Nephron

Experimental Nephrology and Genetics: Review Article

Nephron
DOI: 10.1159/000538241

Received: September 21, 2023
Accepted: March 4, 2024
Published online: March 8, 2024

The Complement C3a and C5a Signaling in Renal Diseases: A Bridge between Acute and Chronic Inflammation

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Keywords
Anaphylatoxin · C3a receptor · C5a receptor · Acute and chronic kidney disease

Abstract
The complement system, a cornerstone of the innate immune defense, typically confers protection against pathogens. However, in various clinical scenarios the complement's defensive actions can harm host cells, exacerbating immune and inflammatory responses. The central components C3 and C5 undergo proteolytic cleavage during complement activation, yielding small active fragments C3a and C5a anaphylatoxins. Traditionally, these fragments were associated with inflammation via the specific receptors C3a receptor (R), C5aR1 and C5aR2. Recent insights, however, spotlight the excessive C3a/C3aR and C5a/C5aR1 signaling as culprits in diverse disorders of inflammatory and autoimmune etiology. This is particularly true for several kidney diseases, where the potential involvement of anaphylatoxins in renal damage is supported by the enhanced renal expression of their receptors and the high levels of C3a and C5a in both plasma and urine. Furthermore, the production of complement proteins in the kidney, with different renal cells synthesizing C3 and C5, significantly contributes to local tissue injury. In the present review, we discuss the different aspects of C3a/C3aR and C5a/C5aR signaling in acute and chronic kidney diseases and explore the therapeutic potential of emerging targeted drugs for future clinical applications.

The Complement Cascade

The complement cascade follows three canonical routes: the classical, lectin, and alternative pathways whose activation occurs through stepwise proteolytic events in a cascade-like progression (Fig. 1) [1, 2]. This process is tightly controlled by a large panel of fluid-phase and cell-membrane regulators to avoid injury of autologous tissues. However, in several pathological conditions, complement system is overactivated driving severe inflammation and tissue injury [1, 2]. The classical activation pathway responds to antigen-antibody recognition via the C1 complex, whereas the lectin pathway is initiated by mannose-binding lectin identifying carbohydrate structures on infectious organisms. The alternative pathway is constitutively weakly activated in the host, through spontaneous hydrolysis known as tick-over. This process enables complement system to stay primed for a fast and robust activation [1, 2]. Despite distinct initiation mechanisms, these pathways converge in the cleavage of the C3 by the classical/lectin and the alternative C3 convertases, yielding active proteolytic fragments and finally the membrane

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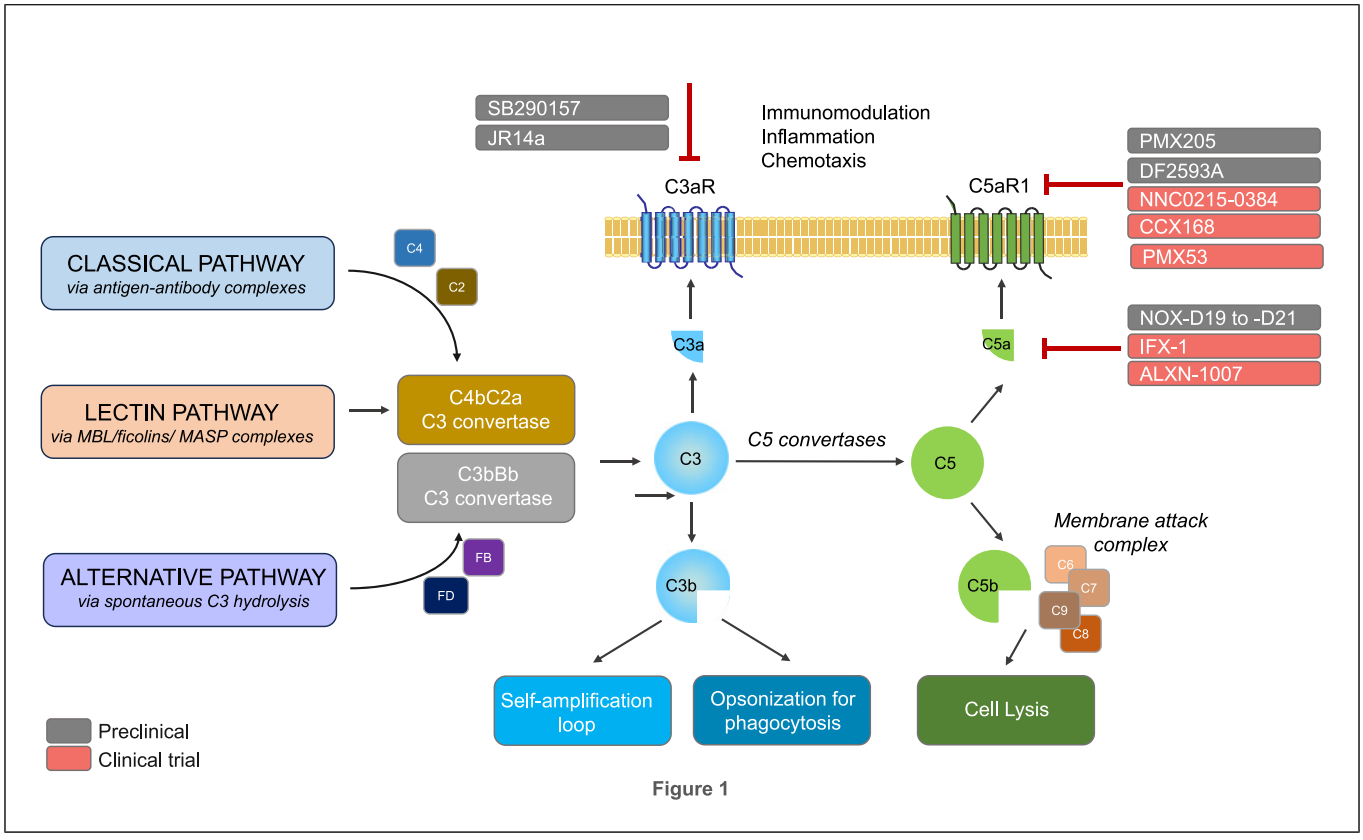


Fig. 1. C3a/C3a receptor and C5a/C5a receptor axis, novel targets for inhibition of the complement cascade. Complement activation via the classical, lectin, and alternative pathway converges to form complement C3 convertases which cleave C3 molecule to generate C3a and C3b in a step that initiates amplification of the signal cascade. C3b also promotes elimination of foreign invaders through opsonization that facilitates contact and recognition by phagocytes. The activation of the terminal complement pathway occurs when the alternative and classical C5 convertases cleave C5 in C5a and C5b. C5b binds to C6, C7, C8, and multiple C9 molecules forming the transmembrane pore C5b-9 also known as membrane attack complex (MAC), which triggers lysis of the microbes or injured cells. The anaphylatoxins C3a and C5a bind to their specific G-protein-couple receptors C3aR and C5aR1, respectively, which activate inflammation, chemotaxis of neutrophils and macrophages, and immune response. Several compounds are available for the inhibition of anaphylatoxin effects and their receptors. The figure shows those ones available for experimental studies and development (in gray) or employed in ongoing or terminated clinical trials (in red). MBL, mannose-binding lectin; MASP, MBL-associated serine proteases; FB and FD, Factor B and Factor D; C3aR and C5aR, C3a receptor and C5a receptor; C, complement.

attack complex (MAC) (Fig. 1). The generated effector products elicit different biological effects, including pathogen opsonization, lysis, and inflammatory cell recruitment (Fig. 1). Beside the conventional pathways of activation, non-complement proteases can locally activate C3 and C5 during inflammation [3].

