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INSIGHTS

Friend or foe? IFNλ drives fibrosis

Ivan Zanoni[1]

Type III IFNs, or IFNλ, are pleiotropic immune mediators that mostly work at mucosal surfaces by signaling in epithelial cells and selected immune cells. Zhou, Zhang, and colleagues (https://doi.org/10.1084/jem.20251858) demonstrate that IFNλ also signals in kidney fibroblasts sustaining renal fibrosis.

Zhou, Zhang, and colleagues describe for the first time the capacity of a group of IFNs, known as type III IFNs or IFNλ, to signal in renal fibroblasts (Zhou, 2026), supporting renal fibrosis and the development of chronic kidney disease, a devastating pathology affecting almost 1/10 of the world population and often causing dependency on dialysis and/or kidney transplantation.

IFNs belong to three families—type I, type II, and type III IFNs—and are master regulators of antibacterial and antiviral responses but have also been involved in playing protective or detrimental roles during infectious and noninfectious diseases, including inflammatory diseases, autoimmunity, and cancer (Boehmer and Zanoni, 2025). Type III IFNs, or IFNλ, are the latest addition to the IFN families. There are four type III IFNs in humans (IFNλ1–4) and only two in mice (IFNλ2 and IFNλ3), and they signal via the IFNλ receptor (IFNLR) which is composed by IFNLR1 and IL-10 receptor β (Boehmer et al., 2026). For a long period of time, type III IFNs were believed to only play redundant roles compared with type I IFNs, especially regarding their capacity to induce antiviral IFN-stimulated genes (ISGs). Nevertheless, in contrast to the almost ubiquitous signaling capacity of type I IFNs across tissues and cells, type III IFNs have a much-restricted group of target cells. Indeed, it was initially thought that the IFNLR was only expressed by epithelial cells and hepatocytes, until three independent groups showed responses also in neutrophils (Blazek et al., 2015; Galani et al., 2017; Broggi et al., 2017). Since then, the capacity of type III IFNs to signal in epithelial cells or in restricted groups of immune cells has been appreciated both in the context of antiviral and antimicrobial responses or during nonmicrobial diseases, particularly at mucosal surfaces (Boehmer et al., 2026). So far, it remained unknown whether type III IFNs had also the capacity to signal in stromal cells.

In their work, Zhou, Zhang, and colleagues (Zhou, 2026) report the capacity of type III IFNs to activate an immune response in kidney fibroblasts in the context of chronic kidney disease. To study this disease in mice, the authors set up the unilateral ureteral obstruction (UUO) model and initially tested type III IFN accumulation over time in fibrotic kidneys, revealing a marked time-dependent increase at the mRNA and protein levels of IFNλ2/3, which positively correlated with fibrotic markers such as α-SMA and fibronectin. Remarkably, the analysis of publicly available RNA-sequencing dataset revealed upregulation of the transcripts of IFNλ2 and IFNλ3 in the kidney of patients with chronic kidney disease compared with controls. These observations were confirmed in newly collected kidney samples from chronic kidney disease patients that showed upregulation at the protein and mRNA levels of IFNλ2/3 in fibrotic areas.

Next, to prove causality of type III IFN signaling in inducing kidney fibrosis, the authors utilized the UUO model in WT mice or in mice lacking the IFNLR and found that WT mice presented significantly increased renal fibrosis and fibrotic markers compared with mice lacking type III IFN signaling.

