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Review Article

Portrayal of the Multitasking Complement Regulator One in Critical Illness

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ABSTRACT

The complement system is one of the evolutionary ancient, primordial components of the immune system. As such, it was destined to fulfill most aspects of the immune response with built-in self-limiting regulatory components. While new and new layers of immune repertoire evolved, complement retained its influential role in recognition, phagocytosis, clearance, antibody diversity, adaptive immune response and regulation. In essence the complement system is an innate patent recognition niché, serving to process pathogens, clearing debris and to condition adaptive immunity. The three complement amplification pathways are individually or in combination regulated by soluble and membrane bound complement regulators, Regulator of Complement Activation (RCAs). Among them Complement Regulator-1(CR1) stands out for diversity of functions, and may be of particular interest for intensivists beyond complement regulatory roles, the emergence of regulatory T cells, a more complex executive function, due to erythrocyte bound clearance mechanisms, to aiding opsonophagocytosis of pathogens, and increasing affinity maturation of monoclonal antibodies. This review article sets out to describe CR1, bridging basic science, with behavior in intensive care related clinical scenarios, that are typically associated with a Systemic Inflammatory Response (SIRS), in which complement is involved by direct engagement or indirectly, in situations when opportunities of modifications have a real potential.

Keywords: Complement regulator one; Systemic inflammatory response syndrome; Regulator of complement activation; Phagocytosis; Red blood cells; Sepsis; Ischemia-reperfusion injury

INTRODUCTION

For a detailed description of the complement system, the reader is advised to reach out for excellent reviews [1,2]. An overall characterization is vital for understanding the intensive care related ramifications of CR1 function and modification. Within the three loading complement pathways, the alternative and Mannose Binding Lectin (MBL) pathways, triggered upon direct attachment to the pathogen had been formed earlier, later upon the development of antibody producing B cells, the classical pathway emerged. The MBL and classical pathways are initiated by lectin and the C1 components respectively, recognizing mannose sugar abundantly present on bacteria in MBL, and recognizing antibodies in the classical route; these pathways culminate in common downstream cascades of C4b2a convertase. The alternative pathway is activated by hydrolysis of C3 on activating surfaces, which is followed by interaction with factor B to create C3bBb *convertase* stabilized by properdin. When these avenues reach and activate C3 by *convertases*, C5 *convertases* emerge, ultimately leading to the formation of the Membrane Attack Complex (MAC) (C5b-C9), responsible for active killing *via* cell or pathogen lysis. The alternative pathway is of particular interest due to activation by Lipopolysaccharide (LPS), zymosan, inulin, virus infected cells, teichoic acid, IgA, cardiopulmonary bypass and hemodialysis membranes. Membrane bound and soluble RCAs function

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in a mutually complementary manner (CR1, CD46, CD55, CD59, factor H, factor I) to set boundaries to complement activation and prevent self from destruction [3]. Absence of main pathway participants, overactivation or deficient regulation leads to pathologies [4]. Defective alternative pathway renders the individual susceptible to infection by encapsulated organisms, such as neisseria and haemophilus, pneumococcus, defective regulation, overt activation is associated with atypical Hemolytic Uremic Syndrome (aHUS), glomerulopathies and age related macular degeneration. Deficiencies in the classical pathway (C1q,C2,4) are associated with systemic lupus erythematosus (SLE). Disproportional membrane bound CR1 deficiency emerges in anemia, in conditions leading to tissue injury, in lupus nephritis, rheumatoid arthritis and various glomerulopathies [5,6].

LITERATURE REVIEW

Functional characterization of CR1

The CR1 or CD35 molecule gene is encoded, together with other RCAs in a cluster on chromosome 1, in mice CR1 is a splice variant of common CR1/2 genes [7].

In humans CR1 is expressed on erythrocytes, glomerular podocytes, epithelial cells and certain leukocytes:neutrophils, macrophages, dendritic cells, T and B cells. Based on human protein atlas and experimental data, the RNA expression of CR1 is high on resident tissue macrophages all through the gut but rectum, Kupffer cells of liver, renal podocytes, B cells, blood monocytes and alveolar type 2 cells, moderate expression is detected in cerebral oligodendrocytes [8].

