Invited Review

T cell subsets in immunologically-mediated glomerulonephritis

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Summary. Until recently, research on the pathogenesis of glomerulonephritis has been mainly focused on the characterization of humoral immune responses in the initiation of glomerular injury. However, there is a growing recognition that both cellular and humoral immune responses, in varying proportions, are involved in the pathogenesis of immunologically-mediated glomerulonephritis.

T lymphocytes are essential cellular elements of cell-mediated immunity. Both in experimental models of immune-mediated renal disease and in histopathological analyses of human nephropathies, the involvement of T cells has been demonstrated in the immunoregulation of nephritogenic immune responses and in the immune injury in the kidney. T cell activation resulting in either delayed-type hypersensitivity, cytolytic reactions, abnormal expression of major histocompatibility complex (MHC) molecules, or B cell activation can result in glomerulonephritis. These different types of responses are exerted by distinct T cell subsets defined by cell surface markers and cytokine profiles.

CD4+ T cells in vivo are functionally heterogeneous with respect to cytokine production and the CD45 isoforms that are found on their surface. Like CD4+ T cells, CD8+ T cells may also be heterogeneous at the level of cytokine production. The roles of CD4+ and CD8+ cells and their cytokine profiles in glomerulonephritis have not been extensively investigated yet, but such studies might improve the understanding of the pathogenesis and possibly lead to new therapeutic approaches of human glomerulonephritis. In this review the role of distinct T lymphocyte subsets in experimental and human glomerulonephritis will be discussed.

Key words: T cells, T cell subsets, Glomerulonephritis

Introduction

Until recently, most research on the pathogenesis of glomerulonephritis has been devoted to the characterization of humoral immune responses in the initiation of glomerular injury (Holdsworth and Tipping, 1991). However, the participation of antibody, immune complexes, complement, and neutrophils alone cannot completely explain many events occurring in experimental and human glomerulonephritis (Rovin and Schreiner, 1991). It is now recognized that both cellular and humoral immune responses, in varying proportions, are involved in the pathogenesis of immunologically-mediated glomerulonephritis (Holdsworth and Tipping, 1991; Rovin and Schreiner, 1991). Cell-mediated immunity can also be the main cause of renal damage in certain forms of glomerulonephritis (Bolton, 1984; Holdsworth and Tipping, 1991; Brouwer et al., 1993; Neilson, 1993; Remke et al., 1994). T lymphocytes are essential cellular elements of cell-mediated immunity. T cell activation resulting in either delayed-type hypersensitivity, cytolytic reactions, abnormal expression of major histocompatibility complex (MHC) molecules, or B cell activation might result in glomerulonephritis (Florquin and Goldman, 1994). These different types of responses are exerted by distinct T cell subsets defined by cell surface markers and cytokine profiles (Florquin and Goldman, 1994). The topic of this review is the role of distinct T lymphocyte subsets in experimental and human glomerulonephritis.

Heterogeneity of CD4+ T cell subsets based on cytokine production

Mosmann and Coffman were able to define two subsets among fully differentiated CD4+ T cell clones in the mouse, on the basis of a restricted cytokine profile in vitro, designated Th1 and Th2 clones (Mosmann and Coffman, 1989). Upon activation, Th1 clones produce interleukin-2 (IL-2), interferon-γ (IFN-γ) and tumor necrosis factor-β (TNF-β), but not IL-4, IL-5, IL-6, or...
IL-10, whereas Th2 clones produce IL-4, IL-5, IL-6, IL-10 and IL-13, but not IL-2 or IFN-γ. Both types of clones are able to produce IL-3, granulocyte-macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor alpha (TNF-α). Apart from this distinction, Th clones which secrete a mixture of Th1 and Th2 cytokines have also been characterized. These Th clones are designated Th0 clones (Mosmann and Coffman, 1989). A clearcut dichotomy, as found in different disease states human CD4+ T cell clones are found which exhibit Th1 or Th2 profiles (Romagnani, 1991), and both Th1 and Th2 cells are shown to be involved in the pathogenesis of immunological disorders (Trembleau et al., 1995). Although the Th1/Th2 model is a valuable model to investigate and explain diverse immune reactions, it is likely that the T-cell responses in vivo are more diverse and sophisticated (Kelso, 1995). However, up till now there is still evidence that CD4+ T cells in vivo are functionally heterogeneous in that responses are essentially either Th1-like or Th2-like (Fowell et al., 1991).

