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Epigenetic Contributions to the Developmental Origins of Adult Lung Disease

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Abstract

Perinatal insults, including intrauterine growth restriction, preterm birth, maternal exposure to toxins, or dietary deficiencies produce deviations in the epigenome of lung cells. Occurrence of perinatal insults often coincides with the final stages of lung development. The result of epigenome disruptions in response to perinatal insults during lung development may be long-term structural and functional impairment of the lung and development of lung disease. Understanding the contribution of epigenetic mechanisms to life-long lung disease following perinatal insults is the focus of the developmental origins of adult lung disease field. DNA methylation, histone modifications, and microRNA changes are all observed in various forms of lung disease. However, the perinatal contribution to such epigenetic mechanisms is poorly understood. Here we discuss the developmental origins of adult lung disease, the interplay between perinatal events, lung development and disease, and the role that epigenetic mechanisms play in connecting these events.

Keywords

Lung development; epigenetic; developmental origins; programming

Introduction

Do the origins of adult lung disease lie in early life events? How is individual susceptibility to adult lung disease programmed by perinatal environmental conditions? Answers to these questions are at the center of the emerging ‘Developmental Origins of Adult Lung Disease’ field. Research is focused on understanding the contribution of perinatal events to adult lung disease, as well as uncovering the *mechanisms* connecting perinatal events to adult lung disease. A key mechanism under investigation involves plasticity of the lung epigenome.

Key Concepts in the Developmental Origins of Adult Lung Disease

The developmental origins of disease field evolved following David Barker’s observation that low birth weight (a surrogate for poor *in utero* conditions) predisposed to adult cardio-metabolic disease and early death (Barker and Osmond, 1986). More recently, the

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developmental origins of disease field has expanded to include lung disease (Joss-Moore et al., 2011, Harding and Maritz, 2012, Stocks et al., 2013).

Two main concepts are associated with the developmental origins of adult lung disease. The first relies on the idea that lung function tracks a predictable percentile over the life course (Figure 1). A consequence of percentile tracking of lung function is that failure to reach normal, maximal lung function by early adulthood results in a lower lung function at later age; deficits that can become significant when considered in combination with the reduction in lung function that accompanies normal aging. When perinatal events alter the growth and development of the lung, thus reducing lung function in the neonatal and childhood period, the result is reduced lung function throughout life. The second concept in the developmental origins of adult lung disease involves the idea that the lung has specialized cells that undergo programing and subsequent remodeling during normal lung development. When lung development is interrupted by noxious stimuli the result is divergence of cellular programming, producing dysfunctional remodeling of the lung, either during development or later in response to injury (Figure 2).

Perinatal insults, including intrauterine growth restriction (IUGR), premature birth, maternal exposure to toxins, or dietary deficiency are linked to several lung disease outcomes and remodeling disorders (Stocks et al., 2013) (Table 1). The pathophysiology of lung disease with perinatal origins is likely a combination of incomplete lung growth and development, as well as reprogramming of specific cells within the lung. Lung growth and development, as well as reprogramming of specific lung cells, involves precise spatial and temporal activation of gene expression programs. Spatial and temporal gene expression programs are regulated by epigenetic mechanisms.

The Epigenetic Contribution to the Developmental Origins of adult lung disease

The interaction between genetics, epigenetics, and the environment contribute to the developmental origins of adult lung disease. We focus on the epigenetic component because epigenetic mechanisms regulate the timing, magnitude, and cell-specificity of gene expression and resulting transcriptomes. Epigenetic regulation of gene expression is accomplished by directing the interactions among the transcription machinery, transcription factors, and specific regions of DNA. Excellent reviews of the general mechanisms of epigenetic regulation of gene expression are available (Klose and Bird, 2006, Zentner and Henikoff, 2013, Voss and Hager, 2014) so we will not review them.

Lung Developmental Timing

To consider the role of epigenetic mechanisms in the developmental origins of adult lung disease, an understanding of the timing of lung development is helpful. Human lung development passes through 5 distinct stages: embryonic (4–7 weeks gestation), pseudoglandular (5–17 weeks gestation), canalicular (16–27 weeks gestation), saccular (28–31 weeks gestation), and alveolar (32 weeks gestation though early postnatal years) (Albertine and Pysher, 2004, Burri, 2006). Because animal models are often used to study

the molecular mechanisms of the developmental origins of adult lung disease, the timing of lung development in non-human mammalian species is also important. Lung development in non-human mammalian species follows the same distinct stages as human lung development. In the sheep, the timing is of lung development is similar to that of the human, with alveolar formation largely complete by, or shortly after, term birth. This is in contrast to the rat and mouse, in which the lung is developmentally more immature at term birth. The rat and mouse lung is in the saccular stage of development at term birth (Figure 3). Distinct from humans and sheep, rats and mice undergo alveolar formation during the second and third weeks of postnatal life after term birth. Normal newborn rats and mice pups do not need ventilation support or supplemental oxygen to live.

