

Chapter 2

Developmental Epigenomics and Metabolic Disease

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Abstract Organisms have evolved the processes of developmental plasticity to adjust their developmental trajectory in response to early life exposure to environmental cues. The potentially adaptive nature of such anticipatory responses is aimed at promoting Darwinian fitness; however, a mismatch between the induced phenotype and the later life environment increases the risk of disease, as evolutionary processes act to maximize reproductive success and not to maintain health and longevity. We focus on the developmental origins of later life metabolic disease in humans particularly with respect to early life under- and overnutrition and review the experimental, epidemiological, and clinical evidence implicating epigenetic mechanisms in the modulation of disease risk. There is growing evidence that epigenetic marks—and hence possibly disease risk—may be transgenerationally transmitted via non-genomic pathways of inheritance. This has implications both for the perpetuation of disease risk across generations and for the potential impact on evolution should epigenetic marks become genomically fixed. We also discuss the potential of developmental epigenomics in identifying prognostic biomarkers and therapeutic targets and raise several technical and methodological caveats to be borne in mind when undertaking and interpreting epigenomic research.

Keywords Childhood abuse • Development • Developmental origins of health and disease • Developmental plasticity • Diabetes • Environmental toxins • Epigenetics •

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Epigenomics • Evolution • Fitness • Health • Intervention • Maternal care • Maternal nutrition • Metabolic disease • Mismatch • Obesity • Overnutrition • Phenotypic inertia • Predictive adaptive response • Stress • Trade-off • Undernutrition

Abbreviations

DOHaD	Developmental origins of health and disease
HPA	Hypothalamic-pituitary-adrenal
IAR	Immediate adaptive response
PAR	Predictive adaptive response

2.1 Introduction

Gene-environment interactions have traditionally been used to explain phenotypic variation in humans, such as differential susceptibility to disease. However, such a dichotomous perspective is increasingly becoming outmoded in light of the accumulating data pointing to the role of early life development in disease causation. In this chapter we discuss how the processes of developmental plasticity—whereby phenotypic development is influenced by developmental experiences—affect an individual's interaction with its environment at maturity and, in turn, its risk of metabolic disease. Developmental plasticity is now well recognized as being underpinned by epigenetic mechanisms, which are phylogenetically old processes that regulate gene expression in response to environmental cues through covalent modification of DNA and its associated molecules. We also discuss how the emerging field of developmental epigenomics may be exploited to identify prognostic biomarkers and indicate targets for therapy and the attendant methodological pitfalls of which to be mindful.

2.2 Developmental Plasticity

Far from passively adhering to a rigid genetic blueprint during early development, the developing organism is receptive to external cues and responds by adjusting its phenotypic development, thus resulting in several different possible phenotypes arising from a single genotype. It achieves this via the processes of developmental plasticity, which are ecologically prevalent and seen across many taxa (Bateson et al. 2004). Examples include the female honeybee which develops into either a queen or a worker according to how the early larva is fed; the water flea which

forms a defensive helmet and tail spike when its mother is exposed to chemicals released by predators, allowing it to cope with a potentially dangerous postnatal environment; the larval desert locust which receives parental chemical signals that act as a proxy for population density and in response develops into either a nocturnal, solitary morph or a diurnal, gregarious morph; and the spade-foot tadpole which undergoes earlier metamorphosis from tadpole to terrestrial form to promote immediate survival when habitat desiccation is imminent. In this review we shall focus on the potential role of the processes of developmental plasticity in humans and consider how these may contribute to the risk of metabolic disease in later life.

Developmental plasticity clearly plays an essential role in coping with changing environments on a time-scale intermediate between coping via homeostasis and responding through phenotype selection. It has evolved to enable an organism to modulate its phenotypic development and life course in potentially adaptive ways (Bateson et al. 2004; Bateson and Gluckman 2011), that is, increasing Darwinian fitness to allow gene flow to the next generation. With respect to cues such as nutritional state, it is likely that there is some level of phenotypic inertia in the formation of responses to environmental cues: taking into account a range of environmental conditions over a longer time scale may enable a more accurate picture of the future environment to be obtained (Kuzawa and Thayer 2011).

