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Transcriptional Control of Lung Morphogenesis

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Maeda Y, Davé V, Whitsett JA. Transcriptional Control of Lung Morphogenesis. *Physiol Rev* 87: 219–244, 2007; doi:10.1152/physrev.00028.2006.—The vertebrate lung consists of multiple cell types that are derived primarily from

endodermal and mesodermal compartments of the early embryo. The process of pulmonary organogenesis requires the generation of precise signaling centers that are linked to transcriptional programs that, in turn, regulate cell numbers, differentiation, and behavior, as branching morphogenesis and alveolarization proceed. This review summarizes knowledge regarding the expression and proposed roles of transcription factors influencing lung formation and function with particular focus on knowledge derived from the study of the mouse. A group of transcription factors active in the endodermally derived cells of the developing lung tubules, including thyroid transcription factor-1 (TTF-1), β-catenin, Forkhead orthologs (FOX), GATA, SOX, and ETS family members are required for normal lung morphogenesis and function. In contrast, a group of distinct proteins, including FOXF1, POD1, GLI, and HOX family members, play important roles in the developing lung mesenchyme, from which pulmonary vessels and bronchial smooth muscle develop. Lung formation is dependent on reciprocal signaling among cells of both endodermal and mesenchymal compartments that instruct transcriptional processes mediating lung formation and adaptation to breathing after birth.

I. INTRODUCTION

A. Transcription and Lung Development

The formation of the lung occurred relatively late in evolution, representing a singular solution to terrestrial survival of vertebrates. From the sequencing of DNA across multiple phyla, it has become readily apparent that a large part of each genome has been committed to the control of gene transcription and that biological diversity has been generated primarily by the elegant control of gene expression rather than by differences in the numbers of genes in each genome. Thus >20% of the human genome has been committed to the regulation of transcription and the signaling molecules that inform transcriptional processes. Organ specification and morphogenesis depend on both tissue-selective and ubiquitous transcription factors and genes that work in interacting networks. The complexity of gene transcription during lung morphogenesis is immediately evident from the multiple cell types that comprise the lung, being derived from ectodermal, mesenchymal, and endodermal compartments, all present in appropriate numbers and sites to support respiration. Transcription factors uniquely specifying lung formation have not been identified to date. Although a number of transcription factors and their binding sites have been characterized and associated with the regulation of lung specific genes, the principles that govern the design and evolution of transcriptional networks operating during lung formation and function have just begun to be understood. Not surprisingly, some of these genes encode proteins that are unique to the lung, namely, proteins critical for pulmonary surfactant homeostasis, which are required for reduction of surface tension at the air-liquid interface and without which gas exchange would not be possible.

Study of lung-selective gene expression is relatively recent, beginning with the recognition that regulatory regions of all the surfactant protein genes, including *Sftpa*, *Sftpb*, *Sftpc*, and *Sftpd*, are controlled by the homeodomain containing protein thyroid transcription factor-1 (TTF-1; Nkx2.1) (24). Knowledge regarding the expression and diversity of transcription factors expressed in the developing lung has expanded in parallel with the recognition that transcription factors function in complex networks, interacting at transcriptional and posttranscriptional levels to regulate gene expression. Functions of transcription factors are influenced in multiple cellular compartments by both transcriptional and posttranscriptional mechanisms, via interactions with proteins regulating their routing, degradation, import, and export from the nucleus and by protein-protein interactions among diverse groups of transcription factors and coactivators. Transcriptional complexes interact with DNA on target genes whose access is influenced by the structure of surrounding chromatin. Chromatin structure itself is regulated by recruitment of remodeling factors, the actions of histone acetylases, deacetylases, and methylase/demethylase that modify histone at unique sites. Knowledge regarding the expression and function of an increasing number of transcription factors important for lung formation is expanding rapidly. This review provides a summary of the roles of a number of transcription factors influencing lung morphogenesis, with particular focus on developmental processes critical for lung formation during embryogenesis and for lung function at the time of birth.

The pulmonary system consists of a tracheal tube, leading to bronchi/bronchioles, that provide inhaled gases to peripheral saccular-alveolar structures, wherein capillaries come in close apposition to epithelial surfaces to facilitate the exchange of oxygen and carbon dioxide required for cellular respiration. As in the organogenesis of all tissues, formation of the lung is dependent on a myriad of interactions among signaling and receiving molecules that mediate cell proliferation, survival, migration, polarity, differentiation, and function (84). While precise knowledge regarding the molecules and cellular events regulating lung formation remains relatively rudimentary, processes mediating lung morphogenesis and homeostasis are actively being studied and identified (30, 45, 209, 249).

B. Spatial and Temporal Control of Lung Morphogenesis

The structure of the lung varies in complexity among vertebrate species but is highly conserved in its position along the foregut, ventral to the esophagus, between the thyroid and stomach (Fig. 1). Lungs are spatially organized along both cephalo-caudal (from the conducting airways to the peripheral saccules) and dorsal-ventral axes. Mammalian lungs are usually asymmetrically lobulated; for example, the mouse lung consists of four right and left main lobes. Pulmonary situs is determined by genes regulating left-right asymmetry (196). Formation of the lung also requires information that regulates right and left asymmetry and the gradual tapering of the conducting airways that lead to ever smaller tubes that lead to the alveoli where gas exchange occurs.

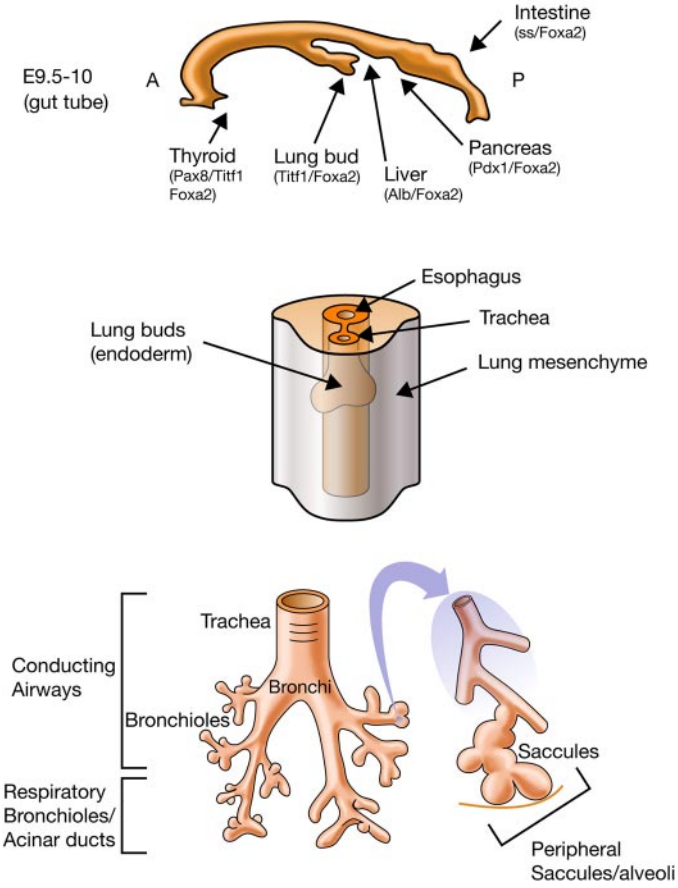

FIG. 1. Patterning of the foregut endoderm: lung bud formation and branching morphogenesis. *Top*: mouse endoderm is depicted at approximately E9.5–10. Transcription factors (Pax8, Titf1, Pdx1, Foxa2) and markers (Alb, albumin; ss, somatostatin) identify cells that contribute to organ formation along the anterior-posterior axis (A-P). TTF-1 (Titf-1 gene) is expressed at sites of lung and thyroid formation, with the latter in cells expressing both PAX8 and TTF-1. *Middle*: lung buds and trachea at E9.5–10, as the early buds evaginate into the mesenchyme. *Bottom*: conducting and peripheral regions of the lung at approximately E12. Later in morphogenesis (E17–18) peripheral saccules are formed (*bottom right inset*). Alveolarization occurs in the postnatal period.

As in other branching organs, proliferation and differentiation of distinct regions of the lung occur at precise times during development. Lung formation has been organized into five structural epochs that are generally shared, but vary temporally and regionally among diverse vertebrate species (Table 1). The sites, levels, and identity of transcription factors controlling morphogenesis change dynamically during these periods. Transcription factors of multiple families are expressed in various cells during lung morphogenesis. While some transcription factors are highly restricted to cell type, for example, in the mesenchyme or epithelium, others are expressed in multiple tissue compartments in a distribution pattern that may also change during development.

C. Transcriptional Anticipation of Lung Formation Along the Foregut Axis in the Early Embryo

The lung buds arise from the lateral-esophageal sulcus that arises between the thyroid and the stomach along the foregut endoderm expressing organ-selective genes (206, 293). Expression of transcription factors or markers characteristic of specific organs are observed along the anterior-posterior axis of the foregut tube before formation of each organ (206; A. M. Zorn and J. M. Wells, unpublished observations). TTF-1, an Nkx2 homeodomain-containing transcription factor, marks the region from which lung buds arise (Fig. 1). As a general theme, many of the transcription factors required for development of the early foregut are reutilized later in lung morphogenesis (283). For example, deletion of the *Foxa2*, *Catnb*, *Sox17*, *Gata-6*, *Stat3* genes, and other transcription factors expressed in endodermally derived cells along the foregut, results in failure of normal embryonic patterning well before the formation of the lung (3, 87, 104, 167, 226). Nevertheless, many of these transcription factors play important roles in lung morphogenesis, functioning later in gestation and in the postnatal period. Because formation of specific organs along the foregut is dependent on paracrine signaling between cells of the endodermally derived tube and cells from neighboring mesenchyme, transcription factors controlling foregut growth and differentiation (e.g., FOXF1, GLI family members, POD-1, and others) are also critical for lung morphogenesis.

D. Fibroblast Growth Factor Signaling Influences Organ Formation Along the Foregut Tube

TTF-1 is the earliest known marker associated with commitment of endodermal cells to pulmonary and thyroid cell lineages, appearing before formation of the definitive lung (120) (Fig. 1). Outgrowth and branching of these TTF-1 expressing cells require fibroblast growth

TABLE 1. *The five structural epochs of lung formation*

Phase	Events	Mouse	Human
Embryonic	Formation of the lung buds and major bronchi, division of tracheal-esophageal tube	E9–11.5	3–7 wk
Pseudoglandular	Proliferation of bronchial branches, acinar tubules and buds; vasculogenesis and innervation	E11.5–16.5	5–17 wk
Canalicular	Organization of the pulmonary vascular bed, pulmonary acinus, and increasing innervation	E16.5–17.5	16–26 wk
Saccular	Dilation of peripheral airspaces, differentiation of the respiratory epithelium and increasing vascularity of the saccules, surfactant synthesis	E17.5–PN5	24–38 wk
Alveolar	Growth and septation of the alveoli, maturation of the pulmonary vascular system	PN5–28	38 wk to maturity

E, embryonic; PN, postnatal.

factor (FGF) signaling. Recent studies support the concept that FGF signaling centers from heart and/or from the splanchnic mesenchyme influence lung formation from foregut endoderm (206). The dose and timing of exposure of endodermal precursors to FGF signaling from the cardiac mesenchyme influences the formation of pulmonary lineages as the gut tube forms at E7–8 in the mouse. Cells receiving less FGF stimulation form other organs, including the gastrointestinal tract, liver, and pancreas (283). Thyroid organogenesis is marked by coexpression of TTF-1 and PAX-8, whereas formation of the lung occurs in a region marked by coexpression of TTF-1 and FOXA2 (24, 58). To date, a lung specific transcription factor has not been identified; however, the process of lung formation is dependent on TTF-1 and its interactions with other transcription factors.