The lung is developmentally dynamic during times of common perinatal insults. Perinatal insults that produce long-term changes in the human lung tend to occur during the second half of gestation and the early postnatal period. Because of this timing, the saccular and alveolar stages of lung development are most relevant to our discussion. Large animal models, such as sheep, provide opportunities for physiologic and molecular studies in a similar developmental context to humans. Sheep models of preterm birth and respiratory support, as well as models of intrauterine growth restriction (IUGR), are used to study the developmental origins of adult lung disease (Albertine et al., 1999, Rozance et al., 2011, Null et al., 2014). Uniquely, the preterm lamb model recapitulates the human clinical occurrence of preterm birth that is frequently associated with respiratory distress and failure. Respiratory failure necessitates **ventilator** support with oxygen-rich gas to keep the preterm neonates alive.

Rat and mouse models are also valuable tools for understanding the developmental origins of adult lung disease, particularly for molecular manipulation. Immaturity of the lungs at birth in rat and mouse allows postnatal manipulation during the saccular and alveolar stages of lung development. Rat and mouse models used to study the effects of perinatal events on lung outcomes include models of IUGR induced by uteroplacental insufficiency, malnutrition, maternal toxins and tobacco smoke, as well as models of postnatal hypoxia and hyperoxia (Bassi et al., 1984, Bhaskaran et al., 2012, Hilgendorff et al., 2012, Olave et al., 2012, Rehan et al., 2012, Joss-Moore et al., 2013).

Epigenetic Effects in the Lung

Environmentally-induced disruptions to the normal epigenetic characteristics of DNA within distinct cells during development leads to alterations in gene expression and thus, changes in development. Three major consequences can arise from changes in lung cell epigenetics and transcriptomes that occur at developmentally sensitive time points. First, the lung can assume an alteration in structure and/or function secondary to changes in cell differentiation and cell-to-cell communications. Secondly, when the epigenome of a cell is altered at a developmentally sensitive time point, this “new” epigenetic platform becomes the basis upon which subsequent epigenetic changes are built. The potential result is an increasing deviation from “normal” during and after development. The final consequence of changing lung cell epigenetics during development is that the new epigenome is also primed to direct gene expression differently in response to future lung injury and repair.

Epigenetic mechanisms include DNA methylation, histone protein modifications, and non-coding RNA's, including microRNA. Involvement of each of these epigenetic mechanisms in the developmental origins of adult lung disease will be considered below.

DNA methylation

DNA methylation occurs primarily as the addition of a methyl group to the 5′ position of a cytosine followed by a guanine (CpG). CpG density in the mammalian genome is relatively low, with CpGs clustered in dense regions known as CpG "islands" (Gardiner-Garden and Frommer, 1987). CpG islands are commonly found in promoter regions of mammalian genes, and are often unmethylated (Klose and Bird, 2006, Huh et al., 2013). Unlike promoter regions, coding regions and regions between genes contain low density CpGs, and are more frequently methylated (Illingworth et al., 2008, Liang et al., 2011, Maunakea et al., 2013). Low density CpGs located in the coding region tend to be associated with exons more often than with introns, and may have a role in alternative exon usage (Choi, 2010).

Changes in DNA methylation following preterm-birth, intrauterine growth restriction (IUGR), or maternal toxin exposure are identifiable in placenta and peripheral tissues such as blood leucocytes (Ferreira et al., 2011, Suter et al., 2011, Hogg et al., 2012, Jiang et al., 2012). However, to our knowledge, no studies document DNA methylation changes in human lung tissue associated with perinatal events.

DNA methylation changes are linked to immune responses associated with the development of adult lung disease. Asthma development is linked to maternal folate intake during pregnancy (Haberg et al., 2009, Whitrow et al., 2009). Dietary intake of folate leads to the production of S-adenosyl-L-methionine (SAM), a universal methyl donor and precursor for DNA methylation. In mice, a maternal diet high in methyl donors increases offspring airway inflammation, serum IgE levels, and airway hyperesponsiveness. Additionally, the phenotypic changes in mice offspring occur in conjunction with hypermethylation of the Run3x gene, a mediator of inflammation (Hollingsworth et al., 2008). Control of activated T-helper cells is also regulated by DNA methylation, again linking epigenetic mechanisms to the development of allergic airway disease (Kabesch et al., 2010, Yang and Schwartz, 2011).

Despite no human evidence of lung DNA methylation changes following perinatal insults, abundant evidence shows lung DNA methylation changes in the presence of adult lung disease. One large study of DNA methylation in peripheral blood of adults (smokers and non-smokers) with chronic obstructive pulmonary disease (COPD) identified numerous differentially methylated genes, compared to matched subjects without COPD (Qiu et al., 2012). Differentially methylated regions identified are generally hypomethylated and 70% of the sites are outside of CpG islands. Gene ontology (GO) analysis identified expected GO pathways associated with the differentially methylated genes, including, response to stress and external stimuli as well as wound healing cascades. Because the study identified differential methylation in non-lung tissue, difficulties arise in assessing whether the changes are causative, a marker of lung injury, or a marker of the initial COPD stimulus.

