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The role of PD-1/PD-L1 axis in idiopathic pulmonary fibrosis: Friend or foe?

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Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease with a bleak prognosis. Mounting evidence suggests that IPF shares bio-molecular similarities with lung cancer. Given the deep understanding of the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway in cancer immunity and the successful application of immune checkpoint inhibitors (ICIs) in lung cancer, recent studies have noticed the role of the PD-1/PD-L1 axis in IPF. However, the conclusions are ambiguous, and the latent mechanisms remain unclear. In this review, we will summarize the role of the PD-1/PD-L1 axis in IPF based on current murine models and clinical studies. We found that the PD-1/PD-L1 pathway plays a more predominant profibrotic role than its immunomodulatory role in IPF by interacting with multiple cell types and pathways. Most preclinical studies also indicated that blockade of the PD-1/PD-L1 pathway could attenuate the severity of pulmonary fibrosis in mice models. This review will bring significant insights into understanding the role of the PD-1/PD-L1 pathway in IPF and identifying new therapeutic targets.

KEYWORDS

PD-1, PD-L1, idiopathic pulmonary fibrosis, profibrotic role, immunomodulatory role, therapeutic target

1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive fibrotic interstitial lung disease characterized by chronic epithelial injury and exhausted repair capacity of the alveolar compartment (1, 2). IPF occurs mainly in individuals over 60, with progressive dyspnea and irreversible pulmonary function damage being the most prevalent manifestations (1). It is estimated that the prevalence of IPF is staggering at 10-20 per 100,000 people in Western countries (3). Currently, although some newly authorized therapeutic drugs such as Pirfenidone and Nintedanib are approved for IPF treatment

(4–6), they only moderately attenuate lung function damage and could not reverse disease progression or reduce case-fatality (3). Hence, IPF is still a lethal "silent killer" and novel treatment strategies are urgently needed to alleviate its impact on patients' lives.

It is well documented that interstitial lung diseases correlate with lung cancer development. Indeed, IPF patients have a fivefold increased risk of lung cancer development compared with ordinary people (7). Besides, accumulating studies have demonstrated that pre-existing IPF hurts the prognosis of lung cancer patients regardless of anticancer modalities (8, 9). Meanwhile, numerous studies also investigated the association between IPF and lung cancer. For example, in a review, Tzouvelekis et al. summarized the common pathogenic mechanisms between IPF and lung cancer, elucidating that they share many pathogenic similarities, including genetic and epigenetic markers (7). Gaining insight into common molecular characteristics between IPF and lung cancer could provide more treatment options for these patients.

The immune homeostasis maintenance role of the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway in human diseases is well elucidated in recent studies. On the one hand, activation of the PD-1/PD-L1 signaling pathway could regulate the intensity of immune response in peripheral tissues and maintain immune tolerance to self-antigens by inhibiting T cells hyperactivation and cytokines secretion (such as IL-10 and IFN-γ) (10). However, on the other hand, in the tumor microenvironment (TME), the PD-1/PD-L1 axis is also employed by cancer cells to escape immunological surveillance (11). TCR signaling upregulates the expression of PD-1 on the T cell surface, which binds to PD-L1 on cancer cells to exert negative regulatory effects and thus impair the antitumor function of T cells (12). Therefore, inhibiting the PD-1/PD-L1 axis has been successfully used to reverse the immunosuppressive TME, thereby restoring the normal antitumor effect of T cells. Given this advantage, immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis have shown promising antitumor effects in various malignancies (11).

Existing evidence identified that aside from cancer cells, PD-L1 is also expressed on some types of immune cells (11) and stromal cells (13–16). Interestingly, recent studies have shown that PD-L1 is aberrantly expressed on human and mouse lung fibroblasts. Given the increased recognition of the similarities between lung cancer and IPF, more and more studies focused on the role of the PD-1/PD-L1 axis in IPF and investigated the potential therapeutic effect of PD-1/PD-L1 blockades on IPF. Nevertheless, the conclusions are equivocal and part of the mechanism remains unclear. In this review, we will summarize the role of the PD-1/PD-L1 axis in IPF based on clinical studies and animal models.

2 PD-1/PD-L1 axis and IPF in clinical studies

Many studies have investigated the relationship between the PD-1/PD-L1 axis and IPF in human samples, and Table 1 summarizes their main findings. Although different methods are applied to measure PD-1 or PD-L1 expression levels, most studies have identified abnormal PD-1 or PD-L1 expression in the lung tissue or peripheral blood samples from IPF patients compared with healthy individuals. Regarding the detailed detecting methods, immunohistochemistry (IHC) was most commonly used to evaluate the expression levels of PD-1 and PD-L1 in the lung samples from IPF patients (19, 22, 23, 25). For instance, Kronborg-White and colleagues detected the cellular membrane PD-L1 (mPD-L1) expression in the lung specimen from IPF patients using the DAKO PD-L1 IHC 22C3 PharmDx Kit. They found positive expression of mPD-L1 in alveolar and/or bronchiolar epithelial cells in the lung tissue of most IPF patients (19). However, in a small sample size study, Jovanovic et al. found that PD-L1 was negatively expressed in fibroblasts and myofibroblasts in lung tissue from IPF patients by IHC staining (23). Intriguingly, they observed that mPD-L1 is overexpressed on alveolar macrophages (23). One study applied IHC to detect the PD-1 expression levels in lung tissue from healthy donors, IPF patients, and lung cancer patients. The results suggested that PD-1 was significantly overexpressed in IPF and lung cancer samples compared to healthy donors (22). Further, Habiel identified a higher infiltration level of $CD8^+$ cytotoxic $CD28^{null}$ T cells in the lung tissue of IPF patients, and these T cells expressed higher levels of PD-1 (26). Several studies also used immunofluorescence (IF) (17, 27), flow cytometry (FCM) (25–27), Western blot (WB) (27), and mass cytometry (20) to explore the expression pattern of PD-1/PD-L1 axis in IPF patients. Interestingly, some studies explored the expression levels of PD-1 and PD-L1 in the peripheral blood of IPF patients and healthy individuals (18, 22, 23). Exploiting FCM, Wang et al. revealed that PD-1 and PD-L1 were overexpressed on the $CD4^+$ T cells of IPF patients' peripheral blood (18). Similarly, Ni et al. also indicated that the percentage of $PD\text{-}1^+$ lymphocytes in the peripheral blood of IPF patients was also elevated (22). However, there was no significant elevation of PD-L1 expression level in the peripheral blood leukocytes of IPF patients compared with healthy donors (22). Furthermore, there were two small sample size studies detected the soluble PD-L1 (sPD-L1) plasma concentration in IPF patients (23, 24). Jovanovic et al. applied a sandwich enzyme-linked immunosorbent assay (ELISA) kit to detect the sPD-L1 plasma concentration in 23 IPF patients who did not undergo surgical biopsy (23). They identified that the serum sPD-L1 concentration of IPF patients was significantly higher compared with healthy donors ($P<0.01$) (23). Besides, another study also observed higher level of sPD-L1 in patients with IPF compared to healthy individuals using

TABLE 1 The expression level of the PD-1/PD-L1 in human studies.

