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Glomerular Injury: Current Topics and Understanding

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Summary. **As is widely accepted, most of glomerulonephritic renal diseases arise from abnormal immunologic processes. Current problems and understanding of the mechanisms underlying the glomerular injury are the focus of this review. Data gathered in the last few years have changed the old view of the kidney as an "innocent bystander". The kidney is a more active contributor to glomerular immune reactions than previously realized. This line of research conducted at our institute is introduced and open to the discussion.**

Introduction

It is still widely accepted that most of glomerulonephritic renal diseases arise from abnormal immunological processes. Immunofluorescent studies have provided important suggestions of mechanisms in renal diseases. By immunofluorescence (IF) microscopic patterns, glomerular diseases can be classed as either an anti-glomerular basement membrane (GBM) disease or circulating immune complex (CIC) nephritis, based on classical investigations of experimental glomerulonephritis (GN) models of Masugi nephritis (nephrotoxic nephritis) and serum sickness nephritis.[1,2] The former shows a distinctly diffuse linear pattern, due to binding of circulating antibodies to GBM. Until recently, it was believed that a granular pattern of localization of immune reactants (immunoglobulins and complements) were caused by conducting glomerular deposition of the CIC. However, pathogenetic mechanisms cannot be explained so simply. Fig. 1 shows typical IF patterns for linear (Fig. 1a) and granular (Fig. 1b) depositions of autologous immunoglobulins. According to the classical view, the anti-GBM antibody is possibly involved in the pathogenesis of the former, linear deposition whereas the latter, granular one may be induced by the deposition of CIC. However, what were actually observed from photos were different phases (Days 1 and 7 following the start of GN) of cationic antigen-induced GN[3] in which a mechanism differing from that of anti-GBM antibody and CIC mediation is involved.

In most human cases, the pathogenetic antigens involved in immune complex GN are virtually unknown. It is only a speculation that the autologous antibody and complements in glomeruli in a granular pattern detected by IF should be immune complexes (IC) formed in the circulation. There is increasing evidence that IF data do not adequately indicate the following pathogenesis: a linear pattern indicates anti-GBM mediation and a granular pattern, CIC. In this paper, assessment is made on recent studies including our own that have changed classical views of the pathogenesis of immune complex glomerulonephritis (ICGN).

Glomerular Capillary Wall As a Size and Charge Barrier

The total net-charge or electrical polarity of macromolecules has great influence on their localization in the glomerular capillary wall, which is comprised of a filamentous network of polyanionic glycoproteins. The staining of GBM with cationic dyes[4,5] and tracer studies using electron dense macromolecules such as cationized ferritin[6] have been conducted to examine morphologically the functions of the GBM not only as a size barrier, but also as a charge-selective barrier for large circulating molecules.[7] The cationic dye, polyethyleneimine (PEI) is a suitable cationic probe for determining the anionic sites of GBM.[8-10] As shown in Fig. 2, PEI particles showing the anionic sites are distributed at

