Contrasting Roles of Complement Activation and Its Regulation in Membranous Nephropathy

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The complement system is involved in defense against microorganisms, the processing of immune complexes and apoptotic debris, and the development of an appropriate immune response. Along with these physiologic effects, complement activation has the potential to result in tissue pathology. To limit this, various complement regulatory proteins (CRP) are present on host cells, including the glomerular podocyte. Experimental data from the Heymann nephritis (HN) rat model of human membranous nephropathy (MN) have shown that IgG antibodies in subepithelial immune deposits initiate complement activation and C5b-9–mediated damage of the overlying podocyte. Although IgG can activate the classical pathway, there also is evidence that alternative pathway activation occurs in MN, which could occur because of absent, dysfunctional, or inhibited podocyte CRP. Related to this are experimental data in HN showing the presence of antibodies that bind and inhibit podocyte CRP; although such antibodies have not been documented in human MN, a decrease in CRI quantity on the podocyte has been observed. As a result of a relative lack of CRP and the exposure of activating complement proteins to tubular cells, alternative complement pathway activation and C5b-9–mediated tubular injury can occur in MN and other proteinuric diseases. Overall, in a disease such as MN, the balance between complement regulation and activation is tipped toward its being activated. Therefore, a number of therapeutic approaches have been developed to counteract this, including recombinant forms of endogenous CRP and complement-inhibitory monoclonal antibodies. There is good reason to be optimistic that approaches to block complement activation will become viable therapy for human MN in the future.

Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults, with as many as half of affected individuals progressing to renal failure over a period of years to decades (1). Although some cases are associated with malignancy, infections, or drugs, most are of a primary “idiopathic” nature and are due to underlying autoimmunity (2). Pathologically, MN is characterized by thickening of the glomerular capillary wall, which is visible by light microscopy, but little in the way of increased cellularity. As seen by electron microscopy, there are subepithelial immune deposits and effacement of the overlying visceral glomerular epithelial cell (podocyte). By immunohistologic techniques, these immune deposits contain IgG as well as complement components. This review details the evidence from human and animal data that the complement system plays a key role in the pathogenesis of MN and speculates on ways in which complement inhibitory strategies could be used as therapy.

Activation and Regulation in the Complement System

The complement system is an important component of both innate and adaptive immunity, consisting of the classical, alternative, and lectin pathways, altogether containing approximately 35 proteins involved in its activation and regulation (Figure 1) (reviewed in references 3–6). Under normal circumstances, complement activation occurs on pathogens and unwanted host material (e.g., apoptotic debris) but not on normal host cells; distinction between the two is based on the molecular repertoire presented, such as antigens to which antibodies are directed or pathogen-associated molecular patterns (PAMP) (5). The classical pathway is initiated on biologic surfaces by the binding of complement component C1q to complement-fixing isotypes of IgG, as well as IgM. The activated C1 engages and activates C4 and C2 in sequence, thereby forming the C3 convertase, which catalyzes the ongoing cleavage of C3 to the C3a anaphylatoxin and C3b, which becomes transiently reactive, allowing it to become bound to the growing immune complex. The C5 convertase, C4b2a3b, in turn cleaves circulating C5 into C5a and C5b; C5a is similar to C3a in its activity as an anaphylatoxin, whereas C5b is like C3b and remains associated with the immune complex, where it recruits C6, C7, C8, and C9 to form the C5b-9 complex. When complement activation occurs in the vicinity of a lipid membrane such as on bacteria, erythrocytes, and nucleated cells, the newly expressed hydrophobic
Figure 1. The complement system. Activation can occur through the classical, lectin, or alternative pathways. Proinflammatory mediators include anaphylatoxins C3a and C5a, C3b (and its cleavage fragments), which can interact with complement receptors, and the C5b-9 membrane attack complex (in boldface). Regulation occurs throughout the pathways by complement regulatory proteins (CRP), which are depicted in boxes adjacent to and matched in black type for the complement proteins that they inhibit. Factor I (fI) can cleave and inactivate C4b and C3b by using C4-binding protein (C4bp), complement receptor 1 (CR1), membrane co-factor protein (MCP), and factor H (fH) as co-factors. CR1-related protein y (Crry) is found exclusively in rodents. Ag, antigen; Ab, antibody; C1inh, C1-inhibitor; MBL, mannose-binding lectin; MASP-2, MBL-associated serine protease-2; DAF, decay-accelerating factor.