First author	PD-1/PD-L1	Patients	Sample	Method	Cell types	Expression level	Ref.
Xia Guo	PD-L1	IPF/normal	Lung	IF	/	Upregulation	(17)
Bing Wang	PD-1	IPF/normal	Peripheral blood	FCM	$CD4^+$ T cells	Upregulation	(18)
	PD-L1	IPF/normal				Upregulation	
Sissel Kronborg-White	mPD-L1	IPF/normal	Lung	IHC	Alveolar and/or bronchiolar epithelial cells	Upregulation	(19)
Lu Cui	PD-L1	IPF/normal	Lung	Mass cytometry	Fibroblasts	Upregulation	(20)
Yan Geng	PD-L1	IPF/normal	Lung	IF WB FCM	Fibroblasts	Upregulation	(21)
Ke Ni	PD-1	IPF/normal	Lung	IHC	/	Upregulation	(22)
			Peripheral blood	FCM	T lymphocytes	Upregulation	
	PD-L1		Peripheral blood	FCM	T lymphocytes	No change	
Dragana Jovanovic	mPD-L1 sPD-L1	IPF/normal	Lung	IHC	Alveolar macrophages	Upregulation	(23)
			Plasma	ELISA	/	Elevation	
M Roksandic Milenkovic	sPD-L1	IPF/normal	Plasma	ELISA	/	Elevation	(24)
Lindsay J. Celada	PD-1	IPF/normal	Lung	FCM	Th17 cells	Upregulation	(25)
				IHC	/	Upregulation	
	PD-L1			IHC	/	Upregulation	
David M. Habiel	PD-1	IPF/normal	Lung	FCM	$CD8^+$ cytotoxic $CD28^{null}$ T cells	Upregulation	(26)

IPF, idiopathic pulmonary fibrosis; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; IF, immunofluorescence; FCM, flow cytometry; mPD-L1, membrane programmed death-ligand 1; sPD-L1, soluble programmed death-ligand 1; IHC, immunohistochemistry; WB, western blot; ELISA, enzyme linked immunosorbent assay; Th17, T helper 17.

ELISA (24). Taken together, these findings suggest abnormal expression of the PD-1/PD-L1 axis in IPF patients. The PD-1/PD-L1 pathway may contribute to the occurrence and development of IPF. However, well-designed and prospective studies should be conducted to make it clear since all currently published studies are retrospectively designed and have a small sample size.

3 PD-1/PD-L1 axis and IPF in animal models

Numerous studies have investigated the expression pattern and role of the PD-1/PD-L1 axis in IPF through animal models. In this part, we will only discuss the expression disorder of the PD-1/PD-L1 axis in IPF animal models, and its roles in IPF will be summarized in the next section. Table 2 depicts current studies focusing on the expression pattern of the PD-1/PD-L1 axis in pulmonary fibrosis *via* animal models. The intratracheal administration of the cytotoxic drug bleomycin to C57BL/6 mice is known to be the most commonly used murine model to simulate the pathological process of human IPF (31). Bleomycin contributes to fibrosis by inducing alveolar epithelial injury *via* DNA cleavage, free radical formation, and deoxynucleotide oxidizing reaction (32). Even though it could not fully reflect the clinical characteristics and pathological process of human lung fibrosis, it remains crucial in preclinical studies of anti-fibrotic compounds screening and pulmonary fibrosis mechanisms investigation (31). As mentioned before, PD-L1 is not only expressed on tumor cells, but can also be detected on some types of immune cells (11) and stromal cells (13–16). Emerging evidence has identified that PD-L1 is also expressed on fibroblasts/myofibroblasts (17, 20, 21, 29) and mesenchymal stem cells (MSCs) (22) in the lung from IPF patients or murine models. In a bleomycin-induced mouse pulmonary fibrosis model, Lu and colleagues observed that the expression level of PD-L1 is significantly upregulated in the lung tissue (29). Besides, they further investigated the protein expression level of PD-L1 in primary mouse lung fibroblasts to confirm PD-L1 upregulation at the cellular level. As expected, the primary mouse lung fibroblasts expressed a higher level of PD-L1 (29). Consistent results were also reported in other studies (17, 20). As a binding molecule of PD-L1 on T cells, several studies have also detected the expression pattern of PD-1 in the bleomycin-induced pulmonary fibrosis murine model (25, 30). Wang et al. observed that PD-1 was significantly upregulated in the lung tissue of the pulmonary fibrosis mice model *via* IHC staining. Besides, they found that PD-1 was also overexpressed on $CD4^+$ T cells of peripheral blood (25, 30). Nevertheless, they failed to quantify the PD-1 expression on T cells in the lung tissue. Celada and colleagues revealed that PD-1 was positively expressed on $CD4^+$ T cells in the mice lung specimen (25). In addition, Cui et al. found that PD-1 was upregulated on $CD8^+$T cells in the lung of the bleomycin chemical injury murine model, indicating an immunosuppressive environment existed in lung fibrosis (20).

In recent years, immunodeficient mice have become increasingly useful as preclinical animal models for studying

human diseases since they are also capable of engrafting human tissues (21, 33–36). Some studies also employed the humanized murine model to investigate the expression pattern and role of the PD-1/PD-L1 axis in IPF (20–22, 26). Geng and colleagues established a humanized murine model of pulmonary fibrosis through intravenous injection of invasive IPF lung fibroblasts into NOD-SCID-IL2Rγc$^{-/-}$ (NSG) mice (21). More severe pulmonary fibrosis was observed in the lung of mice injected with invasive lung fibroblasts than in mice injected with noninvasive IPF lung fibroblasts. By performing RNA sequencing (RNA-*seq*) analysis and experimental validation, they observed that PD-L1 is significantly upregulated on the invasive fibroblasts of the pulmonary fibrosis mice model. Besides, in a humanized mouse model in which the researchers successfully engrafted primary human fibrotic lung fibroblasts in NSG mice underneath the kidney capsule, upregulation of PD-L1 was also observed on the fibroblasts in the lung (20).

