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Invited Review

Human IgA nephritis: immunocytochemical evidence of a chronic inflammatory proliferative disorder

K. Yoshioka and S. Maki
Department of Pediatrics, Kinki University School of Medicine, Osaka-sayama, Japan

Summary. This overview summarizes recent information concerning the biopathology of mesangial cell proliferation and matrix expansion which constitute fundamental features in human IgA nephritis. The currently available knowledge, mainly stemming for immunohistochemical observation of human materials, experimental investigations with laboratory animals, and mesangial cell culture studies, emphasizes the importance of cell to cell, cell to soluble factors, and cell to matrix interactions. Mesangial cells, activated by cytokines and growth factors, express adhesion molecules, stimulate proliferation both of themselves and neighbouring cells, and synthesize extracellular matrix. Matrix components, in turn, may influence the behaviour and proliferation activity of mesangial cells, or act as a receptor or reservoir for growth factors. Expression of protooncogenes, regulating cell proliferation and apoptosis, by glomerular cells could be associated with persistent cell replication and chronic tissue damage. These disease processes seem to be common to a group of diseases termed chronic inflammatory proliferative disorders.

Key words: IgA nephritis, Mesangial cell, Cytokine, Growth factor, Protooncogene

Introduction

IgA nephritis (IgA nephropathy or Berger's disease) (Berger and Hinglais, 1968) is recognized worldwide as the most common form of primary glomerulonephritis in children, adolescents and adults (D'Amico, 1987). The clinical manifestations of this disease vary, ranging from macroscopic hematuria coinciding with an upper respiratory infection to nephrotic syndrome with or without hypertension, but is often asymptomatic (Silva and Hoggs, 1989). The prevalence of IgA nephritis largely depends upon the urinary screening program and biopsy policy. In those countries where renal biopsies are performed fairly routinely to diagnose asymptomatic hematuria and/or proteinuria, the frequency of this disease ranges from several percent to 50% or more (D'amico, 1987; Silva and Hoggs, 1989). High rates of incidence have documented especially in France, Spain, Italy, and Eastern Asia including Japan. Genetic factors and environmental influences may also contribute to the geographical differences in prevalence. The high frequency rate in Japan is certainly influenced by the urine screening system performed annually for all school children.

IgA nephritis is identified by the presence of dominant glomerular mesangial staining for IgA in the absence of systemic lupus erythematosus, Schönlein-Henoch purpura nephritis, or liver disease (D'Amico, 1987; Silva and Hoggs, 1989). Deposition of IgG, C3 and also rarely IgM may be present. The main morphological feature of this disease is mesangial cell proliferation in combination with increases in matrix components. The affected glomeruli may show crescents or focal or global sclerosis accompanying various degrees of tubulo-interstitial changes. The severity of these histological changes are good predictors of the progression of this disease (Silva and Hoggs, 1989). Prognosis of IgA nephritis was initially considered favourable, but recent surveys on the outcome of patients are unanimously emphasizing the slowly progressive nature of this disease. The frequency of endstage renal disease in adult series may be as high as 30%-50% after 10-20 years of follow-up (Silva and Hoggs, 1989).

This article reviews recent immunocytochemical and molecular evidence indicating that IgA nephritis has features of a chronic inflammatory proliferative disorder. The mechanisms of persistent mesangial cell proliferation and matrix accumulation are also discussed.

Triggers of mesangial injury

The etiology of IgA nephritis is still unknown although a quarter of a century has passed since Berger and Hinglais first described this disease (Berger and

Offprint requests to: Dr. Kazuo Yoshioka, M.D., Department of Pediatrics, Kinki University School of Medicine, 377-2 Ohno-highashi, Osaka-sayama 589, Japan

Hinglais, 1968). Patients with IgA nephritis seem to have abnormalities in the amounts of IgA produced and its chemical nature, and also tend to trap this immunoglobulin to the glomerular mesangium (Williams, 1993). The deposition of IgA in the glomeruli may be explained as an immune complex disease or an autoimmune disease (D'Amico, 1987; Silva and Hoggs, 1989). Certain viruses, bacteria, dietary components or self-components existing in the glomerulus are candidate foreign- or self-antigens (Silva and Hoggs, 1989; Montinaro et al., 1992), but their precise nature and role are only speculative. The intraglomerular depositon of IgA due to either trapping of circulating IgA immune complexes or interaction of circulating IgA with resident or «planted» glomerular antigens can trigger the elaboration of an array of chemoattractans by several mechanisms (Couser, 1990). The activation of complement pathways generates C5a (anaphylatoxin), a potent chemotactic peptide. Interaction of Fc region of immunoglobulins with the Fc receptors on the resident glomerular cells and infiltrating phagocytes stimulates the cells to release chemoattractants such as interleukin (IL)-8, monocyte chemotactic protein-1, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor (TNF), platelet-activating factor, and leukotriene B4.

