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REVIEW

Progranulin: A promising biomarker and therapeutic target for fibrotic diseases

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Abstract Progranulin (PGRN), a multifunctional growth factor-like protein expressed by a variety of cell types, serves an important function in the physiologic and pathologic processes of fibrotic diseases, including wound healing and the inflammatory response. PGRN was discovered to inhibit pro-inflammation effect by competing with tumor necrosis factor-alpha (TNF-α) binding to TNF receptors. Notably, excessive tissue repair in the development of inflammation causes tissue fibrosis. Previous investigations have indicated the significance of PGRN in regulating inflammatory responses. Recently, multiple studies have shown that PGRN was linked to fibrogenesis, and was considered to monitor the formation of fibrosis in multiple organs, including liver, cardiovascular, lung and skin. This paper is a comprehensive review summarizing our current knowledge of PGRN, from its discovery to the role in fibrosis. This is followed by an in-depth look at the characteristics of PGRN, consisting of its structure, basic function and intracellular signaling. Finally, we will discuss the potential of PGRN in the diagnosis and treatment of fibrosis.

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1. Introduction

Fibrosis is a consequence of the tissue remodeling response characterized by the deposition of collagen and other extracellular matrix (ECM) molecules[1,2]. If highly progressive and not effectively controlled, fibrosis ultimately results in organ malfunction and death. The most common clinical fibrotic diseases are systemic diseases; systemic sclerosis (SSc); chemical and radiation-induced fibrotic diseases; and organ-specific pathologies such as cardiac, liver, pulmonary, skin and renal fibrosis[3]. According to relevant data, cirrhosis is a leading cause of death worldwide—it was associated with 2.4% of global deaths in 2019[4]. Moreover, idiopathic pulmonary fibrosis (IPF) accounts for over 16,000 deaths per year in the United States[5]. In America, almost 45% of deaths from various disorders can be attributed to tissue fibroproliferative diseases[6]. In addition, the total annual global incidence of fibrotic diseases is nearly 4.968% of the population per year[7]. The incidence of fibrotic disease and the number of fibrosis-related deaths continue to increase with an ever-expanding aging population[8]. Although the etiologies of different fibrotic diseases vary, the pathogenesis of these diseases is consistent. The main pathogenesis is an inordinate accumulation of fibrous connective tissue around inflamed or damaged tissue, leading to an excessive increase in fibronectin and collagen in the ECM and the differentiation of fibroblasts into myofibroblasts, causing permanent scarring and organ dysfunction[9,10]. Notably, fibroblast activation is regulated by various secreted soluble factors. It has been reported that Progranulin (PGRN) acts as a pleiotropic growth factor and its reduction promotes fibrogenesis in skin wound healing[11]. Hence, further elucidation of the mechanism of fibrotic disorders and identification of more effective therapeutic targets for extra fibrosis are needed.

PGRN, a pleiotropic growth factor-like protein produced in assorted tissues, is involved in diverse pathological and physiologic processes, including embryogenesis, wound healing, host defense, tumorigenesis, and cartilage degeneration[12,13]. Furthermore, PGRN has a well-accepted role in inflammatory cell proliferation and has been demonstrated to be involved in the process of immune diseases[14]. It has been reported that overexpressed serum PGRN acts as an independent predictor of the extent of liver fibrosis in nonalcoholic fatty liver disease (NAFLD) patients[15]. Similarly, in models of carbon tetrachloride-induced liver fibrosis and methionine-choline-deficient diet-induced nonalcoholic steatohepatitis, PGRN exhibited protective effects against liver damage, fibrosis and inflammation through inhibiting the phosphorylation of nuclear transcription factor kappa B (NF-κB)[16]. These results increase the understanding of the importance of PGRN in fibrotic diseases and strongly indicate that PGRN is a novel biomarker and treatment target in fibrotic diseases.

The tissue remodeling response is highly dynamic and the cells involved in this process are continuously renewed throughout their lifetime. These findings are consistent with the findings of previous reports on external factors or internal signaling pathways, and accumulating research has explored the role of PGRN in tissue remodeling through the targeting of different molecules[17,18]. Therefore, we reviewed recent studies linking PGRN to fibrotic diseases. We first summarize the knowledge of PGRN, and subsequently provide insight into the functions and regulatory roles of PGRN in fibrotic diseases. Finally, the clinical relevance of PGRN regulation in fibrotic disorders was also explored to provide insight into the development of therapeutic strategies.

2. Overview of PGRN

2.1. Basic structure of PGRN

PGRN, also referred to as granulin-epithelin precursor[19], acrogranin[20], proepithelin, GP88, and PC-cell derived growth factor[21], is an autocrine multifunctional growth factor that includes 593 amino acids and has a molecular weight of nearly 75−80 kDa that contributes to modulating cell proliferation and wound repair[22]. It is encoded by the GRN gene and is located at chromosomal region 17q21.32; this gene 12 exons and results in three isoforms[14]. PGRN consists of $7^1/_2$ domains of a cysteine-rich motif ($CX_{5\text{-}6}CX_5CCX_8CCX_6CCXDX_2HCCPX_4CX_{5\text{-}6}C$, X: any amino acid) in the order P-G-F-B-A-C-D-E, where P is the incomplete motif and A-G are full repeats[23], which are connected by six disulfide bonds, forming four sequentially trapezoidal folded β hairpins structures in the spatial structure[24] (Fig. 1). In addition, PGRN is decidedly expressed in certain types of neurons[25], and macrophages[26] and is also expressed in a broad range of other cells and tissues, containing chondrocytes[27], adipose tissue[28], hematopoietic cells[29], and immune cells[30], including dendritic cells and T cells. In 1998, for the first time, PRGN was demonstrated to promote cell proliferation by directly binding to fibroblasts[31].

2.2. Biological functions of PGRN

PGRN is understood to play an essential role in various physiological and disease processes, including early embryonic development, inflammation and wound healing[32]. The multiple roles of PGRN are mediated by various related proteins[33]. Uniquely, PGRN can bind to a wide range of proteins at distinct levels, ranging from the extracellular fluid and the ECM to intracellular components, including the nucleus and cytoplasm[34]. This adaptability is likely a result of the exceptional structure of the PGRN. For instance, the PGRN F-B domain can be identified by Laminin G and the EGF-like domain of Perlecan domain V[35]. Interestingly, Laminin and Perlecan are the main components of the ECM. So far, more than 20 proteins have been identified as binding partners of PGRN[36-41]; among them are several cell surface proteins, including tumor necrosis factor receptors (TNFRs)[42], sortilin 1[43] and Toll-like receptor 9[44]. According to a previous study, PGRN was found to be a novel ligand that blocks TNF-alpha (TNF-α)-mediated signaling pathways by competing with TNF-α for binding to TNFR1/2, hence inhibiting its proinflammatory effects[45]. Moreover, secretory leukocyte protease inhibitor binds directly to PGRN, blocking the proteolysis by elastase[46]. Increasing evidence has indicated that PGRN is digested into 6 kDa GRN peptides by many proteases, consisting of matrix metalloproteinases 9 and 12, elastase and protease 3[36,47-49]. However, GRN, as opposed to PGRN, promotes the expression of neutrophil-attracting chemokines during inflammation[50]. Therefore, maintaining a balance between PGRNs and GRNs is also an important mechanism through which PGRNs characterize their biological functions.

In many types of diseases, inflammation is the trigger for fibrosis[51]. Activated inflammation leads to the overexpression of inflammatory mediators[52,53]. Fibroblasts and other mesenchymal cells are subsequently transformed to myofibroblasts *via* the enrichment of fibrotic cytokines, where they secrete ECM components[54]. In the normal wound healing response, activated myofibroblasts are removed from the wound site by apoptosis following

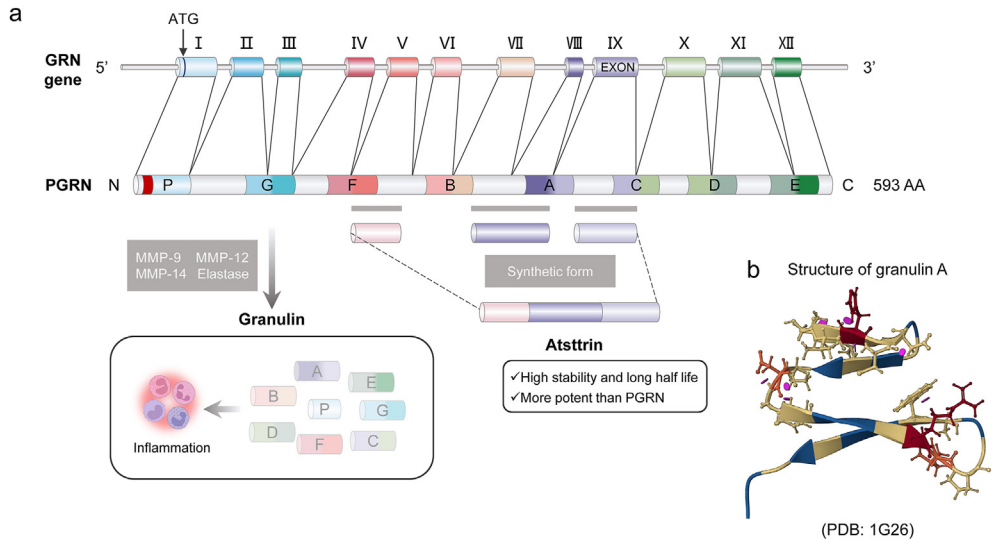

Figure 1 The structure and production of PGRN. (a) PGRN gene (GRN), located on chromosome 17q21.32, consists of 12 exons. PGRN is formed by 7.5 domains (a granulin motif in the order of P−G−F−B−A−C−D−E, where A−G are full repeats and P is the half-motif) of a 12-cysteine motif, which cleavages producing GRNs that promotes inflammation. Atsttrin is the synthetic form derived from FAC domain of PGRN (from Ref. 129). (b) Human granulin A structure (from protein data bank, https://www.rcsb.org/, PDB ID, 1G26). PGRN, progranulin; AA, amino acid; MMP, matrix metalloproteinases.

injury repair[55]. Conversely, during the fibrotic process, myofibroblasts fail to undergo apoptosis and are subsequently activated, ultimately contributing to disproportionate ECM deposition[56]. While PGRN is one of the main anti-inflammatory factors, the specific function of PGRN may differ according to the stage and components involved in inflammatory responses[33]. For example, PGRN affects the development of macrophages, neutrophils, blood vessels, and fibroblasts in acute skin damage[57], but in acute infection, PGRN represses lipopolysaccharide (LPS)-mediated interleukin (IL)-6, TNF-α, and monocyte chemoattractant protein-1 (MCP-1) cytokine release from macrophages[58]. Furthermore, the results of several studies revealed that TNF-α has profibrotic effects in various animal models generated from TNF-α blockers or TNF-receptor deficient mice[59-61]. Therefore, PGRN competitively binds to TNF-α receptors, which may be an underlying mechanism for the inhibition of fibrosis.

As mentioned above, PGRN has potent inflammatory effects in multiple animal models, and thus can downregulate the expression of proinflammatory molecules, leading to decreased injury correlated with fibrosis[16,62]. Moreover, although the exact mechanisms underlying the role of PGRN in some fibrotic diseases have largely not been elucidated, increasing evidence has demonstrated that PGRN is involved in fibrosis[11,16,17]. In brief, PGRN is involved in the generation of fibrosis-related cytokines and products, and plays a significant role in human fibrotic diseases.