Domains of C7, C8, and C9 can insert into the cell membrane. In some circumstances, this can lead to osmotic cellular death. In other instances in which so-called sublytic quantities of C5b-9 have formed, a variety of cellular events can occur, including activation of signaling pathways and induction of the active process of endocytosis and shedding of C5b-9, likely as a protective mechanism. In contrast to the classical pathway, the alternative pathway of complement is independent of antibody and has a low-level constitutive activity, as a result of the spontaneous hydrolysis of C3 in plasma. The alternative pathway C3 and C5 convertases (C3bBb and C3bBb3b) are homologous to those of the classical pathway and similarly generate C3a, C3b, C5a, and C5b-9.

Besides the capacity of complement proteins to be discriminatory in their binding, such as to PAMP or immune complexes that bear IgG, an additional level of security is provided self-tissue by circulating and cell-bound complement regulatory proteins (CRP) (7,8). The various CRP act throughout the complement activation cascades, from prevention of C1 activation by C1 inhibitor to blocking formation of C5b-9 by CD59 (Figure 1). A number of proteins are contained within the regulators of complement activation family and are concentrated at the C3/C5 step, which is where all three pathways converge and generate C3a, C3b, and C5a and begin the formation of C5b-9. These include the plasma proteins C4-binding protein and factor H and the cell membrane proteins decay accelerating factor (DAF; CD55), membrane co-factor protein (CD46), and complement receptor 1 (CR1; CD35). CR2 (CD21) is also a member of this family, whereas CR3 (CD11b/CD18) is a β2 integrin; both have affinity for C3 proteins but do not limit complement activation. Confusing to all but the aficionados is CR1-related gene/protein y (Crry) (9), which is a rodent member of the regulators of complement activation family with fairly broad activity (10). Relevant to MN and this discussion are the CRP located on the podocyte. DAF and CD59 are linked to the rat and human podocyte membrane via a glycosylphosphatidylinositol (GPI) anchor (11–15). As its transmembrane CRP, human podocytes use CR1 (16), whereas rat podocytes have Crry (15). Overall, it seems that human podocytes use DAF and CR1 to limit C3 and C5 activation and CD59 to restrict C5b-9 formation.

Besides inflammation, complement activation clearly is involved in the immune response to foreign antigens or lack of it in tolerance to self and in immune complex processing (17–19). Simplistically, for a productive immune response to be propagated when the B lymphocyte antigen receptor is engaged by antigen, there must be a second signal that can be delivered by the interaction of immune complex-bearing C3d with B lymphocyte CR2 (20). Complement activation is also important for the processing of circulating immune complexes, both by limiting their size and through interactions with erythrocyte CR1 (or platelet factor H in rodents [21]), which shuttles immune complexes to FcγR- and CR3-bearing cells of the mononuclear phagocyte system. Complement activation also can profoundly affect the fate of immune complexes in glomeruli and may well be responsible for the movement of certain immune complexes from subendothelial to subepithelial sites (22). Thus, in addition to the pathophysiologic effects from complement activation products, the complement system has the potential to be involved in earlier immunologic events that occur in MN.

Heymann Nephritis as a Model of MN

We are fortunate to have an excellent animal model of MN, Heymann nephritis (HN) (23). In the active model of HN (AHN), rats are immunized with Fx1A, an extract of rat kidney that contains components of the proximal tubule brush border. Animals respond to this immunization by developing autoantibodies against various brush border proteins, some of which are also expressed on the podocyte. Within 8 to 10 wk, most rats develop clinical aspects seen in humans with MN, namely heavy proteinuria (consisting of albumin and higher molecular weight proteins), features of the nephrotic syndrome, and mild renal insufficiency (24,25). Although initially few changes are visible by light microscopy, immunofluorescence microscopy demonstrates the typical granular peripheral capillary wall deposition of IgG and C3, visible ultrastructurally as electron-dense deposits beneath effaced podocytes. With time, the ongoing generation of immune complexes decreases, but proteinuria remains for the life of the animal. The passive model of HN (PHN) has similar features but is induced by the passive administration into rats of antiserum from sheep or rabbits that
were immunized with Fx1A. This leads to rapid induction of these changes within 5 to 6 d after injection.

