Frontiers in Nephrology

T Cells in Crescentic Glomerulonephritis

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Crescent formation in glomerulonephritis (GN) is a manifestation of severe glomerular injury that usually results in a poor clinical outcome. In humans, crescentic GN is frequently associated with evidence of either systemic or organ-specific autoimmunity. T cells play a major role in initiation of adaptive immune responses that lead to crescentic injury. In experimental models of crescentic GN, Th1 predominant immune responses have been shown to promote crescent formation. Perturbation of regulatory T cell function may contribute to development of autoimmune crescentic GN. The presence of T cells and macrophages in crescentic glomeruli, frequently in the absence of humoral mediators of immunity, suggest a dominant effector role for T cells in crescentic GN. The association of cellular immune mediators with local fibrin deposition implicates cell-mediated "delayed-type hypersensitivity–like" mechanisms in crescent formation. Intrinsic renal cells also contribute to T cell–driven effector mechanisms in crescentic GN, *via* expression of MHC II and co-stimulatory molecules and by production of chemokines and cytokines that amplify leukocyte recruitment and injury.

J Am Soc Nephrol 17: 1253–1263, 2006. doi: 10.1681/ASN.2005091013

Glomerulonephritis (GN) is not a single disease but shows a variety of histologic patterns, clinical features, and outcomes that indicate multiple pathogenic mechanisms. A pivotal role for adaptive immune responses in initiation of GN has been demonstrated in experimental models, but across the spectrum of human GN, direct evidence of immune pathogenesis is more variable. The strongest case that adaptive immune responses drive nephritogenic events in glomeruli in humans has been mounted in crescentic GN, and evidence for involvement of autoimmunity, either organ-specific autoimmunity to glomerular antigens (*e.g.*, anti–glomerular basement membrane [anti-GBM] GN) or systemic autoimmunity to nonglomerular antigens (*e.g.*, ANCA-associated crescentic GN, lupus nephritis) now is emerging for many forms of human crescentic GN.

$CD4^+$ T cells play a central role in adaptive immunity. T cell–independent responses are uncommon. They usually are associated with simple carbohydrate-rich antigens and do not show extensive Ig isotype switching or strong affinity maturation. The known antigens that drive crescentic GN show strong evidence of $CD4^+$ T cell dependence and do not have the characteristics of T-independent antigens. The evidence from glomerular pathology also suggests a prominent role for local $CD4^+$ T cell–driven Th1-type responses in crescentic GN with delayed-type hypersensitivity (DTH)-like cellular effectors (T cells and macrophages) as well as Th1 Ig isotypes in glomeruli. The relative contributions of cellular and humoral $CD4^+$ T cell–driven effectors, particularly in ANCA-associated GN, remains controversial, but it is clear that the nephritogenic immune responses are $CD4^+$ T cell–driven.

T Cells in Experimental Crescentic GN

Although studies of human renal biopsy material provide context and relevance to the study of T cells in crescentic GN, studies in experimental models have been critical to demonstrate their functional contribution. Experimental studies have focused extensively on the role of $CD4^+$ T cells (1–8) and to a lesser extent on $CD8^+$ T cells (2,9–11). More recently, the potential role of regulatory T cells (Treg) has been demonstrated (12–14) and the contributions of T cell subsets that express α/β T cell receptors (TCR) and γ/δ TCR (15–18) to the development of GN have been explored (Table 1).

$CD4^+$ T Cells in Initiation of Nephritogenic Immune Responses

The prominent glomerular accumulation of $CD4^+$ T cells and macrophages in human crescentic GN suggests a potential "helper" T cell role in directing crescentic injury (19,20). The role of $CD4^+$ T cells has been explored extensively in planted antigen models of crescentic GN (1–3) as well as in models involving organ-specific (4,5) and systemic autoimmunity (6,7). These demonstrate that the Th1 or Th2 bias of the $CD4^+$ T cell response exerts a major influence on immune effector mechanisms and resultant patterns of glomerular injury. Th1 cells develop from naive $CD4^+$ (Th0) cells under the influence of IL-12 and IL-18 and play a key role in directing DTH and augmenting production of opsonizing and complement-fixing subclasses of IgG. Th2 cells develop under the influence of IL-4

Published online ahead of print. Publication date available at www.jasn.org.

