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Original article

Interferon-λ3 rs12979860 can regulate inflammatory cytokines production in pulmonary fibrosis

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ABSTRACT

Pulmonary fibrosis (PF) is the last phase of interstitial lung diseases (ILDs), which are a collection of pulmonary illnesses marked by parenchymal remodeling and scarring. Treatment can only halt the functional decline of the lung, raising the necessity of identifying the basic processes implicated in lung fibrogenesis. The Interferon lambda-3 (*IFNL3*) gene variant, rs12979860, was determined to be related to an elevated risk of fibrosis in different organs, but the mechanism through which it mediates fibrogenesis is not clear. In the current research, we aim to figure out some of the mechanistic pathways by which IFN-λ3 mediates ILDs. 100 healthy controls and 74 ILD patients were genotyped for *IFNL3* rs12979860. Then the mRNA expression of IFNL3 and some other proinflammatory mediators was examined according to genotype in the peripheral blood mononuclear cells (PBMCs) of ILDs patients. The *IFNL3* rs12979860 genotype distribution of healthy individuals and ILDs patients was shown to be in Hardy-Weinberg equilibrium (HWE) with a minor allele frequency (MAF) of 0.293 and 0.326, respectively. Furthermore, the CC genotype was demonstrated to be linked to enhanced IFNL3 expression. Also, the CC genotype was linked to an increase in the mRNA expression of TLR4 ($P = 0.03$) and the inflammatory cytokines IL-1β and TNF-α ($P = 0.01$ and 0.04, respectively) and had no effect on the NF-kB level ($P = 0.3$). From these results, we can deduce that IFN-λ3 may mediate tissue fibrosis via increasing the expression of IFN-λ3 itself and other proinflammatory mediators. This stimulates a self-sustaining loop mechanism which includes a reciprocal production of IFN-λ3, TLR4, IL-1β, and TNF-α leading to persistent inflammation and fibrosis.

1. Introduction

PF is the final consequence of several ILDs, which are also called diffused parenchymal diseases (Wuyts et al., 2013). ILDs are a wide collection of chronic pulmonary illnesses marked by lung parenchymal tissue restructuring and/or fibrotic change. ILD patients have a loss in lung function, worsening symptoms, a poor response to therapy, a diminished quality of life, and a high rate of death. ILDs can be idiopathic or linked with systemic or connective tissue diseases (CTDs) such as rheumatoid arthritis (RA), scleroderma, and systemic lupus erythematosus (SLE). Idiopathic pulmonary fibrosis (IPF) is the predominant ILDs type (Ozaki and Glasgow 2022). IPF is a chronic, fatal condition marked by permanent pulmonary fibrosis and decreased lung function. It is most likely caused by numerous loops of epithelial cell damage and unregulated healing (Raghu et al., 2011). Up to 30% of newly diagnosed ILD cases have CTDs in which all lung areas (bronchioles,

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alveoli, and parenchyma) are affected (Kalchiem-Dekel et al., 2018, Mira-Avendano et al., 2019).

Numerous ILDs have an immunopathogenesis that is still poorly understood and may be caused by one or more than one of several factors, e.g., immunological dysregulation, inappropriate regeneration, prolonged inflammation, and frequently in the context of genetic predisposition (Sweis et al., 2023).

ILDs have diverse prognoses in general, although some exhibit fibrosis and are distinguished by disease progression. IPF is the prototype of them, but other ILDs, including autoimmune-related ILDs, may also exhibit a progressive fibrotic pattern (Case 2022). In this study, we will focus on ILDs related to the phenotype of progressive pulmonary fibrosis, especially IPF, rheumatoid arthritis-related ILDs (RA-ILDs), and systemic lupus erythematous-related ILDs (SLE-ILDs).

Fibrogenic mechanisms are still elusive and unsatisfactory, so a limited number of drugs target fibrosis specifically (Bellan et al., 2019). Up until now, only a couple of antifibrotic medicines, nintedanib and pirfenidone, were licensed for the management of progressive fibrosing ILDs (Wilfong and Aggarwal 2021). Unfortunately, these medications are not able to give a full cure and are linked to concerns about tolerability. They have the potential to reduce the pace of functional deterioration in the lungs, but they can't stop the scar tissue from accumulating (Spagnolo et al., 2020). So, there is a great necessity for identifying the possible biological systems involved in fibrogenesis to cover the unmet need for innovative medicines to treat ILDs.