CR1 on resting neutrophils is present in low levels, upon neutrophil activation high CR1 levels are induced. CR1 is cleaved from the surface by *neutrophil elastase*, and released from intravesicular granules, retaining partial functionality.

One of the most important features of CR1 is the adherence promoting and opsogenic capacity, due to high affinity towards C3b and C4b coated surfaces, initializing and enhancing the uptake of pathogens by immune cells for further processing and presentation. The regulatory function of CR1 encompasses the decay acceleration or disintegration of *C3* and *C5 convertases*, thereby limiting their function in time, as well as serving as cofactor in C3b and C4b decomposition. The executive capacity of CR1 enhances attachment, phagocytosis and clearance; at the same time, CR1 limits not only the MAC lytic pathway, but the Systemic Inflammatory Response (SIRS) *via* limiting the production of C3a and C5a anaphylatoxins.

Red blood cell bound function of CR1 BB

Blood Erythrocytes (RBCs) represent a significant source of CR1. Genetic polymorphism determines the expression level from 100 to 500 copies per cell, with erythrocyte age related decline in numbers. Providing the abundance of RBSs, the CR1 pool represents a compelling potential [9]. During anemia this pool shrinks largely. CR1 on RBCs serves to carry immune complexes of microbial origin and debris for presentation and clearance by splenic and liver macrophages (Kupffer cells). Pathogens are recognised by natural antibodies; with subsequent Fc induced C1 mediated classical pathway activation, by mannose binding lectins and by C3. During the process, activated C3b and C4b fragments, MBL, C1q are recognized by CR1 [10,11]. The complement system serves important house-keeping clearance functions for damaged self, when C1q is directly activated, recognising the exposed phosphatidylserine on surfaces, such as apoptotic blebs, mitochondrial membranes, also DNA, uric acid, amyloid, etc, with a limited inflammatory response, due to regulators, such as factor H, and "do not eat me signals", inducing predominantly phagocytosis. Apoptotic cell recognition receptor choice and complement regulation determine the non-or low degree inflammatory response [12]. If the complement cascade becomes activated uninterrupted till the terminal membrane attack complex formation, the adjacent cell becomes lysed. RBCs are protected from lysis due to CR1 and factor I decay activity, which cleaves the active *protease* complexes and degrades C3b and C4b to inactive fragments. CR1 therefore on the surface of erythrocytes serves as an immune complex transporter, while protecting the integrity of erythrocytes. Binding and transport of immune complexes is an energy consuming event, because when CR1 becomes engaged on RBCs, ATP is released to facilitate CR1 clustering and extracellular ATP is a requirement for efficient immune complex (IC) binding to CR1 and for Polymorphonuclear (PMN) phagocytosis. While the lifespan of human RBCs is 120 days, CR1 has a calculated half-life of 11-32 days; hence aged RBCs become relatively depleted in CR1. Comparative measurement of CR1 level on erythrocytes may become challenging, due to the number of variables in cell age, levels and polymorphisms. The CR1 ligation increases erythrocyte deformability [13,14].

An estimated 2/3rd of intensive care conditions, septic patients in particular, acquire during their illness anemia that is typically long lasting. Guidelines are rather conservative in hemoglobin transfusion triggers with few exceptions, such as Acute Coronary Syndrome (ACS) [15,16]. Anemia however worsens survival presenting a yet to be solved predicament.

RBC storage time is associated with increased pneumonia, Acute Lung Injury (ALI) and sepsis rates in some, not all studies. The age of stored red blood cells may have a negative impact on infection incidence in trauma patients [17]. Anemia worsens 90 day Chronic Obstructive Pulmonary Disease (COPD) mortality in mechanically ventilated patients with a conservative cutoff of hemoglobin 120 g/L, after adjusting for comorbidities with elementary tools. Perioperative low hemoglobin is also associated with surgical outcome, based on a metaanalysis of 24 studies, even though clear causative associations are not consistently extrapolated from the studies. Acute and chronic anemia worsens mortality in myocardial infarction by extending oxygen delivery and consumption imbalance [18-20]. Cardiac surgery mortality was associated with the number of blood transfusions, these data are usually adjusted for variables, and nevertheless patients receiving more RBCs are more complex and frail [21]. Due to the number of variables, cumulative evidence serves as a framework in treatment algorithms, serving to deliver decisions in line with best practice opinions of senior experts. Perhaps animal studies with controllable variables could shed more light on the subject

[22]. CR1 , DAF (CD55) and CD59 levels were unchanged on stored human RBCs independent of age , low level alternative complement activation is however noticeable, assumed due to handling and tubing, upon adding not only allogeneic, but even autologous sera [23].