Monocyte/macrophage infiltration

Leukocyte subset analyses in both human renal biopsy specimens and experimental renal diseases show that mononuclear and polymorphonuclear leukocytes infiltrate the glomeruli, and that they significantly contribute to glomerular injury (Shigematsu, 1970; Hook et al., 1987; Wilson, 1991). In IgA nephritis, monocytes/macrophages are the dominant celll types infiltrating glomeruli (Yoshioka et al., 1989a; Arima et al., 1991). There is a significant correlation between macrophage infiltration and the degree of proteinuria (Yoshioka et al., 1989a; Arima et al., 1991). Cytokines, growth factors, oxigen radicals, proteolytic enzymes, and autacoids, released by infiltrating monocytes/macrophages, may induce cell damage directly, alter glomerular hemodynamics, promote mesangial cell proliferation, and stimulate matrix production by resident glomerular cells..

Increased numbers of both $CD4^+$ and $CD8^+$ T cells have also been found in glomeruli of patients with IgA nephritis, but T cells tend to be located in periglomerular and interstitial areas (Li et al., 1990). The $CD4^+/CD8^+$ ratio varies, depending on disease activity and chronicity. In IgA nephritis, the presence of T cells correlated with renal function and the activity of glomerular crescents (Li et al., 1990).

Adhesion molecules

Under physiological conditions, random contact between leukocytes and vascular endothelial cells does not produce adhesion. Adhesion occurs via specific interactions of leukocyte adhesion molecules with counter-receptors on endothelial cells. Major leukocyte adhesion molecules include selectins, carbohydrate-containing selectin ligands, integrins, and immunoglobulin (Ig) superfamily (Brady, 1994). The initial adhesion («rolling») of circulating leukocytes to endothelial cells is facilitated by interaction of selectins with their ligands, and further tight adhesion («immobilization») is mediated by interaction of leukocyte integrins, very late activation antigen-4 (VLA-4) and lymphocyte function-associated antigen (LFA-1) with Ig superfamily, intercellular adhesion molecules-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), on endothelium (Pober and Cotran, 1990).

ICAM-1 is constitutively expressed at low levels by glomerular endothelial cells, mesangial cells, and parietal epithelial cells, and has been reported to be frequently up-regulated in murine autoimmune lupus nephritis and proliferative types of human nephritis including IgA nephritis, crescentic glomerulonephritis, and lupus nephritis (Bishop and Hall, 1989; Wuthrich et al., 1990; Muller et al., 1991; Briscoe and Cotran, 1993). Recent studies of leukocyte-endothelial adhesion in experimental nephritis have indicated that there are selective requirements for adhesion molecules (Mulligan et al., 1993; Brady, 1994). In neutrophils and complement-dependent anti-glomerular basement membrane (GBM)-induced acute nephritis in rats, VLA-4, ICAM-1, and macrophage-1 (Mac-1) are important for full development of injury. ICAM-1 has as its ligands members of the ß2 integrin family; LFA-1, expressed on most leukocytes; and Mac-1 expressed by polymorphonuclear cells and macrophages (Pober and Cotran, 1990).

The potential of ICAM-1 as a target for intervention in inflammatory renal diseases has been tested in experimental models of glomerulonephritis, tubulointerstitial nephritis, and renal allograft rejection. Treatment of animals with anti-ICAM-1 monoclonal antibody alone or in combination with anti-LFA-1 monoclonal antibody, prior to induction of disease, clearly attenuated glomerular injury (Kawasaki et al., 1993; Nishikawa et al., 1993). In rat crescentic nephritis, antibody treatment, even when instituted after the disease was established, retarded progression of the disease (Kawasaki et al., 1993), implying that such antibodies may be clinically useful as new therapeutic tools for human nephritis.

