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REVIEW ARTICLE

Complement regulation and kidney diseases: recent knowledge of the double-edged roles of complement activation in nephrology

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Abstract The complement activation system plays important roles to maintain homeostasis in the host and to fight foreign invaders to protect the host. Therefore, the complement system is considered a core part of innate immunity which also cross-talks to acquired immunity. In the history of nephrology, the complement system is familiar to us, because complement protein or fragment deposition, including C3, C4, C1q, and/or C4d, is routinely estimated by immunohistochemistry to diagnose renal pathologies. The relationships between pathological mechanisms and complement activation have been investigated for renal diseases such as post-infectious glomerulonephritis, lupus nephritis, and primary membranoproliferative glomerulonephritis, which are usually accompanied by hypocomplementemia. However, unregulated complement activation in local areas might be associated with progression of various renal injuries even in the normocomplementemic patient. Recently, attention has focused on dysfunction of complement regulation in various diseases including renal diseases such as atypical hemolytic uremic syndrome and C3 glomerulopathy. Some mechanisms associated with complement activation in these diseases were clarified. In addition, lots of anti-complement agents were developed and some of the agents have become clinically available. Now, anti-complement therapies represent a realistic choice of therapeutic approaches for complement-related diseases. Research on roles of complement activation is proceeding into new stages in the field of nephrology and in other fields involving both basic and clinical research. We herein summarize relationships between the complement activation and regulation systems, their physiological effects and roles in maintenance of homeostasis in the host, and how dysregulation of the complement system triggers disease, especially renal disease.

Keywords Complement · Complement regulator · Complement dysregulation

Introduction

Originally, the roles of the complement (C) system have been known as opsonization to scavenge foreign invaders such as microorganisms, fragments of damaged tissues and pathological immune-complexes, chemoattractant effects causing vasodilation and infiltration/accumulation of inflammatory cells, induction of inflammatory cytokines, and cell lysis of foreign and damaged cells through triggering processes of necrosis and apoptosis [1–3]. These roles are positioned to have important roles in innate immunity, the second defender of the host, after breaching of the first defense of epithelial layers such as skin, to protect the host from various physical stresses. In addition, it was recently shown that the C activation system was in close cross-talk with acquired immunity, the third arm of host defense. Now, in addition to roles in innate and acquired immunity, the relationship between the C and coagulation systems is also realized. From these multiple lines of evidence, it is clear that the C system is one of the most important systems to maintain the host homeostasis.

The C system is constructed from three activation pathways, the classical pathway (CP), the alternative pathway (AP), and the lectin pathway (LP), that each form C5

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convertase enzymes and initiate the terminal pathway (TP) leading to formation of the lytic membrane attack complex (MAC; C5b-9; terminal complement complex; TCC). Historically, the CP was first recognized, followed by the AP and the LP. Although the CP is present in Reptilia/Aves and Mammalia, C3- and the AP-associated proteins are already expressed in primitive animals such as Echinodermata, Protostomia, and Cnidaria during animal evolution [4]. Indeed, parts of the AP were already constructed 1000 million years ago [4]. The CP is now considered to be the most recently evolved C activation pathway.

C activation has the capacity to damage the host, particularly when occurring through the AP which has limited capacity to distinguish targets from the host. Therefore, there are multiple mechanisms to regulate unexpected activation of the C system mediated by an array of C regulators (CReg). However, it has also been clarified that some of these C regulators have additional roles beyond regulation of C activation.

Here, we briefly summarize C activation and regulation, describe recent knowledge about bridging to acquired immunity, discuss aspects of CRegs, and cross-talk to the coagulation system. We also describe pathological conditions related to uncontrolled activation of C system and renal injuries.