II. EMBRYONIC AND PSEUDOGLANDULAR PERIOD: TRANSCRIPTION IN THE RESPIRATORY EPITHELIUM DURING BRANCHING MORPHOGENESIS

Two lung buds appear on the ventral-lateral aspect of the foregut at embryonic day (E) 9–9.5 and evaginate into the splanchnic mesenchyme as the primordial trachea and two main bronchi are formed. The tracheal and bronchial stalks extend to form the main bronchi, a process completed by approximately E10.5 in the mouse.

FGF-10 from the mesenchyme (155), FGF-R2 in the endoderm (53), SHH/GLI 2,3 (132, 188), and retinoic acid receptors (RARs) (151) play important roles during this early period of tracheal-pulmonary morphogenesis. While TTF-1 is required for lung organogenesis per se, the upper trachea and in some cases the main bronchi are formed in mice lacking TTF-1 (112, 157), FGF-10 (155), or FGF-R2IIIb (53). While there is considerable redundancy in retinoic acid receptor (RAR) function, deletion of multiple RARs causes severe tracheal and lung malformations, including lung hypoplasia and agenesis (151). Lung formation is also dependent on SHH produced by the endodermally derived cells that activate Ptch/Smo/Gli in the pulmonary mesenchyme (188). *Shh*$^{-/-}$ mice have tracheoesophageal fistula and simple cystlike lung sacs that fail to branch (132, 188). Like the SHH and FGF pathways, multiple signaling centers control autocrine-paracrine signaling among and between endodermal and mesenchymally derived cells during formation of the lung that drive transcriptional processes to influence gene expression and cell behavior. On the other hand, transcriptional centers guide the production and secretion of signaling molecules that function in a reciprocal manner. Removal of the splanchnic mesenchyme surrounding primordial lung buds blocks growth and branching of bronchial tubules in the embryonic lung, a process that can be restored by provision of an FGF signaling center toward which endodermal cells of the peripheral lung tubules will migrate (12, 255). In the embryonic/pseudoglandular period, pulmonary cells are capable of considerable plasticity; for example, exposure of tracheal tubes to peripheral lung mesenchyme can reprogram their differentiation to that of peripheral lung tubules (55).

A. Complementary Development of Lung Epithelium and Mesenchyme

Stereotypic branching and budding occurs as the bronchial and bronchiolar tubules form between approximately E11 to E16 in the mouse. During this period, pulmonary blood vessels are produced by vasculogenesis and angiogenesis (52). Blood vessels coalesce and extend along the lung tubules to produce pulmonary arteries, veins, and lymphatics. Smooth muscle cells differentiate and migrate along the bronchial tubules (143). Nerves are observed along vascular structures, primarily innervating the conducting regions of the lung. Cartilage appears along the ventral region of the trachea and bronchi in a precisely spaced manner. The lung tubules gradually taper along the cephalo-caudal axis. Cartilaginous regions

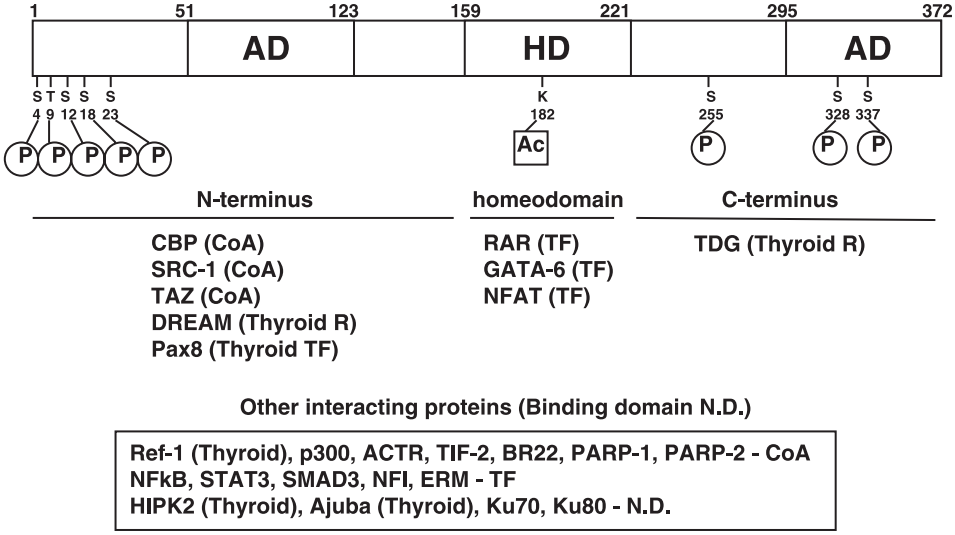

FIG. 2. Structure of TTF-1, its post-translational modifications, and interacting proteins. TTF-1 consists of three domains: NH_2-terminal activation domain (AD), middle DNA-binding homeodomain (HD), and COOH-terminal AD. TTF-1 is phosphorylated on seven serine residues and a threonine residue in the NH_2- and COOH-terminal domain, and acetylated on a lysine residue in the HD. Multiple domains of TTF-1 bind to coactivators and transcription factors in the lung, thyroid, and forebrain. TTF-1 interacts via direct protein-protein interactions with transcription factors and coactivators via distinct domains to regulate gene expression. P, phosphorylation; Ac, acetylation; CoA, coactivator; R, repressor; TF, transcription factor; N.D., not determined.

of the airway are well established by E11–12, being marked by expression of Sox9 in precartilagenous tracheal-bronchial mesenchyme. Deletion or mutation in a number of transcription factors and signaling molecules, including SHH (154), SOX9 (165), RARs (151), and FGF receptors (50), disrupts tracheal cartilage formation in the developing mouse lung. Thus, by E16, the general structure of the lung is well established along multiple axes, providing the scaffolding upon which region-specific differentiation of various pulmonary epithelial cells begins.

B. TTF-1 and Branching Morphogenesis

TTF-1 is a 43-kDa homeodomain-containing protein expressed in forebrain, thyroid, and lung. In the lung, TTF-1 plays a critical role in the regulation of lung morphogenesis, epithelial cell differentiation, and the expression of genes upon which perinatal respiratory adaptation depends. TTF-1 is detected in respiratory epithelial cells throughout lung morphogenesis and at maturity (120, 221, 291). Deletion of TTF-1 in the mouse causes malformations of the forebrain, thyroid, and lung (112). The lungs of *Titf-1*$^{-/-}$ mice consist of a tracheal-esophageal fistula with intact main bronchial tubes and absence of peripheral lung structures, consistent with its requirement for branching morphogenesis. Mutations in the human *TTF-1* gene have been associated with hypothyroidism and respiratory failure in human infants (56). Since the importance of TTF-1 was recognized relatively early in the study of transcriptional pathways regulating lung formation and gene expression (24, 112, 156), knowledge of its role is relatively more developed than that for other transcription factors. The multiple functions of TTF-1 are highly dependent on its temporal-spatial expression, interactions with other transcription factors, and its responses to various external conditions, as occurs during injury after birth.

TTF-1 consists of NH_2- and COOH-terminal transactivating domains and a centrally located homeodomain DNA that binds to CAAG motifs in regulatory regions of its transcriptional targets (Fig. 2). Its multiple domains, phosphorylation, and acetylation modulate interactions with multiple transcription factors and coactivators that, in turn, regulate the expression of genes that are critical for lung formation and function. TTF-1 directly binds and regulates the expression of a number of genes selectively expressed in respiratory epithelial cells, including *Sftpa*, *Sftpb*, *Sftpc*, and *Sftpd* (24, 48). RNA microarray data from a transgenic mouse in which TTF-1 phosphorylation sites were mutated (*Titf-1*^{PM}) revealed that TTF-1 influences expression of groups of genes regulating surfactant homeostasis, vasculogenesis, host defense, fluid homeostasis, and inflammation before birth (51). Transcriptional targets of TTF-1 that are critical for early lung morphogenesis are not known, although BMP-4 expression was shown to be directly regulated by TTF-1 (292).

1. TTF-1 interacts with multiple partners

TTF-1 interacts with a number of regulatory proteins and transcription factors (Fig. 2). The NH_2 terminus of TTF-1 binds to transcriptional coactivators, CBP (173, 174, 276), SRC-1 (NCOA1) (173, 174, 269, 276), TAZ (185), a repressor DREAM (197), and the transcription factor PAX8 (58). The homeodomain of TTF-1 binds to transcription factors RAR (263), GATA-6 (133, 252), and NFAT (48). The COOH terminus of TTF-1 binds to thymine DNA glycosylase (TDG) (159). TTF-1 binds to various coactivators, p300 (8, 75), TIF-2 (NCOA2), ACTR (NCOA3) (173), BR22 (273, 271), REF-1 (230), and transcription factors NFκB (91), STAT3 (264), SMAD3 (123), NFI (8),

and ERM (129). TTF-1 also interacts with the DNA repair proteins TDG, poly(ADP-ribose) polymerase (PARP)-1, and PARP-2. TDG represses TTF-1-activated transcription (159), while PARP-1 and PARP-2 activate it (140). TTF-1 binds to a kinase HIPK2, a LIM domain-containing protein AJUBA (159), DNA repair proteins KU70 and KU80 (140), but the functions of these interactions have not been identified. TTF-1 interacts with multiple DNA repair proteins including TDG, REF-1, PARP-1, PARP-2, KU70, and KU80 (140, 159, 230), supporting its potential role in this process. DREAM, PAX8, TDG, REF-1, HIPK2, and AJUBA were identified as TTF-1 interacting proteins in the thyroid, but similar interactions have not been identified in the lung.

2. Posttranslational modification of TTF-1

TTF-1 is phosphorylated on seven serine residues in HeLa cells. Substitution of seven serine phosphorylation sites (S4, S12, S18, S23, S255, S328, S337) for alanines did not affect TTF-1-mediated activation in vitro (282). In contrast, this substitution in the mice decreased perinatal survival and altered tissue-specific gene expression in vivo (51). TTF-1 is phosphorylated by various kinases, protein kinase A (PKA) (124, 239, 265), MST2 (6), Ras (158, 239), and ERK (158) in vitro. PKA phosphorylates the threonine residue (T9) of TTF-1 and activates TTF-1-mediated activation in vitro (265). Ras inhibits TTF-1 function through ERK, which phosphorylates the serine residues (S18, S328, S337) of TTF-1 (158). TTF-1 is also acetylated by coactivators CBP, SRC-1, and ACTR that may influence its activity (269). Lysine K182 within the homeodomain of TTF-1 is acetylated (269). Taken together, TTF-1 appears to play a central role in lung morphogenesis. The level and intracellular trafficking of TTF-1 as well as its interactions with other transcription factors and coactivators regulate the expression of genes important for lung formation and function (119).

