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Properdin: A multifaceted molecule involved in inflammation and diseases

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Abstract

Properdin, the widely known positive regulator of the alternative pathway (AP), has undergone significant investigation over the last decade to define its function in inflammation and disease, including its role in arthritis, asthma, and kidney and cardiovascular diseases. Properdin is a glycoprotein found in plasma that is mainly produced by leukocytes and can positively regulate AP activity by stabilizing C3 and C5 convertases and initiating the AP. Promotion of complement activity by properdin results in changes in the cellular microenvironment that contribute to innate and adaptive immune responses, including pro-inflammatory cytokine production, immune cell infiltration, antigen presenting cell maturation, and tissue damage. The use of properdin-deficient mouse models and neutralizing antibodies has contributed to the understanding of the mechanisms by which properdin contributes to promoting or preventing disease pathology. This review mainly focusses on the multifaceted roles of properdin in inflammation and diseases, and how understanding these roles is contributing to the development of new disease therapies.

Keywords

Complement system regulation; alternative pathway; properdin; complement regulatory proteins; Factor P

1. Introduction

The complement system is central to immunity and homeostasis. Over 20 candidate drugs that target complement components are being assessed in clinical trials (Ricklin, et al., 2018). Since its discovery 64 years ago, properdin, the only known positive regulator of complement, has undergone significant biological characterization in its serum and microenvironment sources, physiological functions, roles in disease, and biochemical characteristics including expression, translation, post-translational modifications, oligomerization and secretion. Understanding the distinct functions of properdin and its

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opposing negative regulator Factor H, as well as the data surrounding the role of properdin as a potential pattern recognition molecule, will significantly contribute to our understanding of complement regulation. Herein, we review these topics, in addition to the identified roles of properdin in immunity and the status of properdin in complement therapeutics.

2. The complement system

2.1 Three pathways overview

The complement system is composed of over 40 proteins that carry out multiple functions, including participating in a cascade-like activation process, serving as cellular receptors or as important ligands for those receptors, and/or serving as essential complement regulatory proteins. The circulating complement system proteins, complement receptors expressed on human cells (CR1, CR2, CR3, CR4, C5a receptor 1and 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 essential roles in host defense against infection, in homeostasis through the clearance of immune complexes and cell debris, in linking innate and adaptive immunity, as well as in metabolism and in the nervous system (reviewed in (Barnum and Schein, 2018a)). The complement system (Figure 1) can be activated through three pathways: classical, lectin and alternative. The classical pathway (CP) is commonly initiated by binding of the C1 complex (composed of C1q, C1r, and C1s) to immunoglobulins bound on pathogens or cell surfaces, to circulating immune complexes, or to pentraxins (e.g. C-reactive protein, pentraxin 3, serum amyloid P). The lectin pathway (LP) is initiated when mannose-binding lectin (MBL), ficolins or collectins (CL-LK), recognize certain carbohydrates and other ligands on the surface of pathogens. The activation of both the CP and LP leads to cleavage of C4 and C2 by serine proteases (C1s and MBL-associated serine protein 2 (MASP-2)) associated with the recognition molecules C1q or MBL, respectively. The C4b that is formed, binds covalently to the cell surface and the C2b fragment binds to the C4b, generating the C3 convertase of the CP and LP (C4b2b), which then converts native C3 to C3b and C3a, a chemoattractant molecule. C3b has an exposed thioester bond (Pangburn and Muller-Eberhard, 1980; Tack, et al., 1980), which allows C3b to effectively tag certain molecules by covalently binding to hydroxyl (-OH) and amine ($-NH_2$) groups found on cell surfaces. Covalent binding of C3b occurs within sixty microseconds at a minimum distance of 28–30 nm (280–300 Å) (Sim, et al., 1981), before the C3b thioester is quickly inactivated by hydrolysis.

Unlike CP and LP, the alternative pathway (AP) initiates spontaneously on surfaces that are not (or inefficiently) protected by complement regulatory proteins. Spontaneous hydrolysis of C3 (Muller-Eberhard, 1988) as well as contact activation on certain cells (e.g. platelets), and artificial surfaces (Hamad, et al., 2015; Nilsson and Nilsson Ekdahl, 2012), forms $C3(H_2O)$. $C3(H_2O)$ is able to bind to Factor B, forming $C3(H_2O)B$ and Factor B can then be cleaved by the serum protease Factor D, generating the AP fluid-phase C3 convertase $C3(H_2O)Bb$. $C3(H_2O)Bb$ can then cleave additional C3 molecules, generating C3b and C3a. C3b deposited on cell surfaces associates with Factor B to generate C3bB, in which Factor B is cleaved by Factor D to generate the membrane-bound AP C3 convertase C3bBb. C3bBb

cleaves many C3 molecules to C3b allowing efficient amplification of C3b deposition on cell surfaces, which is essential for opsonization (Barnum and Schein, 2018b). C3b can be further cleaved to iC3b and C3dg fragments, which can be recognized by complement receptors (CR1, CR2, CR3, CR4, and CRIg), leading to phagocytosis (Holers, 2014). When C3b binds to or near the C4b2b and C3bBb convertases, C5 convertases are formed (C4b2b3b and C3bBbC3b [$(C3b)_{2\text{-}n}Bb$], respectively). Both the C3 and C5 convertases of the AP are stabilized by properdin, which increases their half-life (Berends, et al., 2015; Fearon and Austen, 1975; Schreiber, et al., 1975). The C5 convertase cleaves C5 into C5a, a potent chemoattractant, and C5b. C5b can form a complex with C6, which is the base for the sequential binding of C7, C8 and C9 to form the membrane attack complex (MAC; C5b-9) (reviewed in (Holers, 2014)). MAC leads to direct microbial killing, while sub-lytic levels of MAC stimulate various cellular responses including pro-apoptotic or anti-apoptotic signaling (Nauta, et al., 2002; Tegla, et al., 2011), and inflammasome activation (Morgan, 2016). C3a and C5a are important factors that bind to specific G-protein-coupled receptors for C3a (C3a receptor 1) and C5a (C5a receptor 1; C5aR1; CD88), respectively. Receptor engagement promotes inflammation and other functions, including cancer progression, cerebellar development, homing of stem cells to the bone marrow, and tissue fibrosis (reviewed in (Ajona, et al., 2017; Klos, et al., 2009)).

2.2 Properdin as a soluble positive regulator via stabilizing C3 and C5 convertases

The AP represents a true safeguard system that is always active and also accounts for approximately 80–90% of terminal pathway activation by forming a powerful amplification loop for the three complement pathways (Harboe, et al., 2009; Harboe, et al., 2004). The C3 convertase, in the fluid phase and on cell surfaces, has a short half-life of ~90 seconds under physiological conditions (Pangburn and Muller-Eberhard, 1986). Properdin, a plasma glycoprotein and the only positive regulator of the complement system, can bind to and stabilize surface-bound AP C3 convertases (C3bBb) (Figure 1 and 2A) and C5 convertases ($(C3b)_{2\text{-}n}Bb$) by extending the half-life of the nascent convertases 5–10-fold, leading to accelerated and efficient amplification of C3b deposition on surfaces. Properdin, a ~50 kDa protein, is found at 4–25 μg/ml in plasma and, under physiological conditions, forms mainly cyclic dimers (P_2), trimers (P_3) and tetramers (P_4) in a 26:54:20 ratio via head-to-tail association of its monomers (Pangburn, 1989; Smith, et al., 1984). The convertase-stabilizing activity of the tetramer is greater than the trimer, and both are greater than the dimer (Pangburn, 1989). The strength of the interaction of properdin with surface-bound C3b is stronger than surface-bound iC3b, but is enhanced on C3bB, and further increases when C3bBb is generated (Farries, et al., 1988). It has been shown, by electron microscopy, that C3bBb convertase molecules were bound to properdin vertexes and thus required properdin to be forming at least a dimer for recognition of the convertase (Alcorlo, et al., 2013). The same study also showed that each properdin oligomer has the potential to use all its vertexes to bind C3bBb convertases (Alcorlo, et al., 2013).

2.3 Factor H: a soluble negative regulator with an essential role in discrimination between self and non-self

Although the AP efficiently activates and amplifies on most pathogens surfaces, it does not on host cell surfaces due to the presence of soluble or membrane-bound complement

regulatory proteins. While the membrane-bound regulators (CD35/CR1, CD55/DAF, CD46/MCP, CD59) are common for regulating all three pathways (reviewed in (Barnum, et al., 2018a)), the process to discriminate self (host) from non-self (pathogens/altered surfaces) by the AP requires the participation of Factor H (reviewed in (Ferreira, et al., 2010b)), C3b (Pangburn, et al., 2008; Sahu and Pangburn, 1994; Sahu and Pangburn, 1995), and potentially properdin, via its possible role as a pattern recognition molecule (reviewed in section 2.4).