Interferon lambda-3 (IFN-λ3) is an interferon lambda family member; it is a protein encoded by the interferon lambda-3 (*IFNL3*) gene and has varied expression caused by single nucleotide polymorphisms (SNPs) (Honda et al., 2010). rs12979860 is a variant in the *IFNL3* gene that was recently found to be related to sever hepatic inflammation and fibrosis in different disease etiologies (Noureddin et al., 2013, Eslam et al., 2015). It was additionally observed that *IFNL3* rs12979860 correlates with the onset of fibrosis across different epithelial tissues. In the lung, it has been related to an elevated hazard of PF caused by systemic sclerosis (Metwally et al., 2019). Regardless of the tissue involved, the pathophysiology of fibrotic diseases is largely the same (Razzaque and Taguchi 2003). As a result, we anticipate that *IFNL3* rs12979860 may also contribute to the pathophysiology of PF in fibrotic ILDs.

Inflammatory cytokines constitute essential elements in the pathological process of PF. They are capable of influencing many biological processes in lung fibrosis (Fathimath Muneesa et al., 2021). It was proved that Inflammatory mediators, e.g., interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) cause epithelial-mesenchymal transition (EMT) in fibrotic foci (Rieder et al., 2011). NF-kB has been linked to the synthesis of proinflammatory cytokines and chemokines, in addition to immune cell attraction (Simmonds and Foxwell 2008). TLR4 is a pattern-recognition receptor (PRR) that induces the release of a variety of proinflammatory cytokines in macrophages and fibroblasts upon activation, resulting in the activation of more fibroblasts and macrophages (Bolourani and Brenner 2021).

In this research, we tried to identify the role of the *IFNL3* rs12979860 genotype in the PF pathogenesis within ILDs patients and tried to identify some of its mechanistic pathways.

2. Materials and methods

2.1. Study population and study design

From November 2021 to January 2023, this study enrolled 174 participants, including 100 healthy controls (49 male and 51 female) have an average age of 35 years and 74 ILDs subjects (19 male and 55 female) have an average age of 51 years. The study included only patients suffering from fibrotic ILDs, according to a CT scan and before starting any antifibrotic drugs regimens. Our exclusion criteria were: 1) non-ILD chronic lung disease patients, e.g., chronic obstructive pulmonary disease (COPD) and chronic asthmatic patients, 2) cases with other organ fibrosis such as kidney or liver fibrosis, and 3) patients with non-fibrotic ILDs. All patients were from Middle and Upper Egypt. The Ethics of Scientific Research committee, Faculty of Pharmacy, Minia University, approved all experiments.

2.2. Sample collection

10 mL of peripheral blood was collected at day time, usually from 10 to 11 a.m., and transferred under cooled conditions and stringent aseptic conditions using EDTA as an anticoagulant and divided into two parts: 2 mL were stored at −20 °C for DNA extraction, followed by a TaqMan® SNP genotyping allelic discrimination assay, and 8 mL of fresh blood for PBMCs separation, then the extracted RNA was kept at −80 °C till the RT-qPCR step.

2.3. Genotyping

Firstly, we extracted the DNA by column extraction with the GeneJET DNA extraction, 50 preparation kit (Cat. No. K0781, ThermoFisher, USA) as the producer's instructions. Secondly, rs12979860 was genotyped by the TaqMan® SNP assay (Cat. No.: 4351379, Assay ID: C-7820464–10, ThermoFiher, USA) following company guidelines using the StepOnePlus™ RT-PCR equipment (Applied Biosystems, USA).

2.4. Quantification of the mRNA expression of the examined genes

Firstly, density gradient centrifugation was used for PBMCs separation on Ficoll® Paque Plus (Cat. No. GE17-1440–03, Sigma-Aldrich, Germany) as producer's instructions. Secondly, we extracted total RNA following the company's protocol by using the RNeasy Kit (Cat. No. 74104, Qiagen, Germany). Thirdly, cDNA was synthesized using the RevertAid First Strand cDNA Kit (Cat. No. K1622, ThermoFisher, USA) in accordance with the company's protocol. After that, SYBR® green qPCR master mix (Cat. No. SQ103-0100, GeneDireX, USA) was used for qPCR in the StepOnePlus™ RT-PCR apparatus (Applied Biosystems, USA). GAPDH was used as a housekeeping gene to normalize the CT values from qPCR. Then gene expression of IFNL3, IL-1β, TLR4, TNF-α, and NF-kB was measured by ΔCT = CT (GAPDH) - CT (target), finally represented as 2 ΔCT. Table 1 lists the utilized experiment's primers.

