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Review Article

The Role of Nephritis-Associated Plasmin Receptor (NAPlr) in Glomerulonephritis Associated with Streptococcal Infection

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It is well known that glomerulonephritis can occur after streptococcal infection, which is classically referred to as acute poststreptococcal glomerulonephritis (APSGN). The pathogenic mechanism of APSGN has been described by so-called immune complex theory, which involves glomerular deposition of nephritogenic streptococcal antigen and subsequent formation of immune complexes *in situ* and/or the deposition of circulating antigen-antibody complexes. However, the exact entity of the causative antigen has remained a matter of debate. We isolated a nephritogenic antigen for APSGN from the cytoplasmic fractions of group A streptococcus (GAS) depending on the affinity for IgG of APSGN patients. The amino acid and the nucleotide sequences of the isolated protein revealed to be highly identical to those of reported plasmin(ogen) receptor of GAS. Thus, we termed this antigen nephritis-associated plasmin receptor (NAPlr). Immunofluorescence staining of the renal biopsy tissues with anti-NAPlr antibody revealed glomerular NAPlr deposition in essentially all patients with early-phase APSGN. Furthermore, glomerular plasmin activity was detected by *in situ* zymography in the distribution almost identical to NAPlr deposition in renal biopsy tissues of APSGN patients. These data suggest that NAPlr has a direct, nonimmunologic function as a plasmin receptor and may contribute to the pathogenesis of APSGN by maintaining plasmin activity.

1. Introduction

Acute poststreptococcal glomerulonephritis (APSGN) develops after streptococcal infection with the obvious latent period of around 10 days. It is mostly accompanied by decrement in serum complement titer and glomerular deposition of C3 and IgG. From these characteristic manifestations, it has been widely accepted that the immunological reaction against streptococcus related antigens is engaged for the initiation of this disease. The most popular theory of the pathogenic mechanism of APSGN has been the immune complex theory, which involves the glomerular deposition of nephritogenic streptococcal antigen and the subsequent formation of immune complexes *in situ* and/or the deposition of circulating antigen-antibody complexes [1, 2]. However, glomerular immunoglobulin deposition is not often prominent in this disease, and the reason for the difference in the site of glomerular cell infiltration and the site of immune complex deposition is unclear; the major site of inflammation in this disease occurs on the inner side of the glomerular tufts (endocapillary site), whereas the immune complex in early phase is localized to the outer side of the glomerular tufts (subepithelial site). Indeed, another type of human glomerulonephritis with subepithelial immune complex deposition, membranous nephropathy, is rarely accompanied by endocapillary cell infiltration. Thus, the actual mechanism of how prominent glomerular endocapillary proliferation occurs in this disease is still unknown, and the most essential and critical issue, "what is the causative entity/antigen," has remained a matter of debate [3–6].

We recently isolated and characterized a nephritogenic antigen from group A streptococcus (GAS) that we call the nephritis-associated plasmin receptor (NAPlr) and is homologous to the streptococcus plasmin(ogen) receptor