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ISSN: 1046-6673/1705-1253

Table 1. Functional evidence of T cell involvement in experimental crescentic GN[a]

Model	Animal	Description
Models involving organ-specific autoimmunity		
EAG	Mice	TCR-deficient mice do not develop GN even after passive transfer of anti-GBM antibodies (5)
	Rats	CD4 depletion attenuates injury in BN rats (4) CD8 depletion attenuates injury in Wky rats (9)
Models involving systemic autoimmunity		
MRL/lpr lupus	Mice	Anti-CD4 treatment suppresses autoimmunity and GN (6) α/βTCR T cell–deficient mice are partially susceptible to disease (15,16), and δ/γ T cell deficiency augments GN (15)
NZB/NZW F1 lupus	Mice	Anti-CD4 treatment prevents autoimmunity and GN (7)
NZM2338 lupus	Mice	Transfer of $CD4^+CD25^+$ Treg does not suppress proliferative GN (14)
(SWR×NZB)F1	Mice	Transfer of $CD4^+CD25^+$ Treg suppresses autoantibodies and GN (12)
BXSB-Yaa lupus	Mice	α/β TCR T cell deficiency prevents autoimmunity and GN (17)
Models initiated by heterologous planted antigens		
NTN	Mice	CD4 T cell deficiency prevents disease (2) CD8 T cell deficiency exacerbates disease (2) Anti-CD4 antibody prevents disease (3) α/β and γ/δ T cell contribute to GN (18) Transfer of $CD4^+CD25^+$ Treg suppresses GN (13)
	Rats	Anti-CD4 antibody attenuates disease (1) CD4 depletion in the effector phase of injury attenuates GN (8) Anti-CD8 antibody attenuates macrophage accumulation and disease in WKY rats (10,11)

[a]EAG, experimental autoimmune anti–glomerular basement membrane glomerulonephritis; GBM, glomerular basement membrane; GN, glomerulonephritis; NTN, nephrotoxic serum nephritis; TCR, T cell receptor; Treg, T regulatory cells.

and IL-13 and promote allergic responses, mast cell/IgE-mediated hypersensitivity responses, and production of IgE and IgG with lower complement-fixing capacity (Figure 1).

The propensity of Th1-biased responses to direct crescentic patterns of injury has been demonstrated in rodent models initiated by heterologous anti-GBM globulin (nephrotoxic nephritis [NTN]) (21,22) and in autoimmune crescentic GN induced by immunization with human α3 chains of type IV collagen (5,23). Th1 cytokine deficiencies (*e.g.*, IL-12 [24], IFN-γ [25]) attenuate crescentic injury, as does blocking Th1 cytokines using antibodies. Conversely, administration of IL-12, the key Th1 cytokine, exacerbates disease (26). IL-18 enhances crescentic GN even in the absence of IL-12 (27). Mice with deficiencies of Th2 cytokines (IL-4 and IL-10) show greater susceptibility to crescentic GN (28,29), and administration of these Th2 cytokines either during the initiation of disease (30) or after glomerular injury is established (31) provides protection from development of crescents. IL-4 administration also attenuates crescent formation in rats with anti-GBM GN (32). The role of T helper subsets in models involving systemic autoimmunity seems to be more complex. IFN-γ receptor–deficient MRL/lpr lupus-prone mice show protection from development of crescentic GN (33), whereas blocking IL-4 but not IL-12 provides protection from GN (34). In human lupus nephritis, there is conflicting evidence for the involvement of Th1/Th2 subsets. Taken together, these data suggest that crescentic GN results from Th1 polarized systemic immune responses directing cell-mediated immune glomerular injury.

Co-stimulatory molecules provide essential second signals to helper T cells that facilitate development of immune responses and also contribute to activation of immune effector cells. CD28 is a co-stimulatory molecule that is expressed by T cells and that interacts with CD80 and CD86 on antigen-presenting cells. CD80-deficient mice showed protection from crescentic NTN (35), whereas CD86 deficiency augmented Th1 responses, glomerular injury, and crescent formation. Similar results were demonstrated by antibody inhibition of CD80 and CD86 (36). It is interesting that combined deficiency of CD80 and CD86 or