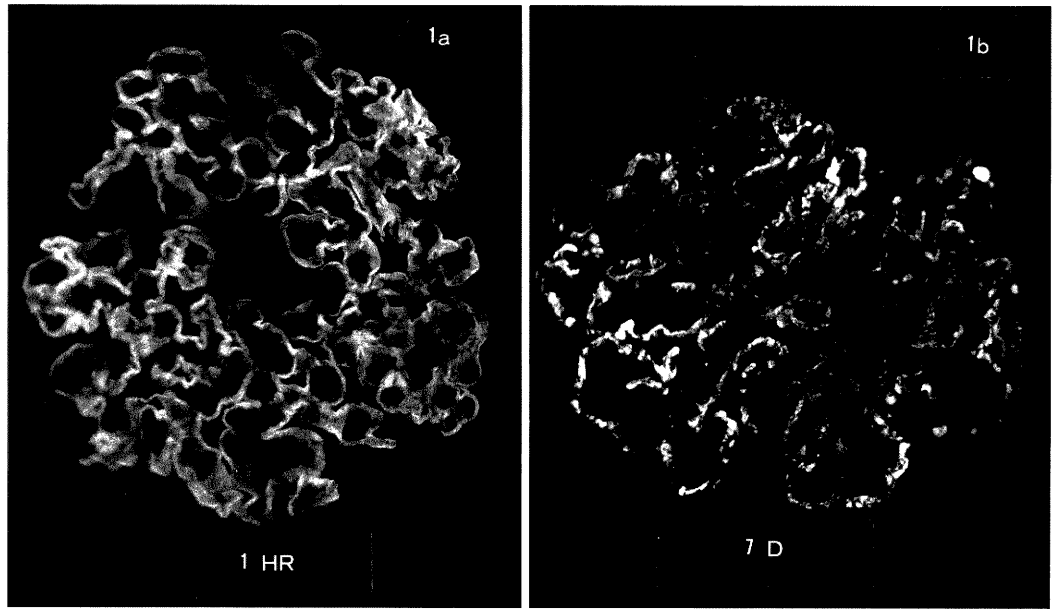

Fig. 1. Cryostat sections of rat glomeruli. One hundred ug of cationized human IgG was perfused via the left renal artery of a rat preimmunized with human IgG. (a) At 1 hr, stained with FITC labeled anti-rat IgG. Glomerular localization was seen in a deffuse pattern along the capillary wall. (b) On day 7, stained with FITC labeled anti-rat IgG. Discrete granular deposition of rat IgG was seen along the capillary wall.

regular intervals along the lamina rarae interna and externa. Occasionally aggregated PEI particles appear at the slit pores and on the surface of epithelial foot processes. An ultrastructural study using cationized ferritin in combination with the PEI stain indicated that the initial binding site of cationized ferritin injected intravenously is on the subendothelial side of GBM, corresponding to anionic sites in the lamina rara interna (Fig.3). The presence of anionic sites has been reconfirmed by a simple model in which the prior application of a low molecular weight polycation, protamine sulfate, inhibits binding of the cationic antigen to the glomerular polyanion.[11]

Cationic probes may also be used to investigate size restriction since they are not subject to electric repulsion when encountering polyanions.[12] The monomer and dimer of cationized ferritin penetrated the lamina densa whereas polymer did not, although it could readily enter the lamina rara interna. Also, a study using other naturally occurring size isomers of lysozyme and ribonuclease, prepared by chemical cross-linking indicated the persistence of cationic macromolecules to largely depend on their molecular weight. IF showed more intense staining along the glomerular capillary when injected with a dimeric or trimeric cationized lysozyme. These findings demonstrate the lamina densa to be a size restrictive barrier where cationic molecules with a Stokes-Einstien radius exceeding a value between 7 to 12 nm are excluded.[12,13]

Immune Complex Formation and Pathogenesis of Glomerulonephritis

Table 1 lists various types of immunologically induced glomerular injuries.[14] At about 1980, we took special attention to two basic forms of antibody-

Table 1. Immunological Mechanisms in Glomerulonephritis

I. Antibody-Mediated Mechanisms
  A. Deposition of circulating immune complexes
    Exogenous antigens (e.g., serum sickness; postinfectious GN)
    Endogenous antigens (e.g., DNA in lupus nephritis; tumor antigens)
  B. *In-situ* immune deposit formation
    1. Antiglomerular basement membrane antibody (Anti-GBM)
    2. Other fixed antigens (e.g., Heymann nephritis)
    3. Planted antigens
II. Activation of the Alternate Complement Pathway (e.g., membrano-proliferative GN)
III. (?) Cell-Mediated Immune Mechanisms

mediated glomerular injury, anti-GBM and CIC-associated damage. Injury resulting from the deposition of CIC has been investigated by the models of serum sickness,[15-18] and Masugi nephritis. Clarification was made by several mechanisms of antibody-dependent glomerular injury.[19-23] Limited space does not permit their discussion here. As described above, IF patterns of immune reactants in glomeruli do not always reliably indicate the pathogenesis of GN. Evidence for this is as follows: first, in many patients with membranous GN, showing homogenous, granular deposits by IF and subepithelial deposits by electron microscopy (EM), it is not possible to detect CIC in the serum even by various techniques.[14] Secondly, injections of preformed immune complexes except of cationic immune complexes were found incapable of inducing membranous GN in experimental animals, in which preformed immune complexes were deposited in mesangium or subendothelial spaces.[14] These findings, however, cannot be taken as direct evidence that other mechanisms are responsible for inducing the immune complex GN.

