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Complement in immune and inflammatory disorders: pathophysiological mechanisms

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Abstract

While acute or chronic inflammation is a common component of many clinical disorders, the underlying processes can be highly distinct. In recent years, the complement system has been associated with a growing number of immunological and inflammatory conditions that include degenerative diseases, cancer and transplant rejection. It becomes evident that excessive activation or insufficient control of complement activation on host cells can cause an immune imbalance that may fuel a vicious cycle between complement, inflammatory cells and tissue damage that exacerbates clinical complications. Although the exact involvement of complement needs to be carefully investigated for each disease, therapeutic modulation of complement activity emerges as attractive target for upstream inhibition of inflammatory processes. This review provides an update about the functional and collaborative capabilities of complement, highlights major disease areas with known complement contribution, and indicates the potential for complement as focal point in immunomodulatory strategies for treating inflammatory diseases.

Inflammation is a recognized hallmark of disease, yet the knowledge about underlying mechanism that shape the inflammatory response and its resolution has been largely extended in recent years. Given the classic perception of complement as defense system against microbial intruders, it may appear surprising that this ancient pillar of innate immunity was identified as a contributor in various inflammatory pathologies. On the other hand, it becomes evident that complement not only acts as sensor of pathogens but also recognizes diseased and damaged host cells, and closely collaborates with other immune and defense systems to eliminate potential danger (1, 2). This interplay serves as vital triage system that tailors the immune response according to the threat level. However, insufficient, excessive or poorly controlled complement activation can tip the balance between health and disease and lead to self-attack of host cells (1–3). In the worst case, a vicious cycle between tissue damage, complement activation and immune attack perpetually recreates inflammatory stimulators rather than resolving them. In view of this upstream position in inflammatory homeostasis, there is growing interest in understanding the role of complement in pathological processes and in exploiting complement targets for therapeutic modulation (3, 4). Fortunately, our knowledge about the functions of complement in health and disease has much improved, and new discoveries revealed a fascinating crosstalk network that ties complement closely into the immune-inflammatory network (1, 5). Here we provide an update on complement and its dialog with associated systems, discuss major

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D.R. and J.D.L. are the inventors of patents and/or patent applications that describe the use of complement inhibitors for therapeutic purposes. J.D.L. is the founder of Amyndas Biotherapeutics and Amyndas Pharmaceuticals, which are developing complement inhibitors for clinical applications.

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disease areas and indicate opportunities for therapeutic intervention (see the accompanying review (6) for more).