Genetically modified and silica-induced lung fibrosis murine models were also applied to investigate the expression pattern and role of the PD-1/PD-L1 pathway in pulmonary fibrosis. Consistent with the PD-L1 expression level in the lung tissue of the bleomycin-driven pulmonary fibrosis murine model, Cui and colleagues observed that PD-L1 was also positively expressed in the lung of IL-6 knockout mice (20). In a silica-induced pulmonary fibrosis mice model, the researchers adopted multiple assays to evaluate the changes in the mRNA and protein expression levels of PD-1 and PD-L1 in the lung (28). They demonstrated that silica exposure resulted in altered proportions and subtypes of T and B cells in immune organs, as well as the abnormalities of PD-1, PD-L1, and CTLA-4 expressions on these cells, leading to an imbalanced systemic immune homeostasis. Taken together, PD-1 and PD-L1 are abnormally expressed on specific cell types in the lung of the pulmonary fibrosis murine model, indicating that the PD-1/PD-L1 axis is vital in lung fibrosis occurrence and disease progression.

4 The profibrotic role of the PD-1/PD-L1 axis in IPF

The immune regulatory role of the PD-1/PD-L1 axis in cancer immunity has been determined. However, its role in IPF remains controversial. The profibrotic environment of IPF is

TABLE 2 The expression level of the PD-1/PD-L1 in animal models.

First author	PD-1/ PD-L1	Animal	Exposure	Sample	Cell types	Method	Expression level	Ref.
Youliang Zhao	PD-1	6-8 weeks male C57BL/6 mice	Silica	Lung	/	WB	Upregulation	(28)
	PD-L1			Lung	/	IHC FCM PCR	Upregulation	
Ye Lu	PD-L1	4-6 weeks female C57BL/6 mice	BLM	Lung	Fibroblasts	WB IHC	Upregulation	(29)
Xia Guo	PD-L1	12-16 weeks male C57BL/6 mice	BLM	Lung	Fibroblasts	IF	Upregulation	(17)
Dong Wang	PD-1	8 weeks male C57BL/6 mice	BLM	Lung	/	IHC	Upregulation	(30)
				Peripheral blood	$CD4^+$ T cells	FCM	Upregulation	
Lu Cui	PD-L1	11-12 weeks male C57BL/6 mice	BLM	Lung	Fibroblasts	Mass cytometry	Upregulation	(20)
		JUN-induced lung fibrosis mice	JUN	Lung	Fibroblasts	IF FCM	Upregulation	
		IL-6 knock out mice and wildtype	BLM	Lung	Fibroblasts		Upregulation	
		NSG mice	Primary human fibrotic lung fibroblasts engraftation	Lung	Fibroblasts		Upregulation	
	PD-1	11-12 weeks male C57BL/6 mice	BLM	Lung	$CD8^+$T cells	Mass cytometry	Upregulation	
Yan Geng	PD-L1	6-8 weeks female NSG mice	$CD274^{high}$ and $CD274^{low}$ IPF lung normal fibroblasts injection	Lung	Fibroblasts	PCR RNA-seq	Upregulation	(21)
Ke Ni	PD-L1	4-6 weeks $Rag2^{-/-}\gamma c^{-/-}$ mice	BLM	Lung	MSC	FCM	Upregulation	(22)
Lindsay J. Celada	PD-1	7-9 weeks old C57BL/6J mice	BLM	Lung	$CD4^+$ T cells	FCM	Upregulation	(25)

IPF, idiopathic pulmonary fibrosis; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; IF, immunofluorescence; FCM, flow cytometry; IHC, immunohistochemistry; WB, western blot; PCR, polymerase chain reaction; BLM, bleomycin; NSG, NOD-SCID-IL2Rγc$^{-/-}$; RNA-seq, RNA sequencing; MSC, mesenchymal stem cell.

shaped by proliferating cells, immune cells, stromal cells, growth factors, and extracellular matrix (ECM) proteins (37). It profoundly determines the onset of fibrosis and its ultimate destiny— control or progression (37). According to currently published studies, the PD-1/PD-L1 pathway plays a double-edged sword effect in IPF. On the one hand, it can trigger lung fibrosis by interacting with multiple cell types and pathways. On the other hand, it could maintain immune homeostasis by interacting with the profibrotic component when fibrosis is initiated. Herein, we will first discuss its profibrotic role in IPF.

4.1 Th17 CD4$^+$ T cells

There are numerous studies regarding the role of T helper 17 (Th17) cells in pulmonary fibrosis (38–52), with a consensus conclusion being made that they are profibrotic and detrimental in IPF (3). A previous study also observed elevated interleukin17A (IL17A), which is the typical cytokine of Th17 cells in the bronchoalveolar lavage (BALF) of IPF patients (53). Furthermore, animal studies illustrated that IL-17A deficiency could mitigate bleomycin and radiation-induced pulmonary fibrosis (54, 55). Sarcoidosis is one of the common idiopathic lung diseases. Braun and colleagues found significantly increased PD-1$^+$ CD4$^+$ T cells during sarcoidosis progression, with Th17 cells being the most predominant cell types expressing PD1 (56). They revealed for the first time the relationship between the PD-1/PD-L1 pathway and sarcoidosis, providing insights for subsequent studies. Hence, in 2018, Celada et al. first investigated the role of PD-1$^+$ CD4$^+$ T cells in IPF and elucidated the intrinsic mechanisms (25). By conducting molecular, immunohistochemical, and FCM analyses of IPF patients and murine specimens, they identified that PD-1$^+$ CD4$^+$ T cells (mainly Th17 subsets) promote pulmonary fibrosis *via* signal transducer and activator of transcription 3 (STAT3)-mediated IL-17A and transforming growth factor–β (TGF-β) production. Interestingly, blockading the PD-1 pathway significantly decreased STAT3, IL-17A, and TGF-β expression levels on Th17 cells, subsequently reducing collagen I production from fibroblasts and attenuating lung fibrosis in a murine model. Consistent results were also verified in a later study (30).

Previous publications demonstrated that the upregulation of PD-1 on CD4$^+$ T cells shaped an immunosuppressive environment in sarcoidosis patients and was correlated with disease aggravation in these individuals (56). Nevertheless, Celada et al. indicated that except for the known immune regulation role of PD-1$^+$CD4$^+$T cells, PD-1 upregulation on CD4$^+$T cells also served a profibrotic role (25). It is well known that STAT3 could regulate PD-1 expression on T cells in various malignancies (57, 58). An increasing body of evidence recently suggests that PD-1 could also regulate STAT3 in pulmonary fibrosis and sarcoidosis (25, 30). Mechanically, STAT3 transcription activity could be negatively regulated by phosphatidylinositol 3kinase (PI3K) (59). This pathway may be correlated with PD-1 manipulation of STAT3 expression in patients with sarcoidosis since a recent study showed that PD- 1 inhibits PI3K expression in CD4$^+$ T cells in sarcoidosis (60). Therefore, the overexpressed PD-1 on Th17 cells might increase STAT3 transcription activity through indirect inhibition of PI3K (25). Besides, there is also a possibility that exosomes derived from Th17 cells could also regulate PD-1 expression (25).