Along with its clinical manifestations, AHN has other similarities to human MN; both are autoimmune diseases characterized by the production of pathogenic autoantibodies (26–28), and both have a genetic susceptibility involving genes both inside and outside the MHC with incomplete penetrance (i.e., not all animals of the same background in any given experiment develop disease) (2,29). Just as must occur in humans, tolerance to self-antigens is lost in AHN; in this model, a fairly specific immunization scheme must be followed, and variations on this can prevent autoimmunity from occurring, including through the induction of antigen-specific T suppressor cells (30). The primary antigenic target in AHN is megalin, which is shared by podocytes and proximal tubular epithelial cells (26–28). Unfortunately, AHN with its anti-megalin autoantibodies is unlikely truly to reflect human MN, as megalin is absent from the human podocyte. In fact, human MN is likely to be a heterogeneous disease, with multiple possible antibody-antigen specificities and routes of subepithelial immune complex accumulation (see also Ronco and Debec in this Frontiers in Nephrology). Antibodies can bind directly to intrinsic glomerular antigens such as megalin in HN or neutral endopeptidase (NEP) in congenital MN (31); antibodies can bind to antigens extrinsic to the glomerulus that have accumulated in this region, including a variety of cationic proteins (32,33), and immune complexes originally formed in the circulation can ultimately end up in this area, such as occurs in serum sickness (34). Related to the latter mechanism, the experimental evidence is overwhelming that circulating immune complexes cannot directly deposit in subepithelial sites but rather must go through intermediate steps, such as binding in subendothelial locations and then dissociating and reforming in the subepithelial space (35) (see also Nangaku, Shankland, and Couser in this Frontiers in Nephrology section). As noted previously, the complement system can profoundly affect the disposition of immune complexes and surely plays a role in this localization and movement of glomerular immune complexes (22,36,37). Given the broad autoantibody repertoire in systemic lupus erythematosus, including to cellular and matrix proteins, positively charged histones, and antigens contained in circulating immune complexes, it is conceivable that lupus MN could involve any one or more of these three possibilities (38,39).

**Complement Activation in Human and Experimental MN**

Relevant to the complement system and the pathogenesis of MN is the presence of IgG contained in the subepithelial immune deposits. Although most of the pathogenicity of IgG is the result of the γ heavy chain constant domains (which form the Fc) interacting with the C1q complement protein and FcγR on inflammatory cells, other effects can be the direct consequence of IgG binding to particular antigens or even its sheer bulk when accumulated in large latticed immune complexes as occurs in MN (40). Examples of antigen reactivities that can be of direct consequence include those to thyroid stimulating hormonereceptor in Graves disease (41) and potentially to podocyte β1 integrins in PHN (42).

Studies in HN have taught us much about the disease process in human MN. Depletion of serum complement with cobra venom factor immediately before induction of PHN prevents foot process effacement and proteinuria almost completely without affecting the quantity of subepithelial immune complexes (43). Complement activation in the subepithelial space produces the C3a and C5a anaphylatoxins and the C3 opsonins. However, as elegantly dissected by Salant et al. (33), these proinflammatory components of complement are not of consequence when generated in the subepithelial space because of its being separated from the blood by the glomerular capillary wall. Thus, MN is a noninflammatory disease. Using an isolated perfused kidney model of PHN, Cybulsky et al. (44) showed that C8 was required in the plasma perfusate for podocyte injury and proteinuria to occur. In further studies, Baker et al. (45) showed that C6-depleted rats did not develop proteinuria in PHN. Overall, because C6 and C8 have no known role other than contributing to the formation of C5b-9 (Figure 1), these provided strong evidence for the role of C5b-9 to result in podocyte injury in HN. This topic is covered in detail by Nangaku, Shankland, and Couser in this Frontiers in Nephrology section.