C. FOXA Family and Branching Morphogenesis

The FOX proteins comprise a family of >50 transcription factors sharing a winged helix DNA binding domain that plays an important role in the regulation of cell differentiation, organogenesis, and gene expression in diverse organisms from *Caenorhabditis elegans* to humans. Many FOX transcription factors, including FOXA1, FOXA2, FOXJ1, FOXM1, FOXF1, and FOXP family members, are expressed in the lung (45). FOXA1 and FOXA2 are expressed in the foregut endoderm before lung formation and are expressed in an overlapping pattern with TTF-1 in respiratory epithelial cells during lung morphogenesis and in the mature lung (17, 291). FOXA2 is required for formation of the foregut in the early embryo (3) and plays critical roles in differentiation of the respiratory epithelium at various times during development. The role of FOXA1 and FOXA2 (also known as HNF-3α and HNF-3β) in the lung was initially recognized by their effects on expression of several genes expressed selectively in respiratory epithelial cells. FOXA1 and FOXA2 bind and activate *Scgb1a1* and *Sftpb* gene promoters (18–20, 178, 203). Increased expression of FOXA2 in respiratory epithelial cells perturbed branching and impaired cell differentiation (290). Later in development, FOXA1 and FOXA2 influence differentiation of respiratory epithelial cells, regulating genes important for lung function at birth. FOXA2 binds and directly regulates the transcription of a number of genes mediating formation or lung function, including *Sftpa*, *Sftpc*, *Sftpd*, *Titf-1*, *Muc5A/C*, *Wnt7b*, E-cadherin, and *Vegfa* (24, 42, 81, 88, 145, 236, 244, 245, 246, 252, 290).

1. Overlapping roles of FOXA1 and FOXA2 during branching morphogenesis of the lung

Cell selective deletion of FOXA2 in the respiratory epithelium did not perturb branching morphogenesis but delayed the maturation of the peripheral lung resulting in death after birth. In contrast, *Foxa1*$^{-/-}$ mice survived after birth, exhibiting stage-specific delays in lung maturation, but did not have defects in branching morphogenesis (18). Deletion of both *Foxa* genes severely disrupted branching morphogenesis in the canalicular period, resulting in lung hypoplasia, cyst formation, and lack of epithelial and smooth muscle differentiation. Deletion of *Foxa1/Foxa2* inhibited SHH signaling resulting in decreased expression of transcription factors controlling pulmonary smooth muscle differentiation, including myocardin (244) that, in turn, regulates smooth muscle differentiation, indicated by α-smooth muscle actin (α-SMA) expression (Fig. 3). Since SHH is required for formation of bronchial and vascular smooth muscle, defects in branching morphogenesis seen after deletion of *Foxa1/Foxa2* genes are likely mediated by the lack of SHH signaling that is required for differentiation or migration of smooth muscle precursors in the lung mesenchyme (Fig. 3).

D. Epithelial β-Catenin Influences Branching Morphogenesis and Cell Differentiation

Epithelial cells lining the lung tubules become increasingly differentiated along the cephalo-caudal axis associated with expression of cell type specific markers in *1*) ciliated, basal, secretory cells in conducting airways; *2*) secretory and ciliated cells in small airways; and *3*) cuboidal pre-type II cells and later squamous type I cells that line peripheral saccules. β-Catenin plays a critical role in establishing this proximal-distal cell fate in the respiratory epithelium. The Wnt/β-catenin pathway is an evolutionarily conserved signaling system that is utilized by

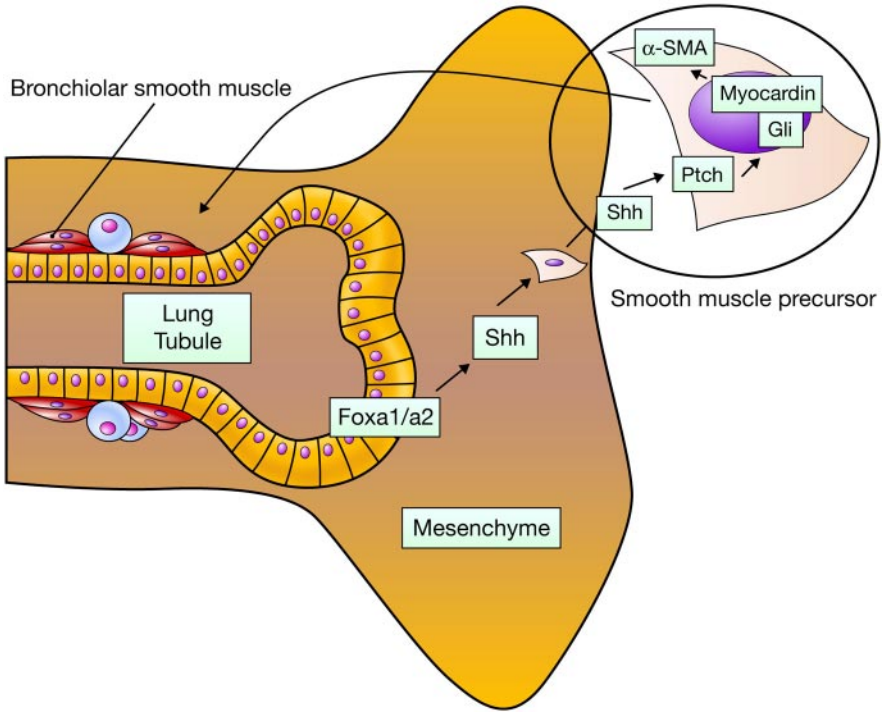

FIG. 3. FOXA regulates SHH required for branching morphogenesis. FOXA1/A2 is expressed in epithelial cells of embryonic lung and is required for SHH production by the epithelium (154). SHH is secreted, binding to PTCH on pulmonary mesenchymal cells, releasing SMO to activate GLIs. SHH is required for the differentiation of pulmonary mesenchymal precursors and regulates smooth muscle differentiation (e.g., myocardin) that activates α-smooth muscle actin (α-SMA), a marker of smooth muscle cells. Thus FOXA activity regulates paracrine signaling via SHH that is required for branching morphogenesis of the lung.

many cell types throughout organogenesis. In the mouse, deletion of β-catenin is lethal in the early embryonic period, well before formation of the lung (87). A number of Wnt ligands and components of the β-catenin signaling pathway are expressed in various pulmonary cells throughout lung morphogenesis (227, 252). Wnt ligands activate Frizzled, Arrow-LRP-5/6, Disheveled (Dsh), causing the uncoupling of β-catenin from the degradation pathway and its entry into the nucleus, where it interacts with T-cell transcription factor (TCF)/lymphoid enhancer-binding factor (LEF) to control transcription (176). Involvement of the Wnt signaling pathway in lung morphogenesis has been recently reviewed (30, 191, 209, 249). TCF/LEF interacts with at least 11 cofactors including β-catenin, to regulate transcription, and β-catenin interacts with at least 25 cofactors (see http://www.stanford.edu/~rnusse/wntwindow.html). β-Catenin is expressed in both proximal and distal regions of the lung in both epithelial and mesenchymal compartments (170, 180, 227). Deletion or inhibition of β-catenin in respiratory epithelial cells impaired branching morphogenesis and inhibited peripheral airway cell differentiation in vivo (170, 214). The effect of activated β-catenin during lung formation was demonstrated in transgenic mice expressing a mutant β-catenin in which the ubiquitination domain was deleted in vivo. Branching morphogenesis was disrupted, and aberrant differentiation and hyperplasia of the airway epithelium were observed (169). In lung, TCF1, TCF4, and LEF-1 are expressed more distally than proximally (180, 227). LEF-1 is required for formation of submucosal glands (63). Expression of a LEF-1-β-catenin fusion protein in respiratory epithelial cells of the embryonic lung enhanced cell proliferation and caused their transdifferentiation into cells with characteristics of gastrointestinal epithelia, demonstrating remarkable cell type plasticity (180). Later in development, increased expression of activated β-catenin in proximal airway epithelial cells caused ectopic differentiation of alveolar type II-like cells in conducting airways, goblet cell hyperplasia, and air space enlargement associated with increased mucin (MUC5AC) expression (169). Shu et al. (214) suggested that Wnt/β-catenin functions upstream of BMP4, FGF signaling, and N-myc (214). Taken together, these experiments support the concept that Wnt signaling and the β-catenin/TCF/LEF pathway regulates branching morphogenesis and airway epithelial differentiation.

E. GATA-6

GATA-6 is a member of the GATA family of zinc finger transcription factors that plays a critical role in visceral endoderm formation (167). Like FOXA2 and TTF-1, GATA-6 is expressed in respiratory epithelial cells throughout lung morphogenesis. GATA-6 is required for survival of endodermally derived progenitors that form the bronchiolar epithelium (167). Later in development, GATA-6 influences sacculation and alveolarization of the lung. Expression of a dominant negative GATA-6 in respiratory epithelial cells of the mouse inhibited lung differentiation in late gestation and decreased expression of aquaporin-5 and surfactant proteins (135) often acting

synergistically with TTF-1 (266). Increased activity of GATA-6 inhibited alveolarization and perturbed pulmonary function (117, 134). GATA-6 binds to the homeodomain region of TTF-1, coactivating various transcriptional targets expressed in the respiratory epithelium (see Fig. 2). TTF-1 and GATA-6 complex with HOP (homeodomain only protein) that serves as a repressor that modifies histone acetylation (277). In vitro, GATA-6 increased the activity of the *Sftpa*, *Sftpb*, *Sftpc*, and *Wnt7b* gene promoters (27, 133, 252).

1. Other zinc finger transcription factors

The zinc finger proteins include a large number of proteins/transcription factors that share structures that interact with zinc ions. More than 10 different classes of zinc-binding motifs have been identified. The tetrahedral coordination of the zinc ion is mediated by four cysteine (C) and/or histidine (H) residues in various arrangements. Archetypal DNA binding structures on fingers are found in the GATA family as well as SP, KLF, and GLI families (C2H2) (61, 71). While numerous zinc fingers proteins are expressed in the lung, only a few have been clearly implicated in lung morphogenesis. GATA-4 is required for formation of foregut endoderm-derived organs, but its precise role in lung morphogenesis is unknown (45). GATA-5 knockout mice do not have defects in lung morphogenesis (164), although GATA-5 is expressed within the pulmonary mesenchyme (166). SP3 is a ubiquitously expressed transcription factor closely related to specificity protein 1 (SP1). SP3-deficient embryos are growth retarded and die at birth of respiratory failure, although the cause of respiratory failure is unknown (26). While deletion of lung Kruppel-like factor causes early embryonic death, lungs of chimeric *Lklf*$^{-/-}$ mice are arrested in the late canalicular stage of lung development resulting in death after birth (248).

