ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

Exploration of IgA Nephropathy from the Perspective of Gd-IgA1 and Complement Alternative Pathway

Qijun Tian[1,a], Jian Shi[2,b,*]

[1]*Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
[2]*Nephropathy Department 1, Shaanxi Academy of Traditional Chinese Medicine, Xi'an, Shaanxi, 710003, China*
[a]*tianqj2023@163.com,* [b]*health133@163.com*
[*]*Corresponding author*

Abstract: *IgA nephropathy is the most common primary glomerular diseases globally, affecting approximately 1.3% of the global population. The pathogenesis is incompletely understood and it has a poor prognosis. The features of IgA nephropathy is IgA deposition in the glomerular mesangium, which initiates inflammatory cytokine release and complement activation. Previous studies have shown that the type of IgA deposited in the glomerulus is Gd-IgA1 and is involved in the occurrence and development of IgA nephropathy. At present, a large number of studies have shown that the activation of complement pathway plays an important role in the pathogenesis of IgA nephropathy, and is related to disease progress, especially the Lectin pathway and alternative pathway. This article mainly describes the relationship between alternative pathways and Galactose deficient IgA1 (Gd-IgA1) in the occurrence and development of IgA nephropathy.*

Keywords: *IgA nephropathy; Complement; Alternative pathway; Galactose-deficient IgA1*

1. Introduction

1.1. IgA nephropathy

Immunoglobulin A nephropathy(IgAN) is the most common form of primary glomerular diseases globally, with diverse clinical manifestations characterized by recurrent gross hematuria or microscopic hematuria, and pathological changes featuring poorly O-galactosylated IgA1 deposition in the glomerular mesangium, and pathological changes featuring IgA1 deposition in the glomerular mesangium, mesangial cell proliferation, and matrix expansion. And in approximately 40-50% of patients, end-stage renal disease (ESRD) within 20 years of diagnosis [1] and is one of the leading causes of chronic renal failure(CRF), although the course usually evolves gradually. Berger and Hinglais discovered in 1968 that IgA (immunoglobulin A) deposits cause IgA nephropathy in the glomerular mesangium. It has been more than 50 years since then [2]. Studies have shown that genetic factors and environmental factors have an important impact on the occurrence of IgA nephropathy[3].

1.2 Factors affecting Gd-IgA1

The most widely accepted hypothesis about the pathogenesis of IgAN has been known as a "four-hit" hypothesis [4], that is, the development of IgAN requires at least four processes (called "hits"): (1)increased synthesis of poorly Ogalactosylated IgA1(also called Galactose-deficient IgA1, Gd-IgA1) in circulation; (2)production of autoantibodies against Gd-IgA1; (3)formation of immune complexes containing pathogenic O-galactosylated IgA1; and (4)mesangial deposition of these immune complexes activating mesangial cells and subsequently impairing glomeruli. Numerous studies have shown Galactose deficient IgA1 (Gd-IgA1) is the main pathogenic factor of IgA nephropathy, Gd-IgA1 is a specific type of immunoglobulin, and its sugar group is deficient in Galactose. However, with the increase of serum Gd-IgA1 levels, it has also been found in healthy individuals, and glomerular IgA1 deposition may occur in populations without obvious clinical disease characteristics, and even in normal individuals, glomerular deposition can be absorbed, indicating that besides Gd-IgA1, other factors are also involved in the pathogenesis of IgA nephropathy [5]. In recent years, a large amount of clinical and animal experimental research evidence has shown that excessive activation of the complement pathway plays an important role in the pathogenesis of IgA nephropathy and is related to disease progression [6].

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

However, an increasing number of studies have found that its pathogenesis is related to multiple factors. Immunological events play a decisive role in the pathogenesis of IgA nephropathy.

After the deposition of Gd-IgA1 in IgA nephropathy patients, not all patients will experience kidney damage. More and more studies are analyzing the involvement of other factors, leading to the true occurrence, development, and progressive deterioration of the disease, ultimately leading to the development of end-stage kidney disease, Multiple immune cells (such as dendritic cells, NK cells, macrophages, T lymphocyte subsets, B lymphocytes, etc.) and molecules (such as IgA receptors, toll like receptors, complements, etc.) in innate and adaptive immunity are involved in the pathogenesis of IgA nephropathy.

The low galactosylated IgA1 molecule is mainly generated from the respiratory tract and intestinal mucosa surface of Mucosa-associated lymphoid tissue(MALT), of which the gut associated lymphoid tissue(GALT) produces the most immunoglobulin A, and is concentrated in the special lymphoid follicles of Peyer's patches at the distal ileum [7]. Therefore, according to the treatment of its source, the phase III clinical trial of Budesonide targeted release preparation(Nefecon), which specifically releases active drugs in the Peyer patches to the distal ileum, has achieved good results, showing a significant role in reducing urinary protein and stabilizing glomerular filtration rate [8]. The good curative effect obtained by Nefecon also proves that Gd-IgA1 plays an important pathogenic role in the occurrence and development of IgA nephropathy.

