Properdin: a regulatory protein that functions beyond immune system regulation

Abstract:

Properdin, a serum glycoprotein, is involved in the immune system regulation particularly alternative pathway activation of the complement system. Properdin is made up of cyclic oligomers of monomeric subunits and is generated by a variety of leukocyte subsets. Properdin promotes complement activation, which leads to alterations in the cellular milieu that contribute to innate and adaptive immunological responses, such as the generation of pro-inflammatory cytokines, immune cell recruitment, and the development of immune cells involved in antigen presentation. While the presence of possible properdin inhibitors in serum and the production of non-physiological aggregates in pure properdin preparations have delayed research of its activity, properdin has still appeared as a key factor in various inflammatory disease models. Using the properdin-deficient murine model has aided in the knowledge of how properdin participates in diseases pathophysiology promotion or prevention. Pharmaceutical therapy for complement-dependent damage such as properdin is possible for a variety of acute and chronic problems, ranging from well-established medicines for rare conditions to prospective future therapies for large patient groups such as the pandemic coronavirus-virus disease 2019. The basics of properdin biology are discussed, with a focus on the major hurdles that have hampered the interpretation of results from properdin-targeted studies.

Keywords: properdin; immune system; infection; complement therapy; inflammation.

Introduction:

It has been clear in recent decades that the complement system is involved in a variety of illnesses [1]. As a result, Complement-inhibiting treatment is becoming increasingly popular [2]. In theory, the complement system is an important component given that it plays a crucial role in the protective immunity in humans. It is made up of various plasma and cell surface proteins, which actively interact in a complex manner, along with several more regulatory (immune) systems to distinguish amongst invasive, changed identity, and healthy self-surfaces. Complement allows for advanced immune surveillance and balance in the body. In order to stand against a complement-attack, most tissues and cells within the human body will produce membrane-bound proteins that serve a regulatory purpose. Regulatory proteins, which are soluble in nature, are then sent off to inflamed spots. This happens through their interaction with not just ligands but also primarily the complement proteins. It is marked through the local mircoenvironment's complex and distinct form. One soluble complement protein is properdin. It is an initiator and regulator of the alternative pathway for the complement, which then has a substantial effect on its activation levels [1].

Clinical trials are now evaluating over 20 potential medicines that target complement components [3]. Found 64 years ago, properdin is essentially the one and only recognized complement regulator that has experienced enormous physiological categorization in aspects of serum and microenvironment inputs, biological capabilities, illness functions, and biochemical characteristics which would include elements such as, transcription, expression post-translational modifications, oligomerization and secretion [1, 3]. In this review, properdins' roles in immunity and its place in complement treatments are discussed.

Comment [MAM1]: Their place

Complement system:

Among the first line of defense against external and abnormal host cells, complement more or less acts as a critical part of an individual's immunity itself [4]. This system is a collection of plasma proteins that are often produced in the liver and membrane proteins that are produced on the surfaces of cells. Complement can be present in blood, cells, and tissues [5]. Complement proteins collaborate for the purpose of opsonizing the pathogens and triggering a sequence of inflammatory

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reactions that aid cells relevant to immunity in combating illness, alongside maintaining homeostasis. Three different pathways – classical (CP), lectin (LP), and alternative (AP) – each leading to a shared terminal pathway – are able to initiate the complement system. For the context of a normal person, AP's seen as always functioning at low levels all of the time to check for infections. Healthy host cells are immune to complement attack and can tolerate low-grade activation for long periods. Apoptotic cells are cells that are continually formed in the body during normal cellular homeostasis; activate the three routes on their surfaces. Complement activation is strictly controlled in order to destroy dying cells without triggering adaptive or innate components and affecting immunity. Complement can become completely active once a pathogen is present. Complement induces inflammation, opsonization, phagocytosis, and pathogen death during an infection, which leads to the adaptive immune response being activated. Autoimmunity, thrombotic microangiopathy, chronic inflammation, graft rejection, and cancerous diseases are all related to increased susceptibility to non-infectious or infectious illnesses due to insufficient or excessive complement stimulation [1, 4, and 5].

Overview of pathway:

Over 40 proteins make up the complement system, which performs a variety of tasks such as contributing to a cascade-like process for activation, which acts as major ligands or cellular receptors. Complement system proteins, complement receptors expressed on human cells (CR1, CR2, CR3, CR4, C5a receptor 1 and 2, C3a receptor 1, C1q receptors, and CRIg), and complement regulatory proteins (Factor H, CD35/CR1, CD55/DAF, CD46/MCP, CD59, C4bp, Factor I, C1-INH, clusterin, vitronectin, CMSD1, CRIg, Factor H-like protein 1, Factor H-related protein 1–5, and properdin) play important roles in the host's defence against infection, in maintaining homeostasis through the clearance of immunological complexes and cell debris, in bridging the gap between innate and adaptive immunity, in metabolism, and in the nervous system [6]. As previously mentioned, there are three mechanisms to activate the complement system: classical, lectin, and alternative. The classical pathway is initiated when the C1 complex (containing C1q, C1r, and C1s) binds to immunoglobulins bound on pathogens or cell surfaces, circulating immune complexes, or pentraxins. The lectin pathway (LP) is initiated when certain carbohydrates and

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other ligands on pathogen surfaces are recognized by mannose-binding lectin (MBL), ficolins, or collectins (CL-LK). When the CP and LP are active, serine proteases associated with the recognition molecules C1q and MBL (C1s and MBL-associated serine protein 2 (MASP-2)) break C4 and C2. The generated C4b attaches to the cell surface, while the C2b fragment binds to the C4b, forming the CP and LP C3 convertase (C4b2b), which converts C3 to C3b and C3a, a chemo-attractant molecule. C3b possesses an exposed thioester bond [7, 8], allowing it to tag specific molecules by covalently binding to hydroxyl (-OH) and amine (-NH2) groups on cell surfaces. Before the C3b thioester is immediately inactivated by hydrolysis, covalent attachment of C3b occurs within sixty microseconds at a minimum distance of 28–30 nm (280–300 nm) [9].

The structure and production of properdin:

Properdin is a significantly positively influenced plasma glycoprotein and is a component of the complement system. It is primarily manufactured by leukocytes, such as T cells [10], monocytes [11], and mast cells [12], in comparison with other complement elements generated by the liver; the protein is also stored in neutrophil auxiliary granules and is produced when the cells are activated [13]. The association between chemotherapy-provoked neutropenia and a reduction in properdin levels in the circulation [14] highlights neutrophils' involvement in total protein levels in plasma. In the healthy control group, normal systemic levels of human properdin are reported to vary from 5 to 45 g/ml [15]. The wide variation between researches is most likely owing to changes in the methodologies and reagents utilized, such as detection methods, antibody combinations, and standard protein preparations. In healthy neonates and babies (under one year old), systemic properdin levels are lower than in adults [24, 25, 28, 33].