Factor H (formerly known as β1H) (Figure 2B) recognizes C3b, iC3b, and C3d in the context of specific host cell markers including polyanions such as glycosaminoglycans (GAGs) and sialic acid. Factor H accelerates the decay of the convertases (by dissociating Bb from C3b or C3(H_2O)) and serves as a cofactor for factor I-mediated cleavage of C3b and C3(H_2O) to "inactive" C3b (iC3b) and iC3(H_2O), which can no longer form new convertases. AP activation will proceed unchecked, on most pathogen surfaces that lack polyanionic markers, due to poor or absent Factor H binding. Thus, the ability of Factor H to bind to a surface is key in protecting host cells and for discriminating self from non-self. Factor H is a ~150 kDa protein that consists of 20 complement control protein (CCP) domains and circulates in blood at approximately 150–550 μg/ml. Factor H regulatory functions are contained within its four most N-terminal domains, while its ability to recognize self from non-self is found mainly in the C-terminal domains, 19 and 20. Additional sites for recognition of C3b and polyanions exist throughout Factor H and likely contribute to how effectively Factor H recognizes different tissues, which vary in their polyanion marker milieu (reviewed in (Ferreira, et al., 2010b)).

Many mutations and single nucleotide polymorphisms have been found in Factor H. Deficiency of Factor H, mainly due to mutations found in the N-terminal domains, are associated with C3 glomerulopathy (dense deposit disease), which is characterized by insufficient fluid-phase regulation that causes rapid consumption of C3 (Pickering, et al., 2002; Ruseva, et al., 2013). Mutations, mainly in the C-terminus, lead to impaired cell surface binding (Ferreira, et al., 2009; Lehtinen, et al., 2009) and have been associated with atypical hemolytic uremic syndrome (aHUS) (reviewed in (Ferreira, et al., 2010b)), while the H402Y polymorphism is linked to an increased risk for developing age-related macular degeneration (Raychaudhuri, et al., 2011).

Factor H and properdin often have opposing regulatory roles and can also directly interfere with each other. For example, properdin can directly limit Factor H cofactor activity (Farries, et al., 1988; Medicus, et al., 1976), and structural data predicts that properdin would affect Factor H decay accelerating activities (Alcorlo, et al., 2013). This suggests that defective Factor H regulation may enhance the positive regulatory functions of properdin.

2.4 Properdin as a potential pattern recognition molecule that initiates the AP and as a ligand with unknown or novel functions

Louis Pillemer (Pillemer, et al., 1954) proposed that properdin acted as an initiator of the AP and called it the "properdin system". This notion was soon after replaced with what is now widely recognized as the AP convertase-stabilizing function of properdin (section 2.2) (Fearon, et al., 1975; Schreiber, et al., 1975). Later, Vuagnat et al. showed that properdin

expressed on the surface of transfected HEK-293 cells could potentially either capture $C3(H_2O)Bb$, initiating the AP activation or could protect the C3b that was already on the surface from negative regulators, promoting convertase assembly and stability (Vuagnat, et al., 2000). More recently, Hourcade et al. showed that properdin does have the ability to initiate the AP through the generation of a C3 convertase *de novo* by recruiting C3b or $C3(H_2O)$ and Factor B (Figure 2A), using surface plasmon resonance (Hourcade, 2006). Multiple studies that followed have suggested that properdin can act as a pattern recognition molecule by binding to and initiating the AP on microorganisms (Cortes, et al., 2011; Spitzer, et al., 2007), cells (Camous, et al., 2011; Gaarkeuken, et al., 2008; Kemper, et al., 2008; Nagamachi, et al., 2014; O'Flynn, et al., 2016; Saggu, et al., 2013; Xu, et al., 2008; Zaferani, et al., 2011), and biological substrates such as LPS, AMRS2, myeloperoxidase (MPO), heparan sulfate proteoglycans, Factor H related-protein 5 (FHR5), acetylated LDL, and zymosan (Chen, et al., 2016; Ferreira, et al., 2010a; Kimura, et al., 2008; Klop, et al., 2014; Micklisch, et al., 2017; O'Flynn, et al., 2014; Zaferani, et al., 2012).

There are other properdin interactions with pathogens and with biological substrates that have been demonstrated, but not yet experimentally shown to lead directly to AP activation, including the interaction of properdin with Mycobacteria (Al-Mozaini, et al., 2018), DNA (Xu, et al., 2008), monomeric C reactive protein (O'Flynn, et al., 2016), and certain GAGs (reviewed in (Blatt, et al., 2016a)).

Caution needs to be taken when interpreting the results of the properdin binding studies cited above for the following reasons: First, large aggregates of properdin are present in purified preparations of the protein (Farries, et al., 1987; Pangburn, 1989), which were used in most of those studies. These large aggregates of properdin, also referred to as "activated" properdin or P_n are non-physiological, induce AP activation in solution, lead to complement consumption (Farries, et al., 1987; Pangburn, 1989) and may account for nonspecific ionic interactions with several surfaces, such as *Neisseria meningitidis* and Jurkat T cells (Agarwal, et al., 2010; Ferreira, et al., 2010a). Thus, size exclusion or ion exchange chromatography is recommended for separating native forms of properdin (P_2, P_3, P_4) from P_n forms (Agarwal, et al., 2010; Ferreira, et al., 2010a) for use in research. Studies where native/physiological forms of purified properdin were used have shown direct binding of properdin, independent of C3 deposition, to zymosan (Ferreira, et al., 2010a), *Chlamydia pneumoniae* (Cortes, et al., 2011), necrotic nucleated cells (Ferreira, et al., 2010a), and activated platelets (Saggu, et al., 2013). Properdin in neutrophil supernatants (another physiological source) can bind to apoptotic T cells and activated platelets (Kemper, et al., 2008; Saggu, et al., 2013).

The second reason why studies examining the ability of properdin to act as a pattern recognition molecule needs to be carefully interpreted is that increasing concentrations of serum inhibit the direct interaction of properdin with all the properdin-binding surfaces tested so far (Cortes, et al., 2011; Ferreira, et al., 2010a; Saggu, et al., 2013), and binding of properdin to certain surfaces, in the presence of serum, requires C3 activity (Agarwal, et al., 2010; Agarwal, et al., 2011; Cortes, et al., 2011; Harboe, et al., 2012; Harboe, et al., 2017). While there is no *in vivo* evidence that properdin-initiated complement activation exists, there is evidence in a murine abdominal aortic aneurism (AAA) model, that the convertase

stabilization function of properdin is sufficient to promote AP-dependent pathogenesis and properdin-initiated complement activation is not required (Zhou, et al., 2012).

It is important to note that it is not known how properdin behaves when released at high concentrations in local microenvironments *in vivo*, which may be different from its behavior in serum. Using physiological P_2-P_4 properdin, anti-C3 fragment antibodies to block any properdin-C3 interactions on surfaces, and inhibiting C3 cleavage (i.e. by Compstatin (Sahu, et al., 1996)), in serum or in biological samples containing locally-expressed properdin, should help define the surfaces that indeed bind properdin, contributing to further understanding of whether properdin is in fact a pattern recognition molecule.

Interestingly, properdin has recently been assigned a complement activation/amplification-independent mode of action. Properdin is a ligand for receptor NKp46 on NKp46$^+$ cells, including natural killer (NK) cells, subsets of innate lymphoid cell group 1 (ILC1) and natural cytotoxicity receptor$^+$ ILC3 and initiates a transduction pathway in NK cells, which is distinct from classical NK cell activation (Narni-Mancinelli, et al., 2017) (Figure 4D). Further studies aimed at identifying other potential complement activation/amplification-independent roles for properdin in nature, are warranted.

3. Properdin gene and protein characteristics

3.1 Properdin gene location and expression

Properdin is a glycoprotein synthesized as a single-chain molecule of 469 amino acids, which includes a 27-amino acid leader sequence, leading to 442 amino acids in the mature protein (Nolan, et al., 1991). Each properdin monomer is composed of six complete thrombospondin type 1 repeat (TSR) domains, in which each TSR consists of a folded core consisting of three antiparallel strands held together by three disulfides, consisting of around 60 amino acids (Goundis and Reid, 1988). The TSR domains are labeled TSR1–6 and a truncated N-terminal domain (TSR0) containing key conserved residues (Sun, et al., 2004). Properdin is post-translated by C-mannosylation, O-fucosylation, N-glycosylation and C-glycosylation (Hartmann and Hofsteenge, 2000; Higgins, et al., 1995; Yang, et al., 2016). The N-glycosylation site, which is the best known post-translational modification, is not essential for properdin activity (Higgins, et al., 1995). Extensive heterogeneity has been found in occupancy of the C-mannosylation sites in the six TSR domains (Yang, et al., 2016).

In line with the fact that complement is an ancient defense system, the properdin gene found in amphioxus *Branchiostoma japonicum*, which represents an archetype of vertebrate properdins, has a similar function as the ones in vertebrates (Gao, et al., 2017; Nolan, et al., 1991). The human properdin gene, which was cloned (Nolan, et al., 1991) and sequenced, contains 10 exons that span approximately 6kb (Nolan, et al., 1992) and is located at the short arm of the X chromosome Xp11.4 (NCBI, 2017). The mouse properdin gene contains 9 exons (NCBI, 2018) and is located on Chromosome X, 16.44 cM, cytoband A3 (Evans, et al., 1990).

