

Pathogenesis of IgA Nephropathy

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In IgA nephropathy (IgAN), there is dysregulation of the IgA response to a wide range of antigens. The dysregulation promotes synthesis of polymeric IgA1 (pIgA1) with physicochemical characteristics that favor mesangial deposition, including altered O-glycosylation of the hinge region. This may be the synthesis of IgA in the systemic compartment, which has the phenotype of mucosal IgA. There is not a change in IgA1 structure to an entirely abnormal form; rather, there is a shift that results in a proportional increase in forms of IgA1 also found in healthy individuals. Altered O-glycosylation could favor pIgA1 deposition by promoting formation of macromolecular IgA and immune complexes. Mesangial injury follows through interactions of pIgA1 with the cells and extracellular matrix proteins of the mesangium and the activation of complement. The final clinical expression of IgAN also depends on generic factors, including hypertension and proteinuria, and a fibrotic renal response. No single "IgAN gene" has been identified, and it is likely that multiple interacting genes will eventually prove to underlie susceptibility to IgAN and the risk of progressive renal disease. These new pathogenic insights have not yet led to new therapeutic opportunities.

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IgA NEPHROPATHY (IgAN) is the most common pattern of glomerulonephritis identified in all parts of the world where renal biopsy is widely practiced. A substantial minority of patients known to have IgAN will develop progressive renal insufficiency and eventually require renal replacement therapy. It follows that the elucidation of the pathogenesis of IgAN is a key research goal that, if followed by the design of successful specific treatment interventions, will have a substantial positive health impact.

The initiating event in the pathogenesis of IgAN is the mesangial deposition of IgA, which is predominantly polymeric IgA of the IgA1 subclass (pIgA1). With or without the additional deposition of IgG and C3 complement, this could be associated with glomerular inflammation and injury with the potential for that injury either to resolve or heal with sclerosis. Codeposits of IgG and complement components are not mandatory for disease activity or progression, and their presence at diagnosis does not correlate with clinical outcome. Subsequently, tubular atrophy and interstitial fibrosis could follow, leading to progressive renal failure (Fig 1). Although the deposition of IgA and the mechanisms by which IgA provokes glomerular inflammation are specific to IgAN, subsequent "downstream" inflammatory events and their consequences are generic and appear to differ little from common mechanisms of progression of chronic renal disease.

INSIGHTS ON PATHOGENESIS FROM CLINICAL OBSERVATION

A number of points must be taken into account if a description of the pathogenesis of IgAN is to be consistent with clinical observations in IgAN.

- Mesangial IgA deposition may be widespread in apparently healthy individuals who have little or no clinical evidence of renal disease at the time the mesangial IgA is identified.
- The extent and intensity of the glomerular injury in response to mesangial IgA deposition are very variable. For example, some individuals have low-grade glomerular inflammation that resolves completely; others have an apparently morphologically similar lesion yet develop slowly progressive renal insufficiency. Still others have a more fulminant necrotizing inflammation with crescent formation, which could occur in the initial phase of the disease or be superimposed on preexisting, more indolent damage.
- Recurrent mesangial IgA deposition is very common after renal transplantation. Recurrence is increasingly frequent with duration of transplantation, occurring eventually in approximately 50% of all patients.¹ In addition, occasional unwitting "experiments" in which cadaveric kidneys with mesangial IgA deposits were transplanted into recipients with primary renal disease other than IgAN have resulted in resolution of the IgA deposits within weeks.^{2,3} These findings strongly suggest that IgAN is a consequence of host susceptibility, including

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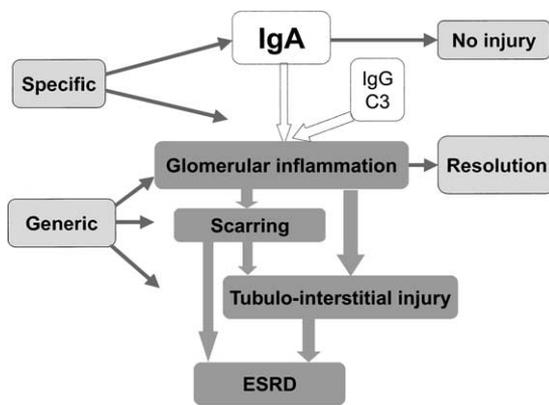


Fig 1. Overview of the pathogenesis of IgA nephropathy. IgA deposition with or without associated IgG and complement leads to mesangial inflammation and injury, which could resolve or lead on to progressive renal scarring and eventually end-stage renal disease (ESRD). Although the deposition of IgA and the initiation of mesangial injury are specific to IgAN, subsequent “downstream” events are likely generic to other progressive renal disease.

abnormalities of the IgA immune system, rather than an intrinsic kidney abnormality.

- Elevated serum IgA per se is not sufficient to cause IgAN. Thus, patients with IgA myeloma, even with a large circulating load of pIgA1, are at risk of developing cast nephropathy rather than IgAN. Likewise, in HIV/AIDS, when there could be very high quantities of circulating polyclonal pIgA, IgAN is only one of a number of patterns of glomerular disease which are seen.⁴
- Some patients with IgAN also develop Henoch-Schönlein purpura. Henoch-Schönlein purpura is a systemic vasculitis in which skin, joint, and gut involvement coincides with a renal lesion that could be indistinguishable from IgAN. Mechanisms by which some individuals develop Henoch-Schönlein nephritis and others a “renal-limited” lesion, IgAN, are not clear. This issue is not further discussed here; the relationship between IgAN and HSP has been recently reviewed.⁵

MAJOR ELEMENTS IN THE PATHOGENESIS OF IgA NEPHROPATHY

There are three elements that can contribute to the development of IgAN, and the extent to which each is operational decides the severity, tempo, and eventual outcome of IgAN in any individual. These elements are:

1. Synthesis and release into the circulation of pIgA1 with characteristics that favor mesangial deposition.
2. The “responsiveness” of the glomerular mesangium as judged by:
 - its susceptibility to mesangial deposition;
 - its capacity to mount an inflammatory response to that deposition; and
 - its capacity to deal with that response by resolution of inflammation rather than ongoing sclerosis.
3. The tendency of the whole kidney to respond to injury by mounting a response favoring progressive renal injury, including hypertension, proteinuria, tubular atrophy, and interstitial fibrosis.

Each of these three elements could have a significant genetic component influencing the eventual phenotype of the disease in any individual. Genetic approaches to analysis of the pathogenesis of IgAN are assuming increasing importance with recent developments in our knowledge of the human genome and are discussed further subsequently.

The likely interactions of these elements of pathogenesis are shown in Figure 2.

IgA “Load” and the Development of IgAN

Some circulating pIgA1 has features that promote mesangial deposition and that will be described in this review as “pathogenic.” The eventual extent and severity of disease could depend on the “load” of pathogenic IgA to which the mesangium is exposed. There could be intermittent large surges of pathogenic IgA into the circulation or continual low-level exposure. The degree of abnormality of the IgA would also influence outcome. Thus, IgA load is a composite of the duration of exposure, the amount of pathogenic IgA that reaches the circulation, and also the extent of the qualitative abnormality of the IgA that circulates. Therefore, intermittent exposure to IgA, which is highly pathogenic, could have the same pathogenic impact as prolonged exposure to IgA, which is only modestly abnormal.

Is IgA Nephropathy a Single Disease?