The pathways of C activation, classical roles as a part of innate immunity

The C system comprises the three activation pathways, the TP, and the regulation system. The three C activation pathways, CP, AP, and LP, consist of enzymatic cascades through to the cleavage of C5, whereas the TP leading to formation of the MAC does not involve enzymatic processes (Fig. 1). The CP is initiated by the binding of C1q to the activating surface. Surface-bound C1q binds antibody attached to particulate antigen but can also bind many other ligands antibody-independently such as components of damaged cells, bacterial lipopolysaccharide, and nucleic acids. C1q is complexed with C1r and C1s; these confer enzymatic activity for cleavage of C4 and C2 to create the C3 convertase, C4b2a and, after addition of C3b, the C5 convertase, C4b2a3b. The AP activates the C pathway in an antibody-independent manner and amplifies C activation on foreign surfaces. An important characteristics of the AP is that it is spontaneously initiated by the phenomenon of "tickover" to generate $C3(H_2O)$ which binds factor (F) B to make a C3 convertase, $C3(H_2O)Bb$, in the fluid phase, ensuring that C is always in a "ready-to-fire" situation. The LP differs from the CP only in that mannose-binding lectin (MBL) and its associated serine proteases (MASPs) in an MBL-MASP complex replace the C1qrs-complex. MBL
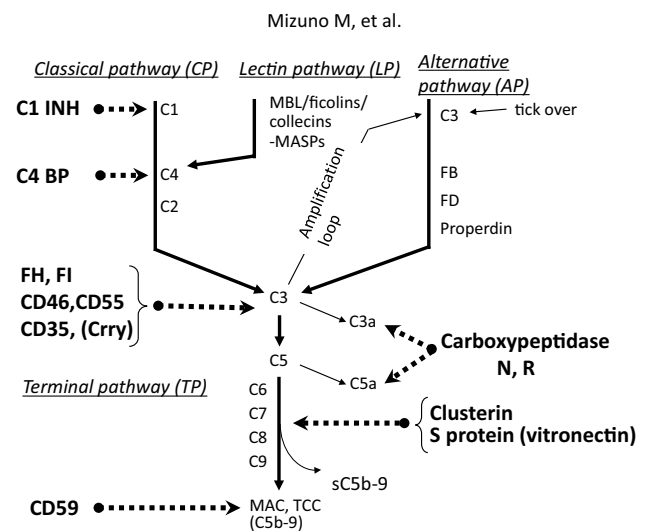

Fig. 1 Pathways of the complement activation system and points of the regulation. Activation of the complement system is three early pathways of the classical pathway (CP), the alternative pathway (AP), and the lectin pathway (LP). These three pathways gather to form C3 convertases following C5 convertases and formation of membrane attack complex [MAC, terminal complement complex (TCC), C5b-9] which following pathway is called as the terminal pathway (TP). *C1-INH* C1 inhibitor, *C4BP* C4 binding protein, *FH* factor H, *FI* factor I, *FB* factor B, *FD* factor D, *MBL* mannose-binding lectin, *MASP* MBL-associated serine protease

binds to mannose-rich microbial surface and is complexed with MASPs 1, 2, and 3 that collaborate to enzymatically cleave later components [5]. In addition, ficolin-1 (M-ficolin), ficolin-2 (L-ficolin), ficolin-3 (H-ficolin, Hakata antigen), collectin-10 (CL-10, CL-L1), and collectin-11 (CL-11, CL-K1), which also have a collagen-like triple helix structure similar to C1q molecule, can activate LP [6]. They gain enzymatic activity by complexing with MASPs, similar in structure to the C1qrs-complex. Interestingly, it was recently reported that the LP might be related to activation of AP. MASP 1/3 cleaves pro-FD into FD which then activates the AP through cleavage of FB to generate the C3bBb C3 convertase of the AP [7, 8]. The three activation pathways form C3 convertases and subsequently C5 convertase, hence converging in the TP to form MAC on the targeted cell surface.