Both Th17 and regulatory T cells (Tregs) have been described as exhibiting the property of plasticity (61). Tregs upregulate TGFβ has been well documented (62). Tregs can reacquire characteristics of Th17 cells when exposed to IL-6 with or without IL-1β and IL-23 (61, 63). The increased IL6 production was observed in PD-1$^+$Th17 cells from IPF patients (25). Besides, Th17 cells that secrete intracellular and membrane-bound TGF-β were also detected in IPF patients' lung samples (25). Thus, it is reasonable that increased IL6 secretion caused Tregs to differentiate into Th17 subsets, thereby increasing IL17 and TGF-β expression levels and ultimately promoting pulmonary fibrosis (Figure 1A).

4.2 Fibroblasts/Myofibroblasts

The pathological process of IPF is intimately related to chronic lung injury and thereby causes a chronic inflammatory response (64). The cytokines and inflammatory mediators produced in this process could hasten the proliferation and differentiation of fibroblasts (64). As a result, fibroblasts are transformed into myofibroblasts, which are responsible for excessive proliferation, epithelial-mesenchymal transition (EMT), ECM deposition, and ultimately resulting in collagen overproduction in the lung (65). Recently, mounting evidence revealed that PD-L1 is upregulated on human and murine lung fibroblasts (17, 20, 21, 29). Most strikingly, these studies indicated that upregulated PD-L1 on lung fibroblasts entitled an invasive phenotype to fibroblasts, thereby promoting IPF progression, and anti-PD-L1 monoclonal antibody (anti-PD-L1 mAb) could reverse this effect. Thus, PD-L1 on lung fibroblasts contributes to pulmonary fibrosis occurrence and progression and may be a novel target for IPF treatment. However, the underlying mechanisms need to be well elucidated.

4.2.1 p53 and FAK pathways

Recently, using RNA-seq analysis, Geng and colleagues revealed that PD-L1 was upregulated on invasive lung fibroblasts and was associated with the invasive phenotype of lung fibroblasts, is regulated by p53 and focal adhesion kinase (FAK) pathways, and drives lung fibrosis in a humanized pulmonary fibrosis murine model (21). *In vivo* and *in vitro* experiments have shown that the invasion ability of invasive

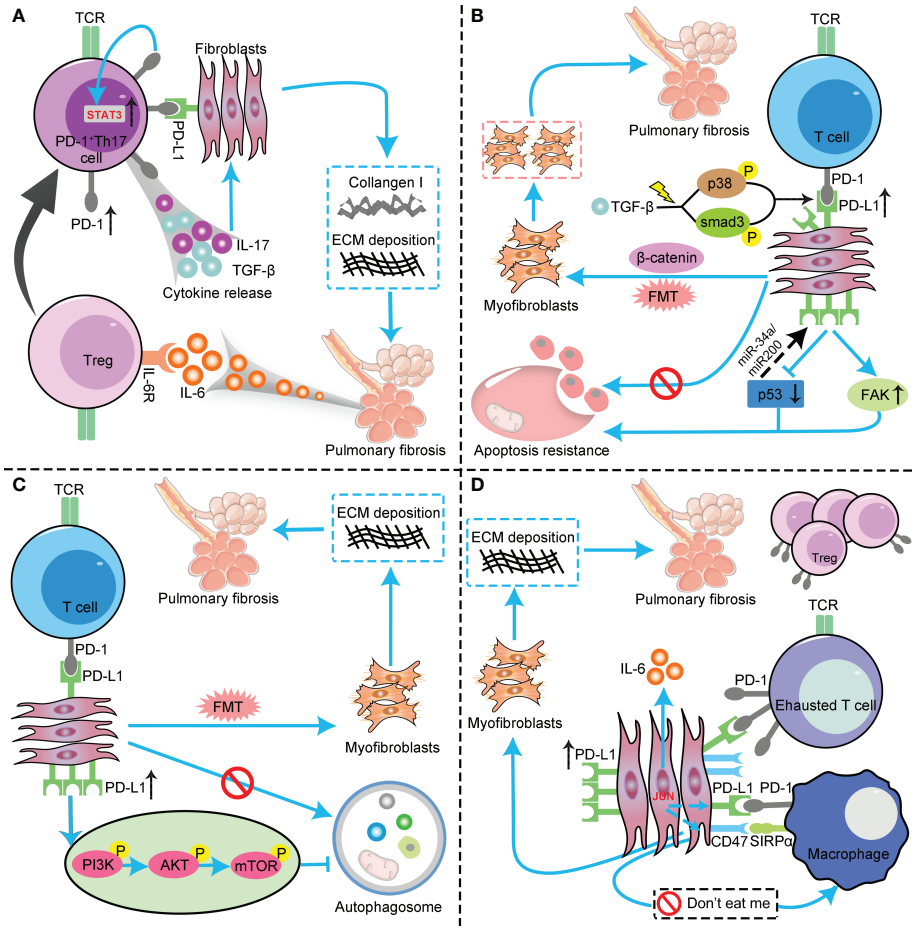

FIGURE 1
The profibrotic role of the PD-1/PD-L1 axis in IPF through interaction with multiple cell types and pathways. **(A)** PD-L1 up-regulation on Th17 T cells promotes pulmonary fibrosis through STAT3-mediated IL-17 and TGF-β production; **(B)** PD-L1 up-regulation on lung fibroblasts promotes pulmonary fibrosis *via* p53, FAK, Smad3, and β–catenin signaling pathways. On the one hand, PD-L1 up-regulation on lung fibroblasts may cause myofibroblasts to apoptosis-resistance and evasion phagocytosis *via* macrophages by inhibiting the p53 pathway and activating the FAK pathway, ultimately leading to excessive proliferation of myofibroblasts to trigger IPF. On the other hand, PD–L1 mediates lung fibroblast to myofibroblast transition (FMT) through Smad3 and β–catenin signaling pathways, thus promoting pulmonary fibrosis; **(C)** PD-L1 up-regulation on lung fibroblasts could induce myofibroblasts proliferation and ECM deposition through inhibiting autophagy, and eventually promotes pulmonary fibrosis; **(D)** PD-L1 up-regulation on lung fibroblasts promotes pulmonary fibrosis by inhibiting adaptive immunity. JUN upregulates the expression levels of PD-L1 and CD47 in fibroblasts and dormant macrophages. As a result, the above cells are converted into exhausted T cells and quiescent macrophages. In this context, myofibroblasts can evade immune clearance and resist macrophage-induced phagocytosis. In addition, JUN can also directly regulate IL-6 at the chromatin level, leading to inhibitory adaptive immune responses— primarily T cell exhaustion and upregulation of activated Tregs. PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; IPF, idiopathic pulmonary fibrosis; Th17, T helper 17; STAT3, signal transducer and activator of transcription 3; IL-17, interleukin-17; TGF-β, transforming growth factor–β; FAK, focal adhesion kinase; ECM, extracellular matrix; Tregs, regulatory T cells ; TCR, T cell receptor; FMT, fibroblast to myofibroblast transition; AKT, protein kinase B; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin.

lung fibroblasts and the severity of pulmonary fibrosis in mice could be attenuated by knocking out PD-L1 in fibroblasts and targeting PD-L1 using anti-PD-L1 mAb and FAK inhibitor.