It is also important to bear in mind that the entity called IgAN is defined by a pattern of glomerular

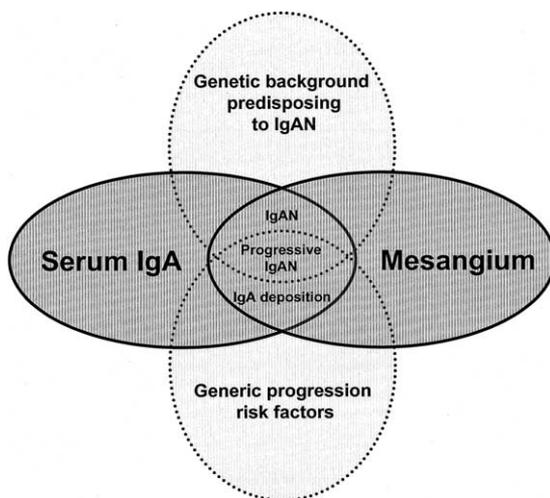


Fig 2. Interactions of major elements of pathogenesis of IgA nephropathy. The interactions of different pathogenic elements required to produce IgA nephropathy are shown. Total circulating serum IgA is the source of mesangial IgA deposits in IgAN. The fraction of total serum IgA that has a propensity for mesangial deposition is however small, and that capable of initiating glomerulonephritis smaller still. The precise physicochemical properties of this IgA and the pathways controlling its production are discussed in the text. The response of the mesangium, and in particular the mesangial cell (MC), to the deposited IgA is critical to the development of IgAN. A failure of MC clearance mechanisms could contribute to mesangial IgA accumulation, whereas MC activation with release of proinflammatory cytokines and extracellular matrix components will drive GN and glomerulosclerosis. Without an appropriate genetic predisposition to develop IgAN, IgA deposition can be a benign process with little to no risk of triggering glomerulonephritis. However, given an appropriate genetic background, serum IgA responses will favor mesangial IgA deposition and the mesangial response will take on a proinflammatory phenotype, resulting in clinically significant IgA nephropathy of varying severity. Finally, if generic progression risk factors coincide, this will increase the likelihood of progressive renal impairment and could ultimately determine the rate of decline in renal function.

morphology and no assumption can be made that it will eventually prove to be one entity with a single pathogenic mechanism. Intuitively, it seems more probable that several mechanisms or combinations of mechanisms can all produce IgAN; our growing understanding of the pathogenesis could eventually allow a more realistic classification of different subsets of IgAN.

We discuss each of these areas of pathogenesis and their genetic background with special emphasis on recently published work.

THE HUMAN IgA IMMUNE SYSTEM

Structure of Human IgA

There are two subclasses of human IgA, IgA1 and IgA2, and two allotypes of the latter, IgA2m1 and IgA2m2.⁶ IgA1 and IgA2 can both exist in monomeric (mIgA) or polymeric (pIgA) forms. IgA polymers are usually dimers (dIgA) (although higher molecular weight forms are also found) and contain the 21-kD joining protein J chain. IgA and J chain are cosynthesized by the plasma cell and the polymers are assembled before secretion.⁷

The main structural difference between the IgA subclasses is the 18-amino acid hinge region situated between the CH1 and CH2 domains of IgA1, which is lacking in IgA2.⁶ Although short, the hinge region forms a distinctive feature of IgA1. It consists of an unusual repeating sequence of proline, serine, and threonine residues, and it carries multiple O-linked carbohydrate side chains (Fig 3). This type of glycosylation is rare in serum proteins and is not found in other serum immunoglobulins, including IgA2. The composition of each O-glycan chain is variable and could consist of GalNAc alone with or without additional galactose and sialic acid (Fig. 3). Therefore, an array of different IgA1 O-glycoforms could be found in serum IgA1 at any time.

Human IgA Production

IgA plasma cells are mainly located at mucosal immune sites, where they produce very large quantities of IgA of both subclasses, the relative proportions varying in different locations. Mucosally produced IgA is rapidly transported across the adjacent epithelial barrier into external secretions with very little entering the blood. This active transport is mediated by the polymeric immunoglobulin receptor (pIgR), which is expressed on the basolateral surface of epithelial cells and recognizes J chain-containing immunoglobulins (pIgA and IgM). Once bound, the pIgR-pIgA complex is internalized and secreted at the luminal side of the epithelial cell. Such transported pIgA retains a portion of the pIgR (now termed the secretory component [SC]), forming secretory IgA (sIgA). J chain is essential for active mucosal IgA secretion, and virtually all mucosally produced IgA is polymeric.⁷

Despite the marked predominance of mucosal IgA production, appreciable quantities of IgA are

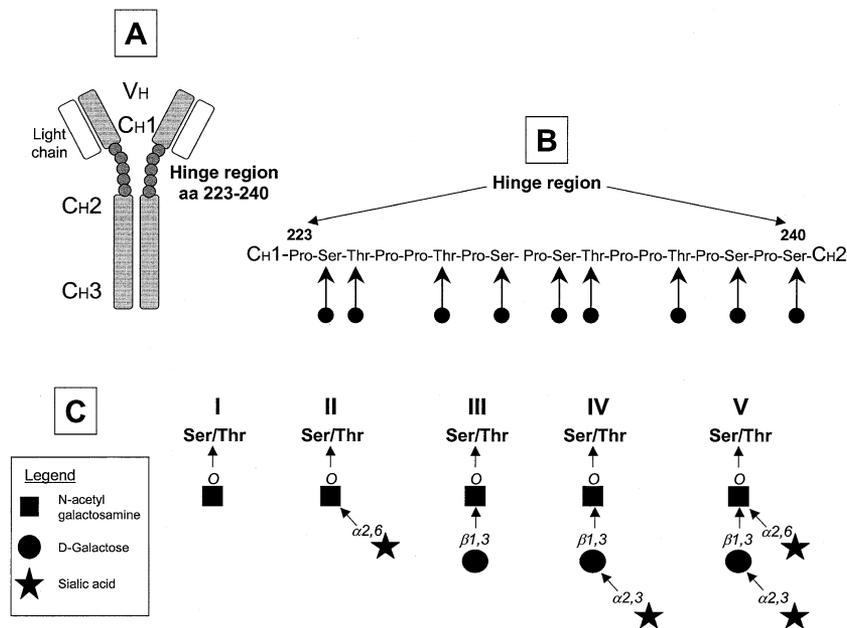


Fig 3. O-glycosylation of human IgA1. (A) Structure of monomeric IgA1. There are two $\alpha 1$ heavy (H) chains and two κ or δ light chains. The $\alpha 1$ heavy chain has a variable (V) region and three constant region domains (CH1–3), with an 18 amino acid (aa) hinge region lying between the CH1 and CH2 domains, from aa 223–240 inclusive. **(B) Amino acid sequence of the IgA1 hinge region.** All nine serine and threonine residues (marked with arrows) are potential sites for O-glycosylation, although the completeness of glycosylation is variable, and no more than five or six sites are likely to be occupied in normal serum IgA1.¹⁵¹ **(C) The O-glycan chain types found in IgA1.** Each O-glycan chain is based on a core N-acetyl galactosamine unit (GalNAc; black squares) O-linked to serine or threonine. This can exist alone (chain type I), but usually carries galactose (black circles) and sialic acid (black stars) to form chain types II–V.¹⁵² Each IgA1 molecule carries a mixture of these five chain types, giving rise to a wide array of possible O-glycoforms.

also made in systemic immune sites, most notably the bone marrow. This IgA is nearly all monomeric IgA1, and is secreted into the circulation. Therefore, human serum IgA is mainly mIgA1.⁶

Functions of Human IgA

The major function of IgA is in mucosal defense. pIgA in mucosal secretions and on the internal side of the mucosal barrier effectively binds microbes and toxins, neutralizing them and preventing invasion further into the body. Although it has been shown to fix complement in some situations, IgA is much less effective at doing so than IgG and IgM. This could help to prevent excessive inflammation at mucosal surfaces, where antigen exposure is continuous but is generally dealt with effectively without the need for acute and damaging inflammatory reactions.⁸

The function of systemic IgA is less well understood. It could act in an antiinflammatory fashion, damping down systemic immune responses and

clearing antigen as IgA immune complexes (IgA-IC), hence the association between IgA synthesis and otherwise immunosuppressive cytokines such as IL-10 and TGF- β .⁹

Control of Human IgA Production

Systemic production of IgA appears to be under similar T cell control mechanisms to IgG production, antigen exposure resulting in serum IgA antibody production showing broadly similar patterns of primary and secondary immune responses and affinity maturation as seen with IgG.¹⁰ As is the case for other immunoglobulin isotypes, type 2 T cell cytokines (IL-4, 5, and 6) promote B cell class switching to IgA, and subsequent proliferation and differentiation of IgA-producing cells.¹¹ However, IgA production is also specifically and potently promoted by the cytokines IL-10 and TGF- β ,¹² which have suppressive effects on IgG production. The control of mucosal IgA production is less well understood, although Th2 T cells are undoubtedly

involved.^{13,14} A variety of cell types probably contribute to the maintenance of a mucosal microenvironment strongly favoring pIgA production. The factors that influence coexpression of J chain by mucosal but not systemic IgA plasma cells are unknown, but could be of great relevance to our understanding of the immunopathogenesis of IgAN.¹⁵

