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Review

Krueppel-like factors transcriptionally regulate idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a devastating interstitial lung disease (ILD) characterized by excessive inflammation and deposition of extracellular matrix (ECM) in the pulmonary niche, ultimately leading to decline of pulmonary function. Even though there are three food and drug administration (FDA) approved drugs for treatment of IPF, these drugs are ineffective against reversal of the disease but rather can only reduce the progression of the disease. As a result, the median survival rate for IPF is extremely low and new therapeutic strategies are urgently needed. Krueppel-like factors (KLFs) are zinc finger containing transcription factors that control the outcome associated with various types of diseases, given their critical role in cellular differentiation and proliferation. The role of KLFs is very cell specific and as a result it finely balances the inflammation associated with various diseases. Even though different members of the KLF family have been reported to have a role in IPF, this review summarizes the role of KLFs in regulation of inflammation associated with idiopathic pulmonary fibrosis.

1. Introduction

Interstitial lung disease (ILD) is a term used for a group of lung diseases characterized by inflammation and/or fibrosis of the lung interstitium [1]. IPF is one of the most common types of ILD. The exact cause of this disease is not known, that's why the term 'idiopathic' and the disease is typically characterized by gradual scarring of the lung tissue [1,2].If left untreated, the survival rate is 3-5 years and the median survival rate is still low even with lung transplant [3]. Even worse, a lot of IPF patients who experience acute exacerbation (AE), only survive for a couple of months [4]. Noteworthy to mention that IPF patients show a steady decline of lung function such as Forced Vital Capacity (FVC) [5] and Diffuse capacity of the lung for carbon monoxide (DLCO) [6] whereas IPF AE shows a rapid decline in FVC and DLCO. More importantly, IPF mostly affects aged individuals (over 60 years of age) and this in turn increases the chance of comorbidity and higher mortality rate [7]. The incidence rate of IPF varies by region. In North America, it ranges from 18.7 per 100,000 people in Canada to 29.8 per 100,000 people in the USA [8,9]. In the European Union, the incidence rate is 25.1 for every 100,000 people [8]. In the east Asia, the incidence rate greatly varies between countries Japan, Taiwan, South Korea and China and it ranges 1.2-4.16 for every 100,000 people [10,11]. An added burden for IPF is that it is often diagnosed very late in the disease progression [12]. There are currently three FDA approved drugs for the treatment of IPF, Nintedanib, Pirfenidone and Nerandomilast, but these drugs only reduce the progression of the diseases [13,14]. Of these three drugs, Nintedanib and Pirfendone has been used for IPF since 2014 [15] and only one drug, Nerandomilast has been approved by the FDA for treatment of IPF in the last 10 years [14].

Dysfunctional alveolar epithelial cells (AECs) are one of the most important triggering factors for development of IPF [16]. Inflammation within the pulmonary niche is a critical process for the development and progress of IPF which often contributes to chronic oxidative stress in AECs, specifically due to reactive oxygen species (ROS) [17]. The chronic oxidative stress (due to the repetitive injury) is responsible for the aberrant alveolar repair and impaired epithelial regeneration. The combination of oxidative stress and aberrant repair often leads to activation of several downstream signaling factors such as NF-kB, STAT3 and Wnt pathways [18–20]. The cytokine milieu as a result of these activated pathways ultimately forces the epithelial cells and partly, the endothelial cells to transition to myofibroblast, referred to as epithelial-mesenchymal transition (EMT) and endothelial-mesenchyme

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Table 1
Classification of KLF family members.

Group No.	KLF family members	Specialized Motif/domain	Type of activity
1	KLF3,8,12	PVDLS [33]	Activator/ Repressor
2	KLF1,2,4,5,6,7	Low complexity regions (LCR) containing Serine/Threonine or Proline [33]	Activator/ Repressor
3	KLF9,10,11, 13,14,16	Sin3a interacting domain (SID) [33]	Repressor

transition (EndMT) respectively, contributing to the development of fibrosis [21–23].Additionally, activation of these key pathways in turn leads to secretion of various cytokines such as IL-1β, IL-6, IL-33 promoting recruitment of immune cells in the pulmonary niche [24,25]. Recruitment of innate immune cells such as macrophages, neutrophils and dendritic cells (DCs), Myeloid derive suppressor cells (MDSCs), in turn secrete a host of factors such as transforming growth factor-β (TGF-β), IL-1β, platelet derived growth factor α (pdgfα), extracellular ATPs, neutrophil elastase, neutrophil extracellular traps (NETs) which in turn not only promotes further oxidative stress and damage to AECs but also the activation of fibroblast to myofibroblast (the key cells responsible for collagen deposition within the lungs), often referred to as fibroblast to myofibroblast transition (FMT) [26] as summarized in our recent review [27]. The repetitive injury to AECs also leads to recruitment of lymphocytes such as T cells subsets and B cells, which releases a host of factors such as IL-6, IL-8, TGF-β which have been reported to promote EMT, EndMT and FMT, as have been summarized in our recent review [28]. Thus, the AECs, due to repetitive injury, oxidative stress & aberrant repair begin a vicious cycle whereby they release inflammatory markers, leading to recruitment of immune cells, which in turn, due to their secreted factors, promote immune-epithelial/fibroblast interaction, leading to aggravation of the disease.

