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REVIEW

Podocytopathy in the mesangial proliferative immunoglobulin A nephropathy: new insights into the mechanisms of damage and progression

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ABSTRACT

Immunoglobulin A nephropathy (IgAN) was defined as a mesangiopathic disease, since the primary site of deposition of IgA immune material is the mesangium, and proliferation of mesangial cells and matrix excess deposition are the first histopathologic lesions. However, the relentless silent progression of IgAN is mostly due to the development of persistent proteinuria, and recent studies indicate that a major role is played by previous damage of function and anatomy of podocytes. In IgAN, the podocytopathic changes are the consequence of initial alterations in the mesangial area with accumulation of IgA containing immune material. Podocytes are therefore affected by interactions of messages originally driven from the mesangium. After continuous insult, podocytes detach from the glomerular basement membrane. This podocytopathy favours not only the development of glomerular focal and segmental sclerosis, but also the progressive renal function loss. It is still debated whether these lesions can be prevented or cured by corticosteroid/immunosuppressive treatment. We aimed to review recent data on the mechanisms implicated in the podocytopathy present in IgAN, showing new molecular risk factors for progression of this disease. Moreover, these observations may indicate that the target for new drugs is not only focused on decreasing the activity of mesangial cells and inflammatory reactions in IgAN, but also on improving podocyte function and survival.

Keywords: chronic kidney disease, IgA nephropathy, podocyte, podocytopathy, proteinuria

INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is defined by the detection of IgA in glomeruli as dominant or co-dominant with respect to the other immunoglobulins [1]. It was classified as mesangiopathic glomerulonephritis, since the primary site of deposition of IgA immune material is the mesangium, and proliferation of mesangial cells and matrix excess deposition are the first histopathologic lesions. Although microscopic or macroscopic haematuria is the most common manifestation, the major risk for progression is proteinuria, which results from derangement of the podocyte-basement membrane [glomerular basement membrane (GBM)] glomerular compartment. In IgAN, persistent proteinuria represents the target for therapy according to kidney disease improving for global outcomes (KDIGO) guidelines [2]. Proteinuria develops mainly due to haemodynamic and immunological factors affecting podocyte function and survival, and the result of sustained harmful events that may lead to podocytopathy and overt focal and segmental sclerotic lesions. The role of these lesions in IgAN progression is also an area of research for the potential new therapeutic drug targets.

The Oxford clinicopathological classification of IgAN and subsequent update detected the predictive value of outcome of histologic lesions related to mesangial cell activation and glomerular inflammation, including mesangial hypercellularity (M), endocapillary hypercellularity (E) and crescents (C), in addition to chronic tubulointerstitial lesions (T) [3, 4]. However, an independent risk value was also found for segmental glomerulosclerosis (S) with the presence of glomeruli showing segmental adhesions or sclerosis, detected in 76% of renal biopsy specimens. In IgAN, S1 lesions develop from the organization of previous segmental necrotizing or endocapillary inflammatory lesions or in response to podocyte injury and detachment, but also from hyperfiltration due to adaptive haemodynamic changes. S1, as well as M1, E1 and C1 scores, were all associated with proteinuria at renal biopsy [3]. In the large European study of validation of the Oxford classification enrolling more than 1147 cases of IgAN of various ages and from 13 different European countries, S1 was confirmed to be the most frequent lesion (70% of cases), compared with lower frequency of typical proliferative changes (M1: 28%, E1: 11%, C1–2: 11%) [5].

The value of S1 lesions was investigated in a recent study that subclassified the cases with S1 enrolled in the original Oxford cohort according to the presence of signs of podocyte

injury (podocytopathy) such as podocyte hypertrophy or tip lesions [6]. Podocytopathic lesions were associated with greater initial proteinuria and more rapid functional decline and worse survival from the combined endpoint compared with patients with S1 without these features. In this S1 subgroup, corticosteroid/immunosuppressive therapy was associated with a better renal survival. Podocytopathic lesions were also found to be a risk factor for progression in children with IgAN [7].

The recent focus on podocyte damage and proteinuria development in IgAN suggested interest in reviewing recent experimental and observational studies on the pathogenetic mechanisms implicated in the development of podocyte injury in this glomerular disease.

PODOCYTES AND GLOMERULAR DISEASES

Podocytes are highly specialized non-divisible cells committed to maintain the glomerular filtration barrier by synthesis of GBM components, formation of the slit diaphragm and interactions securing endothelial cell viability [8]. The main function of podocytes is to avoid the daily loss of circulating proteins.