The mucosal and systemic immune systems are largely under separate control and produce IgA with differing features and functions. The homing of subpopulations of activated T and B cells to the correct effector sites is mediated by highly specific receptor–ligand interactions; lymphocyte cell-surface homing and chemokine receptors interact with location-specific vascular endothelial cell ligands.¹⁶ Mucosally and systemically activated cells migrating through the circulation express distinct receptors and are recruited back to their priming tissue by recognition of the relevant vascular ligands to effect an immune response in the appropriate location. However, there is inevitably and necessarily a degree of “crosstalk” between the different immune compartments, and the human mucosal and systemic IgA immune responses are intricately linked and regulated. There appears to be a “mucosa–bone marrow axis,” in which there is continual trafficking of antigen-specific lymphocytes and antigen-presenting cells between mucosal sites and primary lymphoid tissues such as the tonsils, spleen, and bone marrow.^{17–19} This is illustrated by the phenomenon of oral tolerance, by which systemic immune responses to mucosally encountered antigens are actively suppressed.²⁰ The effect is seen particularly with frequently encountered nonpathogenic antigens that are readily dealt with in the mucosa, for example, those derived from food or commensal bacteria. Oral tolerance has been shown to occur in humans, but most of the evidence on its control comes from experimental animals. Oral tolerance is mediated by antigen-specific T cells that arise in the mucosa but migrate to the systemic compartment. T cell subsets implicated in oral tolerance include Th2 cells, Tr (T-regulatory) and Th3 cells, which produce the immunosuppressive cytokines IL-10 and TGF- β ,²¹ and $\gamma\delta$ T cells.²² $\gamma\delta$ T cells are a minority T cell population in most compartments of the immune system, but they have particular importance in mucosal immunity and play a pivotal role in mucosal IgA production.²³ The surface marker

expression of $\gamma\delta$ T cells is less well defined than that of $\alpha\beta$ T cells, and they are often classified instead by their V region use. The polymorphic V regions of the γ and δ T cell receptor genes are grouped in families, and characteristic V γ and δ families predominate in the $\gamma\delta$ T cell populations found in different immune system compartments. Furthermore, $\gamma\delta$ T cell subsets expressing different V region families also differ in their homing receptor and cytokine expression,²⁴ suggesting that V region use could define functional $\gamma\delta$ T cell subsets.

Interestingly, all the cell types implicated in the control of oral tolerance have also been associated with promotion of IgA production. TGF- β is a key cytokine in the control of IgA production, not only promoting IgA production and suppressing other isotype responses, but also inducing expression of the mucosal retention receptor $\alpha E\beta 7$ by mucosal lymphocytes.²⁵ Functional analysis of these T cell subtypes has not yet made clear the extent of overlap between Th3 cells, Tr cells, and $\gamma\delta$ T cells.

Clearance of Human IgA

IgA and IgA-IC are cleared from the circulation at least partly through the liver. The hepatic asialoglycoprotein receptor (ASGPR) and the Fc α receptor CD89 are IgA-binding receptors expressed in the liver, although in humans, their relative contributions to IgA catabolism have yet to be fully elucidated.^{26–28} IgA is also catabolized by monocytes/macrophages and neutrophils through their expression of CD89, and this is another potentially important route of clearance.²⁹

ANIMAL MODELS OF IgA NEPHROPATHY

Numerous animal models of IgAN have been studied, generally involving immunization with enteral and parenteral antigen, or infusion of preformed immune complexes. However, there are significant differences between animals and humans in the control of IgA production and also the structure of IgA; for example, IgA in all nonprimate mammals is structurally more like human IgA2 than IgA1, and no nonprimate species has a hinge region analogous to human IgA1. Caution should therefore be exercised in extrapolating the mechanisms of IgA deposition in these animal models to human IgAN.

In contrast, animal models have been highly informative about immune and inflammatory

Table 1. Properties of IgA in Normal Subjects and in IgA Nephropathy*

Properties of IgA	Controls		IgAN	
	Serum IgA	Mucosal IgA	Serum IgA	Mesangial IgA*
Size	Mostly mIgA	Mostly pIgA	Increased pIgA	pIgA
Subclass	Mostly IgA1	IgA1 & IgA2	Increased IgA1	IgA1
Proportion of λ light chain compared with normal serum IgA	—	Not known	Increased	Increased
Charge compared with normal serum IgA	—	Not known	Anionic	Anionic
O-glycosylation	Heavily galactosylated and sialylated	Unknown galactosylation decreased sialylation	Reduced galactosylation, increased or decreased sialylation	Reduced galactosylation and sialylation

* The common features of serum and mesangial IgA in IgAN (right-hand columns) constitute the "pathogenic IgA phenotype" [see text].

events that follow IgA deposition, for example, using the anti-Thy 1.1 model of mesangial proliferative GN.

Because of these limitations, this review focuses mainly on information obtained from human studies.

IgA PRODUCTION IN IgA NEPHROPATHY

One of the key factors determining the development of IgAN is the presence in the circulation of IgA molecules with propensity to mesangial deposition (Table 1). Numerous aspects of IgA and IgA production are abnormal in patients with IgAN. However, patient cohorts are highly heterogeneous in respect to many of these abnormalities, displaying great variability both in degree and in the proportion of patients affected, making it difficult to identify a clear and consistent pattern of IgA abnormalities common to all patients. This supports the notion that more than one pathogenic mechanism could result in the production of pathogenic circulating IgA. We therefore propose the concept that there is a "pathogenic IgA phenotype," a theoretical composite of all the characteristics thus far identified as being associated with mesangial IgA deposition and IgAN.

Deposited mesangial IgA must come from the blood. High plasma IgA alone is not sufficient to produce mesangial IgA deposits, and therefore patients with IgAN must produce a pool of circulating IgA molecules with special characteristics, which particularly promote mesangial deposition.

For these molecules to accumulate in the kidney, the rate of their deposition must exceed that of clearance.

Characteristics of Circulating IgA in IgAN

Many studies have demonstrated modestly increased serum levels of IgA in IgAN. However, because raised IgA levels alone do not necessarily produce IgAN, it is likely that some other feature of circulating IgA in IgAN is responsible for mesangial deposition.

Physicochemical Properties of Circulating IgA in IgAN

Serum IgA in IgAN displays a number of unusual physical characteristics (Table 1). The increase in serum IgA is accounted for by pIgA1, with mIgA and IgA2 levels generally being normal.³⁰ The serum IgA of patients is anionic,^{31,32} δ light chains are overrepresented,³³ and the IgA1 O-glycosylation profile is altered in comparison to controls.³⁴

IgA Glycosylation. The abnormal O-glycosylation of IgA1 has been well studied in recent years, and there is increasing evidence for its involvement in the pathogenesis of IgAN. Many studies have investigated the binding of various O-glycan-specific lectins to serum IgA1 from patients with IgAN.³⁵ Although lectins are convenient tools for indicating abnormal glycosylation patterns, they cannot provide precise structural information about the O-glycan chains expressed by IgA1 molecules, because their

specificities are not absolute, and their binding could be affected by factors other than the individual O-glycan moieties present.³⁵ However, such studies have provided useful data, clearly and consistently demonstrating that serum IgA1 in IgAN is abnormally O-glycosylated, and strongly suggesting that this abnormality takes the form of reduced galactosylation of the O-glycans, leading to increased frequency of truncated glycan chains consisting of GalNAc alone and possibly to increased exposure of the hinge region peptide itself.³⁶ More precise analysis of IgA1 O-glycosylation has proved challenging, but studies using carbohydrate electrophoresis,³⁷ chromatography,^{36,38} and mass spectroscopy^{39,40} all support a lack of O-linked galactosyl chains in IgA1 from patients with IgAN. Altered sialylation of the IgA1 O-glycans in IgA1 is more debatable because the specificity of sialic acid-binding lectins is unsatisfactory. Both increased⁴¹ and decreased⁴⁰ O-sialylation have been suggested, and further confirmation will need improved analytical techniques.

There is no evidence that IgAN results from a clonal abnormality of IgA-producing plasma cells. The shift in IgA1 O-glycosylation pattern does not even result in a tightly restricted pattern with IgA1 molecules all showing a specific abnormality. Rather there is a shift that slightly favors the appearance of IgA1 molecules with glycoforms less likely to contain galactose (and perhaps sialic acid).