The MAC comprises a complex of the C proteins C5b to C9; MAC makes holes in the cell membrane and induces targeted cell lysis. This mechanism is very effective to kill foreign invaders such as microorganisms and malignant cells. However, it was recently reported that sublytic MAC worked as a costimulatory molecules to polarize naïve T-cell to Th1-cells [9], to stimulate production of arachidonic acids, IL-1, and TNF-α from renal tubular epithelial cells [10] and to repair/regenerate Schwann cells and glia cells [11]. A detailed 3D MAC structure was recently

published, showing the association of C5b, C6, C7, C8α, β, γ, and 18 molecules of C9 in the complex, and that the formed hole size is variable and approximately 240 Å in the targeted cell membrane [12].

During C activation, the anaphylatoxins C3a and C5a are produced. Although C3a and C5a are well known to play roles as strong chemotactic factors [13], C5a acting through C5a receptor (R) was shown to be neuroprotective by inhibiting apoptotic cell death [14], cause regeneration of liver cells, accelerate fracture healing, and reduce post-injury neural damage [3, 15–17]. It was also suggested that C3a and C5a have opposite effects on the disease process in endotoxin shock [18].

C regulation

The C system can behave as a double-edged sword, both protective and also harmful in the host. Because of this potential to cause harm, the activation cascade of the C system is controlled by many CRegs to maintain homeostasis in the host. The C activation is mainly regulated at the steps of formation of C3 convertase to control all three pathways of C activation, and during formation of MAC. There are multiple CRegs both in the fluid phase and on surfaces (Table 1). Exceptionally, only C1 inhibitor (C1-INH) inhibits the CP at the level of formation of the C1qrs-complex. Interestingly, FH is an abundant protein in serum as a fluid phase CReg at the C3 converse level, but also plays roles

as a CReg on surfaces [19, 20]. FH is a multifunctional CReg, having cofactor activity to work with FI and convertase decay accelerating activity [21]. C4-binding protein (C4BP) which is a ~500 kDa large glycoprotein binds C4b and C3b and inhibits the C activation through decay acceleration of the CP C3 convertase, C4b2a, and as a cofactor for FI cleavage of C4b [19].

CRegs at the C3 convertase level on surfaces include C receptor (CR) 1, CD46, and CD55, together called membrane CRegs; in mouse and rat, Crry is the major membrane regulator of the C3 convertase. CR1 and CD46 are transmembrane molecules. CR1, originally described as a receptor for C3b and C4b, also possesses decay acceleration and FI cofactor activities for C3 convertase regulation. CD46 is an important membrane cofactor of FI cleavage of C3b/C4b; CD46 was also reported as a receptor for several viruses [23]. In human, CD46 is broadly distributed and polymorphic [24, 25]. CD46 has been implicated in recognition of apoptotic and necrotic cells [2], and plays roles in the male reproductive system and sperm maturation—indeed, in rodents, CD46 expression is restricted to testis, on late-phase spermatids and mature sperm [26, 27]. CD55, a glycosyl phosphatidylinositol (GPI)-anchored protein, is a decay accelerator for C3 convertase [28]. A truncated isoform of CD55 was identified in rat genital tissue [29]. In rodents, Crry is broadly expressed and a key CReg at the C3 convertase level, possessing both FI cofactor and decay acceleration activities [30]. C1-INH is also a multifunctional

Table 1 Complement (C) regulators and regulation levels in activation of the C pathway

Category	Regulator (abbreviation* and/or alternative name)	Regulation level of the C pathway
Fluid level regulator		
	C1 inhibitor (C1-INH,C1 inactivator)	C1qrs, MASPs**
	C4-binding protein (C4BP)	C3***
	Factor H (FH)	C3/C5****
	Factor H-related proteins 1–5 (FHR)	C3/C5
	Factor I (FI)	C3/C5
	Clusterin (apolipoprotein J, SP-40)	TCC***** (C5b-8)
	Vitronectin (S-protein, S40)	TCC (C5b-9)
	Carboxypeptidase N, R (TAFI)******	C5a/C3a
Solid level regulator		
	CD46 (membrane cofactor protein; MCP)	C3/C5
	CD55 (decay accelerating factor; DAF)	C3/C5
	CD35 (complement receptor 1; CR1)	C3/C5
	Crry******* (complement receptor-related protein)	C3/C5
	CD59 (HRF20, protectin)	TCC (C5b-9)