Table 1
List of primers sequences used for RT-PCR.

No.	Gene	Sequence
1	*GAPDH*	Fw; 5′-GACTAACCCTGCGCTCCTG-3′ Rev; 5′-GCCCAATACGACCAAATCAG-3′
2	*IFNL3*	Fw; 5′-TGCCTGTCGTGTACTGAACCA-3′ Rev; 5′-GAGCGCGGAGTGCAATTC-3′
3	*TLR4*	Fw; 5′-CCCTTCTCAACCAAGAACCT-3′ Rev; 5′-GCCCTCTAGAGCAGATTTGT-3′
4	*NF-kBp65*	Fw; 5′-TCATGAAGAAGAGTCCTTTCAGC-3′ Rev; 5′-GGATGACGTAAAGGGATAGGG-3′
5	*IL-1β*	Fw; 5′-ACAGATGAAGTGCTCCTTCCA-3′ Rev; 5′-GTCGGAGATTCGTAGCTGGAT-3′
6	*TNF-α*	Fw; 5′-CAGGGACCTCTCTCTAATCA-3′ Rev; 5′- GTAATAAAGGGATTGGGGCA-3′

2.5. Statistical analysis of the study findings

To determine the suitable sample size for this study, the two-sample *t*-test formula was employed. This formula considers a significant level (alpha) of 0.05, a standard deviation (σ) of 1.32, and the desired power of 0.90. For descriptive statistics, the median ± interquartile range (twenty-fifth to seventy-fifth percentile) was used to represent continuous variables. The Mann-Whitney *U* test was used to assess the difference in median values. The dominant model (CC versus CT/TT) was used for the explanation of the functional role of the *IFNL3* rs12979860 genotype on ILDs, as previously reported (Eslam et al., 2015, Metwally et al., 2019). All statistical analysis was carried out using GraphPad Prism version 9 (GraphPad Software, USA). Statistical significance was considered when a *P*-value was less than 0.05.

3. Results

3.1. Patient characteristics

The study enrolled 174 participants, including 100 healthy controls and 74 ILD patients. Genotyping was successful for all samples except one healthy control sample. The *IFNL3* rs12979860 genotype distribution of both healthy control and ILD patients was found to be in HWE with a MAF of 0.293 for healthy control and 0.326 for ILD patients. These findings agreed with those of the 1000 genome project's healthy population (https://browser.1000genomes.org) and show no deviation from HWE ($P = 0.7$).

In terms of rs12979860 genotypes, Table 2 indicates *IFNL3* rs12979860 genotype distribution in both healthy controls and patients.

ILD patients and healthy controls have *P*-values of 0.6 and 0.8, respectively. The chi-square test was employed to determine *P*-values; $P > 0.05$ signifies no divergence from HWE.

3.2. IFNL3 rs12979860 genotype association with the IFNL3 mRNA expression of ILD patients

To investigate the functional effects of *IFNL3* rs12979860 in ILDs, the dominant model of inheritance was used as previously reported, and the rs12979860 variant was classified as CC versus CT/TT (Eslam et al., 2015, Metwally et al., 2019).

Our findings revealed a substantial elevation in IFNL3 mRNA expression in the [CC] genotype over the [CT/TT] genotypes ($P = 0.03$), as shown in Fig. 1.

3.3. Association of IFNL3 rs12979860 genotype with pro-inflammatory mediators' mRNA expression in ILD patients

Based on rs12979860 genotype, we examined the expression of TLR4 and some inflammatory mediators, including NF-kB, IL-1β, and TNF-α in ILD patients' PBMCs to comprehend the potential functional impact of IFN-λ3 in ILDs.

Under the dominant model, the [CC] genotype was found to be linked with a significant increase in the amount of IL-1β mRNA in comparison to the CT/TT genotypes in ILD patients' PBMCs (Fig. 2a; $P = 0.01$). In addition, the [CC] genotype was shown to be related to a substantial elevation of TLR4 mRNA in comparison to the CT/TT genotypes in ILD patients' PBMCs (Fig. 2b; $P = 0.03$). Moreover, the [CC] genotype was linked to a considerable rise in TNF-α mRNA expression over the CT/TT genotypes in ILD patients' PBMCs (Fig. 2c; $P = 0.04$). However, NF-kB mRNA level was not significantly affected by *IFNL3* genotypes in ILD patients' PBMCs (Fig. 2d; $P = 0.3$). Table 3 shows all these data.