The potential reaction norm of induced phenotypes provided by developmental plasticity is presumably limited by the range of environmental exposures previously experienced by the lineage. A further constraint emerges from the likely developmental and energetic costs involved in maintaining the capacity for plasticity. Hence, these processes tend to be limited to windows during early development (Bateson and Gluckman 2011). The mechanisms underlying developmental plasticity include changes in epigenetic marks that modulate the expression of specific genes under specific contexts (Waterland and Jirtle 2003; Gluckman et al. 2011). There are also emerging hints that epigenetic changes may be transgenerationally transmitted through non-genomic mechanisms of inheritance (Low et al. 2011).

2.2.1 Environmental Interactions During Development

Developmental plasticity is one of several responses that organisms employ during development in response to environmental exposures. The type of response elicited is dependent on where on the spectrum of severity and evolutionary novelty the environmental exposures lie. Extreme environmental challenges that overwhelm the adaptive capacity, or which are entirely novel and thus are not countered by evolved defenses, can result in irreversible disruption of the normal developmental program. Limb malformation in children whose mothers were treated with thalidomide during pregnancy is an example of such a teratogenic response. Challenges that are less severe, and particularly those that occur within the normative

ecological context, generally induce a potentially adaptive plastic response (Gluckman et al. 2009).

The phase within the life course when the phenotypic consequences of these responses become apparent allows an additional level of classification into immediate adaptive responses (IARs) or predictive adaptive responses (PARs), although there is no sharp delineation between the two and both can be induced by the same cue (Gluckman et al. 2005b). IARs are made when survival is immediately threatened and a prompt response is needed, but this is usually followed by longer-term trade-offs. For example, the fetus challenged by placental dysfunction may be born prematurely and growth retarded so as to improve its immediate chances of survival, but this incurs an unavoidable trade-off of greater morbidity and mortality postnatally (Gluckman et al. 2005b).

Cues of a more subtle nature may evoke PARs which do not lead to an overt phenotype at birth, but nevertheless bestow potentially adaptive advantages later in life. However, what has often been misunderstood is that these responses are most likely to be fitness enhancing in childhood through to the early reproductive years (Godfrey et al. 2010), as human fitness is largely determined by childhood and adolescent survival (Jones 2009). There may be a loss of potential advantage under some circumstances from the induction of such responses in mismatched environments later in life, but this is inconsequential in evolutionary terms. By adapting the phenotype better to the predicted ecological (e.g., nutrition and stress) environment in childhood and adolescence, fitness is likely to be enhanced. Such a model is supported by the observation that puberty is accelerated in girls of lower birth size (Sloboda et al. 2007).

Anticipatory responses are a widespread phenomenon, and the PAR model is supported by much experimental and clinical evidence. The coat characteristics of the meadow vole are particularly illustrative—using day length cues as transduced by maternal melatonin, voles are born with a thin coat during spring in anticipation of a hot summer or a thick coat in autumn which only confers an advantage later in the winter season (Lee and Zucker 1988). The ability to use prenatal cues to predict the extremes of temperatures encountered in adulthood therefore promotes survival and reproduction. Fetally undernourished rats fed a normal postnatal diet become obese, hypertensive, and insulin and leptin resistant and develop behavioral modifications reflected in increased food consumption and decreased physical activity (Vickers et al. 2000). This set of features comprises an integrated phenotype that had been tailored to cope with the nutritional scarcity anticipated to prevail postnatally. A high-fat diet amplifies these features, but administration of the adipokine leptin to neonatal rats can prevent development of all aspects of metabolic dysfunction (Vickers et al. 2005). In humans, retrospective analysis of a cohort of adults who were gravely undernourished in childhood showed that those who were smaller at birth developed marasmus, a more benign form of malnutrition, compared to those larger at birth who developed kwashiorkor, a form with a poorer survival prognosis (Forrester et al. 2012). They also had persistent changes in metabolic physiology. This suggests that potential marasmics were able to make

PARs enabling the development of a metabolic physiology that is more compatible with a low-nutrient environment.

2.2.2 The Role of Epigenetics in Developmental Plasticity

A rapidly accumulating body of literature indicates that epigenetically mediated modulation of the expression of specific genes and pathways plays a crucial role in the processes of developmental plasticity. This understanding has been considerably aided by next-generation technological advances in sequencing analysis over the past few years (Ku et al. 2011). Epigenetic mechanisms affecting gene dosage underpin several developmental processes including cell differentiation, genomic imprinting, and X-chromosome inactivation in female mammals. It would appear that the same biological processes have been co-opted for a range of core functions. While these other uses of epigenetic processes are generally stable, developmental plasticity involves contingent changes in gene regulation that may be transient or persist across the life course.