Functional heterogeneity of CD4+ T cell subsets based on the expression of CD45

Besides the heterogeneity of CD4+ T cells based on cytokine production, CD4+ T cells are also heterogeneous with respect to the CD45 isoforms that are found on their surface (Fowell et al., 1991; Kampinga et al., 1992; Mason, 1992). The leukocyte-common antigen, CD45, has been shown to exist in man, mouse and rat in a number of different isoforms, generated by differential usage of three exons (A, B, and C) of a single gene (Thomas, 1989). Isoform usage varies with T cell maturation, activation and differentiation (Mason, 1992).

To some extent there is an association between the CD45 phenotype of CD4+ memory T cells and the potential to secrete particular cytokines upon activation, which can be linked to the Th1 and Th2 phenotypes discussed before (O’Garra and Murphy, 1993). It is supposed that there are two memory phenotypes CD4+CD45RAlowB220lowC101high and CD4+CD45RAlowB220highC101high (Mason and Powrie, 1990). They release predominantly IL-4 (memory cells for humoral response) respectively IFN-γ and IL-2 (memory cells for cell-mediated responses) following stimulation (Bottomly et al., 1989; Mason and Powrie, 1990; Fowell et al., 1991; Mason, 1992). However, the association between lymphokine synthesis and CD45R isoform expression is quantitative rather than absolute, and therefore these subsets should not be interpreted as bona fide Th2 and Th1 cells respectively, but more as a Th2-“like” and Th1-“like” cells (Fowell et al., 1991).

Functional heterogeneity of CD8+ T cells

The two major functions of CD8+ cells are cytolyis and immunosuppression. Like CD4+ T cells, CD8+ T cells may also be heterogeneous at the level of cytokine production, and this determines whether they exhibit inflammatory- or suppressor-type properties (O’Garra and Murphy, 1993). CD8+ cells can secrete Th1 cytokines such as IFN-γ and IL-2, and Th2 cytokines such as IL-10 (de Jong et al., 1991; Inoue et al., 1993). They can also produce TGF-β, which mediates at least part of their suppressive function (Miller et al., 1992).

Inoue et al. showed that mouse CD8+ T cell clones could be subdivided into cytotoxic (Tc) and suppressor (Ts) subgroups by the pattern of cytokine production and CD45 expression (Inoue et al., 1993). These mouse CD8+ subsets correspond strongly with the human Mycobacterium leprae-specific Type 1 and Type 2 CD8+ T cell subsets derived from patients with leprosy, as described by Salgame and Bloom (Salgame et al., 1991; Bloom et al., 1992). There is no direct correlation between CD8+ subsets and CD4+ T1 and Th2 subsets, since most alloreactive and antigen-specific CD8+ T cell clones produce large amounts of IFN-γ (Kemeny et al., 1994).

The nephritogenic immune response and the role of T cells in glomerulonephritis

The nephritogenic immune response consists of several interacting elements represented by the components of the immune system, the renal parenchymal cells and a genetic or environmental disturbance that sets it all off (Karp et al., 1991). There is a growing recognition of the importance of T cells in mediating renal injury (Meyers, 1995). The effector cells of the nephritogenic autoimmune response are autoreactive Th cells, capable of activating both B cells and cytotoxic T lymphocytes and recruiting additional leukocytes, such as macrophages (Karp et al., 1991; Rovin and Schreiner, 1991).Suppressor T cells in renal autoimmunity have recently been the focus of interest, especially in experimental anti-tubular basement membrane disease (Kelly et al., 1985) and mercuric chloride-induced anti-glomerular basement membrane disease (Pelletier et al., 1987). Immune injury can induce MHC class II expression on mesangial cells, predominantly through the production of IFN-γ by T lymphocytes (Madrenas et al., 1991). This may enhance the ability of mesangial cells to interact with infiltrating leukocytes and serve as antigen-presenting cells (Rovin and Schreiner, 1991), thus playing a role in the development or maintenance of a nephritogenic T cell response (Karp et al., 1991). Alternatively, renal tubular epithelial cells may promote anergy in autoreactive T cells, thus down-regulating the autoimmune responses within the kidney (Singer et al., 1993).