The tumor suppressor protein p53 plays a crucial role in cell cycle arrest, apoptosis, senescence, and innate immunity (21, 66–70). Numerous studies have shown that the loss function of p53 is related to lung injury and IPF progression (21, 71–73). Besides, mounting evidence also suggests that the expression level of p53 is reduced in myofibroblasts compared to normal lung fibroblasts (74, 75). Emerging evidence indicated a negative regulatory loop between PD-L1 and p53 in invasive lung fibroblasts (21). We all know that p53 could regulate PD-L1 expression in malignancies *via* multiple members of microRNA families, such as miR-34a (76), miR-200 (77), and miRNA-320a (78). It suggests that p53 might contribute to PD-L1 regulation in lung fibroblasts. However, although molecular experiments have demonstrated that inhibition of PD-L1 could upregulate p53 expression level in IPF lung fibroblasts, the underlying

mechanisms are still not well elucidated (21). A dual effect of p53 during normal wound healing has been acknowledged (78). Initially suppressed, it reemerged after healing and reached its peak after reepithelialization (79). On the contrary, myofibroblasts emerge in response to tissue injury and undergo apoptosis at wound closure (80). So, whether p53 determines the fate of myofibroblasts and whether gaining p53 function in myofibroblasts impacts fibrotic lung restoration? Recently, Qu and colleagues revealed that p53 functional restoration sensitizes lung myofibroblasts to apoptosis, promotes the clearance of apoptotic myofibroblasts by macrophages, and eventually results in lung fibrosis resolution in the pulmonary fibrosis murine model (75). Therefore, PD-L1 on lung myofibroblasts may cause myofibroblasts to apoptosis-resistance and evasion phagocytosis *via* macrophages by inhibiting the p53 pathway, ultimately leading to excessive proliferation of myofibroblasts to trigger IPF (Figure 1B).

FAK plays a crucial role in cell survival, proliferation, migration, and adhesion. Lung epithelial cell FAK signaling determines the ultimate destiny of lung epithelial cells and inhibits lung injury and fibrosis. The pharmaceutical intervention of FAK could dramatically inhibit the proliferation of lung myofibroblasts *in vitro* and attenuate the severity of lung fibrosis in IPF murine models *in vivo*. Interestingly, a recent study showed a positive correlation between PD-L1 and FAK mRNA expression levels in PD-L1-positive triple-negative breast cancer (TNBC) (81). Taken together, PD-L1 upregulation on lung fibroblasts aggravates IPF by inhibiting the p53 pathway to allow myofibroblasts to escape macrophage-induced apoptosis. Besides, it also aggravates fibrosis by augmenting the invasive phenotype of fibroblasts by regulating the FAK pathway (Figure 1B).

4.2.2 Smad3 and β–catenin pathways

Recently, Guo and colleagues added new evidence for how PD-L1 on fibroblasts regulates the progression of pulmonary fibrosis (17). *In vitro* and *in vivo* studies demonstrated that PD-L1 is essential in the transition from fibroblast to myofibroblast, and PD-L1 acts through both Smad3-dependent and independent pathways to promote pulmonary fibrosis induced by TGF-β. Smad3 is a crucial transcription factor involved in TGF-β-induced IPF (82). Previous publications indicated that, except for the tumor cell surface, PD-L1 is also expressed in the nuclei of some malignancies (83, 84). Furthermore, treating TGF-β could upregulate PD-L1 expression levels in the nuclei of primary human lung fibroblasts. Ultimately, they identified that PD-L1 might act as a co-transactivator of TGF-β to enhance fibrotic marker gene expression and thus promote pulmonary fibrosis. A previous study elucidated that upregulation of PD-L1 could promote tumor growth and progression by activating the β-catenin pathway (85). Besides, aberrant activation of the GSK3β/β-catenin signaling pathway has been shown to correlate with IPF progression (86). Guo et al. demonstrated that β-catenin signaling was involved in the TGF-β-induced fibroblasts to myofibroblasts transition. Furthermore, they revealed that PD-L1 was involved in TGF-β-induced phosphorylation and inhibition of GSK3β at Serine 9, therefore inhibiting β-catenin degradation (17). Collectively, they identified that PD-L1 might also mediate TGF-β-induced fibroblasts to myofibroblasts transition through the β-catenin signaling (17). Therefore, PD–L1 upregulation on lung fibroblasts may promote IPF progression *via* Smad3 and β–catenin signaling pathways. Mechanically speaking, the activation of TGF-β could recruit and phosphorylate Smad3 by activating the receptor kinases. Activated Smad3 then translocates into the nucleus, which binds with other co-factors to activate fibrotic-related gene transcription. Besides, the downstream Smad3 and p38 pathways of TGF-β could upregulate the PD-L1 expression level on the lung fibroblasts. As a result, the upregulated PD-L1 binds to Smad3 and enhances its transcription activation of fibrotic-related genes. Furthermore, PD-L1 also facilitates GSK3β phosphorylation at Ser9, thus inhibiting GSK3β-dependent degradation of β-catenin. Increased β-catenin may also contribute to TGF-β-induced fibrotic-related gene expression through binding with the T cell factor (TCF) transcription factor (Figure 1B).