The honeybee referred to above provides a good example of how epigenetic processes mediate developmental plasticity. Although early life nutrition in terms of duration of access to royal jelly normally determines whether larvae become queens or workers, experimentally induced silencing of *Dnmt3*, which encodes the DNA methyltransferase enzyme responsible for establishing new methylation marks, causes most larvae to develop into queens with the characteristic enlarged ovaries (Kucharski et al. 2008).

2.2.3 Epigenetics and Evolution

Epigenetic processes, such as DNA methylation and small RNA activity, are thought to have evolved as defense mechanisms to protect the genome against transposable elements—potentially mutagenic mobile DNA segments that move from one location of the genome to another (Slotkin and Martienssen 2007). Epigenetic silencing may have evolved to counter viral infections or to silence the second genome during cell fusion in bacteria. Alternatively, DNA methylation may also have enabled gene dosage rebalance after gene duplication (Chang and Liao 2012). Others have suggested that the epigenetic function of changes in histone structure may have arisen as an incidental outcome from their primary role as regulators of gene expression (Felsenfeld and Groudine 2003). Mattick has also proposed that noncoding RNAs may have evolved as a means of regulating the complex processes of plasticity underpinning cognition and brain function, perhaps in part through their ability to be differentially edited depending on the context (Mattick 2011).

2.2.3.1 Potential Role of Epigenetic Change in Evolutionary Processes

Could epigenetic processes play a role in guiding genetic evolution? West-Eberhard (2003) has suggested that changes in phenotype induced by the environment can lead to adaptive evolution and the origin of evolutionary novelties. Thus, rather than being the originator of evolutionary change, genes may instead serve as “followers” in maintaining developmentally induced phenotypic changes. Indeed, a growing body of evidence points towards the transgenerational transmission of developmentally induced, epigenetically regulated phenotypes (Gluckman et al. 2007a), but the discussion to date on whether heritable induced phenotypes could drive evolutionary change has been limited by insufficient empirical evidence for a mechanism.

A key question is whether changes in epigenetic marks prompted by early life exposures could become incorporated into the genome. Theoretically, this may be achieved through several routes. Firstly, recurrence of the inducing cues over multiple generations may stabilize the phenotype until genomic fixation occurs via genetic accommodation, the processes of which are still poorly defined. Secondly, the propensity of methylated or hydroxymethylated cytosine to spontaneously hypermutate into thymine or uracil, respectively (Pfeifer 2006), causing nonrandom changes to the DNA sequence, may generate a range of phenotypes that undergo natural selection and become genomically fixed. Finally, increasing data from animal studies examining male germline inheritance have suggested that epigenetic marks may pass meiosis by way of microRNAs (Wagner et al. 2008) or of methylation and/or histone marks in sperm (Ng et al. 2010; Morgan and Bale 2011). This supports the plausibility of selection acting on the phenotype induced by a particular epigenetic mark; phenotypes that enhance fitness could conceivably then become genomically fixed and drive evolutionary change.

2.3 Developmental Plasticity, Health, and Disease

2.3.1 *Developmental and Evolutionary Pathways to Disease*

We proposed that PARs act to confer longer-term adaptive advantages that enhance an organism’s fitness (Gluckman et al. 2005a). However, the efficacy of this strategy is dependent on the accuracy of early life cues received. If the cues are not faithfully transmitted or are not reflective of the actual environment, the fetus will consequently make erroneous predictions and adopt a developmental trajectory that is unsuited to its mature environment, thereby elevating risk of disease in later life. This scenario is known as a developmental mismatch (Gluckman and Hanson 2006). For example, if the fetus receives inadequate nutrition, whether due to placental dysfunction, poor maternal diet, or maternal constraint (maternally imposed physiological limitations on fetal growth to reduce the risk of obstructed

labor), an energy-poor environment is predicted, and an energy-conserving metabolic physiology is developed—even though the environment may be nutritionally abundant in reality. It then becomes mismatched to a postnatal obesogenic environment, potentially leading to metabolic disease. The conditions under which predictive responses are evolutionarily protected have been defined—selective advantage is possible even if the prediction is not always accurate (Jablonka et al. 1995).

