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REVIEW

The role of epigenetic dysregulation in the epidemic of allergic disease

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Abstract The epidemic of allergic disease in early life is one of the clearest indicators that the developing immune system is vulnerable to modern environmental changes. A range of environmental exposures epidemiologically associated with allergic disease have been shown to have effects on the foetal immune function in pregnancy, including microbial burden, dietary changes and environmental pollutants. Preliminary studies now suggest that these early effects on immune development may be mediated epigenetically through a variety of processes that collectively modify gene expression and allergic susceptibility and that these effects are potentially heritable across generations. It is also possible that rising rates of maternal allergy, a recognised direct risk factor for infant allergic disease, may be further amplifying the effects of environmental changes. Whilst effective prevention strategies are the ultimate goal in reversing the allergy epidemic, the specific environmental drivers, target genes, and intracellular pathways and mechanisms of early life immune programming are still unclear. It is hoped that identifying genes that are differentially regulated in association with subsequent allergic disease will assist in identifying causal pathways and upstream contributing environmental factors. In this way, epigenetic paradigms are likely to provide valuable insights into how the early environment can be modified to more favourably drive immune development and reverse the allergic epidemic.

Keywords Epigenetics · Allergic disease · Pregnancy · Cord blood · Allergy prevention · Pregnancy

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Introduction

The immune system is exquisitely sensitive to environmental changes. One of the clearest reflections of this is the recent and dramatic rise in virtually all immune diseases with progressive modern urbanisation. Early development of the immune system is dependent on environmental cues, most notably from the colonising microflora, and that other exposures, such as diet and environmental pollutants, may also influence development in both the antenatal period and soon thereafter. There is emerging evidence that the epigenetic mechanisms that govern gene expression during immune differentiation are susceptible to these environmental influences. Whilst this plasticity in gene expression may confer adaptability to environmental change, the dramatic rise in allergic disease suggests that modern environmental pressures could be adversely affecting these developing pathways. Rising rates of allergic immune disease in infancy also suggest that there may be critical early periods of sensitivity. Effects on the epigenetic regulation of these pathways are now being explored as a mechanism for the long-observed gene–environmental interactions.

Changing prevalence of allergic disease

The rise in allergic disease first became evident in the more industrially developed countries of Australasia, Western Europe and North America where more than 40% of the population may be affected at some stage in their lives (Hopper et al. 1995; Peat et al. 1994). However, the same patterns are now emerging in virtually all regions of the world undergoing industrial development and westernization (Asher et al. 2006). Burgeoning rates of allergic disease in populous developing countries in Asia, Africa and South America (Asher et al. 2006) highlight that this is fast becoming a major global health issue. Even remote island populations in Papua New Guinea are experiencing rising rates of allergy as the western lifestyle encroaches (Herbert et al. 2009). This is also an indication that environmental changes can affect immune function irrespective of genetic background. However, there is some evidence that non-Caucasian races may even be more susceptible to allergic disease (Leung et al. 1994; Sicherer et al. 2010). For example, several studies suggest that Asian populations may be more susceptible to allergic disease when living in 'westernised' environments (Leung et al. 1994; Sicherer et al. 2010). Earlier studies of respiratory disease observed that both allergic symptoms and sensitisation were more common in Asian Australians than non-Asian Australians (Leung et al. 1994). Rates were also higher in Australian-born Asians than Asian immigrants, with the prevalence increasing with length of stay in Australia (Leung et al. 1994). Studies in the USA have similarly noted that non-white races are more susceptible to food allergy, particularly Asian populations (Sicherer et al. 2010), suggesting a genetic propensity that may be amplified in a western environment. This has major implications as the heavily populated regions of Asia are becoming rapidly urbanised, westernised and industrialised.

