

TGF- β 1: Gentlemanly orchestrator in idiopathic pulmonary fibrosis (Review)

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Abstract. Idiopathic pulmonary fibrosis (IPF) is a worldwide disease characterized by the chronic and irreversible decline of lung function. Currently, there is no drug to successfully treat the disease except for lung transplantation. Numerous studies have been devoted to the study of the fibrotic process of IPF and findings showed that transforming growth factor- β 1 (TGF- β 1) plays a central role in the development of IPF. TGF- β 1 promotes the fibrotic process of IPF through various signaling pathways, including the Smad, MAPK, and ERK signaling pathways. There are intersections between these signaling pathways, which provide new targets for researchers to study new drugs. In addition, TGF- β 1 can affect the fibrosis process of IPF by affecting oxidative stress, epigenetics and other aspects. Most of the processes involved in TGF- β 1 promote IPF, but TGF- β 1 can also inhibit it. This review discusses the role of TGF- β 1 in IPF.

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1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, lethal and irreversible disease, which is characterized by fibroblast proliferation and excessive deposition of extracellular matrix in the lung (1,2). It was reported that the overall survival of the patients who were diagnosed with IPF was 3-5 years (3). The

annual incidence of IPF is between 0.22 and 7.4 per 100,000 individuals in Europe and North America, but is lower in East Asia and South American (4). The incidence and prevalence of IPF increase with age and are higher in men (Tables I and II), which have been on the increase in recent years (1,5,6). Smoking, silica, and lampblack may be high risk factors for IPF (7). IPF can cause many symptoms such as dyspneal breathlessness, and chest discomfort, which does great harm to human and induces tremendous economic burden (8).

At present, many studies have focused on the pathogenesis mechanisms, which mainly include the Smad, MAPK, and ERK signaling pathways (9). Of these mechanisms TGF- β 1 is of critical significance (10). Researchers have conducted pharmacological studies on TGF- β 1 in IPF, and some new drugs targeting TGF- β 1-relevant signaling pathways have been developed. Such drugs include Nimbolide (11), Tanshinone IIA (Tan IIA) (12), methylsulfonylmethane (13) and Isoliquiritigenin (ISL) (14). However, since none of these medicines can successfully treat IPF, lung transplantation remains the primary method of treatment (15).

Both basic research and clinical research have proven that TGF- β 1 plays an important role in the pathogenesis of IPF (Table III). However, no review systematically summarizing and discussing the role of TGF- β 1 and relevant pathways in IPF has currently been published. The aim of the present review was to summarize the studies concerning the role of TGF- β 1 in the development of IPF in recent decades (16) (Fig. 1). The findings may help researchers to grasp the latest progress in the pathogenesis of IPF related to TGF- β 1 and to provide novel targets and a theoretical basis for the development of IPF clinical drugs.

2. TGF- β 1-involved pathway in IPF

Canonical TGF- β 1/Smad signaling pathway. The Smads family comprises three subfamilies, including five receptor-activated Smads (R-Smads), one common mediator Smad (Co-Smad) and two inhibitory Smads (I-Smads). Smad6 and Smad7 are the third type of Smads known as 'inhibitory Smads' or 'anti-Smads'. They are structurally different from other members of the family, and have been proven to be inhibitors of the Smad signaling pathway by disturbing the activation of R-Smads (17). Usually, TGF- β 1 activates Smads through the transmembrane receptor serine/threonine kinase, successively regulating the transcription of target genes (18).

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When TGF- β type I receptor kinase was activated by TGF- β 1 signal, R-Smads (Smad2 and Smad3) were phosphorylated; of note is that Smad3 is more sensitive to TGF- β 1 than Smad2 (19). Activated Smad2 and Smad3 form a complex, which combines with the Co-Smad (Smad4) and transfers into the nucleus to regulate the expression of target genes (20). The contribution of TGF- β 1/Smad signaling pathway to IPF is mainly dependent on the following three processes: Myofibroblast differentiation, EMT/EndMT, and fibrogenesis.

TGF- β 1-involved myofibroblast differentiation. TGF- β 1 regulates the terminal differentiation of human lung fibroblasts (HLF) and promotes the synthesis of fibroblast extracellular matrix (21). Additionally, TGF- β 1/Smad3 is the chief signaling pathway that regulates fibroblast differentiation (22,23). Transcription of α -smooth muscle actin (α -SMA), a target of myofibroblasts, was stimulated by TGF- β 1 via a Smad3-, but not Smad2, dependent manner, resulting in the increased expression of α -SMA protein in human fetal lung fibroblasts (HFLF) (22). However, Deng *et al* (24) demonstrated that although Smad3 can be activated by TGF- β 1 in HLF, the former did not affect the expression of collagen I or α -SMA. Treating fibroblasts with TGF- β 1 could increase the expression of galectin-1 (Gal-1), which phosphorylated Smad2 and enhanced the nuclear retention of Smad2, promoting myofibroblast differentiation and accelerating fibrosis (25). TGF- β 1 induced upregulation of miR-424 through the Smad3-dependent signaling pathway, which inhibited the expression of Slit2, an inhibitory protein on TGF- β 1 profibrogenic signaling. As a result, miR-424 acts as a positive feedback regulator of the TGF- β 1 signaling pathway, promoting the myofibroblast differentiation of HLF (26). Interestingly, with the treatment of miR-424 inhibitor, Smad3 phosphorylation by TGF- β 1 was reduced in HLFs, indicating miR-424 as a positive feedback regulator of TGF- β 1/Smad3 synergistically (26). Previous findings demonstrated TGF- β 1/Smad3-induced NADPH oxidase 4 (NOX4) mediated the production of H₂O₂, which was necessary for myofibroblast differentiation of lung mesenchymal cells, providing novel insight into the therapeutic targeting in IPF (27,28). In addition, TGF- β 1 was reported to accelerate lung fibrosis by stimulating the production of ROS depending on NOX-4, and the produced ROS promoted the nuclear export of histone deacetylase 4 (HDAC4) and formation of α -SMA fiber in normal human lung fibroblasts (NHLFs) (29). Furthermore, following exposure to ROS, the expression of miR-9-5p, which inhibits the transformation from mesothelial cells to myofibroblast and reduces fibrogenesis via targeting TGF- β receptor type II (TGFBR2) and NOX4, was also upregulated, demonstrating that there may be a self-limiting homeostatic mechanism (28). Moreover, TGF- β 1 can upregulate the level of Sirtuin 6 (SIRT6) protein in HFLF. The overexpression of SIRT6 inhibits TGF- β 1-induced myofibroblast differentiation by suppressing TGF- β 1/Smad2 and NF- κ B signaling pathways (30). Inhibition of TGF- β 1/Smad signal downregulated the expression of Rock1, RhoC and RhoA, demonstrating Rho kinase was a key mediator in myofibroblast differentiation induced by TGF- β 1/Smad (31).