In the last 20 years, over 50 genetic mutations leading to deletion or modification of podocytary proteins have been reported as important causes of podocytopathies. Besides genetic factors, podocyte dysregulation and injury leading to proteinuria may be due to an as yet unidentified permeability factor(s), likely active in minimal change disease or focal segmental glomerular sclerosis (FSGS) leading to modification of the glomerular barrier permselectivity in the absence of any inflammatory changes [9]. Podocytes can also react via specific receptors to a variety of inflammatory mediators, including cytokines, reactive oxygen species and complement products released during glomerular inflammatory conditions [10].

Moreover, podocytes can suffer from haemodynamic challenges due to their downstream localization from the GBM, which expose these cells to a constant stress, which is further amplified in hyperfiltration conditions [10, 11]. In addition, hyperfiltration due to a reduced number of functioning nephrons can also induce haemodynamic and podocytopathic changes, which can be detected in secondary forms of FSGS. In these various conditions, podocyte activation by immunological and/or haemodynamic factors triggers a cascade of protein kinases activity leading to reactive oxygen species release, endoplasmic reticulum stress, protein unfolding abnormalities and mitochondrial damage. The podocyte stress burden impacts on the integrity of the cytoskeleton and slit diaphragm, promoting cell functional and anatomic damage, detachment and death.

PODOCYTE MECHANISMS AIMED AT MAINTAINING INTEGRITY OF THE GLOMERULAR BARRIER

Due to its location in the GBM and to the constant exposure to a fluid flow, podocytes are constantly exposed to the risk of detachment, particularly those located near the opening of Bowman's capsule to the proximal tubule, a region of the highest filtrate flow velocity [11, 12]. Podocyte adaptation to immunological or haemodynamic noxae manifests in cellular hypertrophy and foot process effacement, which represents a protective mechanism to prevent detachment that, if sustained, culminates in cell detachment, which drives adjacent podocytes to cover the denuded GBM [10–12].

It is of interest for understanding the podocyte damage in conditions with expansion of the mesangial area, as it occurs in IgAN, to consider the relationship between glomerular capillaries and the folding pattern of the GBM [13]. The peripheral outpocketings of the GBM form a continuous channel system that is open to the mesangium and contains the capillaries. The mechanical stability of this system is largely maintained by the mesangial cells, which insert along the paramesangial aspect of the GBM. In conditions of increased mesangial area, there is a lengthening of the mesangial axis followed by the prolapse of the capillary and the associated podocyte detachment with loss into the urinary space [13].

Thus, the podocyte stress and adaptation observed in podocytopathies manifest as alterations in podocyte charge or shape, an active process that occurs due to actin cytoskeleton rearrangement that precedes podocyturia [10, 11, 14].

ROLE OF CELL–CELL AND CELL–MATRIX ADHESION IN PODOCYTE SURVIVAL

Integrity and function of the glomerular filtration barrier are due to cell-to-cell and cell-to-matrix adhesions. Podocyte adhesion is promoted by several receptors, including integrins, syndecans and dystroglycan, which interact with cytoskeletal actin [15]. Particularly investigated in proteinuric conditions and in IgAN is the podocyte integrin system, with focus on αVβ3 and α3β1 [16]. Integrins are transmembrane receptors for various extracellular membrane components, including laminin, vitronectin, collagens and fibronectin. They activate kinases that phosphorylate key molecules for cell–cell and cell–matrix interaction.

Integrin αVβ3 binds to cytoskeletal actin and extracellular vitronectin [17]. In addition, it can react on the podocyte surface to urokinase plasminogen activator receptor (uPAR), a multi-domain glycoprotein, which normally binds to urokinase plasminogen activator (uPA). The binding of uPAR to podocytary αVβ3 induces foot process effacement and eventually podocyte detachment [12, 16, 18]. In the experimental model of lipopolysaccharide (LPS)-induced nephropathy, uPAR is the key factor for mediating foot process effacement and proteinuria by interaction with αVβ3, leading to integrin activation and podocyte damage [18, 19].