From the research on the process of glycosylation of IgA molecules to Gd-IgA1, increasing evidence indicates that the abnormal O-glycosylation of IgA1 is involved in the occurrence and development of IgA nephropathy [9,10]. Core 1, β1, 3-Galactose transferase(core 1, β1, 3-galactosyltransfer, C1GALT1) and its molecular chaperone Cosmc play an important role in the glycosylation of IgA1 molecule, and C1GALT1 connects Galactose to IgA1 molecule. The study found that the expression level of C1GALT1 was significantly down regulated in patients with IgA nephropathy, and was negatively correlated with the higher Gd-IgA1 level [5]. Other studies have shown that the common variation of C1GALT1 affects the Gd-IgA1 level in the population [11], which is independently related to the risk of progressive IgA nephropathy, and the pathogenic importance of IgA1 O-glycosylation changes may be different in white people and Chinese IgA nephropathy patients. Gd-IgA1 as a key causative factor in IgA nephropathy. Research [12] shows that the down-regulated Cosmc gene is the basis of abnormal O-glycosylation in IgA1 hinge region. In addition, some studies [13] have shown that after cytokine IL-4 stimulation, Galactose on the O-sugar chain of IgA1 hinge region is significantly deficient, and the gene expression of C1GALT1 and Cosmc and the enzyme activity of C1GALT1 are down regulated. The increase in IgA1 produced after IL-17 stimulation is accompanied by a decrease in IgA1 glycosylation [14]. IL-17, IL-10, IL-6 and other cytokines seem to play a role in the progress of inflammation and kidney damage, and also participate in the pathogenesis of IgA nephropathy. Therefore, it is speculated that the expression and activity of C1GALT1 and Cosmc are important for the O-glycosylation of IgA1, and are regulated by cytokines such as interleukin and (or) other factors, leading to abnormal glycosylation of IgA1. Therefore, the role of cytokines in the pathogenesis of IgA nephropathy needs to be further confirmed.

In addition, B cell activating factor (BAFF), as a positive regulator of B cell function, was used to measure serum BAFF levels in patients with autoimmune diseases such as systemic lupus erythematosus(SLE), primary Sjogren's syndrome(PSS), rheumatoid arthritis(RA), and other autoimmune diseases using a double antibody sandwich ELISA method. It was found that BAFF has an impact on promoting antibody production in autoimmune diseases, rather than on B lymphocyte activation [15]. A large number of studies have shown that there is a correlation between the elevated levels of circulating B lymphocyte activator (BAFF) and proliferation inducing ligand(APRIL) and the elevated levels of circulating low galactosylated IgA1 [16,17], which may play a role in the occurrence and development of IgA nephropathy, and even excessive B cell survival factors can disrupt the balance of the microbial flora. Some studies have shown that the serum BAFF level is related to the degree of tubular atrophy/interstitial fibrosis, and can also be used as a non-invasive indicator to monitor the severity of IgA nephropathy [18].

There are reports about Toll like receptors (TLRs). In patients with IgA nephropathy, TLR9 activation induces abnormal glycosylation of IgA nephropathy through the pathway of increment inducing ligand (APRIL) and IL-6, and it is closely related to Gd-IgA1 synthesis, cytokine secretion, proteinuria and serum creatinine [19]. TLR4 can recognize Lipopolysaccharide(LPS) in Gram-negative bacteria and induce methylation of the molecular chaperone Cosmc gene, which is conducive to the Galactose based defect of IgA [14]. The expression of TLR7 and CD19 protein in the kidney is closely related to renal function(estimated glomerular filtration rate and serum creatinine concentration) and renal tissue pathology(tubular atrophy, leukocyte infiltration, tubulointerstitial fibrosis and glomerulosclerosis) in

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

patients with IgA nephropathy, which shows that the level of TLR7 mRNA in peripheral blood B cells in patients with IgA nephropathy is significantly increased, and the overexpression of GALNT2(N-acetylamino Galactose transferase) can promote the production of Gd-IgA1 in B cells of patients with IgA nephropathy. The mechanism may be that TLR7 activates B cells to produce high levels of Gd IgA1 through the TLR7-GALNT2 axis, thus promoting renal inflammation and the synthesis of Gd IgA1 antibodies [20]. Therefore, inflammatory mediators such as pathogens and damage related molecular patterns(PAMPs and DAMPs, respectively) can activate TLRs present on renal intrinsic cells. Some TLRs can increase IgA levels and promote glycosylation abnormalities, further triggering inflammation and tissue damage to exacerbate renal injury.