TGF- β 1-involved EMT/EndMT. It was also reported that TGF- β 1 stimulated primary human bronchial epithelial cells (HBEC) to the status of EMT *in vitro* mainly through

Smad2/3-dependent mechanism (32). TGF- β 1 induces alveolar epithelial cells (AEC) to EMT in a time- and concentration-dependent manner through Smad2 activation, and this event induced by TGF- β 1 was not relevant to the ERK1/2 signaling pathway (33). In addition, TGF- β 1/Smad2/3 signaling mediated the EMT induced by the high mobility group box 1 (HMGB1) released from injured lung in A549 cells (34). There was a negative feedback mechanism in the TGF- β 1/Smad-involved pulmonary fibrosis. TGF- β 1 upregulates the expression of CXCR7, a seven transmembrane G protein-coupled receptor in endothelial cells, in a Smad2/3-dependent pattern. Overexpression of CXCR7 impeded endothelial-to-mesenchymal transition (EndMT) and lung fibrosis induced by TGF- β 1 through inhibition of the Jag1-Notch pathway (35). TGF- β 1 stimulation significantly upregulated the expression of Resistin-like molecule- β (RELM- β) through the Smad2/3/4 pathway, which was reported to enhance TGF- β 1-induced cell proliferation and EndMT (36). Rho kinase signal transduction activated by TGF- β 1 in EMT was a positive regulator of phosphodiesterase 4 (PDE4), which promoted EMT of AEC (37).

TGF- β 1-involved pulmonary fibrogenesis. The expression of peroxisome proliferator-activated receptor γ (PPAR γ), a negative regulator of TGF- β 1-induced fibrosis, is mainly controlled by TGF- β 1. Cells lacking Smad3 showed that the down-regulation effect of TGF- β 1 on PPAR γ was weakened, suggesting that TGF- β 1 regulates the PPAR γ in a Smad3-dependent manner (38). TGF- β 1 exerted a pro-fibrosis effect by regulating the expression of connective tissue growth factor (CTGF), which was attributed to activation of the TGF- β 1/Smad3 signaling pathway (39). Follistatin-like protein 1 (Fstl1) was a glycoprotein that plays a crucial role in promoting fibrogenesis. At the transcriptional and translational level, the expression of Fstl1 was upregulated by TGF- β 1 via the Smad3-c-Jun signaling pathway in mouse pulmonary fibroblasts, suggesting that TGF- β 1 may contribute to the IPF through a Smad3/c-Jun/Fstl1 axis (40). Huang *et al* (41) reported that TGF- β 1/Smad3 signal inhibited the expression of long noncoding RNA fetal-lethal noncoding developmental regulatory RNA (FENDRR) which can reduce fibrogenesis and inhibit the process of pulmonary fibrosis. The TGF- β 1/Smad3 signal upregulates the phosphorylation level of ERK5 and further leads to the contraction and migration of collagen gel induced by TGF- β 1 (42). miR-29, a downstream target gene of TGF- β /Smad, was capable of inhibiting numerous fibrosis-related genes upregulated by TGF- β 1 including CTGF, Smad3 and TGF- β 1 (43). However, in fibroblasts, the expression of miR-29 was negatively regulated by TGF- β 1/Smad3 signal (43-45). Similarly, Smad7, a negative regulator of TGF- β 1, is suppressed by miR-182-5p which is induced by TGF- β 1, resulting in the development of IPF (46). TGF- β 1 activates Semaphorin (SEMA) 7A and its receptors through a Smad3-independent and Smad 2/3-independent mechanism, respectively, promoting pulmonary fibrosis (47). Activating transcription factor 4 (ATF4) was a pivotal transcriptional regulator for the metabolism of amino acid (48). TGF- β 1/Smad3 signaling could increase the expression of the ATF4 through initiating the mechanistic target of rapamycin complex 1 (mTORC1) and its downstream translation initiation factor 4E binding protein 1 (4E-BP1), promoting collagen

Table I. The association between IPF incidence with age.

Studies	<50 years	50-59 years (%)	60-69 years (%)	>70 years (%)	(Refs.)
Miyake	2.9%	14.7	54.9	27.5	(117)
Kim	NA	17.1	25.7	57.2	(118)

Table II. The association between IPF incidence with sex.

Studies	Male (%)	Female (%)	(Refs.)
Baumgartner	60	40	(119)
Miyake	90.2	9.8	(117)
García-Sancho Figueroa	73.2	26.8	(120)
Awadalla	47.3	42.7	(121)
Kim	75.7	24.3	(118)
Koo	70.5	29.5	(122)
Paolucci	72.5	27.5	(123)

biosynthesis (49). This is one of the key pathways through which TGF- β 1 stimulates collagen synthesis and IPF in HLF (50) (Fig. 2).

PI3K-relevant signaling pathway. A great number of studies indicated that phosphatidylinositol-3-kinase (PI3K) was involved in the pathomechanism of pulmonary fibrosis (51-54). It was also revealed that PI3K may play an important role in TGF- β 1-relevant IPF.

As mentioned previously, CTGF is a functional intermediate product between TGF- β 1 and ECM protein. CTGF derived from epithelial cells can activate fibroblasts and further accelerate the fibrosis process in an autocrine manner (55). It was reported that TGF- β 1 may induce the EMT and synthesis of ECM in lung epithelial cells through the TGF- β 1/PI3K/CTGF signaling pathway (56). Treating human lung epithelial cells with PI3K inhibitor can, not only inhibit the synthesis of CTGF and type I collagen, but also reverse the EMT and fibrogenesis stimulated by TGF- β 1. TGF- β 1 activated PI3K and protein kinase B (PKB)/AKT via SEMA 7A-dependent mechanisms. SEMA 7A plays a central role in the PI3K/PKB/AKT pathway, which contributes to TGF- β 1-induced fibrosis and remodeling (47). TGF- β 1 activated the PI3K/Jun-NH2-terminal kinase (JNK)/AKT and AP-1 synergistically to induce tissue factor (TF) expression in HLF, promoting the process of IPF (57) (Fig. 3).

MAPK-relevant signaling pathway. Mitogen-activated protein kinase (MAPK), mainly consisting of three distinctive cascades, the JNK, p38 and ERK pathways, is a well-known and crucial signaling pathway in multiple diseases (58-61). In the past decades, the role of MAPK cascade in the TGF- β 1-relevant IPF has been gradually elucidated.

