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Developmental Pathways in the Pathogenesis of Lung Fibrosis

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive and terminal lung disease with no known cure. IPF is a disease of aging, with median age of diagnosis over 65 years. Median survival is between 3–5 years after diagnosis. IPF is characterized primarily by excessive deposition of extracellular matrix (ECM) proteins by activated lung fibroblasts and myofibroblasts, resulting in reduced gas exchange and impaired pulmonary function. Growing evidence supports the concept of a pro-fibrotic environment orchestrated by underlying factors such as genetic predisposition, chronic injury and aging, oxidative stress, and impaired regenerative responses may account for disease development and persistence. Currently, two FDA approved drugs have limited efficacy in the treatment of IPF. Many of the genes and gene networks associated with lung development are induced or activated in IPF. In this review, we analyze current knowledge in the field, gained from

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both basic and clinical research, to provide new insights into the disease process, and potential approaches to treatment of pulmonary fibrosis.

Keywords

Lung, development; fibrosis; transforming growth factor-β (TGF-β); sonic hedgehog (SHH); Notch; Wnt; fibroblast growth factor (FGF); platelet derived growth factor (PDGF); Hippo; antagonistic pleiotropy

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is an age-related interstitial lung disease characterized by progressive scarring of lung tissue which reduces gas exchange, and leads to progressive respiratory failure (Lederer and Martinez, 2018; Raghu and Chang, 2004; Thannickal et al., 2004). According to conservative estimates, there are 3–9 new cases reported per 100,000 per year in the European and North American populations, while a lower incidence has been reported in Asia and South America (Hutchinson et al., 2015). The majority of IPF patients are males, above 60 years of age at disease presentation, and survival is limited to between 3–5 years post diagnosis (Raghu et al., 2006; Thannickal, 2013). The etiology of the disease is largely unknown. Current concepts of disease initiation and progression implicate a multifactorial pathogenesis with the intersection genetic susceptibility, aging and environmental factors (Thannickal et al., 2014). Genetics may explain only 20% of the cases, and 75% has a history of smoking (Baumgartner et al., 1997; Wolters et al., 2014). There is recent debate on whether the term “IPF” should be reclassified based on the emerging data on genetic susceptibility and other risk factors (Thannickal et al., 2018; Wells et al., 2018; Wolters et al., 2018).

Recent findings suggest IPF arises from a failure of lung alveolar epithelial regeneration and an abnormal wound healing response (Chambers and Mercer, 2015). In normal lung injury-repair, activated stromal fibroblasts/myofibroblasts deposit extracellular matrix (ECM) composed primarily of fibrillar collagen and fibronectin to form a provisional matrix to facilitate alveolar epithelial type 2 cell (AEC2) progenitor proliferation and differentiation to regenerate the damaged and denuded epithelium (Thannickal, Ann Rev Med 2004). In contrast, a failure of normal re-epithelialization due to chronic injury and/or aging may exhaust mechanisms of epithelial regeneration resulting in aberrant mesenchymal activation. Reciprocally, the aberrantly activated mesenchyme may restrict the ability of the epithelium to regenerate the damaged alveolus.

An aberrant recapitulation of developmental genes has been reported in IPF (Chanda et al., 2016; Lehmann et al., 2016; Selman et al., 2008). The precise role of these developmental pathways in the genesis and progression of IPF is unclear. In the current review, we re-examined the fundamentals of embryonic lung development and regenerative pathways in the adult lung, and compared with aberrant developmental reprogramming in aging, and IPF in order to establish a framework for therapeutic development. Lung development has been studied extensively in recent years, generating new insights into the origins of the different cell lineages that exist in the lung as well as the molecular pathways that regulate these

lineages. This has led to novel insights into congenital lung diseases, lung abnormalities and acquired lung diseases, including asthma and chronic obstructive pulmonary disease (COPD), and the lung's response to acute or chronic injury. In addition, these studies have revealed that specific cell progenitors within the mammalian respiratory system regenerate after injury through the activation of stem/progenitor populations or through proliferation-induced cellular expansion (Barkauskas et al., 2013; Peng et al., 2015; Warburton et al., 2008; Zacharias et al., 2018). Some of the molecular pathways that regulate these regenerative processes have been identified, raising hope that they can be harnessed to promote lung regeneration in humans.

2. Overview of Lung Development

Lung development is a complex process. In mammals, lung development is divided into 2 main stages: the branching stage and the alveolar differentiation stages (Alanis et al., 2014;Chang et al., 2013; Herriges and Morrisey, 2014; Warburton et al., 2010). A schematic overview of mammalian lung development is given in Figure 1. Lung development is initiated with outward budding of the endoderm of the anterior foregut beginning during the fourth week of gestation in humans, and embryonic day 9.0 (E9.0) in mice. Evagination of the endoderm results in the formation of two lung buds and the trachea during this period. The endoderm-derived epithelium in the primitive lung bud differentiates into respiratory epithelium which lines the proximal and distal airways, including the alveoli where gas exchange occurs. Conducting airways are formed by highly regulated and repeated dichotomous branching (branching morphogenesis) from the two lung buds between the seventh to the 16^{th} week of gestation in humans (mouse: E9.5-E16.5 days), generating a tree-like network of airways with thousands of terminal branches. The developing lung at this stage appears conspicuously glandular (pseudoglandular), formed by narrow epithelial lined tubules and surrounded by abundant mesenchyme. Epithelial-mesenchymal interactions become clearly evident during the pseudoglandular stage. Endodermal lung buds undergo branching that is dependent on the amount of mesenchyme present around the lung buds (McCulley et al., 2015; Warburton et al., 2008).

The alveolar differentiation phase of lung development begins between the 16^{th} – 24^{th}week of gestation in humans; E16.5-E17.5 in mouse marks the formation of basic gas exchange surface lined by cuboidal epithelium and vascularization (Herriges and Morrisey, 2014; Warburton et al., 2010). Cytodifferentiation of the bronchial epithelial cells into AEC2s and type 1 (AEC1) pneumocytes occurs during this phase. At 24 weeks of gestation until term in humans (and E17.5 - P5 in mouse), tissue projection into the distal airspaces result in formation of sac-like structures (saccular). These changes are associated with remarkable decrease in the prominence of interstitial tissue and a thinning of airspace walls. The epithelium lining the saccules of human fetal lung at this stage of development are recognizable as AEC1 and AEC2 pneumocytes. Five weeks after birth to adolescence in human (from P5-P30 in mouse), the air-blood barrier between the alveolar walls and capillaries is formed, composed of a thin epithelial cell layer, a basement membrane, and a thin layer of endothelial cells. AEC2s are facultative progenitor cells for AEC1s, and is responsible for surfactant production in the lung. In the lamb it was observed that there is generally one type II cell per alveolus (Flecknoe et al., 2002). Although alveoli are formed at

birth, the maturation process begins approximately 5 weeks after birth (Schittny, 2017). It is believed there are 20 million of these primitive terminal sacs/alveoli are present in the lung at birth, lined by mature alveolar epithelium. These alveoli develop into 300 million mature alveoli by age 8 years in humans (Burri, 1984)). During multiplication of the alveoli in the early years of life, the alveolar size mostly remain constant. Alveolar size increases with the expansion of thoracic cage during adolescence (Herriges and Morrisey, 2014; Schittny, 2017; Warburton et al., 2010).

