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# Checkpoint Imbalance in IGA Nephropathy: Unraveling the Immune Dysregulation Driving Glomerular Injury

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**KEYWORDS**

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**ABSTRACT:**

**Introduction**: IgA nephropathy (IgAN), also known as Berger disease, is the most common form of primary glomerulonephritis and a leading cause of chronic kidney disease and end-stage renal failure worldwide. It is characterized by the deposition of IgA in the glomerular mesangium and subsequent immune-mediated renal injury.

**Objectives**: This review aims to summarize current insights into the immunopathogenesis of IgAN, with particular emphasis on the role of galactose-deficient IgA1 (Gd-IgA1) and the regulatory function of the PD-1/PD-L1 immune checkpoint pathway, as well as its therapeutic implications.

**Methods**: A narrative review of recent experimental and clinical literature was conducted, focusing on mechanisms of immune complex formation, complement activation, and immune checkpoint modulation in IgAN, including evidence from patients receiving immune checkpoint inhibitors.

**Results**: Current evidence indicates that patients with IgAN frequently produce galactose-deficient IgA1 (Gd-IgA1), which is inadequately cleared and recognized as autoantigenic. This leads to the generation of anti-Gd-IgA1 autoantibodies and formation of circulating immune complexes. Deposition of these complexes in the glomerular mesangium triggers complement activation, chronic inflammation, and progressive fibrosis, ultimately contributing to renal failure. Dysregulation of the PD-1/PD-L1 axis—particularly during immune checkpoint inhibitor therapy in cancer patients—can exacerbate autoimmune responses, resulting in disease flare-ups or de novo IgAN. The PD-1/PD-L1 pathway plays a critical role in limiting T-cell–mediated inflammation.

**Conclusions**: The PD-1/PD-L1 axis represents a double-edged sword in IgAN pathogenesis. While inhibition may increase the risk of autoimmune renal injury, therapeutic enhancement of this pathway may reduce excessive immune activation and kidney damage. Targeted immunomodulatory strategies involving PD-1/PD-L1 signaling therefore hold promise as future treatment approaches in IgAN management.

**Keywords:** IgA Nephropathy, PD1/PDL1, Inflammation, Fibrosis, Chronic Kidney Disease

**Abbreviation**

PD1/PDL1- Programmed Death-1/Programmed Death-Ligand 1, IgA- Immunoglobulin A ESRD- End-stage renal disease, Gd-IgA1- Galactose-deficient IgA1, eGFR - Estimated Glomerular Filtration Rate, RAAS- Renin-Angiotensin-Aldosterone System, BAFF- B-cell Activating Factor, ICI- immune checkpoint inhibitor, RIF- Renal interstitial fibrosis, MMP-2- matrix metalloproteinase-2

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## 1. Introduction

Immunoglobulin A (IgA) nephropathy, or IgAN, is a major cause of glomerulonephritis and renal failure. This disease is characterized by IgA deposition in the glomerular mesangium. Damage to the basement membrane by the immune system results in hematuria, proteinuria, and renal insufficiency. Because Berger and Hinglais first described the illness in 1968, it is also known as Berger disease. The most frequently seen alteration is mesangial proliferation with noticeable IgA deposition, though a range of glomerular lesions may be seen pathologically [1]. Recent international collaborative efforts have produced significant findings that have significantly improved our comprehension of the immunopathogenesis of IgAN. Furthermore, the growth of multicenter networks has facilitated the planning and execution of clinical trials in a comprehensive manner, yielding crucial data regarding immunotherapy for IgAN. Although the clinical course typically progresses gradually, between 20% and 50% of affected patients develop end-stage renal disease (ESRD) within 20 years of diagnosis. Prevalence varies by ethnicity, race, geography, and genetics; Asian patients are affected more often and to a greater extent [2]. IgAN, which is produced by aberrant immune responses, results in IgA deposits in the glomerulus, increased podocyte permeability, and interstitial fibrosis. Although IgAN often precedes an infectious disease that results in a dysregulated immune response, it is important to remember that IgAN does not have an infectious etiology. There is no evidence that a specific infectious agent causes IgAN. Instead, the immune system appears to be activated by a range of clinical and subclinical stimuli, as well as genetic factors associated with IgA glycosylation [3]. The most common form of primary glomerulonephritis worldwide is IgA nephropathy (IgAN), also known as Berger's disease. The progressive accumulation of immune complexes, mainly composed of immunoglobulin A (IgA), in the glomerular mesangium of the kidneys is a hallmark of this chronic autoimmune disease. This chronic deposition and the resulting inflammation ultimately lead to end-stage renal disease (ESRD), which necessitates dialysis or kidney transplantation in approximately 30–40% of patients within 10–20 years of diagnosis. It results in glomerulosclerosis, or the scarring of the glomeruli, which are tiny blood filters [4]. The complexity of IgAN is encapsulated in a four-step series of events that begin with the production of an aberrantly glycosylated form of IgA1 galactose-deficient IgA1 (Gd-IgA1) (Hit 1), where O-linked glycans in the hinge region are missing galactose residues. For its pathogenesis, this is the commonly accepted "multi-hit" theory. Once this abnormally structured IgA1 is recognized as a neoantigen, the immune system proceeds to generate autoantibodies, typically of the IgG or IgA class, that specifically target these Gd-IgA1 molecules (Hit 2). Circulating immune complexes containing Gd-IgA1 and anti-glycan antibodies are produced after this binding (Hit 3). Due to ineffective removal from the circulation, these complexes eventually become trapped and lodged within the sensitive mesangium of the kidney glomeruli (Hit 4) [5]. This mesangial deposition triggers the complement cascade, mainly the alternative and lectin pathways, and encourages resident mesangial cells to proliferate and generate inflammatory mediators and extracellular matrix components. Together, these elements drive the fibrosis, progressive kidney damage, and inflammatory process that are characteristics of IgA N [6].