3.2 Protein structure and oligomer studies

As mentioned in section 2.2, under physiological conditions, properdin forms mainly cyclic P_2, P_3 and P_4 in a 26:54:20 ratio via head-to-tail associations of monomers (Pangburn, 1989; Smith, et al., 1984). The P_4 is ten times more active than the P_2 (Pangburn, 1989) and shows a higher activity when inducing complement-mediated platelet-granulocyte aggregate (PGA) formation (Blatt, et al., 2016b). The increased activity is likely due to increased avidity of properdin for the convertases, because of the presence of multiple convertase binding sites in the tetramer (Alcorlo, et al., 2013).

Different approaches have been used to study the functional contribution of properdin domains and oligomerization. Higgins et al. constructed properdin deletion mutants, each lacking a single TSR, and found that recombinant properdin lacking TSR6 cannot form oligomers, deletion of TSR5 or TSR6 makes properdin unable to bind C3b, and properdin lacking TSR4 can bind C3b, but cannot stabilize C3bBb (Higgins, et al., 1995). Antibodies raised against human TSR5 (Perdikoulis, et al., 2001) and mouse TSR 5–6 (Bertram, et al., 2015) effectively inhibited properdin function *in vitro* and *in vivo*, respectively. Likewise, the anti-properdin antibody CLG561, developed by Novartis as an AP inhibitor, also binds TSR5 (Johnson, et al., 2016). Competitive inhibition with recombinant TSR4–5 inhibits AP-mediated hemolysis (Kouser, et al., 2016). Structural studies have shown that TSR5 is needed for interaction with C3b (Pedersen, et al., 2017) and that this binding occurs by docking on top of the C3b C345C domain (Alcorlo, et al., 2013; Pedersen, et al., 2017). Also, properdin docks on the Factor B vWA domain (Alcorlo, et al., 2013) and TSR4 may be responsible for this interaction (Pedersen, et al., 2017) (Figure 3). Structural studies have also proposed models for oligomerization (Alcorlo, et al., 2013; Sun, et al., 2004) that illustrate roles for TSR0–1 and 5–6 in mediating contacts at the vertexes (Alcorlo, et al., 2013) of properdin oligomers, although the exact composition of the vertexes could not be determined.

3.3 Properdin mutations, deficiencies, and polymorphic variants

Properdin deficiency is inherited as an X-chromosomal recessive trait and is highly associated with increased susceptibility to infection with *Neisseria meningitidis* with a significantly higher risk of developing disseminated, fulminant meningococcal infections than normal individuals (reviewed in (Figueroa, et al., 1993)).

Properdin deficiency has been described in more than 25 families with identification of ~ 20 different mutations (Figure 3). Properdin deficiency has been divided into three main categories (Fijen, et al., 1999a): (a) Type I or complete absence of circulating properdin, which is caused by various mutations that either cause a truncated gene product (Helminen, et al., 2012; Westberg, et al., 1995) or changes in protein conformation that do not allow properdin secretion (van den Bogaard, et al., 2000). Nucleotide mutations found on Type I deficient families alter amino acids that are highly conserved in TSRs from human and mice, suggesting that they are essential for the protein structure (Fijen, et al., 1999b); (b) Type II properdin deficiency, which results in reduced levels of properdin (<10%) in serum. Properdin is synthesized and secreted from the cells, but oligomerization has an abnormal pattern with a dominance of dimers (Fredrikson, et al., 1998; Pedersen, et al., 2017). The

reduced properdin concentration in type II deficiency is probably due to rapid extracellular degeneration of abnormal properdin molecules (Fredrikson, et al., 1998); and (c) Type III properdin deficiency, which is characterized by an impaired ability to bind C3b and regulate the AP, even though the plasma levels are normal (Fredrikson, et al., 1996).

Multiple properdin polymorphic variants exist, but the potential functional consequences of most of them have not been studied (reviewed in (Ferreira, 2018)). Recently, the rs1048118 (p.Asn428(p=)-*CFP*) polymorphism has been correlated with higher levels of properdin protein, and is significantly associated with an increased risk of antibody-mediated cardiac allograft rejection (AMR), potentially playing a role in the development of AMR (Marron-Linares, et al., 2017).

4. Properdin sources

Unlike most complement proteins synthesized by hepatocytes, properdin is synthesized and/or secreted mainly by leucocytes (Table 1). Primary T cells (Schwaeble, et al., 1993), monocytes (Fredrikson, et al., 1998; Maves and Weiler, 1992; Uchiyama, et al., 2016; Whaley, 1980), macrophages (Reis, et al., 2006), dendritic cells (DCs) (Dixon, et al., 2017; Li, et al., 2011; Reis, et al., 2006), granulocytes (Camous, et al., 2011; Uchiyama, et al., 2016; Wirthmueller, et al., 1997) and mast cells (Stover, et al., 2008) have been reported to synthesize mRNA only or to also secrete properdin. Mature neutrophils store large amounts of properdin in secondary granules. Properdin levels are reduced by ~19–32% in neutropenic states in patients under chemotherapy. This indicates the importance of neutrophils in contributing to serum properdin levels, while also suggesting significant contribution of other cells as well (Tsyrkunou, et al., 2017).

In addition, endothelial cells (Bongrazio, et al., 2003; Jeon, et al., 2017; Uchiyama, et al., 2016) and adipocytes (Pattrick, et al., 2009; Peake, et al., 1997) also secrete properdin. Properdin expression and secretion by human umbilical vein endothelial cells (HUVECs) is increased when cells are exposed to laminar shear stress for 24 hours, and is enhanced with turbulent flow (Bongrazio, et al., 2003). Properdin is also secreted by HUVECs under IFN-α stimulation, which may partially contribute to properdin level increase in the serum of patients during IFN-α treatment (Uchiyama, et al., 2016). A recent study found that HUVECs are able to secrete properdin through the release of extracellular vesicles under Kaposi’s sarcoma-associated herpesvirus (KSHV) infection, which may participate in early viral defense (Jeon, et al., 2017).

5. Properdin, immune cells, and immune responses

5.1 Properdin and neutrophils

Neutrophils store and rapidly release their intracellular properdin into the extracellular space in response to a variety of inflammatory agonists, including bacterial LPS, the cytokines TNF-α, IL-8 (CXCL8), granulocyte–macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), C5a (Figure 4A), fMLP, PMA, and IFN-α (Camous, et al., 2011; Uchiyama, et al., 2016; Wirthmueller, et al., 1997). In sites of inflammation, where there is local release of cytokines and complement is activated, the

secretion of properdin will elevate the levels of properdin in the microenvironment surrounding activated neutrophils and cells that are in close proximity, with various potential consequences (Figure 4A). Properdin-enhanced AP activation on neutrophils serves as a positive feedback loop to enhance generation of C5a (Camous, et al., 2011). Unfractionated properdin when incubated with isolated resting neutrophils promotes complement activation on neutrophil membranes (Camous, et al., 2011) and neutrophil-secreted properdin and isolated physiological forms (P_2-P_4) can bind to activated platelets, but not resting platelets (Saggu, et al., 2013), and activate the AP. Moreover, P_2-P_4 induces the formation of PGA, when added to whole blood, by inducing complement activation, which leads to C5a generation, C5aR-mediated neutrophil activation, and increased expression of CR3, which is essential for the aggregates to form. On the contrary, inhibition of properdin decreases PGA formation, while inhibition of Factor H increased it (Blatt, et al., 2016b). Interestingly, these events occur despite the presence of membrane-bound complement regulatory proteins on neutrophil and platelet surfaces, illustrating the potential highly significant role of properdin positive regulation in local microenvironments.

The process of Neutrophil Extracellular Traps (NETs) formation (i.e. NETosis) is a specific form of neutrophil cell death in which nuclear DNA undergoes decondensation with subsequent expulsion of chromatin that is coated with cytotoxic granular antimicrobial proteins, such as MPO, elastase, and other proteases. NETs play an important role in the innate immune response (e.g. by immobilizing and killing invading microorganisms). PMA (Yuen, et al., 2016) and ANCA-positive IgG stimulate TNF-α primed neutrophils to release NETs (Wang, et al., 2015a), as well as release key components of the AP such as properdin, Factor B and C3. The released NETs activate the alternative complement cascade and the complement components deposit on NETs (Wang, et al., 2015a; Yuen, et al., 2016). Complement activation on NETs leads to C5 cleavage with formation of the MAC (C5b-9) (Figure 4B) (Wang, et al., 2015a; Yuen, et al., 2016) and pro-inflammatory C3a, C5a and soluble C5b-9 (sC5b-9) release (Wang, et al., 2015a). An antibody that blocks the convertase-stabilizing function of properdin inhibits AP-mediated, but not non-AP-mediated, complement activation on NETs (Yuen, et al., 2016).