Properdin is found in the oligomeric form in the blood and is found on the X chromosome. This last feature is critical to the organism's biological function. Properdin oligomers are composed of a monomer resembling a rod, with molecular weights in the range of 53 kDa [34]. Each monomer has 442 amino acids [35] and one truncated and six complete thrombospondin type I repeat (TSR) domains, which are numbered TSR0 to TSR6 from the N to C terminus [35, 37]. By creating head-to-tail linkages, the elastic monomeric subunits form cyclic dimers, trimers, or tetramers

with curled vertex structures [7, 40, 38]. The oligomers occur in a fixed ratio of around 1:2:1 in normal human plasma, with the trimer being the predominant type [7]. Properdin's flexibility, the oligomeric structure makes biochemical and structure-based studies hard to manage. Since a while, scientists relied on structure-function experiments with recombinant protein that was truncated or mutated, or particular TSR-directed antibodies to learn about the activities of individual TSRs in terms of target binding and oligomerization [36, 39, 40]. Recent developments, when studying properdin's atomic formation, have highlighted that vertex formation is mediated by TSR domains emanating from two monomers. The connecting component will be made up of three TSRs [38, 41]. Based on current information, the most likely structure of properdin is a vertex with TSR0–1/TSR5–6 joined by TSRs 2–4. The complete structure with high resolution of the properdin has, however, not yet been determined.

Properdin deficiencies, mutations, and polymorphic variants:

Properdin deficiency is inherited as a X-chromosomal recessive trait and is closely connected to increased susceptibility to *Neisseria meningitides*, alongside with a substantially augmented risk associated with having spread, fulminant meningococcal infection than healthy persons [42]. Properdin deficiency has been detected in around 25 families, including approximately 20 different mutations [43]. Type I, or absolute lack of circulatory properdin, is triggered by a variety of mutations that lead to a shortened particular gene or alterations in protein structure that impede properdin secretion [44, 45]. Type II, or partial lack of circulatory properdin, is produced by a variety of abnormalities that produce a shortened genetic material or alterations in protein structure that impede properdin release [46]. Nucleotide mutations found in Type I deficient families alter amino acids that are structurally similar in human and mouse TSRs, showing that they are necessary for protein complexes [47]. (b) Type II properdin deficiency, which results in a 10% drop in serum properdin concentrations. Properdin is generated and secreted by cells, but oligomerization takes an unconventional path, with dimers predominating. Despite normal plasma levels, type II properdin deficiency is defined by a diminished capacity to bind C3b and govern the AP. Despite normal plasma levels, type III properdin

deficiency is described by a reduced capacity for binding C3b and control of the AP [48-50].

Properdin and disease:

To prevent the unfavorable inflammation-related and autoimmunological reactions that occur when cell viability is reduced later in apoptosis, as well as the following necrosis, tissues should be eliminated as soon as possible during apoptosis [51]. Without properdin, a higher number of apoptotic cells may proceed to secondary necrosis, potentially contributing to autoimmunity, more prominently the in vivo formation of systemic lupus erythematosus (SLE) [52]. While Properdin-deficient people have lower serum AP activation and end up more vulnerable to *Neisseria meningitides* [53, 54, 55, 56], only a few findings have established a link between properdin deficiency and autoimmune illness [57, 58]. There are a few possibilities for why properdin-deficient people don't have an evident autoimmune phenotype: 1. Considering the importance of removing dead cells as quickly as possible, it comes as no surprise that there are multiple (sometimes overlapping) systems in place to ensure the process's continuous operation. Properdin, recognizes relatively early apoptotic T cells [59], whereas C1 and MBL recognize late apoptotic/necrotic cells [60]. Late apoptotic and necrotic cells are regarded as more harmful than original ones because they lack membrane integrity and release intracellular antigen elements known to trigger an autoimmune response. A progressive apoptotic cell must be identified and designated for elimination by the 'second guard,' C1q and/or MBL, even in the lack of properdin. Apoptotic cells are recognized and removed by a number of extra proteins, such as the class-B scavenger receptor CD36, the classic phosphatidylserine receptor, 2-glycoprotein, and milk-fat globule epidermal growth factor 8 (MFGE8) [61, 62, 63]. Consequently, the effects of properdin deficiency on autoimmunity may not be apparent till the disruption is noticed or experienced in one or more than one of the 'back up' pathways. This deficiency can result in a number of paradoxical results: When it comes to the MRL/lpr lupus nephritis model for mouses, the AP convertase factor D [64] and factor B [65] are necessary for not only the death of the cell but also its pathologic complement deposition. Considering that the protein helps stabilize AP convertases, it's possible that although a deficiency of properdin allows more

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malignant tumors to develop, it also limits necrotic cells' capacity for complement activation. Properdin abnormalities that enable convertase stability but impair apoptotic cell recognition, instead of those that cause complete properdin deficit, are more probable risk factors for autoimmunity. These abnormalities would not be discovered in previous studies as they would not always produce Neisseria susceptibility or interfere with properdin functioning in typical properdin tests. It's worth emphasizing the study at hand has more or less fine-tuned its focus to remain entirely on T cells [59], and it's unknown if it attaches to certain other forms of apoptotic cells. Furthermore, autoimmune illnesses are more common in women [66], However, since properdin is encoded on the X chromosome (and thus almost all documented properdin-deficient people are men), the effect of properdin deficiency in women is unclear [57,58]. Xu et al. [67] looked into the part played by properdin in apoptosis [58]. Using Jurkat cells, the researchers discovered that apoptosis was accompanied by a significant rise in binding of properdin. Research conducted on biochemistry in the future, when it comes to the subject, alongside in vivo model studies, is expected to expand on the mechanism(s) and the part played by the protein's interaction at the time of apoptosis.

If Properdin indeed contributes to the detection of broad danger signals, its spectrum of particular targets might encompass pathogen-infected along with cancerous elements. Sjoblom et al. [68] looked at 13,000 different genes to study and examine their sequencing. The work extended itself from one end to another, i.e. it looked at breast tumors of a primary nature, and went as far as delving into the lines of comparable gene sequencing traces that came from other tissue that match and could be classified as normal. Mutated genes, which were significantly altered during carcinogenesis, were discovered, suggesting that they would typically perform a protective role. This group included the properdin gene. The properdin gene is most likely active in breast cancer development, with the resultant properdin proteins being carried to the cell membrane and designating it for clearing. Breast cancerous cells have been shown to have altered GAG components in growth and may create properdin-binding domains [69]. If abnormalities in the properdin gene accumulated throughout tumor formation, this defensive pathway may be disrupted. As earlier said, a loss of properdin or its ability to recognize possibly lethal antigens can result in a wide range of illnesses and persistent problems. Properdin-induced AP activation, on the other hand, may not always be beneficial, and in certain situations may be harmful:

