# Update on Molecular Biology of Lung Development—Transcriptomics

Thomas J. Mariani, PhD

**KEYWORDS**

• Epithelium • Mesenchyme • Airway • Alveoli • Progenitor cells

**KEY POINTS**

- The past 2 decades have witnessed tremendous growth in our understanding of fundamental regulatory processes and networks responsible for coordinating the development of the mammalian lung; high-throughput, genome-wide analyses have facilitated this growth.
- Recent seminal observations regarding cellular heterogeneity and lineage relationships demonstrate we have much yet to learn.
- Recent developments in single-cell transcriptome analysis are likely to transform our appreciation of cellular heterogeneity with the respiratory system and help to determine whether this heterogeneity is programmed, stochastic, or a combination.
- The precise role of environmental cues, both normal (eg, oxygen) and foreign (eg, microbes), in the coordinated regulation of lung development remains poorly defined.
- Multi-scale integration of molecular information, such as that defined by comprehensive profiling of miRNA and mRNA expression, will ultimately be necessary for a complete explanation of lung development.

## INTRODUCTION

This article highlights some of the significant advances in our understanding of lung developmental biology made over the last few years, which challenge existing paradigms and are relevant to a fundamental understanding of this process. Additional comments address how these new insights may be informative for chronic lung diseases that occur, or initiate, in the neonatal period. This is not meant to be an exhaustive review of the molecular biology of lung development. For a more comprehensive, contemporary review of the cellular and molecular aspects of lung development, readers can refer to recent reviews by others.[1–7]

Disclosure: Dr T.J. Mariani is supported by HL101813 (NHLBI), HL101794 (NHLBI), HL122700 (NHLBI) and HHSN272201200005C (NIAID) grants.
Division of Neonatology and Pediatric Molecular and Personalized Medicine Program, University of Rochester Medical Center, 601 Elmwood Avenue, Box 850, Rochester, NY 14642, USA
*E-mail address:* Tom_Mariani@urmc.rochester.edu

Clin Perinatol 42 (2015) 685–695
http://dx.doi.org/10.1016/j.clp.2015.08.001 **perinatology.theclinics.com**
0095-5108/15/$ – see front matter 

## DISCUSSION

### *Introduction to Lung Development*

Historically, the process of lung development has been conceptualized as a linear set of stages, typically including 4 or 5 discrete parts, aligned with the age of the organism. These stages were defined largely on histologic and morphologic changes in lung structure that occur during fetal development. The embryonic stage of lung development is recognized as encompassing the initiation of lung formation and, as a reference, occurs from 4 to 6 weeks postmenstrual age (PMA) in humans and embryonic day 9.5 (E9.5) to E10.5 in mice. This stage involves budding of a patch of ventral foregut endoderm, located between the thymus and liver, to form a distinct organ primordium. A central role for retinoic acid (RA) in this process has been appreciated, and recent studies uncovered a Wnt/Tgfbeta/Fgf10 regulatory network controlled by RA to drive the formation of the lung bud.[8]

The pseudoglandular stage of lung development largely involves establishment of the airway structure of the mature rodent and occurs from 6 to 16 weeks' PMA in the human and E10.5 to E16.5 in the mouse. Formation of the airways results from recursive branching morphogenesis, similar to that which occurs in other glandular organs with a branched tubular structure (eg, salivary, mammary). Branching morphogenesis in the lung seems to be regulated locally by FGF10/FGFR2 and BMP4/Shh signaling, to promote tube elongation or branch-point formation, respectively. Some investigators have suggested conversely that FGF10 controls epithelial differentiation.[9] Although it was largely presumed that this local regulation occurred stochastically, seminal studies by Metzger and colleagues[10,11] demonstrated that these events are programmed in both time and space.

Once the major airway architecture of the lung has been established during the pseudoglandular stage, the canalicular stage of lung development involves initiation of the formation of the functional (acinar) portion of the lung and initiation of the differentiation of distinct respiratory cell types. This stage occurs from 16 to 26 weeks' PMA in the human; but for some reason, it is much more condensed in mice, occurring from E16.5 to E17.5. The establishment of a proximal-distal differentiation pattern of lung epithelium has been described[12,13] and seems to be regulated by a complex set of regulatory molecules and transcription factors driven by the activation of Wnt/b-catenin signaling. The emergence of morphologically distinguishable alveolar epithelial cell types, which are essential for facilitating gas exchange, also begins at this stage. As discussed later, although it is now clear that mesenchyme undergoes analogous processes to specify various cell types,[14] and can play a direct role in developmentally associated lung diseases,[15,16] an understanding of how this process is regulated for mesenchymal cells is less clear.

The saccular stage of lung development involves the formation of frank, functional airspace capable of gas exchange. This stage is associated with the emergence of the expression of numerous cell type–specific markers and expansion of the density of the alveolar capillary bed. In the human, the saccular stage takes place entirely in utero, initiating at approximately 26 weeks' PMA and continuing through 36 weeks' PMA. In the mouse, for reasons that are not entirely clear, this stage spans birth, initiating at E17.5 and continuing through approximately the first 4 to 7 postnatal days (P4-7). The initiation of functional pulmonary surfactant production and surfactant secretion is a key physiologic event that occurs during this stage. Functional surfactant is essential to maintain airspace patency, and its absence is a major cause of morbidity and mortality in babies born before this time.[17]

The alveolar stage is the ultimate stage of lung development, and it initiates at 36 weeks' PMA in humans and at approximately P4-7 in mice. The major events of