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Genes, environment, and developmental timing: New insights from translational approaches to understand early origins of respiratory diseases

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Abstract

Over the past decade, "omics" approaches have advanced our understanding of the molecular programming of the airways in humans. Several studies have identified potential molecular mechanisms that contribute to early life epigenetic reprogramming, including DNA methylation, histone modifications, microRNAs, and the homeostasis of the respiratory mucosa (epithelial function and microbiota). Current evidence supports the notion that early infancy is characterized by heightened susceptibility to airway genetic reprogramming in response to the first exposures in life, some of which can have life-long consequences. Here, we summarize and analyze

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CONFLICT OF INTERESTS

All the authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

the latest insights from studies that support a novel epigenetic paradigm centered on human maturational and developmental programs including three cardinal elements: genes, environment, and developmental timing. The combination of these factors is likely responsible for the functional trajectory of the respiratory system at the molecular, functional, and clinical levels.

Keywords

airway and lung cell biology; epigenetics

1 | INTRODUCTION: EARLY LIFE AS THE CRITICAL DEVELOPMENTAL PERIOD FOR GENE–ENVIRONMENTAL INTERACTIONS IN THE RESPIRATORY SYSTEM

Studies over the past three decades have established that early life environmental influences define the individual risk for respiratory diseases.[1–5] For instance, severe viral respiratory infections taking place in early life are strongly associated with an increased susceptibility for asthma and chronic obstructive pulmonary disease (COPD).[1,6] Longitudinal birth cohorts have provided conclusive evidence that the molecular phenotype and microenvironment of the respiratory mucosa (e.g., nasal microbial commensals and concomitant inflammation) are predictive of future respiratory health and disease.[7–10] Some studies also suggest that the determinants of respiratory disease may begin during intrauterine life.[11,12] Among these, determinants, maternal obesity seems to have a dramatic impact on the development of respiratory illnesses in the offspring, during infancy, and beyond.[13–15]

The impact of these studies indicates that the traditional “gene–environmental interaction model” must be expanded to include the developmental timing of the human airways. Early life represents a critical time point in which perturbations (e.g., environmental exposures) can have a dramatic impact on the developmental trajectory of a given individual and consequently lead to a life-long risk for respiratory disorders. An example of the complex interplay between genes, environment, and developmental timing can be seen in the relationship between early viral infections and the risk of respiratory diseases. Several studies have shown that genetic variants at the 17q21 locus are strongly associated with asthma risk in children who had rhinovirus wheezing illnesses.[16] However, among young children exposed to animal barns in the first year of life, these genetic variants are protective.[17] These findings indicate that a precise combination of genetic background and early life events may shape the individual life-long risk for respiratory diseases.

In this review, we summarize and analyze the latest insights from studies that have increased our understanding of the mechanisms of early life epigenetic programming of the respiratory system. From the molecular perspective, we are taking a broad approach to include different epigenetic mechanisms with complex interactions, including DNA modifications (e.g. methylation), posttranscriptional changes (e.g., microRNAs [miRNAs]), and the biology of the mucosal barrier as a critical interface for genetic–environmental interactions during early life.

2 | MOLECULAR EVIDENCE OF A STEREOTYPICAL DEVELOPMENTAL PROGRAM AND A "WINDOW OF SUSCEPTIBILITY" FOR GENETIC REPROGRAMMING IN HUMANS

Birth cohorts have shown that the epigenetic influences on human development begin in utero.[18] Results from the Boston birth cohort, one of the largest birth cohorts in the U.S. (>3500 maternal–infant dyads in active follow-up) showed that DNA methylation patterns are largely established in utero as cord blood signatures are more than 99% identical than those observed at 2 years of age.[18] A remarkable exception to this pattern is the DNA methylation of immune genes, which continues to evolve during early infancy showing substantial variability during the first years of life.[18,19] The finding that the developmental program of the immune system is shaped by the environment in early life has been further illustrated by a longitudinal study that included a comprehensive immune analysis of newborns ($n = 100$) with high resolution transcriptomic and functional prospective signatures of infant immune cell populations.[20] This study demonstrated that (1) cord blood signatures are not representative of postnatal immunity, and (2) stereotypical postnatal developmental gene expression trajectories, which seem to be associated with specific microbial interactions, are established during the first weeks of life.[20] Collectively, these studies provide solid evidence that during early life, environmental influences shape the developmental molecular program of the immune system in humans. However, little is still known about the molecular reprogramming of the respiratory system in newborns and human infants. Filling this critical gap may provide unique insights into how the earliest environmental airway exposures can modify stereotypical developmental programs and define individual life-long susceptibility and/or resilience to respiratory disorders during and beyond childhood.

3 | EPIGENETIC MECHANISMS AND EVIDENCE LINKING GENE–ENVIRONMENTAL INTERACTIONS WITH PEDIATRIC RESPIRATORY DISORDERS

Epigenetic information is essential for organogenesis, developmental processes, and postnatal differentiation and maturation.[21–23] Epigenetic changes have been mapped in multiple lineages and developmental windows in which they are essential. For instance, following fertilization, the parental genomes undergo extensive histone modifications and global demethylation, to allow for initial cell totipotency and facilitate the establishment of embryonic patterns.[24,25] Later, embryogenesis and fetal development are characterized by cell lineage-specific epigenetic remodeling that is responsible for cell differentiation.[25] The epigenome is influenced by the environment and undergoes dynamic changes during development and aging.[26–30] Thus, it is important to keep in mind that epigenetic mechanisms are not only referring to "gene–environmental interactions" but also to normal developmental and maturational processes. From the molecular biology perspective, epigenetics has mostly been centered on heritable alterations that are not due to changes in DNA sequence.[21,23] Classical epigenetic mechanisms include histone modifications and DNA methylation,[29] which regulate gene expression in response to the environment,

particularly during early development.[31,32] DNA methylation is almost exclusively found in CpG dinucleotides in mammals,[22,33] and is typically associated with gene repression,[22,33] although it has also been connected to other regulatory gene expression effects such as the regulation of tissue-specific gene expression, promoter use, and alternative splicing in humans.[22,34]