5.2 Properdin, monocytes/macrophages, dendritic cells, and T cells

IFN-α stimulates properdin secretion by monocytes and enhances monocyte-mediated group A *Streptococcus* killing (Uchiyama, et al., 2016). Monocyte-derived DCs, professional antigen presenting cells (APCs) responsible for both the initiation of immunity and immunological tolerance, express mRNA and produce properdin constitutively (Dixon, et al., 2017; Li, et al., 2011; Reis, et al., 2006). Properdin secretion is depressed under IFN-γ stimulation (Dixon, et al., 2017), while Factor H production is enhanced by IFN-γ and IL-27 in DCs (Dixon, et al., 2017). Modulation of DC-derived properdin and Factor H affects T cell responses in opposite ways. Inhibition of Factor H production from DCs induces greater allogenic $CD4^+$ T-cell proliferation, while inhibition of properdin production leads to reduced proliferation (Dixon, et al., 2017), either by modulating complement regulation in the local microenvironment (Figure 4C) or by a direct effect of properdin and Factor H. Several recent studies have confirmed that complement actively plays a role in regulating T-cell immunity (reviewed by (Heeger and Kemper, 2012)). Properdin is also constitutively

expressed and synthesized by T cells (Schwaeble, et al., 1993), which likely participates in this DC - T cell interplay.

5.3 Properdin and natural killer cells

NK cells, essential players in innate immune defense, have recently been shown to bind properdin via the NKp46 receptor (as mentioned in section 2.4). Properdin is not able to induce classical NK cell activation like that induced by an anti-NKp46 monoclonal antibody, but initiates an unknown transduction pathway that leads to up-regulation of the transcripts encoding the Xcl1 chemokine. Data indicate that this interaction is independent from the role of properdin in complement activity. In addition, $NKp46^{+}$ cells are required for mice survival during *N. meningitidis* infection and the cells enhance the effect of exogenously-administered properdin on inhibiting *N. meningitidis* infection in mice (Narni-Mancinelli, et al., 2017) (Figure 4D). Future studies to understand whether additional signals are required for properdin-associated NK cell activation are warranted along with exploring other signaling pathways initiated by properdin.

6. Properdin and diseases

Given the relevance of AP activation in the pathogenesis of many diseases, the role of properdin is widely being evaluated in infectious and non-infectious diseases. A comprehensive summary is included in Table 2. The use of properdin knockout mice, neutralizing antibodies, and administration of exogenous properdin in *in vivo* rodent models, as well as the study of patients with properdin mutations, and thorough biochemical characterization of properdin functions, have all contributed significantly to the understanding of pathophysiological mechanisms of properdin, as well as to the design of therapeutic candidates.

Abundant evidence indicates that properdin plays important roles against infections by pathogens (e.g. bacteria, fungi, viruses, etc.) in *in vitro* and *in vivo* mouse models (Table 2, Infectious diseases). The mechanisms may include complement promotion by properdin by either stabilizing the convertases or potentially initiating complement in local microenvironments, which enhances immune cell infiltration, and modulates maturation of APCs as well as adaptive immune responses. For example, increasing evidence indicates that properdin deficiency leads to macrophages shifting to an M2 phenotype, which contributes to both infectious and non-infectious disease outcomes in various models (Al-Rayahi, et al., 2017; Dupont, et al., 2014; Steiner, et al., 2014). Interestingly, depending on the disease stimulus (i.e. infectious, non-infectious), the lack of properdin may lead to opposite results, such as those from septic and non-septic shock models (Stover, et al., 2008).

In non-infectious diseases (Table 2, Non-infectious diseases), the detection of properdin on tissue samples (indicating likely alternative pathway activation) and decreased levels of properdin levels in serum are often associated with clinical syndrome in humans. While lack of properdin often protects host from exacerbated inflammation, resulting in improved symptoms and decreased mortality in mouse models, lack of properdin exacerbated colonic injury in colitis models, indicating the complexity of modulating properdin in specific diseases (Jain, et al., 2015b). In the case of the role of properdin in kidney diseases (Table 2,

Kidney diseases/damage), a particularly intriguing finding is that lack of properdin leads to more severe renal injury when Factor H is dysfunctional (Lesher, et al., 2013b; Ruseva, et al., 2013), suggesting an intricate balance in complement positive and negative regulation is in play (reviewed in (Lesher, et al., 2013a)). Properdin also contributes to vascular diseases (Table 2, Cardiovascular diseases or associated cardiovascular factors), correlating with the severity of various cardiovascular disease events (such as stroke) by, for example, contributing to endothelial dysfunction (Hertle, et al., 2016). Finally, properdin can also have protective effects. Similar to what is described for C3 glomerulonephritis, above, lack (or reduced levels) of properdin unexpectedly lead to increased atherosclerotic plaque progression (Steiner, et al., 2014) and to increased severity of heart failure (Shahini, et al., 2017).

7. Properdin and disease therapeutics

Only two drugs are currently available in the clinic with connection to the complement system: plasma purified or recombinant preparations of C1-INH (various manufacturers) and anti-C5 monoclonal antibody eculizumab (Soliris®; Alexion Pharmaceuticals Inc.). Over 20 candidate drugs that target complement components are being assessed in clinical trials (reviewed in (Ricklin, et al., 2018)). Eculizumab, the only complement-specific inhibitor that is approved for aHUS (Campistol, et al., 2013) and paroxysmal nocturnal hemoglobinuria (PNH) (Hillmen, et al., 2006), prevents cleavage of C5 and thus blocks generation of C5a and formation of the MAC complex (Jore, et al., 2016) and thus does not block C3 opsonization. However, limited success of clinical trials for rheumatoid arthritis (RA) (Vergunst, et al., 2007) and cardiovascular diseases (Verrier, et al., 2004), and high cost (Ricklin and Lambris, 2016) contribute to the need to find additional treatment options. In addition, upstream complement inhibition (i.e. at the convertase level) needs to be explored, especially in diseases where complement activation is strong and C5 inhibition is insufficient, leading to residual hemolysis in certain PNH patients. The residual hemolysis may be due to the high density of C3b molecules that can compete with C5 inhibitors for recruiting C5 (Harder, et al., 2017). Studies evaluating combination therapy, using more than one complement inhibitor that target different stages of complement activation, are also warranted.

Therapeutic inhibitors of properdin would block complement at an earlier stage by interfering with the amplification of the AP and thus potentially ameliorate human diseases where the AP participates in the pathogenesis, in particular in diseases where properdin levels are increased and where properdin has been shown to play an important role in the pathogenesis (Table 2). In addition, since the AP accounts for ~ 80–90% of terminal pathway activity that was initiated by classical and lectin pathways, inhibiting properdin may be effective in limiting inflammatory-mediated damage in diseases where predominantly the CP and LP play pathogenic roles.

In vivo murine studies support the notion that inhibition of properdin may be a promising treatment for inflammatory diseases (Kimura, et al., 2010; Miwa, et al., 2013; Wang, et al., 2015b). The pathophysiological effects of presence or absence of properdin have been discussed above (section 3.3) and in Table 2 in each specific disease. Various molecules,

including antibodies and fragments thereof that can inhibit properdin have been identified in many laboratories (Blatt, et al., 2016b; Hourcade, et al., 2016; Kouser, et al., 2016; Mendes-Sousa, et al., 2017; Silva, et al., 2016), with potential as future therapeutic candidates. Currently, a fully-human anti-properdin Fab (CLG561) is assessed by Novartis for use in age-related macular degeneration (AMD) (Johnson, et al., 2016); it is currently evaluated as monotherapy or in combination with the fully human anti-C5 monoclonal antibody LFG316 in a phase 2 trial for geographic atrophy (Ricklin, et al., 2016). Moreover, an antibody (NM9401) and small molecules for properdin inhibition are being developed by Novelmed for use in PNH and RA, respectively (reviewed in (Morgan and Harris, 2015)), but efficacy and outcomes have not yet been reported.

Another consequence of properdin inhibition is that it can restrict the formation of PGA (which are known to be pro-thrombotic) in thrombin receptor-activating peptide (TRAP)-stimulated human whole blood *ex-vivo* (Blatt, et al., 2016b). Factor H regulation of complement, via its C-terminus, is essential for limiting excessive PGA formation and aHUS-related C-terminal Factor H mutations pre-dispose patients to the risk of thrombosis. Thus, this risk may be reduced by inhibiting properdin when impaired Factor H cell-surface protection exists (Blatt, et al., 2017).

Although there are many experimental evidences that support the benefits of inhibiting properdin as a potential therapy for certain diseases, properdin inhibition has also shown counterintuitive effects in a murine Factor H-related C3 glomerulopathy (C3G) model; properdin deletion converts a mild C3G to a lethal and rapidly progressing C3G phenotype (Lesher, et al., 2013b; Ruseva, et al., 2013). Thus, anti-properdin therapy may serve as a therapeutic target in several, but not all, complement-mediated pathologies. Another reason for caution when considering properdin inhibition as therapy is the known significant increase in susceptibility to *Neisseria meningitidis* and septicemia when properdin is absent or dysfunctional (reviewed in (Figueroa, et al., 1993)). Vaccination with serogroup B meningococcal vaccine mostly prevents these deleterious consequences and could be used in combination with properdin inhibition therapy in patients (Hellenbrand, et al., 2015), which is already recommended for patients on eculizumab treatment.