Transcriptional regulation forms an important aspect of controlling the above-mentioned inflammation and the cell-cell interactions associated with various types of lung diseases including IPF [29,30]. One of the key transcription factors that controls the inflammation within various cell types is Zinc finger containing KLFs. The Zinc finger motifs of the KLFs bind to specific DNA sequences and in turn control the transcription of the specific gene [31].KLFs were first identified in *Drosophila melanogaster* in 1993 and of the 17 members of the KLF family, they can be subdivided into 3 subgroups [32] as given in Table 1. This Table 1 excludes KLF15 and 17 due to their limited knowledge regarding their physiological role [32]. Additionally, there is also KLF18, but it has been reported to be a pseudogene [34]. All the above KLFs are typically involved in tissue homeostasis and inflammatory responses in addition to cellular proliferation [32,35]. For example, KLF4 and KLF7 regulate neuronal stem cell and axonal growth respectively [36,37]. Similarly, KLF9 has been reported to regulate NLRP3 inflammasome mediated inflammation associated with chronic obstructive pulmonary disease [38]. Previous studies have shown that KLF2 negatively regulates cardiac hypertrophy [39]. A study by Gao et al. has shown that KLF15 controls the outcome of renal fibrosis by imparting an anti-fibrotic effect [40]. A typical structure of the KLF includes a conserved C-terminal region and highly diverse N-terminal region.

The C-terminal region is the DNA binding domain, consisting of Zinc finger motifs which are in turn composed of Zinc atom and two Cysteine and Histidine residues(C_2H_2) [32]. There are three highly conserved zinc finger motifs in the C-terminal region of all the members of the KLF family. Each of the Zinc finger motifs recognize three DNA base pairs sequences with a total of nine sequences for the three Zinc finger motifs [41].Not only DNA binding, the Zinc finger motifs in KLF1,4,8,11 has important function in nuclear localization signaling [42–45].

The N-terminal region, being highly diverse, binds to corepressors or coactivators, leading to functional diversity [32]. The classification of KLFs into 3 subgroups (as given in Table 1) is based on the functional binding motifs found in the N-terminal region. Group 1 KLFs (such as KLF3, 8 and 12) have repressor Proline-Valine-Aspartic Acid--Leucine-Serine (PVDLS) motif which binds to the corepressor C-terminal Binding Protein (CtBP). For example, KLF8 recruit corepressor CtBP to directly regulate TGF-β induced EMT [46]. However, the repressor activity is both CtBP dependent and independent as disrupting the PVDLS domain does not completely reduce the repressor activity of KLF8 [47]. Interestingly, KLF8 has a dual transcription activity as it not only binds to corepressors such as CtBP but also binds to coregulators with acetyl transferases activity such as p300 [48]. Group 2 KLFs (such as KLF1, 2, 4, 5, 6 and 7) have low complexity regions (LCR) containing Serine/Threonine or Proline, acting as transcriptional regulators. Transcriptional activation is mostly because of acetylation, SUMOylation and phosphorylation in the transcriptional activation/repression domain found in the N-terminal region. For example, KLF1 has been reported to interact with p300 which determines its regulatory function [49]. Just like the group 1 KLFs, acetylation of KLFs is finely regulated to determine the activation/repression activity of the group 2 KLFs. KLF4 is acetylated by p300 which is responsible for KLF4 mediated activation whereas binding to suppressors such as histone deacetylase (HDAC) leads to KLF4 mediated repression [50]. This dual role of KLF4 is reflected in the fact that there is opposing roles of KLF4 in pdgfrβ+ cells and α-smooth muscle actin+ (α-SMA+) cells in the fibrotic lungs which may be due to variable activation/repression [51]. Indeed, the role of KLFs is not only disease specific but also cell specific. Our previous studies have shown that while KLF4 imparts a proinflammatory phenotype in myeloid cells such as macrophages and neutrophils during *Streptococcus pneumoniae* induced bacterial infection of the lung [29,30,52], KLF4 has an anti-inflammatory effect on epithelial cells during the same bacterial infection within the lungs [53].