While not distinguishing between causative and marker status, one finding of the study does suggest *specificity* of peripheral blood differential methylation in COPD patients. Mutations

of the SERPINA1 gene, which codes for α1- antitrypsinogen, are causally associated with COPD. Two differentially methylated CpG sites within the SERPINA1 gene were identified by the study. Methylation status of one of the SERPINA1 sites ranked highest in COPD cases, as well as highest for association with lung function (Qiu et al., 2012). These data raise interesting questions. Given that few of the genes identified as being differentially methylated could be predicted based on smoking intensity, what is the trigger for differential methylation and what is the timing of occurrence? A complete understanding of potential perinatal contributions to DNA methylation changes observed in adult lung disease is an important research directive.

Mechanistic insight into myofibroblast differentiation has provided insight into the role of DNA methylation in lung cellular reprogramming and remodeling. The myofibroblast has a pro-fibrotic phenotype characterized by expression of extracellular matrix (ECM) genes such as elastin, collagen, and α-smooth muscle actin (α-SMA). Myofibroblasts have features of both fibroblasts and smooth muscle cells, and appear to be the main source of excessive elastin production in lung diseases, such as bronchopulmonary dysplasia (BPD) and idiopathic pulmonary fibrosis (IPF). Activation of injury cascades result in proliferation of resident fibroblasts, as well as epithelial mesenchymal transitions. The resulting myofibroblast foci exhibit accumulation of ECM, dysregulated wound repair and lung remodeling (Bland et al., 2007, Yang and Schwartz, 2014).

The involvement of DNA methylation in myofibroblast differentiation is exemplified by Thy-1 promoter methylation (Hagood, 2014). Thy-1, also known as CD90, is a cell-surface antigen expressed on fibroblasts. Thy-1 positive fibroblasts have lipid inclusions and an anti-fibrotic phenotype, while Thy-1 negative fibroblasts differentiate into myofibroblasts (Zhou et al., 2004). Thy-1 also independently plays a role in alveolar formation (Nicola et al., 2009). One means by which Thy-1 maintains a lipogenic fibroblast phenotype is by stimulating peroxisome proliferator activated receptor gamma (PPARγ) signaling and PPARγ directed transcription of lipid enhancing genes (Varisco et al., 2012). Hypermethylation of the Thy-1 promoter silences Thy 1, producing myofibroblast differentiation. DNA hypermethylation of Thy 1 is observed in myofibroblasts located in fibroblastic foci in IPF, and in mice exposed to the fibrotic agent bleomycin. Hypermethylation of lung Thy-1 can also be induced by hypoxia (Sanders et al., 2008, Robinson et al., 2012). The perturbation of Thy-1 methylation, PPARγ activity, and subsequent myofibroblast differentiation is likely important in the lung response to perinatal insults.

Histone Modifications

While DNA methylation is one of the better studied and more easily assessed epigenetic modification, histone modifications provide greater variability in effects and often interact with DNA methylation. A core of 8 histone proteins, forming a unit called a nucleosome, is surrounded by two wraps of 147 base pairs of DNA (Luger et al., 1997). Adjacent nucleosomes are connected by short pieces of linker DNA. The nucleosome core is occupied by the globular portion of the histone proteins, while the unstructured, N-terminal “tails” of the histone proteins extend freely from the nucleosome (Luger et al., 1997). Histone tails

provide the location for many (but not all) post-translational, covalent modifications (reviewed in (Zentner and Henikoff, 2013)). The modifications made to histone proteins include acetylation, mono, di and tri methylation, phosphorylation, and ubiquitylation.

The combinatorial complexity of histone modifications along a gene is high because of the potential number of modifications, modifiable amino acids, and the number of nucleosomes along the length of a gene. However, genome-wide mapping of global patterns of histone modifications using chromatin immunoprecipitation with parallel DNA sequencing (ChIP-seq), have revealed that patterns of histone modifications are associated with distinct elements within the DNA of a genome (Huff et al., 2010, Zentner and Henikoff, 2013). For example, promoters tend to have high levels of histone 3 (H3), lysine 4 (K4) trimethylation (me^3), while putative enhancers are characterized by enriched H3K4me^1 alone or with H3K27acetylation (ac) or H3K27me^3 (Rada-Iglesias et al., 2011, Zentner et al., 2011). Gene bodies tend to be enriched with H3K36me^2 (or me^3) in association with transcriptional activation. H3K4me^2 (or me^3) and K36me^2 (or me^3) may contribute to regulating stability of the nucleosome during RNA polymerase II transit (Wagner and Carpenter, 2012, Zentner and Henikoff, 2013). Also enriched in the promoter and body of the gene is H4K20me^1 (Smolle and Workman, 2013). H4K20me^1 may function in transcriptional initiation and promoter clearance as well as nucleosome stability in the body of the gene (Karlic et al., 2010). H4K20me^1 plays a critical role in target gene activation in wingless (Wnt) signaling (Li et al., 2011). Successful Wnt signaling requires H4K20me^1 in enhancer regions of target genes. Because Wnt signaling is essential for both lung development and repair after lung injury, H4K20me^1 and Wnt signaling is particularly interesting in the context of the developmental origins of adult lung disease (Dasgupta et al., 2009, Crosby and Waters, 2010, Villar et al., 2011).