The C3a/C3aR and C5a/C5aR Intracellular Signaling

The bioactive products C3a and C5a, small peptides (77-aa for C3a and 74-aa for C5a) also named anaphylatoxins, are generated by the C3 and C5 cleavage through the canonical pathways [1, 3] (Fig. 1) or intracellular systems [4]. While physiological conditions maintain moderately elevated plasma C3a levels (>100 nM) due to the tick-over C3 degradation, C5a remains nearly undetectable. During inflammation, both anaphylatoxins rise markedly contributing to the intricate cascade of immune responses. The activity of C3a and C5a is regulated by plasma carboxypeptidases that can rapidly metabolize them by removing C-terminal arginine to less-potent forms, C3a desArg and C5a desArg, with limited ability to bind to their specific receptor C3aR and C5aR1 expressed on cell membranes [3]. The engagement of these transmembrane G-protein-coupled receptors

promotes GTP/GDP exchange from the G-protein α subunit, leading to βγ subunit dissociation [3]. Intracellular signaling cascades, propelled by free α and βγ subunits, involve the phosphorylation of MAPKs, which activates NF-κB and cAMP response element-binding protein [3]. Interestingly, C3aR and C5aR1 are also expressed in different subcellular compartments as mitochondria, lysosomes, and endoplasmic reticulum [4]. These receptors, engaged by intracellularly generated C3a and C5a, are crucial for the regulation of basic cell physiological processes, including cell metabolism, autophagy, and gene expression [4], while they may contribute to cell dysfunction under oxidative stress conditions [5]. Importantly, a crosstalk of C3aR and C5aR1 with other receptors like FcR, toll-like receptors (TLRs), and CCR5 has been also described contributing to inflammation and tissue injury [3, 6].

A second receptor, C5aR2 (also named C5L2), has been identified as a G-protein uncoupled receptor for C5a and C5a desArg [7]. Initially thought to be a decoy receptor, more recent studies indicate that C5aR2 can physically interact with C5aR1 and β-arrestin, negatively regulating their signaling with consequent anti-inflammatory effects [7]. Conversely, other groups suggest a pro-inflammatory role of C5aR2 in the release of cytokines, such as IL6 and TNFα, in sepsis models [7]. To date, the biological and pathophysiological functions of C5aR2 are still a topic of debate.

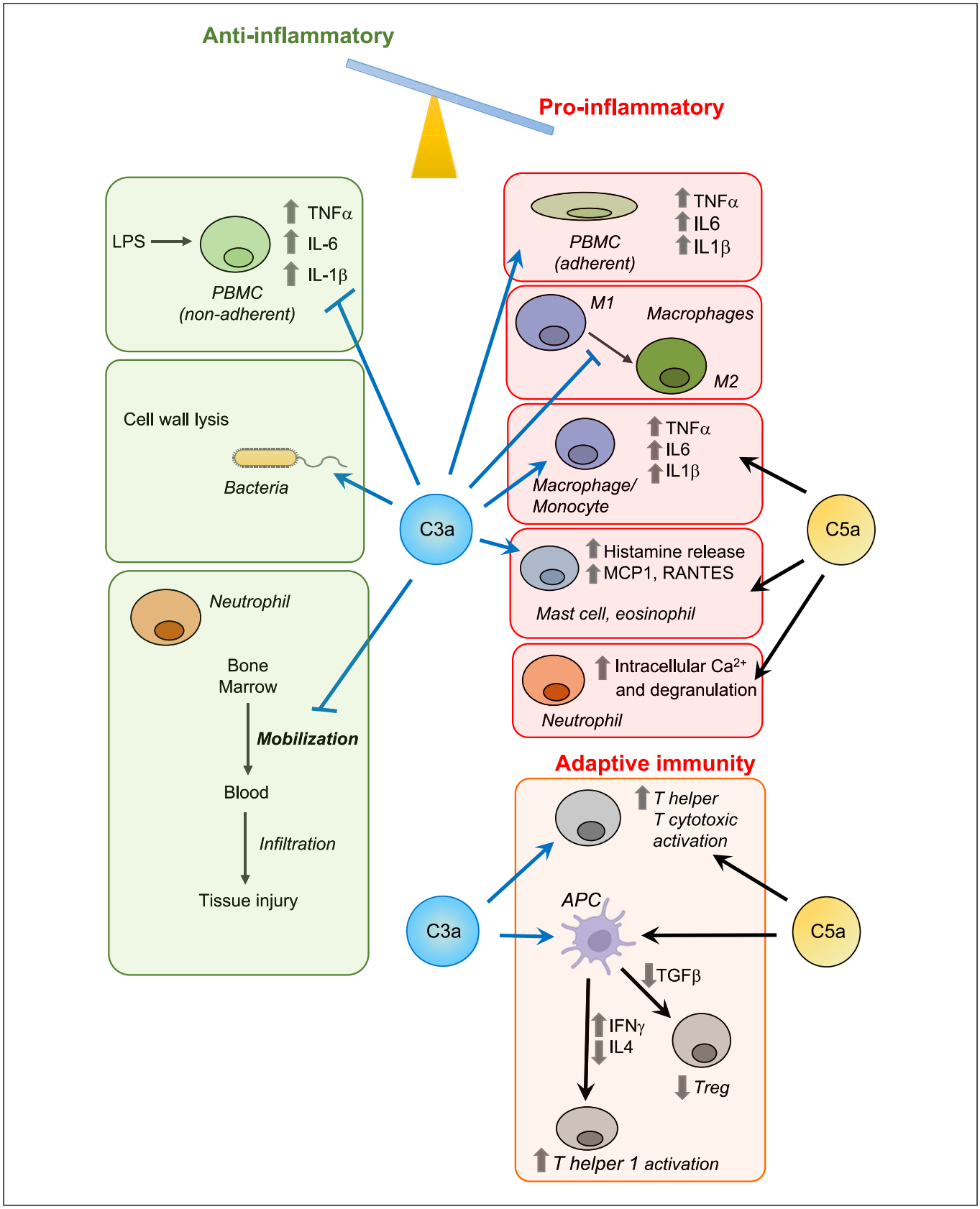
The Role of Anaphylatoxins C3a and C5a in Regulating Innate and Adaptive Immune Responses

C3a and C5a, and their desarginated derivatives, are pivotal signaling effectors, influencing a wide range of biological activities from chemotaxis to immune cell activation, thus playing crucial roles in both innate and adaptive immunity and inflammation [3, 6, 8].

