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The Molecular Mechanisms Underlying IgA Nephropathy: Pathogenesis and Potential Therapeutic Targets

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Abstract

IgA nephropathy (IgAN), also known as Berger's disease, is a primary glomerulonephritis characterized by the deposition of galactose-deficient IgA1 (Gd-IgA1) in the glomerular mesangium, leading to progressive renal damage. This condition is prevalent in young adults and frequently follows respiratory or gastrointestinal infections. Approximately 20-40% of patients with IgAN progress to end-stage renal disease (ESRD) within 20 years of diagnosis. The pathogenesis of IgAN involves genetic, environmental, and immunological factors. Central to the disease is the production of Gd-IgA1, which forms immune complexes with IgG and IgA antibodies. These complexes deposit in the glomeruli, triggering mesangial cell proliferation and inflammation. Environmental triggers, particularly infections, are thought to exacerbate this immune response. Recent research has focused on understanding the molecular mechanisms underlying aberrant glycosylation of IgA1 and the role of immune complexes in disease progression. Targeting these pathways offers promising therapeutic strategies, such as modulating glycosylation enzymes and developing monoclonal antibodies to reduce pathogenic immune complex formation. Advances in diagnostic tools, such as identifying specific glycosylation patterns, are also aiding in early detection and treatment. Despite these advancements, challenges remain in personalizing treatment and addressing the disease's heterogeneous clinical presentation.

1. Overview of IgA Nephropathy

1.1 Definition and epidemiology

IgA nephropathy (IgAN), also known as Berger's disease, is the most prevalent form of primary glomerulonephritis globally, characterized by the deposition of immunoglobulin A (IgA) in the glomerular mesangium (Levy & Berger, 1988). First described in 1968 by Berger and Hinglais, IgAN

predominantly affects young adults, often presenting with episodes of gross hematuria typically following respiratory or gastrointestinal infections (Floege & Feehally, 2000). The disease is more common in Asian populations, with the highest prevalence reported in Japan and Singapore, while it is relatively rare in African populations (Schena & Nistor, 2018).

1.2 Clinical presentation and progression to end-stage renal disease

IgAN presents with a variety of clinical symptoms, ranging from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis. The most common initial presentation is macroscopic hematuria, often triggered by upper respiratory tract infections. About 30-40% of patients present with asymptomatic hematuria with mild proteinuria (Floege & Feehally, 2000). Over time, proteinuria can develop and worsen, and in 20-40% of patients, the disease progresses to end-stage renal disease (ESRD) within 20 years of diagnosis (Gentile et al., 2023). The progression to ESRD is influenced by several factors including the degree of proteinuria, hypertension, and the presence of chronic histological lesions like interstitial fibrosis and tubular atrophy (Roberts, 2014).

1.3 Pathogenesis of IgA Nephropathy

The pathogenesis of IgAN involves a complex interplay of genetic, environmental, and immunological factors. Central to the disease is the production of galactose-deficient IgA1 (Gd-IgA1), which forms immune complexes with IgG and IgA antibodies (Robert et al., 2015). These immune complexes deposit in the glomerular mesangium, leading to mesangial cell proliferation, matrix expansion, and glomerular injury (Suzuki et al., 2011). Genetic predisposition plays a significant role, with studies identifying several susceptibility loci, including those on chromosomes 6p21, 1q32, and 22q22 (Suzuki et al., 2011).

Environmental factors, particularly those that affect the mucosal immune system, also contribute to the disease pathogenesis. Infections, particularly those involving the respiratory and gastrointestinal tracts, are believed to trigger the abnormal immune response that leads to the production of Gd-IgA1 (Gentile et al., 2023).

Emerging evidence suggests that the immune complexes in IgAN may activate the complement system, particularly the alternative and lectin pathways, contributing to glomerular injury (Knoppova et al., 2016). The complement activation is mediated both systemically and locally within the glomeruli, exacerbating the inflammatory response and renal damage.

The understanding of IgAN pathogenesis has evolved significantly over the years, but several key questions remain. The precise molecular mechanisms that lead to the production of Gd-IgA1, the specific triggers for the production of pathogenic antibodies, and the exact pathways leading to mesangial deposition and subsequent renal injury are still being elucidated (Yeo et al., 2017).

2. Role of galactose-deficient IgA1 (Gd-IgA1)

2.1 Mechanisms of aberrant glycosylation

As shown in **Figure 1**, IgAN is a prevalent form of primary glomerulonephritis, characterized by the deposition of IgA1-containing immune complexes in the glomeruli. Central to the pathogenesis of IgAN is the aberrant glycosylation of IgA1, specifically the production of galactose-deficient IgA1 (Gd-IgA1). This abnormal glycosylation is considered the initial pathogenic hit in the multistep

process leading to IgAN (Novak et al., 2018). The IgA1 molecule typically has O-glycans in its hinge region, consisting of N-acetylgalactosamine (GalNAc) with β1,3-linked galactose and variable sialylation. In IgAN patients, IgA1 molecules exhibit deficient galactosylation, resulting in increased levels of Gd-IgA1 in circulation. These Gd-IgA1 molecules have fewer galactose residues, leading to the exposure of terminal GalNAc, which is immunogenic (Ohyama et al., 2021).

Research has identified several factors and mechanisms contributing to this aberrant glycosylation. TLR9 activation in IgA-secreting cells has been shown to induce the production of Gd-IgA1 through APRIL (a proliferation-inducing ligand) and IL-6 mediated pathways. This activation leads to increased production of nephritogenic IgA and exacerbates kidney injury in IgAN-prone models (Makita et al., 2019). Further, downregulation of Golgi matrix protein 130 (GM130) has been linked to deficient glycosylation. GM130 is crucial for the proper glycosylation of IgA1 in the Golgi apparatus, and its reduced expression leads to decreased activity of β1,3-Gal transferase (C1GALT1), the enzyme responsible for attaching galactose to GalNAc, resulting in the production of Gd-IgA1 (Wang et al., 2019).