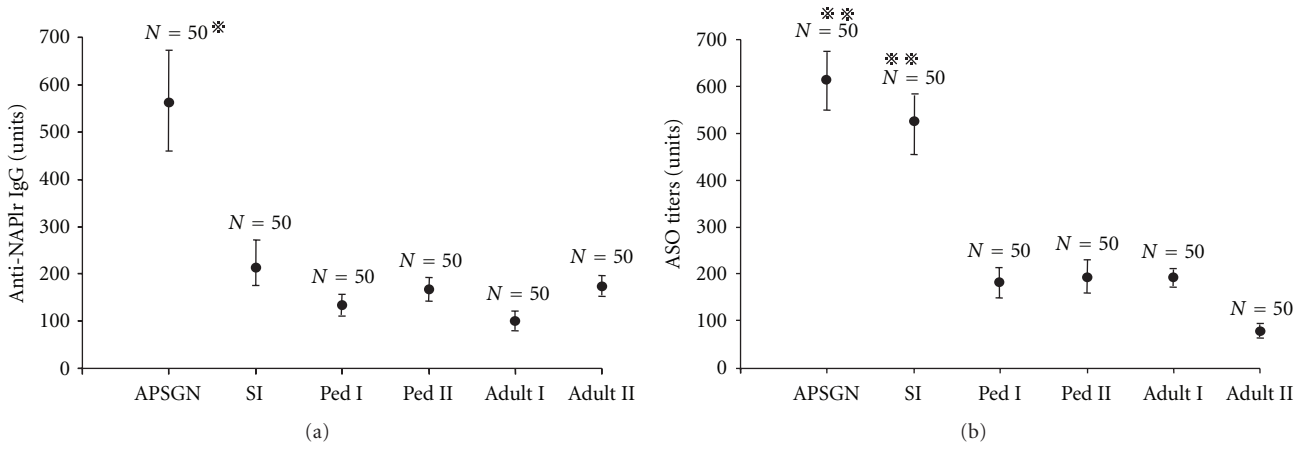

Figure 1: (a) The results of Western blotting assay for anti-NAPlr antibody titers in patients with acute poststreptococcal glomerulonephritis (APSGN), patients with a streptococcal infection (SI) without renal involvement, pediatric patients without renal disease, and normal healthy adults (see Table 1 for ages of subjects in each group). Values are means ± SEM. $^{*}P < 0.05$ for APSGN versus SI, pediatrics, and normal adults by t test. (b) ASO titers for the same groups of patients. The titers in the APSGN and SI groups are significantly higher than those in the normal adults and the pediatric patients without renal disease. Values are means ± SEM. $^{**}P < 0.001$ for APSGN or SI versus those in other groups by t test.

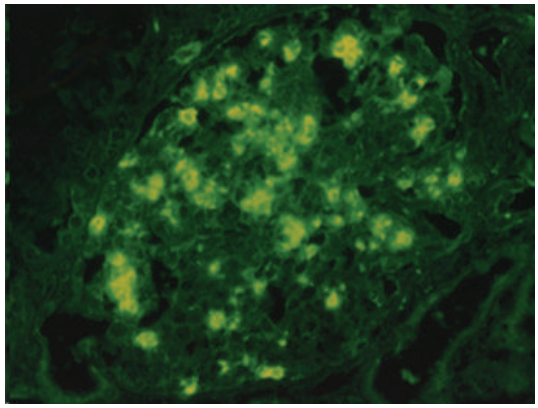

Figure 2: Immunofluorescence staining for NAPlr in tissue sample from a patient with acute poststreptococcal glomerulonephritis. Staining sites, which are thought to represent free antigen, are localized primarily in the mesangium and part of the glomerular basement membrane (GBM), and infiltrating leukocytes show a ring-like granular pattern (original magnification ×200).

(Plr) [7, 8]. The evidence for the important roles of NAPlr and the related plasmin activity in the development of glomerulonephritis associated with streptococcal infection are described.

2. Isolation of Nephritis-Associated Plasmin Receptor (NAPlr)

We postulated that the nephritogenic antigen for APSGN should have affinity for the serum of convalescent APSGN patients. So the fraction from the cytoplasmic proteins of GAS that has high affinity for the IgG of APSGN patients were collected by using affinity chromatography with APSGN patients' IgG-immobilized Sepharose and then purified by ion exchange chromatography. Eventually the 43-kDa protein, a potent nephritogenic antigen for APSGN, was isolated [7, 8]. The amino acid and the nucleotide sequences of the antigen revealed to be highly identical to those of reported Plr, or glyceraldehyde-3-phosphate dehydrogenase (GAPDH) of GAS [7–10]. Thus, we termed this antigen NAPlr. Plr has been shown *in vitro* to bind plasmin and maintain its proteolytic activity by protecting it from physiologic inhibitors like α_2-antiplasmin (α_2-AP) [11]. NAPlr exhibited similar functions as Plr, such as specific binding with plasmin(ogen), and expression of GAPDH activity [7]. Further analysis revealed the nephritogenic characteristics of the isolated antigen as described in the following sections.

3. Antibody Response against NAPlr in APSGN Patients

We analyzed the anti-NAPlr antibody titers by Western blotting in serum samples from 50 APSGN patients, 50 streptococcal infection (SI) patients without nephritis, 50 young pediatric patients (<11 years old), 50 older pediatric patients (11–20 years old), 50 young normal adults (25–35 years old), and 50 older normal adults (52–59 years old). The percentage of those positive for anti-NAPlr antibody was high in APSGN patients, but was also quite high even in healthy older people (Table 1). APSGN patients, however, showed significantly higher antibody titers as demonstrated in Figure 1(a) than other groups, even SI patients without nephritis. Anti-NAPlr antibody titer differed from ASO titer in that the ASO titer was similarly high in both APSGN and SI patients (Figure 1(b)) [8].