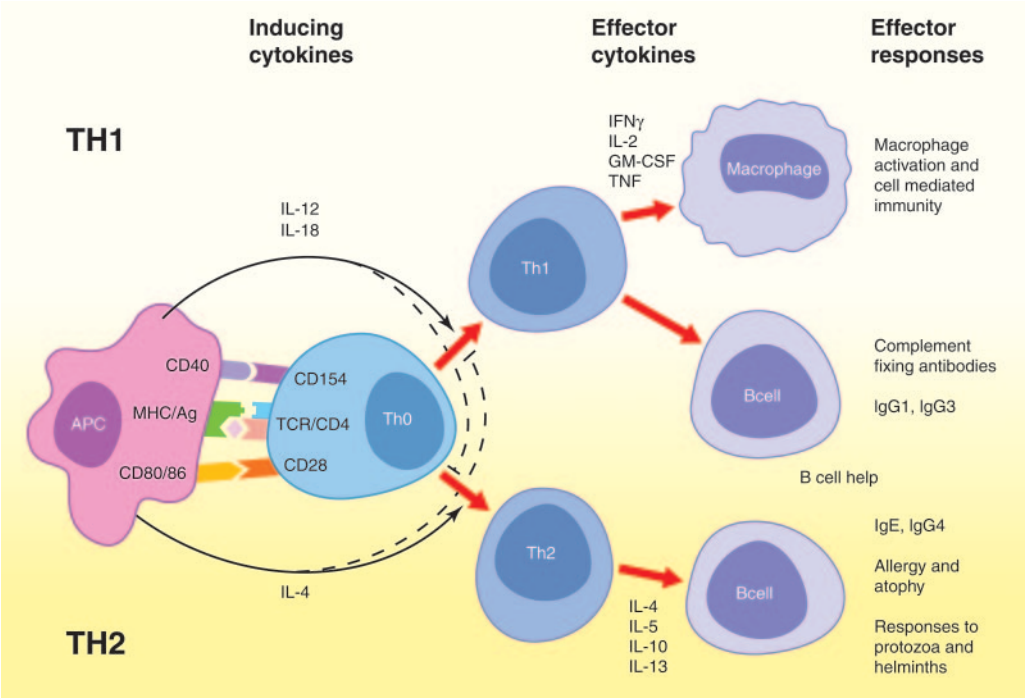

Figure 1. A simplified depiction of the major elements in T helper subset differentiation and effector functions. Th1-directed effector mechanisms play a dominant role in development of crescentic glomerulonephritis (GN). Illustration by Josh Gramling—Gramling Medical Illustration.

combined inhibition of CD28 signaling using CTLA4-Ig did not affect development of crescentic glomerular injury (35,36). Production of autologous nephritogenic antibody was significantly suppressed by combined CD80 and CD86 inhibition, providing further evidence of the independence of severe crescentic injury from humoral immune responses in this model.

Despite the lack of protection afforded by combined CD80/CD86 deficiency and CTLA4-Ig, CD28-deficient mice showed marked attenuation of crescentic NTN (37), suggesting that CD28 may be a potential therapeutic target in human crescentic GN. In murine NTN, mAb inhibition of inducible co-stimulator (ICOS) signaling and administration of CTLA4-Ig to block CD28 was effective in ameliorating noncrescentic GN (38). CTLA4-Ig also significantly reduced circulating autoantibody levels, accumulation of T cells and macrophages in glomeruli, and crescent formation in autoimmune anti-GBM GN in Wistar-Kyoto (Wky) rats (39). Mutant CTLA4-Ig that selectively blocked CD80 (B7.1), reduced the Ig2a (Th1) autoantibody subtype (without significant effects on total IgG) and provided similar protection from crescentic GN to that observed using standard CTLA4-Ig (39), suggesting that Th1-mediated responses may be dominant in this autoimmune crescentic model.

Binding of CD40 on antigen-presenting cells with CD154 on T cells provides co-stimulatory signals that synergize with IL-12 to induce IFN-γ production (40). In crescentic autoimmune anti-GBM GN in Wky rats, a key role for CD154 in both the initiation and the effector phases of the disease has been demonstrated (41). CD40 signaling is essential for development of nephritogenic immune responses that lead to crescentic injury in murine NTN (42) and murine lupus nephritis (43). The requirement for CD40 in the immune initiation phase of murine NTN can bypassed by administration of IL-12, which restores splenocyte IFN-γ production, renal chemokine expression, and glomerular T cell and macrophage recruitment. However, IL-12 failed to restore crescentic glomerular injury as a result of ineffective macrophage activation in the absence of CD40 (42).