There is also a Group 3 KLF, namely KLF9, 10, 11, 13, 14 and 16 which has Sin3a interacting domain (SID) which leads to repression activity of this group of KLFs [54].A study by Yang et al., has shown that KLF13 recruit Sin3a repressor factor to suppress TGF-β target genes. Given the N-terminal functional diversity, it is responsible for the multi-faceted(pro-fibrotic/anti-fibrotic) roles of these KLFs in the pulmonary niche [55]. In this review we summarize how different members of the KLF family regulate the inflammation within the fibrotic lung and discuss how this can be leveraged for development of new therapeutics against pulmonary fibrosis.

2. KLFs and IPF

The exact inducing stimuli for IPF remains unclear but studies have shown that repetitive epithelial injury, aggravated by recruited immune cells, finally leads to collagen deposition by fibroblasts [56]. Thus, the immune cells, fibroblast and epithelial cells form a triad that together with cell-cell interaction and signaling molecules is the key driving force for development and progression of fibrosis. The key component that drives this cell-cell interaction is regulated by transcriptional regulators such as KLFs. The contribution of endothelial cells and its regulation by KLFs also forms a supporting system to the triad described above [21].

2.1. Leukocytes

Leukocytes such as alveolar macrophages (AMs) are one of the key cells involved in regulating fibrosis and have been reported to regulate fibroblast contraction irrespective of the diseased state of the lung and this effect is determined by the proximity of the AMs to fibroblast [57]. There is controversial data about how AMs regulate fibrosis. While one study has shown no outcome of fibrosis when AMs were depleted with intra-tracheal administration of clodronate in bleomycin model of pulmonary fibrosis [58], whereas other studies have shown that AMs releases fibroblast specific protein (FSP1) in the pulmonary fibrotic microenvironment which is in turn responsible for mesenchymal

Table 2
Role of KLFs in leukocytes during IPF.

KLF	Immune cells (including AMs, Mo-Macs, Neutrophils and lymphocytes)					
	Cell Type	Pro-fibrotic	Anti-fibrotic	Key signaling targets	Fibrosis related pathophysiological processes	Type of experiment
KLF2	Neutrophils	☑*	☑#	*HIF-1α #HIF-1α	*Arg1 secretion #NET	*In vivo, ex vivo #In vivo, ex vivo
	B cells	☑		SMAD1	B cell proliferation	In vivo
KLF4	AMs	☑*	☑#	*HDAC8 #MERTK	*Secretion of pro-fibrotic factors such as TGF-β, Resistin-like alpha (Retnla). #Secretion of MMP2	*In vitro, in vivo #In vivo
	MoMacs	☑		NF-kB	Macrophage polarization and secretion of Arg1	In vitro, in vivo, ex vivo
	$CD4^+$	☑		IL17a	Pro-fibrotic cytokines such as IL-17	In vivo
KLF6	MoMacs	☑		NF-kB	Macrophage polarization and secretion of IL-1β, MCP-1	In vitro, in vivo
KLF9	AMs	☑		TREM2	AM survival and secretion of pro-fibrotic factors such as pdgfα	In vivo, ex vivo
KLF10	$CD8^+$	☑		TGF-β	Inflammatory cytokines such as interferon-γ (IFN-γ)	In vitro, in vivo
	Monocytes	☑		Rho	Monocyte recruitment	In vivo