Animal models demonstrate that perinatal events are associated with histone changes along genes within multiple tissues (Fu et al., 2004, Park et al., 2008, Zinkhan et al., 2012). For several reasons, our group has focused on histone changes to the lung PPARγ gene. Firstly, the nuclear receptor family transcription factor PPARγ is a key player in lung development and lung repair, and is involved in epithelial-mesenchymal transitions, lipid homeostasis, and inflammatory control (Lian et al., 2005, Simon et al., 2006, Cerny et al., 2008, Wang et al., 2009, Joss-Moore et al., 2010). Secondly, PPARγ activity is responsive to long chain fatty acids. As such, nutritional status may influence functional output of PPARγ and nutrition may provide a means for manipulating PPARγ activity. Lastly, PPARγ directly regulates the transcription of several chromatin modifying enzymes via PPAR response elements (PPRE) (Wakabayashi et al., 2009). One of these PPARγ responsive genes is the set domain containing histone methyltransferase, Setd8, which places the H4K20me^1.

The expression and epigenetics of lung PPARγ and Setd8 are susceptible to perinatal insults, including IUGR (Joss-Moore et al., 2010). In the rat lung, IUGR decreases PPARγ and Setd8 expression, as well as genome-wide and gene-specific levels of H4K20me^1 in both male and female rat lung (Joss-Moore et al., 2010). The PPARγ-Setd8-H4K20me^1 axis can be enhanced with dietary long chain fatty acid activation of PPARγ. Supplementation of IUGR rats with the PPARγ agonist, docosahexanoic acid (DHA), restores PPARγ and Setd8 levels, as well as global and gene-specific H4K20me^1 (Joss-Moore et al., 2010). Findings

such as these suggest a role for nutritional approaches to treat perturbations in epigenetic regulation of gene expression following a perinatal insult.

IUGR in the rat also induces other histone modification changes along the PPARγ gene in the lung. Sex-specific alterations in H3 methylation along the PPARγ gene in IUGR include decreased H3K9me^3 in male neonatal rats and *increased* H3K9me^3 in female neonatal rats (Joss-Moore et al., 2011). Sex-divergent H3K9me^3 changes occurring in response to IUGR are interesting because basal H3K9me^3 is not different between control male and female rats. Sex-divergent changes in lung PPARγ epigenetics following IUGR demonstrates that males respond differently than females to the insult of IUGR.

IUGR also has sex-divergent effects on the methyl binding protein MeCp2, which bridges DNA methylation and histone modifications. MeCp2 is essential for myofibroblast differentiation and pulmonary fibrosis (Hu et al., 2011). One means by which MeCp2 affects myofibroblast differentiation is by binding to methylated DNA, influencing H3K9me^3 placement, and promoting transcriptional repression of targets such as PPARγ (Fuks et al., 2003). In the developing rat lung, IUGR affects both MeCP2 expression and MeCP2 occupancy of the PPARγ promoters in a sex-divergent manner (Joss-Moore et al., 2011). In female rat lung, IUGR increases MeCP2 expression and MeCP2 occupancy of the PPARγ promoters in conjunction with decreased PPARγ expression. In contrast, in developing male rat lung, IUGR does not affect MeCP2 expression or MeCP2 occupancy of the PPARγ promoters, however PPAR expression is still decreased (Joss-Moore et al., 2011). These results suggest that the sex-divergent responses to IUGR in the lung originate with the regulation of gene expression.

Explanations for sex-divergent PPARγ regulation effects in response to perinatal insults are lacking. In disorders of placental insufficiency and preterm birth, potential explanations include sex-specific abnormalities in placental lipid transfer to the fetus, sex-specific inability to maintain lipid homeostasis ex-utero, and increased estrogen receptor inhibition of PPARγ signaling (Chu et al., 2014, Martin, 2014).

Multiple cues direct placement of histone modifications, including availability and activity of enzymes that place and remove marks. Fine regulation of gene expression relies on the dynamic nature of histone modifications, thus exemplifying the importance of chromatin modifying enzymes. Genes actively transcribed, or genes that are poised for transcription pending an activating signal (such as transcription factor binding to an enhancer), are characterized by rapid acetylation and deacetylation (Zhang and Nelson, 1988, Spencer and Davie, 2001, Barth and Imhof, 2010). Rapid local changes in histone acetylation occur on nucleosomes at or near promoters at the time of activation of transcription from poised genes (Waterborg, 2002). Acetyl groups are placed on histones by histone acetyltransferase (HAT) enzymes and removed by histone deacetylatase (HDAC) enzymes. Under basal conditions, chromatin that is being rapidly acetylated and deacetylated is enriched in HAT and HDAC activity. While mechanisms are still being elucidated, evidence suggests that rapid acetylation and deacetylation may facilitate nucleosome mobilization during polymerase transit, thus physically facilitating transcriptional activation and elongation (Walia et al., 1998, Reinke et al., 2001, Waterborg, 2002).