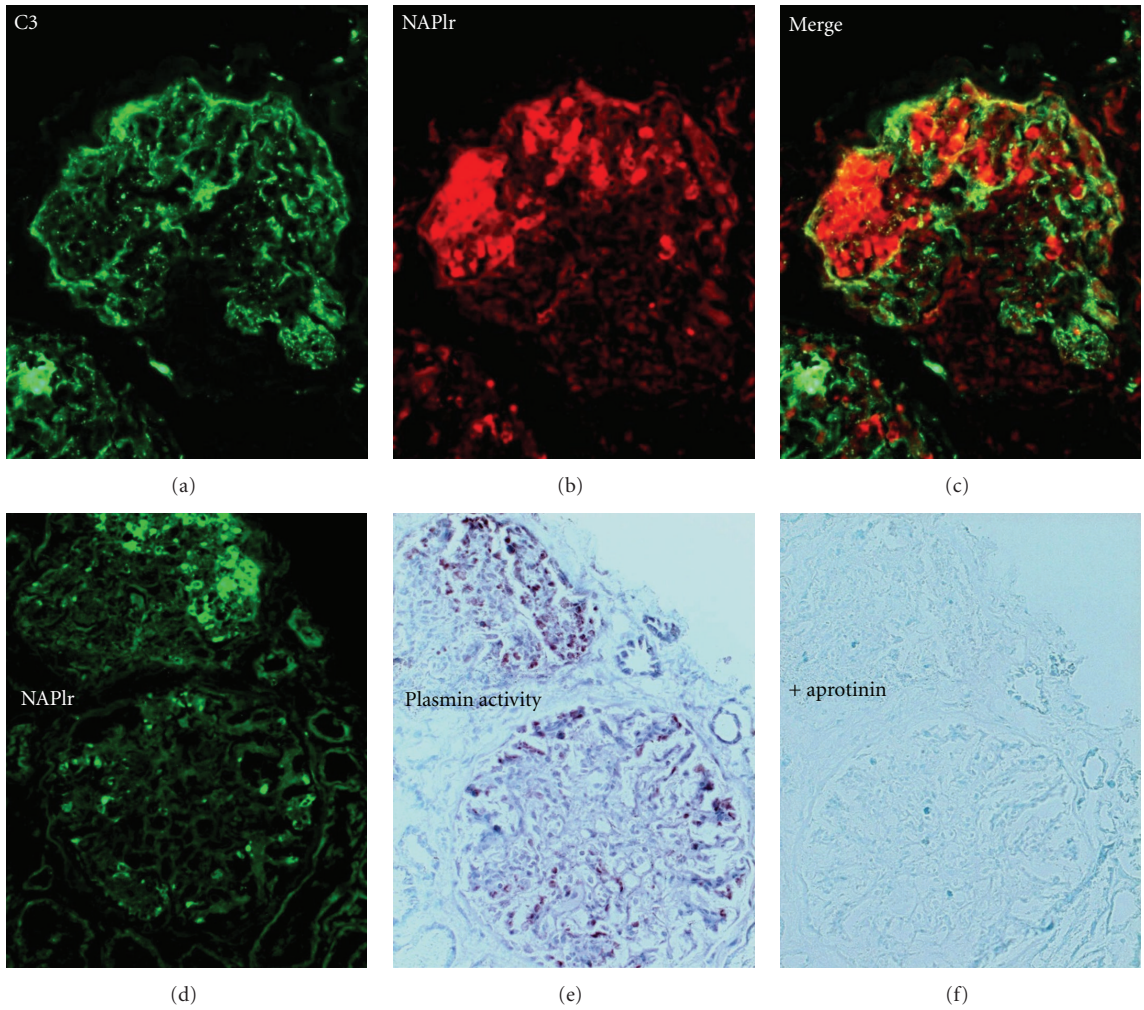

Figure 3: Representative photomicrographs of double immunofluorescence staining for C3 (FITC; green) and NAPlr (Alexa Fluor 594; red) ((a)–(c)). The distributions of C3 (a) and NAPlr (b) were obviously different in the merged image (c). ((d)–(f)). NAPlr IF staining and *in situ* zymography for plasmin activity in serial sections of renal biopsy tissue from an APSGN patient. The distribution of plasmin activity was similar to that of NAPlr deposition ((d) and (e)). Addition of aprotinin inhibited the zymographic activity suggesting the activity to be plasmin (f) (original magnification ×200).

Table 1: Positive rate of serum anti-NAPlr antibody in patients with APSGN, streptococcal infection, pediatric patients, and normal adults.

	Age in years range	Anti-NAPlr antibody (+)
APSGN	5–75 years, mean 29.3	45/50 (90%)
Streptococcal infection	8–64 years, mean 29.0	15/25 (60%)
Pediatric I	0.2–10 years, mean 7.2	13/50 (26%)
Pediatric II	11–20 years, mean 14.1	18/50 (36%)
Normal adults I	25–35 years, mean 30.0	24/50 (48%)
Normal adults II	52–59 years, mean 53.2	36/50 (72%)

4. Glomerular Deposition of NAPlr in APSGN Patients

Direct immunofluorescence staining with rabbit anti-NAPlr antibody in renal biopsy tissue from APSGN patients revealed glomerular NAPlr deposition mainly on mesangial and endocapillary site as ring-like granular pattern (Figure 2). As shown by the values listed in Table 2, glomerular NAPlr deposition was observed in 100% (25/25) of APSGN patients within 2 weeks after disease onset or in 84% (36/43) of APSGN patients within 30 days after disease onset, but the percentage of tissue specimens showing NAPlr deposition decreased over time. On the other hand, no normal kidney was positive for NAPlr and only 4 out of