proliferation and activation [59].AMs have long been reported to be regulated by KLF4. A study by Chakraborty et al. has shown that AM KLF4 upregulates its myeloid-epithelial-reproductive tyrosine kinase (MERTK) expression, a receptor for efferocytosis and restricts lung injury in murine model [60].Another study has shown that pleckstrin homology domain and leucine-rich repeat protein phosphatase 1 (PHLPP1) inhibited KLF4 expression and prevented the pro-fibrotic polarization of AMs [61]. The same study has further shown that intratracheal administration of shRNA targeting KLF4 leads to better outcomes of pulmonary fibrosis [61]. Macrophage polarization is an important process in the prognosis of pulmonary fibrosis. Supporting the earlier studies, it was recently shown in a radiation induced model of pulmonary fibrosis, lung ECM promoted polarization of alveolar macrophages to M1 phenotype instead of M2 phenotype through the NF-kB pathway [62]. There is compelling evidence which shows that KLF4 is critical for macrophage polarization, whereby KLF4 is upregulated in M2 macrophages and downregulated in M1 macrophages [63]. Taken together, these studies show not only that KLF4 is an important regulator of resident macrophages in the fibrotic niche but also that it could be developed as a therapeutic target. Additionally, triggering receptors expressed on myeloid cells 2(TREM2) in AMs have been studied, whereby it was shown that TREM2 promotes pro-fibrotic activity in monocyte-derived AMs [64]. As expected, knockout of TREM2 led to better outcome of pulmonary fibrosis [64]. On a related note, TREM2 is regulated by KLF9 in macrophages [65]. A recent study by Xu et al., shows that downregulation of TREM2 in KLF9 deficient macrophages [65]. Even though there are no direct studies linking the role of KLF9 in macrophages in pulmonary fibrosis, the above two studies imply a possible role of KLF9/TREM2 axis in AMs in pulmonary fibrosis. Not only AMs, KLFs may also drive the inflammatory signature of neutrophils in the fibrotic lungs. Our previous review has highlighted the role of neutrophils in development and progress of pulmonary fibrosis [27]. Briefly, neutrophils release NETs that promote myofibroblast proliferation [66]. Literature reviews suggest that KLF2 is an important transcription factor for neutrophil activation and NETosis [67], suggesting a possible role of KLF2 in pathogenesis of pulmonary fibrosis. Our recent study has also shown that arginase1(Arg1) is highly expressed by pro-fibrotic neutrophils in IPF patients and this Arg1 expression is driven by fibroblast derived IL-6 [68]. There are other groups which have shown that KLF2 is the key regulator of Arg1 in these myeloid cells as myeloid specific KLF2 floxed mice have reduced expression of Arg1 [69]. Arg1 is not only necessary for neutrophil activation but also for polarization of monocyte derived macrophages, typically referred to as MoMacs [63]. There are mainly two subclusters of macrophages in the fibrotic lungs-resident AMs and MoMacs [70]. The role of KLF4 in macrophage polarization and thereby dictating the sequential events in pulmonary fibrosis not only applies to the resident AMs but also to MoMacs. In addition to KLF4, KLF6 has also been reported for its role in macrophage polarization and control release of pro-inflammatory cytokines such as Monocyte-chemoattractant protein-1 (MCP-1) which recruits monocytes and macrophages [71]. This polarization state favors the aggravation of pulmonary fibrosis by secretion of cytokines such as TNF-α, IL-1β and keratinocyte chemoattractant (KC) in the pulmonary microenvironment [29,63]. In fact, the precursors of MoMacs, monocytes, are also regulated by KLFs. Monocytes express Natriuretic peptide receptor A (NPRA) [72] which is regulated by KLF10 [73]. Regulation of pulmonary fibrosis by KLF10 is demonstrated by its mimicking activity of TGF-β [73]. In addition to the myeloid cells above, KLF10 is a transcriptional regulator responsible for TGF-β signaling pathway in T lymphocytes ($CD8^+$) [74,75]. It is well defined that TGF-β is the key driver of tissue fibrosis including IPF [76]. Our recent review has also outlined the key roles of these lymphocytes in the context of pulmonary fibrosis by promoting fibroblast activity in various ways [28]. Th17 cells are a class of CD4 T cells that are responsible for IL17 secretion which drives ECM production in fibroblasts [77,78]. KLF4 is not only necessary for Th17 differentiation but it is present in the promoter region of IL17 gene [79,80]. There are currently three FDA approved drugs for IPF and of these, Nintedanib has been documented to regulate B Cell receptor (BCR) signaling, thereby regulating fibroblast migration/activation [81,82]. A study by Hart et al. has shown that KLF2 is necessary for this BCR signaling as KLF2 deficient B cells showed impaired B cell activation and proliferation [83]. Thus, even though there are no studies which demonstrate the direct role of lymphocyte KLF in pulmonary fibrosis, prevalent literature shows KLF may orchestrate lymphocyte into a pro-fibrotic phenotype. Taken together, the inflammatory signature of immune cells such as AMs, neutrophils, monocytes, MoMacs and lymphocytes is significantly controlled by KLFs (as summarized in Table 2) and their crosstalk with the mesenchyme drives myofibroblast activation.

2.2. *Alveolar epithelial cells*

AECs are another key player in regulating fibrosis. The interaction of these epithelial cells with fibroblast is necessary for lung homeostasis. AECs releases a host of pro-inflammatory factors such as MCP-1/CCL2 which leads to recruitment of monocytes and macrophages which in turn promote fibroblast activation and migration [84,85]. Another aspect of epithelial cells includes EMT, whereby, epithelial cells gradually lose their own characteristics to gain a mesenchymal phenotype [86]. Noteworthy to mention that recent Single-cell RNA sequencing (ScRNA seq) data shows that there is a specific subset of AECs, termed as aberrant basaloid cells [87]. These cells are absent in normal lungs but found in IPF lungs, co-localizing along with the myofibroblast foci [87]. Interestingly these cells express markers of epithelial cells such as Tumor protein 63 (TP63), Keratin 17 (KRT17) and EMT markers such as N-Cadherin (CDH2) and Vimentin [87]. Like the alveolar macrophages,

Table 3
Role of KLFs in AECs during IPF.