The HDAC family of enzymes has received attention in the context of the developmental origins of lung disease. Preterm lambs managed by invasive mechanical ventilation (MV) develop a BPD phenotype, with arrested alveolar development and excessive and disordered elasin deposition (Albertine et al., 1999, Bland et al., 2007). Lungs of preterm lambs managed by MV also have increased HDAC1 and genome-wide histone *hypo*acetylation. In contrast, lungs of preterm lambs managed by non-invasive high-frequency nasal ventilation do not develop BPD, have normal alveolar development and normal EMC deposition. Lungs of preterm lambs managed by high-frequency nasal ventilation have genome-wide histone *hyper*acetylation. Histone modifications H3K14ac, H3K18ac, and H3K27ac, are lower in lungs of preterm lambs managed by MV than high frequency nasal ventilation (Hamvas et al., 2013). Collectively, these data suggest that MV upsets the acetylation-deacetylation equilibrium in the lung by increasing deacetylation.

When preterm lambs are treated with the HDAC inhibitors, valproic acid or trichostatin A, all histone modifications increase in the MV group. Measures of alveolar formation are improved with increased histone acetylation that is triggered experimentally by inhibiting HDACs in preterm lambs managed by MV (Hamvas et al., 2013).

While descriptive studies have initiated the field of epigenetics in developmental origins of adult lung disease, studies assessing phenotypic changes that result from manipulation of epigenetic responses, such as those described above, are critical to moving the field forward.

Non-coding RNA

Non-coding RNA is functional RNA that is not translated into a protein product. Long non-coding RNA and short microRNAs (miRNA) effect the translation of target mRNA's into protein. The involvement of long non-coding RNA in lung disease and development is limited, and what is known is largely in the context of cancerous lung cells (Booton and Lindsay, 2014). miRNA, on the other hand, is better understood in the context of lung disease and development.

miRNA are small non-coding RNAs that bind sequence-specifically to the 3′UTR of target mRNAs and prevent translation by accelerating mRNA degradation, or by blocking the passage of the ribosome (reviewed in (Dogini et al., 2014)). Pre-miRNAs may be transcribed from independent genes, or from within introns or exons of coding genes, either as a single miRNA or in clusters. Pre-miRNAs are processed by Drosha and Dicer to produce miRNAs of approximately 21 base-pairs. The transcription of miRNAs is controlled by the same epigenetic mechanisms as coding genes, including DNA methylation and histone modifications.

Given the number of known miRNA genes, and the ability of a single miRNA to have multiple targets, the involvement of miRNA's in developmental and disease processes is not surprising. One particular aspect relevant to the developmental origins of disease is the role of miRNAs in the response to cellular stress. In response to cellular stressors, miRNAs interact with other cell-stress response pathways and direct translation to stress responses (Leung and Sharp, 2010, Emde and Hornstein, 2014). Interestingly, a subset of miRNAs also controls the expression of chromatin modifying enzymes, including DNA methyltransferases

and histone deacetylases (Sato et al., 2011, Dakhlallah et al., 2013). Taken together, these data suggest an epigenetic-miRNA regulatory circuit that may be important in the transcriptional response to cellular stressors such as those induced by perinatal insults (Leung and Sharp, 2010, Sato et al., 2011, Emde and Hornstein, 2014).

Little is known about the effects of perinatal events on long-term expression and regulation of lung miRNAs. One study reported expression profiles of miRNA in peripheral blood of late-preterm infants with and without BPD (Wu et al., 2013). A 4-miRNA signature was identified as characterizing preterm infants with BPD. The miRNAs that differed in magnitude between preterm infants with BPD and those without were miR-152, miR-30a-3p, miR-133b, and miR-7 (Wu et al., 2013). The presence of a miRNA signature in peripheral blood that might serve as a biomarker is an exciting prospect. However, much more investigation is required to understand the local miRNA status in the human lung under developmental and disease conditions.

Steps toward understanding the effects of perinatal events on lung miRNA expression and regulation have been made in animal models. Differential miRNA expression has been reported in a number of rat and mouse models designed to mimic the histopathology of BPD. Neonatal rat and mouse lungs examined during normal development and in conjunction with injurious stimuli, such as hyperoxia, demonstrate that lung miRNA profiles are dynamic and vary with development and injury (Bhaskaran et al., 2012, Dong et al., 2012, Yang et al., 2012). Neonatal rat lungs exposed to hyperoxia are characterized by down-regulation of miR-342, miR-335, miR-150, miR-126, and miR-151, and up-regulation of miR-21 and miR-34a (Bhaskaran et al., 2012). Similarly, hyperoxia altered miRNA profiles, including increased miR-29. Gene ontology enrichment and pathway analysis demonstrated that genes involved in a variety of lung developmental processes are targets of altered miRNA (Dong et al., 2012).