Another emerging phenomenon is the 'second wave' of allergic disease (Prescott and Allen 2011) now occurring in the most Westernised regions. Whilst the 'first wave' of allergic diseases such as asthma and allergic rhinitis gained momentum over 50 years ago, a 'second wave' of food allergy has emerged only very recently, becoming most evident in the last 10–15 years (Gupta et al. 2007). Over this period, a striking increase in food allergy has been most dramatic in the very same countries that lead the respiratory epidemic, including the UK, Australia and the USA (Gupta et al. 2007; Mullins 2007; Liu et al. 2010a), whereas aeroallergen allergic disease has reached a plateau or even begun to decline (Gupta et al. 2007; Robertson et al. 2004). This increasing burden of food allergy anaphylaxis is most evident in preschool children (Mullins 2007). These temporal difference between different allergic conditions and apparent intergenerational differences in the profile of disease are still puzzling, but could suggest either continuing changes in the environmental pressures over time or other modifying effects between generations (below). At this stage, the specific environmental factors driving this progressive vulnerability to disease have not been clearly defined, but most likely include progressively cleaner environments (Strachan 2000), more pro-inflammatory Western style diets (West et al. 2010), environmental contaminants and pollutants (Baccarelli and Bollati 2009; Ponsonby et al. 2001; Liu et al. 2008), and maternal transmission of antigens during pregnancy or soon thereafter (DesRoches et al. 2010). Most notably, there is now evidence that these environmental exposures can modify early immune gene expression through potentially heritable epigenetic changes (Liu et al. 2008; Schaub et al. 2009; Hollingsworth et al. 2008; Perera et al. 2009; Baccarelli et al. 2009). Although in its infancy in relation to complex diseases, epigenetic research provides a new perspective and likely mediator of the majority of gene–environment interactions.

Developmental origins of allergic disease

Developing systems are especially vulnerable to the effects of adverse environmental exposures. This has led to obvious interest in the early life origins of a wide range of diseases that are linked to environmental change (Barker 1998). Such 'foetal programming' was first described in the context of long-term effects of intrauterine environment on offspring (Koldovsky 1979) and subsequently developed by Barker and colleagues in the early 1990s (Barker and Fall 1993). The 'foetal origins' hypothesis (as it is now known) is supported by a large number of studies in animals and fewer largely epidemiological studies in humans (reviewed in Waterland and Michels 2007). Structure, function and response patterns of many systems are programmed during this period, and early deviations may provide valuable insights into the pathogenesis of disease as well as the pathways of environmental influence. In the context of immune development, there is consistent evidence of differences in the immune function of neonates that go on to develop allergic diseases (Prescott 2003; Prescott and Clifton 2009), also suggesting foetal origins of these common immune disorders. Whilst some of these differences are likely to be conferred, at least in part, by genetic inheritance, this does not explain the significant rise in disease, which is frequently first manifest within only weeks or months of birth. A range of environmental exposure in pregnancy have been shown to modify immune function, including maternal diet (Dunstan et al. 2003), microbial exposure (Schaub et al. 2009; Prescott et al. 2008) and pollutants such as cigarette smoke (Noakes et al. 2003), notably the same culprits identified as potential immune modifiers in epidemiological studies of allergic disease. A

better understanding of these early interactions may also provide opportunities for early intervention and disease prevention.

Epigenetic programmes govern early development

From a single cell, we develop into complex multicellular organisms. This vast cellular diversity is achieved by a tightly regulated, yet imperfect (and plastic), developmental epigenetic programme which contributes to the varied patterns of gene expression both temporally and in a tissue-specific fashion. Achieving the complexity inherent in mammalian development requires the establishment of a 'blank slate' in the very early embryo that can be selectively rewritten ('programmed') as progenitor cells give rise to heterogeneous daughter cells as part of various developmental cascades, producing different cell types and, ultimately, tissues within an individual. To achieve this, genome-wide DNA demethylation occurs twice during mammalian development (Monk et al. 1987): firstly during the generation of germ cells in both males and females and secondly following fertilization prior to blastogenesis. During this time, gene-specific methylation marks of both the maternal and paternal genomes are extensively erased before lineage-specific marks are reestablished (Okada et al. 2010).

