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Full Review

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C3 glomerulonephritis and CFHR5 nephropathy

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Abstract
Complement is an important aspect of defence against infection and its activation and regulation are finely balanced. Disordered complement regulation can lead to C3 glomerulonephritis (C3GN), which is characterized by complement (but not immunoglobulin) deposition in the glomerulus of the kidney. Although only recently recognized as a clinical entity, C3GN is important and elucidation of its molecular causes, by studies of single cases and families, has identified key proteins that protect the kidney from complement-mediated damage. The commonest cause of C3GN is complement factor H-related 5 (CFHR5) nephropathy, which is endemic in Greek Cypriots. Genetic evidence implicates some of the same complement regulators in the aetiology of common immune complex glomerular disorders such as IgA nephropathy and lupus nephritis. Importantly, therapeutic manipulation of the complement pathway is now feasible. An exciting challenge is to determine whether this can be applied to kidney diseases that are caused by complement dysregulation, and also whether they might be used to intervene in other kidney diseases.

Keywords: complement; C3; CFHR5; glomerulonephritis; genetics

Introduction

The complement system is a proteolytic cascade that is an important arm of the innate immune defence system, combining exquisite sensitivity with the potential for massive amplification. These characteristics are balanced by regulatory mechanisms that prevent self-harm from inappropriate activation. It is now clear that some forms of kidney disease are caused by genetic variants that increase the likelihood of complement activation. These findings have important implications. First, they pinpoint the precise molecular cause of disease in a significant and increasing number of patients. Secondly, they provide a rational framework within which to reconsider existing diagnostic categories and disease classification. Thirdly, they provide powerful insight as to how the complement system functions in humans. Fourthly, they have led directly to effective therapeutic interventions in some patients.

Complement activation can be triggered in three ways [1]. The classical pathway is initiated by antibodies binding to antigen. The lectin pathway is initiated by lectins binding to microbial surfaces. Both these result in activation, by cleavage, of circulating C3 to produce C3b. The alternative pathway involves direct cleavage of C3 by an enzyme complex that includes C3b, providing a mechanism for positive feedback and amplification (Figure 1). Activation of C3 leads to the production of molecules that drive an inflammatory response (C3a and C5a) and also to activation of the terminal pathway that leads to assembly of the membrane attack complex (C5b–9), which results in lysis of the targeted cell. An important feature of the complement system is that there is a 'tickover' level of C3 activation due to spontaneous hydrolysis. This is counterbalanced by regulators that act both in the fluid phase and on the cell surface (Figure 1).

Kidney disease related to alterations in the complement alternative pathway

A number of different hereditary and acquired alterations in components and regulators of the alternative pathway are now known to cause kidney diseases. It is useful to consider the kidney diseases under two headings; atypical haemolytic uraemic syndrome (aHUS) and C3 glomerulopathy. Unfortunately, these do not map onto traditional classifications of kidney disease in a completely straightforward way. This illustrates that our existing classification is based largely on morphology, rather than on the underlying pathogenic process.

In aHUS, the characteristic renal lesion is thrombotic microangiopathy [2]. This is not the main focus of this article, but it is interesting to compare and contrast it with C3 glomerulopathy. In aHUS, there is systemic endothelial damage. About 60% of cases are associated with mutations in components of the complement alternative pathway, or with neutralizing autoantibodies directed against the important circulating complement regulator, complement factor H (CFH) [2]. The commonest genetic alterations are missense mutations in *CFH*, which decrease the ability of CFH to bind endothelial cells and protect