The role of membrane bound CR1 during allogeneic and minor mismatch blood transfusions is likely protective, because soluble CR1 treatment protects erythrocytes from hemolysis, setting a limit to the classical pathway that mediates non-compliance reactions [24].

Current guidelines advocate restrictive transfusion strategies for situations other than cardiovascular compromise due to the lack of negative impact on mortality in restrictive arms with Red Blood Cell (RBC) sparing ramification. The paradigm, that even moderate anemia (Hgb<110 g/L) may worsen survival outcome in many chronic conditions, yet at the same time transfusion threshold is around 80 g/L give or take with no negative impact on survival, indicates indirectly that overt transfusion administration may become detrimental. This review is not set to analyze the issue, but the role of CR1 is pertinent to address. The energy depleted state of aged erythrocytes likewise, may be addressed therapeutically.

CR1 and CRP

CR1 during opsonization interacts with the C-reactive Protein (CRP) molecule, in that CRP antigen complexes bind to erythrocyte CR1 and are carried to the liver and splenic Reticulo-Endothelial System (RES) for processing [25,26]. CRP is an evolutionary conserved pentraxin molecule with five globular monomers; primarily production in the liver is transcriptionally controlled by IL-6 and IL-1β. CRP relates to CR1 in its ability to activate the classical complement pathway *via* C1q binding and its opsogenic function upon recognition of phosphocholine moiety on polysaccharide capsules of microbes. As a matter of fact, CRP was discovered in 1930 binding pneumococcal phosphatidylcholine. CRP opsonizes apoptotic cell membranes and nuclear antigens. Importantly CRP preferentially engages in Myeloid-Derived Suppressor Cell (MDSC) expansion and their suppressive effect on mouse T cell proliferation.

Interestingly, CRP has a complement regulatory function by directing factor H (fH) to *C3 convertase* [27]. Moreover CRP binding to apoptotic cells has an antiinflammatory outcome due to CRP dependent fH engagement. In accordance with these observations CRP has been shown to demonstrate a protective function in endotoxin mediated shock and autoimmune conditions. CRP is instrumental in complement dependent phagocytosis and Reactive Oxygen Species (ROS) formation of tested zymosan and streptococcus pneumonia [28]. CRP is important for protection against acetaminophen induced liver injury by complement regulation [29].

Soluble CR1

The soluble form of CR1 (sCR1) arises upon proteolytic cleavage from surface bound CR1 and from intracellular vesicles. *Neutrophil elastase* (NE), *serum tryptase* and *metalloproteinase* have been attributed the function of membrane bound CR1 cleavage. NE aids bacterial killing and formation of bactericidal neutrophil extracellular traps (NET), but NE involvement is usually accompanied with significant tissue destruction, and the cleavage of other surface molecules, such as TLR4, lung surfactant, cleaving epithelial junctions, collagens (II, III, IV) etc, contributing to cartilage damage for example [30-34]. ARDS patients demonstrate very high NE levels and COPD patients too, react with heightened NE response due to synergistic effect of hypoxia and inflammation acting on NE release, contributing to the demolition of alveoli, increased mucus production and impaired ciliary function [35,36]. NE is able to induce the mRNA expression of proinflammatory IL-6, TNFα and MIP-2 [37].

CR1 levels are markedly decreased on PMNs of Cystic Fibrosis (CF) patients, even though CR3 levels are retained. This is due to cleavage of CR1 from the surface, inducing severe defects in phagocytosis and killing of Pseudomonas aeruginosa in CF patients [38].

Structurally sCR1 is analogous to the membrane bound counterpart in LHA-C regions, lacking the D region that is responsible for internalization. The A region binds C4b, B and C regions bind C3b/C4b, while the D region is responsible for binding C1q and MBL, sCR1 therefore demonstrates partial effect as compared to membrane bound counterpart, that is the C3b, C4b binding activity, lagging interaction with the initialization of the classical and mannose binding pathways and internalization, hence phagocytosis [39].