### 1.1 Clinical Presentation and Diagnosis

IgAN's highly variable clinical course, which often manifests silently for years, makes early detection challenging. Males and those with Asian and some European ancestries are more likely to have the disease, which has a strong genetic predisposition and is typically diagnosed in the second or third decades of life. The most recognizable and common clinical sign is hematuria, or blood in the urine. It often appears as cola or tea-colored urine and can be either microscopic, which can only be found by urinalysis, or macroscopic, which is visible to the unaided eye [7]. An episode of macroscopic hematuria that happens concurrently with, or within 1 to 2 days after, an upper respiratory tract infection or other mucosal infection is a classic presentation of synpharyngitic hematuria because the increase in mucosal IgA production contributes to the pathogenic immune complexes. Proteinuria, or the presence of protein in the urine, is another significant feature. A significantly worse renal outcome is linked to high protein levels, particularly those exceeding 1 gram per day, which is a good indicator of the severity of the disease and the risk of its progression. Other symptoms that might point to the onset of nephrotic syndrome

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include edema (swelling), particularly around the ankles and eyes, hypertension, and flank pain [8]. The only test required to make a definitive diagnosis of IgAN is a kidney biopsy. The pathognomonic discovery of dominant or co-dominant IgA deposits in the glomerular mesangium is revealed by immunofluorescence microscopy analysis of the biopsy. Apart from the biopsy, urinalysis is used to measure hematuria and proteinuria, blood tests for serum creatinine and estimated Glomerular Filtration Rate (eGFR) are used to assess kidney function, and sometimes serological tests for components like Gd-IgA1 are used for diagnosis and follow-up. These tests are not standard diagnostic techniques, though [9].

### 1.2 Treatment

Strict supportive care is the cornerstone of treatment for all patients with IgA nephropathy because there is currently no known cure. This care is intended to slow the rate at which kidney function deteriorates and manage associated risks. The main techniques used in this foundational therapy to block the Renin-Angiotensin-Aldosterone System (RAAS) and aggressively control blood pressure in order to reduce proteinuria are angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, which also have a direct anti-proteinuric effect. Another advancement in supportive care is the use of sodium-glucose cotransporter 2 inhibitors, which have demonstrated exceptional effectiveness in reducing proteinuria and major adverse kidney outcomes in patients with chronic kidney disease, including IgAN. Patients who receive the best supportive care possible but still have high-risk, persistent proteinuria may benefit from more therapeutic approaches [10]. Recent developments have enabled the use of targeted-release budesonide, an oral corticosteroid formulation designed specifically to release the drug in the distal ileum to inhibit the overproduction of pathogenic Gd-IgA1 at the source (the gut-associated lymphoid tissue). There are fewer systemic side effects and this immunosuppressive technique is more targeted. Sparsentan, a dual endothelin and angiotensin receptor antagonist that is non-immunosuppressive, has also been approved to reduce proteinuria in this high-risk population. Though their overall effectiveness in non-rapidly progressive IgAN is still up for debate due to side effect concerns, systemic corticosteroids and other strong immunosuppressants, like cyclophosphamide, may be considered for rapidly progressing disease [11]. In the future, the therapeutic landscape is rapidly changing due to the multi-hit hypothesis. Emerging investigational therapies are focusing on novel targets. Potential disease-specific treatments that could drastically alter the course and outcome of IgA nephropathy include blocking the production of the pathogenic IgA by blocking factors like A Proliferation-Inducing Ligand (APRIL) and B-cell Activating Factor (BAFF) and using various inhibitors to target the complement cascade, particularly the alternative pathway [12].