Consistent with complement activation occurring in human and experimental MN is the finding of C3 and C5b-9 in subepithelial immune deposits and in the urine (46–49). In AHN, even if there are large amounts of IgG1 and IgG2c antibodies in glomerular immune deposits, complement is not activated unless IgG2b antibodies are present (25). This complement activation (as evidenced by C3 deposition) is associated with podocyte ultrastructural abnormalities and proteinuria. In keeping with these observations is that rat IgG2b is very effective at binding C1q and leading to subsequent complement activation, whereas IgG1 and IgG2c are not (50). In PHN, injection of the complement-activating sheep γ1 anti-Fx1A leads to disease, whereas the non–complement-activating γ2 anti-Fx1A does not (43). A similar requirement for a classical pathway-activating human IgG isotype is seen in congenital MN. Maternal production of anti-NEP IgG1 seems necessary for disease; if only anti-NEP IgG4 is produced, then proteinuria does not result (51). Of the human IgG isotypes, IgG1 and IgG3 are capable of binding C1q and leading to C4 activation (52).

**Role of CRP and the Alternative Pathway in Human and Experimental MN**

These data in humans and experimental animals would lead one to believe that MN should have a uniform pathogenesis: Irrespective of exact antigen specificity, the presence of subepithelial C1q-fixing IgG leads to classical pathway complement activation all of the way to C5b-9, which exerts its effects on the podocyte. Unfortunately for this simple paradigm, most cases of idiopathic human MN have a predominance of IgG4, with less IgG3 and no IgG1 in subepithelial immune deposits (53,54). In addition, there is little to no demonstrable C1q and C4 in these deposits (55), consistent with the lack of classical pathway-activating capacity of IgG4 (56) and that the large hetero-
ligomeric C1 complex (C1qr,S2, Mr approximately 800 kD) undoubtedly has limited access across the glomerular basement membrane to the subepithelial space. Although hereditary complete C4 deficiency is rare and has been associated with lupus-like and proliferative glomerulonephritis, MN has also been reported in a C4-deficient patient (57).

Thus, the absence of classical pathway-activating IgG isotypes, or C1q and C4 in glomeruli, is evidence against classical pathway activation as predominating in idiopathic MN and that alternative pathway activation may be occurring instead. The alternative pathway is spontaneously active; the presence of CRP on host but not foreign tissue confers the specificity of activation. The podocyte primarily relies on membrane CR1 (Cry in rodents) and GPI-linked DAF; whether circulating factor H has access to the podocyte is not clear but may not occur substantially, given the asymmetry of factor H (58). Perhaps because of this, the podocyte does have the capability to make its own factor H (59) and related proteins (60,61).

Alternative pathway activation and C5b-9 generation on the podocyte in MN could occur because of absent, dysfunctional, or inhibited CRP. Related to the last mechanism, we have found that the crude Fx1A preparation that is used to induce AHN in rats contains Crry and CD59 and that within anti-Fx1A generated in rats (or in sheep as used in PHN), there are antibodies to both Crry and CD59 that can neutralize their complement regulatory activity in podocytes in vitro (15,62,63). In a study by Schiller et al. (63), rats that were immunized with Fx1A lacking Crry generated anti-Fx1A autoantibodies that accumulated in subepithelial immune deposits, but there was no evidence for complement activation in glomeruli and abnormal proteinuria did not result. Disease could be reconstituted through the inclusion of recombinant Crry in the immunogen or by the passive transfer of anti-Crry antibodies. Thus, generation of autoantibodies to functional podocyte CRP could render these cells susceptible to complement activation and C5b-9 formation.

Further support for this concept is our finding that injection of function-neutralizing anti-Crry and anti-CD59 antibodies to rats with preexisting immune deposits that consisted only of anti-megalin antibodies led to development of abnormal proteinuria (64) (Figure 2). The activation of complement through any pathway represents a balance between activating and inhibiting influences; even with a full repertoire of CRP, complement activation can overwhelm its regulation (65). This seems to occur in the PHN model in which immune complex formation occurs rapidly and with a sufficient amount of antibody (66) to overwhelm any protective effect of the CRP, thereby resulting in complement activation and disease (64) (Figure 2). This guides the underlying premise of providing extrinsic CRP to podocytes in therapy (discussed below).

