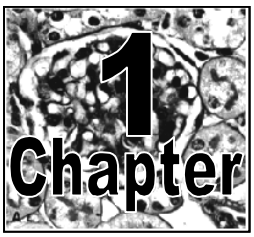
GENERAL INTRODUCTION



I. CLINICAL FEATURES OF HUMAN IGA-NEPHROPATHY

Immunoglobulin A nephropathy (IgAN) is the most common type of glomerulonephritis in large parts of the world. This glomerular disease leads to end stage renal failure (1,2) in approximately 30 – 50 % of the patients (3,4). About 7 to 10% of the patients with renal replacement therapy have IgAN (5). IgAN is a disease of young adults, males are more frequently affected than females. The clinical presentations of this type of glomerulonephritis show a large variability. Forty percent of the patients have recurrent episodes of macroscopic hematuria associated most commonly with infections of the upper respiratory tract (6) but also other infections have been shown to be associated with increasing disease activity (7-10). In contrast to children adults show no spontaneous remission of the disease (4,11,12). During the course of the disease macroscopic hematuria is less frequent, however long term prognosis of the disease with infection-related macroscopic hematuria is better (12-14). In most of the patients with IgAN the disease has an indolent course and is manifested by microscopic hematuria, intermittent or persistent. In the course of IgAN first mild proteinuria occurs which increases during the timecourse and is frequently associated with rising hypertension (15,16). The degree of hypertension and proteinuria are predictive for progression of the decline of renal function.

II. HISTOPATHOLOGICAL FEATURES

During the initial phase of IgAN MC proliferation is a characteristic finding. This acute phase is accompanied by infiltration of few monocytes, however extra and intracapillary inflammatory processes are severe enough and lead to crescent formation (17). Crescents are frequently found during relapses with macroscopic hematuria. More monocytes and T-cells were found in biopsies of activated disease (17) as compared to those without signs of disease activity.

Immunohistologically IgA-Nephropathy is characterized by deposition of IgA in the renal mesangium (18,19). The IgA deposited in the renal mesangium is mainly of the IgA1 subclass (20-25). Other immunoglobulins are frequently codeposited in the glomeruli in IgAN showing more frequently IgG (45-83%) as compared to IgM (9-66%)(24). In these cases the course of the disease is more severe (26,27).

The deposited IgA has been suggested to be mainly of polymeric origin. There is no direct evidence of the polymeric nature of deposited IgA but the presence of J-chain and the ability of secretory component to bind to glomerular areas with IgA-deposition points out that it is most likely IgA of polymeric origin

(28). Furthermore elution studies using glomeruli of patients with IgAN seem to detect a substantial fraction of polymeric IgA (28,29).

In patients with IgAN deposits of C3 have been described at similar glomerular locations as IgA in up to 90% of the patients (21,30-33). The codepostion of factor H and properdin in the absence of complement components of the classical pathway indicates the activation of complement during IgAN by the alternative pathway (32). Detection of the terminal membrane attack complex (MAC) in the glomerulus during IgAN is correlated with progressive renal failure.

III. IGA RELATED ACTIVATION OF MC

Various investigators have pointed out that IgA binds to rat mesangial cells (MC) (34,35). It was been shown that binding of IgA to MC leads to uptake and degradation of IgA and that IgA induces release of different cytokines (36,34). Previous results have demonstrated that IgA binds to human MC (36-38), however no specific receptor could be identified responsible for binding and activating the cells. Binding studies with human monoclonal IgA1 have shown linear binding curves indicating a single population of an IgA-binding protein on human MC with a Ka of $3.2x10^7$ M^{-1}. Quiescent MC bear approximately $2.55x10^5$ sites/cell, and after stimulation of these cells with different recombinant cytokines (Interleukin-6, Tumor Necrosis Factor-α, Interferon-α) binding-sites increased whereas binding curves were not changed (39). Diven and coworkers demonstrated in their study that IgA1, isolated from healthy individuals (polyclonal), binds dose-dependently and in a saturable manner to human MC. They found $1.2x10^6$ binding-sites/cell and an affinity constant for IgA1(Ka) of $2.3x10^6$ M^{-1} and a dissociation constant (Kd) of $4.4x10^7$ M^{-1}. Binding of dimeric and polymeric IgA led dose-dependently to enhanced expression of the protooncogene c-jun (40) which has been shown to be linked to cell proliferation and matrix synthesis (41).

