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Interferon-Stimulated Genes: Novel Targets in Renal Pathogenesis

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Abstract
Background: Kidney diseases are a prevalent global health concern, and despite ongoing research, there remains a lack of fully effective clinical treatments to prevent or halt their progression. Consequently, it is encouraged to identify novel biomarkers, establish early diagnostic methods, pinpoint key molecular pathways, and develop innovative therapeutic targets for more effective management of renal disorders. ***Summary:*** Interferons (IFNs), a group of cytokines, play pivotal roles in immune responses, particularly in antiviral and antiproliferative activities. IFNs trigger a cascade of signaling events that lead to the induction of interferon-stimulated genes (ISGs), which are essential for controlling viral infections and regulating immune responses. This review explores the impact of interferon-related genes on renal disorders, focusing on the mechanisms, therapeutic approaches, and consequences of enhanced interferon signaling in the kidney. ***Key Messages:*** Most diagnostic and therapeutic strategies targeting ISGs are still far from clinical implementation. The better understanding of ISG-regulated pathophysiology and the progress of new intervention approaches are expected to facilitate the clinical translation of ISGs-based diagnosis and therapy of kidney diseases.

Introduction

Kidney diseases, including acute kidney injury (AKI) and chronic kidney disease (CKD), are a major global health concern, affecting millions of people worldwide [1]. Despite significant advances in understanding the pathophysiology of kidney diseases, many patients remain unresponsive to current preventive and therapeutic approaches. Consequently, it is imperative to identify novel biomarkers, establish early diagnostic methods, pinpoint key molecular pathways, and develop innovative therapeutic targets for more effective management of renal disorders [2, 3].

Interferons (IFNs) are crucial cytokines involved in immune modulation, especially in antiviral and antiproliferative activities. Among the three primary IFN families, type I (IFN-α/β) and type III (IFN-λ) are predominantly linked to antiviral responses, while type II (IFN-γ) also exhibits significant antiviral effects [4–6]. IFN activation is triggered by pathogen-associated

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molecular patterns recognized by pattern recognition receptors, initiating a signaling cascade that leads to the transcription of interferon-stimulated genes (ISGs). These genes are essential for antiviral defense, antimicrobial immunity, and anti-neoplastic functions [7]. In the kidneys, tubular epithelial cells, podocytes, mesangial cells (MCs), and endothelial cells produce type I IFNs. Among these cell types, the most pronounced effects of IFN-I are observed in glomerular epithelial cells, particularly podocytes and parietal epithelial cells. These cells are crucial in the pathogenesis of podocytopathies and the progression of CKD [8, 9]. IFN-I signaling in podocytes and pattern recognition receptors induces the expression of numerous ISGs, which are central to the development and progression of kidney diseases. This increased ISG expression highlights the importance of the IFN-I pathway in renal pathology.

The type I interferon (IFN-I) signaling pathway is a cornerstone of innate immunity, exerting profound influence on various biological processes through the induction of ISGs [10, 11]. This pathway has been extensively studied due to its critical role in host defense and its involvement in numerous pathological conditions. Dysregulated IFN-I signaling and aberrant ISG expression have been implicated in a spectrum of diseases, ranging from viral infections to autoimmune disorders like systemic lupus erythematosus (SLE) [12]. Of particular interest are the type I interferonopathies, a group of rare monogenic disorders characterized by persistent activation of the IFN-I pathway and chronic upregulation of ISGs [13]. These conditions result in sustained inflammation and progressive tissue damage, highlighting the deleterious effects of uncontrolled IFN-I signaling. Intriguingly, despite the heterogeneity of underlying causes, IFN-I-related renal disorders often share common pathogenic mechanisms and histopathological features. These similarities can be attributed to the convergence of different disease processes on the IFN-I pathway and the subsequent activation of a common set of ISGs. This shared pathophysiology underscores the central role of IFN-I signaling and ISG expression in the development and progression of renal damage across various conditions.

Recent research has emphasized the role of ISGs in kidney disease, where they contribute to both protective and pathogenic processes. As a vital organ for maintaining homeostasis, the kidney is particularly vulnerable to damage from persistent or dysregulated IFN signaling. In the context of kidney disease, ISGs may drive immune responses that worsen inflammation and fibrosis, ultimately leading to progressive renal impairment. One the other hand, ISGs can enhance the immune response by promoting the activation and recruitment of immune cells to the kidney (Fig. 1). This can be beneficial in fighting infections. Thus, understanding the specific roles and mechanisms of ISGs in kidney disease is essential for developing targeted therapies.

What Is the ISG

The simplest definition of an ISG is any gene that is induced during an IFN response. This encompasses all types of IFNs, including type I (IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, and others), type II (IFN-γ), and type III (IFN-λ1, IFN-λ2, IFN-λ3, IFN-λ4). Type I and III IFNs are recognized as the classical antiviral IFNs [14, 15]. All three types of IFNs activate signaling through the JAK/STAT pathway. Type I and III IFNs stimulate the formation of the ISGF3 complex, which comprises phosphorylated STAT1, STAT2, and IRF9. Variations in this pathway also occur, such as unphosphorylated STAT molecules and IRF9-STAT2 homodimers. In contrast, type II IFN leads to the formation of phosphorylated STAT1 homodimers, known as the IFNγ-activated factor [16, 17]. While ISGs are typically induced by IFN signaling, they can also be directly activated by other factors like IRF1, IRF3, IRF7, NFκB, or IL-1 signaling [18], even in the absence of IFN signaling. Furthermore, several of these factors are themselves inducible by IFNs, leading to multiple pathways for the induction of a single ISG. Some ISGs are expressed at baseline levels and are further upregulated during an IFN response, while others are expressed exclusively in response to IFNs.