Recent studies have demonstrated that aberrant glycosylated IgA1 may affect the formation of macromolecular immune complexes and subsequent activation of complement and other factors, leading to the progress of IgA nephropathy [21]. Although the factors involved in the pathogenesis are complex, complement involvement is one of the main reasons for the progression of IgA nephropathy. Activation of the complement cascade is known to be involved in the pathogenesis of IgA nephropathy. The complement system is activated through the classical pathway(CP), the Lectin pathway(LP) and the bypass pathway(AP), which have a common terminal pathway and play an important role in anti infective immunity. More and more clinical and animal experimental research evidence suggests that the activation of complement pathways plays an important role in the pathogenesis of IgA nephropathy and is related to disease activity and progression. Although IgA deposition in the mesangium is the key diagnosis of IgA nephropathy, mesangial C3 deposition is also common. A large amount of evidence shows that complement activation plays an important role in the development of IgA nephropathy, and the codeposition of C3 and IgA in the mesangium is related to the severity and progress of IgA nephropathy. With the continuous deposition of C3, IgA nephropathy patients are more prone to microscopic hematuria, fibrocrescent, interstitial inflammatory cell infiltration, and have higher scores according to the Oxford scoring system [22]. Some studies have shown that Gd-IgA1 immune complex in circulation can enhance the synthesis and secretion of IL-6 and C3 and the proliferation of mesangial cells, thus promoting the inflammatory progress of IgA nephropathy [23]. There is also evidence that Gd-IgA1 immune complexes can activate alternative pathways of complement [24]. The alternative and lectin pathways dominate the complement activation of IgA nephropathy. Therefore, it is speculated that whether the Gd-IgA1 immune complex will develop into clinically dominant glomerulonephritis after deposition depends partly on the role of the complement system.

Gut microbiota also has a certain impact on the level of Gd-IgA1. Thanks to the development of metagenomics and metabonomics research, we have accelerated our understanding of the importance of gut microbiota in health and disease. Recent studies have linked dysbacteriosis and its damage to the intestinal barrier with chronic diseases outside the digestive system(such as Chronic kidney disease and diabetes). The imbalance of gut microbiota and the damage of intestinal barrier are important links in the intestinal micro ecosystem. The pathogenesis of IgA nephropathy is related to autoimmune disorders and intestinal microbial disorders. A large number of studies have shown that patients with IgA nephropathy have different degrees of intestinal microflora imbalance [25,26], which is manifested by differences in abundance and composition, and an increase in the number of opportunistic pathogens. The imbalance of gut microbiota and its metabolites, food and other antigens lead to changes in the intestinal barrier through various ways, which is conducive to the absorption of toxins by the intestinal mucosa into the body, the activation of intestinal mucosal lymphoid tissue(GALT), the production of a large number of abnormal glycosylated IgA1 [27], and ultimately the formation of immune complexes into the blood circulation and deposition in the kidney. Gd-IgA1 is a key pathogenic factor in IgA nephropathy, and it have shown that the down-regulated Cosmc gene is fundamental for the abnormal O-glycosylation in the IgA1 hinge region. TLR4 can identify lipopolysaccharide(LPS) in Gram-negative bacteria and induce the methylation of the molecular chaperone Cosmc gene, which favors the galactosylation defect of IgA [12]. Urine Gd-IgA1 level is significantly negatively correlated with actinobacillus, bifidobacteria, bifidobacteriaceae, and bifidobacterium. The urine Gd-IgA1 level in patients with IgA nephropathy increases [28], and the significance of the diagnosis and prognosis of Gd-IgA1 in urine was greater than that of blood Gd-IgA1. Therefore, correcting this flora dysbiosis or performing specific flora-targeted interventions may be a potential therapeutic strategy for the prevention and management of IgA nephropathy.

2. IgA nephropathy and complement

Numerous studies have shown that complement activation has a pivotal role in the pathogenesis of IgA nephropathy and is associated with disease progression. Complement components are widely present

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

on serum, tissue fluid, and cell membrane surface, and are highly regulated protease cascade reaction systems composed of more than 30 proteins and are important mediators for inflammation and tissue damage repair [29], It includes complement component proteins (C3, C5, etc.), complement regulatory proteins (factor I, factor H, etc.), and complement receptor proteins (CR1 to CR5, C3aR, C5aR, etc.). The complement system is activated through the classical pathway (CP), lectin pathway (LP) and bypass pathway (AP), which have common terminal pathway. The effective complement regulation plays an important role in targeting response to inflammation and prevention of cell damage [30].

IgA nephropathy is driven by the formation and deposition of immune complexes composed of Gd-IgA1 and Gd-IgAl autoantibodies (anti-Gd-IgA1 antibodies), which deposit in the glomerulus to trigger complement mediated inflammation leading to disease progression [21]. This process often involves activation of the lectin and alternative pathways. The abnormal glycan structure of Gd-IgA1 may lead to its binding to complement components for complex formation in the glomerulus, thereby triggering inflammatory responses, cellular damage and fibrosis.

Although the factors involved in the pathogenesis are complex, complement involvement is one of the main reasons for the progression of IgA nephropathy. The deposition of immune complexes in the Mesangium region activates complement and leads to the release of inflammatory factors and glomerular damage. Complement activated complement component proteins, regulatory proteins, etc. are deposited throughout the whole glomerulus, which is an important mechanism of IgA nephropathy pathogenesis. In IgA nephropathy, its characteristic feature is that IgA is usually codeposited with complement proteins in the mesangium. Although Gd-IgA deposition within the mesangium is a key diagnosis of IgA nephropathy, C3 deposition within the mesangium is also common. In the updated Oxford classification, only the effect of complement C3 on the prognosis of IgA nephropathy was shown. The study found that there was a close relationship between the activation of complement pathway, the concentration of Galactose deficient IgA1(Gd-IgA1) and the clinical severity of IgA nephropathy, and Gd-IgA1 and the activation of complement pathway were considered to be involved in the pathogenesis of IgA nephropathy.