JNK pathway. Coagulation factor XII (FXII) is a serine protease relevant to fibrinolysis, it was demonstrated that the production of FXII induced by TGF- β 1 in HLF was mediated with JNK/Smad3 signaling pathways (62). With the stimulation

of TGF- β 1, the expression of phosphorylated p38, phosphorylated JNK, and interstitial phenotypic markers including desmin, vimentin and α -SMA were significantly increased (63). TGF- β 1-induced primary lung fibroblasts immediately release extracellular fibroblast growth factor-2 (FGF-2), p38 MAPK and JNK phosphorylation. As a result, lung fibroblasts proliferated in response to TGF- β 1 indirectly (64). TGF- β 1 can induce the phenotype of HLF to myofibroblasts in a dose- and time-dependent manner. Although the activity and phosphorylation of c-JNK, p38 MAPK, and ERK increased in response to TGF- β 1, phenotypic modulation from HLF to myofibroblast was only regulated by c-JNK, suggesting that TGF- β 1 induced HLF to myofibroblast via a c-JNK-mediated pathway (65). TGF- β 1 was also reported to contribute to pulmonary fibrosis through down-regulation of the expression of vascular endothelial growth factor-D (VEGF-D) in HLF via the JNK signaling pathway, providing a speculative mechanism in the tissue remodeling of IPF (66). Notably, this protective effect of TGF- β 1 on fibroblasts was independent on endothelin (ET)-1, which also endows fibroblast resistance to apoptosis. TGF- β 1 could induce the deposition of extracellular matrix derived from tracheal basal cells, and the latter promoted EMT via a c-JNK1 involved pathway, which impairs the homeostasis of epithelial cell and the occurrence of IPF (67).

p38 signaling pathway. Notably, TGF- β 1/MAPK signal not only contributed to the phenotypic modulation to myofibroblast, but also showed a protective effect on myofibroblasts. For example, TGF- β 1 attenuates the apoptosis of fibroblast by inducing the production of a p38-dependent growth factor, which activates PI3K/AKT successively (68). It is noteworthy that activation of p38 MAPK induced by TGF β 1 was able to induce α -SMA but not collagen I in HLF (24). Tissue inhibitors of matrix metalloproteinases 3 (TIMP3), an effective angiogenesis inhibitor blocking the binding of VEGF to VEGF receptor 2, may be an important mediator of TGF- β 1-mediated IPF (69). As TGF- β 1 strongly upregulates the expression of TIMP3 in HLF, this process is relevant to p38 but not ERK pathway. The p38-mediated loss of epithelial complement inhibitory protein (CIP) caused by TGF- β 1 led to the expansion of IPF epithelial damage, which in turn led to complement activation, further downregulated CIPs and induced the expression of TGF- β 1 in feedback (70).

ERK signaling pathway. TGF- β 1 regulates the autocrine of basic fibroblast growth factor (bFGF) in HLF, which activated the expression of ERK pathway and the induction of activator protein-1 (AP-1), accelerating pulmonary fibrogenesis (71). It was also reported that TGF- β 1 induces GSK-3 β inhibition and nuclear β -catenin translocation in HLF through ERK1/2 activation, which successively led to the production of γ -SMA and collagen (72). CD44v6 regulates the synthesis of

Table III. Targeting molecules and signaling pathways initiated by TGF- β 1 in IPF.

Author, year	Cell/tissue type	Target gene	Potential signaling pathways	Biological effect	(Refs.)
Canonical TGF- β 1/Smad signaling pathway					
Gu <i>et al.</i> , 2007	Human fetal lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/ α -SMA	Promoting myofibroblast differentiation	(22)
Ramirez <i>et al.</i> , 2012	Murine lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/PPAR γ	Promoting pulmonary fibrogenesis	(38)
Li <i>et al.</i> , 2016	Human embryonic lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/CTGF	Promoting pulmonary fibrogenesis	(39)
Huang <i>et al.</i> , 2020	Human lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/miR-424/Slit2	Promoting myofibroblast differentiation	(26)
Zheng <i>et al.</i> , 2017	Mouse pulmonary fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/c-Jun/ Fstl	Promoting fibrogenesis	(40)
Hecker <i>et al.</i> , 2009	Human fetal lung mesenchymal cells	<i>Smad3</i>	TGF- β 1/Smad3/NOX4/H2O2	Promoting myofibroblast differentiation	(27)
Guo <i>et al.</i> , 2017	Normal human lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/NOX4/ROS	Promoting myofibroblast differentiation	(29)
Fierro-Fernández <i>et al.</i> , 2015	Human fetal lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/NOX4/ROS/ miR-9-5p/NOX4	Attenuating myofibroblast differentiation	(28)
Huang <i>et al.</i> , 2020	Mouse lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/FENDDR	Promoting pulmonary fibrogenesis	(41)
Kadoya <i>et al.</i> , 2019	Human lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/ERK5	Promoting pulmonary fibrogenesis	(42)
Cushing <i>et al.</i> , 2011;	Human fetal lung fibroblast	<i>Smad3</i>	TGF- β 1/Smad3/miR-29	Promoting pulmonary fibrogenesis	(43)
Yang <i>et al.</i> , 2013;					(44)
Xiao <i>et al.</i> , 2012					(45)
Kang <i>et al.</i> , 2007	Murine lung	<i>Smad3</i>	TGF- β 1/Smad3/SEMA 7A	Promoting pulmonary fibrogenesis	(47)
Selvarajah <i>et al.</i> , 2019	Primary human lung fibroblasts	<i>Smad3</i>	TGF- β 1/Smad3/mTORC1/4E- BP1/ATF4	Promoting collagen biosynthesis	(49)
Jiang <i>et al.</i> , 2018	Human endothelial cells	<i>Smad2/3/4</i>	TGF- β 1/Smad2/3/4/RELM- β	Attenuating EndMT	(36)
Câmara and Jarai, 2010	Human bronchial epithelial cells	<i>Smad2/3</i>	TGF- β 1/Smad2/3	Promoting EMT	(32)
Li <i>et al.</i> , 2015	Human alveolar epithelial cell (A549)	<i>Smad2/3</i>	TGF- β 1/Smad2/3	Promoting EMT	(34)
Guan and Zhou, 2017	Mice lung endothelial cells	<i>Smad2/3</i>	TGF- β 1/Smad2/3/CXCR7/TGF- β 1/lag1-Notch	Attenuating EndMT	(35)
Chen <i>et al.</i> , 2020	Human embryonic lung fibroblasts	<i>Smad2/3</i>	TGF- β 1/Smad2/3/miR-182-5p/ Smad7	Promoting pulmonary fibrogenesis	(46)
Kasai <i>et al.</i> , 2005	Human alveolar epithelial cell (A549)	<i>Smad2</i>	TGF- β 1/Smad2	Promoting EMT	(33)
Ji <i>et al.</i> , 2014	Human embryonic lung fibroblasts	<i>Smad2</i>	TGF- β 1/Smad2/RhoA	Promoting myofibroblast differentiation	(31)
PI3K relevant signaling pathway					
Shi <i>et al.</i> , 2016	Human alveolar epithelial cells	<i>PI3K</i>	TGF- β 1/PI3K/CTGF	Promoting EMT and fibrogenesis	(56)
Wygrecka <i>et al.</i> , 2012	Human lung fibroblasts	<i>PI3K</i>	TGF- β 1/PI3K/JNK/AKT/TF	Promoting pulmonary fibrogenesis	(57)
MAPK relevant signaling pathway					
JNK pathway					
Chen <i>et al.</i> , 2013	Human alveolar epithelial	JNK-p38	TGF- β 1/JNK-p38	Promoting EMT	(63)
Khalil <i>et al.</i> , 2005					(64)
Jablonska <i>et al.</i> , 2010	Human lung fibroblasts	JNK	TGF- β 1/JNK/Smad3/FXII	Promoting pulmonary fibrogenesis	(62)

Table III. Continued.