F. Nuclear Factor-1

Nuclear factor-1 (NF-1) proteins constitute a family of eukaryotic DNA binding proteins that share a conserved NH_2-terminal domain. The DNA-binding domain of NF-1 has no obvious sequence similarity to other known classes of DNA-binding proteins. NF-1 binds as a dimer to a palindromic consensus sequence [YTG GCA (N)3 TGC CAR] to regulate gene transcription (118). NF-1B-deficient mice die in the early postnatal period from respiratory failure associated with lung hypoplasia and decreased expression of surfactant proteins (78, 222). Likewise, expression of a dominant negative NF-1-engrailed construct in respiratory epithelial cells impaired lung morphogenesis and inhibited surfactant protein-C (SP-C) expression (8). NF-1 directly interacts with TTF-1 and the coactivator p300 to activate *Sftpc* gene transcription (7, 8).

G. N-Myc

N-Myc, a basic helix-loop-helix protein, is expressed in the developing respiratory epithelium where it is restricted to peripheral lung tubules, being detected at low levels in the developing trachea and bronchi. *N-myc*$^{-/-}$ mice die from cardiac failure, before formation of the lung; however, partial deletion of N-myc disrupted branching morphogenesis of the lung (161, 162). N-Myc is not required for lung bud formation but is required for proliferation of peripheral progenitor cells during lung morphogenesis (181).

III. TRANSCRIPTION FACTORS ACTIVE IN THE LUNG MESENCHYME DURING BRANCHING MORPHOGENESIS

Cells of the splanchnic mesenchyme, although morphologically are a relatively homogeneous and "undifferentiated" group of cells, ultimately form the multiple tissues that comprise the nonendodermal compartment of the lung, including cartilage, arteries, veins, capillaries, lymphatics, bronchial smooth muscle, and other stromal tissues. Transcriptional mechanisms controlling differentiation and proliferation of the multiple cell types derived from the pulmonary mesenchyme are not well understood. Nevertheless, a number of transcription factors have been identified that play important roles in the development of the pulmonary mesenchyme, including FOXF1, FOXM1B, POD1, HIF, GLI, T-BOX, and HOX family members.

A. FOXF1

FOXF1 is expressed in the splanchnic mesenchyme in close apposition to endoderm, suggesting its role in mesenchymal-epithelial interaction during lung and gastrointestinal tract morphogenesis (45). FOXF1 expression is restricted to the distal mesenchyme of the developing lung and the muscle layer of the bronchus, but it is absent in the epithelial cells and mesenchyme of large vessels. FOXF1 plays a critical role in embryonic development. Deletion of FOXF1 is lethal before gastrulation. Severe lung malformations were observed in *Foxf1*$^{+/-}$ mice (101, 142). Expression of a number of genes critical for lung morphogenesis and function, including *Sftpb*, *Vegfa*, *Vegfr2*, *Bmp-4*, *Tbx*, *Lklf*, *Fgf-10*, and *Gli3* were reduced, implicating FOXF1 in the regulation of mesenchyme-epithelial interactions (101, 127, 142). Deletion of the *Foxf1* gene influenced the expression of c-Met, myosin VI, SP3, BMI-1, ATF-2, GR, p53, p21, RB, p107, Notch-2 receptor, and the Notch-2 downstream target hairy enhancer of split-1 (HES-1) in the developing mouse lung (98).

B. FOXM1B

FOXM1B activates genes involved in G_1/S and G_2/M progression through its interaction with Cdk-Cyclin complexes and p300/CBP coactivators (46). FOXM1B is negatively regulated by p19ARF, a tumor suppressor (102). Pulmonary microvasculature abnormalities, associated with diminished levels of the PECAM-1, transforming growth factor (TGF)-β receptor type II, ADAM-17, vascular epidermal growth factor (VEGF) receptors, FLK-1, Aurora B kinase, LAMA4, and the FOXF1 transcription factor were observed in lungs of *Foxm1*$^{-/-}$ mice (111). Increased expression of FOXM1B increased proliferation of alveolar and bronchial epithelial cells, as well as smooth muscle and endothelial cells, activating cell cycle promoting factors, including cyclin A2, cyclin E, cyclin B1, cyclin F, and Cdk1, while decreasing the levels of p21, a Cdk inhibitor (99). Thus FOXM1B regulates pulmonary genes essential for cell proliferation, extracellular matrix remodeling, and vasculogenesis during lung development and repair.

C. POD1

POD1 is a basic helix-loop-helix transcription factor that is highly expressed in the mesenchyme of developing lung. *Pod1*$^{-/-}$ mice die in the perinatal period with severely hypoplastic lungs lacking alveoli. Although POD1 is expressed in the mesenchyme, lung defects in *Pod1*$^{-/-}$ mice were observed in the adjacent epithelia, including abnormalities in cell differentiation and branching morphogenesis (194).

D. HIF-1α and HIF-2α

The hypoxia inducible factors (HIFs) are oxygen-sensitive transcription factors that regulate the expression of genes involved in the control of angiogenesis, glucose metabolism, and cellular proliferation, playing critical roles during development and in response to physiological and pathophysiological stimuli. HIF-1α is expressed at low levels in the fetal lung and in the bronchiolar epithelium of adult lung (44, 65). HIF-1α is induced in bronchial and alveolar epithelium, smooth muscle, and vascular endothelium during hypoxia (280). HIF-1α is required for embryonic vascularization. *Hif-1*$\alpha^{-/-}$ mice die at midgestation in association with defects in VEGFA expression and vasculogenesis (201). Pulmonary hypertension and pulmonary vascular remodeling were observed in *Hif1*$^{+/-}$ heterozygous mice during hypoxic conditions (281). Transcriptional targets of HIF-1α, and its interactions with cofactors, and its role in pulmonary pathophysiology were recently reviewed (79, 199, 205, 253). HIF-2α mRNA is present in endothelial cells and pulmonary mesenchyme at E13.5 and E15.5 (96). HIF-2α increases prior to birth and is abundant in adult lung (65). *Hif-2* gene targeted mice died after birth from atelectasis and decreased surfactant production (44). *Hif2*$^{+/-}$ mice were protected against pulmonary hypertension and right ventricular hypertrophy, indicating a critical role for HIF-2α in hypoxia-induced pulmonary vascular remodeling (29). HIF-2α was detected in endothelial cells, bronchial epithelial cells, and type II cells from E18 and postnatally (242). Taken together, HIF-1α and HIF-2α play critical roles in the regulation of perinatal lung function and hypoxia-induced pulmonary vascular remodeling.

E. GLI Family Members

Signaling via the SHH pathway is critical for normal lung morphogenesis. GLI proteins are members of the zinc finger transcription factor family that mediate Hedgehog (Hh) signaling in target cells. SHH is secreted and binds to extracellular matrix and other proteins, e.g., hedgehog interacting protein (HIP) (41), as well as to its primary receptor Patched-1 (PTC), releasing SMO in responding cells. SMO activates GLI transcription factors to influence target gene expression (138). There are three known GLI family members: GLI1, GLI2, and GLI3. GLI1 and GLI2 are activators of Hh-target genes; GLI3 acts primarily as a repressor, although some GLI3 activator function is also involved in induction of target gene transcription (107). SHH is expressed in the developing lung epithelium, and its primary receptor Patched (PTC) is found in mesenchymal cells. SHH signaling is required for branching morphogenesis, serving as a paracrine signal that regulates smooth muscle differentiation in the lung mesenchyme (188, 251). PTC is expressed in the lung mesenchyme until E13.5 (250) and was detected in the respiratory epithelium at E16.5 (250). PTC was detected in the basal layer of the adult bronchial epithelium where it was localized with calcitonin gene-related peptide (CGRP), a neuroendocrine cell marker (250). Watkins et al. (250) suggested that neuroendocrine cells in the airway epithelial compartment may respond to SHH signaling from adjacent airway epithelial cells (250). GLI1, GLI2, and GLI3 are expressed in an overlapping fashion in the lung mesenchyme. GLI1 is expressed after E16.5 in the respiratory epithelium (76). Foregut defects, including stenosis of the esophagus and trachea, and hypoplasia and lobulation defects of the lung were observed in *Gli2*$^{-/-}$ mice (168). Deletion of GLI3 caused pulmonary hypoplasia and altered lung shape (76). *Gli2*$^{-/-}$,*Gli3*$^{+/-}$ mice have esophageal atresia with tracheoesophageal fistula and severe lung hypoplasia. *Gli2*$^{-/-}$,*Gli3*$^{-/-}$ mice lack esophagus, trachea, and lung (168).

F. T-Box Transcription Factors

T-box (TBX) transcription factor family consists of six members (TBX1 through TBX6) sharing the DNA bind-

ing domain of Brachyury (T). In the lung, TBX1 is expressed in the epithelium, while TBX2–5 are expressed in lung mesenchyme (34). Deletion of the *Tbx-1* gene did not alter lung formation (130). Treatment of embryonic lung cultures with antisense oligonucleotides to TBX4 and TBX5 suppressed the expression of FGF10, an essential growth factor mediating branching morphogenesis. Inhibition of TBX2 and TBX3 did not affect branching morphogenesis in vitro (31).

G. HOX Genes

A subset of HOX genes is expressed in developing lung. In general, Hox genes are expressed in the pulmonary mesenchyme where levels decrease with advancing gestation (22). HOXB3, HOXB4, and HOXB5 are highly expressed in the foregut endoderm in the region where lung buds form. Later in development (E10.5-E14.5), HOXB3 and HOXB4 are expressed in the mesenchyme of the trachea, bronchi, and peripheral lung, while HOXB2 and HOXB5 mRNAs are selectively expressed in the mesenchyme of the peripheral lung tubules (23). Remarkably, deletion of single HOX genes does not perturb lung morphogenesis, a finding that is likely to depend on redundant functions of multiple HOX genes. At present, defects in tracheal-pulmonary morphogenesis have been observed only in $HoxA5^{-/-}$ mice, which showed abnormalities in tracheal and lung structure and decreased expression of surfactant proteins, TTF-1, FOXA2, and N-Myc (5).

IV. THE CANALICULAR PERIOD: TRANSCRIPTIONAL CONTROL OF DIFFERENTIATION OF THE CONDUCTING AIRWAY EPITHELIUM

Before E15 in the mouse fetus, epithelial cells lining the trachea, bronchi, and bronchioles are relatively undifferentiated as defined by the expression of cell-specific markers used to identify epithelial cell types later in development. In contrast, the adult conducting airways are lined by relatively diverse cell types, including squamous, basal, ciliated, brush, goblet, nonciliated/secretory cells (also termed Clara cells), intermediate and neuroepithelial cells, and the relatively cuboidal cells located in the bronchoalveolar duct junctions (Fig. 4). A pseudostratified epithelium lines the trachea and main bronchi. Smaller conducting airways, from bronchioles to acinar ducts, are generally lined by simple columnar-cuboidal epithelia. The numbers and localization of the diversity of these cell types vary developmentally along the proximal-distal axis of the lung and are highly species dependent. The mechanisms determining the complex pattern of cells lining the airways are poorly understood, but are influenced by autocrine-paracrine and cell-cell interactions that regulate transcription factors controlling cell differentiation. The numbers and types of cells lining conducting airways are strongly influenced by infection, cytokines, inflammatory mediators, and injury that are associated with common airway diseases, including chronic obstructive pulmonary disease, asthma, and cystic fibrosis.