KLF	AECs				
	Pro-fibrotic	Anti-fibrotic	Key signaling targets	Fibrosis related pathophysiological processes	Type of experiment
KLF4		☑	TERT*, SMAD2/3#	*AEC senescence, #EMT	In vitro, in vivo, ex vivo
KLF5	☑*	☑#	*RPHN2 #YAP, miR-200	*EMT #AEC differentiation, EMT	*In vitro, in vivo, ex vivo #In vitro, in vivo
KLF8	☑		Four and a half LIM domain 2 (FHL2)	EMT	In vitro
KLF9		☑	Slug	EMT	Ex vivo
KLF14		☑	ERS	AEC senescence	In vitro, in vivo
KLF17		☑	Inhibitor of DNA binding 1 (Id1)	EMT	In vitro, in vivo

Table 4
Role of KLFs in endothelial cells during IPF.

KLF	Endothelial Cells				
	Pro-fibrotic	Anti-fibrotic	Key signaling targets	Fibrosis related pathophysiological process	Type of experiment
KLF2	☑		Phospo-SMAD3	EndMT	In vivo, in vitro, ex vivo
KLF4		☑	Phospo-SMAD3	EndMT	In vivo, in vitro, ex vivo

these epithelial cells are also under the direct control of transcriptional factors such as KLF. KLF4 along with other members of KLFs have been reported to regulate EMT. KLF4 not only regulates AECs activity but it has been reported to suppress TGF-β induced EMT during pulmonary fibrosis [88]. The probable mechanism reported was that KLF4 regulates EMT directly by inhibiting the phosphorylation of SMAD2/3 pathway and Dvl2 in Wnt pathways [88].It's worth mentioning that one of the key target of KLF4 has been reported to be CDH2, a marker, highly expressed by the aberrant basaloid cells [89].Unlike KLF4, the role of KLF5 is very much context dependent. In some studies, KLF5 has been reported to inhibit EMT as knockdown of KLF5 promoted EMT and the proposed mechanism was by regulating microRNA(miR)-200 in keratinocytes [90]. It was recently reported that Yes1 associated transcriptional regulator (YAP) is upregulated in activated AECs, and deletion of YAP in AECs worsens pulmonary fibrosis in bleomycin model of lung fibrosis [91]. Interestingly, the study showed that YAP binding sites are in the promoter region of KLF5, implying the importance of this zinc finger transcriptional factor in AEC differentiation and proliferation during homoeostasis and pulmonary fibrosis [91]. In stark contrast to the former study, a study by Zhang et al., showed that KLF5 promotes EMT in pulmonary epithelial cell line, A549 [92]. In this study, repression of KLF5 led to decrease in EMT markers such as Vimentin and CDH2 in a Rhophilin Rho GTPase binding protein 2 (RHPN2) dependent manner [92]. Supporting the above, it was shown that KLF5 has been reported to regulate the AECs during hyperoxia induced acute lung injury (HALI) [93]. This study by Liberti et al., has shown more widespread fibrosis in the control group with respect to the AEC specific KLF5 knockout group [93]. Literature reviews also suggest the implication of other KLFs such as KLF8, 9 & 17 in EMT in different models of cancer with possible effects on tissue fibrosis [94–97]. However further studies need to be done to understand the role of these additional KLFs in EMT during lung fibrosis. Thus, the fine balance of KLFs may be necessary for the generation of aberrant basaloid cellular subsets which in turn support EMT.

It is well defined how these stressed epithelial cells release TGF-β and the repetitive injury triggers a senescence associated secretory phenotype (SASP) in AECs and thereby triggering fibroblast activity [98–100]. In an animal model of bleomycin induced lung fibrosis, it was shown that AECs express senescent markers such as p16, Mcp1, Matrix Metalloproteinase (Mmp10, Mmp12) [101]. There is strong evidence that the induction of senescence is AECs (along with fibroblasts) sustains the pathophysiology associated with IPF [101–104]. A recent study by Wang et al., has shown that KLF4 expression goes down in AECs and overexpression of KLF4 in AECs reduces the development of pulmonary fibrosis by inducting telomerase reverse transcriptase (TERT) expression [105]. Given the role of KLF4 in regulating TERT, overexpression of KLF4 led to reduced senescence in AECs in bleomycin model of lung fibrosis. [105]. In addition to KLF4, another member of the third type of KLFs, KLF14 reduced endoplasmic reticulum stress (ERS) in AECs and thereby its senescent phenotype [106]. Naturally, knockdown of KLF14 led to higher mortality in bleomycin induced lung injury [106]. It is noteworthy to mention that senescence in AECs and its progenitors impair cellular repair and in turn drive pulmonary fibrosis [100]. Another member from the same group of KLF4, KLF5, has been reported to regulate p53 and thereby, determine whether the epithelial cells will undergo cellular senescence. As a result, KLFs control the fate of transition of AECs to EMT and induction of senescence. Thus, given its role in regulating AECs, KLFs could be developed as therapeutic target in pulmonary fibrosis as summarized in Table 3.