Author, year	Cell/tissue type	Target gene	Potential signaling pathways	Biological effect	(Refs.)
MAPK relevant signaling pathway					
Hashimoto <i>et al</i> , 2001	Human lung fibroblasts	<i>JNK</i>	TGF- β 1/ <i>JNK</i>	Promoting myofibroblast differentiation	(65)
Cui <i>et al</i> , 2014	Human lung fibroblasts	<i>JNK</i>	TGF- β 1/ <i>JNK</i> /VEGF-D	Promoting pulmonary fibrogenesis	(66)
p38 signaling pathway					
Kulasekaran <i>et al</i> , 2009	Human lung fibroblasts	<i>p38</i>	TGF- β 1/ <i>p38</i> /PI3K/ <i>AKT</i>	Attenuates apoptosis	(68)
Deng <i>et al</i> , 2015	Human lung fibroblasts	<i>p38</i>	TGF- β 1/ <i>p38</i> / α -SMA	Promoting pulmonary fibrogenesis	(24)
García-Alvarez <i>et al</i> , 2006	Human lung fibroblasts	<i>p38</i>	TGF- β 1/ <i>p38</i> /TIMP3/VEGF	Promoting pulmonary fibrogenesis	(69)
Gu <i>et al</i> , 2014	Human small airway epithelial cells	<i>p38</i>	TGF- β 1/ <i>p38</i> /CIPs/complement	Promoting epithelial injury in IPF	(70)
ERK signaling pathway					
Caraci <i>et al</i> , 2008	Human lung fibroblasts	<i>ERK1/2</i>	TGF- β 1/ <i>ERK1/2</i> /GSK-3 β / β -catenin	Promoting myofibroblast differentiation	(72)
Ghatak <i>et al</i> , 2017	Human lung fibroblasts	<i>ERK</i>	TGF β 1/ <i>ERK</i> / <i>EGR1-AP-1</i> /CD44v6	Promoting myofibroblast differentiation	(73)
Wnt/β-catenin relevant signaling pathway					
Lu <i>et al</i> , 2019	Lung resident mesenchymal stem cells	β -catenin	TGF- β 1/ β -catenin	Promoting myofibroblast differentiation	(79)
Zhou <i>et al</i> , 2012	Human alveolar epithelial cell	β -catenin	TGF- β 1/ β -catenin/CBP	Promoting EMT	(83)
Wang <i>et al</i> , 2015	Human embryonic lung fibroblasts	<i>Wnt3a</i> / β -catenin	TGF- β 1/ <i>Wnt3a</i> / β -catenin/miR-29	Promoting cell proliferation	(84)
Other signaling pathway					
Arsalane <i>et al</i> , 1997	Human alveolar epithelial cell (A549)	γ -GCS	TGF- β / γ -GCS/ROS	Promoting pulmonary fibrogenesis	(101)
Jardine <i>et al</i> , 2002					(102)
Boustani <i>et al</i> , 1997					(103)
Yu <i>et al</i> , 2020	Mouse alveolar epithelial cells	<i>TRB3</i>	TGF- β / <i>TRB3</i> /Wnt/ β -catenin	Promoting EMT	(97)
Yamasaki <i>et al</i> , 2008	Murine lung epithelial cells	<i>TNF-α</i>	TGF- β / <i>TNF-α</i> /p21	Attenuating fibrosis, and alveolar remodeling	(88)
Zhang <i>et al</i> , 2019	Human fetal lung fibroblasts	<i>SIRT6</i>	TGF- β 1/ <i>SIRT6</i> /TGF- β 1/ <i>Smad2</i>	Attenuating myofibroblast differentiation	(30)
Kang <i>et al</i> , 2007	Murine lung	<i>SEMA 7A</i>	TGF- β 1/ <i>SEMA 7A</i> /PI3K/ <i>PKB</i> / <i>AKT</i>	Promoting pulmonary fibrogenesis	(47)
Kolosonek <i>et al</i> , 2009	Human alveolar epithelial cells	<i>Rho</i>	TGF- β 1/ <i>Rho</i> /PDE4	Promoting EMT	(37)
Wei <i>et al</i> , 2019	Human lung fibroblasts	<i>miR-133a</i>	TGF- β 1/ <i>miR-133a</i> /CTGF-Coll1a1	Attenuating myofibroblast differentiation and pulmonary fibrosis	(87)
Lu <i>et al</i> , 2002	Alveolar interstitial cells	<i>Integrin α8β1</i>	TGF- β 1-LAPT/ <i>Integrin α8β1</i> / <i>ERK</i>	Promoting cell adhesion	(75)
Lim <i>et al</i> , 2014	Fibroblast cell lines	<i>Gal-1</i>	TGF- β 1/ <i>Gal-1</i> / <i>Smad2</i>	Promoting myofibroblast differentiation	(25)

Table III. Continued.

Author, year	Cell/tissue type	Target gene	Potential signaling pathways	Biological effect	(Refs.)
Xiao <i>et al.</i> , 2012	Human alveolar epithelial cell	<i>FGF-2</i>	TGF β 1/FGF-2/ERK1/2	Promoting fibroblast proliferation and fibrogenesis	(74)
Noskovičová <i>et al.</i> , 2018	Human lung fibroblasts	<i>CDCP1</i>	TGF- β 1/CDCP1	Attenuating myofibroblast differentiation	(85)
Hagimoto <i>et al.</i> , 2002	Human bronchiolar epithelial cells	<i>caspase-3</i>	TGF- β /caspase-3/Fas	Promoting cell apoptosis and lung injury	(96)
Finlay <i>et al.</i> , 2000	Human lung fibroblasts	<i>bFGF</i>	TGF- β 1/bFGF/ERK-API	Promoting pulmonary fibrogenesis	(71)
Uhal <i>et al.</i> , 2007	Primary human lung fibroblasts	<i>ANG</i>	TGF- β 1/ANG	Promoting development of IPF	(86)
Zhou <i>et al.</i> , 2012	Human alveolar epithelial cell (A549)	<i>Amphiregulin</i>	TGF- β 1/amphiregulin/EGFR/TGF- β 1	Promoting pulmonary fibrosis	(91)

COL1 and α -SMA in fibroblasts, and it is a potential activation target of TGF- β 1 in lung fibroblasts (73). The induction of CD44v6 by TGF- β 1 not only depends on ERK-induced early growth response-1 (EGR1) signaling, but also requires abundant AP-1 involvement, suggesting that there is a TGF β 1-ERK-EGR1/AP-1-CD44v6 axis (73). TGF- β 1 can induce the expression of FGF-2 and its release from type II AEC. In addition, the FGF-2 signaling is responsible for the fibroblast proliferation and fibrotic activation through the ERK pathway (74). TGF- β 1 binds non-covalently to the latency-related peptide (LAP) to form a complex. Consequently, the interaction of integrin α 8 β 1 and LAP-TGF- β 1 complex induces FAK and ERK phosphorylation and promotes cell proliferation (75) (Fig. 4).

