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Properdin: An Immune System Regulator That Can Be a Therapeutic Target of the Complement System

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Properdin, a serum glycoprotein, is involved in the immune system regulation, particularly in alternative pathways beginning the complement system. Properdin is made up of cyclic oligomers of monomeric subunits and is generated by various leukocyte subsets. Properdin promotes complement activation, which results in changes withinside the cell milieu that makes contributions 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. Despite the presence of potential inhibitors (properdin) in serum and the formation of non-physiological aggregates in pure properdin preparations, properdin has emerged as a critical component in a variety of inflammatory illness 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, fluctuating from entrenched 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 main hurdles that devour hampered the analysis of outcomes as of properdin-targeted studies.

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

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1. INTRODUCTION

It has been evident in recent decades that the complement system is concerned with many illnesses [1]. As a result, Complement-inhibiting treatment is becoming increasingly popular [2]. In theory, the complement system is an imperative component given that it shows a crucial part in the protective immunity in humans. It comprises various plasma and cell surface proteins, which actively interact in a complex manner, along with several more regulatory (immune) systems to distinguish between 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, are sent off to inflamed spots. This happens through their interaction with ligands and primarily the complement proteins. It is marked through the local microenvironment'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 substantially affects 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 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, post-translational expression modifications, oligomerization and secretion [1, 3]. This review discusses properdins' roles in immunity and their place in complement treatments.

2. COMPLEMENT SYSTEM

Complement is one of the first lines of defence against foreign and aberrant host cells, and it also serves as a crucial component of an individual's immunity [4]. This system consists of plasma proteins, which are often produced in the liver, and membrane proteins produced on the cell surfaces. Blood, cells, and tissues all contain complements [5]. Complement proteins collaborate to opsonize the pathogens and trigger a sequence of inflammatory reactions that aid cells relevant to immunity in combating illness, alongside maintaining homeostasis. The complement system can be activated through three separate pathways: classical, lectin, and alternative, leading to a standard terminal route. In the context of a typical human, AP is thought to be constantly functioning at low levels to check for infections. Healthy host cells are immune to complement attack and can tolerate low-grade activation for long periods. Apoptotic cells are continually formed in the body during normal cellular homeostasis; they activate the three routes on their surfaces. Complement activation is strictly controlled 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, 5].

3. OVERVIEW OF PATHWAY

Over 40 proteins make up the complement system, which performs various tasks such as contributing to a cascade-like process for activation, which acts as significant ligands or cellular receptors. "Complement system proteins, complement receptors expressed on human cells such as C5a receptor, CR4, CR3, CR2, CR1, and 2, CRIg, C3a receptor 1 and C1q receptors, and, as well complement regulatory proteins such as Factor I, Factor H, CD55/DAF, C1-INH, CD59, CD35/CR1, C4bp, CD46/MCP, CMSD1, vitronectin, clusterin, CRIg, protein 1 (Factor H-like), protein (Factor H-related) 1–5, and properdin show important parts in the host's defence in contradiction of infection, in keeping homeostasis over and done with the consent of immunological complexes and cell remains, in bridging the gap between immunity (adaptive and innate), in use, and the nervous system [6]. There are three mechanisms to activate the complement system: lectin, alternative and classical. The pathway (classical) is started when the complex (C1) having C1r, C1q, and C1s) binds to immunoglobulin's keep on pathogens or cell exteriors, CIC (circulating immune complexes), or pentraxins. The lectin pathway is triggered when some biological compound (carbohydrates) and additional ligands on

pathogen surfaces are recognized by MBL (mannose-binding lectin), CL-LK (ficolins, or collectins). Serine proteases linked with the recognition molecules C1q and MBL (C1s and MBL-associated serine protein 2 (MASP-2)) cleave C4 and C2 when the CP and LP are activated. The produced C4b binds to the cell surface, and the C2b fragment binds to the C4b, creating the CP and LP C3 convertase (C4b2b), which converts C3 to C3b and C3a, chemoattractant molecules. C3b has an exposed thioester bond [7, 8], allowing it to bind to hydroxyl (-OH) covalently and amine (-NH2) groups on cell surfaces to tag specific molecules. Covalent attachment of C3b occurs within sixty microseconds at a minimum distance of 28–30 nm (280–300 nm) before hydrolysis the C3b thioester is quickly inactivated." [9].

