



Published in final edited form as:

*Immunobiology*. 2025 May ; 230(3): 152915. doi:10.1016/j.imbio.2025.152915.

## Systemic lupus erythematosus as the paradigm for understanding the complex immune relationships and therapeutic opportunities for targeting complement in autoimmune diseases<sup>☆</sup>

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### Abstract

Complement therapeutics have been increasingly tested and approved for human diseases, often in orphan diseases with strong and apparently causal genetic linkage or mutation-associated features. However, the complement system has been demonstrated to be activated in essentially all human inflammatory, ischemic and autoimmune diseases, suggesting the possibility of even wider therapeutic applications. The goal of this manuscript is to review some of the evidence supporting a wide role for complement in the specific treatment of autoimmune diseases, especially as recent approvals in autoantibody-driven diseases are opening the door to others of these indications. However, in part because of a dearth of complement biomarker data obtained during clinical trials, it is not known what findings would help to predict therapeutic success in other autoimmune diseases. To frame the discussion, it is relevant to point out that the disease systemic lupus erythematosus (SLE) has been among the most extensively studied autoimmune disease with regards to the varied roles of the complement system, and there are available both human phenotypic studies and murine model data. Because of that history, SLE will be focused upon herein, the many roles of complement in SLE will be reviewed, and informative comparisons to other autoimmune diseases will be made. In aggregate, experimental and phenotypic data suggest that each human autoimmune disease deserves careful attention to the possibility that a specific complement inhibitor targeting the most relevant complement convertase or component will be of benefit, and thus therapeutic approaches should be tested using informative biomarker-driven clinical trial strategies.

### Keywords

Therapeutics; Autoimmune Disease; Biomarkers; Animal Models; Clinical Trials

<sup>☆</sup>This article is part of a Special issue entitled: 'ICW2025' published in *Immunobiology*.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

CRediT authorship contribution statement

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## 1. Introduction

In science, a paradigm can constitute a distinct set of concepts that centrally contribute to the understanding of a field. The word is Greek in origin and is often used to provide a framework in which broad activities are presented and discussed. This review aims to explore the many activities of the complement system and how they contribute to the development and pathogenesis of human autoimmune diseases. Within that broad context, the disease systemic lupus erythematosus (SLE) has long been extensively studied with regards to the many varied roles of complement in disease risk, immune dysregulation and organ damage (Manderson et al., 2004). Because of that history, it is a fitting disease upon which to focus. Thus, the primary effort herein will be to review how the specific activities of complement that have been studied in SLE and its animal models serve as paradigms around which to understand the broader roles of this intriguing pathway in the immunopathogenesis of other autoimmune diseases and its therapeutic potential (Ricklin et al., 2018). As a direct extension of these studies, working to modulate deleterious activities in SLE and other autoimmune diseases through the incorporation into human studies of informative biomarkers (Nilsson and Ekdahl, 2012) as well as testing the increasing number of approved complement therapeutics (West et al., 2024) in patients in a mechanism-driven manner remain promising areas for further exploration.

### 1.1. Knowledge gained from SLE studies can be used to predict roles of complement in other autoimmune diseases

SLE is a complex female predominant disorder with an incidence of 5–12/100,000 person-years and extensive interactions with components of the complement system (Fanouriakis et al., 2021; Li et al., 2021; Siegel and Sammaritano, 2024). The disease process is characterized by immunologic features, including dysregulation of innate and adaptive immunity, the former characterized in part by continuous neutrophil activation and the latter by the presence of a wide variety of autoantibodies. SLE is generally considered to be a systemic disorder, but with immune-mediated damage that can affect almost every organ system, most often renal (designated lupus nephritis), mucocutaneous, musculoskeletal, serosal, hematologic and neuropsychiatric (Siegel and Sammaritano, 2024). Current therapeutic approaches in SLE include glucocorticoids, hydroxychloroquine, immunosuppressives (cyclophosphamide, azathioprine, mycophenolate mofetil, voclosporin), and targeted biologics (belimumab, anifrolumab, rituximab), as well as additional off label medications when specific clinical situations arise (Siegel and Sammaritano, 2024).

The complement system is understood to play several integral roles in the pathogenesis of SLE, both with regards to risk of development of the disease (Botto et al., 2009) as well as through the engagement of potent effector mechanisms once clinical disease is established (Fig. 1) (Li et al., 2021). These roles have been primarily explored through genetic, biomarker, animal model, and *ex vivo* studies, as well as in some emerging clinical trials.