The consequences of mismatch need not be symmetrical: there is a greater fitness disadvantage for a human in predicting a nutritionally rich environment and being born into a nutritionally poor environment than vice versa. Both survival and fertility are more likely to be compromised in the former, and the Paleolithic human was most likely to be exposed to less nutritionally rich environments. The presence of maternal constraint further biases the prediction. The key issue is when in the life course the disadvantage appears. In general the impact of a nutritionally rich environment does not affect health until after peak fertility, at least in females. As evolution is driven by fitness, and not by health or longevity per se, such late-onset disadvantage is generally of no evolutionary consequence.

Evidence of developmental mismatch in humans abounds and will be discussed in detail below. Migrants or refugees who were born in conditions of poor nutrition and have moved to countries with a more energy-dense, fat- and sugar-laden diet are at greater risk of diabetes and cardiovascular disease (Jeemon et al. 2009). Similar health problems are also increasingly seen in countries undergoing rapid economic growth and hence nutritional transition to a diet more comparable in composition and quantity to the “Western” diet, such as in India and China.

Two points should be noted regarding the nature of mismatch. Firstly, not every individual who is mismatched to their environment will inexorably develop disease. Other factors such as the individual’s specific developmental history, later life environment, and their genome may also play a role. Mismatch simply increases the risk of developing disease in later life. Secondly, because developmental plasticity operates under normal as well as under adverse conditions (Gluckman et al. 2011), the induction of variable risk in a mismatched environment is not limited to extreme scenarios. For instance, risk of death from heart disease is higher among those of low birth weight, but the effect is graded across the normal range of birth weights, indicating that plastic responses are occurring even in uneventful pregnancies (Godfrey 2006). Similar graded effects have also been observed for risk of diabetes, obesity, and hypertension. Since no obvious impact is seen in the fetus or mother, and such effects can be induced by normal physiological cues (i.e., maternal nutritional status throughout the offspring’s early development), “normal” birth weight may well be obscuring subtle developmental effects that nonetheless increase risk of later life disease. It is important to note that the “normal” range in terms of nutrition may include over- as well as undernutrition, either of which can be viewed as unbalanced nutrition leading to potential mismatch in the offspring.

2.3.2 Developmental Origins of Health and Disease

The involvement of a developmental component in determining disease risk in later life—a phenomenon dubbed the Developmental Origins of Health and Disease (DOHaD)—is a relatively new field of research. While there was a series of earlier clinical and experimental papers (reviewed in Gluckman et al. (2010)), it only received more focused attention after the publication of several highly influential papers from David Barker's group. They showed that reduced fetal growth, as measured by low birth weight, was associated with greater risk of cardiovascular-related mortality in later life (Barker et al. 1989). These findings proved provocative as they challenged preconceived assumptions that adverse cues experienced during gestation would only become manifest during the immediate postnatal period and not produce effects after a lag of several decades. However, further research has since verified this phenomenon by demonstrating similar associations for other metabolic disorders including insulin resistance, obesity, hypertension, diabetes, and osteoporosis (Godfrey 2006) coupled with a plethora of studies in a number of animal species. Today there is an increasing appreciation of the importance of DOHaD research in understanding contemporary human morbidity and mortality.

2.3.3 Developmental Origins of Obesity and Related Metabolic Diseases

An extensive body of experimental studies in animals involving maternal dietary and behavioral or hormonal manipulation from pregnancy to weaning has revealed how offspring can be “primed” to develop characteristics akin to that of human cardiometabolic disease in later life. Two widely used rat models involve subjecting pregnant dams to a hypocaloric or protein-restricted diet during pregnancy and/or lactation (Vickers et al. 2000; Lillycrop et al. 2009). Offspring later develop obesity, hypertension, impairments in glucose homeostasis and lipid metabolism, and dietary fat preference. These effects are exacerbated when offspring are fed a high-fat postnatal diet, which simulates a situation of greater mismatch. Recent work in rodents has suggested that such developmental induction can also be effected by paternal factors (Carone et al. 2010; Ng et al. 2010; Morgan and Bale 2011).

In humans, the prolonged study periods required for longitudinal analysis have limited experimental and clinical studies. Therefore, retrospective analysis of so-called natural experiments, such as famines and pandemics which have exposed population groups to a putative inducer of developmental programming, has yielded the most useful data (Vaiserman 2011). A cohort of Dutch individuals whose mothers were subjected to an acute period of famine during pregnancy as a result of Nazi-imposed food restrictions have served as a valuable resource.

