Fgf10 Signaling in Lung Development, Homeostasis, Disease, and Repair After Injury

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The lung is morphologically structured into a complex tree-like network with branched airways ending distally in a large number of alveoli for efficient oxygen exchange. At the cellular level, the adult lung consists of at least 40–60 different cell types which can be broadly classified into epithelial, endothelial, mesenchymal, and immune cells. Fibroblast growth factor 10 (Fgf10) is expressed in mesenchymal stromal niches, between cartilage rings in the upper conducting airways where basal cells normally reside, and in the lipofibroblasts adjacent to alveolar type 2 cells. Fgf10 protects and promotes lung epithelial regeneration after different types of lung injuries. An Fgf10-Hippo epithelial-mesenchymal crosstalk ensures maintenance of stemness and quiescence during homeostasis and basal stem cell (BSC) recruitment to further promote regeneration in response to injury. Fgf10 signaling is dysregulated in different human lung diseases including bronchopulmonary dysplasia (BPD), idiopathic pulmonary fibrosis (IPF), and chronic obstructive pulmonary disease (COPD), suggesting that dysregulation of the FGF10 pathway is critical to the pathogenesis of several human lung diseases.

Keywords: Fgf10, regeneration, epithelium, fibrosis, injury

EPITHELIAL FGF10 SIGNALING DURING LUNG DEVELOPMENT

Fibroblast growth factor 10 (Fgf10) was first detected using whole-mount in situ hybridization 20 years ago in the splanchnic mesoderm surrounding the foregut around E9.5 when the primary lung buds start to emerge. Lung primordial mesoderm-specific transcription factor Tbx4 defines the Fgf10 expression domain, at both the anterior and posterior boundaries (Sakiyama et al., 2003). The importance of Fgf10 in lung development is well illustrated by the total failure of lung formation and perinatal lethality of Fgf10 deficient mice (Min et al., 1998; Xu et al., 1998; Sekine et al., 1999). Even though Fgf10 binds with high affinity to Fgfr2b, it has a weaker affinity for Fgfr1b (Ohuchi et al., 2000). The Fgf10 knockout phenotype is phenocopied in mice lacking Fgfr2b (Arman et al., 1999; De Moerlooze et al., 2000), which is highly expressed in respiratory epithelium from the early embryonic lung bud stages through late fetal lung development (Peters et al., 1992). Intriguingly,
Fgf10 has also been detected in the lung mesenchyme (Al Alam et al., 2015), but its mesenchymal function requires further investigation. Although Fgfr2b is a receptor for both Fgf7 and Fgf10 during lung development, Fgf7 knockout mice do not exhibit an obvious lung defect (Guo et al., 1996), even though Fgf7 is expressed in the developing lung mesenchyme starting at E14.5 (Mason et al., 1994). However, overexpression of Fgf7 in mice using the human Sftpc promoter results in severe pulmonary malformations, including bronchial airway enlargement, cystic lung lesions and impaired branching morphogenesis leading to embryonic lethality (Simonet et al., 1995).

From E10.5 to E12.5, Fgf10 expression is restricted to the distal lung mesenchyme at sites where branching occurs (Belluscì et al., 1997) and the ventral mesenchyme of the trachea (Sala et al., 2011; Figure 1A). For a long time, the localized pattern of Fgf10 expression in the distal lung was thought to determine where new lung buds sprout. However, proper epithelial branching still occurs in developing Fgf10−/− lungs in which Fgf10 is overexpressed in every cell. This indicates that the precise spatial organization of Fgf10 expression is not required for the highly preserved and stereotypical branching morphogenesis. Hence, other mechanical and/or signaling pathways systems must be in place to control bud outgrowth. Instead, localized Fgf10 expression in the distal mesenchyme is required to regulate epithelial lineage commitment (Volckaert et al., 2013) by maintaining the undifferentiated status of the distal Sox9+ expressing epithelial progenitors and preventing them from differentiating into Sox2pos bronchial epithelium (Figure 1A).