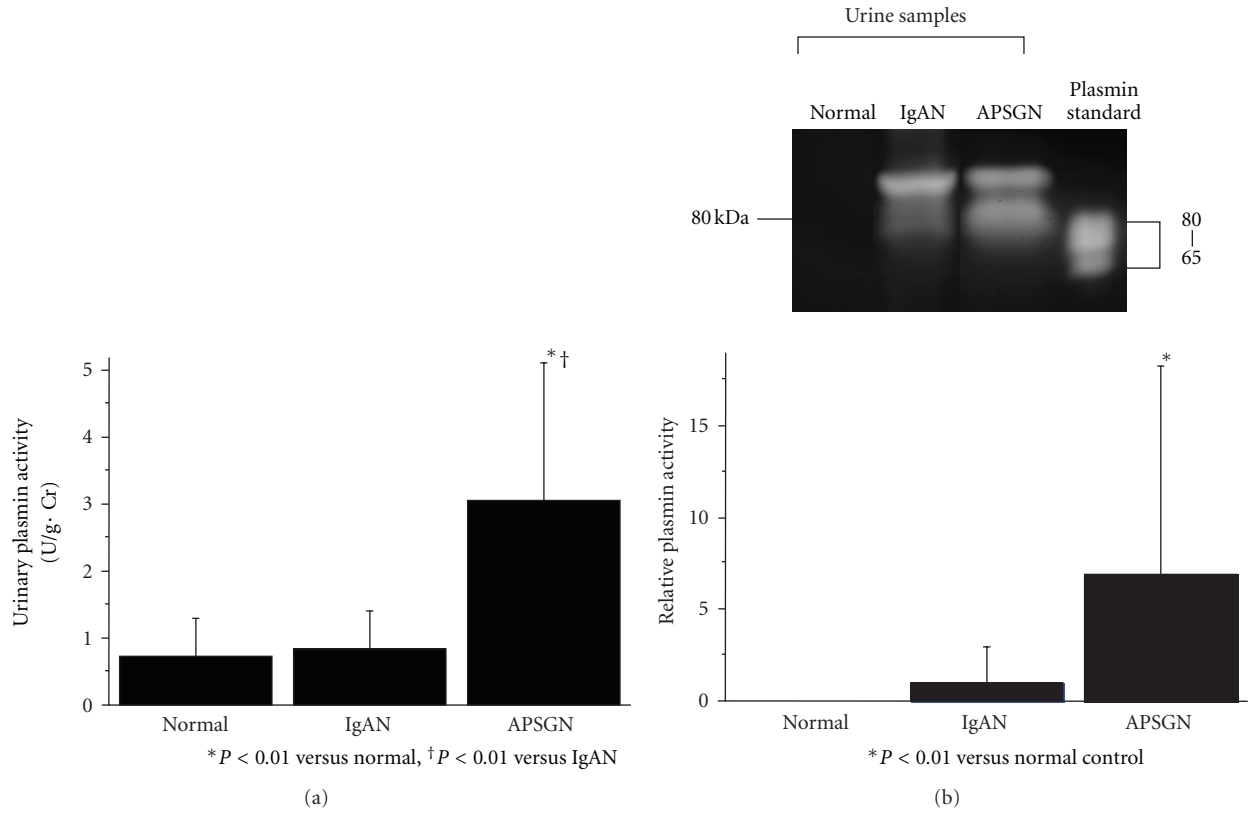

Figure 4: (a) Urinary plasmin activity assessed by chromogenic assay and corrected for urinary creatinine concentration. Results are expressed as corrected mean activity ± SE. $^*P < 0.01$ versus normal control; $^\dagger P < 0.01$ versus IgAN. (b) Representative casein gel zymography results for a plasmin standard and urine supernatants from normal controls, patients with IgAN, and patients with APSGN. Graph shows mean ± SE of the density of 80-kDa bands in casein gel zymography expressed in arbitrary units. $^*P < 0.05$ versus normal controls.

Table 2: Glomerular NAPlr deposition in APSGN, non-APSGN, and normal kidney tissues.

Biopsy specimens	Onset to biopsy	Glomerular NAPlr (+)
APSGN	1–14 days	25/25 (100%)
	15–30 days	11/18 (61%)
	31–90 days	0/7 (0%)
	Total	36/50 (72%)
Non-APSGN		4/100 (4%)
Normal kidneys		0/10 (0%)

100 patients with other glomerulonephritis were positive for NAPlr [7].

5. Localization and Properties of NAPlr, and Pathogenic Mechanism of APSGN

It is worthy of notice that the glomerular distribution of NAPlr was essentially different from that of IgG or C3 in the glomeruli of APSGN patients (Figures 3(a)–3(c)) [8]. In early-phase APSGN, C3 and/or IgG deposits are usually found at a subepithelial site (on the outer side of the glomerular tufts), while NAPlr deposits are always found on the inner side of the glomerular tufts. Using double immunofluorescence staining for more precise analysis, we found NAPlr to be localized mainly on glomerular endocapillary neutrophils, mesangial area, and partially on endothelial cells or glomerular basement membrane [12].