3. Signaling Pathways in Lung Development and IPF

The molecular signaling pathways that regulate the different stages of lung development have been well studied (Herriges and Morrisey, 2014; Morrisey and Hogan, 2010). TGF-β, Wnt, hedgehog, Notch, and fibroblast growth factor (FGF) signaling pathways are implicated in regulating lung specification, branching and patterning during lung development. Many of these pathways remain dormant in the adult, but are activated during injury repair (Selman et al., 2008). Recent evidence also indicate that chronic activation of these developmental pathways in aging is associated with various lung pathologies (Chanda et al., 2016; Joannes et al., 2016; Konigshoff et al., 2008; Selman et al., 2008). In this review, we compare and contrast the role of these pathways during lung development and IPF.

3.1 Transforming Growth Factor

Transforming growth factor-β (TGF-β) is a member of a large family of polypeptides that modulate a variety of cellular functions, including cell proliferation, differentiation, and apoptosis in diverse organ systems (Aschner and Downey, 2016). TGF-β isoforms (β1, β2, and β3) are known to participate in embryonic lung development, in the maintenance of organ homeostasis and in the response to tissue injury. There is increasing evidence for the activation of TGF-β pathways in chronic lung diseases, including IPF (Bartram and Speer, 2004; Broekelmann et al., 1991; Khalil et al., 1991).

Expression of all three TGF-β gene isoforms, receptors (I, II, and III), and signaling mediators (SMAD-2, -3, -4, -6, and -7) occurs throughout lung development (Aschner and Downey, 2016). TGF-β1 gene-deleted mice develop widespread inflammation with pulmonary endothelialitis and interstitial pneumonia within 2 to 3 weeks after birth (Bartram and Speer, 2004). TGF-β1 is secreted by both stromal and epithelial cells of the primordial ducts as early as gestational day E11 in the developing mouse lung, and co-localizes with collagen I and III, fibronectin, and proteoglycans in the ECM (Heine et al., 1990). In mice, TGF-β1 has been shown to inhibit branching morphogenesis (Serra et al., 1994). Upregulation of TGF-β receptor II or SMAD-2, -3, -4, and -6 was also shown to inhibit branching morphogenesis while upregulation of SMAD-7, an inhibitory SMAD, promotes branching *in vitro* (Zhao et al., 1998). On the contrary, in rat lung explants, neutralization of TGF-β2 negatively affected branching (Liu et al., 2000). These findings support a critical role for TGF-βs as key regulators of branching morphogenesis.

Evidence also indicates a more prominent role for TGF-β signaling in the alveolarization phase of lung development (Alejandre-Alcazar et al., 2008). Increased expression of Activin

A receptor like kinase-1 (ALK-1), a type I TGF-β receptor, stimulates angiogenesis via maturation of endothelial cells during late lung development (Hu-Lowe et al., 2011; Lamouille et al., 2002). TGF-β1/SMAD signaling also plays a significant role in differentiation of AEC2s into AEC1s during alveolar phase (Bhaskaran et al., 2007). Blockade of canonical TGF-β signaling by SMAD-3 ablation between postnatal days 7 and 28 impairs alveolar maturation in mice (Ahlfeld et al., 2016; Chen et al., 2005). Interestingly, adenovirus mediated over-expression of TGF-β1 also results in inhibition of alveolarization in the neonatal mouse and rat lungs (Gauldie et al., 2003; Vicencio et al., 2004). Clara cells of the bronchiolar epithelium are known progenitor cells that participate in lung regeneration after injury (Crosby and Waters, 2010; Reynolds and Malkinson, 2010; Rokicki et al., 2016). The activin like kinase-5 (Alk-5) is a gene encoding the TGF-β type I receptor, is expressed in embryonic bronchial epithelium and loss of Alk-5 has been shown to inhibit Clara cell differentiation (Xing et al., 2010). TGF-β1 was reported to disrupt epithelial differentiation and inhibit synthesis of Clara cell secretory protein, phospholipids, and the surfactant proteins A, B, and C (Beers et al., 1998). Exogenously administered TGF-β1 inhibits epithelial maturation and surfactant production in human fetal lung culture (Beers et al., 1998). These observations support pleiotropic actions of TGF-β that may be contextual and concentration dependent in the developing lung.

In the adult human lung, TGF-β1 and TGF-β3 mRNAs are localized in the bronchial epithelium and alveolar macrophages while only TGF-β1 mRNA was detected in mesenchymal and endothelial cells (Coker et al., 1996). In mouse, TGF-β1 and TGF-β3 mRNA expression were observed in bronchiolar epithelium, Clara cells, mesenchymal cells, and alveolar cells, including macrophages. TGF-β1 (not TGF-β3) was localized in the pulmonary endothelium of mouse lungs (Coker et al., 1996). TGF-β1 regulates fibroblast recruitment to sites of tissue injury, and mediates fibroblast-to-myofibroblast differentiation (Thannickal et al., 2003). TGF-β1 stimulates ECM production by myofibroblasts and inhibits ECM degradation by matrix metalloproteinases (Krafts, 2010). These effects of TGF-β1 are modulated by cytokines such as platelet derived growth factor (PDGF), urokinase type plasminogen activator and monocyte chemoattractant protein-1 (Bartram and Speer, 2004).

Upregulation and activation of all TGF-β isoforms, and receptors are reported in IPF, although TGF-β1 is known to play predominant role in the pathogenesis of IPF (Bartram and Speer, 2004; Fernandez and Eickelberg, 2012). While TGF-β expression was detected in a variety of cell types including inflammatory cells, biologically active TGF-β1 released from alveolar epithelial cells is implicated in the pathogenesis of IPF lung disease (Xu et al., 2003). Hyperactivation of TGF-β signaling has been implicated in the pathogenesis of IPF, including myofibroblast differentiation and survival (Horowitz et al., 2007; Thannickal and Horowitz, 2006). Cellular senescence is a well-known mediator of fibrotic lung disease (Hecker et al., 2014; Schafer et al., 2017). Upregulation of markers of senescence was detected in lung fibroblasts and epithelial cells 14 days after bleomycin lung injury. These cells also reported a senescence-associated secretory phenotype (SASP) which included TGF-β1 (Schafer et al., 2017). Repetitive injury of the alveolar epithelium is considered critical for an aberrant wound healing response in IPF (Degryse et al., 2010; Wilson and Wynn, 2009). Consequent platelet activation with fibrin-rich clot formation is associated

with epithelial up-regulation of plasminogen activator inhibitor-1 (PAI-1) via TGF-β1/Smad3 signaling (Dennler et al., 1998). TGF-β1 is a potent inducer of apoptosis in alveolar epithelial cells (Siegel and Massague, 2003). TGF-β1 is secreted in a latent form, bound to latency-associated peptide (LAP). AECs in IPF have been shown to express increased levels of the integrin αvβ6 that binds to LAP and converts TGF-β1 and 3 into an active form (Munger et al., 1999). Overexpression of TGF-β1 in AEC2s resulted in AEC2 hyperplasia, interstitial thickening, fibroblast proliferation and increased ECM production (Xu et al., 2003). Epithelial-to-mesenchymal transition (EMT)-like cellular programs have been proposed to occur in IPF (Willis et al., 2005). However, in-vivo studies in an acute bleomycin injury model indicate that EMT is unlikely to serve as a source of myofibroblasts during lung fibrogenesis (Rock et al., 2011). Primary AECs cultured on fibronectin or fibrin matrix undergo EMT-like phenotypic changes via integrin-dependent activation of endogenous latent TGF-β1, while AECs cultured on laminin/collagen matrix do not activate the TGF-β1 signaling (Kim et al., 2006). Adhesion-dependent FAK signaling is a critical switch that determines TGF-β1-induced EMT vs. apoptosis (Ding et al., 2017). TGF-β1 induction of EMT may be mediated through both SMAD-dependent and -independent pathways, specifically through Erk and JNK activation (Xie et al., 2004; Yamashita et al., 2008). Alveolar macrophages are a significant source of TGF-β1 (Zhu et al., 2017). Co-culture of M2 macrophages with mouse lung epithelial cells results in EMT induction (Zhu et al., 2017); in this study, pre-treatment of macrophages with a TGF-β receptor inhibitor, LY2109761 blocked EMT, suggesting that alveolar M2 macrophages induces EMT through TGF-β/SMAD signaling. There is evidence of dysregulated macrophage signaling driven by TGF-β1 during fibrosis (Larson-Casey et al., 2016). Serum amyloid P, a member of the pentraxin family of proteins, was shown to inhibit bleomycin-induced lung fibrosis by limiting alveolar macrophage accumulation in a TGF-β1 over-expressing transgenic mouse model (Murray et al., 2011).