4 | PRENATAL EXPOSURES AND EPIGENETICS IN PEDIATRIC RESPIRATORY DISEASES

Fetal epigenetic regulation is modifiable by the maternal environment and has been proposed as a mechanism by which prenatal environmental stimuli contribute to the development of respiratory disorders.[35] In support of this notion, mechanistic animal studies have demonstrated that maternal microbial exposures, through DNA methylation and histone modifications, may modulate the expression of important immune factors such as interleukin (IL-4) and interferon-γ genes in the offspring's lungs.[36,37] Increases in histone H3 acetylation linked to an asthma phenotype have been also identified in mice pups after maternal nicotine exposure.[38] In humans, epigenetic modifications (e.g., *SMAD3* methylation) have been proposed as a mechanism mediating the intergenerational risk of asthma in children from asthmatic mothers.[39] Furthermore, epigenetic modifications may also mediate the effect of noninheritable prenatal factors on respiratory outcomes. For example, maternal stress is associated with differential methylation patterns linked to subsequent risk of wheeze or asthma.[40] Maternal smoking, a recognized risk factor for the development of asthma has been linked to epigenome-wide and gene-specific methylation changes.[41,42] For example, Neilsen et al.[42] showed that the effects of maternal smoking on asthma may be mediated by DNA methylation modifications in the *AHHR* gene, a mediator for cell growth and differentiation and Gao et al.[43] showed associations between prenatal smoking, higher methylation level in the *AXL* gene body and increased risk of childhood wheezing, in two independent populations including 1391 children. Furthermore, methylation patterns linked to subsequent risk of wheeze or asthma have been associated with environmental stimuli including, air pollutants, allergens, viruses, and other environmental factors such as season of birth and inner-city living.[6,44,45] Passive smoking exposure may also cause histone acetylation modifications (H3 and H4) in alveolar macrophages of asthmatic children.[46] Conversely, prenatal farm living, has a protective effect on the development of childhood asthma and allergies. The farm environment also affects the epigenome and is linked to differential DNA methylation in genes related to IgE regulation and Th2 differentiation (e.g., *ORMDL1*, *STAT6*, *RAD50*, and *IL13*)[47] prompting questions about whether these changes may explain, at least partly, the protective effect of farm living on the development of childhood asthma and allergies. In summary, these studies suggest that gene-environmental interactions may start in-utero and epigenetic mechanisms may mediate some of the described effects of prenatal environmental exposures on respiratory disease.

5 | EPIGENETIC MECHANISMS AND EARLY LIFE RESPIRATORY DISORDERS

Most of the human-based evidence linking epigenetic mechanisms to the development of early life respiratory disorders has been derived from genome-wide DNA methylation profiles utilizing blood specimens of children with asthma.[45] Interestingly, in an epigenome-wide meta-analysis,[48] Xu et al.[48] examined specific blood cell-specific methylation patterns and demonstrated that hypomethylation of 14 CpG sites in eosinophils is associated with childhood asthma. Thus, the presence of cell-specific methylation patterns may affect the interpretation of most blood methylation studies published to date. An alternative approach to address this issue is the use of emergent single-cell technologies and computational referenced-based and reference-free deconvolution methods to examine DNA methylation at the single-cell level.[49–51] However, a more fundamental problem of the studies using only blood DNA methylation is that epigenetic information, including DNA methylation, is tissue-specific[24] and circulating blood cells may not reflect the diverse gene-environmental and developmental processes of the airways.[52] Thus, epigenetic studies ideally should include airway cell types since the premise of environmentally driven genetic reprogramming of the respiratory system implicates the presence of specific DNA methylation and transcriptomic marks on the airway epithelial barrier. Given that airway epithelial cells are in direct contact with the environment, the analysis of these cell types may reflect better functionally relevant epigenetic effects in the human airways.

6 | THE HUMAN AIRWAY EPITHELIUM TO DEFINE SIGNATURES OF DEVELOPMENT AND GENE–ENVIRONMENTAL INTERACTIONS

An elegant proof of concept study conducted by Nicodemus-Johnson et al.[53] demonstrated that the airway epithelial barrier can be epigenetically “reprogrammed” by environmental stimuli relevant to respiratory diseases.[53] In that study, the investigators used an *in vitro* model of methylation and gene expression response to IL-13 in airway epithelial cells to demonstrate that this pro-asthmatic type 2 cytokine selectively induces long-lasting DNA methylation changes that mirror those found in vivo in the asthmatic airway epithelial cells.[53,54] Recently, Cardenas et al.[55] also demonstrated epigenome-wide associations of asthma and allergic phenotypes with lower DNAm of genes driving Th2 and eosinophilic responses (e.g., *EPX*, *IL4*, and *IL13*) in nasal epithelial cells from 547 children.[55] Interestingly, in this study, the epigenetic age of the nasal epithelium was also accelerated in children with asthma. Additional epigenetic studies in airway epithelial cells of asthmatic individuals have shown differential methylation in the STAT5A transcription factor leading to downregulation of *STAT5A* expression,[56] and hypomethylation of IL-6 and nitric oxide synthase 2 (*NOS2*) associated with increased FeNO.[57] In African American children, arachidonate 15-lipoxygenase (*ALOX15*) and periostin (*POSTN*), two genes involved in Type 2 immune responses, were differentially methylated in the nasal epithelium.[58] Moreover, a large study showed that methylation profiles in the airway epithelium of children with atopy included genes involved in epithelial barrier function (e.g., *CDHR3* and *CDH26*), and airway epithelial integrity and immune regulation (*FBXL7*, *NTRK1*, and *SLC9A3*).[59] This study also demonstrated that a methylation-based classifier in the nasal

epithelium is able to discriminate atopy and atopic asthma in Hispanic, African American, and European children,[59] suggesting that a methylation signature in the nasal epithelium has potential implications in the pathobiology of wheezing and asthma in children.[59] Notably, methylation signatures in the airways may be imprinted by interactions with local factors such as the local microbiota. For example, Morin et al demonstrated lasting effects of the infantile microbiota on DNA methylation patterns in lysosomal and antimicrobial gene pathways in the nasal epithelium of 562 children associated with the development of allergic rhinitis.[60] Importantly, the human neonatal and infant airway epithelium also shows that specific DNA methylation profiles in airway epithelial cells have important functional effects in gene expression during early life.[61] Thus, all this accumulated human-based evidence provides a strong scientific rationale to conduct longitudinal studies in newborns and infants to define the dynamics of the epigenetic reprogramming of the human airway epithelium and the potential impact on long-term gene expression and individual susceptibility to respiratory conditions during infancy and beyond early childhood.