The essential components of cell-mediated immunity are present in both human and experimental glomerulonephritis (Rovin and Schreiner, 1991). Experimental renal pathology demonstrates a correlation between the presence of mononuclear cell infiltrates and glomerular...
dysfunction, particularly with respect to proteinuria, diminished glomerular blood flow, and ultimate effacement of glomerular structure (Rovin and Schreiner, 1991). Characterization of renal inflammatory cells could give further insight into the pathogenesis of distinct forms of glomerulonephritis (Markovic-Lipovski et al., 1990).

**T cell subsets in experimental glomerulonephritis**

*Murine models of lupus nephritis*

Systemic lupus erythematosus is a disease characterized by B cell hyperactivity, autoantibody production and immune complex deposition in vital organs (Theofilopoulos and Dixon, 1981). Murine models of spontaneous lupus (MRL-lpr/lpr, NZBxNZWF1 and BXSB mice) and models of induced lupus, such as the parent-into-F1 model of graft-versus-host disease, have been useful in elucidating the importance of cytokines and cell-cell interactions in the pathogenesis of lupus nephritis (Handwerger et al., 1994).

MRL-lpr/lpr mice spontaneously develop an autoimmune disease characterized by vasculitis, massive lymphadenopathy, glomerulonephritis, and autoantibody production (Jabs et al., 1992). The autoimmune disease was recently identified as a defect in the Fas antigen (Watanabe-Fukunaga et al., 1992). According to Díaz Gallo et al. (1992), the predominant renal interstitial infiltrate in MRL-lpr/lpr is composed of unique lymphoid cells regulated by the lpr gene (Kelley et al., 1993). These MRL-lpr/lpr kidney infiltrating 'double negative' T cell clones (CD3+, TCR α/β+, B220+, CD4+, CD8+) are autoreactive, kidney-specific, exclusively proliferating to renal tubular epithelial and mesangial cells, and they secrete IFN-γ (Díaz Gallo et al., 1992; Kelley et al., 1993). Several observations suggest that these lpr-regulated T cells cause renal disease in MRL-lpr/lpr mice: their accumulation in lymph node, spleen and kidney prior to renal injury; increasing numbers of these cells in the kidney correlate with disease severity; prevention of renal injury can be obtained by therapeutic elimination of these T cells; and they express transcripts of cytokines associated with inflammatory responses (IFN-γ, TNF-α, TNF-β) (Díaz Gallo et al., 1992; Kelley et al., 1993). Although these kidney-infiltrating cells do not express CD4 or CD8, their proliferation is MHC-restricted. Their supernatants induce class II and ICAM-1 on the surface of cultured renal tubular epithelial cell (Díaz Gallo et al., 1992). The cytokine profiles of the clones are heterogeneous, suggesting that there is an oligoclonal population of T cells within the renal interstitium (Díaz Gallo et al., 1992). All clones transcribe mRNA for at least one cytokine capable of inducing MHC Class II and ICAM-1 (IL-4, TNF-α, IFN-γ), suggesting that these T cell clones might cause the up-regulation of MHC Class II and ICAM-1 on tubular epithelial cells (Kelley et al., 1993). The authors speculated that autoreactive kidney-specific T cells recognize a kidney-specific antigen on the surface of tubular epithelial cells (Kelley et al., 1993).

In contrast, Jabs et al. (1992) suggest that CD4+ T cells play a central role in the development of the autoimmune disease in MRL-lpr/lpr mice. They described that the target organ lesions in MRL-lpr/lpr mice, including the kidney, are largely composed of CD4+ cells (Jabs et al., 1992), while only the massively enlarged lymph nodes are composed primarily of 'double negative' T cells. Anti-CD4+ monoclonal antibody therapy demonstrated marked suppression of the autoimmune disease as determined by reversal of the immunopathological lesions, improvement in autoantibody production, and decrease of IgG levels in the group treated with anti-CD4+ monoclonal antibody (Jabs et al., 1992). Glomerulonephritis, interstitial nephritis and proteinuria were either reduced or completely eliminated (Jabs et al., 1992). The authors suggested that the CD4+ cell plays an essential role in the autoimmune process and that the massive accumulation of double-negative T cells is not a primary factor in the development of the autoimmune disease. Recent studies using MRL/lpr mice lacking CD4+ T cells also show a diminished autoimmune disease despite an accumulation of CD4+CD8+ 'double negative' cells in spleen and lymph nodes (Koh et al., 1995).