*Standard abbreviation in international complement society (refer to [22]), **mannose-binding lectin-associated serine protease, ***level of C3 convertase, ****level of C5 convertase, *****TCC is terminal complement component, membrane attack complex, and C5b-9, ******TAFI is thrombin-activatable fibrinolysis inhibitor, carboxypeptidase U, and carboxypeptidase B, ********the expression of Crry was reported in mouse and rat only

protein, originally discovered to inhibit the CP through binding to C1s and C1r, causing dissociation of C1s and C1r from the C1qrs-complex [31]. C1-INH also works to suppress the LP because of its capacity to bind and dissociate MASPs from the MBL-MASPs complexes [32]. C1-INH has also been associated with effects on acquired immunity by preventing T-cell proliferation and cytotoxic T-cell generation [33]. Moreover, C1-INH plays important bridging roles to the coagulation system (see Sect. 6).

Clusterin (apolipoprotein J) and vitronectin (S-protein) in the fluid phase and CD59 on surfaces inhibit the TP and MAC formation; vitronectin and clusterin bind C5b-7 and prevent its association with membranes [34, 35]. Of note, vitronectin is known to be associated with the coagulation system as we describe in the following Sect. 6. CD59 is a GPI-anchored membrane protein that prevents MAC assembly by binding the C5b-8 complex and preventing C9 insertion into the bilayer [36, 37]. In mouse, CD59 has two isoforms; CD59a which is broadly distributed and CD59b which is expressed only in the male genital tissue [1, 38].

CRegs and microorganisms

The membrane CRegs CD46 and CD55 are multifunctional proteins. Both CD46 and CD55 play roles as receptors for some microorganisms; for instance, CD46 works as a receptor for the measles virus and adenoviruses [39–41], CD55 binds echoviruses, coxsackievirus, and hantavirus [42–44]. Moreover, a CD55 polymorphism was reported to be related to severity of H1N1 influenza A virus infection [45] and to infection of Echoviruses 7 and 11 [46, 47]. Interestingly, it was recently shown that vitronectin might be related to Dengue virus infection because of interaction between vitronectin and dengue virus nonstructural protein 1 [48]. Of note, CRs have also been reported to play roles as microorganism receptors; for example, CR2 works as a receptor of Epstein-Barr virus on B-cells [49].

On the other hand, some microorganisms are able to recruit the host CRegs to escape C attack in the host. For example, CD46 was recruited in paramyxoviruses and mumps virus to escape C-mediated attacks [50], while group A streptococcus binds FH, FH-related protein (FHR) 1, C4BP and CD46 in order to escape from the host C activation system [51]. It was also reported that some other bacteria from Gram positives to Gram negatives, fungus and parasites, including *Staphylococcus pneumoniae, Acinetobacter* spp., *Bordetella pertussis, Pseudomonas aeruginosa, Neisseria meningitidis, Haemophilus influenzae, Onchocera volvulus, Echinococcus granulosus*, and

Candida albicans, could acquire CRegs to evade C attack in the infected host [51–54].