7 | MECHANISTIC EVIDENCE OF EPIGENETIC REPROGRAMMING AT THE AIRWAY MUCOSAL BARRIER

Notwithstanding the importance of associating specific airway DNA methylation profiles with respiratory disease in children, there is still a need to conduct mechanistic studies showing that specific environmental clues can induce gene reprogramming in the airways. To date, this has been primarily examined in animal models.[62,63] For instance, a recent study in mice showed that environmental clues regulate epigenetic reprogramming of airway-resident memory CD8+ T cells.[62] Specifically, the combination of transcriptome and chromatin accessibility analyses using Assay for Transposase-accessible Chromatin revealed an enrichment of genes in airway immune tissue-resident cells associated with stress-related programs (e.g., amino acid starvation pathway) in response to changes in the airway microenvironment.[62] Additional animal studies have shown that environmental manipulation can cause early life epigenetic reprogramming of mucosal barriers in an age-specific manner.[64] Pan et al.[64] examined the transcriptomic and epigenetic profiles of epithelial gut cells from mice representing the infant, juvenile, and adult stages in the presence or absence of a germ-free environment.[64] This study showed the presence of microbiota-dependent DNA methylation differences early after birth in genes linked to immune pathways and metabolic processes.[64] Taken together, these mechanistic animal studies demonstrate that there are environment-responsive transcripts in early life that shape stage-specific cellular programs during postnatal development.

8 | EXPANDING THE UMBRELLA OF ENVIRONMENTALLY DRIVEN GENETIC REPROGRAMMING IN THE AIRWAYS: NONCODING RNA AND POSTTRANSLATIONAL MODIFICATIONS

Progress in molecular biology has expanded the umbrella of environmentally driven genetic reprogramming to include noncoding RNAs involved in the regulation of cellular functions.[65–69] Noncoding RNAs (ncRNAs) can be classified by size into long ncRNAs

(>200 nucleotides) and small RNAs (≤200 nucleotides).[70] The most studied family of small noncoding RNAs involved in genetic reprogramming are the miRNAs (≈22 nucleotides). miRNAs are highly evolutionary conserved molecules that play essential roles in RNA silencing and posttranscriptional regulation of gene expression.[71,72] miRNAs bind to recognition elements within the 3′-untranslated region (3′–UTR) of target messenger RNAs (mRNAs).[73] Several studies have confirmed that miRNAs regulate gene expression via base-pairing of complementary mRNA sequences in the 3′-UTR, leading to posttranscriptional silencing and mRNA decay.[71,73] In addition to these intracellular effects, there is also evidence that some miRNAs may be selectively exported in protective extracellular vesicles (exosomes) to induce genetic reprogramming between cells.[74–76] Exosomes containing miRNAs have been isolated from immune cells,[77,78] as well as from body fluids such as nasal and pulmonary secretions.[79,80] Recent evidence also indicates that exosomal miRNAs are taken up by airway epithelial cells and modify their gene expression.[81]

miRNAs share important features with classical epigenetic mechanisms (e.g., DNA methylation), including (1) essential roles regulating gene expression during organogenesis and the development and maturation of the lungs,[82] and (2) responsiveness to environmental clues relevant to the pathogenesis of respiratory disorders.[69,83] Indeed, Solberg et al.,[84] conducted a seminal study using an in vitro model to define miRNA and gene expression responses to IL-13 in airway epithelial cells form healthy and asthmatic individuals. In this study, IL-13 stimulation mirrored changes in many differentially expressed miRNAs observed in asthmatic airways, including repression of miR-34/449 family members,[84] which are molecules with critical roles in airway epithelial cell differentiation.[85–87] In addition, Najrana et al.[88] recently showed that mechanical stretch regulates the expression of specific miRNA in extracellular vesicles released from lung epithelial cells. Other studies have reported additional miRNAs profiles linked to respiratory disorders.[83,89–92] The airway production of miR-155 has been linked to the pathogenesis of cigarette smoke-induced lung inflammation in COPD[93] and the regulation of airway antiviral and pro-inflammatory responses.[92,94] miR-155 has also been associated with TH2 allergic responses in several cellular components, including eosinophils,[95] macrophages,[96] innate lymphoid cells type 2,[97,98] dendritic cells,[99] and mast cells.[100] Several other miRNAs such a miR-126, miR-21, miR-146a, miR-221, and miR-222 have been implicated in the regulation of airway inflammatory responses in different animal models and cell systems.[82,101–104]