The functional effects of altered IgA1 hinge region O-glycosylation are as yet unproven, but could be expected given the pivotal position of the hinge region in the IgA1 molecule. The hinge region is a short sequence consisting of only 18 amino acids, but it typically carries 10 to 12 O-glycan chains, which contribute approximately half of the molecular weight of the region, depending on the completeness of O-glycosylation. As the glycans extend from the peptide core, they shield it from external exposure and will influence the physical shape and electrical charge of the IgA1 molecule, thus potentially affecting interactions with proteins and receptors.⁴² They could also determine the antigenicity of IgA1, as discussed in more detail subsequently. IgA1 glycosylation also appears to influence matrix interactions, molecules lacking terminal sialic acid, and galactose units have been shown *in vitro* to exhibit increased affinity for the extracellular matrix components fibronectin and type IV collagen.⁴³

Functional Characteristics of IgA in IgAN

Antigen Specificity

In some types of human glomerulonephritis, the presence of immunoglobulin within the glomerulus can be directly attributed to autoantibodies binding to an endogenous antigenic target, to trapping of preformed immune complexes from the blood, or to *in situ* formation of immune complexes. In IgAN, there is no convincing evidence of circulating IgA autoantibodies against a mesangial antigen,⁴⁴ but there are reports of increased levels of circulating IgA-IC. This could arise from increased antigen load and persistent IgA antibody production or from failure of IgA-IC clearance from the circulation.

Increases in circulating IgA antibodies against a variety of antigens have certainly been described, although no single pathogenic antigen has been established. As is the case for total serum IgA in IgAN, the increase in IgA antibody titers seems to be restricted to IgA1,^{45,46} and pIgA may be represented.⁴⁷ Because the majority of pIgA is mucosal in origin, particular attention has been paid to mucosally encountered antigens as potential triggers for the development of IgAN, and there is indeed convincing evidence for an increase in circulating pIgA1 antibodies against a variety of mucosal antigens, both microbial and environmental. However, the same can also be seen for systemically encountered antigens,^{45,46,48} suggesting that there is a general tendency to overproduce pIgA1 antibodies in IgAN.

Large immune complexes that persist in the circulation are most susceptible to mesangial trapping. IgA-IC composed of pIgA will be likely to meet these criteria; they will be large by virtue of the polymeric nature of the IgA, and the low efficiency of IgA complement fixation could favor both large size and persistence in the circulation, because complement interrupts IC lattice formation and is involved in complex internalization by phagocytes.

Furthermore, in a study of antibody responses to systemic immunization with tetanus toxoid in IgAN, the pIgA1 antibody response was not only increased and prolonged,⁴⁷ but the IgA was also of low affinity, although IgG affinity was normal.¹⁰ This suggests that some IgA antibodies could be functionally abnormal in IgAN, leading to failure

of antigen clearance and consequent persistence of IgA production and circulating IgA-IC.

Another intriguing explanation for the presence of circulating IgA-IC in IgAN is provided by the demonstration in patients' serum of IgG and IgA antibodies against agalactosyl IgA1 O-glycans and the "naked" IgA1 hinge region peptide.^{49,50} This raises the possibility that in some IgA-IC, abnormally O-glycosylated IgA1 is actually the antigen rather than the antibody, and therefore continued production of abnormally O-glycosylated IgA1 will ensure the persistence of circulating IgA-IC.

Altered IgA Clearance in IgAN

Failure of normal IgA and IgA-IC clearance mechanisms could also facilitate their persistence in the serum. This has not been thoroughly studied in IgAN, because the normal pathways of IgA catabolism in the human are not well understood. *In vivo* studies tracking the clearance of radiolabeled IgA from the circulation have demonstrated that the liver has an important role and that the rate of clearance is reduced in IgAN.⁵¹ The hepatic ASGPR is probably a key hepatic receptor in this process, and its interaction with IgA1 could potentially be affected by abnormal O-glycosylation, although recent reports suggest that the N-linked glycans, elsewhere in the IgA1 molecule, could be the major mediators of IgA1-ASGPR binding.²⁸ However, a recent study of IgA1 binding to the hepatocyte cell line HepG2⁵² demonstrated increased binding of IgA1 from patients with IgAN, arguing against a defective clearance by this route, although it is still possible that a small pool of nephritogenic IgA1 molecules has different clearance properties.

Another route of IgA catabolism is by monocytes and neutrophils, which express Fc α RI, CD89. In IgAN, these cells have been shown to downregulate CD89 expression, which could lead to reduced clearance of IgA from the circulation and potentially contribute to increased serum IgA levels.²⁹ It has also been shown that mIgA purified from patients with IgAN binds less well to CD89 than mIgA from healthy controls, and this could act to disrupt the efficiency of systemic IgA clearance in IgAN.⁵³ Alterations in the posttranslational modification of CD89 have also been reported in IgAN. Myeloid CD89 molecules isolated in IgAN are consistently larger (60-85 kDa) than those of controls (55-75 kDa) and show decreased binding

to a sialic acid-specific lectin indicating impaired sialylation of surface CD89 molecules.²⁹ This could potentially influence the receptor-ligand interaction and could help explain the reduced binding of mIgA seen in IgAN.

Characteristics of Mesangial IgA in IgA Nephropathy

Circulating IgA in IgAN is therefore abnormal in a number of respects. Which of these characteristics might promote mesangial deposition in a given individual?

Examination of the IgA molecules deposited in the kidney will clearly provide crucial insights into this issue, but opportunities for such studies are relatively limited compared with the ease with which serum IgA can be studied. The mesangial deposits always contain IgA1, whereas the presence of IgA2, IgG, and IgM are variable and do not seem to be required for development or progression of glomerulonephritis.⁵⁴ The deposited IgA has been shown to bind SC, and therefore to consist at least partly of J chain-containing pIgA molecules. Compared with serum IgA, IgA eluted from biopsy sections displays a predominance of the δ light chain and is more anionic.⁵⁵ Opportunities to study the O-glycosylation of deposited IgA1 are limited by the modest amount of IgA that can be eluted from a typical renal biopsy core. However, it is clear from two recent studies that the mesangial IgA1 has an O-glycosylation pattern that exaggerates the abnormality seen in serum IgA1, suggesting that altered O-glycosylation is a factor directly promoting mesangial deposition^{40,56} (Table 1).

Attempts to identify the antigen specificity of mesangial IgA have not produced consistent findings. Some viral and bacterial antigens have been detected in mesangial deposits, but the findings are widely variable and could indicate the production of IgA with nephritogenic features during the immune response to certain infections in individual cases rather than implicating these pathogens per se as causative agents.

It is clear that the deposited IgA has the same abnormal physicochemical features as serum IgA in IgAN (summarized in Table 1), the "pathogenic IgA phenotype," but that the mesangial IgA is "enriched" for these abnormalities. This strongly suggests that circulating IgA consists of molecules heterogeneous in all these respects, and it is those

molecules at the most abnormal end of the spectrum that deposit in the mesangium. Therefore, to produce mesangial IgA deposits, a subtle increase in circulating IgA with these characteristics is probably more significant than large changes in total IgA or other physicochemical types of IgA. Which of the pathogenic IgA features are actually responsible for deposition is not clear, but altered O-glycosylation is perhaps the most attractive candidate, because it can affect the three-dimensional shape and charge of the IgA1 molecule, which could modify the interactions of IgA1 with cells and proteins, and there is good evidence for its direct involvement in complex formation.^{49,50}

Control of Production of Pathogenic IgA in IgA Nephropathy

Although it is possible that there are a variety of IgA characteristics that promote deposition, there are no clinically distinct subgroups of patients who might share such differing characteristics and therefore deposit IgA by different mechanisms. How the different elements of the pathogenic IgA phenotype relate to one another is unclear, but it is implausible that each is a totally separate entity; it seems much more likely that they reflect different aspects of a common defect of the IgA immune system. Indeed, there is evidence that some of these properties are coexhibited by the same IgA; for example, the raised serum fraction is restricted to pIgA1, and pIgA1 $\delta\lambda$ is anionic as a result of increased sialylation.⁴¹

Whether the pIgA1 production occurs in the mucosa or the marrow has been a matter of continuing debate. The association of episodic macroscopic hematuria with respiratory and gastrointestinal tract infections that is so characteristic of the disease has led to the suspicion that IgAN is intimately linked with abnormal mucosal antigen handling. This is further suggested by the consistent observation that both mesangial IgA and the increase in serum IgA are polymeric, the type of IgA that is normally produced at mucosal surfaces rather than in systemic immune sites, and several studies that show increased serum levels of pIgA antibodies against mucosal antigens.⁵⁷⁻⁵⁹ However, the presence of pIgA in the circulation cannot be simply attributed to mucosal overproduction and "spillage" into the circulation. Mucosal pIgA plasma cell numbers are normal or even reduced in IgAN,^{60,61} whereas pIgA antibody levels in muco-

sal secretions are not elevated and are sometimes lower than controls.⁶² On the other hand, increased pIgA1 plasma cell numbers are found in the bone marrow in IgAN,^{63,64} and systemic antigen challenge results in increased titers of circulating pIgA1 antibodies^{46,47} with normal levels in mucosal secretions.⁶⁵ Therefore, the overproduction of pIgA1 seems likely to be based in systemic immune sites such as the bone marrow, with both systemic and mucosal antigen challenges resulting in this systemic overresponsiveness. As well as an increase in IgA antibody titers, the IgA immune response to immunization is prolonged in IgAN.⁴⁷ This could be related to a functional defect of IgA antibody affinity¹⁰ leading to antigen persistence in the patients, although IgG function appears to be normal, and the patients do not show any signs of overt mucosal or systemic immunodeficiency.