However, a number of studies reveal a more complex scenario for C3a/C3aR signaling, which shows dual activities in controlling inflammatory processes, depending on cell types and diseases (Fig. 2) [9]. In this context, evidence is available that C3a exerts anti-inflammatory activity by inhibiting the release of cytokines as TNFα, IL1β, and IL6 by LPS-primed non-adherent peripheral blood mononuclear cells [9, 10]. Moreover, during infection C3a promotes pathogen elimination through the induction local macrophage and neutrophil phagocytosis [6, 8, 11], or bacterial lysis as consequence of its direct binding to the pathogen membrane [12]. Understanding the impact of C3a/C3aR activity on neutrophil inflammatory response is complex due to contradictory reports. Following acute damage, C3a mitigates the progression of the inflammation by preventing neutrophil mobilization and tissue infiltration in intestinal ischemia/reperfusion injury [13], whereas it exerts detrimental effects during acute kidney injury [14]. In other granulocytes as mast cells, C3a exerts pro-inflammatory activity by promoting cell migration, cytokine production through PI3K/Akt signaling pathways and histamine release [15], as well as it stimulates eosinophil degranulation, *via* calcium mobilization, and oxidative stress [16]. When monocyte/macrophage responses become predominant compared to neutrophils, C3a may indeed operate as a classical pro-inflammatory mediator [3, 9]. C3aR engagement increases IL6 and TNFα release by monocytes and promotes IL1β secretion, through the NLRP3 inflammasome, by regulating ATP efflux [9, 10, 17]. C3a and C3a desArg increase cytokine production by adherent peripheral blood mononuclear cell activated by LPS, while they suppress that of non-adherent cells [9, 10] (Fig. 2). Interestingly, C3a inhibits differentiation/polarization and migration of M2 macrophages by repressing the PPARγ-dependent transcriptional activation of M2-specific genes [18].

The anaphylatoxin C5a emerges as one of the most potent pro-inflammatory peptides exhibiting chemotactic activity toward neutrophils, phagocytes, and mast cells at the site of inflammation [3]. In response to C5a stimulation, mast cells release histamine, cytokines, and chemokines fostering vasodilation and fluid extravasation [3]. In neutrophils, C5a influences intracellular calcium homeostasis through its mobilization from intracellular stores [3], engendering a more prolonged effect compared to C3a, which instead triggers calcium influx without leading cell degranulation [9]. Additionally, in monocytes and macrophages, C5a boosts TNFα and IL-1β production [8]. Beside the direct effect of these anaphylatoxins on immune cells, exuberant C3a and C5a activation also fosters acute inflammation by affecting endothelial cell behavior, leading to changes in vascular flow, histamine-induced vascular permeability, leukocyte extravasation, and chemotaxis [19, 20].

In the context of innate immunity, C3a and C5a have also regulatory function on antigen presenting cells (APCs) with consequences for the modulation of the adaptive arms of the immune system [1, 6, 8] (Fig. 2). Indeed, C3a and C5a bind to antigen presenting cells, inducing cytokine release and elevating costimulatory molecules, thus intensifying the adaptive immune response and regulating T-cell proliferation and activation [1, 6, 8]. Furthermore, T cells express C3aR and C5aR1



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enabling local C3a and C5a signaling to directly affect T-cell function increasing their proliferation and reducing apoptosis, through the PI3K/Akt signaling pathway [6, 8, 21]. These anaphylatoxins can also influence the balance between different populations of T cells, such as T helper cells and cytotoxic T cells [22], thus shaping the immune response. In addition, C3aR/C5aR1 signal transduction reduces Treg functions, thus sustaining the immunoresponse [23]. While these mechanisms are required for proper T-cell response, excessive generation of C3a and C5a can induce aberrant T-cell activity. As an example, sustained C3a-rich environment has been shown to promote excessive T-cell activation and altered phenotypes which can contribute to infection-associated organ damage, as recently observed during the response to SARS-CoV-2 viral infection [24].

Altogether, these findings uncovered an intricated role of C3a/C3aR and C5a/C5aR1 in the balancing of the proper regulation of innate and adaptive immunity. As a result, unrestrained C3a and C5a activation contributes to the exuberant immune and inflammatory responses in several communicable and noncommunicable diseases [6, 25, 26].

C3a/C3aR and C5a/C5aR1 Activity in Renal Cells

In the kidney, constitutive expression of C3aR and C5aR1 has been described in glomerular cells and, even more, in the tubular epithelium in both humans and rodents [25, 27–30]. However, during the progression of immune and nonimmune-mediated forms of kidney diseases, aberrant C3a/C3aR and C5a/C5aR1 signaling occurs in the renal tissues, in association with high anaphylatoxin levels in the serum and urine. Particularly, the renal expression of C3aR and C5aR1 increases in acute and chronic kidney diseases including focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), lupus nephritis (LN), IgA nephropathy, diabetic nephropathy (DN) at the early time of glomerular injury, and unilateral ureteral obstruction [25, 29–36]. In glomeruli, C3a directly induces podocyte damage by impairing mitochondrial function, antioxidant defense, and increasing cell motility [37]. Podocytes are able to synthesize several complement components, including C3 and complement regulatory factors, some of which increase in response to injury and contribute to potentiate tissue damage [31]. Parietal epithelial cells (PECs) are also susceptible to the detrimental effects of C3a exhibiting abnormal proliferation and capacity to migrate from the Bowman's capsule toward the vascular tuft, leading to glomerular hyperplastic-like lesions, and sclerosis [38]. In glomerular endothelial cells (GECs), C3aR and C5aR1 are constitutively expressed at very low level, while they are greatly upregulated in experimental and clinical DN as well as in LN [29, 34, 37]. In vitro, high levels of C3aR and C5aR1, associated with upregulation of adhesion molecules P-selectin, ICAM1 and VCAM1, are observed in endothelial cells in response to C3a and C5a [20, 39]. Interestingly, high glucose concentration increases significantly C3aR and C5aR1 expression in GEC that undergo endothelial-myofibroblast transition and fibrosis, through TGFβ and Wnt/β-catenin pathways when challenged with C3a or C5a [29].

Among renal cells, proximal epithelial tubular cells are the cell population which physiologically exhibits highest C3aR level in the brush border and basolateral membrane [27]. In pathological conditions, C3 is activated and C3a is formed within the tubules by the intrinsic convertase activity of the proximal tubular cells and by ammonia [40]. Similarly to what occurs in the endothelial cells, C3a and C5a directly increase pro-fibrotic αSMA and TGFβ proteins, favoring tubular cellular dysfunction and fibrosis [41, 42]. Moreover, C3aR signaling activation increases proteoglycan production by cultured tubular cells, through Akt-mediated activation of the β-catenin/TCF transcription factor complex, which in turn promotes proliferation and collagen synthesis in renal fibroblasts [43].

Fig. 2. Effects of C3a and C5a on inflammation and adaptive immunity. C3a exerts its anti-inflammatory action decreasing cytokine production from LPS-primed non-adherent peripheral blood mononuclear cells (PBMCs), promotes the elimination of germs, limits neutrophil mobilization from bone marrow and infiltration, thus preventing tissue injury. C3a induces inflammation by promoting the release of cytokines by activated adherent PBMC and suppressing differentiation and polarization of M1 into M2 macrophages. C3a, together with C5a, promotes cytokine production by monocyte/macrophages and stimulates the degranulation of eosinophils and mast cells. C5a also influences intracellular calcium homeostasis, cell degranulation and activation in neutrophils. In the context of adaptive immunity, both anaphylatoxins directly, or through antigen presenting cells (APC), affect T-cell (T helper, T cytotoxic, and T reg) activation in terms of cell proliferation, cytokine production and reduced apoptosis. PBMCs, peripheral blood mononuclear cells; LPS, lipopolysaccharide; TNF, tumor necrosis factor; IL, interleukin; M, macrophage.