Soluble CR1 levels are increased in patients with liver cirrhosis, possibly due to defective hepatic clearance, the levels correlate with advanced disease stage based on Child-Pugh score and bilirubin [40]. While serum sCR1 levels are increased, Kupffer cell specific membrane bound CRIg levels are decreased. The CRIg receptor is responsible for the uptake of C3b opsonized pathogens and immune complexes from circulation and serves as Pattern Recognition Receptor (PRR) for blood-borne gram positive bacteria, listeria monocytogenes, adenovirus [41]. CRIg levels are downregulated by TLR2, 4 ligation and proinflammatory cytokines typically present in alcoholic steatohepatitis. Alcohol-fed mice had lower levels of CRIg, and CRIg deficient mice had worse hepatitis and bacterial clearance, than wild type or CRIg/TLR2 double KO animals. CRIg has a rate limiting effect on the alternative pathway by blocking *C5 convertase* and consequently decreasing MAC formation [42]. The role of increased sCR1 levels in hepatic failure remains to be understood, it may be a compensatory mechanism in situations of enhanced proinflammatory environment driven by upregulated TLRs, when other complement components, dependent on hepatic production are defective, or it is an induced a deviation of complement regulation and uptake, that worsens hepatitis phenotype.

DISCUSSION

Role of CR1 in sepsis and infections

Sepsis is frequently associated with low RBCs due to a number of mechanisms. The reasons are complex and both pathogen and immune mechanisms contribute to anemia development.

Beyond hemolysis due to bacterial porins and toxins, such as pseudomonas pyocyanin, streptococcal hemolysin, enhanced erythrocyte clearance *via* eryptosis may occur. Eryptosis may be initiated by energy depletion, oxidative stress and osmotic shock. During eryptosis, phosphatidylserine externalizes leading to RBC recognition by macrophages and their clearance [43].

Sepsis is a hallmark presentation of complement activation. Potentially all three pathways participate during the recognition of natural antibody-antigen complexes by C1q, lipid A of bacterial endotoxin, some RNA viruses can directly bind to C1q. The lectin binding pathway receptors (MBL, ficolins 1,2,3, collectin 11) bind mannose , lipoteichoic acid and other carbohydrates of fungi, bacteria(haemophilus, streptococci, neisseria, etc), and viruses (HIV) as well, directly or with the aid of IgA molecule. The sepsis phenotype may be determined by overt and derailed systemic inflammatory response and by the defective pathogen clearance. Clinically, it is important to determine the prevailing immunological phenotype and receptor expression level. More than a single parameter, the ratio of proinflammatory and immune-supressive contributors, phagocytic and killing activity determines the outcome and conditions of potential modifications. A conspicuous immune response that is defective in its finalization represents sometimes an unbearable burden on energy metabolism with rapid muscle wasting and energy exhaustion, a catabolic state that is difficult or impossible to rectify. That is why early and efficient bacterial killing and/or functional neutralization even before entry and processing, and consolidation of SIRS are desired. A prolonged immune-suppressed environment leads to the establishment of chronic infections.

An immunosuppressive phenotype typical for tumor microenvironment may be associated with increased RCA expression, including that of CR1 on malignant endometrial tissue, on nasopharyngeal cancer cells [44,45].

Several clinical studies monitored CD35 alone or with CD64, and CD11b (CR3), attempting a timely distinction between viral and bacterial infections, reaching clinical precision [46]. Such measurements will likely reach significance once comprehensive immune monitoring clinically becomes available.

Murine common CR1/2 gene deficiency leads to aggravated, severe phenotype in Coxsackie B3 virus (CVB3) induced acute myocarditis, with increased IL-1β production, IC deposition , pericarditis, despite the fact that a complementary mouse RCA, CD46 is not affected by the deficiency, hence redundancy among RCAs here is limited, while the replication of CVB3 is not adversely affected [47]. IL-β is the principal cytokine associated with disease pathogenesis in this model.

The deleterious effect of complement activation, particularly driven by C5a- calcium interactions on cardiac action potential, and subsequent systolic and diastolic heart function has been experimentally elegantly demonstrated during polymicrobial sepsis [48].