Fgf10 achieves this, in part, by activating epithelial β-catenin signaling through activation of Akt, which negatively regulates Sox2 expression (Volckaert et al., 2013). Indeed, Wnt/β-catenin signaling is important for the regulation of proximal-distal differentiation in the developing airway epithelium (De Lange et al., 2005; Hashimoto et al., 2012; Ostrin et al., 2018). As the epithelium grows out, cells which become further and further displaced from the source of Fgf10 start to differentiate into Sox2pos bronchial epithelium (Volckaert et al., 2013; Volckaert and De Lange, 2014; Figure 1A). As a corollary, Fgf10 hypomorphs and conditional Fgf10 (Dermo1-cre:Fgf10) and Fgf2 (Sftpc-cre:Fgf2) mutants fail to maintain distal progenitors, resulting in a proximalized lung with impaired alveolar epithelial lineage formation and reduced capacity to produce surfactant proteins (Maillieux et al., 2005; Ramasamy et al., 2007; Abeler et al., 2009). In addition, in lungs overexpressing Fgf10 early on, distal epithelial progenitors fail to differentiate into bronchial epithelium (Volckaert et al., 2013). Taken together, these findings indicate that epithelial-mesenchymal interactions between Fgfr2b and its ligand Fgf10 is required for lung epithelial lineage commitment (Xu et al., 1998; Sekine et al., 1999; Ohuchi et al., 2000).

The localized expression of Fgf10 in the trachea, on the other hand, drives submucosal gland (SMG) and basal cell development and their maintenance (Rawlins and Hogan, 2005; Volckaert et al., 2013; Volckaert et al., 2017). At the onset of lung and trachea initiation, Fgf10 is detected in the ventral mesenchyme of the trachea (Sala et al., 2011), and then becomes restricted to the intercartilage mesenchyme at later stages and into adulthood (Sala et al., 2011). Interestingly, although Fgf10−/− and Fgfr2b−/− embryos are born without lungs, they still develop a trachea (Sekine et al., 1999; De Moerloose et al., 2000; Sala et al., 2011). SMGs are severely reduced in number and size in Fgf10 heterozygotes (Jaskoll et al., 2005; Rawlins and Hogan, 2005). Abnormal function of SMGs of the upper respiratory tract are associated with severe/fatal asthma and cystic fibrosis later in life (Benayoun et al., 2003; Salinas et al., 2005). However, despite the significance of SMGs for human respiratory diseases, little is known about the mechanisms of Fgf10 signaling that controls their growth, differentiation, and homeostasis during early postnatal and adult life.

Overexpression of Fgf10 at later stages of lung development, post-Sox2pos bronchial epithelial specification, directs the differentiation of Sox2pos proximal airway epithelium toward the p63/Krt5pos basal cell lineage while blocking Foxj1pos ciliated cell fate throughout the conducting airway (Volckaert et al., 2013). The cells that express Fgf10 in the mesenchyme are themselves progenitors for airway and vascular smooth muscle cells as well as lipofibroblasts (LIFs) during embryonic development, and a subset of lung resident mesenchymal stem cells during adult life (Maillieux et al., 2005; Taniguchi et al., 2007; El Agha et al., 2014). Interestingly, Fgf10 also directly and indirectly orchestrates differentiation of these mesenchymal progenitors (El Agha and Belluscì, 2014; Chao et al., 2015). Epithelial BMP4, a target of Fgf10, controls the differentiation of cells arising from the distal mesenchymal Fgf10-expression domain into the airway smooth muscle cell (ASM C) lineage (Maillieux et al., 2005). In addition, Fgf10 hypomorphs demonstrate defective formation of alveolar myofibroblasts (aMYFs) at different developmental stages (Maillieux et al., 2005; Ramasamy et al., 2007).