Moreover, certain cytokines have been shown to enhance the production of Gd-IgA1. For instance, IL-6 and APRIL not only increase the synthesis of aberrantly glycosylated IgA1 but also contribute to the formation of nephritogenic immune complexes by promoting the binding of IgG to Gd-IgA1 (Person et al., 2022). Additionally, microRNAs (miRNAs) play a role in the regulation of glycosylation. For example, miR-98-5p targets CCL3, reducing its expression and consequently increasing IL-6 levels, which further decreases C1GALT1 expression, exacerbating the production of Gd-IgA1 (Liu et al., 2020).

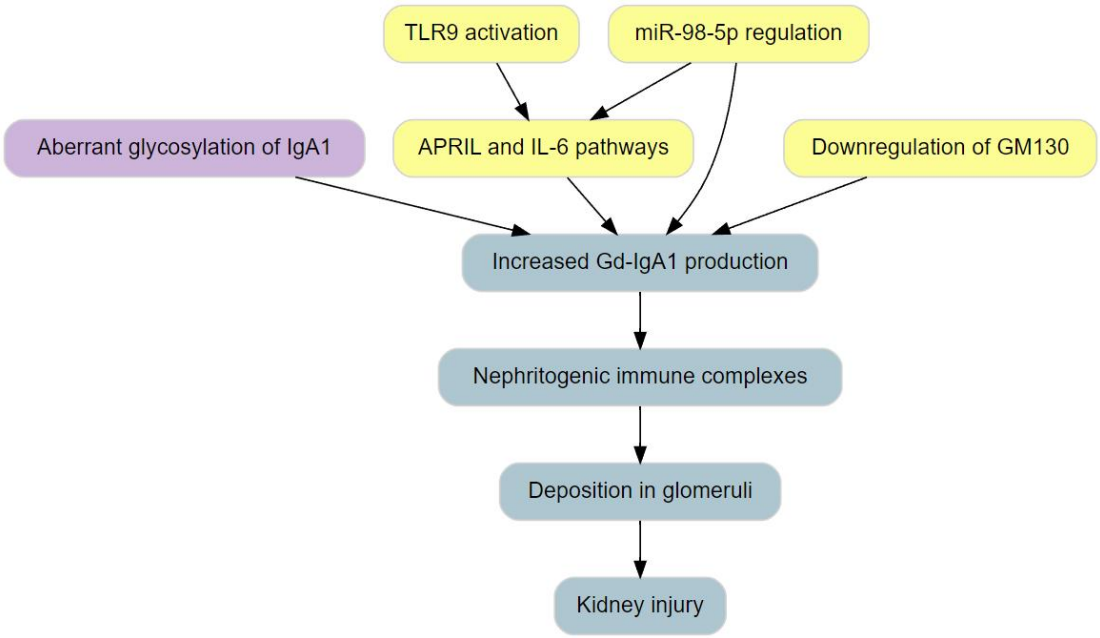

Figure 1 Mechanisms of Aberrant Glycosylation in IgAN

2.2 Impact on immune complex formation and deposition

The presence of Gd-IgA1 in the circulation is a pivotal factor in the formation of pathogenic immune complexes in IgAN. Gd-IgA1 serves as an autoantigen, recognized by naturally occurring anti-glycan antibodies, predominantly IgG. The interaction between Gd-IgA1 and these autoantibodies leads to the formation of large immune complexes that are prone to deposition in the glomerular mesangium (Suzuki & Novak, 2021). These immune complexes initiate a cascade of inflammatory responses within the kidney. Upon deposition, they activate mesangial cells, triggering the release of pro-inflammatory cytokines and growth factors, which promote mesangial cell proliferation and extracellular matrix expansion, hallmarks of glomerular injury in IgAN (Novak et al., 2018). The role of complement activation, particularly through the alternative and lectin pathways, is significant in the pathogenic process. The deposited immune complexes activate these pathways, leading to the generation of pro-inflammatory mediators and further glomerular damage (Suzuki & Novak, 2021).

Interestingly, studies have shown that patients with IgAN have increased numbers of Gd-IgA1 producing B cells expressing λ light chains and homing receptors CCR9 and CCR10. These cells are predisposed to migrate to mucosal tissues of the upper respiratory and digestive tracts, where infections can trigger the production of Gd-IgA1, further linking mucosal immunity to the pathogenesis of IgAN (Zachová et al., 2022). Moreover, the diagnostic potential of plasma IgA1 O-glycans has been explored as biomarkers for distinguishing IgAN from other glomerular diseases and healthy individuals. Specific patterns of O-glycosylation in IgA1 molecules correlate with disease severity and progression, making them valuable for clinical diagnostics (Zhang et al., 2022).

In summary, the role of Gd-IgA1 in IgAN involves its aberrant production through defective glycosylation mechanisms, followed by the formation of pathogenic immune complexes that deposit in the kidneys, leading to glomerular injury through inflammatory and complement-mediated pathways.

3. Immune Mechanisms and Inflammatory Pathways

3.1 Single-cell transcriptomics insights

Single-cell transcriptomics has provided groundbreaking insights into the complex cellular and molecular landscapes of IgAN. This section will detail findings from various studies, highlighting how single-cell RNA sequencing (scRNA-seq) has elucidated the intricate immune mechanisms and inflammatory pathways involved in IgAN pathogenesis.

3.1.1 Overview of Single-cell Transcriptomics in IgAN

Single-cell RNA sequencing (scRNA-seq) has revolutionized our understanding of IgAN by enabling the analysis of gene expression at a single-cell level. This approach has uncovered heterogeneity among cell populations and identified specific cell types and pathways implicated in disease progression. For instance, scRNA-seq of kidney biopsies from IgAN patients has revealed distinct gene expression patterns in various renal cell types, providing insights into the molecular underpinnings of IgAN (Tang et al., 2021).

3.1.2 Mesangial Cell Transcriptomics

Mesangial cells play a pivotal role in the pathogenesis of IgAN. scRNA-seq studies have identified upregulation of genes such as MALAT1, GADD45B, SOX4, and EDIL3 in mesangial cells of IgAN

patients. These genes are associated with cell proliferation and matrix accumulation, suggesting their involvement in mesangial cell activation and extracellular matrix deposition (Tang et al., 2021); (Zhong & Xiao, 2021). Furthermore, the expression of JCHAIN in mesangial cells provides insights into the mechanisms of IgA1 dimerization and deposition, a hallmark of IgAN. This gene is thought to contribute to the formation of pathogenic immune complexes (Zheng et al., 2020).

