CHEST®

Official publication of the American College of Chest Physicians

Epigenetics and Prenatal Influences on Asthma and Allergic Airways Disease

David Martino and Susan Prescott

Chest 2011;139;640-647
DOI 10.1378/chest.10-1800

The online version of this article, along with updated information and services can be found online on the World Wide Web at:
http://chestjournal.chestpubs.org/content/139/3/640.full.html

Chest is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright2011by the American College of Chest Physicians, 3300 Dundee Road, Northbrook, IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder.
(**http://chestjournal.chestpubs.org/site/misc/reprints.xhtml**)
ISSN:0012-3692

AMERICAN COLLEGE OF CHEST PHYSICIANS®

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

CHEST Translating Basic Research Into Clinical Practice

Epigenetics and Prenatal Influences on Asthma and Allergic Airways Disease

David Martino, BSc(Hons); and Susan Prescott, MD, PhD

Uterine life is arguably the most critical time in developmental programming, when environmental exposures may have the greatest potential to influence evolving fetal structure and function. There has been substantial progress in understanding the epigenetic mechanisms through which environmental exposures can permanently alter the expression of fetal genes and contribute to the increasing propensity for many complex diseases. These concepts of "developmental origins" of disease are being applied across virtually all fields of medicine, and emerging epigenetic paradigms are the likely mechanism behind the environment-driven epidemic of asthma and allergic disease. Here, we examine the epigenetic regulation of immune development and the early immune profiles that contribute to allergic risk. In particular we review new evidence that key environmental exposures, such as microbial exposure, dietary changes, tobacco smoke, and pollutants, can induce epigenetic changes in gene expression and alter disease risk. Although most of these factors have already been clearly implicated in epidemiologic studies of asthma and allergic disease, new studies investigating the mechanisms of these effects may provide new avenues for using these pathways for disease prevention. ***CHEST 2011; 139(3):640–647***

Abbreviations: IFN-γ = interferon-γ; NF-κB = nuclear factor κB; Th = T helper; Treg = T regulatory cell

The emerging field of epigenetics provides a new frontier for understanding mechanisms underlying well-recognized gene-environment interactions. Epigenetics refers to the study of heritable changes in gene expression, caused by chemical modifications in a chromosome, which are so termed because they alter the likelihood of gene transcription but do not change the underlying sequence. This particular mechanism of gene regulation is fundamental to all aspects of growth and development, determining the flow of genomic information in a temporal and tissue-specific manner. The epigenetic program is encoded by specific histone modifications (methylation and acetylation) and DNA methylation patterns, which determine the degree of DNA compaction and thus the accessibility of genes for transcription (Fig 1). In addition to histone modifications and DNA methylation, there are also other gene regulatory networks, including microRNAs, small interfering RNAs, and long noncoding RNAs, all of which serve to control gene expression.[1] However, these are distinct from epigenetic traits as it is unclear whether these processes are transmittable across generations. During cellular differentiation, these networks selectively alter the patterns of gene expression to allow considerable cellular diversity while the DNA code remains unchanged. In a general sense the epigenetic code provides plasticity of gene expression in response to environmental changes, allowing more rapid phenotypic adaptations across generations. As developmental changes are most profound during embryonic and fetal life, this is also arguably when the epigenetic program is most vulnerable to environmental changes. Given that these modifications are reversible and sensitive to environmental factors, they provide a mechanistic link between environmental exposures, developmental programming, and risk for disease.

Manuscript received July 14, 2010; revision accepted September 10, 2010.
Affiliations: From the School of Paediatrics and Child Health Research, University of Western Australia, Perth, WA, Australia.
Funding/Support: Dr Prescott is funded by a National Health and Medical Research Fellowship.
Correspondence to: Susan Prescott, MD, PhD, University of Western Australia, School Paediatrics and Child Health Research, Princess Margaret Hospital for Children, GPO Box D 184, Perth, WA, 6840, Australia; e-mail: sprescott@meddent.uwa.edu.au
© 2011 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (http://www.chestpubs.org/site/misc/reprints.xhtml).
DOI: 10.1378/chest.10-1800