Another study demonstrated cytosolic calcium release after stimulation of MC with aggregated monoclonal IgA in a dose-dependent and transient manner. This initial induction of calcium rise was due to calcium mobilisation from inositol trisphosphate (IP_3)-sensitive intracellular stores. Protein tyrosin kinase inhibitors abolished calcium mobilization from these stores (42).

Furthermore IgA immunecomplexes or aggregates of soluble IgA and IgG activate human MC to produce IL-6 and TNFα (34). Also rat MC were stimulated to produce increasing amounts of IL-6 using dimeric and polymeric IgA. IL-6 has been reported to induce matrix protein transcription and autocrine growth in MC in vitro (43,44). In vivo glomerular IL-6 overexpression was detected in human

glomerulonephritis types characterized by MC hypercellularity such as IgAN and some types of lupus nephritis (45-49).

Binding of monoclonal aggregated IgA to MC in vitro furthermore leads to enhanced expression of the nuclear factor-kappa B (NF-kappa B) (50). This increased expression of NF-κB induces e.g. expression of monocyte chemo-attractant protein-1 (MCP-1), IL-8 and interferon-inducible protein 10. Preincubation of MC with Fc-fragments of IgA led to a complete blocking of this effect (49,50).

Enhanced production of the chemoattractant IL-8 (51) may lead to accumulation of polymorphonuclear cells (PMN) in biopsies of patients with IgAN. Evenmore increased numbers of IL-8 and TNFα-positive cells correlate with the amount of proteinuria and the number of IL1α, TNFα and IL-6 positive cells are associated with hypercellularity of the renal mesangium (44,49,52,53).

IV. IGA-RECEPTORS AND IGAN

Because of increasing evidence of receptor mediated activation of mesangial cells it seems more and more likely that binding of IgA or IgA-immunecomplexes is mediated via an receptor on the surface of human renal MC. Therefore the known receptors, especially the Fc receptor for IgA (CD89, FcαRI) will be described in the following paragraph in more detail.

IV.1 FcαRI/CD89

The DNA sequence of a receptor for the Fc-tail of IgA expressed on myeloid cells was published earlier (54). The 1.6 cDNA clone was isolated from PMA-stimulated U937 cells, using a known monoclonal antibody specific for CD89 (My43) (55). The gene of CD89 consists of 5 exons and is located on chromosome 19, at position 19Q13.4 (56), which is different from all other Fc receptors. They are located on chromosome 1.

The protein backbone of CD89 consists of two extracellular Ig-like domains (206 aa) and carries one potential O-linked, and 6 potential N-linked glycosylation sites. The transmembrane part is 19 aa long and has a positive charged arginine which is necessary for association of CD89 with the FcR γ-chain. The FcR γ-chain is a homodimer-signaling unit. Like other Fc receptors lacking an intracellular signaling motif, signaling into the cell is initiated via this dimeric γ-chain with a size of 10 KD (57). Binding to CD89 leads to phosphorylation of the intracellular ITAM motifs on the γ-chains (58) activating the signaling pathways downstream into the cell.

CD89 is expressed on the surface of neutrophils (59,60), eosinophils (61,62) and cells of the monocyte/macrophage lineage (63). The predicted molecular weight of this receptor is 30 KD (54), however the molecular weight of CD89 on monocytes and neutrophils was found to be 55-75 KD and 70 – 100 KD for CD89 expressed on eosinophols.These results and further deglycosylation experiments (61,62,64) indicate that CD89 is highly glycosylated and that its glycosylation is dependent on the CD89 expressing cell.