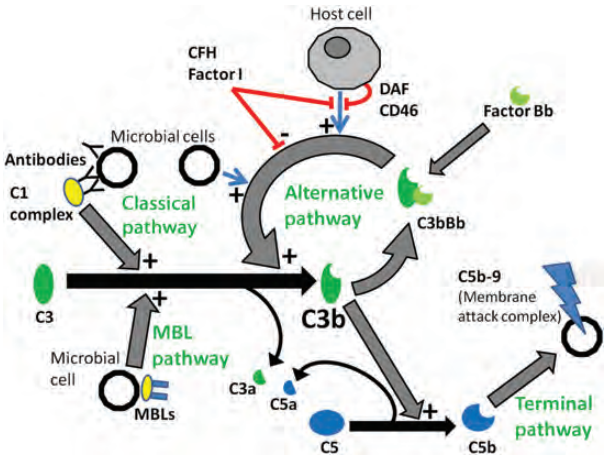

Fig. 1. Central to the activation of complement is the cleavage of abundant circulating C3 to form C3a and C3b. This occurs spontaneously at a low rate in the plasma but is accelerated by: (i) the classical pathway, in which antibodies bound to antigen (for example, on microbial cells) lead to recruitment of the C1 complex which, via activation of C4 and C2 from the circulation, increases C3 cleavage at the antibody-coated surface; (ii) the mannose-binding lectin (MBL) pathway, in which mannose residues on microbial surfaces are recognized by MBL proteins, again leading to recruitment and activation of C4 and C2; (iii) the alternative pathway, in which C3b binds to factor Bb from the circulation to form the C3bBb complex that is stabilized by the presence of a biological surface and provides a mechanism for positive feedback, allowing massive C3 activation. Runaway C3 activation is prevented by circulating alternative pathway regulators, including CFH and Factor I, and cell surface regulators, including decay accelerating factor (DAF) and membrane cofactor protein (CD46). C3b generation also leads to the cleavage of circulating C5 to form C5a and C5b. C5b generation activates the terminal pathway, in which C6–C9 are recruited to form the membrane attack complex—a pore-like structure which lyses the targeted cell. C3a and C5a are anaphylatoxins that recruit and activate cells of the immune system.

them from complement-mediated injury [3]. The penetrance in pedigrees with mutations is incomplete, showing that a mutation on its own is not always sufficient to cause the disease. Importantly, blockade of the terminal pathway, either by deletion of the gene for C5 in a murine model of aHUS [4] or using eculizumab (which is a humanized monoclonal antibody against C5) in patients with aHUS, ameliorates thrombotic microangiopathy and can result in insignificant clinical improvement [5, 6]. The clinical benefit is apparent in groups that include aHUS patients with mutations in a variety of genes, and a significant number in whom a mutation in an alternative pathway regulator is not evident [7]. The combination of the genetic, autoantibody and therapeutic information provides a high degree of certainty implicating complement alternative pathway activation in aHUS. In contrast to C3 glomerulopathy, there is not C3 deposition in the mesangium or basement membrane and the thrombotic microangiopathy is manifest as extensive fibrin deposition.

C3 glomerulopathies: dense-deposit disease and C3 glomerulonephritis

C3 glomerulopathy is a recent term that applies to settings in which there is C3 deposition in the glomeruli without significant immunoglobulins—i.e. there is evidence of complement-mediated injury to the glomerulus not resulting from activation of the classical pathway [8]. C3 glomerulopathy may be associated with normal circulating levels of C3 or may be associated with C3 depletion. Morphologically, C3 glomerulopathy would often be classified as membranoproliferative glomerulonephritis (MPGN), with sub-classification into Type I or Type II MPGN, depending on the nature and location of the accumulation of electron-dense material visualized by electron microscopy. Several points are noteworthy: first, C3 glomerulopathy may be associated with morphological appearances that do not conform to MPGN. This has led to the replacement of the term 'MPGN Type II' with the label 'dense-deposit disease' (DDD) that refers to the accumulation of highly osmiophilic (i.e. electron dense) material within the glomerular basement membrane (GBM). Secondly, DDD is often associated with runaway activation (and hence consumption) of C3 in the fluid phase, reinforcing the role of complement in the pathophysiology of the disease. Thirdly, C3 glomerulopathy *without* dense transformation of the GBM is referred to as C3 glomerulonephritis (C3GN) and only accounts for a proportion of cases of MPGN Type I; in the majority of MPGN Type I, there is clear evidence of immunoglobulin deposition (and usually an underlying infective or autoimmune process can be identified) [9].