Properdin produced from newly discharged neutrophil granules has a high target-binding capability (as compared to indigenous serum properdin), which might explain neutrophils' crucial involvement in AP-dependent disease models for diseases, including rheumatoid arthritis [70, 71] and anti-phospholipid syndrome [72]. Neutrophil-derived properdin may also promote AP activation in glomerulonephritis and vasculitis caused by anti-neutrophil cytoplasmic autoantibodies (ANCA disease) [73], as well as play a role in kidney transplant rejection, which is characterized by massive neutrophil infiltration in the presence of dying tissue [74]. Mast cells were recently discovered to be a novel source of properdin [75]. Properdin-directed complement activation might potentially be used in circumstances involving mast cells. It has recently been discovered that the AP C3 convertase is involved in the worsening of injury and disease. As a result, the AP C3 convertase has emerged as a potential therapeutic target. Antibodies that inhibit factor B [76], factor D [77), and properdin [78] have been presented as potential treatments in humanized form. Given the importance of the AP in preserving health, there is concern about the approach's potential adverse effects. We're only scratching the surface of the biological implications of properdin: target recognition. It's probable that this recently discovered properdin activity is involved in one or more of the various AP-dependent neutrophil-dependent illnesses. Properdin is made up of six TSRs, the majority of which appear to be ligand-binding sites. As a result, each target may be recognized by a unique set of TSRs. This scenario suggests the development of reagents that inhibit certain properdin: target interactions while leaving other properdin activities unaffected, avoiding unwanted side effects and restricting the therapeutic intervention's impact on the relevant therapeutic intervention. Structure studies examining properdin: target recognition, as well as investigations aimed at elucidating properdin target recognition inhibition in the serum, could be crucial in this regard. In an added note, the presence of a tiny animal plan would help with this kind of study.

Systemic Inflammation:

Complement inhibition has only proven successful in rare disorders so far. One rationale for this is that the pathophysiology of several uncommon illnesses is commonly discovered to be more or less complement-triggered, and a single therapy with a complement blocker may be adequate to control the problem. The pathophysiology of trauma and sepsis is significantly more convoluted, however,

complement is undoubtedly essential. Complement acts as an upstream first-line sensor of risk, perhaps amplifying the inflammatory outburst. Nevertheless, due to the alternative first-line sensors (such as Toll-like receptors) exist, a combination of inhibitors of many of these sensors may be required necessary, as demonstrated with complement and CD14 [79]. CD14 inhibition has been recommended as a possible therapy for coronavirus disease 2019 (COVID-19) [80]. Prospective complement suppression techniques in septic infections or conditions will face the difficulty of identifying subgroups of patients who are characterized by complement activation. Other upstream bottlenecks, i.e. the sensor molecules, can then be combined with this, however, inhibiting elements such as cytokines, which are single downstream mediators, have a lower likelihood of working owing to their abundance. Given the numerous studies that strived to demonstrate and show that inhibiting specific downstream mediators is ineffective. Inherent immunity, especially complement, plays a pivotal role in the pathogenesis of trauma, and its therapeutic efficacy is equivalent to those of sepsis; nevertheless, DAMPs are more essential at first [80]. Recurrent infection, however, is usually discovered when sepsis advances to its final stages.

Among the first investigations of increased complement activation in people with COVID-19 found an increase in the activation of components sC5b-9 and C5a, with the former acting for a longer period of time [81]. The presence of C5a in bronchoalveolar fluid and the prevention of lung injury in a human C5aR1 knock mice model further suggested a role for the Ca-C5aR1 axis [82]. Five separate complement activation products from all routes were assessed in hospitalized patients in a clinical investigation of 39 patients. All activation products were uniformly raised across the board in all patients [83], and C5b-9 was linked to respiratory performance. Antibody titers, surprisingly, were also substantially linked with respiratory function, albeit to a lesser level. It's unclear how much the classical versus lectin pathways contributed to C4 activation, although they were very certainly both engaged. Furthermore, the C3 convertase C3bBbP was greatly enhanced, showing that a COVID-19 therapy strategy should be wide and encompass all routes (i.e., C3 or C5). [84) and [85] reviewed the interaction between the complement system and coronaviruses (2020). Treatment for COVID-19 has so far been restricted to case studies, the majority of which demonstrate inhibition at the C5 level [86, 87, 88].

Although the results of an open-labeled randomized study with 15 patients treated with an inhibitory anti-C5a antibody and 15 controls [89] are promising, bigger randomized control studies are needed to determine whether complement inhibition is a viable therapy option for COVID-19 [90].

Mode of expression of complement:

Targets to be suppressed:

Some diseases, like cold agglutinin syndrome and PNH, demonstrate greater dependence on complement, while others are only partially dependent on complement, varying from strongly to a little, and there are almost certainly no circumstances in which immune inflammatory response is involved when complement is missing. Thus, the guidelines for treating a problem will be dependent primarily on the quantity of the complement implicated on a scale [91]. Moreover, a disparity exists when it comes to chronic, lifelong diseases when the person who is ill is typically bound to their house and other diseases where there is an intense need for immediate care because of life-threatening issues at play, where the person who is ill is in the hospital or even the ICU, where they are monitored closely and given antibiotics, and where suppression is just required for a smaller period of time. In addition, the cost of suppressing complement has typically been exceptionally high, and it has been utilized in rare illnesses. New and less expensive pharmaceuticals are on their way to the market, and the ramifications for healthcare costs must be considered. [92]. When discussing this important topic in the future, there will be many other issues to consider.

We have listed a few of the target molecules found in the cascade, which will be important in the coming future, as per our belief. Because the scientific field is rapidly evolving, this may alter. We must underline that a designed humanized monoclonal antibody targeting C5 cleavage is the only medication for complement suppression that has been accessible for routine usage. As a result, the expertise of blocking other targets was limited until now [93].

Classical and Lectin Pathway:

MBL has been the most researched protein in the lectin system and may be an option in some circumstances, but MASP-2 has recently been proposed as an

interesting candidate to inhibit the lectin pathway. MBL, like C1q, is a recognition molecule with several roles, and MASP-2 could be a viable option because the lectin pathway is recognized by a variety of different molecules, with MASP-2 serving as the primary activation pathway. The fundamental risk with stopping the lectin pathway is that a significant portion of the complement's danger recognition function is lost [94].

C3 and the Alternative Pathway:

The fundamental difficulty with blocking C3 and alternate components is that it reduces opsonization and, therefore, increases the danger of infection. This should not be a concern if the patient is in an acute condition and is being watched and treated with antibiotics. A child will not be concerned about this short-term treatment. C3 is critical for accelerating B-cell antibody production; however, inhibiting C3 for a short period would have little effect. Another issue with C3 is its abundance in circulation, as well as the fact that it is produced locally in numerous tissues, making inhibition difficult [95].

The terminal pathway:

To be suppressed, the terminal pathway's ultimate goal is to stop C5b-9 from combining, inhibiting membrane attack complex development yet enabling C5a to be released. This might be achieved by blocking C6 or C7, for example. The leakage process via the membrane begins after C8 has bonded [96].