The epigenetic programme involves multiple 'layers' of regulation. Primary and secondary epigenetic marks include covalent changes to DNA (methylation and hydroxymethylation of cytosine within CpG dinucleotides) and DNA-associated packaging proteins (histone methylation, acetylation, ubiquitination, phosphorylation). These marks in turn attract macromolecular complexes that together determine the higher order structure and function of a genomic region, whether at the level of a gene promoter, whole chromosome, or the entire genome. Higher order epigenetic state encompasses the degree of DNA compaction, replication timing and spatial positioning within the cell nucleus (Klose and Bird 2006). The result is the highly coordinated control of genomic activities such as gene expression, DNA replication and cell division.

These mechanisms are all potentially subject to modification in response to environmental changes, and this may provide an adaptive advantage in some settings, allowing changes in gene expression that may be more beneficial under altered environmental conditions (Symonds et al. 2009). Moreover, these epigenetic modifications are potentially heritable, conferring the same advantages to the offspring. In this way, the epigenetic code provides plasticity of gene expression in response to environmental changes, allowing more rapid (yet potentially reversible) phenotypic adaptations across generations than those associated with Darwinian selection. Equally so, maladaptive changes as a result of potentially adverse environmental exposures may also be transmitted to future generations, increasing the risk of disease, as demonstrated in animal models of allergic disease (Hollingsworth et al. 2008).

Epigenetic regulation of immune development

The cellular differentiation that leads to immune system development is also under clear epigenetic control. Best characterised for T cells, differentiation into T helper 1 (Th1), Th2, Th17 and regulatory T cells (Treg) is governed by underlying changes in DNA/histone methylation and/or histone acetylation (as recently reviewed by Janson et al. 2009). In uncommitted naive $CD4^+$ T cells, key cytokine promoter regions are methylated and transcriptionally repressed. Patterns of subsequent demethylation associated with gene activation depend on the direction of lineage commitment. When these cells progress into Th-1 lineage commitment, they undergo progressive demethylation of the interferon γ (*IFN*γ) gene promoter, with associated increased transcriptional activity and production of IFNγ, the defining signature of this lineage (White et al. 2002, 2006; Winders et al. 2004; Yano et al. 2003). Conversely, commitment to the Th2 lineage (the predominant lineage at birth) is associated with demethylation of Th2-associated genes such as *IL-4* (Janson et al. 2009), with concomitant silencing (DNA methylation) of *IFN*γ (Janson et al. 2009; Zhu et al. 2003; Sanders 2006). Chromatin remodelling at the Th2 cytokine locus (*IL4/IL5/IL13/RAD50*) is also essential for Th2 lineage commitment (Yamashita et al. 2004). The mechanics of this process are not fully understood, but involve changes in permissive histone modifications following T cell receptor signalling. These modifications are orchestrated by site-specific enzymes including histone acetyltransferases (HATs) and histone deacetylases (HDACs). Removal of acetyl groups by HDACs is generally associated with gene silencing, whereas acetylation by HATs is associated with a more open chromatin structure and enhanced gene transcription. GATA-3 transcription factor appears essential to initiate the cascade of epigenetic modifications that stabilize Th2 gene expression signature and lineage commitment (Yamashita et al. 2004). Commitment to the more recently identified pro-inflammatory Th17 lineage is also regulated through changes in histone acetylation (Janson et al. 2009). Although the developmental role of this lineage is not clear, there are significant correlations between Th17 and Th2 function in early life (Schaub et al. 2008a), and it appears likely that epigenetic processes similar to those involved in Th1/Th2 commitment also control Th17 cell fate determination (Akimzhanov et al. 2007). Finally,