The current classification of ISGs is complicated by these diverse induction mechanisms and expression patterns. Additionally, IFNs can induce noncoding RNAs, such as long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), and repress certain genes during IFN stimulation. The terms "interferon-repressed genes" (IRGs or IRepGs) have been used inconsistently, sometimes referring specifically to genes downregulated by IFNs and other times to all IFN-regulated genes [10, 19, 20].

The Role of ISG in Kidney Disease

ISG15

ISG15, a 15 kDa ubiquitin-like protein, plays a crucial role in kidney diseases and immune responses. Induced by IFN-α through the activation of interferon regulatory

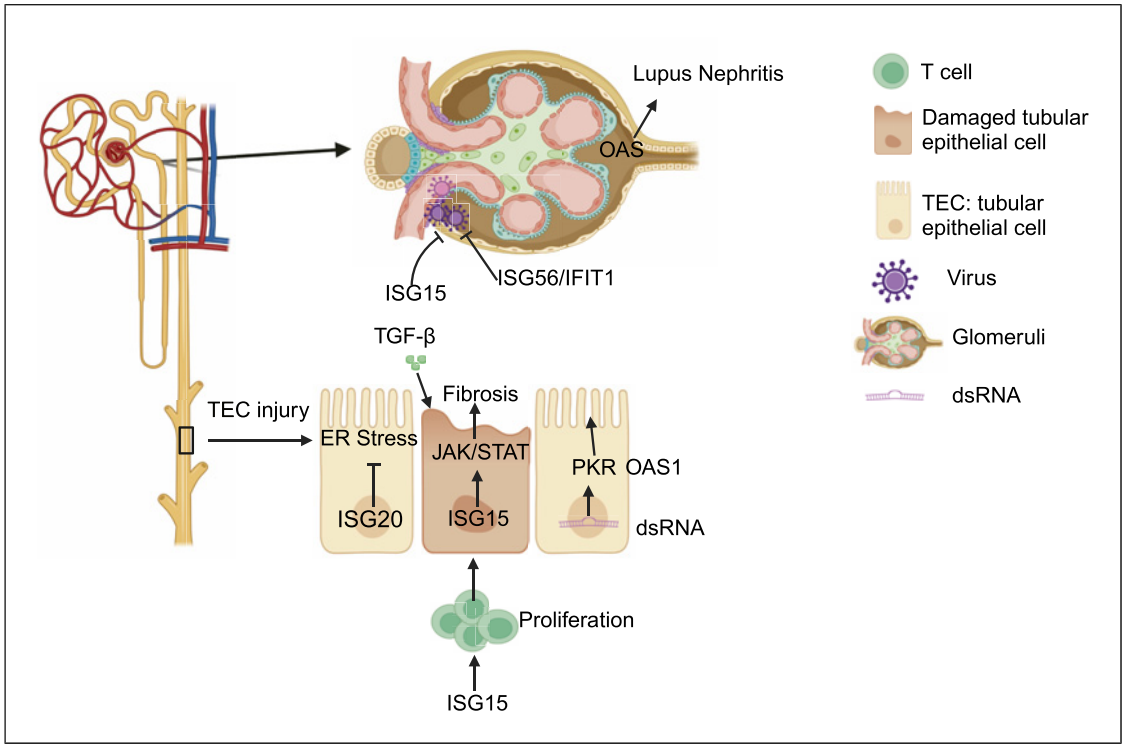

Fig. 1. Simplified overview of ISGs and their actions in kidney diseases. ISGs play a crucial role in kidney diseases. dsRNA, a common viral signature, triggers the activation of ISGs through pathways such as JAK/STAT and PKR. This activation cascade leads to a series of pathological events in the kidney, including tubular injury, fibrosis, and ER stress. Among the ISGs, ISG15 stands out for its significant contribution to fibrosis promotion and cellular proliferation. Additionally, ISG56 and OAS1 have been implicated in glomerular damage. The intricate interplay between these ISGs and their downstream effects underscores the complex nature of kidney pathology, suggesting that ISGs may serve as novel therapeutic targets in the treatment of kidney injury.

factors (IRFs) and interferon-stimulated response elements [21], ISG15 was initially discovered in IFN-treated Ehrlich ascites tumor cells [22]. Under normal physiological conditions, ISG15 expression is low, but it becomes significantly upregulated in various kidney injury models, including ischemia-reperfusion injury, cisplatin-induced nephrotoxicity, and unilateral ureteral obstruction [23]. ISG15 plays an important role in the intervention of hederagenin in CKD. Subsequently, some researchers found that knockdown of ISG15 in TCMK1 cells significantly inhibited TGF-β-induced fibrotic protein expression and JAK/STAT activation, suggesting it as a potential target for CKD treatment [24].

