Unexpected Role for Properdin in Complement C3 Glomerulopathies

Mohamed R. Daha
Leiden University Medical Center, and University Medical Center, Groningen, The Netherlands


doi: 10.1681/ASN.2012111110

The complement system is a major component of innate immunity and plays a key role in our defense against foreign pathogens.1 In normal steady state conditions, the complement system has no significant biologic activity. There are three main pathways to generate biologic activity by initiation of complement activation, including the classic pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). Whereas antigen-antibody complexes mainly activate the CP, the LP is initiated by pattern recognition of exposed complex carbohydrate moieties. The AP is constitutively active at a low grade due to the spontaneous tick-over of C3. Once C3 is activated into C3b and C3a, the C3b fragment is able to covalently bind to foreign and host cell surfaces and serve as focus for amplification of complement activation by the interaction with factor B (fB) and factor D (fD). The C3bBb convertase that is generated is labile and requires stabilization by properdin (P) to extend its half-life for additional C3 activation.2

AP complement activation is regulated by several membrane and fluid phase moieties such as factor H (fH), which enhances decay dissociation of fB from the convertase resulting in loss of C3 activating potential, both in the fluid phase and on cell surfaces. fH is a glycoprotein composed of 20 consensus repeats (SCRs) that interact with surface deposited C3b and polyanionic molecules on host cells and thereby determines its affinity for tissues.3–4 N-terminal 1–4 SCRs are essential for regulation of complement activity, whereas SCRs 19–20 are required for tissue interaction.

Mutations in fH in murine models and humans associate with severe kidney disease including C3 GN, such as dense deposit disease (DDD) and atypical hemolytic uremia (aHUS).3,6 Initial insight into the mechanism through which uncontrolled C3 activation results in accumulation of C3 activation products in the kidney was obtained through the investigation of mice with gene-targeted fH mutations. fH-deficient mice develop uncontrolled AP activation and a
secondary deficiency of C3. Elegant studies from Pickering et al.6 demonstrate that these mice develop marked accumulation of C3 along the glomerular basement membrane (GBM) and glomerular inflammation resembling membranoproliferative GN. A similar pathology has also been described in a breed of pigs with spontaneous flH deficiency.7

Renal accumulation of C3 in the murine model is dependent on AP activation, because mice with a combined deficiency of flH together with a deficiency in fB do not develop renal injury or hypercatabolism of C3.8 In addition, deposition of C3 along the GBM is dependent on factor I (flI), an enzyme that cleaves C3b to inactive C3b (iC3b), rendering it incapable of binding fB and initiating further AP and terminal pathway activation. Studies in mice with a combined deficiency of flH and flI suggest that it is iC3b that deposits along the GBM during uncontrolled activation of the AP.

Studies from the 1970s demonstrate that fP stabilizes the C3bBb convertase and counteracts the function of flH.5 More recent studies show that next to its stabilizing function, fP may also serve as an initiator of AP activation on certain surfaces like bacteria and apoptotic and necrotic cells.9 Deficiencies of properdin are associated with severe meningococcal and neisserial infections, implicating the crucial role of fP in defense against foreign pathogens.

One of the main questions in C3 glomerulopathies and aHUS is how to treat these diseases that share hypercatabolism of C3 through the AP, and how to downregulate C3 activation. Because fP is the only positive regulator of C3bBb function, the thought is that attenuation of C3bBb function by elimination of fP would be a good choice.

In this issue of JASN, two leading research groups report on their studies on the effects of fP deletion in gene-targeted mice.10,11 Using comparable murine models, both Ruseva et al.10 and Lesher et al.11 come to the same unexpected findings, namely that fP deletion or depletion with mAbs, in contrast to what one would have expected, results in more severe renal pathology in fH−/− mice. The study by Ruseva et al.10 reports that fH−/− mice have complete depletion of circulating C3 and C5 and that the fH−/−/fP−/− mice have a predominant depletion of C3. This profile is in agreement with the complement profile seen in patients with fP-independent C3 nephritic factors (C3NeFs).12 Unexpectedly, however, glomerular inflammation, capillary wall thickening, and glomerular C3 staining were significantly increased in fH−/−/fP−/− mice compared with fH−/− mice. Earlier on, these investigators had already shown that administration of exogenous fH ameliorates GBM deposition of C3 in fH−/− mice and triggers the appearance of mesangial C3 deposits. These studies demonstrate that fP influences the intraglomerular localization of C3.