Aging-associated increases in TGF-β1 has been observed in the sera of human and mice (Carlson et al., 2009). IPF is a disease of aging and increased TGF-β1 remains central to the disease process. Although therapeutic approaches targeting activation of latent TGF-β and signaling reduce lung fibrosis in murine models, such efforts have not been translated into the clinic. TGF-β performs numerous normal physiologic functions and inhibition of TGF-β activities may lead to aberrant immune activation, epithelial hyperplasia and impaired wound healing (Varga and Pasche, 2008). Therefore, identification of the downstream TGF-β signaling effectors that mediate fibrosis without interfering with homeostatic functions of TGF-β may be more effective as therapeutic targets.

3.2 Wnt

The Wnt family of genes represents 19 secreted glycoproteins which regulate mammalian embryonic development and regenerative responses to injury in postnatal life (Logan and Nusse, 2004; Nusse and Clevers, 2017; Reya and Clevers, 2005). Aberrant Wnt signaling has been reported to cause birth defects and adult-onset diseases in humans (Clevers, 2006; Moon et al., 2004; Reya and Clevers, 2005). Wnt family of glycoproteins bind to cell surface receptors called Frizzled and activate intracellular signaling cascades (Hlsken and Behrens, 2000; Pongracz and Stockley, 2006). There are 10 Frizzled receptors encoded by 9 genes

that are members of seven-loop transmembrane family of receptors (Pongracz and Stockley, 2006). Canonical Wnt signaling pathway is initiated when Wnt binds to Frizzled on the plasma membrane along with the co-receptor low density lipoprotein related protein (LRP) 5/6; this results in inhibition of phosphorylation of β-catenin in the cytoplasm and its subsequent translocation into the nucleus, where it activates transcription factors of the T Cell factor (TCF)/LEF family of genes. In the absence of Wnt, β-catenin gets phosphorylated and degraded through the ubiquitin-proteasome pathway (Nusse and Clevers, 2017; Pongracz and Stockley, 2006). Canonical Wnt signaling regulates a diverse set of genes that include, matrix metalloproteinases (MMPs) (Wu et al., 2007), cell-cycle regulators (Davidson and Niehrs, 2010), oncogenes (Zhan et al., 2017), and angiogenic growth factors (Qu et al., 2014).

There are two non-canonical Wnt pathways: the planar cell polarity (Wnt/PCP) and Wnt/calcium (Wnt/Ca_2^+) pathways. The Wnt/PCP pathway activates JNK and Rho-kinases (Kuhl et al., 2000; Pandur et al., 2002). The Wnt/ Ca_2^+ pathway increases intracellular calcium concentration and activates protein kinase C, calcineurin and CaMKII signaling pathways. These non-canonical Wnt signaling pathways regulate cell migration, cell polarity and stem cell maintenance. Non-canonical Wnt signaling also engages LRP-5/6, but differs from canonical signaling in requiring different G-proteins for signal transduction (Liu et al., 2001; Liu et al., 2005; Malbon et al., 2001; Regard et al., 2011). Wnt1, Wnt2/2b, Wnt3/3a, Wnt7a/7b, Wnt8 and Wnt10a/10b typically signal via the canonical pathway, while Wnt5a, Wnt4 and Wnt11 participate in non-canonical Wnt signaling pathway, with few exceptions (Pongracz and Stockley, 2006; Torres et al., 1996).

Both canonical and non-canonical pathways are activated during lung organogenesis (De Langhe and Reynolds, 2008; Li et al., 2015). Five Wnt genes were found to be expressed in the developing lung: Wnt2/2b, Wnt7b, Wnt5a, and Wnt11 (Goss et al., 2009; Lako et al., 1998; Li et al., 2002; Rajagopal et al., 2008; Shu et al., 2002; Weidenfeld et al., 2002). Among the canonical Wnt ligands, Wnt2 is produced by the mesenchyme (Monkley et al., 1996), Wnt11 by both mesenchyme and epithelium (Lako et al., 1998), and Wnt7B was detected exclusively in the epithelium (Weidenfeld et al., 2002). Canonical Wnt/β-catenin signaling appears in the anterior foregut as early as embryonic day E9.0 and regulates formation of the trachea and two lung buds (E9.5); this is mediated via expression of Nkx2.1 transcription factor in the endodermal cells on the ventral side of the anterior foregut. Wnt2/2b$^{-/-}$ mutants or mice lacking endoderm-specific β-catenin expression or mice overexpressing Wnt antagonist, DKK-1, show complete lung agenesis and lack of Nkx2.1 expression (Goss et al., 2009; Harris-Johnson et al., 2009; Volckaert et al., 2013). Early endoderm-specific deletion of Ctnnb1, the gene encoding β-catenin, leads to a complete failure to specify lung progenitors (Goss et al., 2009). Retinoic acid signaling in the foregut mesoderm suppresses activities of DKK-1, and TGF-β to promote endodermal Wnt signaling and mesodermal FGF-10 production respectively, both critical for the formation of lung primordium (Chen et al., 2010; Chen et al., 2007). Epithelial-specific inactivation of β-catenin during pseudoglandular stage of lung development leads to reduced branching, defective proximal–distal patterning, and development of peripheral airways via down-regulation of critical pathways such as BMP-4 and FGF signaling (Hashimoto et al., 2012; Mucenski et al., 2003; Ostrin et al., 2018; Shu et al., 2005; Ustiyan et al., 2016). The non-

canonical Wnt5A stimulates migration, proliferation and differentiation of lung endothelial cells (Cheng et al., 2008). Over-expression of Wnt5A results in increased levels of fibroblast growth factor-10 (FGF-10) in the mesenchyme and decreased sonic hedgehog (SHH) in the epithelium, supporting its role in branching morphogenesis of the developing lung (Li et al., 2005; Li et al., 2002). Wnt7b promotes epithelial and mesenchymal expansion during lung development and modestly induces mesenchymal FGF-10 expression (Rajagopal et al., 2008).

In the adult lung, Wnt signaling maintains homeostasis by regulating stem and progenitor cell functions during quiescence and injury repair (Borthwick et al., 2001; Flozak et al., 2010; Pongracz and Stockley, 2006; Reya and Clevers, 2005; Zhang et al., 2008). Functional studies indicate a role for Wnt signaling in epithelial cell proliferation, EMT, myofibroblast differentiation, and collagen synthesis (Kim et al., 2002; Konigshoff et al., 2008). In the epithelium, Wnt5a facilitates AEC2 to AEC1 differentiation and surfactant production (Xu et al., 2015). In normal lung fibroblasts, Wnt5a promotes proliferation, increased fibronectin expression, and inhibits H_2O_2-induced apoptosis (Vuga et al., 2009). Reduction of canonical and increase in non-canonical Wnt signaling have been observed in hematopoietic stem cells and lungs of aged mice (Florian et al., 2013; Paxson et al., 2013). Increase in non-canonical Wnt signaling has been also found in aging human lungs (Kovacs et al., 2014). Interestingly, increase in canonical Wnt signaling was observed in the muscle cells of aged mice (Brack et al., 2007). Increased Wnt signaling was also shown to induce cellular senescence (Zhang et al., 2013a).

