invariant cysteine residues and several conserved amino acids.[23] FH contains three C3b binding sites (SCRs 1–4, SCRs 6–10 and SCRs 16–20) and two heparin binding sites (near SCR 13 and SCR 6-10). SCR 1-4 also exhibits cofactor activity for factor I.[27] Pathogens can hijack FH by expressing FH binding proteins (streptococcal M6 protein, Yad A protein and glycoprotein (gp) 120) to evade from complement-mediated damage.[9, 28] A similar 42-kDa protein, FHL-1 is also encoded by the same gene. FHL-1 is smaller than FH and comprised of seven identical SCRs that are identical, with the exception of 4 amino acids at the C terminus, to SCR1 through SCR7 of FH. FH and FHL-1, each regulate complement activity by at least three mechanisms **Figure 04.** First, these regulatory proteins can bind the opsonin C3b, thereby blocking the interaction of C3b with complement factor B and with C3b receptors on phagocytes. Secondly, they function as cofactors in the factor I-mediated cleavage of C3b. C3b cleavage blocks formation of the C3 convertase C3bBb, thereby blocking the amplification mechanism of the alternative complement pathway. Thirdly, both RCAs promote the decay acceleration of C3bBb **Figure 02.**

C4 binding protein (C4BP):

C4BP is a proline-rich, chymotrypsin-labile, macromolecule glycoprotein (450-590 kDa).[29] C4BP is a chief RCA for CP/LP and three isoforms circulate in plasma; 7 alpha chains and 1 Beta chain, 6 alpha chains and 1 Beta chain, and 7 alpha chains without a Beta chain. The 7 identical α-chains (70 kDa) and one β-chain (45 kDa) is the most abundant C4BP isoform.[30] C4BP is synthesized in the liver, exhibits lipid binding properties and exist in triglyceride-rich particles. C4BP reveals positive correlation with total cholesterol, triacylglycerol and VLDL cholesterol. It averts C4b from binding C2b thus preventing the formation of CP/LP C3 convertase (C4bC2b).[26] Furthermore, it accelerates the natural decay of CP/LP C3 convertase and enhances the cleavage of soluble and surface-bound C4b by serving as a cofactor for FI[31] **Figure 04.** Chymotrypsin cleaves C4BP into a large (160 kDa) carbohydrate-containing core domain and a small (48 kDa) functional domain which exhibits cofactor activity for FI.[29] Murine C4BP domain acts as an adjuvant and its fusion with malarial merozoite surface protein has shown promising protection against malaria in mice[32] **Figure 02.**

Factor I (FI) or C3b/C4b inactivator:

Factor I (FI) is the decisive, soluble-circulating RCA for all complement pathways. Complete absence of FI is rare while physiological relevance of FI deficiency is demonstrated by severe illnesses such as autoimmune disorders, recurrent infections, and glomerulonephritis. The *CFI* gene which encodes FI is located on chromosome 4. FI is mostly synthesized in the liver but also in fibroblast, monocytes, keratinocytes and endothelial cells. FI is an 88 kDa serum serine proteinase, mainly synthesized in the liver and utilizes the cofactors such as FH, C4bBP, CR-1 and MCP to degrade the α-chain of complements C4b and C3b to generate iC4b and iC3b respectively[22, 33] **Figure 04.** FI is an acute phase protein and its concentration (~35 µg/ml) markedly increases during inflammation **Figure 02.**

C1 inhibitor (C1-INH):

C1-INH is the 76 kDa, highly glycosylated serpin or serine protease inhibitor mainly synthesized in the liver and other cells including endothelial cells, monocytes, fibroblasts[34], microglial cells, megakaryocyte[35] and the placenta.[36] C1-INH is composed of 478 amino acids and two domains: N-terminal, non-serpin, mucin-like domain (113 amino acids), and a serpin domain (365 amino acids). Although the configuration of serpin domain is homologous to other plasma serpins and is crucial for the activity; relatively it is a poor inhibitor and its activity can be triggered by heparin and other glycosaminoglycans (37). The N-terminal domain binds to lipopolysaccharides and E-selectin. C1-INH synthesis can be induced by several factors including Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) Interferon- α and γ and colony stimulating factor-1.[36] C1-INH regulates the CP by inhibiting two serine proteases; C1r and C1s thus preventing the C1 complex formation. C1-INH also regulates the LP by inhibiting MASP-1 and MASP-2[38] **Figure 04.** Beside inactivating complement pathways C1-INH also inactivates the different proteases in the coagulation, contact and fibrinolytic system.[39] Broadly, C1-INH suppresses inflammation, gram negative sepsis, endotoxic shock and regulates vascular permeability.[40, 41] Human plasma-purified C1-INH has been used in treating hereditary heterozygous angioedema since 1970's[42] and studies have shown promising beneficial effects in preventing graft rejection with minimal toxicity.[43] Recombinant C1-INH has recently been produced and clinical trials are in progress[39] **Figure 02.**

Factor B (FB):

FB is a single chain, 100 kDa serine protease glycoprotein, which is extremely specific and tightly

regulated, mainly synthesized and secreted by the cells outside the liver.[44] FB is mainly synthesized by skin keratinocytes[45] and released into human saliva and contributes in the local immune and inflammatory responses of the oral cavity.[46] FB consists of three N-terminal complement control protein domains (CCP-1, CCP-2, and CCP-3), a VWA (Von Willebrand factor A) domain and a C-terminal serine protease (SP) domain. The CCP-3 domain is connected to VWA domain by a 45-residue linker. CCP-1 through CCP-3 and the linker form fragment Ba (234 amino acids) while the VWA and SP domains constitute fragment Bb (505 amino acids). FB regulates AP and its activation requires its association with fluid-phase C3 convertase; C3(H2O) or surface-bound C3b and the presence of Mg^{+2}, after which it is cleaved by factor D into fragments Ba and Bb[47] **Figure 04.** Fragment Ba detaches, leaving behind the 60kDa catalytically active component Bb which binds with C3b and forms AP C3 convertase C3bBb[48, 49] **Figure 02.**

Factor D (FD):
Factor D is a 24 kDa[50] chymotrypsin-like, member of the serine protease superfamily essentially requires for the activation of the AP. FD is constitutively synthesized in the hepatocytes[51] and is unique among serine proteases in that it lacks an activation peptide and is not obliged to regulation by activating enzyme or protease inhibitor. Furthermore, it acts on extremely restricted natural substrate, C3b-bound FB.[52] FD cleaves FB only when it is in a Mg++-dependent complex with C3b[53] **Figure 04.** Due to the atypical structural conformations of the active site, FD regulation instead requires a novel mechanism. FD activation (resting zymogen state to catalytically active conformation) relies on natural substrate which induces reversible conformational changes in the catalytic triad and substrate binding sites (52, 54). Individuals lacking FD are more susceptible to recurrent Neisseria infections[55] **Figure 02.**