Median and interquartile range (twenty-fifth to seventy-fifth percentiles) were used for statistical representation of our data. The two-tailed Mann-Whitney *U* test was used to figure out the difference in median values. Statistical significance was defined as *P*-values less than 0.05.

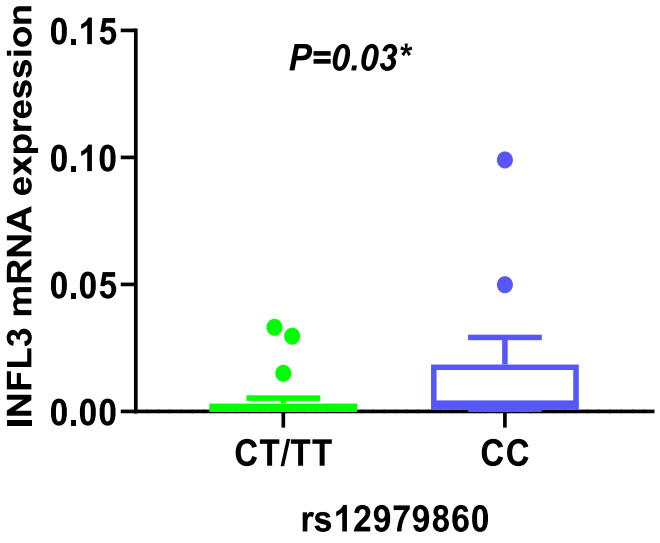

Fig. 1. *IFNL3* rs12979860 genotype association with IFNL3 mRNA expression in ILD patients' PBMCs. The IFNL3 mRNA expression was relative to GAPDH by RT-qPCR. The two-tailed Mann-Whitney test was utilized for calculating the result, which was visualized using GraphPad Prism 8 software. *P* value less than 0.05 was chosen as the measure of significance. (*) denotes a *P*-value less than 0.05.

Table 2
IFNL3 rs12979860 genotype distribution in healthy controls and ILD patients.

IFNL3 rs12979860	ILD (n = 74)	Healthy control (n = 99)
CC	34 (46%)	49 (49.5%)
CT	31 (42%)	42 (42.4%)
TT	9 (12%)	8 (8.1%)
[C]	67.4 %	70.7 %
[T]	32.6 %	29.3 %

4. Discussion

The mechanistic pathway of IFNL3 in mediating fibrosis in general and lung fibrosis due to ILDs in particular has not been obvious until now and needs further investigation. In this study, initially, we elucidated the genotype distribution of *IFNL3* rs12979860. Genotype distribution was found in HWE. Our results showed that there was a non-significant difference in the MAF of ILD patients (MAF = 0.326) compared to healthy controls (MAF = 0.293). These results revealed no deviance from HWE and were consistent with those of the healthy population from the 1000 Genome Project (Auton et al., 2015).

PBMCs can reflect the response of the body to various diseases. So, it can be used for gene expression profiling as a source for biomarkers (Bolen et al., 2011, Mosallaei et al., 2020). Hence, we demonstrated that the *INFL3* rs12979860 genotype and INFL3 mRNA expression in PBMCs from ILDs individuals are related. We found the CC genotype enhances the expression of IFNL3 significantly more than the CT/TT genotypes. This result supports prior studies that indicated patients who have the *IFNL3* rs12979860 CC genotype secrete higher amount of INFL3 in their serum and livers than these ones with CT or TT genotypes (Langhans et al., 2011, Eslam et al., 2017, Metwally et al., 2019). Thus, the risk CC genotype has been found to enhance IFN-λ3 expression.

The lung has a completed set of toll-like receptors (TLRs) that can distinguish between self-danger-associated molecular patterns

