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Epigenetics and the Developmental Origins of Lung Disease

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Abstract

The developmental origins of disease hypothesis has recently been expanded to include the early origins of lung disease, particularly early events that alter lung development. Intrauterine growth restriction (IUGR), preterm birth with the need for prolonged mechanical ventilation, and maternal tobacco smoke (MTS) or nicotine exposure produce neonatal and adult lung disease. These perinatal insults are characterized by alterations in alveolar formation and changes in the expression of genes that regulate alveolarization, including IGF1 and PPAR γ . A potential mechanism for such changes in gene expression is epigenetics. IGF1 and PPAR γ have altered epigenetic states in response to these perinatal insults. Identification of the specific epigenetic mechanisms involved in the developmental origins of lung disease may facilitate identification of molecular biomarkers with the potential to personalize respiratory disease risk assessment and treatment. The purpose of this review is to summarize what is known about the developmental origins of lung disease, the epigenetic contributions to lung disease, and areas that need further investigation.

The developmental origins of disease hypothesis describes the origins of adult disease in terms of perinatal “plasticity” in the face of sub-optimal environmental conditions [1]. While the majority of focus in the field has been on the development of metabolic disease, recent attention has included the early origins of lung disease, particularly early events that alter lung development as well as lung injury and repair processes.

Susceptible genes and gene networks that are important in lung development, as well as lung injury and repair processes, have been identified using animal models. The developmental timing and level of transcription of genes is regulated by epigenetic mechanisms. Perturbations in epigenetic regulation of gene transcription in the lung are associated with several models of perinatal lung disease. This review focuses on evidence supporting a mechanistic role for epigenetics in the developmental origins of lung disease.

1.1 The Basics of Epigenetics

Epigenetics influences developmental and cell-specific gene transcription, gene silencing, as well as modulation of the level of transcription of genes that are being transcribed. During normal development, precisely timed regulation of gene transcription is required. Only genes specific to a particular cell type and developmental stage are transcriptionally active, while others are silenced. While transcriptional activation and gene silencing are “on or off”

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states, epigenetics is important in modulating the transcriptional level of genes being actively transcribed. The ability to modulate gene transcription provides “plasticity” during development.

Gene transcription relies on the transcription machinery identifying and accessing appropriate regulatory regions within a gene, including promoter regions. Epigenetic modifications help direct the transcription machinery and associated factors to the appropriate location within a gene. To appreciate the role of epigenetics in the regulation of gene transcription, familiarity with the environment of DNA within the eukaryotic nucleus is helpful. In the nucleus, double-stranded DNA is packaged in an increasingly complex protein scaffold, collectively known as chromatin. At its lowest level, the DNA is wrapped twice around a protein core, forming a unit called a nucleosome (Figure 1) [2]. The protein core of the nucleosome contains 8 proteins, two copies each of histone proteins H2A, HB2, H3 and H4. Nucleosomes are then packaged in increasing complexity to finally form a chromosome. Epigenetic modifications occur at the level of the nucleosome.

DNA methylation is one of the better understood epigenetic modifications. DNA methylation occurs primarily on the cytosine (C) of a C-guanine(G) dinucleotide. This dinucleotide is referred to as a CpG, where p represents the phosphate group, indicating that the C and G are on the same DNA strand. In the mammalian genome, CpG's are often clustered in CpG “islands”, consisting of a greater than 200 base pair region with a CG content of at least 50% [3].

CpG islands are commonly found in the promoter region of mammalian genes and, while associated with gene silencing when methylated, are often unmethylated. DNA methylation-mediated gene silencing may occur via physical inhibition of transcription factor binding to methylated DNA. Alternatively, methylated DNA may provide a specific binding site for methyl-CpG-binding domain proteins that recruit other chromatin remodeling proteins that repress transcription. Interestingly, unmethylated CpG islands have been associated with genes in the active and silent states [4–6]. In the mouse genome, for example, only about 5% of promoter CpG dense regions are used to silence genes [7]. Recently, non-promoter methylation has been implicated in the regulation of transcription. Frequently, CpG's found elsewhere within a gene (intragenic) and in other intergenic regions, are methylated [8]. As well as enhancing transcription, these inter- and intragenic CpGs appear to be involved in the regulation of alternative promoter usage [8–9].

