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Renal Diseases and the Role of Complement – Linking Complement to Immune Effector Pathways and Therapeutics

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Abstract

The complement system is an ancient and phylogenetically conserved key danger sensing system that is critical for host defense against pathogens. Activation of the complement system is a vital component of innate immunity required for the detection and removal of pathogens. It is also a central orchestrator of adaptive immune responses and a constituent of normal tissue homeostasis. Once complement activation occurs, this system deposits indiscriminately on any cell surface in the vicinity and has the potential to cause unwanted and excessive tissue injury. Deposition of complement components is recognized as a hallmark of a variety of kidney diseases, where it is indeed associated with damage to the self. The provenance and the pathophysiological role(s) played by complement in each kidney disease is not fully understood. However, in recent years there has been a renaissance in the study of complement, with greater appreciation of its intracellular roles as a cell-intrinsic system and its interplay with immune effector pathways. This has been paired with a profusion of novel therapeutic agents antagonizing complement components, including approved inhibitors against complement components (C)1, C3, C5 and C5aR1. A number of clinical trials have investigated the use of these more targeted approaches for the management of kidney diseases. In this review we present and summarize the evidence for the roles of complement in kidney diseases and discuss the available clinical evidence for complement inhibition.

Keywords

Kidney disease; Immunology; Complement system; Complosome; C3; C5; Complement inhibitors; Eculizumab; Avacopan

Introduction

Kidney diseases are highly prevalent worldwide, and significant causes of morbidity and mortality. Chronic kidney disease (CKD), defined as kidney damage or decreased renal function lasting for more than three months, affects 1 in 7 adults in the United States. Acute kidney injury (AKI), which occurs over a shorter period, often days or weeks, is estimated

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to affect 1 in 5 adults hospitalized with acute illness (Centers for Disease Control and Prevention, 2021; Saran et al., 2020). Both CKD and AKI can progress to end-stage kidney disease (ESKD), requiring renal placement therapy (RRT), and have significant implications for health. CKD, for example, is a significant independent risk factor for cardiovascular disease, which has double the prevalence in the CKD, compared to the non-CKD, population (Chronic Kidney Disease Prognosis Consortium et al., 2010). AKI, despite improvements in clinical care, greater awareness and earlier diagnosis, continues to have an associated mortality of over 20% in adults (Rewa & Bagshaw, 2014; Susantitaphong et al., 2013). Despite these epidemiological predicates, the mainstay of therapy for kidney diseases is supportive care, management of hypertension, cardiovascular risk, electrolyte and endocrine abnormalities. This is because the underlying pathogenesis of most kidney diseases remain complex and largely undefined. Where there are clear features showing overactivation of the immune system directed against kidney tissues, such as infiltration by inflammatory immune cells, or deposition of immune complex, broad-spectrum immunosuppression has historically been employed. While undoubtedly effective in some individuals, such strategies, by nature of their broad-spectrum function, predispose patients to infections, neoplastic transformation and further cardiovascular injury. In the modern era, concerted efforts and sophisticated methods to study kidney diseases have shed light on some of the pathogenic mechanisms at play and highlighted some that are amenable to targeted therapy using more specific inhibitors. The complement system is an exemplar of an immunological system intimately associated with kidney diseases that is undergoing a renaissance in both the basic science and the clinical spheres and in which a profusion of novel therapeutic agents is currently occurring. Here, we review the role of the complement system in kidney diseases and discuss some of the newer agents targeting complement components.

The complement system

The complement system is an evolutionarily ancient and highly conserved component of immunity (Noris & Remuzzi, 2013). It is broadly acknowledged as a key component of innate immunity required for the detection and removal of pathogens. However, complement is also a central orchestrator of adaptive immune responses and recent work identified this system as key to normal tissue homeostasis. Since perturbations in any of these complement activities are connected with kidney disease on some level or the other, we will give a relatively broad introduction into the complement system here.

Complement was originally discovered as a plasma-based protein system that “complemented” antibody-based immune reactions (Silverstein, 1986) and is discussed at length in other chapters in this series (note to editorial team: please add link here to the most appropriate chapter for the interested reader to access). Briefly, at its core, it is a system of proteins that are enzymatically cleaved and activated following recognition of danger signals into bioactive components in a cascade-like fashion. Conceptually, the plasma-based complement system can be activated by three distinct pathways, the classical (triggered by recognition of immune complexes), lectin (triggered by pattern recognition signals) and the alternative (triggered by recognition of altered-self or tick-over) pathways (Holers, 2014). The result of these pathways is formation of the C3 and, consecutively, C5 convertases, protein complexes that cleave and activate the central components C3 and C5,

respectively. This process initiates the terminal pathway, which includes formation of a lytic membrane attack complex (MAC). The terminal pathway should not be understood as the only effector pathway, as many complement fragments generated during activation of this system also have effector functions. Among those are the important anaphylatoxins C3a and C5a, which have mostly proinflammatory functions, and the opsonins (C3b and C4b and further breakdown products) which mediate antigen/target opsonization and removal by scavenger cells. Because complement, once activated, has the potential to also harm healthy host tissue, it is tightly controlled by a number of regulators that block complement activation or limit the half-life of the convertases. Considering the complement system as compartmentalized into three main activation pathways aids the understanding of function and regulation of this system (Figure 1).

The classical pathway is initiated by binding of antibodies to a pathogen or autoantigen to generate an immune complex, which is then detected by the C1 complex. This complex circulates in serum as a complex containing C1q, C1r and C1s (Noris & Remuzzi, 2013), which are assembled into a multimeric structure resembling a bouquet. C1q can attach to the Fc portion of antibodies in immune complexes, initiating a confirmation change in C1 that enables autoactivation of C1r, which in turn cleaves C1s. C1s can then cleave C4 and C2. The C4bC2b complex represents the classical pathway C3 convertase that initiates C3 cleavage. In healthy conditions only IgG and IgM are known to be able to activate complement. Among the subclasses, IgG1 and IgG2 feature a stronger activation, IgG2 a lesser and IgG4 none.

The lectin pathway is activated by pattern recognition. These patterns can derive from invading pathogens (pathogen associated molecular patterns, PAMPs) or from dangerously altered host cells, such as dying, stressed, or infected cells (danger associated molecular patterns, DAMPs) (Garred et al., 2016). Lectins bind to repetitive carbohydrate patterns within PAMPs and DAMPs (Holmskov et al., 2003). Among the lectins of the lectin complement pathway pattern are mannose-binding lectin (MBL), the ficolins ficolin-1, ficolin-2, ficolin-3 and ficolin-10 and collectin-11 (Świerzko & Cedzyński, 2020). The recognition complexes of the lectin pathway (MBL, ficolins and collectins) are, like C1, each assembled into a bouquet like structure (Garred et al., 2016). However, MBL-associated serine proteases (MASPs)-1, -2 and -3 (instead of C1r and C1s) are the associated proteases that cleave C4 and C2 after binding to generate C4bC2b, the lectin (and classical) C3 convertase.

In contrast, the alternative pathway is not dependent on pattern recognition but rather detects amino groups present on all living cells. Low levels of C3 are constantly activated in serum into C3b via hydrolysis of the thioester, in a process termed “tick over”. Such tonically generated C3b activation fragments can then deposit on any surface. This ensures rapid detection of invading pathogens or noxious self and irritants. Under physiological conditions, attack of healthy host tissue by C3b is prevented through the expression of complement regulators that inactivate C3b (see below). However, if C3b binds to the surface of pathogens or cell debris (which are mostly devoid of complement regulators), C3 activation will amplify as a positive feedback loop involving Factors B, D (CFB and CFD) and properdin to generate the alternative pathway C3 convertase C3bBb. The alternative

pathway is phylogenetically considered as the most ancient complement activation pathway and the C3 gene is the earliest complement molecule gene detected across the evolutionary development of the animal kingdom and is present in invertebrates (Al-Sharif et al., 1998; Zarkadis et al., 2001).

The formation of C3 convertase and further local C3 activation generally leads to the rapid assembly of C5 convertases, which then cleave C5 into C5a and C5b. The classical and lectin pathway C3 convertases form the classical and lectin pathway C5 convertase (C4bC2bC3b) and the alternative pathway C3 convertase generates the alternative pathway C5 convertase (C3bBbC3b). This latter pathway is also a potent amplification mechanism for both the classical and lectin pathways (Merle, Church, et al., 2015). The C5 convertases are key in the initiation of the terminal pathway as the generated C5b, in conjunction with serum complement components C6 to C9, assembles the membrane attack complex (MAC, C5b-9) – which can kill pathogens via direct lysis (Bajic et al., 2015). Cleavage of C5 also generates C5a, a potent anaphylatoxin. It is important to note that both C3 and C5 can also be activated in a convertase-independent fashion by non-canonical complement activators comprising a number of proteases, including those belonging to the coagulation system, as well as granzymes and cathepsins (Huber-Lang et al., 2018; Lupu et al., 2014; Minta et al., 1977).

As mentioned, once complement activation occurs, this system deposits on any cell surface in the vicinity indiscriminately. To prevent detrimental complement attack on healthy host cells and tissues, complement activation needs to be controlled, a task mediated by a range of fluid phase and cell membrane bound regulators. The required regulation occurs at the level of initial binding of complement components to targets (initiation), convertase assembly (propagation) and membrane attack complex formation (lysis). For example, C1 Inhibitor (C1Inh), a serine protease inhibitor blocking C1 as well as MASPs, controls unwanted C1 activation in serum. Complement Factor H (CFH) and C4B binding protein (C4BP) can detect surface deposited C3b and C4b, respectively, and act as cofactors in the inactivation of C3b and C4b by the serum protease Factor I (CFI). Surface expressed regulators, such as CD46 (membrane cofactor protein, MCP) function in a similar fashion as co-factors for CFI to inactivate C3b and C4b by proteolytic cleavage (Liszewski et al., 1991, 2005). It is important to note that rodent hematopoetic cells do not express a molecule performing identical functions to human CD46. In case C3b and C4b deposition cannot be kept in check, regulation also happens at the level of convertase formation. Regulators such as CD46, CD55 (decay acceleration factor, DAF) and CD35 (complement receptor 1, CR1) accelerate the decay of formed convertases and thus hamper amplification of complement activation. C4BP limits the function of C4b and accelerates the decay of the C3 convertase generated by classical or lectin pathways (Podack & Müller-Eberhard, 1978).

Finally, should the first two steps of control prove ineffective, MAC formation is inhibited by CD59 and vitronectin. Of note, there is only one known positive regulator of complement activation, properdin, which specifically stabilizes the alternative pathways C3 convertase, an activity that makes properdin an attractive therapeutic target in inflammatory diseases. Importantly, the CD55 and CD59 genes are duplicated in the mouse, with different patterns of tissue expression, highlighting a discrepancy to human (D. D. Kim & Song, 2006).

Regulation on the level of membrane attack/lysis can be mediated by vitronectin which prevents MAC attachment to the cell membrane (Podack & Müller-Eberhard, 1978).

Effector mechanisms recruited by complement

Once complement activation has been achieved, the biologically active fragments generated recruit key components of the immune system, including innate and adaptive mechanisms, to mount an effector response against the inciting danger signal. These are all of relevance when considering the pathological effects of complement in kidney diseases and the potential adverse effects of complement-targeting therapies.