Vitronectin (Vn, S protein):
Vitronectin is a 75 kDa, multifunctional, extracellular matrix (ECM) glycoprotein[56], present in high concentration in plasma (200–700 µg/ml), α-granules of platelets and other organs (liver, heart, lung, duodenum, tonsil and skeletal muscle).[57] Vn is crucial for several pathophysiological processes including cell adhesion, migration, spreading and angiogenesis. Vn blocking in cancerous tissue has been shown promising therapeutic for malignant carcinomas.[19] Vn is synthesized in the liver as a 478 residue precursor polypeptide of which 459 amino acids (aa) are mature protein and 19 aa are signal peptide.[56] The major part of Vn molecule (residues 51–310) regulates the formation of MAC by interacting with the components of terminal complement complex (TCC) at two stages **Figure 04.** First, Vn mask a polar surface on the nascent C5b-7 with its non-heparin-binding domains and halts its transition from hydrophilic to hydrophobic state thus preventing its insertion into the cell membrane.[58] Second, vitronectin's positive charge domain binds its corresponding negative charge domain on C9 and prevents C9 polymerization, necessary for lytic pores.[59] Vn also exerts regulatory effects on coagulation, plasminogen activation and fibrinolysis and recently reduced plasma Vn level was associated with autoimmune skeletal muscle disease, Myasthenia gravis (MG).[60] Vn accumulation has been suggested an important mediator in the coronary atherosclerosis[56] **Figure 02.**

Clusterin (40, SP-40, Apo J or cytolysis inhibitor):
Clusterin is an enigmatic 75-kDa, heterodimeric, complement regulatory glycoprotein for which the biosynthetic origin is not yet been established however initially it was identified as a major aggregating protein--hence the name clusterin, in the rete testis fluid.[61, 62] Clusterin circulates in the blood and physiological fluids in association with lipoproteins. Multiplicity in the clusterin names indicate complexity in interpretation of its biological roles and its multiple functions.[63] Although a number of physiologic functions have been proposed including complement regulation, sperm maturation, membrane protection, initiation of apoptosis and lipid transport[64], clusterin's established function is to prevent the MAC-mediated cellular lysis[65] **Figure 04.** In all three pathways, complement fragment C5b provides binding site for C6 and C7, to form C5b-7. The newly synthesized C5b-7 complex either gets attached to the cell membrane (C5b−7m) or prevented from attachment by vitronectin and clusterin. C5b-7 binds with clusterin and vitronectin and forms soluble C5b−7 (C5b−7s).[59] Later, complement proteins C8 and C9 either binds to C5b−7m to form membrane-MAC (mMAC) or to C5b−7s to form soluble-MAC (sMAC).[66] A hydrophilic to amphiphilic transition in the nascent sMAC and mMAC exposes the clusterin and vitronectin binding site. The binding of clusterin and vitronectin to newly synthesized, amphiphillic, mMAC or sMAC renders C5b−9 complex lytically inactive[67] **Figure 02.**