Integrins are a family of related proteins that are composed of α and ß chains, and participate in contact between cells and the extracellular matrix. At least eight distinct ß chains noncovalently linked to fifteen different α chains with different ligand specificities have been identified (Ruoslahti et al., 1994): ß1 integrins participate mainly as cell membrane receptors for extracellular matrices (ECM); α1ß1, α2ß1, and α3ß1 are capable of mediating the binding of cells to more than one matrix component (type IV collagen, laminin, etc.);

and α5ß1 and α6ß1 favour fibronectin and laminin, respectively, as a ligand. Previous studies have established the preferential localization of ß1 integrins in the human kidney (Kerjaschki et al., 1989; Korhonen et al., 1990). α1ß1, α2ß1, and α3ß1 are distributed in mesangial cells, and α3ß1 is also present on the glomerular endothelial and epithelial cells. In proliferative types of human glomerulonephritis, including IgA nephritis, expression of ß1 integrins and αvß3 (vitronectin receptor) is augmented in the mesangium (Kerjaschki et al., 1989). The functional role of integrins is difficult to demonstrate *in vivo*, but it is assumed that overexpression of ß1 integrins and αvß3 are responsible for firm cell-matrix adhesion (Roth et al., 1993), ECM accumulation, and trapping terminal complement complex, S-protein (vitronectin)-C5b-9 (Okada et al., 1993).

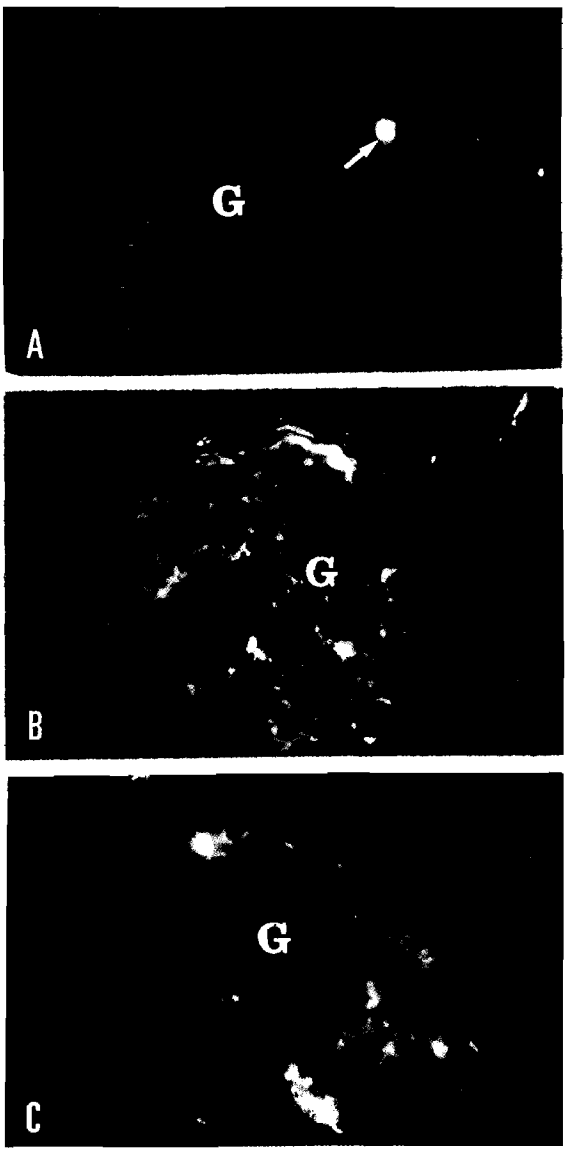

Fig. 1. Glomerular expression of IL-1α **(A)**, TNF-α **(B)**, and TGF-ß **(C)** in IgA nephritis, detected by immunofluorescence. Note cytoplasmic staining for IL-1α (A, arrow), glomerular resident cell staining for TNF-α (B), and mesangial staining for mature form of TGF-ß (C). G: glomerulus. x 400

Proinflammatory cytokines

Cytokines are polypeptides secreted by specific cells which act as growth promoters and biological modifiers. IL-1, IL-6, IL-8, and TNF-α are major cytokines which initiate immunological and inflammatory events. These proinflammatory cytokines can be produced by infiltrating monocytes/macrophages or mesangial cells themselves. IL-1 and TNF-α share some biological properties (Baud et al., 1992; Sedor et al., 1992); both stimulate mesangial cells to generate IL-6 and IL-8, induce the formation of oxygen radicals by mesangial cells, enhance tissue factor expression by endothelial and mesangial cells, and promote the synthesis of the vasodilator prostaglandin E2.