NAPlr is a 43 kD protein with a pI of 4.7, and its most characteristic feature *in vitro* is that it binds to plasmin and maintains the proteolytic activity of plasmin by protecting the enzyme from physiological inhibitors such as α_2-AP. Actually, plasmin is engaged in many physiological phenomenon, such as, fibrinolysis, extracellular-matrix turnover, cell migration, wound healing, angiogenesis, and neoplasia [13–16], but because it is easily inhibited and tightly regulated by physiological inhibitors it is not normally found in an active form *in vivo*. We found significant glomerular NAPlr deposition in the early phase of APSGN, which led us to speculate that deposited NAPlr would trap plasmin and cause glomerular damage by keeping it in an active condition *in vivo*. To evaluate this hypothesis, we performed an *in situ* zymography with a plasmin-sensitive synthetic substrate (*p*-toluenesulfonyl-L-lysine α-naphthyl ester), and found prominent intraglomerular plasmin activity only in NAPlr-positive APSGN patients (Figure 3(e)) [17]. This activity was completely inhibited by aprotinin (Figure 3(f)), a plamin inhibitor, but was resistant to α_2-AP. In contrast to the different distributions of NAPlr and C3 or

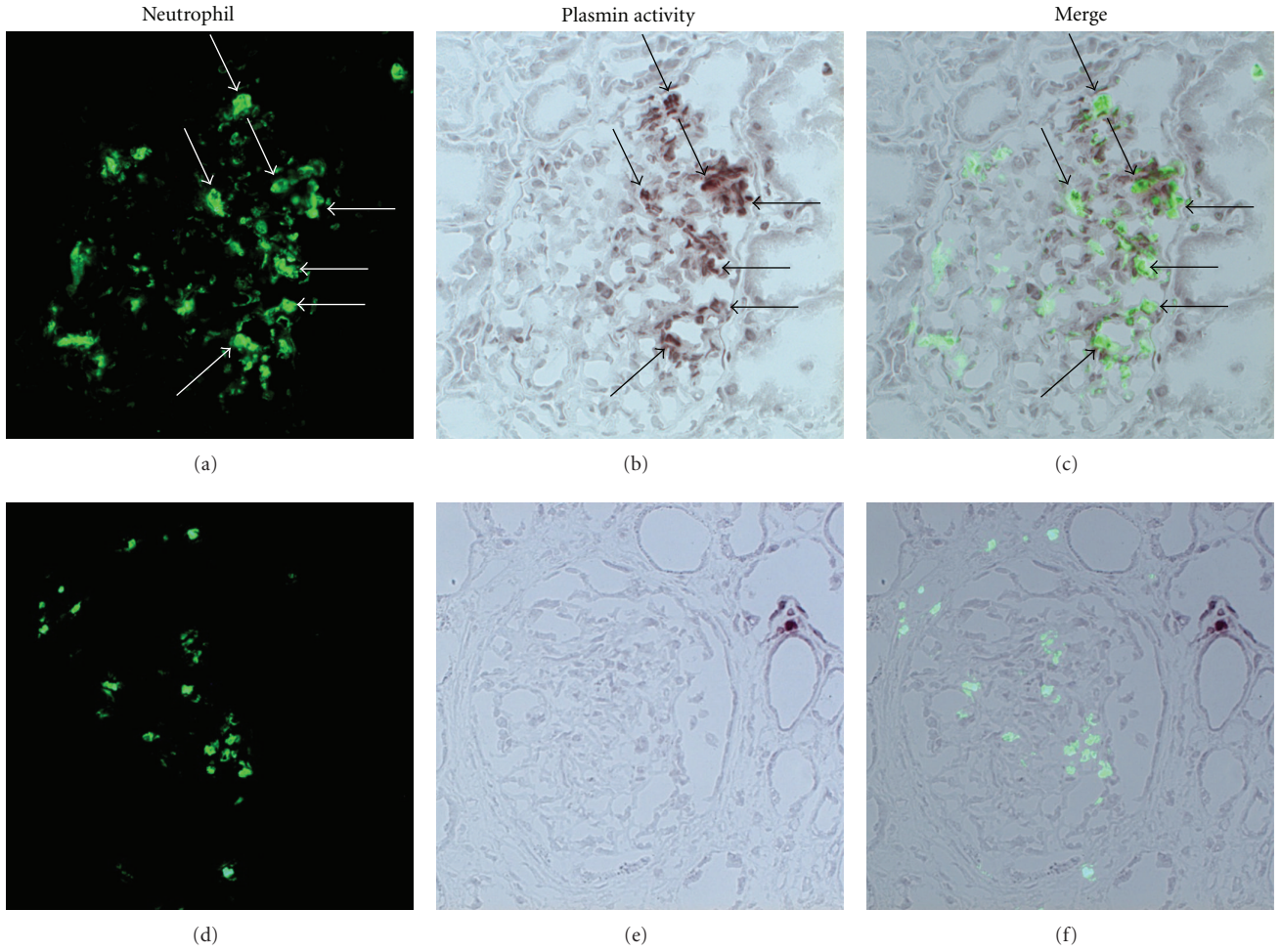

Figure 5: Glomerular infiltrating neutrophils and plasmin activity in APSGN and rapidly progressive glomerulonephritis. Representative photomicrographs of double staining for neutrophil elastase ((a) and (d), indirect immunofluorescence staining) and plasmin activity ((b) and (e), *in situ* zymography) from a patient with APSGN ((a)–(c)) and with rapidly progressive glomerulonephritis ((d)–(f)). The same fields were observed under fluorescence microscopy ((a) and (d)) and light microscopy ((b) and (e)) and were merged ((c) and (f)). The merged image (c) shows upregulated plasmin activity in a large portion of glomerular neutrophils in APSGN patients (indicated by arrows) but not in rapidly progressive glomerulonephritis patients (f) (original magnification ×260).

