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Review

Developmental plasticity and developmental origins of non-communicable disease: Theoretical considerations and epigenetic mechanisms

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ABSTRACT

There is now evidence that developmental influences have lifelong effects on cardiovascular and metabolic function and that elements of the heritable or familial component of susceptibility to cardiovascular disease, obesity and other non-communicable diseases (NCD) can be transmitted across generations by non-genomic means. In animals the developmental environment induces altered phenotypes through genetic, physiological (especially endocrine) and epigenetic mechanisms. The latter include DNA methylation, covalent modifications of histones and non-coding RNAs. Such 'tuning' of phenotype has potential adaptive value and may confer Darwinian fitness advantage because it either adjusts the phenotype to current circumstances and/or attempts to match an individual's responses to the environment predicted to be experienced later. When the phenotype is mismatched to the later environment, e.g. from inaccurate nutritional cues from the mother or placenta before birth, or from rapid environmental change through improved socio-economic conditions, risk of NCD increases. Such mechanisms are also thought to play roles in ageing and early onset of puberty, reinforcing a life-course perspective on such adaptive responses, especially the detrimental later effects of trade-offs. Epigenetic changes induced during development are highly gene-specific and function at the level of individual CpG dinucleotides in both gene promoter and intergenic regions. Evidence is accruing that endocrine or nutritional interventions during early postnatal life can reverse epigenetic and phenotypic changes induced, for example, by unbalanced maternal diet during pregnancy. Elucidation of epigenetic processes may permit perinatal identification of individuals most at risk of later NCD and enable early intervention strategies to reduce such risk.

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1. The worldwide burden of non-communicable disease

Non-communicable disease (NCD) such as diabetes, cardiovascular disease and the metabolic syndrome, account for 60% of all deaths globally (World Health Organisation). In low to middle income countries, NCD are becoming particularly important as a rapid increase in their prevalence has been observed as these countries undergo socio-economic improvement (Ramachandran et al., 2010). Recently the UN General Assembly agreed that an international summit should be held to address the challenge of NCD, especially in low and middle income countries (UN General Assembly webpage). Whilst the increase in NCD arises primarily through adopting a western lifestyle, there is growing recognition of the role played by developmental factors. This is in accordance with the fundamental principles of life-course biology (Gilbert and Epel, 2009), whereby developmental trajectories established in early life influence the response of the individual to later exposures, such as adult lifestyle (Fig. 1)(Gluckman et al., 2009). Moreover, it is now widely accepted that fixed genomic variations such as single nucleotide polymorphisms and copy number variations explain only a fraction of the variation in NCD risk in a population (Manolio et al., 2009).

Links between prenatal growth and the later risk of NCD are thought to reflect variations in the quality of the intra-uterine environment (Gluckman et al., 2008; Hanson and Godfrey, 2008). As well as the limiting effects of small uterine size, constrained growth may reflect other aspects of the intra-uterine environment such as nutrition, oxygen supply and hormonal exposure. While both intra-uterine growth restriction and preterm birth appear to have long-term consequences for NCD risk (Hofman et al., 2004; Hovi et al., 2007), it is important to stress that the associations between prenatal development and future risk are seen across the range of birth size typical for each population (Gluckman et al., 2008). The precise nature of the underlying environmental cues is still being defined, but this review focuses on the central role of nutrition in inducing altered phenotypes. It is important to emphasise that we are considering environmental variation during development that is physiological, rather than pathological exposures that are disruptive to development (see Gluckman et al., 2005 for review).