Diagnostic and follow-up

Complement Activation Detection:

The complement system can be evaluated using a variety of methods [97, 98]. The first is an in vivo test for measuring the degree of complement activation. There are a variety of assays available to identify specific activation products, but the TCC is a useful biomarker because it signals that C5 is activated and that both C5a and C5b-9 are produced. When C9 is included in the complex but not present in the original C9 molecule, this can be identified in plasma as sC5b-9 using a simple ELISA based on a monoclonal antibody interacting with a neoepitope exposed in C9 [99]. The advantage of this test is that this complex has a longer half-life (1 hour) than

the C5a molecule, which has a much shorter half-life (1 minute). It will also identify the activation of the entire cascade from beginning to conclusion. The use of EDTA to acquire blood samples and the collection and snap-freezing of plasma at 270°C is vital [100, 101].

Total Complement Activity (TCA) testing

This collection of assays evaluates the complement system's overall functional activity. They used to be based on complement hemolytic testing, however increasingly sensitive and reliable enzyme immunoassays, such as the entire complement screen, gradually supplanted it. However, unlike the sC5b-9 test, this assay measures complement properties in vitro and so requires serum (fresh or freshly maintained and kept at a temperature of 27°C). The detecting method is similar to C5b-9 ELISA, but the structure is different [102]. The wells are covered with activators specific to each of the three pathways, and if all 3 elements are present and active, the C5b-9 complex will form in the well and be identified using the same anti-C9 neoepitope antibody. The complement system will be recognized as 100 percent activity in the wells if it is normal. The C5b-9 complex will not form if a terminal component or C3 is genetically faulty, such as in a patient lacking C5. Because the detection antibody does not recognize a C9 neoepitope, all three pathways will show 0% activity. If one or more of the tests come out negative, additional testing is required to identify the lacking component [103].

Therapeutic Complement Inhibition's Consequences:

A. Adverse Effects and Safety

1. **Established C5 Inhibition:**

Eculizumab was the sole complement blocker approved for therapeutic usage till 2020. In 2007, it was approved to treat paroxysmal nocturnal hemoglobinuria. These patients will be treated for the rest of their lives, and the treatment has proven to be extremely safe. The medicine was shown to be safe and well-tolerated in a 66-month study of 196 patients, without any indication or confirmation for cumulative toxicity [104]. Four deaths were unrelated to the treatment, and no evidence of Neisseria infection was identified. A similar finding was discovered in a Japanese investigation of PNH patients [105]. A study conducted a thorough evaluation of 12

databases and revealed that no deaths or Neisseria infections occurred as a result of the treatments [106]. A number of other research back up the safety of the product. However, three incidences of Neisseria infection were discovered in significant research conducted over five years, with 1,321 participants, including both pediatric and adult patients, with one case resulting in death [107]. Ultimately, a study that was done over a decade and included 28,518 individual years confirmed the medication's efficacy all while emphasizing the risk of Neisseria infection. Other infections were discovered, but the cause was unknown [108]. As a result, C5 inhibition with eculizumab is a relatively safe treatment with few side effects, but the minor risk of Neisseria infection should be kept in mind at all times.

2. New Inhibitors Could Have Negative Side Effects:

When novel inhibitors are approved for clinical usage, various potential side effects should be considered. It is impossible to rule out the possibility that inhibiting all three pathways' initial recognition phases, or inhibiting C3, had the likelihood of raising the risks associated with added infectious events, caused by reduced opsonization. Short-term therapy although the person is still under observation may be less of a worry in some acute phases, and it might potentially be the most beneficial therapy [109].

B. Efficacy of Treatment

1. Fully Complement-Dependent Diseases:

Once the condition is predominantly complement-dependent, such as in paroxysmal nocturnal hemoglobinuria and aHUS, complement inhibition is very effective and even life-saving. Complement has a substantial (albeit not only) part in the pathophysiology of a variety of disease possibilities, as previously indicated. Before adding additional disorders to the list, controlled clinical trials should be done. Off-label use may be permitted in severely sick patients if there is a reason to suspect the presence of complement-mediated pathology, particularly if the condition is uncommon and medical trials with appropriate power are difficult to undertake [110,111].

2. Diseases with Complex Pathophysiology:

Complement activation may have a smaller role in pathophysiology in such complicated disorders, thus the goal will be to employ a combination of laboratory models and clinical trials to see if complement suppression might lower disease activity [112].

Conclusion

The complicated role of properdin in various key immune processes increases the demand for new research on both levels in vitro and in vivo. Among these would be a reassessment of sickness frequency, particularly for people with properdin deficiency. Moreover, more examination of the impacts of properdin deficiency in animal studies is also required. Properdin DNA polymorphism in people who present with illnesses of autoimmune disorders typically associated with issues with apoptotic cell clearance, or in those with particular cancerous cells or tumors, should get greater focus, with a special emphasis on polymorphisms that affect the identification of the target. The body's immune system consists of various components such as complement to quickly recognize and destroy infections and other dangerous organisms.

There has been for a long time an assumption that complement is a primitive "stop-gap" measure to stop infection while waiting for the complete activation of the adaptive immune system. It is now clear how naïve this assumption was: effective immune defence is considered as a complex system wherein the intrinsic system plays critical roles in instructing and directing the adaptive system. The discovery of complement receptors, such as CRIg [113], and the revealed new roles complement proteins like C1q in the development of the neuronal synapse [114], the importance of DAF, CD46, and C5a in modulating T cell responses [115-119], the properdin capability of recognizing dangerous antigens [59,119]: all of these findings show how closely complement and adaptive immunity are linked, implying that there will be many more intriguing discoveries at the complement/adaptive immunity interface in the future.

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We believe that this review has provided the reader with enough information to investigate complement as an intriguing and thoroughly studied topic for treatment of a variety of illnesses in the clinical setting, instead of merely as "an elegant model system." It is also important to note the significance of intensifying research activities

in this area is for establishing the framework for clinical investigations in the future. It is reasonable to expect that as the number of complement-modulating drugs increases, so will the number of diseases that can be treated with complement-modulating therapies.

References:

1. Ricklin D, Reis ES, Lambris JD (2016) Complement in disease: a defence system turning offensive. Nat Rev Nephrol 12:383–401.

2. Ricklin D, Mastellos DC, Reis ES, Lambris JD (2018) The renaissance of complement therapeutics. Nat Rev Nephrol 14:26–47.