Complement beyond microbial defense

The past decade revealed a new perception of complement that reaches beyond the elimination of pathogens and includes key functions in immune surveillance, homeostasis, and mediation of inflammatory responses (1, 2). The hub-like organization of complement and its cell-surface-directed action (Fig. 1), involving some fifty constituents such as pattern-recognition molecules (PRM), protein components, proteases, regulators, and cell-surface receptors, is essential for adjusting the complement response to different triggers (Fig. 2A). When faced with foreign intruders, binding of PRM to molecular surface patterns can trigger distinct initiation pathways. In the classical pathway (CP), this is mainly mediated by binding of the C1 complex, consisting of the PRM C1q and the proteases C1r and C1s, to immunoglobulin patches on the pathogen. In the lectin pathway (LP), microbial carbohydrates are recognized by mannose-binding lectin (MBL) or ficolins in complex with MBL-associated serine proteases (MASP). Through activation of C2 and C4, both pathways lead to the assembly of C3 convertase complexes, which cleave the abundant plasma protein C3 into an anaphylatoxin fragment (C3a) and the opsonin C3b. The alternative pathway (AP), is induced by conversion of C3 to its hydrolyzed form C3(H_2O), either spontaneously at a low rate in solution or accelerated by contact of C3 with various surfaces (tick-over (7)), which leads to the formation of initial AP C3 convertases. Once C3b is deposited on target surfaces, it promotes amplification of the response via the AP by forming additional C3 convertases via a tiered mechanism that involves binding of factor B (FB) and proteolytic activation by factor D (FD) to result in the C3bBb complex (8). Properdin (factor P; FP) further supports AP-mediated amplification by stabilizing the C3bBb convertase. Continuous deposition of C3b favors generation of C5 convertases that convert component C5 into C5b, which initiates formation of membrane attack complexes (MAC; C5b-9) that lyse susceptible cells (*e.g.,* Gram-negative bacteria). Cleavage of C5 releases the chemokine C5a that, together with C3a, attracts immune cells to sites of activation via binding to the anaphylatoxin receptors C5aR (CD88) and C3aR, respectively. Carboxypeptidases rapidly convert C3a and C5a into their desarginated forms, resulting in a shift in their activity/specificity profiles. Phagocytic cells recognize C3b-opsonized surfaces via complement receptor 1 (CR1; CD35), which facilitates phagocytosis and mediates the degradation of C3b to iC3b, C3c and C3dg by factor I (FI). Whereas iC3b is the primary ligand for the integrin receptors CR3 (CD11b/CD18) and CR4 (CD11c/CD18), both iC3b and C3dg also interact with CR2 (CD21) that is part of the B cell co-receptor complex and reduces the threshold of B cell activation. Additional receptors for C3b/iC3b (*i.e.,* CR of the immunoglobulin superfamily; CRIg) and for C1q (*e.g.,* gC1qR) also participate in the recognition and elimination of opsonized cells. While host cells are probed by a constant low level of AP activation (referred to as “tick-over” mechanism), they express membrane-bound regulators of complement activation (RCA) that either destabilize convertases (CD35, CD55) or act as cofactors for the FI-mediated degradation of C3b to iC3b (CD35, CD46) and C3dg (CD35) and of C4b to iC4b (CD35, CD46) (1, 9). In addition, the soluble RCAs C4b-binding protein (C4BP) and factor H (FH) recognize host cell-surface patterns and contribute to the regulation of the CP/LP and AP convertases, respectively. Finally, the membrane regulator CD59 and soluble vitronectin and clusterin prevent MAC formation on host cells. Apoptotic cells induce yet another response that lies in between that observed for foreign and host cells; while the recognition of surface modifiers on apoptotic cells by PRMs induces opsonization, the presence of RCA prevents excessive amplification and, consequently, the generation of C5a or MAC. Thereby, complement facilitates the elimination of apoptotic cells, immune complexes and cellular debris without inducing inflammatory triggers (Fig. 2B) (1).

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While complement was first described decades ago, recent discoveries have challenged key concepts, revealed new players and redefined roles for established ones. For example, pentraxins were identified as mediators of complement activation (10), properdin was attributed PRM functionality (leading to AP initiation by recruiting C3b from the plasma pool to the surface) (11), and C5L2 (GPR77) was classified as an anaphylatoxin receptor, though its functional implication is still under investigation (12). The LP recently gained interest due to the discovery of new PRM (*e.g.,* PTX3), regulators, and bypass routes that contributed to our understanding of this pathway and to the identification of therapeutic targets and templates (13, 14). In addition, LP components have been associated with a role in AP modulation, as MASP-1 was shown to mediate the maturation of FD from its inactive pro-form in mice and *in vitro* (15). Finally, the contribution of central (*i.e.*, hepatic) versus peripheral complement production (*e.g.*, by migratory and tissue-resident cells) in complement-driven pathologies is increasingly investigated, particularly in the context of transplantation (16).