Wnt/ β -catenin relevant signaling pathway. The Wnt/ β -catenin pathway is the canonical Wnt signaling pathway, also known as the ' β -catenin-dependent' Wnt pathway. Wnt/ β -catenin has been proven to play an important role in body development and growth, tumor, cardiovascular disease, musculoskeletal diseases, and also respiratory disease (76-78). In normal conditions, the glycogen synthase kinase-3 β (GSK-3 β) combines with the β -catenin, axis inhibition protein (Axin) and adenomatous polyposis coli (APC) to form a complex. When the Wnt/ β -catenin was activated, the complex degraded, while β -catenin was not degraded and translocated into the nucleus (77).

Increasing evidence suggested that Wnt/ β -catenin was involved in the TGF- β 1-relevant IPF. TGF- β 1 initiated the Wnt/ β -catenin cascade via upregulating β -catenin and GSK-3 β , promoting the fibrotic differentiation of lung resident mesenchymal stem cells (LR-MSCs) (79). In addition, it was found that, Wnt/ β -catenin was required for the initiation of Smad2/3 induced by TGF- β 1, suggesting that there may be a crosstalk between the two mechanisms in the myofibroblast differentiation (80). GSK-3 signaling decreases the phosphorylation of cAMP-response element binding protein (CREB) and attenuates its antagonism function on TGF- β /Smad signaling, promoting the myofibroblast differentiation in HLF (81). However, Liu *et al* suggested that in the transition of human normal skin fibroblast to myofibroblast induced by TGF- β 1, Wnt/ β -catenin played the role of negative regulator (82). TGF- β 1 was capable of inducing the accumulation of β -catenin in the nuclear, facilitating EMT in a CREB-binding protein (CBP)-depending pattern in AEC (83). This revealed a potential cascade of TGF- β 1/ β -catenin/CBP. miR-29 negatively regulated the proliferation of IMR-90 cells induced by TGF- β 1, but TGF- β 1 inhibited the expression of all three members of the miR-29 family via Wnt3a/ β -catenin pathway (84) (Fig. 5).

Feedback regulation mechanism. Feedback regulation is a crucial aspect in molecule cascades. Both positive and negative feedback are revealed in TGF- β 1-involved pathway in IPF.

TGF- β 1 strongly downregulated Cub domain-containing protein 1 (CDCP1), which promoted myofibroblast differentiation through inhibition of the potential negative feedback effect of CDCP1 expression on TGF- β 1 stimulation (85). Similarly, TGF- β 1 activated the autocrine mechanism of angiotensin (ANG) and angiotensinogen (AGT) peptide, which upregulated the expression of TGF- β 1 to form an 'autocrine loop', promoting the development of IPF (86). miR-133a was

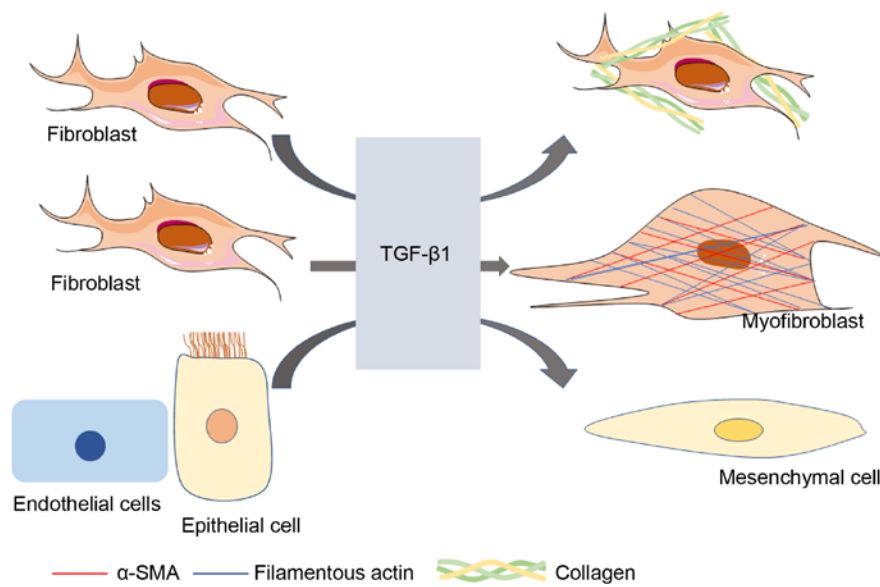


Figure 1. Role of TGF-β1 in Idiopathic pulmonary fibrosis. TGF-β1 plays a crucial role in idiopathic pulmonary fibrosis. It promotes the transformation of fibroblast into myfibroblast, epithelial cell into mesenchymal cell, and it promotes the production of collagen, filamentous actin and α-SMA.

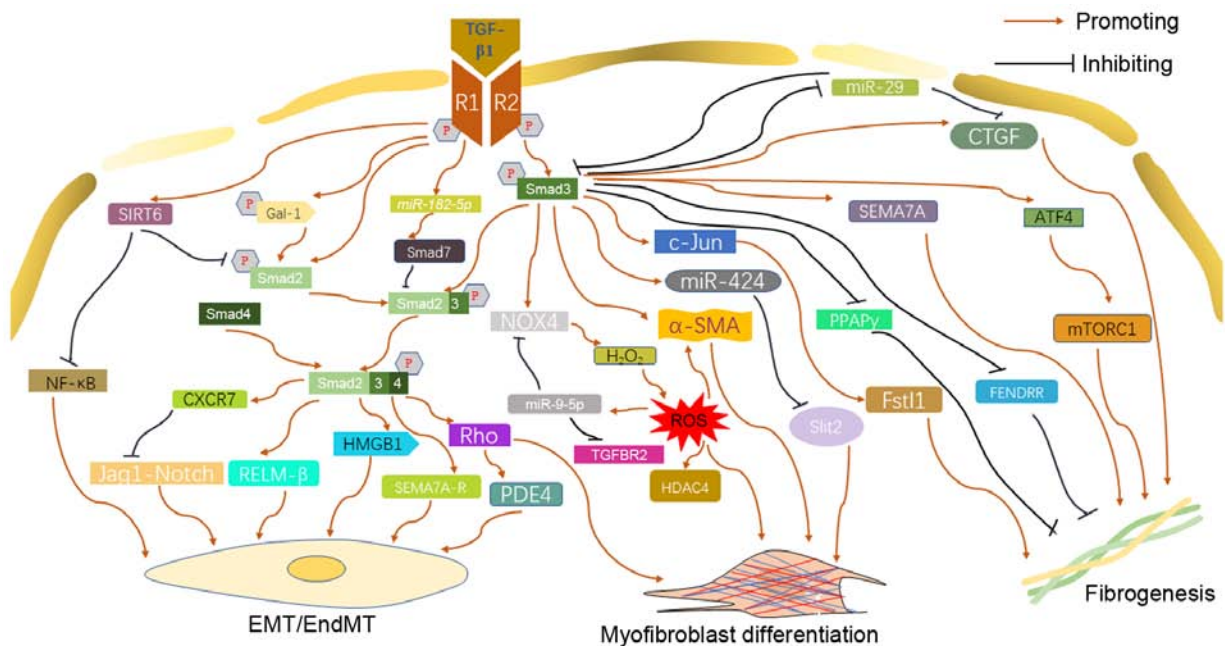


Figure 2. TGF-β1/Smad signaling pathway. TGF-β1 influences the three key steps of idiopathic pulmonary fibrosis: EMT/EndMT, myfibroblast differentiation, and fibrogenesis by participating in Smad-related signaling pathways. TGF-β1 activates HMGB1, RELM-β, Slit2, and Fst11 by combining with Smad2 and Smad3. However, this combination has both a positive promotion role, as well as an inhibitory role. In addition, Smad7 plays a negative regulatory role in these mechanisms. These are not three independent pathways, there are places where they cross each other.