Histone modifications are also important in regulating transcription. Epigenetic modifications to histone proteins occur largely, but not exclusively, on the unstructured, N-terminal “tails” of the histone proteins (Figure 1) [2]. Modifications are diverse and include acetylation, methylation, ubiquitination and phosphorylation (reviewed in [10]). While some histone modifications are associated with specific effects, such as high levels of histone (H) 3 lysine 4 (K4) trimethylation and H3K27 acetylation (Ac) being associated transcriptional activation, the effects of individual histone modifications are complex and significant cross-talk between modifications exists. Due to the three-dimensional nature of chromatin, cross-talk can occur between closely spaced nucleosomes as well as those far apart with respect to the genomic DNA. Given, the presence of two tails from each histone within a nucleosome, each with many modifiable residues, the number of potential combinations of modifications along any given gene is staggering. Efforts are currently underway to analyze patterns of modifications and their effect on transcription [11–12].

A corollary of this large potential combination of modifications is that a greater level of information can be stored in histone modifications than in DNA methylation. Like DNA methylation, histone modifications outside promoter regions are critical for the epigenetic

modulation of gene expression. Epigenomic data demonstrate that different histone modifications associate with discrete regions of genes highlighting the importance of evaluating the entire gene [13].

Appropriate development of the lung relies on precisely timed gene expression that is, in part, due to the extensive combination of DNA methylation and histone modifications that occur along the length of key genes. Disruption of the normal epigenetic modifications during a developmentally sensitive time can alter transcription and may contribute to changes in lung development.

Developmental Origins of Lung Disease

Neonatal lung disease is characterized by multi-factorial etiology. For the purposes of this review, however, we limit the focus on the effects of intrauterine growth restriction (IUGR), maternal tobacco smoke (MTS) or nicotine exposure, and preterm birth with the need for prolonged mechanical ventilation.

In term infants, IUGR increases the need for respiratory support [14–17]. Additionally, IUGR and preterm birth are closely associated co-morbidities. An estimated 5–12% of preterm births in the United States are IUGR [18]. IUGR, with preterm birth and mechanical ventilation with oxygen exposure, increases the risk and severity of the chronic lung disease of infancy (bronchopulmonary dysplasia, BPD), with male infants being more severely affected [19–23, 24, 25–27]. Further, BPD survivors have impaired lung function and increased susceptibility to lung injury in adolescence and adulthood [28–32]. Fetal exposure to MTS also increases postnatal lung disease. In humans, MTS exposure has been causally linked to the development of asthma [33–37], airway hyper-responsiveness [38], and a decline in lung function [34, 39–41]. MTS exposure may also increase the risk of developing adult-onset lung diseases, such as chronic obstructive pulmonary disease (COPD) [36].

While the mechanisms by which these perinatal insults predispose to adult lung disease are incompletely understood, altered alveolar formation is implicated. Animal models of IUGR, MTS exposure, and preterm birth with prolonged mechanical ventilation and/or oxygen exposure display impaired alveolarization [42–51]. In the rat, alveolarization occurs entirely in the postnatal period, thus affording an opportunity to examine an immature lung without the complications of preterm birth. In a rat model of IUGR, immature neonatal lungs have increased distal airspace wall thickness [42]. MTS and/or maternal nicotine exposure alter lung growth and alveolarization in non-human primates [52–53], sheep [54] and rats [47–50]. Finally, studies show that postnatal mechanical ventilation of preterm baboons or sheep, in the absence of IUGR, produces alveolar simplification [51, 55].

Elastin is important for alveolarization, and is altered in IUGR, MTS exposure and preterm birth with need for prolonged mechanical ventilation. The IUGR rat lung has decreased elastin expression and elastic fiber deposition, and increased static lung compliance at maturity [56]. Similarly, maternal nicotine exposure decreases rat lung elastin content during development [57]. Decreased elastin expression in these models likely contributes to observed changes in alveolar formation. Of note, both IUGR and MTS often involve hypoxia. In contrast, mechanical ventilation is often associated with recurring hypoxia and hyperoxia and volume trauma. Interestingly, mechanical ventilation of preterm baboons or sheep results in *increased* elastin expression, and disordered and excessive lung elastin deposition [51, 58–59]. This excessive lung elastin deposition is accompanied by decreased expression of vascular endothelial growth factor (VEGF) and its receptor in the lung (VEGFR2), also crucial for alveolar formation [58]. These data suggest that IUGR, MTS exposure, and preterm birth with prolonged mechanical ventilation and oxygen exposure,

alter the expression of lung genes that are important for alveolar formation. Additionally, while these insults affect the homeostasis of many cellular metabolites, oxygen availability may play a key role.