Recent studies have elucidated ISG15's significant impact on AKI and the AKI-to-CKD transition [23]. ISG15 knockout mice exhibit reduced renal injury and fibrosis in multiple AKI models, suggesting a protective effect of ISG15 deficiency [23]. The mechanism involves ISG15's promotion of TGFβR1 ISGylation, a post-translational modification that alters the stability, localization, and function of target proteins. This process plays a crucial role in the development of AKI and subsequent AKI-to-CKD transition. Furthermore, ISG15 modulates the JAK/STAT pathway, which is vital for the kidney's response to injury. Activation of STAT3, in particular, mediates renal fibrosis in the UUO model [24].

In addition to its role in kidney injury, ISG15 has been implicated in immune responses and transplant rejection. It exhibits high expression in various immune cells, including neutrophils, monocytes, lymphocytes, and dendritic cells, suggesting a significant role in modulating immune responses within the kidney [25]. Recent research has identified ISG15 as a promising marker for detecting rejection in kidney transplantation through integrated analysis of cell-specific gene expression in peripheral blood [26]. ISG15 also showed a critical role in promoting the proliferation of T cells. T cell is a major component of the adaptive immune system and is increasingly recognized for their involvement in various kidney pathologies, including AKI [27, 28], CKD [29],

and autoimmune kidney disorders like lupus nephritis (LN) [30] and IgA nephropathy [31]. ISG15 plays a critical role in modulating cytokine signaling pathways, which are essential for T-cell differentiation and function [32]. ISG15 also plays a critical role in T-cell proliferation and differentiation, influencing the balance between pro-inflammatory and regulatory T cells in renal diseases.

These findings highlight ISG15 as a potential therapeutic target in kidney diseases. Recent research has demonstrated that inhibition of ISG15 can significantly reduce TGF-β-induced fibrotic protein expression and JAK/STAT activation 3. Moreover, a novel DRD4-ISG15-NOX4 axis has been identified in the progression of AKI, where DRD4 activation suppresses the ISG15/NOX4 pathway, alleviating oxidative stress and preserving mitochondrial function 8. While these discoveries offer promising avenues for treatment, further research is essential to unravel the complex signaling pathways and identify specific therapeutic targets within the ISG15 cascade, ultimately translating these insights into clinical applications for patients with kidney diseases.

ISG20

ISG20 is a 3′-5′ exoribonuclease that primarily degrades single-stranded RNA and plays a crucial role in infectious diseases [33]. ISG20 serves as a crucial effector molecule in the innate immune response, demonstrating broad-spectrum activity against various pathogens, including viruses, bacteria, and parasites. Its antiviral prowess is most directly evidenced by its capacity to substantially reduce intracellular viral RNA levels. Moreover, ISG20 exhibits remarkable efficiency in degrading synthetic viral RNA analogs, further underscoring its potent antiviral properties [34].

While many studies have explored ISG20's role in antiviral defense and other physiological and pathological processes, highlighting its potential as a biomarker, drug target, or immunotherapy candidate, its precise biological activity and mechanisms in disease contexts remain largely unclear. Recent research has shifted attention to the involvement of lncRNAs and proteins like ISG20 in kidney pathology, further expanding our understanding of its function.

ISG20 is predominantly localized in the nucleolus and Cajal bodies, suggesting its involvement in the biogenesis and maturation of ribosomal RNA and small nuclear RNA. This subcellular distribution underscores ISG20's potential role in critical RNA processing pathways [35]. Recent studies have shown that ISG20 expression is upregulated in the kidneys following ischemia-reperfusion injury, likely as a protective response to RNA oxidation. Enhancing ISG20 activity could represent a novel therapeutic strategy for AKI. By degrading oxidized RNA, ISG20 reduces cellular stress and helps prevent further damage to renal cells [36]. The Exo II motif of ISG20 mediates its enzymatic activity, which can be completely abolished by replacing aspartic acid 94 (D94) in the Exo II motif with glycine (D94G) [33]. ISG20 relies on its 3′-5′ exoribonuclease activity to mitigate endoplasmic reticulum stress/unfolded protein response pathway activation, thereby improving kidney injury. This study is the first to identify ISG20 as a key regulator of RNA oxidative damage in AKI kidneys, confirming its important role in AKI and expanding its biological functions. As a 3′-5′ exoribonuclease, intervening with ISG20 activators to modulate its enzymatic activity is the most ideal therapeutic approach for diseases like AKI, which have a rapid onset and a short therapeutic window. The study utilized AAV-mISG20 injections into mice before AKI onset, and 30 days later, an ischemia/reperfusion-induced AKI model was constructed. While this method has limitations, it is the first attempt to target ISG20-mediated degradation of oxidized RNA as a therapeutic strategy for AKI. It provides an experimental data foundation for the effectiveness of this strategy. The feasibility of this approach depends on the further development of ISG20 activators, kidney-targeted delivery techniques, and efficient expression systems in the future.