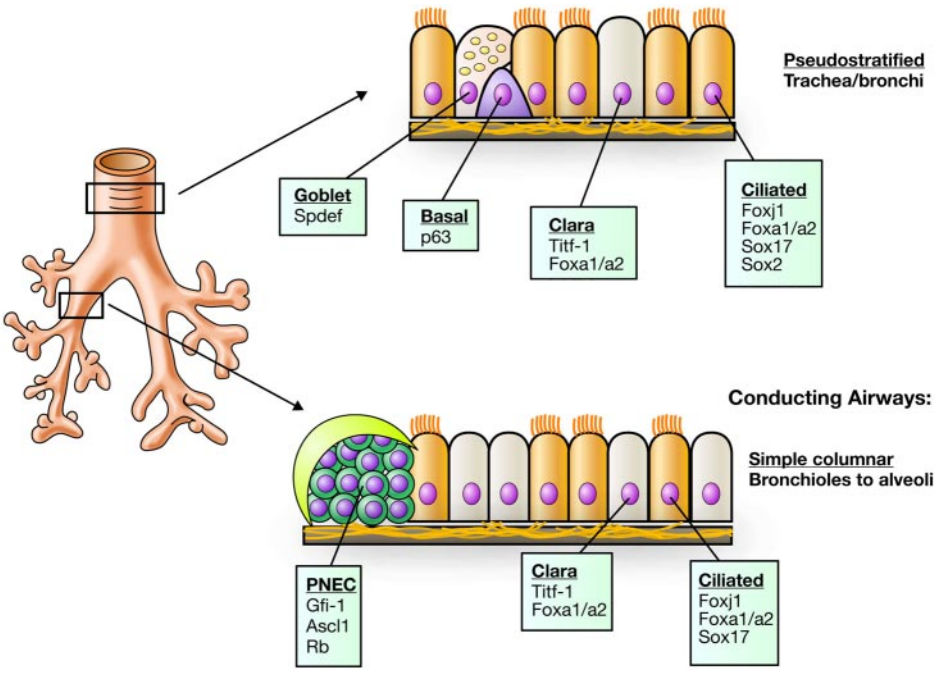

FIG. 4. Selective expression of transcription factors in the respiratory epithelium. In the mouse, large conducting airways (trachea and bronchi) are lined by a pseudostratified epithelium consisting primarily of goblet, basal, Clara (secretory), and ciliated cells. Peripheral conducting airways (bronchioles-acinar ducts, proximal to the alveoli) are lined by a simple columnar epithelium comprised primarily of ciliated and nonciliated cells (Clara cells). Pulmonary neuroendocrine cells (PNEC), some clustered in neuroendocrine bodies (NEBs), are a relatively rare cell type that express serotonin, bombesin, calcitonin gene-related peptide (CGRP), and other neuroendocrine peptides (*top panel*). Transcription factors influencing cell type differentiation and gene expression are depicted.

Transcriptional mechanisms controlling epithelial cell differentiation in the conducting airways during lung morphogenesis and repair remain less completely understood; however, TTF-1, NF-1β, GATA-6, and other transcription factors, including RB, ETS, SOX, and FOX family members play roles in cell specific differentiation and gene expression in the conducting airways. Concentrations of these transcription factors vary among distinct cell types along the cephalo-caudal axis of the conducting airways where differentiation is influenced by their concentration, activation, and interactions with other transcription factors (Fig. 5).

A. Differentiation of Basal Cells (p63)

The p63 transcription factor, a homolog of tumor suppressor p53, is highly expressed in embryonic ectoderm and in epithelial cells in various tissues including the trachea and bronchi. p63 binds p53 response elements and can positively or negatively regulate p53 target genes. In contrast to the tumor suppressor functions of p53, increased expression of p63 splice variants is observed in many squamous carcinomas (256). Differentiation of the conducting airway begins prior to birth. At this time, the pseudostratified epithelium of the upper airway contains basal cells that selectively express p63. Deletion of p63 in the mouse results in formation of a simple columnar epithelium that lacks basal cells. Thus p63 plays a critical role in the development of normal tracheobronchial epithelium (47). Ectopic expression of an isoform of p63 containing only the transactivation domain caused squamous metaplasia and induced keratin-14 expression, a marker of stratified epithelia (116).

B. FOXJ1 and Ciliogenesis

FOXJ1 (HFH-4) is required for the establishment of right-left asymmetry in the early embryo and ciliogenesis in various organs including the lung (232, 233, 279). FOXJ1 regulates a number of genes required for ciliogenesis in ciliated cells in the conducting airways, such as ezrin and calpastatin (73, 86). In the early embryo, FOXJ1 regulates gene(s) controlling left-right asymmetry, such as *Lrd* (38). Lack of FOXJ1 results in the failure of cilia formation in the node, resulting in failure to express lefty-2 and the randomization of sites of Nodal and PITX2, proteins that control situs, in turn influencing lung lobulation (285). FOXJ1 also regulates IkB-β, inhibiting NFκB activation, thereby inhibiting inflammation during lung repair (128). Absence of cilia, bronchiectasis, sinusitis, and situs inversus are features of Kartagener's syndrome in humans; however, defects in the *Foxj1* gene have not been directly linked to this disorder.

C. Pulmonary Neuroepithelial Cells and Neuroendocrine Bodies

The pulmonary neuroendocrine system consists of a relatively rare subset of specialized airway epithelial cells, some of which are closely associated with nerve fibers. Pulmonary neuroendocrine cells (PNEC) are found as

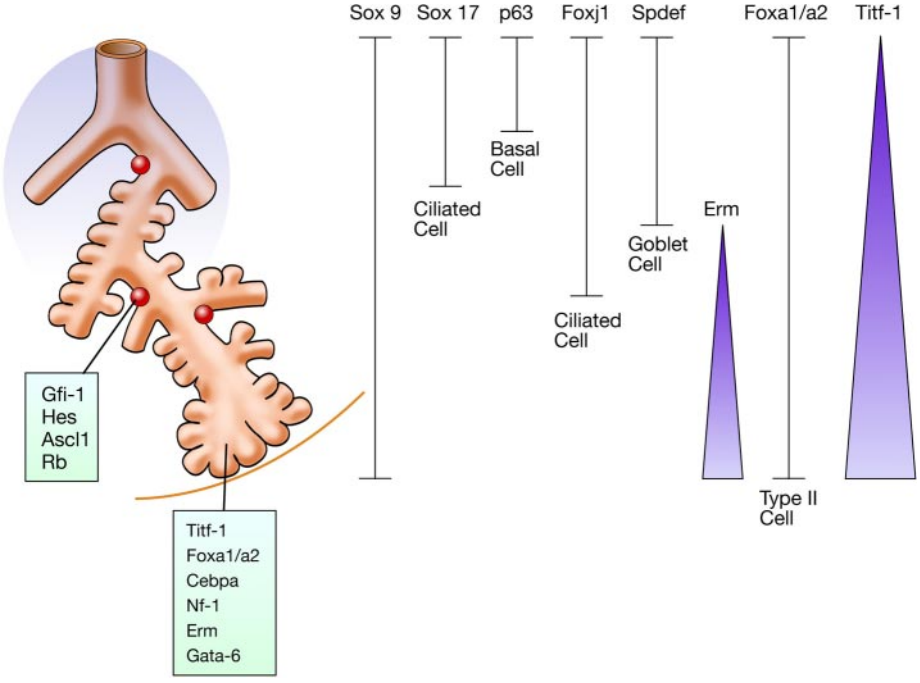

FIG. 5. Distribution of transcription factors in respiratory epithelial cells. Conducting and peripheral airways are depicted (*left*). The distribution of transcription factors varies among distinct cell types along the cephalocaudal axis of the lung. GFI-1, HES, MASH, and RB influence differentiation/growth of neuroendocrine cells (circles). Alveolar type II cells, but not type I cells, express TTF-1, FOXA1/2, C/EBPα, NF-1, ERM, and GATA-6. TTF-1, SOX family members, p63, FOXJ1, SPDEF, and other transcription factors vary in concentration along the airways where they influence epithelial cell differentiation and gene expression.

isolated cells or in clusters termed neuroendocrine bodies (NEB) (238). A number of transcription factors (MASH1/HASH1, HES1, GFI1, pRB) are known to influence pulmonary neuroendocrine development. MASH1/HASH1 is expressed in normal fetal pulmonary neuroendocrine cells. MASH1/HASH1-deficient mice have no detectable pulmonary neuroendocrine cells and lack of expression of neuroendocrine markers including CGRP (25, 95). Increased expression of MASH1/HASH1 in nonendocrine airway epithelial cells, using the CCSP promoter, caused progressive airway hyperplasia and metaplasia (131). Hairy and enhancer of split1 (HES1), expressed in nonneuroendocrine epithelial cells, represses expression of MASH1/HASH1 (37, 95). Increased numbers of pulmonary neuroendocrine cells and induction of both MASH1/HASH1 and NeuroD were observed in *Hes*$^{-/-}$ mice. Notch-1 expression was suppressed in *Hes*$^{-/-}$ mice, suggesting MASH1/HASH1 and HES1 regulates neuroendocrine versus nonneuroendocrine cell fate specification in the lung epithelium via Notch signaling (95). Growth factor independent-1 (GFI1) is a transcription factor coexpressed with MASH1/HASH1 in neuroendocrine cells in the developing and mature lung. Decreased numbers of PNECs and a reduction in the size of NEB were observed in *Gfi1*$^{-/-}$ mice, indicating its role in growth and maturation of PNEC/NEBs (109). Increased numbers of neuroendocrine cells were observed in the airways of *Rb*$^{-/-}$ mice and in mice expressing Sox17 (184, 258), indicating their potential roles in PNEC differentiation.

D. SOX Family of HMG Containing Transcription Factors

A number of SOX genes are expressed in the developing lung, including SOX2, -4, -9, -11, and -17 (90). SOX9 is widely expressed in epithelial cells throughout lung morphogenesis, while SOX2 is more abundantly expressed in ciliated cells in conducting airways (181, 183, 190). *Sox9*$^{-/-}$ mice have multiple anomalies of the skeleton and cartilage and have severe tracheal cartilage malformations (165). While SOX9 is widely expressed in respiratory epithelial cells in the fetal lung, deletion of SOX9 in the respiratory epithelium did not alter lung morphogenesis or function (190). SOX17 interacts with β-catenin in the regulation of transcription of endodermal genes and is required for anterior-posterior axis formation in *Xenopus* (216). Both SOX17 and SOX2 are relatively abundant in ciliated cells in the perinatal lung. SOX17 is first detected in the lung mesenchyme (E10–11) and later (E16–17) in the epithelium of conducting airways in the mouse. Their expression changes dynamically during repair and redifferentiation of the bronchiolar epithelium following injury (183). Expression of SOX17 in the fetal mouse lung disrupted peripheral lung formation. When expressed in the postnatal lung, SOX17 induced focal hyperplasia and caused ectopic expression of proximal airway markers, supporting its potential role in respecification of progenitor cells. Increased staining for SOX17 and SOX2 were observed during repair of the conducting airways. *Sox11*$^{-/-}$ mice die at birth from cyanosis and have lung hypoplasia (219); however, the genes and processes regulated by SOX11 during lung formation are not known.