3. PGRN in fibrotic diseases

Fibrotic diseases are characterized by the activation of ECM-producing myofibroblasts, and include SSc, liver fibrosis, kidney fibrosis and other related diseases[63]. Although increasing in-depth research has focused on these diseases, the underlying mechanisms have not been fully elucidated, hampering advances in biomarker and therapeutic target research for fibrotic disease. As a consequence, there is an urgent need to obtain a better understanding of the mechanisms underlying fibrosis to design new therapies that postpone or prevent disease progression. Additionally, current works have revealed that PGRN participates in the pathogenesis and development of them, including liver fibrosis[16] and cardiovascular fibrosis[64,65], etc.[17] (Table 1). Recent studies have shown that the expression level of PGRN was increased in several fibrotic diseases and exhibited anti-inflammatory effects, thereby inhibiting organ fibrosis.

3.1. *Hepatic fibrosis*

Hepatic fibrosis is a reversible wound-healing response characterized by the abnormal accumulation of ECM proteins containing collagen owing to most chronic liver injuries[66,67]. In terms of the complex and diverse pathogenesis of liver fibrosis, although the exact function of PGRN in this disease is unknown, there is no doubt that PGRN has a great influence on the progression and pathogenesis of liver fibrosis[16,68] (Fig. 2).

In a study consisting of 95 patients with biopsy-proven NAFLD and 80 age- and sex-matched controls, Yilmaz et al. found that the serum PGRN concentration was positively related to the degree of hepatocyte fibrosis. Moreover, Yilmaz et al.[15] illustrated that PGRN could serve as a predictor of hepatocyte fibrosis in NAFLD patients after adjustment for a broad spectrum of probable confounders. Nevertheless, this study did not elucidate the causal relationship between serum PGRN levels and the occurrence of liver fibrosis. Notably, several studies have shown that PGRN suppresses hepatic fibrosis[16,69,70]. Yoo et al.[16] have suggested that PGRN could attenuate liver fibrosis by reducing the inflammatory response. Researchers have investigated the role of PGRN by establishing two models of chronic liver disorders, methionine-choline-deficient diet-induced nonalcoholic steatohepatitis and carbon tetrachloride-induced liver fibrosis. Several studies have shown that disturbances in macrophage function can result in aberrant repair, which can lead to the progression of pathological fibrosis[71]. In both models, PGRN decreased

Table 1 Progranulin in fibrotic diseases.

Organ	Disease	Subject	Expression level	Link to PGRN	PMID
Liver	NAFLD	NAFLD patients	↑	An independent predictor of the degree of hepatic fibrosis in patients	22045426
	MCD-induced NASH	Mice RAW264.7, HepG2, Huh7	↑	PGRN attenuated liver fibrosis by reducing hepatic steatosis and injury	31591383
	CCl_4-induced liver fibrosis	Mice RAW264.7, HepG2, Huh7, human primary stellate cells	↑	PGRN reduced liver fibrosis by inhibiting inflammation	31591383
	GD	GD patients	↓	Negatively correlated with clinical disease severity and liver stiffness	32652633
	Thioacetamide-induced liver cirrhosis	Rats	↑	PGRN was upregulated in cirrhotic livers *in vivo*	19784507
Heart	CAVD	Patients	↑	PGRN significantly reduced the fibrosis markers	32247641
		hVICs, pVICs	↓		
		$grn^{-/-}$MEFs	NA		
	AMI	Mice, rabbits	↑	PGRN decreased fibrosis size in myocardium	32678228
Lung	AE-IPF	AE-IPF patients	↑	A possible marker of disease activity in AE-IPF	34462814
	ALI	Mice	↑↓[a]	Pro-inflammatory mediators were decreased	33941562
		Mice RAW164.7	NA	Anti-inflammatory factor was upregulated	32565732
		Mice	↑↓	PGRN/TNFR2 interaction played a protective role in ALI	22969170
Bronchus	HDM-induced chronic asthma	Mice BEAS-2B	NA	Administration mitigated inflammation and fibrosis	34408470
Skin	Skin wound healing	Mice	↑	Downregulation enhanced the fibrosis degree	30561754
	SSc	SSc patients Mice	↑	Increased in diseased tissue, inhibition improved disease in mice models	31108104
	LSc	LSc patients Human dermal fibroblasts	↑	Overproduction induced the pro-fibrotic phenotype in dermal fibroblasts	30268392

"NA" indilegecates that changes in the expression level are not mentioned in the reference.

NAFLD, nonalcoholic fatty liver disease; MCD, methionine-choline-deficient diet; NASH, non-alcoholic steatohepatitis; CCl_4, carbon tetrachloride; GD, Gaucher disease; CAVD, calcific aortic valve disease; AMI, acute myocardial infarction; AE-IPF, acute exacerbation of idiopathic pulmonary fibrosis; ALI, acute lung injury; HDM, house dust mite; SSc, systemic sclerosis; LSc, localized scleroderma; PGRN, progranulin; TNFR2, tumor necrosis factor-alpha receptor 2.

[a]"↑↓" indicates that the expression level of PGRN increases first and then decreases significantly.

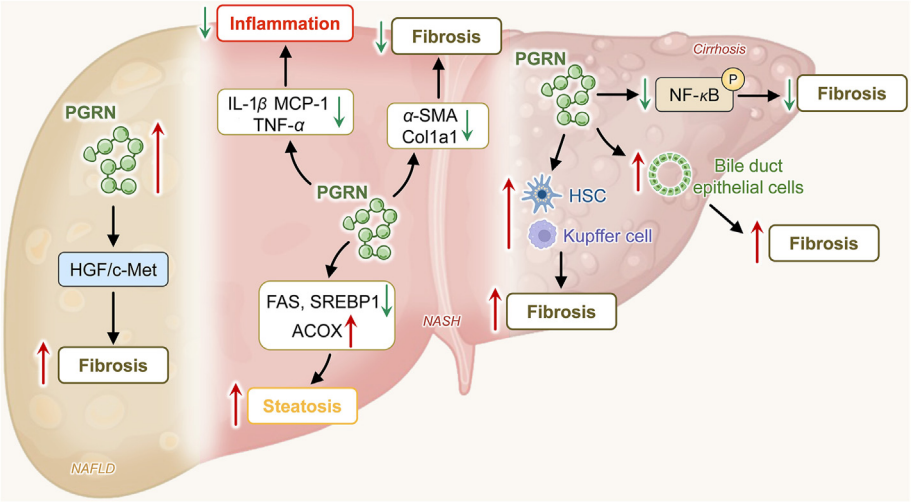

Figure 2 PGRN in hepatic fibrosis. Upregulated serum PGRN acted as an independent marker of liver fibrosis in patients with NAFLD, which could occur *via* the regulation of the HGF/c-Met signaling pathway. Moreover, PGRN attenuated liver fibrosis by downregulating hepatic steatosis and inflammation in NASH. PGRN was up-regulated in cirrhotic livers and positivity was strong in hepatic areas of bile duct proliferation and in fibrous septa, suggesting the involvement of this growth factor in bile duct epithelial cell and non-parenchymal cell proliferation, which contributes to the fibrotic process. PGRN, progranulin; NAFLD, nonalcoholic fatty liver disease; HGF, hepatocyte growth factor; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; α-SMA, α-smooth muscle actin; FAS, fatty acid synthase; SREBP1, sterol regulatory element-binding protein-1; ACOX, (acyl-CoA oxidase; HSC, hepatic stellate cell; NF-κB, nuclear transcription factor kappa B.

macrophage activation and infiltration, contributing to reduced hepatic fibrosis. Moreover, the results of the *in vitro* and *in vivo* experiments indicated that the expression levels of TNF-α, interleukin-1beta (IL-1β), MCP-1, alpha-smooth muscle actin (α-SMA), and collagen type I alpha 1 chain were significantly downregulated in the PGRN-treated group than in the blank group. Additionally, in Gaucher disease (GD) patients, Tantawy et al.[69] reported a further negative correlation between serum PGRN and liver stiffness as well as the potential of PGRN as a biomarker of liver fibrosis in GD patients.

Conversely, a previous study by Guerra et al.[72] revealed that both PGRN protein and mRNA positivity were unmistakable in hepatic areas of bile duct proliferation and in fibrous septa by using in situ hybridization and immunohistochemistry. These results indicated that growth factors contributed to the fibrotic process. Several reasons may explain the conflicting results: First, different modeling methods could cause deviations in the results. Second, animal experiments cannot completely explain the conditions in humans. Furthermore, sample size and group limitations may partially account for such contradictory findings.

3.2. *Cardiovascular fibrosis*

3.2.1. *Calcific aortic valve disease*

Calcific aortic valve disease is a universal valvular heart diseases that encompasses a disorder spectrum ranging from aortic valve sclerosis to gross left ventricular (LV) outflow obstruction by calcific aortic valve stenosis, which is characterized by the presence of mineralized nodules and fibrosis (*i.e.*, progressive mineralization and fibrosis in the aortic leaflets)[73,74]. Many studies on PGRN expression have shown that PGRN is produced and secreted from macrophages, endothelial cells, neuronal cells, etc.[75]. Of note, one study by Huang et al.[64] provided the first report to state that PGRN is expressed in valve interstitial cells. In addition, data from the study showed that PGRN expression increased in valves from calcific aortic valve disease patients but decreased in primary porcine valve interstitial cells. The results suggested that increasing concentrations of PGRN elicited continuous reductions in intracellular TNF-α expression until the maximum peak was reached in response to 800 ng/mL PGRN, and the fibrosis marker α-SMA was also downregulated. As mentioned above, the expression of PGRN has also been reported to be upregulated under some conditions, including hypoxia[76] and traumatic brain injury[77]. Therefore, the overexpression of PGRN may be the consequence of a compensatory response, as analyzed by Yin et al.[78] Taken together, these findings suggest that PGRN might constitute a novel biomarker for mitigating valve fibrosis.

3.2.2. *Acute myocardial infarction*

Acute myocardial infarction (AMI) can present as myocardial necrosis caused by acute thrombotic obstructions of coronary artery blood flow[79]. AMI arises when blood ceases to suddenly flow to a part of the heart, and the myocardium is injured owing to a lack of oxygen supply[80]. AMI always results in varying degrees of ventricular remodeling. Approximately three days post-MI, the beginning of fibroblast proliferation and replacement fibrosis cause the formation of a collagen I-rich scar[81]. Unlike healthy myocardium, the fibrotic scar is electrically inert and less contractile, exacerbating myocardial fibrosis and deteriorating cardiac function, which leads to no fundamental improvement in clinical symptoms or prognosis[82]. As such, the prevention of myocardial fibrosis post-AMI is essential for patient survival. It has been demonstrated that PGRN ameliorates fibrosis after myocardial ischemia/reperfusion (I/R) in rabbits[65]. To our knowledge, the LV internal diameter is correlated with an index of adverse cardiac repair[83]. Sasaki et al.[65] have suggested that recombinant PGRN markedly weakens the deterioration of the internal diameter of the

LV at diastole and systole according to echocardiography analysis. Moreover, Masson's trichrome staining revealed that, compared with vehicle, PGRN strongly reduced the extent of fibrosis in the myocardium by 10% after myocardial I/R. In conclusion, PGRN might have therapeutic potential for fibrosis in myocardial I/R injury.