IgG (Figures 3(a)–3(c)), the glomerular distributions of plasmin activity and NAPlr are essentially identical (Figures 3(d) and 3(e)), suggesting that deposited NAPlr does indeed cause glomerular damage in APSGN by trapping plasmin and maintaining its activity [17]. Plasmin might damage renal tissue directly by degrading extracellular matrix proteins such as fibronectin or laminin but might also exert an indirect effect on variety of extracellular matrix proteins by activating promatrix metalloproteases [13]. Plasmin can also mediate inflammation by activating monocytes and neutrophils and causing their glomerular accumulation [18, 19]. Thus we think that glomerular damage may initially be induced by deposited NAPlr, which can bind plasmin and maintain its proteolytic activity, rather than by subepithelial immune-complexes. In this respect, the finding that NAPlr is localized on the inner side of glomerular tufts (endocapillary) is consistent with the predominantly endocapillary glomerular inflammation in APSGN. In other words, endocapillary localization of NAPlr might account for the different sites of glomerular inflammation and immune-complex deposition in APSGN. NAPlr thus acts not only as a component of the immune complex but also as a plasmin receptor and might contribute to the pathogenesis of APSGN by maintaining proteolytic activity. This is consistent with previous clinical findings that proteinuria and microscopic hematuria are occasionally found in the dormant phase of APSGN, when antibody against the nephritogenic antigen has not yet developed. The incidence of APSGN in streptococcal infection patients with these manifestations (proteinuria and hematuria in the dormant phase) is higher than that in streptococcal infection patients without these symptoms [20]. In keeping with these results, urinary

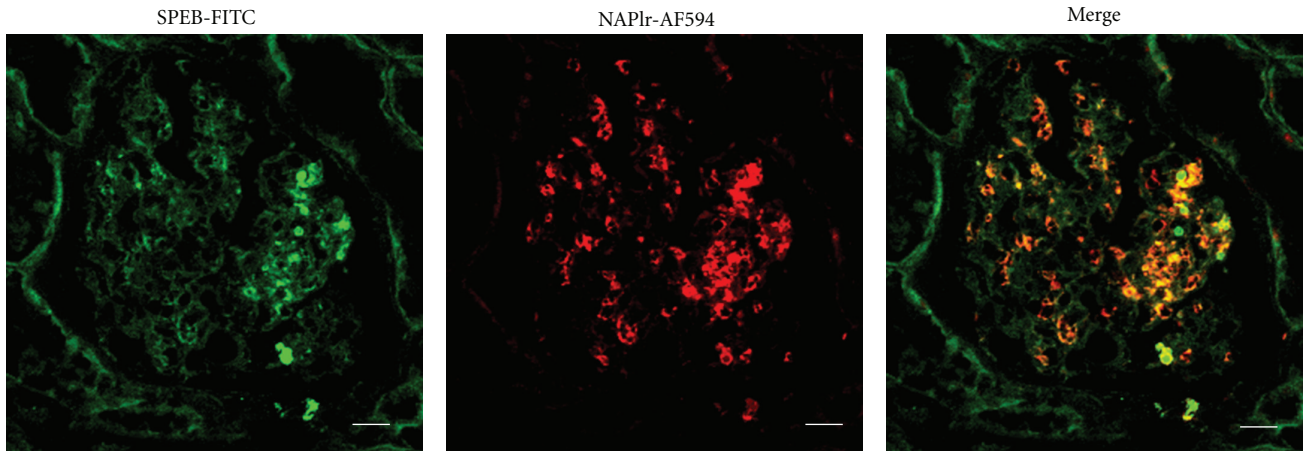

Figure 6: Representative photomicrographs of double IF staining for streptococcal pyrogenic exotoxin B (SPEB) ((a), FITC) and NAPlr ((b), Alexa Fluor 594) in an APSGN patient. A similar but not identical distribution of NAPlr and SPEB was observed in the merged image (c). Generally, NAPlr staining results were rather stronger than SPEB staining results (scale bar = 20 μm).

plasmin activity assessed by chromogenic assay (Figure 4(a)) and casein gel zymography (Figure 4(b)) was upregulated in APSGN patients than that in the urine of healthy subjects and IgA nephropathy patients, which support the pathogenic role of NAPlr and plasmin activity in APSGN [21].