## 1.2. Historic and next generation complement genetic studies have contributed to understanding of the risk of SLE and other autoimmune diseases

Although complement effector functions are often considered to be most relevant to lupus clinical manifestations, deficiencies of classical pathway (CP) proteins remain among the most impactful genetic associations with SLE (Macedo and Isaac, 2016). Specifically, although individual studies present varied levels of association, development of SLE is highly associated with complete deficiencies of C1q (90–95 %) and C4 (75 %). Additional associations with SLE are found with complete deficiencies of C1r/C1s (60–66 %) and C2 (~10 %). Perhaps the most fascinating association with SLE occurs with the C4 genes *C4A* and *C4B*, which exhibit substantial variation in risk for SLE, with *C4A* protecting more strongly than *C4B*, but also very impressive sex-biased risk in their effects (Kamitaki et al., 2020). In that situation, C4 alleles appear act more strongly in men than in women when assessing risk for SLE as well as the disease schizophrenia. With regards to complement regulatory proteins, the genetics of the factor H (FH) and FH-related (FHR) family have been studied in patients with SLE, with the finding that the *FH* locus is linked to SLE risk (Zhao et al., 2011) and also that the relatively common linked deletion of *FHR3* and *FHR1* genes contributes an elevated risk to the development of SLE across multiple ethnic populations (Zhao et al., 2011). Although the mechanisms of effects of complement gene variants in patients are unknown, they are often considered to reflect defects in clearance of immune complexes and apoptotic bodies (Botto and Walport, 2002), promoting loss of self-tolerance and inappropriate tissue deposition (Fig. 1A). However, more recent experimental models have suggested that the complete C1q and the *C4A/C4B* polymorphic variant effects regulate the development of loss of self-tolerance through effects on CD8 T cell metabolism (Ling et al., 2018) and autoantibody producing B cell development (Simoni et al., 2020), respectively. The mechanism of effects of the *FHR3/FHR1* deletion are unknown, but are likely due to as yet uncharacterized immunomodulatory effects.

Acquired alterations in C1q functions are also found in patients, typically associated with anti-C1q autoantibodies that are present in an especially high proportion of patients with lupus nephritis (Beurskens and van Schaarenburg, 2015). Other acquired associations include the loss of complement receptor 1 (CR1/CD35) from the surface of erythrocytes that is apparently secondary to excessive levels of C3 fragment-coated immune complex clearance and cleavage of CR1 in the liver (Schifferli et al., 1989). Although the associations of complement deficiencies with SLE are most often commented upon in publications, it is relevant to emphasize that patients with CP deficiencies are also at risk for severe infections that can be fatal (Macedo and Isaac, 2016).

With this extensive background in SLE, other autoimmune diseases have also demonstrated substantial genetic associations with the complement pathway (Coss et al., 2024; Jia et al., 2022). The most impactful associations are gene mutations, often found in the renal diseases atypical hemolytic uremic syndrome (aHUS) and C3 glomerulopathy (C3G), present in the alternative pathway (AP) activation and regulatory proteins, as well as inhibitory autoantibody generation (Noris et al., 2010). Other intriguing associations are found with the FHR family (Poppelaars et al., 2021a), where as opposed to the deletion of *FHR3/FHR1* being associated with a higher risk of SLE, there is a lower risk of developing IgA

nephropathy (IgAN) (Gharavi et al., 2011). Clinically useful next generation sequencing approaches are now available to evaluate patients with these thrombotic microangiopathies (TMA) and other potential complement-related renal diseases (Java and Kim, 2023). Importantly, the use of these approaches more broadly in autoimmune diseases should increase our understanding of disease pathogenesis and the potential for complement pathway therapeutic intervention.

### 1.3. Biomarkers of complement activation are readily detected in patients with SLE and other autoimmune diseases

Complement biomarkers can be used to discern the functional and activation status of specific activation pathways as well as common effector mechanisms (Nilsson and Ekdahl, 2012). Examples include C1, C4 and C2 for the CP, factor B (FB) and factor D (FD) for the AP, and ficolins, mannose-binding lectin (MBL) and MBL-associated serine proteases (MASPs) for the lectin pathway (LP). Activation products include C4d (CP and LP), and Bb and Ba (AP), while other effector mechanism components [C3a, C5a and C5b-9/membrane attack complex (MAC)] are products of the common pathway that follows the initiation mechanisms. Additional biomarkers consisting of measures of the intact multi-protein convertases are also increasingly available.