Preclinical and Clinical Evidence of the Role of C3a and C5a in Renal Diseases

The kidney is particularly vulnerable to complement overactivation, due to the low expression of complement regulators and the local production of functionally active complement components, both in the tubular and glomerular compartments, which directly contribute to renal inflammation and fibrosis [44]. Complement has been studied in kidney diseases for decades and a great deal of data has been collected regarding the activation at C3 and C5 level and deposition of C3b and C5b [45, 46]. More recently, the pathogenic contributions of C3a and C5a in the onset and progression of acute and chronic renal damage, are emerging. C5a mediates the early phase of acute inflammation, through rapid neutrophil recruitment and activation, while C3a, together with C5a, coordinates and amplifies the acute inflammatory and immune response later on, when monocytes/macrophages are recruited, leading to tissue injury [6, 25]. In this scenario, both anaphylatoxins, through their integrating actions, may also promote directly renal tissue injury by activating intracellular signaling in the different renal cell populations. These processes contribute to bridge from an acute response toward a pro-fibrotic signaling cascade leading to chronic renal damage, as detailed below.

Acute Kidney Injury

Growing evidence suggests that both anaphylatoxins C3a and C5a are important effectors in the onset of acute tubular injury [47]. In a model of renal ischemia-reperfusion injury (IRI), the contribution C3a and C5a are sustained by the increased expression of their receptors in tubular cells associated with inflammatory cell infiltration and the production of TNFα, IL-1β, and IFNγ, as well as chemotactic factors [14]. The role of C3a and C5a is also demonstrated by the reduction of inflammatory mediators and tubulointerstitial $GR1^+$ neutrophil and $F4/80^+$ macrophage infiltration in mice lacking C3aR or C5aR1 and, to a greater extent, in C3aR/C5aR1 double knockout mice, leading to an improvement in tubular cell damage [14]. Previous studies in IRI models show that the silencing of C5aR1 gene preserves renal function and reduces inflammation [48].

Although a pathogenic role of C5a has been demonstrated in experimental IRI, in the clinical practice the inhibition of C5 with eculizumab does not prevent delayed graft function induced by IRI in deceased donor kidney transplants [49]. The reasons why eculizumab is not effective in these patients may be attributed to the upstream activity of the C3 convertase, which is not inhibited by the treatment. This promotes the activation of C3a/C3aR signals possibly effectors of oxidative stress, cytokine production, and innate immune activation leading to renal injury in delayed graft function [49].

Focal Segmental Glomerulosclerosis

FSGS is an important cause of end-stage renal disease in children and adolescents and typically presents with nephrotic range proteinuria. Complement activation occurs in FSGS patients as documented by the increased plasma and urine levels of C3a and C5a, associated with C3b accumulation in areas of renal tissue injury, which correlates with renal function decline [43, 50].

That C3a and C5a play a pathogenic role in this disease, is highlighted by preclinical data showing that in mice with adriamycin (ADR)-induced FSGS, a marked activation of both the C3a/C3aR and C5a/C5aR1 signaling is associated to podocyte injury and glomerulosclerosis [51]. One of the mechanisms leading to C3a formation on podocytes in ADR mice involves defective regulation of the decay-accelerating factor, an important regulator/inhibitor of C3 activation [52]. Treatment of ADR mice lacking decay-accelerating factor in podocytes with C3aR antagonist abrogates the disease, thus implying a key role for locally produced C3a that, upon binding to podocyte C3aR, induces glomerular injury in this model [52]. The C3a/C3aR signaling is also critical for the aberrant adaptive response of PEC to podocyte damage occurring in the early phases of the glomerulosclerotic process. In this regard, increased glomerular C3a/C3aR expression is associated with the activation of the GDNF/c-Ret axis and podocyte-dependent PEC dysfunction and migration in mice with proteinuric nephropathy [38]. Engagement of C3a/C3aR signaling is also instrumental to the development of tubular interstitial fibrosis, albuminuria, and renal dysfunction [41].

Membranous Nephropathy

Patients with autoimmune MN exhibited heightened deposition of C3b and MAC, a phenomenon that correlates with increased proteinuria [53], as well as C3aR overexpression on the podocytes [32]. Seven fold higher levels of C3a and C5a are detected in the serum of these patients compared to those with FSGS or minimal change disease [54], suggesting that complement activation is a defining feature of MN that distinguishes it from other forms of nephrotic syndrome.

Preclinical studies have shown that complement activation is a determinant factor for the development of glomerular damage in MN and that inhibition of C3 is more effective in reducing podocyte damage than the blockade of MAC formation, suggesting an important role of C3 in

sustaining immunological glomerular injury [55]. Furthermore, a causal role of C3a/C3aR signaling in inducing glomerular injury has been demonstrated by the finding that increased C3a in the plasma of MN patients leads to loss of synaptopodin and NEHP2, as well as to cytoskeletal alterations in cultured podocytes [32]. Consistently, gene silencing of C3aR and C5aR1 protects podocytes against sublytic complement-mediated injury in vitro [56]. The recent evidence that administration of two C3aR antagonists, SB290157 or JR14a, attenuates proteinuria, foot process effacement, and electron-dense deposits at a similar extent in rats with Heymann nephritis [32], highlights the clinical potential of treatments targeting C3aR in primary MN.

Lupus Nephritis

Numerous studies have highlighted the detrimental impact of complement activation on LN. Deficiencies in complement components (C1, C2, C4) increase the risk of developing systemic lupus erythematosus (SLE) due to the essential role of an intact complement system in clearing apoptotic cell bodies and immune complexes, crucial for preventing autoimmunity [57]. High levels of glomerular C3aR expression have been detected in kidney specimens from LN patients and these correlate with disease severity and activity [34]. Plasma and urinary C3a levels are increased in patients with active LN compared to patients in remission [58]. As for C5a, enhanced C5aR1 mRNA expression has been assessed in glomeruli, whereas only a slight increase in circulating and urinary C5a occurs in active LN [30, 59].

In experimental LN spontaneously developed by MRL/Ipr mice, the upregulation of C3aR expression in both glomerular and tubular cells has been observed [35]. In these mice, C3aR blockade by SB290157 decreases the renal expression of IL-1β and RANTES, limiting renal damage and improving survival [35]. Conversely, MRL/Ipr mice knockout for C3aR shows an accelerated onset of renal damage, though not associated to increased severity in the long-term, suggesting a protective role of C3a in early phase of the disease [60]. In these C3aR knockout animals, a wide range of chemokines and chemokine receptors increases in association with a more rapid rise in serum creatinine in the early but not late stage of the disease compared to control MRL/Ipr mice [60]. These data that C3aR deficiency accelerates the onset of chronic inflammation and tubulointerstitial fibrosis highlight the complexity of the role of C3a/C3aR axis in promoting renal damage in LN. As for C5aR1, its renal expression increases in MRL/Ipr mice, before and upon developing kidney disease, and its blockade reduces albuminuria, preserves renal function, limits renal inflammatory cell infiltration, and delays mortality [61].

Diabetic Nephropathy

Clinical studies have shown that the complement system is activated systemically and locally during progressive DN [62]. In DN patients, plasma levels of C1q, mannose-binding lectin, Bb, C3a, C5a, as well as their urinary levels except for C1q, are higher compared with diabetic patients without renal involvement [62]. In the kidney, glomerular C3a is associated with increased C3aR expression in advanced phase of DN and correlates with glomerular lesions and renal disease progression [29, 62]. In experimental model of DN, a harmful activity of C3a is demonstrated by data that C3aR blockade (SB290157) significantly reduces proteinuria and limits glomerular podocyte injury, through the maintenance of mitochondrial function [37]. Similarly, C3aR deficiency in mice with a high fat diet and streptozotocin-induced DN alleviates the disease by suppressing macrophages and T-cell inflammatory response [63]. Further, C3aR and C5aR antagonists significantly reduce glomerular endothelial-myofibroblast transition by limiting the expression of α-SMA, TGFβ, and fibronectin through Wnt/β-catenin signaling in DN rats [29]. Other compounds targeting C5a/C5aR1, the mixed RNA/DNA aptamer NOX-D21 and the specific C5aR1a PMX53, significantly improve renal function and limit glomerulosclerosis and tubulointerstitial damage reducing lipid accumulation [64], and mitochondrial reactive oxygen species [65].