### 1.3 Factors Effecting Iga Nephropathy

Genetic, immunological, environmental, lifestyle, clinical, and pathological factors all play a role in the onset and course of IgA nephropathy (IgAN). Genetic factors are important because people who have certain HLA gene polymorphisms or a family history of IgAN are more likely to be affected. Disease susceptibility has also been connected to variations in genes controlling complement pathways and mucosal immunity. The development of IgA-containing immune complexes, the overactivation of the complement system, especially components C3, C4, and C5a, which promote inflammation, and the increased production of galactose-deficient IgA1 are all immunological factors that play a key role in pathogenesis. Environmental factors that can cause or exacerbate IgAN include respiratory or gastrointestinal infections, particularly those caused by viruses or streptococci, and these conditions frequently exhibit seasonal variation. Table 1 provides the specifics [13].

## 2. Pathophysiology of IgA nephropathy

IgA immune complexes are deposited in the renal mesangium in IgA nephropathy (IgAN), commonly referred to as Berger's disease, a chronic glomerular disorder. The aberrant production of galactose-deficient IgA1 (Gd-IgA1), which has compromised O-linked glycosylation in the hinge region, is the first step in the pathogenesis. Because these abnormal IgA1 molecules are not sufficiently removed from the bloodstream, they build up in the blood. IgG and/or IgA autoantibodies are produced against Gd-IgA1 because the immune system perceives it as a foreign antigen. Large circulating immune complexes that tend to deposit in the glomerular mesangium are created when Gd-IgA1 interacts with these autoantibodies. Local inflammation is started when

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mesangial cells are activated by mesangial deposition. The alternative and lectin pathways, which include elements like C3, C4, and C5a, are the primary means of complement activation, which intensifies inflammatory damage [14]. Leukocyte infiltration, extracellular matrix expansion, and mesangial cell proliferation are caused by the release of different cytokines, chemokines, and growth factors by activated mesangial cells. Proteinuria and hematuria are caused by these inflammatory reactions that weaken the glomerular filtration barrier. Continuous damage causes tubulointerstitial fibrosis and progressive glomerulosclerosis, which eventually result in end-stage renal disease (ESRD) or chronic kidney disease (CKD). Accordingly, IgA nephropathy develops through a series of inflammatory and immunological processes, starting with aberrant IgA1 production and ending with irreversible renal damage [15].

In IgA nephropathy, an autoimmune disease, immune complexes containing an abnormal form of immunoglobulin A (IgA) are deposited in the kidney's filtering units, or glomeruli. This deposition triggers an inflammatory response that damages the kidney filters, leading to blood and protein in the urine and eventually a decline in kidney function. The disease mechanism is best described by the Four-Hit Hypothesis [16]. A multi-hit pathogenic mechanism that includes aberrant IgA1 production, autoantibody formation, immune complex deposition, and progressive glomerular injury leads to IgA nephropathy (IgAN). Galactose-deficient IgA1 (Gd-IgA1) is produced in the initial step, referred to as Hit 1 [17]. Sugar chains [O-glycans] with terminal galactose residues are typically found in the hinge region of the IgA1 molecule. However, the IgA1 molecules produced in people who are predisposed to IgAN—due to genetic and environmental factors like mucosal infections [like a cold or sore throat]—do not contain galactose residues. Because of this flaw, N-acetyl galactosamine (GalNAc) residues are exposed, giving the immune system the impression that the molecule is alien. The immune system responds to Hit 2 by generating autoantibodies, mostly of the IgG and IgA classes, that target Gd-IgA1 specifically after identifying these exposed GalNAc residues as antigens. These anti-Gd-IgA1 autoantibodies attach to the circulating Gd-IgA1 molecules during Hit 3, forming large immune complexes (ICs). The severity and activity of the disease are directly correlated with the blood levels of these pathogenic immune complexes [18]. The circulating immune complexes ultimately settle in the mesangium, the glomerulus's central region, in Hit 4. Their deposition sets off a series of inflammatory events by activating mesangial cells and the complement system, specifically the lectin and alternative pathways. These include the growth of the extracellular matrix, the proliferation of mesangial cells, and the release of inflammatory mediators like growth factors, chemokines, and cytokines [19]. The glomerular structure gradually deteriorates due to the subsequent infiltration of inflammatory cells. Glomerulosclerosis, tubulointerstitial fibrosis, and eventually chronic kidney disease or end-stage renal disease are caused by the kidney's filtration ability being compromised over time by this ongoing inflammation and proliferation. Therefore, IgAN is a stepwise autoimmune process that leads to chronic glomerular injury through aberrant IgA1 production and immune complex deposition [20].