specific epigenetic signatures (DNA hypomethylation) are associated with FOXP3 expression, a defining signature of the Treg lineage (Janson et al. 2008; Polansky et al. 2008). It has been shown that selective demethylation of the evolutionarily conserved Treg-specific demethylated region within the FOXP3 locus determines the expression of this gene, which is critical for the establishment of a stable Treg lineage (Polansky et al. 2008). Furthermore, the level of FOXP3 demethylation is associated with more efficient functional activities (suppressive capacity) of Tregs (Liu et al. 2010b). Less is known about the epigenetic determinants of other immune cell types, although specific epigenetic marks are likely to play a key role in a broad range of immune-related processes (Yang et al. 2008). Similarly, there is still little understanding of the epigenetic events that predispose to the tissue-specific manifestation of allergic disease, i.e. in the skin, airways and other mucosal surfaces. There is evidence that some antenatal exposures (such as maternal smoking) affect airway development in the foetus (Gilliland et al. 2000; Hylkema and Blacquiere 2009), but the exact mechanisms are not clear. The dose, timing and reversibility of any potential adverse exposure are also important factors that still need further investigation.

The well-defined profile of epigenetic modifications associated with Th lineage commitment, coupled with the sensitivity of the early developmental period, has led to speculation that factors that disrupt these pathways may increase the risk of allergic disease (Vuillermin et al. 2009). Specifically, effects on DNA methylation and endogenous HDAC that selectively inhibit certain pathways (Th1 and T regulatory cell differentiation) may favour Th2-associated allergic differentiation (Bousquet et al. 2004; Miller and Ho 2008).

Developmental differences in gene expression in allergic disease

Complex immunological mechanisms have evolved to allow the foetal and maternal immune systems to coexist during pregnancy. $FOXP3^+$ Tregs are attracted to the materno-foetal interface by human chorionic gonadotrophin (Schumacher et al. 2009), and the maternal cellular immune system adapts subtly to a 'Th2 state' in order to downregulate Th1 IFNγ cell-mediated immune responses to foetal antigens (Breckler et al. 2008; Wegmann et al. 1993). Neonatal immune responses reflect these maternal events, with reduced Th1 function and relative dominance of Th2 activity, with underlying epigenetic changes driving these patterns of gene expression (Zaghouani et al. 2009). This reduced IFNγ expression in neonatal $CD4^+$ T cells (relative to adults) is associated with silencing (hypermethylation) of the IFNγ promoter (White et al. 2002). In the postnatal period, there is suppression of the Th2 dominance with progressive Th1 maturation (Prescott et al. 1999), and this $CD4^+$ maturation is accompanied by progressive demethylation within the IFNγ promoter and upregulated IFNγ transcriptional activity (White et al. 2006).

Allergic disease is associated with significant differences in this pattern of immune development: firstly, in the neonatal T cell function and, secondly, in the postnatal maturation patterns. As noted above, in the neonatal period, there is consistent evidence of *presymptomatic* differences in newborns that later develop allergic disease. Of these, immaturity of Th1 function has been the most consistent observation (reviewed in Prescott 2003). However, there is now preliminary evidence of attenuated Treg function (Smith et al. 2008; Schaub et al. 2008b) and excessive innate inflammatory responses (Tulic et al. 2011) compared with infants that remain non-allergic. These abnormalities appear to culminate in an increased propensity for uncontrolled Th2 immune responses in the postnatal period, which is associated with attenuated Th1 maturation in early childhood (Tulic et al. 2011).

Because differences in immune function are evident at birth in newborns that develop allergic disease, there is intense interest in the prenatal factors that may be alternatively programming neonatal immunity, particularly exposures that can disrupt normal gene activation or silencing associated with balanced neonatal immune responses (Martino and Prescott 2010, 2011).