That immune complexes may be formed locally, i.e., "in situ", is a concept originating more than 75 years ago. For example, the early researchers considered that antigen-antibody reaction took place at the site of tissue damage,[24] and also, there was the autologous phase of Masugi nephritis.[25] Research on glomerular immune aggregates has indicated the possibility of in situ immune complex formation. For instance, a lectin-induced GN model using concanavalin-A (Con A) in which Con A-sugar residues interact, followed by passive injection with a specific (anti-Con A) antibody, was found to give rise to immune complex formation quite close to the blood-endothelial interface.[26] In addition, the Heymann nephritis model has been found to apparently be a prototype of human membranous nephropathy, in which the cell-associated antigen, 330 kd of glycoprotein (gp 330), shared by glomerular and proximal tubular cells serves as a target for the circulating antibody, following by local immune complex formation.[27] Experimental models involving extrinsic antigens, particularly planted polycationic antigens, have been proposed to indicate the pathogenesis of a various GN with subepithelial immune deposits.[28] As described above, negatively charged components in the GBM act as a charge barrier. These fixed anionic sites also function as receptors for cationic substances subsequently to be planted, followed by local binding of the corresponding circulating antibody.[3,28] In this model, the in situ formation of an immune complex leads to a typical immune complex glomerulonephritis with heavy proteinuria.[3] Detailed quantitative studies show that severe GN with a proteinuria of at least 100 mg per 24 hours can be regularly induced on Day 1 or 2 following injection, when 4.0 ug of antigen and 31.9 ug of antibody are present in a diseased kidney.[3] The persistence of

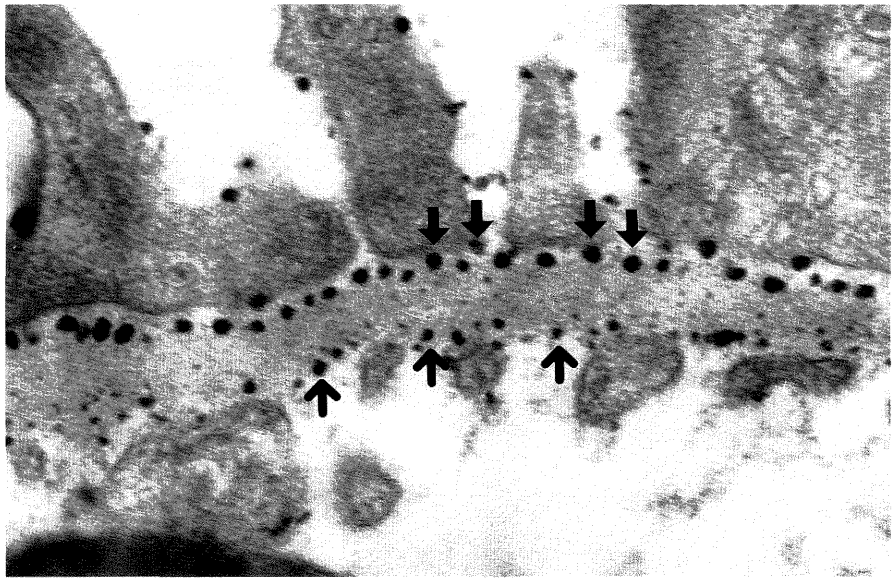

Fig. 2. A section of the glomerulus from a normal rat injected with PEI. PEI particles were distributed along the lamina rarae of the GBM and on the surface of epithelial foot processes. (×40,000)