$CD4^+$ T Cell–Driven Effector Mechanisms in Crescentic GN

In addition to their critical role in initiation of immune responses in crescentic GN, $CD4^+$ T cells have key effector roles, particular *via* their capacity to recruit macrophages. In NTN, $CD4^+$ T cell depletion in the effector phase of the disease (after the nephritogenic immune response is established) is effective in preventing glomerular macrophage recruitment and crescentic injury (8). Potential contributions of proinflammatory cytokines such as IFN-γ (44), IL-12 (45), IL-1b (46), and TNF (47) from T cells, macrophages, and intrinsic renal cells during the effector phase of crescentic GN have been explored in murine NTN (Figure 2).

Effector T cells are memory cells that direct immune responses after recognition of their cognate antigen presented on MHC II. Studies using MHC II "chimeric" mice (created by bone marrow transplantation) demonstrated a critical role for MHC class II expression by intrinsic renal cells in the development of murine NTN. Despite high circulating levels and glomerular deposition of nephritogenic antibody, T cells did not localize in glomeruli, and glomerular macrophage recruitment and crescentic GN failed to develop in the absence of renal expression of MHC II (48). In immune complex–initiated mu-

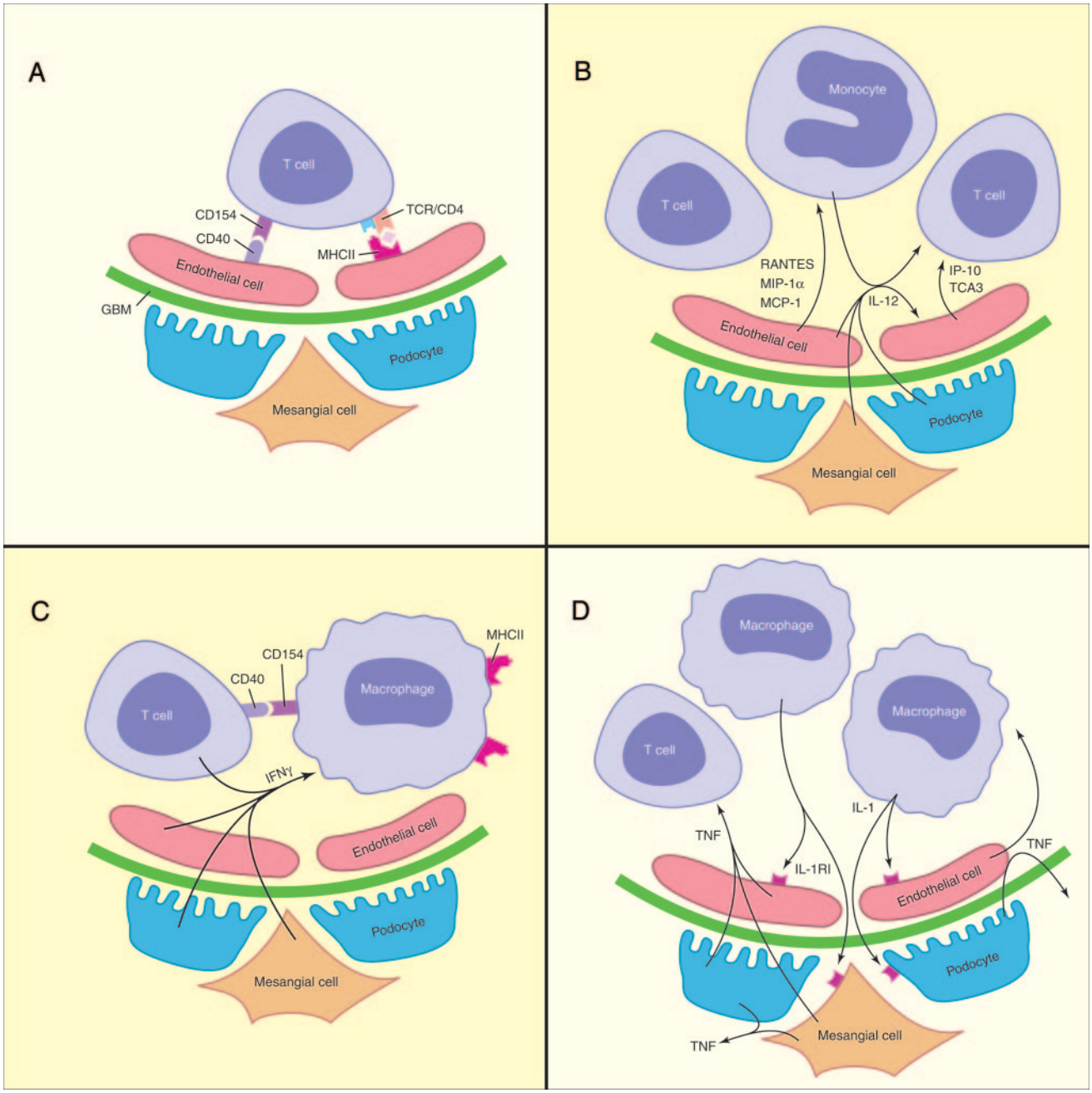

Figure 2. Mechanisms of effector T cell–directed injury in crescentic nephrotoxic nephritis have been demonstrated using chimeric mice with selective leukocyte or intrinsic renal cell deletions of MHC II (48), CD40 (50), IL-12 (45), IFN-γ (44), TNF (47), and IL-1β and IL-1 receptor I (46). (A) Effector T cells require MHC II and CD40 expression by intrinsic renal cells to recognize nephritogenic antigens and initiate injury. (B) Intrinsic renal cell production of monocyte and T cell chemoattractant chemokines and IL-12 directs further leukocyte influx. (C) T cell expression of CD40 and IFN-γ from T cells and intrinsic renal cells activate monocytes to macrophages. (D) Macrophages produce IL-1, which acts *via* IL-1 receptor I on intrinsic renal cells to induce TNF production and crescentic injury. Illustration by Josh Gramling—Gramling Medical Illustration.

rine lupus nephritis, however, transplantation of MHC II– or MHC I–deficient kidneys into MRL/lpr mice demonstrated that renal expression of these molecules is not required for development of renal injury, although some protection from development of renal failure was observed in mice with MHC II–deficient kidneys (49).