## 3. Role of pd1 and pdl1 in various inflammatory diseases

One important immune checkpoint that preserves self-tolerance and inhibits excessive immune activation is the PD-1/PD-L1 pathway. Numerous inflammatory and autoimmune disorders have been linked to the dysregulation of this pathway. Reduced PD-1/PD-L1 signaling causes hyperactive T and B cells in Systemic Lupus Erythematosus (SLE), which in turn causes excessive production of autoantibodies (such as ANA and anti-dsDNA) and extensive tissue inflammation. Defective synovial T cell PD-1 signaling in RA leads to chronic inflammation and progressive joint degradation. Similar to this, MS is characterized by a decreased PD-1/PD-L1 interaction, which permits autoreactive T cells to damage myelin sheaths and result in demyelination [21]. Insulin deficiency results from autoreactive T cells destroying pancreatic β-cells due to impaired PD-1/PD-L1 function in Type 1 Diabetes Mellitus (T1DM). Immune regulation against gut flora is disrupted in Inflammatory Bowel Disease (IBD) by altered PD-1/PD-L1 expression in the intestinal mucosa, which leads to chronic intestinal inflammation. Reduced PD-1 expression in psoriasis promotes effector T-cell activation and cytokine release, especially TNF-α and IL-17, which fuel skin inflammation. Airway inflammation is maintained in asthma by the overexpression of PD-L1 on airway epithelial cells, which inhibits regulatory T cells but increases Th2/Th17

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responses. Reduced PD-1/PD-L1 signaling causes T- and B-cell hyperactivation in IgA Nephropathy (IgAN), which in turn causes an excess of galactose-deficient IgA1 and immune complex deposition in glomeruli. Finally, chronic renal inflammation and fibrosis are promoted by the dysregulation of PD-1/PD-L1 in renal and immune cells in diabetic nephropathy (DN). As a result, the PD-1/PD-L1 pathway is an essential immune balance regulator, and the pathophysiology of many autoimmune and inflammatory diseases is greatly influenced by its dysfunction, Table 2 provides the specifics [22].

## 4. Impact of PD1 and PDL1 in IgA nephropathy

Programmed cell death 1 (PD 1) is an immune checkpoint receptor expressed by activated T cells and B cells, and its ligand, PD L1, is widely expressed by antigen-presenting cells and other tissues. PD 1 engagement by PD L1 usually transmits an inhibitory signal that decreases T cell activation and maintains tolerance. By regulating hyperactive immunity, the PD 1/PD L1 axis normally protects against autoimmunity. For example, when the cancer drug nivolumab blocks PD 1, autoreactive T cells may be released. It has been demonstrated that this results in de novo IgA nephropathy (IgAN) in some patients. This suggests that PD 1 signaling normally suppresses the pathogenic immune responses that can activate IgAN. The pathophysiology of IgAN depends on persistent immune activation [23]. Several studies have shown that active IgAN is associated with increased expression of PD 1 and PD L1 on lymphocytes, especially in more severe (proliferative) cases. Grywalska et al. (2018) found that patients with proliferative glomerulonephritis's (PGN, including IgAN) had significantly higher levels of PD $1^+$ T cells (both $CD4^+$ and $CD8^+$) and PD $1^+$ B cells than either non-proliferative GN or healthy controls. Additionally, these lymphocytes expressed more PD-L1. The authors concluded that "deregulation of the PD-1/PD-L1 axis may contribute to PGN pathogenesis" and that high levels of PD 1/PD-L1 are linked to persistent T cell activation and a worse prognosis [24].