2.1. Classical pathway and Lectin pathway

Complement is an important defense mechanism in the immune system, and the activation of complement can trigger the classical pathway (CP), lectin pathway(LP), or bypass pathway(AP). The complement pathway can recognize and eliminate pathogens, promote the phagocytosis function of immune cells, and participate in the inflammatory response. Clinical observations suggest that variations in AP and LP activity may provide a link between the deposition of glomerular IgA and glomerular inflammation and injury.

CP is activated by pattern recognition molecules (PRM) C1q and pathogen associated molecular patterns (PAMPs), damage associated molecular patterns(DAMPs), or immune complexes containing IgM and IgG, or by molecules such as CRP [31]. Therefore, whether CP is activated can be determined through C1q detection.

LP is triggered by the interaction of PRM with carbohydrate PAMPs and DAMP located on non self-cells. These LP proteins are named MBL related Serine protease MASP-1, MASP-2 and MASP-3 [32]. In IgA nephropathy, different research teams found that about 25% of patients with IgA nephropathy exhibited positive renal local MBL staining, suggesting the presence of complement activation of LP. MBL, L-ficolin, M-ficolin, and H-ficolin are all complementactivating soluble pattern recognition molecules, which interact with PAMPs and/or DAMPs and initiate complement activation through MBL-associated serine protease (MASP)-1, MASP-2, and MASP-3, activating C4 and C2 and leading to C4b2a formation and C3 cleavage. LP activation on the surface of pathogens plays a first-line role in host defense. The abnormal glycosylation of IgA1 is characterized by high levels of GalNac exposure, which may interact with ficolins to activate LP.

2.2. Alternative pathways

The alternative pathway is a part of the complement, also known as the bypass pathway(AP), which plays an important role in anti-infection immunity. On the one hand, the alternative pathway forms the C3 convertase(C3bBb) through the hydrolysis of C3 by itself and combined with the hydrolysis of factor B, in which factor P can stabilize the alternative pathway C3 convertase and promote complement activation. After the formation of C3 invertase, it is cleaved into C5, and then C5b forms a membrane attack complex(MAC) with C6, C7, C8, and C9 to exert a cytolytic effect. On the other hand, the

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

alternative pathway is to combine C3b bound to the surface of antigen foreign bodies such as pathogenic microorganisms with factor B, and with the participation of factors P and D, form C3 invertase(C3bBb), which subsequently activates the enzymatic cascade reactions of C3, C5-C9. At the same time, the cleavage products C3a and C5a of C3 and C5 are also potent inflammatory effectors, which can initiate inflammatory reactions and exacerbate tissue damage.

Alternative pathways are one of the most common complement activation pathways in IgA nephropathy. Multiple studies have found that there are alternative pathway complement components such as B factor, P factor, and regulatory protein H factor in the renal tissue of IgA nephropathy patients. There are also significantly elevated B and P factors in the circulation of IgA nephropathy patients [33]. There is also an increase in circulating C3 products in 70% of pediatric IgA nephropathy patients [34]. Studies have also found that the levels of complement related proteins, including C3a, C5a, H-factor, and MAC, in the urine of severe IgA nephropathy patients are higher than those of mild cases [35,36]. Alternative pathways can be directly activated in situ in renal immune deposition. In pathological cases, the bypass pathway is overactivated. Studies have shown that glomerular C3 deposition may be affected by regulatory deficiencies in the bypass pathway triggered by immune complexes; In addition, individual C3 deposition can induce glomerular injury similar to that in IgA nephropathy [37].

As shown in Figure 1, the complement system is activated by three different pathways: the classical pathway (Cla ssical pathway, CP), the lectin pathway (Lectin pathway, LP), and the alternative pathway (Alternative pathway, AP). The classical pathway is activated by lgM and (or) lgG and antigen antibody complex with C1q to form C3 convertase (C4 b 2 b) (N-amino acid) (MBL ficolin), and then activate MBL-related serine protease (MASP-1 / MASP-2), C4, C2, to form C3 convertase (C4b2b), the same as the classical pathway. The alternative pathway forms C3 convertase (C3 b B b) through the hydrolysis of C3 and the enzymatic hydrolysis of factor D. Factor P can stabilize the alternative pathway C3 convertase and promote live complement. After the formation of C3 convertase, the three pathways cleave into C5, and then C5b forms a membrane attack complex (MAC) with C6, C7, C8, and C9 to play a cytolytic effect.