One miRNA cluster, the miR17~92 cluster, is particularly interesting from a lung disease perspective. While not studied in the context of perinatal insults, the miR17~92 cluster has been studied in the context of lung repair and remodeling (Mendell, 2008, Jevnaker et al., 2011, Dakhlallah et al., 2013). The miR17~92 cluster codes for 6 miRNAs in a single open reading frame, miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92–1. The miR17~92 cluster is altered in human IPF and in mouse models of bleomycin-induced fibrosis, and is important in fibrotic gene expression. In an elegant study, lung tissue from IPF patients was compared to controls and showed significant down regulation of the miR17~92 cluster in IPF relative to control lung (Dakhlallah et al., 2013). Furthermore, the miRNA changes were inversely proportional to DNA methylation levels within the CpG-dense promoter of the cluster. Interestingly, the DNA methyltransferase DNMT1, which is a predicted target of the cluster, inversely correlated with expression of the cluster, suggesting that miR17~92 cluster may play a role in regulation of DMNT1 expression in the lung (Dakhlallah et al., 2013). Finally, DNA methylation was manipulated with the DNA demethylating compound 5′-aza-2′deoxyctidine and effects were reversed (Dakhlallah et al., 2013). Studies, such as this one, highlight the need for research that examine the presence and persistence of lung epigenetic-miRNA regulatory pathways in animal models of perinatal insults.

Conclusions and Research Priorities

The developmental origins of adult lung disease field is at a critical point in understanding the epigenetic mechanisms leading to adult lung disease after perinatal insult. More importantly, mechanistic understanding will lead to the development of targeted, specific, interventions that may alleviate, or even prevent, the development of adult lung disease in susceptible individuals.

Despite this positive outlook, the developmental origins of adult lung disease field faces many challenges. Human clinical research into the developmental origins of adult lung disease is needed. However, to design informative human studies, several concepts must be addressed. First, accessible tissue sources for study need to be validated. Secondly, potential epigenetic processes need to be identified as either biomarkers or causative agents.

Much of the mechanistic work needed to facilitate informative human studies in the developmental origins of adult lung disease field will fall to research using animal models. Animal models successful for understanding the developmental origins of adult lung disease require several characteristics. Perinatal insults should be administered to mimic the human scenario as closely as possible. In response to the perinatal insult, animal models should display a clinically relevant lung disease phenotype, with objective measures of disease severity, including structural, functional, and molecular characteristics. Objective measures of disease severity within animal models, will facilitate short and long-term studies examining the effects of perinatal insults, and potential interventions, on disease of the lung. Manipulation of epigenetic modifications performed in the perinatal period, may have positive effects on the lung in the short-term. However, manipulation of epigenetic modifications in the perinatal period may also have detrimental effects in the long-term. Long-term studies will clarify whether a particular intervention is effective in alleviating adult disease in the developmental origins of lung disease. An extension of these long-term studies involves addition of an adult lung injury or a “second hit” on the lung, after the perinatal insult.

Techniques utilized to understand the involvement of epigenetic modifications in the developmental origins of lung disease are varied and include genome wide and site-specific approaches. Choice of approach will be influenced by cost, resolution of data, and contribution to understanding the biological phenomena. Combined understanding of DNA methylation in the context of histone modifications will be important, as will the role of non-coding RNA in the context of specific targets. High resolution sequencing based approaches to understanding DNA methylation and histone modifications are promising and yield high quality information. However, sequencing based approaches to genome wide methylation and histone modifications are expensive and highly dependent upon sophisticated bioinformatics to ensure that accurate conclusions are derived from the data. Single molecule approaches, such as targeted bisulfite sequencing and traditional chromatin immunoprecipitation are useful in the context of understanding disruptions to select genes. An important caveat for single gene epigenetic analysis, however, is the need to consider the entire gene of interest and not just 5′ regulatory regions.

A significant challenge to the field lies in distinguishing epigenetic phenomena that are event biomarkers, from epigenetic phenomena with a causative role. Once causative epigenetic mechanisms are identified, selective focus on mechanisms that are amenable to manipulation will be important. Furthermore, potential interventions need to be considered in the context of non-lung organs. This concept is particularly important in the developmental origins of adult lung disease because the timing of perinatal insults coincides with not only lung development, but also development of brain, kidney, and other susceptible organs. One way to minimize “collateral damage” in treating the lung in the context of developmental origins of adult lung disease is to aim at normalizing conditions that are perturbed in sequence or in parallel by the perinatal event. For this reason, approaches involving nutritional manipulation may prove promising.

In summary, perinatal insults such as IUGR, preterm birth, maternal toxin exposure and dietary deficiency that occur during critical periods of lung development predispose to impaired lung function, structure, and molecular characteristics in later life. The development of adult lung disease following perinatal insults involves plasticity of the epigenome and subsequent alterations in lung cell transcriptomes. A comprehensive understanding of the epigenetic mechanisms driving the developmental origins of adult lung disease has the exciting potential to lead to treatments that reduce or eliminate lung disease in susceptible individuals.