Complement and the innate immune system

Complement activation initiates a number of mechanisms for removal of the inciting danger signal. These include direct lysis of pathogens by insertion of MAC into outer membranes, recruitment and activation of innate immune cells by anaphylatoxins, and directing phagocytosis of pathogens via engagement of opsonins by specific complement receptors (Merle, Church, et al., 2015; Schifferli et al., 1988; Walport, 2001). The chief anaphylatoxins are C3a and C5a. These are chemoattractant molecules that engage cognate G protein-coupled receptors leading to recruitment and activation of immune cells (Klos et al., 2009). C3a binds the C3a receptor (C3aR), while C5a can bind either C5a receptor 1 (C5aR1, CD88) or receptor 2 (C5aR2, or C5L2) (Cain & Monk, 2002; Crass et al., 1996, 1999; Gerard & Gerard, 1991). C3aR is expressed by both myeloid (including neutrophils, basophils, eosinophils, mast cells, monocytes/macrophages and dendritic cells (DCs)) and non-myeloid (including endothelial and epithelial) cells (Klos et al., 2009). C3aR signaling recruits classical signaling moieties that are intimately associated with immune activation, including MAPK and PI3K, but this receptor also plays a role in negative regulation of immune cells (Coulthard & Woodruff, 2015). C5aR1 also has broad tissue expression, but is especially present on myeloid cells, where it is also coupled to a number of signaling pathways involved in immune activation, including MAPK and PI3K (Klos et al., 2009; Langkabel et al., 1999; Norgauer et al., 1993). C5aR1 expression and its activation on endothelial cells is recognized as a key player in vascular inflammation (D. Jayne, 2019). C5aR2 is also broadly expressed but has less well characterized functions. Although there is consensus that it mostly portents anti-inflammatory functions, one of which is to suppress expression of C5aR1, it can clearly also have pro-inflammatory activities in certain settings, such as sepsis (X. X. Li et al., 2019). In general, ligation of receptors for C3a and C5a activate endothelial surfaces (Dobrina et al., 2002; Tedesco et al., 1997) and chemoattract and activate innate immune cells, resulting in degranulation, generation of reactive oxygen species and production of inflammatory cytokines (Asgari et al., 2013; Brekke et al., 2007; Haggadone et al., 2016; Mollnes et al., 2002). Complement activation also generates a number of opsonins, which are factors that facilitate phagocytosis, including C4b, C3b and additional C3 processed fragments, such as iC3b, C3dg and C3d. These complement components deposited on the surface of target cells are recognized by specific receptors (for example, CD11b/CD18, CR3 or Mac-1 and CD11c/CD18, CR4) expressed on phagocytic cells that are attracted to these sites by anaphylatoxins (Holers, 2014; Merle, Noe, et al., 2015).

Complement fragments are clearly essential for appropriate recruitment, activation and maturation of antigen-presenting cells, as evidenced by the ability of the anaphylatoxins C3a and C5a to upregulate co-stimulatory molecules (HLA-DR, CD86 and CD40) on monocyte-derived DCs and to enhance their capacity for allo-stimulation (K. Li et al., 2012), together with the clear impairment of DC maturation seen in patients with C3 deficiency (Ghannam et al., 2008). However, they also have a role to play in tolerogenic functions as well. For example, ligation of the complement C3 activation product iC3b to CR3 on APCs results in sequential production of transforming growth factor-β2 and interleukin (IL)-10, which are essential for induction of tolerance (Sohn et al., 2003). Likewise, C3 is necessary for the induction and tolerogenicity of myeloid derived suppressor cells (MDSCs), immature myeloid cells characterized by the ability to suppress immune responses, in murine transplant models (Hsieh et al., 2013). Thus, there is considerable complexity in ascribing broad roles to complement, i.e. inflammatory or anti-inflammatory, when found at sites of inflammation. This is an important point when considering complement inhibition in the context of disease. An additional factor is that cells of the immune system also produce complement components when appropriately activated. Many immune cells of the have this ability, including T lymphocytes, neutrophils, monocytes/macrophages, NK cells, DCs, and mast cells, as reviewed elsewhere (Lubbers et al., 2017).

Another important concept is that, as a sophisticated danger recognition system, complement engages into considerable cross-talk with other danger sensing systems. For example, many PAMPs activate not only toll like receptors (TLRs) but also complement factors (Reis et al., 2019). These include components of all three of the complement activation pathways, including C1q, MBL, ficolins, collectins and properdin (Ghiran et al., 2002; M. Howard et al., 2018; Köhl, 2006). Properdin, for example, quite apart from its role in stabilizing C3 convertase, binds to PAMPs (Spitzer et al., 2007), potentially in a manner independent from C3b deposition (Harboe et al., 2017; Kemper et al., 2008; O'Flynn et al., 2018). Once TLRs and complement receptors are recruited, there can be significant cross-talk, resulting in synergistic or antagonistic outcomes, which are cell- and context-specific. There are several examples of this. The C1q receptor, gC1gR, for example, signals through the PI3-K pathway to repress LPS-dependent TLR4-induced production of IL-12 from macrophages and dendritic cells (DCs) (Waggoner et al., 2005), but enhances maturation of monocyte-derived immature DCs and promotes their secretion of IL-12 (Csomor et al., 2007). In mice, knockout of CD55 (DAF) or inactivation of C3 modulates cytokine production after TLR stimulation (X. Zhang et al., 2007) indicating co-dependence between the two. Likewise, activation of AP-1 and NF-kB by receptors for C3a and C5a interacts with signals derived from TLR4, amplifying pro-inflammatory effects in monocytes but antagonizing them in macrophages (Bosmann et al., 2012; Hawlisch et al., 2005; Seow et al., 2013). This cell-specific effect may promote the sentinel function of monocytes, but limit tissue damage conveyed through macrophages (Reis et al., 2019). C5 receptors further interact with the TLR system, both directly and indirectly. For example, C5aR1 and TLR2 act synergistically to transduce cAMP and PKA signaling (M. Wang et al., 2010), while TLR4 enhances the pro-inflammatory effects of C5a by negatively regulating the inhibitory alternate C5a receptor, C5aR2 (Raby et al., 2011). The functional cross-talk between TLRs and complement receptors have both direct and indirect effects on the immune system,

which are often difficult to dissect. Notably, while they may directly modify the maturity and function of antigen presenting cells (APCs), an indirect effect is to influence T helper cell polarization after these APCs present antigen to T cells bearing their cognate receptors. The consensus is that complement receptor signaling on APCs, in a context-specific fashion, endows these cells with Th1 or Th17 polarizing capacity. Thus, for example, global C3 and C5 deficiency leads to impaired Th1 polarization highlighting indirect effects on T cells (Drouin et al., 2006; Ghannam et al., 2008; Karp et al., 2000, p. 2000) despite C5aR1 signaling on DCs.

Complement and the adaptive immune system

Complement receptor mediated signals shape the functional phenotype of APCs and, by extension, ensuing T cell responses. However, the complement system also has direct effects on T cells, which are essential for mediation of effector responses. T cells express both receptors for C3a and C3b, C3aR and CD46 on human T cells. Deficiency of either of these in T cells renders them unable to differentiate to Th1 cells (Ghannam et al., 2014; Le Friec et al., 2012). In fact, $CD4^+$ T cells transcribe their own C3 at low levels while in circulation (Kolev et al., 2020) and take up a small percentage of their C3 stores from the extracellular space in the form of C3(H2O) (Elvington et al., 2017). Migration into tissues across activated endothelial surfaces results in interactions between ICAM-1 and LFA-1, which is the signal to augment C3 transcription and C3 protein stores, a process termed ‘C3-licensing’ (Kolev et al., 2020). Basal levels of C3 in T cells constantly tick-over, generating C3 breakdown products that maintain tonic mTOR signaling. This is essential for $CD4^+$ T cell survival in the periphery. When the T cell receptor is then engaged upon antigen presentation, together with appropriate co-stimulation (e.g. through CD28), intracellular stores of C3 are mobilized and targeted to lysosomes, where they are processed to active C3a and C3b by cathepsin L (CTSL), before being targeted for secretion form the cell. The intracellularly generated C3a and C3b can translocate to the cell surface and engage with C3aR and CD46, respectively, but C3a also engages C3aR intracellularly. The overall effect is to change the bioenergetic state of the cell, by enhancing nutrient influx and activation of the mTOR pathway, allowing the cell to synthesize proteins required for Th1 induction and IFN-γ expression (Liszewski et al., 2013). Thus, patients deficient for C3 can also not mount a sufficient Th1 response (Ghannam et al., 2014).

The support of protective Th1 responses is somewhat intuitive for complement activation. However, cell-intrinsic complement is also significantly involved in the timely contraction of T cell immunity. Specifically, sustained CD46 signaling, together with IL-2, also initiates transition of inflammatory Th1 cells to a regulatory phenotype, shutting down IFN-γ production and switching on IL-10 secretion (Cardone et al., 2010; Kemper et al., 2003; Liszewski et al., 2013). Thus, C3b signaling through CD46 is part of a complex lifecycle of $CD4^+$ T cells and required for both initiation and shutdown of inflammation. While some of the molecular mechanisms of the versatility of CD46 is now known, it is possible that alternative splicing of the pre-mRNA, resulting in four different isoforms, may in part be responsible for its complex behavior (Choileain et al., 2011; Kolev et al., 2015; Le Friec et al., 2012; Liszewski & Atkinson, 1996).

Human $CD4^+$ T cells also contain stores of C5, although how the C5 gene is regulated or how C5 is processed inside cells is currently unknown. Intracellular ligation of C5a to C5aR1 induces mitochondrial ROS production in these cells, which is an upstream activator of NLPR3 inflammasome assembly and required for IL-1-β maturation and secretion. These events are required for optimal IFN-γ production and Th1 polarization of human $CD4^+$ T cells and thus control the magnitude of Th1 responses (Arbore et al., 2016).

Human $CD8^+$ T cells also contain intracellular stores of C3. Here, C3 processing, also triggered following stimulation through the TCR and co-stimulation, generates C3b and engages CD46. Ligation of CD46 in $CD8^+$ T cells also mediated metabolic shifts, in this case activating fatty-acid reprogramming, which supports cytotoxic effector function with granzyme B and IFN-γ production in these cells (Arbore et al., 2018).

Importantly, mice do not express CD46 on somatic tissue and a functional homologue that recapitulates the activity of CD46 in mice has not yet been identified. Thus, the cell-intrinsic mechanism of CD46 engagement as an integral part of the Th1 program is a human-specific pathway. There are other notable species-specific differences in the contribution of complement to T cell regulation. In humans T cells, C5aR1 is only expressed intracellularly, differing to murine T cells which express C5aR1 on the surface. In contrast, human C5aR2 is expressed both intra- and extracellularly, while the murine protein is limited to the intracellular compartment (Arbore et al., 2016; Strainic et al., 2013). Despite lack of a functional CD46 molecule in mouse $CD4^+$ T cells, engagement of anaphylatoxin receptors C3aR and C5aR1/2 similarly results in IL-12 receptor expression and activation of mTOR complex 1 through the PIK3 pathway, which are required for Th1 differentiation (Lalli et al., 2008; Strainic et al., 2008). The criticality of these receptors is shown by double knockout mice, where simultaneous absence of C3aR and C5aR1 diminishes Th1 responses and enhances secretion of IL-10 and TGF-b. In line with these findings, these mice also show increased frequency of FoxP3+ regulatory T cells in vitro (Kwan et al., 2013; Strainic et al., 2013; van der Touw et al., 2013). T cells also express other complement receptors, including CR1/CR2 and C1q receptor, but these are either expressed on subsets of T cells or are inducible on activation (A. Chen et al., 1994; Erdei et al., 2009; Pekalski et al., 2017). Their roles remains largely unexplored, but may mediate sensitivity to IL-2, modulation of mitochondrial metabolism, or denote recent thymic émigrés (Ling et al., 2018; Pekalski et al., 2017; Török et al., 2015).

In B cells, complement receptor activation plays similarly important roles. In fact, CD19 and CD21 (CR2) are part of the B cell co-receptor complex and are also integral to normal B cell activation. CD21 binds to opsonized antigens through attached C3d (or iC3b or C3dg) when the B-cell receptor (BCR) binds antigen. Ligation of C3d to CD21 and co-engagement with CD19 lowers the threshold for BCR signaling (Carter & Fearon, 1992; Dempsey et al., 1996) and enables antigen-specific B cell responses, specifically when antigen concentrations are low. Uncoupling of CD21 from CD19 or a knockout of CD21 and CD35 diminishes survival of germinal center B cells and secondary antibody titers in mice (Barrington et al., 2009; M. B. Fischer et al., 1998; Molina et al., 1996). Of note, in humans, CD21 and CD35 are encoded by separate genes, where mice express it from a single gene known as Cr2 (Jacobson & Weis, 2008). These mice have proven very

useful in the dissection of the important role of complement in the formation and function of germinal centers (GCs), a prime site for antibody manufacture. For example, in the lymph nodes, macrophages patrol the subcapsular sinus (SCS) and capture C3d-opsonized immune complexes or antigens via CR3. They then transfer these through the SCS to CD21 expressed by naïve/non-cognate B cells in the B cell follicles. These B cells transfer C3d-opsonized antigens to follicular dendritic cells in the dark zone, which retain antigen long enough for (re)presentation to cognate primed B cells during the germinal center reaction; events required for induction of antibody producing plasma cells and memory B cells (Z. Chen et al., 2000; Heesters et al., 2016). Interestingly, germinal center B cells physiologically repress expression of CD55 and other complement C3/C5 convertase regulators via the transcription factor BCL6, but increase expression of the C5b-9 MAC inhibitor CD59. These changes permit C3 to be cleaved on the surfaces of GC B cells without formation of MAC and activate C3a- and C5a-receptor signals required for positive selection. Genetic disruption of this pathway causes premature GC collapse and impaired affinity maturation (Cumpelik et al., 2021).