Alternatively, the systemic immune microenvironment could have an inherent bias toward pIgA production. A number of studies have shown that peripheral blood mononuclear cells and circulating T cells overexpress Th2 cytokines⁶⁶⁻⁶⁸ as well as IL-10 and TGF- β ,⁶⁹⁻⁷¹ both of which are potent promoters of IgA. Studies of circulating lymphocyte populations must, however, be interpreted with caution, because of the diversity of subsets represented. It is not always possible to be confident which subpopulation of lymphocytes are represented, and what are the origin and destination of such cells.

Abnormalities in the specific factors that influence the type of IgA produced in a given situation would be of great relevance in IgAN, but these control mechanisms remain unknown. Normally, mucosal IgA production is almost exclusively polymeric, whereas systemic IgA is monomeric. Presumably, elements of the mucosal microenvironment promote J chain expression. It is also possible that other features of the pathogenic IgA phenotype such as light chain use and O-glycosylation are under similar control to polymer production, and that the pathogenic IgA is actually a "mucosal phenotype" aberrantly occurring in the circulation.

O-glycosylation is of particular interest in this context, because it has the potential directly to influence IgA deposition. IgA1 is O-glycosylated as part of the synthetic process within the plasma cell by the action of various intracellular glycosyltransferases. Abnormal IgA O-glycosylation in

IgAN arises from a synthetic defect; there is no evidence for excess postsecretory degradation of the O-glycan chains,⁷² and the amino acid sequence of the IgA1 hinge region, which provides the template for O-glycosylation, also appears to be normal.⁷³ The O-glycosylation defect in IgAN appears to take the form of reduced galactosylation. The enzyme β 1,3-galactosyltransferase catalyzes the addition of galactose to O-linked GalNAc. We have found some evidence of a functional defect in β 1,3-galactosyltransferase in peripheral blood B cells,⁷⁴ but we have not found any evidence for an overt defect in the activity of this enzyme in bone marrow B cells in IgAN (Buck KS, unpublished observations). However, these studies investigated total B cells from patients and controls, and it is still possible that a minority B cell subpopulation with abnormal β 1,3GT function is responsible for the production of abnormally glycosylated IgA1 in IgAN. The glycosylation of secretory IgA appears to differ from that of serum IgA in normal human subjects with lower sialylation,⁷⁵ demonstrating that the degree of O-galactosylation could well vary between immune sites, although the factors controlling this remain unknown. This is supported to some extent by reports showing that in murine systems, Th2 cytokines have been shown to influence IgA N-glycosylation,⁷⁶ although this data is difficult to extrapolate to the human situation because mouse IgA lacks O-glycosylation.

If this supposition is correct, “aberrantly” glycosylated pIgA1 could be normal in some immune sites such as the mucosa, and its excess presence in the serum in IgAN could be a consequence of defective or misplaced IgA immune responses. In view of the evidence for an imbalance between the mucosal and systemic IgA systems in IgAN, we speculate that mucosal-type antigen handling or regulatory influences could be aberrantly displaced to systemic sites in IgAN. One particularly interesting possibility is that IgAN results from a breakdown of oral tolerance, perhaps on a genetic background favoring IgA production. Support for this theory includes the presence in the circulation of IgA antibodies against food and mucosal environmental antigens^{59,77-80} and evidence of low-level chronic inflammatory activity in intestinal mucosa.^{81,82} $\gamma\delta$ T cells are particularly implicated as mediators of oral tolerance in the mouse,²² and although their role in human oral tolerance is un-

proven, there are several reports of aberrant $\gamma\delta$ T cell populations in IgAN. Cells expressing V δ 3 are deficient from both the duodenal mucosa and the bone marrow in IgAN.^{83,84} Another study found that total circulating $\gamma\delta$ T cell numbers were increased in IgAN and further increased during a systemic immune response,⁴⁸ although the functional subset of these $\gamma\delta$ T cells was not investigated. Finally, peripheral blood $\gamma\delta$ T cells from patients with IgAN have been shown to express TGF- β (an important cytokine in murine oral tolerance) and specifically to promote IgA production by B cells in culture.⁸⁵

THE ROLE OF THE MESANGIUM IN IgAN

The Normal Mesangium

The mesangium, consisting of mesangial cells (MC) and the surrounding mesangial matrix, plays a key role in the maintenance of glomerular homeostasis. The mesangium provides structural support for the glomerular capillary loops; MC contractility controls glomerular filtration, and MC contribute to the continual remodelling, which helps maintain the integrity of the mesangial matrix and the GBM. In addition to these physiological functions, the MC has also been implicated in coordinating the local response to glomerular injury because it is capable of generating a plethora of inflammatory mediators and cytokines and can respond to a number of different hormonal, paracrine, and autocrine signals.^{86,87}

Mechanisms of Mesangial IgA Deposition

Although accumulation of IgA in the mesangium is the pathogenic hallmark of IgAN, not all IgA deposition is associated with the development of glomerulonephritis.⁸⁸ Furthermore, IgA deposition is not necessarily an irreversible phenomenon; mesangial IgA deposits in kidneys inadvertently transplanted into recipients who originally did not have IgAN disappear^{2,3} and sequential biopsy studies suggest that clinical remission is accompanied by disappearance of IgA deposits.⁸⁹ Together this suggests that the mesangium is normally capable of clearing finite amounts of IgA and that processes distinct from IgA deposition are necessary for the development of glomerulonephritis. In IgAN, mesangial IgA accumulation occurs because the rate of IgA deposition either exceeds this clearance capacity and/or the deposited IgA is in some way resistant to mesangial clearance.

IgA deposition cannot be explained by a simple flooding of the glomerulus with high levels of serum IgA that overwhelm mesangial clearance mechanisms. Accepting that the process of IgA deposition is not directed against mesangial antigens, the IgA molecule must therefore possess certain intrinsic physicochemical features that promote mesangial deposition in IgAN, the “pathogenic IgA phenotype” (Table 1). Not all features of this pathogenic IgA will apply to all IgA molecules, perhaps explaining the poor correlation between total serum IgA levels and mesangial IgA deposits. Indeed, the levels of circulating pathogenic IgA could be very low; however, because pathogenic IgA is continuously present in the circulation as a result of intrinsic abnormalities in regulation of IgA production, glomeruli will have a prolonged pathogenic IgA exposure, ie, a high IgA load, resulting in incessant mesangial IgA accumulation and glomerular damage.