Aetiology of C3 glomerulopathies

DDD is rare, occurring with a frequency of ∼2–3 per million population. Up to 80% of cases are associated with a circulating C3 nephritic factor (C3NeF) [10], an autoantibody that binds to and stabilizes activated C3 in the plasma. This can lead to persistent alternative pathway activation, C3 consumption and low plasma C3 levels. Other causes of complement activation, including genetic deficiency of CFH [11], mutations in genes for complement components (including *CFH* and *C3* [12–14]) and autoantibodies directed against CFH, factor B and C3, have all been described [10, 15, 16]—attesting to a central role for complement in the pathogenesis of DDD.

C3GN is also associated with abnormalities of complement alternative pathway regulation. Compared with DDD, a C3NeF is detected less frequently in C3GN (around 40–50% of cases), and antibodies directed against CFH have very rarely been reported. In contrast, genetic abnormalities, including mutations in the genes *CFH*, *CFHR5*, *Factor I* and *CD46*, are described in a greater proportion (around 20%) of patients [14, 17]. Some of these genetic changes have also been identified in patients with immune complex glomerulonephritis (i.e. MPGN with glomerular immunoglobulin deposition), suggesting that variation in the regulation of the complement alternative pathway may influence susceptibility to immune complex-mediated kidney disease. Furthermore, some mutations identified in patients with C3GN and MPGN are reported in patients with DDD and aHUS [9, 14]. This variability in disease phenotype, together with the lack of family history in most cases of DDD and C3GN (even

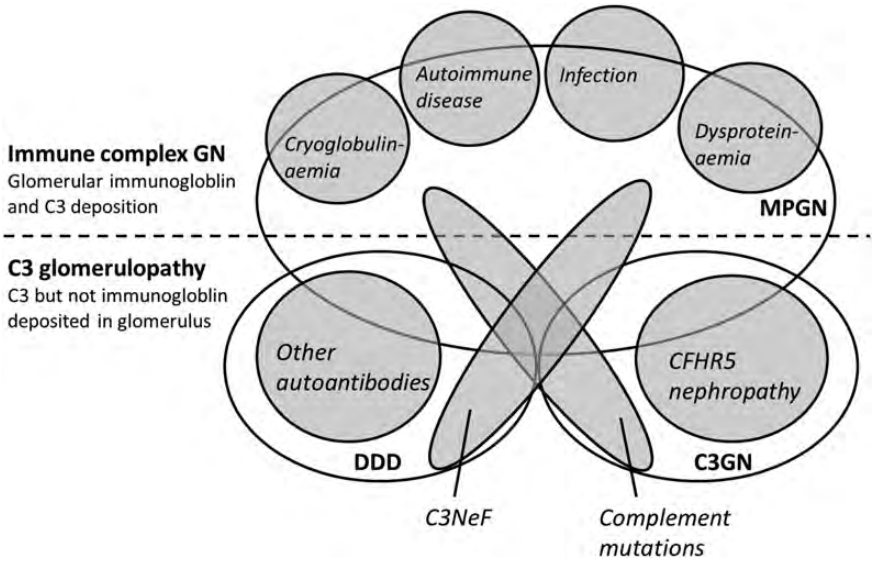

Fig. 2. The histological categories of MPGN, DDD and C3GN are shown as unfilled circles. Grey circles represent disease aetiologies, including CFHR5 nephropathy; C3NeF; and mutations in genes for complement regulators, such as *CFH* and *Factor I*, which may either result in deficiency or defective function of the proteins. In some patients, both a C3NeF and a complement mutation can be identified, and the histological pattern may demonstrate DDD, C3GN or MPGN with glomerular immunoglobulin deposition. In addition, rare patients with autoantibodies to C3 and Factor B have been described in association with DDD.