Evidence of aberrant activation of components of Wnt signaling in IPF is documented in multiple studies. β-catenin expression in normal adult lung is confined to endothelial and epithelial cells; however, in IPF lungs, nuclear accumulation of β-catenin was observed in proliferative epithelial lesions as well as in fibroblastic foci (Chilosi et al., 2003). Wnt1, 7b and 10b, Frizzled-2, -3 and LEF-1 expression were found to be significantly increased in IPF (Konigshoff and Eickelberg, 2010). Conversely, in the bleomycin model, inhibition of Wnt/beta-catenin signaling resulted in attenuation of lung fibrosis (Henderson et al., 2010; Kim et al., 2011). Wnt1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with IPF (Konigshoff et al., 2009).

Wnt family of genes may contribute to IPF pathogenesis through multiple mechanisms. Wnt/β-catenin signaling induces anti-apoptotic and pro-fibrotic phenotypes in lung fibroblasts, promoting fibroblast proliferation, and myofibroblast differentiation and survival (Hamburg-Shields et al., 2015; Lam and Gottardi, 2011). Wnt/β-catenin pathway activation in AEC2 results in increased production of IL-1β, leading to an inflammatory and pro-fibrotic response (Aumiller et al., 2013). MMP-7 is activated by upregulation of Wnt/β-catenin pathway facilitating breakdown of ECM and directional fibroblast movement (Chilosi et al., 2003; Konigshoff et al., 2008; Rosas et al., 2008). Non-canonical Wnt5a has been shown to promote proliferation and survival of lung fibroblasts as well as increase in ECM production (Vuga et al., 2009). TGF-β and Wnt crosstalk play important roles in IPF pathogenesis. TGF-β1 has been shown to synergize with Wnt/β-catenin signaling pathway to induce epithelial-mesenchymal transition (Zhou et al., 2012). TGF-β1 induced expression of ECM metalloproteinase inducer (EMMPRIN, a glycosylated transmembrane protein) in

AEC2 cells further stimulates production of certain MMPs by stromal fibroblasts acting through Wnt/β-catenin signaling pathway (Hasaneen et al., 2016). ICG-001, a small molecule that inhibits T-cell factor (TCF)/β-catenin transcription, was found to inhibit TGF-β1-induced EMT and reverse pulmonary fibrosis in mice (Henderson et al., 2010), suggesting that targeting TGF-Wnt crosstalk might be a useful therapeutic strategy.

3.3 Sonic Hedgehog

The hedgehog pathway is one of the major developmental pathways regulating organ morphogenesis in various organisms (Ingham and McMahon, 2001). The hedgehog gene was first described in fruit fly *Drosophila melanogaster*, where it regulates dorsal–ventral differentiation and segment polarity (Heussler and Suri, 2003; Nusslein-Volhard and Wieschaus, 1980). Three vertebrate orthologs were identified namely sonic hedgehog (SHH), indian hedgehog (IHH), and desert hedgehog (DHH) (Kugler et al., 2015). Among the hedgehog orthologs, SHH is the most abundantly expressed hedgehog ligand and plays a critical role in organ morphogenesis, including the lung (Fernandes-Silva et al., 2017; McMahon et al., 2003). Canonical hedgehog signaling is activated when one of the hedgehog ligands bind to Patched1 (PTCH1) receptor on the plasma membrane (Fernandes-Silva et al., 2017). In the absence of ligand, PTCH1 sequesters Smoothened (SMO), a G-protein coupled transmembrane protein, at the base of the primary cilia on the plasma membrane, resulting in inhibition of hedgehog pathway (Taipale et al., 2002). PTCH1 is inhibited upon binding of the hedgehog ligand, thereby freeing SMO to signal to the glioma-associated transcription factors (GLI-1/2/3) to dissociate from suppressor of fused (SUFU) in the cytosol (Humke et al., 2010). GLI-2/3 translocate to the nucleus and express SHH responsive genes, namely secreted signaling proteins such as bone morphogenetic protein-4 (BMP-4), cell cycle genes like N-Myc, and transcription factors such as forkhead box A2 (FoxA2) (Astorga and Carlsson, 2007; Oliver et al., 2003; Rohatgi et al., 2007; Sasaki et al., 1997). Non-canonical hedgehog signaling, independent of GLI transcription factors, during organogenesis has also been proposed (Jenkins, 2009).

During lung development, SHH is expressed in the ventral foregut endoderm as early as embryonic day E10 in mice (Kugler et al., 2015; Litingtung et al., 1998), while receptor PTCH1 and the GLI transcription factors are abundantly expressed in the adjacent mesenchyme starting day E11.5 (Bellusci et al., 1997a; Grindley et al., 1997). Endodermal expression of SHH in the ventral foregut is regulated by retinoic acid produced by the adjacent mesoderm (Rankin et al., 2016). SHH induces mesodermal expression of Wnt2/2b and BMP-4 via paracrine signaling leading to endodermal expression of Nkx2.1 which is critical for the formation of the initial lung buds (Rankin et al., 2016). In mice, highest expression of SHH was found to be restricted in the distal epithelium of the developing lung between E10.5 to E16.5 which also coincides with the period of branching morphogenesis (Miller et al., 2001). PTCH1, SMO, and the GLI transcription factors are also elevated in the mesenchyme during branching proportional to the SHH level (Bellusci et al., 1997a; Grindley et al., 1997; Zhang et al., 2010). Gene deletion of SHH or its signaling intermediates (PTCH1, GLI-2/3) results in lung abnormalities including lung hypoplasia and defective lobe formation (Bai et al., 2002; Goodrich et al., 1997; Grindley et al., 1997; Litingtung et al., 1998; Motoyama et al., 1998; Pepicelli et al., 1998). SHH levels decline

during late gestation although robust SHH expression was observed in subsets of the respiratory epithelial cells (Miller et al., 2001). Inhibition of hedgehog signaling during early postnatal lung development results in larger airspaces without affecting alveolar septation (Liu et al., 2013). SHH signaling is also tightly regulated by the mesenchyme-derived Hedgehog interacting protein (HHIP) which prevents branch outgrowth (Chuang et al., 2003; Chuang and McMahon, 1999). Overexpression of SHH in mice during lung development leads to an abundance of mesenchyme and the absence of typical alveoli resulting respiratory death soon after birth (Bellusci et al., 1997a).

Hedgehog signaling maintains adult stem cells in diverse adult tissues/organs (Petrova and Joyner, 2014). SHH signaling has been reported to be active in the adult lung and maintain quiescence of the progenitor cells (Peng et al., 2015). In this study, SHH signaling is downregulated following acute lung injury, which allows for mesenchymal expansion. Attenuation of this response negatively affects epithelial repair, supporting the concept dysregulation of hedgehog signaling may lead to aberrant repair and regeneration in the lung (Peng et al., 2015).