IL-1 is a co-mitogen for cultured mesangial cells (Sedor et al., 1992). Rat IL-1 enhances the rate of proliferation of mesangial cells only in the presence of serum or other growth factors such as fibroblast growth factor (FGF). TNF-α can either enhance or inhibit growth of cultured mesangial cells, whose effects appear to be influenced by the endogenous prostaglandin production (Baud et al., 1992). IL-6 is another cytokine that mediates proliferative glomerular diseases. Rat mesangial cells in culture can synthesize IL-6 and proliferate in response to IL-6 (Horii et al., 1989). Immunoreactive IL-6 has been detected in mesangium, parietal epithelial cells, synechiae, damaged tubular epithelium, and arterial muscle cells in human mesangial proliferative glomerulonephritis (Fukatsu et al., 1991). Our own data (Yoshioka et al., 1993a,b; Takemura et al., 1994) indicate a more restricted distribution of IL-6, and that monocytes/macrophages are a major source of glomerular IL-6. Mice transgenic for IL-6 have been shown to develop plasmacytosis and mesangial proliferative glomerulonephritis (Suematsu et al., 1989). On the other hand, SCID mice transgenic for IL-6 lack mesangial proliferation, suggesting other immunological factors in addition to IL-6 are necessary to induce mesangial cell proliferation. Urinary excretion of IL-6 is increased in the active phase of IgA nephritis and lupus nephritis, possibly reflecting the presence and severity of mesangial proliferation (Horii et al., 1989; Dohi et al., 1991; Iwano et al., 1993). In addition to its mesangial origin, excretion from tubular epithelial cells might also contribute to urinary IL-6 level (Fukatsu et al., 1993).

Using immunofluorescence and immunoperoxidase-*in situ* hybridization double-labelling techniques, we recently demonstrated the concurrent expression of IL-1α, IL–1ß, IL-6, IL-8 and TNF-α in glomeruli of patients with IgA nephritis (Yoshioka et al., 1993a,b). IL-1α (Fig. 1A), IL-6, and IL-8 were expressed dominantly by monocytes-macrophages infiltrating glomeruli rather

than resident glomerular cells. TNF-α was expressed by resident glomerular cells (Fig. 1B) and infiltrating leukocytes (Yoshioka et al., 1993b). The number of IL-1α, IL-6, and TNF-α positive cells infiltrating glomeruli showed a significant correlation with mesangial hypercellularity. The frequency of IL-8- and TNF-α positive intraglomerular cells and that of IL-1α-, Il-6, Il-8-, and TNF-α positive interstitial cells were significantly associated with histological changes in glomeruli and interstitium, respectively. IL-8 is a chemoattractant for lymphocytes as well as neutrophils (Matsushima et al., 1992). Thus, IL-8 may play a role in the infiltration of neutrophils and T cells, which are occasionally found in tissues of patients with IgA nephritis (Kincaid-Smith et al., 1989; Li et al., 1990).

Growth factors

The role of growth factors in mesangial cell proliferation and tissue remodelling have been well studied in experimental nephritis and also in materials biopsied from patients. Evidence indicates that platelet-derived growth factor (PDGF) (Johnson et al., 1993) and transforming growth factor-ß (TGF-ß) (Border et al., 1992) are factors crucial for mesangial cell proliferation and matrix accumulation