Another application for using properdin inhibition in therapeutic settings comes from the fact that complement activation on nanoparticles often leads to their opsonization and removal before they reach their intended destination, limiting their development as tissue-specific drug delivery platforms. Some properdin-related strategies have been developed to potentially overcome this problem. For example, recombinant TSR4+5 (Kouser, et al., 2018) or inhibitory anti-properdin antibodies (Wang, et al., 2016), when coated on nanoparticles, inhibited complement activation on the nanoparticles. These nanoparticles that inhibit properdin activity, may even have potential therapeutic applications for regulating local inflammatory responses.

Properdin-related therapeutics can also potentially benefit from using properdin itself, either locally or systemically, as a therapeutic weapon. While delivery methods would be important for avoiding complement consumption, an experimental example of the potential for using properdin therapy comes from a study showing that low-dose recombinant

properdin therapy markedly reduced susceptibility to *Streptococcus pneumoniae* and *Neisseria meningitidis* infection in mice (Ali, et al., 2014). This raises the possibility that supplementation of properdin might be effective in sepsis and other severe infections in humans. Targeting properdin to bind to certain surfaces (i.e. tissues or probes for delivery to tissues) may also have potential beneficial therapeutic effects, by promoting complement-dependent elimination of unwanted (i.e. cancer) cells. In support of this notion, there are data showing that transfected HEK293 cells expressing membrane-bound properdin (Vuagnat, et al., 2000) and properdin-coated nanoparticles (Kouser, et al., 2018) initiate complement activation, and that properdin insufficiency promotes a microenvironment that helps tumor cells evade the immune response (Al-Rayahi, et al., 2017).

8. Concluding remarks

The discoveries surrounding properdin characteristics and functions have progressed significantly beyond its role as a convertase stabilizer. The opposite effects of properdin deficiency in certain murine disease models elucidate the complexity of the role of properdin in health and disease. Continuing to discover and study the various sources of properdin, the regulation of its production, and the molecular mechanisms of its physiological and pathological functions in circulation and particularly in local microenvironments will significantly increase our understanding of complement regulation and host immune responses. These findings will also continue to prove useful in the critical design and evaluation of the use of properdin modulation in therapeutics.

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Abbreviations:

aHUS	atypical hemolytic uremic syndrome
AAA	abdominal aortic aneurysm
AAV	ANCA-associated vasculitis
AMD	age-related macular degeneration
AMR	antibody-mediated rejection
ANCA	anti-neutrophil cytoplasmic antibody
AP	alternative pathway
APC	antigen presenting cells

C3G	C3 glomerulopathy
C5aR1	C5a receptor 1
CP	classical pathway
DCs	dendritic cells
HUVEC	human umbilical vein endothelial cells
GAGs	glycosaminoglycans
HF	heart failure
KSHV	Kaposi's sarcoma-associated herpesvirus
LP	lectin pathway
MAC	membrane attack complex (C5b-9)
MPO	myeloperoxidase
NETs	Neutrophil Extracellular Traps
NK cells	natural killer cells
$P^{-/-}$	properdin-deficient mice
P_2	dimeric form of properdin
P_3	trimeric form of properdin
P_4	tetrameric form of properdin
PGA	platelet-granulocyte aggregates
P_n	non-physiological aggregated form of properdin
PNH	paroxysmal nocturnal hemoglobinuria
sC5b-9	soluble C5b-9
TSR	thrombospondin type 1 repeat
WT	wild type

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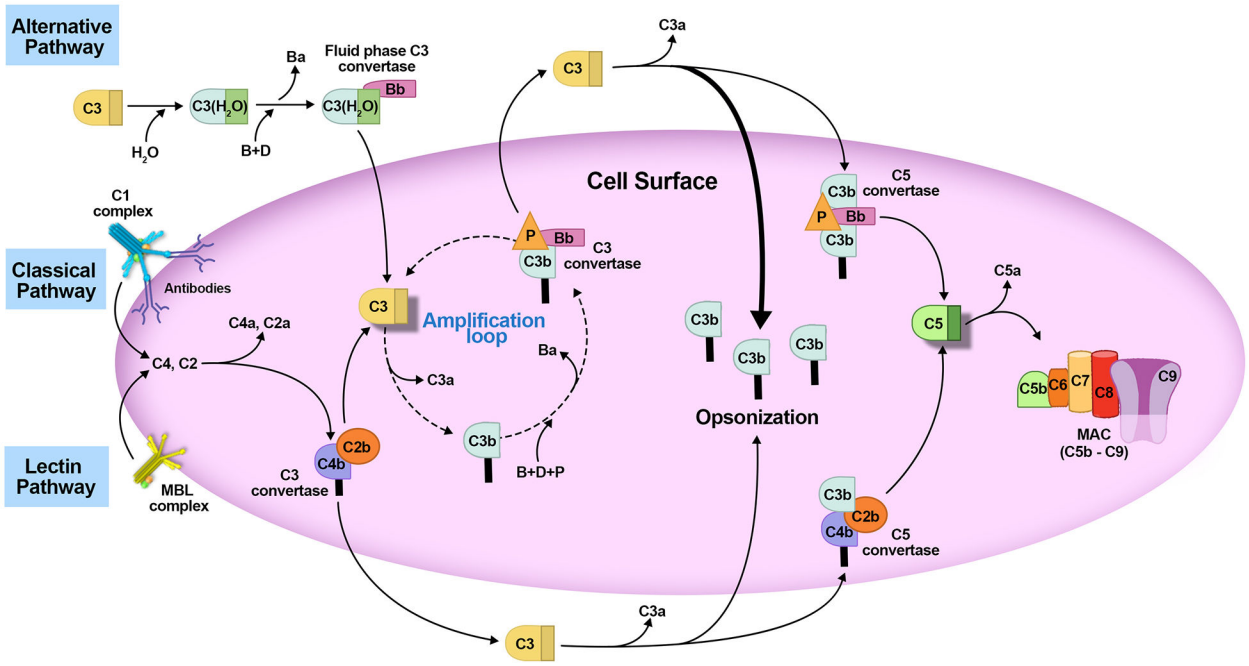

Fig. 1.

An overview of complement system and the role of the alternative pathway (AP) in the amplification loop. Complement activation is initiated by three different pathways: classical, lectin and alternative pathway. In the classical pathway (CP), C1 complex [C1q, C1s(2) and C1r(2)] recognizes two IgGs or one pentamer IgM (not shown) to form an antigen-antibody complex. In the lectin pathway (LP), mannose-binding lectin (MBL), ficolins or collectins, in association with MBL-associated serine proteins (MASPs), recognize carbohydrates on pathogens. Recognition of these molecules leads to the generation of the C3 convertase C4b2b. Unlike the CP and LP, the alternative pathway (AP) is spontaneously activated in fluid phase through hydrolysis of C3 to C3(H_2O). C3(H_2O) recruits Factor B (labeled B) that is cleaved by Factor D (labeled D) to form the fluid-phase AP C3 convertase C3(H_2O)Bb. C4b2b and C3(H_2O)Bb cleave C3 molecules found in plasma to generate C3a and C3b, which covalently attach to the cell surface. The C3b derived from all pathways can be used to generate the AP C3b convertase (C3bBb) (amplification loop). Properdin binds to C3bBb and C3bBbC3b extending the half-life of the convertase and thus promoting efficient C3b deposition on the cell surface (represented by the thick line). If C3b binds to or near any C3 convertase, it will form the AP C5 convertase (C3bBb3b) and the LP and CP C5 convertase (C4b2b3b). These C5 convertases cleave C5 to form C5b and C5a, leading to the formation of the membrane attack complex (MAC) that is common to all pathways. Anaphylatoxins C3a and C5a play important roles in inflammation.

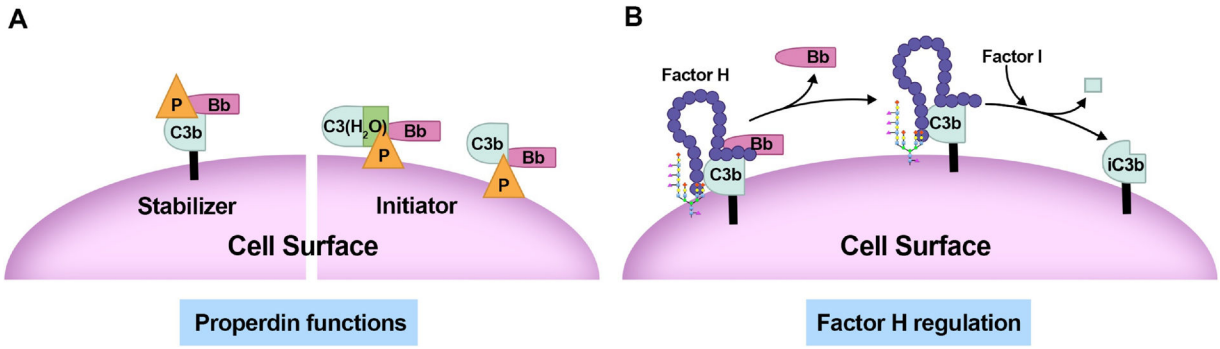

Fig. 2.