It remains unclear which physicochemical characteristics of the pathogenic IgA phenotype dictate mesangial deposition, and could therefore be found in individuals with mesangial IgA but no glomerulonephritis, and which features are responsible for the initiation of a proinflammatory glomerular response in susceptible individuals. In animal models of glomerulonephritis, it has been known for some time that macromolecular Ig-containing complexes are particularly prone to mesangial deposition. It seems likely therefore that the increased levels of serum IgA macromolecules in IgAN will promote mesangial deposition through nonspecific size-dependent mesangial trapping. The exaggerated O-glycosylation defect detected in mesangial IgA1 could promote this phenomenon; it has been shown that aberrantly glycosylated IgA1 molecules have an increased tendency both to self-aggregate⁴³ and form antigen-antibody complexes with IgG antibodies directed against IgA1 hinge epitopes.⁵⁰ Furthermore, altered IgA1 O-glycosylation is a feature also seen in other conditions associated with glomerular IgA deposition.^{34,90} There is also evidence from transgenic mice that soluble CD89-IgA complexes generated after binding of IgA to membrane bound CD89 are associated with massive mesangial IgA deposition.⁹¹ It is possible that circulating Fc α RI-IgA complexes could form part of the circulating pool of macromolecular “pathogenic” IgA in human IgAN, although more recent data suggest

that CD89-IgA complexes might not be specific to IgAN.⁹²

In addition to nonspecific, size-dependent mesangial trapping, there is also evidence that IgA deposition could be influenced by interactions between IgA and specific mesangial matrix components. Studies in renal biopsy material show re-binding of IgA eluates to autologous glomeruli and to some other IgAN samples but not to normal glomeruli, suggesting that specific IgA-matrix interactions could be present.⁹³ IgA1 glycosylation again appears to influence matrix interactions; molecules lacking terminal sialic acid and galactose units *in vitro* have increased affinity for the extracellular matrix components fibronectin and type IV collagen.⁴³ The anionic pI of mesangial IgA could also promote interactions with such mesangial proteins.

Although immunoglobulins with λ light chains do seem to predominate in glomerular deposits in various renal diseases,⁹⁴ it is unlikely that λ light chain use *per se* is the driving force behind deposition in IgAN, because significant amounts of IgA1 λ is found in the circulation of all individuals

Mesangial Cell IgA Receptors and IgA Clearance

For IgA accumulation to develop, the rate of mesangial IgA deposition must exceed that of mesangial clearance. The principal candidate pathway for IgA clearance is through mesangial cell (MC) receptor-mediated endocytosis and catabolism of IgA deposits. Unfortunately, the published data concerning the interaction of IgA with MC and the expression of IgA receptors by MC is inconsistent (Table 2). It is clear, however, that human MC express at least one type of IgA receptor and that this differs from the other IgA receptors thus far characterized: CD89 (Fc α RI), polymeric Ig receptor, and hepatic ASGPR. It has been reported that human MC express the transferrin receptor (CD71) and that this could act as a receptor for IgA in IgAN.^{95,96} There is also preliminary evidence that human MC could in addition express an ASGPR, an Fc α/μ receptor and a novel Fc α R..⁹⁷⁻⁹⁹ Independent of the receptor involved, there is *in vitro* evidence that MC are capable of receptor-mediated endocytosis and catabolism of IgA, supporting the role of the MC as a major contributor to mesangial IgA clearance.^{97,100} It is not yet known whether there are abnormalities of MC IgA binding in IgAN; however, it is possible that impaired binding

Table 2. Review of Evidence on Identification of the Mesangial Cell (MC) IgA Receptor(s)*

Receptor	Demonstration of Receptor mRNA Using Human MC or Renal Biopsies	Demonstration of Receptor Protein Using Human MC or Renal Biopsies	Functional Effects of MC Receptor Crosslinking
pIgR	No	No	N/A
Hepatic ASGPR	No	No	N/A
Fc α RI (CD89)	Yes	No	N/A
Transferrin receptor (CD71)	Yes	Yes	Not known
Novel Fc α R	N/A	Yes	MC proliferation, cytokine & ECM synthesis, activation of second messenger pathways and upregulation of transcription factors.†
Fc α/μ R	Yes	No	No
Novel ASGPR	N/A	Yes	Catabolism of desigA

Abbreviation: N/A; not applicable.

* Only studies using human MC or human renal biopsy data have been included ([reviewed by Monteiro, 2002]¹⁰⁹

pIgR, polymeric immunoglobulin receptor; ASGPR, asialoglycoprotein receptor; Fc α R, receptor binding the Fc region of IgA; Fc α/μ R, receptor binding both IgA and IgM; ECM, extracellular matrix components; desigA, desialylated IgA; NA,

† These functional effects of receptor crosslinking have been observed with whole IgA molecules and most have been shown to be Fc α dependent. This does not therefore exclude the possibility that the observed effects could have been The result of crosslinking of CD71 or Fc α/μ R.

could lead to defective mesangial IgA clearance and thereby contribute to IgA accumulation and the development of glomerulonephritis.

Mechanisms of Initiation and Progression of Glomerular Inflammation in IgA Nephropathy

Although IgG and complement components are often codeposited, IgA alone appears sufficient to provoke glomerular injury in the susceptible individual. In animal models, it has been shown that passive transfer of either “pathogenic” IgA or T cell-depleted allogeneic bone marrow cells from IgAN-prone mice can trigger the development of IgAN in previously normal animals.^{101,102} Furthermore, bone marrow transplanted from normal donors lowers total serum IgA, including the macromolecular IgA fraction, while simultaneously attenuating the glomerular lesions seen in these IgAN-prone mice.¹⁰³ Separately it has been shown that deposition of pIgA, but not mIgA, initiates glomerulonephritis, suggesting that those IgA macromolecules prone to mesangial trapping are also capable of initiating inflammation.¹⁰⁴

The development of glomerulonephritis following IgA deposition is believed to result from both IgA-induced activation of MC and local complement activation.

Mesangial Cell Activation

There is strong in vitro evidence that crosslinking of MC IgA receptors with macromolecular IgA elicits a proinflammatory and profibrotic phenotypic transformation in MC. Consistent with the mesangial hypercellularity seen in renal biopsy specimens, MC proliferate in response to IgA.^{105,106} Furthermore, exposure to IgA has been shown to upregulate secretion of both extracellular matrix components and the profibrotic growth factor TGF- β .¹⁰⁷ IgA is also capable of altering MC-matrix interactions by modulating integrin expression, and this could have an important role in remodelling of the mesangium following glomerular injury.¹⁰⁸ Exposure of MC to IgA is also capable of initiating a proinflammatory cascade involving MC secretion of PAF, IL-1 β , IL-6, TNF- α , and MIF; the release of the chemokines MCP-1, IL-8, and IP-10; and development of an amplifying proinflammatory loop involving IL-6 and TNF- α -induced upregulation of MC IgA receptors.¹⁰⁹ There is also evidence that activation of MC by codeposited IgG could synergistically contribute to the development of a proinflammatory MC phenotype and thereby influence the degree of glomerular injury.¹¹⁰

It is not yet clear which specific physicochemical properties of mesangial IgA affect MC activation; however, there is some *in vitro* evidence that undergalactosylated IgA glycoforms from patients with IgAN reduce proliferation, increase nitric oxide synthesis and the rate of apoptosis, and enhance integrin synthesis in cultured MC.^{108,111} This, together with the overrepresentation of aberrantly glycosylated IgA in mesangial IgA, suggest IgA1 O-glycosylation plays a role in both the deposition of IgA and the subsequent injury.

Complement

Although involvement of the complement cascade is not essential for the development of IgAN, there is evidence that local complement activation can influence the extent of glomerular injury. In rats, dIgA and pIgA, but not mIgA, can activate complement to induce glomerular damage.¹⁰⁴ Mesangial IgA activation of C3 probably occurs through the mannan-binding lectin (MBL) pathway and this ultimately leads to the generation of C5b-9, sublytic concentrations of which can activate MC to produce inflammatory mediators as well as matrix proteins.^{112,113} C3 and MBL are not only deposited in the kidney in IgAN,^{54,112,114} but can also be synthesized locally by the MC, and in the case of C3, by podocytes as well.¹¹⁵ It is likely, therefore, that once MC have bound IgA, they are capable of activating complement, independent of any systemic complement activity, by using endogenously generated C3 and MBL.¹¹⁵ MC also synthesize complement regulatory proteins,¹¹⁶ which could explain why C5b-9 generation in IgAN does not usually result in mesangiolysis. By contrast, the downregulation of complement receptor 1 (CR1) by podocytes in IgAN could render podocytes highly sensitive to complement attack.¹¹⁷

Cellular Effector Mechanisms

In contrast to some other patterns of proliferative glomerulonephritis, IgAN is not generally associated with a marked glomerular cellular infiltrate, suggesting that most of the glomerular injury is mediated by an expansion in resident glomerular cells. However, as glomerular lesions become more severe, the number of mononuclear cells increases both in the mesangium and Bowman's space.^{118,119} In crescentic IgAN, not only macrophages, but also activated T cells, can be detected in glomeruli.¹²⁰ Like with other forms of glomer-

ulonephritis, the number of glomerular macrophages has been correlated both with the presence of crescents and the degree of renal dysfunction.¹¹⁹