reported to attenuate the differentiation of myfibroblasts by targeting many components of the TGF-β1 pro-fibrosis pathway, including α-SMA, CTGF and collagen. There seems to be a negative-feedback loop in the TGF-β1 pro-fibrogenesis pathway, because TGF-β1 upregulates the expression of miR-133a (87). Additionally, p21, a key regulator of apoptosis induced by TGF-β1 through tumor necrosis factor-α (TNF-α) signaling pathway, negatively regulates TNF-α expression induced by TGF-β1, participating in the fibrosis and alveolar remodeling induced by TGF-β1 (88). TNF-α could enhance the process of EMT induced by TGF-β1 in A549 cells through

combination with TGF-β1 (89). However, TGF-β1 was also reported to inhibit the release of TNF-α from mast cells (90). TGF-β1 stimulates the EGFR ligand, amphiregulin, which regulates the classical and non-classical TGF-β1 signaling pathway through the activation of EGFR (91) (Fig. 6).

Other signaling pathways. Besides the signaling pathways discussed above, other molecules cascades were also revealed to be involved in the TGF-β1 relevant mechanisms of IPF.

The proliferation of fibroblasts is mainly mediated by platelet-derived growth factor (PDGF) isoforms, whose activity

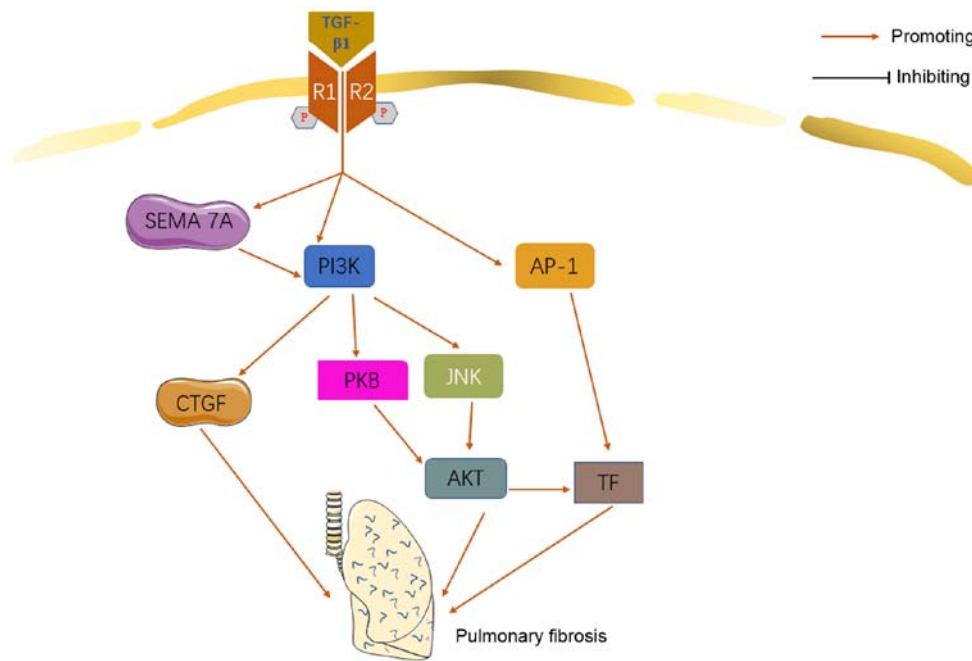


Figure 3. PI3K signaling pathway. TGF- β 1 activates the PKB, JNK, and AKT signaling pathways through the PI3K signaling pathway, and also activates AP-1 to promote the production of tissue factor, which ultimately lead to the formation of idiopathic pulmonary fibrosis.

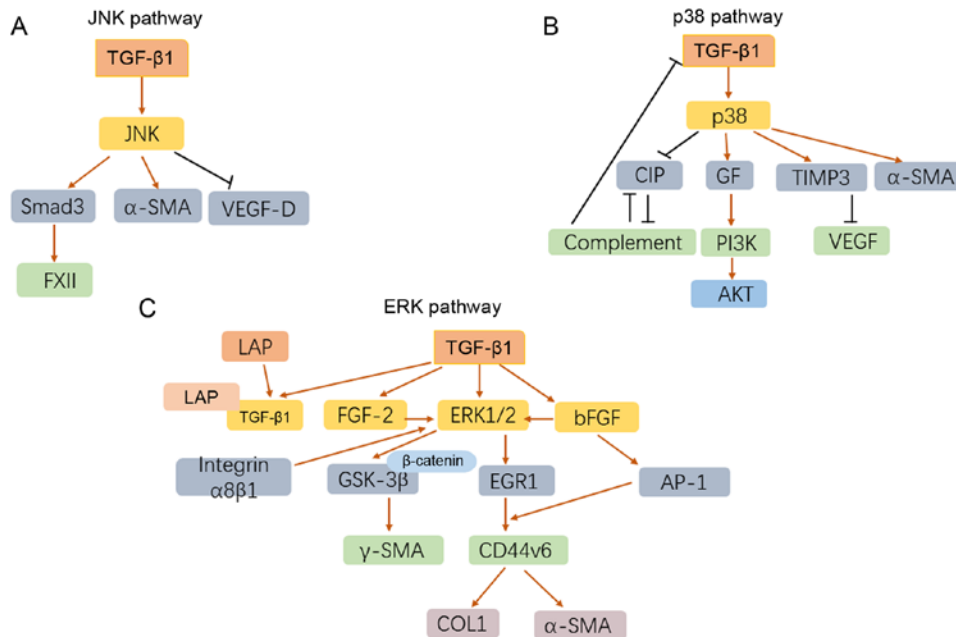


Figure 4. MAPK signaling pathway. The JNK, P38 and ERK pathways constitute the canonical MAPK signaling pathway. The downstream of JNK signaling pathway has Smad3, α -SMA, and VEGF-D, which promote the former two and inhibit VEGF-D. Downstream of p38 are CIP, GF, TIMP3 and α -SMA. P38 inhibits CIP, CIP inhibits complement, and complement in turn inhibits TGF- β 1. The ERK pathway is a very complex signaling pathway, in which there are many molecules, including FGF-2, AP-1, and γ -SMA. The final effect of these pathways is to promote the production of α -SMA and COL1, leading to idiopathic pulmonary fibrosis.