where a likely pathogenic mutation in a complement regulating gene has been identified), suggests that additional genetic or environmental factors are important in determining disease susceptibility. Recent detailed investigations have demonstrated multiple potential abnormalities of complement regulation in a significant proportion of patients with C3 glomerulopathies [14]. Histological and aetiological classifications of these glomerular disorders are summarized in Figure 2. Interestingly, while genetic defects that impair alternative pathway regulation at surfaces are more commonly identified in aHUS and C3GN, absolute deficiency of CFH and abnormalities (such as a particular C3 activating mutation [12] or C3NeF) that impair alternative pathway regulation in the circulation tend to be associated with DDD. This has led to the suggestion that DDD is a particular consequence of C3 dysregulation in the fluid phase (for review see [18]).

There is some evidence that common genetic variation at loci encoding complement regulators such as CFH and CD46 can modulate the risk of C3 glomerulopathy [14, 19], and although the statistical evidence from the small cohorts of patients involved is weak, there is *in vitro* evidence of altered complement regulation in the presence of some of these variants [19–21]. While genotyping for these variants is unlikely to contribute clinically to the diagnosis or management of individual patients, these findings do reinforce the importance of even subtle variation in complement regulation in the pathogenesis of C3 glomerulopathies.

Clinical features of C3 glomerulopathy

Clinical features of C3 glomerulopathies are variable and do not seem to correlate well with the histological type (i.e. whether the biopsy shows DDD or C3GN). Presentation is usually before the age of 30 years, and while some patients exhibit hypertension, nephrotic range proteinuria and progressive renal impairment, in others there are discrete episodes of haematuria and acute renal dysfunction, sometimes without significant proteinuria. Extra-renal manifestations include retinal drusen, which are caused by the accumulation of material containing C3 within Bruch's membrane. Drusen may be associated with late-onset visual impairment and are recognized in both DDD and C3GN when associated with a C3NeF. In addition, partial lipodystrophy (that is destruction of the fat cells in the upper half of the body) is seen in a small number of patients with a C3NeF.

Renal failure is a common outcome in C3 glomerulopathies, with around 50% of patients reaching end-stage renal disease within 10 years of diagnosis [22]. Recurrence of disease in renal allografts is common, presumably because the aetiological factors that cause the disease (such as a C3NeF or *CFH* mutation) are still present post-transplantation.

The heterogeneity in clinical features, response to treatment and outcomes in patients with DDD or C3GN, has probably contributed to the difficulty in validating therapeutic strategies in C3 glomerulopathies [9, 23]. In addition, there is not a good correlation between the clinical course of disease and the histological type of C3 glomerulopathy: it seems likely that identifying the underlying aetiology is of more clinical relevance than determining whether or not the biopsy shows dense transformation of the GBM. This is especially pertinent when determining therapy: aggressive immunosuppression with antibody depletion (for instance by targeting B-cells using rituximab) has been used with some evidence of success in DDD where autoantibodies have been

identified [15], but this approach seems unlikely to be efficacious where there is an underlying genetic defect of a complement regulator.

Identification of a mutation in *CFHR5* in Greek Cypriot kindreds with C3 glomerulopathy

We undertook genetic studies of two families with C3 glomerulopathy who originated from Cyprus. In both families, the index case had a renal biopsy showing MPGN, and immunolabelling which showed striking glomerular C3 deposition without immunoglobulins. Electron microscopy revealed mesangial and characteristic, elongated, subendothelial electron-dense deposits, without dense transformation of the GBM—appearances consistent with C3GN. The family structure was consistent with autosomal dominant transmission. We showed that disease in these families cosegregated with part of the regulators of complement activation cluster of genes on Chromosome 1. There was a common haplotype across the region in the two families, suggesting inheritance from a single common ancestor. Within the linked region, we identified a 6.3 kbp internal duplication in the complement factor H-related 5 (*CFHR5*) gene. This included exons 2 and 3 and was predicted to encode a protein that was larger than CFHR5 due to duplication of the first two short consensus repeat domains. Consistent with this, when serum from patients is analysed by western blot, there is a reduced amount of normal CFHR5, and an additional species of the predicted higher molecular weight [24].