Many informative biomarkers have been studied in patients with SLE. For instance, while low C3, C4 and total hemolytic complement (THC) are most often associated with active disease, the plasma levels of FH are inversely associated with clinical disease activity scores and positively associated with serum C3 levels, reflecting likely decreases in complement activation (Wang et al., 2012). Whether this kind of FH/C3 level relationship exists for diseases without systemic activation is not clear. Additionally, there is an inverse relationship between the injury scores in lupus renal biopsies, including those patients with TMA, and serum FH levels. When comparing the levels of complement activation factors in SLE patients with glomerulonephritis as compared to those without this target organ involvement, plasma levels of Bb, C3a, C5a and sC5b-9 were all significantly increased, and Bb levels were the most highly associated with worse outcomes and renal pathology scores. Beyond this, the ratio of iC3b to C3 was found to be increased as a biomarker of elevated disease activity (Kim et al., 2019), and evidence of AP activation acted as an antecedent predictor of future flares (Buyon et al., 1992). In addition to blood levels of biomarkers, renal mRNA expression has been studied in the kidneys of patients with proliferative lupus nephritis, pre- and post-treatment for a renal flare (Parikh et al., 2017). Notably, in therapeutic non-responders complement *C3* and *FD* mRNA levels were substantially elevated, while mRNA from the *FI* gene was decreased. In addition to mRNA levels, the presence of both FH and FB proteins in the glomerulus were associated with interstitial fibrosis, and those biopsies with localized properdin (P) exhibited higher proteinuria (Sato et al., 2011). Not surprisingly, the presence of C3 fragments in the first renal biopsy is associated with the doubling of serum creatinine in the future (Hill et al., 2001). Beyond the kidney and blood findings, even in early classic studies complement C3 fragments were found to be associated with local IgG deposition in patients with SLE in the liver, spleen, heart and other organs (Walport, 2002; Paronetto and Koffler, 1965). More recently, covalently cell-bound C3d and C4d have been identified in patients with

SLE on erythrocytes and other circulating cell types, and the relative levels exhibit the potential to portend disease flares (Ramsey-Goldman et al., 2017). In sum, the systemic and tissue-specific autoimmunity in SLE is associated with widespread evidence of complement dysregulation and deposition.

With regards to complement elevations in other autoimmune diseases, many diseases are characterized by the presence of activation in the specific target organs (Coss et al., 2024; Jia et al., 2022). Perhaps the most relevant to review are the autoimmune diseases in which complement therapeutics have been approved. These include cold agglutinin disease (CAD), generalized myasthenia gravis (gMG), neuromyelitis optica (NMO), and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV).

With regards to CAD, the disease is typically characterized by cold-reactive IgM autoantibodies of monoclonal origin that function as hexamers, and an associated anemia that has been considered for decades to be due to the clearance of IgM and CP derived C3 fragment-bound cells by complement receptors in the reticuloendothelial system in a process designated extravascular hemolysis (Shi et al., 2014). Recent clinical trials using the C1s monoclonal antibody (mAb) inhibitor sutimlimab were successful in reducing hemolysis and improving fatigue, and led to the approval of this drug in patients with CAD (Röth et al., 2021). With regards to complement biomarkers, C4 levels are often decreased due to the presumed CP consumption as it activates C3 as the C3b fragment on the erythrocyte surface, and the “surviving” erythrocytes are found to be coated with the terminal C3d cleavage fragment after the surface C3b is proteolytically processed to this fragment (Berentsen et al., 2022).

With regards to gMG, the pathogenesis of experimental MG has been studied for decades and shown to involve anti-acetylcholine receptor antibodies that are present in the neuromuscular junction (Nakano and Engel, 1993). These autoantibodies fix complement through the CP and cause neuromuscular dysfunction in experimental models, primarily through MAC formation (Morgan et al., 2006). More recently, complement biomarkers have been measured in patients with gMG, demonstrating that C2 and C5 levels are significantly reduced, and C3, C3b and C5a increased (Iacomino et al., 2022). Beyond these findings, gMG patients have demonstrated higher plasma C3a and soluble C5b-9, as well as correlations of a composite disease severity score with levels of plasma FB, FI, and FH Huang et al., 2024. With this extensive experimental background, the finding that ravulizumab demonstrated clinical benefit sufficient for approval was not unexpected (Vu et al., 2023).