3.3. *Respiratory system fibrosis*

3.3.1. *Idiopathic pulmonary fibrosis*

IPF is a progressive chronic interstitial pneumonia of unknown pathogenesis characterized by incessant scarring of the lung parenchyma triggering reduced quality of life and earlier mortality[84]. In particular, acute exacerbation of IPF (AE-IPF) is an acute, clinically significant, respiratory exacerbation of unexplained causes[85] and may even occur in individuals with limited fibrosis and well-preserved lung function[86]. Interestingly, a study based on patients with AE-IPF hospitalized at Hainan General Hospital between January 2017 and June 2020, demonstrated that PGRN expression in the study group was dramatically greater than that in matched controls[12]. According to guidelines from the European Respiratory and American Thoracic Society, decreased diffusing capacity of carbon monoxide (DLCO) is often observed in patients with structural lung diseases, consisting of chronic obstructive lung disease and interstitial lung disease (ILD)[87]. Hence, DLCO is used to indicated to measure the progression of pulmonary fibrosis. Xie et al.[12] has also found an obvious negative correlation between PGRN and DLCO, suggesting that the PGRN concentration increases as fibrosis worsens. As discussed previously, the mechanism underlying the increase in PGRN may involve in the inflammatory response to AE-IPF, and PGRN could be useful as a clinical marker of AE-IPF (Fig. 3). Another study has shown that serum PGRN levels were significantly higher in non-IPF ILD patients compared to healthy subjects and stable IPF patients[88]. The difference can be explained by the mechanism of PGRN in acute exacerbation.

3.3.2. *Asthma*

Asthma is a chronic, heterogeneous condition that may result from exposure to allergens or other environmental irritants[89,90]. It has been demonstrated that airway remodeling is a cardinal feature of asthma in which airways undergo structural changes, and are capable of causing variable airflow limitation in patients with asthma[91]. Additionally, previous studies demonstrated that fibrosis is an important characteristic of airway remodeling[92,93]. Earlier work by Minshall et al. confirmed that a progressive increase in fibrosis was correlated with increasing severity of asthma[94]. Thus, the suppression of airway fibrosis would be beneficial for relieving airway remodeling, thereby improving asthma symptoms and prognosis. A study conducted by Liu et al.[17] indicated that PGRN protected against remodel of the asthmatic airway by inhibiting autophagy. The findings indicated that the increased mRNA expression of the fibrosis-related genes collagen-I, α-SMA, transforming growth factor beta 1 (TGF-β1) and matrix metalloproteinase-9 (MMP9) in house dust mite-induced mice was greatly suppressed by PGRN treatment. Meanwhile, PGRN dramatically reduced the expression levels of collagen-I, α-SMA and collagen-III induced by TGF-β1 in BEAS-2B cells (a cell from the human airway epithelium)[17]. Overall, PGRN may function as a potential treatment option for chronic asthma (Fig. 3).

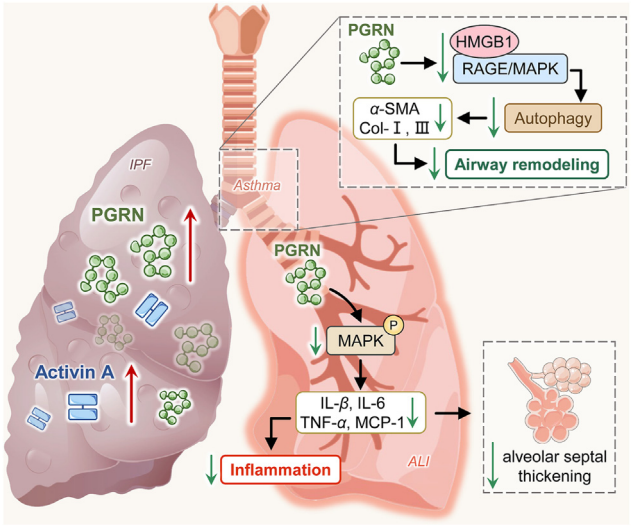

Figure 3 PGRN in respiratory system fibrosis. In AE-IPF, PGRN concentration increased as fibrosis worsen, which functioned as possible markers of disease activity together with activin A. For patients with asthma, PGRN significantly reduced collagen-I, α-SMA and collagen-III in TGF-β-induced airway epithelial cells *via* autophagy, thereby preventing airway remodeling and improving asthma. Furthermore, PGRN attenuated the formation of inflammatory molecules and alveolar septal thickening by inhibiting the MAPK signaling pathway in ALI. PGRN, progranulin; HMGB1, high-mobility group box protein 1; RAGE, The receptor for advanced glycation end product; MAPK, mitogen-activated protein kinase; α-SMA, α-smooth muscle actin; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; TNF-α, tumor necrosis factor-alpha.

3.3.3. *Acute lung injury/acute respiratory distress syndrome*

Acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) is characterized by diffuse alveolar injury, which causes excessive pulmonary inflammation and pathological changes in lung tissues[95-97]. Previous observations suggested that injury and repair mechanisms occur synchronously rather than in sequentially[98,99]. More importantly, Marshall et al. demonstrated that 24 h following disease onset, the level of N-terminal procollagen peptide III, an indicator of collagen turnover, was significantly greater in the bronchoalveolar lavage fluid (BALF) of ARDS patients than in that of controls[100]. Accumulated evidence has shown that pulmonary tissue morphology, including fibrin deposition and alveolar wall thickening, is altered from a normal state to fibrosis in ALI model mice[101,102]. Therefore, fibrosis may be an early response to ALI/ARDS and a crucial therapeutic target for improving patient prognosis. It is generally accepted that PGRN has antifibrotic effects[65,103]. Nevertheless, the mechanisms of PGRN in ALI/ARDS remained uncertain. In a study by Lu et al.[102], PGRN markedly suppressed the formation of inflammatory molecules including IL-1β, IL-6, TNF-α, and MCP-1. In accordance with the theory that dysregulated or chronic inflammation may contribute to the progression of pathological fibrosis or scarring[104], the above study revealed that treatment with PGRN also significantly attenuated alveolar septal thickening and transparent membrane formation. Similarly, Chen[105] and Guo et al.[106] also showed that PGRN could significantly reduce intra-alveolar fibrin in ALI mouse models. Apparently, the antifibrotic efficacy of PGRN in the ALI model indicates that PGRN is a promising therapeutic approach for fibrosis in ALI/ARDS (Fig. 3).

3.4. Skin fibrosis

As the body's main external barrier, the skin is a common site of tissue damage[107]. Following injury, a complex wound repair reaction occurs in the skin, which is generally imperfect, with some degree of fibrosis or scarring[108]. This outcome leads to the replacement of native tissue with dense connective tissue, ultimately resulting in loss of normal tissue function[109]. Although the effect of PGRN on the fibrosis process in skin remains poorly understood, the PGRN gene is expressed in dermal fibroblasts, endothelial cells and infiltrating leukocytes and is a mediator of the wound response[110]. Notably, data from a study by Li et al.[11] found that the protein and mRNA levels of PGRN were elevated after injury and that the downregulation of PGRN augmented the fibrosis area, skin thickness and collagen I expression during cutaneous wound healing. Similarly, Li et al.[18] demonstrated that PGRN upregulation decreased both the area and thickness of granulation/fibrosis tissue in a mouse model.

Nevertheless, this is inconsistent with the findings based on a study about on skin sclerosis carried out by Yang et al[111]. It is well known that SSc is a rare, complex and chronic connective tissue disease of unknown etiology, the cardinal symptom of which is skin fibrosis[112,113]. Using a bleomycin (BLM)-induced dermal fibrosis mouse model, researchers have shown that a decrease in PGRN expression ameliorates fibroblast activation and skin fibrosis. Additionally, compared with those in BLM-induced wild-type (WT) mice, there was a distinct reduction in dermal thickness and a great attenuation of collagen fibers in skin tissue in BLM-induced PGRN$^{-/-}$ mice [111]. By coincidence, based on the current data about the double-edged role of TNF-α on fibrosis[114,115], Miyagawa et al.[116] investigated the impact of PGRN on localized scleroderma (LSc), the results of which indicated that PGRN overproduction aggravated skin fibrosis *via* blockade of the anti-fibrotic function of TNF-α on skin fibroblasts; the same was true for SSc. Interestingly, it was reported that PGRN can both act as an anti-inflammatory factor and a proinflammatory factor[117]. Thus, it was speculated that PGRN maintained the pro-fibrotic phenotype due to the special anti-fibrosis mechanism of SSc and LSc dermal fibroblasts.

Given that the above studies involved different disease models and complex pathogenesis, PGRN seems to have dual modes of action, such as acting as a promoter and inhibitor in the development of skin fibrosis. Overall, the present findings provide new insights into the complicated effects of PGRN in skin fibrotic disorders.

4. PGRN expression and mechanisms in fibrotic diseases

Previous studies have demonstrated that patients with fibrotic diseases exhibit elevated plasma PGRN levels compared with healthy individuals. A study carried out by Yilmaz et al. suggested that serum PGRN levels were significantly greater in NAFLD patients than in controls[15]. Moreover, in a recent cross-sectional study, serum PGRN levels were significantly greater in non-IPF ILD patients compared to healthy subjects and IPF. By coincidence, Xie et al.[12] reported that PGRN levels were greater in AE-IPF patients than in healthy individuals, which indicates a possible pathogenetic role of PGRN in this disease, as noted by Tanaka et al.[118]. Therefore, it can be assumed that PGRN expression is lower in chronic and stable IPF patients compared to non-IPF ILD and AE-IPF patients, but still higher than that in the control population.

Analysis of the human promoter of the GRN revealed that its expression is likely regulated by inflammation[119]. Based on the data thus far, inflammation may be an important mechanism for bridging PGRN and fibrosis. There are potential factors such as IL-6[120,121] and TNF-α[121] that can influence serum PGRN levels. Although PGRN has been extensively studied as an anti-inflammatory factor, increased PGRN levels are likely to be a compensatory response to the inflammatory response[77]. Additionally, some researchers have speculated that altered levels of PGRN with hepatic fibrogenesis can occur *via* regulation of the hepatocyte growth factor/mesenchymal−epithelial transition factor system signaling pathway[15].

5. Regulatory mechanism of PGRN in fibrotic diseases

5.1. PGRN signaling pathways

The global understanding of signal transduction regulatory networks in biological processes is highly important for exploring the molecular mechanisms of disease[122-124]. Notably, the onset and progression of fibrotic diseases are regulated by complex molecular mechanisms and different signaling pathways[2], while our present understanding of fibrosis is incomplete, which causes the treatment of fibrosis is currently at a bottleneck stage. Hence, an increasing number of studies have focused on the effect of PGRN on fibrosis at the molecular level and revealed that mitogen-activated protein kinase (MAPK), the TGF-β/Smad pathway, and the NF-κB signaling pathway are activated during the development of fibrotic diseases (Fig. 4).