3. Ricklin D, Mastellos DC, Reis ES, Lambris JD, 2018 The renaissance of complement therapeutics. Nat Rev Nephrol 14, 26–47. [PubMed: 29199277]

4. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol (2010) 11:785–97. doi:10.1038/ni.1923

5. Kolev M, Le Friec G, Kemper C. Complement – tapping into new sites and effector systems. Nat Rev Immunol (2014) 14:811–20. doi:10.1038/nri3761

6. Barnum SR, Schein TN, 2018a The Complement FactsBook (Second Edition), Academic Press.

7. Pangburn MK, Muller-Eberhard HJ, 1980 Relation of putative thioester bond in C3 to activation of the alternative pathway and the binding of C3b to biological targets of complement. J. Exp. Med 152, 1102–1114. [PubMed: 6903192]

8. Tack BF, Harrison RA, Janatova J, Thomas ML, Prahl JW, 1980 Evidence for presence of an internal thiolester bond in third component of human complement. Proc. Natl. Acad. Sci. U. S. A 77, 5764–5768. [PubMed: 6934510]

9. Sim RB, Twose TM, Paterson DS, Sim E, 1981 The covalent-binding reaction of complement component C3. Biochem. J 193, 115–127. [PubMed: 7305916]

10. Schwaeble W, Dippold WG, Schafer MK, Pohla H, Jonas D, Luttig B, Weihe E, Huemer HP,Dierich MP, Reid KB (1993) Properdin, a positive regulator of complement activation, is expressed in human T cell lines and peripheral blood T cells. J Immunol 151:2521–2528

11. Whaley K (1980) Biosynthesis of the complement components and the regulatory proteins of the alternative complement pathway by human peripheral blood monocytes. J Exp Med 151:501–516

12. Stover CM, Luckett JC, Echtenacher B, Dupont A, Figgitt SE, Brown J, Mannel DN, Schwaeble WJ (2008) Properdin plays aprotective role in polymicrobial septic peritonitis. J Immunol 180: 3313–3318

13. Wirthmueller U, Dewald B, Thelen M, Schafer MK, Stover C, Whaley K, North J, Eggleton P, Reid KB, Schwaeble WJ (1997) Properdin, a positive regulator of complement activation, is released from secondary granules of stimulated peripheral blood neutrophils. J Immunol 158:4444–4451

14. Tsyrkunou A, Agarwal S, Koirala B, Finberg RW, Nath R, Barton B, Levitz SM, Wang JP, Ram S (2017) Properdin levels in individuals with chemotherapy-induced neutropenia. Open Forum Infect Dis. https://doi.org/10.1093/ofid/ofw250

15. Pangburn MK (1989) Analysis of the natural polymeric forms ofhuman properdin and their functions in complement activation. J Immunol 142:202–207

16. Corvillo F, Bravo Garcia-Morato M, Nozal P, Garrido S, Tortajada A, Rodriguez de Cordoba S, Lopez-Trascasa M (2016) Serum properdin consumption as a biomarker of C5 convertase dysregulation in C3 glomerulopathy. Clin Exp Immunol 184:118–125

17. Zhang Y, Nester CM, Martin B, Skjoedt MO, Meyer NC, Shao D, Borsa N, Palarasah Y, Smith RJ (2014) Defining the complement biomarker profile of C3 glomerulopathy. Clin J Am Soc Nephrol 9:1876–1882

18. Zhang Y, Meyer NC, Fervenza FC, Lau W, Keenan A, CaraFuentes G, Shao D, Akber A, Fremeaux-Bacchi V, Sethi S, Nester CM, Smith RJH (2017) C4 nephritic factors in C3 glomerulopathy: a case series. Am J Kidney Dis 70:834–843

19. Stover CM, McDonald J, Byrne S, Lambert DG, Thompson JP (2015) Properdin levels in human sepsis. Front Immunol 6:24

20. Somani R, Richardson VR, Standeven KF, Grant PJ, Carter AM (2012) Elevated properdin and enhanced complement activation in first-degree relatives of South Asian subjects with type 2 diabetes. Diabetes Care 35:894–899

21. Shahini N, Michelsen AE, Nilsson PH, Ekholt K, Gullestad L, Broch K, Dahl CP, Aukrust P, Ueland T, Mollnes TE, Yndestad A, Louwe MC (2017) The alternative complement pathway is dysregulated in patients with chronic heart failure. Sci Rep 7: 42532

22. Xu W, Berger SP, Trouw LA, de Boer HC, Schlagwein N, Mutsaers C, Daha MR, van Kooten C (2008) Properdin binds to late apoptotic and necrotic cells independently of C3b and regulates alternative pathway complement activation. J Immunol 180: 7613–7621

23. Poppelaars F, Gaya da Costa M, Berger SP, Assa S, Meter-Arkema AH, Daha MR, van Son WJ, Franssen CF, Seelen MA (2016) Strong predictive value of mannose-binding lectin levels for cardiovascular risk of hemodialysis patients. J Transl Med 14:236

24. de Paula PF, Barbosa JE, Junior PR, Ferriani VP, Latorre MR, Nudelman V, Isaac L (2003) Ontogeny of complement regulatory proteins - concentrations of factor h, factor I, c4b-binding protein, properdin and vitronectin in healthy children of different ages and in adults. Scand J Immunol 58:572–577

25. Grumach AS, Ceccon ME, Rutz R, Fertig A, Kirschfink M (2014) Complement profile in neonates of different gestational ages. Scand J Immunol 79:276–281

26. Gou SJ, Yuan J, Chen M, Yu F, Zhao MH (2013) Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. Kidney Int 83:129–137

27. Onda K, Ohi H, Tamano M, Ohsawa I, Wakabayashi M, Horikoshi S, Fujita T, Tomino Y (2007) Hypercomplementemia in adult patients with IgA nephropathy. J Clin Lab Anal 21:77–84

28. Minta JO, Jezyk PD, Lepow IH (1976) Distribution and levels of properdin in human body fluids. Clin Immunol Immunopathol 5: 84–90

29. Sonntag J, Brandenburg U, Polzehl D, Strauss E, Vogel M, Dudenhausen JW, Obladen M (1998) Complement system in healthy term newborns: reference values in umbilical cord blood. Pediatr Dev Pathol 1:131–135

30. Davis CA, Vallota EH, Forristal J (1979) Serum complement levels in infancy: age related changes. Pediatr Res 13:1043–1046

31. Wolach B, Dolfin T, Regev R, Gilboa S, Schlesinger M (1997) The development of thecomplement system after 28 weeks' gestation. Acta Paediatr Scand 86:523–527

32. Prellner K, Sjoholm AG, Truedsson L (1987) Concentrations of C1q, factor B, factor D and properdin in healthy children, and the age-related presence of circulating C1r-C1s complexes. Acta Paediatr Scand 76:939–943

33. Drew JH, Arroyave CM (1980) The complement system of the newborn infant. Biol Neonate 37:209–217

34. Smith CA, Pangburn MK, Vogel CW, Muller-Eberhard HJ (1984) Molecular architecture of human properdin, a positive regulator of the alternative pathway of complement. J Biol Chem 259:4582– 4588

35. Nolan KF, Schwaeble W, Kaluz S, Dierich MP, Reid KB (1991) Molecular cloning of the cDNA coding for properdin, a positive regulator of the alternative pathway of human complement. Eur J Immunol 21:771–776