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

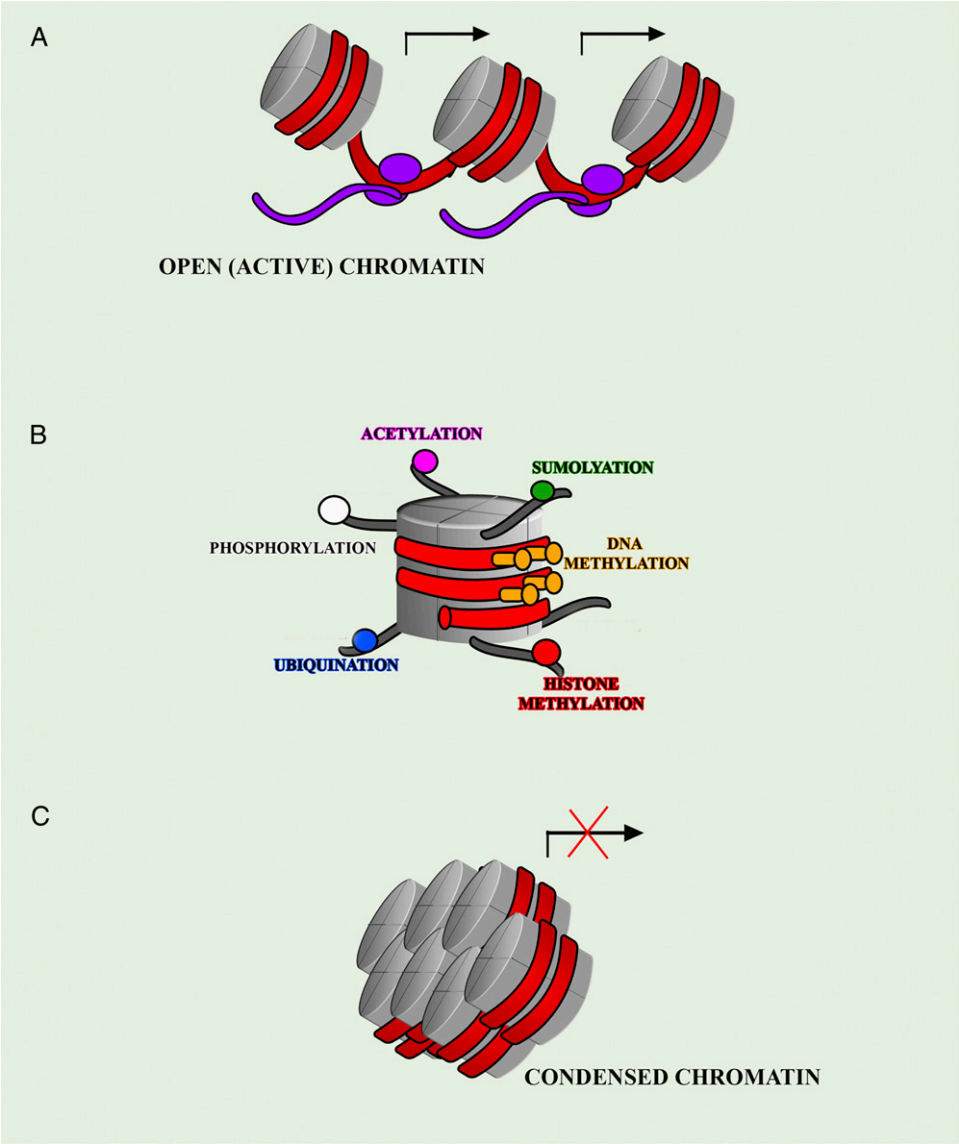

FIGURE 1. A, Transcriptionally active chromatin contains a subset of modifications listed in B and is accessible to DNA polymerase. C, Condensed chromatin contains a different subset of these modifications, and the DNA is transcriptionally silent. A combination of modifications to histone tail domains together with DNA methylation will determine the conformation, and these are not mutually exclusive.

In the context of asthma and allergic disease, a substantial body of work suggests a link between epigenetic gene regulation, immunity, and physiologic development. Around the turn of this century, cellular immune studies described a role for histone and DNA methylation changes in the control of cellular immune development.[2,3] The increasing rates of early childhood allergy led to the novel hypothesis that environmental changes can promote allergic predisposition through epigenetic effects on gene expression, and that this begins in fetal life.[4] Since then, epigenetics has become the cornerstone in the quest to understand the "developmental origins" of complex modern diseases, such as asthma and allergy.[5,6]

It has already been established that maternal exposures, such as cigarette smoke, can modify both fetal lung development[7] and fetal immune function,[8] contributing to an increased risk of subsequent asthma and respiratory disease.[9] Other important intrauterine exposures, including the maternal diet[10,11] and microbial exposures,[12] are also known to modify the risk of allergic disease in the offspring. Recent studies now show that these prenatal exposures (diet, microbial infections, tobacco smoke, and other pollutants)

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

can epigenetically activate or silence immune-related genes with substantial effects on immune programming.[7,13-16] These new studies provide a novel framework to understand the mechanisms by which the environment influences developmental and immune programming and determines the risk for subsequent disease. The new hope is that these pathways may also provide a foundation for targeted early interventions to prevent disease.

Developmental Programming, Epigenetics, and Immune Function

There is now substantial evidence that early immune development is altered in children affected by asthma and allergic diseases. These alterations lead to dysregulated immunity characterized by a deficiency of interferon γ (IFN-γ) production,[17,18] altered innate immunity,[19] and deficient T regulatory cell (Treg) networks,[20] which culminate in a propensity for uncontrolled T helper (Th) 2 immune responses. These differences are evident at birth,[21,22] suggesting that prenatal factors may be particularly important in alternatively programming neonatal immunity. There is now conclusive evidence that immune development is epigenetically regulated. These mechanisms are known to control both Th1 and Th2 cell differentiation[2,3] and are also a prerequisite for FoxP3 expression and Treg differentiation.[23] There is, therefore, growing interest in exposures during pregnancy that can activate or silence these genes and alter the balance of neonatal immune responses.