2.3. Endothelial cells

Like epithelial cells, endothelial cells also lose their phenotype and transition to mesenchyme, referred to as EndMT which contributes to fibroblast accumulation during pulmonary fibrosis [21]. There are two transcription factors from the same family, KLF2 and KLF4, which synergistically contribute to the EndMT process, whereby loss of one transcription factor, KLF4, is compensated by increased KLF2 expression [107]. This is most probably possible because KLF4 binds to the transactivation domain of KLF2. In fact, because of this overcompensation, knockout of KLF4 leads to exacerbation of pulmonary fibrosis [107]. Even though there are limited literature available, endothelial cells are regulated by KLFs within the lungs during pulmonary fibrosis as summarized in Table 4.

2.4. Fibroblasts

Fibroblasts are instrumental in regulating the outcome of pulmonary fibrosis. The role of fibroblasts is multidimensional; it is not only responsible for ECM production leading to decline of lung function but also interacts with other cell types. Fibroblast have been reported to cross talk with macrophages whereby macrophages secrete pdgfα which binds to its receptor, pdgfrα, promoting fibroblast proliferation. Fibroblast in turn secrete colony stimulating factor 1(csf1) to promote macrophage proliferation [108,109]. Similarly, Arg1 expression in neutrophils is driven by fibroblast derived IL-6 and Arg1 expression in neutrophils serves as a substrate for collagen synthesis in fibroblasts. [68]. Just like the other cell types in the pulmonary niche, fibroblasts are highly controlled by KLFs. KLF15 is one of the key transcription factors in this regard. It has been recently shown that KLF15 controls fibroblast proliferation, migration and in turn ECM production [110]. The probable mechanism in this study by Han et al., is that KLF15 inhibits ERS in fibroblast and thereby prevents TGF-β induced fibroblast proliferation. [110]. Review of literature suggests that ERS is an important trigger for development of pulmonary fibrosis and is linked to EMT, macrophage polarization and most importantly myofibroblast activation [111].Not

Table 5
Role of KLFs in (myo)fibroblast during IPF.

KLF	(Myo)fibroblast				
	Pro-fibrotic	Anti-fibrotic	Key signaling targets	Fibrosis related pathophysiological processes	Type of experiment
KLF2		☑	Activating Protein-1 (AP-1): c-Jun and c-Fos	Collagen secretion and pro-inflammatory cytokine such as IL-6	In vitro, in vivo
KLF4	☑*	☑#	*TGF-β #SMAD2/3, HIF-1α	*ECM production #FMT	*In vitro, in vivo, ex vivo #In vitro, in vivo, ex vivo
KLF6		☑	p53	Fibroblast senescence	In vitro
KLF7	☑		SMAD3	FMT	In vitro, in vivo
KLF15		☑	ERS	Fibroblast proliferation and ECM production	In vitro

only KLF15, KLF4 also binds to the promoter site of hypoxia inducible factor-1α (HIF-1α), which is also known as the ERS signaling pathway [112]. Naturally, KLF4 expression was significantly reduced in injured lung fibroblasts and overexpression of KLF4 in lung fibroblast led to decrease in expression of HIF-1α [112]. This is supported by another study which have shown diminished expression of KLF4 in fibroblasts and conditional knockout of KLF4 in fibroblast using *Col1α2 cre* worsened pulmonary fibrosis [113].In stark contrast to the two former studies above, a recent report has shown that KLF4 is upregulated in pdgrβ+ cells (a major source of myofibroblasts) and this upregulation is directly correlated with TGF-β signaling and lung fibrosis [51].As expected deletion of KLF4 in pdgrβ+ cells leads to reduction of pulmonary fibrosis given its role in controlling the phosphorylation of SMAD2/3 pathways [51].The probable reason for the discrepancy is that there are various subclusters of fibroblasts in the fibrotic lungs [114] and whereas as *Col1α2 cre* targets activated myofibroblast, pdgfrβ is expressed by smooth muscle cells, pericytes in addition to fibroblast [115–117]. Even though KLF7 has not been reported in lung fibroblasts and pulmonary fibrosis, one such study has shown that ubiquitin-specific protease 7 (usp7) interacts with KLF7 in promoting FMT in a model of myocardial infarction induced fibrosis [118]. Another member from the same group of the former KLF, KLF2, has also been reported in regulating fibrosis. The study reported an overall reduction of KLF2 expression in lung tissues post bleomycin induced lung injury in mice [119]. Additionally, overexpression of KLF2 in pulmonary fibroblast reduced their collagen secretion induced by TGF-β [119]. This is supported by another study which has shown expression of KLF2 in lung fibroblast negatively correlates with its pro-fibrotic connective tissue growth factor (CCN2) expression [120].