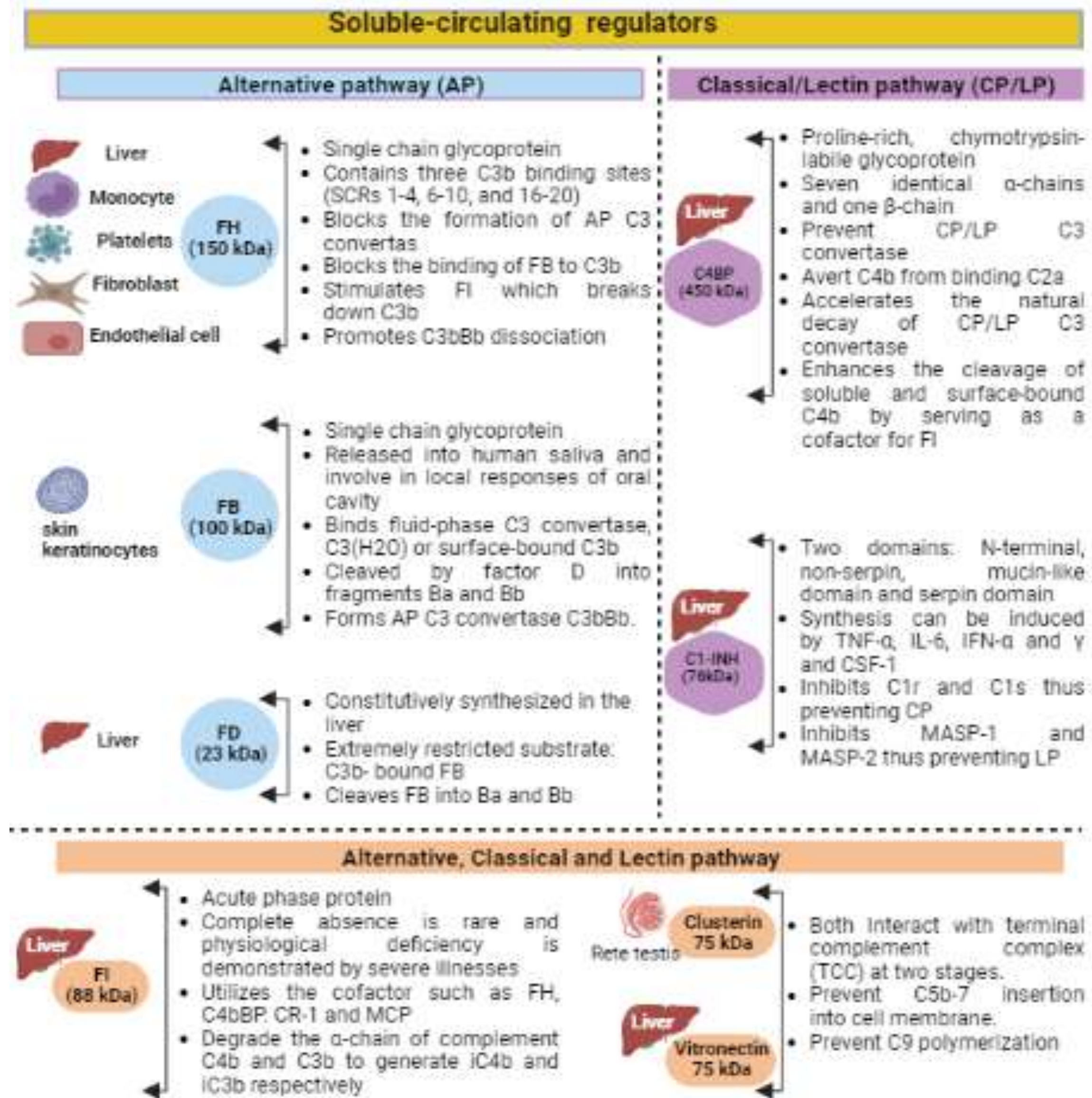

Figure 02: Shows the sites of synthesis and functions of the Soluble-circulating regulators of complement system. FH= Factor H, FB= Factor B, FD= Factor D, C4BP= C4 binding protein, C1-INH= C1 inhibitor, FI= Factor I.

Membrane-bound Regulators of complement activation (mRCA)

It has long been known that membrane-bound complement regulators are fascinating proteins, expressed throughout the body and prevent the complement over-activation and destruction of self-cells. Although the mRCA expression varies across tissue, these are essentially naturally-designed to exert tight regulatory functions on the complement system. The mRCA may act as a double-edged sword and the expression of mRCA on tumor cells and pathogens or their over-regulatory function allow them to proliferate unchecked.[68] The well-studied mRCA include complement receptor 1 (CR-1 or CD35), complement receptor 2 (CR-2 or CD21), CD46, CD55 and CD59.

Complement receptor 1 (CR-1, CD35):

Complement receptor 1 (CR-1 or CD35) is a polymorphic, 210-290 kDa, trans-membrane glycoprotein expressed on a variety of cells including B lymphocytes, phagocytes, erythrocytes[69], glomerular podocytes, follicular dendritic cells and small sub-set of T lymphocytes.[70] The function varies with different cell types and CR-1 expression on erythrocytes is unique to humans and other primates. Patients treated with erythropoietin express progressive increase in the average number of CR-1 on their erythrocytes[71] and reduced expression of CR-1 appears to be an important event in autoimmune disease; systemic lupus erythematosus (SLE).[72] CR-1 prevents the formation of CP and AP C3 convertases, serves as a cofactor for FI[71], clears C3/C4-opsonized immune complexes[73] and regulates antibody formation.[74] CR-1 is an important

RCA protein with two distinct sites and 30 short consensus repeats (SCRs). Site-1 comprises SCR-1 and SCR-2 and binds C4b while site-2 contains SCR-8 and SCR-9 and binds C3b.[75] CR-1 promotes FI mediated degradation of C3b to iC3b and subsequently to C3c and C3dg and of C4b to C3c and C3d **Figure 04.** CR-1 also promotes differentiation of activated B cells to immunoglobulin-secreting cells and triggers phagocytic cells. CR-1 is exclusively expressed on a subset of $CD4^+$ but not on $CD8^+$ T lymphocytes and it has been noted that all $CR\text{-}1^+$ lymphocytes express Fcγ receptors. Co-expression of Fcγ and CR-1 on a subset of $CD4^+$ T lymphocytes has been associated with an enhanced ability to bind and respond to C3-bearing complex[76] **Figure 03.**

Complement receptor 2 (CR-2, CD21):

Complement receptor 2 (CR-2, CD21) is a 145 kDa trans-membrane protein, primarily expressed on mature and immature B cells however it is also expressed by subset of T cells[77] and follicular dendritic cells.[78] On B cells, CR-2 is co-expressed with CD19 and B cell receptor (BCR). CR-2 is made of 15 short consensus repeats (SCRs) and binds four classes of ligands (C3 activation fragments, IgE receptor CD23, Epstein-Barr virus (EBV) glycoprotein gp350/220 and the cytokine interferon alpha (IFN-a). The preferred ligand for CR-2 is C3 breakdown product, C3d. CR2 along with its ligand C3d, is the linkage between adaptive and innate immunity.[79] C3d tags the invading microorganisms which can be recognized by CR2 and this C3d ligated CR2 can trigger the CD19 or BCR mediated, calcium-dependant, B cell intracellular signaling. B cell activation results in amplified humoral immune response[80] **Figure 03.**

Membrance cofactor protein (MCP, CD46):

CD46 (membrane cofactor protein; MCP) is a genetically, structurally and functionally related member of the regulators of complement activation (RCA). MCP is a 60–65 kDa trans-membrane glycoprotein that is expressed on all nucleated cells particularly endothelial, epithelial and hematopoietic cells and the reproductive tissues and is absent on erythrocytes.[81] MCP exhibits tissue-specific heterogeneity and is composed of approximately 350 amino acids which are such arranged that approximately 60 cysteine-rich amino acids link tandemly and form four short consensus repeats termed complement control protein repeats (CCP1–4).[33, 82] CCP are important for MCP inhibitory activity. MCP triggers the factor I-mediated C3b and C4b degradation deposited on host cells **Figure 04.** Owing to its regulatory rule and abundant expression, MCP is the preferred target for several pathogens. Human herpes virus, measles virus, S. pyogenes and Neisseria species[83] use MCP from immune evasion. The underlying mechanisms involved in cytoprotection by MCP are areas of interest for transplant, cancer and reproductive immunologists **Figure 03.**

Decay-accelerating factor (DAF, CD55):

Decay-accelerating factor (DAF) or CD55 was first isolated by Hoffmann in 1969 from human erythrocytes[84] and was later described as a 70-kDa, glycosylphosphatidylinositol (GPI)-anchored complement inhibitory glycoprotein. The gene for DAF is located on chromosome 1q32 within same locus encoding for other regulatory proteins.[85] DAF has four, membrane-distal, short consensus repeats (SCR) domains, of which domain 2 and 3 contacts the CP convertase while domain 2,3 and 4 adheres the AP convertase. The third short consensus repeat is responsible for DAF's regulatory activity and signaling. Similar to other GPI-anchored proteins, DAF is associated with tyrosine kinases.[86] DAF primarily inactivates the CP and AP C3 and C5 convertases by dissociating these proteins as well as prevent their assembly[68, 87] **Figure 04.** DAF is highly expressed on all serum-exposed cells and protect the self-cells from autologous complement-mediated lysis. DAF also serves as a receptor for different viruses.[96] DAF acts a binding partner for CD97 which is widely expressed on lymphocytes, granulocytes and broad range of tumor cells. CD55-CD97 interaction triggers the activation, migration, and attachment of these cells in the inflammatory processes in multiple sclerosis.[88] The adhesion between seven-span transmembrane protein CD97 and CD55 has also been associated with many diseases, including autoimmune diseases, cancer, malaria[89] and paroxysmal nocturnal hemoglobinuria (PNH).[90, 91] Patient's erythrocytes with life-threatening disorder, PNH are devoid of CD55 and CD59. As high serum levels of DAF are strongly associated with the progression of many cancers, recently chimeric monoclonal antibodies i.e. anti-CD55 were suggested potential therapeutic agent for cancer immunotherapy (92) **Figure 03.**