Another condition with extensive connections to complement is NMO, a disease associated with IgG autoantibodies directed to aquaporin 4 that typically presents with transverse myelitis and optic nerve dysfunction (Wingerchuk and Lucchinetti, 2022). In a clinical trial, eculizumab demonstrated a significant decrease in relapse rates (Pittock et al., 2013), which led to regulatory approval. Local evidence of complement activation in the central nervous system is provided by findings of elevations of C3a and C5a in the cerebrospinal spinal fluid as well as MAC deposition within the NMO lesions (Bennett and Owens, 2017).

Circulating activation products from the classical (C4d, iC3b), alternative (Bb, iC3b) and terminal pathways (C5a, sC5b-9) are elevated in patients (Hakobyan et al., 2017).

The fourth autoimmune disease example is provided by AAV, a potentially life threatening disorder characterized by small vessel inflammation, endothelial dysfunction, and related organ complications (Kitching et al., 2020). Patients with subtypes of AAV exhibit variable rates of autoantibodies to proteinase 3 (PR3) and/or myeloperoxidase (MPO), which are neutrophil cytoplasmic proteins. Significant clinical benefit has been shown to occur in clinical trials using the C5aR1 inhibitor avacopan in AAV, where it was paired with rapid glucocorticoid decreases (Jayne DRW, Merkel PS, Schall TJ, Bekker P, Group AS, 2021), resulting in approval in this patient population.

With regards to complement biomarkers in AAV, deposition of C3 fragments and MAC has been found in the kidney, as well as significant elevations of circulating C3a, C5a and sC5b-9 whose levels correlate with disease activity (Wu et al., 2019; Kallenberg and Heeringa, 2012). In addition, an increase in circulating C5a has been detected prior to the onset of a clinical flare (Johansson et al., 2022). In histologic studies, the presence of renal Bb correlates with crescents, interstitial infiltrates and fibrosis, as well as tubular atrophy (Gou et al., 2013). Beyond these sites, urinary levels of Bb correlate with the serum creatinine, and the presence of renal C3 fragments is associated with worse disease outcomes (Oba et al., 2021).

#### 1.4. Functions of the complement system likely involved in the pathogenesis of SLE and other autoimmune diseases

From experimental models and clinical studies, the complement system is known to affect many aspects of the innate and adaptive immune systems. Here these various activities are described, initially as they have been studied in SLE but also providing examples of similar roles in other autoimmune diseases.

**Complement Activation Pathways and the Key Role of the Alternative Pathway and Amplification Loop.** The clinical success of therapeutics targeting the classical pathway, as well as the C3/C5 convertases, the AP and C5aR1, has provided substantial impetus to understanding the mechanisms by which complement activation is initiated and regulated in human disease states. Certainly the success of C1s-targeted CP inhibition in CAD, and nascent studies of C2 inhibition in experimental models and patients with neurologic diseases such as multifocal motor neuropathy (Budding et al., 2022) indicates that IgM and complement fixing isotypes of IgG can play important roles in human autoimmune diseases (Gewurz et al., 1995). In contrast, LP initiation through the binding to ligands by mannose-binding lectin (MBL) and activation of the MASPs plays a less certain role (Reid and Turner, 1994; Matsushita et al., 2000).

In contrast, AP auto-activation through “tickover” has the capacity to be engaged in many settings (Muller-Eberhard, 1988; Elvington et al., 2019). Regardless of the nature of the initiators, all three activation pathways will generate C3b molecules that will engage the amplification loop. Although the absence of published trials in patients with SLE limits understanding of the role of the AP in this disease, murine models have been extensively



studied to evaluate mechanisms potentially involved in the development of the human disease, including lupus nephritis (McGaha and Madaio, 2014). In this setting, although SLE is considered to be an autoantibody driven disease, support for the essential role of the AP and amplification loop was provided by the finding that *FB*<sup>-/-</sup> MRL/*lpr* mice demonstrated substantial protection from development of nephritis (Fig. 1B) (Watanabe et al., 2000). Similarly, *FD*<sup>-/-</sup> MRL/*lpr* mice lacking the key AP protein FD were protected (Elliott et al., 2004). Subsequently, another AP inhibitor, CRIg-Fc, was also found to ameliorate development of glomerulonephritis in MRL/*lpr* mice (Lieberman et al., 2015). These findings are in contrast to findings that *C3*<sup>-/-</sup> mice were not protected in this model (Sekine et al., 2001), and that *C4*<sup>-/-</sup> mice in a separate model of SLE demonstrated enhanced autoimmunity (Einav et al., 2002).