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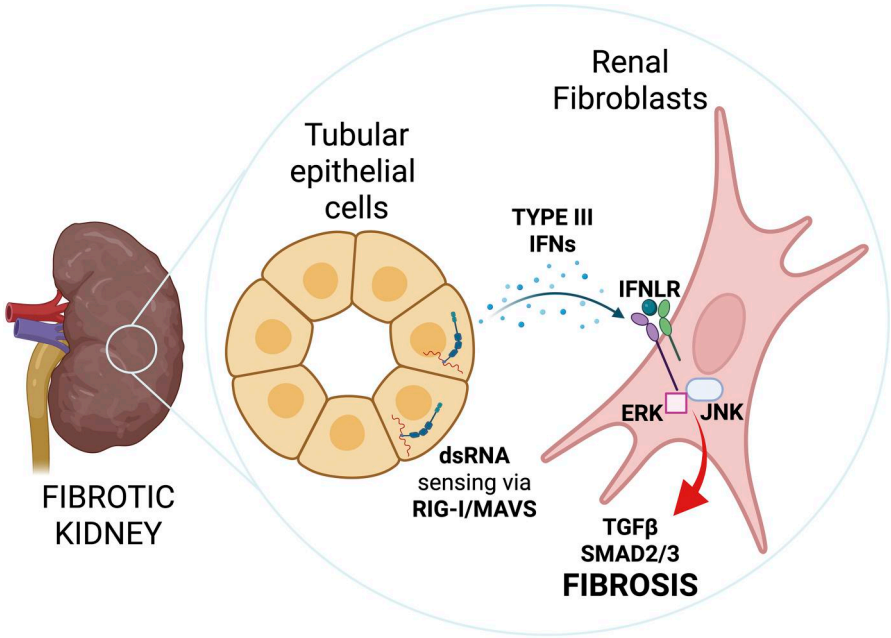
Furthermore, they demonstrated that exogenous administration of recombinant (r)IFNλ2 accelerated renal fibrosis.

To identify the cells that responded to type III IFNs increasing fibrosis of the kidney, bone marrow chimera experiments were performed, demonstrating that type III IFN signaling in nonimmune cells was necessary to favor fibrosis. Interrogation of publicly available single-cell RNA-sequencing datasets of patients with chronic kidney disease demonstrated that the IFNLR was primarily expressed by fibroblasts or fibrosis-associated myofibroblasts. Since fibroblasts were previously reported to express no IFNLR, the authors isolated these cells from different tissues and compared them with mouse embryo fibroblasts (MEFs), which are often used as a reference to study fibroblasts. Surprisingly, only skin and kidney fibroblasts, but not MEFs or peritoneal fibroblasts, responded to

[1]Harvard Medical School, Boston Children's Hospital, Boston, MA, USA.

Correspondence to Ivan Zanoni: ivan.zanoni@childrens.harvard.edu.



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During kidney fibrosis, dsRNA is sensed via RIG-I/MAVS by tubular epithelial cells, which produce type III IFNs. Type III IFNs are sensed by renal fibroblasts via the IFNLR that activates ERK/JNK inducing the production of TGFβ, which in turn activates SMAD2/3, fostering renal fibrosis.

rIFNλ2, upregulating ISGs and, more importantly, pro-fibrotic factors.

Based on these data, the authors generated a new conditional knock out mouse model in which type III IFN signaling was solely deleted in fibroblasts, making the extraordinary finding that, in response to UUO, these mice were protected against fibrotic lesions of the kidney.

But how do type III IFNs drive fibrosis by directly acting on fibroblasts? Since TGFβ is a major driver of fibrosis, Zhou, Zhang, and colleagues speculated type III IFNs affect its production and indeed found upregulation of TGFβ at the gene and protein levels in renal fibroblasts treated with rIFNλ2, as well as WT mice, treated or not with rIFNλ2, compared with mice lacking type III IFN signaling in the UOO model (Zhou, 2026). Mechanistically, type III IFNs led to TGFβ production via ERK and JNK, but not p38 MAPK or PI3K-mTOR, inducing TGFβ-dependent SMAD2/3 signaling in renal fibroblasts, also increasing their migratory capacity and upregulating fibrotic markers. Blocking TGFβ with an antibody protected mice against renal fibrosis, leading the authors to conclude that type III IFN signaling in fibroblasts brings to increased TGFβ, supporting fibrosis.

The authors also identified activation of the RIG-I–MAVS pathway in tubular epithelial cells of the kidney as the major driver of type III IFNs in their UUO model and proved in vitro that double stranded RNA (dsRNA) can activate RIG-I/MAVS to induce type III IFNs.