Expression of co-stimulatory molecules is important for T cell effector functions as well as their initial activation. Intrinsic renal cell expression of CD40 (which signals *via* CD154 on T cells) was demonstrated to play a key role in renal production of chemokines, glomerular T cell and macrophage recruitment, and crescentic injury in murine NTN (50). Production of IL-12 by intrinsic renal cell also contributes to glomerular T cell recruitment and development of crescentic NTN (45). Admin-

istration of IL-12 restores initiation of nephritogenic immune responses in the absence of CD40 but fails to overcome the defective effector cell activation in murine crescentic NTN (50). These studies indicate important and independent roles for expression of CD40 and IL-12 by intrinsic cells in the recruitment and activation of effector cells in crescentic GN.

Studies in murine lupus suggest antibody-independent (probably T cell directed) effector mechanisms in development of lupus nephritis. In MRL/lpr mice, B cells are necessary for development of GN (51). However, this role may be independent of their involvement in autoantibody production (52) as lupus-prone mice with B cells that fail to make Ig still develop GN. Depletion of kidney-autoreactive T cells by intrathymic injection of syngeneic renal cells (but not splenocytes) into neonatal MRL/lpr mice attenuated development of GN without altering the levels of autoantibodies (53). In lupus-prone NZ mixed 2410 (NZM2410) mice, deficiency of the T cell intracellular signaling molecule Stat 6 or treatment with anti–IL-4 antibody decreased Th2 responses and GN despite enhanced levels of anti-DNA antibodies (54). Stat 4 deficiency decreased Th1 cytokines and accelerated development of GN in the absence of high levels of anti-DNA antibodies (54). The dissociation of GN from autoantibody production in these models of lupus nephritis is consistent with an effector role for T cells in directing glomerular inflammation.

$CD8^+$ T Cells

The presence of $CD8^+$ T cells in human and some experimental models of crescentic GN raises the prospect of T cell–mediated cytotoxicity as an effector mechanism of injury. Cytotoxic T cells recognize antigens presented on MHC I and induce injury by secretory molecules such as perforin and granzyme, which induce cellular cytotoxicity, and by cell surface molecules such as lymphotoxin (TNFβ) and Fas ligand, which interact with receptors of the TNF receptor family on the target cell to induce apoptosis.