In conclusion, lymphocytes that express more PD 1/PD L1 in IgAN patients are indicative of chronic immune stimulation. More recent studies have identified specific subsets of T cells. A 2020 study (Wang et al., Sci. Rep.) found that circulating PD 1hi CXCR5^– "peripheral helper" [T_PH] $CD4^+$ T cells were more common in IgAN patients than in healthy controls. These PD 1 hi T cells aid B cells in producing IL 21 and maturing into plasma cells that secrete antibodies. PD 1hi Patients with newly diagnosed IgAN had significantly higher levels of CD138-B cells and CXCR5-T cells than controls. Notably, although their numbers decreased following treatment, higher levels of these PD 1hi T cells were associated with worse renal function (lower eGFR) and higher proteinuria [25]. The authors concluded that "subsets of circulating PD-1hi CXCR5- T cells contribute to the progression and pathogenesis of IgAN by regulating the differentiation of $CD138^+$ B cells." In other words, PD 1hi helper T cells may unnaturally stimulate IgA-producing B cells in IgAN. This new finding links the PD 1 marker to active disease rather than immune inhibition. Overall, human data suggest a paradox: even though PD 1 is an inhibitory receptor, IgAN patients have upregulated levels of PD 1 and PD-L1 on immune cells. This is most likely due to compensatory exhaustion markers on chronically activated T and B cells [26]. Increased expression of PD 1/PD-L1 is associated with more aggressive disease. PD 1/$PDL1^+$ lymphocyte counts were higher in proliferative GN patients (including IgAN) and "deregulation of PD-1/PD-L1 may contribute to pathogenesis," according to Grywalska et al. Wang et al. also showed a relationship between PD 1 hi T cells and B cells and the severity of the illness. These results imply that chronic PD-1/PD-L1 signaling is present in IgAN, which could indicate a pathogenic but exhausted immune state [27].

Particularly when taking immune dysregulation into account, research on the role of the Programmed Death-1 (PD-1) and its ligand, Programmed Death-Ligand 1 (PD-L1), axis in IgA Nephropathy (IgAN) is expanding. PD-1 is an essential inhibitory immune checkpoint receptor that is primarily expressed on T-cells. It promotes self-tolerance and prevents immune system overreactions when it binds to its ligands, PD-L1 or PD-L2. Although the primary pathogenesis of IgAN is the deposition of galactose-deficient IgA1 immune complexes in the glomerular mesangium, which results in local inflammation and damage, the PD-1/PD-L1 axis may be implicated in the persistent chronic injury and inflammatory processes [28]. According to research, the pathophysiology and possibly worse prognosis of some

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proliferative forms of glomerulonephritis, such as IgAN, may be associated with a deregulation of this axis, which frequently shows up as changed frequencies of T and B lymphocytes that are PD-1-positive and PD-L1-positive. High proportions of lymphocytes expressing PD-1 and PD-L1 could be an indication of persistent glomerular inflammation and ongoing T-cell activation [29]. Reports of IgAN emerging as an uncommon but severe immune-related adverse event (irAE) in patients receiving cancer treatment with immune checkpoint inhibitors (ICIs) that block the PD-1/PD-L1 pathway (e.g., anti-PD-1 antibodies) further emphasize the clinical significance of this pathway .The axis's function in renal immune homeostasis is demonstrated by the fact that blocking this inhibitory pathway, which is meant to improve anti-tumor immunity, can impair immunological self-tolerance and cause the onset or worsening of autoimmune diseases like IgAN. All of these results point to the PD-1/PD-L1 axis as a key regulatory pathway in the kidney, and its disruption could be a factor in the immune-mediated damage that IgAN is known for [30]. Research on the effects of the Programmed Death-1 (PD-1) and Programmed Death-Ligand 1 (PD-L1) pathways in Immunoglobulin A Nephropathy (IgAN) is just getting started, but it may play a part in the immunopathogenesis and prognosis of the condition. While its ligand, PD-L1, is present on a variety of immune and non-immune cells, including renal parenchymal cells, PD-1 is a crucial inhibitory immune checkpoint receptor that is mainly expressed on T cells. By suppressing T-cell activation, this pathway typically preserves immunological homeostasis and averts autoimmunity [31]. Research points to a deregulation of this axis in the context of IgAN, a disease caused by the accumulation of aberrant IgA-containing immune complexes in the kidney's glomeruli. Research has shown that PD-1-positive and PD-L1-positive T and B lymphocytes are more common in patients with primary proliferative glomerulonephritis, which can include aggressive forms of IgAN, than in non-proliferative forms and healthy controls. It is believed that this elevated expression is linked to persistent glomerular inflammation and ongoing T-cell activation, which aid in the onset and advancement of kidney damage. A further indication of the pathway's crucial role in renal immune tolerance is the fact that the therapeutic use of immune checkpoint inhibitors (ICIs), which block the PD-1/PD-L1 interaction, in cancer patients has occasionally resulted in the development or aggravation of glomerulonephritis, including IgAN. Thus, the PD-1/PD-L1 axis seems to play a key role in the immune dysregulation that characterises IgAN, and its constituents could serve as novel therapeutic targets for reducing the kidneys' harmful inflammatory response as well as possible prognostic biomarkers. The impact of PD-1/PD-L1 are depicted in Figure 1 and 2 [32].