Increased hedgehog pathway activity has been demonstrated in IPF (Bolanos et al., 2012; Chanda et al., 2016; Cigna et al., 2012; Selman et al., 2008). Significantly higher expression of SHH and its signaling effectors was detected in the alveolar epithelium and underlying fibroblasts, respectively, in areas undergoing fibrotic remodeling (Bolanos et al., 2012; Cigna et al., 2012; Selman et al., 2008). SHH pathway has been reported to stimulate myofibroblast differentiation and collagen production in tissue fibroblasts from systemic sclerosis (Horn et al., 2012). In the lung, SHH treatment increased fibroblast proliferation, survival, migration, and ECM production without elevating α-SMA expression (Bolanos et al., 2012; Chanda et al., 2016). Higher SHH expression in airway and alveolar epithelial cells has been reported in the bleomycin-induced experimental model of lung fibrosis (Moshai et al., 2014). While inhibition of hedgehog signaling fails to prevent fibrosis in the bleomycin model, SHH overexpression during the fibrotic phase worsens lung fibrosis (Liu et al., 2013; Moshai et al., 2014). Thus, although SHH signaling is essential for normal lung development and maintains quiescence of the mesenchyme, it is also chronically activated in IPF.

3.4 Notch

Notch signaling is essential for normal development and homeostasis of multiple organs, including the lung (Xu et al., 2012). Dysregulation of Notch signaling has been implicated in tissue fibrosis and cancer (Dang et al., 2000; Kavian et al., 2012; Noseda et al., 2006; Xu et al., 2012). A detailed account of canonical Notch signaling is reviewed elsewhere (Ables et al., 2011; Bray, 2016). Briefly, Notch pathway facilitates juxtacrine signaling between neighboring cells via single-pass transmembrane receptors, thereby regulating cell fate decisions during organ development through intercellular communications. There are four Notch receptors (Notch 1–4) and five ligands, Jagged 1, Jagged 2, Delta-like canonical Notch Ligands (Dll1, Dll3, and Dll4) in mammals (Bray, 2016; Kopan and Ilagan, 2009). Notch receptors are composed of functional extracellular, transmembrane and intracellular domains. Following ligand-receptor interaction, the Notch intracellular domain (NICD) is

cleaved by γ-secretase from the transmembrane domain and associates with nuclear CSL to activate Notch pathway target genes which include c-Myc, p21, Hes, and Hey family of genes (Ables et al., 2011; Kopan and Ilagan, 2009; Lubman et al., 2007).

Notch pathway genes are expressed in the developing lung as early as bud formation. While Notch1, Jagged 1 and Jagged 2 are restricted to the distal part of the budding endoderm, Dll1 expression is detected in the proximal region (Kong et al., 2004; Tsao et al., 2008; Xu et al., 2012). Although Notch signaling is not required for initial lung bud formation, it specifies epithelial cell fate decisions along the proximodistal axis. Using explant cultures, it was shown that pharmacological inhibition of Notch signaling in the foregut or lung results in an expansion of the distal epithelial progenitor pool that interferes with proximal structure formation (Tsao et al., 2008). In contrast, transgenic mice overexpressing a dominant active Notch3 intracellular domain in the distal lung epithelium show impaired differentiation of distal epithelial progenitor cells by preventing maturation (Dang et al., 2000).

During late lung development, Notch signaling regulates alveologenesis (Tsao et al., 2016). In mice, inactivation of Notch signaling in the lung epithelium interfered with alveolar formation marked by significantly reduced AEC2 surfactant protein-C production and emphysema-like enlargement of distal airspaces resulting in death by 2–3 weeks after birth (Tsao et al., 2016). Conditional deletion of Notch signaling intermediates, Jagged-1 or glycosyltransferase lunatic fringe (*Lfng*) causes only mild defect in alveolar epithelium which slows alveologenesis due to delayed differentiation of AEC2 to AEC1 (Xu et al., 2010). Interestingly, Notch over-expressing mutants die before onset of alveologenesis (Guseh et al., 2009). During neonatal life, Notch2, as compared to Notch1, is primarily activated in AEC2s to induce PDGF-α expression and paracrine signaling of alveolar myofibroblasts progenitors, critical for secondary septa formation during alveologenesis (Tsao et al., 2016)8681381;. In the postnatal lung, epithelial Notch signaling prevents airway club (Scgb1a1 positive/Clara) cells from differentiating into goblet cells and is critical for airway regeneration after injury (Tsao et al., 2009). Notch signaling, therefore, plays a major role in the epithelial–mesenchymal interactions during alveologenesis and maintenance of the integrity of the epithelial and smooth muscle layers of the distal conducting airways in the developing lung (Tsao et al., 2016). Deletion of Jaggged-1 in the lung epithelium negatively affects alveolar septation, without apparently compromising differentiation of epithelial progenitors (Zhang et al., 2013b). Further studies of cell-specific activation of Notch signaling during lung development is required to fully understand the role of this important pathway.

In the adult lung, Notch signaling preserves progenitor cell niches in coordination with other developmental pathways and participates in tissue injury repair (Noseda et al., 2006; Xu et al., 2012). Experimental activation of Notch signaling has been shown to reduce adherence of the germ line stem cells to the niche with aging (Tseng et al., 2014), suggesting that Notch participates in niche maintenance that may contribute to the age-related decline in stem cells. Marked decline in cell adhesiveness and development of anoikis resistance is well known in cancer progression and metastasis (Buchheit et al., 2014), and increased Notch signaling has been reported in this process (Hu et al., 2012). Elevated Notch-mediated signaling has also been reported in IPF (Hu et al., 2015; Zhou et al., 2016). Myofibroblast

apoptosis resistance play a key role in the pathogenesis of pulmonary fibrosis (Thannickal et al., 2004; Xie et al., 2015). Notch/CSL activation stimulates α-SMA expression in vascular smooth muscle cells, and during endothelial-to-mesenchymal transformation (Noseda et al., 2006). *Lfng* gene deletion in lung fibroblasts inhibits myofibroblast differentiation (van Tuyl et al., 2005), and inhibition of Jagged1/Notch1 signaling in mesenchymal stromal cells attenuates bleomycin-induced lung fibrosis (Hu et al., 2015; Zhou et al., 2016). Notch signaling is upregulated in surviving Clara cells after naphthalene injury, where it facilitates epithelial repair (Volckaert et al., 2011). In contrast, inactivation of Notch signaling in Clara cells stimulates goblet cell differentiation in the postnatal lung (Tsao et al., 2011; Zhang et al., 2013). The role of non-canonical Notch pathways are currently being studied, and appear to participate in organ development and postnatal tissue repair via Wnt/β-catenin signaling (Andersen et al., 2012).