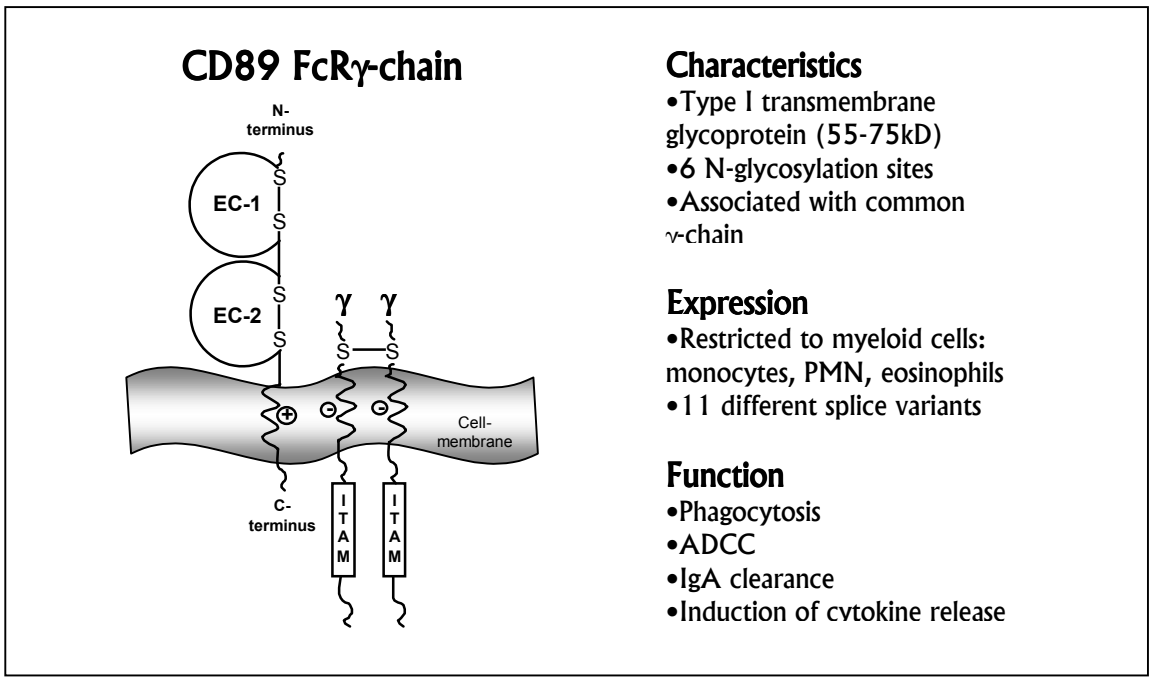


Figure 1: Structure and characteristics of the Fc-Receptor for IgA (FcαRI/CD89): The extracellular domain 1 and 2 (EC-1 and EC-2), as well as the associated pair of γ-chains with their signaling (ITAM) motifs are depicted. Furthermore the characteristics of CD89 the cellular distribution and its known functions are summarized.

The expression of CD89 on human renal MC is controversial. Expression of mRNA of the Fc receptor CD89 has been suggested on human MC (38,39). Activation of human MC with IL6 or TNFα led to increased binding of IgA accompanied by an increase of mRNA expression of CD89. However, no evidence was provided for the direct involvement in the binding of IgA to these cells via CD89 (39). Further mRNA expression of CD89 was demonstrated in whole human glomeruli in 40% of patients with IgAN. In healthy individuals and patients with mesangial proliferative glomerulonephritis distinct from IgAN no CD89-expression was found suggesting an absence of CD89 expression on human MC *in situ* (65,66). Even more CD89-surface expression was not detectable on human MC using known monoclonal antibodies against CD89. However binding of IgA let to activation of MC independent of CD89 (40).

CD89 has different functions dependent on the cell. In macrophages and neutrophils IgA mediated phagocytosis is evident as shown by several investigators (55,63,67-69), Furthermore release of cytokines initiated by crosslinking of CD89 with IgA or monoclonal antibodies has been shown. Release of TNFα, IL1α, IL-6 and some other cytokines from macrophages has been stated (70). All the cells mentioned above and expressing CD89 show antibody dependent cell-mediated cytotoxicity (ADCC) as another effector function of this receptor (71-75). CD89 dependent degranulation is reported for neutrophils and eosiniphils using aggregated IgA resulting in e.g. release of neurotoxins from eosinophils (55,76-80). The ligand for CD89, human IgA1, has been studied for its binding domain. It has been found that the Leu^{257}-Gly^{259} region in Cα2 and the Pro^{440}-Phe^{443} region in Cα3 is crucial for binding to CD89 (81,82).