3.1.3 Tubular Cell Inflammation

scRNA-seq analyses have also highlighted significant changes in tubular cells of IgAN patients. These cells exhibit upregulation of inflammatory pathways, including TNF signaling, IL-17 signaling, and NOD-like receptor signaling, which are critical in mediating inflammatory responses within the kidney (Tang et al., 2021); (Zhong & Xiao, 2021). Additionally, receptor-ligand interaction analyses have shown enhanced crosstalk between mesangial and tubular cells, suggesting a coordinated inflammatory response that exacerbates kidney damage (Zheng et al., 2020).

3.1.4 Immune Cell Involvement

The role of immune cells in IgAN has been further elucidated through scRNA-seq. In particular, studies have shown significant involvement of kidney-resident macrophages and CD8+ T cells, with these cells displaying abnormal gene expression profiles related to proliferation and inflammation. Transitional cell types among intercalated cells, characterized by fibrosis signatures, have also been identified, indicating potential pathways leading to interstitial fibrosis and adverse renal outcomes (Zheng et al., 2020). Moreover, scRNA-seq of circulating leukocytes from IgAN patients has identified differential gene expression in monocytes and natural killer (NK) cells, highlighting their role in interferon signaling and antigen presentation. This suggests a prominent role for innate immune cells in the pathogenesis of IgAN (Post et al., 2023).

3.1.5 Differential Gene Expression and Pathway Enrichment

Several studies have employed scRNA-seq to perform differential gene expression and pathway enrichment analyses, revealing critical pathways involved in IgAN. For instance, differentially expressed genes (DEGs) in IgAN are enriched in pathways such as NF-κB signaling, MAPK pathways, and apoptotic processes. These pathways are implicated in the regulation of immune responses and cell survival, further underscoring their relevance in IgAN pathogenesis (Gholaminejad et al., 2020); (Park et al., 2020).

3.1.6 B-cell Receptor Repertoire

High-throughput sequencing of B-cell receptors (BCR) has revealed significant insights into the clonal diversity and specificity of B cells in IgAN. Studies have shown that the BCR heavy-chain complementarity-determining region 3 (CDR3) repertoire in IgAN patients is characterized by shorter CDR3 lengths and increased variant frequencies, indicating altered B-cell responses (Chen et al., 2019). Additionally, IgAN patients exhibit increased frequencies of B cells expressing λ light chains and mucosal homing receptors, suggesting that these cells originate from mucosal sites and contribute to the formation of pathogenic IgA1 complexes (Zachová et al., 2022).

3.1.7 Regulatory Networks and Biomarker Identification

Integrative analyses combining scRNA-seq data with other omics approaches have identified key

regulatory networks and potential biomarkers for IgAN. For example, several microRNAs (miRNAs) have been implicated in the regulation of genes involved in immune responses and glycosylation of IgA1. These miRNAs, including miR-98-5p, target critical genes such as CCL3, IL-6, and C1GALT1, influencing the production and glycosylation of IgA1 (Liu et al., 2020). Additionally, machine learning algorithms have identified RNA-binding proteins (RBPs) such as DDX27, RCL1, and TFB2M as characteristic RBPs in IgAN, highlighting their potential as diagnostic markers and therapeutic targets (Zhang et al., 2022).

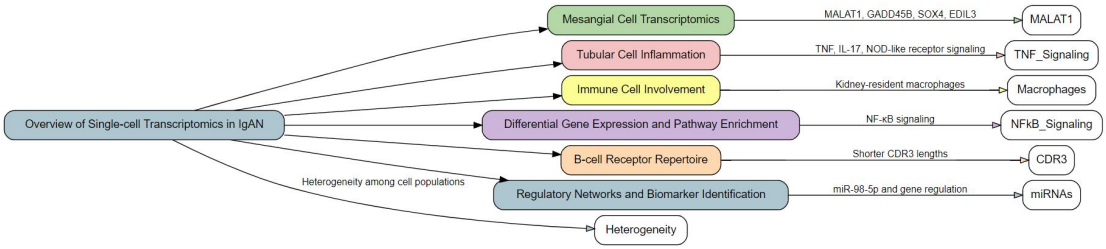

Figure 2 Single-cell transcriptomics insights in IgAN

3.2 Role of Fcα receptor (CD89) and other IgA receptors

3.2.1 Introduction to Fcα Receptor (CD89)

The Fcα receptor (CD89) is an essential component in the pathogenesis of IgAN, the most common form of primary glomerulonephritis worldwide. CD89 is expressed predominantly on myeloid cells, such as neutrophils, eosinophils, monocytes, and macrophages, where it mediates various immune responses upon binding to IgA (Moresco et al., 2016). The receptor's role is significant in both protective immune functions and pathological processes associated with IgAN.

3.2.2 Structure and Binding Mechanism of CD89

CD89 is a transmembrane glycoprotein with a molecular weight ranging between 55 to 75 kDa, depending on its glycosylation status (Xu et al., 2016). It binds to both subclasses of IgA (IgA1 and IgA2) in various molecular forms, including monomeric, dimeric, and secretory IgA. The binding affinity of CD89 to IgA is mediated through its membrane-distal EC1 domain, and this interaction is crucial for initiating downstream immune responses (Papista et al., 2015).

3.2.3 Pathogenic Role of Soluble CD89-IgA Complexes

In the context of IgAN, soluble CD89-IgA complexes have been identified as critical pathogenic factors. These complexes are found in the serum of patients with IgAN and are implicated in the mesangial deposition of IgA, a hallmark of the disease (Wu et al., 2020). The pathogenic mechanism involves the release of soluble CD89 following its interaction with IgA, forming complexes that deposit in the glomeruli and trigger inflammatory responses (Lechner et al., 2016).