Compared to their unexposed siblings, these people as adults tend to have higher plasma lipid levels and higher rates of obesity and coronary artery disease (Heijmans et al. 2009). Comparable observations have also been made in Nigerian individuals exposed to conditions of famine during early life, who were then at higher risk of hypertension and impaired glucose tolerance in adulthood (Hult et al. 2010).

Prenatal undernutrition is not the only developmental route by which predisposition to metabolic disease could occur. Early life overnutrition, maternal adiposity, gestational diabetes, and excessive weight gain during pregnancy are also risk factors for a similar outcome (Boney et al. 2005). The downstream metabolic effects of early life overnutrition have been corroborated by many animal studies. For example in mice, offspring of mothers fed a high-fat diet from weaning until lactation developed hypertension, fatty liver, and lipid metabolism dysregulation in adulthood (Elahi et al. 2009). In rats, a maternal high-fat diet induced hepatic fat deposition and insulin insensitivity in offspring at adulthood (Bruce et al. 2009; Dunn and Bale 2009).

The apparent paradox of diametrically different exposures giving rise to similar health outcomes in later life suggests that multiple developmental pathways are at play. Our understanding of the biological basis of how early life overnutrition is linked to adverse health outcomes is rudimentary. There are suggestions that disruption of mitochondrial function, oxidative stress, and upregulated placental transport could contribute (Bruce and Hanson 2010); however, there is now also growing evidence that epigenetic factors contribute to both pathways, as discussed later.

Although gestational diabetes has adverse consequences on offspring health, evolutionary explanations could account for the lack of negative selection against it: as mild fetal hyperinsulinemia is growth promoting, the placenta may have evolved to buffer against fetal undernutrition rather than overnutrition; furthermore obesogenic environments would have been highly unlikely during the course of our evolutionary history, and it is only with the current ubiquity of nutritional overload that an evolutionary mismatch has arisen (Ma et al. submitted).

The trends towards poorer dietary quality and increasing rates of maternal obesity and gestational diabetes in many developing and developed countries are raising concerns about the health impact on the next generation and in particular the perpetuation of a vicious cycle of “diabesity” (Poston 2011). Paternal influences at the time of conception may also play a role: daughters of male rats chronically fed a high-fat diet have impaired pancreatic function, suggesting that the generational effects must have been caused by altered sperm development or molecular programming in the father’s germline (Ng et al. 2010). Food preferences may be shaped by the nature of maternal diets and the foods onto which children are weaned (Beauchamp and Mennella 2009). Infant diet can also modulate disease risk. For example, an early transition from breast milk to formula feeding increases the risk of being overweight in adolescence (Gillman et al. 2001).

2.3.3.1 Epigenetics: Experimental Evidence

The initial resistance towards the idea that disease with a later life onset could have developmental origins was partially due to the lack of evidence for a tenable biological mechanism that could account for the epidemiological observations. However, a wealth of animal data have now identified modifications of specific epigenetic marks in association with alterations in gene expression and disease susceptibility. In the rat undernutrition model described above, increased methylation at the promoter region of *Ppara*, which encodes a major regulator of lipid metabolism, was seen in conjunction with decreased gene expression in hepatocytes (Gluckman et al. 2007b). Additionally, both epigenetic and phenotypic changes in these rats could be reversed if leptin was administered at the neonatal stage (Vickers et al. 2005; Gluckman et al. 2007b). This suggests that the presence of an adipose-derived hormone may act as a cue to alter fetally made predictions of a scarce nutritional environment and thus adopt a different developmental trajectory to adapt accordingly. A similar approach found hypomethylation of hypothalamic *Pomc*, encoding an anorexigenic peptide, in association with the rescuing effects of orally administered leptin (Palou et al. 2011). The degree of nutritional deficit need not be severe for epigenetic effects to be seen. In baboons, moderate undernutrition that did not affect birth weight—that is, no overt phenotypic change was induced—nevertheless led to molecular changes as reflected by hypomethylation at the *PCK1* promoter, the gene product of which is crucial for normal gluconeogenesis (Nijland et al. 2010).