PDGF is a 30 kD cationic protein consisting of two disulphide-bonded chains existing as a homodimer (PDGF-AA or PDGF-BB) or as a heterodimer (PDGF-AB). PDGF is stored in the alpha granules of platelets, and released into the extracellular environment following activation of the platelets by various stimuli. PDGF is also synthesized by many other cell types, including macrophages, glomerular mesangial cells, renal microvascular endothelial cells, and smooth muscle cells. PDGF induces mesangial cell proliferation through autocrine and paracrine mechanisms. In addition to its potent mitogenic effect, PDGF possesses other biological activities suh as chemoattraction, inflammatory cell activation, and vasoconstriction (Johnson et al., 1993). Studies from several laboratories have indicated that PDGF is involved in mesangial proliferation in both animal models and human IgA nephritis. Johnson and co-workers (Iida et al., 1991; Johnson et al., 1992) have demonstrated a crucial role of PDGF for mesangial proliferation in rat anti-Thy 1 nephritis, which has certain morphological similarities with human IgA nephritis in its proliferative phase. Increased expression of PDGF protein and PDGF-B chain mRNA was observed in mice with IgA nephritis induced by immunization with anionic and cationic dextrans, or dextran sulphate (Gesualdo et al., 1991), or in rats with Habu snake venon-induced glomerulo-nephritis (Barnes and Abboud, 1993). PDGF protein and PDFG-B-chain mRNA were also demonstrated in the mesangium of patients with IgA nephritis (Gesualdo et al., 1991; Waldherr et al., 1993).

TGF-ß is a multifunctional regulator of cell growth and functions (Roberts and Sporn, 1990). TGF-ß is secreted by various types of cells, mostly in a latent form which is composed of three components; mature (functionally active) TGF-ß, latency associated peptide

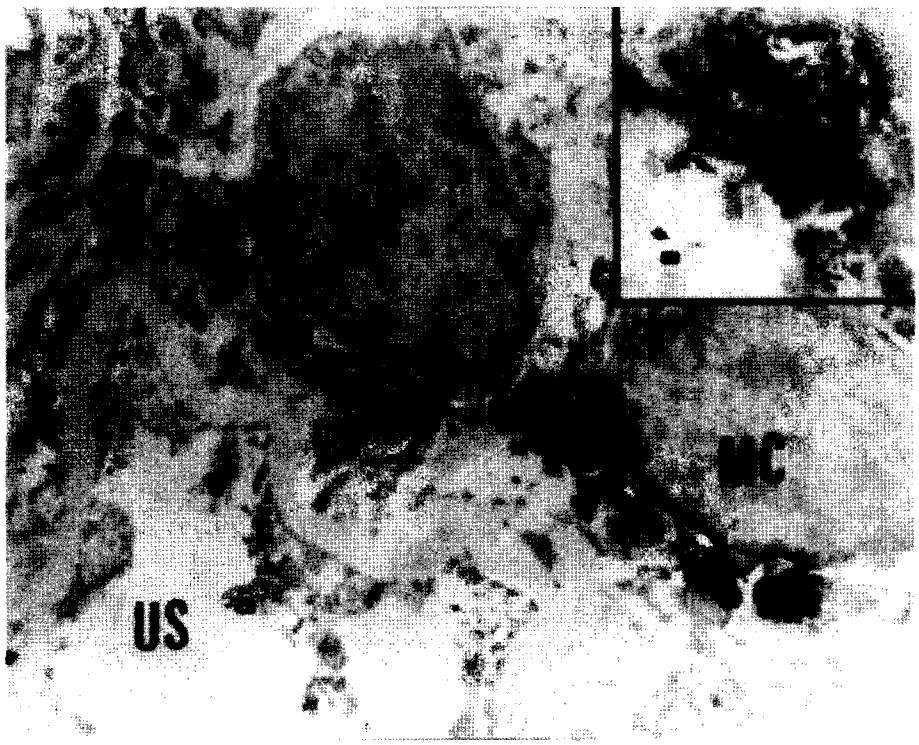

Fig. 2. Immunoelectron microscopic observation of type III collagen within the glomerular mesangium in a patient with IgA nephritis, stained with monoclonal antibody to type III collagen and peroxidase-labelled secondary antibody. The reaction products were distributed in the mesangial area **Inset:** a higher magnification. The reaction products are shown by arrows. MC: mesangial cell. US: Urinary space. x 5,000 (inset, x 10,000).

(LAP), and latency-associated peptide binding protein (Miyazono and Helden, 1991). Mature TGF-ß can be cleaved and activated *in vitro* by heat, proteolytic enzymes, low or high pH, and denaturation with chemical agents. Glomerular mesangial cells and possibly epithelial cells can express TGF-ß. Platelets and monocytes/macrophages, both of which are high-level sources of TGF-ß, are often found within nephritic kidneys. TGF-ß stimulates the synthesis of collagen, fibronectin, and proteoglycans in cultured mesangial cells. Our immunocytochemical studies in human IgA nephritis have shown that mature TGF-ß (Fig. 1C) and TGF-ß LAP are localized in association with matrix components of GBM or mesangium, and within immune deposits, and that mesangial staining for TGF-ß LAP protein shows a significant correlation with increase in the mesangial matrix (Yoshioka et al., 1993a). Waldherr et al. (1993) reported increased TGF-ß immunoreactivity in mesangium, blood vessels, and interstitium in IgA nephritis. *In situ* hybridization studies (Waldherr et al., 1993; Yoshioka et al., 1993a) further confirmed TGF-ß mRNA expression by glomerular resident cells, rather than by infiltrating monocytes/macrophages.