3.2.4 Role of CD89 in Immune Regulation and Inflammatory Pathways

CD89-mediated immune responses are complex, with both pro-inflammatory and anti-inflammatory

effects. Cross-linking of CD89 by multimeric IgA complexes induces a high-intensity signaling pathway, activating immune cells and producing inflammatory cytokines (Papista et al., 2015). Conversely, monovalent engagement of CD89 can trigger inhibitory ITAM (ITAMi) signaling, recruiting tyrosine phosphatase SHP-1 and suppressing immune cell activation (Wu et al., 2020).

3.2.5 CD89 Expression in Mesangial Cells

The expression of CD89 in mesangial cells has been a subject of considerable interest. Recent studies have identified a novel Fcα receptor expressed by human mesangial cells that recognizes the Fc portion of IgA. This receptor binds polymeric IgA with high affinity and may mediate mesangial injury following IgA deposition (Moresco et al., 2016). Although immunogenically distinct from CD89, the mesangial Fcα receptor shares some molecular homology, as evidenced by the presence of CD89-related mRNA transcripts in mesangial cell cultures (Papista et al., 2015).

3.2.6 Genetic Variants and Soluble CD89 Levels

Genetic variations in the CD89 gene have been explored in relation to IgAN susceptibility and disease progression. Specific single-nucleotide polymorphisms (SNPs) in the CD89 gene have been associated with variations in soluble CD89 levels, which correlate with the severity of IgAN (Wu et al., 2020). However, these genetic variants do not appear to affect overall susceptibility to the disease.

3.2.7 Role of Other IgA Receptors in IgAN

In addition to CD89, several other IgA receptors have been implicated in the pathogenesis of IgAN. The transferrin receptor (CD71) is highly expressed in the mesangium of patients with IgAN and preferentially binds polymeric IgA1 complexes (Papista et al., 2015). This interaction promotes mesangial cell proliferation and the production of inflammatory cytokines, contributing to the disease process (Makita et al., 2019).

3.2.8 Therapeutic Implications of Targeting CD89

Given the central role of CD89 in the pathogenesis of IgAN, targeting this receptor offers potential therapeutic benefits. Strategies to block the interaction between CD89 and IgA or to inhibit the formation of soluble CD89-IgA complexes are being explored as potential treatments for IgAN (Lechner et al., 2016). Additionally, understanding the dual regulatory functions of CD89 can help develop therapies that modulate its signaling pathways to either enhance or suppress immune responses as needed (Papista et al., 2015).

3.2.9 Summary

The Fcα receptor (CD89) plays a multifaceted role in the immune regulation and pathogenesis of IgA nephropathy. It mediates both pro-inflammatory and anti-inflammatory responses, depending on the nature of its engagement with IgA. The presence of soluble CD89-IgA complexes in patients with IgAN underscores its significance in disease progression. Targeting CD89 and its associated pathways offers promising therapeutic avenues for managing IgAN. Further research into the molecular mechanisms and genetic factors influencing CD89 function will enhance our understanding and treatment of this complex disease.

Table 1. Role of Fcα receptor (CD89) and other IgA receptors in IgAN

Section	Key Points
Introduction to Fcα Receptor (CD89)	CD89 is critical in IgA nephropathy, expressed on myeloid cells, and mediates immune responses by binding IgA.
Structure and Binding Mechanism	CD89 is a glycoprotein (55-75 kDa) that binds IgA1 and IgA2, initiating immune responses.
Pathogenic Role	Soluble CD89-IgA complexes in patients trigger inflammation and are key in disease progression.
Immune Regulation	CD89 mediates complex immune responses, with both pro-inflammatory and anti-inflammatory effects.
Expression in Mesangial Cells	A novel receptor in mesangial cells binds polymeric IgA, contributing to mesangial injury.
Genetic Variants	CD89 gene SNPs affect soluble CD89 levels and IgAN severity, not overall susceptibility.
Other IgA Receptors	CD71 also plays a role in IgAN by binding IgA1 and promoting inflammation.
Therapeutic Implications	Targeting CD89 interactions and pathways offers potential IgAN treatments.
Summary	CD89 is pivotal in IgAN, with therapeutic targeting offering promising treatment avenues.

4.Genetic and Environmental Factors

4.1 Genetic Predisposition and Loci Associated with IgAN

IgAN is a complex disease with a significant genetic component. Numerous studies have identified various genetic loci and polymorphisms that contribute to the susceptibility and progression of this disease. This section will provide a comprehensive review of the genetic predispositions and loci associated with IgAN, highlighting the latest findings and their implications for understanding the pathogenesis and potential therapeutic targets.

4.1.1 Genome-Wide Association Studies (GWAS) and Identified Loci

Genome-wide association studies (GWAS) have been instrumental in uncovering the genetic underpinnings of IgAN. To date, over 30 risk loci have been identified through these studies, emphasizing the importance of genetic factors in the disease's pathogenesis (Xu et al., 2023). One

significant finding is the identification of the MHC locus on chromosome 6p21, which is strongly associated with genetic susceptibility to IgAN and other immune-mediated glomerulopathies (Sanchez-Rodriguez et al., 2020).

GWAS have also revealed that IgAN has a complex polygenic architecture with nearly 20 genome-wide significant loci identified to date (Sanchez-Rodriguez et al., 2020). For example, a recent study involving over 10,000 cases and nearly 30,000 controls identified 30 independent genome-wide significant risk loci, explaining 11% of the disease risk (Kiryluk et al., 2021). Among these, 16 loci were novel, including TNFSF4, REL, CD28, CXCL8/PF4V1, LY86, LYN, ANXA3, TNFSF8/15, REEP3, ZMIZ1, RELA, ETS1, IGH, IRF8, TNFRSF13B, and FCAR.

4.1.2 Rare Variants and Exome Sequencing

Next-generation sequencing technologies have allowed for the identification of rare variants associated with IgAN, accounting for some of the missing heritability. A study focusing on protein-coding variants in IgAN found a rare variant in the gene encoding vascular endothelial growth factor A (VEGFA), which was significantly associated with a two-fold increased risk of IgAN (Li et al., 2023). This study also identified a novel common variant in PKD1L3, linked to lower haptoglobin protein levels and an increased risk of kidney disease progression in IgAN.

Similarly, an exome-wide association study in pediatric patients identified significant associations with several genes, including PRAG1 and UBR3, emphasizing the role of multiple genes in the disease's etiology (Buianova et al., 2023).