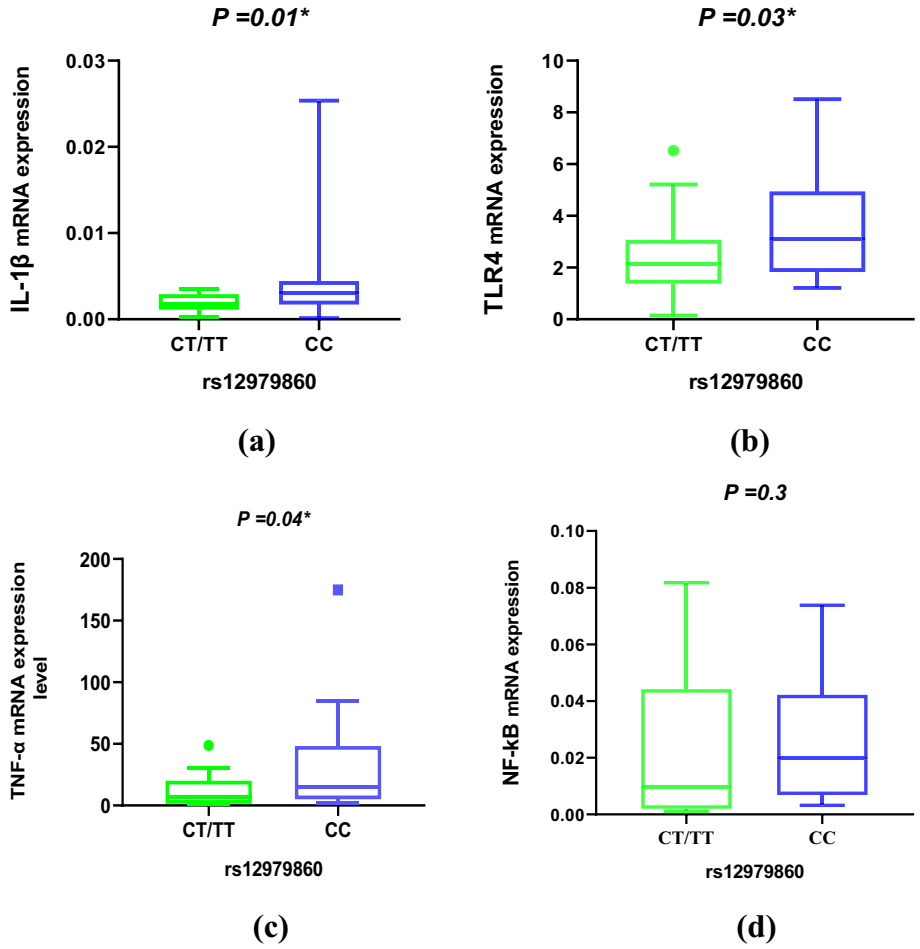

Fig. 2. Association of the *IFNL3* rs12979860 genotype with mRNA expression levels of proinflammatory cytokines in ILD patients' PBMCs: (a) IL-1β mRNA expression level according to rs12979860 genotype, (b) TLR4 mRNA expression level according to rs12979860 genotype, (c) TNF-α mRNA expression level according to rs12979860 genotype, and (d) NF-kB mRNA expression level according to rs12979860 genotype. The mRNA expression was normalized to GAPDH by RT-qPCR. The two-tailed Mann-Whitney test was utilized for calculating the result, which was visualized using GraphPad Prism 8 software. *P* less than 0.05 was chosen as the measure of significance. (*) denotes a *P*-value less than 0.05.

Table 3
Quantification of mRNA expression of IFNL3, IL-1β, TLR4, NF-kB, and TNF-α in PBMCs of ILD patients according to the rs12979860 genotype under the dominant model.

Genotype	*IFNL3*	IL-1β	TLR4	NF-kB	TNF-α
CC	0.0033 ± (0.0008–0.0185)	0.0031 ± (0.0017–0.0044)	3.109 ± (1.831–4.943)	0.0199 ± (0.0068–0.0422)	14.94 ± (5.144–48.33)
CT/TT	0.0006 ± (0.0002–0.0032)	0.0081 ± (0.0011–0.0029)	2.145 ± (1.380–3.069)	0.0097 ± (0.0020–0.0442)	7.154 ± (1.471–20.15)
P-value	0.03	0.01	0.03	0.3	0.04

(DAMPs) and exogenous pathogen-associated molecular patterns (PAMPs) because it is continually exposed to a variety of host-derived risk stimulator and foreign bodies. Furthermore, TLRs are involved in the pathogenesis of non-infectious lung illnesses like ILDs (Kovach and Standiford 2011). TLR4, one of the most researched TLRs in lung fibrosis, has been demonstrated to have a pro-fibrotic effect whenever triggered by DAMPs and PAMPs (Lu et al., 2008, He et al., 2009). LPS stimulation of TLR4 in monocyte-derived dendritic cells (MDDC) has been shown to increase the synthesis of IFN-λ3 (Coccia et al., 2004). Accordingly, we expect TLR4 to be one of the mechanistic pathways through which IFN-λ3 mediates lung fibrosis. In concordance with this, we observed a substantial elevation in TLR4 mRNA expression in the rs12979860 CC genotype over the CT/TT genotypes. In line with our findings, earlier *in vitro* research deduced that IFN-λ3 induces a pro-inflammatory phenotype in macrophages, resulting in overexpression of TLR4, TNF-α, and IL-1β (Read et al., 2019). In addition, IFN-λ3 enhanced interferon-stimulated genes' (ISGs) expression and the response to bacterial, fungal, and viral PAMPs, according to *in vitro* findings. This could be done via synergistic activation of inflammasome pathways (Caspase 1 activity and IL-1β cleavage) (Read et al., 2021). This data, together with our findings, show that IFN-λ3 has a crucial role to maintain the inflammatory responses.