Experimentally, infusion of recombinant PDGF-BB into rats which had received a subnephritogenic dose of anti-Thy 1 antibody, induced mesangial cell proliferation along with increased ECM deposition (Floege et al., 1993). Administration of anti-PDGF and anti-TGF-ß antibodies or an inhibitor (decorin) of TGF-ß to rats with anti-Thy-1 nephritis suppressed mesangial cell proliferation and matrix increase, respectively (Border et al., 1990; Border and Ruoslahti 1992; Johnson et al., 1992). Recent studies by Isaka et al. (1993), using the *in vivo* gene transfection technique, more directly demonstrated their role in glomerular cell proliferation and progression of glomerulosclerosis.

Epidermal growth factor (EGF), insulin-like growth factor (IGF)-I and basic FGF also have mitogenic effects on cultured mesangial cells (Floege et al., 1993b). Although EGF and its receptor are immunolocalized to the glomerular endothelial cell surface in normal and nephritic human kidneys, little is known at present concerning the *in vivo* effects on mesangial cells (Yoshioka et al., 1990b). Mice transgenic for IGF-I did not develop glomerular lesions or glomerular hypertrophy (Doi et al., 1990). Recent studies using the anti-Thy-1 model have shown the capability of basic FGF to mediate mesangial proliferation (Floege et al., 1993a).

Protooncogenes

Protooncogenes, cellular homologues of oncogenes, have been implicated in the control of normal cell proliferation and differentiation (Bishop, 1983). One class of protooncogenes including *c-myc*, *c-max*, *c-fos*, and *c-jun* encode nuclear proteins (Weinberg, 1985). Mitogenic stimuli such as growth factors and phorbol acetate, activate signal transduction pathways that induce expression of these genes. *c-myc*, *c-max*, *c-fos* and *c-jun* have been identified as immediate early genes in several in vivo models of cell proliferation. The complex of *c-myc* and *c-max*, and that of *c-fos* and *c-jun* (activator protein-1 complex) promptly stimulate quiescent cells to switch from the G0 phase entering the G1 stage of the cell cycle. The other group of protooncogenes of which protein products act in the cytoplasm includes *c-raf*, *c-ras*, and *c-mos* (Weinberg, 1985). These regulate the second messenger molecules in the cytoplasm. overexpression of protooncogenes such as *c-myc*, *c-raf*, *c-fos*, and *c-jun* have been detected in peripheral mononuclear cells from patients with lupus nephritis (Boumpas et al., 1986) and IgA nephropathy (Ebihara et al., 1991). We recently identified and localized cells expressing *c-myc*, *c-fos*, and *c-raf* mRNA and their protein products in glomeruli of patients with IgA nephritis (Takemura et al., 1993). The frequency of protoncogene-positive cells showed a strong correlation with the population of glomerular cells positive for proliferating cell nuclear antigen and increases in mesangial cells and matrix. These results indicate that

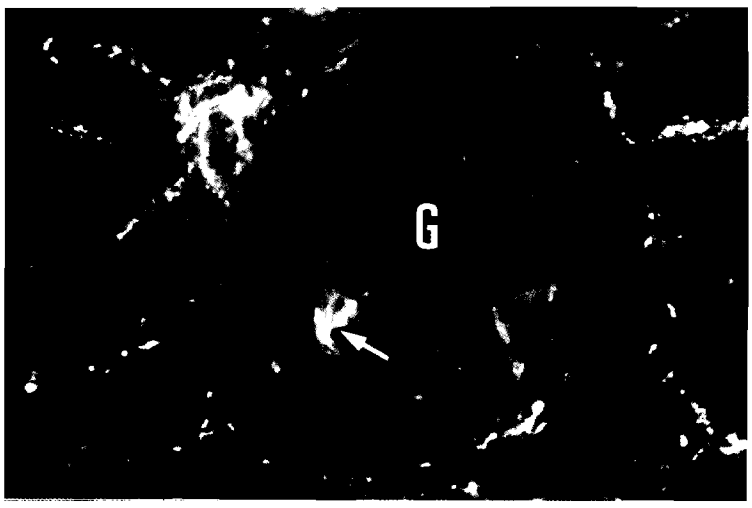

Fig. 3. Immunofluorescent staining for α-smooth muscle actin isoform in IgA nephritis. Segmental glomerular staining (arrow) and expression by interstitial cells are seen. G: glomerulus. x 400