36. Higgins JM, Wiedemann H, Timpl R, Reid KB (1995) Characterization of mutant forms of recombinant human properdin lacking single thrombospondin type I repeats. Identification of modules important for function. J Immunol 155:5777–5785

37. Sun Z, Reid KB, Perkins SJ (2004) The dimeric and trimeric solution structures of the multidomain complement protein properdin by X-ray scattering, analytical ultracentrifugation and constrained modelling. J Mol Biol 343:1327–1343

38. Alcorlo M, Tortajada A, Rodriguez de Cordoba S, Llorca O (2013) Structural basis for the stabilization of the complement alternative pathway C3 convertase by properdin. Proc Natl Acad Sci U S A 110:13504–13509

39. Bertram P, Akk AM, Zhou HF, Mitchell LM, Pham CT, Hourcade DE (2015) Anti-mouse properdin TSR 5/6 monoclonal antibodies block complement alternative pathway-dependent pathogenesis. Monoclon Antib Immunodiagn Immunother 34:1–6

40. Perdikoulis MV, Kishore U, Reid KB (2001) Expression and characterisation of thethrombospondin type I repeats of human properdin. Biochim Biophys Acta 1548:265–277

41. Pedersen DV, Roumenina L, Jensen RK, Gadeberg TA, Marinozzi C, Picard C, Rybkine T, Thiel S, Sorensen UB, Stover C, Fremeaux-Bacchi V, Andersen GR (2017) Functional and structural insight into properdin control of complement alternative pathway amplification. EMBO J 36:1084–1099

42. Figueroa J, Andreoni J, Densen P, 1993 Complement deficiency states and meningococcal disease. Immunol. Res 12, 295–311. [PubMed: 8288947]

43. Fijen CA, Kuijper EJ, te Bulte MT, Daha MR, Dankert J, 1999a Assessment of complement deficiency in patients with meningococcal disease in The Netherlands. Clin. Infect. Dis 28, 98–105. [PubMed: 10028078]

44. Helminen M, Seitsonen S, Jarva H, Meri S, Jarvela IE, 2012 A novel mutation W388X underlying properdin deficiency in a Finnish family. Scand. J. Immunol 75, 445–448. [PubMed: 22229731]

45. Westberg J, Fredrikson GN, Truedsson L, Sjoholm AG, Uhlen M, 1995 Sequence-based analysis of properdin deficiency: identification of point mutations in two phenotypic forms of an X-linked immunodeficiency. Genomics 29, 1–8. [PubMed: 8530058]

46. van den Bogaard R, Fijen CA, Schipper MG, de Galan L, Kuijper EJ, Mannens MM, 2000 Molecular characterisation of 10 Dutch properdin type I deficient families: mutation analysis and Xinactivation studies. Eur. J. Hum. Genet 8, 513–518. [PubMed: 10909851]

47. Fijen CA, van den Bogaard R, Schipper M, Mannens M, Schlesinger M, Nordin FG, Dankert J, Daha MR, Sjoholm AG, Truedsson L, Kuijper EJ, 1999b Properdin deficiency: molecular basis and disease association. Mol. Immunol 36, 863–867. [PubMed: 10698340]

48. Fredrikson GN, Gullstrand B, Westberg J, Sjoholm AG, Uhlen M, Truedsson L, 1998 Expression of properdin in complete and incomplete deficiency: normal in vitro synthesis by monocytes in two cases with properdin deficiency type II due to distinct mutations. J. Clin. Immunol 18, 272–282. [PubMed: 9710744]

49. Ferreira VP, 2018 Properdin, in: Barnum SR, Schein TN (Eds.), The Complement FactsBook (Second Edition). Academic Press, pp. 283–293.

50. Marron-Linares GM, Nunez L, Crespo-Leiro MG, Barge-Caballero E, Pombo J, Paniagua-Martin MJ, Suarez-Fuentetaja N, Cid J, Grille-Cancela Z, Muniz-Garcia J, Tan CD, Rodriguez ER, VazquezRodriguez JM, Hermida-Prieto M, 2017 Polymorphisms in genes related to the complement system and antibody-mediated cardiac allograft rejection. J. Heart Lung Transplant, 37, 477–485. [PubMed: 2878432

51. Savill J, Dransfield I, Gregory C, Haslett C. A blast from the past: clearance of apoptotic cells regulates immune responses. Nat Rev Immunol 2002;2:965–975. [PubMed: 12461569]

52. Korb LC, Ahearn JM. C1q binds directly and specifically to surface blebs of apoptotic human keratinocytes. J Immunol 1997;158:4525–4528. [PubMed: 9144462]

53. Braconier JH, Sjoholm AG, Soderstrom C. Fulminant meningococcal infections in a family with inherited deficiency of properdin. Scandinavian Journal of Infectious Diseases 1983;15:339–345. [PubMed: 6658381]

54. Densen P, Weiler JM, Griffiss JM, Hoffmann LG. Familial properdin deficiency and fatal meningococcemia. Correction of the bactericial defect by vaccination. New England Journal of Medicine 1987;316:922–926. [PubMed: 3102964]

55. Densen P. Interaction of complement with Neisseria meningitidis and Neisseria gonorrhoeae. Clinical Microbiology Reviews 1989;2:S11–S17. [PubMed: 2497954]

56. Kolble K, Reid KB. Genetic deficiencies of the complement system and association with disease--early components. International Reviews of Immunology 1993;10:17–36. [PubMed: 8340675]

57. Holme ER, Veitch J, Johnston A, Hauptmann G, Uring-Lambert B, Seywright M, Docherty V, Morley WN, Whaley K. Familial properdin deficiency associated with chronic discoid lupus erythematosus. Clin Exp Immunol 1989;76:76–81. [PubMed: 2736801]

58. Sjoeholm AG, Kuijper EJ, Tijssen CC, Jansz A, Bol P, Spanjaard L, Zanen HC. Dysfunctional properdin in a dutch family with meningococcal disease. New England Journal of Medicine 1988;319:33–37. [PubMed: 3380115]

59. Kemper C, Mitchell LM, Zhang L, Hourcade DE. The complement protein properdin binds apoptotic T cells and promotes complement activation and phagocytosis. Proceedings of the National Academy of Sciences of the United States of America. 2008In Press

60. Trouw LA, Blom AM, Gasque P. Role of complement and complement regulators in the removal of apoptotic cells. Mol Immunol 2008;45:1199–1207. [PubMed: 17961651]

61. Fadok VA, Bratton DL, Rose DM, Pearson A, Ezekewitz RA, Henson PM. A receptor for phosphatidylserine-specific clearance of apoptotic cells. Nature 2000;405:85–90. [PubMed: 10811223]

62. Ren Y, Silverstein RL, Allen J, Savill J. CD36 gene transfer confers capacity for phagocytosis of cells undergoing apoptosis. J Exp Med 1995;181:1857–1862. [PubMed: 7536797]