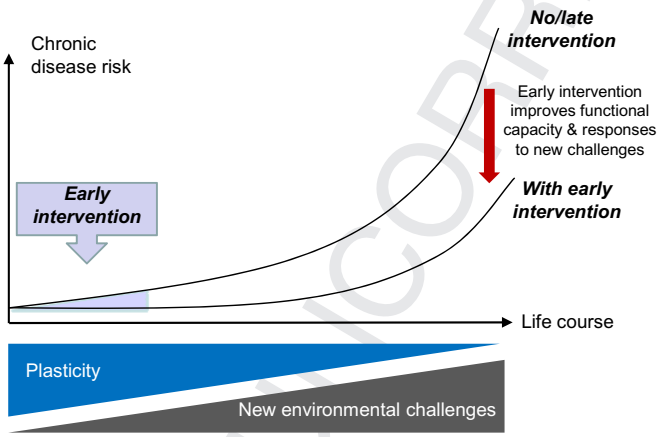

Fig. 1. Chronic non-communicable disease does not fit the medical model whereby an individual is healthy until they contract the disease. Risk increases throughout the life-course as a result of declining plasticity and accumulative effects of inadequate responses to new environmental challenges. However, whilst the greatest increase occurs in adult life, the trajectory is set much earlier: epigenetic processes are induced by cues such as mother's diet and body composition before and during pregnancy, and fetal infant and childhood nutrition and development. Adopting a life-course perspective allows identification of phenotype and markers of risk earlier, with the possibility of nutritional and other lifestyle interventions. In early life relatively modest interventions can have a large impact on disease risk later. Such preventative measures require a long-term investment, but are more likely to be effective than treatments administered after disease is manifest, or screening programmes which identify early stages of disease, again after it has arisen.

2. The role of developmental plasticity

Developmental plasticity in the strictest sense forms a component of phenotypic plasticity, the property of a given genotype to produce different phenotypes in response to distinct environmental conditions (see Pigliucci, 2001 for review of this and subsequent ideas). The theoretical concepts underpinning this definition, and their implications, are worthy of consideration. First, the focus of the definition is very much on genotype and thus processes controlled by inherited alleles. Such processes are likely to have been selected through evolution, and so even groups of a species may develop very different phenotypes under similar environmental conditions (Semlitsch and Wilbur, 1989), representing different fitness-optimising strategies between species. Secondly, it implies that the processes are controlled, rather than being the result of random variations or 'noise' in the developmental programme. The history of developmental biology was dominated in the early 20th century by what we can now see as an artificial separation between heritable 'factors' (now termed genes) determining phenotype through the developmental programme and environmental influences which could disrupt that programme. This is not to say that developmental processes should not be viewed as being 'canalised', in the sense used by Waddington (Waddington, 1942) whereby the developmental programme operates to limit small variations in the final phenotype, even though very distinct phenotypes can be produced. Indeed, striking examples of such polyphenisms occur in insects: the caterpillar of the Emerald moth *Nemoria arizonaria* is camouflaged to resemble oak catkins in spring but to resemble oak twigs if it develops in the summer, phenotypes which are induced by the tannin content of the leaves and catkins consumed (Greene, 1989). Recent evidence suggests that similar processes might also operate in mammals (Gluckman et al., 2007a).

A further implication is that the phenotype is induced by a specific environment. This is not to say that the phenotype induced is necessarily that conferring optimal fitness in the face of a specific environmental challenge, although the parsimony of selection would suggest that it should. However, because both pleiotropism (where one gene can influence a range of phenotypic aspects) and epistasis, (where one gene can influence others) the situation may not be simple. However, without over-complicating the issue, we can recognize that there are sometimes similar phenotypic results induced from a range of environmental challenges during development, and that they may involve similar signalling processes (e.g., the role of glucocorticoids – see Drake et al., 2005 for review) and underlying epigenetic mechanisms. As with the well-established examples from plants and non-mammalian animals, the developmental effects are adaptive. Thus, the ability to demonstrate developmental plasticity must itself have been selected, such that there will be genetic, heritable components to it. This latter point seems to have been overlooked by those who have focused purely on the disruptive effects of the developmental environment (in the DOHaD field epitomized by an excessive emphasis on IUGR) (Gluckman et al., 2008).

Thus, without dismissing the effects of developmental disruption under severe environmental conditions, we can recognize that many species exhibit environmental effects on development even within the normal range. For any genotype, there will be a range of possible phenotypes developing in any particular environment. This is the concept of the reaction norm, originally proposed by Woltereck (Woltereck, 1909) who first reported what would now

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be called adaptive phenotypic plasticity in the protective 'helmet' developing in *Daphnia* exposed to chemical cues indicating the presence of predators. This phenotype is not the result of disruption, because it is a normal occurrence for these species, and appears adaptive. Similar developmental phenotypic responses to predators occur in many other phyla (see Sheriff et al., 2010). In mammals, much of the developmental environment is transduced through the mother, or more strictly through her phenotype as this can affect the transmission of external stimuli such as nutrition to her fetus or infant. Such processes can be summarized under the heading of maternal effects, and their evolution and adaptive significance has been reviewed (Uller, 2008; Badyaev and Uller, 2009). As with many adaptive strategies, the effects on offspring phenotype however also bring a cost. For *Daphnia* this is probably in terms of metabolic or swimming efficiency, and this explains why the organism does not display the helmet phenotype in the absence of predators. Such costs are reminiscent of the trade-offs of antagonistic pleiotropy (Kirkwood and Rose, 1991) in which early survival and reproductive function is prioritised at the expense of repair and prevention of ageing in many species, including humans.