4. 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, monocytes, and mast cells [10,11, 12], compared to 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 finding that chemotherapy-induced neutropenia is associated with a decrease in properdin stages in the circulation emphasizes neutrophils' role in total protein levels in plasma. Normal systemic levels of human properdin in the healthy control group have been reported to range from 5 to 45 g/ml [14,15-25]. 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 present in the blood in the oligomeric form and on the X chromosome. This last characteristic is crucial to the organism's biological activity. Properdin oligomers are made up of a monomer that looks like a rod and has a molecular weight of 53 kDa [34]. Respectively monomer contains 442 amino acids [35], as well as one truncated and six full TSR-domains (thrombospondin type I repeat) (labeled TSR0 to TSR6 from the N to C terminus [35-37]. By creating head-to-tail linkages, the elastic monomeric subunits are cyclic, such as dimers, trimers, or tetramers with set 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 and the oligomeric structure make biochemical and structure-based studies hard to manage. For 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]. When studying properdin's atomic formation, recent developments have highlighted that vertex formation is mediated by TSR domains emanating from two monomers. The connecting component will be three TSRs [38, 41]. According to current data, the most likely structure of properdin is a vertex with TSR0–1/TSR5–6 linked by TSRs 2–4. However, the properdin's complete structure with high resolution has yet to be established.

5. PROPERDIN DEFICIENCIES, MUTATIONS, AND POLYMORPHIC VARIANTS

Properdin lack is inherited, for instance, a X-chromosomal recessive trait linked to a higher sensitivity to *Neisseria meningitides* and a significantly greater risk of having spread, fulminant meningococcal illness than healthy people [42]. Properdin absence has been detected in around 25 families, including approximately 20 different mutations [43]. Type I, or complete absence of circulatory properdin, is caused by several mutations that result in a truncated specific gene or changes in protein structure that prevent properdin secretion. [44, 45]. Type II, or partial lack of circulatory properdin, is produced by various abnormalities that produce a shortened genetic material or alterations in protein structure that impede properdin release [46]." Nucleotide mutations reported in Type I deficient families modify structurally identical amino acids in human and mouse TSRs, indicating that they are required for protein complexes. [47]. (b) Type II properdin insufficiency causes a 10% reduction in serum properdin concentrations. Properdin is produced and released by cells, but oligomerization occurs unusually, with dimers predominating. Type II properdin deficiency is characterized by a reduced ability to bind C3b and regulate the AP despite normal plasma levels. Despite normal plasma levels," type III properdin insufficiency is

defined by a decreased ability to bind C3b and govern the AP [48-50].

6. PROPERDIN AND DISEASE

To prevent the unfavorable inflammation-related and auto immunological 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 detects comparatively initial apoptotic T cells [59], whereas MBL and C1 become aware of late apoptotic/necrotic cells [60]. Because they lack membrane reliability and leak intracellular antigen components known to elicit an autoimmune response, late apoptotic and necrotic cells are considered more dangerous than original ones. Even in the absence of properdin, a progressing apoptotic cell must be detected and marked for removal by the'second guard,' C1q and/or MBL. A variety of additional proteins identify and eliminate apoptotic cells, including 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 mouse, 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 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 disease models (AP-dependent) for diseases, including RA (rheumatoid arthritis) and anti-phospholipid syndrome [70, 71, 72]. " In glomerulonephritis and vasculitis induced by anti-neutrophil cytoplasmic autoantibodies, neutrophil-derived properdin may also enhance AP activation (ANCA disease) [73], In addition, neutrophils play a role in kidney transplant rejection, which is characterised by significant neutrophil infiltration in the presence of dying tissue [74]. Mast cells have recently been identified as a new 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, AP C3 convertase has emerged as a promising therapeutic target. Humanized antibodies that block factor B [76], factor D [77], and properdin have been proposed as possible therapies [78]. Given the AP's role in health preservation, there is worry about the approach's possible negative repercussions. We're merely scraping the surface of properdin's biological implications: target recognition. This freshly identified properdin activity is most likely implicated in one or more of the many AP-dependent neutrophil-dependent diseases. Properdin is composed of six TSRs, the vast majority of which appear to be ligand-binding sites. As a consequence, each target may be identified by a distinct collection of TSRs. This scenario suggests the development of reagents that inhibit specific properdin: target interactions while leaving other properdin activities unaffected, thereby avoiding unwanted side effects and limiting the impact of the relevant therapeutic intervention on the relevant therapeutic inter-vention. Studies on the structure of properdin: target recognition, as well as soundings aimed at elucidating properdin target recognition inhibition in the serum, could be crucial in this regard." In addition, the availability of a miniature animal plan might aid in this type of research.