A functional role for $CD8^+$ cells has been demonstrated best in Wky rats using NTN (11) and autoimmune (9) models of crescentic GN. Depletion of $CD8^+$ cells using mAb blocked development of GN in both models without significant effects on circulating levels of nephritogenic antibodies. The observation that increased glomerular expression of granzyme B is reduced by CD8 depletion (9) provides further evidence for involvement of T cell–mediated cytotoxicity. However, macrophage depletion studies demonstrate that macrophages also are important cellular effectors of injury NTN in Wky rats (55). The ability of IL-18 treatment to increase glomerular macrophage proliferation and aggravate injury (56) and IL-4 treatment to reduce macrophage accumulation and ameliorate injury (32) is consistent with a role for Th1-directed immune mechanisms in crescentic GN in Wky rats. A similar role for $CD8^+$ cells has not been demonstrated in crescentic NTN in mice as CD8-deficient mice show more severe injury (2) and MHC I deficiency (57) does not affect development of crescentic GN in this model.

T Regulatory Cells

T regulatory cells (Treg) are a subset of T cells involved in the induction and maintenance of peripheral tolerance. Several types of Treg have been described, including Tr1 cells, characterized by production of high levels of IL-10 and TGFβ, and $CD4^+CD25^+$ Treg, characterized by constitutive expression of CD25 and Foxp3. Impairment of Treg function has the potential to contribute to the development of autoimmune forms of GN, and augmentation of Treg function has been suggested as potential therapeutic strategy. Treg activity has been demonstrated in the peripheral blood of patients after remission of Goodpasture's syndrome but not during the acute illness (58). These cells were capable of suppressing autoreactive T cells, and their activity was associated with a $CD4^+CD25^+$ phenotype. The potential for $CD4^+CD25^+$ Treg to attenuate experimental anti-GBM GN has been demonstrated in mice that develop NTN (13). Transfer of $CD4^+CD25^+$ cells from naive mice decreased glomerular T cells and macrophage accumulation and suppressed development of GN, but $CD4^+CD25^+$ cells from nephritic mice aggravated disease (13). Transferred cells trafficked predominantly to secondary lymphoid organs and could not be detected in nephritic kidneys (13).

Evidence for a role for Treg in autoimmune GN associated with lupus also has been provided from murine models. In NZM2328 lupus-prone mice, depletion of $CD25^+CD4^+$ Treg by neonatal thymectomy accelerated development of autoimmunity and GN. Transfer of $CD25^+$ cells suppressed development of anti-DNA autoantibodies and features of autoimmunity but not proliferative GN or sialoadenitis (14). In (SWR×NZB)F1 lupus-prone mice, $CD4^+CD25^+$ and $CD8^+$ alloantigen-specific Treg could be induced by immunization with very low doses of nucleosome peptide, and these Treg were capable of suppressing autoantibody production and development of GN after adoptive transfer (12).

T Cells in Crescentic Human GN

Recognition of the important role of autoimmunity in most forms of human crescentic GN has led to renewed interest in identification of the antigenic epitopes and the mechanisms of initiation and regulation of autoimmune (nephritogenic) responses. Recent work has characterized some of the autoantigens in human crescentic GN at the molecular level. Target antigens may be endogenous glomerular antigens (*e.g.*, the noncollagenous domain [NC1] of the α chain of type IV collagen [α3(IV)NC1] in anti-GBM disease) or endogenous systemic antigens (myeloperoxidase [MPO] or proteinase 3 [PR3] in vasculitis and nuclear epitopes in lupus nephritis). These nonrenal antigens may be targeted to glomeruli as immune complexes, antibody-coated neutrophils (ANCA), or passively deposited antigens in the glomerular filter, where they subsequently bind antibody and thereby act as *in situ* immune complexes.

T Cells in Autoimmune Anti-GBM GN

Characterization of the nephritogenic peptides of α3(IV)NC1 has highlighted the role of T cells in this uncommon form of autoimmune crescentic GN. Studies in Wky rats have demonstrated the capacity of recombinant α3(IV)NC1 to elicit nephri-

togenic responses (59) and the ability of transferred Th1 cell lines to induce crescentic disease in the absence of glomerular antibody deposition (60), confirming the primary role of autoreactive T cells in this model of autoimmune crescentic GN. Peptide mapping has defined a potent T cell epitope pCol (28–40) that induced severe glomerulonephritis in rats (61).