4.2.3 Autophagy

Autophagy is a highly conserved and pivotal catabolic process in eukaryotic cells (87, 88). It maintains the homeostasis of the intracellular environment by forming autophagosome vesicles, engulfing dysfunctional cytoplasm and organelles, and forming autolysosomes to degrade the contents of vesicles (89, 90). Autophagy disorder involves various diseases, also including IPF (91–96). Accumulating evidence revealed that autophagy activity was impaired in IPF, and inhibition of autophagy could induce myofibroblast proliferation and ECM deposition, thus leading to fibrosis (97, 98). On the contrary, pharmaceutical administration of autophagy activators could attenuate fibrotic severity (99). Interestingly, a recent study indicated that anti-PD-L1 mAb significantly inhibited the invasive ability and ECM deposition of TGF-β1-induced lung fibroblasts by downregulating the PI3K/Akt/mTOR signaling pathway to induce autophagy (29). It is well elucidated that PI3K/Akt signal pathway plays a pivotal role in regulating cell growth, proliferation, motility, metabolism, and survival (1). Most importantly, recent studies have identified that PI3K/Akt activation significantly correlated with the expression of the fibrotic-related gene alpha-smooth muscle actin (α-SMA) (100). Further, it is also suggested that the interaction between PI3K/Akt and TGF-β involves pulmonary fibrosis formation (101). The mammalian target of rapamycin (mTOR) is downstream of the PI3K/Akt signal pathway. Activation of the PI3K/Akt signaling pathway could activate

mTOR, which inhibits autophagy in myofibroblasts and ultimately promotes the formation of pulmonary fibrosis (102) (Figure 1C).

Recently, several studies have revealed subtle crosstalk between PD-L1 and autophagy in cancer cells (103, 104). In mouse melanoma and human ovarian cancer, tumor cell-intrinsic PD-L1 upregulates mTOR complex 1 signaling to inhibit autophagy and sensitizes tumor cells to clinically available autophagy inhibitors (103). Meanwhile, another study demonstrated that autophagy regulates PD-L1 expression in gastric cancer through the p62/SQSTM1-NF-κB pathway (104). *In vitro* and *in vivo* studies indicated that inhibition of autophagy upregulated the expression of PD-L1 in gastric cancer cells. Hence, there might be an interaction between PDL1 expression on myofibroblasts and autophagy in IPF, and they could be novel biomarkers and therapeutic targets in IPF diagnosis and treatment. Besides, more relevant studies are warranted to make this clear.

4.2.4 Inhibition of adaptive immunity

Adaptive immunity has been shown to orchestrate existing fibrotic responses, and various subsets of T cells are enriched in fibrotic lungs (20). In a recent review, Shenderov and colleagues demonstrated that immune dysregulation served as a driver of IPF, and several cell types were involved in this process (3). They indicated that M2 macrophages, Th17 cells, $CD8^+$T cells, and possibly Tregs promote fibrosis, while Th1 and tissue-resident memory (TRM) $CD4^+$ T cells appear to be protective (3). Besides, there is growing evidence that increased levels of activated Tregs infiltration are associated with disease progression in pulmonary fibrosis (105–107). As an essential immune checkpoint molecule, the immunosuppressive role of PD-L1 in cancer immunity is elucidated. In a recent publication, Cui et al. revealed that fibroblasts PD-L1 also elicit adaptive immunity dysfunction in the transcription factor JUN inducted pulmonary fibrosis murine model (20). By employing a single-cell protein screening approach in human and murine fibrotic lungs, JUN expression in fibroblasts increased IL-6 expression and secretion, which plays pivotal roles in adaptive and innate immunity. Besides, JUN expression in fibroblasts also upregulated the expression levels of PD-L1 and CD47, suggesting that these two immune regulatory pathways are dysregulated in IPF. Surprisingly, they identified that blockade of PD-L1, CD47, and IL-6 significantly alleviated the severity of pulmonary fibrosis not only in bleomycin-induced pulmonary fibrosis mice model but in IL-6 knockout and humanized NSG mice models. CD47 is a crucial molecule that mediates malignant cells or impaired cells to resist phagocytosis (108, 109). JUN expression in lung myofibroblasts directly controls the promoters and enhancers of CD47 and PD-L1. The direct consequence is increased expression of these immune-checkpoint proteins in fibroblasts and dormant macrophages. Therefore, these immunomodulatory pathways are hyperactivated. As a result, in the fibrotic environment, T cells and macrophages become exhausted and quiescent. In this context, myofibroblasts could evade immune clearance and resist macrophage-induced phagocytosis. In addition, JUN could also directly regulate IL-6 at the chromatin level, which results in the inhibitory adaptive immune response— chiefly T-cell exhaustion and upregulation of activated Tregs. Ultimately, pulmonary fibrosis initiates and continues to worsen in this vicious circle (Figure 1D).

5 The immune regulatory role of the PD-1/PD-L1 axis in IPF

As mentioned in the previous section, current evidence indicates that the PD-1/PD-L1 pathway has dual effects in the IPF— profibrotic and immune regulatory roles. We have discussed the profibrotic role of the PD-1/PD-L1 pathway in IPF initiating and disease progression. Here, we will review its immune regulatory role in IPF.

5.1 $CD28^{null}$ T cells

Although the exact role of the immune system in the development and progression of IPF is currently under debate, existing evidence suggests that this disease is associated with the hyperactivation of immune-related pathways (26, 110) and aberrant infiltration of some subsets of immune cells (111). Clinical investigations have demonstrated abnormal infiltration of T cells in the lung tissue of patients with IPF (22, 112). Currently, the phenotype of T cells in IPF is not well characterized (26). It has been reported that one or more co-stimulatory molecules, such as CD28 and ICOS receptors, are absent on the surface of T cells in the peripheral blood of IPF patients (113, 114). Furthermore, several studies have shown that $CD28^{null}$ T cell abundance in T cells is associated with the bleak prognosis of these individuals (113, 114).

$CD28^{null}$ T cells are antigen-experienced memory T cells present in the pathological process of various diseases (26). These cells have been observed to share similar phenotypes with $CD8^+$ cytotoxic T cells (115, 116). In a recent study, Habiel and colleagues identified that the populations of $CD8^+$ $CD28^{null}$ T cells in explanted lung cellular suspensions from IPF patients were significantly elevated than normal donor lungs (26). *In vivo* study indicated that IPF $CD28^{null}$ T cells may promote dexamethasone-resistant lung fibrosis. Besides, they observed that intravenous administration of $CD28^{null}$-enriched T cells purified from IPF lung explants could induce severe lung remodeling by targeting alveolar type II epithelial cells or by modulating surfactant protein C production by these cells in

humanized NSG mice model. Most importantly, FCM and transcriptional analysis detected higher levels of PD-1 and CTLA-4 on $CD28^{null}$ cytotoxic T cells relative to $CD28^{+}$ cytotoxic T cells. Furthermore, it showed that PD-L1 was overexpressed on structural cells in IPF lungs compared to normal lung samples. Interestingly, anti-CTLA-4 or anti-PD-1 mAb intervention significantly exuberated the severity of pulmonary fibrosis in humanized NSG mice. Therefore, IPF $CD28^{null}$ T cells may serve as a profibrotic component in lung fibrosis, but the immune checkpoint molecules CTLA-4 and PD-1 appear to limit this effect.