Kidney Infection

Distinct and opposing activities of C3a and C5a have been described during infection. At variance with the well-documented inflammatory role of the C5a/C5aR1 axis, a protective effect of C3a, in virtue of its antimicrobial activity, has been reported in experimental models of infection-induced renal injury. In acute pyelonephritis induced by inoculation of *Escherichia coli*, C3aR is required for protection against renal injury [11]. The finding that C3aR deficient mice develop a more severe disease supports the evidence that the C3a/C3aR axis confers protection during kidney infection through suppression of local inflammatory response and enhancement of bacterial phagocytosis [11]. The protective role of C3a is also demonstrated in experimental chronic pyelonephritis [66]. Here, the lack of C3aR (global or myeloid cell specific) induces more pronounced renal lesions, tissue inflammation, and extracellular matrix deposition, whereas treatment with C3aR agonist reduces disease severity [66]. Conversely, C5aR1 favors the pathogenesis of chronic kidney infection by *Escherichia coli* by increasing bacterial

colonization of tubular epithelium, local inflammatory responses, and fibrosis as well as impairment of macrophage phagocytic function [67].

C3a- and C5a-Targeted Therapeutics in Renal Diseases: Clinical Perspectives

The preclinical studies described above have underscored the therapeutic potential of inhibiting C3a and C5a signaling in acute and chronic kidney diseases; however, their clinical translation remains largely unexplored. Numerous strategic approaches have emerged to counteract the effects of C3a and C5a, as summarized in Figure 1. While impeding complement activation at the C3 and C5 levels avoids the generation of C3a and C5a, the prolonged clinical use of these inhibitors could heighten the risk of recurrent, life-threatening infections [2]. Specifically, blocking the classical and alternative pathways at C3 or the terminal pathway can affect opsonization capacity and the clearance of immune complexes and apoptotic cells, as well as the activation of the immune response [2]. However, it is more advantageous to target C3a and C5a signaling with specific antibodies or through the neutralization of the activity/engagement of the respective receptors with selective antagonists and/or small peptides as well as the silencing of the receptor expression.

Several C5a-targeted therapeutics have been proposed for different disorders as delineated in the Table 1 [68]. Completed phase II trials with the anti-C5a antibody IFX-1 have provided promising results in patients with granulomatosis with polyangiitis, in severe COVID-19 pneumonia, in hidradenitis suppurativa and pyoderma gangrenosum. Another anti-C5a antibody, ALXN1007, entered in phase II clinical trials for the treatment of graft-versus-host disease and antiphospholipid syndrome. Aptamer technology has been applied to obtain C5a inhibitors, including NOX-D19 and NOX-D21, which exhibited efficacy exclusively in models of sepsis and transplant rejection [69, 70]. Despite their high selective characteristics and low immunogenicity, these L-RNA aptamers have not progressed to human trials. Focused study on the regulation of C5a/C5aR1 signals led to the development of specific C5aR1 inhibitors and/or antagonists (Table 1). The cyclic peptide PMX53 is one of the first C5aR1 antagonist described extensively in experimental inflammatory pathologies with promising results. However, its clinical translation has not been widespread or very effective in rheumatoid arthritis, psoriasis, and age-related macular degeneration [2]. A new molecule, PMX205, has been developed with higher lipophilia, enhanced gastrointestinal stability and therapeutic effects in experimental neurodegenerative disorders [71]. Another compound, CCX168 (avacopan), a non-peptidic C5aR1 inhibitor, demonstrates favorable outcomes in phase II studies on ANCA-associated vasculitis, leading to an advantageous reduction of the glucocorticoid requirement and improvements in renal parameters. Encouraged by these positive results, a phase III study has been performed and completed. Other phase II/III clinical trials have focused on the effect of CCX168 in autoimmune disorders with renal involvement, such as ANCA vasculitis, atypical HUS, IgA nephropathy, and C3 glomerulopathy [72]. Based on the current evidence, avacopan is now recommended as adjunctive treatment in combination with standard therapy for severe active ANCA-associated vasculitis. More recently, a potent and selective inhibitor has been designed, DF2593A, targeting the allosteric "minor pocket" of C5aR1 which is hypothesized to be highly conserved in G-protein-coupled receptor class [73]. This compound has been described as controlling chronic inflammation and neuropathic pain in a mouse model [73]. The humanized monoclonal antibody that targets C5aR1 (NNC0215-0384) has demonstrated safety and tolerability in patients with rheumatoid arthritis. Another anti-C5aR1 antibody, avdoralimab, has produced disappointing results when given to patients with COVID-19.

Despite their success in experimental models, translation in clinical practice of inhibitors of the C3a/C3aR axis is still to be explored. In this regard, the first developed C3aR antagonist, SB290157, has been extensively studied and has shown protective effects in multiple models of acute and chronic inflammatory disorders including kidney diseases. Nevertheless, in some contexts, off-target effects and the agonist function of SB290157 have been observed [74]. Recently, another compound has been developed, the C3aR antagonist JR14a, which exhibited beneficial effects in experimental MN, akin to SB290157 [32]. This novel compound could open new therapeutic perspective for the clinical use. However, one of the major concerns that limits the use of these compounds derives from the evidence of a "dual role" of C3a/C3aR pathway (as depicted in Fig. 2) in the regulation of acute and chronic inflammatory cell responses which underscores the complexity of this intracellular axis. While C3aR engagement contributes to renal tissue damage in acute tubular injury [14] and chronic glomerular inflammation [25], in specific pathological settings, C3aR mediates protection by inhibiting

Table 1. Clinical trials of C5a-C5aR1 targeted therapeutics under active development

Compound	Target	Class	Disease	Clinical phase	Status (completed trials)	References
IFX-1	C5a	Antibody	Granulomatosis with polyangiitis (GPA)	II	With results	
			Granulomatosis with polyangiitis (GPA)	II	With results	
			Severe COVID-19 Pneumonia	II/III	With results	Vlaar APJ, Lancet Rheumatol 2020 Vlaar APJ, Lancet Respir Med 2022
			Hidradenitis suppurativa	II	With results	Huang C, Biomedicines 2022
			Hidradenitis suppurativa	II	No results	
			Septic organ dysfunction	II	No results	
			Cardiac surgery	II	No results	
			Pyoderma fangrenosum	II	With results	
ALXN1007	C5a	Antibody	Antiphospholipid (aPL) syndrome	II	With results	
			Acute-graft-versus-host disease	II	With results	
CCX168 (Avacopan)	C5aR1	Small molecule	aHUS	II	No results	
			ANCA-associated vasculitis	II	With results	Jayne DRW, JASN 2017
			ANCA-associated vasculitis	II	With results	Merkel PA, ACR Open Rheumatol 2020
			ANCA-associated vasculitis	III	With results	Merkel PA, JMIR Res Protoc 2020 Jayne DRW, N Engl J Med 2021 Soulsby WD, ACR Open Rheumatol 2022 Harigai M, Mod Rheumatol 2023
			C3 glomerulopathy	II	With results	Zotta F, Pediatr Nephrol, 2023
			IgA Nephropathy	II	With results	Bruchfeld A, Clin Kidney J 2022
			Hidradenitis suppurativa/acne inversa	II	With results	Huang C, Biomedicines 2022
NNC0215-0384	C5aR1	Antibody	Rheumatoid arthritis	I	No results	
			Rheumatoid arthritis	I	No results	
PMX53	C5aR1	Cyclic peptide	Rheumatoid arthritis	Ib	With results	Vergunst CE, Rheumatol Oxf Engl 2007
			Psoriasis	I/IIa	No results	
			Age-related macular degeneration	I/IIa	No results	
AVDORALIMAB		Antibody	Severe COVID-19 pneumonia	II	With results	Carvelli J, Lancet 2022