VI.2 Asialoglycoprotein-receptor and mannose receptor

Other receptors, such as the asialoglycoprotein-receptor (ASGP-R) and mannose receptor could be involved in binding of IgA to MC. Since reliable poly- and monoclonal antibodies against the mannose receptor have been generated (83,84) and it has been suggested that activated mouse MC express this receptor (84), we investigated its expression on human MC. Neither on resting nor on activated human MC we detected protein expression of the mannose receptor using flowcytometry.

ASPG-R, a 44 KD single subunit receptor of the C-type lectin family, is known to be exclusively expressed on human and rat hepatocytes and involved in the clearance of galactose-terminal glycoproteins for example human IgA1 (85-87) which is eliminated via endocytosis (88). IgA1 has sialic acid residues in its O-linked oligosacharide side chains located in the prolanged hinge region of the immunoglobulin with which it can bind to the receptor. IgA2 on the other hand can not bind to this receptor (89-91). It is thought that clearence of IgA1 by ASGP-R is one of the main routes of clearance of this subclass of IgA.

Recently it was reported that ASGP-R is expressed on human and rat MC using RT-PCR (92). In this study binding and catabolism of IgA by human and rat MC was saturable and partly inhibitable by galactose but no other carbohydrates.

IV.3 Secretory component

Secretory component is expressed on the basolateral site of secretory epithelial cells and also known as poly-IgA receptor facing the blood compartment. This receptor specifically binds to J-chain associated dimeric/polymeric IgA and pentameric IgM. After binding of e.g. dimeric IgA it is transported through the cell to the apical site

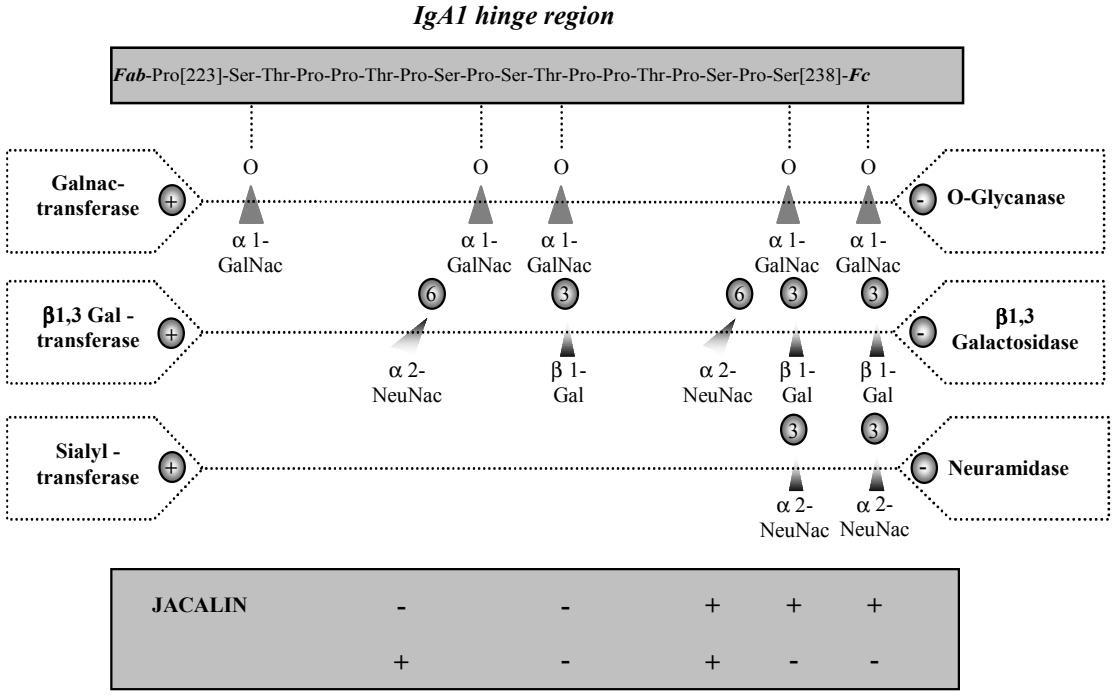
via endocytosis. There, after cleavage of the membrane-anchoring domain of the membrane bound secretory component sIgA is released into the glandular secretions (93,94). There it is responsible for neutralisation of microbes and toxins and prevents unwanted antigens to pass the mucosal barrier (95,96). Until now there is no evidence for expression of this receptor in the kidney.