Yet it is the discovery of the dialogue between complement and other physiological systems that has profoundly changed how we perceive complement as inflammatory mediator and therapeutic target (1). For example, it is evident that during injuries and certain disease conditions, complement and coagulation act in a concerted manner (17). While some coagulation enzymes directly cleave and activate C3 or C5 (18), thereby bypassing traditional initiation pathways, the products of such activation may themselves influence coagulation as shown for the stimulation of tissue factor expression by C5a (19). The LP may also play a linking role as MASP-2 can activate prothrombin and induce clot formation, while MBL and ficolins were described to bind fibrinogen and fibrin (20, 21). Furthermore, there are links between platelet activation and the activity of complement and contact systems through an interplay involving hydrolyzed C3, RCA, chondroitin sulfate, P-selectin, gC1qR and other components (22). Although complement and the Toll-like receptors (TLR) have both been described as ‘first line of defense’ systems, it is only recently that the extent of cooperation between these two pathways has been realized. The crosstalk between TLR, CD14 and MyD88 on the Toll side and complement components including C5aR, CR3, CD46, CD55 and gC1qR is important for antimicrobial defense but also contributes to inflammatory disorders (23). Despite its classification as a part of humoral innate immunity, complement strongly mediates adaptive and cellular immune responses. The role of complement in the stimulation and maturation of B cells via CD21 is well described and critically contributes to autoimmune and other diseases (24). Our knowledge about the crosstalk between complement and T cells, however, is still unfolding (25). Complement appears to modulate T cell immunity during induction, contraction and effector phases by acting directly on T cells or by affecting antigen-presenting cells (APC). The interaction between T cells and APC induces a concerted reaction (enhanced secretion of C3, FB, FD and C5 with downregulation of CD55) that favors complement activation on immune cells, local generation of C3a and C5a, enhanced T cell proliferation, and cytokine release on APC that provokes a shift towards Th1 immunity (25). Moreover, CD46 has been identified as a central element in the IL2-dependent transformation of Th1 cells into a regulatory state (25), and C5aR and CD46 signaling have been associated with the function of γδT-cells (26, 27). New insight was also achieved concerning the cooperation between complement and Fcγ receptors (FcγR) in the removal of immune complexes (IC). For example, a positive feedback loop has been reported, in which C5aR stimulation promotes the expression of activating FcγR; binding of autoantibodies induces the local secretion of C5 by activated cells, thereby increasing the generation of C5a and, consequently, C5aR signaling (28). More recently, a negative feedback mechanism has been discovered, in which high-galactose IC bridge inhibitory FcγRIIB and the lectin receptor dectin-1 to induce signaling that counteracts C5aR-mediated responses (29, 30). Finally, complement was shown to modulate the activities of other key players of cellular immunity such as NK and NKT cells

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(31), myeloid-derived suppressor cells (32), or mast cells (33). These observations underscore the importance of complement in physiological processes but also explain why dysregulation of the complement system may result in far-reaching clinical consequences.

A balancing act between health and disease

Though complement is considered a 'master of sensing' that discriminates between foreign, altered and healthy self surfaces, several triggers may lead to a dysfunctional triage of potential danger (Fig, 2B). Dysfunctions, deficiencies or polymorphisms of complement components are often factors that tip the balance (3), but tissue damage or confrontation with non-self surfaces (*e.g.,* biomaterials, transplants) can also lead to excessive activation. Importantly, disruption of the complement balance with increased production of effector molecules may trickle down the immune system and contribute to autoimmune, inflammatory, degenerative, hematological, and ischemic disorders. Despite the variety of disease manifestations, the involvement of complement typically follows a common scheme that involves the recognition of potential (though not always "real") danger patterns, an insufficiently controlled amplification loop, and the stimulation of downstream inflammatory responses. The activated immune system, in addition to complement attack itself, may exacerbate the problem by further disrupting tissue integrity and creating additional danger patterns, thereby fueling a vicious cycle between complement activation, immune stimulation and inflammation. What varies between individual disorders, however, are the triggers, dynamics, extent and localization of complement involvement.

In the case of **age-related and degenerative diseases**, it is the slow but steady accumulation of debris that can act as a promoter. While disease etiologies are often complex, the "fitness" of the complement system is considered a key determinant in how fast a symptomatic threshold is reached. Age-related macular degeneration (AMD), a degenerative eye disease and major cause of blindness in elderly people, has evolved into a focal point of complement drug discovery. Initiated by the discovery of complement proteins in the characteristic subretinal drusen deposits and strong disease correlations with polymorphisms in FH, research has meanwhile identified additional genetic associations (*e.g.*, C3, FB) and established an imbalanced complement system as key contributor to the development of both geographic atrophy (dry AMD) and choroidal neovascularization (wet AMD) (34). While questions about disease triggers and the role of systemic versus locally produced complement remain controversial (35), a recent study suggested a contribution of the oxidative stress adduct malondialdehyde as initiator and provided a functional explanation about the disease correlation of the FH Y402H polymorphism (36). Although complement inhibition at various levels has shown promise in models of AMD, the translation into a clinical application has proven challenging. Another age-related disease that gained interest is Alzheimer's disease (AD), especially after genome-wide association studies (GWAS) revealed disease correlations with CR1 and clusterin (37). Indeed, the importance of locally synthesized complement in the brain becomes increasingly evident and encompasses physiological functions such as synapse formation but also inflammatory roles in trauma, stroke and AD (38). For example, accumulation of amyloid proteins in AD was shown to trigger complement primarily via C1q-mediated CP activation; the role of the AP, and the contribution of individual pathways, may vary in different models of AD and requires further examination (38, 39). The C5a-C5aR axis seems to play an important role in this neuropathology by modulating inflammatory responses, and C5aR antagonists have shown beneficial effects in AD models (38, 40).