5.1.1. MAPK signaling pathway

The MAPK signaling pathway has been widely studied and is generally divided into four branches: the extracellular signal-related kinase (ERK1/2), p38 MAPK, c-Jun N-terminal kinase (JNK1/2/3), and ERK5[125]. Recent studies have reported that the activated MAPK signaling pathway may play a role in the pathogenesis of fibrosis[126-128]. Moreover, it was reported that activation of the MAPK signaling pathway in proinflammatory M1 macrophages was related to the production of the profibrotic mediators IL-1β, IL-6 and TNF-α[129,130], which stimulate fibroblast activation and survival, thus, exacerbating fibrosis[131]. Interestingly, Liu et al.[132] found that PGRN significantly inhibited LPS-activated JNK and p38 to complete its reversal of LPS-promoted M1 polarization. Based on these findings, it was reasonable to deduce that the activation of MAPK signaling pathways might be a potential mechanism of fibrosis. Similarly, in a study on ALI, PGRN suppressed the phosphorylation of ERK, JNK and p38 in the process of alleviating ALI[102]. In addition, Liu et al.[17] demonstrated that high-mobility group box protein 1 (HMGB1) significantly exacerbates fibrosis formation in house dust mite-induced chronic asthma, while the upregulation of HMGB1 and subsequent RAGE/MAPKs signaling activation are restrained in PGRN-treated asthmatic mice. Overall, the mechanisms linking PGRN with fibrotic diseases are not fully understood, but given such findings, it is conceivable that PGRN might attenuate fibrosis by modulating MAPK signaling.

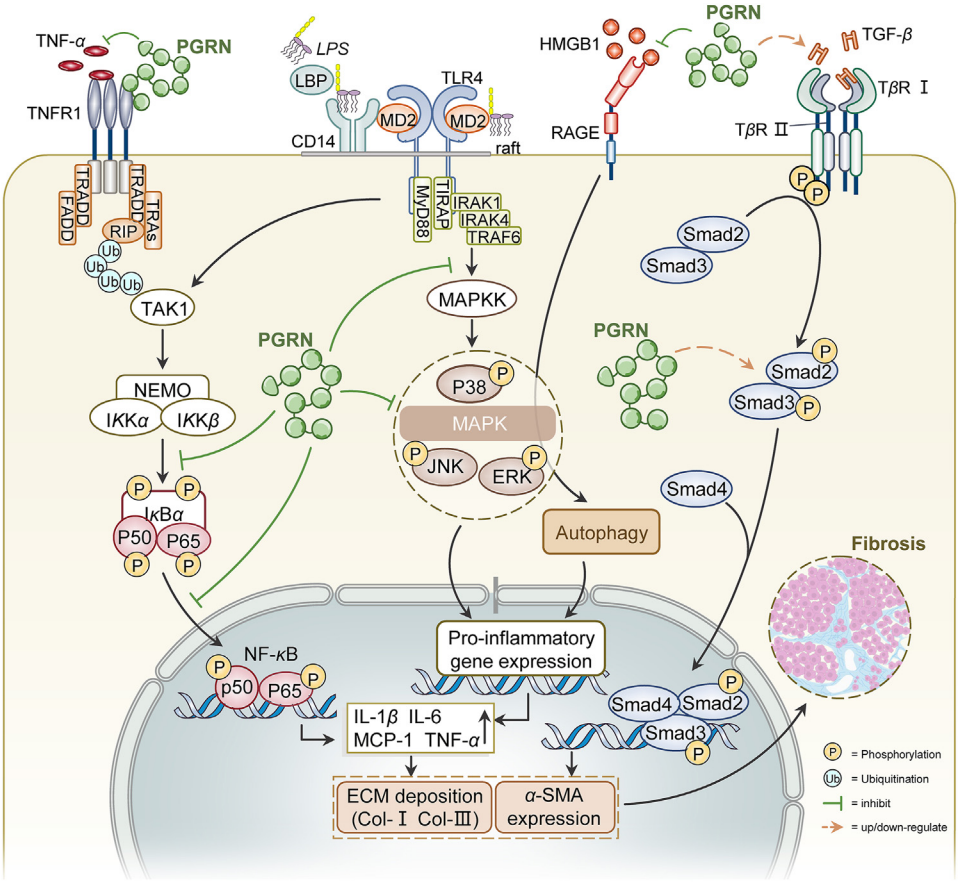

Figure 4 Functions and signaling pathways associated with PGRN in fibrogenesis. (1) PGRN inhibited competitively TNF/TNFR1, followed by the suppression of the NF-κB pathway. Besides, PGRN significantly reduced phosphorylation of IκBα, p65 and the nucleus translocation of NF-κB p65. (2) PGRN also delayed the inflammatory process through inhibiting the increase of HMGB1 and the activation of RAGE/MAPKs signaling pathway. In another study about ALI, PGRN inhibited the activation of the MAPK signaling pathway *via* decreasing phosphorylation of ERK, JNK and p38. (3) PGRN played dual roles in modulating the TGF-β/Smad signaling pathway. Abbreviations: PGRN, progranulin; TNF-α, tumor necrosis factor-alpha; TNFR1, TNF receptor 1; TRADD, TNFR1-associated death domain protein; FADD, Fas-associated protein with death domain; TRAFs, TNFR-associated factors; RIP, receptor interacting protein; NF-κB, nuclear transcription factor kappa B; NEMO, NF-κB essential modulator; IL-1β, interleukin-1 beta; MCP-1, monocyte chemoattractant protein-1; α-SMA, againstα-smooth muscle actin; ECM, extracellular matrix; LPS, lipopolysaccharide; LBP, LPS-binding protein; MD2, myeloid differentiation protein 2; MyD88, myeloid differentiation primary response gene 88; TLR4, Toll-like receptor 4; TIRAP, Toll/IL-1 receptor domain containing adaptor protein; IRAK, IL-1 receptor-associated kinase; MAPK, mitogen-activated protein kinase; JNK, c-Jun N-terminal kinases; ERK, extracellular signal-related kinases; HMGB1, high-mobility group box protein 1; RAGE, The receptor for advanced glycation end product; TGF-β, transforming growth factor beta; TβR, TGF-beta receptor; TAK1, TGF-β-activated kinase 1.

5.1.2. *TGF-β/Smad signaling pathway*

The TGF-β family of cytokines, which consists of TGF-βs, bone morphogenic proteins, and activins, regulates a wide array of biological activities in various cell types and at different developmental stages[133]. In general, canonical intracellular signaling activated by TGF-β ligands is mediated by SMAD family proteins, which are divided into three groups: receptor-associated SMADs (R-SMADs), cooperating SMADs (Co-SMADs), and inhibitory SMADs (ISMADs)[134]. However, a large amount of previous research into the signaling pathway has concentrated on its effect on fibrogenesis[135,136]. For example, a reduction in PGRN was shown to considerably increase the extent of fibrosis and collagen I accompanied by the upregulation of the expression of TGF-β1, Smad3 and P-Smad3, indicating that PGRN likely inhibited the degree of fibrosis *via* the TGF-β/Smad signaling pathway[11]. However, Zhou et al.[137] found that PGRN induced TGF-β1 and p-SMAD2&3 protein expression in fibroblasts, and the stimulatory effect of PGRN on fibroblasts could be subsequently suppressed by a TGF-β signaling pathway inhibitor (HY-10431), as proven by the decreases in the α-SMA and collagen I and III levels. Interestingly, these findings are consistent with those of a previous investigation, which revealed that PGRN promoted the development of dermal fibrosis through the activation of TGF-β/Smad3 signaling[111]. Considering that different fibrotic diseases have complex molecular mechanisms, PGRN may play disparate roles, even if it only modulates the TGF-β/Smad signaling pathway.

5.1.3. NF-κB signaling pathway

The NF-κB signaling pathway is a highly conserved evolutionary pathway, activated by various stimuli that potentially endanger the host and has key functions in the initiation of immune, inflammatory and wound-healing responses[62]. Furthermore, there is an ever-increasing body of research evidence demonstrating that NF-κB signaling is a promising therapeutic method for treating various fibrotic diseases[138,139]. Based on a typical study on fibrosis investigated by Yoo et al.[16], it has been shown that the phosphorylation of NF-κB was strongly decreased in PGRN-treated fibrosis mouse models compared with control groups, which suggested that PGRN reduces hepatic fibrosis by inhibiting inflammation activated by the NF-κB signaling pathway. Coincidentally, Liu et al.[132] also illustrated the anti-inflammatory role of PGRN through the repression of NF-κB signaling. Given the complexity of the NF-κB signaling pathway, further comprehensive research is needed to assess the interaction between PGRN and NF-κB signaling in regulating fibrotic diseases.

5.2. PGRN/TNFR interactions

As we all know, no biologically active ligand functions in isolation but acts through its interaction with binding partners. There is no direct evidence that PGRN and TNFR binding modulate the fibrotic process. However, inflammation is believed to be an important mechanism in the development of fibrosis[140]. The importance and validity of PGRN-TNFR interactions in inflammatory diseases and conditions are supported by more recent experimental and epidemiological evidence[42,45,141]. There are two distinct TNFRs, TNFR1 and TNFR2[142], which bind TNF-with comparable affinities but have different expression patterns and mediate different intracellular pathways[143,144]. After TNF binds to TNFR1, several adaptor proteins are recruited, followed by the activation of inflammatory signaling pathways[145]. In contrast, TNFR2 signaling is thought to mediate anti-inflammatory responses. In an LPS-induced acute lung injury model, PGRN markedly reversed LPS-induced lung permeability, as assessed by reductions in total protein, albumin, and IgM in BALF, as well as body weight loss[106]. This function is mediated through TNFR2, since neutralizing an antibody against TNFR2, but not TNFR1, completely blocks the therapeutic function of PGRN[106]. Furthermore, TNF-α and IL-β can induce NF-κB signaling in HSCs, promoting their survival and differentiation into myofibroblasts[146]. Consistent with this, TNFR1-deficient mice exhibit decreased liver fibrosis in response to bile duct ligation[147]. This is consistent with the data found by Sundaram et al.[148]. They revealed a mechanism to protect against liver fibrosis *via* the inhibition of TNFR signaling. Apparently, the interaction of PGRN with TNFR may modulate the fibrotic process. Although PGRN clearly has anti-inflammatory and antifibrotic effects on several diseases, it is unclear how PGRN exerts these effects. The finding that PGRN directly binds to TNFR and blocks the binding of TNF-α to its receptors provides new insight into the molecular mechanisms underlying PGRN-mediated antifibrosis.

6. Potential clinical significance of PGRN

6.1. PGRN as a biomarker for fibrosis

Fibrosis in the early stage is typically clinically reticent, and by the time patients reach clinical attention, fibrotic organs usually progress to a degree in which the physiologic functions of the affected tissue are impaired[149]. However, there is a problem that until now, no adequately exact biomarkers displaying the activity or condition of the fibrotic process have been identified. Hence, specific biomarkers are urgently needed to immediately diagnose fibrotic disorders, enhance clinical treatment, and expedite the advancement of effective therapeutic approaches[150]. Furthermore, specific biomarkers could accurately stratify fibrosis severity in high-risk individuals, closely reflect fibrosis progression, and could be utilized to establish customized treatments most appropriate for a specific subpopulation of fibrosis patients[151].