inflammatory cell infiltration and tissue injury [13, 75]. For all these reasons, in-depth investigations and awareness on the activity of C3a and its receptor in the different pathological contexts are needed.

Altogether these findings highlight the detrimental role of anaphylatoxins in the progression of renal diseases through their vasoactive, pro-inflammatory, and chemoattractant activity perpetuating the immune

response. While C5a blockade primarily addresses the acute effects of inflammation, targeting C3a signaling may hold promise in mitigating inflammation and immune response as well as in limiting renal fibrosis over time in chronic renal diseases thus supporting the rationale for future clinical translation of the complement inhibitors.

Acknowledgments

We would like to thank Kerstin Mierke for the manuscript's editing and Antonella Piccinelli for figure preparation.

Conflict of Interest Statement

The authors have declared they have no conflicts of interest.

Funding Sources

None.

Author Contributions

S.B., B.I., and M.M. conceived the review, drafted the manuscript, and create figures and table.

References

1 Noris M, Remuzzi G. Overview of complement activation and regulation. Semin Nephrol. 2013;33(6):479–92. doi: 10.1016/j.semnephrol.2013.08.001.
2 Morgan BP, Harris CL. Complement, a target for therapy in inflammatory and degenerative diseases. Nat Rev Drug Discov. 2015;14(12):857–77. doi: 10.1038/nrd4657.
3 Klos A, Wende E, Wareham KJ, Monk PN. International union of basic and clinical pharmacology. [corrected]. LXXXVII. Complement peptide C5a, C4a, and C3a receptors. Pharmacol Rev. 2013;65(1):500–43. doi: 10.1124/pr.111.005223.
4 West EE, Kemper C. Complosome: the intracellular complement system. Nat Rev Nephrol. 2023;19(7):426–39. doi: 10.1038/s41581-023-00704-1.
5 Ishii M, Beeson G, Beeson C, Rohrer B. Mitochondrial C3a receptor activation in oxidatively stressed epithelial cells reduces mitochondrial respiration and metabolism. Front Immunol. 2021;12:628062. doi: 10.3389/fimmu.2021.628062.
6 Peng Q, Li K, Sacks SH, Zhou W. The role of anaphylatoxins C3a and C5a in regulating innate and adaptive immune responses. Inflamm Allergy Drug Targets. 2009;8(3):236–46. doi: 10.2174/187152809788681038.
7 Li R, Coulthard LG, Wu MCL, Taylor SM, Woodruff TM. C5L2: a controversial receptor of complement anaphylatoxin, C5a. FASEB J. 2013;27(3):855–64. doi: 10.1096/fj.12-220509.
8 Zhou W. The new face of anaphylatoxins in immune regulation. Immunobiology. 2012;217(2):225–34. doi: 10.1016/j.imbio.2011.07.016.
9 Coulthard LG, Woodruff TM. Is the complement activation product C3a a proinflammatory molecule? Re-evaluating the evidence and the myth. J Immunol. 2015;194(8):3542–8. doi: 10.4049/jimmunol.1403068.
10 Takabayashi T, Vannier E, Burke JF, Tompkins RG, Gelfand JA, Clark BD. Both C3a and C3a (desArg) regulate interleukin-6 synthesis in human peripheral blood mononuclear cells. J Infect Dis. 1998;177(6):1622–8. doi: 10.1086/515316.
11 Wu KY, Zhang T, Zhao GX, Ma N, Zhao SJ, Wang N, et al. The C3a/C3aR axis mediates anti-inflammatory activity and protects against uropathogenic E. coli-induced kidney injury in mice. Kidney Int. 2019;96(3):612–27. doi: 10.1016/j.kint.2019.03.005.
12 Zipfel PF, Reuter M. Complement activation products C3a and C4a as endogenous antimicrobial peptides. Int J Pept Res Ther. 2009;15(2):87–95. doi: 10.1007/s10989-009-9180-5.
13 Wu MCL, Brennan FH, Lynch JPL, Mantovani S, Phipps S, Wetsel RA, et al. The receptor for complement component C3a mediates protection from intestinal ischemia-reperfusion injuries by inhibiting neutrophil mobilization. Proc Natl Acad Sci U S A. 2013;110(23):9439–44. doi: 10.1073/pnas.1218815110.
14 Peng Q, Li K, Smyth LA, Xing G, Wang N, Meader L, et al. C3a and C5a promote renal ischemia-reperfusion injury. J Am Soc Nephrol. 2012;23(9):1474–85. doi: 10.1681/ASN.2011111072.
15 Venkatesha RT, Berla Thangam E, Zaidi AK, Ali H. Distinct regulation of C3a-induced MCP-1/CCL2 and RANTES/CCL5 production in human mast cells by extracellular signal regulated kinase and PI3 kinase. Mol Immunol. 2005;42(5):581–7. doi: 10.1016/j.molimm.2004.09.009.
16 Takafuji S, Tadokoro K, Ito K, Dahinden CA. Degranulation from human eosinophils stimulated with C3a and C5a. Int Arch Allergy Immunol. 1994;4 Suppl(1):27–9. doi: 10.1159/000236743.
17 Asgari E, Le Friec G, Yamamoto H, Perucha E, Sacks SS, Köhl J, et al. C3a modulates IL-1β secretion in human monocytes by regulating ATP efflux and subsequent NLRP3 inflammasome activation. Blood. 2013;122(20):3473–81. doi: 10.1182/blood-2013-05-502229.
18 Mogilenko DA, Danko K, Larionova EE, Shavva VS, Kudriavtsev IV, Nekrasova EV, et al. Differentiation of human macrophages with anaphylatoxin C3a impairs alternative M2 polarization and decreases lipopolysaccharide-induced cytokine secretion. Immunol Cell Biol. 2022;100(3):186–204. doi: 10.1111/imcb.12534.
19 Shivshankar P, Li YD, Mueller-Ortiz SL, Wetsel RA. In response to complement anaphylatoxin peptides C3a and C5a, human vascular endothelial cells migrate and mediate the activation of B-cells and polarization of T-cells. FASEB J. 2020;34(6):7540–60. doi: 10.1096/fj.201902397R.
20 Propson NE, Roy ER, Litvinchuk A, Köhl J, Zheng H. Endothelial C3a receptor mediates vascular inflammation and blood-brain barrier permeability during aging. J Clin Invest. 2021;131(1):140966. doi: 10.1172/JCI140966.
21 Strainic MG, Liu J, Huang D, An F, Lalli PN, Muqim N, et al. Locally produced complement fragments C5a and C3a provide both costimulatory and survival signals to naive CD4+ T cells. Immunity. 2008;28(3):425–35. doi: 10.1016/j.immuni.2008.02.001.
22 Vieyra M, Leisman S, Raedler H, Kwan WH, Yang M, Strainic MG, et al. Complement regulates CD4 T-cell help to CD8 T cells required for murine allograft rejection. Am J Pathol. 2011;179(2):766–74. doi: 10.1016/j.ajpath.2011.04.038.
23 Kwan W, van der Touw W, Paz-Artal E, Li MO, Heeger PS. Signaling through C5a receptor and C3a receptor diminishes function of murine natural regulatory T cells. J Exp Med. 2013;210(2):257–68. doi: 10.1084/jem.20121525.
24 Georg P, Astaburuaga-García R, Bonaguro L, Brumhard S, Michalick L, Lippert LJ, et al. Complement activation induces excessive T cell cytotoxicity in severe COVID-19. Cell. 2022;185(3):493–512.e25. doi: 10.1016/j.cell.2021.12.040.
25 Gao S, Cui Z, Zhao M-H. The complement C3a and C3a receptor pathway in kidney diseases. Front Immunol. 2020;11:1875. doi: 10.3389/fimmu.2020.01875.