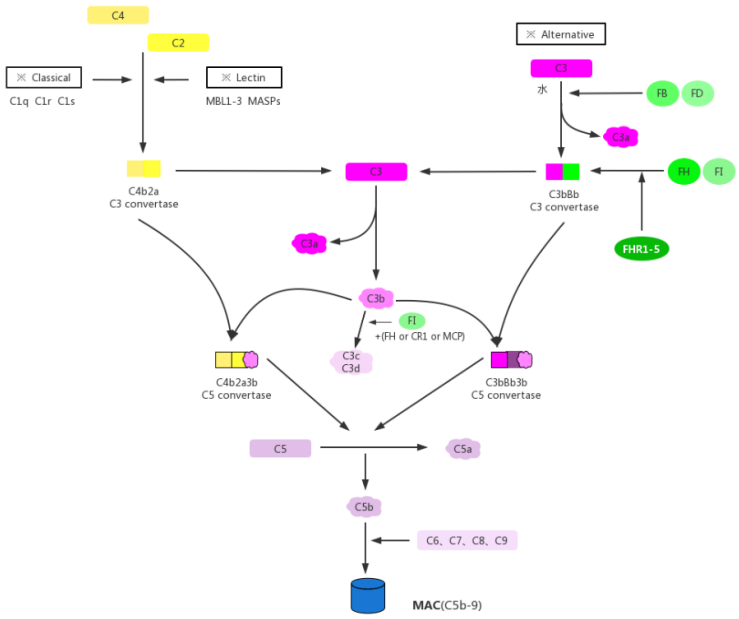

Figure 1: The complement activation pathway

2.3. Evidence of complement pathway activation

Although the three complement pathways have common terminal pathways, they are activated through different substances, so it can be judged whether the pathways are involved through the deposited protein components. Immunohistochemical evidence shows deposition of C3, C4d, mannan-binding lectin pathway (MBL, MASP1, MASP2 and Ficolin2), and the factor H(FH), complement H factor-related protein 2(FHR2), complement H factor-related protein 5(FHR5), and the membrane attack complex(MAC) in the IgA nephropathy mesangium, as well as commonly lacking C1q [38]. The presence of these proteins is evidence of the activation of the complement system.

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

The activation of the classical pathway (CP) can be detected by tissue immunostaining to identify the complement component C1q. Although some studies [39] suggest that glomerular mesangial C1q deposition is associated with poor renal prognosis and severe pathological features in IgA nephropathy patients. However, the vast majority of IgA nephropathy renal biopsy tissues did not detect C1q, indicating that the classical pathway does not play an important role in the pathogenesis of IgA nephropathy [40]. Additionally, glomerular C3, C4, C1q, and IgG can also demonstrate CP activity [41]. The presence of isolated glomerular C3 deposition suggests AP activity, and the presence of C4 and C3 in the absence of C1q is evidence of lectin pathway (LP) activation [41,42].

A study identified a total of 27 complement proteins associated with IgA nephropathy in the urine of IgA nephropathy patients, and showed an increase in relative abundance of C3, membrane attack complex(MAC), complement regulatory proteins, MBL(mannose binding lectin), and MASP1(MBL associated serine protease 2) in the lectin pathway and alternative pathways [43]. There have also been studies linking complement proteins in urine with clinical and pathological aspects, and found that complement-related protein 12 (colec12), complement factor H (CFH), complement H factor-related protein 2(CFHR2), and complement factor B(CFB) are positively correlated with serum creatinine. colec12, CFHR2, CFB, and C8g are positively correlated with glomerulosclerosis, while CFH, CFHR2, C8g, and C9 are positively correlated with renal tubular atrophy/interstitial fibrosis. Urinary complement proteins may become biomarkers for evaluating the progression of IgA nephropathy [44].

The presence of complement proteins in serum, urine, and kidneys indicates that complement activation is involved in the occurrence and development of IgA nephropathy. Evidence of complement activation and necessary effector molecular regulation of IgA nephropathy through alternative pathways suggests that Gd-IgA1 immune complexes have complement activation effects. AP is considered the most important pathway of action in the pathogenesis of IgA nephropathy. It has been proposed that PIgA (polymeric IgA), IgA complexes, and abnormally glycosylated IgA have strong ability to activate AP.

2.4. Correlation of complement pathway activation with Gd-IgA1

A large number of previous studies have shown that Galactose deficient IgA1(Gd-IgA1) is the main pathogenic factor of IgA nephropathy, and subsequent studies have also shown that complement pathway activation is also involved in the occurrence and development of IgA nephropathy [40]. Some studies have found a correlation between the activation of alternative pathways, Gd-IgA1 levels, and their clinical and pathological severity in IgA nephropathy patients, and both Gd-IgA1 and complement alternative pathway activation are believed to be involved in the pathogenesis of IgA nephropathy. Schmitt [23] hypothesized that Gd-IgA1 exposed to mesangial cells or aggregated IgA1 secretes C3 and matrix components through interaction with the C3a receptor of mesangial cells, leading to interstitial cell proliferation and excessive production of extracellular matrix, leading to the occurrence and development of IgA nephropathy.