For reasons not fully resolved, the kidney appears to be particularly susceptible to complement attack, and several **glomerular diseases** show strong correlation with disturbed AP activity (41). In atypical hemolytic uremic syndrome (aHUS), a rare disease

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characterized by hemolytic anemia, thrombocytopenia and renal impairment, complement polymorphisms (*e.g.,* FH, CD46, C3), deletions (*e.g.,* FH-related proteins; FHR) or autoantibodies (*e.g.,* against FH) can cause perpetual self-attack (41, 42). More recently, two other forms of thrombotic microangiopathies, *i.e.,* hemolytic uremic syndrome caused by Shiga toxin-producing *E. coli* (STEC-HUS) and thrombotic thrombocytopenic purpura (TTP), have been more closely linked to AP activation via mechanisms involving P-selectin and platelet thrombi, respectively (43). While dysfunctional AP activity is a driving force of these diseases, activation of C5 appears to be fueling the cycle by causing endothelial cell damage. Indeed, C5-targeted inhibition has shown promising effects in these disorders, and Eculizumab has meanwhile been approved for the treatment of aHUS (44). Another series of kidney disorders characterized by dense renal deposits of C3 in the absence of CP markers have recently been classified under the name *C3 glomerulopathy* and include dense deposit disease (DDD) and CFHR5 nephropathy, among other forms (41).

Disruption or exhaustion of complement-mediated clearance of immune complexes and apoptotic cells, and of its bridging to adaptive immunity, are contributing factors of **autoimmune diseases**, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) or antiphospholipid antibody syndrome (APS) (45, 46). Bidirectional crosstalk between complement and Fcγ R appears to be of particular importance in this disease class as they cooperate in shaping B cell responses (47). The participation of complement pathways and components may differ considerably. In SLE, CP activation and complement consumption by autoimmune complexes can be influenced by autoantibodies against C1q or deficiencies in CP components, whereas AP involvement appears to be more prominent in the case of RA. Finally, certain forms of anti-neutrophil cytoplasmic antibody (ANCA)-induced vasculitis, inflammatory small-vessel disorders caused by autoantibodies against neutrophil constituents, were linked to complement: When affected vascular endothelial surfaces trigger complement activation, the generated C5a attracts and primes neutrophils, which in turn adhere to the endothelium. Primed neutrophils express antigens that are recognized by ANCAs, which leads to their activation and release of factors that induce cell damage, thereby fueling an amplification cycle that culminates in necrotizing inflammation (48). C5aR-directed therapy has shown success in a glomerular ANCA vasculitis model (49) and drugs blocking at the level of C5 or C5aR are currently evaluated.

Some autoimmune diseases also impose a higher risk for developing **pregnancy-related complications**, and important roles have been revealed for complement in both healthy and pathological pregnancy (50). Whereas complement is important for the protection of mother and fetus from pathogens, pregnancy also seems to be a state particularly vulnerable to excessive complement activity (50). For example, complement is suspected to be a major factor in both antibody-dependent (*i.e.,* in women with APS) and –independent pregnancy loss, via mechanisms that likely involve C5a-mediated impairment of placental angiogenesis. Similar dysregulation of angiogenesis may also be involved in preeclampsia, a major pregnancy complication characterized by sudden onset of hypertension and proteinuria. In contrast to C5a signaling, which is considered a detrimental factor in the etiology of preeclampsia, C1q has recently been attributed a preventive role against abnormal placentation in a mouse model of the disease (51). Finally, complement activation was found significantly elevated in preterm birth, and complement activation products such as Bb or C3a have been described as predictive markers of preterm delivery; however, it is not yet clear whether and under which circumstances complement activation is a contributor to or a consequence of events leading to premature delivery (50). While complement therapeutics have shown encouraging effects in models of pregnancy disorders (52–54), the translation into the clinic is often challenging when involving pregnant patients.