Following upon the results in murine models of SLE, the role of the AP has been explored in a number of other autoimmune diseases. Perhaps most relevant is IgA nephropathy (IGAN), the most common form of primary glomerulonephritis in the world (Penfold et al., 2018). Therein, recent clinical trials and approvals have provided great insights into the roles of complement, in particular the C3/C5 convertase (Dixon et al., 2023) and AP (Perkovic et al., 2025), the latter leading to approval of the small molecule FB inhibitor iptacopan. The pathogenesis of IgAN appears to be a systemic disorder that targets the kidneys (Suzuki et al., 2011). Renal histologic features include immune complexes containing galactose-deficient IgA1 (Gd-IgA1), IgG and C3 activation fragments. In patients, elevated circulating C3b, iC3b and C3dg are found in ~30 % of patients, and renal biopsies typically contain FH, FB and P (Le Stang et al., 2021; Poppelaars et al., 2021b). The role of the AP remains to be explored in other autoimmune disorders associated with and/or driven by autoantibodies. However, hope for beneficial effects comes from various animal models, for instance AAV where *FB*<sup>-/-</sup> mice are protected in the highly informative murine model of this disease (Xiao et al., 2007), and the CAIA model of RA, where similarly *FB*<sup>-/-</sup> but not *C4*<sup>-/-</sup> mice are protected from the development of arthritis (Banda et al., 2006).

### **Regulation of B and T Cell Autoimmune Responses, as Well as Effector Functions, by Complement Activation Fragments and Their Receptors. In**

addition to the effects of C1q discussed above, there are other well-defined intersections between complement activation fragments and the adaptive immune system. One consists of the complement receptor type 2 (CR2/CD21), which is most highly expressed on B cells and follicular dendritic cells. CR2 plays a key role in the development of high affinity antibodies and long-lasting memory to foreign antigens (Carroll and Isenman, 2012). When CR2 is bound by its primary C3 activation fragment-derived ligand, designated C3d, it co-associates with CD19 on B cells to amplify B cell receptor (BCR) signaling. C3d and CR2 also mediate immune complex binding to follicular dendritic cells.

As the development of SLE involves subversion of normal B cell tolerance checkpoints, it was expected that CR2 ligation by C3d-bound immune complexes would promote the development of autoantibodies and a worsened outcome in models of SLE. However, prior studies in murine models of SLE using gene-targeted *Cr2*<sup>-/-</sup> mice, which lack both CR2 and complement receptor 1 (CR1/CD35), demonstrated variable results, possibly due to the associated lack of interactions by C4b itself with CR1 being a dominant effect (Einav et al.,

2002). As an alternate approach to address this question, a highly specific mouse anti-mouse C3d monoclonal antibody was created that blocks interaction with CR2 (Thurman et al., 2013). With this tool, disruption of the critical C3d-CR2 ligand-receptor binding step alone substantially delayed autoimmunity and renal disease progression in the MRL/*lpr* model of SLE (Fig. 1C) (Kulik et al., 2019).

Recent data have also highlighted another potential role for CR2 in its interactions with targets. One study suggested that this receptor could also interact with DNA and result in interferon alpha, a major cytokine driver of SLE pathogenesis, release (Fig. 1D) (R. A. Banda N, Szakonyi G, Chen XS, Holers VM., 2013). A second suggested that engagement of CR2 on follicular dendritic cells would allow a TLR7-dependent mechanism to be triggered, resulting in production by these cells of interferon alpha (Fig. 1D) (Das et al., 2017).

With regards to other models, CR2 engagement has been found to be essential for the development of the human rheumatoid arthritis (RA) model collagen-induced arthritis (CIA) (Kuhn et al., 2008) and experimental autoimmune myocarditis (Kaya et al., 2001). Unfortunately, this target has not been explored yet in patient studies.