In the graft-versus-host disease model of systemic autoimmune disease, depending on the parent and F1 strain combinations used, mice develop either an acute illness, with T cell activation patterns similar to those reported in allograft rejection, or a chronic, lupus-like graft-versus-host disease, with anti-DNA antibody production and deposition of immune complexes in skin and glomeruli (Via et al., 1987). In chronic graft-versus-host disease only donor CD4+ allogenic MHC Class II-reactive T cells appear to be activated, resulting in the delivery of help to host allogeneic MHC Class II-bearing B cells, including autoreactive B cells (Handwerger et al., 1994). Chronic graft-versus-host disease is characterized by a selective deficiency in cells secreting IL-2 and IFN-γ and a hyperactivation of Th2 cells (de Wit et al., 1993; Charlton and Lafferty, 1995). Mice suffering from this disease spontaneously produce lymphokines of Th2 origin, such as IL-4, IL-10, and possibly IL-6 (Goldman et al., 1991; de Wit et al., 1993; Handwerger et al., 1994; Rus et al., 1995). The disease can be prevented by administration of either IFN-γ or IL-12 at the time of cell transfer (Donckier et al., 1994; Via et al., 1994). IL-4 was shown to be responsible for the increased expression of class II antigen on B cells (de Wit et al., 1993).

**Mercury-induced anti-glomerular basement membrane disease**

In the mercuric chloride (HgCl2)-induced autoimmune model of anti-glomerular basement membrane nephritis in Brown Norway rats, polyclonal B-cell...
of loss of suppression, anti CD8+ therapy neither prolonged the disease in Brown Norway rats, nor induced it in Lewis rats (Pelletier et al., 1990). A possible suppressor function of the RT6.2+ T cell subset was reported by Kosuda et al. (1991), who examined this subset in mercury-induced glomerulo-nephritis in the rat. RT6.2+ T cells constitute 45% of the CD4+ T cell population and 80% of the CD8+ cell population, and can passively transfer protection from mercury-induced glomerulonephritis in rats lacking RT6.2+ T cells (Angeullo et al., 1988). They found that there was a decrease in the RT6.2+ T cell population over the course of the disease in Brown Norway rats that correlated with the peak in anti-glomerular basement membrane antibody titer (Kosuda et al., 1991). If RT6.2+ T cells (which include both CD4+ and CD8+ cells) are the only suppressor population in this model they may not have been depleted adequately by a CD8+ therapy (Karp et al., 1991). The factors that cause the differential effects of HgCl2 on the immune dysregulation in susceptible versus non-susceptible rats are largely unknown, but differences in both MHC and non-MHC-linked genes are implicated in the control of susceptibility (Druet et al., 1977; Sapin et al., 1984; Bigazzi, 1992).

Heymann’s nephritis

Active Heymann’s nephritis is induced by immunization of susceptible rat strains with crude preparations of renal tubular epithelium in complete Freund’s adjuvant (CFA) (Heymann et al., 1959). The pathology of Heymann’s nephritis in the rat closely resembles idiopathic membranous nephropathy in man (Alousy et al., 1969). The disease is caused by a CD4+ helper T cell-dependent (Cheng et al., 1988) humoral autoimmune response which results in the in situ deposition of auto-antibodies in glomeruli (Couser and Salant, 1980) and complement activation (De Heer et al., 1985a). The autoimmune response in Heymann’s nephritis is under regulatory influence by T lymphocyte subsets (De Heer et al., 1985b). Insights into the role of CD4+ and CD8+ T cell subsets in Heymann’s nephritis are obtained from T cell depletion (Cheng et al., 1988; Quiza et al., 1991, 1992) and transfer (De Heer et al., 1985b, 1986; Cheng et al., 1988) experiments.