E. ETS Family

ETS family members, including ETS-1, SPDEF, ELF-3, ESE-3, ERM, and PEA3, are expressed in lung epithelial and/or mesenchymal cells (108, 136). PEA3 and Erm were selectively expressed in peripheral lung buds during mouse lung morphogenesis, and expression of a dominant negative form of Erm inhibited type II cell differentiation (136). SPDEF is expressed in epithelial cells in extrapulmonary airways and is excluded from the lung periphery, contrasting to the distribution of ERM that is expressed predominantly in the lung periphery (129, 186). ERM is coexpressed with SP-C and strongly activates the *Sftpc* gene promoter in type II alveolar epithelial cells. Both ERM and SPDEF bind to TTF-1 and interact both directly and synergistically in the regulation of transcriptional target genes (129; K. S. Park, T. R. Korfhagen, M. D. Bruno, J. A. Kitzmiller, H. Wan, S. E. Wert, G. K. K. Hershey, G. Chen and J. A. Whetsett, unpublished observations). SPDEF coactivates the expression of a number of genes expressed in conducting airways. Taken together, these findings support the concept that the spatial distribution of members of the ETS family of transcription factors influence cell differentiation in the lung.

V. SACCULAR-ALVEOLAR STAGES: TRANSCRIPTIONAL CONTROL OF PERINATAL LUNG MATURATION AND RESPIRATORY ADAPTATION

The saccular-alveolar period of lung morphogenesis represents a particularly vulnerable time in mammalian development, marking the transition from a fluid-filled to air-filled lung upon which survival depends following birth. Supportive structures of the peripheral air saccules become more gracile as type I epithelial cells become increasingly squamous, providing close apposition between pulmonary blood vessels and the respiratory epithelium. Peripheral lung tissues thin as lung saccules dilate and pulmonary capillaries come into increasingly close contact with the epithelial lining where gas exchange is facilitated. At the time of birth, pulmonary vascular resistance falls, pulmonary blood flow increases, lung fluid is resorbed, and pulmonary surfactant is secreted into the peripheral saccules of the lung, the latter

reducing surface tension that prevents alveolar collapse once the lung is filled with air. Lack of surfactant causes respiratory distress syndrome (RDS) in preterm infants, an important cause of morbidity and mortality in newborns. The importance of surfactant for perinatal survival is further supported by the findings that inherited disorders of surfactant metabolism, including mutations in the *ABCA3*, *SFTPC*, and *SFTPB* genes cause lethal respiratory distress in mature infants after birth (257). A number of transcription factors influence perinatal lung maturation, including TTF-1, FOXA2, NFATc3, C/EBPα, and the glucocorticoid receptor (GRα), regulating the expression of genes critical for respiratory adaptation at birth.

A. TTF-1, C/EBPα, NFATC3, and FOXA2 Participate in a Transcriptional Network Regulating Perinatal Lung Maturation

Mutation of TTF-1 (phosphorylation site mutation *Titf-1*^{PM}) or cell-selective deletion of C/EBPα, FOXA2, or calcineurin b1 (Cnb1) did not substantially alter early branching morphogenesis of the mouse lung, but impaired pulmonary maturation in the saccular-alveolar stage of development, each mutation resulting in respiratory failure at birth (10, 49, 51, 147, 246). While subtle differences in lung maturation and differentiation were observed in these mutant mice, marked deficits in expression of genes regulating surfactant homeostasis were observed in each mouse model. Maturation of the peripheral lung saccules was delayed, as evidenced by lack of differentiation of type II and type I epithelial cells and the absence of lamellar bodies and tubular myelin, indicating the lack of surfactant lipid synthesis and packaging. Groups of genes regulating (I) surfactant protein and lipid synthesis (e.g., *Abca3*, *Scd-1*, *Pon-1*, *Kdap*, *Sftpa*, *Sftpb*, *Sftpc*, and *Sftpd*), (II) fluid and solute transport, including *Aq5*, *Scnn1g*, *Slc34a2*, (III) vasculogenesis, *Vegfa*, and (IV) innate host defense (e.g., *Lys*, *Sftpa*, *Sftpd*, and *Scgb1a1*) were variably influenced by mutation or deletion of the *Titf-1*, *Cebpα*, and *Foxa2* genes during lung morphogenesis (Fig. 6). While these transcription factors bind to distinct *cis*-active elements on target genes, the similarity of the maturational defects and transcriptional targets suggest that TTF-1, C/EBPα, CNB1/NFATC3, and FOXA2 interact either directly or via complex formation at transcriptional targets, as well as by influencing the expression of one another. For example, FOXA2 directly regulated the TTF-1 promoter in vitro (88). Targeted mutation or deletion of TTF-1 or deletion of FOXA2 blocked C/EBPα and CNB1 expression in the peripheral respiratory epithelial cells prior to birth (49, 51, 147). Taken together, these transcription factors may interact in a network to influence lung maturation that is critical for postnatal survival. Likewise, other partners of TTF-1 (e.g., NF-1, NFATc3, GATA-6) and coactivators play roles in the regulation of perinatal lung maturation, influencing type II cell function and the differentiation of type I epithelial cells in the alveoli (Fig. 6).

B. Glucocorticoid Receptors and Perinatal Lung Maturation

Glucocorticoid administration to the mothers of preterm fetuses induces lung maturation, a finding that has

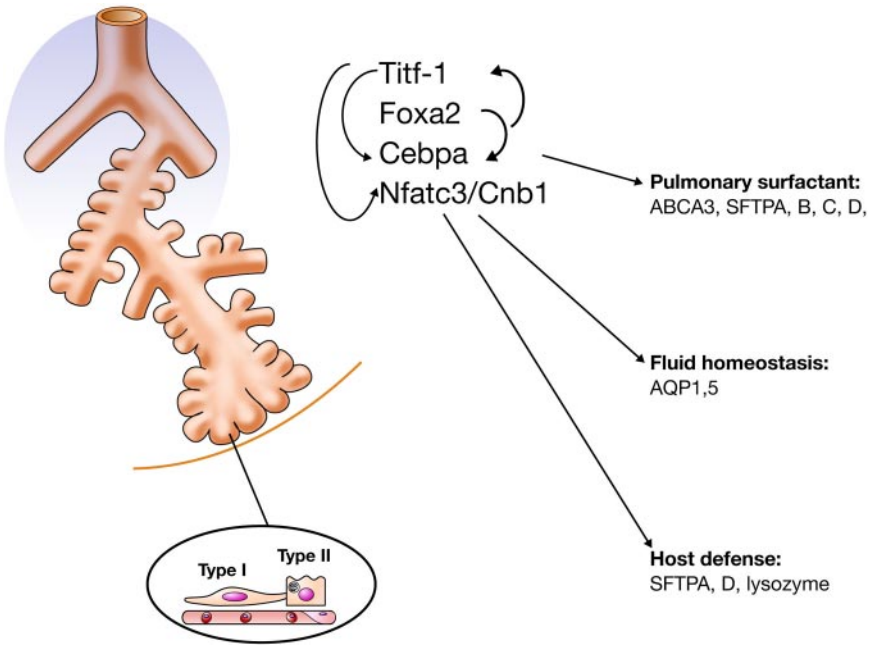

FIG. 6. TTF-1, FOXA2, NFATC3, and C/EBPα participate in a network regulating perinatal lung maturation and adaptation to airbreathing at birth. Prior to birth, the peripheral lung saccules differentiate and the mesenchyme thins as sacculation and alveolarization proceed. Type I cells (squamous cells) come into close contact with pulmonary capillaries to facilitate gas exchange. Surfactant lipids and proteins expressed by the type II cells are required to reduce surface tension at the air-liquid interface in the alveoli. TTF-1, FOXA2, NFATC3 (activated by CNB1-calcineurin), and C/EBPα are expressed by pre-type II cells and type II cells where they coregulate genes required for perinatal respiratory function. TTF-1, FOXA2, NFATC3, and C/EBPα influence expression of genes regulating surfactant synthesis, fluid and electrolyte homeostasis, and innate defense.

TABLE 2. *List of transcription factors associated with abnormalities in lung morphogenesis or function*