26 Perico L, Benigni A, Casiraghi F, Ng LFP, Renia L, Remuzzi G. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021;17(1):46–64. doi: 10.1038/s41581-020-00357-4.

27 Braun MC, Reins RY, Li T-B, Hollmann TJ, Dutta R, Rick WA, et al. Renal expression of the C3a receptor and functional responses of primary human proximal tubular epithelial cells. J Immunol. 2004;173(6):4190–6. doi: 10.4049/jimmunol.173.6.4190.

28 Zahedi R, Braun M, Wetsel RA, Ault BH, Khan A, Welch TR, et al. The C5a receptor is expressed by human renal proximal tubular epithelial cells. Clin Exp Immunol. 2000;121(2):226–33. doi: 10.1046/j.1365-2249.2000.01249.x.

29 Li L, Chen L, Zang J, Tang X, Liu Y, Zhang J, et al. C3a and C5a receptor antagonists ameliorate endothelial-myofibroblast transition via the Wnt/β-catenin signaling pathway in diabetic kidney disease. Metabolism. 2015;64(5):597–610. doi: 10.1016/j.metabol.2015.01.014.

30 Abe K, Miyazaki M, Koji T, Furusu A, Nakamura-Kurashige T, Nishino T, et al. Enhanced expression of complement C5a receptor mRNA in human diseased kidney assessed by in situ hybridization. Kidney Int. 2001;60(1):137–46. doi: 10.1046/j.1523-1755.2001.00780.x.

31 Li X, Ding F, Zhang X, Li B, Ding J. The expression profile of complement components in podocytes. Int J Mol Sci. 2016;17(4):471. doi: 10.3390/ijms17040471.

32 Gao S, Cui Z, Zhao MH. Complement C3a and C3a receptor activation mediates podocyte injuries in the mechanism of primary membranous nephropathy. J Am Soc Nephrol. 2022;33(9):1742–56. doi: 10.1681/ASN.2021101384.

33 Liu L, Zhang Y, Duan X, Peng Q, Liu Q, Zhou Y, et al. C3a, C5a renal expression and their receptors are correlated to severity of IgA nephropathy. J Clin Immunol. 2014;34(2):224–32. doi: 10.1007/s10875-013-9970-6.

34 Mizuno M, Blanchin S, Gasque P, Nishikawa K, Matsuo S. High levels of complement C3a receptor in the glomeruli in lupus nephritis. Am J Kidney Dis. 2007;49(5):598–606. doi: 10.1053/j.ajkd.2007.02.271.

35 Bao L, Osawe I, Haas M, Quigg RJ. Signaling through up-regulated C3a receptor is key to the development of experimental lupus nephritis. J Immunol. 2005;175(3):1947–55. doi: 10.4049/jimmunol.175.3.1947.

36 You D, Weng M, Wu X, Nie K, Cui J, Chen Y, et al. C3aR contributes to unilateral ureteral obstruction-induced renal interstitial fibrosis via the activation of the NLRP3 inflammasome. Life Sci. 2022;308:120905. doi: 10.1016/j.lfs.2022.120905.

37 Morigi M, Perico L, Corna D, Locatelli M, Cassis P, Carminati CE, et al. C3a receptor blockade protects podocytes from injury in diabetic nephropathy. JCI Insight. 2020;5(5):e131849. doi: 10.1172/jci.insight.131849.

38 Morigi M, Locatelli M, Rota C, Buelli S, Corna D, Rizzo P, et al. A previously unrecognized role of C3a in proteinuric progressive nephropathy. Sci Rep. 2016;6:28445. doi: 10.1038/srep28445.

39 DiScipio RG, Schraufstatter IU. The role of the complement anaphylatoxins in the recruitment of eosinophils. Int Immunopharmacol. 2007;7(14):1909–23. doi: 10.1016/j.intimp.2007.07.006.

40 Nath KA, Hostetter MK, Hostetter TH. Pathophysiology of chronic tubulointerstitial disease in rats. Interactions of dietary acid load, ammonia, and complement component C3. J Clin Invest. 1985;76(2):667–75. doi: 10.1172/JCI112020.

41 Tang Z, Lu B, Hatch E, Sacks SH, Sheerin NS. C3a mediates epithelial-to-mesenchymal transition in proteinuric nephropathy. J Am Soc Nephrol. 2009;20(3):593–603. doi: 10.1681/ASN.2008040434.

42 Peng Q, Wu W, Wu KY, Cao B, Qiang C, Li K, et al. The C5a/C5aR1 axis promotes progression of renal tubulointerstitial fibrosis in a mouse model of renal ischemia/reperfusion injury. Kidney Int. 2019;96(1):117–28. doi: 10.1016/j.kint.2019.01.039.

43 Han R, Hu S, Qin W, Shi J, Hou Q, Wang X, et al. C3a and suPAR drive versican V1 expression in tubular cells of focal segmental glomerulosclerosis. JCI Insight. 2019;4(13):e130986. doi: 10.1172/jci.insight.130986.

44 Portilla D, Xavier S. Role of intracellular complement activation in kidney fibrosis. Br J Pharmacol. 2021;178(14):2880–91. doi: 10.1111/bph.15408.

45 Poppelaars F, Thurman JM. Complement-mediated kidney diseases. Mol Immunol. 2020;128:175–87. doi: 10.1016/j.molimm.2020.10.015.

46 Cerullo D, Rottoli D, Corna D, Rizzo P, Abbate M, Macconi D, et al. Characterization of a rat model of myeloperoxidase-anti-neutrophil cytoplasmic antibody-associated crescentic glomerulonephritis. Nephron. 2021;145(4):428–44. doi: 10.1159/000515421.

47 Stenson EK, You Z, Reeder R, Norris J, Scott HF, Dixon BP, et al. Complement activation fragments are increased in critically ill pediatric patients with severe AKI. Kidney 360. 2021;2(12):1884–91. doi: 10.34067/KID.0004542021.

48 Zheng X, Zhang X, Feng B, Sun H, Suzuki M, Ichim T, et al. Gene silencing of complement C5a receptor using siRNA for preventing ischemia/reperfusion injury. Am J Pathol. 2008;173(4):973–80. doi: 10.2353/ajpath.2008.080103.