LncRNAs are a class of RNAs longer than 200 nucleotides in length and have limited or no protein-coding potential [37]. Increasing evidence has demonstrated that lncRNAs play vital roles in kidney diseases, including diabetic kidney disease (DKD). Lnc-ISG20, a newly identified lncRNA, has gained attention for its regulatory functions in various physiological and pathological processes [38]. In CKD, lnc-ISG20 has been found aberrantly upregulated in the glomerular in the patients with diabetic nephropathy [39]. Recent studies have highlighted the involvement of lncRNAs and microRNAs in regulating gene expression during fibrosis. Among these, the lnc-ISG20/miR-486-5p/NFAT5 axis has emerged as a significant pathway influencing kidney fibrosis. The lnc-ISG20 has been identified as a critical regulator in various physiological and pathological processes, including kidney fibrosis. Mechanistic studies have demonstrated that miR-486-5p is a downstream miRNA of lnc-ISG20 [40]. This interaction plays a pivotal role in modulating the expression of NFAT5, a transcription factor known to be involved in cellular responses to hypertonic stress. Both long noncoding ISG20 and protein ISG20 play significant roles in kidney disease, particularly in the context of fibrosis and acute injury.

Lnc-ISG20 modulates fibrotic signaling pathways, while ISG20 protects against oxidative RNA damage. Understanding the distinct and overlapping functions of these molecules provides valuable insights into kidney disease mechanisms and offers potential therapeutic avenues for treating AKI and CKD.

Preclinical studies have identified ISG20 as a potential mediator of CX3CL1 production in glomerular endothelial cells, particularly in LN [41]. Inhibition of ISG20 could potentially reduce glomerular inflammation in LN patients. For the mechanism, ISG20 is involved in regulating CX3CL1 production, which contributes to glomerular inflammation. It is crucial to note that these therapeutic approaches are still in the preclinical stage and require further research. The efficacy and safety of these approaches need to be rigorously tested in human clinical trials before any therapeutic applications can be considered.

ISG56/IFIT1

IFN-stimulated gene 56 (ISG56) is one of the first identified proteins induced by viruses and type I IFNs. The ISG56/IFIT1 family of genes, clustered on human chromosome 10, includes four members: ISG56/IFIT1, ISG54/IFIT2, ISG60/IFIT3, and ISG58/IFIT5, with homologs conserved across mammals to amphibians [42]. ISG56 is produced by various renal cells and may function together in physiological and pathological antiviral innate immunity. ISG56 was expressed by poly IC treatment, and IFN-beta-mediated CXCL10 expression is positively regulated by ISG56 in cultured human renal proximal tubular epithelial cells [43]. This finding suggests that ISG56 may play a critical role in the positive regulation of antiviral immune and inflammatory responses in renal proximal tubular epithelial cells. TLR3 recognizes double-stranded RNA (dsRNA) of viral origin as exemplified by polyriboinosinic:polyribocytidylic acid [poly(I:C)] RNA, a synthetic analog of viral dsRNA. In adult healthy kidneys, TLR3 can also be found on MCs, vascular smooth muscle cells and collecting duct epithelium. Therefore, TLR3-ISG56 signaling may be important for the clearance of any viral RNA reaching the glomerular mesangium [44].

Interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) is one of the interferon-inducible genes, typically showing extremely low mRNA levels under normal conditions. However, its mRNA levels can be significantly induced by interferon and viral infections. Elevated expression of IFIT1 has been observed in peripheral blood samples from patients with SLE, and similar increases have been noted in the renal tissue of patients with LN [45]. A study further corroborated this finding, showing a correlation between increased IFIT1 expression, significant podocyte loss, and compromised renal function in the renal tissue of MRL/lpr mice [46]. IFIT1 is recognized as an important gene with antiviral properties and immune regulatory functions. Further research, including cell transfection and transcriptome analysis, is needed to elucidate the signaling pathways involved in the renal pathological changes caused by IFIT1 expression and to provide evidence for the development of novel therapeutic strategies targeting SLE.

Protein Kinase R

Double-stranded RNA activated protein kinase R (PKR) is a recognized inducer of inflammation, oxidative stress, and apoptosis. PKR activates inflammatory signaling cascade through activation of NF-κB and JNK causing fibrosis and cellular apoptosis [47, 48]. Some studies showed PKR regulates the metabolism especially promotes obesity and insulin resistance in diabetic mice [49], which indicated PKR might involve in DN. One recent study found the expression of PKR and its downstream genes are decreased in L-NAME-induced kidney injury. Imoxin, also known as C16 or 2-aminopurine, is a small molecule inhibitor specifically targeting PKR. The imoxin treatment attenuated L-NAME-induced kidney injury. PKR is a core contributor in the pathogenesis of L-NAME-induced renal damage and tubular apoptosis. Therapeutically targeting of PKR could be an attractive approach to treat the renal complications associated with hypertension [50].