During pregnancy, complex immunologic mechanisms have evolved to allow the fetal and maternal immune systems to coexist. The maternal cellular immune system adapts subtly during pregnancy to a "Th2 state" to down-regulate Th1 IFN-γ cell-mediated immune responses to fetal antigens.[24,25] This is achieved by the suppression of fetal IFN-γ production via hypermethylation (gene silencing) of the *IFNG* gene promoter in $CD4^+$ T cells at the maternofetal interface.[3] $FOXP3^+$ cells are also attracted to the maternofetal interface[26] by human chorionic gonadotrophin, and recent studies now provide preliminary evidence that the *FOXP3* gene is expressed at lower levels in the placentas of allergic women (and allergic infants) (S. L. Prescott, MD, PhD; A. Osei-Kumah, PhD; T. Richman, BSc; D. Martino, BSc; J. A. Dunstan, PhD; M. K. Tulic, PhD; et al, unpublished data, February 2010).

Neonatal immunity reflects these maternal events, with reduced Th1 function and relative dominance of Th2 activity, with underlying epigenetic changes driving these patterns of gene expression.[27] This has fueled speculation that factors that increase gene methylation may increase the risk of disease by silencing pathways (Th1 and Treg differentiation) that normally inhibit Th2 allergic differentiation and propensity for allergic airways disease.[28]

Early Events and Epigenetic Regulation of Airway Development

Asthma and allergic respiratory disease are the culmination of both local epithelial dysfunction and generalized Th2 atopic propensity. Although systemic proclivity for allergy is a major contributor to allergic airways disease, there is accumulating evidence that local mucosal expression of disease occurs through independent processes in Th2-predisposed individuals. Local epithelial-mesenchymal interactions are now believed to play a critical role in asthma pathogenesis,[29] and a number of early life influences are believed to contribute to abnormal local tissue function in response to inflammation (Fig 2).

In the antenatal period, maternal environmental exposures have the capacity to influence lung development. There is very strong evidence that maternal smoking in pregnancy has adverse effects on fetal lung development and asthma risk.[9,30] This includes increased responsiveness to methacholine, smooth muscle layer thickness, and collagen deposition. Altered DNA methylation patterns have been observed in several genes in buccal cells from children exposed in utero to tobacco smoke, which may be a likely mechanism for increased risk for disease.[9] Similarly, maternal infections and the use of antibiotics have been associated with an increased risk for allergic airways disease,[31] as have specific aspects of maternal diet,[11,14] maternal stress levels,[32] and exposure to pollutants,[15] all of which have been associated with epigenetic changes (as discussed in the "Specific Environmental Exposures Can Modify Epigenetic Programming and Susceptibility to Allergic Airways Disease" section).

After birth, environmental exposures also influence local events in the developing airways. Viral infection, particularly with respiratory syncytial virus, is one of the strongest postnatal associations with asthma.[33] Wheezing lower respiratory infection in the first year of life is a strong risk factor for asthma at 6 years of age in both nonatopic (OR, 4.1; $P < .0005$) and atopic (OR, 9.0; $P < .0005$) children.[34] This strongly suggests that viral-induced lower airway inflammation during the early period of postnatal development can have profound long-term effects that are more marked than effects of inflammation at later ages.

Currently there is very little evidence about whether early-life infection with respiratory syncytial virus is associated with epigenetic changes that might predispose to the development of a systemic Th2 immunologic profile. There is some evidence that adenoviral