Collectively, complement is clearly essential for the control of adaptive immune responses.

Complement and the coagulation system

Aside from significant crosstalk with other classic danger sensors such as the TLRs and inflammasomes, the complement system also has an intimate relationship with another prominent plasma-effector system, the coagulation cascade. Not only is there a striking commonality in the way the clotting and complement systems are activated (both are zymogen systems activated in a cascade like manner), but they interact on a number of different levels. This includes bi-directional activation and cross-regulation which are particularly important for diseases in which immune activation and thrombosis (‘immunothrombosis’) are coincident, a good example being COVID-19 (Bonaventura et al., 2021). As discussed above, propagation of complement activation is not solely dependent on convertases but can be driven by other proteases. In particular, several components of the coagulation cascade, including thrombin, factors XIa, Xa, IXa, and plasmin are known to cleave C3 or C5, generating their biologically active forms (Ekdahl et al., 2016; Huber-Lang et al., 2006; Markiewski et al., 2007). Conversely, C3a and C5a both promote activation of platelets and epithelial cells, secretion of tissue factor and von Willebrand factor, all of which have pro-coagulant functions (Keragala et al., 2018). Although negative feedback loops are often in place to maintain homeostasis, some inflammatory states result in self-perpetuating feed forward loops. For example, activated platelets express complement receptors (Martel et al., 2011) and are stimulated by complement deposition to release α-granules and microparticles (Sims & Wiedmer, 1995) which, in turn, further activate the complement system (Del Conde et al., 2005). The involvement of complement with healthy functioning of the coagulation system is perhaps best demonstrated by lectin pathway components. MASPs1-3 have pro-coagulant properties, behaving like thrombin and support clot formation and reduce bleeding time upon wounding (Jenny et al., 2018). Deficiency of MBL, which normally does not evoke a spontaneous phenotype, has, however, detrimental consequences when patients are challenged by specific infections, resulting in disseminated intravascular coagulation (Takahashi et al., 2011). Although the close functional relationship

between complement and the coagulation system has long been known, it has only recently been the focus of intense attention as a causative factor for endothelial and epithelial damage and local and systemic microangiopathy – hallmarks of a range of human pathologies, including some kidney diseases.

Local production of complement by kidney cells

Complement was classically described as a plasma operative system secreted by the liver. More recently, it is being recognized that many other tissues produce complement factors (Friščić et al., 2021; K. Li et al., 2007; Morgan & Gasque, 1997). In fact, expression of complement factors from endothelial, mesangial and epithelial cells of the kidneys have all been demonstrated in the 1980s and 1990s (Passwell et al., 1988; S. Sacks et al., 1993; S. H. Sacks, Zhou, Pani, et al., 1993; S. H. Sacks, Zhou, Andrews, et al., 1993; Welch et al., 1993, 1996; Witte et al., 1991; Zhou et al., 1993). In culture, human tubular epithelial cells can be induced to produce C3 in response to IL-2 (Brooimans et al., 1991; Welch et al., 1993), IL-1 (Castellano et al., 2005; Gerritsma et al., 1996), IFN-γ (Castellano et al., 2005), CD40 (Castellano et al., 2005), and IL-17 (Van Kooten et al., 1998) and to repress both C3 and C4 production in response to TGF-b (Gerritsma et al., 1998). Additional complement factors, such as C2, C4, CFB and CFH, can also be induced by cytokines such as IFN-γ (Gerritsma et al., 1997; S. Sacks et al., 1993; Zhou et al., 1993) and IL-1 (Gerritsma et al., 1996). That complement production, notably C3 and C4, from intrinsic kidney cells could be induced or amplified by leukocyte-derived immune activators, such as IFN-γ and IL-2, lead to the postulate that local complement production could enhance local inflammatory responses initiated by other insults. A case in point was demonstration of C3 mRNA induced in kidney cells of rat allografts undergoing ischemic injury or rejection coinciding with peaks in leukocyte-derived factors, such as IL-2 and IFN-γ (Pratt et al., 2000). These observations were extended by an elegant series of experiments that confirmed that locally produced complement, rather than serum derived complement, plays an important role in kidney transplant rejection (Pratt et al., 2002). Here, the investigators performed MHC-mismatched mouse allografts in which grafted kidneys were from wild-type or C3−/− mice. The absence of C3 in allografted kidneys significantly hindered acute transplant rejection, a phenomenon attributed to defective T cell priming in the absence of C3 produced locally (Pratt et al., 2002). As has been discussed, immune cells of both the lymphoid and myeloid lineages have significant capacity for transcription of complement genes and rely on autocrine/paracrine complement receptor signaling for appropriate immune responses. So, while these experiments demonstrated the potential importance of C3 produced within kidneys as pathogenic factors, they did not directly attribute this to intrinsic kidney cells, as opposed to C3-producing resident or infiltrating immune cells. In fact, until recently, a C3floxed mouse was not available to enable conditional deletion of C3 in kidney cells themselves. This is also true of other complement components that can be produced by intrinsic cells of the kidneys – until tissue-specific deletion of these have been made in animal models, it is difficult to know the importance and role(s) of kidney-derived complement under both physiological and pathological conditions and to predict the likely benefit or disadvantage of therapeutic interventions directly targeting these.

Drugs targeting the complement system

In the recent 15 years several drugs directly targeting complement components (Table 1) have been developed and marketed, thus establishing new and promising therapeutic options for patients with complement-mediated diseases (Mastellos et al., 2019; Ricklin et al., 2018). The C5 inhibitor Eculizumab, the first complement inhibitor marketed, marked a milestone, and was initially approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), in which its clinical benefit has been clearly demonstrated (Brodsky et al., 2008). The most common mutations in PNH affect the PIGA gene, which encodes phosphatidylinositol glycan A, an enzyme required for the synthesis of glycosyl phosphatidylinositols (GPIs), glycolipids that anchor come proteins to the cell membrane. Absence of GPI anchoring results in membrane deficiency of the complement inhibitory proteins CD55 and CD59, making red blood cells particularly susceptible to chronic complement-mediated hemolysis, as well as activating platelets, monocytes, and granulocytes (Brodsky, 2014). Eculizumab is a monoclonal antibody that works by binding to C5, blocking C5 activation, and thereby the terminal complement pathway with formation of the MAC. Recently, the C3 inhibitor Pegcetacoplan, a pegylated peptide that binds C3 and C3b and inhibits C3 cleavage, was approved for use in PNH as an upstream regulator of complement activation. Pegcetacoplan was superior to Eculizumab regarding clinical and hematologic outcomes of PNH in the PEGASUS trial (Hillmen et al., 2021). Meanwhile, Eculizumab has been additionally approved for treatment of atypical hemolytic uremic syndrome (see below) and myasthenia gravis after successful trials (J. F. Howard et al., 2017; Legendre et al., 2013; Muppidi et al., 2019). A number of additional drugs, ranging from small molecules, peptides and antibodies, that target complement components are in development, have been developed and/or are being trialed in different settings (Ricklin et al., 2018). They are summarized in Table 1. These include the C5aR1 inhibitor Avacopan, which is in the approval process for ANCA-associated vasculitis, as outlined below.

Impact of complement on kidney diseases

Complement components are frequently found within injured kidneys across a range of different pathologies. In most cases, the functional consequences of local complement deposition are unknown, but inferred from animal models approximating human diseases and knowledge of basic complement biology. It is important to note that some complement components are more stable than others and covalently bound to surfaces, so these are often the components that are looked for and found in clinical diagnostic laboratories. This bias can make it difficult to know whether a component is present on its own in a clinical biopsy sample or whether it is part of broad complement activation and includes the full terminal complement components and anaphylatoxins.

Thrombotic microangiopathies

Thrombotic microangiopathies (TMA) are heterogeneous diseases all characterized by distinctive histological appearances of small vessel (arterioles and capillaries) injury and microvascular thrombosis. They share the same clinical features of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and end-organ dysfunction. These are the

sequelae of platelet consumption in microthrombi, shearing injury to red blood cells as they navigate the microthrombi-containing microvasculature and occlusion of blood vessels in major organs. Clinical features, although heterogeneous, typically include hypertension, acute kidney injury and MAHA (Noris et al., 2014; Ruggenenti et al., 2001). In all, a trifecta of pathogenic mechanisms converges to cause clinical syndrome, namely endothelial injury, genetic predisposition and microvascular immunothrombosis. Multiple factors can cause endothelial injury, including pathogenic toxins, viruses, immune complexes and drugs (Goldberg et al., 2010). Genetic predispositions include inherited mutations in complement components or von Willebrand factor (vWF) (Fakhouri & Frémeaux-Bacchi, 2021; Noone et al., 2018). Microvascular immunothrombosis is the term used to refer to local activation of endothelial surfaces, leading to loss of endothelial thrombo-resistance, abnormal vWF aggregation, platelet activation, leukocyte adhesion, complement activation and micro-thrombus formation (Noris et al., 1992; P. E. Rose et al., 1984). Mouse models of TMA are available but suffer from high mortality and do not faithfully reproduce the human clinical picture (Pickering et al., 2007; Smith-Jackson et al., 2019; Ueda et al., 2017). The role of complement factors expressed locally within kidney or immune cells has not been investigated in these diseases.

The three most commonly recognized TMAs are thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome caused by Shiga toxin-producing Escherichia coli (STEC-HUS) or complement-mediated TMA, all of which demonstrate features of complement activation. The non-specific term atypical hemolytic uremic syndrome (aHUS) is commonly used and refers to all TMA that are not associated with Shiga-toxin or ADAMTS13 deficiency. Complement-mediated TMA and TTP can be difficult to distinguish from each other clinically due to their many overlapping features (McFarlane et al., 2021). In general, however, TTP features minimal to no kidney injury, but in the majority of patients includes neurological abnormalities or other signs of organ injury, whereas complement-mediated TMA commonly and predominantly affects the kidneys (Page 2017, George 2014).

TTP is especially characterized by microthrombi containing abnormally large multimers of vWF. vWF is normally sequestered as ultra-large multimers (ULvWF) in special storage compartments of endothelial cells (known as Weibel–Palade bodies) and platelets (a-granules). On endothelial activation, vWF is released into the circulation where it is normally cleaved into smaller multimers by a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13), a metalloprotease also known as vWF-cleaving protease (Furlan et al., 1996; Plaimauer et al., 2002; Tsai, 1996). Because ULvWF agglutinate circulating platelets at sites with high levels of shear stress, a failure to break down ULvWF results in platelet clumping in the microvasculature (Moake et al., 1982) and the clinical syndrome of TTP. This syndrome can be caused by either congenital deficiency of ADAMTS13 through inherited mutations (G. G. Levy et al., 2001) or autoantibodies directed against this protein (Furlan et al., 1996; Tsai, 1996), but a vascular stressor is also required to trigger an episode. These include drugs, infections and pregnancy (Veyradier et al., 2001). Complement activation is observed in TTP (Reti et al., 2012; Ruiz-Torres et al., 2005), deposition of complement fragments is seen in tissues (Chapin et al., 2012) and sera from these patients also has the capacity to activate complement

components in vitro and has a pro-thrombotic effect on endothelial cells (Ruiz-Torres et al., 2005) which can be abrogated by pre-incubation with complement inhibitors (Ruiz-Torres et al., 2005). Although the exact mechanisms of complement activation in TTP are not known, it is likely that coagulation factors, such as thrombin, or other proteases recruited following endothelial injury play a part in activating C3 and C5 (see above) (Ekdahl et al., 2016; Huber-Lang et al., 2006; Markiewski et al., 2007).