Fibroblast senescence along with the AECs and endothelial cells supports inflammation driven development and progression of fibrosis in the pulmonary niche [101]. There is a probable synergism between different KLFs to regulate senescence in fibroblast. A study by Sabatino et al. has shown knock down of KLF6 leads to enhanced senescence in fibroblasts [121]. Similarly, another group has shown that KLF4 knockout fibroblasts enters senescence earlier than KLF4 wild type fibroblasts [122]. Taking together, it is well established that KLFs regulate the activation of fibroblast to myofibroblast in the wounded lung tissue as summarized in Table 5.

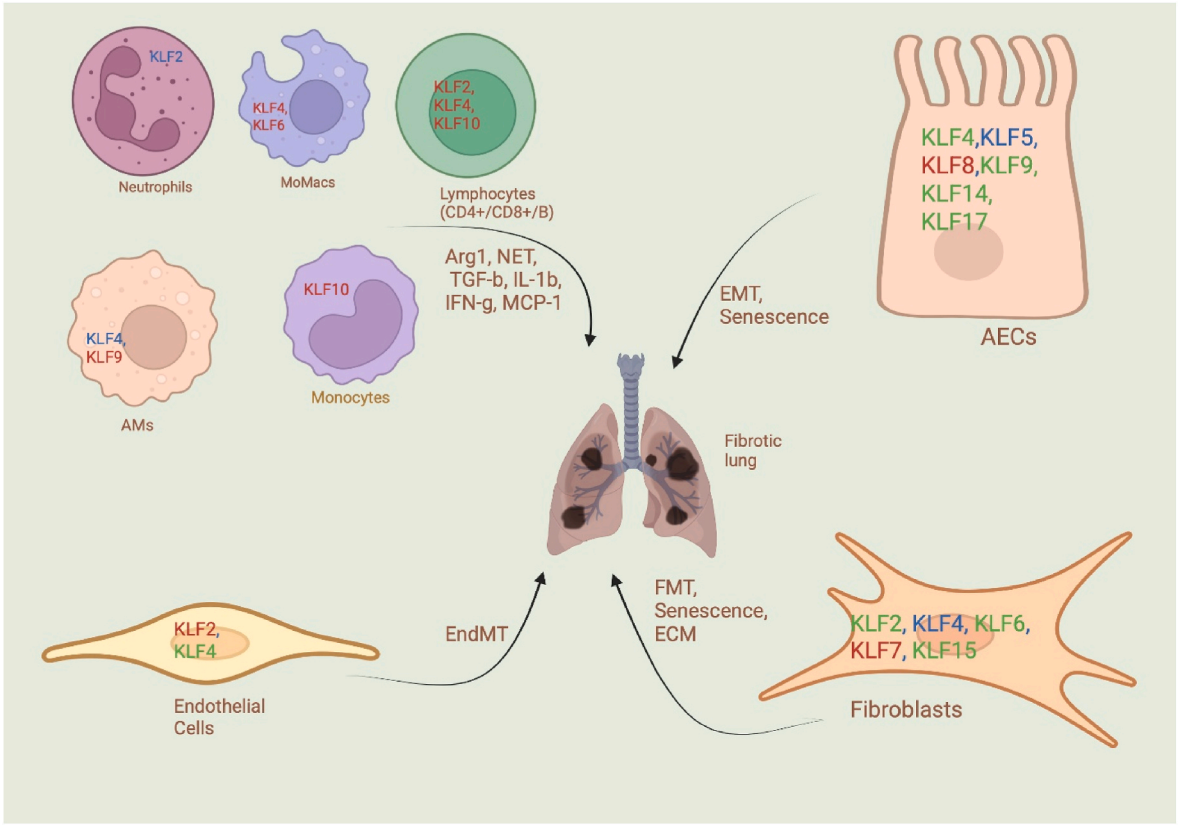

Fig. 1. KLFs regulate cell-cell interaction of immune cells, epithelial cells, endothelial cells and fibroblasts leading to deposition of ECM in IPF. KLFs in green impart an anti-fibrotic phenotype and red colored KLFs impart a pro-fibrotic phenotype whereas KLFs which are blue colored have been reported to have both pro-fibrotic and anti-fibrotic effects.