IFN-λ3 is mostly produced by immune cells (Yoshio et al., 2013). Also, the *IFNL3* CC, or risk variant, has been found to increase the involvement of immune cells at the inflammation site, which in turn results in more IFN-λ3 synthesis by these cells and explains its role in mediating inflammation and fibrosis progression (Eslam et al., 2017). It has been clearly suggested, based on the evidence gathered from numerous human studies and animal models, that immune cells can regulate the inflammatory and fibrotic responses already present in ILDs via inflammatory cytokines generated by

these cells (Bagnato and Harari 2015, Desai et al., 2018). Thus, to figure out the potential importance of the *IFNL3* rs12979860 variant in ILD pathogenesis, we investigated the expression levels of some inflammatory mediators, e.g., TNF-α, NF-kB, and IL-1β in PBMCs from ILD patients based on the rs12979860 genotype. From our results section, we observed that the *IFNL3* CC genotype considerably boosts IL-1β and TNF-α mRNA expression in the PBMCs of ILD patients when compared to the CT/TT genotypes. However, while the NF-kB mRNA level was found to be higher in the CC genotype, the difference was not statistically significant when compared to the CT/TT genotypes.

Based on these findings, we may conclude that the risk genotype has been related to greater levels of pro-inflammatory mediators' expression that aid in the occurrence and progression of PF. Further, the rs12979860 CC genotype appears to perform its profibrotic role through its impact on TLR4, IL-1β, and TNF-α. In agreement with our results, an *in vitro* study found that after being treated with IFN-λ3, plasmacytoid dendritic cells survive longer and release CXCL10, IFN-α, and moderate amounts of TNF-α (Finotti et al., 2016). Furthermore, In bleomycin-induced PF mice model, we reported in previous research that IFNL3 mRNA was remarkably increased in this model and positively linked to the expression of TGF-β, IL-1β, and TNF-α (Hamdi et al., 2022).

Our study has limitations, particularly the absence of lung biopsies from ILD patients, as currently the diagnosis of ILDs is done using non-invasive techniques like lung CT scan.

From our current study findings, we can deduce that IFNL3 has a vital contribution to the fibrotic and inflammatory pathways of ILDs because of its effect on immune cells. It transforms the lung's homeostatic milieu into a self-sustaining loop of IFN-λ3 secretion followed by TLR4, TNF-α, and IL-1β upregulation. Moreover, the rs12979860 CC genotype was linked to increased expression of IFN-λ3 itself and other inflammatory markers connected to the onset and progression of PF.