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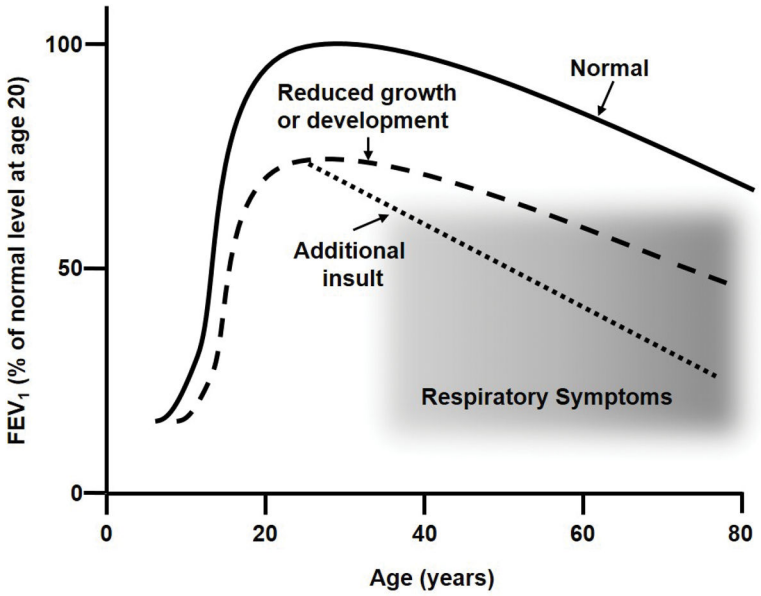

Figure 1. Variance of lung function with age

Lung function, represented by FEV_1 as a % of maximal value, varies with age and reaches a maximum in the early 20s. The solid line represents FEV_1 variation with age under conditions of normal growth, and in the absence of disease or additional insults (e.g. smoking). The dashed line represents FEV_1 in the case of reduced lung growth and/or development during early in life. Failure to achieve normal maximal lung function, even with normal age-related decline, produces respiratory symptoms (shaded area). The dotted line represents a more rapid decline in lung function as a result of additional insults (e.g. smoking), in which case respiratory symptoms are observed at earlier ages. Figure adapted from (Weiss, 2010, Stocks et al., 2013).