Preliminary evidence of epigenetic modifiers in allergic disease

New findings suggest that a number of environmental exposures can induce stable epigenetic changes in gene expression, which can be passed to offspring and subsequent generations (Schaub et al. 2009; Hollingsworth et al. 2008; Vuillermin et al. 2009; Breton et al. 2009; Bobetsis et al. 2007). Many of these factors (Fig. 1) have previously recognised effects, both on foetal immune function (Dunstan et al. 2003; Noakes et al. 2003; Blumer et al. 2005, 2007) and epidemiologic links with the allergy epidemic, including microbial burden (Strachan 2000; Braun-Fahrlander et al. 2002), dietary changes (West et al. 2010) and environmental pollutants (Ponsonby et al. 2001; Nowak et al. 1996). Emerging epigenetic paradigms provide a new mechanism for the observed effects on gene expression (Schaub et al. 2009; Hollingsworth et al. 2008; Vuillermin et al. 2009; Breton et al. 2009; Bobetsis et al. 2007).

Microbial exposure in pregnancy

As one of the leading candidates in the allergy epidemic, there has been a long-standing interest in the role of

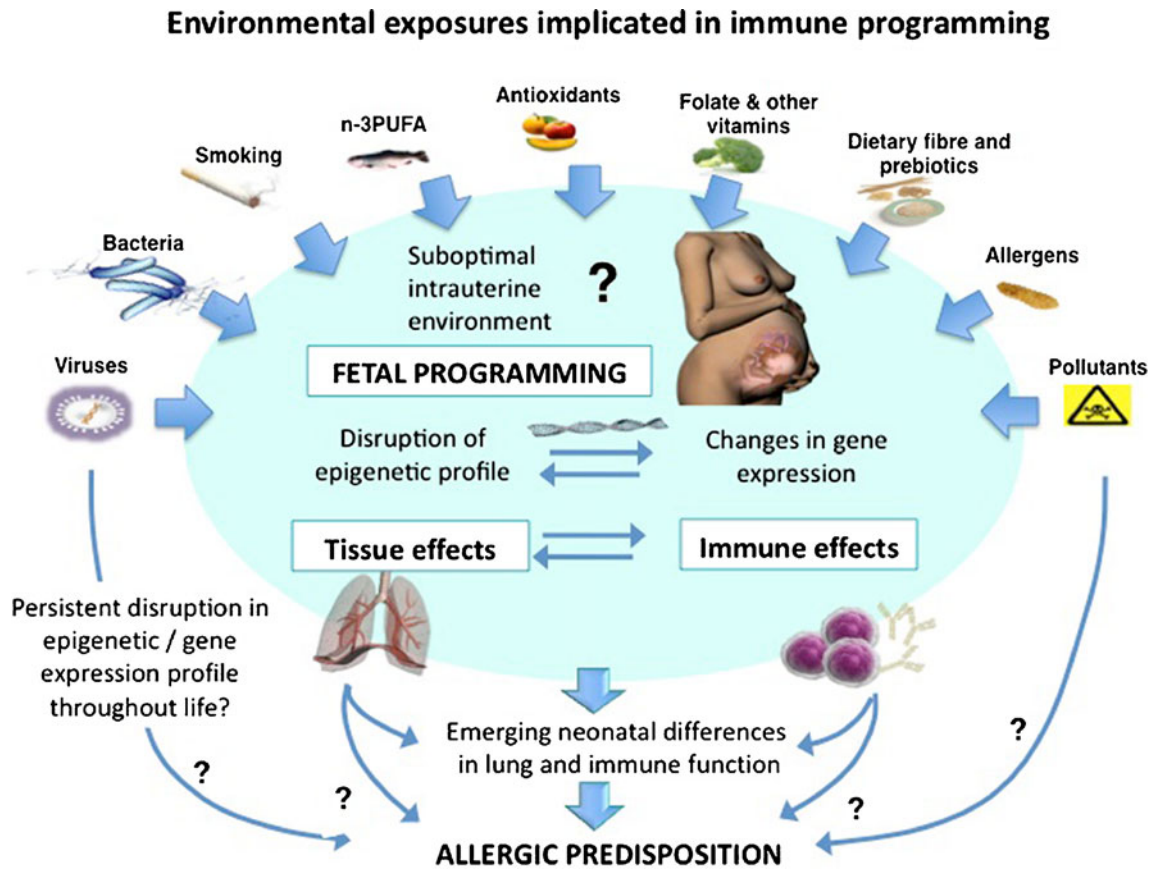

Fig. 1 Environmental influences on early immune programming: an epigenetic perspective. This illustrates the environmental factors that have been implicated as potential immune modifiers during early development in the prenatal and/or postnatal periods