Galactose-deficient IgA1(Gd-IgA1) and alternative complement pathway activation are considered to be involved in the pathogenesis of IgA nephropathy. Nevertheless, the relationships between alternative pathway activation and disease activity or Gd-IgA1 level remains unclear. The study [45] found that in IgA nephropathy patients, serum Gd-IgA1, Gd-IgA1/CFH and Gd-IgA1/C3 concentrations were significantly higher than those of the other groups and had some significance for the diagnosis of IgA nephropathy, Gd-IgA1/C3 had the highest diagnostic value, serum CFHR 1 and CFH concentrations were higher than the healthy group, and serum Gd-IgA1/CFH, Gd-IgA1/C3, CFHR1/CFH and CFHR1 and C3 were associated with the pathological severity of IgA nephropathy. Research has found that IgA nephropathy patients with high CFHR1 and CFHR1/CFH have higher serum Gd-IgA1 levels and faster renal function progression [46]. In a study [47] of 75 IgA nephropathy patients, compared with the healthy group, the plasma Gd-IgA1 level of IgA nephropathy patients increased and the Mesangium Gd-IgA1 was positive. In addition, the plasma Gd-IgA1 level was positively correlated with the concentration of Bb, C3a, C4d and MAC, and the high plasma Gd-IgA1 level was correlated with the deposition of mesangial Gd-IgAl. In 84 newly detected IgA nephropathy patients [48], it was found that the level of Proteinuria was positively correlated with the updated Oxford mesangial cell proliferation classification(M), intracapillary cell proliferation(E), tubular atrophy /interstitial fibrosis(T) and crescent(C). In addition, the plasma Gd-IgA1 titer of IgA nephropathy patients with tubular atrophy/interstitial fibrosis(T) was significantly increased, and both Gd-IgA1 and B factors could independently predict higher T scores. A comparative study was conducted between 98 IgA nephropathy patients and 25 patients with primary focal segmental sclerosis (FSGS) [49]. It was found that plasma C5a, B factor, and Gd-IgA1 levels in IgA nephropathy patients were higher than those in the control group.

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

Gd-IgA1 levels were positively correlated with plasma C5a and Bb, but not significantly in FSGS patients, indicating a close correlation between the activation of alternative complement pathways, Gd-IgA1 concentration, and clinical severity of IgA nephropathy. It has also been shown that the levels of Gd-IgA1 antibodies and the complement bypass activation of the biomarkers reflect the Oxford IgA nephropathy classification [8].

The above studies all indicate a correlation between serum Gd-IgA1 and complement factor levels. The deposition of Gd-IgA1 and its immune complexes triggers the activation of the complement pathway, especially the role of C3 and complement regulatory proteins in the alternative pathway, such as CFH, complement H factor related proteins, and B factor. The increase in local inflammatory response leads to and promotes the occurrence and progression of IgA nephropathy. In addition, Gd-IgA1 and B factors can independently predict higher renal tubular atrophy/interstitial fibrosis (T) scores, suggesting that the main site of action of the alternative pathway may be the renal tubulointerstitium. It does not rule out that compared with the deposition of Gd-IgA immune complex in healthy people, gene factors or environmental and dietary factors can activate the complement system. (Figure 2)

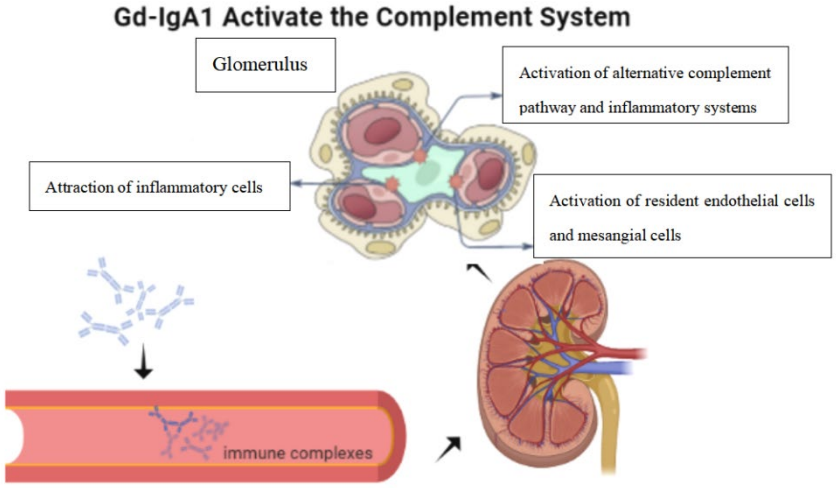

Figure 2: Gd-IgA1 deposition in the glomerulus activated the occurrence of the complement-induced inflammatory response, and the glomerular injury

3. Discussions

There is a specific correlation between serum Gd-IgA1 levels and biomarker levels activated by complement replacement pathways. Changes in Gd-IgA1 levels affect the deposition and expression of C3 and complement regulatory proteins in the replacement pathway in the kidneys, and both are correlated with the occurrence and development of IgA nephropathy and the pathological manifestations of renal glomeruli and tubules. These biomarkers may be used to guide treatment decisions. However, the mechanism by which Gd-IgA1 induces complement pathway activation, leading to local inflammatory response and kidney damage, remains unclear. In clinical trials for the treatment of IgA nephropathy, the observation of biomarkers activated by the complement replacement pathway during Gd-IgA1 treatment (in the NEFIGAN study [8]) may reveal the role between Gd-IgA1 and the complement pathway, suggesting that this can lead to dual inhibition of Gd-IgA1 and the complement pathway, maximizing the treatment of the disease. Therefore, more in-depth research is needed to explore this issue.

References

[1] Berthoux C F, Mohey H, Afiani A. Natural History of Primary IgA Nephropathy[J]. Seminars in Nephrology, 2007, 28(1).
[2] Berger J, Hinglais N. Intercapillary deposits of IgA-IgC[J]. Journal of the American Society of Nephrology: JASN, 2000, 11(10).
[3] Floege, Jürgen., Rauen, Thomas., Tang, Sydney C W, et al. Current treatment of IgA nephropathy. Seminars in immunopathology, 2021, 43(5):717-728.