63. Verhoven B, Schlegel RA, Williamson P. Mechanisms of phosphatidylserine exposure, a phagocyte recognition signal, on apoptotic T lymphocytes. J Exp Med 1995;182:1597–1601. [PubMed: 7595231]

64. Watanabe H, Garnier G, Circolo A, Wetsel RA, Ruiz P, Holers VM, Boackle SA, Colten HR, Gilkeson GS. Modulation of renal disease in MRL/lpr mice genetically deficient in the alternative complement pathway factor B. J Immunol 2000;164:786–794. [PubMed: 10623824]

65. Elliott MK, Jarmi T, Ruiz P, Xu Y, Holers VM, Gilkeson GS. Effects of complement factor D deficiency on the renal disease of MRL/lpr mice. Kidney International 2004;65:129–138. [PubMed: 14675043]

66. Hochberg, MC. Epidemiology of systemic lupus erythematosus. In: Lahita, RG., editor. Systemic lupus rythematosus. New York: Churchill Livingstone, Inc; 1992. p. 103-117

67. Xu W, Berger SP, Trouw LA, de Boer HC, Schlagwein N, Mutsaers C, Daha M, van Kooten C. Properdin binds to late apoptotic and necrotic cells independently of C3b and regulates alternative pathway complement activation. Journal of Immunology 2008;180:7613–7621.

68. Sjoblom T, Jones S, Wood LD, Parsons DW, Lin J, Barber TD, Mandelker D, Leary RJ, Ptak J, Silliman N, Szabo S, Buckhaults P, Farrell C, Meeh P, Markowitz SD, Willis J, Dawson D, Willson JK, Gazdar AF, Hartigan J, Wu L, Liu C, Parmigiani G, Park BH, Bachman KE, Papadopoulos N, Vogelstein B, Kinzler KW, Velculescu VE. The consensus coding sequences of human breast and colorectal cancers. Science 2006;314:268–274. [PubMed: 16959974]

69. Fuster MM, Esko JD. The sweet and sour of cancer: glycans as novel therapeutic targets. Nat Rev Cancer 2005;5:526–542. [PubMed: 16069816]

70. Ji H, Ohmura K, Mahmood U, Lee DM, Hofhuis FM, Boackle SA, Takahashi K, Holers VM, Walport M, Gerard C, Ezekowitz A, Carroll MC, Brenner M, Weissleder R, Verbeek JS, Duchatelle V, Degott C, Benoist C, Mathis D. Arthritis critically dependent on innate immune system players. Immunity 2002;16:157–168. [PubMed: 11869678]

71. Wipke BT, Allen PM. Essential role of neutrophils in the initiation and progression of a murine model of rheumatoid arthritis. J Immunol 2001;167:1601–1608. [PubMed: 11466382]

72. Girardi G, Berman J, Redecha P, Spruce L, Thurman JM, Kraus D, Hollmann TJ, Casali P, Caroll MC, Wetsel RA, Lambris JD, Holers VM, Salmon JE.

Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. J Clin Invest 2003;112:1644–1654. [PubMed: 14660741]

73. Xiao H, Schreiber A, Heeringa P, Falk RJ, Jennette JC. Alternative complement pathway in the pathogenesis of disease mediated by anti-neutrophil cytoplasmic autoantibodies. Am J Pathol 2007;170:52–64. [PubMed: 17200182]

74. Sacks SH, Zhou W. Locally produced complement and its role in renal allograft rejection. Am J Transplant 2003;3:927–932. [PubMed: 12859526]

75. Stover CM, Luckett JC, Echtenacher B, Dupont A, Figgitt SE, Brown J, Mannel DN, Schwaeble WJ. Properdin plays a protective role in polymicrobial septic peritonitis. J Immunol 2008;180:3313–3318. [PubMed: 18292556]

76. Thurman JM, Kraus DM, Girardi G, Hourcade D, Kang HJ, Royer PA, Mitchell LM, Giclas PC, Salmon J, Gilkeson G, Holers VM. A novel inhibitor of the alternative complement pathway prevents antiphospholipid antibody-induced pregnancy loss in mice. Mol Immunol 2005;42:87–97. [PubMed: 15488947]

77. Fung M, Loubser PG, Undar a, Mueller M, Sun C, Sun WN, Vaughn WK, Fraser CD Jr. Inhibition of complement, neutrophil, and platelet activation by an anti-factor D monoclonal antibody in simulated cardiopulmonary bypass circuits. Journal of Thoracic and Cardiovascular Surgery 2001;122:113– 122. [PubMed: 11436043]

78. Gupta-Bansal R, Parent JB, Brunden KR. Inhibition of complement alternative pathway function with anti-properdin monoclonal antibodies. Mol Immunol 2000;37:191–201. [PubMed: 10930626]

79. Huber-Lang M, Barratt-Due A, Pischke SE, Sandanger Ø, Nilsson PH, Nunn MA, Denk S, Gaus W, Espevik T, and Mollnes TE (2014) Double blockade of CD14 and complement C5 abolishes the cytokine storm and improves morbidity and survival in polymicrobial sepsis in mice. J Immunol 192:5324–5331.

80. Martin TR, Wurfel MM, Zanoni I, and Ulevitch R (2020) Targeting innate immunity by blocking CD14: novel approach to control inflammation and organ dysfunction in COVID-19 illness. EBioMedicine 57:102836.

81. Cugno M, Meroni PL, Gualtierotti R, Griffini S, Grovetti E, Torri A, Panigada M, Aliberti S, Blasi F, Tedesco F, et al. (2020) Complement activation in patients with COVID-19: A novel therapeutic target. J Allergy Clin Immunol 146:215–217.

82. Carvelli J, Demaria O, Vely F, Batista L, Benmansour NC, Fares J, Carpentier S, Thibult ML, Morel A, Remark R, et al.; Explore COVID-19 IPH group; Explore COVID-19 Marseille Immunopole group (2020) Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature 588:146–150

83. Holter JC, Pischke SE, de Boer E, Lind A, Jenum S, Holten AR, Tonby K, BarrattDue A, Sokolova M, Schjalm C, et al. (2020) Systemic complement

activation is associated with respiratory failure in COVID-19 hospitalized patients. Proc Natl Acad Sci USA 117:25018–25025.

84. Java A, Apicelli AJ, Liszewski MK, Coler-Reilly A, Atkinson JP, Kim AH, and Kulkarni HS (2020) The complement system in COVID-19: friend and foe? JCI Insight 5:e140711.

85. Noris M, Benigni A, and Remuzzi G (2020) The case of complement activation in COVID-19 multiorgan impact. Kidney Int 98:314–322.

86. Potlukova E and Kralikova P (2008) Complement component c1q and anti-c1q antibodies in theory and in clinical practice. Scand J Immunol 67:423–430

87. Kulasekararaj AG, Lazana I, Large J, Posadas K, Eagleton H, Lord Villajin J, Zuckerman M, Gandhi S, and Marsh JCW (2020) Terminal complement inhibition dampens the inflammation during COVID-19. Br J Haematol 190:e141–e143.