5. Conclusion

The *IFNL3* rs12979860 CC, risk genotype, is shown to be related to enhanced expression of IFNL3, TLR4, IL-1β, and TNF-α. However, it has no significant impact on NF-kB mRNA levels in PBMCs from ILD patients. Furthermore, IFN-λ3 may be mediating tissue inflammation and fibrosis by maintaining a self-perpetuating loop of IFN-λ3 release and TLR4, IL-1β, and TNF-α upregulation. To sum up the main implications of our findings, our research highlighted IFN-λ3 blockade as a novel target for new drug development. These drugs targeting IFN-λ3 will have limited side effects as the expression pattern of IFNL receptors has been restricted to epithelial tissues, limiting the action of IFNLs to these tissues (Eslam and George 2015). Also, early screening of ILD patients for the rs12979860 CC genotype will be beneficial for identifying patients who are at higher risk for pulmonary inflammation and fibrosis, which will be a helpful advance in personalized therapy for these patients and enhance their lives.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Auton, A., Brooks, L.D., Durbin, R.M., et al., 2015. A global reference for human genetic variation. Nature 526, 68–74. https://doi.org/10.1038/nature15393.
Bagnato, G., Harari, S., 2015. Cellular interactions in the pathogenesis of interstitial lung diseases. European respiratory review : an official journal of the European Respiratory Society. 24, 102–114. https://doi.org/10.1183/09059180.00003214.
Bellan, M., M. G. Cittone, S. Tonello, et al., 2019. Gas6/TAM System: A Key Modulator of the Interplay between Inflammation and Fibrosis. 20, https://doi.org/10.3390/ijms20205070.
Bolen, C.R., Uduman, M., Kleinstein, S.H., 2011. Cell subset prediction for blood genomic studies. BMC Bioinf. 12, 258. https://doi.org/10.1186/1471-2105-12-258.
Bolourani, S. and Brenner, M. 2021. The interplay of DAMPs, TLR4, and proinflammatory cytokines in pulmonary fibrosis. 99, 1373-1384. https://doi.org/10.1007/s00109-021-02113-y.
Case, A.H., 2022. Clinical Overview of Progressive Fibrotic Interstitial Lung Disease. Front. Med. 9,. https://doi.org/10.3389/fmed.2022.858339 858339.
Coccia, E.M., Severa, M., Giacomini, E., et al., 2004. Viral infection and Toll-like receptor agonists induce a differential expression of type I and lambda interferons in human plasmacytoid and monocyte-derived dendritic cells. Eur. J. Immunol. 34, 796–805. https://doi.org/10.1002/eji.200324610.
Desai, O., Winkler, J., Minasyan, M., et al., 2018. The Role of Immune and Inflammatory Cells in Idiopathic Pulmonary Fibrosis. Front. Med. 5, 43. https://doi.org/10.3389/fmed.2018.00043.
Eslam, M., George, J., 2015. Genome-Wide Association Studies and Hepatitis C: Harvesting the Benefits of the Genomic Revolution. Semin. Liver Dis. 35, 402–420. https://doi.org/10.1055/s-0035-1567830.
Eslam, M., Hashem, A.M., Leung, R., et al., 2015. Interferon-λ rs12979860 genotype and liver fibrosis in viral and non-viral chronic liver disease. Nat. Commun. 6, 6422. https://doi.org/10.1038/ncomms7422.
Eslam, M., McLeod, D., Kelaeng, K.S., et al., 2017. IFN-λ3, not IFN-λ4, likely mediates IFNL3-IFNL4 haplotype-dependent hepatic inflammation and fibrosis. NatureCommunications. 49, 795–800. https://doi.org/10.1038/ncomms15245 10.1038/ng.3836.
Fathimath Muneesa, M., Shaikh, S.B., Jeena, T.M., et al., 2021. Inflammatory mediators in various molecular pathways involved in the development of pulmonary fibrosis. International Immunopharmacology 96,. https://doi.org/10.1016/j.intimp.2021.107608 107608.
Finotti, G., Tamassia, N., Calzetti, F., et al., 2016. Endogenously produced TNF-α contributes to the expression of CXCL10/IP-10 in IFN-λ3-activated plasmacytoid dendritic cells. J. Leukoc. Biol. 99, 107–119. https://doi.org/10.1189/jlb.3VMA0415-144R.
Hamdi, E., Abdelrehim, A.B., Higazi, A., et al., 2022. Interferon lambda-3 as a new candidate gene involved in the progression of idiopathic pulmonary fibrosis. Bulletin of Pharmaceutical Sciences. Assiut. 45, 1109–1119 https://doi.org/10.21608/bfsa.2022.271824.
He, Z., Zhu, Y., Jiang, H., 2009. Inhibiting toll-like receptor 4 signaling ameliorates pulmonary fibrosis during acute lung injury induced by lipopolysaccharide: an experimental study. Respir. Res. 10, 126. https://doi.org/10.1186/1465-9921-10-126.
Honda, M., Sakai, A., Yamashita, T., et al., 2010. Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. Gastroenterology 139, 499–509. https://doi.org/10.1053/j.gastro.2010.04.049.
Kalchiem-Dekel, O., Galvin, J.R., Burke, A.P., et al., 2018. Interstitial Lung Disease and Pulmonary Fibrosis: A Practical Approach for General Medicine Physicians with Focus on the Medical History. J. Clin. Med. 7. https://doi.org/10.3390/jcm7120476.
Kovach, M.A., Standiford, T.J., 2011. Toll like receptors in diseases of the lung. International Immunopharmacology 11, 1399–1406. https://doi.org/10.1016/j.intimp.2011.05.013.
Langhans, B., Kupfer, B., Braunschweiger, I., et al., 2011. Interferon-lambda serum levels in hepatitis C. J. Hepatol. 54, 859–865. https://doi.org/10.1016/j.jhep.2010.08.020.
Lu, Y.C., Yeh, W.C., Ohashi, P.S., 2008. LPS/TLR4 signal transduction pathway. Cytokine 42, 145–151. https://doi.org/10.1016/j.cyto.2008.01.006.
Metwally, M., Thabet, K., Bayoumi, A., et al., 2019. IFNL3 genotype is associated with pulmonary fibrosis in patients with systemic sclerosis. Sci. Rep. 9, 14834. https://doi.org/10.1038/s41598-019-50709-9.
Mira-Avendano, I., Abril, A., Burger, C.D., et al., 2019. Interstitial Lung Disease and Other Pulmonary Manifestations in Connective Tissue Diseases. Mayo Clin. Proc. 94, 309–325. https://doi.org/10.1016/j.mayocp.2018.09.002.
Mosallaei, M., Ehtesham, N., Rahimirad, S., et al., 2020. PBMCs: a new source of diagnostic and prognostic biomarkers. Arch. Physiol. Biochem. 1–7. https://doi.org/10.1080/13813455.2020.1752257.