Human erythrocyte CR1 binds adenovirus 5 with high affinity, this leads to rapid clearance of the virus with inhibited hepatic and overall systemic infection [49]. CR1 is particularly sensitive to trypsin-mediated cleavage, and during severe acute pancreatitis, when increased trypsin levels enter the bloodstream; associated complement regulator cleavage is a potential driver of SIRS and Multiple Organ Dysfunction Syndrome (MODS). In Wistar rat model of necrotising pancreatitis, induced by retrograde injection of glycodeoxycholic acid and intravenous cerulein, sCR1 treatment led to decreased levels of C3a, decreased complement-hemolytic activity, diminished pancreatic and pulmonary injury [50].

Lastly CR1 engagement in Plasmodium infections is imperative to mention, because CR1 on erythrocytes serves as plasmodium falciparum receptor, participating in the parasite infectivity and rosetting of red blood cells in endemic areas, leading to a positive selection for low CR1 expressing alleles [51,52]. Soluble CR1 treatment experimentally concluded in diminished red blood cell invasion by plasmodium falciparum, particularly in sialic acid independent strains. Low erythrocyte CR1 expression contributes to severe anemia in this population [53,54].

CR1 function in phagocytosis

Enhancement of pathogen phagocytosis is a plausible approach in fighting infections [55]. Phagocytosis is initiated upon the engagement of pathogen associated molecular patterns with non-opsogenic receptors directly and with the opsogenic ones, such as CR1, CR3, CR4, Fc receptors (FcγRI,II,III). CRs orchestrate the uptake of C3b or immunoglobulin coated particles, that are destroyed in lysosomes by tissue resident macrophages, circulating monocytes, neutrophils and by non-professionals, albeit with low efficiency. Membrane bound CR1 on the surface of neutrophils enhances the attachment and CR3 mediated phagocytosis. Upon introduction of pathogens to blood, erythrocyte bound CR1 promptly engages in carriage; later neutrophil bound CR1 takes over, both acting in a complementary manner [56]. Membrane bound CR1 on the surface of neutrophils enhances the attachment and CR3 mediated phagocytosis.

A vast proportion of pathogens developed strategies in an attempt to evade phagocytosis, often interfering with the complement system. Group A streptococcal evasion techniques are discussed below [57]. Golden staphylococcus has evolved multiple immune evasion strategies, such as conditioning macrophages towards an antiinflammatory phenotype, or enhancement of regulatory factor H attachment to bacterial surface [58,59]. Staphylococcal Ecb protein experimentally aborted C3b and CR1 interaction on the surface of neutrophils with the aftermath of impaired phagocytosis and defective bacterial killing [60]. The Extracellular Complement Binding protein (Ecb) is present in the majority of Staphylococcus aureus strains. Neisseria porins inhibit phagocytosis; they impair the upregulation of CR1 and CR3 receptor molecules [61].

CD89 and CD35 expressions were evaluated in children with dental caries. CD89 serves as a receptor for IgA immunoglobulin, providing immune surveillance on mucosal surfaces. On the neutrophils from the saliva of caries prone children under age five, CD89 levels were statistically increased, while CD35 levels remained unchanged [62]. The reason may be

the presence of Streptococcus mutant strains, carrying complement evasion factors, disabling C3b deposition and CR1/CR3 mediated phagocytosis.

When mucosal barriers are broken, Str.mutans entrance to the bloodstream has the potential to conclude in the damage of the coronary arterial endothelial layer, further aggravating atherosclerosis or heart valve damage [63].

While phagocytosis is a desirable feature in pathogen elimination, if a pathogen is capable of surviving chronically intracellularly due to evasion techniques evolved to overcome intracellular killing, CR1 may paradoxically support survival (HIV) and establishment of chronic infection or carrier state. Obligate intracellular bacteria, surviving in macrophages, such as Mycobacterium leprae, tuberculosis or avium, Francisella tularensis can gain access to macrophages *via* complement receptors [64-66]. Francisella tularensis, due to presence of the protein IgIC, is able to survive and replicate inside macrophages [67].