49 Schröppel B, Akalin E, Baweja M, Bloom RD, Florman S, Goldstein M, et al. Peritransplant eculizumab does not prevent delayed graft function in deceased donor kidney transplant recipients: results of two randomized controlled pilot trials. Am J Transplant. 2020;20(2):564–72. doi: 10.1111/ajt.15580.

50 Huang J, Cui Z, Gu Q-H, Zhang Y-M, Qu Z, Wang X, et al. Complement activation profile of patients with primary focal segmental glomerulosclerosis. PLoS One. 2020;15(6):e0234934. doi: 10.1371/journal.pone.0234934.

51 Liu G, Wang Q, Shi Y, Peng X, Liu H, Peng Y, et al. Resveratrol attenuates adriamycin-induced focal segmental glomerulosclerosis through C3aR/C5aR- sphingosine kinase 1 pathway. Pharmacology. 2017;100(5–6):253–60. doi: 10.1159/000479525.

52 Angeletti A, Cantarelli C, Petrosyan A, Andrighetto S, Budge K, D'Agati VD, et al. Loss of decay-accelerating factor triggers podocyte injury and glomerulosclerosis. J Exp Med. 2020;217(9):e20191699. doi: 10.1084/jem.20191699.

53 Zhang XD, Cui Z, Zhang MF, Wang J, Zhang YM, Qu Z, et al. Clinical implications of pathological features of primary membranous nephropathy. BMC Nephrol. 2018;19(1):215. doi: 10.1186/s12882-018-1011-5.

54 Zhang M-F, Huang J, Zhang Y-M, Qu Z, Wang X, Wang F, et al. Complement activation products in the circulation and urine of primary membranous nephropathy. BMC Nephrol. 2019;20(1):313. doi: 10.1186/s12882-019-1509-5.

55 Salant DJ, Belok S, Madaio MP, Couser WG. A new role for complement in experimental membranous nephropathy in rats. J Clin Invest. 1980;66(6):1339–50. doi: 10.1172/JCI109987.

56 Haddad G, Lorenzen JM, Ma H, de Haan N, Seeger H, Zaghrini C, et al. Altered glycosylation of IgG4 promotes lectin complement pathway activation in anti-PLA2R1-associated membranous nephropathy. J Clin Invest. 2021;131(5):e140453. doi: 10.1172/JCI140453.

57 Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity. 2007;40(8):560–6. doi: 10.1080/08916930701510673.

58 Song D, Guo WY, Wang FM, Li YZ, Song Y, Yu F, et al. Complement alternative Pathway's activation in patients with lupus nephritis. Am J Med Sci. 2017;353(3):247–57. doi: 10.1016/j.amjms.2017.01.005.

59 Edelbauer M, Kshirsagar S, Riedl M, Haffner D, Billing H, Tönshoff B, et al. Markers of childhood lupus nephritis indicating disease activity. Pediatr Nephrol. 2011;26(3):401–10. doi: 10.1007/s00467-010-1720-x.

60 Wenderfer SE, Wang H, Ke B, Wetsel RA, Braun MC. C3a receptor deficiency accelerates the onset of renal injury in the MRL/lpr mouse. Mol Immunol. 2009;46(7):1397–404. doi: 10.1016/j.molimm.2008.12.004.

61 Bao L, Osawe I, Puri T, Lambris JD, Haas M, Quigg RJ. C5a promotes development of experimental lupus nephritis which can be blocked with a specific receptor antagonist. Eur J Immunol. 2005;35(8):2496–506. doi: 10.1002/eji.200526327.

62 Li XQ, Chang DY, Chen M, Zhao MH. Complement activation in patients with diabetic nephropathy. Diabetes Metab. 2019;45(3):248–53. doi: 10.1016/j.diabet.2018.04.001.

63 Li XQ, Chang DY, Chen M, Zhao MH. Deficiency of C3a receptor attenuates the development of diabetic nephropathy. BMJ Open Diabetes Res Care. 2019;7(1):e000817. doi: 10.1136/bmjdrc-2019-000817.
64 Yiu WH, Li RX, Wong DWL, Wu HJ, Chan KW, Chan LYY, et al. Complement C5a inhibition moderates lipid metabolism and reduces tubulointerstitial fibrosis in diabetic nephropathy. Nephrol Dial Transplant. 2018;33(8):1323–32. doi: 10.1093/ndt/gfx336.
65 Tan SM, Ziemann M, Thallas-Bonke V, Snelson M, Kumar V, Laskowski A, et al. Complement C5a induces renal injury in diabetic kidney disease by disrupting mitochondrial metabolic agility. Diabetes. 2020;69(1):83–98. doi: 10.2337/db19-0043.
66 Zhao SJ, Wu KY, Min XY, Wang CX, Cao B, Ma N, et al. Protective role for C3aR in experimental chronic pyelonephritis. FASEB J. 2022;36(11):e22599. https://doi.org/10.1096/fj.202201007R.
67 Choudhry N, Li K, Zhang T, Wu KY, Song Y, Farrar CA, et al. The complement factor 5a receptor 1 has a pathogenic role in chronic inflammation and renal fibrosis in a murine model of chronic pyelonephritis. Kidney Int. 2016;90(3):540–54. doi: 10.1016/j.kint.2016.04.023.
68 Home - ClinicalTrials.gov [Internet]. [cited 2023 Jun 14]. Available from: https://www.clinicaltrials.gov/.
69 Hoehlig K, Maasch C, Shushakova N, Buchner K, Huber-Lang M, Purschke WG, et al. A novel C5a-neutralizing mirror-image (l-)Aptamer prevents organ failure and improves survival in experimental sepsis. Mol Ther. 2013;21(12):2236–46. doi: 10.1038/mt.2013.178.
70 Khan MA, Maasch C, Vater A, Klussmann S, Morser J, Leung LL, et al. Targeting complement component 5a promotes vascular integrity and limits airway remodeling. Proc Natl Acad Sci U S A. 2013;110(15):6061–6. doi: 10.1073/pnas.1217991110.
71 Woodruff TM, Crane JW, Proctor LM, Buller KM, Shek AB, de Vos K, et al. Therapeutic activity of C5a receptor antagonists in a rat model of neurodegeneration. FASEB J. 2006;20(9):1407–17. doi: 10.1096/fj.05-5814com.
72 Lee A. Avacopan: first approval. Drugs. 2022;82(1):79–85. doi: 10.1007/s40265-021-01643-6.
73 Moriconi A, Cunha TM, Souza GR, Lopes AH, Cunha FQ, Carneiro VL, et al. Targeting the minor pocket of C5aR for the rational design of an oral allosteric inhibitor for inflammatory and neuropathic pain relief. Proc Natl Acad Sci. 2014;111(47):16937–42. doi: 10.1073/pnas.1417365111.
74 Lee JD, Taylor SM, Woodruff TM. Is the C3a receptor antagonist SB290157 a useful pharmacological tool? Br J Pharmacol. 2020;177(24):5677–8. doi: 10.1111/bph.15264.
75 Boos L, Campbell IL, Ames R, Wetsel RA, Barnum SR. Deletion of the complement anaphylatoxin C3a receptor attenuates, whereas ectopic expression of C3a in the brain exacerbates, experimental autoimmune encephalomyelitis. J Immunol. 2004;173(7):4708–14. doi: 10.4049/jimmunol.173.7.4708.