Another gene that is important for alveolar formation is IGF1. IGF1 is increased in the lung in infants who died from BPD [60]. Preterm lambs with prolonged mechanical ventilation also have increased IGF1 [61]. IGF1 is located in mesenchymal cells. Importantly, a characteristic of the BPD lung phenotype is increased thickness and cellularity of the mesenchyme [51, 55]. These characteristics could be due to increased IGF1 mRNA transcript and protein abundance in the lung.

The IGF1 gene produces several different mRNA variants, using multiple transcriptional start sites, multiple promoters, alternative splicing, and multiple 3' untranslated regions (UTR's) [62]. The normal tissue and developmentally-specific expression IGF1 variants relies on epigenetic mechanisms. These epigenetic mechanisms may be sensitive to perinatal insults such as those described above.

2.2 The Role of Epigenetics in the Developmental Origins of Lung Disease

To understand the role of epigenetics in the developmental antecedence of adult lung disease, molecular targets common to normal lung development as well as lung injury and repair need to be identified. Research studies should address not only the epigenetic states of target genes but also the epigenetic regulators acting to influence these states. While the field is in its infancy, evidence demonstrates that perinatal insults alter both gene expression and epigenetic determinants in the lung.

Epigenetic determinants and the effects of perinatal insults have most frequently been assessed in animal models of IUGR. The emerging picture is that IUGR alters the epigenetics of susceptible genes in association with changes in gene transcription and subsequently phenotype [63–64]. There are two long-term implications when epigenetics and gene transcription are disrupted developmentally. The first is that altered gene transcription can change the final structure and function of an organ, via changes in transcription from apoptotic or proliferative genes. Secondly, when the epigenetics of a gene are altered during development, the “new” epigenetic code becomes the platform for future epigenetic modifications that would normally accompany development. Long-term changes in epigenetics are an important implication because of the potential to alter expression of susceptible genes long removed from the insult, or in the face of subsequent stressors.

In the rat lung, IUGR induces epigenetic modifications to the PPAR γ gene. PPAR γ , a member of the nuclear receptor family of transcription factors, contributes to epithelial-mesenchymal interactions that are crucial for lung development [65–66]. The PPAR γ gene is susceptible to epigenetic changes because it relies on epigenetics for normal tissue and developmentally-specific transcription of mRNA variants. PPAR γ gives rise to multiple tissue-specific mRNA variants via expression from two promoters and alternatively exon usage (Figure 2). In the neonatal rat lung, IUGR decreases mRNA transcript levels of all PPAR γ variants. Importantly, changes in PPAR γ transcription are associated with alterations in H3 and H4 methylation along the PPAR γ gene, often in a sex-specific manner [67–68]. IUGR decreases H3K9 trimethylation (Me3) along the PPAR γ gene in male neonatal IUGR rats. Interestingly, in female neonatal rats, IUGR increases H3K9Me3 along the PPAR γ gene [68]. This apparent dichotomy is intriguing, given that in control rats, H3K9Me3 is not different between males and females, implying that both genders have similar basal epigenetic regulation of PPAR γ but respond differently to the IUGR insult. Interestingly, altered H3K9Me3 levels along the PPAR γ gene in IUGR, are directly associated with changes in the H3K9Me3 regulator, methyl CpG binding protein 2 (MeCP2).

MeCP2 can bind to PPAR γ promoters and repress transcription [69]. When MeCP2 is present at the promoters, histones of PPAR γ are characterized by increased H3K9Me3 [69]. In association with changes in PPAR γ H3K9Me3 described above, IUGR alters MeCP2 expression as well as MeCP2 occupancy of the PPAR γ promoters in rat lung [68]. In female whole lung, MeCP2 expression is increased and MeCP2 occupancy at the PPAR γ promoters is increased. In male lung however, levels of MeCP2 and occupancy at the PPAR γ promoters is unaltered by IUGR [68]. Again, a sex-specific response to the IUGR insult occurs. The molecular basis for a sex-specific epigenetic response in the face of a stressor such as IUGR is currently unknown and represents an important area of ongoing research.