The role of T cells in the mediation of Heymann’s nephritis was investigated by treatment with monoclonal antibody specific for T cell subsets for 6 weeks after immunization (Quiza et al., 1992). Anti-CD4 monoclonal antibody therapy totally prevented proteinuria. Moreover, it reduced antibody and complement deposition in the glomerulus and auto-antibody titers in serum. Anti-CD8+ monoclonal antibody therapy markedly reduced proteinuria, but had no effect on auto-antibody titers or on the deposition of antibody and complement in the glomerulus (Quiza et al., 1992). This suggest that both cytotoxic CD8+ and CD4+ effector T cells may have a direct role in the mediation of glomerular dysfunction in Heymann’s nephritis (Quiza et
resulted in a significant suppression of the autoimmune response and prevented or only minor proteinuria in subsequently challenged animals (De Heer et al., 1986).

Tolerance to Heymann’s nephritis can be induced by immunization with renal tubular antigen in incomplete Freund’s adjuvant (IFA) (Harmon et al., 1980; De Heer et al., 1985b, 1986; Cheng et al., 1988). When tolerant rats are rechallenged with renal antigen in CFA, the onset of Heymann’s nephritis is either completely prevented or only minor proteinuria will develop (Harmon et al., 1980). This unresponsiveness is mediated by antigen-specific thymus-derived CD8+ suppressor T cells (De Heer et al., 1985b). Transfer experiments with splenic CD8+ T cells from tolerant rats resulted in a significant suppression of the autoimmune response in subsequently challenged recipients, while transfer of splenic CD8- T helper cells enhanced the autoimmune response (De Heer et al., 1985b).

Quiza et al. (1991) investigated the effects of therapy with monoclonal antibody to T cell subsets on induction of tolerance of Heymann’s nephritis following preimmunization with renal tubular antigen in IFA (Quiza et al., 1991). Anti-CD4 monoclonal antibodies given for 2 weeks after the preimmunization abolished the capacity of renal tubular antigen in IFA pretreatment to induce unresponsiveness to Heymann’s nephritis. CD4+ cells are thus critical for the induction of tolerance to Heymann’s nephritis (Quiza et al., 1991). Furthermore, in non-tolerant animals, anti-CD4 therapy administered prior to immunization did not prevent the induction of Heymann’s nephritis, but even enhanced the severity of the disease (Quiza et al., 1991). The authors suggested that the monoclonal antibody used for the depletion of CD4+ cells (MRC OX35) might mainly remove suppressor CD4+ cells or that after the therapy new thymus-derived CD4+ cells provide better help to the B cells. Anti-CD8 monoclonal antibodies did not prevent induction of tolerance and had no effect on the severity of the disease in responsive animals (Quiza et al., 1991). This suggests that there is no requirement for CD8+ cells in the induction phase immediately after preimmunization with renal tubular antigen in IFA (Quiza et al., 1991). However, CD8+ T cells may participate in the maintenance of long-term unresponsiveness, as was shown by the transfer experiments with splenic CD8+ T cells discussed earlier (De Heer et al., 1985b).

All together it is clearly shown that T lymphocyte subsets play an important role in the regulation of Heymann’s nephritis. It appears that CD4+ T cells play a critical role both in the induction of Heymann’s nephritis (Cheng et al., 1988) and in induction of unresponsiveness to the disease (Quiza et al., 1991). CD8+ T cells are involved in the mediation of glomerular barrier dysfunction (Quiza et al., 1992), in the spontaneous down-regulation of the active disease (De Heer et al., 1986) and in maintenance of suppression after induction of tolerance (De Heer et al., 1985b). Further investigation is required on the cytokine profiles and regulation of the different T cell subsets in order to obtain more insights in the mechanisms by which the cells exercise their suppressive or effector functions. In addition, the role of T cells in human membranous glomerulonephritis has to be assessed.