7. 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 principal investigations of increased complement activation in people infected with COVID-19 found a rise in the activation of components sC5b-9 and C5a, through the former acting for a time-consuming period [81]. "The presence of C5a in bronchoalveolar fluid and the prevention of lung harm in a human C5aR1 knock mice model further suggested a title part for the Ca-C5aR1 axis [82]. Five different complement initiation products commencing all routes were assessed in hospitalized patients in a medical investigation of patients (39). All initiation 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 is unclear how much the classical versus lectin

involved in the to activation of C4, although they remained mutually engaged.

Furthermore, the C3 convertase C3bBbP improved, indicating that a COVID-19 therapeutic plan should be broad and include all channels (i.e., C3 or C5). Examined the relationship between the complement system and coronaviruses (2020). So far, COVID-19 treatment has been limited to case studies, the bulk of which show inhibition at the C5 level [84, 85,86, 87, 88]. Although the findings of an open-labeled randomized trial with 15 patients treated with an inhibitory anti-C5a antibody and 15 controls [89] are promising, more extensive randomized control trials are required to evaluate if complement inhibition is a feasible therapeutic option for COVID-19" [90].

8. CAN COMPLEMENT BE INHIBITED?

8.1 Targets to be Suppressed

Like cold agglutinin syndrome and PNH, some diseases demonstrate a greater need for accompaniment. In contrast, others are only partially dependent on complement, varying from powerfully to a little, and there are almost certainly no circumstances in which an inflammatory immune response is involved when complement is missing. Thus, the guidelines for treating a problem will depend 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. 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 critical topic in the future, many other issues will be considered.

As per our belief, we have listed a few of the target molecules found in the cascade, which will be important in the coming future. 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 in blocking other targets was limited until now [93].

8.2 Classical and Lectin Pathway

MBL is the best-studied protein of complement and may be an alternative in some cases, while MASP-2 has recently been recognized as an intriguing possibility for inhibiting the lectin pathway. MBL, like C1q, is a recognition molecule with several functions, and MASP-2 might be a potential choice since the lectin route is recognized by multiple molecules, with MASP-2 functioning as the principal activation pathway. The primary hazard of interrupting the lectin route is that a significant percentage of the complement's danger sensing function is impaired [94].

8.3 C3 and the Alternative Route

The major difficulty with inhibiting C3 and alternate components is that it diminishes opsonization and, consequently, the danger of infection increases. This should not be a concern if the patient is in an acute condition and is being observed and under antibiotic treatment. A child will not be concerned about this short-term treatment. C3 is essential for accelerating B-cell antibody production; yet inhibition of C3 for a short time would have no effect. Another challenge with C3 is its widespread distribution, as well as the fact that it is secreted locally in a variety of tissues, making inhibition difficult [95].

8.4 The Terminal Pathway

The terminal pathway's ultimate objective is to prevent C5b-9 from joining, preventing membrane attack complex growth while allowing C5a to go on the rampage. This may be accomplished by, for example, blocking C6 or C7. After C8 has joined, the leaking process via the membrane commences [96].