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

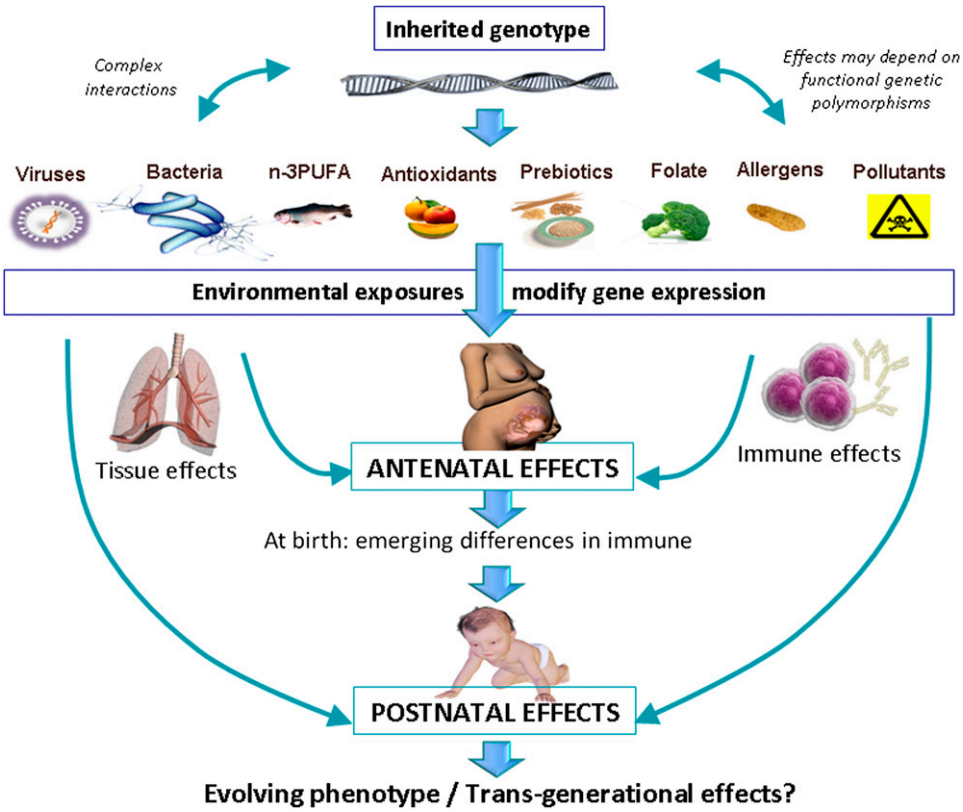

FIGURE 2. Complex gene-environmental interactions modify gene expression and phenotype during early development. PUFA = polyunsaturated fatty acid.

infections increase the expression of inflammatory genes via surface coat proteins, which are capable of interacting with histone modifiers,[35] and play a role in the pathogenesis of COPD.[36] In general, infection with viral agents has also been associated with DNA methylation events in the host.[37] Although the development of better animal models will clarify the issue, it is likely that early viral infections may induce epigenetic changes in inflammatory pathways, which synergize with allergen sensitization, to contribute to the development of a Th2-biased asthmatic phenotype.[38]

SPECIFIC ENVIRONMENTAL EXPOSURES CAN MODIFY EPIGENETIC PROGRAMMING AND SUSCEPTIBILITY TO ALLERGIC AIRWAYS DISEASE

Environmental changes that have been epidemiologically linked with the allergy epidemic, including microbial burden,[39,40] dietary changes,[41,42] and environmental pollutants,[15,43,44] have also been shown to have effects on fetal gene expression and immune function.[8,10,45,46] Moreover, emerging epigenetic effects of these exposures[7,13,14,16,47] provide a new mechanism for the observed effects on gene expression. These new findings suggest that these exposures can induce stable epigenetic changes in gene expression, which can be passed to offspring and subsequent generations (Fig 2).

Maternal Diet in Pregnancy

Modern dietary changes appear to be providing less tolerogenic conditions during early immune programming and may also provide important avenues for preventing disease. Modern diets differ in many aspects from more traditional diets, with more processed and synthetic foods and less fresh fish, fruits, and vegetables. These changes in nutrients have been implicated in the increase in asthma and allergic disease, including the decline in polyunsaturated fatty acids,[10] soluble fiber,[48] antioxidants,[49] and other vitamins,[50] based on recognized immunologic effects as well as epidemiologic associations.

In one of the first epigenetic models of allergic disease, the role of folic acid in the pathogenesis of asthmatic airways disease has recently come to the forefront. This model was based on the capacity of folate to epigenetically modify gene expression through its role as a dietary methyl donor for DNA.[51] Supplementation of pregnant mice with a high-folate diet resulted in altered gene methylation patterns

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

and decreased transcriptional activity in the lung tissue of progeny mice with increased airways hyperreactivity, airways eosinophilia, and production of chemokine and inflammatory macrophage proteins.[14] One of the genes implicated was runt-related transcription factor 3, which several independent studies have indicated has a protective role in airways disease through the induction of FOXP3$^+$ Tregs.[52] This has been followed by reports in humans[53,54] linking folic acid supplementation during pregnancy with increased risk of asthma and respiratory disease in infants. However, until this is confirmed and the mechanisms more closely studied it is premature to make changes in the current practice aimed at using folate to prevent neural tube defects. This highlights the urgent call for more studies in this area. These studies should be considered in the context of other related dietary nutrients, such as vitamins B2, B6, B12, methionine, and choline, which may also be implicated through their effects on folate-mediated one-carbon metabolism.