In the maternal protein restriction rat model, decreased methylation at the *Ppara* and *GR* promoters was observed together with corresponding increases in gene expression (Lillicrop et al. 2005, 2007, 2008); histone modifications biased towards *GR* transcription were also detected. In a similar mouse model, offspring showed hypermethylation at the *Lxra* promoter and reduced expression of its gene product, a key protein in lipid metabolism (van Straten et al. 2009). Lower levels of leptin gene transcription and protein expression were found in adipose tissue of offspring of protein-starved mice. This was also associated with demethylation of specific CpGs at the leptin gene promoter (Jousse et al. 2011). Of potential functional relevance to hypertension, hypomethylation at the promoter of mouse brain *Ace-1*, coding for a component of the renin-angiotensin system, has been observed alongside upregulation of microRNAs that regulate its translation (Goyal et al. 2010).

Placental insufficiency can be experimentally simulated by uterine ligation during pregnancy. Offspring of these rats eventually become diabetic. Molecular investigations demonstrate that this outcome is underpinned by multiple epigenetic changes. These included histone deacetylation and reconfiguration of histone methylation and, in parallel, gradual *Pdx1* promoter hypermethylation leading to underexpression of a transcription factor necessary for pancreatic development (Park et al. 2008). Neonatal treatment of offspring with exendin-4, a glucagon-like

peptide-1 analogue, could normalize the histone modifications and *Pdx1* transcription, preventing the onset of diabetes (Pinney et al. 2011).

There is increasing evidence for the epigenetic basis by which early life overnutrition gives rise to metabolic dysfunction in adulthood. In a study of knockout rats that lack apolipoprotein E and are hypercholesterolemic, it was shown that offspring fed a high-cholesterol diet had as adults differential histone marks in the vasculature compared to counterparts from wild-type mothers fed an identical diet (Alkemade et al. 2010). Changes appear to manifest early in postnatal life in the rat model of maternal high-fat nutrition since hypomethylation of *Cdkn1a*, which encodes for the hepatic cell cycle inhibitor, was observed at postnatal day two (Dudley et al. 2011). Various changes in histone marks have been detected for hepatic *Pck1* (Strakovsky et al. 2011), which codes for a key regulator of plasma glucose homeostasis. A neurobehavioral link has been suggested wherein mice born to maternal high-fat diet dams showed both global and gene promoter-specific hypomethylation in the brain, including that of opioid- and dopamine-related genes (Vucetic et al. 2011). The altered epigenetic regulation within the mesocorticolimbic reward circuitry may likewise account for dietary preferences biased towards sucrose and fat.

In a nonhuman primate model, Japanese macaques fetuses, which were exposed to a high-fat diet during gestation, showed symptoms of nonalcoholic fatty liver disease. Molecular investigations revealed hyperacetylation of the histone mark H3K14 in hepatocytes and decreased expression of the histone deacetylase HDAC1 (Aagaard-Tillery et al. 2008).

2.3.3.2 Epigenetics: Clinical Evidence

The obvious constraints of using humans as experimental subjects in investigations of the developmental induction of later life disease have limited the availability of high-quality molecular evidence. Adult offspring born during the Dutch Hunger Winter famine cohort were examined for their epigenetic state of several genes known to be linked to growth and metabolic disease. A birth weight-independent decrease in DNA methylation was seen at the promoter of *IGF2*, an imprinted gene that promotes cell proliferation, when compared to that in unexposed siblings (Heijmans et al. 2008). While the effect size was very small, these data suggest that an epigenetic change can persist for at least six decades after transient exposure to the inducing cue. Interestingly, *IGF2* methylation is not affected in preterm babies born small for gestational age, suggesting some caution in interpretation (Tobi et al. 2011).

Molecular support for the concept that maternal preconceptional body composition influences offspring metabolic profile has been provided by a study which found that prepregnancy BMI was moderately correlated with methylation of umbilical cord *PPARGC1A*, the gene product of which regulates energy metabolism (Gemma et al. 2009). Since none of the mothers was diabetic, it can be inferred that developmental influences may still be exerted in unexceptional pregnancies.

Perhaps the strongest data come from a recent clinical study following children born to normal pregnancies from birth to up to 9 years, to determine potential associations between early life epigenetic marks and possible prodromal markers of metabolic disease. It was found in two independent cohorts and in two independent replicates within one cohort that in DNA extracted from the umbilical cord at term, the methylation level at a specific site in the *RXRA* promoter correlated with childhood body fat (Godfrey et al. 2011). *RXRA* is a transcription factor involved in fat metabolism and insulin sensitivity, providing physiological relevance. Maternal carbohydrate consumption in early pregnancy has previously been linked to neonatal adiposity, and in this study higher *RXRA* promoter methylation was indeed linked to low-carbohydrate intake. That the association was detected in healthy subjects and not dependent on birth weight underscores the normative nature of developmentally plasticity. As a substantial proportion of the variance in adiposity could be accounted for by the epigenetic state, epigenotypic measures may lead to the ability to quantify the importance of the developmental contribution.