Despite the data in AHN discussed above, there has been no evidence that podocyte CRP are the target of autoantibodies in human MN. As an alternative possibility, a reduction in CRP could enhance susceptibility to complement activation; such a mechanism underlies paroxysmal nocturnal hemoglobinuria, a clonal abnormality in hematopoietic cells in which there is an inability to anchor GPI-linked proteins, including DAF and CD59, to the plasma membrane (67). An alteration in podocyte CR1 has long been associated with glomerular diseases, in particular lupus nephritis (68,69). The possibility that CR1 is cleaved at its membrane proximal site such as by inflammatory cell proteases (leaving a “stump”) or that it is absent altogether has been investigated by Schifferli et al. (70), who have shown that the entire CR1 protein is absent in glomerular diseases, including MN. As the authors have postulated, the absence of CR1 on podocytes could render these cells “highly sensitive to complement attack.” Whether absence of CR1 in glomerular diseases such as MN represents an intrinsic or acquired defect and, importantly, whether this contributes to disease pathogenesis remain to be established.

**Role of Complement in the Tubulointerstitial Injury in MN**

In addition to the pivotal role of complement in mediating injury to the podocyte in MN, complement activation seems to be involved in the tubular injury that culminates in the histologic picture of tubulointerstitial atrophy and fibrosis (71–73). It has long been known that progression in MN and other glomerulopathies correlates closely with the degree of proteinuria (74,75). Increasingly, evidence suggests that proteinuria per se may actually be responsible for this tubulointerstitial injury,
through exposure of the luminal surface of tubules to albumin, transferrin, lipoproteins, and proteins of the complement system (76,77). Because of their large size, key complement components such as C3 and C5 are not normally present in the glomerular ultrafiltrate; therefore, nature has limited expression of CRP on the apical membrane of tubular cells to only weak expression of CD59 (12). The relative imbalance between CRP and proactivating complement proteins results in the alternative pathway’s being activated on proximal tubular cells, which can be modeled in vitro (78,79) and also detected in vivo (71,80). Compelling evidence that C5b-9 activation occurs and is injurious to tubular epithelia comes from the studies of Nangaku and colleagues (81–83) in which rats deficient in C6 were protected from tubulointerstitial injury in the puromycin, adriamycin, and remnant kidney proteinuric models. Thus, strategies to inhibit the complement system in MN may protect not only against glomerular damage but also directly against tubular injury.

**CRP as Therapy for MN**

Current therapy for MN consists primarily of immunosuppressive drugs such as corticosteroids, cytotoxic agents, and calcineurin inhibitors, aimed mainly at decreasing the production of the autoantibodies presumed to be present in MN (84,85). These immunosuppressive therapies come at the cost of serious side effects, such as bone marrow suppression and an increase in the risk for infection. Furthermore, despite intensive effort and study, available treatment has limited efficacy (86); the topic of conventional management of MN is covered by Catran in this Frontiers in Nephrology section. One potential clue to why rational (albeit, nonspecific) therapy targeting the immune system for an autoimmune disease such as MN has not consistently shown a benefit again comes from the AHN model and studies by Noble et al. (87) of its natural course. As time passes after immunization with Fx1A, autoantibodies that are detectable in blood wane as does glomerular complement activation, yet basement thickening and disorganization occur, incorporating these immune deposits, and proteinuria persists. Upon reimmunization with Fx1A, there is the prompt reappearance of anti-Fx1A antibodies forming fresh immune deposits and another wave of glomerular complement activation. Related to this concept are the findings of Schulze et al. (88) that the presence of C3c reflects ongoing complement activation and tracks with disease activity, whereas the presence of C3d is a marker for past complement activation and those of Makker and Kanalas (89) in which kidneys that were from rats with AHN and transplanted into normal hosts had prompt disappearance of glomerular C3 but persistent glomerular IgG and proteinuria up to 28 wk posttransplantation. Similar findings of apparent disease activity and inactivity are seen in human MN, as C3d is present in nearly all cases of MN, whereas C3c is found much less frequently in biopsy specimens and is associated with higher levels of proteinuria (55). The presence of C3d in subepithelial immune deposits presumably reflects the action of podocyte CR1 to act as a factor I co-factor for the cleavage of iC3b. It seems logical that targeting immunologic aspects with therapy should be timed when disease activity is highest, which is difficult to predict in a disease such as MN, particularly given our ignorance of target antigens. One intriguing possibility is to identify periods of disease activity as reflected by ongoing complement activation on the podocyte by measuring the appearance of C5b-9 in the urine (48,49,90,91).