Starting at E16.5, Id2pos Sox9pos Sftpcpos Pdpnpos alveolar/bipotent epithelial progenitors give rise to alveolar type I and II (AT1/AT2) cells (Desai et al., 2014; Treutlein et al., 2014). Alveolar epithelial differentiation is coordinated by both mechanical forces and growth factors. In this context, it was recently shown that mechanical forces generated by fetal breathing movements stimulate AT1 cell differentiation, whereas Fgf10-mediated ERK1/2 signaling in distal progenitor cells prevents them from differentiating, thereby ensuring their AT2 fate (Li et al., 2018). In the mesenchyme, Glilpos Pdgfra pos mesenchymal progenitor cells give rise to aMYFs and LIFs (Li et al., 2015; Chao et al., 2016). Although aMYFs and LIFs are both derived from Glilpos Pdgfra pos mesenchymal progenitors, LIFs exhibit lower Pdgfra pos expression and higher levels of Fgf10 expression in association with its receptors Fgfr1b and Fgfr2b. This suggests that different Fgf and ligand profiles might mediate the direction of differentiation from Pdgfra pos mesenchymal progenitors toward LIF or aMYF (McGowan and McCoy, 2015). Interestingly, it has been shown that LIFs consist of both Fgf10pos and Fgf10pos subpopulations (Al Alam et al., 2015). Fgf10 reduction in Fgf10 hypomorphs as well as knockdown of Fgfr2b ligand in vivo led to significantly decreased expression of LIF marker Adrp at E18.5 in global LIF subpopulations (Fgf10pos and Fgf10pos). This suggests that Fgf10 signals promote the formation of LIFs in an autocrine
A Wnt7b-Fgf10 epithelial-mesenchymal crosstalk maintains distal epithelial progenitors during lung development and becomes reactivated in the adult lung to regenerate injured airway epithelium. (A) During the branching stage of lung development, Fgf10 is expressed by mesenchymal progenitor cells, which depends on Wnt/β-catenin signaling, and acts on the distal epithelium to induce Bmp4 and Sox9 expression to keep them in an undifferentiated state. As the epithelial tube grows toward the Fgf10 source, Sox9+ progenitors acquire more proximal positions, switch on Sox2 expression and acquire bronchial epithelial fate. Simultaneously, distal Fgf10-expressing airway smooth muscle (ASMC) progenitors encounter epithelial Bmp4 and Shh (not shown) causing them to stop expressing Fgf10 and differentiate into mature ASMCs. (B) In the adult, basal stem cells (BSCs) generate their own Fgf10-expressing niche mediated by Yap-Wnt7b, and their maintenance is critically dependent on Fgf10-Fgfr2b signaling. The non-cartilaginous airway epithelium is kept quiescent during homeostasis, by active Integrin-linked kinase (Irk)-Hippo signaling, which prevents Fgf10 expression in ASMCs. In response to injury, surviving epithelial cells spread out, leading to a destabilization of Merlin and inactivation (dephosphorylation) of Hippo kinases Mst1/2. This increases nuclear Yap in spreading epithelial cells causing these cells to secrete Wnt7b. Epithelial-derived Wnt7b then acts on ASMCs to induce Fgf10 expression, which is required for epithelial regeneration. Solid cell borders represent lineage labels to follow the fate of epithelial cells in response to injury.

and/or paracrine fashion (Al Alam et al., 2015). Additionally, constitutive Fgfr1b knockouts and conditional partial loss of Fgfr2b in lung mesenchyme revealed that Fgfr1b and Fgfr2b are likely to play redundant roles in LIF formation (Al Alam et al., 2015). Finally, Apert syndrome mice, which exhibit a splicing switch defect resulting in increased mesenchymal Fgfr2b expression, demonstrate increased Fgf10 expression and signaling in the mesenchyme. These mice display reduced epithelial branching, arrested development of terminal airways and an “emphysema like” phenotype in post-natal lungs resulting from decreased canonical Wnt signaling (De Langhe et al., 2006), likely due to sequestering of the Fgf10 ligand by the misexpressed Fgfr2b receptor.

**FGF10 SIGNALING DURING LUNG AND TRACHEA HOMEOSTASIS**

During homeostasis, adult mouse lungs harbor three main stem cell populations that maintain the lung epithelium: basal stem/progenitor cells (BSCs) in the cartilaginous airways, club cells in the conducting airways and subsets of AT2 cells in the...
alveoli (Rawlins et al., 2009; Rock et al., 2010; Barkauskas et al., 2013). During homeostasis Fgf10 is expressed in mesenchymal stromal niches, between cartilage rings in the upper conducting airway where basal cells normally reside, and in the LIFs adjacent to AT2 cells in the alveoli (El Agha et al., 2014; Figures 1B, 2).