Chronic serum sickness

Chronic serum sickness in rats, induced by subcutaneous injections of BSA in Freund’s incomplete adjuvant as described by Van Liew, Brentjens and Noble (Van Liew et al., 1983), is a model of proliferative immune complex glomerulonephritis, which progresses to death from kidney failure in three distinct stages: a mild, moderate and a final, severe stage (Van Liew et al., 1983). In the mild stage of the disease, histology and kidney function are normal. In the moderate stage, immune complex deposits accumulate in the peripheral capillary wall and the glomeruli become enlarged and hypercellular, finally resulting in segmental glomerular and tubular necrosis in the severe stage (Van Liew et al., 1983). T lymphocyte accumulation in glomeruli is a consistent and significant feature of chronic serum sickness nephritis, although T cells are present only in low numbers, only for a brief period and only in the moderate stage, before the development of severe kidney insufficiency (Noble et al., 1990). As long as T cells are present in glomeruli, inflammation has relatively benign functional consequences. This suggests that T cells might have an immunosuppressive function, preventing severe glomerular dysfunction by blocking the differentiation of macrophages along abnormal pathways (Noble et al., 1990). Therefore, this model promises to be an excellent tool with which to evaluate the possible immunoregulatory role of glomerular T cells in proliferative immune complex glomerulonephritis (Noble et al., 1990).

Tubulo-interstitial glomerulonephritis

Murine anti-tubular basement membrane disease, induced in susceptible mouse strains, is an autoimmune kidney disease mediated by tubular antigen–specific CD8+ nephritogenic effector T cells which are delayed-type hypersensitivity-reactive and cytotoxic to renal epithelial cells (Meyers and Kelly, 1994). Recently, the 3M-1 target antigen, secreted and expressed by proximal tubular cells, of murine anti-tubular basement membrane disease has been sequenced and a major nephritogenic domain has been identified (Neilson et al., 1991).

Both CD4+ Th-cell clones and CD8+ effector T cell clones have been evaluated in this model (Meyers and Kelly, 1991, 1994; Heeger et al., 1994). The Th cell response in this model is predominantly a Th1
phenotype, with IL-2 and IFN-γ expression in the absence of IL-4 excretion (Heeger et al., 1994). These Th cells also secrete an antigen-binding T helper factor, ThF, that induces the CD8⁺ nephritogenic effector T cell response (Hines et al., 1990). Meyers and Kelly (1991) have derived a CD8⁺, 3M-I-specific, class I-restricted nephritogenic effector T cell line from susceptible mice immunized with renal tubular antigen. The cells display cytotoxicity against tubular cells in vitro and can mediate both interstitial nephritis and delayed-type hypersensitivity to the 3M-I target antigen (Meyers and Kelly, 1991). Some subclones of this cell line show differential activity: one clone is cytotoxic but not delayed-type hypersensitivity-reactive, and several are delayed-type hypersensitivity-reactive with less cytotoxic activity (Meyers and Kelly, 1994). Adoptive transfer experiments demonstrated qualitative differences in the tubulo-interstitial lesions induced by the distinct clones (Meyers and Kelly, 1994). The delayed-type hypersensitivity-reactive clones induced inflammatory cellular lesions, whereas the cytotoxic clone elicited a more diffuse pattern of injury characterized by tubular dilatation and atrophy (Meyers and Kelly, 1994). The two phenotypes also expressed different cytokine profiles (Meyers and Kelly, 1991). The delayed-type hypersensitivity-reactive clones expressed IL-2, IL-4, IL-6, IFN-γ, TNFα, and TGF-β; the cytotoxic subset expressed a similar profile, except for IL-2 and TGF-β (Meyers and Kelly, 1994).

Non-susceptible strains of mice also develop 3M-I-specific T cells, but these are CD4⁺ and do not infiltrate and mediate inflammatory interstitial lesions (Neilson et al., 1985a). The development of CD4⁺ and the suppression of CD8⁺ effector T cells appears to be mediated by CD8⁺ suppressor T cells (Kelly et al., 1988). In susceptible mice these suppressor cells are also present, but they are counteracted by Vicia villosa lectin-adherent contrasuppressor cells, thus allowing for preferential maturation of nephritogenic CD8⁺ effector T cells (Kelly et al., 1988).