This work is innovative in multiple ways. This is the first report of type III IFNs signaling in stromal cells. Also, it links type III IFNs to renal fibrosis and chronic kidney disease, expanding detrimental activities of this group of IFNs beyond the ones previously described for acute respiratory distress syndrome (ARDS) or inflammatory bowel diseases (IBD) (Boehmer et al., 2026; Major et al., 2020; Jena et al., 2024; Sposito et al., 2021; Broggi et al., 2020). This is particularly relevant in light of the possibility to develop new therapies aimed at targeting type III IFNs in pathological contexts. The authors gave particular attention to this aspect and described four different therapeutic strategies. Initially, they used small molecules to block either JNK or ERK, showing, both in vitro and in vivo, reduced TGFβ production/signaling and amelioration of UUO. Next, they used a RIG-I inhibitor to prevent type III IFN production, obtaining similar results. As an additional therapeutic intervention, type III IFNs were silenced during UUO by using an adenovirus expressing short harpin RNA (shRNA) directed against IFNλ2/3, which led to significant reduction in fibrotic areas of the kidney and TGFβ signaling. Finally, direct blockade of type III IFN signaling using an anti-IFNλ2/3 antibody also protected mice against renal fibrosis.

The findings described by Zhou, Zhang, and colleagues also raise new important questions.

The authors found that patients with chronic kidney disease upregulate in their kidneys only IFNλ2 and IFNλ3, but not IFNλ1 or IFNλ4. This is particularly intriguing since in the context of ARDS and IBD in human patients a similar trend was also previously described (Jena et al., 2024; Sposito et al., 2021). This leaves open a major question that is how distinct members of the type III IFN family are regulated and whether they differentially signal via their common IFNLR, allowing protective antimicrobial or detrimental inflammatory/fibrotic responses.

Another intriguing observation is the distinct capacity of fibroblasts derived from different tissues to respond, or not, to type III IFNs. These findings suggest that tissue-specific factors play fundamental roles in shaping the responses of cells to type III IFNs. On top of tissue-specific responses, the inflammatory status should also be taken into consideration when assessing the capacity of cells to respond to type III IFNs, as previously shown in the context of TNF stimulation for mouse and human neutrophils that increases their responsiveness to type III IFNs (Broggi et al., 2017). Overall, this mandates to more comprehensively assess responses to type III IFNs across tissues and inflammatory conditions.

The unique capacity of type III IFNs to upregulate TGFβ via ERK/JNK compared with type I or II IFNs, while all IFNs induce ISGs in fibroblasts and/or in vivo, is also an interesting observation. Signaling downstream of type I and III IFN receptors is very similar, although some differences have been described (Boehmer and Zanoni, 2025; Odendall et al., 2014; Broggi et al., 2017; Schnepf et al., 2021). Of note, type III IFNs also modulate non-transcriptional and non-translational programs (Lazear et al., 2015; Broggi et al., 2017; Sebina et al., 2022), which may contribute to the unique responses elicited by type III IFNs compared with other IFNs.

Always related to differences across IFN families, how lacking responses to type I IFNs also ameliorates UOO, while lacking responses to type II IFN worsens this pathology, and the cross talk between the IFN families to overall control renal fibrosis will need to be more carefully investigated in the future.

Another important question is what is the source of agonists activating pattern recognition receptors (PRRs) (Brubaker et al., 2015) that drive pathology in vivo in the models of UUO and in human patients with chronic kidney disease. The authors proved that, in vitro, dsRNA induces type III IFNs in tubular epithelial cells via RIG-I/MAVS. In vivo, dsRNA was also detected, but its source in the absence of a viral infection remains unknown. Also, why in the UUO model only RIG-I, but not other PRRs tested such as TLR3, drives type III IFNs will need to be elucidated.

In all, this study sheds new light on an important and unknown funciton of type III IFNs, while future studies will be needed to better understand protective and detrimental roles played by type III IFNs in different inflammatory contexts and the physiological functions of type III IFNs that supported their positive selection during evolution, which remain largely unknown in humans (Zhang et al., 2024).

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