2.3.4 Epigenetic Contributions to the Developmental Origins of Other Disorders

2.3.4.1 Early Life Stress

Early life stresses in humans can lead to dysfunctions in neurodevelopment and behavior (Champagne 2010). Furthermore, maternal rat behaviors including tactile stimulation, such as licking and grooming of pups, influence their later life behavioral and hypothalamic-pituitary-adrenal (HPA) responses to stress. Higher levels of maternal care lead to lower methylation levels at the hippocampal *GR* promoter and lower expression of GR, which plays a role in the regulation of HPA activity (Weaver et al. 2004). These rats are better able to cope with stressors and grow up to demonstrate a similar level of care towards their offspring, inducing the same epigenetic changes in them. Known as niche re-creation, this is one pathway by which developmentally induced epigenetic changes can be passed onto subsequent generations. Maternal separation, another inducer of early life stress in mice, caused hypomethylation at the enhancer region of brain *Avp*, which codes for the neuropeptide arginine vasopressin linked to mood and cognitive behaviors (Murgatroyd et al. 2009). Alterations were particularly apparent at CpGs located in the MeCP2 binding site. The epigenetic changes, together with the induced endocrine and behavioral phenotypes, persisted for at least 1 year.

In recent years, a number of human studies have been published that draw some parallels with the animal work. Hypermethylation at the promoter of hippocampal *GR*, and a reduction in its expression, was found in individuals who had suffered childhood abuse compared with those who did not experience such adversity (McGowan et al. 2009). Furthermore, newborn children whose mothers

experienced depression in late pregnancy had hypermethylated cord blood *GR* and at 3 months of age showed heightened HPA stress responses as determined by salivary cortisol after stress exposure (Oberlander et al. 2008). This study did not examine if the epigenetic changes endured past the neonatal period. Recently, a positive association was found between methylation levels in blood samples from adolescent children and maternal experience of violence from an intimate partner during pregnancy (Radtke et al. 2011), which highlights the durability of epigenetic marks established in utero. Finally, other work focusing on the impact of childhood abuse found an influence on methylation at the promoter region of *5HTT*, encoding the serotonin transporter; degree of methylation also correlated with symptoms of antisocial personality disorder (Beach et al. 2011).

2.3.4.2 Environmental Toxins

It is now well established that prenatal exposure to environmental toxins affects global and gene-specific DNA methylation. Children whose mothers were tobacco smokers during pregnancy showed global hypomethylation in cord blood (Guerrero-Preston et al. 2010). Moreover, these changes appear to be durable, as suggested by a preliminary report showing lower genomic methylation of *Sat2* and *Alu* in adults who had been prenatally exposed to smoke (Flom et al. 2011). Traffic-related airborne polycyclic aromatic hydrocarbon exposure is also linked to increased *ACSL3* methylation in cord blood, concomitant with lowered gene expression in fetal placental tissue (Perera et al. 2009). It is of concern that the degree of methylation is associated with incidence of childhood asthma, although it is unclear if the physiological functions of ACSL, an enzyme involved in fatty acid metabolism, directly affect asthma.

2.4 Developmental Epigenomics

2.4.1 Problems and Pitfalls

The literature reviewed above points to a role for epigenetics in developmental processes of functional significance in humans; however, these studies are at an early stage and several caveats are needed. Experimental studies generally involve a single large manipulation, making it potentially difficult to translate the findings to humans. The field of epigenomic epidemiology likewise needs to benefit from the experience of genomic research and become more aware of the importance of experimental replication. To date it appears that only the study by Godfrey et al. (2011) has validated a finding by replication both within and between cohorts.