PKR is a serine/threonine protein kinase that is activated by IFNs, dsRNAs. Upon binding to dsRNA, PKR undergoes autophosphorylation, forming a dimer and activating its kinase activity. This activation leads to the phosphorylation of various substrates, including eIF2α, protein phosphatase 2A (PP2A), and inhibitor of nuclear factor kappa-B (IκB) kinase (IKK). The PKR inhibitor C16 can also alleviate LPS-induced AKI through inhibiting NF-kB and NLRP3 pyroptosis signal pathways [51]. PKR inhibits translation and promotes apoptosis through the substrates and downstream effectors [52]. Phosphorylated eIF2α blocks translation initiation but activates some selected proteins critical to cell survival, including transcription factor 4 (ATF4), growth arrest, and DNA damage gene (GADD34) and C/EBP-homologous protein (CHOP). Autosomal dominant polycystic kidney disease is one of the most common inherited renal diseases and characterized by the development of fluid-filled cysts. One study found knockdown of PKR abolishes PC1-inhibited proliferation and translation.

Inhibition of cell proliferation and protein synthesis by PC1 is mediated by the total expression of PKR, rather than its kinase activity [53].

Transposable elements (TEs), often called "jumping genes," are DNA sequences capable of changing their position within a genome. Discovered by Barbara McClintock in the 1940s, TEs' ability to move within the genome has become a key factor in shaping genomic architecture and evolution. TEs can be classified into two main categories: retrotransposons and DNA transposons [54]. Endogenous retroviruses (ERVs) are a specific class of TEs that originate from ancient viral infections. ERVs are remnants of retroviruses that integrated into the germline cells of an ancestor, enabling them to be inherited by subsequent generations as part of the host genome. Over time, these viral sequences have become fixed in the genome, passed down through generations. Evolutionarily inherited ERVs have the potential to trigger an immune reaction [55] and comprehensive RNA-sequencing of control and diseased kidneys from human and mouse disease models indicated higher expression of TEs and ERVs in diseased kidneys. One recent study observed a positive correlation with cytosolic nucleotide sensors and TE/ERV expression in human CKD samples, which was particularly strong between PKR, and TE expression [56]. Thus, PKR may be a novel target for the treatment of kidney diseases [57].

2′-5′-Oligoadenylate Synthetase 1

2′-5′-oligoadenylate synthetase 1 (OAS1) is a crucial enzyme in the innate immune response [58], particularly in antiviral defense. It belongs to the OAS family, which is activated by the presence of dsRNA, a molecular pattern associated with viral infections [59]. Upon activation, OAS1 catalyzes the synthesis of 2′-5′-linked oligoadenylates (2-5A) from ATP [60]. OAS1 is encoded by the *OAS1* gene, which is stimulated by IFNs, particularly type I IFNs (IFN-α and IFN-β) [61]. This gene is one of the many ISGs that form a rapid and robust antiviral response during infections. OAS1 was identified as a protein associated with the risk of COVID-19, The measured mRNA levels of OAS1 were associated with reduced numbers of susceptibility, hospitalization, ventilation, and death [62, 63]. DKD has irreversible damage, and its risk factor increases with SARS-CoV-2 infection. By interactome analysis and Hub genes identification, one study found the highly expression of OAS1 in DKD groups [64]. OAS1 module participates in muscle cell proliferation and positive regulation of transcription [65]. In addition, another bioinformatic study reveals that the OAS family is also highly expressed in LN [66]. The OAS family genes were revealed to be closely associated with LN progression. Therefore, OAS1 might play a critical role in regulating the development of CKD and it is the key biomarker for the early diagnosis of DKD.

RSAD2/Viperin

RSAD2, commonly known as viperin (virus inhibitory protein, endoplasmic reticulum-associated, interferon-inducible), is a multifaceted protein that plays a significant role in the innate immune response against viral infections [67]. Encoded by the RSAD2 gene, viperin is well-known for its ability to inhibit a broad spectrum of viruses by disrupting various stages of the viral life cycle. While its antiviral functions have been extensively studied, recent research has started to explore its involvement in other physiological and pathological processes, including its potential role in kidney disease.

The kidney is highly susceptible to immune-mediated injury due to its exposure to circulating immune cells and inflammatory mediators. Inflammatory cytokines and IFNs play crucial roles in the pathogenesis of both AKI and CKD. Given that viperin is highly inducible by IFNs, its expression is often elevated in response to inflammation [68]. Studies have shown that viperin can modulate the production of pro-inflammatory cytokines, potentially influencing the inflammatory milieu in the kidney. Viperin's interaction with the Toll-like receptor (TLR) signaling pathway could contribute to the amplification of the inflammatory response in renal tissues [69].

Apoptosis and fibrosis are key pathological features of kidney disease. Viperin has been implicated in the regulation of cell death pathways, including apoptosis, which is a critical process in the progression of kidney injury [70]. Viperin can induce apoptosis in infected or damaged cells, a mechanism that might help limit tissue damage during acute injury but could contribute to fibrosis and CKD if dysregulated. Additionally, viperin's involvement in the regulation of cellular metabolism and its impact on mitochondrial function could influence the development of renal fibrosis, a hallmark of CKD.

Viperin has been identified as a key player in the innate immune response against Zika virus (ZIKV). A recent study demonstrated that endogenous viperin is overexpressed in HK-2 cells cultured under high glucose conditions, which is linked to the inhibition of ZIKV growth. This finding provides new insights into the mechanism by which high glucose environments contribute to ZIKV growth suppression in HK-2 cells [71].