9. DIAGNOSTIC AND FOLLOW-UP

9.1 Complement Activation Detection

Several methodologies can evaluate the complement system [97, 98]. "The first is an in vivo test to assess the level of complement initiation. In attendance are other assays available to identify particular initiation products, but the TCC is an important biomarker since it

indicates that C5 has been initiated and that both C5b-9 and C5a are generated. When C9 is present in the complex but not in the original molecule (C9), it may be detected as sC5b-9 in plasma using a simple standard enzyme-linked immunoassay (ELISA) based on an antibody (monoclonal) reacting with a neoepitope wide-open in C9 [99]. This test benefits from having a longer half-life (1 hour) than the C5a molecule, which has a significantly shorter half-life. It will also detect the initiation of the full cascade from start to finish." It is critical to utilize EDTA to obtain blood samples and to collect and snap-freeze plasma at 270°C [100, 101].

9.2 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 examination measures complement components in-vitro and requires serum (fresh or freshly maintained and kept at a temperature of 27°C). The detecting method is similar to C5b-9 enzyme-linked immunoassay (ELISA); on the other hand, the structure is dissimilar [102]. The wells are coated with activators unique to each of the three routes, and if all three components are present and active, the C5b-9 complex forms in the well and can be recognized using the same antibody (anti-C9 neoepitope). If everything is normal, the complement system will be identified as having 100 percent activity in the wells." If a terminal component or C3 is genetically defective, such as in a patient lacking C5, the C5b-9 complex will not form. All three pathways will be inactive because the detection antibody does not identify a C9 neoepitope. If one or more tests are negative, further testing is necessary to identify the missing component [103].

10. THERAPEUTIC COMPLEMENT INHIBITION'S CONSEQUENCES

A. Adverse Effects and Safety

1. Conventional C5 Inhibition

Eculizumab was the sole complement blocker appropriate 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 unconnected to the therapy, and there was no indication of *Neisseria* infection. 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 hazard of *Neisseria* infection. Other infections were detected, but the source of them remained unexplained [108]. As a result, C5 inhibition with eculizumab is a generally safe therapy with few side effects, although the modest risk of Neisseria infection should always be considered."

11. 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 is 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. Although the person is still under observation, short-term therapy may be less of a worry in some acute phases, and it might potentially be the most beneficial therapy [109].

B. Treatment efficacy

1. Diseases that are completely complement-dependent:

When a condition is mostly complement-dependent, 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].

12. 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 investigation of the impacts of properdin lack 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 original "stop-gap" ration 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 shows critical roles in educating and directing the adaptive structure. The detection of accompaniment receptors, such as CRIg [113], and the revealed new roles complement proteins like C1q in the change of the neuronal synapse [114], the significance of CD46, DAF, and C5a in modulating responses (T cell) [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 numerous supplementary intriguing detections at the balance/adaptive immunity interface in the future.

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 medical 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 medical investigations in the yet to come. The aforementioned is practical 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ricklin D, Reis ES, Lambris JD. Complement in disease: A defence system turning offensive. Nat Rev Nephrol. 2016; 12:383–401.
2. Ricklin D, Mastellos DC, Reis ES, Lambris JD. The renaissance of complement therapeutics. Nat Rev Nephrol. 2018;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. The complement factsbook (Second Edition), Academic Press; 2018a.
7. Pangburn MK, Muller-Eberhard HJ. 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. 1980;152:1102–1114. [PubMed: 6903192]