Table 1. Chronic inflammatory proliferative disease (Hirano, 1994)

Characteristics	
Chronic inflammation	
Immune response	
Proliferation of tissue-specific cells	
Matrix accumulation	
Proliferating tissue-specific cells -	***Typical diseases in humans***
Mesangial cell	Mesangial proliferative Glomerulonephritis (IgA nephritis)
Synovial cell	Rheumatoid arthritis
Vascular smooth muscle cell	Atherosclerosis
Keratinocyte	Psoriasis
Participants	
Leukocytes (monocytes/macrophages, T cells, polymorphonuclear cells), platelets	
Adhesion molecules	
Cytokines	
Growth factors	
Protooncogenes	
Extracellular matrix	

protooncogene expression is associated with glomerular cell proliferation and matrix increase in IgA nephritis.

Apoptosis

«Apoptosis» or «programed cell death» is a tightly controlled mechanism of cellular self-destruction. It has become clear that cell death through this process is crucial to cell proliferation and differentiation in the fields of immunological tolerance, embryology, infection, and oncology. Cells undergoing apoptosis are characterized by a cascade of genetic and biochemical events that cause cell shrinkage, cytoplasmic condensation, cleavage of chromosomal DNA, and formation of apoptotic bodies. Apoptotic cells/bodies are cleared by phagocytosis by macrophages or neighbouring cells in epithelia and tumors. Depending on the cell type, apoptosis can be initiated by either steroid hormones, irradiation or TNF-α, and inhibited by IL-1 and endotoxins. Certain proto-oncogenes modulate apoptosis. For instance, *p53* and *bcl-2* have been shown to be an inducer and suppresser of apoptosis, espectively (Cohen, 1993). It is possible that apoptosis is a part of a remodelling process relevant to glomerular injury. A previous study by Harrison (1988) showed that apoptotic cells are present within the glomeruli of patients with various types of nephritis, especially in those infiltrated by neutrophils. In rats with anti-Thy-1 nephritis, proliferating mesangial cells seem to undergo apoptosis in the resolving phase (Shimizu et al., 1993). On the other hand, defective regulation of apoptosis might be linked to prolonged tissue injury. We very recently detected *bcl-2*-expressing glomerular cells in patients with progressive type of IgA nephritis (Yoshioka, K., unpublished observation). *Bcl-2* is known to contribute to oncogenesis by promoting tumor cell longevity and inducing resistance to anti-cancer drugs (Korsmeyer, 1992). We speculate that suppression of apoptosis by *bcl-2* or other unknown factors may represent a new mechanism by which both infiltrated leukocytes and intrinsic glomerular cells survive in diseased kidney, leading to delayed healing of inflammation.

Accumulation of extracellular matrix

Glomerular ECM accumulation seems to be a final common pathway to glomerular destruction in a variety of glomerular diseases. Immunohistochemical studies in human chronic forms of glomerulonephritis (Yoshioka et al., 1987a,b, 1989b; Oomura et al., 1989) and relevant animal models (Ebihara et al., 1993) have shown that: (1) normal ECM components are overexpressed, due to either increased synthesis (Okuda et al., 1990; Floege et al., 1991; Nakamura et al., 1991; Ebihara et al., 1993) or imbalance between matrix proteases and their inhibitors (Jones et al., 1992; Nakamura et al., 1993), or both; and (2) ECM molecules, such as type I and III collagens, normally undetectable in the glomerulus, participate in the sclerotic process (Ebihara et al., 1993; Minto et al., 1993). These alterations seem to be common to various types of glomerular diseases, except for passive Heymann nephritis (Fogel et al., 1991). In both immune- and non-immune-mediated glomerulonephritis, major normal ECM components, including type IV collagen, laminin, and fibronectin, and also minor components such as tenascin, are accumulated in expanded mesangium and glomerular crescents (Yoshioka et al., 1987a,b; Oomura et al., 1989; Truong et al., 1994). Type I and III collagens, due to *de novo* synthesis by intrinsic glomerular cells (Ebihara et al., 1993; Minto et al., 1993) or migration from interstitium through damaged basement membrane of the Bowman's capsule into glomeruli (Wiggins et al., 1993; Striker et al., 1984), are also deposited in the glomerulus.