4.1.3 HLA and Non-HLA Genetic Associations

The association of HLA alleles with IgAN has been well-documented. For instance, specific HLA-DRB1 and -DQB1 alleles have been linked to IgAN susceptibility in various populations (In et al., 2022). In Korean patients, alleles such as HLA-DRB10405 and HLA-DQB10401 were found to be significantly higher in IgAN patients compared to controls, suggesting a strong genetic predisposition (In et al., 2022).

Non-HLA loci also play a crucial role in IgAN pathogenesis. For example, SNPs in the DEFA1A3 region, which includes multiallelic copy number variations, have been associated with IgAN in both European and Asian populations (Shwan et al., 2022). Another study identified genetic interactions between G ALNT12 and C1GALT1, which are involved in the regulation of serum galactose-deficient IgA1 levels, further supporting the role of genetic dysregulation in IgAN development (Wang et al., 2021).

4.1.4 Epigenetic and Multifactorial Influences

In addition to genetic factors, epigenetic modifications and environmental triggers also contribute to IgAN pathogenesis. Studies have shown that epigenetic mechanisms, such as DNA methylation and histone modifications, may influence gene expression and susceptibility to IgAN (Xu et al., 2023). For instance, variants in the MIR31HG gene have been linked to increased IgAN risk in the Chinese population (Yuan et al., 2020).

A systematic review and meta-analysis of immune and inflammatory gene polymorphisms also highlighted the role of genetic variants in the immunologic and inflammatory pathways contributing

to IgAN pathogenesis (Ding et al., 2021).

4.1.5 Genetic Studies in Diverse Populations

Genetic studies in diverse populations have provided insights into the genetic basis of IgAN. For example, a study conducted in a Chinese Han population identified significant associations between IgAN and several single nucleotide polymorphisms (SNPs) in the MIR3142HG gene (Cao et al., 2022). These findings underscore the importance of considering ethnic and genetic diversity in IgAN research.

Additionally, a study on the gut microbiota and host genetics revealed associations between genetic variants controlling gut microbiota composition and IgAN susceptibility, suggesting a link between the gut-renal axis and disease pathogenesis (He et al., 2021).

4.1.6 Summary

The genetic landscape of IgA nephropathy is complex and multifaceted, involving numerous loci and polymorphisms that contribute to disease susceptibility and progression. Genome-wide association studies have been pivotal in identifying over 30 risk loci, highlighting the polygenic nature of IgAN. Rare variants and epigenetic modifications further add to the genetic complexity, underscoring the need for comprehensive and integrative approaches to understand the disease. These genetic insights not only enhance our understanding of IgAN pathogenesis but also pave the way for the development of targeted therapies and personalized medicine. Future research should focus on expanding genetic discovery efforts to more diverse populations and integrating genetic, epigenetic, and environmental factors to fully unravel the complex etiology of IgAN.

Table 2. The genetic factors in IgAN.

GWAS and Identified Loci	GWAS have identified over 30 risk loci, including the MHC locus on chromosome 6p21, and genes such as TNFSF4, REL, and CD28.	Xu et al., 2023; Sanchez-Rodriguez et al., 2020; Kiryluk et al., 2021
Rare Variants and Exome Sequencing	Rare variants in genes like VEGFA and PKD1L3 have been associated with increased risk and progression of IgAN.	Li et al., 2023; Buianova et al., 2023
HLA and Non-HLA Genetic Associations	Specific HLA alleles (e.g., HLA-DRB1 and -DQB1) and non-HLA loci (e.g., DEFA1A3) are associated with IgAN susceptibility.	In et al., 2022; Shwan et al., 2022; Wang et al., 2021
Epigenetic and Multifactorial Influences	Epigenetic mechanisms like DNA methylation and histone modifications influence IgAN susceptibility; variants in MIR31HG increase IgAN risk.	Xu et al., 2023; Yuan et al., 2020; Ding et al., 2021
Genetic	Studies in diverse populations reveal significant	Cao et al., 2022; He et

Studies in Diverse Populations	associations with genes like MIR3142HG; gut microbiota and host genetics link to IgAN susceptibility.	al., 2021

4.2 Environmental triggers and their impact on disease progression

4.2.1 Overview of Environmental Triggers

Environmental factors play a significant role in the progression of IgAN. These triggers include industrial pollutants, infectious agents, allergens, and nephrotoxic xenobiotics, all of which can lead to epigenetic changes affecting both cellular and humoral immunity (Svirskaya et al., 2021). The impact of these environmental factors on the immune system is multifaceted, influencing various pathways that contribute to disease progression.

4.2.2 Infectious Agents

Infectious agents are a well-documented environmental trigger in IgAN. Several studies have highlighted the connection between infections, particularly of the respiratory and gastrointestinal tracts, and IgAN exacerbations. For instance, synpharyngitic hematuria is a common clinical manifestation associated with IgAN, indicating an active mucosal immune system response to upper respiratory tract infections (Person et al., 2022). The pathogenic mechanism involves the production of aberrantly O-glycosylated IgA1, the main autoantigen in IgAN, driven by abnormal cytokine signaling in response to infections (Person et al., 2022).

4.2.3 Industrial Pollutants and Nephrotoxic Xenobiotics

Exposure to industrial pollutants and nephrotoxic xenobiotics is another crucial factor in IgAN progression. These substances can disrupt immunoglobulin A production in mucosae and alter the composition of microbiota and mucosal lymphoid cells, including γδT-lymphocytes (Svirskaya et al., 2021). The role of environmental toxins in IgAN is linked to their ability to induce chronic autoimmune inflammation, thereby accelerating disease progression through the activation of immune responses and promotion of tissue injury.

4.2.4 Allergens

Allergens also contribute to the progression of IgAN by triggering immune responses that enhance the production of pathogenic IgA1. The interplay between allergens and the mucosal immune system can lead to the activation of specific immune pathways that promote inflammation and tissue damage in the kidneys. This is supported by evidence showing that exposure to certain allergens correlates with increased levels of circulating immune complexes and subsequent renal deposition (Chang & Li, 2020).