microbial exposure in early life. There is now compelling evidence that several pathogens can disrupt host cell epigenetic profile (Bobetsis et al. 2007; Gutierrez et al. 2004; Kitajima et al. 2008), influencing or mimicking mechanisms involved in DNA methylation (Tao and Robertson 2003; Graessmann and Graessmann 1988; Kruger et al. 1989) and histone modification (Arbibe et al. 2007). Although most of the focus has been on postnatal microbial effects, there is emerging evidence of intrauterine effects. Human studies also show that allergy protection by in utero microbial exposure in rural farming environments is associated with enhanced neonatal Treg function, *FOXP3* expression and associated epigenetic effects (hypomethylation) of the *FOXP3* gene (Schaub et al. 2009). Non-pathogenic microbial strains (*Acinetobacter lwoffii*) have been isolated from these environments and their effects examined further in animal models. When administered to pregnant rodents, these bacteria also have allergy-protective effects in the offspring, an effect which is dependent on the increased expression of IFNγ (Renz, 2010, personal communication). Furthermore, this effect is epigenetically mediated by an increase in H4 acetylation of the *IFNγ* promoter and abolished by the inhibition of histone acetylation following Garcinol treatment. These observations have provided new dimensions to the 'hygiene hypothesis' and suggest that declining microbial exposures may be contributing to allergic predisposition by epigenetically modifying the patterns of immune gene expression during critical periods of early development (Vuillermin et al. 2009).

Maternal diet in pregnancy

Diet and nutrition in pregnancy have been central to the cross-discipline notions of the 'developmental origins' of many diseases (Waterland and Michels 2007). In the context of allergic disease, modern dietary changes appear to be providing less tolerogenic conditions during early immune programming (reviewed in West et al. 2010). A range of specific nutritional changes have been implicated in the rising allergic propensity, including the decline in omega 3 polyunsaturated fatty acids (n-3PUFA) (Dunstan et al. 2003), soluble fibre (Maslowski et al. 2009), antioxidants and other vitamins (Devereux et al. 2007), based on epidemiological associations and recognised immunological effects. Variations in nutrient factors such as PUFA have recognised immunological effects which are mediated by

changes in eicosanoid derivates and other metabolic products (resolvins; Calder 2009), oxidative cell membrane fluidity, surface marker expression (Calder et al. 2002) and cell signal transduction (Prescott et al. 2007). We have shown that maternal supplementation with fish oil (*n*-3 PUFA) is associated with effects on immune function (Dunstan et al. 2003) and T cell signalling (Prescott et al. 2007). However, at this stage, it is not clear how/whether this is related to epigenetic modifications. Similarly, antioxidants have been shown to have effects on T cell regulation (Tan et al. 2005) and induction of IL-12 production by antigen-presenting cells (Utsugi et al. 2003). Theoretically, this could favour development of Th1 and inhibit Th2 responses. There are only limited data on the immunomodulatory role of maternal dietary antioxidants during pregnancy (Devereux et al. 2002), but evidence that oxidative stressors can induce epigenetic changes in disease risk (below) indirectly highlights a role for these pathways (Breton et al. 2009).