STEC-HUS is by far the commonest cause of HUS in children. Many different strains of E. coli are associated with STEC-HUS, but two of the most well-recognized are E. coli 0157:H7 and E. coli O104:H4 (Banatvala et al., 2001; Frank et al., 2011; Soysal et al., 2016; Tarr et al., 2005; Ylinen et al., 2020). Transmission of these strains to human usually occurs via cattle, either from consumption of undercooked, contaminated meat, dairy produce, fruit and vegetables or via water or person-to-person spread (Bell et al., 1994; Vaillant et al., 2009). Commonly, a prodromal syndrome consisting of gastrointestinal symptoms, such as diarrhea, is followed by clinical features consistent with TMA. Shiga toxins produced by STEC bind globotriaosylceramide, a globoside expressed on glomerular vascular endothelial cells, and are both directly cytotoxic and transduce signals that enhance local inflammation (Johannes & Römer, 2010). Together with platelet activation and recruitment of inflammatory cells, ensuing events cause immunothrombosis (Karpman et al., 2001; Nestoridi et al., 2005). In STEC-HUS, there is ample evidence for activation of complement, with elevations in processed fragments of CFB clearly pointing to hyper-activation of the alternative pathways of complement activation (Ståhl et al., 2011; Thurman et al., 2009). One postulated mechanism includes upregulation of endothelial P-selectin by Shiga toxin, which can bind C3b and assemble the alternative pathway convertase (Del Conde et al., 2005; Morigi et al., 2011). Indeed, CFB deficient mice or mice treated with inhibitors of P-selectin are protected from disease (Morigi et al., 2011). Shiga toxin can also directly activate complement via the alternative pathway by binding CFH and complement factor H related protein (CFHR) (Poolpol et al., 2014; Orth et al., 2009).

STEC-HUS is relatively rare in adults. Complement-mediated TMA, although rare, is the more common form of TMA in adult patients. This syndrome is the archetypal disease of dysregulated complement activation. The majority of cases are caused by uncontrolled activation of the alternative pathway, either from loss of complement regulatory proteins (CFH, CFI, CD46, THBD, CFHR1, CFHR3, CFHR5) or from gain-of-function in effector proteins (e.g. CFB, C3) (Bu et al., 2018; Caprioli et al., 2006; de Jorge et al., 2007; Delvaeye et al., 2009; Esparza-Gordillo et al., 2005; Frémeaux-Bacchi et al., 2008; Hofer et al., 2013; Osborne et al., 2018; Zipfel et al., 2007). The majority of cases are genetic, with the most common mutation (~10% of cases) being in complement factor H (CFH), but the disease can also be acquired secondary to development of antibodies against CFH or CFI proteins are (Dragon-Durey et al., 2005; Józsi et al., 2008). Importantly, most genetic mutations show incomplete penetrance. As expected, complement-mediated TMA is also predominantly a disease characterized by hyperactivation/persistence of the alternative pathway of complement activation, resulting in deposition of terminal complement components on endothelial surfaces and consequent immunothrombosis (Landau et al., 2001).

The pathogenic role of complement in TTP, STEC-HUS and complement-mediated TMA indicates that these entities should respond to complement-targeting drugs. Certainly, complement-mediated TMA responds to the C5 targeting drugs, Eculizumab or Ravulizumab (Barbour et al., 2021; Fakhouri et al., 2021; Legendre et al., 2013; Rondeau et al., 2020). This is less clear for STEC-HUS, so Eculizumab is reserved for patients with life-threatening or CNS-involving STEC-HUS, based on anecdotal evidence of potential benefit (Monet-Didailler et al., 2019; Percheron et al., 2018; Walsh & Johnson, 2019). TTP has the highest mortality of any of these conditions, so rapid initiation of therapy aimed at repletion of ADAMTS13 is important. This can take the form of plasma exchange, permitting repletion with ADAMTS13-containing fresh frozen plasma, or infusion of factor VIII concentrate, which also has high concentration of ADAMTS13 (Rock et al., 1991). Complement inhibition is not routinely used in TTP. It has been reported to have additional benefits in patients with TTP that are refractory to plasma exchange (Chapin et al., 2012).

Primary membranous nephropathy

Primary membranous nephropathy is a common glomerulonephritis of adults with characteristic features of glomerular basement membrane thickening (a “membranous” appearance) in the absence of proliferative lesions or cellular infiltration (Fogo et al., 2015; Glassock, 2012). Here, there are granular deposits of immune complexes (of immunoglobulins and complement) in the sub-epithelial and intramembranous regions of the glomerular basement membrane. Patients mostly present with proteinuria with or without loss of kidney function and either recover spontaneously (1/3 of patients), achieve partial remission (1/3 of patients) or have progressive disease (1/3 of patients). Clues as the pathogenesis of this disease was provided by passive Heymann nephritis, a rat experimental model approximating human membranous nephropathy, in which sheep are immunized with crude proximal tubular cell proteins. The resulting antibodies, among them anti-megalin antibody, are injected into rats where they cause immune-complex glomerulonephritis (Barabas & Lannigan, 1974). These immune complexes contain active components of complement, including MAC, resulting in injury to podocytes, which produce extracellular matrix components in response and lose their structural contribution to the glomerular filtration barrier, resulting in proteinuria (Cybulsky et al., 2005; Floege et al., 1992; Nangaku et al., 2005). In this model, blocking the alternative pathway of complement activation using a small-molecule factor B inhibitor (LNP023), or infusion of soluble recombinant complement receptor 1 (which both blocks C3b and C4b and also dissociates C3 and C5 convertases), ameliorates disease (Couser et al., 1995; Schubart et al., 2019), indicating the dependence on complement fixation for the pathogenesis of this model.

While rats express megalin on their podocyte cell surfaces, human podocytes do not. In fact, identification of the auto-antigen(s) responsible for human membranous nephropathy was not successful until recently. In 70–80% of cases of human membranous nephropathy, antibodies appear to be directed against the phospholipase A2 receptor (PLA2R) on podocytes (Beck et al., 2009; Glassock, 2012). A variety of other auto-antibody targets including THSD7A, EXT1/EXT2, NELL1, SEMA3B, HTRA1 and PCDH7 have also been characterized (Al-Rabadi et al., 2021; S. Sethi et al., 2019; S. Sethi, Debiec, Madden, Charlesworth, et al., 2020; S. Sethi, Debiec, Madden, Vivarelli, et al., 2020; S. Sethi et

al., 2021; Tomas et al., 2014). However, some of these, such as THSD7A, the second most common target in membranous nephropathy, features no complement C3 deposition in mouse (Tomas et al., 2017). The auto-antibodies are of the IgG4 subtype, which are not commonly known to activate complement (Tao et al., 1993). Nevertheless complement C3, C4, CFH, CFB, properdin, MBL, and C5b-9 deposition, signifying complement activation, are commonly seen in affected glomeruli (Endo et al., 2004; Kawata et al., 2020; Ravindran et al., 2020; Segawa et al., 2010; R. Zhang et al., 2012). A new study suggests that altered glycosylation of IgG4 could promote lectin complement pathway activation leading to podocyte damage, partially resolving this conundrum (Haddad et al., 2021). However, disease and complement activation has also been reported in cases with MBL deficiency, indicating that the alternative pathway may be sufficient on its own to induce disease (Bally et al., 2016). Another method of complement activation could be by IgG1 through the classical pathway, but C1q is only inconsistently seen in the kidneys, (Reinhard et al., 2020). In support, in a cytotoxicity assay with patient sera and rabbit complement in HEK293 cells, higher IgG subclass diversity and higher total IgG titer is associated with increased cytotoxicity. Furthermore, blocking of the classical and alternative pathway in this assay with Mg-EDTA significantly decreased toxicity (Lateb et al., 2019). A very small subset of patients with membranous nephropathy feature anti-CFH antibodies, but no correlation has been found between the presence of these antibodies and disease severity (Seikrit et al., 2018; A. Sethi et al., 2021; Valoti et al., 2019). Similarly, complement levels in the urine or serum are not routinely measured in clinical practice. When measured, elevated levels of C3a, C4d, C5a, Bb and C5b-9 are observed in the plasma and urine of patients compared to controls, however none of these was predictive for treatment response (M. Zhang et al., 2019).

Because of the significant chance of spontaneous remission in primary membranous nephropathy, the mainstay of treatment is supportive management initially followed by immunosuppressive therapies should there be evidence of progression or no evidence of remission. Anti-B cell therapy with Rituximab is a common first-line treatment, as are combinations of cyclophosphamide with steroids or a calcineurin inhibitor. Complement inhibition in primary membranous nephropathy has only been trialed in a small study, which was never published because of negative outcomes. Some of the details are described in review articles, including the possibility that adequate complement-inhibiting doses were not used (Cunningham & Quigg, 2005; H. Ma et al., 2013).

Lupus nephritis

Systemic lupus erythematosus (SLE) is a common systemic autoimmune disease. Up to 40% of patients with SLE develop kidney disease (lupus nephritis), which has a significant impact on morbidity (Fanouriakis et al., 2019; Hanly et al., 2016). The clinical picture is highly variable, ranging from asymptomatic proteinuria or hematuria on the one hand to rapid and progressive loss of kidney function from glomerulonephritis on the other. This is because lupus nephritis can cause several different patterns of injury, and frequently more than one, to kidneys.

Although there is considerable literature surrounding the immunology of lupus nephritis and the undoubted involvement of cells of the myeloid lineage (Almaani et al., 2017; Arazi et al., 2019; Hakkim et al., 2010; Leffler et al., 2012), lupus nephritis is classically thought of as an immune-complex-mediated disease, with complement activation in response to immune complexes mediating kidney inflammation and endothelial injury (Birmingham et al., 2016). For this reason, almost all activated components of the complement system are found within the glomeruli of patients with active lupus nephritis. Tellingly, C1q and C4d, commonly seen together, indicate activation of the classical pathway (M.-K. Kim et al., 2013), but evidence from murine models also indicates a role played by the alternative pathway in lupus nephritis (Elliott et al., 2004; Watanabe et al., 2000). Not surprisingly, low serum complement C3 and C4 are markers of complement consumption and are routinely measured (Mahmoud et al., 2015).

Many specificities of autoantibodies have been described in the context of lupus nephritis, and some can even be produced locally within the kidneys (Espeli et al., 2011), but the most common remain anti-dsDNA antibodies recognizing DNA (Lefkowith & Gilkeson, 1996; Mannik et al., 2003). Activation of complement generates local injury directly and recruits immune cells via anaphylatoxins, which exacerbate the glomerular injury (Bao, Osawe, Haas, et al., 2005; Bao, Osawe, Puri, et al., 2005). The degree and histological pattern of injury depends very much on the precise location of immune deposits within the glomerular structure. Some antibodies, including anti-dsDNA, also directly activate mesangial cells, which secrete inflammatory mediators and contribute to local inflammation (Du et al., 2006; Yung et al., 2006).

The role of complement in lupus nephritis is complex as it can both promote and suppress disease (Leffler et al., 2014). Activation of complement through the classical pathway, following binding of C1q to the Fc portion of autoantibodies on deposited immune complexes, is a hallmark of the disease (Duncan & Winter, 1988). Altered nucleosomes potentially also enhance direct antibody binding and complement activation on the glomerular basement membrane (J. H. M. Berden et al., 1999). Fcγ receptors expressed on effector cells, and processed fragments of C3d, then help to recruit the cellular immune response (Chauhan & Moore, 2012; Jovanovic et al., 2009).

Not surprisingly, either genetic or acquired defects in C1 inhibitor, a serpin family member that protects proteolytic cleavage of C4 and C2 by C1 and MBL, are associated with development of SLE (Cacoub et al., 2001; Mészáros et al., 2010; Shukla & Gaur, 2020). Likewise, deletions of CFHR1-CFHR3 increase the risk of SLE (J. Zhao et al., 2011). Paradoxically, C1q deficiencies are also associated with SLE (Topaloglu et al., 1996), although genetic C1q deficiency is very rare It is more common to find anti-C1q autoantibodies (Trendelenburg et al., 2006). In fact, almost a quarter of patients have autoantibodies to C1q and to C3b (Birmingham et al., 2016). The association of C1q deficiency with SLE is partially explained by impairment of clearance of apoptotic cells (Botto et al., 1998; Pang et al., 2014), which may also predispose to the development of autoimmunity (Manderson et al., 2004), but probably also involves loss of the repression of $CD8^+$ T cells mediated by C1q (Ling et al., 2018) and defective suppression of IFN-α in response to nucleoprotein containing immune complexes (Lood et al., 2009; Santer et

al., 2010). Of course, anti-C1q antibodies can also directly recognize C1q deposited in glomerular immune complexes and initiate further complement activation via the classical pathway (Trouw et al., 2004).