8. Tack BF, Harrison RA, Janatova J, Thomas ML, Prahl JW. Evidence for presence of an internal thiolester bond in third component of human complement. Proc. Natl. Acad. Sci. U. S. A. 1980;77: 5764–5768. [PubMed: 6934510]
9. Sim RB, Twose TM, Paterson DS, Sim E. The covalent-binding reaction of complement component C3. Biochem. J 1981;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. Properdin, a positive regulator of complement activation, is expressed in human T cell lines and peripheral blood T cells. J Immunol. 1993;151:2521–2528.
11. Whaley K. Biosynthesis of the complement components and the regulatory proteins of the alternative complement pathway by human peripheral blood monocytes. J Exp Med. 1980;151:501–516.
12. Stover CM, Luckett JC, Echtenacher B, Dupont A, Figgitt SE, Brown J, Mannel DN, Schwaeble WJ. Properdin plays aprotective role in polymicrobial septic peritonitis. J Immunol. 2008;180:3313–3318.
13. Wirthmueller U, Dewald B, Thelen M, Schafer MK, Stover C, Whaley K, North J, Eggleton P, Reid KB, Schwaeble WJ. Properdin, a positive regulator of complement activation, is released from secondary granules of stimulated peripheral blood neutrophils. J Immunol 1997;158:4444–4451.
14. Tsyrkunou A, Agarwal S, Koirala B, Finberg RW, Nath R, Barton B, Levitz SM, Wang JP, Ram S. Properdin levels in individuals with chemotherapy-induced neutropenia. Open Forum Infect Dis; 2017. Available:https://doi.org/10.1093/ofid/ofw250
15. Pangburn MK. Analysis of the natural polymeric forms ofhuman properdin and their functions in complement activation. J Immunol . 1989;142:202–207.
16. Corvillo F, Bravo Garcia-Morato M, Nozal P, Garrido S, Tortajada A, Rodriguez de Cordoba S, Lopez-Trascasa M. Serum properdin consumption as a biomarker of C5 convertase dysregulation in C3 glomerulopathy. Clin Exp Immunol. 2016; 184:118–125.
17. Zhang Y, Nester CM, Martin B, Skjoedt MO, Meyer NC, Shao D, Borsa N, Palarasah Y, Smith RJ. Defining the complement biomarker profile of C3 glomerulopathy. Clin J Am Soc Nephrol. 2014;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. C4 nephritic factors in C3 glomerulopathy: A case series. Am J Kidney Dis. 2017;70:834–843.
19. Stover CM, McDonald J, Byrne S, Lambert DG, Thompson JP. Properdin levels in human sepsis. Front Immunol. 2015;6:24.
20. Somani R, Richardson VR, Standeven KF, Grant PJ, Carter AM. Elevated properdin and enhanced complement activation in first-degree relatives of South Asian subjects with type 2 diabetes. Diabetes Care. 2012;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. The alternative complement pathway is dysregulated in patients with chronic heart failure. Sci Rep. 2017;7:42532.
22. Xu W, Berger SP, Trouw LA, de Boer HC, Schlagwein N, Mutsaers C, Daha MR, van Kooten C. Properdin binds to late apoptotic and necrotic cells independently of C3b and regulates alternative pathway complement activation. J Immunol. 2008; 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. Strong predictive value of mannose-binding lectin levels for cardiovascular risk of hemodialysis patients. J Transl Med. 2016;14:236.
24. de Paula PF, Barbosa JE, Junior PR, Ferriani VP, Latorre MR, Nudelman V, Isaac L. 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. 2003;58:572–577.
25. Grumach AS, Ceccon ME, Rutz R, Fertig A, Kirschfink M. Complement profile in neonates of different gestational ages. Scand J Immunol. 2014;79:276–281.