## 5. Therapeutic Implications

While PD-1 receptors on T cells normally interact with PD-L1 on the surface of other cells to deliver inhibitory signals that reduce inflammation and help preserve organ integrity, including within the kidneys, cancer therapy drugs known as immune checkpoint inhibitors (ICIs) disrupt this interaction to enhance the body's ability to attack tumor cells. However, interrupting PD-1/PD-L1 signaling can also remove natural checks on immune activity, sometimes triggering or worsening autoimmune conditions like glomerulonephritis and IgA nephropathy, as observed in some cancer patients receiving these treatments [33]. Given the PD-1/PD-L1 pathway's protective function, scientists have started looking into how it might be modulated in non-cancer settings, particularly in relation to autoimmune kidney disorders like IgA nephropathy (IgAN). Excessive T cell activation in IgAN leads to harmful kidney inflammation. According to preliminary experimental research, treatments that use substances known as agonists to improve rather than inhibit PD-1/PD-L1 signaling may be able to prevent this detrimental immune activation and preserve renal tissue. In contrast to the broad-acting immunosuppressive medications currently used in clinical practice, PD-1/PD-L1 agonists may offer a more selective and possibly safer option by selectively targeting the pathways in the kidney that maintain immune homeostasis [34]. Although these results are encouraging, preclinical research provides the majority of the supporting data, and additional clinical research is required to completely comprehend the safety and effectiveness of such treatments in patients with IgAN and associated glomerular diseases. The PD-1/PD-L1 immune checkpoint, a critical modulator of kidney immune homeostasis, offers both a risk factor and a potential new target in IgAN, which has paradoxical therapeutic implications [35].

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## 6. Discussion

In IgA nephropathy (IgAN), our research shows that soluble PD-1 (sPD-1) plays a profibrotic and proinflammatory role. Extremely elevated serum sPD-1 levels were found to be a distinct risk factor for renal interstitial fibrosis (RIF) in patients with progressive IgAN. Elevated sPD-1 levels were significantly linked to a worsened decline in renal function. Concurrently, it was found that both sPD-1–high IgAN patients and mouse models of renal fibrosis caused by unilateral ureteral obstruction (UUO) had overexpressed PD-L1, the natural ligand of PD-1, in renal tubulointerstitial tissues. This suggests that sPD-1 and PD-L1 may have a pathological relationship that promotes renal fibrosis [36].