We have developed a simple PCR test that detects the presence of the mutant *CFHR5* allele and that is now available with a 2-week turnaround time from the North East Thames Regional Molecular Genetics Service in London. This DNA test enabled us and our collaborators to identify a large number of additional families [25] and over 100 individuals with kidney disease who carry this mutation. Haplotype analysis is consistent with all the families inheriting the mutation from a single common ancestor. To date, all the families and individuals that we have identified are of Greek Cypriot ancestry, and our studies suggest that the founder mutation occurred in Cyprus between 500 and 3000 years ago. Importantly, we estimate that at least 1 in 6500 people of Greek Cypriot ancestry carry the mutation, and that over an individual's lifetime the penetrance for renal disease (ranging from isolated microscopic haematuria to end-stage renal failure) is over 90% [25]. Unlike most other causes of C3 glomerulopathy, CFHR5 nephropathy therefore seems to be genuinely monogenic, at least in the Cypriot population.

Clinical characteristics of CFHR5 nephropathy, in contrast to C3 glomerulopathies in general, are consistently limited to persistent microscopic haematuria with or without episodic synpharyngitic macroscopic haematuria in the early stages followed by hypertension and progressive renal failure. Neither high-grade proteinuria (>3 g per day) nor the nephrotic syndrome have been reported in any patients with the disease. Circulating levels of C3 have been normal in all individuals where this has been measured and in all cases where renal biopsy has been performed there is C3 glomerulopathy without dense transformation of the GBM. Males have a strikingly higher risk of developing renal impairment than females (80% of men over 50 years old, compared with 20% of women in this age group). A number of patients have been transplanted and, in all the allografts which have been biopsied, there was evidence of glomerular complement deposition in the graft. Nevertheless, graft outcomes using standard immunosuppression regimens have generally been good, possibly reflecting the slow pace of the disease.

What links the mutation in *CFHR5* to glomerular complement deposition?

The association between the *CFHR5* mutation and C3 glomerulopathy is striking. But precisely how the two are linked is not yet fully understood. The two most likely possibilities are either that the problem is caused by a reduction in the effective concentration of active CFHR5 protein, or that the mutant CFHR5 protein acts in a dominant negative manner. An overlapping challenge is to understand precisely how CFHR5 participates in regulating complement activation. CFHR5 protein was first isolated in 2001 when it was established that it is present in complement deposits in humans and *in vitro* studies showed that it binds C3b [26, 27]. We postulate that CFHR5 plays a prominent role in inhibiting C3 activation at the GBM, and have shown that the mutant CFHR5 protein binds to membrane-associated C3b less effectively than does the wild-type protein [24].

As yet, knowledge of the mechanism of action of CFHR5 as an inhibitor of complement activation is limited. It is synthesized in the liver and is present at a much lower concentration than CFH in the circulation. Studies to date have been based on the hypothesis that its actions will be similar to CFH, and it has been shown to bind heparin and CRP, to exhibit cofactor activity for the Factor I-mediated degradation of C3b and to accelerate decay of the C3 convertase [28]. Further *in vitro* studies of CFHR5 function should be fruitful in understanding what CFHR5 does.

In parallel with biochemical approaches, we anticipate insights from further studies of humans with *CFHR5* gene variants. These can be considered in three broad categories. First, understanding what causes the marked difference in disease progression in men compared with women with this *CFHR5* mutation, and why a few women do and a few men do not develop significant renal impairment. Secondly, identifying individuals with other mutations in *CFHR5* who have C3 glomerulopathy. Thirdly, understanding whether genetic variation in *CFHR5* may contribute to susceptibility to other diseases besides C3 glomerulopathy.