As NAPlr was found to be localized mainly in neutrophils, we examined the plasmin activity of glomerular neutrophils and found that many were positive for plasmin activity in renal tissues from APSGN patients (Figures 5(a)–5(c)). On the other hand, glomerular neutrophils were not positive for plasmin activity in renal tissues from rapidly progressive glomerulonephritis patients (Figures 5(d)–5(f)), which suggests disease specificity of the relationship between plasmin activity and neutrophils [12]. With respect to the pathogenic role of NAPlr on neutrophils, the hyperproteolytic state of NAPlr-positive neutrophils in the present study indicates a possible role of these neutrophils in the induction of proteolytic glomerular damage. Specifically, plasmin activity of NAPlr-positive neutrophils may damage mesangium and glomerular basement membranes from inner side of glomerular tufts by promoting plasmin-catalyzed proteolysis. Regarding the mechanism of localization of NAPlr on neutrophils, we suggest two possibilities. NAPlr may bind the urokinase-type plasminogen activator receptor expressed on neutrophils [22], which has recently been shown to be the receptor for streptococcal GAPDH (NAPlr) [23]. Alternatively, NAPlr may be phagocytosed by neutrophils as a foreign bacterial antigen.

6. Comparison of NAPlr and Streptococcal Pyrogenic Exotoxin B (SPEB) as Nephritogenic Antigens for APSGN

Despite the previously mentioned evidence that NAPlr is a potent nephritogenic antigen that could cause APSGN, Batsford et al. [24] hypothesize that the nephritogenic antigen responsible for APSGN is streptococcal pyrogenic exotoxin B (SPEB). SPEB is a cationic cysteine protease secreted as a 42-kDa zymogen that is subsequently cleaved to a 28-kDa active proteinase. It is a toxin in severe invasive streptococcal infections [25] but has also been suggested by several groups [3, 6, 24, 26] to be a potent nephritogenic antigen of APSGN. Because of its cationic character, it is suspected to pass easily through the glomerular basement membrane and be deposited at a subepithelial site, where it would then induce immune complex formation. Cu et al. [6] were able to demonstrate glomerular localization of SPEB in 67% of APSGN patients by indirect IF staining with polyclonal anti-SPEB antibody. Batsford et al. recently compared NAPlr and SPEB in the renal biopsy tissues from a series of APSGN patients with anti-SPEB and antistreptococcal GAPDH (NAPlr) antibodies that they generated [24]. In contrast to our previous findings [7, 8], they found rare glomerular positivity for streptococcal GAPDH compared to those for SPEB. In contrast, they demonstrate that SPEB is the principal nephritogenic antigen. It is important to note that they used an indirect immunofluorescence staining method with the antistreptococcal GAPDH antibody that they generated, whereas we performed direct immunofluorescence staining with the anti-NAPlr antibody that we generated. Immunostaining results can vary with the use of different antibodies, so the comparison may be inappropriate [27]. Nonetheless, we compared glomerular localization profiles of SPEB and NAPlr by using an SPEB antibody provided by Dr. Batsford (Department of Immunology, Institute of Medical Microbiology, Freiburg, Germany) and our NAPlr antibody. Double staining showed an extremely similar distribution of both antigens in the glomeruli of APSGN tissues, although NAPlr staining appeared to predominate (Figures 6(a)–6(c)) [12, 28]. These results were surprising because many researchers, including us, have been assuming that APSGN is the result of a single nephritogenic streptococcal antigen.

Therefore, we should consider the possibility that two or more antigens interact in the induction of this disease. It is also interesting that NAPlr and SPEB share a common function. Both bind plasmin, thereby protect it from physiological inhibitors, and thus might cause chemotaxis of inflammatory cells and degradation of glomerular basement membranes, due to the activity of plasmin [17, 26]. Plasmin activity may be a common final pathway in APSGN [29], or those antigens may cooperate from different mechanisms for the development of APSGN as recently suggested by Rodríguez-Iturbe and Batsford [30].