The study by Lesher et al.11 describes the generation of mice with a deletion of SCRs 19–20 of flH, a region of flH involved in carbohydrate interaction on cell surfaces. These fHm/m mice, in contrast to the fH−/− of Pickering et al.,6 have small amounts of truncated flH and significantly higher levels of C3 than the fH−/− mice. Like fH−/− mice, the fHm/m mice also exhibit prominent C3 and C9 deposition in the kidney with very weak IgG deposition. It is not clear why these IgG deposits are found but the investigators reason that this is not due to an antibody response against factor H. At 2–3 months of age, these mice develop mild glomerular hypercellularity and some evidence of an inflammatory infiltrate. By 10–12 months, fHm/m mice develop signs of GN, characterized by increased glomerular hypercellularity, inflammatory infiltrate, and thickening of the GBM together with heavy proteinuria.

To test the hypothesis that amelioration of fP would potentially prevent the occurrence of pathology in the fHm/m mice, Lesher et al.11 proceeded to generate a fHm/m;fP−/− mouse model. Like the findings of Ruseva et al.,10 these investigators11 also found that deletion of fP did not result in prevention of renal disease but in aggravation of disease activity. The investigators concluded that additional factors that affect the AP complement activation pathway critically determine the nature and severity of the kidney pathology.

It is important to mention that depletion of fP with a mAb specific for mouse fP also shows an enhanced renal disease in fHm/m mice. On the other hand one should be aware of the finding by Kimura et al.12 and Zhou et al.13 that the absence of fP protects against complement-mediated tissue injury in diseases such as complement-mediated embryonic lethality, experimental collagen arthritis, and abdominal aortic aneurysm.

How do these studies on amelioration of fP activity contribute to our understanding of C3 glomerulopathy? As pointed out by Ruseva et al.,10 DDD associates with uncontrolled activation of C3, most commonly due to C3NeF, an IgG antibody that stabilizes the AP C3 convertase. It was found that C3NeF activity is heterogeneous because some C3NeFs activate C3 without affecting terminal pathway activation while other C3NeFs clearly affect C5–9 activation. The latter ones are caused by stabilization of the C3bBb convertase both by C3NeF and fP.14 In the murine model, there is predominant C3 depletion analogous with the first type of C3NeF patients. In this sense, the murine model of Ruseva et al.10 would be compatible with the fP-independent C3NeF patients. Together with the findings of Lesher et al.,11 it is clear that fP influences the intraglomerular fate of C3 during dysregulation of fluid phase C3 activation. The most important conclusion from these two novel and elegant studies is that inhibition of fP in situations of uncontrolled fluid phase activation of complement may be disadvantageous to the host, whereas absence of fP in models of tissue-bound activation of the AP is favorable. Therefore, most probably, one has to proceed with the development of agents that control fluid phase AP activation in diseases with hypercatabolism of C3 using analogs with comparable function of fH.15

DISCLOSURES
None.
Corticosteroid Therapy for Steroid-Sensitive Nephrotic Syndrome in Children: Dose or Duration?

Elisabeth M. Hodson and Jonathan C. Craig

Centre for Kidney Research, The Children’s Hospital at Westmead, Sydney, Australia; and Sydney School of Public Health, University of Sydney, Sydney, Australia


Idiopathic nephrotic syndrome, although a rare disease, is the most common primary glomerular disease among children. It causes substantial morbidity because it typically runs a relapsing course punctuated with prolonged periods of corticosteroids and other immunosuppressive medication. It affects about 2 children per 100,000 aged <16 years in Europe and North America, with higher rates reported among children from the Indian subcontinent.

Approximately 80% of children achieve complete remission with 4 weeks of corticosteroid therapy after their first presentation and are considered to have steroid-sensitive nephrotic syndrome (SSNS), but a similar proportion relapse ≥1 times. Among children who relapse, about 50% will relapse frequently (defined by the International Study of Kidney Disease in Children [ISKDC] as ≥2 relapses within 6 months of initial response, or ≥4 relapses in any 12-month period) or will have a steroid-dependent disease (defined by Arbeitsgemeinschaft für Pädiatrische Nephrologie [APN] as ≥2 consecutive relapses either during corticosteroid therapy or within 2 weeks of ceasing it). Despite relapses, most children continue to be steroid responsive, maintain normal kidney function, and ultimately, will be cured as they age into adolescence and early adult life.

Over 40 years ago, the ISKDC proposed a regimen for the initial episode of SSNS, which comprised 60 mg/m² per day of prednisolone for 4 weeks followed by 40 mg/m² administered on 3 of 7 days for a further 4 weeks. Subsequently, a randomized trial coordinated by the APN demonstrated that alternate-day prednisolone was more effective in maintaining remission than prednisolone given on consecutive days. Most pediatric nephrologists adopted a regimen of daily prednisolone for 4 weeks followed by 4 weeks of alternate-day prednisolone as their standard regimen for the treatment of the first episode of SSNS.

See related articles, “Loss of Properdin Exacerbates C3 Glomerulopathy Resulting from Factor H Deficiency,” and “Combination of Factor H Mutation and Properdin Deficiency Causes Severe C3 Glomerulonephritis,” on pages 43–52 and 53–65, respectively.