Microbial Exposure In Utero

Although postnatal exposures are recognized as the largest source of direct microbial exposure to the developing infant, it is becoming clearer that the epigenetic influences of bacteria begin in utero. In humans, exposure to a high microbial burden in rural farming environments is protective against asthma and allergy.[40] New studies show that nonpathogenic microbial strains (*Acinetobacter lwoffii*) isolated from these farming environments can induce epigenetic effects when administered to pregnant animals and protect the offspring from experimental postnatal asthma (H. Renz, MD, personal communication, May 2010). This effect depends on increased expression of IFN-γ mediated by an increase in H4 acetylation of the IFN-γ promoter. Notably, these effects were abolished by inhibition of histone acetylation following garcinol treatment. Human studies also show that allergy protection by in utero microbial exposure is associated with enhanced neonatal Treg function, FOXP3 expression, and associated epigenetic effects (demethylation) of the *FOXP3* gene.[16] Based on these and other observations, it has been recently proposed that microbial exposures may epigenetically modify the patterns of immune gene expression during critical periods of early development and contribute to allergic predisposition.[47]

Exposure to Tobacco Smoke and Air Pollutants

Oxidative stress produced by exposures such as cigarette smoke and air pollution can have significant epigenetic effects by altering nuclear factor κB (NF-κB) activation or by histone modification and chromatin remodeling of proinflammatory genes. As a potent source of oxidative stress, cigarette smoke contributes to reduced histone deacetylase activity, which results in differential activation of NF-κB and the expression of proinflammatory cytokines IL-6 and IL-8 in peripheral lung tissue.[55] NF-κB is ubiquitous in cells and can induce histone modifications that activate or silence inflammatory genes and other signal-transduction pathways. In pregnancy, the induction of inflammatory genes can influence placental function and fetal programming.[56] Oxidative stress from traffic exhaust particles can also have epigenetic effects in pregnancy. Studies in mice demonstrated that exposure to diesel exhaust particles augmented the production of IgE following allergen sensitization (*Aspergillus fumigatus*) through hypermethylation of *IFNG* and hypomethylation of the *IL4* locus.[15] Of note, Perera et al[57] recently reported that high levels of maternal exposure to traffic particles correlate with methylation of the acyl coenzyme A synthetase long-chain family member 3 and with the development of asthma symptoms in children.

Ingested Persistent Organic Pollutants With Epigenetic Effects

Organic products of industry and agriculture (including polychlorinated biphenyl compounds, organochlorine pesticides, dioxins, and phthalates) contaminate modern homes, food, clothing, and water sources, accumulating in human tissue with age. Although they have immunosuppressive effects at high doses in humans,[58] low levels of contamination may more selectively inhibit Th1 immune responses[59] and favor allergic Th2 immune responses through their "estrogenic" hormonal activity. Some of these products have been readily measured in breast milk, cord blood, and placental tissue, highlighting the potential to influence early development.

Notably, many of these and other contaminants have more recently been associated with epigenetic effects (reviewed in Reference 60), including effects on global DNA methylation patterns at the low-dose exposure found in the ambient environment.[61] We have recently measured persistent organic pollutants (particularly organochlorine pesticides) in 94% of adipose samples from mothers undergoing caesarean section and 62% of breast milk samples.[62] Although we observed that levels have declined since the 1970s, this does not exclude a role in the intervening increase in allergic disease, particularly since the effects may not be apparent for several generations. This is a difficult area to study in humans, in whom only correlative studies are possible, but these "modern" exposures should remain an important consideration in the increase of modern diseases.

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

Other Factors That May Modify Early Gene Expression and Disease Risk

In the context of asthma and allergic disease, the maternal phenotype is particularly important as a well-recognized risk factor for infant disease. Maternal asthma and allergic status has a much stronger effect than paternal allergy on both allergic disease and Th1 IFN-γ production by the neonate.[63] We have also shown that maternal allergy modifies immune interactions between mother and fetus and reduces Th1 activation to the human leukocyte antigen mismatch of fetal alloantigens.[64] This may affect the cytokine milieu at the maternofetal interface and could be implicated in the attenuated Th1 responses commonly observed in infants of atopic mothers. Foreseeably, the increase in maternal allergy may also be amplifying the effect of other environmental changes.

Many other changes in the intrauterine environment can have direct effects on placental gene expression and potentially phenotypically modify the offspring. Preeclampsia, corticosteroid use, and stress have been all associated with epigenetic changes in gene expression, placental immune function, growth retardation, and congenital defects.[32] Maternal stress has an important role in placental gene expression since adrenal glucocorticoid production through the hypothalamic-pituitary-adrenal axis modulates inflammatory gene expression, with recognized effects on glutathione metabolism and DNA methylation.[32,65] Inflammatory disease during pregnancy can also alter placental immune function through cortisol production in a sex-specific manner.[66] Our recent studies also indicate that early induction of innate inflammatory genes in the neonate (including IL-1β and tumor necrosis factor α) is strongly related to the subsequent development of allergic disease.[67] These inflammatory mediators, which are important for immune programming, induce histone modifications and may be responsible for alternatively programming neonatal immunity.