26. Gou SJ, Yuan J, Chen M, Yu F, Zhao MH. Circulating complement activation in patients with anti-neutrophil cytoplasmic antibody-associated vasculitis. Kidney Int 2013;83:129–137.
27. Onda K, Ohi H, Tamano M, Ohsawa I, Wakabayashi M, Horikoshi S, Fujita T, Tomino Y. Hypercomplementemia in adult patients with IgA nephropathy. J Clin Lab Anal. 2007;21:77–84.
28. Minta JO, Jezyk PD, Lepow IH. Distribution and levels of properdin in human body fluids. Clin Immunol Immunopathol. 1976; 5:84–90.
29. Sonntag J, Brandenburg U, Polzehl D, Strauss E, Vogel M, Dudenhausen JW, Obladen M. Complement system in healthy term newborns: Reference values in umbilical cord blood. Pediatr Dev Pathol. 1998;1:131–135.
30. Davis CA, Vallota EH, Forristal J. Serum complement levels in infancy: Age related changes. Pediatr Res. 1979;13:1043–1046.
31. Wolach B, Dolfin T, Regev R, Gilboa S, Schlesinger M. The development of thecomplement system after 28 weeks' gestation. Acta Paediatr Scand. 1997;86: 523–527.
32. Prellner K, Sjoholm AG, Truedsson L. 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 1987;76:939–943.
33. Drew JH, Arroyave CM. The complement system of the newborn infant. Biol Neonate. 1980;37:209–217.
34. Smith CA, Pangburn MK, Vogel CW, Muller-Eberhard HJ. Molecular architecture of human properdin, a positive regulator of the alternative pathway of complement. J Biol Chem. 1984;259:4582– 4588.
35. Nolan KF, Schwaeble W, Kaluz S, Dierich MP, Reid KB. Molecular cloning of the cDNA coding for properdin, a positive regulator of the alternative pathway of human complement. Eur J Immunol 1991;21:771–776.
36. Higgins JM, Wiedemann H, Timpl R, Reid KB. Characterization of mutant forms of recombinant human properdin lacking single thrombospondin type I repeats. Identification of modules important for function. J Immunol. 1995;155:5777–5785.
37. Sun Z, Reid KB, Perkins SJ. The dimeric and trimeric solution structures of the multidomain complement protein properdin by X-ray scattering, analytical ultracentri-fugation and constrained modelling. J Mol Biol. 2004;343:1327–1343.
38. Alcorlo M, Tortajada A, Rodriguez de Cordoba S, Llorca O. Structural basis for the stabilization of the complement alternative pathway C3 convertase by properdin. Proc Natl Acad Sci U S A 2013;110:13504–13509.
39. Bertram P, Akk AM, Zhou HF, Mitchell LM, Pham CT, Hourcade DE. Anti-mouse properdin TSR 5/6 monoclonal antibodies block complement alternative pathway-dependent pathogenesis. Monoclon Antib Immunodiagn Immunother. 2015;34:1–6.
40. Perdikoulis MV, Kishore U, Reid KB. Expression and characterisation of thethrombospondin type I repeats of human properdin. Biochim Biophys Acta. 2001;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. Functional and structural insight into properdin control of complement alternative pathway amplification. EMBO J. 2017;36: 1084–1099.
42. Figueroa J, Andreoni J, Densen P. Complement deficiency states and meningococcal disease. Immunol. Res 1993;12:295–311. [PubMed: 8288947]
43. Fijen CA, Kuijper EJ, te Bulte MT, Daha MR, Dankert J. Assessment of complement deficiency in patients with meningococcal disease in The Netherlands. Clin. Infect. Dis. 1999a;28:98–105.
[PubMed: 10028078]
44. Helminen M, Seitsonen S, Jarva H, Meri S, Jarvela IE. A novel mutation W388X underlying properdin deficiency in a Finnish family. Scand. J. Immunol. 2012; 75:445–448.
[PubMed: 22229731]
45. Westberg J, Fredrikson GN, Truedsson L, Sjoholm AG, Uhlen M. Sequence-based analysis of properdin deficiency: identification of point mutations in two phenotypic forms of an X-linked immunodeficiency. Genomics. 1995;29:1–8.
[PubMed: 8530058]
46. van den Bogaard R, Fijen CA, Schipper MG, de Galan L, Kuijper EJ, Mannens MM. Molecular characterisation of 10 Dutch properdin type I deficient families: mutation

analysis and Xinactivation studies. Eur. J. Hum. Genet. 2000;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. Properdin deficiency: Molecular basis and disease association. Mol. Immunol. 1999b;36:863–867.
[PubMed: 10698340]
48. Fredrikson GN, Gullstrand B, Westberg J, Sjoholm AG, Uhlen M, Truedsson L. 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. 1998;18:272–282.
[PubMed: 9710744]
49. Ferreira VP. Properdin, in: Barnum SR, Schein TN (Eds.), The Complement FactsBook (Second Edition). Academic Press. 2018;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, Vazquez Rodriguez JM, Hermida-Prieto M. Polymorphisms in genes related to the complement system and antibody-mediated cardiac allograft rejection. J. Heart Lung Transplant. 2017;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; 2008. In 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. Mechanismsof 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;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, Mollnes TE. Double blockade of CD14 and complement C5

abolishes the cytokine storm and improves morbidity and survival in polymicrobial sepsis in mice. J Immunol. 2014;192: 5324–5331.