	Family	Location	Downstream Genes	Lung Morphogenesis/ Defect	Disorder	Reference Nos.
HIF1A	bHLH	M, E, enth	Vegf	Vascularization	Die at midgestation(−/−)	201, 280, 281
HIF2A	bHLH	M, E, enth	Vegf, Sftpb	Sacculation/ vascularization	RD/atelectasis(−/−)	29, 44, 65, 242
N-MYC/MYCN	bHLH	dE	Sftpa, Sftpb, Aqp5, Sox9, Rog	Structure/branching	PN(−/−, OE)	161, 162, 181
POD1/TCF21	bHLH	M	Scgb1a1, Bmp4, Sftpc	Branching	PN(−/−)	194
ASCL1/MASH1	bHLH	PNEC	Calca, Dll1	PNEC	PNEC absent(−/−)	25, 95
HES1	bHLH	E(noPNEC)	Ascl1, NeuroD, Notch1	No PNEC	Unknown	95
CREB1	bZIP	SAEC	Sftpd	Sacculation	RD/atelectasis(−/−)	2, 200
CEBPA	bZIP	Type II & AM	Surfactant protein	Sacculation	RD/atelectasis(−/−)	10, 14, 57, 147, 179, 223
CEBPB	bZIP	Lung	Scgb1a1, Cyp2b1	Unknown	COPD, CB	13, 15
CEBPD	bZIP	Lung	Scgb1a1, Cyp2b1	Unknown	Unknown	13
SREBP-1c/SREBF1	bZIP	Type II	Fasn, Scd1	Normal	Lipid metabolism	33, 148, 285
ATF2	bZIP	Lung	Sftpb	Unknown	RD/atelectasis(−/−)	16, 141, 237
JUNB	bZIP	Lung	Sftpb	Unknown	Unknown	163, 207
C-JUN	bZIP	Lung	Sftpb	Unknown	Unknown	207, 259
JUNDI	bZIP	H292	Sftpb	Unknown	Unknown	72, 207
NRF2/NFE212	bZIP	Unknown	Nqo1, Ugt1a6	Normal	AL1, inflammation, emphysema	32, 90
FOXA1	Fox	E	Sftpa, Sftpb, Sftpc, Sftpd, Scgb1a1	Differentiation	Normal function/differentiation delay(−/−)	16, 17, 19, 123, 244
FOXA2	Fox	E	Sftpa, Sftpb, Sftpd, Scgb1a1, Wnt7b, Titf1	Goblet cell/ alveolarization	RD/atelectasis(−/−)	42, 88, 244–246, 252, 290, 291
FOXF1	Fox	dM	GII3, Fgf10, Tbx	Vascularization/ alveolarization	PN, RD, hemorrhage, AL1(−/−)	42, 82, 100–108, 127
FOXJ1	Fox	Cillated E	Dnahc11, Sftpb, Sftpc, Tubb, Nodal, Pitx2, Ezrin/Vit2	Cillogenesis/L-R asymmetry	PN, PostN, autoimmune(−/−)	38, 86, 128, 232, 279, 285
FOXM1	Fox	M	Cyclin, Flk1/Kdr, Pecam1	Vascularization	Air space enlargement (−/−)	99, 100, 110, 111, 275
FOXP1	Fox	pE, dE	Scgb1a1, Sftpc	Normal	Unknown	125, 137, 215, 247
FOXP2	Fox	dE	Scgb1a1, Sftpc	Unknown	Unknown	125, 137, 215
FOXP4	Fox	pE, dE	Scgb1a1	Unknown	Unknown	125, 137
HOXA5	Homeo	M	Sftpb, Sftpc, Titf1, Foxa2, Nmyc/Mycn	Sacculation	RD/atelectasis(−/−)	5
HOXB2, 3, 4, 5	Homeo	M	Unknown	Unknown	Unknown	22, 23
TTF-1/TITF1	Homeo	E	Sftpa, Sftpb, Sftpc, Sftpd, Scgb1a1, Bmp4, Wnt7b	Structure/ differentiation	RD/hypoplasia(−/−)	24, 51, 112
CUTL1	Homeo	E	Unknown	Sacculation/ alveolarization	RD	64
HOP/HOD	Homeo	E	Surfactant protein	Structure	Hemorrhage/alveolar disruption(−/−)	277
PROP1	Homeo	Pituitary gland	Titf1	Sacculation	RD/atelectasis(−/−)	175
PITX2	Homeo	Left bud	Unknown	L-R asymmetry	Situs inverses(−/−)	113, 278
GR/NR3C1	NR	E	Unknown	Sacculation	RD/atelectasis(−/−)	43, 115, 192, 195
ERbeta/ESR2	NR	E(adult)	Sftpc, Pdgf, Gm-csf/ Csf2	Alveolarization	Surfactant accumulation(−/−)	187
RAR	NR	E	Sftpb, elastin	Structure/agenesis	PN/hypoplasia(−/−)	149, 151, 263
LXR/NR1H	NR	?	Unknown	Normal	Foam cell accumulation(−/−)	204
VDR	NR	E	Unknown	Normal	Inflammation(−/−)	177, 260
PPAR	NR	E(adult)	Sftpb, Gata3	Normal	Inflammation(−/−)	153, 261, 271
GATA6	Zinc	dE	Sftpc, Scgb1a1, Foxa2, Aqp5, Foxp2, Wnt7b, Titf1	Differentiation/ sacculation	PN or RD(−/−)	27, 117, 133, 166, 210, 252, 266
SP1	Zinc	bE(adult)	Sftpb	Unknown	Unknown	105, 145
SP3	Zinc	bE(adult)	Scgb1a1	Sacculation	RD(−/−)	26, 105
LKLF/KLF2	Zinc	Lung	Unknown	Branching	Die at midgestation(−/−)	248
GLI1	Zinc	M, E	Foxm1	PNEC/normal	Normal(−/−)	182, 228, 250
GLI2	Zinc	M	GII1, Ptch	Structure	Hypoplasia/agenesis/die at birth(−/−)	76, 168, 182
GLI3	Zinc	M	Unknown	Structure	Hypoplasia/agenesis/extra digits(−/−)	76, 127, 168, 182

TABLE 2—*Continued*

	Family	Location	Downstream Genes	Lung Morphogenesis/Defect	Disorder	Reference Nos.
ZIC3	Zinc	Cerebellum (adult)	Nodal, Pitx2	L-R asymmetry	Pulmonary reversal or isomerism(−/−)	4, 193
PLAGL2	Zinc	Lung	Sftpc	Unknown	Unknown	209
GFI1	Zinc	PNEC	Unknown	PNEC	PNEC hyperplasia	109
STAT1	STAT	E(adult)	Unknown	Normal	Pulmonary fibrogenesis, asthma	202, 243
STAT3	STAT	E(adult)	Sftpa, Sftpb	Normal	ALI	85, 208, 264, 269
STAT4	STAT	E(adult)	Unknown	Normal	Inflammation, COPD	59, 224, 229
STAT6	STAT	E(adult) & more	Unknown	Normal	Inflammation, asthma	1, 21, 122, 160
HDAC	CoA	Lung	Tnf, I/8, Mmp9, Sftpa	Unknown	Asthma, COPD	92–94, 277
NCOR/SMRT	CoA	Lung	Sftpa	Unknown	Unknown	92
SRC1/TIF2/NCOA	CoA	E, M	Sftpa, Sftpb	Sacculation	RD/atelectasis(−/−)	98, 146, 173, 276
P300/EP300	CoA	E, M	Scgbia1, Sftpc, Sftpd	Sacculation	RD(mut)	8, 106, 213
CBP/CREBBP	CoA	E, M	Sftpa, Sftpb, Sftpd	Sacculation	Atelectasis(mut)	92, 106, 173, 213, 276
CARM1	CoA	Lung	Unknown	Sacculation	PN/atelectasis	262
MRG15/MORF4L1	CoA	Lung	Unknown	Sacculation	PN/atelectasis	284
PARP1/PARP2	CoA	E, AM	Sftpb	Unknown	Unknown	140
BR22/TAP26	CoA	E(adult)	Sftpb	Unknown	Unknown	270, 273
TAZ/WWTR1	CoA	E	Sftpc	Unknown	Unknown	135
RCD1	CoA	Lung	Unknown	Branching	Unknown	83
CATENIN/CTNNB1	CoA	E, M	Sftpa, Sftpb, Sftpc, Vegf, Pecam, Foxa2, Nmyc/Mycn, Bmp4	Branching/goblet cell	Pulmonary tumor/pulmonary fibrosis/ALI	40, 60, 169, 170, 181, 183, 214, 287
TCF/LEF	HMG	E, M	Sftpb, Cdx1, Atoh1	Submucosal glands	ALI/no submucosal gland(−/−)	60, 62, 63, 180, 227
SOX2	HMG	E	Unknown	Unknown	Unknown	90, 183
SOX7	HMG	Lung	Unknown	Unknown	Unknown	225
SOX9	HMG	E, M	Unknown	Normal	Normal	190
SOX11	HMG	E, M	Unknown	Sacculation	RD/atelectasis	219
SOX17	HMG	E, M?	Foxa1, Foxa2	Branching, PNEC	Focal epithelial hyperplasia (OE)	183, 216
SMAD1	SMAD	E, M	Sftpc	Branching	Inflammation	36, 211
SMAD2	SMAD	E	Unknown	Branching	ALI/inflammation/ pulmonary fibrosis	150, 240, 287
SMAD3	SMAD	E	Sftpb	Branching/alveolarization	ALI/pulmonary fibrosis/emphysema	36, 123, 240, 287, 289
SMAD4	SMAD	E, M	Unknown	Branching	ALI	240, 287
SMAD5	SMAD	Lung	Unknown	Branching	Unknown	211
SMAD6	SMAD	Vessel E	Unknown	Unknown	COPD	70, 220, 288
SMAD7	SMAD	daE	Sftpc	Branching	ALI/inflammation/ pulmonary fibrosis/ COPD	150, 172, 220, 240, 288
PU.1/SPI1	ETS	AM	Cd32/Fcgr2a, M-csfr/ Csflr	Alveolar macrophage	Alveolar proteinosis	212
ETS1	ETS	Lung	Caveolin-1/Cav1	Unknown	Unknown	108
ELF3	ETS	Lung	Unknown	Unknown	Unknown	108
ESE3/EHF	ETS	Lung	Unknown	Unknown	Unknown	108
SPDEF	ETS	E	Foxj1	Goblet cell differentiation	Inflammation	108; Park, unpublished data
PEA3	ETS	E, M	Aqp5, caveolin-1/ Cav1	Normal	Unknown	108, 134
ERM	ETS	dE	Sftpc, caveolin-1/ Cav1	Branching	RD	108, 129, 134
NF1	Nfl	M, E	Sftpa, Sftpb, Sftpc, Sftpd, Aqp1, ENaC/Scnn1	Sacculation	PN/RD/atelectasis	7, 8, 78, 222
RB1	Rb	Lung	Calca	PNEC	PNEB hyperplasia	258
TBX1	T-box	E	Unknown	Unknown	DiGeorge's syndrome	34, 97, 130, 152
TBX4/5	T-box	M	Fgf10	Branching	Unknown	31, 34
NFATC3(w/CNB1)	NFAT	bE	Sftpa, Sftpb, Sftpc, Sftps, Abca3	Sacculation	RD	48
NFKB	Rel	M	Sftpa	Unknown	Inflammation	91, 92
B-MYB/MYBL2	Myb	dbE	Sftpa	Unknown	Unknown	28
E2F1	E2F	Lung?	Unknown	Structure(W/Rb) (sacculation)	Unknown	121, 135
RUNX3	Runt	D	Ccr7	Dendritic cell	Inflammation	66, 67

TABLE 2—*Continued*

	Family	Location	Downstream Genes	Lung Morphogenesis/Defect	Disorder	Reference Nos.
P63/TP73L	p53	Basal cell	K[4/Krt]-14	Basal epithelial cell	Squamous carcinoma/no basal cells(−/−)	47, 116
DICER	RNase	E	Unknown	Branching/differentiation	Branching/differentiation defects(−/−)	80

M, mesenchyme; E, epithelia; Enth, endothelia; dE, distal epithelia; PNEC, pulmonary neuroendocrine; SAEC, small airway epithelial cells; AM, alveolar macrophage; dM, distal mesenchyme; bE, bronchial epithelia; daE, distal airway epithelia; dbE, distal bronchial epithelia; D, dendritic cells; pE, proximal epithelia; RD, respiratory distress at birth; PN, perinatal death; PostN, postnatal death; ALI, susceptible to acute lung injury; COPD, chronic obstructive pulmonary disease; CB, chronic bronchitis.

led to a standard therapy for the prevention of respiratory distress in preterm human infants (126). The actions of glucocorticoids are mediated by the glucocorticoid receptor α and β (GRα, GRβ) present on target cells (115, 192). The effects of glucocorticoids on maturation of surfactant biosynthesis by fetal type II cells are dependent on mesenchymal cells, which are likely to provide paracrine signals inducing epithelial maturation (11, 217). In mice, deletion of GRα delays lung maturation causing respiratory distress at birth (43). Stimulatory effects of glucocorticoids on surfactant lipid synthesis are associated with increased expression of enzymes mediating lipid biosynthesis. Likewise, glucocorticoids influence the expression of epithelial sodium channels and Na^+-K^+-ATPase that mediate the resorption of lung liquid at birth. Thus transcriptional control of both the respiratory epithelium exerted via TTF-1 and its partners, as well as glucocorticoids in the pulmonary mesenchyme, play distinct but important roles in perinatal lung maturation and function.