Protectin (CD59):

Protectin is a small (18-20 kDa), membrane-bound[93], highly glycosylated, GPI-linked complement regulator, expressed almost on all cells which are in contact with body fluids.[94, 95] While AP always remain in a state of activation without any stimulant to prevent the host from infection or it can be triggered under some pathogenic surroundings such as ischemia, severe infection or autoimmune disorders, it is imperative to thwart the complements directed against self-tissue. One of the manoeuvre to avert the complement-mediated host cell damage is to inhibit the MAC formation. Active C5b offers binding site for C6 and C7, to form C5b-7 which subsequently gets attached to the target cell membrane and form C5b-7m. The C5b-7m subsequently provides binding site for C8 and 3-18 molecules of C9 sequentially. Consequently, the CSb-9 designated as membrane attack complexes (MAC) forms and damages the membrane barrier (96). CD59 regulates the MAC formation at the final step of TCC, by inhibiting the insertion of C9 into membrane C5b-9 complexes[93, 97] **Figure 04.** While CD59 role in complement regulation is

well-defined, studies have shown strong evidence for alternative functions such as GPI-linked, lipid-raft associated and tyrosine kinase-mediated signalling properties.[94] Protectin has also been documented as the chief restriction factor for complement-mediated lysis of cutaneous melanoma and other solid malignancies.[98]

The observation that Paroxysmal nocturnal hemoglobinuria (PNH) erythrocytes are easily lysed by complements led to identification that PNH erythrocytes are defective in two membrane proteins (DAF and CD59)[99] **Figure 03.**

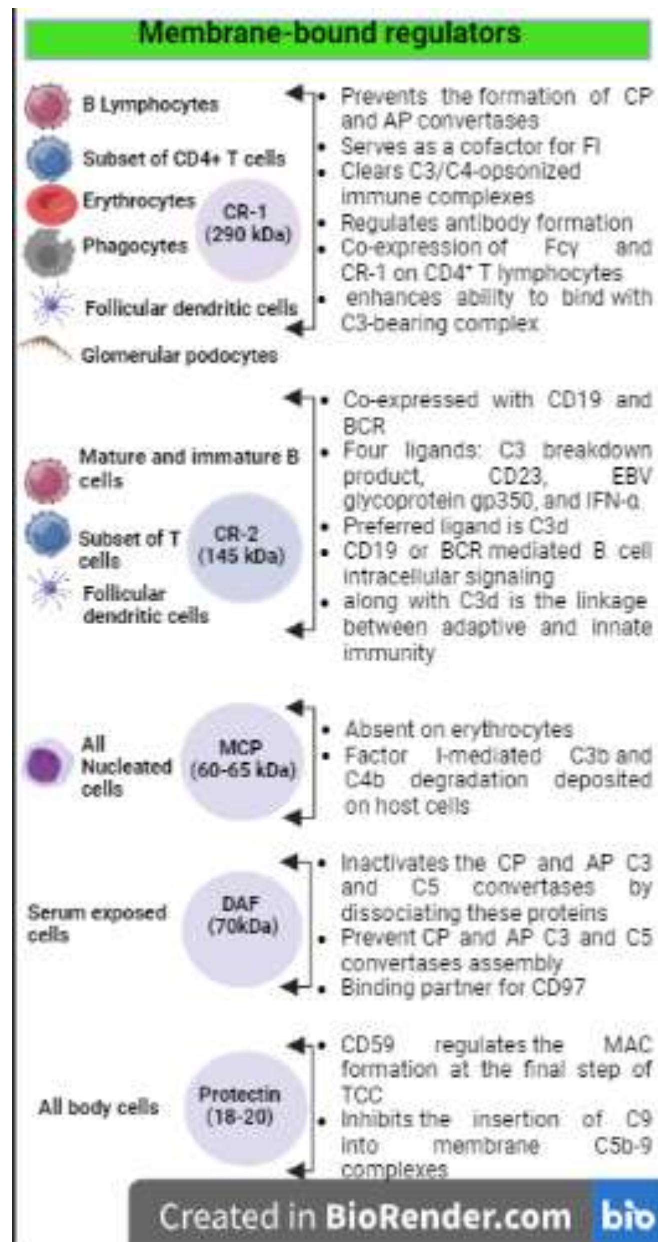

Figure 03: Shows the sites of synthesis and functions of the Membrane-bound regulators of complement activation. CR-1= complement receptor-1 (CD35), CR-2= complement receptor-2 (CD21), MCP= membrane cofactor protein (CD46), DAF= decay accelerating factor (CD55), Protectin= CD59.