Increased expression of serum PGRN has been detected in a variety of fibrotic illnesses and its benefit as a prognostic biomarker for dissimilar clinical parameters has been broadly investigated in many cohorts (as concluded above). It is likely that a single biomarker can predict the prognosis of fibrosis. Thus, the use of a group of biomarkers could increase the accuracy of fibrosis diagnosis and incorporation of PGRN may provide more vital information in diagnosis. A case in point is that PGRN together with activin A, which are possible markers, increase the accuracy of assessing the activity of the AE-IPF[12]. It has been shown that in stable IPF, PGRN levels did not differ from healthy controls[88], while the expression level of activin A was elevated[152]. In AE-IPF, PGRN level was significantly higher than that in stable IPF and much higher than activin A expression (83.7 ± 10.0 *vs.* 14.2 ± 1.7 ng/mL)[12]. It is conceivable that this biomarker could be more extensively applied, for example, in the appraisal of cardiac remodeling after MI[65]. Importantly, serum PGRN was found to function as an independent marker of liver fibrosis in NAFLD[15]. In addition, decreased serum PGRN has been validated to be correlated with clinical disorder severity and increased liver stiffness in patients with GD[69].

Taken together, these findings indicate that the application of PGRN as a proxy for successful treatment is promising but supplementary studies are needed to confirm these findings and to assess its use as a biomarker for the efficacy of experimental antifibrotic therapies.

6.2. PGRN as a therapeutic target in fibrotic diseases

A large number of clinical trials on PGRN have been registered worldwide in the treatment of frontotemporal dementia, advanced solid tumors, etc. (Table 2)[153,154]. Moreover, PGRN itself may contribute to the pathology of fibrotic diseases and is therefore a beneficial therapeutic target. For example, several investigations have noted that PGRN protects against fibrogenesis by inhibiting several profibrotic signaling pathways, which might provide new insights into the treatment of fibrotic diseases[11,17]. Moreover, follow-up studies have shown that PGRN and TNF-α can bind to the same TNFRs[45]. More importantly, compared to TNF-α, PGRN exhibited an even greater binding affinity for TNFRs. Based on these findings, Atsttrin, an engineered protein derived from PGRN[42], was utilized to inhibit subchondral sclerosis which was worsened by the upregulation of MMP-13[27]. Moreover, it has been proved that PGRN decreased MMP-13 expression by inhibiting the binding of TNF-α to its receptor[155]. In another study on fibrosis, blocking MMP-13 also had potential therapeutic implications for preventing liver fibrosis[156]. As a result, the usage of PGRN can serve as a novel approach for targeting fibrosis.

Another potential method to target PGRN is by applying microRNAs (miRNAs). It has been demonstrated that miRNAs are involved in multiple disease processes through targeting

Table 2 Current, known clinical trials about PGRN in diseases.

Disease	Subject	Targeting strategy	Result	Ref./clinical trial name
Frontotemporal dementia (FTD)	Patients in a phase 1 clinical trial	Compound enhancing PGRN expression, nimodipine	Unavailable	NCT01835665
	Patients in a phase 1/2 clinical trial	Compound enhancing PGRN expression, LY3884963	Recruiting	NCT04408625
	Patients in a phase 1/2 clinical trial	Compound enhancing PGRN expression, PBFT02	Recruiting	NCT04747431
	Patients in a phase 1/2 clinical trial	Compound enhancing PGRN expression, AAV:PGRN (AVB-101)	Recruiting	NCT06064890
	Patients in a phase 2 clinical trial	Compound enhancing PGRN expression, FRM-0334	Unavailable	NCT02149160
	Patients in a phase 3 clinical trial	Compound enhancing PGRN expression, AL001	Unavailable	NCT04374136
	Patients in a phase 3 clinical trial	Compound enhancing PGRN expression, PI-2620	Recruiting	NCT05456503
Advanced solid tumors	Patients in a phase 1 clinical trial	Binding to human PGRN/GP88, AG01 (an anti-PGRN/GP88 antibody)	Recruiting	NCT05627960
Sepsis	Patients with sepsis	NA	Upregulated during the early stages of sepsis; a biomarker for sepsis	NCT03280576, Ref. 153
Breast cancer	Eligible healthy women $\geq$40 years old at average risk for developing breast cancer	NA	Unavailable	NCT02700776
Metabolic Syndrome	Patients with metabolic syndrome healthy subjects	NA	An independent predictor for atherosclerosis in subjects without metabolic syndrome	NCT01668888, Ref. 154
		NA	Unknown status	NCT04451616

FTD: frontotemporal dementia, PGRN: progranulin, AAV: adeno-associated virus.
NA, the targeting strategy for PGRN is not mentioned in the clinical trial data.

PGRN[157,158]. This finding indicates the occurrence of a negative feedback mechanism limiting the production of PGRN following some cytokine stimulation. As the underlying mechanisms will be explored in greater depth, such a negative feedback mechanism could conceivably be lost or enhanced in fibroblasts from patients with fibrosis. However, the translation of miRNA-based therapeutics into the clinic has been hampered by issues associated with specificity and delivery. A limitation is that the approach of treatment targeting PGRN can have undesired off-target effects because of a miRNA downstream effect on multiple genes. Other issues are related to delivery: the instability of 'naked', chemically unmodified miRNA structures and the lack of suitable delivery vehicles[159]. Thus, reorganizing these miRNAs will be another method to suppress or increase PGRN enrichment with possible therapeutic benefit.

Collectively, PGRN can directly bind to TNFR or indirectly be targeted by miRNAs to affect the occurrence and progression of fibrotic diseases.

7. Conclusion and future perspectives

PGRN expression is usually elevated when fibrosis develops in organs, including the liver, lung, skin and heart. Considering the abnormal expression of PGRN in patients with fibrotic diseases and its clinical significance in the process of this disease, PGRN could be a biomarker for identifying patients with fibrotic diseases and evaluating the severity and procession of this disease. Notably, overexpression of PGRN is likely to alleviate fibrotic processes by limiting the biological functions (proinflammatory and profibrotic) of PGRN targets, which validates the therapeutic potential of modulating PGRN.

However, many unresolved questions about the role of PGRN in fibrotic diseases remain to be further explored. Serum PGRN level is usually low, being up-regulated in the inflammatory state[160]. It has been demonstrated that PGRN was involved in chronic subclinical inflammation associated with the pathogenesis of diabetic microangiopathy and correlated with changes in disease metrics over time[161]. From the above, inflammation is an important mechanism for the occurrence of fibrosis. Interestingly, it remains to be investigated whether PGRN can be a biomarker for fibrosis progression and prognosis. Within the central nervous system, insights into the processing of PGRN into its granulin cleavage products in the lysosome have been relatively recent, but much remains to be learned about the interplay between PGRN and granulins, as well as the contribution of PGRN to fibrosis. As described above, several studies have reported the abnormal expression of PGRN in fibrotic diseases, but the outcomes are contradictory and inconclusive. For example, additional efforts are warranted to elucidate the dual role of PGRN in skin fibrosis. Mechanistically, in addition to acting on the TGF-β/Smad, MAPK and NF-κB signaling pathways, PGRN has been shown to be involved in the modulation of the Wnt/β-catenin signaling pathway, which affects inflammatory functions[162]. However, whether Wnt/β-catenin and PGRN are directly or indirectly related to fibrosis has yet to be determined. Given that TNF signaling is known to be involved in various kinds of diseases, and TNF inhibitors have been used to treat several kinds of inflammatory diseases, including osteoarthritis and skin inflammation, we envisage potential applications of PGRN, especially its derivative Atsttrin, in fibrotic diseases, such as skin fibrosis. As TNF inhibitors, PGRN and Atsttrin selectively target TNFR, and it is worthwhile to determine whether blockage of both ligand and receptors simultaneously will be more effective through comparing the effects of Atsttrin alone or with current TNF inhibitors. Finally, a crucial point is represented by the timing of the therapeutic interventions. A growing body of evidence suggests that fibrosis occurs in the early stage and is accompanied by inflammation. Therefore, ideally, treatment should be administered not only to patients but also to high-risk people.

In conclusion, notwithstanding these urgent problems, the available evidence strongly supports that PGRN may be a novel biomarker and therapeutic target for reversing the course of multiple fibrotic diseases. More in-depth mechanistic studies are still needed to validate the clinical relevance of PGRN and the potential for therapeutic effectiveness of PGRN in fibrotic diseases.

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Author contributions

Fan Yang: Writing − original draft. Ming-Han Cheng: Writing − review & editing. Hai-Feng Pan: Conceptualization. Jian Gao: Conceptualization, Supervision.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012;**18**:1028−40.
2. Henderson NC, Rieder F, Wynn TA. Fibrosis: from mechanisms to medicines. *Nature* 2020;**587**:555−66.
3. Piera-Velazquez S, Mendoza FA, Jimenez SA. Endothelial to mesenchymal transition (EndoMT) in the pathogenesis of human fibrotic diseases. *J Clin Med* 2016;**5**:45.
4. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis—aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol* 2023;**20**:388−98.
5. Lynch JP 3rd, Huynh RH, Fishbein MC, Saggar R, Belperio JA, Weigt SS. Idiopathic pulmonary fibrosis: epidemiology, clinical features, prognosis, and management. *Semin Respir Crit Care Med* 2016;**37**:331−57.
6. Shi N, Wang Z, Zhu H, Liu W, Zhao M, Jiang X, et al. Research progress on drugs targeting the TGF-beta signaling pathway in fibrotic diseases. *Immunol Res* 2022;**70**:276−88.
7. Zhao X, Kwan JYY, Yip K, Liu PP, Liu FF. Targeting metabolic dysregulation for fibrosis therapy. *Nat Rev Drug Discov* 2020;**19**:57−75.
8. Murtha LA, Morten M, Schuliga MJ, Mabotuwana NS, Hardy SA, Waters DW, et al. The role of pathological aging in cardiac and pulmonary fibrosis. *Aging Dis* 2019;**10**:419−28.
9. Pardali E, Sanchez-Duffhues G, Gomez-Puerto MC, Ten Dijke P. TGF-beta-induced endothelial-mesenchymal transition in fibrotic diseases. *Int J Mol Sci* 2017;**18**:2157.