The considerations above suggest that the processes of developmental plasticity can be summarized conceptually, leading to models for which the clinical implications can be investigated in humans. Fig. 2, modified from Pigliucci (Pigliucci, 2001) for explaining phenotypic plasticity, attempts to do this.

3. Epigenetics during development and ageing

There are several fundamental ways in which the developmental environment can affect phenotype of the individual. These include alterations in developmental trajectories induced by changes in gene expression arising from interactions between the inherited genotype itself and environmental influences such as nutritional or endocrine factors (Schmalhausen, 1986), and also direct effects of the environment in terms of hormones, nutrient provision etc. The artificial separation of gene and environment factors has limited our understanding of phenotypic development and there is a growing understanding of epigenetic effects during development and of their role in plastic processes. These were shown, initially in animal studies, to be important in mediating effects on adult phenotype from perturbations of the developmental environment, including maternal diet (Lillycrop et al., 2005; Waterland and Jirtle, 2003; Gluckman et al., 2007a), uterine blood flow (Pham et al., 2003) and maternal nursing behavior (Weaver et al., 2004). The role of epigenetic processes in some forms of cancer is well-established (Laird, 2005), but these changes are usually large when measured for a sample containing many cells. We are only now starting to appreciate that more subtle epigenetic processes, perhaps affecting only a subset or clone of cells, also have major roles in human and animal development. In animal studies effects of epigenetic changes induced experimentally during development produce lifelong physiological changes of relevance to human disease, such as metabolic alterations and exaggerated stress responses, and a coherent theory for a role of epigenetic mechanisms in the developmental origins of NCD is thus emerging (Gluckman et al., 2008; Godfrey et al., 2007).

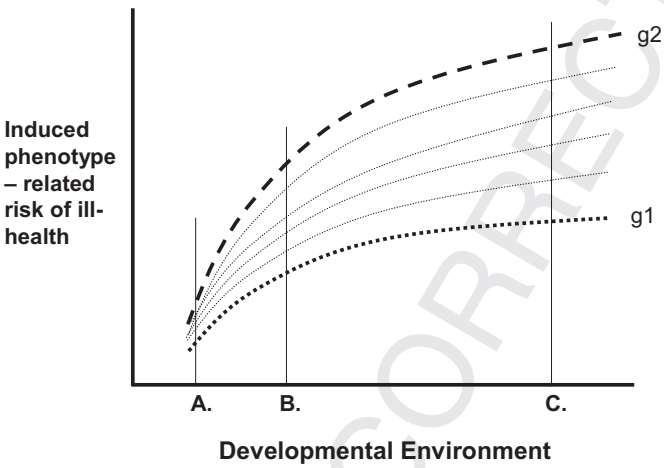

Fig. 2. Effects of developmental environment within the normal range on induced phenotype and thus, for phenotypes or epigenotypes such as fat mass, insulin sensitivity etc., on risk of later disease. Plasticity is shown for two distinct genotypes, g1 and g2 representing the extremes of the population. For mammals at least, we anticipate that there are also many intermediate genotypes, shown as fainter broken lines. In this range of environments, the degree of plasticity (slope of line) is not constant across the range, but decreases in moving from environment A to B to C. In any environment plasticity is greater for genotype g2 than g1. The phenotype which develops is thus influenced by genotype, by plasticity and by genotypically determined plasticity, each interacting with the developmental environment. Note that because the environments are within the normal range, the induced phenotypes will be adaptive (or their induction by genotype and plasticity would have been deselected). For any environment, the potential range of reaction norms for the population will be indicated by the vertical distance between the lines for g2−g1, indicating the range of environments for which phenotypes are adapted. Phenotypes can thus be seen to have been induced in prediction of optimal adaptation to this environment. Thus in concept such a classical diagram (derived from Pigliucci, (2001)) for evolutionary biology becomes very similar to the predictive adaptive response diagram of Gluckman and Hanson, (2005). which was developed to explain the consequences of environmental mismatch and the DOHaD phenomenon in humans.