Beyond CR2, C5a and C3a have been most often considered as targets due to their effects on promoting innate immune-generated inflammation (Wetsel, 1995; Pandey et al., 2020). C5a exhibits its immunoregulatory properties through its primary receptor designated C5aR1/CD88, through which it will promote chemotaxis, neutrophil activation and platelet degranulation, among other largely pro-inflammatory effects (Fig. 1E). Prior studies have demonstrated, however, that C5aR1 and C5aR2 can also affect adaptive immune responses (Kohl, 2006). C3a manifests its effects through its C3aR and can typically play in experimental models either pro-inflammatory or immunomodulatory roles (Humbles et al., 2000; Gao et al., 2020). Studies in the MRL/*lpr* model with C5aR1 deficient animals led to prolonged survival, less renal disease and decreased autoantibodies (Wenderfer et al., 2005). Conversely, MRL/*lpr* mice deficient in C3aR demonstrated accelerated renal disease and increased autoantibody generation, but no effects on survival (Wenderfer et al., 2009).

With regards to other autoimmune disease models, C5aR1 has been successfully targeted in patients with AAV, and it has also been studied in many other autoimmune disease models. These include collagen antibody-induced arthritis (Banda et al., 2012), anti-phospholipid antibody-induced fetal loss (Girardi et al., 2003) and epidermolysis bullosa acquisita, although in this syndrome both C5aR1 and C5aR2 appear to be involved in promoting pathogenesis (Seiler et al., 2022). Thus, this ligand and receptor could well be effective in diseases in which adaptive immunity and complement effector functions are co-drivers of organ damage.

**Engagement of Pro-Inflammatory Pathways Through the Membrane Attack Complex.** Although the MAC is most often considered in the context of cell lysis, it has been known for decades to deposit on nucleated cells and initiate a large number of activation events that are typically pro-inflammatory and can disrupt tissue homeostasis (Morgan et al., 2017). With regards to SLE, although experimental C5 inhibition has long



been known to ameliorate the (NZBxNZW)<sub>F1</sub> experimental model (Wang et al., 1996), and as shown above the C5a product of C5 activation promotes renal injury (Wenderfer et al., 2005), the role of the MAC itself beyond C5a does not appear to have been studied in either patients or published models through inhibitory approaches (Fig. 1F). However, another way to understand the role of the MAC is through gene targeting of the MAC inhibitor CD59, where for example the lack of expression accelerated autoimmunity and target organ damage in the MRL/*lpr* model (Miwa et al., 2012).

Perhaps the best studied example demonstrating a role for the MAC in an autoimmune disease comes from studies of experimental multiple sclerosis and patients with this disease (Morgan et al., 2021; Morgan and Harris, 2015). Specifically, the brains of patients demonstrate extensive immune infiltration, local production of complement factors, and complement activation. In experimental models, inhibition of proximal activation steps can ameliorate models; however, these are relatively unique in demonstrating through specific inhibition approaches a role for the MAC in disease pathogenesis. In addition, when using the CD59 knockout approach, a rat passive transfer model of NMO was greatly accentuated in deficient mice (Yao and Verkman, 2017).

**Clearance of Circulating Immune Complexes.** In addition to the effects of complement on innate and adaptive immunity, a number of important inter-linked “housekeeping” functions are undertaken by this system. One important function is the clearance from the circulation of circulating immune complexes, most often containing IgG antibodies and infectious organisms or their antigens through binding to erythrocyte CR1, in this activity known as the immune adherence receptor (Fig. 1G) (Miyakawa et al., 1981; Nelson, 1953). This function is very much diminished in patients with SLE, as noted above, and also dysfunctional in other systemic diseases such as large vessel vasculitis associated with mixed essential cryoglobulinemia, which is characterized by excessive immune complex formation and their presence in the circulation and abnormal tissue deposition (Schifferli and Taylor, 1989).

**Extrinsic Complement Activation Mechanisms.** Although not extensively studied in SLE, mention of other mechanisms of complement activation is relevant. One of the most important is the extrinsic pathway that is primarily initiated by a number of proteases that are generated in disease settings (Mastellos and Lambris, 2025). A recent example is the observation that granzyme K can cleave C4 and C2 to create the CP/LP C3 convertase C4b/2a Donado et al., 2025.