10. Zhao X, Chen J, Sun H, Zhang Y, Zou D. New insights into fibrosis from the ECM degradation perspective: the macrophage−MMP−ECM interaction. *Cell Biosci* 2022;**12**:117.
11. Li SS, Zhang MX, Wang Y, Wang W, Zhao CM, Sun XM, et al. Reduction of PGRN increased fibrosis during skin wound healing in mice. *Histol Histopathol* 2019;**34**:765−74.
12. Xie T, Han L, Chen Y, Wu H. Progranulin and activin A concentrations are elevated in serum from patients with acute exacerbations of idiopathic pulmonary fibrosis. *Lung* 2021;**199**:467−73.
13. Wang C, Zhang L, Ndong JC, Hettinghouse A, Sun G, Chen C, et al. Progranulin deficiency exacerbates spinal cord injury by promoting neuroinflammation and cell apoptosis in mice. *J Neuroinflammation* 2019;**16**:238.
14. Pogonowska M, Poniatowski LA, Wawrzyniak A, Krolikowska K, Kalicki B. The role of progranulin (PGRN) in the modulation of anti-inflammatory response in asthma. *Cent Eur J Immunol* 2019;**44**: 97−101.
15. Yilmaz Y, Eren F, Yonal O, Polat Z, Bacha M, Kurt R, et al. Serum progranulin as an independent marker of liver fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Dis Markers* 2011;**31**: 205−10.
16. Yoo W, Lee J, Noh KH, Lee S, Jung D, Kabir MH, et al. Progranulin attenuates liver fibrosis by downregulating the inflammatory response. *Cell Death Dis* 2019;**10**:758.
17. Liu M, Shan M, Zhang Y, Guo Z. Progranulin protects against airway remodeling through the modulation of autophagy *via* HMGB1 suppression in house dust mite-induced chronic asthma. *J Inflamm Res* 2021;**14**:3891−904.
18. Li S, Liu J, Guo J, Xu Y, Zhou Z, Li Z, et al. Progranulin inhibits fibrosis by interacting with and up-regulating DNAJC3 during mouse skin wound healing. *Cell Signal* 2023;**109**:110770.
19. Zanocco-Marani T, Bateman A, Romano G, Valentinis B, He ZH, Baserga R. Biological activities and signaling pathways of the granulin/epithelin precursor. *Cancer Res* 1999;**59**:5331−40.
20. Baba T, Hoff 3rd HB, Nemoto H, Lee H, Orth J, Arai Y, et al. Acrogranin, an acrosomal cysteine-rich glycoprotein, is the precursor of the growth-modulating peptides, granulins, and epithelins, and is expressed in somatic as well as male germ cells. *Mol Reprod Dev* 1993;**34**:233−43.
21. Zhou J, Gao G, Crabb JW, Serrero G. Purification of an autocrine growth factor homologous with mouse epithelin precursor from a highly tumorigenic cell line. *J Biol Chem* 1993;**268**:10863−9.
22. Tanimoto R, Lu KG, Xu SQ, Buraschi S, Belfiore A, Iozzo RV, et al. Mechanisms of progranulin action and regulation in genitourinary cancers. *Front Endocrinol* 2016;**7**:100.
23. Williams A, Wang EC, Thurner L, Liu CJ. Review: novel insights into tumor necrosis factor receptor, death receptor 3, and progranulin pathways in arthritis and bone remodeling. *Arthritis Rheumatol* 2016; **68**:2845−56.
24. Hrabal R, Chen Z, James S, Bennett HP, Ni F. The hairpin stack fold, a novel protein architecture for a new family of protein growth factors. *Nat Struct Biol* 1996;**3**:747−52.
25. Rhinn H, Tatton N, McCaughey S, Kurnellas M, Rosenthal A. Progranulin as a therapeutic target in neurodegenerative diseases. *Trends Pharmacol Sci* 2022;**43**:641−52.
26. Fu W, Hu W, Yi YS, Hettinghouse A, Sun G, Bi Y, et al. TNFR2/14-3-3epsilon signaling complex instructs macrophage plasticity in inflammation and autoimmunity. *J Clin Invest* 2021;**131**:e144016.
27. Fu W, Hettinghouse A, Chen Y, Hu W, Ding X, Chen M, et al. 14-3-3 epsilon is an intracellular component of TNFR2 receptor complex and its activation protects against osteoarthritis. *Ann Rheum Dis* 2021;**80**:1615−27.
28. Schmid A, Hochberg A, Kreiss AF, Gehl J, Patz M, Thomalla M, et al. Role of progranulin in adipose tissue innate immunity. *Cytokine* 2020;**125**:154796.
29. Yabe K, Yamamoto Y, Takemura M, Hara T, Tsurumi H, Serrero G, et al. Progranulin depletion inhibits proliferation *via* the transforming growth factor beta/SMAD family member 2 signaling axis in Kasumi-1 cells. *Heliyon* 2021;**7**:e05849.
30. Fang W, Zhou T, Shi H, Yao M, Zhang D, Qian H, et al. Progranulin induces immune escape in breast cancer *via* up-regulating PD-L1 expression on tumor-associated macrophages (TAMs) and promoting $CD8^+$ T cell exclusion. *J Exp Clin Cancer Res* 2021;**40**:4.
31. Xia X, Serrero G. Identification of cell surface binding sites for PC-cell-derived growth factor, PCDGF, (epithelin/granulin precursor) on epithelial cells and fibroblasts. *Biochem Biophys Res Commun* 1998; **245**:539−43.
32. Wang C, Zhou W, Su G, Hu J, Yang P. Progranulin suppressed autoimmune uveitis and autoimmune neuroinflammation by inhibiting Th1/Th17 cells and promoting treg cells and M2 macrophages. *Neurol Neuroimmunol Neuroinflamm* 2022;**9**:e1133.
33. Wang Z, He Q, Zhang X, Ma Y, Fan F, Dong Y, et al. Innate antimicrobial and anti-chemotaxis properties of progranulin in an acute otitis media mouse model. *Front Immunol* 2018;**9**:2952.
34. Tadagavadi RK, Reeves WB. NODding off in acute kidney injury with progranulin?. *Kidney Int* 2015;**87**:873−5.
35. Gonzalez EM, Mongiat M, Slater SJ, Baffa R, Iozzo RV. A novel interaction between perlecan protein core and progranulin: potential effects on tumor growth. *J Biol Chem* 2003;**278**:38113−6.
36. Zhu J, Nathan C, Jin W, Sim D, Ashcroft GS, Wahl SM, et al. Conversion of proepithelin to epithelins: roles of SLPI and elastase in host defense and wound repair. *Cell* 2002;**111**:867−78.
37. Okura H, Yamashita S, Ohama T, Saga A, Yamamoto-Kakuta A, Hamada Y, et al. HDL/apolipoprotein A-I binds to macrophage-derived progranulin and suppresses its conversion into proinflammatory granulins. *J Atherosclerosis Thromb* 2010;**17**:568−77.
38. Sui D, Wilson JE. Interaction of insulin-like growth factor binding protein-4, Miz-1, leptin, lipocalin-type prostaglandin D synthase, and granulin precursor with the N-terminal half of type III hexokinase. *Arch Biochem Biophys* 2000;**382**:262−74.
39. Lam CY, Yip CW, Poon TC, Cheng CK, Ng EW, Wong NC, et al. Identification and characterization of tropomyosin 3 associated with granulin-epithelin precursor in human hepatocellular carcinoma. *PLoS One* 2012;**7**:e40324.
40. Almeida S, Zhou L, Gao FB. Progranulin, a glycoprotein deficient in frontotemporal dementia, is a novel substrate of several protein disulfide isomerase family proteins. *PLoS One* 2011;**6**:e26454.
41. Guo F, Lai Y, Tian Q, Lin EA, Kong L, Liu C. Granulin-epithelin precursor binds directly to ADAMTS-7 and ADAMTS-12 and inhibits their degradation of cartilage oligomeric matrix protein. *Arthritis Rheum* 2010;**62**:2023−36.
42. Tian Q, Zhao Y, Mundra JJ, Gonzalez-Gugel E, Jian J, Uddin SM, et al. Three TNFR-binding domains of PGRN act independently in inhibition of TNF-alpha binding and activity. *Front Biosci* 2014;**19**: 1176−85.
43. Miyakawa S, Sakuma H, Warude D, Asanuma S, Arimura N, Yoshihara T, et al. Anti-sortilin1 antibody up-regulates progranulin *via* Sortilin1 down-regulation. *Front Neurosci* 2020;**14**:586107.
44. Moresco EM, Beutler B. Special delivery: granulin brings CpG DNA to Toll-like receptor 9. *Immunity* 2011;**34**:453−5.
45. Tang W, Lu Y, Tian QY, Zhang Y, Guo FJ, Liu GY, et al. The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. *Science* 2011;**332**:478−84.
46. Voshtani R, Song M, Wang H, Li X, Zhang W, Tavallaie MS, et al. Progranulin promotes melanoma progression by inhibiting natural killer cell recruitment to the tumor microenvironment. *Cancer Lett* 2019;**465**:24−35.
47. Xu D, Suenaga N, Edelmann MJ, Fridman R, Muschel RJ, Kessler BM. Novel MMP-9 substrates in cancer cells revealed by a label-free quantitative proteomics approach. *Mol Cell Proteomics* 2008;**7**:2215−28.
48. Kessenbrock K, Frohlich L, Sixt M, Lammermann T, Pfister H, Bateman A, et al. Proteinase 3 and neutrophil elastase enhance inflammation in mice by inactivating antiinflammatory progranulin. *J Clin Invest* 2008;**118**:2438−47.