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Whereas the lytic power of complement on most eukaryotic cells is restricted, erythrocytes are comparatively susceptible to MAC attack, and several **hemolytic disorders** have ties to complement (55). In paroxysmal nocturnal hemoglobinuria (PNH), a somatic mutation disables the synthesis of glycosyl-phosphatidylinositol anchors and prevents the expression of CD55 and CD59 on mature blood cells. As erythrocytes naturally lack CD46, PNH erythrocytes show a very low capacity for complement regulation and are prone to intravascular lysis with severe hemolytic and thrombotic consequences. Whereas treatment of this orphan disease has long been limited to transfusion and allogeneic stem cell transplantation, the introduction of Eculizumab to the clinic has drastically changed disease management; nevertheless, complement inhibition at the level of C5 appears not to be sufficient for all patients and inhibitory strategies that act on the C3 level are currently considered (55). In addition to PNH, complement-mediated hemolysis is also observed in aHUS (see above), and in cold-agglutinin disease (CAD), in which IgM autoantibodies against certain erythrocyte antigens bind at low temperature (i.e., mainly in peripheral capillaries) and lead to CP activation and lysis (55).

Ischemic diseases constitute another widespread pathological area in which complement is integrally involved. **Ischemia-reperfusion injury** (IRI) occurs when blood flow to tissue is restored after a prolonged time of occlusion, and is relevant in clinical conditions ranging from stroke and myocardial infarction to trauma, sepsis, shock and cardiopulmonary bypass (CPB) surgery (56, 57). The pathological mechanisms behind IRI are multifactorial and complex, and current models suggest that the ischemic phase leads to cellular changes, exposition of neoepitoes, adhesion of polymorphonuclear cells, release of cytokines and production of reactive oxygen species that can trigger apoptosis and necrosis; reperfusion, on the other hand, is characterized by leukocyte adhesion and increased permeability. Complement is considered to be involved in aspects of both phases from the recognition of neoepitopes with subsequent opsonization and amplification to the C5a-mediated modulation of cellular responses and upregulation of adhesion molecules. While the exact contribution of individual complement pathways may vary depending on the model or disorder, recent studies have reemphasized the importance of the LP, and in particular the MBL:MASP-2 complex in complement-mediated effects of IRI (56, 57).

IRI is also a major and inevitable contributor to **transplant-related complications**, especially when organs are transplanted after circulatory arrest of the donor, which can lead to the induction of IRI as described above (16). In addition to the chemotactic and inflammatory effects of C5a, deposition of sublytic MAC has also been shown to induce direct cell activation with release of mediators such as IL-6 or TNF. Importantly, complement activation is a major culprit in allograft rejection, via direct tissue damage or by shaping the alloreactive T cell response. Peripheral synthesis of complement components by the donor organ has a strong impact in this context. Both the production (via B cell-costimulation) and effect of alloantibodies (via CP/LP activation) are complement-driven events in antibody-mediated rejection (AMR) (16). In the case of Langerhans islet transplantation in diabetic patients, the occurrence of a thromboinflammatory response known as ‘instant blood-mediated inflammatory reaction’ is caused by rapid complement activation and limits transplantation efficiency due to islet destruction (58). A particularly interesting, yet still incompletely understood, phenomenon in the context of transplantation is accommodation, in which transplant cells become ‘resistant’ to complement-mediated destruction; the promise of therapeutic complement inhibition for inducing accommodation of renal allografts was shown both for C5 inhibition (59) and after C3 depletion via cobra venom factor (60) in mice and non-human primates, respectively. Yet transplants are not the only non-self surfaces that trigger defense responses by complement and coagulation; products of modern medicine such as biomedical devices and implants, drug delivery vehicles, extracorporeal circuits and other artificial materials can all induce **biomaterial-**

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induced thromboinflammatory reactions (61). Such incompatibility responses are known to influence the outcome of CPB surgery, during which circuit materials, blood/air interfaces in the oxygenator, activated platelets, and protamine complexes (generated to neutralize soluble heparin at the end of the procedure) can activate complement and contribute to systemic inflammatory response syndrome (SIRS; see below) (61, 62). Despite moving out of the spotlight of complement-targeted therapy after years of clinical evaluation with soluble CR1 and anti-C5 antibodies (63, 64), CPB surgery remains a clinical problem and a promising indication for complement therapeutics (62). Another emerging area is hemodialysis; even modern dialyzer membranes activate complement significantly and contribute to perpetual inflammation in patients suffering from end-stage renal disease; therapeutic C3 inhibition was shown to prevent complement activation and reduced markers of immune cell activation, inflammation and coagulation (65, 66). Alongside soluble inhibitors, the coating of materials with passive (*e.g.*, polyethyleneglycol) or active (*e.g.*, FH-binding peptides) moieties is considered an attractive strategy (61, 67).