5.2 Mesenchymal stem cells

MSCs are multipotent stromal cells in multiple human tissues and are characterized by differentiating into mesodermal lineage cells (117, 118). Human MSCs have immunomodulation capacities and have been proven to regulate the activity and function of major immune cell populations, including T cells (22, 119). As such, human MSCs have brought light to cell therapy and tissue regeneration in many diseases, also including pulmonary fibrosis (22, 120). Recently, Ni et al. observed that lymphocytes, especially $CD8^{+}$ T cells, were overactivated at the early stage of bleomycin administration in a humanized NSG pulmonary fibrosis mice model (22). At the late stage, myofibroblasts were activated and accompanied by ECM deposition and lung reconstruction, suggesting the occurrence of IPF. Most strikingly, human MSCs intervention could attenuate the severity of pulmonary fibrosis and improve lung function *via* inhibiting bleomycin-induced T cell infiltration and pro-inflammatory cytokine production in the humanized mice model. Ultimately, they revealed that the PD-1/PD-L1 pathway mediated the alleviation of pulmonary fibrosis by human MSCs.

Human MSCs only play a constitutively immunomodulatory role with proper licensing from the inflammatory environment, especially *in vivo* (121). In the humanized pulmonary fibrosis mice model, the pro-inflammatory microenvironment during pulmonary fibrosis, characterized by high inflammatory cytokines production and high infiltration of $CD8^{+}$ T cells, could maintain the immune regulatory ability of human MSCs (122). In response, human MSCs might express immunomodulatory factors to restrict the profibrotic effect to the lung (22). As one of the most crucial inhibitory immune checkpoints expressed on T cells, once PD-1 is engaged with its ligand PD-L1, it can inhibit the PI3K/Akt pathway and the phosphorylation of ZAP70 and PKCθ and subsequently suppress T cell activation by inhibiting TCR signaling (123). As mentioned before, PD-L1 is also expressed on MSCs. Ni and colleagues demonstrated that PD-1 is significantly overexpressed on T cells in the humanized pulmonary fibrosis mice model, while PD-L1 is highly expressed on activated MSCs (22). Besides, they observed that the interaction of PD-1 and PD-L1 was involved in the immunosuppression of IFN-γ-licensed human MSCs on T cell activation *in vitro*. Hence, PD-L1 upregulated on human MSCs could engage with PD-1 on the $CD8^{+}$T cells in the profibrotic environment of the lung, subsequently delivering an inhibitory signal to the immune system to limit $CD8^{+}$T cells' hyperactivation and pro-inflammatory cytokines secretion. However, there are still some issues that deserve our attention. First, although *in vitro* study indicated that human MSCs have an anti-fibrotic role in IPF *via* the immunomodulatory role of the PD-1/PD-L1 axis, whether the PD-1/PD-L1 axis is involved in human MSC immunoregulation *in vivo* remains unclear. Second, the above study showed that human MSCs only bring therapeutic benefits at the early stage of pulmonary fibrosis. Third, the profibrotic environment is complicated and shaped by multiple cell types and factors. The author only highlighted the role of PD-L1 on human MSCs. However, the fact is that PD-L1 is also expressed on other cells in the lung of IPF patients and murine models (such as myofibroblasts). Taken together, the PD-1/PD-L1 axis participates in ameliorating pulmonary fibrosis by human MSCs in the humanized pulmonary fibrosis mice model. Considering the complexity of the fibrotic environment in IPF and the administration time of human MSCs, relevant studies should be performed to address the above problems.

6 Is it rational to target the PD-1/PD-L1 axis for IPF treatment?

Studies in individuals with IPF and mouse models suggest that the PD-1/PD-L1 axis has a more predominant profibrotic role than its immunomodulatory role in IPF. Thus, numerous preclinical studies were conducted to investigate the feasibility of treating IPF by targeting the PD-1/PD-L1 axis in mice models (20, 21, 25, 26, 28, 29). The majority of studies identified that blockade of the PD-1/PD-L1 axis using PD-L1 mAb could attenuate the severity of pulmonary fibrosis in mice models. Interestingly, as we mentioned before, IPF and lung cancer share common bio-molecular characteristics, and the PD-1/PD-L1 axis is one of the common pathways between them. Recently, one study investigated the therapeutic role of pirfenidone combined with PD-L1 blockade in the pulmonary fibrosis-lung cancer mice model (124). They observed that this combination treatment significantly facilitated the infiltration of immune cells, delayed tumor growth, and improved the prognosis of the mice. Most excitingly, combination therapy attenuated the pulmonary fibrosis of the mice. Therefore, combining anti-fibrotic agents with ICIs may bring potential benefits for IPF. Nevertheless, not all combination therapies are beneficial for relieving pulmonary fibrosis, and sometimes it could be hazardous. For instance, human MSCs contribute to immunomodulatory and are employed in IPF treatment in many preclinical studies (125). However, the combination of human MSCs and PD-1/PD-L1 inhibitors should be avoided since animal studies implicated that the administration of PD-1/PD-L1 inhibitors could reverse the anti-fibrotic role of human MSCs (22).

Although current studies indicated that the PD-1/PD-L1 axis plays a crucial role in promoting IPF, this does not imply that ICIs targeting the PD-1/PD-L1 pathway could become a new strategy for treating IPF in clinical practice. The progression of fibrosis is determined by a dynamic balance between anti-fibrotic and profibrotic mediators within a microenvironment composed of diverse cellular subtypes (20). According to current studies, PD-L1 downregulation on fibroblasts could relieve pulmonary fibrosis through multiple pathways. However, the subsequent immune response due to T cell hyperactivation might break this balance. Up to now, the role of immune cells and immune cell activation in IPF remains controversial (26). However, increased $CD8^+$ T cells in the lung and the airway of IPF patients were found to correlate with severe pulmonary function damage (126, 127). Most importantly, current clinical trials revealed that anti-PD-1/PD-L1 agents increase the risk for severe and potentially life-threatening adverse effects in cancer patients (128). Among them, the incidence of immune checkpoint inhibitor-associated pneumonitis is staggering at 3% to 10% in cancer patients (128). It is worth noting that pre-existing pulmonary fibrosis is a commonly recognized risk factor for immune checkpoint inhibitor-associated pneumonitis (129). Therefore, targeting the PD-1/PD-L1 axis to mitigate pulmonary fibrosis might be a novel insight into IPF treatment. However, there is still a long way to go before finding an optimal balance between immunity activation and PD-L1 degradation.