In summary, these six ISGs – ISG15, ISG56/IFIT1, ISG20, OAS1, PKR, and RSAD2/viperin – form a complex network of antiviral defense mechanisms that are rapidly

Table 1. The role of major ISG in kidney disease

ISG	Kidney condition	Function
ISG20	AKI	Degraded oxidized RNA, reduced ER stress, decreased cell damage [36]
ISG15	CKD, AKI	Involved in renal fibrosis. ISG15 knockout mice show reduced kidney injury and fibrosis [23, 72]
	Kidney transplantation	Regulated T-cell proliferation [26]
ISG56/IFIT1	LN	Antiviral immune and inflammatory responses [43] Associated with podocyte loss and impaired renal function in LN [46]
PKR	L-NAME-induced hypertensive nephropathy	PKR is activated by interferons, dsRNA and contributes to L-NAME-induced kidney injury [50]
	Autosomal dominant polycystic kidney disease	PKR, as a regulator of cell fate, inhibits translation and promotes apoptosis [52]
	Virus-associated kidney injury	PKR may involve in virus-induced renal inflammation [57]
	Sepsis-induced AKI	PKR promotes LPS-induced renal inflammation and injury [51]
OAS1	DKD	Highly expression of OAS1 in DKD groups, in LN [66]
	LN	Regulating the development of CKD [64]
RSAD2/ viperin	Renal fibrosis, CKD	Induces apoptosis, regulates cell metabolism, affects mitochondrial function, potentially influences renal fibrosis [70, 71]

induced by type I IFNs (Table 1). They work in concert to inhibit viral replication through diverse mechanisms, including protein modification, RNA degradation, translation inhibition, and disruption of viral assembly. These ISGs also interact with key signaling pathways involved in kidney disease, such as NF-κB, JAK-STAT, and RIG-I/MDA5, creating a positive feedback loop that amplifies antiviral responses. Their functions extend beyond direct antiviral activity, as they can modulate cellular processes like inflammation and ER stress, which are relevant to various kidney pathologies. For instance, ISG15 and ISG56 have been linked to LN progression, while PKR activation has been implicated in diabetic nephropathy. Additionally, genetic variations in these ISGs, such as OAS1 polymorphisms, may influence susceptibility to certain kidney diseases, highlighting their potential as therapeutic targets or biomarkers in nephrology.

Treatment Approaches Targeting the ISGs

The involvement of ISGs in kidney diseases presents potential therapeutic opportunities. Targeting the IFN signaling pathway and specific ISGs may provide novel treatment strategies for both AKI and CKD. Given the diverse roles of ISGs in kidney disease, therapeutic strategies can be broadly categorized into those aiming to inhibit or enhance ISG activity, depending on the desired outcome (Fig. 2).

Inhibition of Pathogenic ISG Activity

Targeting ISG15: ISG15 has been identified as a pro-inflammatory molecule in various kidney disease models. Therapeutic approaches that inhibit ISG15 expression or function could potentially reduce inflammation and fibrosis, slowing the progression of CKD. Small molecules or monoclonal antibodies designed to target ISG15 could be developed as novel anti-fibrotic therapies. With advancements in gene editing technologies like CRISPR-Cas9, more precise and effective ISG15-targeted drugs are expected to be developed in the future, offering new therapeutic options for a range of kidney diseases.

JAK-STAT Pathway Inhibitors

Since the JAK-STAT pathway is essential for ISG induction, inhibitors of this pathway have the potential to reduce the expression of pathogenic ISGs. These inhibitors, already being explored in other inflammatory and autoimmune diseases, could be repurposed for kidney disease treatment. Originally developed as oral, target-specific DMARDs for immune-mediated arthritis, JAK inhibitors (like ruxolitinib and baricitinib) are also used to treat skin and blood disorders such as atopic dermatitis, polycythemia vera, and graft-versus-host disease. A trial with baricitinib in patients with SAVI, CANDLE, and other type I interferonopathies showed promising results. Case reports and studies have also supported its effectiveness in treating AGS-related neurological symptoms. However, there is limited information on the efficacy of JAK inhibitors for kidney issues in T1Is. In a phase