Role of complement regulators properdin and Factor H. (A) Properdin stabilizes AP C3 convertase C3bBb by increasing the half-life of the convertase by 5 to 10- fold. Properdin also functions as an initiator of AP by binding selectively to cell surface and recruiting $C3(H_2O)$ or C3b. (B) Factor H regulates complement activation by accelerating the dissociation of Bb from the AP C3 convertase C3bBb (and soluble $C3(H_2O)Bb$, not shown) and by serving as a cofactor for Factor I-mediated cleavage of C3b to iC3b (and C3dg (not shown)). Factor H protects host cells by recognizing both polyanions (i.e. glycosaminoglycans (GAGs)) and C3b/C3d found on host cells.

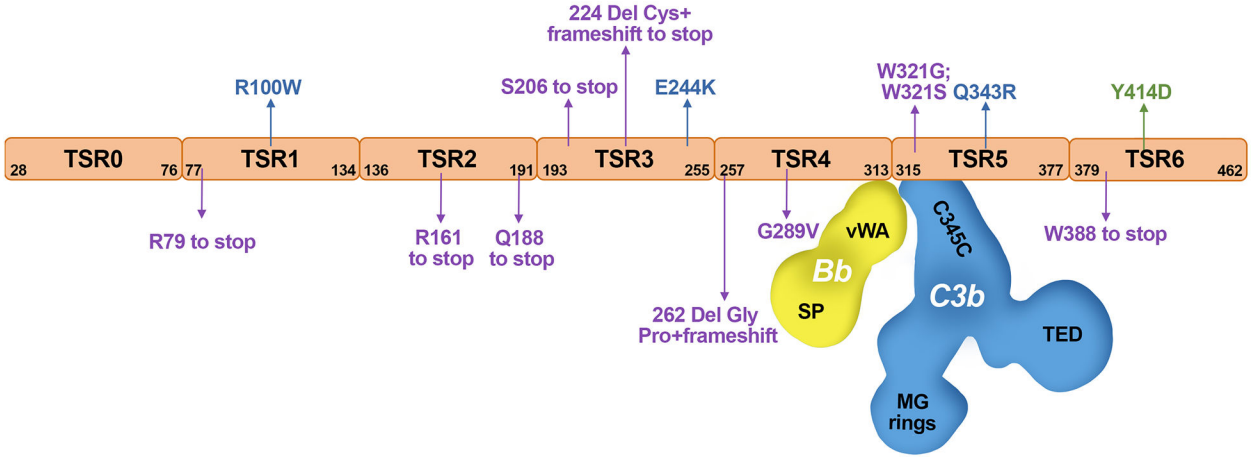

Fig. 3.

Properdin domain function and mutations. The properdin monomer consists of seven thrombospondin type I repeats (TSRs) denoted as TSR0-TSR6 (Orange). The amino acid sequence numbering includes the signal peptide. Properdin docks the C3b C345C domain via TSR5 domain, while properdin docks the Factor B vWA domain potentially via TSR4. C3b domains (TED, MG rings and C345C) are displayed as blue. Factor B domains (vWA and SP) are displayed as yellow. Properdin deficiency type I, II and III are indicated on properdin TSR domains in purple, blue and green arrows/letters, respectively. Approximately twenty mutations of properdin have been reported. Type I deficiency includes R79 to stop, R161 to stop, S206 to stop, 224 Del Cys + frameshift to stop, 262 Del Gly Pro + frameshift, G298V, W321G and W321S (reviewed in (Fijen, et al., 1999b)), Q188 to stop (Schejbel, et al., 2009), and W388 to stop (Helminen, et al., 2012). Type II deficiency includes mutations R100W (Sjoholm, et al., 1988b; Truedsson, et al., 1997), E244K (Pedersen, et al., 2017) and Q343R (Fredrikson, et al., 1998). Type III deficiency includes a Y414D mutation (Fredrikson, et al., 1996; Sjoholm, et al., 1988a).

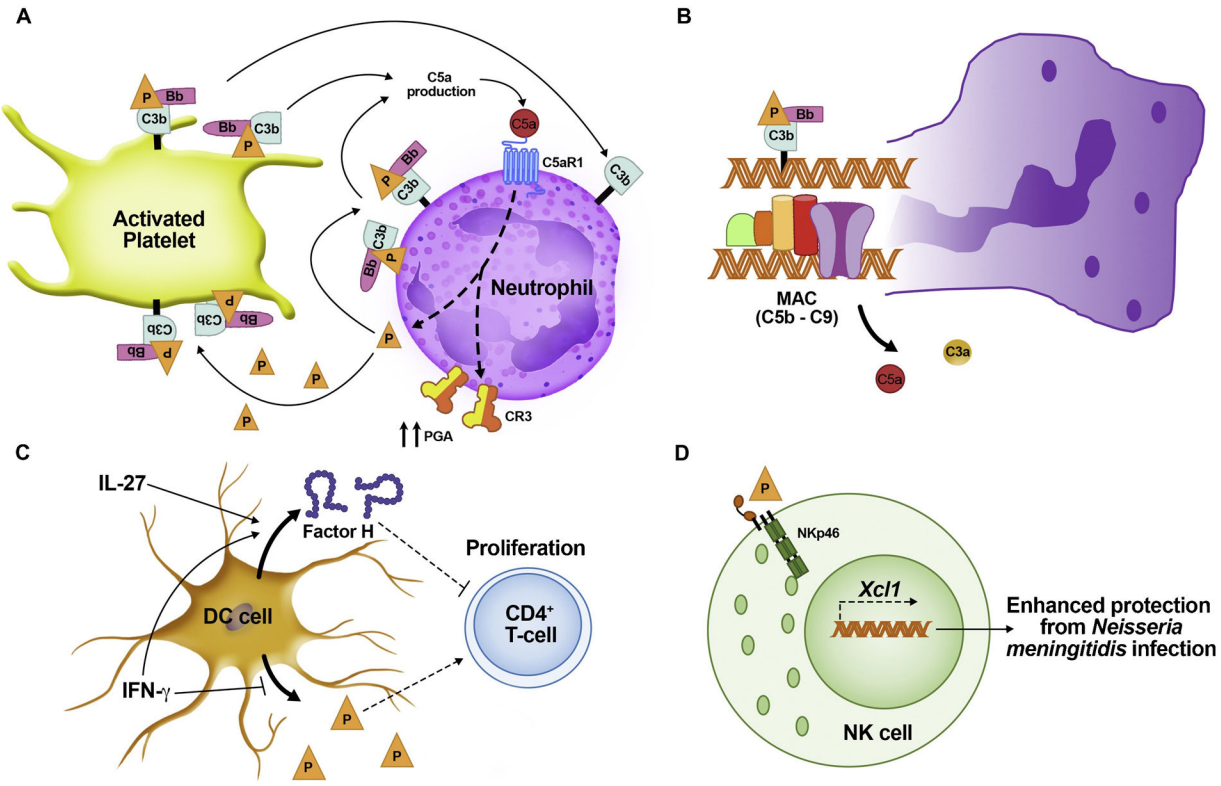

Fig. 4.

Properdin functions in immune responses. (A) Model of properdin roles in neutrophil and platelet microenvironments. Properdin can promote the activation of the AP on platelets either by acting as an initiator or as a convertase stabilizer, leading to C5a generation and C5aR-mediated neutrophil activation, upregulation of CR3 expression, which promotes the formation of platelet-granulocyte aggregates (PGA), and properdin release into the microenvironment. This local properdin may bind directly to platelets and/or neutrophils, leading to additional complement activation or convertase stabilization, while the C3b that is generated in the microenvironment may deposit on the surfaces and serve as a focal point for additional AP amplification. (B) Neutrophils, Neutrophil Extracellular Traps (NETs) and properdin. Complement components released by neutrophils, including properdin, Factor B and C3, are deposited on neutrophil-formed NETs (only the DNA component is shown, for illustration purposes). AP is activated on NETs, leading to C5b-9 deposition. (C) Properdin and dendritic cells (DCs). Properdin secretion by dendritic cells (DCs) is inhibited by IFN-γ. Factor H production by DCs is enhanced by IL-27 and IFN-γ. Inhibition of properdin reduces $CD4^+$ T cell proliferation while inhibition of Factor H increases $CD4^+$ T cell proliferation. (D) Properdin and natural killer (NK) cells. Properdin is recognized by NKp46 receptor on NK cells and subsets of innate lymphoid cells (ILCs) 1 and 3 (not shown). This interaction leads to up-regulation of *Xcl1* expression (dashed line) and also may protect host from *Neisseria meningitidis* infection.

Table 1.