Other **inflammatory diseases** with complement contribution include allergic asthma and periodontitis. The ties between complement and asthma have long been recognized, yet the involvement appears to be complex. Under asthmatic conditions, complement is not only activated through the CP via allergen-antibody complexes but C3 and C5 might also be cleaved by proteases derived from certain allergens (*e.g.*, house dust mites). The resulting C3a and C5a act synergistically in creating a proallergenic immune environment, yet C5a may also protect from maladaptive Th2 immunity during allergen sensitization (68). An important yet complex role in asthma has also been attributed to C5L2 (69). Whereas previous therapeutic attempts focused on C5aR, the scope has recently been expanded to include inhibitors at the levels of C5 and C3 (68). Relatedly, C5a has also been implicated in the exacerbation of chronic obstructive pulmonary disease (70). Though an involvement of complement in periodontal disease was proposed before (71), the intricate mechanisms behind the pathogenesis of periodontitis have only recently been revealed. In this biofilm-driven chronic inflammatory disease that leads to progressive bone loss of the teeth, an intense dialogue between complement effectors and receptors (C5aR, CR3), the TLR system (TLR4, CD14) and the oral microbiome with its keystone pathogen *Porphyromonas gingivalis* shapes the disorder (72). As C5a signaling is at the center of immune evasion and inflammatory activities, C5aR-directed therapies have been evaluated and shown encouraging results (73, 74). Finally, complement-mediated processes have been recognized critical for bone-related disorders and injury (*e.g.,* via anaphylatoxin effects on osteoclast formation), thereby suggesting another potential indication area for complement therapeutics (75).

Perhaps the most severe effects of complement activation are seen in **acute-phase conditions**, often associated with SIRS (see above), in which the host is confronted with a dramatic increase of damage- and/or pathogen-associated molecular patterns (76). In trauma, for example, the initial traumatic impact combined with posttraumatic IRI can trigger a devastating cascade of immuno-inflammatory reactions with complement contribution, which may sustain SIRS (77). As a complication of trauma, or as an independent incident, massive infection may overwhelm the protective functions of complement and other innate immunity components (*e.g.*, TLR) and provoke sepsis (78). The early pathogen-induced hyperinflammatory response with complement and immune cell activation, a cytokine storm and coagulopathy may result in SIRS and persist even after the pathogen is cleared; C5a-dependent signaling seems to be a major player in those devastating events. Independent of the trigger, SIRS can induce secondary tissue damage, multi-organ failure and, ultimately, death (76–78). Despite the prevalence and severity of sepsis, treatment of this condition has proven to be difficult, though complement therapies at the level of initiation (*e.g.*, C1-INH),

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amplification (targeting C3) or signaling (blocking the C5a-C5aR axis) have shown promising results.

While complement plays a dual role in many diseases, the dilemma between beneficial and adverse effects is especially pronounced in **cancer** (79). On the one hand, complement may recognize altered surface pattern and attack cancer cells. Complement can also be therapeutically engaged for the killing of tumor cells via complement-dependent cytotoxicity (CDC); for example, antibodies directed against the surface antigen CD20 that is statically expressed on mature and malignant B cells, induce a CP-mediated complement attack and trigger FcγR activation and other mechanisms that lead to cell death, thereby making them valuable tools for the therapy of lymphoma or certain autoimmune disorders when applied in a well-adjusted dose regimen (80, 81). On the other hand, tumor cells may increase the expression of complement regulators as evasion mechanism, and strategies to increase the efficiency of CDC via regulator-specific inhibitors or knock down via siRNA have been investigated (82). Importantly, though, complement appears to be more intricately involved in tumor progression than originally anticipated, with several studies demonstrating that complement activation and release of C5a may actually create a more favorable environment for tumor growth by shaping immune cell populations and/or angiogenesis in certain cancer models (32, 83, 84).