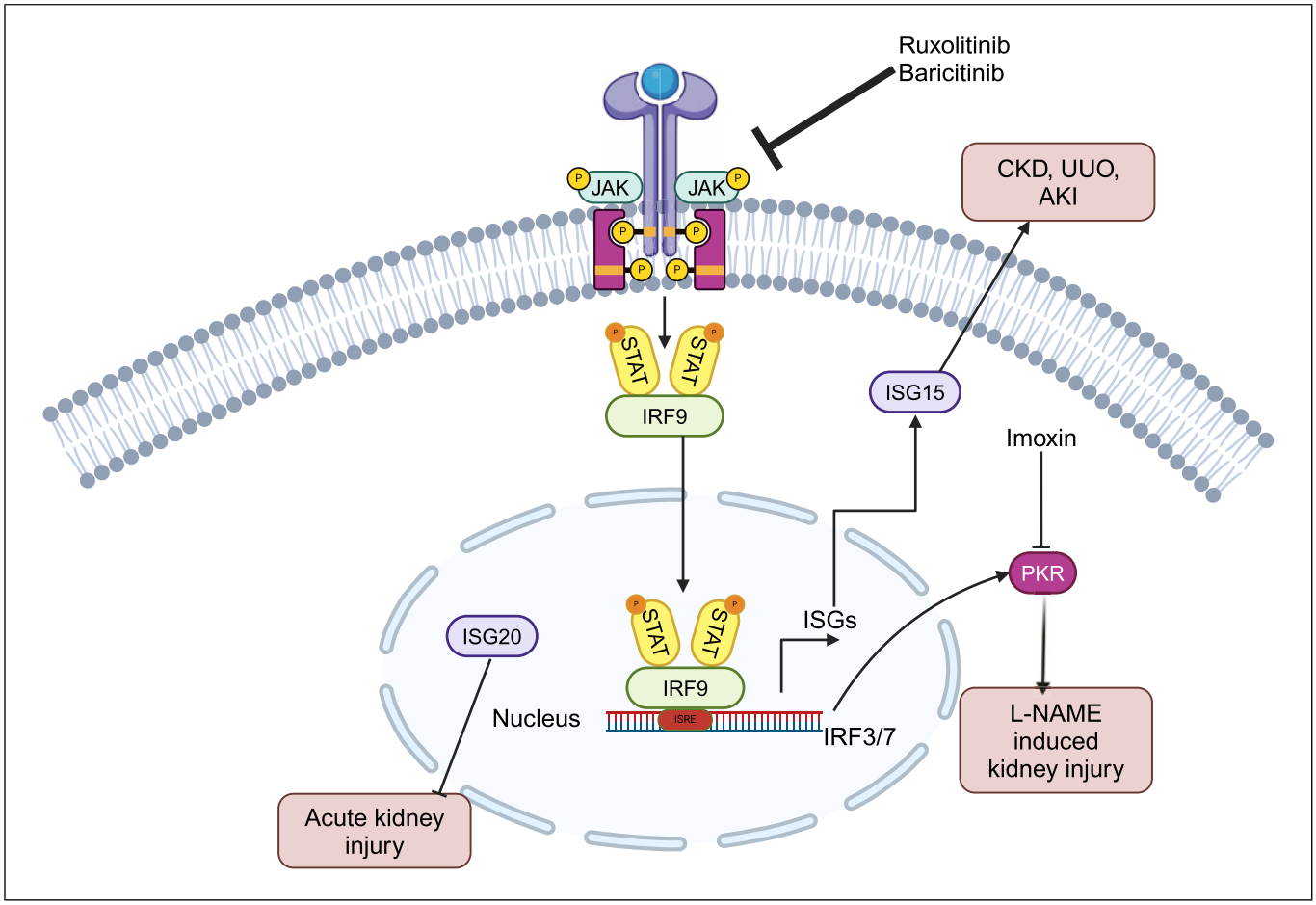

Fig. 2. Therapeutic agents targeting ISGs. The JAK/STAT signaling pathway, activated by various stimuli, leads to the expression of ISGs such as ISG15, ISG20, and PKR, which have been implicated in various forms of kidney injury. ISG15 is associated with CKD, UUO, and AKI, while ISG20 plays a role specifically in AKI. PKR, which can be inhibited by imoxin, contributes to kidney injury in L-NAME-induced models. Targeting this pathway with JAK inhibitors like ruxolitinib and baricitinib offers promising therapeutic potential by disrupting the cascade that leads to ISG expression and subsequent renal damage. These findings highlight the importance of ISGs as therapeutic targets and underscore the potential of pathway-specific inhibitors in mitigating kidney injury and fibrosis.

2 trial of SLE patients with low-to-moderate disease activity, baricitinib was superior to placebo in achieving the primary endpoint of resolving arthritis or rash. Since the trial participants had a low frequency of kidney involvement, no conclusions about kidney response can be drawn [73].

Enhancement of Protective ISG Activity

Boosting antiviral ISG responses: in cases where viral infections contribute to kidney injury, enhancing the expression of antiviral ISGs could provide therapeutic benefits. For example, viral infections are important causative agents in renal disease and are responsible for significant morbidity and mortality. Epstein-Barr virus, cytomegalovirus, adenovirus, and polyomavirus (type BK) are prominent members of this group causing specific diseases. Kidney diseases can be exacerbated by viral infections, where ISGs play a critical role in defense. Elevated IFN signaling is associated with kidney diseases including COVID-19, HIV, and apolipoprotein-L1 nephropathy [74]. Therefore, boosting ISG expression in the kidney could enhance the clearance of viral pathogens and reduce associated kidney damage.

Modulation of Immune Regulatory ISGs

Some ISGs have immunomodulatory functions that could be harnessed to protect against kidney injury. For instance, certain ISGs may help modulate the immune response to prevent excessive inflammation and autoimmunity, which are implicated in conditions like LN. In

patients with SLE, monocytes, B cells, dendritic cells, and granulocytes were significantly increased, while T-cell subsets were decreased. Neutrophils and low-density granulocytes showed the highest ISG activity [75].

Future Perspectives

The role of ISGs in kidney disease is an emerging field of research with the potential to significantly advance both our understanding and treatment of these conditions. Future studies are likely to focus on several key areas, each contributing to a comprehensive approach in addressing ISG-related kidney diseases.