Sources of properdin

Cellular Source		Form	Stimulus	Reference
Primary cells				
Monocytes		mRNA; Protein	Constitutive	(Fredrikson, et al., 1998; Maves, et al., 1992; Uchiyama, et al., 2016; Whaley, 1980)
Dendritic cells	Monocyte-derived	mRNA; Protein	Constitutive	(Dixon, et al., 2017; Li, et al., 2011; Reis, et al., 2006)
	Plasmacytoid, Dermal, Langerhans, Myeloid	mRNA	Constitutive	(Li, et al., 2011)
Primary T cells		mRNA	Constitutive	(Schwaeble, et al., 1993)
Mast cells		Protein	Constitutive	(Stover, et al., 2008)
Granulocytes		mRNA	Constitutive	(Wirthmueller, et al., 1997)
		Protein	TNF-α, C5a, IL-8 (CXCL-8), fMLP, PMA, TNF-α/fMLP, IFN-α	(Camous, et al., 2011; Uchiyama, et al., 2016; Wirthmueller, et al., 1997)
Macrophages		mRNA	Constitutive	(Reis, et al., 2006)
Adipocytes		mRNA; Protein	Constitutive	(Pattrick, et al., 2009; Peake, et al., 1997)
Endothelial cells				
	Human primary cells (HUVECs)	mRNA; Protein	Shear stress; IFN-α	(Bongrazio, et al., 2003; Jeon, et al., 2017; Uchiyama, et al., 2016)
		Protein	IFN-α	(Uchiyama, et al., 2016)
Cell lines				
H-9 (T cell), HuT78, Jurkat, T-ALL		mRNA	Constitutive	(Schwaeble, et al., 1993)
HL-60 (promyelocyte)		Protein	DMSO	(Farries and Atkinson, 1989)
U-937 (monocyte)		Protein	PMA, LPS, IFN-γ	(Minta, 1988)
MonoMac6 (Monocyte)		mRNA;Protein	IFN-γ (mRNA only), IL-1β, LPS, TNF-α, PMA	(Schwaeble, et al., 1994)
3T3-L1 adipocytes		mRNA	Constitutive	(Peake, et al., 1997)

Table 2.

Properdin and related diseases

Disease	Study model	Main findings	References
Infectious diseases			
Neisseria meningitidis	Patients with properdin deficiency	Properdin-deficient patients are highly vulnerable to *N. meningitides* infection. The risks of meningococcal disease in properdin-deficient patients is 250-fold more than the general population.	(Reviewed in (Fijen, et al., 1999b))
N. meningitidis and *N. gonorrhoeae*	*In vitro* study using physiological properdin	Physiological properdin does not directly bind to *N. meningitides* and *N. gonorrhoeae*, but does increase AP-dependent C3 deposition on the bacteria as a stabilizer.	(Agarwal, et al., 2010)
N. gonorrhoeae	*In vitro* study	Properdin is required for antibody-dependent killing of C4b-binding *N. gonorrhoeae* strains.	(Gulati, et al., 2012)
Chlamydia pneumoniae	*In vitro* study using physiological properdin	Physiological properdin directly binds to *C. pneumoniae* and enhances complement activation on *C. pneumonia*e surfaces as measured with C3 and C9 deposition.	(Cortes, et al., 2011)
Mycobacteria	*In vitro* study, THP-1 macrophage cells and purified properdin from human plasma and recombinant TSR4+5	Properdin and recombinant properdin domain TSR4+5 binds to *Mycobacterium bovis* BCG bacteria, in a dose-dependent manner. Properdin inhibits uptake of *M. bovis* BCG by THP-1 cells mainly via domain TSR4+5. Properdin increases the inflammatory response of THP-1 cells to *M. bovis* BCG, by up-regulating pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) and down-regulating anti-inflammatory cytokines (IL-10 and TGF-β).	(Al-Mozaini, et al., 2018)
Citrobacter rodentium-induced colitis	*C. rodentium*-induced colitis in properdin knockout ($P^{-/-}$) mice and wild type (WT) mice	$P^{-/-}$ mice have exacerbated infectious colitis, reduced IL-6 levels from epithelial cells, and increased bacterial colonization versus WT mice. Injection of exogenous WT serum to $P^{-/-}$ mice re-establishes IL-6 production and ameliorates colonic inflammation and bacterial burden. $P^{-/-}$ mice have reduced C5a production after *C. rodentium*-induced colitis. C5a production is required for protection during *C. rodentium* and production of IL-6 derived from epithelial cells.	(Jain, et al., 2015a)
Streptococcus pneumoniae and *Listeria monocytogenes*	Septicemia models: $P^{-/-}$ and WT mice	In *S. pneumoniae* infection, lack of properdin increases survival and has less severe clinical signs of pneumococcal septicemia despite higher bacteria from blood when compared with WT mice. In *L. monocytogenes* infection, properdin deficiency leads to reduced survival and impaired maturation of bone marrow-derived macrophages and a dendritic cell-like population. $P^{-/-}$ mice have skewed macrophage activity toward M2 phenotype.	(Dupont, et al., 2014)
Septic and non-septic shock	Polymicrobial septic peritonitis in $P^{-/-}$ mice; human serum	$P^{-/-}$ mice have less survival in sub-lethal cecal ligation and puncture-induced polymicrobial sepsis as compared with WT mice. Properdin is produced by connective tissue mast cells. Human serum properdin associates with *E. coli* DH5α.	(Stover, et al., 2008)
	LPS-induced and zymosan-induced shock in $P^{-/-}$ mice	$P^{-/-}$ mice have impaired survival, reduced NO production in peritoneal lavage and plasma C5a, increased TNF-α and decreased IL-10 production by peritoneal macrophages in LPS-induced shock. $P^{-/-}$ mice have more % of survival, reduced NO production in peritoneal lavage and plasma C5a, decreased TNF-α and increased IL-10 production by alveolar and peritoneal macrophages in zymosan-induced inflammation.	(Ivanovska, et al., 2008)
Fungal cell wall	Fungal glycans, zymosan *in vitro* study	Properdin binds to glucan particles and zymosan in a C3-dependent manner leading to AP-mediated complement activation.	(Agarwal, et al., 2011)
Kaposi's sarcoma-associated herpesvirus (KSHV)	*de novo* KSHV infection model; HUVECs *in vitro* study	Extracellular vesicles, which contain C3 and properdin, derived from KSHV-infected HUVECs, promote C5b-9 deposition on HUVECs. Silence target gene expression of properdin via RNA interference in HUVECs reduces C5b-9 deposition during KSHV infection. Complement activation enhances the KSHV-infected cell survival and inhibits viral lytic genes expression by activating the NF-κB pathway.	(Jeon, et al., 2017)

Disease	Study model	Main findings	References
Otitis media and pneumonia	Case study on properdin-deficient patients	Patients with nonfunctional properdin developed recurrent otitis media and pneumonia.	(Schejbel, et al., 2009)
Non-infectious diseases			
Rheumatoid arthritis (RA)	Serum and synovial fluid from RA and osteoarthritis patients	Rheumatoid arthritis patients have decreased properdin, C3 and C5 levels, but increased complement cleavage products (Ba and C3d) levels in synovial fluid as compared with levels in patients with degenerative joint diseases.	(El-Ghobarey and Whaley, 1980)
Arthritis	Collagen antibody-induced arthritis (CAIA) in $P^{-/-}$ mice	$P^{-/-}$ mice have less severe CAIA clinical symptoms, decreased receptor activator of Nuclear factor κ B ligand (RANKL) on neutrophils, reduced $Ly6G^{+}CD11b^{+}$ neutrophils in bone marrow, synovial fluid and blood than of WT. $P^{-/-}$-$CD4^{+}$ T cells in both spleen and blood have reduced expression of IL-17 and IFN-γ than WT. Decreased C5a production was found in synovial fluid of $P^{-/-}$ mice in CAIA, which resulted in reduced numbers of $C5aR^{+}$-bearing neutrophils, in comparison with WT. Reduced tartrate-resistant acid phosphatase osteoclast was found in $P^{-/-}$ bone marrow cells cultures.	(Dimitrova, et al., 2012)
	Zymosan-induced arthritis in $P^{-/-}$ mice	$P^{-/-}$ mice have less cell infiltration and bone erosion during arthritis development as compared with WT mice after intra-articular zymosan injection. $P^{-/-}$ mice have elevated IFN-γ production and STAT1 signaling in popliteal lymph nodes and splenocytes, decreased C5a and IL-6 levels in synovium, and decreased circulating zymosan-specific IgG antibodies than WT mice. $P^{-/-}$ mice have significant proteoglycan loss in the joints, less CD4 staining and more CD5aR staining in the joints as compared with WT mice in chronic phase.	(Dimitrova, et al., 2010)
	K/BxN arthritis mice model; properdin global ($P^{-/-}$) and tissue-specific ($P^{fl/fl}$) mice; *Crry*$^{-/-}$ mice	Properdin deletion protects $Crry^{-/-}$ mouse from AP-mediated embryonic death. $P^{-/-}$ mice have reduced arthritis severity, IL-1β level in ankles and C3 deposition in the joints than WT mice. Exogenous properdin purified from plasma restores arthritis sensitivity. Neutralizing antibodies against properdin ameliorates K/BxN arthritis development. Properdin-derived from bone marrow is responsible for K/BxN arthritis.	(Kimura, et al., 2010)
Neutropenia	Blood from patients undergoing IFN-α therapy	Properdin in plasma is increased in patients undergoing IFN-α therapy. IFN-α stimulates the production of properdin in neutrophils, monocytes and HUVECs. Properdin increases killing of Group-A *Streptococcus* in plasma, and this is reduced by the addition of an anti-properdin neutralizing antibody.	(Uchiyama, et al., 2016)
Asthma	Patients with allergic asthma and rhinitis; $P^{-/-}$ allergic asthma mice model; Properdin monoclonal antibody	Properdin production is increased in bronchoalveolar lavage (BAL) of asthmatic patients and mice challenged with ragweed Ag E and OVA, respectively. Properdin promotes allergen-induced airway inflammation and increases Th2 and Th17 responses. Neutralizing mAb anti properdin is sufficient to reduce OVA-mediated airway inflammation. Exogenous properdin in $P^{-/-}$ mice reestablishes sensitivity to lung injury and inflammation.	(Wang, et al., 2015b)
	Subjects with a confirmed history of seasonal allergic rhinitis	Properdin expression is increased in subjects during late allergic reaction after nasal grass allergen challenge.	(Leaker, et al., 2017)
Colitis	Piroxicam and dextran sodium sulfate-induced colonic injury in IL-10 and properdin double knockout mice ($IL\text{-}10^{-/-}P^{-/-}$)	$IL\text{-}10^{-/-}P^{-/-}$ mice have exacerbated colonic injury both in piroxicam-induced acute colonic injury and DSS-induced chronic injury. $IL\text{-}10^{-/-}P^{-/-}$ mice have reduced numbers of infiltrating neutrophils in the inflamed colon, increased bacterial burden and translocation, which subsequently increased the ability of $CD4^{+}$ T cells to release IFN-γ.	(Jain, et al., 2015b)
Abdominal aortic aneurysm (AAA)	Elastase-induced mice model of AAA; human AAA tissues	On human stained AAA specimens, properdin is observed on all layers of the aortic wall but not in normal individuals.	(Pagano, et al., 2009)
	Elastase-induced AAA in hemizygous properdin-deficient male mice ($P^{-/o}$)	Properdin is required for the development of elastase-induced AAA in mice. Plasma properdin is sufficient for AAA development. The role of properdin in the promotion of AP to	(Zhou, et al., 2012)