Conclusions

The progression in GWAS, the availability of improved disease models, and the unprecedented insight into molecular details of humoral and cellular immunology have changed our perception of the role of complement in health and disease. While complement-mediated pathologies so far have often been looked at in an isolated manner, common pattern within a wide spectrum of disease forms begin to emerge. In this context, the importance of the intense crosstalk between complement and other physiological systems and the interplay between complement, infection, immunity, and inflammation has become particularly evident. In view of the upstream and mediating position of complement in inflammatory events, it is expected that the list of diseases with association to imbalanced complement will continue to grow in the years to come. Unquestionably, complement may not be the main driving force in some of these disorders, yet may still be a critical factor that can tip the balance between induction and resolution of inflammation. Even in knowledge of strong complement involvement and with identified risk genes, the translation into disease mechanisms or even therapeutic strategies may remain challenging, as the case of AMD has shown. Profound investigation of involved triggers and complement pathways in each disease, and a holistic interpretation in the context of inflammation and immunity will be required to rapidly achieve clinical benefit. Fortunately, an impressive body of research in recent years has created a broad arsenal of complement inhibitors that can be used to dissect molecular pathways but may also pave the way to complement-targeted immunomodulatory therapies (see accompanying review (6)).

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Abbreviations used in this article

AD	Alzheimer's disease
aHUS	atypical hemolytic uremic syndrome
AMD	age-related macular degeneration
ANCA	anti-neutrophil cytoplasmic antibodies
AP	alternative pathway
APC	antigen-presenting cells
APS	antiphospholipid antibody syndrome
C3aR	C3a receptor
C4BP	C4b-binding protein
C5aR	C5a receptor
CAD	cold agglutinin disease
CPB	cardiopulmonary bypass
CDC	complement-dependent cytotoxicity
CP	classical pathway
CR	complement receptor
CRIg	complement receptor of the immunoglobulin superfamily
DDD	dense deposit disease
FB	factor B
FD	factor D
FH	factor H
FI	factor I
FP	properdin
GPI	glycosylphosphatidylinositol
IC	immune complex
IRI	ischemia/reperfusion injury
LP	lectin pathway
MAC	membrane attack complex
MASP	MBL-associated serine proteases
MBL	mannose-binding lectin
PNH	paroxysmal nocturnal hemoglobinuria
PRM	pattern-recognition molecule
PTX	pentraxin
RA	rheumatoid arthritis
RCA	regulator of complement activation
SIRS	systemic inflammatory response syndrome

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SLE	systemic lupus erythematosus
STEC	shiga toxin-producing E. coli
TLR	Toll-like receptor

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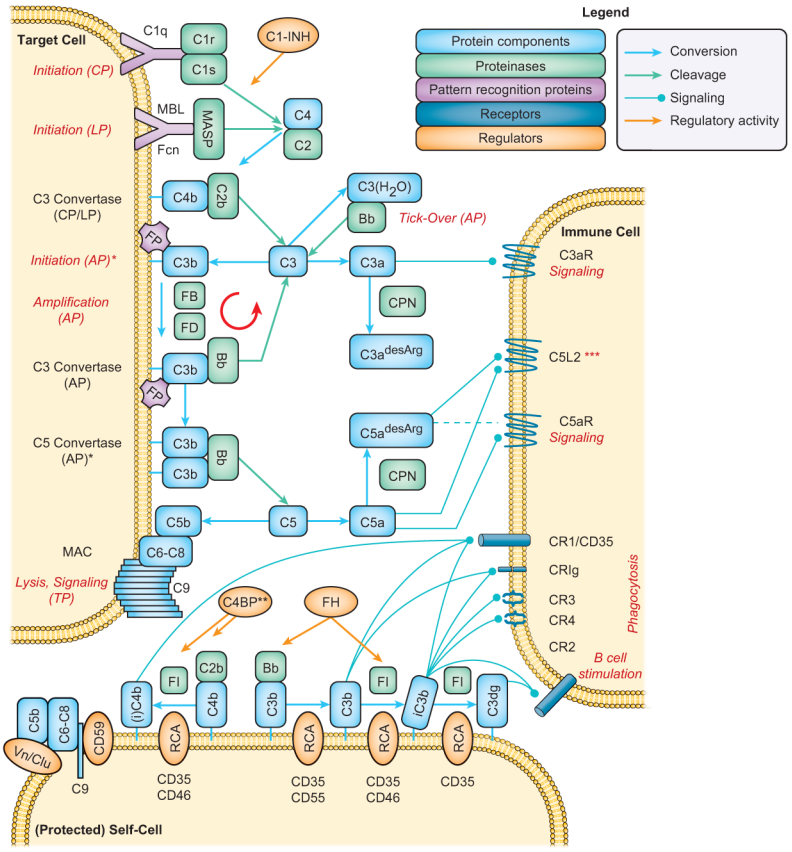

FIGURE 1.