Concluding Remarks

Effective prevention strategies are the ultimate goal in reversing the allergy epidemic. This will require a better understanding of environmental drivers, target genes, and mechanisms of early life immune programming. Preliminary studies strongly suggest that early events can have a defining influence on subsequent immune development and allergic susceptibility, and that many of these effects are mediated by epigenetic modifications. Emerging epigenetic paradigms in allergic disease are likely to provide further novel insights into the mechanisms and pathways through which the early environment can be harnessed to modify immune development and prevent allergic disease.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Prescott has worked as a consultant to companies such as Nestle Nutrition, Nutricia (Danone), and Fonterra. These relationships have not influenced the content of this manuscript in any way. Mr Martino has reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We thank Prof Peter Smith for the images used in Figure 2 and Dr Richard Saffery for his advice on Figure 1.

References

1. Mattick JS. A new paradigm for developmental biology. *J Exp Biol*. 2007;210(pt 9):1526-1547.
2. Fields PE, Kim ST, Flavell RA. Cutting edge: changes in histone acetylation at the IL-4 and IFN-gamma loci accompany Th1/Th2 differentiation. *J Immunol*. 2002;169(2):647-650.
3. White GP, Watt PM, Holt BJ, Holt PG. Differential patterns of methylation of the IFN-gamma promoter at CpG and non-CpG sites underlie differences in IFN-gamma gene expression between human neonatal and adult CD45RO- T cells. *J Immunol*. 2002;168(6):2820-2827.
4. Bousquet J, Jacot W, Yssel H, Vignola AM, Humbert M. Epigenetic inheritance of fetal genes in allergic asthma. *Allergy*. 2004;59(2):138-147.
5. Shaheen SO, Adcock IM. The developmental origins of asthma: does epigenetics hold the key? *Am J Respir Crit Care Med*. 2009;180(8):690-691.
6. Waterland RA, Michels KB. Epigenetic epidemiology of the developmental origins hypothesis. *Annu Rev Nutr*. 2007;27:363-388.
7. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. *Am J Respir Crit Care Med*. 2009;180(5):462-467.
8. Noakes PS, Holt PG, Prescott SL. Maternal smoking in pregnancy alters neonatal cytokine responses. *Allergy*. 2003;58(10):1053-1058.
9. Hylkema MN, Blacquière MJ. Intrauterine effects of maternal smoking on sensitization, asthma, and chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2009;6(8):660-662.
10. Dunstan JA, Mori TA, Barden A, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol*. 2003;112(6):1178-1184.
11. Chatzi L, Torrent M, Romieu I, et al. Mediterranean diet in pregnancy is protective for wheeze and atopy in childhood. *Thorax*. 2008;63(6):507-513.
12. Barnes PJ. Reduced histone deacetylase in COPD: clinical implications. *Chest*. 2006;129(1):151-155.
13. Bobetsis YA, Barros SP, Lin DM, et al. Bacterial infection promotes DNA hypermethylation. *J Dent Res*. 2007;86(2):169-174.
14. Hollingsworth JW, Maruoka S, Boon K, et al. In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest*. 2008;118(10):3462-3469.
15. Liu J, Ballaney M, Al-alem U, et al. Combined inhaled diesel exhaust particles and allergen exposure alter methylation