V. IGA GLYCOSYLATION AND IGA-IMMUNECOMPLEX-FORMATION IN IGAN

Human IgA1 has an O-glycosylated hinge region unique to circulating immunoglobulins. There is raising evidence of changes of the glycosylation of the hinge region of IgA1 in IgAN. Observations of altered lectin binding to IgA1 in IgAN suggest that the O-glycan chains may be undergalactosylated (97-101). More precise structural investigations using fluorophore-assisted carbohydrate electrophoresis (FACE) to analyze IgA1 O-glycans in IgAN and controls demonstrates that in IgAN, the IgA1 O-glycan chains contain increased terminal GalNAc. This could provide evidence that the well-described alterations of lectin binding to IgA1 in IgAN are due to increased occurrence of ungalactosylated GalNAc units which may be due to an absolute increase in the number of O-glycans carried by IgA1, or to a reduced frequency of O-glycan galactosylation (102). So, the deficiency of galactose in the hinge region of the IgA1 molecule may result in the generation of antigenic determinants containing GalNAc residues that are recognized by naturally occurring IgG and IgA1 antibodies followed by the generation of immune complexes (97,98). The IgG antibodies detected in these immunecomplexes are mainly of the IgG2-subclass, however the mesangial IgG-deposits in human IgAN contain mainly IgG of the subclasses one and three. This failure of deposition of IgG2 in the renal mesangium is most likely dependent of the lack of human MC to express the Fc□RII. The relevance of these immunecomplexes is not clear because it has been shown that complement is activated in IgAN via the alternative pathway (103-105) Furthermore the formation of IgA1-IgGcomplexes may affect the plasma level of IgA1 by reducing the rate of its elimination and catabolic degradation by the liver (97,98). Another study found immunoglobulin A-fibronectin complexes to be elevated in patients with IgAN (106). In a recent study using two independent mouse models (gene knockout and antisense transgenic), both manifesting deficiency of an anti-inflammatory protein, uteroglobin (UG), were shown to develop almost all of the pathologic features of human IgA nephropathy. They demonstrate that fibronectin-uteroglobin heteromerization, reported to prevent abnormal glomerular deposition of fibronectin and collagen, also abrogates both the formation of IgA-fibronectin

complexes and their binding to glomerular cells. Moreover, UG prevents glomerular accumulation of exogenous IgA in UG-null mice (107).

Figure 2: Scheme of the IgA1 hinge region from proline [223] upto serine [238] (adapted from Emancipator 1999)



Furthermore it has been shown that the production of polymeric IgA is reduced in the mucosal immune system of patients with IgA-N. This effect could be due to a mucosal gamma delta T cell defect, and could explain the impaired mucosal IgA responses to immunisation, however polymer IgA1 production by the bone marrow is increased (108-110).

Therefore altered production rates of IgA and binding-characteristics of IgA/IgA-immunecomplexes to a suggested FcR for IgA on human MC in patients with IgAN could lead to an explanation on deposition of IgA(-immune)-complexes and inflammation in the renal mesangium. Furthermore, altered hinge region glycosylation may alter IgA1 structure, modifying interactions with matrix proteins, IgA receptors and complement, and therefore influence mesangial deposition and subsequent injury through mechanisms other than classical antigen-antibody reactions. Furthermore the clearance of IgA through the hepatic ASGP-receptor or Fc alpha receptors on circulating white cells may also be impaired (109).