Suppressor T cells can be experimentally induced in anti-tubular basement membrane disease (Neilson et al., 1985b). Intravenous injection of tubular antigen-coupled splenocytes into anti-tubular basement membrane disease-susceptible mice prevents development of the disease. Moreover it improves the histological lesions in animals with established disease by induction of two phenotypically and functionally distinct populations of suppressor T cells (Neilson et al., 1985b). The development of CD4⁺ suppressor T cells (Ts1) inhibit an early stage in the differentiation of the nephritogenic CD8⁺ effector T cells, and also induce a population of CD8⁺ suppressor T cells. These CD8⁺ suppressor T cells (Ts2) or soluble proteins secreted by these cells (TsF₂) directly inhibit the function of the nephritogenic CD8⁺ effector cells through a non-cytotoxic mechanism (Neilson et al., 1985b).

TsF₂ was shown to functionally inhibit both 3M-I specific cytotoxic and delayed-type hypersensitivity-reactive clones (Meyers and Kelly, 1994). The loss of function of the clones was an active cellular process, since it was dependent upon new mRNA and protein synthesis. In the cytotoxic clone, exposure to TsF₂ induced expression of TGF-β1 mRNA (Meyers and Kelly, 1994). Neutralizing antisera to TGF-β1 completely abrogated the suppression of the cytotoxicity, demonstrating that TGF-β1 is required for TsF₂-induced suppression of cytotoxicity and nephritogenicity (Meyers and Kelly, 1994). However, delayed-type hypersensitivity-reactive clones, expressing TGF-β1 themselves following activation, are not inactivated by exogenous TGF-β1. Therefore, TsF₂ may inactivate such clones by other mechanisms (Meyers and Kelly, 1994).

**T cell subsets in human glomerulonephritis**

There is accumulating, although still limited, evidence that cellular immunity is active in human glomerular disease, particularly of a chronic or sclerosing nature (Rovin and Schreiner, 1991). Many forms of human glomerulonephritis are characterized by hypercellularity, of which infiltrating leukocytes constitute a significant proportion (Rovin and Schreiner, 1991). Analysis of leukocyte subsets in glomerulonephritis (Nolasco et al., 1987; Tuazon et al., 1987) has documented the presence of T lymphocytes in rapidly progressive glomerulonephritis with crescent formation, lupus nephritis, Henoch–Schönlein purpura, and transplant glomerulopathy. T lymphocytes of both the suppressor/cytotoxic and helper subsets are represented in glomerular lesions (Rovin and Schreiner, 1991). Glomerular leukocyte infiltrates typically do not correlate with the presence or absence of glomerular deposits of immune complexes (Nolasco et al., 1987; Rovin and Schreiner, 1991). A good example is immune-complex-negative rapidly progressive glomerulonephritis which can exhibit large numbers of glomerular mononuclear leukocytes (Nolasco et al., 1987; Holdsworth and Tipping, 1991). It has been emphasized that many glomerular lesions classified as primary glomerulonephritides are frequently accompanied by highly significant interstitial infiltrates, consisting principally of T lymphocytes and lesser numbers of macrophages (Hooke et al., 1987; Tuazon et al., 1987). Glomerular dysfunction often correlates even better with the intensity of the T cell interstitial infiltrate than the degree of glomerular hypercellularity (Hooke et al., 1987). Immunophenotyping of mononuclear leukocytes in kidney tissue revealed significant increases of CD4⁺ and CD8⁺ T cells in glomeruli of rapidly progressive glomerulonephritis, membranoproliferative glomerulonephritis and focal glomerulosclerosis (Markovic-Lipovski et al., 1990, 1991). Interstitial cells were mostly T lymphocytes in all forms of glomerulopathies investigated (minimal change, membranous nephropathy, membranoproliferative glomerulonephritis type I, mesangiocapillary glomerulonephritis, rapidly progressive glomerulonephritis, focal glomerulo-
sclerosis, IgA nephritis) (Markovic-Lipovski et al., 1990, 1991; Yoshioka and Maki, 1995). A high expression of HLA class II antigens was observed on interstitial mononuclear leukocytes, as a sign of their activation (Markovic-Lipovski et al., 1990). In all forms of glomerulonephritis with interstitial infiltrates the cells surrounded glomeruli like a corona, irrespective of their presence within the glomeruli (Markovic-Lipovski et al., 1990). In membranous nephropathy and mesangio-capillary glomerulonephritis, there was no evident increase of glomerular mononuclear leukocytes despite observed interstitial infiltrates in some patients (Markovic-Lipovski et al., 1990). The variable presence of interstitial cell infiltrates in these patients might reflect a different timing of biopsy or heterogeneity of detected within the glomerular tuft with a slight time of onset, suggesting a correlation between the presence of these cells and the duration of the disease (Markovic-Lipovski et al., 1990). In focal glomerulosclerosis, CD8+ T cells were predominant and usually peripherally distributed within the glomerular tuft or at capillary adhesions and the glomerular T lymphocyte counts were not related to disease duration (Markovic-Lipovski et al., 1990). In IgA nephropathy the CD4+/CD8+ ratio varied and the presence of T cells correlated with renal function and the activity of glomerular crescents (Yoshioka and Maki, 1995). The number of interstitial inflammatory cells in focal segmental glomerulosclerosis was shown to correlate with the degree of impaired renal function (plasma creatinine level) at the time of biopsy (Markovic-Lipovski et al., 1991).