### 1.5. Thoughts on creating more informed therapeutic strategies to facilitate broadening the use of complement targeted drugs in autoimmune diseases

Despite increasing therapeutic benefits being demonstrated in autoimmune diseases, what is lacking in the field is a comprehensive approach to collecting and publishing results of complement-related biomarkers (Mastellos et al., 2019). That is especially relevant when there are pro-inflammatory mediators from this pathway whose levels are intended to be modulated through therapeutic intervention, and when there is a need to understand the specific relationships of such biomarker changes to the relative improvement in a patient

clinical status. Such studies would also provide important confirmation for the field that the intended effects are found when undertaking a targeted therapy, for instance demonstrating in a disease setting that FB cleavage products Ba and/or Bb are altered to the expected level by inhibitors of FB or FD. One such informative approach was recently illustrated by the finding that alternative pathway inhibition of FB by the small molecule iptacopan resulted in the expected decrease in C3 fragment binding to red blood cells (Peffault de Latour et al., 2024) in patients with paroxysmal nocturnal hemoglobinuria (PNH), which was an effect found when patients are treated only with C5 inhibition and C3 activation continues unabated (Risitano, 2012). Without this knowledge in general, there remain many questions such as whether it requires essentially 100 % inhibition to see maximal clinical benefit, which is apparently the requirement for targeting C5 in PNH Gaya et al., 2023. In addition, as many diseases are focused in tissues and organs, and not peripheral blood where samples are relatively accessible, it is unknown as to whether control of complement activation in tissue samples reflects the changes seen in peripheral blood, or other fluids such as urine. Thus, linking immunohistochemistry of organ biopsies to assess changes in local complement activation to tissue damage to peripheral blood biomarkers is much needed in the field. ‘Beyond these questions, other considerations arising from such studies would potentially support the use of combination therapy, for instance to block AP activation in addition to C5aR1 engagement, with the goal to block the deleterious effects of C3 activation in addition to potential C5a effects through extrinsic activation or specific effects on neutrophils as seen in AAV (Jayne DRW, Merkel PS, Schall TJ, Bekker P, Group AS, 2021).

Additional approaches to understanding the level of local control of complement activation in target organs are emerging. One organ that is of particular interest is the kidney, as one can biopsy this organ with reasonable safety and thus directly compare results from tissue samples to those derived from emerging minimally invasive imaging approaches. The ability to specifically detect and quantitate complement *in situ* using an imaging approach was recently shown by the ability of a mAb specific for C3d/iC3b to detect renal deposition of the specific target (Renner et al., 2023). As the field expands to other organs and other complement pathway targets, it is anticipated that the ability to image key activation fragments such as C3d, C4d and the MAC, as well as receptors such as C5aR1 will also have to expand in order to provide additional information about the extent and location(s) of activation, and assure target coverage at the site(s) of interest.

## 2. Conclusions

The complement pathway is activated in many if not all autoimmune diseases. As several autoantibody-driven autoimmune diseases have been shown to benefit from C5 or FB inhibition, it is likely that many others will exhibit similar amelioration following treatment with inhibitors that target specific proteins or convertases. Although patients with SLE, and especially lupus nephritis, have not yet been shown to benefit from a complement inhibitor, some trials are underway. Regardless, this disease has been extensively studied to understand the roles of complement in disease risk, adaptive autoimmunity, evolution and organ damage. Thus, like other diseases, it is hoped that patients with at least some form of SLE will similarly benefit. There are additional studies that would improve the likelihood

of successful outcomes, mostly focused on improving the use and utility of complement biomarkers, including molecular imaging approaches.

## Acknowledgements

The author thanks his many academic and industry collaborators in the complement field for providing many varied viewpoints over his career that influenced the concepts discussed in this manuscript.

## Funding sources

This work was supported by the National Institutes of Health R01 AR051749.

## Data availability

No data was used for the research described in the article.

## Glossary

<b>SLE</b>	systemic lupus erythematosus
<b>FH</b>	factor H
<b>FHR</b>	factor H-related
<b>C3G</b>	C3 glomerulopathy
<b>IGAN</b>	IgA nephropathy
<b>TMA</b>	thrombotic microangiopathy
<b>THC</b>	total hemolytic complement
<b>CAD</b>	cold agglutinin disease
<b>NMO</b>	neuromyelitis optica
<b>ANCA</b>	anti-neutrophil cytoplasmic antibody
<b>AAV</b>	ANCA-associated vasculitis
<b>PR3</b>	proteinase 3
<b>MPO</b>	myeloperoxidase
<b>FB</b>	Factor B
<b>MBL</b>	mannose-binding lectin
<b>MASP</b>	(MBL-associated serine protease)
<b>FD</b>	factor D
<b>P</b>	properdin
<b>BCR</b>	B cell receptor