Noureddin, M., Wright, E.C., Alter, H.J., et al., 2013. Association of IL28B genotype with fibrosis progression and clinical outcomes in patients with chronic hepatitis C: a longitudinal analysis. Hepatology (Baltimore, MD) 58, 1548–1557. https://doi.org/10.1002/hep.26506.

Ozaki, M., Glasgow, A., 2022. Sexual Dimorphism in Interstitial Lung Disease. 10. https://doi.org/10.3390/biomedicines10123030.

Raghu, G., Collard, H.R., Egan, J.J., et al., 2011. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 183, 788–824. https://doi.org/10.1164/rccm.2009-040GL.

Razzaque, M.S., Taguchi, T., 2003. Pulmonary fibrosis: cellular and molecular events. Pathol. Int. 53, 133–145. https://doi.org/10.1046/j.1440-1827.2003.01446.x.

Read, S.A., Wijaya, R., Ramezani-Moghadam, M., et al., 2019. Macrophage Coordination of the Interferon Lambda Immune Response. Front. Immunol. 10, 2674. https://doi.org/10.3389/fimmu.2019.02674.

Read, S.A., Gloss, B.S., Liddle, C., et al., 2021. Interferon-λ3 Exacerbates the Inflammatory Response to Microbial Ligands: Implications for SARS-CoV-2. Pathogenesis. 14, 1257–1270. https://doi.org/10.2147/jir.s301476.

Rieder, F., Kessler, S.P., West, G.A., et al., 2011. Inflammation-Induced Endothelial-to-Mesenchymal Transition: A Novel Mechanism of Intestinal Fibrosis. The American Journal of Pathology 179, 2660–2673 10.1016/j.ajpath.2011.07.042.

Simmonds, R.E., Foxwell, B.M., 2008. Signalling, inflammation and arthritis: NF-kappaB and its relevance to arthritis and inflammation. Rheumatology (Oxford) 47, 584–590. https://doi.org/10.1093/rheumatology/kem298.

Spagnolo, P., Bonella, F., Ryerson, C.J., et al., 2020. Shedding light on developmental drugs for idiopathic pulmonary fibrosis. Expert Opin. Invest. Drugs 29, 797–808. https://doi.org/10.1080/13543784.2020.1782885.

Sweis, J.J.G., Sweis, N.W.G., Alnaimat, F., et al., 2023. Immune-mediated lung diseases: A narrative review. Front. Med. 10, 1160755. https://doi.org/10.3389/fmed.2023.1160755.

Wilfong, E.M., Aggarwal, R., 2021. Role of antifibrotics in the management of idiopathic inflammatory myopathy associated interstitial lung disease. Therapeutic advances in musculoskeletal disease. 13,. https://doi.org/10.1177/1759720x211060907 1759720x211060907.

Wuyts, W.A., Agostini, C., Antoniou, K.M., et al., 2013. The pathogenesis of pulmonary fibrosis: a moving target. Eur. Respir. J. 41, 1207–1218. https://doi.org/10.1183/09031936.00073012.

Yoshio, S., Kanto, T., Kuroda, S., et al., 2013. Human blood dendritic cell antigen 3 (BDCA3) (+) dendritic cells are a potent producer of interferon-λ in response to hepatitis C virus. Hepatology (Baltimore, MD) 57, 1705–1715. https://doi.org/10.1002/hep.26182.