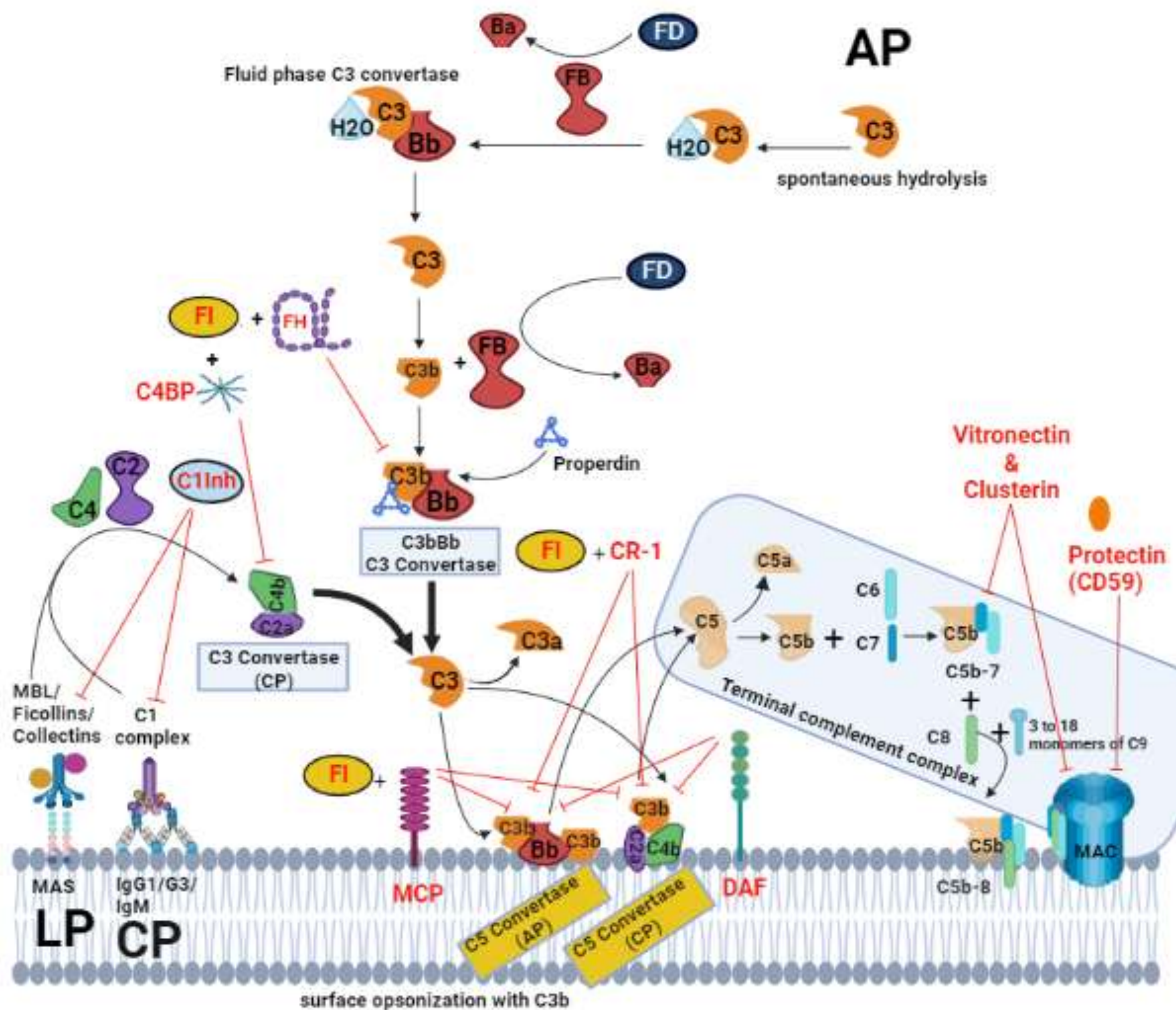

Figure 04: Shows the schematic representation and interplay of complement and their regulators in the body fluids and on the cell surface in all three pathways. Complement inhibitors are highlighted by red color.

CONCLUSION

Complements are one of the human's body first line of defense mechanisms and are crucial for homoeostasis and preventing infections. Complement pathways are classically activated through interacting with antigen-antibody complexes however alternative pathway is activated through spontaneous degradation of complement C3. Most of the complement proteins are serine proteases and are synthesized in an inactive form. Tight control of complement activation and regulation is necessary and complement over activation and deficiencies in regulators may lead to severe autoimmune illnesses. Two types of regulators play their role in controlling complements in the body. Most of the regulators are synthesized in the liver and are glycoproteins. In depth knowledge of complement cascades and how complement proteins are tightly controlled by regulators may help in understanding the different diseases.

DECLARATIONS:

Ethical Approval And Consent To Participate:
Not applicable

Consent For Publication:
Not applicable

Availability Of Data And Materials:
We have provided all data in the form of references and figures and further will be provided on request

Competing Interest:
The authors have no conflicts of interest to declare

Funding:
This research was not funded by any agency

Author's Contributions
Khan RMA designed, wrote, edited, checked, analyzed, interpreted, revised, drafted and finally approved this study. Kulsoom S interpreted, revised, checked, drafted and finally approved this manuscript. Mukhtar R revised, checked, analyzed, and finally approved this study. Faisal M analyzed, interpreted, checked and finally approved this study. Yaseen M checked, analyzed, interpreted, drafted, revised and finally approved this

study. Iqbal MS revised, interpreted and finally approved this study. All authors read and agreed to be accountable of all aspects of the final manuscript.

ACKNOWLEDGEMENT
This research was not funded by any agency.