Roles of C receptors in cross-talk to acquired immunity

During the process of C activation, the products such as C3b and C4b and the degradation products such as iC3b, C3dg, and C3d are generated to target through opsonization invading microorganisms, cell debris, and immune complexes for removal by phagocytes; key phagocyte CRs include CR1 (CD35), CR2 (CD21), CR3 (CD11b/CD18, Mac-1), and/or CD4 (CD11c/CD18) [55–58]. The CRs are expressed on blood cells such as erythrocytes, neutrophils, monocytes, macrophages, T- and B-cells, and follicular dendritic cells (reviewed in [59, 60]). CR1 binds C3b and C4b; CR2 binds iC3b, C3d, and C3dg; CR3 binds iC3b and C4b; and CR4 binds iC3b. The binding interactions enable capture of circulating immune-complexes and foreign cells, resulting in phagocytosis for macrophages, interaction between dendritic cells and B-cells, and differentiation of cellular immunity in the reticuloendothelial system. For example, in the process of opsonization, it was reported that CR2 on B-cell promoted the survival of both mature and transitional B-cells and antibody production [61, 62]. CR2 bound with C3 opsonized immune-complex on the follicular dendritic cell surface might relate to internalization and recycling of immune-complexes to be retained for long period [63]. CD46 is also involved in induction of regulatory T-cells with CD4+ T-cells contributing to immune homeostasis [64, 65]. CR on microglia protects the host through phagocytosis of opsonized amyloid β from cerebral plaques induced by iC3b and CR3, suggesting microglia protection from Alzheimer's disease [66].

Cross-talking between the C system and the coagulation pathway/fibrinolysis system

It has recently become clear that the C system is closely related to the coagulation system/fibrinolysis system, including thrombi formation and fibrinolysis. It was reported that C5a might be directly generated through activation of the coagulation system [67]. C5a upregulates the coagulation system on endothelial cells through activation of tissue factor [68] and platelet aggregation progresses with interaction between C5a and neutrophils [69]. In our report, interaction between C5a and thrombus formation in glomerulus was demonstrated by the inhibitory effects of C5aR antagonist on thrombus formation in an anti-GBM model [70]. In addition, we also reported that C5a promoted liver injuries in a histone-induced lethal thrombosis

model which is a DIC model [71]. In contrast, C5a may promote fibrinolysis with expression of plasminogen activator inhibitor-1 (PAI-1) [72]. Interaction between C3 and fibrinogen in fibrin networks may prevent fibrinolysis and proceed clot formation [73, 74]. Thus, C molecules such as C3, C3a, and C5a appear to play multiple roles during both activation of the coagulation pathways and fibrinolysis system. Carboxypeptidases (N, R) are key protease for inactivation of C5a/C3a to the des-Arg forms, decreasing biological activities of C5a/C3a [75]. Notably, serum carboxypeptidase R was also reported as an inhibitor of fibrinolysis [75] and is alternatively called as thrombin-activatable fibrinolysis inhibitor (TAFI) [75]. In the LP, it was also reported that MBL/MASP complex was related to thrombus formation [76].

Some CRegs are also associated with the coagulation system; C1-INH was originally reported as an inhibitor of the CP to dissociate C1qrs and of the LP to bind MASPs [32]. C1-INH also works to regulate the coagulation system at the levels of factor (F) XIIa [77], thrombin formation, and modification of kallikrein to bradykinin [78]. Vitronectin does not only bind the complex of C5b-7, but also PAI-1 [79] to prevent fibrosis [80].

On the other hand, some of the coagulation factors potentially accelerate the C system. For example, FXa, FXIa, and plasmin may cleave both C5 and C3 accompanied with production of C5a and C3a [81].

Deficiency/mutation and autoantibodies of the C activation pathways and the related various disorders

Dysfunction of the C activation is related to lose of classical roles, opsonization, production of anaphylatoxins, and cell lysis. Deficiencies of the activation components of the C system are associated with autoimmune diseases such as systemic lupus erythematosus (SLE) because of loss of opsonization function leading to accumulation of pathological immune-complexes, and impaired protection from foreign invaders such as microorganisms [82, 83]. Impairment of capacity to form MAC also increases risk of infection; specifically, loss of MAC formation is a strong risk for infection with *Neisseria meningitidis* [84, 85].