7 Conclusion and prospects

Despite the advances in IPF pathogenic mechanism and treatment that have been achieved in recent decades, it is still a lethal disease and needs novel therapeutic strategies to be developed. In recent years, with the discovery of bio-molecular similarities between IPF and lung cancer and the role of the PD-1/PD-L1 axis in cancer immunity, more and more studies have begun to focus on the role of the PD-1/PD-L1 axis in IPF. *In vitro* and *in vivo* studies demonstrated that the PD-1/PD-L1 axis plays a more predominant profibrotic role than its immune regulatory role in IPF by interacting with multiple cell types and pathways. Most murine studies indicated that blockade of the PD-1/PD-L1 axis could attenuate pulmonary fibrosis and improve the prognosis of pulmonary fibrosis mice. Although the pathogenesis of IPF remains largely unknown, the current findings imply that the PD-1/PD-L1 pathway might be a candidate therapeutic target for IPF treatment in the future.

Although we comprehensively summarized the role of the PD-1/PD-L1 axis in IPF for the first time and provided potential insights into this field, the following issues need to be well investigated in future studies. First, despite the majority of published studies illustrating that the PD-1/PD-L1 axis serves a profibrotic role in IPF and pharmaceutical intervention of this pathway could alleviate pulmonary fibrosis, all results were obtained based on murine studies, and the evidence from clinical studies remains lacking. Besides, it is growing recognized that cytokine IL-6 plays a crucial role in pulmonary fibrosis (130). Meanwhile, the preclinical study demonstrated that the blockade of IL-6, CD47, and PD-L1 together could ameliorate pulmonary fibrosis by increasing phagocytosis of profibrotic fibroblasts and by eliminating suppressive effects on adaptive immunity (20). As we know, a clinically tested blocking antibody against IL-6 is available, and the Food and Drug Administration (FDA) approved it for rheumatoid arthritis and acute cytokine release syndrome treatment (130, 131). Many pharmaceutical companies also developed reagents to target both CD47 and PD-L1 immune checkpoint molecules, and a growing number of studies are also conducted to evaluate the therapeutical potential of antibodies that target CD47 and PD-L1 in various malignancies (132–137). How about the effect of IL-6 antibody combination with CD47 and PD-L1 ICIs in patients with IPF or lung cancer combined with IPF? Clinical studies could be designed to answer this question. Furthermore, both PD-1 and PD-L1 exist in two forms: membrane bound (mPD-L1) and soluble (sPD-L1) forms (138, 139). Recent studies reported that sPD-1 and sPD-L1 could be detected in the plasma or serum of patients with lung cancer (138, 140, 141). Meanwhile, sPD-L1 was associated with the prognosis and treatment response in lung cancer (138, 140, 141). To our regret, there were only two small sample size studies reported the abnormal elevation of sPD-L1 in the serum of IPF patients. Hence, large scale prospective studies could be designed to detect the expression levels of sPD-L1 and sPD-1 in IPF patients and explore their prognostic significance in these patients. Second, IPF is a highly complex disease, and multiple factors participate in its occurrence and progression. For instance, it is well documented that lung macrophages and its subpopulations play pivotal roles in pulmonary fibrosis pathogenesis (142–145). Recently, Hartley and colleagues investigated PD-L1 signaling in macrophages and the effects of PD-L1 antibody treatment on tumor-associated macrophages (TAM) responses (146). They elucidated that PD-L1 delivers a constitutive negative signal to macrophages, resulting in an immune-suppressive cell phenotype. Treatment with PD-L1 antibodies reverses this phenotype and triggers macrophage-mediated antitumor activity. However, there was only one study directly reported the role of the crosstalk between the PD-1/PD-L1 pathway and lung macrophages in the pathogenesis of pulmonary fibrosis in our review (20). Hence, more relevant studies could be designed to provide more insights into this field. Besides, the contributions of diverse cell populations in the lung to pulmonary fibrosis pathogenesis are poorly understood. Recently, as an innovative technology, single-cell RNA sequencing (scRNA-*seq*) has been adopted to investigate the transcriptome heterogeneity of different cell types in many diseases (147), also including IPF (20, 145, 148–157). Taking advantage of genomics technology, especially the advances of scRNA-*seq* in recent decades, relevant studies could be designed

to confirm the role of the PD-1/PD-L1 axis in IPF, identify the involved cell populations, and clarify the underlying regulatory mechanisms. Third, we identified that the PD-1/PD-L1 axis plays a more predominant profibrotic role than its immune regulatory role in IPF. It appears that lung fibroblast/myofibroblast PD-L1 upregulation is at the core of this process. Therefore, is there a role of PD-L1 degradation in treating IPF? Until now, genetic knockout strategies, including RNA interference (RNAi), antisense oligonucleotides, and CRISPR/Cas9 are the most explored methods to decrease cellular protein levels (158). Recently, chemical knockout strategies have emerged as promising approaches because of their improved efficacy and reduced side effects (158). Among them, as a novel therapeutic strategy to target traditionally "undruggable" proteins, proteolysis targeting chimeras (PROTACs) have been widely used to deplete a protein of interest (35, 159–161). Recently, Cotton and colleagues designed an antibody-based PROTACs (AbTACs) that could induce the lysosomal degradation of PD-L1 in multiple cancer cell lines by recruiting the membrane-bound E3 ligase RNF43 (159). Nevertheless, targeted degradation of membrane PD-L1 is still challenging for PROTACs. To overcome this bottleneck, Wang et al. recently developed a novel strategy that could achieve precise degradation of the membrane protein PD-L1 in cancer cells by using enzyme-instructed self-assembly (EISA) and surface-induced self-assembly (158). Inspired by the successful applications of the targeted protein degradation technology in this field, is it feasible to use these strategies to selectively degrade PD-L1 in lung fibroblasts/myofibroblasts for IPF treatment? We think relevant preclinical studies could be designed to verify its feasibility. Furthermore, with the rapid development of material science today, especially the insightful understanding of nanomedicine, many nano-drugs and nanotechnologies are developed for disease diagnosis and treatment (162–165). In this context, many approaches and designs have been developed to target the PD-1/PD-L1 axis in tumors to improve the efficacy of immunotherapy (166). Many active agents such as antibodies, peptides, siRNAs, miRNAs, and small molecules have been routinely incorporated into various nanosystems for therapeutic, targeting, or diagnostic purposes (166, 167). Given the crucial role of the PD-1/PD-L1 pathway in IPF, will it be a feasible strategy to apply the above nanomedicines or methods for treating IPF? It will be challenging and needs a long way to go.

Author contributions

YY, WZ, and AJ conceived and designed the manuscript, provided guidance, and edited the manuscript. AJ wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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