<b>CR2</b>	complement receptor 2
<b>CR1</b>	complement receptor 1
<b>CR3</b>	complement receptor 3
<b>MAC</b>	membrane attack complex
<b>PNH</b>	paroxysmal nocturnal hemoglobinuria

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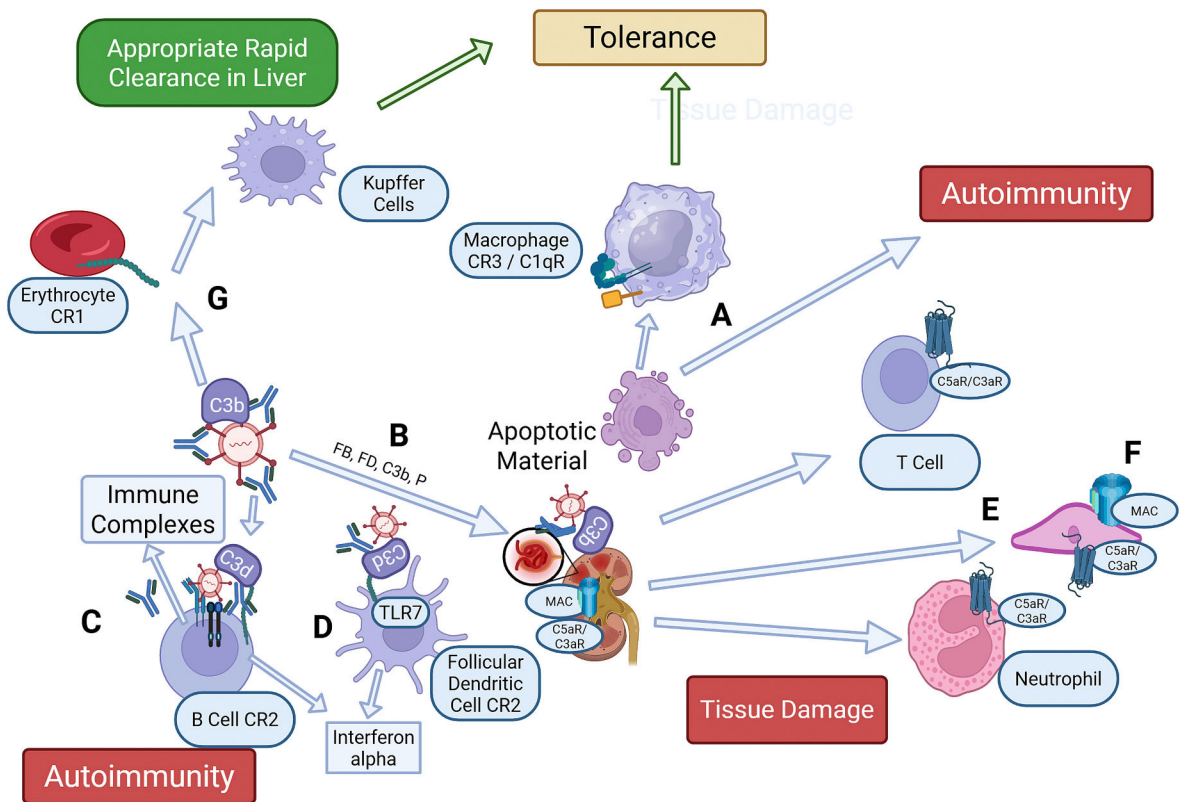
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**Fig. 1.**

Illustration of the many roles of the complement system in the development of SLE, and by inference other autoimmune diseases. (A) Apoptotic material if appropriately cleared through interactions with C1q and its receptor will lead to tolerance, and if not will lead to autoimmunity; (B) In complement activation, the alternative pathway is necessary in SLE and some settings to lead to tissue damage, for instance in the kidney where immune complexes also deposit; (C) CR2 can amplify B cell responses to both foreign and apparently self antigens; (D) CR2 on B cells and follicular dendritic cells amplifies interferon-alpha production; Tissue injury and modulation thereof occurs through complement system C5aR1 and C3aR (E), as well the MAC (F); (G) Appropriate clearance of circulating immune complexes in SLE requires C3b-coated immune complexes to bind to CR1 on erythrocytes and be transported for clearance in the liver. Created in BioRender. Holders, V. (2025) <https://BioRender.com/mm8szox>.