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

of T helper genes and IgE production in vivo. *Toxicol Sci*. 2008;102(1):76-81.
16. Schaub B, Liu J, Hoppler S, et al. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J Allergy Clin Immunol*. 2009;123(4):774-782.
17. Tang ML, Kemp AS, Thorburn J, Hill DJ. Reduced interferon-gamma secretion in neonates and subsequent atopy. *Lancet*. 1994;344(8928):983-985.
18. Martinez FD, Stern DA, Wright AL, Holberg CJ, Taussig LM, Halonen M. Association of interleukin-2 and interferon-gamma production by blood mononuclear cells in infancy with parental allergy skin tests and with subsequent development of atopy. *J Allergy Clin Immunol*. 1995;96(5 pt 1):652-660.
19. Yerkovich ST, Wikström ME, Suriyaarachchi D, Prescott SL, Upham JW, Holt PG. Postnatal development of monocyte cytokine responses to bacterial lipopolysaccharide. *Pediatr Res*. 2007;62(5):547-552.
20. Smith M, Tourigny MR, Noakes P, Thornton CA, Tulic MK, Prescott SL. Children with egg allergy have evidence of reduced neonatal CD4(+)CD25(+)CD127(lo/-) regulatory T cell function. *J Allergy Clin Immunol*. 2008;121(6): 1460-1466.
21. Ohshima Y, Yasutomi M, Omata N, et al. Dysregulation of IL-13 production by cord blood CD4+ T cells is associated with the subsequent development of atopic disease in infants. *Pediatr Res*. 2002;51(2):195-200.
22. Rinas U, Horneff G, Wahn V. Interferon-gamma production by cord-blood mononuclear cells is reduced in newborns with a family history of atopic disease and is independent from cord blood IgE-levels. *Pediatr Allergy Immunol*. 1993;4(2):60-64.
23. Baron U, Floess S, Wieczorek G, et al. DNA demethylation in the human FOXP3 locus discriminates regulatory T cells from activated FOXP3(+) conventional T cells. *Eur J Immunol*. 2007;37(9):2378-2389.
24. Breckler LA, Hale J, Taylor A, Dunstan JA, Thornton CA, Prescott SL. Pregnancy IFN-gamma responses to foetal alloantigens are altered by maternal allergy and gravidity status. *Allergy*. 2008;63(11):1473-1480.
25. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? *Immunol Today*. 1993;14(7):353-356.
26. Schumacher A, Brachwitz N, Sohr S, et al. Human chorionic gonadotropin attracts regulatory T cells into the fetal-maternal interface during early human pregnancy. *J Immunol*. 2009; 182(9):5488-5497.
27. Zaghouani H, Hoeman CM, Adkins B. Neonatal immunity: faulty T-helpers and the shortcomings of dendritic cells. *Trends Immunol*. 2009;30(12):585-591.
28. Martino DJ, Prescott SL. Silent mysteries: epigenetic paradigms could hold the key to conquering the epidemic of allergy and immune disease. *Allergy*. 2010;65(1):7-15.
29. Holt PG. Key factors in the development of asthma: atopy. *Am J Respir Crit Care Med*. 2000;161(3 pt 2):S172-S175.
30. Gilliland FD, Berhane K, McConnell R, et al. Maternal smoking during pregnancy, environmental tobacco smoke exposure and childhood lung function. *Thorax*. 2000;55(4):271-276.
31. McKeever TM, Lewis SA, Smith C, Hubbard R. The importance of prenatal exposures on the development of allergic disease: a birth cohort study using the West Midlands General Practice Database. *Am J Respir Crit Care Med*. 2002; 166(6):827-832.
32. Gheorghe CP, Goyal R, Mittal A, Longo LD. Gene expression in the placenta: maternal stress and epigenetic responses. *Int J Dev Biol*. 2010;54(2-3):507-523.
33. Kumar RK, Hitchins MP, Foster PS. Epigenetic changes in childhood asthma. *Dis Model Mech*. 2009;2(11-12):549-553.
34. Oddy WH, de Klerk NH, Sly PD, Holt PG. The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. *Eur Respir J*. 2002;19(5):899-905.
35. Higashimoto Y, Elliott WM, Behzad AR, et al. Inflammatory mediator mRNA expression by adenovirus E1A-transfected bronchial epithelial cells. *Am J Respir Crit Care Med*. 2002; 166(2):200-207.
36. Hogg JC. Role of latent viral infections in chronic obstructive pulmonary disease and asthma. *Am J Respir Crit Care Med*. 2001;164(10 pt 2):S71-S75.
37. Mikovits JA, Young HA, Vertino P, et al. Infection with human immunodeficiency virus type 1 upregulates DNA methyltransferase, resulting in de novo methylation of the gamma interferon (IFN-gamma) promoter and subsequent downregulation of IFN-gamma production. *Mol Cell Biol*. 1998;18(9):5166-5177.
38. Siegle JS, Hansbro N, Herbert C, et al. Early-life viral infection and allergen exposure interact to induce an asthmatic phenotype in mice. *Respir Res*. 2010;11:14.
39. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259-1260.
40. Braun-Fahrländer C, Riedler J, Herz U, et al; Allergy and Endotoxin Study Team. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med*. 2002;347(12):869-877.
41. Matsui EC, Matsui W. Higher serum folate levels are associated with a lower risk of atopy and wheeze. *J Allergy Clin Immunol*. 2009;123:1253-1259.
42. Husemoen LL, Toft U, Fenger M, Jørgensen T, Johansen N, Linneberg A. The association between atopy and factors influencing folate metabolism: is low folate status causally related to the development of atopy? *Int J Epidemiol*. 2006; 35(4):954-961.
43. Nowak D, Heinrich J, Jörres R, et al. Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: west and east Germany. *Eur Respir J*. 1996;9(12): 2541-2552.
44. Noakes PS, Thomas R, Lane C, et al. Association of maternal smoking with increased infant oxidative stress at 3 months of age. *Thorax*. 2007;62(8):714-717.
45. Blümer N, Herz U, Wegmann M, Renz H. Prenatal lipopolysaccharide-exposure prevents allergic sensitization and airway inflammation, but not airway responsiveness in a murine model of experimental asthma. *Clin Exp Allergy*. 2005;35(3):397-402.
46. Blümer N, Sel S, Virna S, et al. Perinatal maternal application of Lactobacillus rhamnosus GG suppresses allergic airway inflammation in mouse offspring. *Clin Exp Allergy*. 2007;37(3):348-357.
47. Vuillermin PJ, Ponsonby AL, Saffery R, et al. Microbial exposure, interferon gamma gene demethylation in naïve T-cells, and the risk of allergic disease. *Allergy*. 2009;64(3):348-353.
48. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009;461(7268):1282-1286.
49. Miller RL. Prenatal maternal diet affects asthma risk in offspring. *J Clin Invest*. 2008;118(10):3265-3268.
50. Devereux G, Litonjua AA, Turner SW, et al. Maternal vitamin D intake during pregnancy and early childhood wheezing. *Am J Clin Nutr*. 2007;85(3):853-859.
51. Ulrey CL, Liu L, Andrews LG, Tollefsbol TO. The impact of metabolism on DNA methylation. *Hum Mol Genet*. 2005; 14(Spec No 1):R139-R147.
52. Klunker S, Chong MM, Mantel PY, et al. Transcription factors RUNX1 and RUNX3 in the induction and suppressive function of Foxp3+ inducible regulatory T cells. *J Exp Med*. 2009;206(12):2701-2715.