was potentially regulated by TGF- β 1 (92). It was reported that TGF- β 1 downregulated the expression of PDGF- α receptor (PDGF-R α) transcript. However, TGF- β 1 facilitated the transcription of PDGF-R α in HLF, suggesting that TGF- β 1 may contribute to IPF through a PDGF-R α -involved complex network (92). It was reported that the IL-11 secreted by fibroblasts in the lungs of patients with IPF was significantly upregulated (93), and results demonstrated that TGF- β 1

significantly increases IL-11 receptor expression in mouse fibroblasts (94), suggesting that IL-11 may be an important mediator of TGF- β 1 involved IPF. Fas pathway-mediated apoptosis of lung epithelial cells is involved in the pathogenesis of pulmonary fibrosis (95). In lung tissues of patients with IPF, Fas- and FasL-induced apoptosis occurs in AEC and infiltrated inflammatory cells. TGF- β 1 enhances the Fas-mediated pulmonary epithelial cell apoptosis through

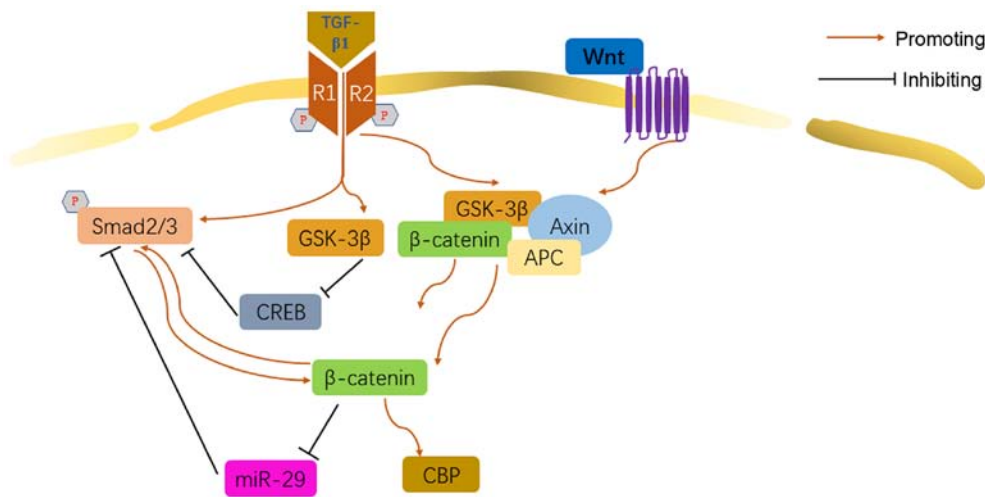


Figure 5. Wnt/ β signaling pathway. The Wnt/ β signaling pathway plays an important role in idiopathic fibrosis promoted by TGF- β 1. After TGF- β 1 activates Wnt/ β -catenin, it degrades the complex formed by GSK-3 β and β -catenin, axin and APC, then β -catenin is released. Additionally, TGF- β 1 promotes the production of β -catenin by combining with Smad2/3, which ultimately leads to an increase in the production of CBP.

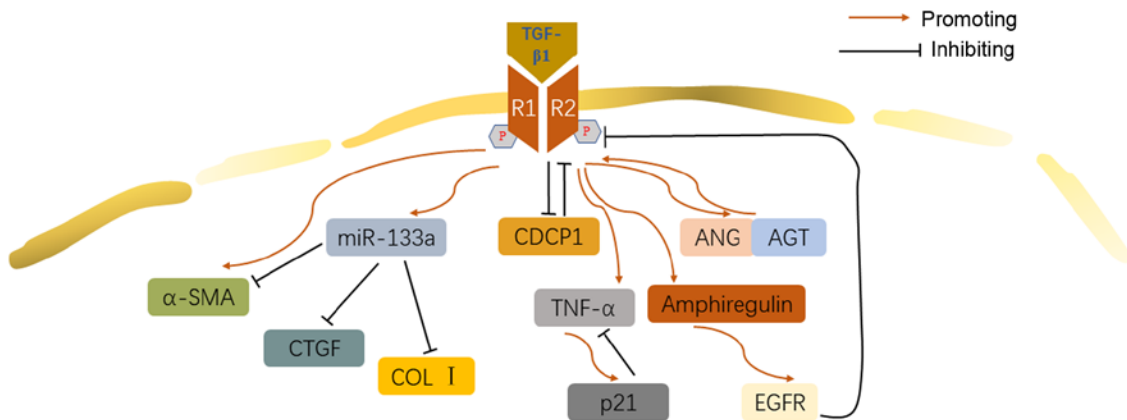


Figure 6. Feedback regulation signaling pathway. TGF- β 1 promotes the production of EGFR by promoting the production of amphiregulin, but EGFR plays a negative feedback role, inhibiting the process by which TGF- β 1 promotes the production of amphiregulin. TGF- β 1 promotes the production of p21 by promoting the production of TNF- α , but p21 in turn inhibits the process that promotes its production. TGF- β 1 promotes miR-133, but miR-133 inhibits the production of α -SMA, CTGF and COL I.

caspace-3, resulting in lung injury and pulmonary fibrosis (96). TGF- β 1 induces the expression of exogenous tribbles homolog 3 (TRB3), which stimulates EMT and promotes the onset of IPF. In addition, TRB3 may participate in the regulation of EMT in MLE-12 cells induced by TGF- β 1 through the Wnt/ β -catenin signaling pathway (97). Insulin-like growth factor-1 (IGF-I) can co-operate with TGF- β 1 to enhance the proliferation of lung fibroblast (98).

Currently, findings have shown that TGF- β 1 may contribute to the development of IPF through epigenetic regulation. In fibroblasts from patients with IPF, TGF- β 1 induces the upregulation of DNA methyltransferase (DNMT3a) and tetmethylcytosine dioxygenase 3 (TET3) (99). TGF- β 1 inhibits Caveolin (Cav)-1 gene via histone modifications, contributing to fibroblast proliferation and apoptosis resistance (100).

TGF- β 1 may promote IPF by reducing the production of antioxidant substance and inducing oxidative stress. TGF- β 1 disturbs the homeostasis of the messenger RNA (mRNA) of the γ -glutamylcysteine synthase (γ -GCS) gene and downregulates the transcription of the gene, inducing the production of ROS

in epithelial cells (101,102). It was also reported that TGF- β 1 reduced the production of glutathione by downregulating precursor amino acid transport and synthesis rate (103). These results are consistent with previous reports of Guo *et al* (29) and Hecker *et al* (27) (Fig. 7).