Increasing evidence indicates a crucial role for T cells, particularly CD4+ cells, in driving B cell hyperactivity in systemic lupus erythematosus (Handwerger et al., 1994). T cell abnormalities are multiple and prominent in patients with systemic lupus erythematosus, and are crucial in the pathogenesis of the disease (Tsokos, 1992). These abnormalities include, among others, T lymphopenia, decreased suppressor cell activity, decreased cytotoxic responses and increased CD4+DR+ and 'double negative' T helper cell activity (Tsokos, 1992). Moreover, T lymphocytes show enhanced proliferative responses when stimulated via the CD3 pathway, which can contribute to the autoimmune activity in human systemic lupus erythematosus (Stekman et al., 1991). IL-2 production by stimulated peripheral blood T cells is decreased and the response of lymphocytes to IL-2 also seems to be decreased, possibly through decreased IL-2 receptor expression (Linker-Israeli, 1992; Tsokos, 1992; Horwitz and Jacob, 1994).

Although chronic murine graft-versus-host disease is obviously Th2 cell-mediated, the Th1/Th2 cytokine paradigm only partially explains the dichotomy between humoral and cellular immunity in human systemic lupus erythematosus (Horwitz and Jacob, 1994). In human systemic lupus erythematosus IgE is not increased and there is no convincing evidence that the production of IL-4 is increased (Horwitz and Jacob, 1994). However, there is preliminary evidence for elevated serum IL-10 levels (Horwitz and Jacob, 1994).

Further investigations on the role of T cells and cytokines in lupus nephritis will provide a framework for the development of more specific immunotherapeutic approaches to the treatment of this disease (Handwerger et al., 1994).

Summary and Conclusion

Both in experimental models of immune-mediated renal disease and in histopathological analyses of human nephropathies, the involvement of T cells has been demonstrated in the immunoregulation of nephritogenic immune responses and in the immune injury in the kidney. The roles of CD4+ and CD8+ cells and their cytokine profiles have not been extensively investigated, but such studies might improve the understanding of the pathogenesis and possibly lead to new therapeutic approaches of human glomerulonephritis (Florquin and Goldman, 1994).

Several approaches to the development of immunosuppressive modalities targeting injurious cellular immune responses have been taken in both autoimmune disease models and experimental transplant rejection (Meyers and Kelly, 1994). An ideal immunosuppressive modality, however, would be antigen or clone specific, targeting only those T cells involved in the autoimmune, or alloreactive, response (Meyers and Kelly, 1994). This type of immunosuppression could theoretically be achieved through preferential expansion of specific suppressor T cells in the host (Meyers and Kelly, 1994).

Further work in the area of cell-mediated immunity in renal disease will be required to develop specific therapies designed to interrupt immunologically sustained glomerular damage (Rovin and Schreiner, 1991).

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T cell subsets in glomerulonephritis

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T cell subsets in glomerulonephritis

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T cell subsets in glomerulonephritis

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