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

53. Håberg SE, London SJ, Stigum H, Nafstad P, Nystad W. Folic acid supplements in pregnancy and early childhood respiratory health. *Arch Dis Child*. 2009;94(3):180-184.
54. Whitrow MJ, Moore VM, Rumbold AR, Davies MJ. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. *Am J Epidemiol*. 2009; 170(12):1486-1493.
55. Rahman I, Adcock IM. Oxidative stress and redox regulation of lung inflammation in COPD. *Eur Respir J*. 2006;28(1): 219-242.
56. Osei-Kumah A, Ammit AJ, Smith R, Ge Q, Clifton VL. Inflammatory mediator release in normal bronchial smooth muscle cells is altered by pregnant maternal and fetal plasma independent of asthma. *Placenta*. 2006;27(8):847-852.
57. Perera F, Tang WY, Herbstman J, et al. Relation of DNA methylation of 5′-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLoS ONE*. 2009;4(2):e4488.
58. Daniel V, Huber W, Bauer K, Opelz G. Impaired in-vitro lymphocyte responses in patients with elevated pentachlorophenol (PCP) blood levels. *Arch Environ Health*. 1995; 50(4):287-292.
59. Daniel V, Huber W, Bauer K, Suesal C, Conradt C, Opelz G. Associations of blood levels of PCB, HCHS, and HCB with numbers of lymphocyte subpopulations, in vitro lymphocyte response, plasma cytokine levels, and immunoglobulin autoantibodies. *Environ Health Perspect*. 2001;109(2): 173-178.
60. Baccarelli A, Bollati V. Epigenetics and environmental chemicals. *Curr Opin Pediatr*. 2009;21(2):243-251.
61. Kim K-Y, Kim D-S, Lee S-K, et al. Association of low-dose exposure to persistent organic pollutants with global DNA hypomethylation in healthy koreans. *Environ Health Perspect*. 2010;118(3):370-374.
62. Noakes PS, Taylor P, Wilkinson S, Prescott SL. The relationship between persistent organic pollutants in maternal and neonatal tissues and immune responses to allergens: A novel exploratory study. *Chemosphere*. 2006;63(8):1304-1311.
63. Prescott SL, Holt PG, Jenmalm M, Björkstén B. Effects of maternal allergen-specific IgG in cord blood on early postnatal development of allergen-specific T-cell immunity. *Allergy*. 2000;55(5):470-475.
64. Prescott SL, Breckler LA, Witt CS, Smith L, Dunstan JA, Christiansen FT. Allergic women show reduced T helper type 1 alloresponses to fetal human leucocyte antigen mismatch during pregnancy. *Clin Exp Immunol*. 2010;159(1):65-72.
65. Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions in utero. *Curr Opin Allergy Clin Immunol*. 2009;9(5):417-426.
66. Scott NM, Hodyl NA, Murphy VE, et al. Placental cytokine expression covaries with maternal asthma severity and fetal sex. *J Immunol*. 2009;182(3):1411-1420.
67. Tulic M, Forsberg A, Hodder M, et al. Differences in the developmental trajectory of innate microbial responses in atopic and normal children: new insights into immune ontogeny. *J Allergy Clin Immunol*. In press. doi:10.1016/j.jaci.2010.09.020.

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians

Epigenetics and Prenatal Influences on Asthma and Allergic Airways Disease

David Martino and Susan Prescott

Chest 2011;139; 640-647
DOI 10.1378/chest.10-1800

This information is current as of March 6, 2011

Updated Information & Services
Updated Information and services can be found at:
http://chestjournal.chestpubs.org/content/139/3/640.full.html

References
This article cites 66 articles, 30 of which can be accessed free at:
http://chestjournal.chestpubs.org/content/139/3/640.full.html#ref-list-1

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.chestpubs.org/site/misc/reprints.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.chestpubs.org/site/misc/reprints.xhtml

Citation Alerts
Receive free e-mail alerts when new articles cite this article. To sign up, select the "Services" link to the right of the online article.

Images in PowerPoint format
Figures that appear in *CHEST* articles can be downloaded for teaching purposes in PowerPoint slide format. See any online figure for directions.

AMERICAN COLLEGE OF
CHEST
PHYSICIANS®

Downloaded from chestjournal.chestpubs.org at Swets Information Services Inc on March 6, 2011
© 2011 American College of Chest Physicians