An additional unanswered question is whether the high frequency of this *CFHR5* mutation in Cyprus is a consequence of genetic drift within the island (where random

sampling effects within a small population can lead to a rapid increase in the frequency of rare alleles over time), or if enhanced complement activation in patients with the disease causes enhanced innate defence against some endemic infection, thereby conferring (at least in the pre-antibiotic era) a survival advantage on those people harbouring the mutation. It is well recognized that selection pressure from endemic infections can maintain disease-causing alleles in human populations—examples being malaria and haemoglobinopathies, and trypanosomiasis and renal failure-associated *APOL1* allotypes in sub-Saharan Africa [29].

What factors govern disease severity in CFHR5 nephropathy?

At present it is not known why women with the mutation only rarely develop kidney failure (despite urinary and histological evidence of active disease). Possibilities include differences between the sexes in response to infections, in the regulation of complement in the circulation, or in how complement is processed in the kidney.

While it is possible that environmental factors, such as frequency of exposure to infections, are primarily responsible for determining the age at which patients develop clinically significant renal failure, this large group of patients with a monogenic disease drawn from a relatively homogeneous island community provides an ideal population in which to study how other genetic factors can influence response to renal injury. Constantinos Deltas' group in Cyprus is investigating how variation in other genes influences the phenotype of patients with CFHR5 nephropathy. They recently reported an association between the severity of the renal phenotype and a *NPHS2* polymorphism which results in a nonsynonymous substitution in podocin [30]. In a second study, they have implicated a polymorphism in the 3′ untranslated region of the gene encoding heparin-binding epidermal growth factor, which they suggest alters the ability of a microRNA to regulate expression of this growth factor that plays a role in podocyte biology [31]. The extent to which these genetic factors play a role in determining the risk of renal failure in the context of other renal diseases remains to be determined.

Studies of *CFHR5* in other patients with C3 glomerulopathy

Recently, Vernon *et al.* [32] reported a child who presented with an acute poststreptococcal nephritis. Evidence of renal inflammation persisted and renal biopsies showed C3 glomerulopathy. The patient was found to be heterozygous for a single-nucleotide insertion in exon 4 of *CFHR5*, which is predicted to result in a frameshift and premature stop codon, and was found to have reduced circulating CFHR5 measured by ELISA. In contrast to our patients with the internal duplication in *CFHR5*, this patient had persistently reduced levels of circulating C3. The authors speculate that the genetic variant in *CFHR5* made the patient susceptible to developing C3 glomerulopathy, which was triggered by the streptococcal infection. Importantly, two first degree relatives also carried the gene variant in *CFHR5*, but did not have any evidence of renal disease and their circulating levels of C3 were in the normal range. Furthermore, their levels of CFHR5 were also normal. This establishes that this genetic variant in *CFHR5* is not sufficient to cause renal disease and is not sufficient to cause a reduction in CFHR5 or C3 levels. This is further supported by the fact that the same variant in *CFHR5* was identified in a patient who acted as a normal control in an investigation of aHUS [33].

Vernon *et al.* [32] also reported that patients with C3 glomerulopathy who did not have a mutation in *CFHR5* had a statistically significant reduction in levels of circulating CFHR5 than controls without renal disease. It will be interesting to establish whether this is specific to C3 glomerulopathy, or whether CFHR5 is also reduced in other glomerular diseases.

Abrera-Abeleda *et al.* [34] have investigated whether genetic variation in *CFHR5* may contribute to DDD. Allele frequencies of three single-nucleotide polymorphisms in *CFHR5* were significantly different between groups consistent with the possibility that variants in *CFHR5* may contribute to the risk of developing DDD.

Contribution of genetic variation in *CFHR5* to other conditions

Two studies have identified rare genetic variants in *CFHR5* in patients with aHUS. Maga *et al.* [35] analysed 144 patients with aHUS cohort and found three non-synonymous coding variants in *CFHR5*, Glu75Xaa, Val277Asn, Val379Leu, which were not present in controls. Westra *et al.* [36] screened a collection of 65 individuals with aHUS. They found three novel single amino acid substitutions in *CFHR5*, which are strong candidates for disease-causing mutations: Ser195Thr, Leu105Arg and Trp436Cys. Monteferrante *et al.* [33] identified genetic variants in *CFHR5* in 9 of 45 aHUS patients and 4 of 80 controls. While further studies will clearly be necessary to establish whether *CFHR5* mutations are sufficient to cause aHUS, these findings suggest that *CFHR5* variants could contribute to aHUS in a proportion of patients.