Simplified scheme of the complement activation network. *Only part of the functional spectrum of properdin (FP) is visualized: FP may act as pattern recognition molecule and recruit C3b from plasma to the target surface (AP initiation); in addition, it stabilizes both the AP C3 and C5 convertases. Only the AP C5 convertase (C3bBb3b) is shown; a CP/LP C5 convertase (C4b2b3b) is also formed. **The regulation of the CP/LP C3 convertase is depicted a one-step process but follows a two-step mechanism similar to C3b, including decay acceleration (C4BP, CD35) and FI-mediated degradation to iC4b (C4BP, CD35, CD46). ***The function of C5L2 is not fully described and may be content-specific; C5a and C5a-desArg bind equally well to C5L2 whereas their binding and signaling profiles on C5aR is distinct. The binding of C3a-desArg to C5L2 remains controversial. Abbreviations: AP, alternative pathway; C1-INH, C1 inhibitor; C3aR, C3a receptor; C4BP, C4b-binding protein; C5aR, C5a receptor; C5L2, C5a receptor-like 2; Clu, clusterin; CP, classical pathway; CPN, carboxypeptidase-N; CR, complement receptor; FB, factor B; Fcn, ficolins; FD, factor D; FH, factor H; FI, factor I; LP, lectin pathway; MAC, membrane attack complex; MASP, MBL-associated protease; MBL, mannose-binding lectin; RCA, regulator of complement activation; Vn, vitronectin.

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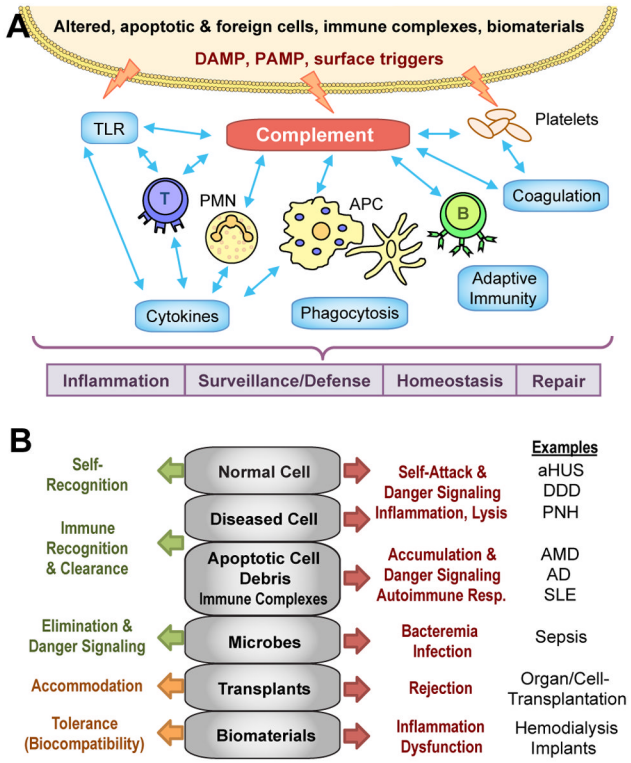

FIGURE 2.

(**A**) Triggered directly by foreign and altered surfaces, the complement network resides upstream of most defense and homeostatic systems, thereby acting as an important mediator in physiological and pathophysiological processes. Abbreviations: DAMP, damage-associated molecular patterns; PAMP, pathogen-associated molecular pattern; PMN, polymorphonuclear cells; TLR, Toll-like receptor. (**B**) While complement-mediate immune surveillance and mediation usually provides adequate physiological response (green arrow) to distinct surfaces (grey), any excessive trigger or inadequate regulation (*e.g.,* due to deficiencies or polymorphisms) may lead to pathophysiological reactions (red arrow) that require therapeutic intervention. In the case of foreign surfaces (*i.e.,* transplants, materials), complement-targeted modulation (orange arrow) may improve tolerance and compatibility. Abbreviations: AD, Alzheimer's disease; aHUS, atypical hemolytic uremic syndrome; AMD, age-related macular degeneration; DDD, dense deposit disease; PNH, paroxysmal nocturnal hemoglobinuria; SLE, systemic lupus erythematosus.