3.5 Fibroblast Growth Factors

Fibroblast growth factors (FGFs) are primarily secreted proteins that are critical in controlling cell proliferation, survival, migration and differentiation during embryonic development and postnatal life (Beenken and Mohammadi, 2009; Ornitz and Itoh, 2015). FGF signals via the activation of a set of cell surface receptors (FGFRs) (Ornitz and Itoh, 2015). FGFRs are single-pass transmembrane proteins with tyrosine kinase activity (Coughlin et al., 1988; Huang and Huang, 1986) and FGF-FGFR interactions are stabilized by heparin sulfate proteoglycans at the cell surface (Ornitz, 2000). FGF signaling through FGFR regulates cellular functions acting via Ras/MAPK/ERK-1,−2, PI3K/AKT, PLCγ/DAG/IP3/PKC, and JAK/STAT pathways (Ornitz and Itoh, 2015; Ornitz and Marie, 2015; Teven et al., 2014). Sprouty (Spry-1 and Spry-2) family of proteins negatively regulates FGF-FGFR signaling, primarily the activation of the Ras/MAPK/ERK1/2 pathway (Hanafusa et al., 2002). Eighteen secreted FGFs have been identified, and are subdivided into seven subgroups based on sequence homology and phylogeny (Itoh and Ornitz, 2011; Ornitz and Itoh, 2015; Popovici et al., 2005). Most FGFs mediate their activities through paracrine signaling; although members of the FGF-19 subgroup (FGF-19, FGF-21, FGF-23) mediate endocrine actions (Beenken and Mohammadi, 2012), and members of the FGF-11 subgroup (FGF-11, FGF-12, FGF-13, FGF-14) do not bind/activate any of the FGFRs and signal intracellularly (Olsen et al., 2003; Smallwood et al., 1996). There are four FGFRs (1–4) identified in the vertebrates which bind specific FGF ligands, except FGF-1 which binds to all FGFRs (Ornitz and Itoh, 2015). Mesenchyme-derived FGF-7 and FGF-10, interact with epithelial FGFR2-IIIb with very high specificity (Lebeche et al., 1999; Peters et al., 1994). FGF signaling through mesenchymal FGFR3 and FGFR4 regulates alveolarization by restricting elastogenic machinery and controlling ECM organization (Li et al., 2017; Ornitz and Itoh, 2015; Weinstein et al., 1998). .

FGF-10 null mice do not form lungs (Min et al., 1998; Sekine et al., 1999). Mesenchyme-derived FGF-10 maintains the niche of distal epithelial progenitors (Bellusci et al., 1997b; Hogan et al., 1997; Lu et al., 2005; Min et al., 1998; Park et al., 1998; Volckaert and De Langhe, 2014). Targeted expression of a dominant negative FGFR2 in the lung epithelium or expression of a soluble dominant-negative FGFR2 mutant in transgenic mice also prevents lung branching morphogenesis (Celli et al., 1998; Peters et al., 1994). In the fetal rat lung,

FGF-2 stimulates surfactant protein gene expression in alveolar epithelial progenitor cells via the PI3K/AKT pathway (Matsui et al., 1999). While targeted FGF-9 gene deletion in the developing lung results in lung hypoplasia (Colvin et al., 2001), FGF-18 is involved in specification of proximal structures (Whitsett et al., 2002).

FGF signaling has been implicated in the pathogenesis of IPF (Joannes et al., 2016; Kadono et al., 1996; Shimbori et al., 2016). In the adult lung, FGF-2 is normally expressed in the epithelium, vascular endothelium, smooth muscle, and epithelial basement membrane (Cordon-Cardo et al., 1990; Guzy et al., 2015; Kranenburg et al., 2005). Increased expression of FGF-2 is reported in IPF lungs (Inoue et al., 1996; Kadono et al., 1996; Qu et al., 1995). It was later demonstrated that FGF-2 is required for epithelial recovery after bleomycin injury in mice,rather than directly contributing to the fibrogenic process (Guzy et al., 2015). Elevated FGF-1 levels are also detected in IPF lungs (MacKenzie et al., 2015). FGF-1 inhibits TGF-β1 stimulated myofibroblast differentiation, and EMT (Hoyles et al., 2011). FGF-1 exerts anti-fibrotic effects by inhibition of myofibroblast differentiation and EMT via proteosomal degradation of TGF-β receptor I both *in vitro* and *in vivo* (Shimbori et al., 2016). In the adult lung, FGFR2b signaling maintains the basal stem cell population and FGF-10 released from the airway smooth muscle cells drives regeneration after naphthalene injury (Volckaert et al., 2011). FGF-10 maintains clonal expansion and differentiation of the alveolar epithelial progenitors and protects them against oxidative stress, asbestos-induced DNA damage and apoptosis (Upadhyay et al., 2004; Upadhyay et al., 2005). Marked reduction in FGF-10 expression in the lung alveolar mesenchymal stromal cells was demonstrated in progressive IPF patients compared to stable IPF (Chanda et al., 2016). FGF-9 and FGF-18 promote survival and migration of human lung fibroblasts, and inhibit myofibroblast differentiation *in vitro* (Joannes et al., 2016). Requirement of cell autonomous mesenchymal FGFR signaling was recently demonstrated during the development of lung fibrosis, and accumulation of Col1α2 positive mesenchymal lineage in fibrotic tissue following bleomycin exposure (Guzy et al., 2017). Therapeutic strategies aimed at targeting mesenchymal FGF signaling may represent an effective strategy to attenuate fibrosis; indeed, the FDA-approved triple angiokinase inhibitor, nintedanib, is well known to inhibit FGFR signaling (Richeldi et al., 2014).

4. Cooperation between TGF-β and Major Developmental Pathways in IPF

Activation of TGF-β, Wnt, SHH, Notch, and FGF signaling pathways are critical for regulating several stages of lung development. In the postnatal lung, many of these pathways maintain progenitor cell niches and actively participate in tissue injury repair. Aberrant recapitulation of these pathways, which may be exacerbated with aging, may contribute to adverse chronic lung diseases such as IPF. While each of these pathways function via their cognate receptors and signaling intermediates, it is important to recognize that they do not act in isolation, but interact with other stress-related or regenerative pathways to determine the ultimate outcome of cellular and tissue responses. Since TGF-β1 has been identified as a central mediator of tissue fibrosis, including IPF (Bartram and Speer, 2004; Fernandez and Eickelberg, 2012; Thannickal et al., 2004), we will examine some of the key pro-or anti-fibrotic signaling pathways that crosstalk with TGF-β signaling.

TGF-β1 was shown to amplify Wnt signaling in the mesenchyme via increased nuclear translocation of β-catenin (Guo and Wang, 2009; Warner et al., 2005). In Xenopus embryos, TGF-β1 and Wnt co-regulate the production of connective tissue growth factor (CTGF), which mediates tissue remodeling and fibrosis (Lipson et al., 2012; Luo et al., 2004). Co-activation of the two pathways occurs via formation of SMAD/β-catenin/TCF-4 complex in the nucleus (Lei et al., 2004). In human bone marrow, SMAD-3/β-catenin signaling in mesenchymal stromal cells promotes self-renewal and inhibits osteocytic and adipocytic differentiation (Jian et al., 2006). SMAD-7, an inhibitor of canonical TGF-β1 signaling, has been shown to promote degradation of β-catenin in the cytoplasm, thereby inhibiting Wnt signaling (Shi and Massague, 2003). Wnt/βcatenin signaling has been implicated in lung fibrosis (Chilosi et al., 2003; Konigshoff et al., 2008). Mice deficient in LRP-5, a Wnt co-receptor, express lower levels of TGF-β1 in the alveolar epithelium after bleomycin injury and are protected from fibrosis (Lam et al., 2014). Thus, pro-fibrotic effects of hyperactive Wnt signaling appear to be, at least in part, mediated through TGF-β1.

TGF-β1 induces the expression of several Notch receptor ligands and co-regulates their shared gene targets in many cell types (Guo and Wang, 2009). SMAD-3, a TGF-β1 signaling mediator forms a complex with Notch signaling intermediates, NICD and CSL in the nucleus to activate Notch-target genes (Blokzijl et al., 2003). Jagged-1, a Notch ligand, augments TGF-β1 mediated upregulation of the cell cycle inhibitor, p21, which confers cytostatic effects on human breast epithelial cells (Niimi et al., 2007). Loss of Notch activity in aged muscle cells is associated with increased TGF-β/SMAD-3 signaling which interferes with regeneration due to activation of the cyclin-dependent kinase inhibitors, p15, p16, p21, and p27 (Carlson et al., 2008). Muscle regenerative capacity was restored when SMAD-3 binding to the promoters of cell-cycle inhibitor genes was inhibited after Notch pathway activation (Carlson et al., 2008). Interaction between Jagged-1/Notch and TGF-β1/SMAD pathways promotes myofibroblast differentiation and EMT during experimentally induced lung fibrosis in mice (Liu et al., 2009; Zavadil and Bottinger, 2005; Zavadil et al., 2004). Together, these studies support cooperative and synergistic effects between the TGF-β and Notch pathways in fibrogenesis.