49. Suh HS, Choi N, Tarassishin L, Lee SC. Regulation of progranulin expression in human microglia and proteolysis of progranulin by matrix metalloproteinase-12 (MMP-12). *PLoS One* 2012;**7**:e35115.
50. Wang J, Van Damme P, Cruchaga C, Gitcho MA, Vidal JM, Seijo-Martinez M, et al. Pathogenic cysteine mutations affect progranulin function and production of mature granulins. *J Neurochem* 2010;**112**:1305−15.
51. Cunha PS, Laranjo S, Heijman J, Oliveira MM. The atrium in atrial fibrillation—a clinical review on how to manage atrial fibrotic substrates. *Front Cardiovasc Med* 2022;**9**:879984.
52. Zhao M, Wang L, Wang M, Zhou S, Lu Y, Cui H, et al. Targeting fibrosis, mechanisms and cilinical trials. *Signal Transduct Targeted Ther* 2022;**7**:206.
53. Lee HN, Na HK, Surh YJ. Resolution of inflammation as a novel chemopreventive strategy. *Semin Immunopathol* 2013;**35**:151−61.
54. Xu CG, Zhu XL, Wang W, Zhou XJ. Ursolic acid inhibits epithelial-mesenchymal transition *in vitro* and *in vivo*. *Pharm Biol* 2019;**57**:169−75.
55. Mascharak S, Talbott HE, Januszyk M, Griffin M, Chen K, Davitt MF, et al. Multi-omic analysis reveals divergent molecular events in scarring and regenerative wound healing. *Cell Stem Cell* 2022;**29**:315−27.e6.
56. Hinz B, Lagares D. Evasion of apoptosis by myofibroblasts: a hallmark of fibrotic diseases. *Nat Rev Rheumatol* 2020;**16**:11−31.
57. Zhou X, Kukar T, Rademakers R. Lysosomal dysfunction and other pathomechanisms in ftld: evidence from progranulin genetics and biology. *Adv Exp Med Biol* 2021;**1281**:219−42.
58. Wang BC, Liu H, Talwar A, Jian J. New discovery rarely runs smooth: an update on progranulin/TNFR interactions. *Protein Cell* 2015;**6**:792−803.
59. Wen Y, Lu X, Ren J, Privratsky JR, Yang B, Rudemiller NP, et al. KLF4 in macrophages attenuates TNFalpha-mediated kidney injury and fibrosis. *J Am Soc Nephrol* 2019;**30**:1925−38.
60. Therrien FJ, Agharazii M, Lebel M, Lariviere R. Neutralization of tumor necrosis factor-alpha reduces renal fibrosis and hypertension in rats with renal failure. *Am J Nephrol* 2012;**36**:151−61.
61. Osawa Y, Hoshi M, Yasuda I, Saibara T, Moriwaki H, Kozawa O. Tumor necrosis factor-alpha promotes cholestasis-induced liver fibrosis in the mouse through tissue inhibitor of metalloproteinase-1 production in hepatic stellate cells. *PLoS One* 2013;**8**:e65251.
62. Luedde T, Schwabe RF. NF-kappaB in the liver—linking injury, fibrosis and hepatocellular carcinoma. *Nat Rev Gastroenterol Hepatol* 2011;**8**:108−18.
63. Tschumperlin DJ, Lagares D. Mechano-therapeutics: targeting mechanical signaling in fibrosis and tumor stroma. *Pharmacol Ther* 2020;**212**:107575.
64. Huang G, An L, Fan M, Zhang M, Chen B, Zhu M, et al. Potential role of full-length and nonfull-length progranulin in affecting aortic valve calcification. *J Mol Cell Cardiol* 2020;**141**:93−104.
65. Sasaki T, Shimazawa M, Kanamori H, Yamada Y, Nishinaka A, Kuse Y, et al. Effects of progranulin on the pathological conditions in experimental myocardial infarction model. *Sci Rep* 2020;**10**:11842.
66. Bataller R, Brenner DA. Liver fibrosis. *J Clin Invest* 2005;**115**:209−18.
67. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol* 2011;**6**:425−56.
68. Parola M, Pinzani M. Liver fibrosis: pathophysiology, pathogenetic targets and clinical issues. *Mol Aspect Med* 2019;**65**:37−55.
69. Tantawy AA, Adly AA, Ismail EA, Salah NY, Abdel Alem S, Elsantiel HI. Serum progranulin levels in paediatric patients with Gaucher disease; relation to disease severity and liver stiffness by transient elastography. *Liver Int* 2020;**40**:3051−60.
70. Afinogenova Y, Ruan J, Yang R, Kleytman N, Pastores G, Lischuk A, et al. Aberrant progranulin, YKL-40, cathepsin D and cathepsin S in Gaucher disease. *Mol Genet Metabol* 2019;**128**:62−7.
71. Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. *Immunity* 2016;**44**:450−62.
72. Guerra RR, Trotta MR, Parra OM, Avanzo JL, Bateman A, Aloia TP, et al. Modulation of extracellular matrix by nutritional hepatotrophic factors in thioacetamide-induced liver cirrhosis in the rat. *Braz J Med Biol Res* 2009;**42**:1027−34.
73. Mathieu P, Boulanger MC. Basic mechanisms of calcific aortic valve disease. *Can J Cardiol* 2014;**30**:982−93.
74. Kraler S, Blaser MC, Aikawa E, Camici GG, Luscher TF. Calcific aortic valve disease: from molecular and cellular mechanisms to medical therapy. *Eur Heart J* 2022;**43**:683−97.
75. De Muynck L, Van Damme P. Cellular effects of progranulin in health and disease. *J Mol Neurosci* 2011;**45**:549−60.
76. Piscopo P, Rivabene R, Adduci A, Mallozzi C, Malvezzi-Campeggi L, Crestini A, et al. Hypoxia induces up-regulation of progranulin in neuroblastoma cell lines. *Neurochem Int* 2010;**57**:893−8.
77. Olczak M, Poniatowski LA, Siwinska A, Kwiatkowska M, Chutoranski D, Wierzba-Bobrowicz T. Elevated serum and urine levels of progranulin (PGRN) as a predictor of microglia activation in the early phase of traumatic brain injury: a further link with the development of neurodegenerative diseases. *Folia Neuropathol* 2021;**59**:81−90.
78. Yin F, Banerjee R, Thomas B, Zhou P, Qian L, Jia T, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. *J Exp Med* 2010;**207**:117−28.
79. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation* 2015;**131**:e29−322.
80. Lu L, Liu M, Sun R, Zheng Y, Zhang P. Myocardial infarction: symptoms and treatments. *Cell Biochem Biophys* 2015;**72**:865−7.
81. Hume RD, Chong JJH. The Cardiac injury immune response as a target for regenerative and cellular therapies. *Clin Therapeut* 2020;**42**:1923−43.
82. Jiao J, He S, Wang Y, Lu Y, Gu M, Li D, et al. Regulatory B cells improve ventricular remodeling after myocardial infarction by modulating monocyte migration. *Basic Res Cardiol* 2021;**116**:46.
83. Meloni M, Caporali A, Graiani G, Lagrasta C, Katare R, Van Linthout S, et al. Nerve growth factor promotes cardiac repair following myocardial infarction. *Circ Res* 2010;**106**:1275−84.
84. Spagnolo P, Kropski JA, Jones MG, Lee JS, Rossi G, Karampitsakos T, et al. Idiopathic pulmonary fibrosis: disease mechanisms and drug development. *Pharmacol Ther* 2021;**222**:107798.
85. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;**183**:788−824.
86. Kreuter M, Maher TM. Treatment of acute exacerbation of idiopathic pulmonary fibrosis. a call to arms. *Am J Respir Crit Care Med* 2020;**201**:1030−2.
87. Martinez FJ, Flaherty K. Pulmonary function testing in idiopathic interstitial pneumonias. *Proc Am Thorac Soc* 2006;**3**:315−21.
88. Toth NM, Muller V, Nagy T, Polivka L, Horvath P, Bohacs A, et al. Serum progranulin level might differentiate non-IPF ILD from IPF. *Int J Mol Sci* 2023;**24**:9178.
89. Zeng Z, Huang H, Zhang J, Liu Y, Zhong W, Chen W, et al. HDM induce airway epithelial cell ferroptosis and promote inflammation by activating ferritinophagy in asthma. *Faseb J* 2022;**36**:e22359.
90. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;**391**:783−800.
91. Pascoe CD, Green FHY, Elliot JG, James AL, Noble PB, Donovan GM. Airway remodelling with spatial correlations: implications for asthma pathogenesis. *Respir Physiol Neurobiol* 2020;**279**:103469.
92. Poon AH, Choy DF, Chouiali F, Ramakrishnan RK, Mahboub B, Audusseau S, et al. Increased autophagy-related 5 gene expression is associated with collagen expression in the airways of refractory asthmatics. *Front Immunol* 2017;**8**:355.

93. Li BB, Chen YL, Pang F. MicroRNA-30a targets ATG5 and attenuates airway fibrosis in asthma by suppressing autophagy. *Inflammation* 2020;**43**:44−53.
94. Redington AE. Fibrosis and airway remodelling. *Clin Exp Allergy* 2000;**30**(Suppl 1):42−5.
95. Xiao K, He W, Guan W, Hou F, Yan P, Xu J, et al. Mesenchymal stem cells reverse EMT process through blocking the activation of NF-kappaB and Hedgehog pathways in LPS-induced acute lung injury. *Cell Death Dis* 2020;**11**:863.
96. Butt Y, Kurdowska A, Allen TC. Acute lung injury: a clinical and molecular review. *Arch Pathol Lab Med* 2016;**140**:345−50.
97. Zoulikha M, Xiao Q, Boafo GF, Sallam MA, Chen Z, He W. Pulmonary delivery of siRNA against acute lung injury/acute respiratory distress syndrome. *Acta Pharm Sin B* 2022;**12**:600−20.
98. Kral JB, Kuttke M, Schrottmaier WC, Birnecker B, Warszawska J, Wernig C, et al. Sustained PI3K activation exacerbates BLM-induced lung fibrosis *via* activation of pro-inflammatory and pro-fibrotic pathways. *Sci Rep* 2016;**6**:23034.
99. Zeng Z, Xiang M, Guan H, Liu Y, Zhang H, Xia L, et al. Early fibroproliferative signs on high-resolution CT are associated with mortality in COVID-19 pneumonia patients with ARDS: a retrospective study. *Ther Adv Chronic Dis* 2021;**12**:2040622320982171.
100. Marshall RP, Bellingan G, Webb S, Puddicombe A, Goldsack N, McAnulty RJ, et al. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med* 2000;**162**:1783−8.
101. Zheng F, Wu X, Zhang J, Fu Z, Zhang Y. Sevoflurane reduces lipopolysaccharide-induced apoptosis and pulmonary fibrosis in the RAW264.7 cells and mice models to ameliorate acute lung injury by eliminating oxidative damages. *Redox Rep* 2022;**27**:139−49.
102. Lu J, Huang J, Shan M, Hu X, Guo W, Xie W, et al. Progranulin ameliorates lung inflammation in an LPS-induced acute lung injury mouse model by modulating macrophage polarization and the MAPK pathway. *Ann Clin Lab Sci* 2021;**51**:220−30.
103. Zhao YP, Wei JL, Tian QY, Liu AT, Yi YS, Einhorn TA, et al. Progranulin suppresses titanium particle induced inflammatory osteolysis by targeting TNFalpha signaling. *Sci Rep* 2016;**6**:20909.
104. Eming SA, Wynn TA, Martin P. Inflammation and metabolism in tissue repair and regeneration. *Science* 2017;**356**:1026−30.
105. Chen YQ, Wang CJ, Xie K, Lei M, Chai YS, Xu F, et al. Progranulin improves acute lung injury through regulating the differentiation of regulatory T cells and interleukin-10 immunomodulation to promote macrophage polarization. *Mediat Inflamm* 2020;**2020**:9704327.
106. Guo Z, Li Q, Han Y, Liang Y, Xu Z, Ren T. Prevention of LPS-induced acute lung injury in mice by progranulin. *Mediat Inflamm* 2012;**2012**:540794.
107. Gu Y, Han J, Jiang C, Zhang Y. Biomarkers, oxidative stress and autophagy in skin aging. *Ageing Res Rev* 2020;**59**:101036.
108. Hu MS, Borrelli MR, Lorenz HP, Longaker MT, Wan DC. Mesenchymal stromal cells and cutaneous wound healing: a comprehensive review of the background, role, and therapeutic potential. *Stem Cell Int* 2018;**2018**:6901983.
109. Talbott HE, Mascharak S, Griffin M, Wan DC, Longaker MT. Wound healing, fibroblast heterogeneity, and fibrosis. *Cell Stem Cell* 2022;**29**:1161−80.
110. He Z, Ong CH, Halper J, Bateman A. Progranulin is a mediator of the wound response. *Nat Med* 2003;**9**:225−9.
111. Yang T, Zhang X, Chen A, Xiao Y, Sun S, Yan J, et al. Progranulin promotes bleomycin-induced skin sclerosis by enhancing transforming growth factor-beta/Smad3 signaling through up-regulation of transforming growth factor-beta type I receptor. *Am J Pathol* 2019;**189**:1582−93.
112. Denton CP, Khanna D. Systemic sclerosis. *Lancet* 2017;**390**:1685−99.
113. Bukiri H, Volkmann ER. Current advances in the treatment of systemic sclerosis. *Curr Opin Pharmacol* 2022;**64**:102211.
114. Meldrum KK, Misseri R, Metcalfe P, Dinarello CA, Hile KL, Meldrum DR. TNF-alpha neutralization ameliorates obstruction-induced renal fibrosis and dysfunction. *Am J Physiol Regul Integr Comp Physiol* 2007;**292**:R1456−64.
115. Wen Y, Rudemiller NP, Zhang J, Robinette T, Lu X, Ren J, et al. TNF-alpha in T lymphocytes attenuates renal injury and fibrosis during nephrotoxic nephritis. *Am J Physiol Ren Physiol* 2020;**318**:F107−16.
116. Miyagawa T, Ichimura Y, Nakamura K, Hirabayashi M, Yamashita T, Saigusa R, et al. Progranulin overproduction due to constitutively activated c-Abl/PKC-δ/Fli1 pathway contributes to the resistance of dermal fibroblasts to the anti-fibrotic effect of tumor necrosis factor-α in localized scleroderma. *J Dermatol Sci* 2018;**92**:207−14.
117. Liu C, Li J, Shi W, Zhang L, Liu S, Lian Y, et al. Progranulin regulates inflammation and tumor. *Antiinflamm Antiallergy Agents Med Chem* 2020;**19**:88−102.
118. Tanaka A, Tsukamoto H, Mitoma H, Kiyohara C, Ueda N, Ayano M, et al. Serum progranulin levels are elevated in dermatomyositis patients with acute interstitial lung disease, predicting prognosis. *Arthritis Res Ther* 2015;**17**:27.
119. Ungurs MJ, Sinden NJ, Stockley RA. Progranulin is a substrate for neutrophil-elastase and proteinase-3 in the airway and its concentration correlates with mediators of airway inflammation in COPD. *Am J Physiol Lung Cell Mol Physiol* 2014;**306**:L80−7.
120. Jing C, Zhang X, Song Z, Zheng Y, Yin Y. Progranulin mediates proinflammatory responses in systemic lupus erythematosus: implications for the pathogenesis of systemic lupus erythematosus. *J Interferon Cytokine Res* 2020;**40**:33−42.
121. Qiu F, Song L, Ding F, Liu H, Shu Q, Yang N, et al. Expression level of the growth factor progranulin is related with development of systemic lupus erythematosus. *Diagn Pathol* 2013;**8**:88.
122. Xin P, Xu X, Deng C, Liu S, Wang Y, Zhou X, et al. The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int Immunopharm* 2020;**80**:106210.
123. Ma S, Meng Z, Chen R, Guan KL. The Hippo pathway: biology and pathophysiology. *Annu Rev Biochem* 2019;**88**:577−604.
124. Lin X, Farooqi AA. Cucurbitacin mediated regulation of deregulated oncogenic signaling cascades and non-coding RNAs in different cancers: spotlight on JAK/STAT, Wnt/β-catenin, mTOR, TRAIL-mediated pathways. *Semin Cancer Biol* 2021;**73**:302−9.
125. Sun Y, Liu WZ, Liu T, Feng X, Yang N, Zhou HF. Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. *J Recept Signal Transduct Res* 2015;**35**:600−4.
126. Salloum S, Jeyarajan AJ, Kruger AJ, Holmes JA, Shao T, Sojoodi M, et al. Fatty acids activate the transcriptional coactivator YAP1 to promote liver fibrosis *via* p38 mitogen-activated protein kinase. *Cell Mol Gastroenterol Hepatol* 2021;**12**:1297−310.
127. Li R, Guo Y, Zhang Y, Zhang X, Zhu L, Yan T. Salidroside ameliorates renal interstitial fibrosis by inhibiting the TLR4/NF-κB and MAPK signaling pathways. *Int J Mol Sci* 2019;**20**:1103.
128. Wang D, Deng B, Cheng L, Li J, Zhang J, Zhang X, et al. A novel and low-toxic peptide DR3penA alleviates pulmonary fibrosis by regulating the MAPK/miR-23b-5p/AQP5 signaling axis. *Acta Pharm Sin B* 2023;**13**:722−38.
129. Goda C, Balli D, Black M, Milewski D, Le T, Ustiyan V, et al. Loss of FOXM1 in macrophages promotes pulmonary fibrosis by activating p38 MAPK signaling pathway. *PLoS Genet* 2020;**16**:e1008692.
130. Zhang X, Fan L, Wu J, Xu H, Leung WY, Fu K, et al. Macrophage p38α promotes nutritional steatohepatitis through M1 polarization. *J Hepatol* 2019;**71**:163−74.
131. Zhang WJ, Chen SJ, Zhou SC, Wu SZ, Wang H. Inflammasomes and fibrosis. *Front Immunol* 2021;**12**:643149.
132. Liu L, Guo H, Song A, Huang J, Zhang Y, Jin S, et al. Progranulin inhibits LPS-induced macrophage M1 polarization *via* NF-κB and MAPK pathways. *BMC Immunol* 2020;**21**:32.
133. Luo K. Signaling cross talk between TGF-beta/Smad and other signaling pathways. *Cold Spring Harbor Perspect Biol* 2017;**9**:a022137.