PPAR γ may also contribute to lung development by direct transcriptional regulation of epigenetic modifying enzymes. A number of chromatin modifying enzymes have PPAR response elements (PPRE) in their promoters and are bona fide transcriptional targets of PPAR γ [70]. One of these PPAR γ responsive genes is the set domain containing histone methyltransferase, Setd8, which places the H4K20Me mark [70]. In the rat lung, IUGR decreases levels of Setd8 in parallel with reductions in PPAR γ expression. Importantly, global levels of H4 methylation are also reduced [67]. The observed changes in PPAR γ , MeCP2, and Setd8 in the IUGR rat lung occur in association with changes mRNA transcript levels of other genes such as elastin and retinoic acid receptors [71]. If and how IUGR influences the epigenetic regulation of elastin and retinoic receptors still needs to be determined.

The epigenetic regulation of IGF1 is also susceptible to perinatal insults [62]. In rat liver, IGF-1 is characterized by expression of transcripts from two distinct promoters as well as transcripts with exon 5 either present or spliced out [62]. Recently, IGF1 has been characterized in the lungs of preterm sheep undergoing alternative forms of respiratory support, either mechanical ventilation or high frequency nasal continuous positive airway pressure (CPAP) [61]. Term and preterm sheep lungs contain transcripts from both IGF1 promoters as well as the transcript lacking exon 5. Interestingly however, the transcript containing exon 5, is absent from the sheep lung under all conditions [61]. Studies are currently underway to assess the effects of mechanical ventilation versus CPAP on DNA methylation and the histone code of IGF1 in the lung of preterm sheep.

The contribution of immune responses to the development of lung disease has received a great deal of attention and epigenetic mechanisms are indicated. In humans, origins of asthma have been linked to maternal folate intake during pregnancy [72–73]. Dietary intake of folate leads to the production of S-adenosyl-L-methionine (SAM), a universal methyl donor and precursor for DNA methylation. A diet high in methyl donors during gestation increases airway inflammation, serum IgE, and airway hyperresponsiveness in mice [74]. A potential molecular mediator of the phenotypic response to methyl donors is the Runx3 gene, which is hypermethylated in mice receiving a high methyl donor diet [74]. Control of Th1/Th2 lineage also likely links epigenetic mechanisms to the development of allergic airway disease [75–76].

Less is known about the effects of MTS on gene specific epigenetic modifications. However, human epithelial cells and immortalized epithelial cells exposed to tobacco smoke condensate have dose dependent changes in global histone modifications as well as altered DNA methyltransferase enzyme expression [77]. Global methylation is also altered in buccal cells from children who had MTS exposure [78].

An important note is that the perinatal insults discussed here are part of a spectrum of perinatal insults that include inflammation as well as hypoxia/hyperoxia. Responses to inflammation, including that produced by neonatal ventilator support, affect lung

development and injury as well as postnatal airway responsiveness in sheep [79–81]. The role of epigenetic mechanisms in the regulation of inflammation in mechanical ventilation still needs to be elucidated.

Conclusions

The epigenetic and environmental influences affecting lung development as well as injury and repair have been recognized as a priority research area by the National Heart Lung and Blood Institute (NHLBI) [82]. While evidence supports a connection, a priority research direction is to understand *how* epigenetics and the environment interact to influence lung development and later susceptibility to lung injury and repair. An understanding of these mechanisms will require specialized investigations in animal models of perinatal lung injury, and will lead to elucidation of potential therapies, as well as identification of biomarkers.

Molecular biomarkers have the potential to personalize respiratory disease risk assessment and treatment. Potential biomarkers need to be amenable to a variety of perinatal insults and be part of an integrative approach to diagnosis and treatment. The translational application of appropriate biomarkers, and an understanding of the molecular mechanisms driving the developmental origins of lung disease, will improve our ability to understand and treat lung disease.

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Figure 1.

A) DNA is packaged within a protein scaffold, collectively known as chromatin. DNA is wrapped around a protein core forming a unit called a nucleosome. The protein core consists of eight histone proteins. Epigenetic modifications include methylation of the DNA as well as modifications to the histone proteins. B) Schematic of the H3 and H4 tails and with potential modification sites indicated.

Figure 2.

Schematic of the rat PPAR γ gene and mRNA transcripts. Exons A1, A2, B, C and 1–6 give rise to three splice variants, PPAR γ 1a, PPAR γ 1b and PPAR γ 2. PPAR γ 1a consists of exons A1, B and 1–6, and PPAR γ 1b consists of exons A2, B and 1–6. The ATG start codon for both –g1 transcripts is positioned at the beginning of exon 1. PPAR γ 2 utilizes exons C and 1–6 with the start codon positioned within exon C.