Beyond these cautionary points, the issues of which epigenetic marks to study are pertinent. In general metabolic disease and obesity involve the gradual

appearance of pathophysiology over many years. As the physiology of metabolic homeostasis is complex and only subtle physiological change is needed for symptoms to appear over time, epigenetic changes of an on/off nature would not be expected to occur as they do in cell differentiation. Rather, one would anticipate context-dependent changes in regulation of sensitive components within complex networks. Thus, we may be looking for epigenetic marks distal to the proximal promoter which may have no effect on expression changes, except in particular contexts. The search strategy used by Godfrey et al. (2011) was an attempt to be unbiased. A microarray discovery approach was used to define genomic regions where DNA methylation showed high variance within a population; then phenotypic correlates were searched for. Since then the potential for better and more complete scanning by whole genome approaches has grown, but the challenges are no less diminished. Ultimately, whatever epigenetic marks are identified, their functional importance will need to be validated by in vitro experiments since the presence or absence of expression changes under basal conditions may not be informative given the context-specific nature of the change.

A further problem concerns which tissue to study and the need to consider potential changes in the number of cells of any type within the tissue since this may be the developmental change of interest, rather than simply being a confounder. A further problem will be how best to analyze the data since its complexity will be orders of magnitude higher than that associated with genomic analyses. Furthermore, we have recently found that many epigenetic measures do not follow normative distributions and require more complex forms of analysis (Sheppard et al. submitted for publication). Such concerns mean that caution must be exercised, particularly when subtle changes in methylation are reported, as seen in the study of *IGF2* in the Dutch Hunger Winter study (Heijmans et al. 2008).

There inherently seems to be greater confidence in data when the magnitude of the epigenetic change is large, and the phenotypic change is strongly associated in a graded manner with the change in the epigenetic mark (Godfrey et al. 2011). Nevertheless, some epigenetic changes may occur in stepwise fashion or follow U-shaped relationships to the phenotype or cue. This might either reflect a canalization process or show that the epigenetic change measured is distal to the induction pathway and of secondary importance.

Beyond the birth period when perinatal tissues can be collected, the range of sample types from which DNA can be extracted is limited. This creates another potential complication. We have found that epigenetic marks in umbilical tissue do not necessarily correlate with those from buccal smear samples, and validation techniques may have to be age and tissue specific. Unless these issues are addressed, we will soon have an obfuscating, confused literature where the technical issues could obscure important biological phenomena.

2.4.2 The Potential of Developmental Epigenetics

Notwithstanding these difficulties, the application of developmental epigenetics has enormous potential in more clearly defining the etiology of metabolic diseases. The reality is that we have little knowledge of the optimal nutritional management of mother and infant to reduce long-term risk of metabolic diseases in contemporary environments. To date, we have mainly used crude measures of birth outcomes and infant growth. It seems feasible to use epigenetic marks to profile infants in relationship to their nutritional exposures and use such measures to better address the issues of preconceptional, gestational, lactational, and infant feeding. Interventional studies which have long-term disease outcomes as their endpoints are clearly impractical, and epigenetic measures may become useful biomarkers of desirable changes in the developmental trajectory.

Birth weight provides a very limited assessment of the neonatal state and intrauterine history, as evidenced by many children who are neither very large nor small at birth having altered development. We are currently evaluating the potential of epigenetic measures made at birth to interrogate the developmental history further. This may be useful in stratifying subjects for intervention, potentially at any stage in the life course.

There remains much uncertainty regarding the relative importance of developmental as opposed to genetic and lifestyle factors in the etiology of noncommunicable disease. The data of Godfrey et al. (2011) indicate a greater developmental component than was generally thought. Nevertheless, much more data, together with various approaches to validation across different populations, will be needed to reach firm conclusions.

As epigenetic biology evolves, the potential for it to identify new therapeutic targets will become clearer. Epigenetic manipulation has already found utility in cancer therapy. If therapeutic strategies are also discovered that allow for the specific targeting of epigenetic changes involved in the genesis of metabolic diseases, the ability to improve human health will be greatly enhanced.

2.5 Final Comments

An in-depth understanding of the developmental origins of obesity, diabetes, and other related metabolic diseases will have important implications for intervention strategies to deal with the epidemic of noncommunicable disease. There is low adherence in the UK to a prudent diet among women of reproductive age, even if pregnancy was planned (Inskip et al. 2009). There is also little appreciation of the importance of nutritional influences in early infancy on lifelong health among first-time mothers (Gage et al. 2011). This suggests that effective nutritional and health education programs targeted at young women could be of immense value in mitigating the soaring rates of obesity and related metabolic diseases. Epigenetic

measurements could well assist in the development of optimal nutritional strategies for health improvement both in the mother and infant, to stratify at-risk populations and to monitor interventions. As global approaches to interrogate the epigenome become more available, novel epigenetic targets for therapeutic intervention will continue to be identified.

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