TGF-β/SMAD signaling was shown to activate Gli-1, −2 genes, effectors of the SHH pathway, in human dermal fibroblasts and keratinocytes (Dennler et al., 2007). SHH signaling in lung fibroblasts stimulates fibroblast proliferation, migration, survival and ECM deposition (Bolanos et al., 2012). Exogenous TGF-β1 stimulates SHH expression in human gingival fibroblasts and inhibition of TGF-β signaling abrogates cyclosporine-induced SHH upregulation (Chung and Fu, 2013). This suggests cooperation between SHH and TGF-β signaling may occur in IPF. Increased TGF-β and SHH signaling is cooperatively suppresses FGF-10 expression in normal human lung fibroblasts (Bolanos et al., 2012; Chanda et al., 2016; McQualter et al., 2013). T-box transcription factors-4, −5 (TBX-4, −5) induce mesenchymal FGF-10 gene expression in embryonic mouse lung (Cebra-Thomas et al., 2003). TBX-4 lineage mesenchymal progenitors are a primary source of myofibroblasts in injured adult lung and ablation of TBX-4 expressing mesenchymal cells attenuates fibrosis following bleomycin lung injury in mice (Xie et al., 2016). Interestingly, levels of TGF-β1 and TGF-βR1 are decreased in TBX-4 expressing lung fibroblasts, while TGF-β2 and TGF-βR2 are upregulated (Xie et al., 2016). Conditional deletion of TGF-β receptor II in

COL1α2 or TBX-4 expressing lung fibroblasts significantly reduces lung fibrosis (Hoyles et al., 2011). Understanding the interactions between TGF-β, SHH and FGF-10 may uncover novel opportunities for therapeutic intervention.

Hippo signaling is an evolutionarily conserved pathway that determines organ size by regulating cell proliferation, apoptosis, and stem cell self-renewal (Badouel et al., 2009). Hippo pathway involves a series of phosphorylation steps leading to inactivation of transcriptional co-activators YAP/TAZ. Dephosphorylated YAP/TAZ translocated into the nucleus and induces expression of genes (CTGF, amphiregulin, survivin, FGF, and GLI-2) commonly associated with cellular growth, differentiation, and apoptosis inhibition (Dawes et al., 2018; Dupont et al., 2011; Fujii et al., 2012; Tsuneki et al., 2017; Zhang et al., 2009; Zhao et al., 2010). In the lung, nuclear YAP was reported to prevent differentiation of embryonic and adult lung progenitor cells (Mahoney et al., 2014; Volckaert et al., 2017; Zhao et al., 2014). TGF-β1 targets Hippo pathway facilitating nuclear translocation of YAP/SMAD-2 (Pefani et al., 2016) which is also associated with F-actin polymerization and stress fiber formation in mesenchymal stromal cells on stiff matrices (Dupont et al., 2011). Nuclear translocation of YAP/TAZ was observed in IPF fibroblasts and in lung fibroblasts grown on stiff matrices which stimulates ECM synthesis, contraction and proliferation (Liu et al., 2015).

5. Therapeutic Targeting of Developmental Pathways in IPF

Impaired alveolar epithelial regeneration and a heightened fibroblastic response are considered key hallmarks of pulmonary fibrosis. Although aberrant recapitulation of major lung developmental pathways has been implicated in the pathogenesis of IPF (Selman et al., 2008), therapeutic approaches to limit tissue remodeling and fibrosis have been challenging. Transplantation of Sox-9^{+} airway basal stem cells has been shown to stimulate regeneration of functional alveoli in mice following bleomycin injury (Ma et al., 2018). Suppression of TGF-β signaling by an FDA-approved anti-fibrotic drug, Pirfenidone, further improved efficiency of the transplanted progenitors (Ma et al., 2018). In addition to TGF-β, Pirfenidone has also been shown to act via inhibition of FGF-2 and IL-1β (Oku et al., 2008; Schaefer et al., 2011). The mechanism of the action of another approved anti-fibrotic drug, Nintedanib, is not well understood, although effects on TGF-β signaling and non-canonical autophagy has been demonstrated (Rangarajan et al., 2016), as well as on PDGF receptor signaling (Wollin et al., 2015). Nintedanib also targets FGF and vascular endothelial growth factor receptor tyrosine kinases as well as Src family of kinases (Kim et al., 2017; Richeldi et al., 2014). Inhibition of FGFR1 activity by NP603, a tyrosine kinase inhibitor, reduced carbon tetrachloride induced hepatic fibrosis in rats (Lin et al., 2011).

Activation of ECM-bound latent TGF-β is dependent on αv integrins on the epithelium, and treatment with antibodies against αvβ6 integrin prevented development of fibrosis in an experimental model of lung fibrosis (Horan et al., 2008; Puthawala et al., 2008; Wipff and Hinz, 2008). Inhibition of TGF-β receptors, ALK-4/5, or SMAD-3 reduced fibrosis in animal models (Ishida et al., 2006; Jinnin et al., 2006).

DKK-1 is a negative regulator of Wnt signaling (Akhmetshina et al., 2012). TGF-β induced fibrogenic response is mediated via activation of Wnt/β-catenin signaling in the fibroblasts which is associated with very low expression of DKK-1 (Akhmetshina et al., 2012). The SHH pathway is upregulated in IPF (Bolanos et al., 2012). Inhibition of SMO (SHH signaling mediator) by cyclopamine, SMO-specific RNA, or small molecule inhibitor LDE223 promotes fibrosis resolution (Rosenbloom et al., 2013). Activated Notch signaling is also reported in IPF (Xu et al., 2012), and suppression of Notch signaling by DAPT, an inhibitor of γ-secretase reduces lung fibrosis in mice (Kavian et al., 2012). Ectopic overexpression of FGF-10 in the alveolar epithelium protects from development of lung fibrosis in murine model following bleomycin injury (Gupte et al., 2009). Re-epithelialization potential of a combination of a glycosaminoglycan (dermatan sulfate) and FGF-10 has been demonstrated in burn wounds in clinical trials (Plichta and Radek, 2012). Thus, in addition to TGF-β1 signaling, targeting other developmental pathways that mediate pro-fibrotic effects in IPF may be an effective therapeutic strategy.