Treatment of CFHR5 nephropathy

Elucidation of the likely molecular cause of CFHR5 nephropathy raises the exciting possibility of targeted treatment for the condition. Based on the rationale that replacing the abnormal CFHR5 protein in the circulation might ameliorate disease, plasma exchange has been utilized in a very small number of patients. Our impression is that this manoeuvre does have a beneficial effect, based on terminating macroscopic haematuria and stabilizing or reducing the level of creatinine. To date, we are not aware of any patient with CFHR5 nephropathy being treated

with eculizumab. This was developed as a treatment for paroxysmal nocturnal haemoglobinuria, and has now been approved for use in aHUS (see above). In a recent report, three patients with C3GN and diverse aetiological factors (but without *CFHR5* mutations) were treated with eculizumab, with limited evidence of response [37]. This provides direct evidence that therapies that control complement activation could provide benefit in treating C3 glomerulopathies, at least in a proportion of patients. However, the lack of response in some patients (despite biopsy evidence of C3 deposition in the glomerulus) suggests that, in contrast to aHUS, terminal pathway activation may not be necessary for renal damage to occur in C3 glomerulopathies. An alternative explanation for the observed lack of clinical response in some patients is the slow rate of kidney damage in these diseases compared with aHUS: longer-term (or larger) studies in C3 glomerulopathies might be needed to demonstrate robust evidence of benefit with complement inhibition.

Wider implications

Complement components are almost always seen in kidney biopsies that show antibody deposition and renal injury (such as proliferative glomerulonephritis related to infection, autoimmune or alloimmune disease). The observation that complement activation due to defective regulation of the alternative pathway is sufficient to cause renal disease in C3 glomerulopathies provides evidence that complement could be an important part of the pathophysiology of these diseases. More recently, variation in genes for complement regulators has been shown to be associated with the common antibody-related kidney diseases IgA nephropathy [38] and systemic lupus erythematosus [39] as well as with MPGN Type 1 [14]. In addition, a trial of eculizumab in antibody-mediated renal allograft rejection has shown evidence of benefit [40]. Together, these findings suggest that developing strategies that modulate complement activation in the kidney might offer new therapies to patients with both rare and common kidney diseases.

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Resistant hypertension: baroreflex stimulation as a new tool

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Abstract
Uncontrolled hypertension remains a significant public health challenge. In recent years, a new baroreflex stimulator has been used to treat these patients. Initial observations suggest that the electrical field stimulation of carotid baroreceptors acutely attenuates sympathetic activation of the vasculature, heart and kidney while augmenting cardiac vagal regulation. During the long-term treatment an average blood pressure (BP) drop of 30–40/15–25 mmHg was observed with a responder rate (>10 mmHg reduction in BP) of up to 80% after 1 year of treatment. Some of this effect can be explained by a 'placebo' effect as suggested by the double-blind Pivotal Trial. The complication rate with the first generation device was 20–30%. With a second generation device, these problems have been reduced to <10%. Even though additional data from controlled clinical trials will be required before more widespread use can be recommended, this treatment option is now approved in Europe for the treatment of severe resistant hypertension and is performed in selected centres with experienced vascular surgeons and hypertension specialists.

Keywords: resistant hypertension; autonomic nerve system; baroreflex activation; therapy; renal denervation

Hypertension affects 20–30% of the adult population in the Western civilization. Beside recommendations to change life style, different antihypertensive drug classes are the main tools to treat this condition. Unfortunately, 10–30% of hypertensive patients—depending on the population analysed—have resistant hypertension [1]. Treatment resistant arterial hypertension is defined as blood pressure (BP) that remains above target in spite of the concurrent use of three antihypertensive agents of