Defective phagocytosis is an attribute of the COPD pathology [68]. In its essence COPD is yet another example of the dysregulated immune phenotype. The disease is represented by chronic inflammation, increased macrophage numbers, but despite the abundance in numbers defective phagocyte function predominates. There is some evidence regarding the level and functionality of CR1 in COPD patients [69]. Another membrane bound complement regulator, CD46, acting by factor I mediated inactivation of C3b and C4b experimentally protected against COPD [70].

CR1 in B cell function

CR1 on the surface of Follicular Dendritic Cells (FDC), together with TLR4, decisively participates in shaping antibody repertoire by enhancing somatic hypermutation and affinity maturation of B cells for antibody production, with importance particularly in recall responses. Preformed immune complexes, carrying native antigens travel to splenic and lymph node germinal centers, where they get attached to filiform protrusions on FDCs *via* the abundantly present surface CR1, lately alternative routes of attachments are hypothesized, too. The ICs may recirculate in the endosomes of FDC, but they are not processed, but remain expressed on the surface in their native form. They trigger cells through a process of somatic hypermutation *via* CD40-CD40L interaction with helper T cells, and establishment of antigen specific memory B cells with enhanced affinity towards antigen [71]. Previous antigen encounters for immunization facilitate this process. Mice lacking CR1 and CR2 demonstrate defective induced humoral responses to pathogens, particularly of IgG subgroups, even though their baseline immunoglobulin levels are normal [72]. Moreover, germinal centers of mice, selectively deficient in CR1, have defective T cell dependent antibody responses; therefore constitutive CR1 presence is an essential component of optimal antibody responses [73]. A more complex regulatory role of CR1 on B cells is elaborated by experimental works, beyond the scope of this article [74]. Experiments have shown regulatory T cell phenotype emergence upon CR1 engagement [75].

CR1 during hypoxia and ischemia-reperfusion injury

Ischemia-reperfusion injury (IRI) accompanies heterogeneous conditions, a transitional state of tissue oxygen deprivation and subsequent restoration, occasionally even to supraphysiologic level. Regardless if it is due to pulmonary hypoxia, cardiogenic low cardiac output states, microcirculatory defects in tissue oxygenation during sepsis, arterial-occlusive conditions, a SIRS is triggered contributing to organ dysfunction.

Hypoxia leads to complement activation, this has been clinically correlated to the survival of post cardiac arrest patientsin that higher complement activation was present in non-survivors [76,77].

A randomized controlled trial had been completed in lung transplant patients, with the pre-reperfusion application of 10mg/kg soluble sCR1 in 28 patients. The treatment resulted in 11 fewer mechanical ventilation days in a significant number of patients, and 50% of patients were extubated after 24 hours in the treatment group as opposed to 19% in the control group, at the same time, the infection rates were not significantly different among groups [78].

In a clinical environment preemptive sCR1 application is not always feasible, because treatment can be started upon established ischemia/hypoxia. Experimental application of sCR1 and following the outcome in real time, after injury is highly desirable.

The kidney is particularly sensitive to complement mediated attack and when membrane bound CR1 is shed due to cell death and/or *neutrophil elastase* release, complement mediated damage is offered a free ride. While CR1 is expressed on podocytes, MCP (CD46) and DAF (CD55) expressions are relatively more widespread, offering some degree of interchangeability in function, importantly glomeruli are more abundantly covered by complement regulators, than tubular cells [79]. Podocyte injury is associated with IRI induced Acute Kidney Injury (AKI) and with LPS induced AKI, leading to CR1 shedding and relative insufficiency that may adversely manifest under circumstances of enhanced demand [80].

Several clinical studies touched upon CR1 involvement in kidney disease, but comprehensive immuno- pathological characterisation of variable faces of acute kidney injury awaits realization [81]. CR1 sheds to urine from podocyte vesicles and its measurement has been proposed to signal kidney injury, in preeclampsia for instance. Deficiency in complement activators alleviates Ischemia-Reperfusion Injury (IRI), and allograft rejection except for C5aR2r deficiency. This was demonstrated on assorted knockout mouse models (C3, C4, C5, C6, C5aR1, fH deficiency). It is now clinically applied historical expertise that “immune suppression” dampens transplant rejection. Can we blunt the immune response in circumstances of ischemia and reperfusion in a way that has minimal negative impact on pathogen defense? Can we find a reasonable compromise or common denominator?