In the LP, an autosomal-recessive disease caused by dysfunction of MASP-1 and MASP-3 has been described; Carnevale, Mingarelli, Malpuech, and Michels (3MC) syndrome presents with multiple abnormalities [86–89].

Autoantibodies against C components are also associated with autoimmune diseases. For example, anti-C1q antibodies are frequent in SLE [90]. Associated with membrane CRegs, development of immune thrombocytopenia

was recently linked with production of autoanti CD55 and CD59 [91].

Deficiency/mutation and autoantibodies of CRegs and the related diseases

This category of diseases is divided into deficiencies or dysfunction caused by mutations of the molecules and autoantibodies that prevent function of the CRegs or cause excessive C activation [such as nephritic factors (Nef)]. Each can cause dysregulation of the C system leading to development of various diseases. For example, deficiency of C1-INH which causes decreased serum C1-INH leads to increased C activation with increased anaphylatoxin production, and also dysregulation of the kinin pathway with over-production of bradykinin. Together, these lead to type 1 hereditary angioedema (HAE) as the pathological appearance [92]. In contrast, dysfunction of C1-INH causes similar symptoms, termed type 2 HAE but C1-INH levels in serum remain in the normal range [92]. The presence of autoantibodies against C1-INH was also reported as a cause of HAE [93]. Polymorphism in FH was first reported to be related to development of age-related macular degeneration in 2005 [94]. Later, it was shown that the dysfunction of FH and disrupted C regulation was also a cause of atypical hemolytic uremic syndrome (aHUS) and C3 glomerulonephropathy (C3GN) [95–97]. CD46 and FI dysfunctions were also reported as reasons to develop aHUS or C3GN. In addition, production of autoantibodies against FH and FI was also reported as the reasons of dysregulation of C activation associated with aHUS and C3GN [98, 99]. Neurological diseases such as Alzheimer's disease and multiple sclerosis were also reported to be related to dysregulation of the C system in humans and animal models [100, 101]. Mutation of *CFHR1* altered circulating FHR oligomerization and caused C dysregulation in some C3GN patients [102]. In addition, acceleration of C activation can occur even if function of CReg is preserved. Mutations of C3 and FB have been shown to prevent interactions of CRegs with the convertase and induce excessive C activation leading to the development of aHUS and/or C3GN [103–105]. Until now, it was reported that mutation of C3 was more common than those of the other CRegs in Japan, compared with the other centuries [106]. Thus, when deficiencies or polymorphism/mutation of CRegs or proteins affects function this can cause dysregulation of C activation and induce pathological conditions.

There are several ways by which autoantibodies can accelerate C activation: (a) the autoantibodies directly affect the targeted CRegs and prevent C regulatory functions, (b) the autoantibodies block binding sites of the associated CRegs to interfere with binding between the targeted

C component and the associated CRegs, and (c) the autoantibodies bind and stabilize the produced C convertases to induce continuous C activation. In the field of nephrology, production of autoantibodies against anti-FH is associated with aHUS and C3GN as an example of (a). Generation of antibodies against C3 and FB to stabilize C3 convertases, accelerate the AP, and induce C3GN as examples of (b). As the example of (c), Nef, for example, C3 Nef which stabilizes C3 convertases C3bBb and C3bBbP [98].

Interestingly, in some aHUS patients with autoantibodies against FH, deficiencies in FHR1 and FHR3 were reported; this is termed deficiency of FHR proteins and autoantibody positive form of HUS (DEAP-HUS) [107].