Although patients with lupus nephritis can develop a membranous pattern of kidney injury, referred to as lupus membranous nephropathy (histologically classified as class V lupus nephritis), this entity, like other patterns of injury seen in lupus nephritis, also has a “full-house” pattern of staining, which distinguishes it from primary membranous nephropathy. This includes an abundance of C1q found here, which is usually absent in primary membranous nephropathy, and indicates that the classical pathway is unlikely to be operative in primary disease (see above) (Ponticelli et al., 2021). This is supported by sub-typing of IgG, which is mainly IgG1 to IgG3 in lupus membranous nephropathy, which have complement fixing ability, compared to IgG4 in primary membranous nephropathy (R. Ma et al., 2014).

The current gold-standard for management of lupus nephritis remains broad-spectrum immunosuppressive drugs. A specific role for complement inhibition in lupus nephritis has not yet been established, as clinical trials, for example of OMS721 and APL-2, are currently ongoing. However, terminal complement inhibition using Eculizimab has been used for the treatment of TMA (see above) occurring in association with SLE, with favorable outcomes (Wright et al., 2020). Mouse models suggest that proximal inhibition of C3, for example by using CRIg/FH, may also have some efficacy (Shi et al., 2019).

C3 Glomerulopathies

C3 glomerulopathies describe a spectrum of rare diseases with complement C3 deposition in the absence of immune-complex deposition and are comprised of dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) (Goodship et al., 2017; R. J. H. Smith et al., 2019). Membranoproliferative glomerulonephritis type II, a morphological pattern of injury and strictly speaking not a disease, falls now under the umbrella of C3 glomerulopathy, too (Floege & Amann, 2016). The diagnosis is made by immune-fluorescent renal biopsy examination and genetic studies of the complement system. The hallmarks of these disease are endocapillary proliferation and double-contouring of the glomerular basement membrane, coupled with subendothelial and mesangial electron dense deposits on electron microscopy that stain brightly for C3 but not immunoglobulins. This is an area in which classifications are evolving, since there are also reports indicating that low level immunoglobulin deposits can actually be detected in a majority of biopsies with DDD or C3GN (Hou et al., 2014), and since a subset of patients with ostensible C3 glomerulopathy also suffer from systemic diseases that can fix complement, such as SLE (see above) (Alexander et al., 2016).

While its pathophysiology is not completely understood, evidence points towards a role for the alternative pathway C3 convertase in mediating this disease. In patients the activity of the C3 convertase can be increased by convertase stabilizing antibodies called C3 nephritic factors (C3NeFs), which are found in the majority of patients with C3GN, and result in increased complement activation (Servais et al., 2012). Additionally, C5 nephritic factors that are correlated with sC5b9 levels are found in some patients (Marinozzi et al., 2017).

Furthermore, autoantibodies that stabilize the C3 convertase by binding to CFB have been described (Q. Chen et al., 2011; Strobel et al., 2010; Y. Zhang et al., 2012). There is also some evidence that renin can enzymatically cleave C3 and that, as described in 3 pediatric patients with DDD, renin inhibition with aliskiren (an orally active renin inhibitor used to treat hypertension and diabetic nephropathy (Parving et al., 2008; Sullivan et al., 2013)) can decrease C3, C3a and C5a in the plasma, as well as reduce complement deposition in the kidneys (Békássy et al., 2018). In some cases, mutations in genes that regulate the alternative pathway C3 convertase, i.e. CFH, C3, CFI, CFHR1, CFHR3, CFHR4 and CFHR5, can be present (Abrera-Abeleda et al., 2011; Bu et al., 2016; Gale et al., 2010; Martínez-Barricarte et al., 2010; Piras et al., 2021; Servais et al., 2012). It should be noted, however, that despite convincing evidence for a role of CFH in the disease, only a minority of patients have a detectable mutation in the CFH gene (Ravindran et al., 2018). Terminal complement pathway activation is evident in C3GN by deposition of C9 (S. Sethi et al., 2009).

Mechanistic evidence stems from Cfh knock out experiments in mice. Cfh knock out mice have a C3 glomerulopathy phenotype, which can be precluded by knocking out Cfb, confirming the role of the alternative pathway (Pickering et al., 2002). Contrary to expectations, Cfd knockout does not rescue the phenotype (Y. Zhang et al., 2020). Also surprisingly, knockout of regulatory Cfi actually prevents disease, instead of causing it (K. L. Rose et al., 2008), clearly indicating this to be a complex model (R. J. H. Smith et al., 2019). A single nucleotide mutation in the porcine CFH gene can cause a similar disease (Hegasy et al., 2002; Høgåsen et al., 1995; Jansen et al., 1998). Likewise, murine models incorporating dominant gain of function human mutant CFHR5 develop a C3GN-type disease (Malik et al., 2021). The knockout of properdin, another alternative pathway complement factor, modifies the phenotype to DDD-like in mice (Lesher et al., 2012; Ruseva et al., 2013). Interestingly, treatment with anti-C5 antibody has the potential to ameliorate, but not to resolve, disease in those mice (Pickering et al., 2006), suggesting that terminal complement components are somewhat redundant in these models.

In general, because this is a rare disease, high quality trial data showing efficacy for immunosuppressive treatments are scant. Most patients are treated with supportive management and blood pressure control, together with steroids and/or mycophenolate mofetil (Rabasco et al., 2015; Tarshish et al., 1992). Data from small studies indicate that complement targeting with Eculizumab is likely to be effective in some, but not all, patients (Herlitz et al., 2012; Payette et al., 2015; Quintrec et al., 2015, 2018; Rousset-Rouvière et al., 2014). Eculizumab is not usually used as a first-line agent for C3GN at present. Preliminary data from a recent phase II trial of APL-2 in C3GN was presented at the American Society of Nephrology’s annual meeting in 2019, showing some efficacy, but these data have not yet been peer-reviewed and published. A number of other trials are currently ongoing evaluating a number of additional complement inhibitors (see Table 1)

IgA nephropathy

IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide (Working Group of the International IgA Nephropathy Network and the Renal Pathology Society et al., 2009). Presentation can vary from asymptomatic discovery of abnormal

kidney function or hematuria to episodic frank hematuria, with or without flank pain, sometimes triggered by upper respiratory tract bacterial infections. A related condition, IgA vasculitis (IgAV, formerly known as Henoch-Schönlein purpura), also involves the skin and gastrointestinal tract, presenting with abdominal pain and purpuric skin rashes, but shares indistinguishable kidney features with IgAN. The glomerular changes evident on light microscopy can be variable, but there is usually mesangial cell proliferation and expansion of extracellular matrix (Working Group of the International IgA Nephropathy Network and the Renal Pathology Society et al., 2009). The prototypical finding is on immunofluorescence microscopy, in which there is dominant deposition of IgA. The IgA can be present alone or together with other antibody classes, but it needs to be either dominant or co-dominant for a diagnosis of IgA nephropathy (Emancipator, 1994; Wyatt & Julian, 2013).

The most commonly accepted hypothesis for the pathophysiology of IgAN entails a sequential set of events. Abnormal activity of glycosyltransferase enzymes in patients with IgAN result in aberrant glycosylation of O-linked glycans in the hinge region of IgA1 causing an in increased serum levels of galactose-deficient IgA1 (Gd-IgA1) (A. C. Smith et al., 2006). These galactose-deficient IgA1 generate an autoimmune response characterized by formation of IgG antibodies recognizing these regions (Tomana et al., 1999). Autoantibodies either form circulating immune complexes and are deposited in the renal mesangium or are formed there (Glassock, 2011). The presence of immune complexes activates mesangial cells, which produce inflammatory factors and injure podocytes (Lai et al., 2008, 2009). IgA1-containing immune complexes also activate complement, either via the alternative or lectin pathways, perpetuating glomerular injury (W. Zhang & Lachmann, 1994). In most cases of IgAN (~90%), therefore, mesangial C3 deposition is found, which is also a risk factor for worse renal outcome (Jennette, 1988; Roberts, 2014; Wu et al., 2021). This is an important finding, as up to 16% of individuals have asymptomatic IgA deposition and of those less than 3% exhibit C3 deposition (Suzuki et al., 2003; Varis et al., 1993). An additional mechanism for complement activation through aberrant IgA may also exist, as studies have shown that, in vitro, galactose-deficient IgA1 and Streptococcus M protein can bind human mesangial cells together and induce C3 secretion (Schmitt et al., 2014). Local deposition of terminal complement components, for example C5b-9, as evidence for downstream complement cascade activation, is sometimes also found (Alexopoulos et al., 1995; Paunas et al., 2017; Rauterberg et al., 1987). In the serum, most patients with IgAN have normal or elevated C3 levels, but evidence of C3 activation fragments is common (Sølling, 1984), indicating systemic complement activation as well.

Evidence of classical pathway activation with C1q deposition is only observed in a subgroup of patients (2–14%), which appears to have a worse outcome (Katafuchi et al., 2019; Tan et al., 2021; Wu et al., 2021). In contrast, lectin pathway activation with MBL and MASP deposition appears more common, in up to 25% of subjects (Endo et al., 1998; Matsuda et al., 1998; Roos et al., 2006). Of note, although MBL is a lectin and can bind to sugars on IgA molecules it does not bind to the aberrant galactose which is found in IgAN (Roos et al., 2001; Wallis, 2007). C4d deposition, which in the absence of C1q signifies lectin pathway activation, is found in 39% of the cases and is a risk factor for progressive disease leading to ESRD (Espinosa et al., 2014; Segarra et al., 2018).

A genetic predisposition to IgAN includes polymorphisms in genes of both innate and adaptive immunity and the alternative complement pathway. A “second hit”, however, may be needed in predisposed individuals, since macroscopic bleeding often coincides with mucosal inflammation, including upper respiratory tract (synpharyngitic) or gastrointestinal infections. Complement factor H related protein genes (CFHR) CFHR1, CFHR3 and CFHR5 are known risk loci for IgAN, which point to a central role of the alternative complement pathway (Gharavi et al., 2011; Zhai et al., 2016). CFHR5 protein itself can compete with C3b for binding to CFH or directly activate C3, a mechanism that augments alternative pathway activation (Gyapon-Quast et al., 2021; Maillard et al., 2015). Apart from CFH and related genes being risk factors, deposition of Properdin and CFH also indicate alternative pathway activation (Itami et al., 2020; Miyazaki et al., 1984; Rauterberg et al., 1987; Roberts, 2014).

There is no consensus on the optimal management of IgAN, especially in those with progressive disease. Immunosuppressive drugs, in general, do not show great benefit in IgA and there is little compelling evidence for B cell depletion with Rituximab (Lafayette et al., 2017; Rauen et al., 2015). Given the evidence for a role of the complement system in IgAN, it is not surprising that there are a number of active clinical trials evaluating the efficacy of complement inhibitors as treatment for patients. Compounds under trial include APL-2 (a C3 inhibitor), Avacopan (a C5aR1 antagonist), LNP023 (CFB inhibitor), IONIS-FB-LRx (CFB inhibitor), Ravulizumab (a C5 antagonist) and Narsoplimab/OMS721 (a MASP-2 inhibitor). Preliminary outcomes from published case reports show mixed results, which may reflect the complexity of the disease (Herzog et al., 2017; Ring et al., 2015; Rosenblad et al., 2014).

Antineutrophil cytoplasmatic autoantibody-associated vasculitis

The antineutrophil cytoplasmatic autoantibody (ANCA)-associated vasculitides (AAV) are a group of disorders that includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA) and renal-limited vasculitis. ANCAs are antibodies directed against epitopes found in the cytoplasm of myeloid cells, typically neutrophils and monocytes. The most common ANCAs are anti-proteinase 3 (PR3) and anti-myeloperoxidase (MPO). Most anti-MPO ANCAs produce a cytoplasmic staining pattern, and most anti-PR3 ANCAs a peri-nuclear pattern, on immunofluorescence. These diseases cause vascular inflammation (vasculitis), which can affect the kidneys, usually causing glomerulonephritis. They can be severe and fulminant, resulting in rapidly progressive loss of kidney function and can also be life-threatening when they affect other organs, such as the lungs. The characteristic of AAV is a pauci-immune pattern of staining in injured glomeruli, with minimal or no immunoglobulin deposition (A. E. Berden et al., 2010).