BSCs are progenitors for club, Tuft1/2, neuroendocrine and ionocyte cells (Rock et al., 2009, 2010; Montoro et al., 2018). In the developing trachea, Fgf10 secreted by the inter-cartilage ionocyte cells (Rock et al., 2009, 2010; Montoro et al., 2018). Intra-tracheal administration of Fgf10 attenuates lipopolysaccharide (LPS)-induced acute lung injury (Tong et al., 2014). Lung resident mesenchymal stromal cells (MSCs) isolated from Fgf10 pretreated rats are protected against LPS-induced acute lung injury (Tong et al., 2016). However, the mechanism underlying these protective effects of Fgf10 signaling during injury and regeneration in adult lung have not yet been fully elucidated.

Fgf10-expressing cells were identified as a subset of LIF progenitors during embryonic development (El Agha et al., 2014). Fgf10-expressing LIFs have been shown to differentiate into activated MYFs upon bleomycin injury, while simultaneously upregulating their Fgf10 expression levels (El Agha et al., 2017). Fgf10-expressing MYFs dedifferentiate back into LIFs but do not downregulate their Fgf10 expression levels during the resolution phase of lung fibrosis (El Agha et al., 2017) suggesting that they retain a memory of the injury which might protect against further injury. This supports the concept that LIFs serve as a source of activated MYFs during fibrogenesis which revert back to LIFs during fibrosis resolution (El Agha et al., 2017; Figure 2).
Naphthalene injury is a well-established injury model to study conducting airway epithelial regeneration by selectively ablating club cells except for a few naphthalene-resistant club stem cells located at bronchoalveolar duct junctions (BADJs) and adjacent to neuroendocrine bodies (NEBs). In the adult lung, Fgf10 is not expressed in mature ASMCs during homeostasis (Figure 1B). However, upon conducting airway epithelial injury, when surviving differentiated epithelial cells spread in an attempt to maintain barrier function, they downregulate their Hippo pathway to drive Yap into the nucleus, and induce the secretion of Wnt7b. Epithelial-derived Wnt7b, in turn, induces Lgr6\textsuperscript{pos} ASMCs to release Fgf10 (Volckaert et al., 2011, 2017; Volckaert and De Langhe, 2014; Lee et al., 2017), which activates Notch and β-catenin signaling in surviving club cells to drive their amplification to promote regeneration (Volckaert et al., 2011; Lee et al., 2017; Figure 1B). Together, these findings provide strong evidence that ASMCs function as a niche for conducting airway epithelial stem cells. Besides club cell regeneration, the induction of Fgf10 expression by the ASMC niche in non-cartilaginous airways extends the BSC niche, allowing the recruitment of tracheal BSCs and/or driving the differentiation of Sox2\textsuperscript{pos}p63\textsuperscript{pos}Krt5\textsuperscript{neg} progenitors along the BSC lineage (Volckaert et al., 2017; Yang et al., 2018). In summary, the Fgf10-Hippo epithelial-mesenchymal crosstalk ensures maintenance of stemness and quiescence during homeostasis and recruitment of BSCs to promote regeneration in response to injury (Volckaert et al., 2017; Figure 1B).

A similar tonic Hedgehog signal maintains lung airway epithelial and mesenchymal quiescence in the distal mouse airways (Peng et al., 2015). In this model, loss of Hedgehog signaling drives regeneration in response to naphthalene-induced epithelial injury via a mesenchymal feedback mechanism, and deregulation of hedgehog during naphthalene induced epithelial lung injury leads to aberrant repair and regeneration (Peng et al., 2015). These findings imply that the Wnt-Fgf10 epithelial-mesenchymal cross-talk and Shh pathway may function as an interactive signaling network in airway and alveolar remodeling responses to chronic injury in asthma, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis.