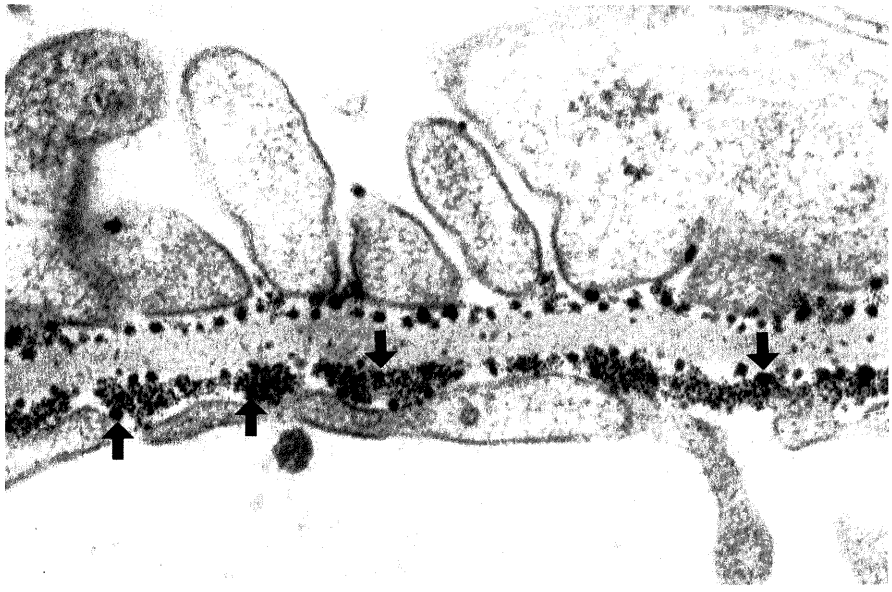

Fig. 3. A section of the glomerulus from a preimmunized rat 1 hr after renal perfusion with 500 ug of cationized ferritin. Most of ferritin aggregates were associated with the anionic sites of the lamina rara interna, detected with PEI (arrows). (×40,000)

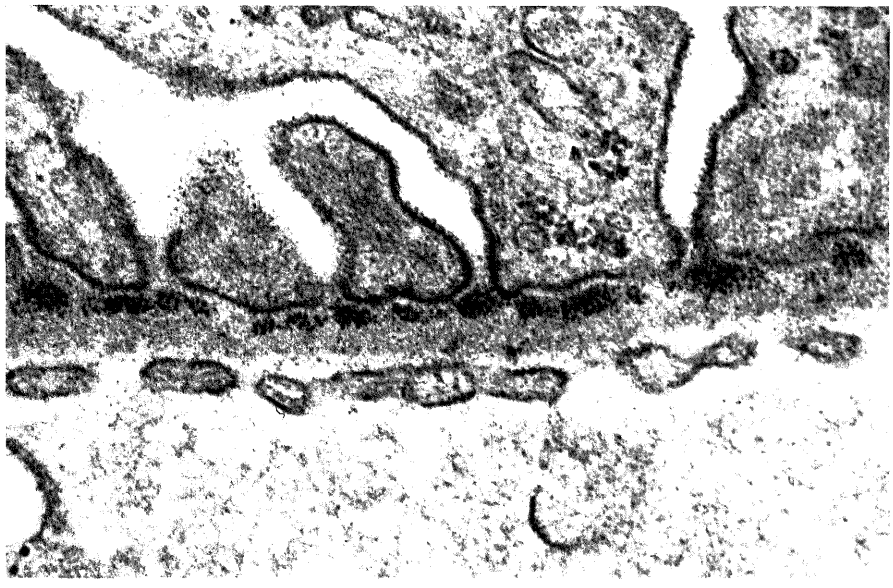

Fig. 4. A section of the glomerulus from a preimmunized rat 24 hr after renal perfusion with 500 ug of cationized ferritin. The ferritin aggregates were found subepithelially and intramembranously. (×40,000)

the cationic antigen in the diseased kidney is markedly prolonged when complexed with the antibody and 12 days are required for removing half the antigen from the kidney. Injection of microgram quantities of cationized antigen into the left renal artery of a preimmunized rat was found to result in a severe unilateral immune complex GN with heavy proteinuria (active model).[29,30] Renal perfusion with native antigen (isoelectric point, <8.5) failed to cause any damage whatever. In this active model, severe proliferative lesion with crescent formation were noted in 10-20% of the glomeruli. Adhesions of the

glomerular capillary loops to Bowman's capsule were commonly observed and with time, spike formation in the GBM became quite prominent. Immune deposits containing the cationic antigen, host antibody and complements appeared confluent along the glomerular capillary wall on the first 2 days and became granular during the course of the disease, as described above (Figs. 1a and 1b).