C activation and regulation are associated with development and progression of renal injuries

As in other tissues, the balance between C activation and regulation is known to be important in kidney to maintain the homeostasis, because the C system has potential to be a double edge sword [1, 82, 108]. In normal human kidney and diseased kidney, membrane CRegs such as CD46, CD55, and CD59 are broadly distributed [109–112]. It was reported that renal injuries were induced and/or accelerated in glomerular and interstitial pathologies when the balance between C activation and regulation was broken in animal models (reviewed in [1, 113, 114]). As another point, it is considered that local (including kidney) production of C components is important for local homeostasis and pathogenesis, although most C components are produced in liver and delivered to systemic circulation [59]. Recently, dysregulation of C caused by genetic abnormalities and autoantibodies of CRegs was demonstrated to be involved in development of renal pathologies such as aHUS and C3GN as we summarized in session 8. However, it was also shown in other renal diseases that most glomerular injuries are related to excessive C activation, although the host did not have genetic abnormalities in or autoantibodies against CRegs. It was also shown that the secondary dysregulation of the membrane CRegs caused by glomerular endothelial damage could induce severe renal injuries accompanied with abundant deposition of C activation products [115]. As supportive evidence, various experimental glomerulonephritidies and interstitial injuries were shown to be dependent on excessive C activation in various types of animal models, including anti-GBM nephritis [116], endothelial injuries caused by MAC formation [117], thrombus formation in glomerular capillaries [70], malarial infection-related nephritis [118], and proteinuria-related interstitial damages (reviewed in [113]). In addition, even if genetic deficiencies and dysfunction of membrane CRegs were

absent, dysfunction of membrane CRegs could be secondary consequences. For example, renal injuries induced by sea anemone toxins PsTX-T and PsTX-115 were caused by impairment of CRegs' expression along glomerular capillaries secondary to glomerular endothelial damage, resulting in severe C activation in glomeruli [115]. However, in the recovering phase, the C activation was diminished with recovery of CRegs' expression along glomerular capillaries [119]. When secondary dysregulation of CRegs was restored, progression of the C activation-dependent renal injuries was prevented.

We know that C deposition in glomeruli occurs in various human renal diseases in both pathogenic immune-complex dependent and independent manner; as references of the former cases, glomeruli in lupus nephritis, post-infectious glomerulonephritis, and membranous proliferative glomerulonephritis (MPGN) have C activation products and accompanying hypocomplementemia, and as references of latter cases, toxin-dependent renal injuries such as Shiga-toxin [120] and the other venoms originated from animals (reviewed in [119]). Part of pathological changes during induction/development of these renal injuries may be caused by the CP, the AP, and/or the LP of the C pathway (Table 2).

Regarding the relationship between anaphylatoxins and kidney, it is known that receptors for C3a and C5a, C3aR and C5aR1 (C5aR), which are G-protein-coupled receptors with seven transmembrane domains [134, 135], and C5aR2 (C5aL2), which is not a coupled G-protein receptor with seven transmembrane domains [136], distribute in kidney [137–139]. Both C3a-C3aR and C5a-C5aR interactions were important in lupus nephritis [138, 140] and interaction between C5a and C5aR is implicated as an amplification loop to induce glomerular injuries in anti-neutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis [130, 141]. The other reports were also supported the C activation system to proceed ANCA-associated glomerulonephritis, especially through the AP [142, 143]. In a report using C3aR-deficient mice, onset of renal injuries was accelerated by C3aR knock-out in MRL/lpr mice [144]. Thus, early components can also be important to preserve homeostasis and suppress renal injuries. Indeed, up-regulation of clusterin in mesangial cells was suggested to protect from C-mediated renal injuries [145].

Current therapeutic approaches using anti-C agents and possibilities in future

As an example of the 1st line of anti-C agents in end of the twentieth century, recombinant soluble CR1 (TP10) was tried in phase I and II clinical trials for various diseases in human, because it had been shown to be an efficient CReg

Table 2 Complement pathway in initiation/development of renal diseases in human and animal models