4.2.5 Microbiota and Mucosal Immunity

The composition of microbiota in the gut and other mucosal sites plays a critical role in modulating the immune responses involved in IgAN. Dysbiosis, or the imbalance of microbial communities, has been linked to the pathogenesis of IgAN through its effects on the production and regulation of IgA (Selvaskandan et al., 2020). Alterations in the microbiota can lead to changes in mucosal immunity,

promoting the production of galactose-deficient IgA1 and enhancing the formation of pathogenic immune complexes (Gentile et al., 2023).

4.2.6 Epigenetic Changes and Immune Modulation

Environmental factors can induce epigenetic changes that modulate immune responses and contribute to the progression of IgAN. These changes can affect the expression of genes involved in immune regulation, leading to persistent inflammation and tissue damage. For instance, exposure to pollutants and infectious agents can result in the upregulation of pro-inflammatory cytokines and other immune mediators, which drive the progression of IgAN (Zheng et al., 2020).

4.2.7 Conclusion

The impact of environmental triggers on the progression of IgAN is profound, involving a complex interplay of factors that influence immune responses and epigenetic regulation. Infectious agents, industrial pollutants, allergens, and changes in microbiota composition all contribute to the exacerbation of disease through various mechanisms. Understanding these environmental influences is crucial for developing targeted therapeutic strategies to manage IgAN effectively.

Table 3. The environmental factors in IgAN.

Aspect	Details	References
Infectious Agents	Respiratory and gastrointestinal infections are linked to IgAN exacerbations, driven by abnormal cytokine signaling and production of aberrantly O-glycosylated IgA1.	Person et al., 2022
Industrial Pollutants and Nephrotoxic Xenobiotics	Exposure to industrial pollutants and nephrotoxic substances disrupts IgA production and microbiota composition, promoting chronic autoimmune inflammation.	Svirskaya et al., 2021
Allergens	Allergens trigger immune responses that enhance pathogenic IgA1 production, leading to renal inflammation and tissue damage.	Chang & Li, 2020
Microbiota and Mucosal Immunity	Gut microbiota composition affects IgAN pathogenesis by modulating immune responses and influencing the production of galactose-deficient IgA1.	Selvaskandan et al., 2020; Gentile et al., 2023
Epigenetic Changes and Immune Modulation	Environmental triggers induce epigenetic changes that modulate immune responses, driving persistent inflammation and tissue damage in IgAN.	Zheng et al., 2020

5. Novel Therapeutic Approaches

5.1 Targeting Aberrant Glycosylation and Immune Complexes

IgAN is characterized by the deposition of immune complexes, specifically those containing galactose-deficient IgA1 (Gd-IgA1), in the glomerular mesangium. Aberrant glycosylation of IgA1 plays a critical role in the pathogenesis of IgAN, making it a key target for novel therapeutic approaches. This section reviews recent advancements in targeting aberrant glycosylation and immune complexes, focusing on innovative strategies that offer promise for improving patient outcomes.

5.1.1 Mechanisms of Aberrant Glycosylation in IgA1

Aberrant glycosylation in IgA1, particularly the under-galactosylation of its hinge region, is pivotal in the formation of pathogenic immune complexes. Research has demonstrated that specific cytokines can enhance the production of aberrantly glycosylated IgA1. For instance, abnormal cytokine signaling in IgA1-producing cells from IgAN patients leads to increased production of these pathogenic forms (Person et al., 2022). Additionally, peripheral blood B cells in IgAN patients express predominantly lambda light chains and mucosal homing receptors, contributing to the production and secretion of Gd-IgA1 (Zachová et al., 2022).

5.1.2 Diagnostic and Therapeutic Implications

The development of robust diagnostic tools for detecting aberrant glycosylation is crucial. A novel automated sandwich immunoassay system utilizing Wisteria floribunda agglutinin (WFA) and anti-IgA1 monoclonal antibodies has shown promise in identifying aberrantly glycosylated IgA1 in IgAN patients (Uenoyama et al., 2022). Similarly, single-molecule fluorescence microscopy has been employed to characterize glycosylation patterns, providing insights into the heterogeneity of IgA1 glycosylation and its role in disease progression (Rubin et al., 2023).

5.1.3 Immune Complex Dissociation and Modulation

Targeting the dissociation of pathogenic immune complexes is a promising therapeutic strategy. Novel glycomimetic compounds that mimic the Tn antigen of Tn(+)IgA1 have shown efficacy in dissociating these immune complexes, thereby reducing their proliferative activity on mesangial cells (Matsumoto et al., 2022). Additionally, treatment with Nefecon® has been reported to selectively modify the composition of circulating IgA-immune complexes, altering their pathogenic potential and reducing proteinuria in patients (Molyneux et al., 2022).

5.1.4 Targeting Glycosylation Enzymes

Modulation of glycosylation enzymes presents another therapeutic avenue. The suppression of β-1,3-galactosyltransferase has been implicated in the production of Gd-IgA1, highlighting the potential of enzyme inhibitors in managing IgAN (Jash et al., 2023). Furthermore, understanding the precise role of these enzymes could lead to the development of targeted therapies that normalize IgA1 glycosylation patterns.

5.1.5 Monoclonal Antibodies and B Cell Depletion

Monoclonal antibodies that target B cells and plasma cells responsible for producing Gd-IgA1 and anti-Gd-IgA1 antibodies represent a novel therapeutic strategy. For example, therapies that deplete

CD38-positive plasma cells, which are central to the production of pathogenic antibodies, have shown potential in modifying the disease course of IgAN (Maixnerova et al., 2022). Additionally, emerging treatments with monoclonal antibodies such as atacicept, sibeprenlimab, and felzartamab are under investigation for their efficacy in targeting the immunopathogenesis of IgAN (Maixnerova & Tesar, 2023).

5.1.6 Glycoengineered Therapeutics

Advancements in glycoengineering have led to the development of therapeutic antibodies with modified glycosylation patterns. These engineered antibodies can potentially modulate immune responses and reduce the formation of pathogenic immune complexes (Ding et al., 2022). Such approaches highlight the potential of precision medicine in tailoring treatments based on individual glycosylation profiles.