Another relevant integrin member playing a role in podocyte survival and involved in acquired damage is α3β1, which binds with its intracellular domain cytoskeletal actin and with the extracellular domain fibronectin, collagen and laminin, reacting also with activated T cells via CD80 (B7-1), a costimulatory receptor on antigen-presenting cells. This molecule was found to be induced in experimental models of glomerular diseases with proteinuria, following the activation of innate immune signalling via toll-like receptor 4 (TLR-4) by bacterial endotoxin (LPS) [19]. CD80 modifies the actin cytoskeleton of podocytes and modulates slit diaphragm disposition. Addition of tumour necrosis factor alpha (TNF-α) to cultured podocytes causes

CD80 upregulation, actin reorganization and podocyte injury [20]. In humans, CD80 was upregulated in several proteinuric states, including primary FSGS [21]. Under podocyte stress conditions, the increased expression of CD80 on the podocyte surface leads to high urinary CD80 excretion, as detected in different proteinuric conditions [22, 23].

PODOCYTOPATHY IN IgAN

Podocyte hypertrophy or glomerular sclerosis at the tubular pole (tip lesions) are considered as the typical features of podocytopathy in renal biopsies of patients with IgAN [6]. These lesions were found to be associated with elevated levels of proteinuria and disease progression, particularly in patients not treated with corticosteroid/immunosuppressive drugs, suggesting a possible responsiveness to this treatment. Even though segmental glomerulosclerosis (S1 according to Oxford classification) was initially thought to be mostly due to the sclerotic repair inflammatory lesions, this morphologic pattern of injury was found to be similar both in IgAN and in lesions detected in primary FSGS, without evidence of inflammatory cell infiltration [24]. Podocytopathy and denudated GBM areas due to podocyte detachment were observed in IgAN [25]. In this disease, a decrease in podocyte number was also found to be associated with global sclerosis [26]. Some studies have detected an increased number of podocytes in urine of patients with IgAN and increased urine excretion of podocalyxin, a protein located in the glycocalyx of podocytes [27]. Urinary podocin was found to be increased in patients with IgAN and severe proteinuria [28]. Though these findings were shared with other proteinuric renal diseases, they underscore the involvement of podocytes in mesangiopathic IgAN [23, 29, 30].

Some recent studies including ours have showed a higher degree of proteinuria in patients with IgAN and S1 in addition to M1, compared with those with M1 but without segmental sclerosis. Patients with S1 had a more rapid decline in estimated glomerular filtration rate (eGFR) and more persistent proteinuria and podocyturia after 7.5 years of follow-up [23]. Moreover, in a pilot study, we have found that in stable conditions, IgAN (unchanged eGFR and proteinuria persistently <0.75 g/day in the last 12 months) presented the highest rates of urinary podocyte loss compared with other primary or secondary glomerulopathies and controls [31].

MECHANISMS INVOLVED IN THE DEVELOPMENT OF PODOCYTOPATHY IN IgAN: ROLE OF MESANGIAL–PODOCYTE CROSS-TALK

The damage to podocytes in IgAN that drives the development of podocytopathy has been supposed to originate from a cross-talk between mesangial cells and podocytes [32, 33].

The initial hit in the pathogenesis of IgAN is thought to be the production of galactose-deficient IgA1 (Gd-IgA1), which triggers an IgG autoimmune response forming Gd-IgA1/IgG immune complexes, induces the cleavage of the extracellular domain of IgA soluble receptor FcαR (CD89), forming Gd-IgA1/CD89/IgG immune complexes [34, 35]. IgA1-containing macromolecules interact with transferrin 1 receptor (TfR1) and transglutaminase 2 (TGase2) receptor expressed on mesangial cells, leading to immune deposits formation, complement activation and inflammation [34]. This immune complex deposition causes activation of mesangial cells with transcription of an array of cytokines—the most important of them being interleukin 6 (IL-6) and TNF-α; meanwhile, the nuclear transcription factor kappa B (NF-κB) is activated with release of chemokynes determining influx of inflammatory cells and the development of a highly immunologic active mesangial 'milieu'.

The interaction between macromolecular IgA isolated from patients with IgAN and human mesangial cells in culture induce an increased production of chemokine ligand 1, and transforming growth factor β1 (TGF-β1) and TNF-α, which in synergy reduce in cultured podocytes the expression of nephrin and erzin, pivotal proteins in the podocyte-regulated slit diaphragm [36, 37]. Moreover, TNF-α acts as an autocrine stimulus with the consequences of increasing podocyte TNF-α and IL-6 synthesis and release. TNF-α and TGF-β1 synergically contribute to podocyte injury in cell culture experiments, leading to cell death [36].