Despite being traditionally regarded as a pauci-immune vasculitis, classically without immunoglobulin or complement deposition in the tissue, and absence of hypocomplementemia, the complement system does play a role in the pathogenesis of AAV (M. Chen et al., 2017). In passive murine models of AAV (transfer of ANCA produced by MPO−/− mice into immunodeficient Rag2−/− recipients (H. Xiao et al., 2002),

causing focal necrotizing and crescentic glomerulonephritis with a paucity of glomerular Ig deposition)) complement depletion with cobra venom factor (Kock et al., 2004), C5 blockade with anti-C5 antibodies, genetic CFB or C5 deficiency all protect against disease (Huugen et al., 2007; H. Xiao et al., 2007), indicating the importance of complement for development of AAV, at least in this model. Since C4 deficiency in the same model does not protect against disease, it is likely that the alternative complement pathway is the key pathogenic mechanism (H. Xiao et al., 2007). Interestingly, C5aR1 blockade or deficiency protects against MPO AAV whereas C6 deficiency does not (Schreiber et al., 2009; H. Xiao et al., 2014), which indicates that it is the anaphylatoxin effects of C5a and not MAC formation that is the pertinent effector mechanism of complement activation in experimental AAV. Mechanistically, C5a signaling through its receptor on ANCA-primed neutrophils activates the p38MAPK, ERK and PI3K pathways in this setting, which facilitate the translocation of ANCA antigens and neutrophil activation (Hao et al., 2012). Depleting C5aR2, in contrast, has mixed results, but sometimes worsens disease (Hao et al., 2013; H. Xiao et al., 2014), which indicates that C5a can also have protective roles by acting on the alternative C5a receptor. Indeed, the two C5a receptors, C5aR1 and C5aR2 are mainly found on infiltrating neutrophils and macrophages in this model, where C5aR1 if often downregulated and C5aR2 upregulated (Yuan et al., 2012). Downregulation of C5aR1 by internalization can occur after C5a stimulation and thus can signify activation of that axis (Huey & Hugli, 1985). Upon stimulation with ANCA, neutrophils release neutrophil extracellular traps (a mechanism designed for contained release of cytotoxic granules) and degranulate (Kessenbrock et al., 2009; Papayannopoulos, 2018). The C5a anaphylatoxin is an activator of extravasation and the respiratory burst in neutrophils (Miyabe et al., 2017). Contrary, C5aR1 inhibition in the mouse model ameliorates not only the autoimmunity but also intra-renal neutrophil activation in ANCA-associated vasculitis (Dick et al., 2018). This is relevant because C5a primed neutrophils release tissue factor within microparticles and NETs (Huang et al., 2015), which causes hypercoagulability (‘immunothrombosis’ – see above), a clinical feature of a subgroup of patients. A caveat in the evidence provided by these mouse models is that most are based on MPO-ANCA and not on PR3-ANCA. PR3-ANCA mouse models generally do not replicate the phenotype of AAV (Geld et al., 2007).

Despite the usual lack of immune complex deposits, glomerular deposits of C3d, C5b-9, CFB, properdin and C4d can be detected in patients with more severe disease (Gou, Yuan, Wang, et al., 2013; Hilhorst et al., 2017; Xing et al., 2008) and complement activation products can be found in both urine and serum (Gou, Yuan, Chen, et al., 2013; Gou, Yuan, Wang, et al., 2013). When present, low serum C3 levels and histologic TMA – a common overlap - are associated with a poor prognosis (Manenti et al., 2015). Likewise, more severe disease is associated with reduced plasms levels of CFH (S.-F. Chen et al., 2018b, 2018a) and there may be a similar reciprocal association between expression of other complement regulators on kidney cells, including CD46 and CD55, and disease severity (Cheng et al., 2018).

In the pre-steroid era, AAV had a close to 100% mortality. The mainstay of current treatment is broad-spectrum high-dose immunosuppression, often coupled with plasma exchange in severe cases. B cell depletion is also effective, when used in combination with other drugs.

Avacopan, a C5aR1 antagonist, has been tested in the CLEAR trial for a ≥50% reduction of the Birmingham Vasculitis Activity Score by week 12 and found non-inferior to high dose prednisolone, in combination with cyclophosphamide or Rituximab (Jayne 2017). In a follow-up study, the ADVOCATE trial, furthermore it was found to be superior in sustaining remission at week 52 highlighting its role as a potential alternative to prednisone (Jayne 2021) (D. R. W. Jayne et al., 2017, 2021; Merkel et al., 2020). Trials of other agents targeting the C5 system, such as Vilobelimab /IFX-1 (anti-C5a), are ongoing.

Anti-glomerular basement membrane disease

Anti-glomerular basement membrane (GBM) disease is a rare, but potentially life-threatening, disease that can cause a severe pulmonary-renal syndrome. This is an autoantibody-mediated disease targeting the non-collagenous domain 1 of the a3 chain of collagen type IV (Greco et al., 2015; Pedchenko et al., 2010). Severe injury to the glomerulus typically causes a rapidly progressive glomerulonephritis and acute kidney injury, which may be accompanied with pulmonary hemorrhage, as the lungs also express the same epitope recognized by the autoantibody. Histological sections of the kidneys show linear deposition of IgG in glomerular capillary walls (Kluth & Rees, 1999), often together with C3 and C1q and occasionally with other factors, indicating local activation of complement (Batal et al., 2009; E. G. Fischer & Lager, 2006). Additional complement components, including C4d, CFB, MBL, Properdin and MAC can also be present (R. Ma et al., 2014), signifying use of all three complement activation pathways. A pathogenic role of complement activation in disease is suggested by passive transfer anti-GBM animal models, in which C1q, C3, C4 and C6 deficiency are protective (Groggel et al., 1985; Hébert et al., 1998; Otten et al., 2009; Sheerin et al., 1997). MAC concentrations are elevated in both the plasma and urine of patients with anti-GBM disease but, because C3 and C4 concentrations are normal in plasma but elevated in the urine, it is reasonable to conclude that activation of the complement cascade occurs in the kidneys of patients with anti-GBM and not systemically (R. Ma et al., 2013).

Because this is a potentially life-threatening disease, aggressive treatment is the standard of care, using high-dose broad-spectrum immunosuppressants and plasma exchange to remove pathogenic antibodies (Pusey, 2003). Addition of Eculizumab as rescue therapy has been published in case reports to potentially be helpful (Nithagon et al., 2021).

Post-streptococcal glomerulonephritis

Many infectious diseases have been documented to cause post-infectious immune-mediated kidney diseases. Post-streptococcal glomerulonephritis (PSGN) is a common cause of acute nephritic syndrome that develops after an infection, mainly by group A beta-hemolytic Streptococcus bacteria. Patients usually develop a glomerulonephritis mediated by immune complex deposition. These immune complexes are either formed in situ or in the circulation. A number of hypotheses have been proposed for the nephritogenicity of Streptococci and potential antigens, as reviewed elsewhere (Rodríguez-Iturbe & Batsford, 2007).

Histologically, bright granular C3 and IgG immunofluorescence is found in glomeruli (Eison et al., 2011). Electron microscopy shows these to form characteristic dome-shaped

sub-epithelial deposits known as “humps”. Because C3 deposition precedes IgG deposition it has been argued that complement activation in triggered through the alternative or lectin pathway (Nordstrand et al., 2009). Supporting a role of the alternative pathway, deposits often contain C3, properdin and C5 (Wyatt et al., 1979), but classical and lectin pathway components, such as C1q, C4 and MBL/MASP-1, are much more rarely evident (Hisano et al., 2007). Terminal complement deposits, co-localized with C3, suggest generation of MAC in situ (Matsell et al., 1994; Wyatt et al., 1979). Most patients have depressed serum C3 and C5 levels in the first weeks (Cameron et al., 1973; Endre et al., 1984; E. J. Lewis et al., 1971) but reduction of classical pathway components, notably C1q, C2 and C4, is rarer (M. Levy et al., 1985; Wyatt et al., 1988). Many children are found to harbor anti-CFB antibodies (Chauvet et al., 2020), which enhance convertase activation in vitro, but their pathophysiological role still needs to be determined.

There is some overlap with C3GN (see above) in the initial presentation, suggesting that both diseases could represent different ends of a common spectrum and making a differential diagnosis challenging (Al-Ghaithi et al., 2016). Treatment for this condition is usually supportive, plus management of the infection with antibiotics. Most patients recover, although there may be some long-term sequelae, such as hypertension and chronic kidney disease. However, because the prognosis is generally so good and there is clear risk of using complement inhibition in the face of active infection, there is no published literature on the use of complement inhibiting drugs to treat pure post-Streptococcal glomerulonephritis. Occasionally, pure post-streptococcal glomerulonephritis presents together with another syndrome, such as aHUS, in which case complement inhibition, for example with Eculizumab, can be beneficial (Kakajiwala et al., 2016; Parekh et al., 2018).

Diabetic Nephropathy

Diabetic nephropathy is now the most common cause of chronic kidney disease in the world. The pathology is heterogenous as are the pathological pathways that are involved. The classic histological changes of diabetic nephropathy involve glomerular changes that reflect alterations in local hemodynamics, inflammation and fibrosis. Classically, there is progressive thickening of glomerular basement membranes, endothelial injury, loss of podocytes and expansion of the mesangium. Injury from hyperglycemia, altered glomerular hemodynamics and advanced glycation end-products results in marked increase in mesangial matrix and appearance of nodular glomerulosclerosis (Riser et al., 2000).

There are reports indicating complement activation in the kidneys of most patients with diabetic kidney disease. In human renal biopsies transcriptomic analysis shows upregulation in expression of complement genes (Sircar et al., 2018), particularly C3 (Woroniecka et al., 2011), compared to healthy donors. Glomerular C1q, C3c and C5a deposits are observed and associated with more severe renal damage in diabetic kidney disease (Sun et al., 2019; Yiu et al., 2018), as well as components of the lectin pathway (J.-M. Zheng et al., 2018). In some cases, tubular C5a deposition can also be seen (Yiu et al., 2018) and complement activation components detected in the urine (Morita et al., 2000; J. Zheng et al., 2019). Importantly, blood levels of C3a, C5a, and C5b-9 can be elevated (Tan 2020). These are not normalized

by angiotensin converting enzyme inhibitors, a mainstay of management for diabetic kidney disease, and may reflect complement activation systemically, and not just in the kidneys.

Mouse models of diabetic kidney disease show varying patterns of complement deposition. In the streptozotocin mouse model, a toxin pancreatopathy causing type I diabetes, C3 deposition has been demonstrated, which can be reversed after pancreatic islet transplantation (Lee et al., 1974; Mauer et al., 1974, 1975). Unfortunately, these findings could not be replicated by others (J. A. Østergaard et al., 2016). In contrast, the non-obese diabetic and the OVE26 mouse models both feature C3 deposition (X. Xiao et al., 2009; Yang et al., 2011), and in other models C5a inhibition ameliorates tubulointerstitial damage (Yiu et al., 2018). In rat models, C5 inhibition also reduces C3 staining and mesangial expansion (Fujita et al., 1999) and treatment with C3aR and C5ar antagonists led to downregulation of alpha smooth muscle actin, TGF-b, fibronectin and beta catenin, which are major components of kidney scarring, and preserved renal function (L. Li et al., 2014, 2015).

Two main mechanisms to trigger complement activation in diabetic nephropathy have been proposed (Flyvbjerg, 2017; S. C. W. Tang & Yiu, 2020; J.-M. Zheng et al., 2018), first, activation of the lectin pathway by altered glycation of cell surface proteins by hyperglycemia; and second, glycation of complement regulatory proteins diminishing their regulatory properties. In support of a role of the lectin pathway, MBLs can bind to fructoselysine, a glycation product (Fortpied et al., 2010). Furthermore, in streptozotocin-induced diabetes, a murine model of T1DM, MBL knockout status protects against renal damage (J. Østergaard et al., 2007; J. A. Østergaard et al., 2012). In this model, MBL levels are higher after induction of diabetes, but don’t correlate with complement deposition (J. A. Østergaard et al., 2013, 2015). In patients with diabetes, MBL is also elevated, as are levels of MASP-1 and MASP-2, compared to controls (Guan et al., 2015; Hansen et al., 2003, 2006; Jenny et al., 2015; N. Zhang et al., 2013; J.-M. Zheng et al., 2018). Likewise, in the setting of simultaneous kidney pancreas transplantation, circulating MBL levels are associated with diabetic nephropathy, but not creatinine, and are dependent on glycemic control (Bijkerk et al., 2016). It remains unclear whether MBL is associated, or not, with complications of diabetes (Hansen et al., 2006, 2010; Kaunisto et al., 2009; J. A. Østergaard et al., 2015). Other alternative pathway components, such as H-ficolin, are also associated with risk of progression to microalbuminuria or macroalbuminuria in a patient cohort with diabetes (J. A. Østergaard et al., 2014), but deleting ficolins in mouses model of diabetes has no effect on diabetic nephropathy (Holt et al., 2015). Abnormal function of CD59 by glycation has also been suggested as a mechanism for MAC deposition within glomeruli (Acosta et al., 2000; Ghosh et al., 2014; Qin et al., 2004; Uesugi et al., 2004). Thrombomodulin, an inhibitor of coagulation, has also a lectin binding domain that inhibits complement activation. More severe diabetic nephropathy occurs in mice which bare a knockout of thrombomodulin’s lectin domain (H. Wang et al., 2012). Interestingly, both C3 and C4 are glycated in diabetes but this does not appear to alter their activity (Peake et al., 1989). Furthermore, C4 plasma levels are not convincingly associated with diabetic nephropathy and C4 haplotypes are not associated with diabetic complications in human (Lhotta, Auinger, et al., 1996; Lhotta, Schlögl, et al., 1996) which contradict findings from

an earlier study showing lower C4 levels correlated with microangiopathy complications (Barnett et al., 1984).