FGF10 SIGNALING IN HUMAN LUNG DISEASES

Several syndromic craniosynostoses have been associated with dominantly acting mutations of FGFR1, FGFR2, and FGFR3 (Hajihosseini et al., 2001). FGFR2B is up-regulated in cultured fibroblasts of some Apert’s and Pfeiffer’s syndrome patients (Oldridge et al., 1999). Gain-of-Fgfr2b function mice Fgfr2\textsuperscript{c/+}\textsuperscript{bA} show phenotypic resemblance to Apert’s and Pfeiffer’s syndromes, including visceral and growth defects, neonatal growth retardation and death, coronal synostosis, ocular proptosis, precocious sternal fusion, and abnormalities in secondary branching in lung and kidney that undergo branching morphogenesis (Hajihosseini et al., 2001; De Langhe et al., 2006).

In humans, haploinsufficiencies for FGF10 or FGFR2B result in autosomal dominant aplasia of lacrimal and salivary glands and lacrimo auriculo-dentoidal syndrome, respectively (Entezarian et al., 2005; Klar et al., 2011). In the former syndrome, patients exhibit irreversible airway obstruction, indicating that genetic variants affecting the FGF10 signaling pathway are important determinants of lung function which ultimately contribute to COPD (Klar et al., 2011). Notably, an airway branch variant with absence of the right medial-basal airway associated with polymorphisms within the FGF10 gene is associated with COPD among smokers (Smith et al., 2018). Interestingly, increased nuclear YAP levels, along with FGFR2B and Wnt7b expression, were observed in squamous metaplastic areas within the airway epithelium of COPD subjects (Volckaert et al., 2017), suggesting that the Hippo pathway is inactivated to induce FGF10 expression and BSC amplification in human COPD.

Bronchopulmonary dysplasia (BPD) is a chronic pulmonary disease of prematurely born infants characterized by arrested alveolar development (Chao et al., 2017). BPD biopsy samples show reduced FGF10 expression (Benjamin et al., 2007), implicating that FGF10 signaling may be involved in BPD. By using hyperoxia-induced neonatal lung injury from post-natal day 0 (P0) to P8 as a mouse model of BPD, Chao et al. (2017) have shown that Fgf10 deficiency causes lethality from P5 in Fgf10\textsuperscript{+/−} pups due to impaired AT2 formation after hyperoxic injury. In this study, overexpression of a secreted dominant negative Fgfr2b, demonstrated that post-natal deficiency of Fgfr2b ligands in the context of hyperoxia-exposure causes decreased SftpC expression and eventually leads to significant lethality. This indicates that Fgfr2b ligands are important for repair after hyperoxia exposure in neonatal lung.

Idiopathic pulmonary fibrosis (IPF) is a chronic interstitial lung disease characterized by the loss of alveolar epithelial integrity, progressive invasion of the lung parenchyma by myofibroblasts and increased extracellular matrix (ECM) deposition leading to respiratory failure, and death often within 5 years of diagnosis (Thannickal et al., 2004; King et al., 2011; Steele and Schwartz, 2013; Yang et al., 2013). Gene expression profiles of MSCs from IPF patient lungs revealed that FGF10 expression in MSCs is suppressed in IPF subjects with progressive disease, along with upregulation of both TGF-β1 and SHH signaling. This suggests that FGF10 deficiency is a potentially critical factor in disease progression (Chanda et al., 2016). However, recently it has been shown that FGF10 is significantly upregulated at both mRNA and protein level in IPF lungs compared to the donor lungs, especially in dense fibrotic islands where ACTA2\textsuperscript{pos} cells accumulate (El Agha et al., 2017).

CONCLUSION

Fgf10 signaling is essential for lung development and adult stem cell maintenance. Important questions remain regarding the mechanisms that regulate Fgf10 expression in the niche to unleash the full therapeutic potential of Fgf10. In addition, very little is known about the importance of FGF10 signaling in human lung development and homeostasis. During homeostasis,
BSCs are restricted to the cartilaginous airway in mice as they require Fgfr2b signaling for their maintenance, whereas in humans they can be found deep in the lung. However, upon different types of injury BSCs are deployed throughout the mouse lung as ASMcs in the non-cartilaginous airways re-express Fgf10 to regenerate the airway epithelium. It is therefore likely that the apparent restricted BSC pattern in the mouse lung is due to it being housed in a fairly sterile environment rather than constantly being exposed to environmental insults as is the case for humans.

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

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