The process of glomerular accumulation of ECM is affected by a variety of factors that are active either at the level of ECM generation or removal. Soluble mediators (IL-1, PDGF, IGF-1, and basic FGF) from either infiltrating inflammatory cells or resident glomerular cells may directly stimulate ECM production by mesangial cells, or induce the synthesis of matrix degrading enzymes, matrix metalloproteases and plasminogen activators, and their respective inhibitors, tissue inhibitors of metalloproteases and plasminogen inhibitors (Border and Ruoslahti, 1992; Sedor et al., 1992; Floege et al., 1993a,b). Accumulated ECM may in turn influence glomerular cell behaviour; experimental evidence from cell and organ culture models indicates a variety of cellular responses to ECM; adhesion and spreading, changes in cytoskeleton and cell shape, induction of polarity and differentiation, stimulation of proliferation and migration, induction of proteases, and platelet migration (Sterzel et al., 1992).

Phenotypic transformation of mesangial cells

Intrinsic mesangial cells act as a framework within the glomerular tuft, a cellular source of growth factors and cytokines, and a modulator of glomerular hemodynamics. They also synthesize and secrete ECM components. After exposure to a variety of stimuli such as immune complexes, complement components and proinflammatory cytokines, they undergo striking phenotypic transformations. Mesangial cells upon various types of experimental glomerular injury such as anti-Thy-1 nephritis (Johnson et al., 1991; Alpers et al., 1992), aminonucleoside nephrosis with glomerular sclerosis (Ebihara et al., 1993), 5/6 nephrectomy (Floege et al., 1992), and streptozotocin-induced diabetes (Fukui et al., 1992), express *de novo* types I and III collagen, α-smooth muscle actin (Alpers et al., 1992; Johnson et al., 1991), and embryonic type myosin isoform (SMemb) (Kuro-o et al., 1991), although the expression of these molecules by mesangial cells are normally repressed and undetectable in normal glomeruli by immunohistochemical means. Temporal analysis of ECM expression in the puromycin nephrosis model of focal and segmental glomerulosclerosis indicated that the expression of normally expressed ECM components is enhanced with time, and that there is a delayed *de novo* expression of types I and III collagen, not normally found within the glomeruli (Ebihara et al., 1993). In human IgA nephritis, appearance of type III collagen (Yoshioka et al., 1989b) (Fig. 2), α-smooth muscle actin (Fig. 3) and SMemb (Kimura et al., 1993) within mesangium parallels mesangial expansion. Type I collagen tends to emerge in sclerotic glomeruli at the advanced stage (Yoshioka et al., 1990a). Certain cytokines and transcription factors might be responsible for phenotypic modulation, but detailed mechanisms are unclear.

Chronic inflammatory proliferative disorder

Although not in general use, the term «chronic inflammatory proliferative disorder (CIPD)», was originally introduced by Hirano (1994) to describe a set of diseases characterized by (1) chronic infiltration of inflammatory cells, (2) provocation of immune response, and (3) persistent proliferation of a tissue-specific cell type (Table 1). This disease process accompanies the participation of a variety of mediators such as adhesion molecules, cytokines and growth factors. Expression of protooncogenes and accumulation of extracellular cellular matrix are also observed. CIPD typically includes rheumatoid arthritis, atherosclerosis, and psoriasis, where the dominant proliferating tissue-specific cell types are synovial cells, vascular smooth muscle cells, and keratinocytes, respectively (Hirano, 1994). Mesangial proliferative IgA glomerulonephritis may also be a CIPD due to the pathologic features described above.

In CIPD, details of why cell proliferation persists are still unclear. Future studies to elucidate the regulatory mechanisms of cell replication and cell death at the molecular level are awaited. The development of manoeuver to control cell growth *in vivo* will introduce a novel way to the treatment of chronic kidney inflammation.

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