In contrast to DNA methylation, and despite the strong evidence demonstrating that miRNAs play essential roles in lung development,[102] only a few studies have explored the potential role of the miRNA-driven genetic programming of the human airways during early life. Lal et al.[105] demonstrated that premature newborns with severe bronchopulmonary dysplasia have reduced levels of airway exosomal miR 876–3p. Complementary studies showed that miR-876–3p treatment led to reduced alveolar hypoplasia and neutrophilic inflammation in mice after exposure to hyperoxia and LPS, environ mental challenges previously linked to the pathogenesis of bronchopulmonary dysplasia.[105] Davis et al.[106] examined serum samples obtained at randomization in 160 children aged 5–12 years from the Childhood Asthma Management Program cohort and identified that eight serum miRNAs were associated with airway hyperresponsiveness to methacholine challenge (PC20) in asthmatic children. Studies in human infants and young children have also

reported specific miRNA signatures during viral respiratory infections.[92,94] Hasegawa et al.[107] identified that in infants with rhinovirus and RSV infections had different nasal airway miRNA profiles associated with NF-κB signaling. A separate study demonstrated that in vivo and in vitro differentiated human airway epithelial cells[92] show a baseline "airway secretory exosomal miRNAome" that primarily encompasses the production of miR-630, miR-302d-3p, miR-320e, and miR-612.[92] Furthermore, this study identified abundant nasal airway production of exosomes containing miR-155 in response to rhinovirus infection in young children.[92] These findings were recently expanded in a larger study (n = 150 young children) that confirmed that miR-155 is strongly associated with the presence of TH1 inflammation against different viruses, including RSV.[94] An independent study reported that miR-155 is highly upregulated in the nasal mucosa of infants with RSV infection.[108] The latter study also showed that miRNA expression in nasal epithelium of RSV-positive infants exhibits a distinct profile of miRNAs, including the repression of miR-34/449 family members, as previously described in the asthmatic condition.[108]

In summary, current evidence demonstrates that in human infants, there are airway miRNA responses to environmental cues (e.g., premature birth or viral infections). Thus, translational and systems biology studies are critically needed to (1) establish specific early human life miRNA profiles and corresponding transcriptomic signatures in different airway cell types as well as in response to various environmental stimuli, and (2) provide mechanistic evidence of miRNA-driven genetic programming of the human airways during early life.

9 | FUTURE DIRECTIONS

Over the past decade, transdisciplinary "omic" approaches have advanced our understanding of the molecular programming of the airways in humans. Several studies have identified potential molecular mechanisms that contribute to early life epigenetic reprogramming, including DNA methylation, histone modifications, miRNAs, and the homeostasis of the respiratory mucosa (epithelial function and microbiota). Future studies must utilize the progress in systems biology and methodologies to obtain and examine samples in human newborns and infants[20,26,109] to conduct prospective and mechanistic studies that define the normal development and maturation of the human airways along with the effect of the environment on this fundamental process. This novel epigenetic paradigm centered on human maturational and developmental programs must include three cardinal elements: genes, environment, and developmental timing in early life. The combination of these factors is likely what really determines the functional trajectory of the respiratory system at the molecular, functional, and clinical levels.

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REFERENCES

1. de Marco R, Accordini S, Marcon A, et al. Risk factors for chronic obstructive pulmonary disease in a European cohort of young adults. Am J Respir Crit Care Med 2011;183(7):891–897. 10.1164/rccm.201007-1125OC [PubMed: 20935112]
2. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med 2016;375(9):871–878. 10.1056/NEJMra1603287 [PubMed: 27579637]
3. Saglani S, Bush A. The early-life origins of asthma. Curr Opin Allergy Clin Immunol 2007;7(1):83–90. 10.1097/ACI.0b013e32801297e6 [PubMed: 17218816]
4. Tsai HJ, Wang G, Hong X, et al. Early life weight gain and development of childhood asthma in a prospective birth cohort. Ann Am Thorac Soc 2018;15(10):1197–1204. 10.1513/AnnalsATS.201712-921OC [PubMed: 29979628]
5. O'Connor GT, Lynch SV, Bloomberg GR, et al. Early-life home environment and risk of asthma among inner-city children. J Allergy Clin Immunol 2018;141(4):1468–1475. 10.1016/j.jaci.2017.06.040 [PubMed: 28939248]
6. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 2008;178(7):667–672. 10.1164/rccm.200802-309OC [PubMed: 18565953]
7. Arrieta MC, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015;7(307):307ra152. 10.1126/scitranslmed.aab2271
8. Bisgaard H. The Copenhagen Prospective Study on Asthma in Childhood (COPSAC): design, rationale, and baseline data from a longitudinal birth cohort study. Ann Allergy Asthma Immunol 2004; 93(4):381–389. 10.1016/S1081-1206(10)61398-1 [PubMed: 15521375]
9. Ta LDH, Yap GC, Tay CJX, et al. Establishment of the nasal microbiota in the first 18 months of life: correlation with early-onset rhinitis and wheezing. J Allergy Clin Immunol 2018;142(1):86–95. 10.1016/j.jaci.2018.01.032 [PubMed: 29452199]
10. Teo SM, Mok D, Pham K, et al. The infant nasopharyngeal microbiome impacts severity of lower respiratory infection and risk of asthma development. Cell Host Microbe 2015;17(5):704–715. 10.1016/j.chom.2015.03.008 [PubMed: 25865368]
11. Burke H, Leonardi-Bee J, Hashim A, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics 2012;129(4):735–744. 10.1542/peds.2011-2196 [PubMed: 22430451]
12. Baïz N, Just J, Chastang J, et al. Maternal diet before and during pregnancy and risk of asthma and allergic rhinitis in children. Allergy Asthma Clin Immunol 2019;15:40. 10.1186/s13223-019-0353-2 [PubMed: 31285746]
13. Liu S, Zhou B, Wang Y, Wang K, Zhang Z, Niu W. Pre-pregnancy maternal weight and gestational weight gain increase the risk for childhood asthma and wheeze: an updated meta-analysis. Front Pediatr 2020;8:134. 10.3389/fped.2020.00134 [PubMed: 32309270]
14. Rajappan A, Pearce A, Inskip HM, et al. Maternal body mass index: relation with infant respiratory symptoms and infections. Pediatr Pulmonol 2017;52(10):1291–1299. 10.1002/ppul.23779 [PubMed: 28816002]
15. Castro-Rodriguez JA, Forno E, Casanello P, Padilla O, Krause BJ, Uauy R. Leptin in cord blood associates with asthma risk at age 3 in the offspring of women with gestational obesity. Ann Am Thorac Soc 2020;12(12):1583–1589. 10.1513/AnnalsATS.202001-080OC

16. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 2007;448(7152):470–473. 10.1038/nature06014 [PubMed: 17611496]
17. Ober C, Sperling AI, von Mutius E, Vercelli D. Immune development and environment: lessons from Amish and Hutterite children. Curr Opin Immunol 2017;48:51–60. 10.1016/j.coi.2017.08.003 [PubMed: 28843541]
18. Wang D, Liu X, Zhou Y, et al. Individual variation and longitudinal pattern of genome-wide DNA methylation from birth to the first two years of life. Epigenetics 2012;7(6):594–605. 10.4161/epi.20117 [PubMed: 22522910]
19. Martino DJ, Tulic MK, Gordon L, et al. Evidence for age-related and individual-specific changes in DNA methylation profile of mononuclear cells during early immune development in humans. Epigenetics 2011;6(9):1085–1094. 10.4161/epi.6.9.16401 [PubMed: 21814035]
20. Olin A, Henckel E, Chen Y, et al. Stereotypic immune system development in newborn children. Cell 2018;174(5):1277–1292. 10.1016/j.cell.2018.06.045 [PubMed: 30142345]
21. Feinberg AP. The key role of epigenetics in human disease prevention and mitigation. N Engl J Med 2018;378(14):1323–1334. 10.1056/NEJMra1402513 [PubMed: 29617578]
22. Greenberg MVC, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol 2019; 20(10):590–607. 10.1038/s41580-019-0159-6 [PubMed: 31399642]
23. Holliday R, Pugh JE. DNA modification mechanisms and gene activity during development. Science 1975;187(4173):226–232. [PubMed: 1111098]
24. Zhang X, Gan Y, Zou G, Guan J, Zhou S. Genome-wide analysis of epigenetic dynamics across human developmental stages and tissues. BMC Genomics 2019;20(suppl 2):S221. 10.1186/s12864-019-5472-0
25. Smith ZD, Meissner A. DNA methylation: roles in mammalian development. Nat Rev Genet 2013;14(3):204–220. 10.1038/nrg3354 [PubMed: 23400093]
26. Merid SK, Novoloaca A, Sharp GC, et al. Epigenome-wide meta-analysis of blood DNA methylation in newborns and children identifies numerous loci related to gestational age. Genome Med 2020;12(1):25. 10.1186/s13073-020-0716-9 [PubMed: 32114984]
27. Pal S, Tyler JK. Epigenetics and aging. Sci Adv 2016;2(7): e1600584. 10.1126/sciadv.1600584 [PubMed: 27482540]
28. Field AE, Robertson NA, Wang T, Havas A, Ideker T, Adams PD. DNA methylation clocks in aging: categories, causes, and consequences. Mol Cell 2018;71(6):882–895. 10.1016/j.molcel.2018.08.008 [PubMed: 30241605]
29. Cavalli G, Heard E. Advances in epigenetics link genetics to the environment and disease. Nature 2019;571(7766):489–499. 10.1038/s41586-019-1411-0 [PubMed: 31341302]
30. Hannon E, Knox O, Sugden K, et al. Characterizing genetic and environmental influences on variable DNA methylation using monozygotic and dizygotic twins. PLoS Genet 2018;14(8):e1007544. 10.1371/journal.pgen.1007544 [PubMed: 30091980]
31. Klosin A, Casas E, Hidalgo-Carcedo C, Vavouri T, Lehner B. Transgenerational transmission of environmental information in *C. elegans*. Science 2017;356(6335):320–323. 10.1126/science.aah6412 [PubMed: 28428426]
32. Ge C, Ye J, Weber C, et al. The histone demethylase KDM6B regulates temperature-dependent sex determination in a turtle species. Science 2018;360(6389):645–648. 10.1126/science.aap8328 [PubMed: 29748283]
33. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet 2012;13(7):484–492. 10.1038/nrg3230 [PubMed: 22641018]
34. Luo C, Hajkova P, Ecker JR. Dynamic DNA methylation: in the right place at the right time. Science 2018;361(6409):1336–1340. 10.1126/science.aat6806 [PubMed: 30262495]
35. Miller RL, Lawrence J. Understanding root causes of asthma. perinatal environmental exposures and epigenetic regulation. Ann Am Thorac Soc 2018;04(suppl 2):S103–S108. 10.1513/AnnalsATS.201706-514MG