5.1.7 Gut-Kidney Axis and Intestinal Immunity

The gut-kidney axis plays a significant role in the pathogenesis of IgAN, with recent studies emphasizing the impact of mucosal immunity and microbiota on disease progression. Targeted intestinal therapies, such as dexamethasone-encapsulated extracellular vesicles, have demonstrated efficacy in reducing proteinuria and alleviating pathological lesions in IgAN by modulating intestinal lymphocytes (Zhang et al., 2022).

5.1.8 Summary

Targeting aberrant glycosylation and immune complexes offers a promising avenue for the treatment of IgA nephropathy. Advances in diagnostic tools, immune complex dissociation, enzyme modulation, monoclonal antibody therapies, glycoengineered therapeutics, and intestinal immunity highlight the potential for novel therapeutic strategies. These approaches, grounded in a deeper understanding of the molecular mechanisms underlying IgAN, hold promise for improving patient outcomes and advancing towards personalized medicine.

5.2 Anti-inflammatory and immunomodulatory therapies

IgAN is primarily driven by the deposition of galactose-deficient IgA1 (Gd-IgA1) in the glomeruli, leading to an inflammatory response and subsequent kidney damage. To combat this, anti-inflammatory and immunomodulatory therapies have been developed and are continuously being refined to target various mechanisms involved in IgAN pathogenesis. This section provides an in-depth review of these therapies, organized under several subheadings.

5.2.1 Corticosteroids

Corticosteroids are among the first-line immunosuppressive treatments used to manage IgAN due to their potent anti-inflammatory effects. They work by suppressing the immune response and reducing the production of inflammatory cytokines. Systemic corticosteroids, such as prednisone, have been shown to reduce proteinuria and slow the progression of renal impairment in patients with IgAN. However, their use is often limited by significant side effects, including increased risk of infection, osteoporosis, and metabolic disturbances (Floege, Rauen, & Tang, 2021).

Recent studies have explored targeted delivery methods to minimize systemic exposure and side effects. For instance, delayed-release budesonide, designed to release the drug in the distal ileum, has

shown promise in reducing proteinuria while limiting systemic adverse effects (Roberts, 2023).

5.2.2 B-cell Targeted Therapies

The central role of B cells in the production of pathogenic Gd-IgA1 antibodies has made them a key target in IgAN treatment. Monoclonal antibodies targeting B-cell activation and survival factors, such as BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand), are being evaluated for their therapeutic potential.

Atacicept, a fusion protein that inhibits BAFF and APRIL, has demonstrated efficacy in reducing serum levels of IgA, IgG, and Gd-IgA1, thereby decreasing proteinuria in IgAN patients. A Phase II study reported significant reductions in proteinuria and stable estimated glomerular filtration rate (eGFR) over 24 weeks (Barratt et al., 2020).

Similarly, BION-1301, a humanized monoclonal antibody that blocks APRIL, has shown promising results in early-phase trials by significantly reducing levels of Gd-IgA1 and proteinuria with minimal adverse effects (Barratt et al., 2022).

5.2.3 T-cell Modulation and Cytokine Inhibition

T-cell imbalances, particularly in the Th1/Th17 and Treg/Th17 ratios, have been implicated in IgAN pathogenesis. Therapeutic strategies aimed at modulating T-cell responses and inhibiting pro-inflammatory cytokines like interleukin-17 (IL-17) are under investigation. A study by Uriol et al. (2020) evaluated the sequential use of paricalcitol, a selective vitamin D receptor activator, followed by secukinumab, an IL-17A blocker, in patients with refractory IgAN. This regimen resulted in significant reductions in proteinuria and hematuria, highlighting the potential of cytokine inhibition in managing IgAN (Uriol et al., 2020).

5.2.4 Complement System Inhibitors

The activation of the complement system, particularly the alternative and lectin pathways, plays a critical role in the inflammatory response in IgAN. Targeting complement components to inhibit their activation has emerged as a novel therapeutic approach.

Narsoplimab, a monoclonal antibody targeting mannan-binding lectin-associated serine protease-2 (MASP-2), has shown efficacy in reducing proteinuria and improving renal function in early-phase trials. This inhibition of the lectin pathway provides a targeted approach to mitigate complement-mediated damage in IgAN (Maixnerova & Tesar, 2023).

Similarly, eculizumab, an inhibitor of the terminal complement protein C5, has been investigated for its potential to prevent the formation of membrane attack complexes and reduce glomerular inflammation. Clinical trials have demonstrated promising results in reducing proteinuria and preserving kidney function (Zhuang, Lu, & Li, 2023).

5.2.5 Emerging Biological Agents

The development of biological agents targeting various aspects of the immune response in IgAN represents a significant advancement in treatment options. These agents include monoclonal antibodies targeting specific immune pathways involved in the disease.

Felzartamab, a monoclonal antibody targeting CD38, has shown promise in depleting pathogenic

plasma cells that produce Gd-IgA1. Early-phase studies have reported reductions in proteinuria and improvements in renal function with manageable safety profiles (Maixnerova et al., 2022).

Another promising agent is sibeprenlimab, a monoclonal antibody that inhibits IL-6, a cytokine involved in the inflammatory response. Clinical trials have shown that sibeprenlimab can significantly reduce proteinuria and inflammation in patients with IgAN (Takahata et al., 2020).

5.2.6 Traditional Chinese Medicine

Traditional Chinese Medicine (TCM) has also been explored for its potential benefits in IgAN. Zhen-wu-tang (ZWT), a well-known TCM formula, has been reported to ameliorate kidney diseases by regulating immune responses and reducing inflammation.

A study by Li et al. (2020) demonstrated that ZWT could protect against IgAN in rat models by promoting the release of exosomes that inhibit the NF-κB/NLRP3 signaling pathway. This mechanism helps reduce glomerular inflammation and improve renal function, suggesting that ZWT may offer a complementary therapeutic approach for IgAN (Li et al., 2020).

5.2.7 Summary

The treatment landscape for IgAN is rapidly evolving, with numerous anti-inflammatory and immunomodulatory therapies showing promise in clinical trials. These therapies target various aspects of the immune response, including B-cell activation, T-cell modulation, complement inhibition, and cytokine suppression. Emerging biological agents and traditional medicine approaches further expand the arsenal of treatments available for managing IgAN. Continued research and clinical trials will be essential to refine these therapies and improve outcomes for patients with this challenging disease.