Blood pressure and glycemic control is the mainstay of therapy for management of diabetic nephropathy. In patients with albuminuria an angiotensin converting enzyme inhibitor or angiotensin II receptor blocker are recommended. If control of albuminuria is not achieved, SGLT2 inhibitors are recommended for patients with type II diabetes. Data from murine models, in particular, and observational studies in humans support a potential role for complement targeting therapies in the management of diabetic nephropathy, but to date there are no published reports of clinical complement targeting therapies in humans.

Ischemic acute tubular injury

Acute kidney injury (AKI) is a common clinical entity and is characterized by an abrupt decrease in kidney function. A major cause of AKI is acute tubular injury (ATI) which is causes by ischemic or toxic injury to the tubule. Any prolonged cause of kidney hypo-perfusion can lead to ATI, while the duration of injury that is needed to cause ATI is variable. Histologically, ATI is characterized by brush border diminishment, varying degrees of necrosis, with sloughing of the epithelium and casts and cell debris, that can occlude the tubular lumen.

Complement activation in the ischemic kidney appears to predominantly affect the proximal tubules (McCullough et al., 2013). A number of mechanisms for complement activation have been suggested. Uninjured endothelium produces complement-regulatory factors, which can be shed during ischemic injury (Hindmarsh & Marks, 1998; Rehm et al., 2007). During re-perfusion and re-oxygenation significant quantities of reactive oxygen species are produced, exacerbating inflammation (Kapitsinou & Haase, 2015). Another injury mechanism is the detection of altered fucose patterns by collectin-11, which then initiates lectin pathway complement activation (Farrar et al., 2016). In mice undergoing renal ischemia reperfusion injury (IRI) that are then challenged with alloantigens, humoral IgG1 responses are amplified against the alloantigen, providing a possible mechanism for complement activation through the classical pathway (Fuquay et al., 2013). Of note, increasing the local pH during in vitro experiments reduces complement activation on PTECs (Peake et al., 2002; Sim & Sim, 1983), presumably because pH changes alters enzymatic processes.

The capacity of tubular cells to produce their own C3 and other complement components upon injury was already shown in 1988 (Passwell et al., 1988) and has been discussed above. In patients with acute tubular necrosis tubular deposits of C3b, but not C4b are pronounced, which points to activation through the alternative pathway (Thurman et al., 2005). (W.-T. Zhao et al., 2019)

It is noteworthy that blockade of C3aR with the chemical inhibitor SB290157 in renal proximal tubular epithelial cells lessens epithelial to mesenchymal transition induced by serum (Z. Tang et al., 2009) (as a caveat it should be mentioned that the inhibitor has also been shown to have off target effects and act as an agonist on C3aR and C5aR2 (X. X. Li et al., 2021)). Consistent with these findings, complement inhibition shows benefits in animal

models of ischemia reperfusion injury. Most pertinently, in the mouse ischemia reperfusion injury (IRI) model, C3, C3ar or CFB knockout status are all protective (Park et al., 2001; Peng et al., 2012; Thurman et al., 2003). A blocking antibody against CFB prevents C3b deposition in mouse kidneys (Thurman et al., 2006). Likewise, C5 inhibition or knockout status for C5ar1 ameliorates kidney function and even upstream complement deposition (Arumugam et al., 2003; Bongoni et al., 2019; De Vries et al., 2003; Peng et al., 2012). MAC formation appears to also play a role as C6 deficient mice, which cannot generate MAC, are also protected from renal IRI (Zhou et al., 2000).

In the IRI model, loss of polarity of Crry, a mouse complement regulatory protein, which is considered to have some functions in common with human CD46, in the tubular epithelium precedes activation of the alternative pathway along the basolateral aspect of tubular cells (Thurman et al., 2006) but treatment with Crry does not reduce injury despite reducing C3 deposition (Park et al., 2001). A caveat in this observation is that delivery of the 160kD molecule to the site of complement activation was not demonstrated. Conversely, deletion of Cd55 and Cd59, key regulators of complement, significantly exacerbate disease mediated by IRI (Yamada et al., 2004). An important addendum to these observations is that treatment of Cd55−/−Cd59−/− mice with anti-C5 or anti-properdin monoclonal antibodies, or deletion of C3, CFB, Properdin, C3ar, or C5ar significantly ameliorates renal IRI, whereas deficiency of C4, Immunoglobulins, or MBL has no effect (Miwa et al., 2013). These findings all point to a critical role mediated by the alternative, rather than the lectin or classical pathways, in kidney injury mediated by ischemia. Consistent with this, is the observation that CFH binds to tubular epithelial cells and limits interstitial complement activation in ischemic injury (Renner et al., 2011).

Although there appears to be significant literature supporting the alternative pathway as the major driver of complement fixation contributing to IRI, this cannot be the whole story. What the above do not explain is the role played by profuse kidney deposits of MBL evident in the IRI model, which are recapitulated in ischemically-injured allografted human kidney transplants (de Vries et al., 2004; Møller-Kristensen et al., 2005) if their purpose is not to contribute to complement fixation. Nor do they explain the role played by the C-type lectin collectin-11, which recognizes an abnormal pattern of L-fucose on post-ischemic renal tubule cells and triggers complement activation through MASP-2 (Farrar et al., 2016).

At present, treatment of ischemic ATI is mostly supportive and aimed at reversing the underlying causes. To our knowledge, there is no compelling clinical data in favor of the use of complement targeting therapies in this setting.

Complement in transplantation

Kidney transplantation is the treatment of choice for most patients with end stage renal disease (ESRD). The quality of the donated organ and ischemia time influence outcomes in transplantation (Giblin et al., 2005; Ojo et al., 2000; Opelz, 1988; Port et al., 2005; Summers et al., 2013). This is highlighted by the superior outcome of living donor transplant programs (SRTR report 2009, http://www.ustransplant.org/annual_reports/current/). After transplantation, immunologically-mediated acute and chronic rejection have significant implications for transplant outcomes.

Complement activation can be related to distinct donor and recipient factors (Biglarnia et al., 2018). Ischemia of the transplant organ during harvest and transport, coupled with pre-existing vascular damage from hypertension and atherosclerosis can be common. The circumstances of death can lead to hemodynamic instability and inflammatory states around the time of organ recovery. Specifically, shock can cause complement activation (Burk et al., 2012; Huber-Lang et al., 2018). Ischemia can lead to complement activation through several mechanisms, as discussed above. In general, expression of C3 in donor kidneys is increased in deceased compared with living donors, suggesting a role for ischemia time (Damman et al., 2011). In mouse and nonhuman primate models of transplantation, complement inhibition pre-transplantation reduce delayed graft function. In both nonhuman primate and porcine models, targeted C1 complement inhibition in the donor reduced occurrence of delayed graft function (Danobeitia et al., 2020; Delpech et al., 2016). Likewise, TT30, a Cr2-Factor H fusion protein, reduces delayed graft function and including C5ar1 blockade in the kidney preservation solution improves graft survival in mouse transplant models (A. G. Lewis et al., 2008; Yu et al., 2016). The fact that knockout of C4 does not protect against IRI, whereas knock-outs of MASP2 does, in a mouse model of isogenic transplantation, indicates a critical role for the lectin pathway in ischemic transplant injury (Asgari et al., 2014).

In recipients of transplanted organs, recurrence of the underlying primary kidney disease that led to organ failure may be a significant cause of complement fixation. A good example is complement-mediated TMA, which can recur in transplanted kidneys (Alasfar & Alachkar, 2014). Equally important is the association of complement activation with acute rejection. Antibody mediated rejection (ABMR) and hyperacute rejection specifically has been studied in this regard. Recipients are screened for the presence of pre-transplant complement-fixing donor specific antibodies (DSA) against donor human leukocyte antigens (HLA), traditionally by a complement-dependent cytotoxicity (CDC) crossmatch test, specifically to prevent hyperacute rejection. This is rejection that occurs within minutes after transplantation, as recipient antibodies recognize HLA expressed on vascular endothelium of the donor, fix complement and initiate immunothrombosis, resulting in rapid loss of the transplant from rejection and thrombosis. Interestingly, pre-transplant C3d-fixing or C1q-binding ability of donor-specific anti-HLA antibodies are not associated with increased risk for kidney graft failure (Kamburova et al., 2018; Tambur et al., 2015). In contrast, post-transplant the complement-fixing ability of de-novo DSA is a risk factor for graft loss (Loupy et al., 2013; Sicard et al., 2015). Deposition of C4d is correlated with development of DSA and with histopathologic changes that imply antibody-mediated rejection (Feucht et al., 1991, 1993; Zwirner et al., 1989). In fact, C4d deposition in the peritubular capillaries is a sensitive and specific marker for the presence of DSA (Collins et al., 1999; Feucht et al., 1991; Mauiyyedi et al., 2002) and has been incorporated into the BANFF classification as a marker of antibody-mediated rejection (Racusen et al., 2003). However, it is recognized that a subset of patient with evidence of antibody mediated rejection have transplant biopsies that are C4d negative (Haas, 2011; Sis et al., 2007, 2009). These cases show significant glomerulopathy too (Haas & Mirocha, 2011). A caveat with C4d staining is that C4 epitopes can also be locally expressed in the absence of antibody-mediated activation via cytokine stimulation of endothelial cells (Hamer et al., 2012).

Local production of complement C3 is a prerequisite for acute renal transplant rejection is mouse models (Farrar et al., 2006; Pratt et al., 2002). Current single cell RNA sequencing approaches highlight complement signatures in donor-derived macrophages from recipient allograft tissue biopsies (Malone et al., 2020). However, two *C3* allelic variants, termed fast and slow, present in donor-derived tissues, were initially thought to be independent determinants of transplant outcomes; unfortunately this has not been convincingly born out by follow-up studies (Brown et al., 2006; Damman et al., 2012; Varagunam et al., 2009).

Current standard of care treatment of ABMR consists of plasmapheresis, intravenous immunoglobulin infusion and high dose corticosteroids (Schinstock et al., 2020). The use of Eculizumab has been demonstrated in smaller cohorts of acute ABMR, however randomized controlled trials are lacking. In the case of post-transplant complement-activating DSA, complement inhibition with eculizumab reduces the incidence of 3-month rejection (Lefaucheur et al., 2018). There is anecdotal evidence for both treatment success and failure with Eculizumab (Bentall et al., 2014; Burbach et al., 2014; Cornell et al., 2015; Locke et al., 2009). Furthermore its effects appears to depend on C4d positivity (Burbach et al., 2014; Cornell et al., 2015; Kulkarni et al., 2017). A role of upstream complement effects as a reason cannot be excluded to explain the mixed results of Eculizumab. In a smaller controlled clinical trial of C1-Inhibitor (C1INH) in ABMR there was no effect on kidney function achieved, but a subgroup analysis suggested less glomerulopathy in the treatment arm (Montgomery et al., 2016). In non-human primates Yunnan-cobra venom factor (Y-CVF), a complement depleting protein, also prevented antibody mediated-rejection in MHC-sensitized recipients (Chen (Song) et al., 2011).

Conclusions

The field of complementology has undergone many paradigm shifts since the first descriptions of complement in 1896. Initially described as a plasma-based pattern recognition system aiding the cytotoxic effects of antibodies, it is now recognized as a tightly regulated and integral component of the immune system, metabolism and development. As outlined in this review there is evidence for pathophysiologic involvement of the complement system in a broad set of kidney diseases through an interplay with diverse immune effector mechanisms.