88. Laurence J, Mulvey JJ, Seshadri M, Racanelli A, Harp J, Schenck EJ, Zappetti D, Horn EM, and Magro CM (2020) Anti-complement C5 therapy with eculizumab in three cases of critical COVID-19. Clin Immunol 219:108555.

89. Mastaglio S, Ruggeri A, Risitano AM, Angelillo P, Yancopoulou D, Mastellos DC, Huber-Lang M, Piemontese S, Assanelli A, Garlanda C, et al. (2020) The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. Clin Immunol 215:108450

90. Vlaar APJ, de Bruin S, Busch M, Timmermans SAMEG, van Zeggeren IE, Koning R, Ter Horst L, Bulle EB, van Baarle FEHP, van de Poll MCG, et al. (2020) Anti-C5a antibody IFX-1 (vilobelimab) treatment versus best supportive care for patients with severe COVID-19 (PANAMO): an exploratory, open-label, phase 2 randomised controlled trial. Lancet Rheumatol 2:e764–e773.

91. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. Frontiers in immunology. 2020 Apr 7;11:590.

92. Hughes, Ronda, ed. "Patient safety and quality: An evidence-based handbook for nurses." (2008).

93. Wong EK, Kavanagh D. Anticomplement C5 therapy with eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. Translational Research. 2015 Feb 1;165(2):306-20.

94. Dobó J, Pál G, Cervenak L, Gál P. The emerging roles of mannose- binding lectin- associated serine proteases (MASP s) in the lectin pathway of complement and beyond. Immunological reviews. 2016 Nov;274(1):98-111

95. Janeway Jr CA, Travers P, Walport M, Shlomchik MJ. The complement system and innate immunity. InImmunobiology: The Immune System in Health and Disease. 5th edition 2001. Garland Science.

96. Albazli K, Kaminski HJ, Howard Jr JF. Complement inhibitor therapy for myasthenia gravis. Frontiers in Immunology. 2020 Jun 3;11:917

97. Lo MW, Kemper C, and Woodruff TM (2020) COVID-19: complement, coagulation, and collateral damage. J Immunol 205:1488–1495.

98. Mollnes TE, Jokiranta TS, Truedsson L, Nilsson B, Rodriguez de Cordoba S, and Kirschfink M (2007) Complement analysis in the 21st century. Mol Immunol 44:3838–3849

99. Harboe M, Thorgersen EB, and Mollnes TE (2011) Advances in assay of complement function and activation. Adv Drug Deliv Rev 63:976–987.

100. Frazer-Abel A (2018) The effect on the immunology laboratory of the expansion in complement therapeutics. J Immunol Methods 461:30–36

101. Prohászka Z, Kirschfink M, and Frazer-Abel A (2018) Complement analysis in the era of targeted therapeutics. Mol Immunol 102:84–88.

102. Mollnes TE, Jokiranta TS, Truedsson L, Nilsson B, de Cordoba SR, Kirschfink M. Complement analysis in the 21st century. Molecular immunology. 2007 Sep 1;44(16):3838-49.

103. Garred P, Tenner AJ, Mollnes TE. Therapeutic Targeting of the Complement System: From Rare Diseases to Pandemics. Pharmacological reviews. 2021 Apr 1;73(2):792-827.

104. Kanakura Y, Ohyashiki K, Shichishima T, Okamoto S, Ando K, Ninomiya H, Kawaguchi T, Nakao S, Nakakuma H, Nishimura J, et al. (2013) Long-term efficacy and safety of eculizumab in Japanese patients with PNH: AEGIS trial. Int J Hematol 98:406–416.

105. Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, and Cantrell A (2013) A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). BMJ Open 3:e003573.

106. Rondeau E, Cataland SR, Al-Dakkak I, Miller B, Webb NJA, and Landau D (2019) Eculizumab safety: five-year experience from the global atypical hemolytic uremic syndrome registry. Kidney Int Rep 4:1568–1576.

107. Socié G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, Mujeebuddin A, Hillmen P, Vande Walle J, and Haller H (2019) Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10- year pharmacovigilance analysis. Br J Haematol 185:297–310.

108. Nolfi-Donegan D, Konar M, Vianzon V, MacNeil J, Cooper J, Lurie P, Sedivy J, Wang X, Granoff DM, and McNamara L (2018) Fatal nongroupable Neisseria meningitidis disease in vaccinated patient receiving eculizumab. Emerg Infect Dis 24: 1561–1564.

109. Patriquin CJ, Kuo KH. Eculizumab and beyond: the past, present, and future of complement therapeutics. Transfusion medicine reviews. 2019 Oct 1;33(4):256-65.

110. Zelek WM, Xie L, Morgan BP, Harris CL. Compendium of current complement therapeutics. Molecular immunology. 2019 Oct 1;114:341-52.

111. Helmy KY, Katschke KJ Jr, Gorgani NN, Kljavin NM, Elliott JM, Diehl L, Scales SJ, Ghilardi N, van Lookeren Campagne M. CRIg: a macrophage complement receptor required for phagocytosis of circulating pathogens. Cell 2006;124:915–927. [PubMed: 16530040]

112. Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. Nature reviews Drug discovery. 2015 Dec;14(12):857-77.

113. Stevens B, Allen NJ, Vazquez LE, Howell GR, Christopherson KS, Nouri N, Micheva KD, Mehalow AK, Huberman AD, Stafford B, Sher A, Litke AM, Lambris JD, Smith SJ, John SWM, Barres BA. The classical complement cascade mediates CNS synapse elimination. Cell 2007;131:1164–1178. [PubMed: 18083105]

114. Hawlisch H, Kohl J. Complement and Toll-like receptors: key regulators of adaptive immune responses. Mol Immunol 2006;43:13–21. [PubMed: 16019071]

115. Heeger PS, Lalli PN, Lin F, Valujskikh A, Liu J, Muqim N, Xu Y, Medof ME. Decay-accelerating factor modulates induction of T cell immunity. Journal of Experimental Medicine 2005;201:1523–1530. [PubMed: 15883171]

116. Kemper C, Atkinson JP. T-cell regulation: with complements from innate immunity. Nat Rev Immunol 2007;7:9–18. [PubMed: 17170757]

117. Liu J, Miwa T, Hilliard B, Chen Y, Lambris JD, Wells AD, Song WC. The complement inhibitory protein DAF (CD55) suppresses T cell immunity in vivo. Journal of Experimental Medicine 2005;201:567– 577. [PubMed: 15710649]

118. Strainic MG, Liu J, Huang D, An F, Lalli PN, Muqim N, Shapiro VS, Dubyak GR, Heeger PS, Medof ME. Locally produced complement fragments C5a and C3a provide both costimulatory and survival signals to naive CD4+ T cells. Immunity 2008;28:425–435. [PubMed: 18328742]

119. 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. Journal of Immunology 2007;179:2600–2608.