80. Martin TR, Wurfel MM, Zanoni I, and Ulevitch R. Targeting innate immunity by blocking CD14: novel approach to control inflammation and organ dysfunction in COVID-19 illness. EBioMedicine. 2020;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. Complement activation in patients with COVID-19: A novel therapeutic target. J Allergy Clin Immunol. 2020;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. Association of COVID-19 inflammation with activation of the C5a-C5aR1 axis. Nature 2020;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. Systemic complement activation is associated with respiratory failure in COVID-19 hospitalized patients. Proc Natl Acad Sci USA. 2020;117:25018–25025.
84. Java A, Apicelli AJ, Liszewski MK, Coler-Reilly A, Atkinson JP, Kim AH, and Kulkarni HS. The complement system in COVID-19: friend and foe? JCI Insight. 2020;5:e140711.
85. Noris M, Benigni A, Remuzzi G. The case of complement activation in COVID-19 multiorgan impact. Kidney Int. 2020;98: 314–322.
86. Potlukova E, Kralikova P. Complement component c1q and anti-c1q antibodies in theory and in clinical practice. Scand J Immunol. 2008;67:423–430.
87. Kulasekararaj AG, Lazana I, Large J, Posadas K, Eagleton H, Lord Villajin J, Zuckerman M, Gandhi S, and Marsh JCW. Terminal complement inhibition dampens the inflammation during COVID-19. Br J Haematol. 2020;190:e141–e143.
88. Laurence J, Mulvey JJ, Seshadri M, Racanelli A, Harp J, Schenck EJ, Zappetti D, Horn EM, and Magro CM. Anti-complement C5 therapy with eculizumab in three cases of critical COVID-19. Clin Immunol. 2020;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. The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. Clin Immunol. 2020; 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. 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. 2020;2:e764–e773.
91. Berentsen S. New insights in the pathogenesis and therapy of cold agglutinin-mediated autoimmune hemolytic anemia. Frontiers in Immunology. 2020;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;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; 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;11:917
97. Lo MW, Kemper C, and Woodruff TM. COVID-19: complement, coagulation, and collateral damage. J Immunol. 2020;205: 1488–1495.
98. Mollnes TE, Jokiranta TS, Truedsson L, Nilsson B, Rodriguez de Cordoba S, and Kirschfink M. Complement analysis in the 21st century. Mol Immunol. 2007;44:3838–3849

99. Harboe M, Thorgersen EB, and Mollnes TE. Advances in assay of complement function and activation. Adv Drug Deliv Rev. 2011;63:976–987.
100. Frazer-Abel A. The effect on the immunology laboratory of the expansion in complement therapeutics. J Immunol Methods. 2018;461:30–36.
101. Prohászka Z, Kirschfink M, and Frazer-Abel A. Complement analysis in the era of targeted therapeutics. Mol Immunol. 2018; 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;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;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. Long-term efficacy and safety of eculizumab in Japanese patients with PNH: AEGIS trial. Int J Hematol. 2013;98:406–416.
105. Rathbone J, Kaltenthaler E, Richards A, Tappenden P, Bessey A, Cantrell A. A systematic review of eculizumab for atypical haemolytic uraemic syndrome (aHUS). BMJ Open. 2013;3:e003573.
106. Rondeau E, Cataland SR, Al-Dakkak I, Miller B, Webb NJA, Landau D. Eculizumab safety: Five-year experience from the global atypical hemolytic uremic syndrome registry. Kidney Int Rep. 2019;4:1568–1576.
107. Socié G, Caby-Tosi MP, Marantz JL, Cole A, Bedrosian CL, Gasteyger C, Mujeebuddin A, Hillmen P, Vande Walle J, Haller H. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10- year pharmacovigilance analysis. Br J Haematol. 2019;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. Fatal nongroupable Neisseria meningitidis disease in vaccinated patient receiving eculizumab. Emerg Infect Dis. 2018;24: 1561–1564.
109. Patriquin CJ, Kuo KH. Eculizumab and beyond: The past, present, and future of complement therapeutics. Transfusion medicine reviews. 2019;33(4):256-65.
110. Zelek WM, Xie L, Morgan BP, Harris CL. Compendium of current complement therapeutics. Molecular Immunology. 2019; 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;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.

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