Our perceptions of the pathophysiological functions of complement in kidney diseases have made a leap forward, including broader appreciation of the interplay between complement and both the adaptive and innate immune systems, as well as the coagulation cascade. Exemplars of the gains that have been made include improved understanding of the roles of complement regulators in complement-mediated TMA and the functions of C5 in neutrophil recruitment and activation in AAV. These insights have been met with innovation from the pharmaceutical industry, leading to the development of a broad range of complement inhibitors, with the capacity to enable targeting of specific complement components in disease. There are several questions regarding the roles of complement in kidney diseases that haven’t been satisfactory answered yet. The description of the existence of an intracellular complement system in kidney and immune cells sparks the question of whether complement components of intracellular or extracellular origin are responsible for

the tissue deposition seen. This is an important question because complement inhibitors that work exclusively in the extracellular space may be therapeutically less effective if complement processing is occurring intracellularly. A case in point is respiratory epithelial cells infected with SARS-CoV2. These cells are induced by signals generated by viral infection to transcribe C3 and CFB and to process C3 intracellularly to C3a and C3b (Yan et al., 2021). Using a cell-permeable CFB inhibitor effectively nullifies this response (Yan et al., 2021). A second important and unanswered question is whether complement activation in a given kidney is an epiphenomenon of the disease of a key cause of pathology. Here, animal models can provide some insights, with the caveat that very few animal models of kidney disease faithfully recapitulate their homologous human diseases. Akin to this is the inherent historical weakness of studying complement deficiency in animal models using global knockouts. These models discount the cell type from which complement is chiefly being produced and can obfuscate outcomes. The increasing availability of tissue targeted conditional knock-outs of complement components are now enabling the dissection of molecular mechanisms of disease at a more granular level and will provide greater insights on disease processes. A third factor is the considerable heterogeneity of several established diseases, for example lupus nephritis, which could very well represent multiple diseases with a common final pathway. This heterogeneity is a potential confounder in the outcomes from clinical trials.

The availability and development of drugs to target virtually all parts of the complement cascade signifies a unique window of opportunity for the field of nephrology to make a leap forward in the next decade. We are excited about the development of intracellular acting inhibitors to make use of the recent advances in our understanding. Given the range of complement inhibitors on offer, the profusion of intracellularly acting inhibitors and our future ability to distinctly target alternative and/or lectin complement activation pathways, it may become increasing important to accurately determine an individual's predominant pathway of complement activation in a given disease.

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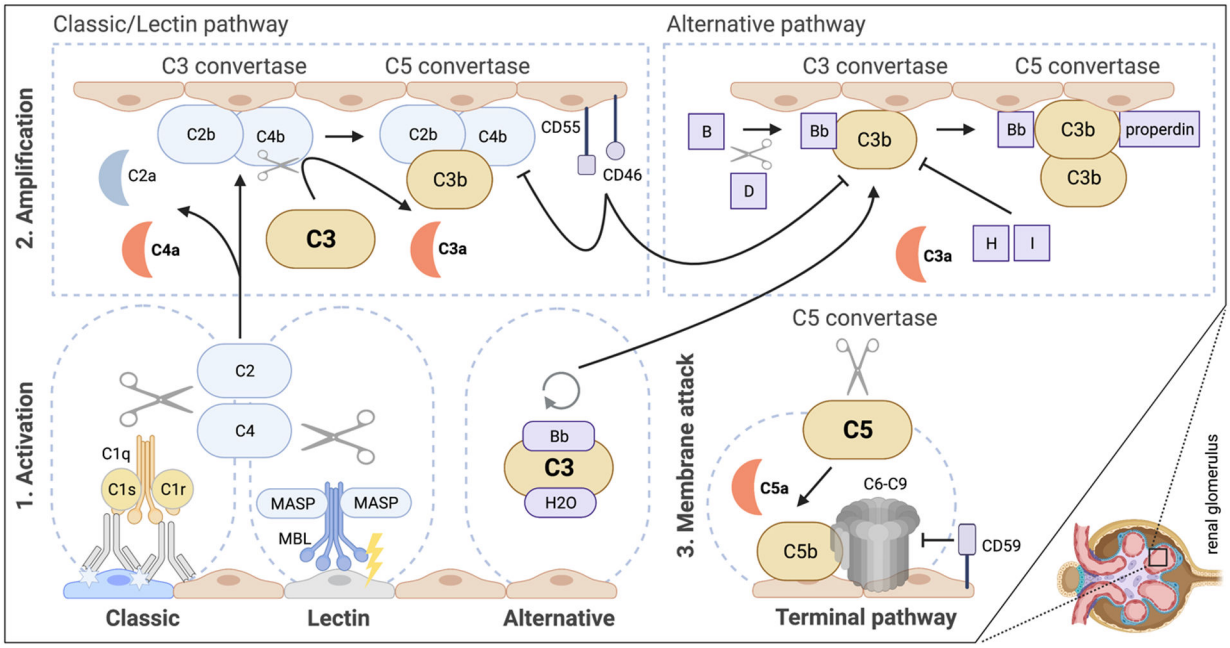

Figure 1. Mechanisms of complement activation.

Shown is a schematic of the classical, alternative and lectin pathways of complement, focusing on **1**. Complement system activation, **2**. Amplification, and **3**. Membrane attack complex assembly. The regulatory proteins CD55, CD59 and CD46 are shown. C, complement factor; MASP, Mannose-Binding Lectin-Associated Serine Protease; B, complement factor B; D, complement factor D; H, complement factor D; I, complement factor I. Figure created with BioRender.com.

Table 1.

Clinically employed complement modulating drugs.

Included are drugs that are approved or in clinical development. Data sourced from Mastellos *et al.*, 2019; Ort *et al.*, 2020; Zelek *et al.*, 2019; Zipfel *et al.*, 2019 and publicly available data from AdisInsight database (http://adisinsight.springer.com). Biosimilars have been omitted.

Target	Name	Developer	Mechanism	Class	FDA approved	Active trials in kidney disease
Classical/Lectin pathway						
C1r/s, MASPs	C1INH/Berinert	CSL Behring	C1 inhibitor	Protein	HAE (2009)	Phase III (Transplant rejection)
C1r/s, MASPs	C1INH/Cinryze/Cetor	Sanquin Blood Supply Foundation; Shire; Shire ViroPharma; Takeda; ViroPharma Incorporated	C1 inhibitor	Protein	HAE (2008)	Phase III (Transplant rejection)
C1r/s, MASPs	C1INH/Conestat alfa/ Ruconest	Pharming Group NV	C1 inhibitor	Protein	HAE (2014)	Phase II (AKI), Phase I (DGF)
C1s	Sutimlimab/BIV009	Bioverativ; True North Therapeutics	CP inhibition/inhibition of C1s protease	mAb		Phase I (Renal transplant rejection)
MASP-2	Narsoplimab/OMS 721	Omeros Corporation; Quantum Leap Healthcare Collaborative	LP inhibition, blockage of MASP2 activity	mAb		Phase III (HUS, IGAN), Phase II (GN, LN, MPGN)
Alternative pathway						
Factor B	Iptacopan/LNP 023	Novartis Pharmaceuticals	Inhibition of AP C3 convertase	Small molecule		Phase III (IGAN, PNH), Phase II (aHUS, MPGN, MN)
Factor B	IONIS-FB-LRX	Ionis Pharmaceuticals	Inhibition of hepatic FB expression	Antisense oligonucleotide		Phase II (IGAN)
Factor D	Lampalizumab	Genentech	Blockage of AP C3 convertase formation	Fab		
Factor D	Vemircopan/ACH-5228	Achillion; Alexion AstraZeneca Rare Disease	Inhibition of AP C3 convertase	Small molecule		Phase II (PNH)
Factor D	Danicopan/ACH-4471	Achillion Pharmaceuticals; Alexion AstraZeneca Rare Disease; National Institute of Allergy and Infectious Diseases	Inhibition of AP C3 convertase	Small molecule		Phase III (PNH)
Properdin	CLG561/NOV-7	MorphoSys; Novartis	Inhibition of AP amplification	mAb		
Other						
C3	AMY 101	Amyndas	Inhibition of C3 activation	Non-PEGylated peptide		
C3	Pegcetacoplan/APL-2	Apellis Pharmaceuticals	Inhibition of C3 activation	PEGylated peptide	PNH (2021)	Phase II (GN, IGAN, LN, MN)
C3	APL 9	Apellis Pharmaceuticals	Inhibition of C3 activation	PEGylated peptide		Phase I (Immunological disorders)

Target	Name	Developer	Mechanism	Class	FDA approved	Active trials in kidney disease
C3/C5 convertases	Mirococept/APT 070	Adprotech/Inflazyme	C3/C5 convertase inhibitor (CR1 domains targeted to endothelium)	Protein		
C3/C5 convertases	TP10/CDX 1135	Celldex Therapeutics	C3/C5 convertase inhibitor (soluble complement receptor 1)	Protein		
C5	Zilucoplan/RA 101495	Amgen; Ra Pharmaceuticals; Takeda; UCB	Allosteric inhibition of C5 activation	Macrocyclic peptide		
C5	Crovalimab/SKY59	Roche; Chugai Pharmaceutical	Blockage of C5 activation (different C5 epitope)	mAb		Phase III (aHUS, PNH)
C5	Pozelimab/REGN 3918	Regeneron; Alnylam Pharmaceuticals	Blockage of C5 activation (different C5 epitope)	mAb		Phase III (PNH)
C5	Tesidolumab/LFG316	Novartis	Blockage of C5 activation (different C5 epitope)	mAb		Phase II (PNH)
C5	Ravulizumab/Ultomiris	Alexion AstraZeneca Rare Disease	Blockage of C5 activation (same epitope on C5)	mAb	PNH (2018)	Phase III (TMA), Phase II (IGAN, LN)
C5	Eculizumab/Soliris	Alexion AstraZeneca Rare Disease	C5 Blockage of C5 activation	mAb	PNH (2007), aHUS (2011), MG (2017), NMA (2019)	Phase III (DGF), Phase II (Renal transplant rejection)
C5	IFX 2	InflaRx	C5 inhibitor	mAb		Preclinical (Autoimmune disorders)
C5	Zilucoplan	Amgen; Ra Pharmaceuticals; Takeda; UCB	C5 inhibitor	Macrocyclic peptide		
C5	Avacincaptad pegol/Zimura	IVERIC bio	Inhibition of C5 expression	RNA aptamer		
C5	Cemdisiran/ALN-CC5	Alnylam Pharmaceuticals; Regeneron Pharmaceuticals	Inhibition of hepatic expression of C5	RNA interference therapeutic		Phase II (HUS, IGAN, PNH)
C5a	Vilobelimab/IFX 1	InflaRx	Blocking binding of C5a to C5aR1	mAb		Phase II (GPA, MPA)
C5a	Olendalizumab/ ALXN-1007	Alexion AstraZeneca Rare Disease	C5a inhibitor	mAb		Phase II (APS)
C5a, MAC, leukotriene	Nomacopan/Coversin	Akari Therapeutics; Evolutec; US Army Institute of Surgical Research	C5a, MAC, leukotriene inhibitor	Protein		Phase III (HUS, PNH, TMA)
C5aR1	Avacopan/CCX 168	ChemoCentryx; Mario Negri Institute for Pharmacological Research	Antagonist of the C5aR1 receptor	Small molecule	[AAV (decision expected 10/21)]	Phase III (MPGN), Phase II (GN, HUS, IGAN)
C5aR1	Avdoralimab	AstraZeneca; Innate Pharma; Novo Nordisk	Blockade of C5aR1 signalling	mAb		
CD59	AAVCAGsCD59/HMR59	Hemera Biosciences	Expression of soluble CD59	Gene therapy		

(a)HUS, (atypical) hemolytic uremic syndrome; AAV, ANCA-associated vasculitis; AKI, acute kidney injury; AP, alternative pathway; APS, antiphospholipid syndrome; C1INH, C1 inhibitor; DGF, delayed graft function; Fab, antigen-binding fragment; GN, glomerulonephritis; GPA, granulomatosis with polyangiitis; HAE, hereditary angioedema; IGAN, IgA nephropathy; LN, lupus nephritis; mAb, monoclonal antibody; MAC, membrane attack complex; MG, myasthenia gravis; MGN, membranous nephropathy; MPA, microscopic polyangiitis; MPGN, membranoproliferative glomerulonephritis; NMA, neuromyelitis optica; PNH, paroxysmal nocturnal hemoglobinuria; TMA, thrombotic microangiopathy.