Progression or Resolution of Mesangial Injury

Although mesangial IgA deposition and the initiation by IgA of glomerular inflammation are specific to IgAN, mechanisms of the subsequent mesangial injury followed either by resolution or progressive sclerosis are likely to be generic, not differing substantially from those seen in other forms of chronic mesangial proliferative GN unrelated to IgA. These processes have been extensively studied *in vitro* and in animal models of mesangial proliferative GN (particularly the anti-Thy1.1 model). MC have a tremendous capacity to reconstitute normal mesangial morphology, even after pronounced mesangial proliferative changes. This occurs through MC apoptosis and the production of antimitogenic factors, the removal of excess matrix through the action of mesangial proteases and antifibrotic factors, and the production of factors that will counteract various proinflammatory products.¹²¹ Recent experimental evidence supports the notion that a crucial factor that determines whether mesangial injury resolves or progresses is the extent of secondary podocyte damage following the primary mesangial injury.¹²² Unlike MC, podocytes have little regenerative capacity and the consequences of podocyte injury, namely, proteinuria and segmental glomerulosclerosis, are well-recognized mechanisms of progressive renal disease.^{123,124}

Tubulointerstitial Injury and Progressive Chronic Renal Failure

Progressive chronic renal failure supervenes in IgAN when persistent proteinuria and hypertension develop in association with vascular and interstitial injury. Available data suggest that these "downstream" events are likewise not specific to IgAN, although this supposition is largely based on circumstantial evidence. First, the pathologic features of progression do not differ in IgAN compared with other chronic proteinuric renal diseases. They include progressive glomerulosclerosis (predominantly global but sometimes segmental) with tubular atrophy, interstitial fibrosis, and vascular sclerosis. Specific features of IgAN such as the extent and location of glomerular IgA deposits are not predictive of progression, with the possible excep-

tion of capillary wall deposits, which could mark a poor prognosis. The extent of mononuclear cell infiltration into the tubulointerstitium again does not differ from that seen in other forms of progressive GN, reflecting the final common pathway of renal parenchymal disease.¹²⁵ There is, however, evidence in IgAN that these infiltrating $\gamma\delta$ - and $\alpha\beta$ -T cells could be proliferating oligoclonally in response to a particular antigen, although the nature of this antigen is currently unknown.^{126,127}

Clinical parameters predicting risk of progression likewise are nonspecific, proteinuria and hypertension being the best predictors both when present at diagnosis and also when occurring during follow up.¹²⁸ Clinical features specific to IgAN such as a history of episodic macroscopic hematuria or elevated serum IgA levels do not predict risk of progression.

These mechanisms of progressive renal failure have been widely studied in the context of many renal diseases, including IgAN. Modification of these processes is a major target for currently available therapies for progressive renal failure. They are not further discussed here.

THE GENETICS OF IgA NEPHROPATHY

There is little doubt that there are genetic components to the pathogenesis and clinical expression of IgAN. This has been inferred from the existence of familial forms of IgAN,¹²⁹ the presence of elevated serum IgA levels and overproduction of IgA by cultured peripheral blood B lymphocytes in otherwise unaffected family members of patients with IgAN,¹³⁰ and the failure of exposure to mesangial IgA deposits to lead to IgAN in all individuals.⁸⁸ However, population studies have failed to show a consistent association with any single genetic marker, suggesting that IgAN does not have classic Mendelian inheritance attributable to a single gene locus but is a complex polygenic disease probably involving both MHC (major histocompatibility complex) and non-MHC susceptibility alleles.

Most population studies in IgAN to date have been relatively small case-control genetic association studies examining single nucleotide polymorphisms (SNPs) in single candidate gene (reviewed by Hsu, 2000).¹³¹ The lack of concordance across many of these studies reflects both small sample sizes (most included fewer than 150 patients) and the methodologic limitations of using such a strat-

egy in studying a complex polygenic disease.¹³¹ This is compounded by the difficulty in defining IgAN as a single disease in light of both its varied clinical presentation and the range of injury as assessed by light microscopy. Identification of non-MHC susceptibility alleles has proved particularly difficult, predominantly because of extensive genetic heterogeneity and the possibility of epistatic interactions among the multiple genes involved in a complex genetic disease.¹³² Furthermore, many of the published studies have reported on genetic factors influencing progression of renal failure in IgAN rather than on disease pathogenesis. It is preferable that these two processes should be viewed as separate, the former being generic to all GN and the latter specific to IgAN.

In a move away from case-control genetic association studies, Ghavari et al., using genome-wide linkage analysis in 30 multiplex kindreds, have demonstrated linkage of IgAN to 6q22-23.¹³³ Linkage to this locus (IGAN1) could only, however, be demonstrated using a dominant mode of inheritance with incomplete penetrance and locus heterogeneity. Interestingly, there are no obvious candidate genes within the linked interval, and no linkage could be found in the same kindreds for a number of candidate genes all implicated in the pathogenesis of IgAN. Further definition of the genes involved within the IGAN1 locus is awaited.

The MHC and IgA Nephropathy

Which genes might contribute to the genetic background in IgAN? It might be predicted that the MHC, and in particular, MHC class I and II, are involved. Certainly class II polymorphisms could restrict peptide-binding specificity and thereby lead to the selection of pathogenic T cell subsets in IgAN. Indeed, there is evidence that T cells in IgAN display restricted T cell receptor $V\beta$ chain CDR3 sequences.¹²⁶ However, case-control genetic association studies of single class I and II loci have failed to identify a consistent association with IgAN.¹³¹ This is perhaps not surprising as MHC polymorphisms are thought to be both gender- and geography-specific. Furthermore, it is recognized that haplotypes crossing MHC class I, II, and probably III (which includes the TNF cluster and various complement components) could be inherited as an extended haplotype. HLA A1-B8-DR3-DQ2 is frequently seen in autoimmune rheumatic diseases (particularly SLE) in the white population

and has been linked with high TNF- α production.¹³⁴ Polymorphisms within the TNF cluster are increasingly being associated with susceptibility to and severity of a variety of diseases, including renal allograft rejection,¹³⁵ SLE,¹³⁴ and inflammatory bowel disease.¹³⁶ TNF- α expression is known to be upregulated in glomeruli in IgAN.¹³⁷ Like with MHC class I and II, the limited studies in IgAN have thus far failed to clarify the role, if any, of class III polymorphisms in IgAN and have not begun to address the possibility of an extended HLA disease haplotype in IgAN. To have any hope of identifying a genuine association between the MHC and IgAN, future work must address the failings of these earlier studies by ensuring there is simultaneous testing for multiple polymorphisms across the entire MHC, and that the populations studied are well defined and large enough to allow robust statistical analysis.

Non-MHC Genes and IgA Nephropathy

Increasing recognition that most, if not all, components of the immune system are highly polymorphic, and that these polymorphisms can affect immune activity has promoted the study of non-MHC susceptibility alleles in complex genetic diseases. Currently there is no convincing evidence for an association between IgAN and polymorphisms within genes integral to the production of IgA itself; genes studied include the immunoglobulin heavy chain cluster, immunoglobulin heavy chain switch region gene, relevant galactosyltransferases, and CD89.^{131,133} However, we propose that in IgAN, there is a broader dysregulation of pIgA1 production in response to environmental triggers rather than a specific qualitative defect in the IgA molecule itself. More reasonable pathogenic candidates might therefore be the highly polymorphic cytokine, growth factor, and their counterreceptor genes, which play a pivotal role throughout the immune response. A number of these polymorphisms are associated with variant levels of gene expression, and any qualitative or quantitative effect on cytokine or growth factor production will inevitably impinge on the synthesis and secretion of other members of the cytokine cascade and could therefore alter the IgA immune response to viral and bacterial infections.¹³⁸ Indeed, polymorphisms of both non-MHC and MHC genes have been associated with phenotypic differences in response to infection.¹³⁹⁻¹⁴¹ Like with the

MHC, it is postulated that cytokine allele frequencies vary among racial and/or geographic groups, implying that different cytokine polymorphisms could act in different populations in IgAN. Furthermore, polymorphisms in the genes encoding surface costimulatory molecules are being identified, and associations between membrane-bound accessory molecules on peripheral blood cells and disease incidence, including renal allograft rejection, have been described.^{142,143} Polymorphisms within the adhesion molecule ICAM-1 have also recently been implicated in the susceptibility to some vasculitides.¹⁴⁴ Studies examining such polymorphisms in IgAN are limited¹⁴⁵⁻¹⁴⁸; all have been small case-control association studies limiting interpretation of their findings for the reasons already mentioned.