The site of immune complex formation and deposition, possibly differing according to the GN models, may be an important factor for determining the mediator and nature of glomerular injury. Devising our experimental model using cationic antigens was facilitated by an ultrastructural analysis of glomerular locations. From electron microscopic studies using cationized ferritin, the initial site of the in situ immune complex formation was found to be primarily on the subendothelial side of GBM, corresponding to anionic sites in the lamina rara interna (Fig. 3).[10,13,30] Local immune complex formation was followed by the infiltration of blood-born cells such as polymorphonuclear leukocytes and monocytes. Representatives of inflammatory mediator systems including complements, coagulation and cellular factors are easily accessible to immune reactants deposited on the subendothelial side of GBM through the fenestrated endothelium. Some monocytes were in direct contact with immune complexes containing ferritin aggregates associated with anionic sites of the lamina rara interna. With time, numerous ferritin aggregates came to be present suepithelially, preferentially beneath the slit membrane. However, the subepithelial location of ferritin did not always correspond to the anionic sites of the lamina rara externa (Fig. 4). The accumulation of macromolecules, including immune complexes, at this locus may possibly affect the point at which the foot process-slit diaphragms are attached to GBM.

Detailed qualitative and quantitative analyses of excreted urinary protein provide data essential for determining the nature of glomerular inflammation and the degree of injury. Electrophoretic patterns of urinary protein using SDS-polyacrylamide gel electrophoresis could be classed as either active in situ ICGN and Masugi GN (low selectivity group) or active Heymann GN and chronic serum siskness GN (high selectivity group).[31] These two groups correspond to diffrences in morphological expression such as proliferative changes rather than the degree of proteinuria. Salant et al. using transplant models found antigen distribution to influence the mediation and morphological features of glomerular injury.[31] They consequently chose Masugi GN and passive

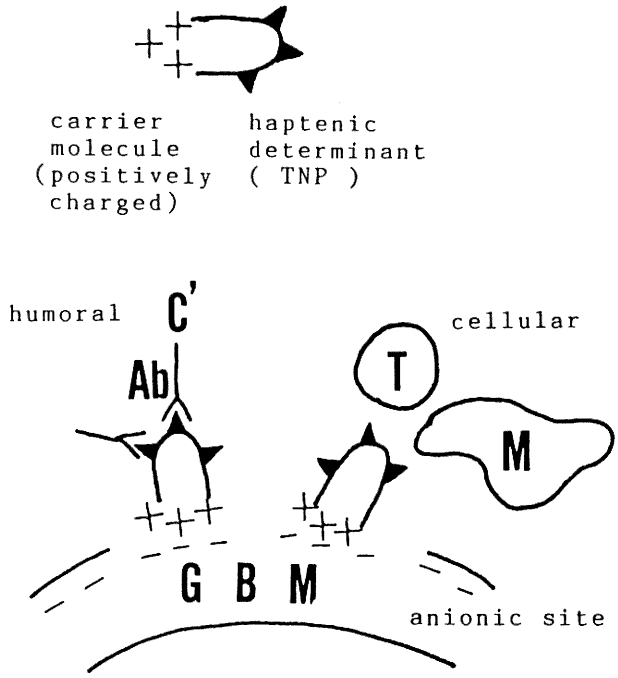

Fig. 5. Hapten-specific immune reaction producing glomerular injury.

Heymann GN as models induced by local immune complex formation on the subendothelial and subepithelial sides of GBM, respectively. The former model exhibits a cell-dependent injury, whereas the latter is cell independent.