The first direct evidence that maternal dietary changes in pregnancy can alter immune function and allergic outcomes through epigenetic changes came from an animal model of folate supplementation (Hollingsworth et al. 2008). This model was based on the capacity of folate supplementation to epigenetically modify gene expression through its role as a dietary methyl donor for DNA (Ulrey et al. 2005). Folate and other one-carbon transfer agents (choline and methionine) function as essential methyl donors in all cells. Available evidence from both animal and human studies suggests that the effects of folate deficiency on DNA methylation are very complex, being cell type- and target organ-dependent, and are gene- and site-specific (Kim 2004; Jhaveri et al. 2001). Multiple lines of evidence suggest a link between disruption in the folate/one-carbon metabolism, changes in DNA methylation, altered gene expression and disease predisposition. Animal studies have shown that prenatal feeding of a methyl supplemented diet can increase DNA methylation and decrease expression of genes in offspring (Cooney et al. 2002; Cropley et al. 2006; Waterland and Jirtle 2004; Wolff et al. 1998), whilst limiting folate supply in humans results in increasing levels of homocysteine and reduced DNA methylation (Jacob et al. 1998). A high folate diet in pregnant mice resulted in altered gene methylation patterns and decreased transcriptional activity in the lung tissue of the progeny with increased airways hyper reactivity, airway eosinophilia and production of inflammatory chemokines (Hollingsworth et al. 2008). These effects were associated with increased methylation (silencing) of the runt-related transcription factor 3 (*Runx3*), which has been separately shown to protect against airway disease through the induction of $FOXP3^{+}$ Tregs (Klunker et al. 2009). Notably, the effects were also heritably transmitted to subsequent generation (Hollingsworth et al. 2008). The significance of this in humans is not clear, although there have been several epidemiological studies to correlate folic acid supplementation during pregnancy with increased risk of asthma and respiratory disease in the infants (Håberg et al. 2009; Whitrow et al. 2009). However, until this is understood more fully, it is premature to change the current recommendations aimed at preventing neural tube defects. The effects of diet are potentially complex, and more studies are also needed to examine the effects of related dietary nutrients, such as vitamins B2, B6, B12, methionine and choline, which may also be implicated in epigenetic effects through the effects on folate-mediated one-carbon metabolism. These and other dietary influences remain an important avenue of research, with the potential to provide simple noninvasive strategies to reduce the risk of disease.

Exposure to tobacco smoke and air pollutants

Cigarette smoke and inhaled pollutants have recognised adverse effects in pregnancy, including effects on foetal lung growth (Gilliland et al. 2000) and immune development (Noakes et al. 2003). New studies now provide preliminary evidence of epigenetic effects in pregnancy (Breton et al. 2009). Maternal smoking in pregnancy is associated with early-onset wheezing and reduced lung function in the offspring (Magnusson et al. 2005; Bisgaard et al. 2009). The effects of smoking on health can also be passed to grandchildren, as evidenced from studies where grandmothers but not mothers have smoked (Li et al. 2005). Furthermore, children exposed to maternal tobacco smoke in utero may develop aberrant DNA methylation on a global and gene-specific scale (Breton et al. 2009). Limited data also suggest that exposures to the ultrafine particulate matter found in pollution may also change DNA methylation in maternal and foetal DNA, possibly associated with altered inflammatory response pathways (Belinsky et al. 2002a, b). High levels of maternal exposure to traffic exhaust particles have been associated with increased methylation of the acyl-CoA synthetase long-chain family member 3 (ACSL3) and with the development of asthma symptoms in children (Perera et al. 2009). New studies in mice also show that exposure to diesel exhaust particles augments the production of IgE after allergen sensitization through the hypermethylation of *IFNG* and hypomethylation of the *IL4* locus (Liu et al. 2008). It is also likely that effects of these pollutants are mediated, at least in part, by recognised epigenetic effects of oxidative stress on NF-κB activation, which can induce histone modifications and chromatin remodelling of pro-inflammatory genes other signal transduction pathways. As a potent source of oxidative stress, cigarette smoke reduces HDAC activity with NF-κB-induced expression of pro-inflammatory cytokines in peripheral lung tissue (reviewed in Rahman et al. 2004). In placental tissue, nicotine has also been

shown to alter cytokine production via NFκB (Dowling et al. 2007). Changes in the cytokine milieu at the materno-foetal interface could have further implications for foetal immune programming and disease susceptibility (as further discussed below). Although there is much to be clarified in this field, there is no doubt that exposure to toxic exposures such as cigarette smoke is harmful and should be avoided.