7. Glomerular NAPlr Deposition in Other Glomerulonephritis Related with Streptococcal Infection

As described above, NAPlr is originally isolated as the putative nephritogenic antigen for APSGN. Indeed, glomerular NAPlr deposition can be found with extraordinary frequency in early-phase APSGN patients. However, recent observation has revealed that glomerular NAPlr deposition and plasmin activity could be found in a similar fashion also in other glomerular diseases, such as dense deposit disease (DDD) [31, 32], Henoch-Schonlein Purpura nephritis (HSPN) [7, 33] and membranoproliferative glomerulonephritis (MPGN) [7], in which recent streptococcal infection has been suggested by serological tests. The histological characteristics common to these cases are prominent endocapillary proliferation. We believe that there is a subgroup of patients in these diseases (DDD, MPGN, and HSPN) in which glomerulonephritis is induced by streptococcal infection and subsequent glomerular deposition of NAPlr and related plasmin activity. We would like to refer to these diseases collectively as streptococcal-infection related nephritis (SIRN).

8. Conclusion

In light of our recent finding on nephritogenic antigen responsible for APSGN, we propose the following mechanisms for the development of APSGN (Figure 7). Infection of the throat or skin with streptococcus induces the release of a nephritogenic antigen, such as NAPlr, into the circulation. Circulating NAPlr accumulates in the renal glomeruli on the mesangial matrix and glomerular basement membrane, probably by adhesion [7]. NAPlr then traps and maintains the activity of plasmin, which might induce glomerular damage by degrading the glomerular basement membrane by itself or by activating promatrix metalloproteases. Plasmin activity may also mediate neutrophil and macrophage infiltration [18, 19]. Therefore we believe that an antibody-independent direct effect of the nephritogenic antigen is important for the initiation of the disease. Such glomerular damage may induce urine abnormalities during the latent period of the disease. The host immune reaction (both humoral and cell-mediated) against the nephritogenic antigen also develops during this latent period. The circulating antibody forms immune complexes, either *in situ* or in the circulation that can readily pass through the altered glomerular basement membrane and accumulate in the subepithelial space as humps. These final steps of immune cell accumulation and immune complex deposition are accompanied by the activation of complement and lead to the overt disease state. The mechanisms localizing NAPlr specifically to the glomeruli and possible contributions and interactions of other nephritic antigens in APSGN must be elucidated in future studies.

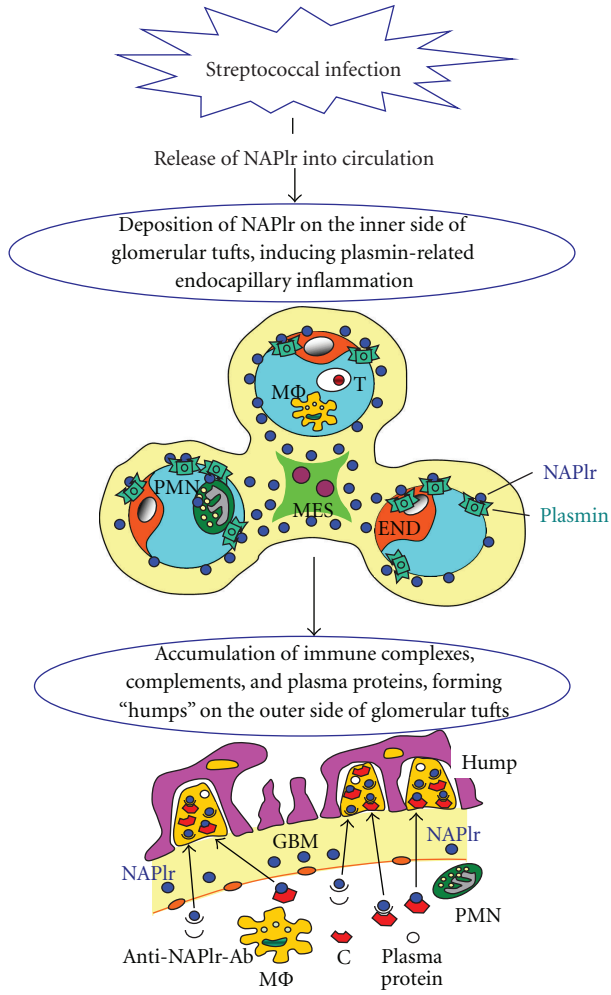

Figure 7: Schematic representation of proposed mechanisms involved in the development of APSGN. MES: mesangial cell; END: endothelial cell; PMN: polymorphonuclear cell; MΦ: macrophage; T: T lymphocyte; GBM: glomerular basement membrane; C: complement; Anti-NAPlr-Ab: Anti-NAPlr-antibody.

Glomerular NAPlr deposition and plasmin activity could be observed in a similar fashion in other glomerular diseases, such as DDD, HSPN, and MPGN, in which recent streptococcal infection has been suggested. We propose to refer to these diseases (glomerulonephritis induced by streptococcal infection and subsequent glomerular deposition of NAPlr and plasmin activity) collectively as SIRN.

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