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

[4] Suzuki H, Kiryluk K, Novak J, et al. The pathophysiology of IgA nephropathy[J]. J Am Soc Nephrol. 2011(22):1795–803.
[5] Yue X, Lina L, Yaru Z, et al. C1GALT1 expression is associated with galactosylation of IgA1 in peripheral B lymphocyte in immunoglobulin a nephropathy[J]. BMC nephrology, 2020, 21(1).
[6] Gharavi AG, Moldoveanu Z, Wyatt RJ, et al. Aberrant IgA1 glycosylation is inherited in familial and sporadic IgA nephropathy[J]. J Am Soc Nephrol. 2008, 19:1008–14.
[7] Suzuki, Keiichiro, Kawamoto, Shimpei, Maruya, Mikako, et al. GALT: organization and dynamics leading to IgA synthesis [J]. Advances in immunology, 2010, 107.
[8] Jonathan B, Richard L, Jens K, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy[J]. Kidney international, 2022.
[9] Kokubo T, Hiki Y, Iwase H, et al. Evidence for involvement of IgA1 hinge glycopeptide in the IgA1-IgA1 interraction in IgA nephropathy[J]. J Am Soc Nephrol 1997; 8: 915–919.
[10] Jan N, Milan T, Karel M, et al. IgA1-containing immune complexes in IgA nephropathy differentially affect proliferation of mesangial cells[J]. Kidney international, 2005, 67(2).
[11] P D G, Karen M, David W, et al. Galactosylation of IgA1 Is Associated with Common Variation in C1GALT1 [J]. Journal of the American Society of Nephrology : JASN, 2017, 28(7).
[12] Qin Wei, Zhong Xiang, Fan Junming, et al. External suppression causes the low expression of the Cosmc gene in IgA nephropathy [J]. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association, 2008, 23(5):1608-14.
[13] Yamada Koshi, Kobayashi Noriyoshi, Ikeda Tomomi, et al. Down-regulation of core 1 beta1, 3-galactosyltransferase and Cosmc by Th2 cytokine alters O-glycosylation of IgA1[J]. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association, 2010, 25(12):3890-7.
[14] Lin Jiaru, et al. Interleukin-17 promotes the production of underglycosylated IgA1 in DAKIKI cells [J]. Renal failure, 2018, 40(1):60-67.
[15] Pers Jacques-Olivier, Daridon Capucine, Devauchelle Valérie, et al. BAFF overexpression is associated with autoantibody production in autoimmune diseases [J]. Annals of the New York Academy of Sciences, 2005, 1050:34-9.
[16] McCarthy, Douglas D., Kujawa, Julie. , Wilson, Cheryl. , et al. Mice overexpressing BAFF develop a commensal flora-dependent, IgA-associated nephropathy[J]. The Journal of clinical investigation, 2011, 121(10).
[17] Li Weiwei, Peng Xiaofei, Liu Yuyuan, et al. TLR9 and BAFF: their expression in patients with IgA nephropathy [J]. Molecular medicine reports, 2014, 10(3):1469-74.
[18] Xin Gang, Shi Wei, Xu Lixia, et al. Serum BAFF is elevated in patients with IgA nephropathy and associated with clinical and histopathological features[J]. Journal of nephrology, 2012, 26(4).
[19] Makita Yuko, Suzuki Hitoshi, Kano Toshiki, et al. TLR9 activation induces aberrant IgA glycosylation via APRIL- and IL-6-mediated pathways in IgA nephropathy[J]. Kidney international, 2019, 97(2):340-349.
[20] Zheng N, Xie K, Ye H, Dong Y, et al. TLR7 in B cells promotes renal inflammation and Gd-IgA1 synthesis in IgA nephropathy [J]. JCI Insight. 2020 Jul 23; 5(14):e136965.
[21] Hashimoto, Azusa. , Suzuki, Yusuke. , Suzuki, Hitoshi. , et al. Determination of severity of murine IgA nephropathy by glomerular complement activation by aberrantly glycosylated IgA and immune complexes [J]. The American journal of pathology, 2012, 181(4).
[22] Xie Minhua, et al. Predictive prognostic value of glomerular C3 deposition in IgA nephropathy[J]. Journal of nephrology, 2022, 36(2).
[23] Schmitt, Roland. , Ståhl, Anne-Lie. , Olin, Anders I. , et al. The combined role of galactose-deficient IgA1 and streptococcal IgA-binding M Protein in inducing IL-6 and C3 secretion from human mesangial cells: implications for IgA nephropathy[J]. Journal of immunology (Baltimore, Md. : 1950), 2014, 193(1).
[24] Russell, M W. , Mansa, B. . Complement-fixing properties of human IgA antibodies. Alternative pathway complement activation by plastic-bound, but not specific antigen-bound, IgA[J]. Scandinavian journal of immunology, 1989, 30(2):175-83.
[25] Dong Ruijuan, Bai Ming, Zhao Jin, et al. A Comparative Study of the Gut Microbiota Associated With Immunoglobulin a Nephropathy and Membranous Nephropathy[J]. Frontiers in cellular and infection microbiology, 2020, 10.
[26] Weng Junxiong, Liu Cuiyun, Ding Xiaoyan, et al. Comparison of Gut microbiota between IgA nephropathy patients and healthy people[J]. Chinese Journal of Microecology, 2021, 33(10):1126-1133.
[27] Coppo R. The intestine-renal connection in Ig A nephropathy[J]. Nephrol Dial Transplant, 2015, 30:360-366.
[28] Tang Yuyan, Tang Yuyan, Zhu Yifan, et al. Gut Dysbiosis and Intestinal Barrier Dysfunction