6. Discussion and Perspective

The intricate molecular mechanisms underlying IgA nephropathy (IgAN) have been the subject of extensive research, revealing a complex interplay of genetic, environmental, and immunological factors. While significant strides have been made in understanding these processes, several critical areas demand further investigation and consideration for future therapeutic strategies. This section will discuss the current understanding of IgAN pathogenesis, highlight the challenges that remain, and propose potential future directions for research and treatment.

6.1 Current Understanding of Pathogenesis

At the heart of IgAN lies the aberrant production of Gd-IgA1, which forms immune complexes with IgG and IgA antibodies. These complexes deposit in the glomerular mesangium, leading to a cascade of pathological events including mesangial cell proliferation, extracellular matrix expansion, and glomerular injury. This understanding has been pivotal in identifying potential therapeutic targets and developing novel treatments aimed at reducing the formation and deposition of these immune complexes.

The genetic predisposition to IgAN has been well-documented, with multiple susceptibility loci identified through genome-wide association studies (GWAS). These loci include regions on chromosomes 6p21, 1q32, and 22q22, among others. Genetic studies have also highlighted the role of certain genes involved in the regulation of IgA1 glycosylation, immune response, and complement activation.

Environmental factors, particularly those affecting the mucosal immune system, such as infections, play a crucial role in triggering the abnormal immune response leading to IgAN. The role of the complement system, especially the alternative and lectin pathways, has been increasingly recognized as a significant contributor to glomerular injury in IgAN.

6.2 Challenges in Current Research and Treatment

Despite the advancements, several challenges persist in the study and management of IgAN:

6.2.1 Heterogeneity in Clinical Presentation and Disease Progression: IgAN exhibits considerable variability in its clinical manifestations and progression. Some patients may experience asymptomatic microscopic hematuria, while others progress to end-stage renal disease (ESRD). Identifying biomarkers that can accurately predict disease course and response to therapy is critical for personalized treatment approaches.

6.2.2 Detailed Mechanisms of Gd-IgA1 Production: While the role of Gd-IgA1 in IgAN is established, the precise molecular mechanisms leading to its production remain unclear. Understanding these mechanisms could open new avenues for targeted interventions.

6.2.3 Long-term Efficacy and Safety of Emerging Therapies: Many of the new therapeutic strategies, including those targeting aberrant glycosylation and immune complex formation, are still in the early stages of clinical evaluation. Long-term studies are necessary to assess their efficacy and safety comprehensively.

6.2.4 Integration of Omics Data: Integrating data from genomics, transcriptomics, proteomics, and metabolomics will provide a more holistic understanding of IgAN pathogenesis and help identify novel therapeutic targets. However, this requires sophisticated analytical tools and interdisciplinary collaboration.

6.2.5 Impact of Environmental Factors: The role of various environmental factors, such as diet, infections, and pollutants, in the initiation and progression of IgAN needs further exploration. Understanding these factors could lead to preventive strategies and improved management of the disease.

6.3 Future Directions

To address these challenges and advance the understanding and treatment of IgAN, the following future directions are proposed:

6.3.1 Identification of Predictive Biomarkers: Research should focus on discovering and validating biomarkers that can predict disease progression and therapeutic response. This would enable personalized treatment plans, improving patient outcomes.

6.3.2 Elucidation of Gd-IgA1 Production Mechanisms: Detailed studies are needed to uncover the molecular pathways leading to the production of Gd-IgA1. This could involve exploring the roles of various cytokines, glycosylation enzymes, and regulatory networks.

6.3.3 Long-term Clinical Trials: Rigorous, large-scale, multi-center clinical trials are essential to evaluate the long-term efficacy and safety of emerging therapies. This will help in establishing these treatments as standard care options for IgAN.

6.3.4 Integration of Omics Data: Advanced computational tools and interdisciplinary collaboration should be utilized to integrate data from various omics studies. This comprehensive approach will provide deeper insights into the molecular mechanisms of IgAN and identify potential therapeutic targets.

6.3.5 Exploration of Environmental Factors: Further research into the impact of environmental factors on IgAN is needed. Studies should investigate how infections, pollutants, and diet influence the mucosal immune response and the production of Gd-IgA1.

6.3.6 Development of Preventive Strategies: Understanding the role of environmental triggers could lead to the development of preventive strategies. Public health measures aimed at reducing exposure to these triggers could help in preventing the onset or progression of IgAN.

6.3.7 Personalized Medicine Approaches: The future of IgAN treatment lies in personalized medicine. By tailoring treatment plans based on individual genetic, molecular, and environmental profiles, it will be possible to achieve better outcomes and improve the quality of life for patients.

6.3.8 Innovative Therapeutic Strategies: Continued research into novel therapeutic strategies, including targeted enzyme inhibitors, monoclonal antibodies, and gut microbiota modulation, is essential. These approaches should be based on a deep understanding of the molecular mechanisms underlying IgAN.

7. Conclusion

IgA nephropathy is a complex disease characterized by the deposition of galactose-deficient IgA1-containing immune complexes in the glomerular mesangium, leading to progressive kidney damage. The pathogenesis of IgAN involves a multifaceted interplay of genetic, environmental, and immunological factors. While significant progress has been made in understanding these mechanisms and developing new therapeutic approaches, several challenges remain.

Future research should focus on identifying predictive biomarkers, elucidating the detailed mechanisms of Gd-IgA1 production, and conducting long-term clinical trials to evaluate the efficacy and safety of emerging therapies. Integrating omics data and exploring the impact of environmental factors will provide a comprehensive understanding of IgAN pathogenesis and identify novel therapeutic targets. Personalized medicine approaches, combined with innovative therapeutic strategies, hold promise for improving patient outcomes and advancing the treatment of IgAN. Through a multidisciplinary approach that combines advanced molecular techniques, innovative therapeutic strategies, and personalized medicine, the future of IgAN research and treatment looks promising, aiming to improve patient prognosis and quality of life.

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