36. Brand S, Teich R, Dicke T, et al. Epigenetic regulation in murine offspring as a novel mechanism for transmaternal asthma protection induced by microbes. J Allergy Clin Immunol 2011;128(3): 618–625. 10.1016/j.jaci.2011.04.035 [PubMed: 21680015]
37. Niedzwiecki M, Zhu H, Corson L, et al. Prenatal exposure to allergen, DNA methylation, and allergy in grandoffspring mice. Allergy 2012;67(7):904–910. 10.1111/j.1398-9995.2012.02841.x [PubMed: 22583153]
38. Leslie FM. Multigenerational epigenetic effects of nicotine on lung function. BMC Med 2013;11:27. 10.1186/1741-7015-11-27 [PubMed: 23379695]
39. DeVries A, Wlasiuk G, Miller SJ, et al. Epigenome-wide analysis links SMAD3 methylation at birth to asthma in children of asthmatic mothers. J Allergy Clin Immunol 2017;140(2):534–542. 10.1016/j.jaci.2016.10.041 [PubMed: 28011059]
40. Kinel E, Kotwicki T, Podolska A, Białek M, Stryła W. Polish validation of Brace Questionnaire. Eur Spine J 2012;21(8):1603–1608. 10.1007/s00586-012-2188-0 [PubMed: 22349968]
41. Suter M, Ma J, Harris A, et al. Maternal tobacco use modestly alters correlated epigenome-wide placental DNA methylation and gene expression. Epigenetics 2011;6(11):1284–1294. 10.4161/epi.6.11.17819 [PubMed: 21937876]
42. Nielsen CH, Larsen A, Nielsen AL. DNA methylation alterations in response to prenatal exposure of maternal cigarette smoking: a persistent epigenetic impact on health from maternal lifestyle? Arch Toxicol 2016;90(2):231–245. 10.1007/s00204-014-1426-0 [PubMed: 25480659]
43. Gao L, Liu X, Millstein J, et al. Self-reported prenatal tobacco smoke exposure, AXL gene-body methylation, and childhood asthma phenotypes. Clin Epigenetics 2018;07(1):98. 10.1186/s13148-018-0532-x
44. Tang WY, Levin L, Talaska G, et al. Maternal exposure to polycyclic aromatic hydrocarbons and 5'-CpG methylation of interferon-γ in cord white blood cells. Environ Health Perspect 2012;120(8): 1195–1200. 10.1289/ehp.1103744 [PubMed: 22562770]
45. Yang IV, Pedersen BS, Liu A, et al. DNA methylation and childhood asthma in the inner city. J Allergy Clin Immunol 2015;136(1):69–80. 10.1016/j.jaci.2015.01.025 [PubMed: 25769910]
46. Kobayashi Y, Bossley C, Gupta A, et al. Passive smoking impairs histone deacetylase-2 in children with severe asthma. Chest 2014; 145(2):305–312. 10.1378/chest.13-0835 [PubMed: 24030221]
47. Michel S, Busato F, Genuneit J, et al. Farm exposure and time trends in early childhood may influence DNA methylation in genes related to asthma and allergy. Allergy 2013;68(3):355–364. 10.1111/all.12097 [PubMed: 23346934]
48. Xu CJ, Söderhäll C, Bustamante M, et al. DNA methylation in childhood asthma: an epigenome-wide meta-analysis. Lancet Respir Med 2018;6(5):379–388. 10.1016/S2213-2600(18)30052-3 [PubMed: 29496485]
49. Houseman EA, Molitor J, Marsit CJ. Reference-free cell mixture adjustments in analysis of DNA methylation data. Bioinformatics 2014;30(10):1431–1439. 10.1093/bioinformatics/btu029 [PubMed: 24451622]
50. Titus AJ, Gallimore RM, Salas LA, Christensen BC. Cell-type deconvolution from DNA methylation: a review of recent applications. Hum Mol Genet 2017;26(R2):R216–R224. 10.1093/hmg/ddx275 [PubMed: 28977446]
51. Houseman EA, Accomando WP, Koestler DC, et al. DNA methylation arrays as surrogate measures of cell mixture distribution. BMC Bioinformatics 2012;13:86. 10.1186/1471-2105-13-86 [PubMed: 22568884]
52. Brugha R, Lowe R, Henderson AJ, et al. DNA methylation profiles between airway epithelium and proxy tissues in children. Acta Paediatr 2017;106(12):2011–2016. 10.1111/apa.14027 [PubMed: 28833606]
53. Nicodemus-Johnson J, Naughton KA, Sudi J, et al. Genome-wide methylation study identifies an IL-13-induced epigenetic signature in asthmatic airways. Am J Respir Crit Care Med 2016;193(4): 376–385. 10.1164/rccm.201506-1243OC [PubMed: 26474238]
54. Wills-Karp M, Luyimbazi J, Xu X, et al. Interleukin-13: central mediator of allergic asthma. Science 1998;282(5397):2258–2261. 10.1126/science.282.5397.2258 [PubMed: 9856949]

55. Cardenas A, Sordillo JE, Rifas-Shiman SL, et al. The nasal methylome as a biomarker of asthma and airway inflammation in children. Nat Commun 2019;07(1):3095. 10.1038/s41467-019-11058-3
56. Stefanowicz D, Hackett TL, Garmaroudi FS, et al. DNA methylation profiles of airway epithelial cells and PBMCs from healthy, atopic and asthmatic children. PLoS One 2012;7(9):e44213. 10.1371/journal.pone.0044213 [PubMed: 22970180]
57. Baccarelli A, Rusconi F, Bollati V, et al. Nasal cell DNA methylation, inflammation, lung function and wheezing in children with asthma. Epigenomics 2012;4(1):91–100. 10.2217/epi.11.106 [PubMed: 22332661]
58. Yang IV, Pedersen BS, Liu AH, et al. The nasal methylome and childhood atopic asthma. J Allergy Clin Immunol 2017;139(5): 1478–1488. 10.1016/j.jaci.2016.07.036 [PubMed: 27745942]
59. Forno E, Wang T, Qi C, et al. DNA methylation in nasal epithelium, atopy, and atopic asthma in children: a genome-wide study. Lancet Respir Med 2019;7(4):336–346. 10.1016/S2213-2600(18)30466-1 [PubMed: 30584054]
60. Morin A, McKennan CG, Pedersen CT, et al. Epigenetic landscape links upper airway microbiota in infancy with allergic rhinitis at 6 years of age. J Allergy Clin Immunol 2020;12(6):1358–1366. 10.1016/j.jaci.2020.07.005
61. Nino CL, Perez GF, Isaza N, Gutierrez MJ, Gomez JL, Nino G. Characterization of sex-based DNA methylation signatures in the airways during early life. Sci Rep 2018;8(1):5526. 10.1038/s41598-018-23063-5 [PubMed: 29615635]
62. Hayward SL, Scharer CD, Cartwright EK, et al. Environmental cues regulate epigenetic reprogramming of airway-resident memory CD8(+) T cells. Nat Immunol 2020;21(3):309–320. 10.1038/s41590-019-0584-x [PubMed: 31953534]
63. Puttur F, Denney L, Gregory LG, et al. Pulmonary environmental cues drive group 2 innate lymphoid cell dynamics in mice and humans. Sci Immunol 2019;4(36):eaav7638. 10.1126/sciimmunol.aav7638 [PubMed: 31175176]
64. Pan WH, Sommer F, Falk-Paulsen M, et al. Exposure to the gut microbiota drives distinct methylome and transcriptome changes in intestinal epithelial cells during postnatal development. Genome Med 2018;10(1):27. 10.1186/s13073-018-0534-5 [PubMed: 29653584]
65. Shamovsky I, Ivannikov M, Kandel ES, Gershon D, Nudler E. RNA-mediated response to heat shock in mammalian cells. Nature 2006; 440(7083):556–560. 10.1038/nature04518 [PubMed: 16554823]
66. Vrijens K, Bollati V, Nawrot TS. MicroRNAs as potential signatures of environmental exposure or effect: a systematic review. Environ Health Perspect 2015;123(5):399–411. 10.1289/ehp.1408459 [PubMed: 25616258]
67. Bi H, Zhou J, Wu D, et al. Microarray analysis of long non-coding RNAs in COPD lung tissue. Inflamm Res 2015;64(2):119–126. 10.1007/s00011-014-0790-9 [PubMed: 25542208]
68. Martinez-Guitarte JL, Planello R, Morcillo G. Overexpression of long non-coding RNAs following exposure to xenobiotics in the aquatic midge *Chironomus riparius*. Aquat Toxicol 2012;110–111: 84–90. 10.1016/j.aquatox.2011.12.013
69. Qiu C, Chen G, Cui Q. Towards the understanding of microRNA and environmental factor interactions and their relationships to human diseases. Sci Rep 2012;2:318. 10.1038/srep00318 [PubMed: 22428086]
70. Han Li C, Chen Y. Small and long non-coding RNAs: novel targets in perspective cancer therapy. Curr Genomics 2015;16(5):319–326. 10.2174/1389202916666150707155851 [PubMed: 27047252]
71. Baltimore D, Boldin MP, O'Connell RM, Rao DS, Taganov KD. MicroRNAs: new regulators of immune cell development and function. Nat Immunol 2008;9(8):839–845. 10.1038/ni.f.209 [PubMed: 18645592]
72. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol 2018;9:402. 10.3389/fendo.2018.00402
73. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009; 19(1):92–105. 10.1101/gr.082701.108 [PubMed: 18955434]