134. Zhang J, Zhang X, Xie F, Zhang Z, van Dam H, Zhang L, et al. The regulation of TGF-β/SMAD signaling by protein deubiquitination. *Protein Cell* 2014;**5**:503−17.
135. Zhang T, He X, Caldwell L, Goru SK, Ulloa Severino L, Tolosa MF, et al. NUAK1 promotes organ fibrosis *via* YAP and TGF-β/SMAD signaling. *Sci Transl Med* 2022;**14**:eaaz4028.
136. Yang Y, Sun M, Li W, Liu C, Jiang Z, Gu P, et al. Rebalancing TGF-β/Smad7 signaling *via* compound kushen injection in hepatic stellate cells protects against liver fibrosis and hepatocarcinogenesis. *Clin Transl Med* 2021;**11**:e410.
137. Zhou Y, Pang H, Wang J, Wu H, Xu Z, Liu X, et al. Progranulin promotes the formation and development of capsules caused by silicone in Sprague−Dawley rats. *Clin Cosmet Invest Dermatol* 2022;**15**:1561−73.
138. Peng L, Wen L, Shi QF, Gao F, Huang B, Meng J, et al. Scutellarin ameliorates pulmonary fibrosis through inhibiting NF-κB/NLRP3-mediated epithelial−mesenchymal transition and inflammation. *Cell Death Dis* 2020;**11**:978.
139. Wang Y, Mou Q, Zhu Z, Zhao L, Zhu L. MALAT1 promotes liver fibrosis by sponging miR-181a and activating TLR4-NF-κB signaling. *Int J Mol Med* 2021;**48**:215.
140. Zhang M, Haughey M, Wang NY, Blease K, Kapoun AM, Couto S, et al. Targeting the Wnt signaling pathway through R-spondin 3 identifies an anti-fibrosis treatment strategy for multiple organs. *PLoS One* 2020;**15**:e0229445.
141. Zhao YP, Tian QY, Frenkel S, Liu CJ. The promotion of bone healing by progranulin, a downstream molecule of BMP-2, through interacting with TNF/TNFR signaling. *Biomaterials* 2013;**34**:6412−21.
142. Brenner D, Blaser H, Mak TW. Regulation of tumour necrosis factor signalling: live or let die. *Nat Rev Immunol* 2015;**15**:362−74.
143. Mundra JJ, Jian J, Bhagat P, Liu CJ. Progranulin inhibits expression and release of chemokines CXCL9 and CXCL10 in a TNFR1 dependent manner. *Sci Rep* 2016;**6**:21115.
144. Wei F, Zhang Y, Jian J, Mundra JJ, Tian Q, Lin J, et al. PGRN protects against colitis progression in mice in an IL-10 and TNFR2 dependent manner. *Sci Rep* 2014;**4**:7023.
145. Aggarwal BB. Editorial: balancing tumor necrosis factor receptor I and tumor necrosis factor receptor II jointly for joint inflammation. *Arthritis Rheumatol* 2014;**66**:2657−60.
146. Pradere JP, Kluwe J, De Minicis S, Jiao JJ, Gwak GY, Dapito DH, et al. Hepatic macrophages but not dendritic cells contribute to liver fibrosis by promoting the survival of activated hepatic stellate cells in mice. *Hepatology* 2013;**58**:1461−73.
147. Tarrats N, Moles A, Morales A, Garcia-Ruiz C, Fernandez-Checa JC, Mari M. Critical role of tumor necrosis factor receptor 1, but not 2, in hepatic stellate cell proliferation, extracellular matrix remodeling, and liver fibrogenesis. *Hepatology* 2011;**54**:319−27.
148. Sundaram B, Behnke K, Belancic A, Al-Salihi MA, Thabet Y, Polz R, et al. iRhom2 inhibits bile duct obstruction-induced liver fibrosis. *Sci Signal* 2019;**12**:eaax1194.
149. Penke LR, Peters-Golden M. Molecular determinants of mesenchymal cell activation in fibroproliferative diseases. *Cell Mol Life Sci* 2019;**76**:4179−201.
150. Marshall RP, Simpson JK, Lukey PT. Strategies for biomarker discovery in fibrotic disease. *Biochim Biophys Acta* 2013;**1832**:1079−87.
151. Hardy T, Zeybel M, Day CP, Dipper C, Masson S, McPherson S, et al. Plasma DNA methylation: a potential biomarker for stratification of liver fibrosis in non-alcoholic fatty liver disease. *Gut* 2017;**66**:1321−8.
152. Myllarniemi M, Tikkanen J, Hulmi JJ, Pasternack A, Sutinen E, Ronty M, et al. Upregulation of activin-B and follistatin in pulmonary fibrosis—a translational study using human biopsies and a specific inhibitor in mouse fibrosis models. *BMC Pulm Med* 2014;**14**:170.
153. Brandes F, Borrmann M, Buschmann D, Meidert AS, Reithmair M, Langkamp M, et al. Progranulin signaling in sepsis, community-acquired bacterial pneumonia and COVID-19: a comparative, observational study. *Intensive Care Med Exp* 2021;**9**:43.
154. Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, Choi DS, et al. Implication of progranulin and C1q/TNF-related protein-3 (CTRP3) on inflammation and atherosclerosis in subjects with or without metabolic syndrome. *PLoS One* 2013;**8**:e55744.
155. Wang S, Wei J, Fan Y, Ding H, Tian H, Zhou X, et al. Progranulin is positively associated with intervertebral disc degeneration by interaction with IL-10 and IL-17 through TNF pathways. *Inflammation* 2018;**41**:1852−63.
156. George J, Tsutsumi M, Tsuchishima M. MMP-13 deletion decreases profibrogenic molecules and attenuates *N*-nitrosodimethylamine-induced liver injury and fibrosis in mice. *J Cell Mol Med* 2017;**21**:3821−35.
157. Xie W, Lu Q, Wang K, Lu J, Gu X, Zhu D, et al. miR-34b-5p inhibition attenuates lung inflammation and apoptosis in an LPS-induced acute lung injury mouse model by targeting progranulin. *J Cell Physiol* 2018;**233**:6615−31.
158. Chen L, Li Q, Wang J, Jin S, Zheng H, Lin J, et al. MiR-29b-3p promotes chondrocyte apoptosis and facilitates the occurrence and development of osteoarthritis by targeting PGRN. *J Cell Mol Med* 2017;**21**:3347−59.
159. Winkle M, El-Daly SM, Fabbri M, Calin GA. Noncoding RNA therapeutics—challenges and potential solutions. *Nat Rev Drug Discov* 2021;**20**:629−51.
160. Xu L, Zhou B, Li H, Liu J, Du J, Zang W, et al. Serum levels of progranulin are closely associated with microvascular complication in type 2 diabetes. *Dis Markers* 2015;**2015**:357279.
161. Albeltagy ES, Hammour AE, Albeltagy SA. Potential value of serum progranulin as a biomarker for the presence and severity of micro vascular complications among Egyptian patients with type 2 diabetes mellitus. *J Diabetes Metab Disord* 2019;**18**:217−28.
162. Tian R, Li Y, Yao X. PGRN suppresses inflammation and promotes autophagy in keratinocytes through the Wnt/beta-catenin signaling pathway. *Inflammation* 2016;**39**:1387−94.