In experimental conditions on animal models ischemic damage to kidneys is often associated with alternative complement

pathway activation preceded by acquired complement regulator defect due to ischemia induced cell damage. The continuous tick over activation of the alternative pathway *via* surface attachment of C3 is hereby insufficiently suppressed due to acquired CR1 deficiency.

Importantly hemodialysis patients have worse outcomes, when CR1 is expressed in low levels on erythrocytes and recombinant erythropoietin treatment induces complement regulator one expression [82].

CR1 and autoimmunity

Patients suffering from autoimmune diseases tend to have worse disease continuance; they more often succumb to sepsis and ischemia-reperfusion injury complications. Complement component deviations are intimately involved in their pathogenesis. Low CR1 levels have been reported on erythrocytes, leukocytes and podocytes of Systemic Lupus Erythematosus (SLE) patients, particularly during flare ups, for acquired reasons such as consumption, decreased transcriptional activity, enhanced proteolytic surface cleavage and defective membrane translocation [83-85]. CR1 levels on erythrocytes recover upon disease remission. SLE deficiency on both erythrocytes and leukocytes is associated with defective immune complex clearance and deposition [86]. Significantly low CR1 levels were present on neutrophils, monocytes and T cells of psoriasis vulgaris patients as opposed to healthy controls [87,88]. Complement inhibition by C5 depletion, disabling the MAC, has been used experimentally in Guillain-Barre syndrome (GBS), and its proximal form, Miller-Fisher Syndrome. sCR1 application produced positive results in the reversal of phenotype. The terminal complex components are present in the peripheral nerves of GBS patients and they likely lead to MAC mediated demyelination [89]. C5a levels are increased in the sera of these patients indicating the terminal MAC self- destructive activation that is aggravated by CR1 deficiency [90].

CONCLUSION

The uniqueness of intensive care associated disease entities is the intensity, complexity and often transient nature of severe acute pathology. Biological therapy is predominantly present in conditions pertinent to chronic infection, autoimmunity, genetically determined deficiencies or malignancies. The nature of treatment is characterized by length, often long half-life and the aspiration for inducible modification is its permanent position. In contrast, in intensive care we desire relatively short term treatment, early and profound influences tilting the balance to minimizing collateral damage, to lifting a headmost wall to detrimental cascade of pathology culminating in often irreversible organ damage, or later boosting an exhausted organism. In intensive care time and complexity is of essence. Reflection on the molecule of interest from several aspects, and analysis in context is important. A recent work offers an extensive overview of trials aimed at the therapeutic application of sCR1. Mostly, the trials were conducted on animal models, using often prophylactic sCR1 treatment, the indications are widespread and particularly ischemia- reperfusion injury of different organs, transplants, autoimmunity, shock and ARDS were included in these studies. The therapeutic goal of SIRS modification during sepsis was seldom targeted. The soluble CR1 molecule does not fully substitute for phagocytic and clearance functions of the membrane bound molecule that are fundamental for optimal disease resolution. From the above it becomes perceivable, that membrane bound and soluble CR1 levels may be wavering depending on disease etiology, site and stage, and they may reflect variable state of immune activation and suppression. Substitution for sCR1 appears a plausible approach in situations of ischemia - reperfusion and autoimmunity with over complement activation and MAC mediated pathologies, during severe necrotising pancreatitis.

In fulminant, hyperactive sepsis, renal failure and pathologies associated with defective immune complex clearance; conditioning membrane bound CR1 would be optimal to maintain the phagocytic and immune complex clearance potential. It remains to be understood however whether CR1 contributes to deep and long standing immune suppression present in post septic patients. Regardless, monitoring CR1 levels and correlating to overall immune response are imperative for assessment and guiding of potential therapies. It would be desirable to address how CR1 enhancement reflects on ROS production and whether it is possible to blunt hyperinflammation, while maintaining the phagocytic and microbial clearance functions. Despite the abundance of promising positive results under experimental conditions, the translation and clinical interpretation of CR1 role in health and disease, is far from conclusive. The functions attributed to complement regulator one can be substituted by other immune components. However, under circumstances of enhanced demand absolute or relative insufficiency of CR1 is detrimental. Searching for novel approaches and avenues is fundamental in critical care practice.

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