We investigated the effects of incubation of human glomerular epithelial cells with supernatants of human mesangial cells cultured with Gd-IgA or with IgA isolated from sera of patients with IgAN. We detected a loss of nephrin expression and the induction of cytoskeletal actin downregulation, which were mediated by increased synthesis of platelet-activating factor (PAF), acting as a secondary mediator of TNF-α [33], which enhances glomerular permeability. The downregulation of nephrin was abrogated by the PAF receptor antagonist, WEB2170.

Another actor in the mesangial–podocyte cross-talk is angiotensin II (AngII), released by cultured human mesangial cells after incubation with IgA and Gd-IgA1 [38]. AngII modulates the α3β1 integrin expression on podocytes by reducing their adhesiveness and these changes are partially reversed by renin–angiotensin blockers [39]. It is of interest that the risk of progression in IgAN was found to be associated with higher expression of endothelin-1, a factor that can promote renal vessel vasoconstriction, cell proliferation and extracellular matrix deposition in this entity [40].

The integrin system plays a pivotal role in podocyte stability and survival as discussed above. One of the mechanisms implicated in podocytopathy of IgAN as well as in other proteinuric nephropathies is supposed to be uPAR, because of its interaction with αVβ3 integrins. Recent studies have been addressed to investigate the relationship between uPAR and proteinuria in IgAN. We reported an association between S1 lesions and high uPAR excretion in urine and podocyte loss in patients with IgAN [23]. Other studies from China detected that soluble urokinase plasminogen activator receptor (suPAR) levels, the circulating soluble fraction of uPAR, were not different in patients with IgAN with or without S1 lesions, though suPAR was significantly correlated with proteinuria and negatively correlated with eGFR decline (in univariate analysis) [41]. In any case, suPAR, a split product of upregulated podocyte uPAR, is a

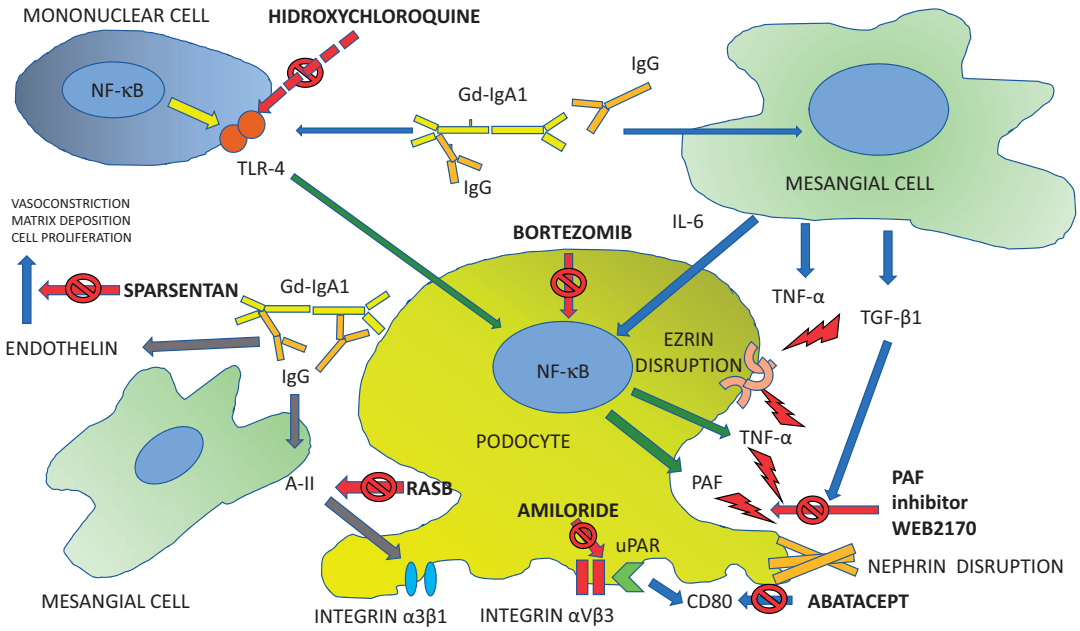

FIGURE 1: Possible targets in the treatment of podocytopathy in IgAN.

marker of podocyte damage, significantly correlated with signs of podocytopathy, such as podocyte hypertrophy and foot process effacement [12].