3. Conclusion and future directions

IPF is an inflammatory lung disease affecting mostly aged individuals with high mortality rates [3,7]. The exact etiology is not known and as result, the number of therapeutics is extremely limited with only three FDA approved drugs. In the last ten years or so, only one new drug has been approved by the FDA among those three drugs, Nintedanib, Pirfenidone and Nerandomilast [14]. Pulmonary tissue is an oasis of heterogeneous cells, of which the immune cells, epithelial cells and endothelial cells cross talk with each other and with the fibroblast, leading to the development of pulmonary fibrosis [27,28]. Overall, all the above cells exert various pro-fibrotic and sometimes anti-fibrotic effects depending on the phase of the disease but ultimately it leads to fibroblast activation and deposition of ECM and failure of pulmonary function [27,28]. Transcription factors such as KLFs tightly regulate the phenotype and function of these diverse cell types, contributing to IPF pathogenesis through multiple, cell type-specific mechanisms.

In this current review, we summarize how different KLFs regulate the inflammatory state of the immune cells, AECs and endothelial cells and (myo)fibroblast. KLFs family consists of 17 family members, and the different members can act as co-suppressors or co-activators [31,32]. The list of possible KLFs which may regulate immune cells, AECs & endothelial cells and fibroblasts with respect to pulmonary fibrosis is given in Tables 2–5. Prevalent literature, even though limited, suggests these KLFs regulate the above cell types but whether all the KLFs work in tandem is not known. For example, it has been reported that KLF4, 5 and 14 regulate the fibrotic profile of AECs [93,105,106] but whether they work synergistically or not is not known. There are also a lot of other KLFs like KLF8,9 which have been reported to regulate EMT (one of the key processes in IPF) in other cancer models but whether it is also applicable for IPF is not yet known. However, it should be mentioned that IPF increases the chance of lung cancer [123], implying that in all probable the process of EMT may have overlapping impacts on lung cancer and IPF. Similarly, myeloid cells such as MoMacs and neutrophils are often referred to as the “bad players of fibrosis” given their pro-fibrotic phenotype [68,109,114]but nothing has been reported about how KLFs regulate their phenotype in the context of pulmonary fibrosis. It is noteworthy to mention that how KLFs regulate the inflammatory profile of MoMacs and neutrophils in other disease types is well defined [29,30,52,124]. The most widely used model of murine fibrosis is bleomycin induced lung injury, which is referred to in this current review, but it must be considered that even though the bleomycin model partly mimics the inflammation associated with fibrosis, this model has a natural resolution unlike the IPF patients [125].

Going forward, ScRNA seq [70] can be used to have a holistic understanding of the entire networks of KLFs regulating a specific cell type in the fibrotic lung. The use of these cutting-edge technologies should be used not only for murine models but also for human samples. It is very important to note regarding patient samples that since IPF is multistage disease, most of the patient samples are available are at the end stage of IPF. To have a comprehensive understanding of how KLFs regulate/balance the inflammation associated with the heterogenous cell population, patient samples need to be used from various stages of IPF using lung biopsies [126] or broncho-alveolar lavage fluid (BALF) [127].

Understanding the role of KLFs in regulating the different cell types during pulmonary fibrosis will open new avenues for treatment for IPF. However, given a lot of the members of the KLF family have a significant role in tumorigenesis [128–131], caution should be taken about therapeutic strategies targeting the KLFs. Another key thing to remember is that the same KLF is very cell and context specific. [30,53]. This is especially important, given that IPF is a multi-stage disease with diverse roles of the same type of cell, for example, macrophages and its secretory profile have been reported to be both pro-fibrotic and anti-fibrotic depending on the phase of the disease [109,114,132]. Thus, taken together, KLFs provide a valuable tool for the development of therapeutics against pulmonary fibrosis as illustrated in Fig. 1, provided comprehensive knowledge is known about them.

Disclosure

No Large language model (LLM) was used in preparing this manuscript.

Author contribution

AB did the conception of the work. AB did the review of literature. AB and AKS contributed to writing. AB drafted the original manuscript. All authors have approved the submitted version of the manuscript and agreed to be accountable for any part of the work.

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Declaration of competing interest

The authors have no conflicts of interest.

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