Other modern pollutants with possible epigenetic effects

Less is known about other modern products of industry and agriculture that contaminate modern homes, food, clothing and water sources. These include polychlorinated biphenyl compounds (PCBs), organochlorine pesticides, dioxins and phthalates, which are highly lipid-soluble and accumulate in human tissue with age. Some of these products have been readily measured in breast milk, cord blood and placental tissue, highlighting the potential to influence early development (Noakes et al. 2006). Many are described as recognised 'hormonal imposters' because of their potentially pro-Th2 'oestrogenic' activity. These have recognised immunosuppressive effects and may favour IgE allergic responses (Narita et al. 2007) and sensitisation (Fukuyama et al. 2010). Prenatal exposure to pesticides has been associated with increased cord blood IgE levels (Reichrtova et al. 1999) and with increased risk of childhood asthma (Sunyer et al. 2005). Exposure to heavy metals in this period has also been correlated with changes in genomic DNA methylation in cord blood (Pilsner et al. 2009). In contaminated regions, PCB exposure has also been linked with higher IgE levels in early childhood (Grandjean et al. 2010). Of relevance here is that these and other contaminants have now been associated with epigenetic effects (reviewed by Baccarelli and Bollati 2009), including effects on global DNA methylation patterns at the low-dose exposure found in the ambient environment (Kim et al. 2010). In many regions, strategies are being developed to reduce levels of environmental contamination, with an associated decline in the levels measurable in human adipose tissue since the 1970s (Noakes et al. 2006). Although allergic disease has continued to rise in this period, this does not exclude a role of these factors, particularly as epigenetic effects may persist for several generations. These 'modern' exposures are an important consideration in the rise of 'modern' diseases, although this will remain difficult to investigate as only correlative studies are possible in humans.

Maternal allergy as an additional immune modifier

Maternal allergy is a strong determinant of allergic risk and has a stronger influence than paternal allergy. This, together with significant effects on neonatal immune function, suggests direct materno-foetal interactions or other maternally imprinted effects. It is possible that the rise in maternal allergy may also be amplifying the effect of environmental changes. This could be an additional factor influencing the observed changes in the age of onset, phenotype and severity of disease seen in the most recent generations (Prescott and Allen 2011).

Allergic women appear to have modified immune interactions with their foetus in pregnancy, with reduced Th1 IFNγ responses to foetal antigens compared with non-allergic women (Prescott et al. 2010). Differences in the cytokine milieu at the materno-foetal interface could therefore be implicated in the attenuated neonatal Th1 responses observed commonly in infants of atopic mothers (Rinas et al. 1993). This suggests that the endogenous effects of the maternal allergic phenotype may compound the increasingly pro-allergic exogenous environment. Perhaps more significantly, epigenetic changes induced by environmental changes can be inherited across generations, as seen in animal models of allergic disease (Hollingsworth et al. 2008). It is possible that the increase in allergic disease could reflect the epigenetic effects of environmental changes in preceding generations, inducing heritable changes in gene expression patterns that confer increased disease risk. This phenomenon could add to the difficulties in identifying causal pathways as relationships between exposures and phenotype within a generation may not reflect any temporal distortions of transgenerational effects.

Conclusion

The dramatic and recent rise in allergic diseases and the very early onset of disease suggest that in utero events have a more critical influence on immune development and allergic propensity than genomic inheritance. This is supported by growing evidence that antenatal exposures (such as maternal diet, microbial exposure and smoking) can modify neonatal immune function and the risk of subsequent disease. Now, new evidence that environmental exposures may be altering disease predisposition through epigenetic effects on foetal gene expression provide novel insights into the mechanisms and causal pathways. Most importantly, as epigenetic modifications are generally reversible, this may lead to the development of novel therapeutic interventions that may be effective in the ultimate goal of arresting, or even reversing, the allergy epidemic.

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Conflict of interest None.

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