REFERENCES

1. Laabei M, Ermert D. Catch me if you can: Streptococcus pyogenes complement evasion strategies. Journal of innate immunity. 2019; 11(1) :3-12.
2. Shariat M, Heydrzadeh M, Abolhassani H, Bemanian MH, Yazdani R. Complement deficiencies. Inborn Errors of Immunity: Elsevier; 2021. p. 291-315.
3. Arkwright PD. Primary Immunodeficiencies of Complement. Primary and Secondary Immunodeficiency: Springer; 2021. p. 313-30.
4. Vignesh P, Rawat A, Sharma M, Singh S. Complement in autoimmune diseases. Clinica Chimica Acta. 2017; 465: 123-30.
5. Agrawal P, Nawadkar R, Ojha H, Kumar J, Sahu A. Complement evasion strategies of viruses: an overview. Frontiers in microbiology. 2017; 8: 1117.
6. Hourcade D, Liszewski MK, Krych-Goldberg M, Atkinson JP. Functional domains, structural variations and pathogen interactions of MCP, DAF and CR1. Immunopharmacology. 2000; 49(1-2): 103-16.
7. Giuntini S, Reason DC, Granoff DM. Combined roles of human IgG subclass, alternative complement pathway activation, and epitope density in the bactericidal activity of antibodies to meningococcal factor H binding protein. Infection and immunity. 2012; 80(1): 187-94.
8. Ermert D, Ram S, Laabei M. The hijackers guide to escaping complement: Lessons learned from pathogens. Molecular immunology. 2019; 114: 49-61.
9. !!! INVALID CITATION !!!
10. Hourcade DE. The role of properdin in the assembly of the alternative pathway C3 convertases of complement. Journal of Biological Chemistry. 2006; 281(4): 2128-32.
11. Hartmann S, Hofsteenge J. Properdin, the Positive Regulator of Complement, Is HighlyC-Mannosylated. Journal of Biological Chemistry. 2000; 275(37): 28569-74.
12. Kemper C, Hourcade DE. Properdin: new roles in pattern recognition and target clearance. Molecular immunology. 2008; 45(16): 4048-56.
13. Spitzer D, Mitchell LM, Atkinson JP, Hourcade DE. Properdin can initiate complement activation by binding specific target surfaces and providing a platform for de novo convertase assembly. The Journal of Immunology. 2007; 179(4): 2600-8.
14. Lachmann PJ. The amplification loop of the complement pathways. Advances in immunology. 2009; 104: 115-49.
15. Lambris JD. The multifunctional role of C3, the third component of complement. Immunology today. 1988; 9(12): 387-93.
16. Janssen BJ, Huizinga EG, Raaijmakers HC, Roos A, Daha MR, Nilsson-Ekdahl K, et al. Structures of complement component C3 provide insights into the function and evolution of immunity. Nature. 2005; 437(7058): 505-11.
17. Lynskey NN, Reglinski M, Calay D, Siggins MK, Mason JC, Botto M, et al. Multi-functional mechanisms of immune evasion by the streptococcal complement inhibitor C5a peptidase. PLoS pathogens. 2017; 13(8): e1006493.
18. Bjanes E, Nizet V. More than a pore: Nonlytic antimicrobial functions of complement and bacterial strategies for evasion. Microbiology and Molecular Biology Reviews. 2021; 85(1): e00177-20.
19. Singh B, Su YC, Riesbeck K. Vitronectin in bacterial pathogenesis: a host protein used in complement escape and cellular invasion. Molecular microbiology. 2010; 78(3): 545-60.
20. Sharma S, Bhatnagar R, Gaur D. Complement evasion strategies of human pathogenic bacteria. Indian journal of microbiology. 2020; 60(3): 283-96.
21. Gialeli C, Gungor B, Blom AM. Novel potential inhibitors of complement system and their roles in complement regulation and beyond. Molecular immunology. 2018; 102: 73-83.
22. Nilsson SC, Sim RB, Lea SM, Fremeaux-Bacchi V, Blom AM. Complement factor I in health and disease. Molecular immunology. 2011; 48(14): 1611-20.
23. Ram S, Sharma AK, Simpson SD, Gulati S, McQuillen DP, Pangburn MK, et al. A novel sialic acid binding site on factor H mediates serum resistance of sialylated Neisseria gonorrhoeae. The Journal of experimental medicine. 1998; 187(5): 743-52.
24. Ferreira VP, Pangburn MK, Cortés C. Complement control protein factor H: the good, the bad, and the inadequate. Molecular immunology. 2010; 47(13): 2187-97.
25. Parente R, Clark SJ, Inforzato A, Day AJ. Complement factor H in host defense and immune evasion. Cellular and Molecular Life Sciences. 2017; 74(9): 1605-24.
26. Syed S, Viazmina L, Mager R, Meri S, Haapasalo K. Streptococci and the complement system: interplay during infection, inflammation and autoimmunity. FEBS letters. 2020; 594(16): 2570-85.
27. Sharma AK, Pangburn MK. Identification of three physically and functionally distinct binding sites for C3b in human complement factor H by deletion mutagenesis. Proceedings of the National Academy of Sciences. 1996; 93(20): 10996-1001.
28. Stoiber H, Schneider R, Janatova J, Dierich MP. Human complement proteins C3b, C4b, factor H and properdin react with specific sites in gpl20 and gp4l, the envelope proteins of HIV1. Immunobiology. 1995; 193(1): 98-113.

29. Nagasawa S, MIZUGUCHI K, ICHIHARA C, KOYAMA J. Limited chymotryptic cleavage of human C4-binding protein: isolation of a carbohydrate-containing core domain and an active fragment. The Journal of Biochemistry. 1982; 92(4): 1329-32.
30. Monte G, Moerschell R, Ghatak A, Melissari E. C4b-binding protein: an update. Thrombosis and haemostasis. 1993; 69(01): 086-.
31. Ermert D, Laabei M, Weckel A, Mörgelin M, Lundqvist M, Björck L, et al. The molecular basis of human IgG-mediated enhancement of C4b-binding protein recruitment to group A Streptococcus. Frontiers in Immunology. 2019: 1230.
32. Ogun SA, Dumon-Seignovert L, Marchand J-B, Holder AA, Hill F. The oligomerization domain of C4-binding protein (C4bp) acts as an adjuvant, and the fusion protein comprised of the 19-kilodalton merozoite surface protein 1 fused with the murine C4bp domain protects mice against malaria. Infection and immunity. 2008; 76(8): 3817-23.
33. Hakulinen J, Junnikkala S, Sorsa T, Meri S. Complement inhibitor membrane cofactor protein (MCP; CD46) is constitutively shed from cancer cell membranes in vesicles and converted by a metalloproteinase to a functionally active soluble form. European journal of immunology. 2004; 34(9): 2620-9.
34. Katz Y, Strunk R. Synthesis and regulation of C1 inhibitor in human skin fibroblasts. The Journal of Immunology. 1989; 142(6): 2041-5.
35. Schmaier AH, Amenta S, Xiong T, Heda GD, Gewirtz AM. Expression of platelet C1 inhibitor. 1993.
36. Prada AE, Zahedi K, Davis III AE. Regulation of C1 inhibitor synthesis. Immunobiology. 1998; 199(2): 377-88.
37. Bos IG, Hack CE, Abrahams J. Structural and functional aspects of C1-inhibitor. Immunobiology. 2002; 205(4-5): 518-33.
38. Beinrohr L, Dobó J, Závodszky P, Gál P. C1, MBL–MASPs and C1-inhibitor: novel approaches for targeting complement-mediated inflammation. Trends in molecular medicine. 2008; 14(12): 511-21.
39. Cicardi M, Zingale L, Zanichelli A, Pappalardo E, Cicardi B, editors. C1 inhibitor: molecular and clinical aspects. Springer seminars in immunopathology; 2005: Springer.
40. Davis III AE, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. Thrombosis and haemostasis. 2010; 104(11): 886-93.
41. Davis III AE, Mejia P, Lu F. Biological activities of C1 inhibitor. Molecular immunology. 2008; 45(16): 4057-63.
42. Csuka D, Munthe-Fog L, Skjoedt M-O, Kocsis A, Zotter Z, Gál P, et al. The role of ficolins and MASPs in hereditary angioedema due to C1-inhibitor deficiency. Molecular immunology. 2013; 54(3-4): 271-7.
43. Berger M, Baldwin III WM, Jordan SC. Potential roles for C1 inhibitor in transplantation. Transplantation. 2016; 100(7): 1415.
44. Kaczorowski DJ, Scott MJ, Pibris JP, Afrazi A, Nakao A, Edmonds RD, et al. Mammalian DNA is an endogenous danger signal that stimulates local synthesis and release of complement factor B. Molecular medicine. 2012; 18(5): 851-60.
45. Pasch MC, van den Bosch NH, Bos JD, Asghar SS, Daha MR. Synthesis of complement components C3 and factor B in human keratinocytes is differentially regulated by cytokines. Journal of investigative dermatology. 2000; 114(1): 78-82.
46. Andoh A, Fujiyama Y, Kimura T, Uchihara H, Sakumoto H, Okabe H, et al. Molecular characterization of complement components (C3, C4, and factor B) in human saliva. Journal of clinical immunology. 1997; 17(5): 404-7.
47. Curman B, Sandbert-Tragardh L, Peterson PA. Chemical characterization of human factor B of the alternate pathway of complement activation. Biochemistry. 1977; 16(24): 5368-75.
48. Campbell RD, Porter RR. Molecular cloning and characterization of the gene coding for human complement protein factor B. Proceedings of the National Academy of Sciences. 1983; 80(14): 4464-8.
49. Milder FJ, Gomes L, Schouten A, Janssen BJ, Huizinga EG, Romijn RA, et al. Factor B structure provides insights into activation of the central protease of the complement system. Nature structural & molecular biology. 2007; 14(3): 224-8.
50. Kaiser J, Oppermann M, Götze O, Deppisch R, Göhl H, Asmus G, et al. Significant reduction of factor D and immunosuppressive complement fragment Ba by hemofiltration. Blood purification. 1995; 13(6): 314-21.
51. Kitano E, Kitamura H. Synthesis of factor D by normal human hepatocytes. International archives of allergy and immunology. 2000; 122(4): 299-302.
52. Jing H, Macon KJ, Moore D, DeLucas LJ, Volanakis JE, Narayana SV. Structural basis of profactor D activation: from a highly flexible zymogen to a novel self-inhibited serine protease, complement factor D. The EMBO Journal. 1999; 18(4): 804-14.
53. Lesavre PH, Müller-Eberhard HJ. Mechanism of action of factor D of the alternative complement pathway. The Journal of experimental medicine. 1978; 148(6): 1498-509.
54. Xu Y, Narayana SV, Volanakis JE. Structural biology of the alternative pathway convertase. Immunological reviews. 2001; 180(1): 123-35.
55. Hiemstra P, Langeler E, Compier B, Keepers Y, Leijh PC, Van den Barselaar MT, et al. Complete and partial deficiencies of complement factor D in a Dutch family. The Journal of clinical investigation. 1989; 84(6): 1957-61.