ISSN 2706-6819 Vol.5, Issue 8: 100-108, DOI: 10.25236/IJFM.2023.050814

Promotes IgA Nephropathy by Increasing the Production of Gd-IgA1[J]. Frontiers in medicine, 2022.
[29] Davies, K A. . Complement[J]. Bailliere's clinical haematology, 1991, 4(4):927-55.
[30] Walport, M J. . Complement. First of two parts[J]. The New England journal of medicine, 2001, 344(14).
[31] Merle, Nicolas S. , Church, Sarah Elizabeth. , Fremeaux-Bacchi, Veronique. , et zl. Complement System Part I - Molecular Mechanisms of Activation and Regulation[J]. Frontiers in immunology, 2015, 6:262.
[32] Kjaer, Troels R. , Thiel, Steffen. , Andersen, Gregers R. . Toward a structure-based comprehension of the lectin pathway of complement[J]. Molecular immunology, 2013, 56(4).
[33] Onda K, Ohi H, Tamano M, et al Hypercomplemia in adult patients with IgA nephropathy [J]. J Clin Lab Anal, 2007, 21(2): 77-84.
[34] Tanaka C, Suhara Y, Kikkawa Y. Circulating immune complexes and complement breakdown products in childhood IgA nephropathy[J]. Nippon Jinzo Gakkai Shi, 1991, 33(3) : 709-717.
[35] Wang Zhen, Xu Zhe, Liu Guohui. The relationship between strength of complement C3 deposition in mesangial regions and degree of disease in patients with IgA nephropathy[J]. The Bethune Journal of Medicine, 2020, 18(05):429-432.
[36] Kim SJ, Koo HM, Lim BJ, et al. Decreased circulating C3 levels and mesangial C3 deposition predict renal outcomes in patients with IgA nephropathy [J]. PLoS One, 2012, 7(7):e40495.
[37] Pickering MC, D'Agati VD, Nester CM, et al. C3 glomerulopathy: Consensus report[J]. Kidney Int, 2013, 84(5) : 1079-1089.
[38] Medjeral-Thomas, Nicholas R. , Cook, H Terence. , Pickering, Matthew C. . Complement activation in IgA nephropathy[J]. Seminars in immunopathology, 2021, 43(5):679-690.
[39] Hong-Joo L, Young S C, Hwan K J, et al. Association of C1q deposition with renal outcomes in IgA nephropathy[J]. Clinical nephrology, 2013, 80(2).
[40] Maillard, Nicolas. , Wyatt, Robert J. , Julian, Bruce A. , et al. Current Understanding of the Role of Complement in IgA Nephropathy[J]. Journal of the American Society of Nephrology : JASN, 2015, 26(7):1503-12.
[41] Tortajada A, Gutierrez E, Pickering C M, et al. The role of complement in IgA nephropathy[J]. Molecular Immunology, 2019, 114:123-132.
[42] Peter G, Ninette G, Katrine P, et al. A journey through the lectin pathway of complement-MBL and beyond[J]. Immunological reviews, 2016, 274(1):74-97.
[43] Xia N, Shuyu Z, Chen S, et al. Urinary complement proteins in IgA nephropathy progression from a relative quantitative proteomic analysis[J]. PeerJ, 2023, 11.
[44] Dongqing W, Changwei W, Sipei C, et al. Urinary complement profile in IgA nephropathy and its correlation with the clinical and pathological characteristics[J]. Frontiers in immunology, 2023, 14.
[45] Wang Weiqing. The value of serum Gd-IgA 1, complement C3, and complement regulatory proteins in the diagnosis and disease evaluation of IgA nephropathy[D]. Ningbo University, 2021.
[46] Moldoveanu, Z, Wyatt, R J, Lee, J Y. , Tomana, M. , et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels[J]. Kidney international, 2007, 71(11):1148-54.
[47] Zhang Kai, Li Qiongqiong, Zhang Yaru, et al. Clinical Significance of Galactose-Deficient IgA1 by KM55 in Patients with IgA Nephropathy[J]. Kidney & blood pressure research, 2019, 44(5):1196-1206.
[48] Juan YT, Chiang WC, Lin WC, et al. Associations between biomarkers of complement activation, galactose-deficient IgA1 antibody and the updated Oxford pathology classification of IgA nephropathy[J]. J Clin Med. 2022;11:4231.
[49] Chiu YL, Lin WC, Shu KH, et al. Alternative complement pathway is activated and associated with galactose-deficient IgA1 antibody in IgA nephropathy patients[J]. Front Immunol , 2021, 12:638309.