Experimental studies in mice have demonstrated the role of MHC class II in susceptibility to autoimmunity and the ability of splenocytes and Th1 antibody isotypes to transfer disease (5). Human studies show association between HLA DRB1*15 and DRB1*04 and susceptibility to anti-GBM disease, whereas expression of DRB1*07 confers protection (62). T cells from patients with acute disease react to a limited number of peptides of α3(IV)NC1 (α3 71 to 90 and α3 131 to 150), suggesting that these are the likely natural immunodominant peptides (63). However, these are not the peptides that induce the strongest responses in T cells from patients with anti-GBM GN when presented by DR15 on Epstein–Barr virus-transformed human B cells, suggesting that factors other T cell receptor affinity determine selection of immunodominant autoreactive epitopes (64). The cytokine profile of autoreactive α3(IV)NC1 T cells from patients in the acute phase of the disease is Th1 predominant (producing IFN-γ); whereas during resolution of disease, IL-10 production is predominant (65). Studies of anti-GBM antibody from patients with anti-GBM GN (66) suggest the B cell epitope is different from that seen by T cells.

The maintenance of tolerance involves peripheral mechanisms, including antigen ignorance, Th2 deviation, and Treg. The mechanisms for maintaining tolerance to autoantigens such as α3(IV)NC1 are both central (clonal deletion) and peripheral. α3(IV)NC1 is expressed in the thymus (67), so clonal deletion would be expected. However, deletion is incomplete, and patients with anti-GBM GN (as well as normal individuals) have nondeleted T cells that are reactive with α3(IV)NC1 (68). The unexpected reduced MHC II presentation of immunodominant α3(IV)NC1 epitopes by human antigen-presenting cells suggests peripheral tolerance through ignorance. The absence of $CD25^+foxp3^+$ Treg during acute disease and the appearance during the recovery phase of human anti-GBM GN suggest that changes in the Treg balance may be involved in the development of Goodpasture's disease (58). The predominance of IL-10–secreting T cells during the resolution of anti-GBM GN is also consistent with the appearance of Treg (65). Mucosal presentation of autoantigens has been shown to be effective in induction of tolerance, and in experimental autoimmune anti-GBM GN in rats, oral feeding of α3(IV)NC1 collagen provides protection (69). These human and experimental observations suggest the possibility of immune modulation therapy for this rare but severe form of autoimmune crescentic GN.

T Cells in ANCA-Associated Crescentic GN

A number of observations suggest a role for $CD4^+$ T cell–directed autoimmunity in crescentic GN associated with small-vessel vasculitis and ANCA. Perhaps the most obvious is the presence of circulating antibodies to neutrophil MPO in this group of diseases and the presence of $CD4^+$ T cells and DTH effectors and relative paucity of antibody in affected glomeruli (70–72). The capacity for MPO autoimmunity to induce crescentic GN has been established in experimental models. Rats that are immunized with MPO develop crescentic GN after infusion of a crude preparation of this antigen into their kidneys (73). Splenocytes or antibodies from MPO-deficient mice that are immunized with murine MPO induce a necrotizing and crescentic GN after passive transfer to immunodeficient mice (74).

The prominent isotype switching that is observed with ANCA (75) and the predominance of Th1 isotypes of ANCA in Wegener's granulomatosis (76) are consistent with Th1-directed responses in the genesis of the autoimmunity. The cytokine profile of mononuclear cells (high IFN-γ, IL-12, and TNFα, which is suppressed by IL-10) in the blood and affected tissues of patients with ANCA-associated GN is consistent with a Th1 response (77). The phenotype of T cells from blood, bronchial lavage, and nasal biopsy specimens of patients with Wegener's granulomatosis also is consistent with Th1-driven cell-mediated immunity (78,79). Immunohistochemistry of affected tissues also demonstrates the presence of IFN-γ (79) and IL-8 (79,80). However, these observations are not uniform, and predominance of $CD3^+$ cells, eosinophils, and Th2 cytokines has been reported in a study of nasal biopsies from patients with Wegner's granulomatosis (81).

The presence of T cells that respond to the likely target antigens, MPO and PR3, in patients with ANCA-associated GN provides evidence for the involvement of T cell–directed autoimmunity (82–86). The immunodominant epitopes have not been defined precisely, but for PR3, predominant T cell–reactive residues in three peptide regions involving the C terminal of the propeptide and the signal sequence have been identified (87). The efficacy of therapies that are targeted to T cells, including anti-CD4 mAb (88) and T cell leukophoresis (89), also suggest involvement of cell-mediated immunity.