74. Wang P, Hou J, Lin L, et al. Inducible microRNA-155 feedback promotes type I IFN signaling in antiviral innate immunity by targeting suppressor of cytokine signaling 1. J Immunol 2010;185(10): 6226–6233. 10.4049/jimmunol.1000491 [PubMed: 20937844]
75. Pillai DK, Sankoorikal BJ, Johnson E, et al. Directional secretomes reflect polarity-specific functions in an in vitro model of human bronchial epithelium. Am J Respir Cell Mol Biol 2014;50(2):292–300. 10.1165/rcmb.2013-0188OC [PubMed: 24010916]
76. Nino G, Huseni S, Perez GF, et al. Directional secretory response of double stranded RNA-induced thymic stromal lymphopoetin (TSLP) and CCL11/eotaxin-1 in human asthmatic airways. PLoS One 2014; 9(12):e115398. 10.1371/journal.pone.0115398 [PubMed: 25546419]
77. Hsu S-D, Lin F-M, Wu W-Y, et al. miRTarBase: a database curates experimentally validated microRNA–target interactions. Nucleic Acids Res 2010;39:gkq1107–gkq1109.
78. Proud D, Turner RB, Winther B, et al. Gene expression profiles during in vivo human rhinovirus infection: insights into the host response. Am J Respir Crit Care Med 2008;178(9):962–968. [PubMed: 18658112]
79. Brown KJ, Seol H, Pillai DK, et al. The human secretome atlas initiative: implications in health and disease conditions. Biochim Biophys Acta 2013;1834(11):2454–2461. 10.1016/j.bbapap.2013.04.007 [PubMed: 23603790]
80. Bondanese VP, Francisco-Garcia A, Bedke N, Davies DE, Sanchez-Elsner T. Identification of host miRNAs that may limit human rhinovirus replication. World J Biol Chem 2014;5(4):437–456. 10.4331/wjbc.v5.i4.437 [PubMed: 25426267]
81. Dragovic RA, Gardiner C, Brooks AS, et al. Sizing and phenotyping of cellular vesicles using nanoparticle tracking analysis. Nanomed: Nanotechnol, Biol Med 2011;7(6):780–788.
82. Sessa R, Hata A. Role of microRNAs in lung development and pulmonary diseases. Pulm Circ 2013;3(2):315–328. 10.4103/2045-8932.114758 [PubMed: 24015331]
83. Foster PS, Plank M, Collison A, et al. The emerging role of microRNAs in regulating immune and inflammatory responses in the lung. Immunol Rev 2013;253(1):198–215. 10.1111/imr.12058 [PubMed: 23550648]
84. Solberg OD, Ostrin EJ, Love MI, et al. Airway epithelial miRNA expression is altered in asthma. Am J Respir Crit Care Med 2012; 186(10):965–974. 10.1164/rccm.201201-0027OC [PubMed: 22955319]
85. Marcet B, Chevalier B, Luxardi G, et al. Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway. Nat Cell Biol 2011;13(6):693–699. 10.1038/ncb2241 [PubMed: 21602795]
86. Lize M, Herr C, Klimke A, Bals R, Dobbelstein M. MicroRNA-449a levels increase by several orders of magnitude during mucociliary differentiation of airway epithelia. Cell Cycle 2010;9(22): 4579–4583. 10.4161/cc.9.22.13870 [PubMed: 21088493]
87. Guseh JS, Bores SA, Stanger BZ, et al. Notch signaling promotes airway mucous metaplasia and inhibits alveolar development. Development 2009;136(10):1751–1759. 10.1242/dev.029249 [PubMed: 19369400]
88. Najrana T, Mahadeo A, Abu-Eid R, et al. Mechanical stretch regulates the expression of specific miRNA in extracellular vesicles released from lung epithelial cells. J Cell Physiol 2020;235: 8210–8223. 10.1002/jcp.29476 [PubMed: 31970782]
89. Levänen B, Bhakta NR, Torregrosa Paredes P, et al. Altered microRNA profiles in bronchoalveolar lavage fluid exosomes in asthmatic patients. J Allergy Clin Immunol 2013;131(3):894–903. 10.1016/j.jaci.2012.11.039 [PubMed: 23333113]
90. Lu TX, Rothenberg ME. Diagnostic, functional, and therapeutic roles of microRNA in allergic diseases. J Allergy Clin Immunol Jul;132:3–13. 10.1016/j.jaci.2013.04.039
91. Kulshreshtha A, Ahmad T, Agrawal A, Ghosh B. Proinflammatory role of epithelial cell-derived exosomes in allergic airway inflammation. J Allergy Clin Immunol 2013;131(4):1194–1203. 10.1016/j.jaci.2012.12.1565 [PubMed: 23414598]
92. Gutierrez MJ, Gomez JL, Perez GF, et al. Airway secretory microRNAome changes during rhinovirus infection in early childhood. PLoS One 2016;11(9):e0162244. 10.1371/journal.pone.0162244 [PubMed: 27643599]