56. Ekmekçi ÖB, Ekmekçi H. Vitronectin in atherosclerotic disease. Clinica chimica acta. 2006; 368(1-2): 77-83.
57. Schvartz I, Seger D, Shaltiel S. Vitronectin. The international journal of biochemistry & cell biology. 1999; 31(5): 539-44.
58. Sheehan M, Morris C, Pussell B, Charlesworth J. Complement inhibition by human vitronectin involves non-heparin binding domains. Clinical & Experimental Immunology. 1995; 101(1): 136-41.
59. Milis L, Morris C, Sheehan M, Charlesworth J, Pussell B. Vitronectin-mediated inhibition of complement: evidence for different binding sites for C5b-7 and C9. Clinical & Experimental Immunology. 1993; 92(1): 114-9.
60. Lepedda AJ, Deiana GA, Lobina O, Nieddu G, Baldinu P, De Muro P, et al. Plasma vitronectin is reduced in patients with myasthenia gravis: Diagnostic and pathophysiological potential. Journal of Circulating Biomarkers. 2019; 8: 1849454419875912.
61. Tschopp J, Chonn A, Hertig S, French L. Clusterin, the human apolipoprotein and complement inhibitor, binds to complement C7, C8 beta, and the b domain of C9. The Journal of Immunology. 1993; 151(4): 2159-65.
62. Fritz IB, Burdzy K, Sétchell B, Blaschuk O. Ram rete testis fluid contains a protein (clusterin) which influences cell-cell interactions in vitro. Biology of reproduction. 1983; 28(5): 1173-88.
63. Jones SE, Jomary C. Clusterin. The international journal of biochemistry & cell biology. 2002; 34(5): 427-31.
64. Jenne DE, Lowin B, Peitsch M, Böttcher A, Schmitz G, Tschopp J. Clusterin (complement lysis inhibitor) forms a high density lipoprotein complex with apolipoprotein AI in human plasma. Journal of Biological Chemistry. 1991; 266(17): 11030-6.
65. Høgåsen K, Homann C, Mollnes TE, Graudal N, Høgåsen AKM, Hasselqvist P, et al. Serum clusterin and vitronectin in alcoholic cirrhosis. Liver. 1996; 16(2): 140-6.
66. Bhakdi S, Käflein R, Halstensen T, Hugo F, Preissner K, Mollnes T. Complement S-protein (vitronectin) is associated with cytolytic membrane-bound C5b-9 complexes. Clinical and experimental immunology. 1988; 74(3): 459.
67. Chauhan A, Moore T. Presence of plasma complement regulatory proteins clusterin (Apo J) and vitronectin (S40) on circulating immune complexes (CIC). Clinical & Experimental Immunology. 2006; 145(3): 398-406.
68. Geller A, Yan J. The role of membrane bound complement regulatory proteins in tumor development and cancer immunotherapy. Frontiers in immunology. 2019; 10: 1074.
69. Iida K, Nussenzweig V. Complement receptor is an inhibitor of the complement cascade. The Journal of experimental medicine. 1981; 153(5): 1138-50.
70. Rødgaard A, Thomsen S, Bendixen G, Bendtzen K. Increased expression of complement receptor type 1 (CR1, CD35) on human peripheral blood T lymphocytes after polyclonal activation in vitro. Immunologic research. 1995; 14(1): 69-76.
71. Hebert LA, Birmingham DJ, Dillon JJ, Cosio FG, Shen X-P. Erythropoietin therapy in humans increases erythrocyte expression of complement receptor type 1 (CD35). Journal of the American Society of Nephrology. 1994; 4(10): 1786-91.
72. Arora V, Verma J, Dutta R, Marwah V, Kumar A, Das N. Reduced complement receptor 1 (CR1, CD35) transcription in systemic lupus erythematosus. Molecular immunology. 2004; 41(4): 449-56.
73. Java A, Liszewski MK, Hourcade DE, Zhang F, Atkinson JP. Role of complement receptor 1 (CR1; CD35) on epithelial cells: a model for understanding complement-mediated damage in the kidney. Molecular immunology. 2015; 67(2): 584-95.
74. RajU KR, Sivasankar B, Anand V, Luthra K, Tiwari SC, Dinda AK, et al. Use of complement receptor 1 (CD35) assay in the diagnosis and prognosis of immune complex mediated glomerulopathies. Asian Pacific Journal of Allergy and Immunology. 2001; 19(1): 23.
75. Krych M, Clemenza L, Howdeshell D, Hauhart R, Hourcade D, Atkinson JP. Analysis of the functional domains of complement receptor type 1 (C3b/C4b receptor; CD35) by substitution mutagenesis. Journal of Biological Chemistry. 1994; 269(18): 13273-8.
76. Cohen JH, Aubry JP, Revillard JP, Banchereau J, Kazatchkine MD. Human T lymphocytes expressing the C3b/C4b complement receptor type one (CR1, CD35) belong to Fcγ receptor-positive CD4-positive T cells. Cellular immunology. 1989; 121(2): 383-90.
77. Levy E, Ambrus J, Kahl L, Molina H, Tung K, Holers V. T lymphocyte expression of complement receptor 2 (CR2/CD21): a role in adhesive cell-cell interactions and dysregulation in a patient with systemic lupus erythematosus (SLE). Clinical & Experimental Immunology. 1992; 90(2): 235-44.
78. Marchbank KJ, Kulik L, Gipson MG, Morgan BP, Holers VM. Expression of human complement receptor type 2 (CD21) in mice during early B cell development results in a reduction in mature B cells and hypogammaglobulinemia. The Journal of Immunology. 2002; 169(7): 3526-35.
79. Morikis D, Lambris JD. The electrostatic nature of C3d-complement receptor 2 association. The Journal of Immunology. 2004; 172(12): 7537-47.
80. Kovacs JM. Investigating complement receptor 2 (CD21/CR2)-ligand interactions and inhibitors thereof: University of Colorado Health Sciences Center; 2010.
81. Seya T, Hirano A, Matsumoto M, Nomura M, Ueda S. Human membrane cofactor protein (MCP, CD46): multiple isoforms and functions. The