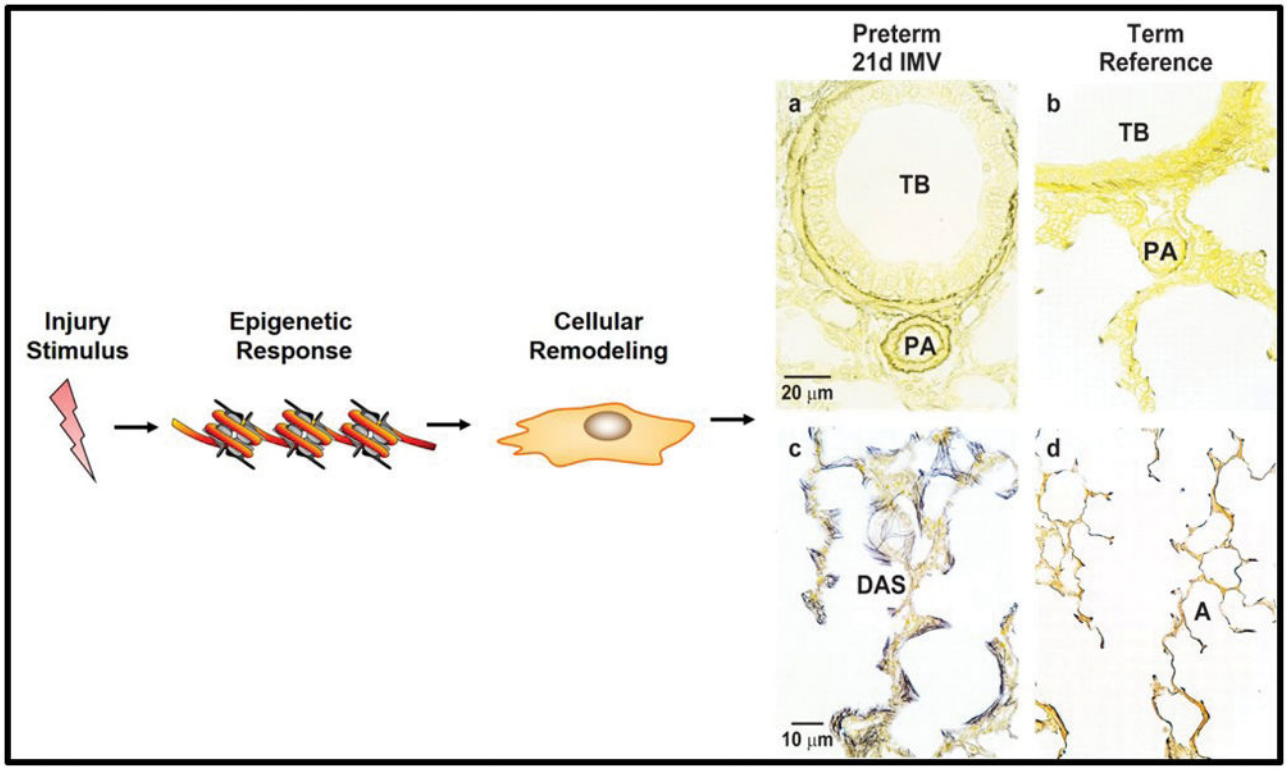

Figure 2. The impact of an injury stimulus to the immature lung

An injury stimulus to the immature lung may prompt an epigenetic response and subsequent cellular remodeling. The schematic shows cellular remodeling for the lamb lung mesenchyme in response to preterm birth with support by intermittent mandatory ventilation with oxygen-rich gas for 21days. Histopathological outcomes are shown in panels a–d. Panel a illustrates accumulation of smooth muscle cells surrounding a terminal bronchiole (TB) and its adjacent pulmonary arteriole (PA) compared to an age-matched term reference lamb (panel b). Panel c shows distended distal airspaces (DAS) with aberrant, excessive accumulation of mature cross-linked elastic fibers (black). This architecture is unlike the normal delicate, lacy features of an age-matched term reference lamb (panel d) with anatomic alveoli (A), thin walls and concentrated elastin at the tip of secondary septa.

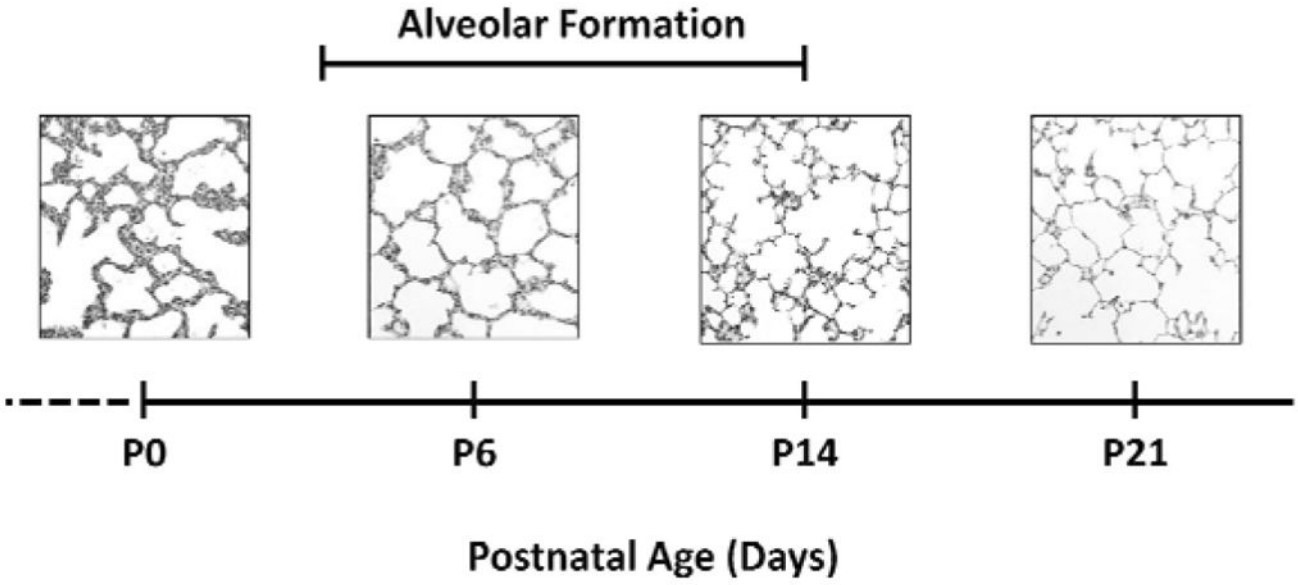

Figure 3. Timeline of rat lung development

Representative images of female rat lungs at postnatal day 0 (P0), P6, P14 and P21. At P0, the rat lung is at the saccular stage of lung development. Alveolar formation takes place from approximately P4 to P14. At P21 alveoli have characteristic histological features of long, straight alveolar walls and numerous, long secondary septa. All panels original magnification 80 × (scale bar is 50 μm).

Table 1

Perinatal insults and associated lung disease reported in human subjects.

Perinatal Insult	Associated Lung Disease	Representative References
Intrauterine growth restriction with and without preterm birth	Bronchopulmonary Dysplasia Reduced Lung Function Chronic Obstructive Pulmonary Disease	(Barker et al., 1991, Caudri et al., 2007, Hancox et al., 2009, Kindlund et al., 2010, Jobe, 2012)
Maternal Tobacco Smoke Exposure	Reduced Lung Function Asthma and Wheezing Airway Reactivity	(Gilliland et al., 2003, Jaakkola and Gissler, 2004, Alati et al., 2006, Hylkema and Blacquiere, 2009)
Air Pollution	Asthma Allergic Airway Disease Chronic Obstructive Pulmonary Disease	(Miller and Marty, 2010, Jedrychowski et al., 2013, Wright and Brunst, 2013, Gaffin et al., 2014, Urman et al., 2014)
Maternal Diet	Asthma Allergic Airway Disease	(Erkkola et al., 2009, Checkley et al., 2010, Nwaru et al., 2010)