Mechanistically, elevated levels of collagen and α-SMA, two important markers of fibrosis, demonstrated that inflammation and hypoxia significantly raised the expression of PD-L1 in renal tubular epithelial (HK-2) cells. These results suggest that PD-L1 overexpression is a direct cause of in vitro fibrotic progression. Notably, intraperitoneal injection of a PD-L1 fusion protein, an inhibitor of sPD-1, prevented renal fibrosis in UUO mice. This bolsters the notion that blocking circulating sPD-1 can restore PD-1/PD-L1 signaling and inhibit fibro genic and inflammatory pathways [37]. Subsequent investigation showed that matrix metalloproteinase-2's (MMP-2) proteolytic cleavage of cell-bound PD-1 may be the cause of elevated serum sPD-1 in IgAN. MMP-2 expression was elevated in renal tubular epithelial cells in response to pro-inflammatory cytokine stimulation, specifically IL-6. The subsequent cleavage of PD-1 from T cells increases the amount of circulating sPD-1, worsening interstitial fibrosis. PD-L1 fusion protein therapy decreased fibrosis by inhibiting T-cell activation, reducing the expression of proteins associated with fibrosis, limiting the deposition of extracellular matrix, and preventing inflammation [38]. Our results indicate that the proinflammatory cytokine sPD-1 stimulates the formation of RIF in IgAN. Even though the PD-1/PD-L1 axis is well known for its tumor immunomodulatory role, recent research also suggests that sPD-1 is involved in autoimmunity and inflammation, including rheumatoid arthritis and systemic lupus erythematosus. Our results corroborate these theories by demonstrating that sPD-1 interferes with PD-1/PD-L1-dependent immune suppression to increase T-cell proliferation and inflammatory responses in the kidney [39]. In chronic renal inflammation, tubular epithelial cells (TECs) are often exposed to cytokines produced by immune cells that have invaded the kidneys. These stimuli encourage the recruitment of more inflammatory cells and change the behavior of TEC. PD-L1 expression is low in healthy tissues but significantly elevated in inflammatory stress or fibrosis. PD-L1 on TECs can provide protection by reducing the cytotoxic immune attack on the renal parenchyma. Our study and other studies demonstrate increased PD-L1 expression in experimental UUO models and fibrotic kidney tissue, which is consistent with the lung [40]. Furthermore, we found a relationship between the level of fibrosis and MMP-2 expression induced by IL-6, suggesting the crucial role that MMP signaling plays in tissue remodeling. MMPs are involved in the processing of different cell-surface materials, including chemokines and CD proteins, as well as the degradation of extracellular matrix. Our results indicate that MMP-2 is responsible for the shedding of membrane-bound PD-1 (CD279) and generates sPD-1 during the progression of fibrosis. Although the precise mechanism of cleavage requires further explanation, these results are consistent with a critical role for MMP-2-driven sPD-1 generation in renal fibrosis. It is likely that other members of the MMP family take part in this process in different disease contexts, since at least 24 MMPs have been identified in humans [41]. By opposing the PD-1/PD-L1 interaction, sPD-1 seems to promote chronic inflammation and suppress immune regulation. In our animal model, exogenous PD-L1 fusion protein efficiently bound sPD-1, restored the balance of PD-1/PD-L1 signaling, and decreased kidney fibrosis. However, since the UUO model is an acute fibrotic process and human renal fibrosis develops over decades, additional dosing, delivery route, and timing optimization is needed for clinical application [42]. This study also points out certain drawbacks. Although PD-L1 upregulation on TECs seems to aid in tissue repair, more research is necessary to determine the precise mechanism causing its induction. We also found that hypertension, a known risk factor for the progression of chronic kidney disease, significantly impacted the association between sPD-1 levels and RIF progression. To confirm these results and lower individual variability, larger clinical cohorts with more disease representation are needed [43]. Our study concludes that elevated serum

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sPD-1 is both a biomarker and a pathogenic driver of renal interstitial fibrosis in IgAN. Tubular epithelial cells' expression of PD-L1 plays a major role in this disease process, and therapeutic targeting of sPD-1 by PD-L1 fusion protein holds promise for preventing or lessening renal fibrosis in chronic kidney diseases [44,45].

## 7. Conclusion

Renal interstitial fibrosis (RIF), a significant problem in chronic kidney disease, is often linked to ongoing inflammation and immune cell activity, especially from T cells. Unfortunately, there isn't a known treatment for this fibrosis once it starts. We found that elevated blood levels of soluble PD-1 (sPD-1) were associated with a faster decline in kidney function and a higher risk of kidney scarring in patients with IgA nephropathy (IgAN). We looked into the cause and found that the PD-1/PD-L1/MMP-2 axis is a critical pathway. In response to inflammatory cues like IL-6, kidney tubular cells produce more MMP-2, an enzyme that can remove PD-1 molecules from the surface of T cells. During this process, soluble PD-1 is released into the bloodstream. Excess sPD-1 interferes with normal PD-1/PD-L1 "braking" signals, which normally keep T cells under control. T cells become hyperactive in the absence of this check, leading to inflammation and kidney fibrosis. To test a possible treatment, we employed a PD-L1 fusion protein, a molecule that can stop the harmful effects of sPD-1. In animal studies, this treatment slowed down T cell activation, reduced inflammatory and fibrosis-related proteins, and dramatically reduced kidney scarring.

Overall, our findings suggest that targeting this pathway with a PD-L1 fusion protein could become a novel therapeutic strategy for kidney fibrosis in chronic kidney disease.

**Declaration**

Conflict of interest- There is no potential conflict of interest among the authors Ethics approval – Not applicable

Informed consent – Not applicable.