international journal of biochemistry & cell biology. 1999; 31(11): 1255-60.
82. Liszewski MK, Leung M, Cui W, Subramanian VB, Parkinson J, Barlow PN, et al. Dissecting sites important for complement regulatory activity in membrane cofactor protein (MCP; CD46). Journal of Biological Chemistry. 2000; 275(48): 37692-701.
83. Källström H, Liszewski MK, Atkinson JP, Jonsson AB. Membrane cofactor protein (MCP or CD46) is a cellular pilus receptor for pathogenic Neisseria. Molecular microbiology. 1997; 25(4): 639-47.
84. Hoffmann EM. Inhibition of complement by a substance isolated from human erythrocytes—II: Studies on the site and mechanism of action. Immunochemistry. 1969;6(3):405-19.
85. Mikesch J-H, Schier K, Roetger A, Simon R, Buerger H, Brandt B. The expression and action of decay-accelerating factor (CD55) in human malignancies and cancer therapy. Analytical Cellular Pathology. 2006; 28(5-6): 223-32.
86. Nicholson-Weller A, Wang C. Structure and function of decay accelerating factor CD55. The Journal of laboratory and clinical medicine. 1994; 123(4): 485-91.
87. Lublin DM, Atkinson J. Decay-accelerating factor: biochemistry, molecular biology, and function. Annual review of immunology. 1989; 7(1): 35-58.
88. Visser L, de Vos AF, Hamann J, Melief M-J, van Meurs M, Van Lier RA, et al. Expression of the EGF-TM7 receptor CD97 and its ligand CD55 (DAF) in multiple sclerosis. Journal of neuroimmunology. 2002; 132(1-2): 156-63.
89. Egan ES, Jiang RH, Moechtar MA, Barteneva NS, Weekes MP, Nobre LV, et al. A forward genetic screen identifies erythrocyte CD55 as essential for Plasmodium falciparum invasion. Science. 2015; 348(6235): 711-4.
90. Dho SH, Lim JC, Kim LK. Beyond the role of CD55 as a complement component. Immune network. 2018; 18(1).
91. Windyga J. Thromboembolic events in paroxysmal nocturnal hemoglobinuria—pathophysiology and new therapeutic options. Journal of Transfusion Medicine. 2022; 15(1): 67-8.
92. Dho SH, Cho EH, Lee JY, Lee SY, Jung SH, Kim LK, et al. A novel therapeutic anti‑CD55 monoclonal antibody inhibits the proliferation and metastasis of colorectal cancer cells. Oncology Reports. 2019; 42(6): 2686-93.
93. Meri S, Morgan B, Davies A, Daniels R, Olavesen M, Waldmann H, et al. Human protectin (CD59), an 18,000-20,000 MW complement lysis restricting factor, inhibits C5b-8 catalysed insertion of C9 into lipid bilayers. immunology. 1990; 71(1): 1.
94. Kimberley FC, Sivasankar B, Morgan BP. Alternative roles for CD59. Molecular immunology. 2007; 44(1-3): 73-81.
95. Meri S, Waldmann H, Lachmann P. Distribution of protectin (CD59), a complement membrane attack inhibitor, in normal human tissues. Laboratory investigation; a journal of technical methods and pathology. 1991; 65(5): 532-7.
96. Sugita Y, Masuho Y. CD59: its role in complement regulation and potential for therapeutic use. Immunotechnology. 1995; 1(3-4): 157-68.
97. Rollins S, Sims P. The complement-inhibitory activity of CD59 resides in its capacity to block incorporation of C9 into membrane C5b-9. The Journal of Immunology. 1990; 144(9): 3478-83.
98. Fonsatti E, Altomonte M, Coral S, De Nardo C, Lamaj E, Sigalotti L, et al. Emerging role of protectin (CD59) in humoral immunotherapy of solid malignancies. La Clinica terapeutica. 2000; 151(3): 187-93.
99. Ruiz-Argüelles A, Llorente L. The role of complement regulatory proteins (CD55 and CD59) in the pathogenesis of autoimmune hemocytopenias. Autoimmunity reviews. 2007; 6(3): 155-61.