93. De Smet EG, Van Eeckhoutte HP, Avila Cobos F, et al. The role of miR-155 in cigarette smoke-induced pulmonary inflammation and COPD. Mucosal Immunol 2020;13(3):423–436. 10.1038/s41385-019-0241-6 [PubMed: 31819170]
94. Arroyo M, Salka K, Chorvinsky E, et al. Airway mir-155 responses are associated with TH1 cytokine polarization in young children with viral respiratory infections. PLoS One 2020;15(5):e0233352. 10.1371/journal.pone.0233352 [PubMed: 32442188]
95. Malmhäll C, Alawieh S, Lu Y, et al. MicroRNA-155 is essential for T (H)2-mediated allergen-induced eosinophilic inflammation in the lung. J Allergy Clin Immunol 2014;133(5):1429–1438. 10.1016/j.jaci.2013.11.008 [PubMed: 24373357]
96. Martinez-Nunez RT, Louafi F, Sanchez-Elsner T. The interleukin 13 (IL-13) pathway in human macrophages is modulated by microRNA-155 via direct targeting of interleukin 13 receptor alpha1 (IL13Ralpha1). J Biol Chem 2011;286(3):1786–1794. 10.1074/jbc.M110.169367 [PubMed: 21097505]
97. Johansson K, Malmhall C, Ramos-Ramirez P, Radinger M. MicroRNA-155 is a critical regulator of type 2 innate lymphoid cells and IL-33 signaling in experimental models of allergic airway inflammation. J Allergy Clin Immunol 2017;139(3):1007–1016. 10.1016/j.jaci.2016.06.035 [PubMed: 27492144]
98. Knolle MD, Chin SB, Rana BMJ, et al. MicroRNA-155 protects group 2 innate lymphoid cells from apoptosis to promote type-2 immunity. Front Immunol 2018;9:2232. 10.3389/fimmu.2018.02232 [PubMed: 30356668]
99. Lu C, Huang X, Zhang X, et al. miR-221 and miR-155 regulate human dendritic cell development, apoptosis, and IL-12 production through targeting of p27kip1, KPC1, and SOCS-1. Blood 2011; 117(16):4293–4303. 10.1182/blood-2010-12-322503 [PubMed: 21355095]
100. Qayum AA, Paranjape A, Abebayehu D, et al. IL-10-induced miR-155 targets SOCS1 to enhance IgE-mediated mast cell function. J Immunol 2016;196(11):4457–4467. 10.4049/jimmunol.1502240 [PubMed: 27183599]
101. Yang M, Shen H, Qiu C, et al. High expression of miR-21 and miR-155 predicts recurrence and unfavourable survival in non-small cell lung cancer. Eur J Cancer 2013;49(3):604–615. 10.1016/j.ejca.2012.09.031 [PubMed: 23099007]
102. Perry MM, Moschos SA, Williams AE, Shepherd NJ, Larner-Svensson HM, Lindsay MA. Rapid changes in microRNA-146a expression negatively regulate the IL-1beta-induced inflammatory response in human lung alveolar epithelial cells. J Immunol 2008; 180(8):5689–5698. 10.4049/jimmunol.180.8.5689 [PubMed: 18390754]
103. Lambert KA, Roff AN, Panganiban RP, Douglas S, Ishmael FT. MicroRNA-146a is induced by inflammatory stimuli in airway epithelial cells and augments the anti-inflammatory effects of glucocorticoids. PLoS One 2018;13(10):e0205434. 10.1371/journal.pone.0205434 [PubMed: 30300399]
104. Wang T, Jiang L, Wei X, et al. Inhibition of miR-221 alleviates LPS-induced acute lung injury via inactivation of SOCS1/NF-kappaB signaling pathway. Cell Cycle 2019;18(16):1893–1907. 10.1080/15384101.2019.1632136 [PubMed: 31208297]
105. Lal CV, Olave N, Travers C, et al. Exosomal microRNA predicts and protects against severe bronchopulmonary dysplasia in extremely premature infants. JCI Insight 2018;3(5), 10.1172/jci.insight.93994
106. Davis JS, Sun M, Kho AT, et al. Circulating microRNAs and association with methacholine PC20 in the Childhood Asthma Management Program (CAMP) cohort. PLoS One 2017;12(7): e0180329. 10.1371/journal.pone.0180329 [PubMed: 28749975]
107. Hasegawa K, Pérez-Losada M, Hoptay CE, et al. RSV vs. rhinovirus bronchiolitis: difference in nasal airway microRNA profiles and NFkappaB signaling. Pediatr Res 2018;83(3):606–614. 10.1038/pr.2017.309 [PubMed: 29244796]
108. Inchley CS, Sonerud T, Fjaerli HO, Nakstad B. Nasal mucosal microRNA expression in children with respiratory syncytial virus infection. BMC Infect Dis 2015;15:150. 10.1186/s12879-015-0878-z [PubMed: 25884957]
109. Burel JG, Apte SH, Doolan DL. Systems approaches towards molecular profiling of human immunity. Trends Immunol 2016;37(1): 53–67. 10.1016/j.it.2015.11.006 [PubMed: 26669258]