Disease	Study model	Main findings	References
		AAA development is to stabilize the AP convertase. Polyclonal rabbit anti-mouse properdin injection prevents AAA phenotype.	
Age-related macular degeneration (AMD)	Choroidal neovascular membranes from AMD patients	Properdin is detected in 50% of choroidal neovascular membranes of AMD patients. Patients with properdin-positive membranes have a longer decreased duration of best-corrected visual acuity (BCVA) and larger atrophic retinal pigment epithelium (RPE) areas than properdin-negative membranes.	(Wolf-Schnurrbusch, et al., 2009)
Cancer	Macrophages from $P^{-/-}$ mice; B16F10 melanoma cell line	Macrophages from $P^{-/-}$ mice shift to M2 phenotype, have increased type II cellular immune responses and decreased MHC-II expression when exposed to B16F10 conditioned medium as compared with macrophages from WT mice.	(Al-Rayahi, et al., 2017)
Transplantation	Biopsies of heart transplantation (HT) patients	More properdin transcripts are detected in Grade 3 biopsies than Grade 0 or 1 heart biopsies from heart transplantation patients.	(Keslar, et al., 2008)
	Patients with heart transplantation	Patients with a properdin nucleotide polymorphism p.Asn428(p=)-*CFP* have higher properdin level as compared with control patients. The increased properdin level is positively associated with antibody-mediated cardiac allograft rejection.	(Carbone, 2017; Marron-Linares, et al., 2017)
Neurological Diseases	Alzheimer's disease (AD) mouse models	Properdin staining is associated with amyloid plaques in the AD mouse models and is also found on the plaques from the $C1q^{-/-}$ AD mice.	(Fonseca, et al., 2011)
Nonalcoholic steatohepatitis (NASH)	Patients biopsies	Properdin accumulates around the areas where steatotic hepatocytes surrounded by neutrophils in NASH while no or little extracellular properdin is observed in healthy livers. Properdin level is positively associated with C3 activation and lobular inflammation.	(Segers, et al., 2014)
Kidney diseases/damage			
IgA nephropathy	Biopsies of IgA-glomerulonephritis patients	Properdin is co-deposited with IgA and C3 in 75–100% of IgA nephropathy patients.	(Maillard, et al., 2015; Rauterberg, et al., 1987)
Membranous nephropathy (MN)	Biopsy from patients with MN; *in vitro* study with HK-2 cell line and proximal tubular epithelial cells (PTECs)	Strong properdin staining is observed on the brush border of tubular epithelium in patients with MN. Properdin purified from human serum directly binds to HK-2 and primary PTECs. Properdin mediates complement activation on HK-2 and on PTECs.	(Gaarkeuken, et al., 2008))
Various kidney diseases	*In vivo* studies with patients with renal diseases and purified properdin	Properdin and MAC levels in urine are significantly higher in patients with renal diseases than normal individuals. High properdin levels are associated with tubular damage markers. Properdin binds to PTECs in a dose-dependent manner. Pre-incubating properdin with PTECs augments complement activation on PTECs.	(Nagamachi, et al., 2014)
C3 Glomerulopathy	Mouse model with reduced FH expression due to a deletion of SCR19–20 ($FH^{m/m}$), $FH^{m/m}/P^{-/-}$ and $FH^{-/-}/P^{-/-}$	The absence of properdin unexpectedly converts mild C3 Glomerulonephritis to severe renal injury in $FH^{-/-}$ and $FH^{m/m}$ mice. $FH^{m/m}/P^{-/-}$ and $FH^{-/-}/P^{-/-}$ mice have increased C3 deposition on glomerular surface.	(Daha, 2013; Lesher, et al., 2013a; Lesher, et al., 2013b; Ruseva, et al., 2013)
	Biological samples from C3G patients	Around 50% C3G patients with low properdin levels have reduced C3 and C5, and increased sC5b-9 plasma levels compared to control groups. Properdin consumption is negatively correlated with high levels of proteinuria.	(Corvillo, et al., 2016)
Renal ischemia reperfusion injury (IRI)	DAF and CD59 double knockout mice ($DAF^{-/-}CD59^{-/-}$) crossed with $P^{-/-}$ mice; mAb against properdin.	$DAF^{-/-}CD59^{-/-}P^{-/-}$ mice have reduced blood urea nitrogen (BUN) level, neutrophil infiltration, and C3 and C9 deposition on kidney as compared to $DAF^{-/-}CD59^{-/-}$ mice. Injection of properdin mAb before, not after IRI, reduces renal IRI in $DAF^{-/-}CD59^{-/-}$ mice.	(Miwa, et al., 2013)
Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)	Clinical study on AAV patients	AAV patients in active stage have lower plasma properdin levels compared with patients in remission and normal controls. Patients at remission stage have higher levels of properdin in plasma than normal controls. Properdin	(Gou, et al., 2013)

Disease	Study model	Main findings	References
		concentration inversely correlates with the proportion of crescents (glomerular lesions) in renal specimens of AAV.	
ANCA-associated glomerulonephritis	Biopsies of patients positive for PR3-ANCA or for MPO-ANCA	Biopsies and immunofluorescence assays to detect properdin deposition show that properdin is associated with higher percentage of cellular crescents, proteinuria, and abnormal glomeruli in patients positive for ANCA. Properdin is more positive in crescentic or mixed renal biopsies than in focal biopsies.	(Hilhorst, et al., 2017)
Cardiovascular diseases or associated cardiovascular factors			
Platelet-leukocyte (PLA)/ Platelet-granulocyte (PGA) aggregates	*Ex vivo* model with human blood	Exogenous properdin, assessed in unfractionated form, and later with P_2-P_4, enhances PLA/PGA formation. Inhibiting properdin impairs thrombin receptor-activating peptide (TRAP)-mediated PGA formation *ex-vivo*, and has the potential to the reduce thrombosis risk associated with high circulating PGA.	(Blatt, et al., 2016b; Ruef, et al., 2008)
Atherosclerosis	$LDLR^{-/-}$ mice crossed with $P^{-/-}$ mice	Properdin deficiency enhances macrophage infiltration in atherosclerotic lesions in male mice fed with a low-fat diet and promotes macrophages shifting to M2 type, resulting in increased atherosclerosis burden in aortae and at aortic root.	(Steiner, et al., 2014)
Heart Failure (HF)	Clinical study on HF patients	HF patients have reduced plasma properdin. Low levels of properdin are associated with increased systemic inflammation and neuro-hormonal deterioration, decreased cardiac function, and increased diastolic dysfunction as compared with HF groups with normal properdin levels.	(Shahini, et al., 2017)
Cardiovascular events	Cohort study in patients with one or more cardiometabolic risk factors	Properdin is positively associated with cardiovascular events (including myocardial infarction, stroke, cardiac angioplasty and/or cardiac bypass), low-grade inflammation and endothelial dysfunction.	(Hertle, et al., 2016)