The staining of GBM with cationic dyes, particularly PEI, as described above, was conducted to provide some morphological clarification of the functions and injury of the anionic sites of GBM in experimental animals and human GN.[9,10,33-35] However, the mechanisms of anionic site-injury associated with hyperpermeability through glomerular capillary walls still are not virtuallly understood.

Clarification of Immunological Mechanisms That Induce Glomerular Injury and Accumulation of Immune Deposits in Glomeruli at Molecular and Cellular Levels

We recently reported a new model of experimental GN in which a cell-mediated (delayed-type) reaction predominates (Fig. 5).[36] In general, macromolecules such as high molecular weight proteins are composed of complex, structural determinants and structural riquirements for antigenicity differ from those determining net charge.[37] Attachment of the hapten to a cationic carrier protein enables its plantation in the

glomerular capillary wall.[36,38,39] Cationized trinitrophenyl (TNP) bovine serum albumin (BSA) conjugates were planted in the glomerular capillary walls of rats previously sensitized intradermally with TNP in ethanol. Histologically, marked exudative and proliferative changes in glomeruli and cellular influx containing Ia-positive leukocytes were noted without any deposition of autologous immunoglobulins. Using this hapten-carrier system, the role of epitope density in cationic antigen can be investigated (Fig.5).[38,39] Rats preimmunized with TNP conducted endocapillary proliferative GN with proteinuria when being administered a high-valency antigen (TNP31. 3-cationized human IgG). In contrast, no significant abnomalities in renal histology or urinalysis could be found following the injection of a low-valency (TNP7.2-cationized human IgG) antigen. Electronmicroscopically, the kidneys of rats given the high-valency antigen showed marked subepithelial dense deposits with foot process retraction. This is in marked contrast to rats which after being given the low valency antigen, showed only small subepithelial electron dense deposits beneath the slit membrance. Epitope specificity and density on the cationic antigen is thus conducted to strongly influence the hapten-specific cellular immune response that leads to glomerular injury and subepithelial dense deposit formation.

Functional Molecules Associated with Glomerular Injury

The use of monoclonal antibodies greatly facilitates the elucidation of specific epitopes on intrinsic cells and the matrix associated with glomerular injury.[40,41] Glomerular injury with heavy proteinuria using two kinds of monoclonal antibodies (mAbs) has been reported in recent studies.[38,39] A single intravenous injection of mAb 5-1-6, produced by immunization with collagenase-treated rat glomeruli, was found to induce massive though transient proteinuria. The recognized antigenic molecule was present on the surface of glomerular epithelial foot process and around slit diaphragms. Linear binding along the glomerular capillary walls was recognized evident 2 hr following injection. Three days later, the immunofluorescent pattern shifted to a fine granular one. Rat IgG and C3 could not be detected during the period of observation. Another nephritogenic mAb, designated as 1-22-3, was recognized on the rat mesangial cell surface. Abnormal proteinuria started immediately following the injection of 500 ug of mAb injection. Glomerular histology indicated diffuse mesangiolytic lesions, similar to those of anti-Thy1-1 antibody induced glomerulopathy.[40,41] The mechanism of mesangiolysis does not involve the classical mediators of immune injury, as exemplified by Habu-venom induced glomerular lesions.[47,48] Investigations should be conducted into the possible mechanisms of structural and functional abnormalities using mAbs against glomerular, intrinsic components.

Concluding Remarks

Mechanisms for the initiation and progression of human glomerulonephritides remain unclear at present. As stated in the preface of the Proceedings of the Second Niigata Symposium of Nephrology, entitled "Cell Proliferation in the Renal Glomerulus and its Mechanism",[48] such clarification will doubtlessly prove difficult but essential for understanding the proliferative changes and prognosis of diseases from both basic and clinical points of view. This in turn will lead to greater understanding of the pathogenesis, clinical treatment and prevention of kidney diseases. Interest in the representative organ of microvasculature, "renal glomeruli", has been spurred by the enormous amount of biologic data obtained using modern techniques such as cell culture,[21,22,49,50] genetic engineering, immune EM and computer analysis. Data which will be accumulated over the last decade of the 20th century should serve greatly to promote study of glomerular diseases.

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