Identifying Cellular Sources of IFN-I Is Crucial for Understanding Their Role in Various Kidney Diseases

This involves pinpointing the primary sources of IFN-I production in renal tissue for LN, investigating the role of resident kidney cells in IFN-I production for DN, and examining the contribution of MCs to IFN-I signaling in IgA nephropathy. These insights will provide a foundation for targeted interventions and more precise disease management strategies.

Characterizing ISG Involvement in Disease Pathogenesis Is Another Critical Area of Focus

This includes elucidating the pathways through which ISGs mediate glomerular inflammation and injury in glomerulonephritis, investigating their role in tubular cell damage and repair mechanisms in AKI, and studying the impact of sustained ISG activation on progressive renal fibrosis in CKD. A deeper understanding of these processes will help in developing more effective therapeutic approaches.

Clinical identification and diagnosis of ISG involvement are essential for improved patient care. This involves developing and standardizing biomarkers for early detection and monitoring of disease activity in LN, creating diagnostic tools to differentiate ISG activation due to viral infections versus autoimmune processes in viral-associated nephropathies, and exploring ISG signatures as potential markers for early detection of allograft rejection in transplant cases. These advancements will enable more accurate diagnosis and timely interventions.

Exploring therapeutic implications of ISG modulation opens new avenues for treating CKDs. This includes developing drugs that selectively inhibit pathogenic ISGs while preserving protective immune responses in LN, investigating ISG-targeted therapies to mitigate inflammation and fibrosis in DN, and exploring the potential of ISG modulation in reducing renal damage in ANCA-associated vasculitis. These targeted approaches promise more effective and potentially less toxic treatment options.

Integrating These Findings with Personalized Medicine Approaches Will Revolutionize Kidney Disease Management

This involves tailoring treatments based on individual ISG expression profiles in LN, developing personalized therapies targeting specific ISG pathways involved in disease progression for IgA nephropathy, and exploring genetic factors influencing ISG responses to guide treatment strategies in focal segmental glomerulosclerosis. This personalized approach will enable more precise and effective treatments, potentially improving outcomes for patients with various kidney diseases.

The Promise and Challenges of ISG-Targeting Therapies in Kidney Diseases

ISG-targeting therapies have the potential to complement existing treatments for various kidney diseases: In LN, where interferon signaling plays a crucial role, anti-IFN therapies could be used alongside standard immunosuppressive regimens to enhance efficacy [76]. For IgA nephropathy, where complement activation is important, ISG-targeting therapies could be combined with complement inhibitors to address multiple pathways of kidney injury [77]. In DKD, where inflammation contributes to progression, ISG-targeting therapies might be used in conjunction with SGLT2 inhibitors or GLP-1 receptor agonists to provide additional renoprotection [78].

In some cases, ISG-targeting therapies might replace current treatments: for patients with interferon-related nephropathies who are intolerant to or have failed conventional therapies, ISG-targeting drugs could serve as an alternative first-line treatment [79]. In C3 glomerulopathy, where current treatments are often ineffective, ISG-targeting therapies might become a primary treatment option if shown to be more effective in clinical trials [80].

Recent clinical trials have shown promising outcomes for ISG-targeting therapies: In LN, anifrolumab (an anti-type I interferon receptor antibody) has demonstrated improved renal responses compared to standard therapy [76]. For IgA nephropathy, iptacopan (a factor B

inhibitor) has shown sustained reductions in proteinuria and preservation of eGFR in long-term studies.

While ISG-targeting therapies show promise, potential side effects and risks must be considered. Inhibiting interferon signaling may compromise the body's ability to fight viral infections [79], increasing susceptibility to infections. Paradoxically, interferon inhibition might lead to the development of other autoimmune conditions in some patients [76]. Some ISG-targeting therapies might have direct nephrotoxic effects, necessitating careful monitoring of kidney function [36]. Altering interferon signaling could potentially impact cardiovascular health, requiring long-term safety studies. Given the role of IFNs in tumor surveillance, there is a theoretical risk of increased malignancy with long-term ISG inhibition [76]. These potential risks underscore the need for careful patient selection, monitoring, and long-term follow-up studies to ensure the safety and efficacy of ISG-targeting therapies in LN treatment.

Conclusion

ISGs play a pivotal role in the pathogenesis of various kidney diseases, including AKI, CKD, and autoimmune nephropathies. The complex interplay between IFN-I signaling and ISGs expression contributes to both protective and pathogenic processes within the kidney. The identification of common ISGs expressed in both peripheral blood and kidneys of patients with LN offers promising biomarkers for disease activity and progression. Future research should focus on understanding the specific roles of individual ISGs in different kidney diseases, developing refined classification systems, and exploring cell-specific modulation of ISG expression as therapeutic strategies. Additionally, investigating ISG expression profiles as biomarkers and evaluating the long-term efficacy of IFN-targeted therapies will be crucial. As our understanding deepens, it will pave the way for personalized and effective treatments, potentially revolutionizing the management of kidney disorders.

Conflict of Interest Statement

The authors declare no competing interests.

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Author Contributions

Meng Jia and Shuangxu Han wrote the manuscript; Liang Li and Yi Fu prepared the figures and tables; and Di Zhou decided on the topics and wrote the manuscript.

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