The Genetics of Progressive Renal Failure

Finally, a genetic predisposition to progressive renal failure must be considered. There are a number of candidate genes, of which the most widely studied have been genes controlling production of proteins in the renin-angiotensin system, including ACE and angiotensinogen. Other candidate genes include nitric oxide synthase, kallikrein, and some cytokines (interleukin-1 β and tumor necrosis factor- α), as well as growth factors such as TGF- β 1 known to have renal fibrogenic effects.

The ACE gene has received most attention, especially its insertion/deletion (I/D) polymorphisms. Individuals who carry the DD allele have higher levels of circulating and tissue ACE, and could also have a higher risk of progression in response to hypertension. However, the proposal that DD was significantly associated with risk of progression in IgAN has not been confirmed consistently, and at present, there is no convincing evidence that ACE or other related gene polymorphisms predict the risk of progressive renal failure in individuals with IgAN.^{131,149} It is more probable that synergistic interactions between a number of gene polymorphisms will influence the risk of progression of IgAN and contribute to the genetics IgAN, but as yet, such synergisms are only just emerging.¹⁵⁰

Clearly, the list of candidate susceptibility and progression alleles is enormous and will increase as more polymorphisms are identified. Their contribution will vary not only between individuals, but also across populations, making elucidation of

an "IgAN haplotype" a daunting task. However, with the publication of an almost complete nucleotide sequence of the human genome, the generation of detailed physical and molecular maps of the majority of human linkage groups, and improving technology, it should prove possible to identify disease genes in IgAN and build understanding of an IgAN genotype over the next decade.

An IgAN Genotype/Phenotype

In the absence of single "IgAN gene(s)," we propose that it could be more helpful to consider that individuals with IgAN must have an IgAN genotype/phenotype. This constellation of features represents a composite of all genetic loci contributing to the development of IgAN and includes genes influencing IgA deposition, those controlling the mesangial inflammatory response, and still others modifying progression of renal failure. Together they generate a global phenotype that predisposes to the development of IgAN after interaction with as-yet undefined environmental factors. The contribution of loci will vary from individual to individual; however, the sum of all loci, including epistatic interactions between loci, will determine whether mesangial IgA deposition is benign or initiates GN. An individual's IgAN genotype/phenotype will also determine the extent of glomerular damage in response to IgA deposition and the degree of subsequent glomerulosclerosis.

SUMMARY

Figure 4 summarizes our current understanding of the pathogenic pathways in IgAN, showing the major features at each stage in the process from exposure of the IgA immune system to the end point of progressive IgAN.

Systemic IgA Response

There is no convincing evidence for the involvement of specific antigens; rather, there is dysregulation of the IgA response to a wide range of antigens. The abnormal systemic IgA immune response promotes synthesis of pIgA1 with physicochemical characteristics, which favors mesangial deposition, the pathogenic IgA phenotype. We propose that this constitutes the synthesis of IgA in the systemic compartment, which has the phenotype of mucosal IgA. The reasons for this shift of IgA1 production require further elucidation but likely

include abnormalities of T cell regulation. Persistence of such pIgA1 in the circulation could also be favored by defects in IgA clearance. Altered O-glycosylation of the hinge region of IgA1 is a striking feature of the circulating pIgA1 and could reflect the shift to mucosal-type IgA. There is not an absolute change in structure of IgA1 to an entirely abnormal form; rather, there is a shift that results in a proportional increase in forms of IgA1 also found in healthy individuals.

Mesangial IgA Deposition

The altered O-glycosylation of the hinge region of IgA1 appears to be the main factor promoting IgA deposition, perhaps by favoring the development of IgA-IC and other macromolecular forms of IgA. Passive trapping of IgA remains the most likely mechanism of IgA deposition, but modification of interaction with mesangial components could also contribute.

Mesangial Injury Subsequent to IgA Deposition

Once IgA1 is deposited, the principal pathways for glomerular injury are through interactions of the pIgA1 with the cells and extracellular matrix proteins of the mesangium and the activation of complement.

Progressive Renal Failure

The final clinical expression of IgAN will also depend on the extent to which generic factors influencing progression risk, including hypertension and proteinuria, produce a renal fibrotic response.

Genetics of IgA Nephropathy

Crucially, the interaction between all these elements is played out on a complex genetic background in which the interactions of a large number of gene polymorphisms produce an IgAN genotype, which likely has a major impact on the eventual disease phenotype.

CONCLUSION

This review demonstrates the exciting progress that has been made in our appreciation of the pathogenesis of IgAN over recent years. However, as yet, these insights have not had any impact on the clinical management of IgAN. We are not yet close to a position in which rational treatments can be designed to interrupt these disease processes at an early stage, which will allow the prevention of

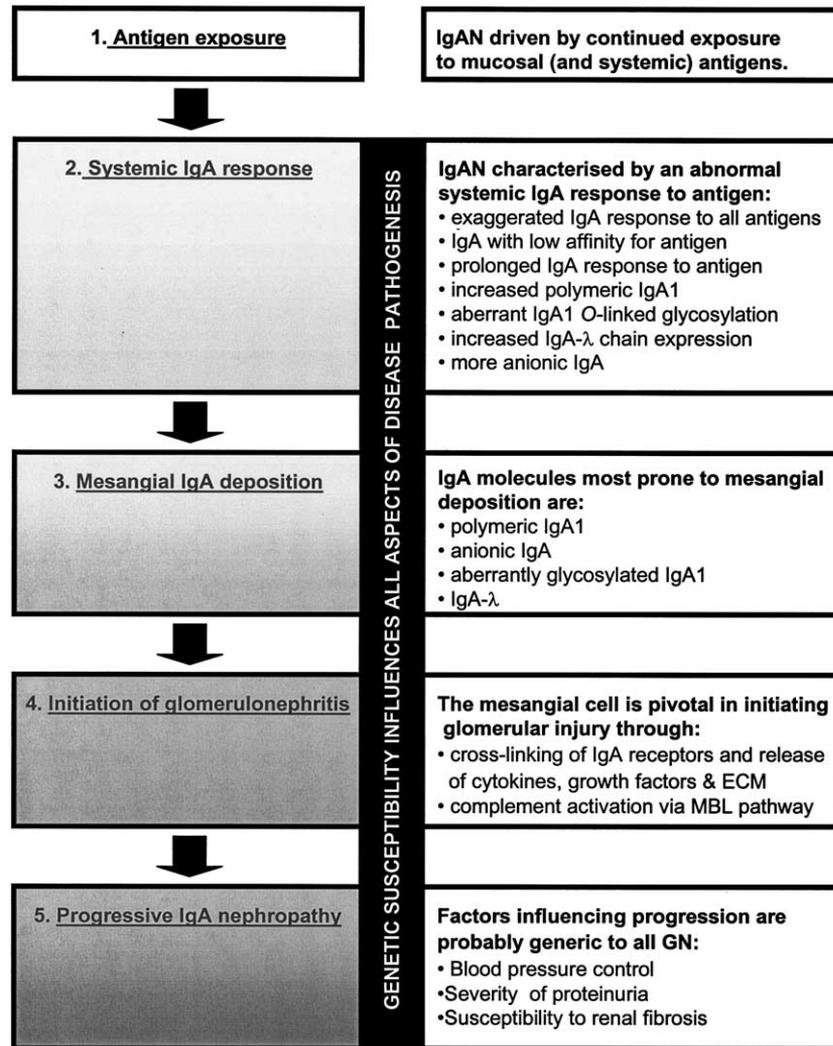


Fig 4. Current understanding of the pathogenesis of IgA nephropathy. For each of the five steps in pathogenesis, the right-hand column summarizes the features best documented in patients with IgAN. The central bar emphasizes that the entire process is played out against a complex genetic background, which likely influences all aspects of the pathogenic pathway.

clinically significant renal disease. Treatment for IgAN, as exemplified in other contributions to this publication, for the present predominantly relies on strategies that interrupt “downstream” events that are generic to other forms of chronic, progressive renal disease, rather than specific to IgAN.

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