C. FOXP Family Members

FOXP1, FOXP2, and FOXP4 are expressed in respiratory epithelial cells (137, 215). FOXP1, FOXP2, and FOXP4 homo- and/or heterodimerize and repress the activity of the CCSP and SP-C promoters (125, 215). The corepressor COOH-terminal binding protein 1 (CtBP-1) interacts with and represses the activity of FOXP1 and FOXP2 but not FOXP4 (125). FOXP2 was increased in the lung of mice expressing a dominant-negative GATA-6 (266). FOXP1-deficient mice have defects in cardiac but not lung morphogenesis, suggesting that other FOXP family members compensate for its loss in respiratory epithelial cells (247).

VI. ALVEOLARIZATION-POSTNATAL LUNG MORPHOGENESIS

Formation of the highly septated and alveolarized structures comprising the alveolar gas exchange area occurs primarily in the postnatal period in mice and humans. Recent gene targeting experiments have identified several transcription factors influencing alveolarization. Cellular processes, signaling mechanisms, and transcription factors controlling alveolarization are relatively poorly understood; however, GATA-6, TTF-1, ERβ, RARs, SMAD3, FOXA2, and FOXF1 have been implicated in the process. In mice expressing increased levels of either GATA-6 or TTF-1 in respiratory epithelial cells, postnatal alveolarization was disrupted, resulting in airspace enlargement (134, 254). ERβ-deficient lungs have larger and fewer alveoli than normal lungs, indicating the importance of ERβ in alveolarization (187). Expression of dominant negative RARα in respiratory epithelial cells caused alveolar abnormalities consisting of increased airspace size and decreased alveolar surface area (268). Centrilobular emphysema, associated with decreased tropoelastin and increased MMP-9 production, was observed in *Smad3*$^{-/-}$ mice (36). Defects in alveolarization were observed after deletion of FOXA2 in respiratory epithelial cells and in heterozygous *Foxf1*$^{+/-}$ targeted mice and *RAR*$\beta^{-/-}$ mice (101, 218, 245).

VII. LISTING OF OTHER TRANSCRIPTION FACTORS INFLUENCING PULMONARY FORMATION/FUNCTION

In this review, we have organized the expression patterns, gene targets, and roles of transcription factors in the context of major events in lung morphogenesis, focusing the discussion to those pathways and processes that have been relatively well established. Nevertheless, as research continues in this area, particularly with increasing insights derived from transgenic mouse models in the study of lung development, the number of transcription factors influencing lung formation and function is increasing at a rapid pace. In this section of the review, we have briefly summarized knowledge regarding transcription factors that influence lung morphogenesis and function. Table 2 provides a list of transcription factors associated with abnormalities in the lung morphogenesis or function. Groups of some of these transcription factors are summarized below.

A. E2F1 and RB

E2F1 is a member of a family of seven related proteins that bind and regulate the promoters of genes regulating cell proliferation. RB associates with E2Fs and suppresses the activation of genes regulating cell cycle progression (69). E2F-RB also influences differentiation and development (114). E2F is converted into a transcriptional suppressor by retinoic acid, causing inhibition of the growth of normal human bronchial epithelial cells (121). E2F1/RB double mutant mice die from respiratory failure at birth, indicating a requirement for E2F1-RB for normal lung differentiation (235).

B. SMADs and the TGF-β Superfamily

Many ligands of the TGF-β superfamily, including a number of bone morphogenic proteins (BMPs), TGF-β1, -2, -3, and activin, are expressed in the developing lung. The SMAD proteins are nuclear effectors of the TGF-β superfamily ligands regulating transcription in various tissues. Eight SMAD proteins have been identified in mammals and have been divided into three classes based on their structure and function: receptor-regulated SMADs (R-SMADs: SMAD1, SMAD2, SMAD3, SMAD5, SMAD8), common-partner SMAD (co-SMAD: SMAD4), and inhibitory SMADs (I-SMADs: SMAD6, SMAD7). Mechanisms mediating TGF-β-Smad signaling have been recently reviewed (74, 231). SMAD1 and SMAD7 positively regulated branching morphogenesis of the lung (35, 286, 288), while SMAD2, SMAD3, and SMAD4 negatively regulate branching morphogenesis (287). SMADs have been implicated in the regulation of inflammation (77).

C. Transcriptional Coactivators

Transcription factors bind to their target DNA elements present in regulatory regions of DNA, directing RNA synthesis by RNA polymerase. Two processes are critical for the activation of transcription. First, tightly compacted chromatin structures consisting of histone and DNA must be opened. Second, the factor or complex of factors interact with RNA polymerase to produce RNA. A number of coregulators that open up closed chromatin structures and interact with transcription factors and RNA polymerase have been identified, including factors that mediate ATP-dependent chromatin remodeling and histone modification. RNA polymerase II-associating factors as well as cell-specific cofactors and negative cofactors function as either coactivators or corepressors in partnership with transcription factors. Some coactivators act either through chromatin modification (e.g., p160, CBP/p300/PCAF histone acetyltransferases, and PRMT/CARM methyltransferases) or more directly (e.g., Mediator) to interact with the general transcription machinery and RNA polymerase II (198). Four chromatin modifiers p160 (SRC-1/TIF2), CBP/p300, CARM1, and MRG15 are required for normal lung morphogenesis. Many of these cofactors are recruited with TTF-1 to transcription sites on target genes (Fig. 2). SRC-1 and TIF2 are members of the p160 coactivator family. The p160 complex contains acetyltransferase (e.g., p300 and CBP) and methyltransferase (e.g., CARM1). Deletion of *Src-1* and *Tif2* in the mouse caused respiratory distress and death at birth (146). Neonates carrying a single acetyltransferase activity (AT)-deficient allele of p300 became cyanotic within minutes following birth (213). Embryos lacking p300 died between E8.5 and E11 (274). Lungs of most *p300* $AT^{-/-}$ mice were arrested in the early saccular stage of morphogenesis, indicating that the lung remodeling at the saccular stage requires p300 AT activity (213). Lung hypoplasia and delayed thinning of the pulmonary mesenchyme were observed in mice bearing a nonfunctional *Cbp* mutant gene (106). CARM1 is a coactivator-associated arginine methyltransferase 1 that binds to the p160 family. *Carm1*$^{-/-}$ mice die from respiratory failure at birth (262). MRG15 associates with at least two nucleoprotein complexes that include histone acetyltransferases and/or histone deacetylase. *Mrg*$^{-/-}$ mice also die from respiratory failure at birth (234).

D. Nuclear Receptors

Nuclear receptors are DNA-binding transcription factors whose nuclear transport and activity are directly modulated by ligand binding to either activate or repress gene expression. The mammalian nuclear receptor superfamily comprises more than 45 transcription factors. Members of the nuclear receptor superfamily include the following: receptors for steroid hormones, such as the estrogen receptor (ER), the glucocorticoid receptor (GR), and the vitamin D receptor (VDR); receptors for nonsteroidal ligands, such as the RAR; and receptors that bind diverse lipid and lipid metabolites including fatty acids and prostaglandins [peroxisome proliferators activated receptors (PPARs) and liver X receptors (LXRs)] (189). Nuclear receptors are involved in the regulation of lung morphogenesis, homeostasis, and inflammation. Lung agenesis/hypoplasia and tracheal cartilage malformations were observed in compound RAR gene-targeted mice, indicating the important role of retinoic acid in lung morphogenesis (139, 151). Compound genotype LXR-deficient mice accumulate foam cells, filled with lipids, in the alveolar sacs of the lungs, indicating the LXR involvement with lung homeostasis (204). Both VDR and PPAR are involved in lung inflammation. *Ppar*$\gamma^{-/-}$ mice are susceptible to allergy-induced lung inflammation (261). In contrast, *Vdr*$^{-/-}$ mice were resistant to experimentally induced asthma in the lungs (260).

E. BZIP Family

The bZIP transcription factors have a basic leucine zipper (bZIP) DNA binding motif that binds to sequence-specific double-stranded DNA to either activate or repress transcription (241). In the lung, bZIP transcription factors including cAMP response element binding protein (CREB), CCAAT/enhancer binding protein (C/EBP), ATF-2, JunB, c-Jun, JunD, and NRF2 regulate gene expression. *Creb* null mice were cyanotic after birth and died from respiratory distress. Atelectasis and respiratory failure were observed in both $Creb^{-/-}$ (200) and $Cebp\alpha^{-/-}$ mice (68). ATF-2-deficient mice also died after birth with severe respiratory distress with lung filled with "meconium"; however, the mechanisms by which deletion of ATF-2 influence perinatal lung homeostasis are unknown (141). NRF2 is expressed mainly in tissues that express phase 2 detoxification genes. NRF2-deficient mice were viable but died from acute respiratory distress after treatment of the antioxidant butylated hydroxytoluene, a chemical agent causing DNA breakage (32).

F. Other Homeodomain Proteins

The homeodomain family of transcription factors plays fundamental roles in morphogenesis, influencing segmentation organogenesis patterning and cell fate determination required for metazoan development. Members of this family share the helix-turn-helix DNA-binding motif known as the homeodomain. Homeodomain proteins regulate various cellular processes by specifically binding to the transcriptional control regions of target genes. The homeodomain proteins are classified into six distinct classes: HOX, Extended HOX, NK, Paired, LIM, POU, and atypical class (9). Six homeodomain transcription factors, HOXA5, TTF-1 (previously discussed in this review), Prophet of PIT1 (PROP1), PITX2, CUTL1, and HOP, affect lung morphogenesis and function. A number of Hox genes are expressed in the lung; however, single deletions of host Hox genes are not associated with severe lung malformations, a finding likely related to overlapping functions of the many Hox genes. PROP1 and PITX2 belong to the Paired class in the homeodomain family. PROP1-deficient mice die from respiratory failure at birth. Lungs of $Prop\text{-}1^{-/-}$ mice are lined by cuboidal epithelial cells and the lung mesenchyme is thickened (175). PITX2 is regulated by Lefty-1, that regulates left-right (L-R) asymmetry in vertebrates (278). In the lungs of normal mice, PITX2 is expressed at E9.5, but only in the left bud. The normal asymmetric pattern of lung lobulation is altered in the $Pitx2^{-/-}$ embryos resulting in right pulmonary isomerism (113).

G. STAT Family

Signal transducer and activator of transcription (STAT) proteins are a group of transcription factors mediating signaling from multiple growth factors, cytokines, and other extracellular molecules (39). Based on findings from gene targeted mice, lung morphogenesis is not dependent on STAT1, -3, -4, or -6. STATs (STAT1, STAT3, STAT4, and STAT6) play an important role in lung inflammation and repair (1, 21, 54, 85, 224, 229, 243).

VIII. CONCLUSION

Concepts regarding regulation of gene transcription are continually advancing. In less than a few decades, our conception of simple molecular "switches" that were proposed to control gene transcription have matured to elaborate, complex networks of interacting transcription factors and their activators/coactivators that together bind to chromatin-DNA, whose structure also changes dynamically during development. The lung is an extraordinarily complex organ, comprised of dozens of distinct cell types. The lung plays a singular but critical role in gas exchange. Understanding the identities of the many transcription factors regulating lung formation and function will provide the concepts that will fuel progress in understanding the pathogenesis of inherited and acquired pulmonary diseases in the future.

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