3. Discussion

IPF is an irreversible lung disease, and there is no exact cause (1). In recent years, the incidence of IPF has gradually increased. There are numerous reasons for the increasing incidence of IPF. Firstly, IPF susceptibility is closely related to aging, which may lead to telomeres shortening and mitochondrial dysfunction. At present, the aging population is on the rise, resulting in an increasing incidence of IPF (104). Secondly, the development of medical technology has led to easy, convenient, and precise diagnosis of IPF, resulting in increasing incidence of IPF (105). Additionally, accumulating exposures to numerous risk factors such as smoking, occupational dust, drug stimulation, bacterial and virus infection, also play a role (106). The

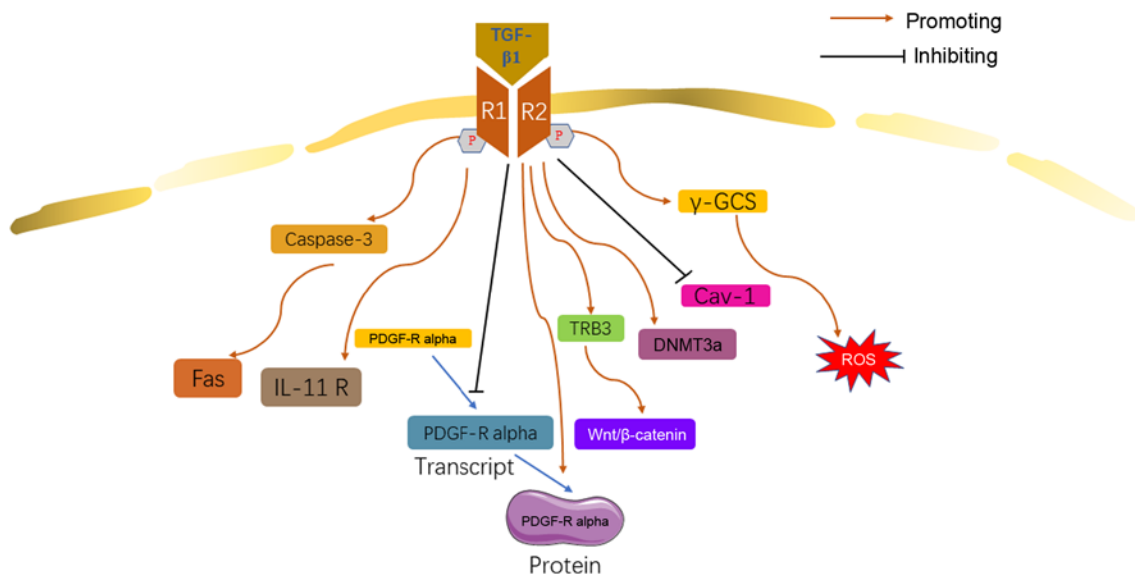


Figure 7. Other signaling pathways. TGF- β 1 promotes Fas by activating caspase-3, and it can also promote the Wnt/ β signaling pathway by promoting TRB3. In addition to positive promotion of idiopathic pulmonary fibrosis, it also has a negative inhibitory effect, such as TGF- β 1 through the inhibition of PDGF-R α protein transcription and inhibition of Cav-1 production to play a negative role in idiopathic pulmonary fibrosis.

increased incidence of IPF has had a significant impact on the economic development of human society and the physical and mental health of people (4). The drugs currently studied can only delay the progression of the disease and maintain lung function but cannot cure the disease (107). In the pathogenesis of IPF, there are many mechanisms, of which TGF- β 1 plays an important role (16). The IPF incidence of male was higher than that of female; this may be because of exposure to smoking, which is an acknowledged risk factor (106). Regarding the association between the IPF incidence and age, as mentioned previously, IPF is an age-associated disorder (1). Accumulated environmental exposures and cellular functional alteration with aging, for example, telomeres shortening, would facilitate the injury of lung (104). Although lung transplantation is the single most effective way to treat IPF, age is an influencing factor as older patients are less tolerant to surgery. According to the current study, age has become a limiting condition for lung transplantation in IPF patients, and the survival rate after lung transplantation in elderly patients older than 65 years is relatively low (108). Therefore, it is of great significance to develop effective early diagnostic methods and innovative therapeutic strategies, such as applications of mesenchymal stem cells (109).

TGF- β 1 activates Smads through the transmembrane receptor serine/threonine kinase, thereby continuously regulating the transcription of target genes (110). The TGF- β 1/Smad signaling pathway functions in IPF mainly through the following three processes: Myofibroblast differentiation, EMT/EndMT and fibrogenesis (111). TGF- β 1 activates PI3K and protein kinase B (PKB)/AKT through a SEMA7A-dependent mechanism, thereby inducing the formation of EMT and ECM in lung epithelial cells (47). TGF- β 1 mediates the production of FXII through the JNK/Smad3 signaling pathway (62). It also attenuates the apoptosis of fibroblasts by inducing the production of p38-dependent growth factor, which continuously activates PI3K/AKT. At the same time, it also initiates the Wnt/ β -catenin cascade by upregulating β -catenin

and GSK-3 β (79). TGF- β 1, not only regulates various mechanism pathways, but also affects IPF by regulating epigenetics, oxidative stress, and miRNA (112-115). Some research suggested that Smad3 activation has no effect on collagen I or α -SMA (24). However, Liu *et al* suggested that in the transition of human normal skin fibroblast to myofibroblast induced by TGF- β 1, Wnt/ β -catenin played a role of negative regulator, but had different functions in the lung, thereby promoting the hypothesis that Wnt/ β -catenin is tissue-specific (82).

There are crosstalks and self-regulating loop in different pathways involved in TGF- β 1-induced IPF. The Rho/Rock and Smad signaling pathways may cross talk in lung fibroblast differentiation (31). The Rho/Rock inhibitor downregulated Smad2 expression and the TGF- β /Smad inhibitor downregulated RhoA, RhoC and Rock1 expression. There may be a complex network between the Rho/Rock pathway and Smad signaling in the process of lung fibroblasts to myofibroblasts induced by TGF- β 1. TGF- β 1 mainly promotes IPF, but there are also some self-regulating mechanisms that can induce miR-133a expression which acts as an antifibrosis regulator of TGF- β 1, which induces IPF (87). Activation of the MAPK family is mediated by TGF- β 1, which affects Smad signaling. ERK1/2 activation directly phosphorylates and activates p90RSK, which is a set of serine/threonine kinases that play a key role in the MAPK signaling pathway (116).

However, some mechanisms and pathways involved in TGF- β 1 have not been clarified; thus, greater efforts to identify these should be made with regard to TGF- β 1. Although some pathways have been proven, fewer drugs are actually converted into clinical applications. As for further studies on TGF- β 1 in IPF, the focus should be on the intersection of various pathways, to facilitate the development of more effective drugs. At the same time, in addition to study on the various signal pathways involved in TGF- β 1, an in-depth study of its role in epigenetics, and oxidative stress should also be conducted. After all, the purpose of research is to serve the clinic and solve the problem of clinical IPF treatment.

4. Conclusion

TGF- β 1 plays a crucial role in the development of IPF as it regulates the pathomechanism of IPF through a number of signaling pathways, including Smad, MAPK, Wnt, and ERK pathways. The effect of TGF- β 1 on IPF is one of stimulation. Nevertheless, there are some self-limiting mechanisms. Furthermore, some TGF- β 1-relevant mechanisms in IPF remain to be elucidated.

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Authors' contributions

ZY substantially contributed to the conception and design of the work and wrote the manuscript. YH revised the manuscript critically for important intellectual content. Both authors approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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