VI. INFILTRATING CELLS DURING GLOMERULONEPHRITIS

VI.1 Neutrophils

There is accumulating evidence that neutrophils are involved in inflammatory injury in IgAN. Histologic examination revealed increased neutrophils and monocyte/macrophage infiltration in IgAN compared with other glomerulonephritides. Higher numbers of infiltrating neutrophils were associated with higher levels of serum levels of IL-8 and IL-8 autoantibodies and was correlated with more severe pathology (111). Furthermore it appeared that the increased renal infiltration of PMN which have a high potential for production of reactive oxygen species might induce the glomerular injuries in patients with IgA nephropathy (112,113). Others found a strong correlation between episodes of macroscopic hematuria and the glomerular influx of neutrophils and monocytes/macrophages. They conclude that, in the acute phase of mesangial IgA nephropathy, PMN and monocytes are present and presumably participate in glomerular injury (6,114).

Glomerular infiltration by neutrophils is also characteristic of acute experimental glomerulonephritis (115). Proteinuria resulting from neutrophil-mediated glomerular injury has been shown in nephrotoxic serum nephritis (116,117), crescentic glomerulonephritis (118) and after intra renal injection of phorbol myristate acetate (PMA) (119), or of cobra venom factor, which causes complement activation and subsequent PMN chemotaxis (120,121). In each of these described models, PMN depletion markedly diminished proteinuria and resulted in reduction or attenuation of renal disease (118).

VI.2 Monocytes/Macrophages

In idiopathic IgAN, infiltration of macrophages is rarely found or absent in the renal mesangium (115,122,123). However, in patients with IgAN with severe mesangial hypercellularity accompanied by glomerulosclerosis, numbers of infiltrating glomerular macrophages are increased (114,124).

Furthermore the involvement of monocytes and macrophages in various glomerulonephritides has been clearly established (125). In particular their involvement has been associated with proliferative forms of glomerulopathies (126,127). Experimental evidence has been provided by rodent models of glomerulonephritis (128-130). In contrast in some cases infiltrating monocytes may serve merely to remove immune complexes and do not contribute to the glomerular injury (131). Recent interest has focused on the role of macrophages in the pathogenesis of focal glomerulosclerosis (132,133). Both glomerular hypercellularity and expansion of the extracellular matrix are thought to be of

primary importance in the development of capillary obsolescence and glomerulosclerosis. In the remnant kidney model in the rat Van Goor and colleagues (125) showed that macrophages play a central role in the development of focal glomerulosclerosis. As described by Floege et al., the development of glomerulosclerosis in this model is preceded by mesangial proliferation and mesangial matrix expansion (134).

VII. SCOPE OF THIS THESIS

For a better understanding of the pathogenesis of human IgA-Nephropathy, we focussed on different questions in the course of this disease. We set up different experimental approaches to clarify the role of interleukin-6 during mesangial development and mesangial cell proliferative glomerulonephritis using an experimental rat anti-Thy-1 model (Chapter 2). During IgAN the role of infiltrating cells is not yet clear therefore we performed selective monocyte/neutrophil-depletion experiments to be able to point out the possible differential roles of infiltrating inflammatory cells during experimental mesangial cell proliferative glomerulonephritis (Chapter 3).

During IgA-N deposition of IgA and IgA-IC in the glomerulus takes place. To evaluate interactions of human IgA with its known Fc-receptor (CD89) which had been suggested to be expressed on human renal MC we developed novel specific reagents for further characterization of this receptor on mononucleated cells and found that the activated receptor CD89 is shedded from the cell surface. This process is FcR γ-chain dependent (Chapter 6). Furthermore we demonstrated that human mesangial cells fail to express CD89 in culture and in kidney sections(Chapter 4). After generating new monoclonal antibodies against IgA-binding proteins derived from neutrophils we observed also binding of this antibody to human MC. This and further experiments demonstrate the presence of an other molecule (s) able to bind IgA on the surface of human renal mesangial cells (Chapter 5).

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