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**Table1.** Factors affecting IgA Nephropathy

| **Category** | **Factors** | |
|---|---|---|
| Genetic Factors | - Family history of IgAN, - HLA gene polymorphisms, - Variants in genes regulating mucosal immunity and complement pathways | |

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| | | |
|---|---|---|
| Immunological Factors | - Increased production of aberrantly glycosylated IgA1, - Formation of IgA immune complexes, - Overactivation of complement system (especially C3, C4, C5a) | |
| Environmental Factors | - Infections (respiratory or gastrointestinal, e.g., streptococcal, viral),<br>- Seasonal variations (exacerbations during infections) | |
| Lifestyle/Dietary Factors | - High salt intake, - High protein diet, - Alcohol consumption – Smoking | |
| Clinical Factors | - Hypertension, - Proteinuria (severity correlates with progression),<br>-Reduced renal function (eGFR decline) | |
| Pathological Factors | - Mesangial proliferation – Glomerulosclerosis, - Tubulointerstitial Fibrosis | |
| Demographic Factors | - Male predominance, - Age (common in 2nd–3rd decade of life),<br>-Ethnicity (higher in Asians and Caucasians compared to Africans) | |

| **Disease** | **Role of PD-1/PD-L1 Pathway** | |
|---|---|---|
| **Systemic Lupus Erythematosus [SLE]** | ↓ PD-1/PD-L1 signaling → Hyperactive T and B cells → Autoantibody production [anti-dsDNA, ANA] → Tissue inflammation. | **[49,50]** |
| **Rheumatoid Arthritis [RA]** | Defective PD-1 signaling in synovial T cells → Uncontrolled inflammation and joint destruction | |
| **Multiple Sclerosis [MS]** | Reduced PD-1/PD-L1 interaction → Enhanced autoreactive T-cell activity against myelin → Demyelination. | |
| **Type 1 Diabetes Mellitus [T1DM]** | Impaired PD-1/PD-L1 pathway → Autoreactive T cells attack pancreatic β-cells → Insulin deficiency [49]. | |

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| | | |
|---|---|---|
| **Inflammatory Bowel Disease [IBD – Crohn's & UC]** | Altered PD-1/PD-L1 expression in gut mucosa → Dysregulated T-cell response to intestinal flora → Chronic intestinal inflammation. | |
| **Psoriasis** | Decreased PD-1 expression → Increased effector T-cell activation and cytokine release [IL-17, TNF-α]. | |
| **Asthma** | Overexpression of PD-L1 on airway epithelial cells → Suppresses Tregs but enhances Th2/Th17 responses → Chronic airway inflammation. | |
| **IgA Nephropathy [IgAN]** | Reduced PD-1/PD-L1 signaling → Hyperactivation of T and B cells → Excessive production of aberrant IgA1 → Immune complex deposition in kidney. | |
| **Diabetic Nephropathy [DN]** | Dysregulation of PD-1/PD-L1 in renal cells and immune cells→Promotes chronicrenal inflammation and fibrosis. | |

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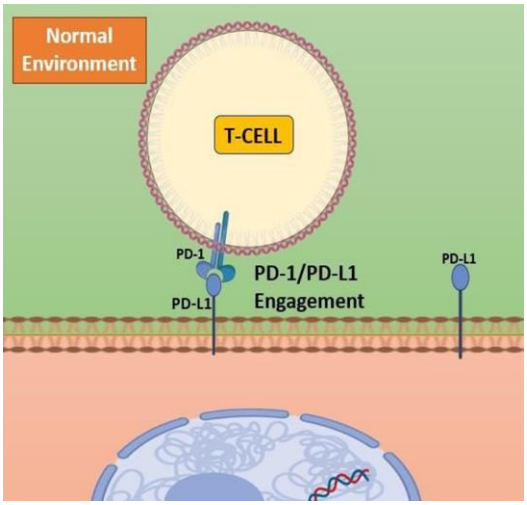


**Figure 1.** Interaction of PD1 and PDL1 in IgA nephropathy

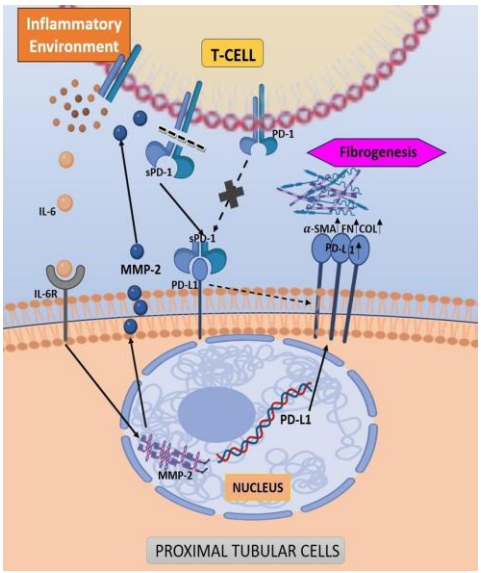


**Figure 2.** Impact of PD1 and PDL1 in inflammation and fibrosis