Lupus Nephritis

Experimental studies have demonstrated that autoimmune responses that lead to murine lupus are T cell dependent (7,17). Deficiency of α/β T cells has been demonstrated to inhibit development of lupus nephritis is some experimental models (17,90), but α/β T cell–independent mechanisms also may be involved (16,91). Failure of deletion of B cells after polyclonal activation by superantigens has been suggested as an alternative mechanism for development of autoantibodies (92). Reduced apoptosis of B cells is a feature of some murine models but has not been detected in human lupus (93). The involvement of Treg imbalance in human disease induction is suggested by decreased Treg in the blood of patients with systemic lupus erythematosus (94). Deficiency of $CD25^+$ Treg does not seem to be involved in some models of murine lupus (95).

The role of T cells as effectors of glomerular injury is not clear in lupus. T cells are present in crescentic glomeruli as well as in the interstitium in lupus-prone mice (95) and in World Health Organization class IV human lupus nephritis (96). In human disease, there is a positive correlation among interstitial T cell accumulation, the histologic severity of injury, and renal function (97). The presence of restricted TCR Vβ gene usage by T

cells in renal biopsies of patients with lupus nephritis suggests that these T cells are not nonspecifically recruited but are oligoclonal and potentially antigen specific (98,99). Human studies provide conflicting evidence for the role Th1- and Th2-biased responses in human lupus nephritis. Higher serum and glomerular IL-18 levels in patients with lupus nephritis compared with nonnephritic patients and high IFN-γ and low IL-4 levels in peripheral blood lymphocyte suggest that a Th1-biased response is associated with development of nephritis (100). Glomerular expression of CD40 and a high ratio of Th1/Th2 cytokine-expressing cells in class IV proliferative lupus nephritis compared with class V lupus nephritis (101) are consistent with involvement of Th1 responses in crescentic injury. However, in children with lupus nephritis, both Th1 and Th2 antibody isotypes were observed in glomeruli (102). Expression of IL-4 and IL-10 mRNA in the absence of IFN-γ (99) in patients with class IV lupus nephritis is consistent with a Th2 phenotype, as is expression of the CCR4 chemokine receptor on intrarenal $CD4^+$ cells (103). However, another study of class IV lupus nephritis reported high expression of the Th1-associated chemokine receptor CCR5 in extracapillary lesions and decreased expression after glucocorticoid therapy (104).

Other Forms of Human Crescentic GN

Information about the contribution of T cells in other forms of human GN associated with crescent formation is scarce. Mesangial deposition of polymeric IgA is the hallmark of IgA nephritis, and crescent formation is a marker of disease severity. It is unclear whether adaptive immune responses are involved directly in the pathogenesis of IgA nephritis, as "circulating IgA-immune complexes" do not seem to contain antigen (105), and glomerular deposits of IgA seem to be polyclonal (106). However, a role for γ/δ T cells and dysregulation of mucosal immunity has been suggested. Circulating γ/δ T cells are increased in patients with IgA nephritis (107). They show evidence of clonal expansion with restricted TCR Vγ usage and produce TGF-β, which stimulates IgA class switching (107). Abnormal glycosylation of IgA may be implicated in this disease (108), and experimental studies suggest the capacity of Th2 cytokines (IL-4 and IL-5) to alter glycosylation of IgA (109,110). Enhanced IL-10 production by peripheral blood mononuclear cells in patients with IgA nephritis would be consistent with increased Th2 or Treg activity (111). Glomerular T cells and macrophages are more frequent in crescentic forms of IgA nephritis than in noncrescentic disease (112). Both α/β and γ/δ T cells are present in glomeruli of patients with IgA nephritis, and the presence of γ/δ T cells correlates with progression of disease (113), although, in children, disease progression has been reported to correlate with the presence of $CD8^+$ T cells (114).

Other forms of human GN associated with crescent formation include cryoglobulinemia, infection-associated GN, and (infrequently) membranous GN. In cryoglobulinemia associated with chronic hepatitis C infection and other chronic infective diseases that result in persistent antigenemia, T cells direct the adaptive immune responses that underpin the formation of circulating immune complexes that deposit in glomeruli. Cryoglobulins that result from plasma cell dyscrasias are generated independent of adaptive T cell–driven immunity. In the case of crescentic transformation of membranous nephritis, the presence of $CD4^+$ and $CD8^+$ T cells in crescentic glomeruli points to their active participation in the pathogenic process (115).

Conclusions

T cell–directed adaptive immunity underpins many forms of GN and particularly crescentic GN. T cell–driven autoimmunity and T cell–driven effector mechanisms play an important role in crescentic human GN, and therapeutic interventions to target selectively these aspects of T cell function may prove particularly beneficial in this severe form of glomerular injury.

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