Given these limited options, strategies to inhibit complement, such as through the use of recombinant CRP or anti-complement antibodies, could potentially offer a significant advance in the therapy of MN. There is growing evidence in animal models that such an approach would be effective and feasible. A recombinant soluble form of human CR1 was used successfully by Couser et al. (92) to decrease the extent of glomerular complement deposition and proteinuria in PHN. Similarly, the rodent molecule Crry, which inhibits the C3 and C5 convertases of the classical and alternative pathways in a manner similar to human CR1, has been used successfully to prevent injury in various mouse models of glomerular diseases. Specifically, daily administration of the fusion protein Crry-Ig, comprising two molecules of Crry linked to the constant region of mouse IgGl, decreased multiple markers of renal injury in mouse models of nephrotic and lupus nephritis (93,94). In addition, a monoclonal antibody that blocked C5 activation had a significant effect on renal disease and survival in murine lupus (95). As with the latter studies in murine lupus models in which homologous proteins were administered chronically, use of endogenous CRP or antibodies in which all but antigen-binding variable regions are “humanized” would avoid any concern of immunogenicity. Given the multiple beneficial roles of the complement system, including its activity against infectious agents, its ability to enhance a normal humoral immune response while maintaining tolerance, and its processing of immune complexes, alteration of any one of these theoretically could occur when inhibition of the complement system is used in therapy. Clues to which of these may occur in human therapy comes from our relatively long-term treatment with Crry-Ig in a mouse model of lupus nephritis, in which there was no change in autoantibody levels or apparent infectious complications, yet there was markedly altered immune complex handling, in this case, protecting the glomerulus (94). Because it does not affect the generation of C3, anti-C5 is unlikely to affect immune complex metabolism, although this was not specifically addressed in its study in lupus mice (95). Unfortunately, because there is no universally accepted mouse model of MN, comparable studies for MN in the mouse have not been performed.

Potentially even more promising is the strategy of targeting CRP specifically to the site where complement is being activated, which can decrease systemic toxicity of complement inhibitors while at the same time increasing their potency. Such an approach has been used to target CR1 to cell membranes with addressins (96) and to selectins with sialyl Lexis x (sLex) glycosylation (97). More recently, the Tomlinson group developed a chimeric protein that consists of DAF or CD59 fused to CR2, the latter targeting the protein to C3d (and iC3b) present at the site of complement activation (98). This targeted inhibitor is approximately 20 times more potent at inhibiting complement-mediated lysis of cells compared with soluble DAF or CD59 alone, and when injected into lupus-prone MRL/lpr
mice, the inhibitor bound with great specificity to sites of complement activation within the glomerulus (98). An alternative approach to creating CRP with natural ligands such as sLe\textsuperscript{x} or CR2 is to use monoclonal antibodies that target specific antigens on cells that are the object of complement activation (99,100). We recently used this approach to target either Crry or CD59 to proximal tubular cells in the puromycin model of proteinuria in the rat; as previously mentioned, tubular injury in this model is dependent on C5b-9 formation (81). Animals in which Crry or CD59 was targeted to the proximal tubular cell had preserved renal function that was not evident in animals that received buffer, targeting antibody, or soluble Crry (Figure 3), illustrating the increased potency available when the CRP is present at the site of complement activation (101). In addition, CD59 is not effective as a soluble recombinant protein (102), likely because it must be placed close to the plasma membrane to exert its effect on C5b-9, as these various approaches allow (98,99,103).

Even though it was not directly studied in animal models of MN, given the compelling story that C5b-9–mediated podocyte injury is relevant in human MN, the humanized inhibitory anti-C5 monoclonal antibody eculizumab (104) was recently studied in a multicenter, double-blind, placebo-controlled trial in idiopathic MN. Unfortunately, there was no difference in proteinuria between patients who received eculizumab or placebo over 16 wk of treatment, perhaps because of incomplete C5 inhibition and/or the aforementioned difficulties proving that any therapy is efficacious in MN, particularly in such an abbreviated study. More encouraging was the reduction in proteinuria with open-label use of eculizumab for up to 1 yr in some of the patients (including two of our patients who went into complete remission), providing optimism that eculizumab will be effective therapy for MN. Thus, despite all of the evidence favoring that complement mediates MN in humans, whether eculizumab or any other complement inhibitory strategy such as those presented here will be used as therapy in human MN remains a question for the future.

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