6. Conclusions

Major pathways that drive embryonic lung development play an important role throughout postnatal life by maintaining progenitor cells niches during quiescence and regeneration following diverse injuries. Animal models support an essential role for these developmental pathways in regulating self-renewal and differentiation of mesenchymal and epithelial stem cells in the normal reparative/regenerative response. Paradoxically, in the aberrant repair process that characterizes IPF, there is also an upregulation of many of these developmental pathways (Figure 2). The significance of this upregulation in IPF is not well understood. However several possibilities may be considered. First, the nature of the injury – acute vs. chronic – may be sufficient to activate these pathways without achieving normal tissue structure and function. For example, repetitive bleomycin injury results in a more durable and persistent fibrosis when compared to the resolving nature of a single dose bleomycin injury (Degryse et al., 2010). Second, the regenerative response may shift from canonical to non-canonical signaling with aging, thereby favoring fibrogenesis. Increased Wnt signaling alters muscle stem cell fate and promotes fibrosis with aging (Brack et al., 2007). Indeed, aging mice have less capacity to resolve fibrosis when compared to their younger counterparts (Hecker et al., 2014). Additionally, age-related alterations in metabolic sensing, mitochondrial dysfunction, and autophagy insufficiency may interfere with the capacity for fibrosis resolution (Rangarajan et al., 2018). Third, a blunted or insufficient response of a particular regenerative pathway may result in fibrosis. For example, the levels of FGF-10 appear to be markedly reduced in progressive IPF (Chanda et al., 2016). Finally, all signaling is contextual, and the aging lung may favor fibrosis over regeneration. The pleiotropic nature of signaling components or genes may offer beneficial effects in early, reproductive years, while inducing more harmful effects in late life when their selective advantage has waned. This concept is commonly referred to as “antagonistic pleiotropy” and has been proposed as a theory of aging (Williams, 1957); however, the antagonistic pleiotropic actions of developmental genes may better serve as an explanation for age-related diseases rather than aging itself.

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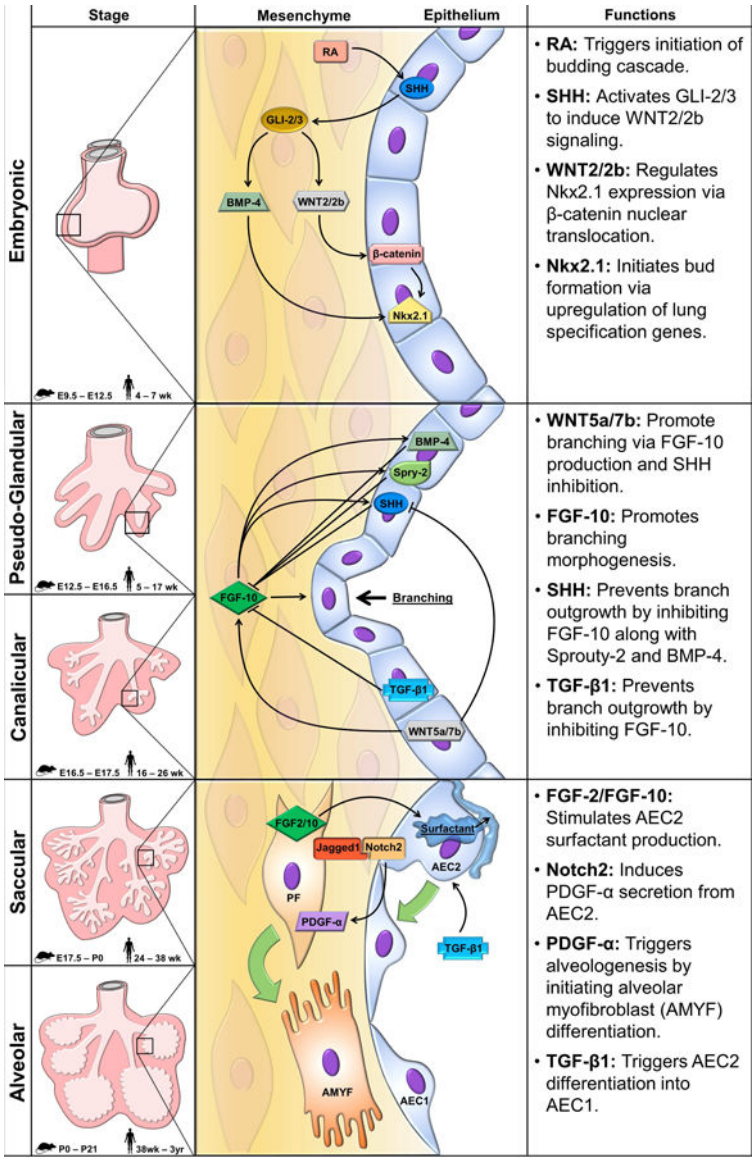

Figure 1: Major signaling pathways during mammalian lung development.

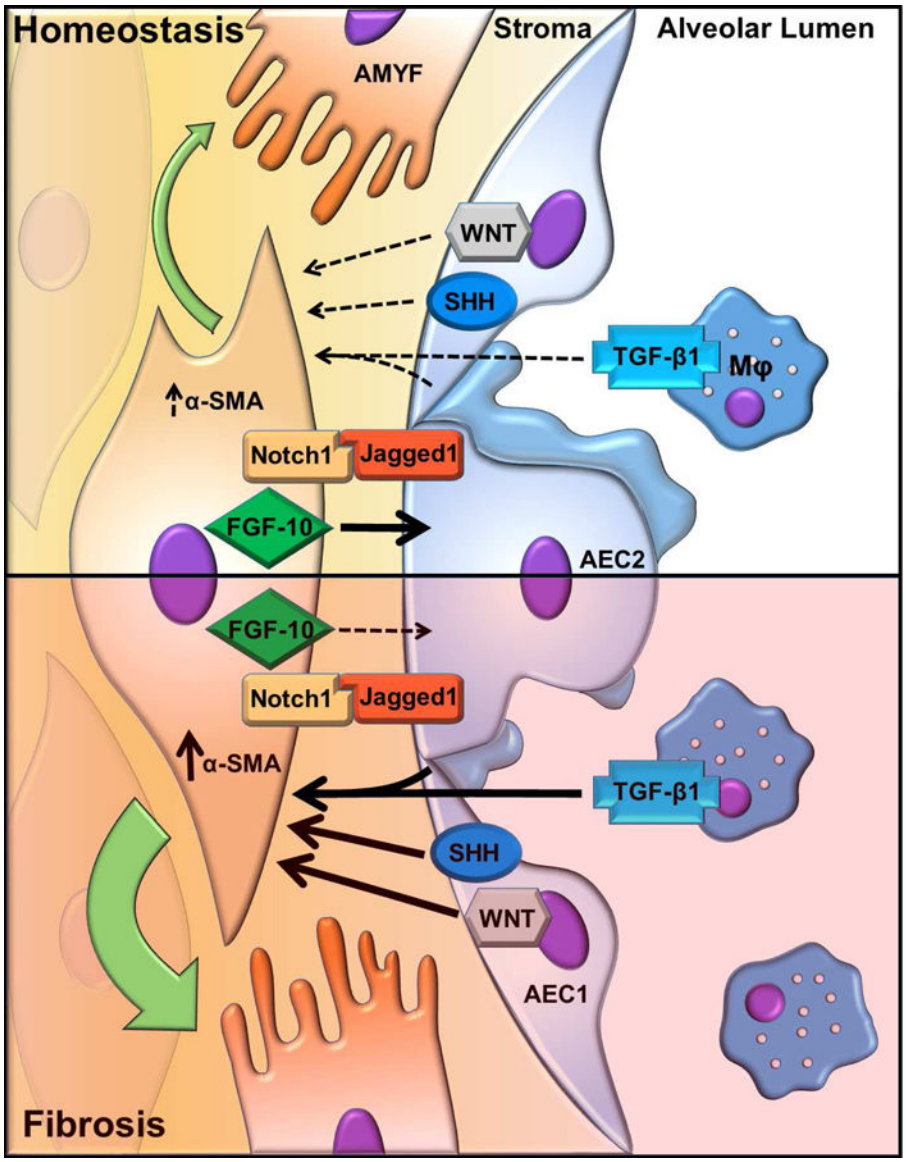

Figure 2: Epithelial-mesenchymal interactions during lung homeostasis and fibrosis.