	References
1. Renal injuries which are thought to be related to the classical pathway	
Post-infectious glomerulonephritis	[121, 122]
Anti-GBM* glomerulonephritis	[123]
Lupus nephritis	[124, 125]
Membranous nephropathy	[126]
IgG4-related diseases	[127]
MPGN** (immune-complex associated)	[122]
2. Renal injuries which are thought to be related to the alternate pathway	
Atypical HUS***	[20]
C3 glomerulonephropathy	[20, 122]
Lupus nephritis (partly)	[124, 125]
Post-infectious glomerulonephritis	[121]
Anti-GBM glomerulonephritis	[123, 128]
IgA nephropathy	[129]
ANCA****-related glomerulonephritis	[130, 131]
Membranous nephropathy (IgG4)	[126, 132]
Nephrotoxin induced nephritis (Habu snakes toxin, Shiga-toxin, et al.)	[115, 119]
Progression of interstitial damages associated with proteinuria	[113]
3. Renal injuries which are thought to be related to the lectin pathway	
IgA nephropathy (partly)	[129]
Membranous nephropathy (partly)	[126]
Acute tubular necrosis	[133]
IgG4-related diseases	[127]

*Glomerular basement membrane, **, ***hemolytic uremic syndrome, ****anti-neutrophil cytoplasmic antibodies

to protect from C activation-dependent injuries in various animal models [146]. Following development from TP10, TP20, APT070 (Microcept), and the other CR1 derivatives were developed and studied to show the therapeutic effects [1, 3, 147, 148]. In the present, C1-INH and a neutralizing anti-C5 antibody have reached clinical use as anti-C therapies. In Japan, C1-INH [Berinert P (CSL Behring)] as a C1 inhibitor is available for HAE [92, 149] and eculizumab as a neutralizing C5 antibody [Soliris (Alexion Pharm.)] is now also used for PNH and aHUS [150]. Usefulness of another form of the C5 antibody, pexelizumab, was shown in a clinical trial of acute myocardial infarction [151]. Different from neutralizing monoclonal antibodies, OmCI originated from *Ornithodoros moubata* was reported as an interesting powerful C5 inhibitor [152]. In the field of nephrology, anti-C therapies have lots of possibilities to prevent renal injuries possibly dependent on excessive activation of C system, such as progression of glomerular and interstitial injuries in glomerulonephritis, ischemia–reperfusion injuries, and antibody-mediated rejections for renal transplantation; usefulness of C5 antibody has been reported for some of them [153–155] in addition to aHUS and C3GN. Of note, patients with some C5 polymorphisms were reported to be refractory for usage of eculizumab in Asian population including Japan, because the polymorphisms prevented to bind between eculizumab and C5 [156].

Despite these advances, C activation remains a double-edged sword playing both protective and damaging roles in the host. Long-term and/or total suppression of the C system may not always be beneficial in the host because of risk of infections and the other C-dependent protective effects. As regards the other aspects, more targeted effective agents, for example, C3 inhibitors such as compstatin and staphylococcal C inhibitor, C5a inhibitors or C5aR antagonists such as PMX-58 and AcePepA, soluble CD59, and clusterin may find roles in therapy [3, 13, 157, 158]. Recently, it was reported that FD inhibition protected in PNH and aHUS [159]. New developing agents including inhibition of FD may be expected to be effective on PNH which is refractory for usage of eculizumab. To develop anti-C agents in future, consideration of these different properties of anti-C therapies may be important to select the right drug, perform appropriate timing, and to regulate.

Conclusion

We are facing to a new stage in understanding of the C system. We understand much more the relevance to disease of dysregulation of the C system. Dysfunction of the C system may be a result of genetic factors and/or anti-antibodies, but excessive C activation may also be secondary to other

factors but nevertheless contribute to induction and development of tissue injuries. In recognizing the double-edged sword nature of C activation, we understand that intervention to regulate the C activation may not only show good effects to protect the host from attacks caused by excessive C activation but also have bad effects by eliminating C effects to maintain homeostasis. To develop new therapeutic agents, care must be taken to balance these outcomes, perhaps, by targeting to disease sites, inhibiting the appropriate C pathway, relevant steps of the C pathways, and timing therapy specifically for each pathological condition amenable to anti-C therapies.

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