We have also recently observed that IgAN patients with S lesions at renal biopsy had elevated CD80 urinary excretion in comparison with patients without S lesions, and CD80 excretion significantly correlated with uPAR-positive podocyturia in all patients [23]. CD80 expression is associated with renal tissue damage of IgAN and was associated with T-cell activation and infiltration [42]. These data are in agreement with the activation of innate immunity in IgAN [43]. Indeed, the LPS-induced experimental model of podocyte damage and proteinuria demonstrated that CD80 was upregulated on podocyte surface via TLR-4, an LPS-specific ligand. Several data also indicate an involvement of TLRs in IgAN [44]. We have previously reported an increased expression of mRNA encoding for Toll-like receptor-4 (TLR-4) in peripheral blood mononuclear cells of patients with IgAN, accompanied by a significant positive correlation with proteinuria [45]. This was also confirmed in children with IgAN and IgA vasculitis (Henoch–Schönlein purpura) [46].

One of the targets of TLR activation is NF-κB. Renal biopsies from patients with IgAN present have shown increased detection of p50 or p65 NF-κB subunits [47]. We found an increased expression of active subunits of NF-κB in peripheral blood mononuclear cells of patients with IgAN [48] and a significant increase of NF-κB in cultured human podocytes after incubation of TNF-α or LPS. In addition, NF-κB is activated in the LPS-induced nephropathy, and it leads to foot process effacement. This interaction correlates with uPAR engagement [49].

Moreover, some previous and new data suggest a modulation of integrins by Gd-IgA1. We demonstrated that human mesangial cells cultured with Gd-Gal IgA or with IgA glycoforms isolated from patients with IgAN induce an upregulation of αVβ3 integrins, which may modify the relationship with the extracellular matrix favouring sclerosis [50]. In IgAN, Gd-IgA1 can increase integrin expression of cultured podocytes, which is followed by podocyte instability ending in cellular detachment [39]. Hence, a direct role of aberrant Gd-IgA1 modifying the integrin system at the mesangial and podocytary level can be envisaged.

CONSEQUENCES DERIVED FROM THE UNDERSTANDING OF THE PODOCYTOPATHY IN IGAN: NEW INSIGHTS INTO THE TREATMENT OF PODOCYTOPATHY IN IgAN

The hypothesis of the role of podocytopathy in the development of proteinuria and focal and segmental sclerosis in IgAN and the association between a better renal survival and the use of corticosteroid/immunosuppressive therapy in these patients have elicited interest in considering podocytes as a target for treatment of IgAN.

Considering the multiple mechanisms leading to podocyte damage in IgAN, new insights into the future therapeutic approaches may be proposed (Figure 1). Podocytary integrins may be modulated by interactions with various mediators released by activated mesangial cells that can be targeted by treatment. There is a high level of evidence for the usefulness of Renin-angiotensin system blockade (RASB) in IgAN, also with the possible association with sparsentan, which can target endothelin as a promising approach [51].

The mediation of podocytary damage by TNF-α and PAF suggests a possible therapeutic target with specific inhibitors [33, 52]. Proteasome inhibitors can target NF-κB activation, and the results obtained in a pilot study with bortezomib in patients with persistent steroid-resistant proteinuria are promising [53, 54]. The inhibition of TLRs is another new approach, and hydroxychloroquine—an antimalarial agent targeting TLR—resulted in a significant and safe reduction in proteinuria in patients with IgAN [55].

Amiloride may be an option, since this drug inhibits the synthesis of uPAR at the mRNA level [56]. As a consequence of this inhibition, the activation of αVβ3 integrins would be dampened and podocyte detachment decreased [57–59]. The CD80-nephrin coupling is another potential therapeutic target [20]. Abatacept (which interferes with the lymphocyte CD28–antigen-presenting cell CD80 coupling) was reported to be associated with the development of IgAN. Thus, CD80 emerges as another potential target to assess in the therapy of IgAN [60].

CONCLUSIONS

IgAN is a mesangiopathic disease; however, recent studies indicate that a progression due to development of persistent proteinuria may follow the engagement of podocytes in a silent damage, which favours not only the development of glomerular focal and segmental sclerosis, but also relentless renal function loss. Recent data suggest focusing on podocytopathy to assess the risk of progression of IgAN as well as looking for new drugs, with the aim not only of decreasing the activity of mesangial cells and inflammatory reactions, but also of improving podocyte function and survival.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part.

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