The term epigenetics as now used refers to processes that induce heritable changes in gene expression without altering the gene sequence. Epigenetic processes are integral in determining when and where specific genes are expressed (Bird, 2001) alterations in the epigenetic regulation of genes may lead to profound changes in phenotype. The major epigenetic processes are DNA methylation, histone modification and microRNAs. To date, most studies on the effect of early life nutrition on the epigenetic regulation of genes have focussed on DNA methylation. Methylation at the 5′ position of cytosine in DNA within a CpG dinucleotide (the p denotes the intervening phosphate group) is a common modification in mammalian genomes and constitutes a stable epigenetic mark that is transmitted through DNA replication and cell division (Bird, 2002). CpG dinucleotides are not randomly distributed throughout the genome but are clustered at the 5′ ends of genes/promoters in regions known as CpG islands. Hypermethylation of these CpG islands is generally associated with transcriptional repression, while hypomethylation of CpG islands is generally associated with transcriptional activation (Bird, 2001). Additionally isolated CpGs can occur in the promoter and intergenic regions and can have regulatory significance. DNA methylation however is intimately linked to histone modifications. Methylated DNA is bound by Methyl CpG binding protein-2 (MeCP2) which can recruit histone modifying complexes to the DNA. MeCP2 recruits both histone deacetylases (HDACs), which remove acetyl groups from the histones, a signal of transcriptionally active chromatin (Strahl et al., 1999; Lachner et al., 2001; Fuks et al., 2000) and histone methyl transferases (HMTs) such as Suv39H (Nakayama et al., 2001; Fuks et al., 2000) which methylates lysine 9 on H3, resulting in a closed chromatin structure and transcriptional silencing. MicroRNAs (miRNAs) which are small non-coding RNAs, can also regulate gene expression, they have been shown to modulate gene expression at the post-transcriptional level through the induction of mRNA degradation or translational repression of a target mRNA (Kuehbacher et al., 2008). However more recent studies have shown that the human miRNAs can also induce chromatin remodelling (Kim et al., 2008) and direct DNA methylation (Bayne and Allshire, 2005), suggesting that DNA methylation, histone modification and miRNAs may work in concert to regulate gene expression.

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Patterns of DNA methylation are established early in development and methylation plays a key role in cell differentiation by silencing the expression of specific genes. In mammals, the zygote undergoes rapid demethylation of the male genome with a few hours of fertilization (Mayer et al., 2000; Oswald et al., 2000). The female genome is passively demethylated during subsequent mitotic divisions (Li, 2002). This is followed by global methylation *de novo* just prior to blastocyst implantation during which 70% of CpGs are methylated, mainly in repressive heterochromatin regions and in repetitive sequences such as retrotransposable elements (Reik and Walter, 2001) At this stage of development, the PcG proteins,which are a group of histone modifying proteins play a critical role in maintaining the pluripotential nature of the embryonic stem cells by silencing cell determination genes such as Pax, Hox and Dlx (Azuara et al., 2006) which are required for development, by polycomb induced H3K27 methylation. Loss of PcG proteins from their target genes (Tiwari et al., 2008) together with lineage specific DNA methylation leads to the establishment of structurally and functionally distinct cell types.

In addition to gene silencing by promoter methylation, differential methylation of individual CpG dinucleotides can induce more subtle modulation of transcriptional activity. In mammals, DNA methylation is induced and maintained by DNA methyltransferases. Deletion or mutation of the genes encoding these enzymes results in embryonic death or severe disruption of development, and loss of imprinting (Jaenisch and Bird, 2003). DNA methylation *de novo* is catalyzed by Dnmt3a and 3b (Okano et al., 1999). DNA methyltransferase (Dnmt)-1 is responsible for maintaining patterns of CpG dinucleotides methylation through replication cycles. Genomic imprinting describes the monoallelic expression of specific gene loci in a manner dependent upon the parental origin (Reik and Walter, 2001). The majority of the human genes known to be imprinted are located in CpG-rich domains termed Imprinting Centres, in which methylation of CpG dinucleotides results in repression of either the maternal or paternal allele (Delaval and Feil, 2004; Morison et al., 2001). Because these methylation patterns are established in the gamete before fertilization, they are excluded from the genome-wide demethylation which occurs after fertilization (Brandeis et al., 1993; Lane et al., 2003). Impaired imprinting leading to biallelic expression is causally—associated with disorders including Angelman, Prader—Willi and Beckwith—Weidemann syndromes (Temple 2007; Tycko and Morison, 2002).

Epigenetic marks induced during development largely persist into adulthood. However, ageing is associated with tissue-specific epigenetic changes. Senescence is associated with decreasing Dnmt1 activity and generalized hypomethylation, leading to activation of oncogenes such as c-Myc and c-N-ras (Lopatina et al., 2002). However, hypermethylation of specific tumor-suppressor gene promoters also occurs in ageing (Richardson, 2003), and is thought to contribute to age related increases in many malignancies. These findings show that ageing is not simply associated with a progressive decline in capacity to maintain methylation of CpG dinucleotides but also involves selective dysregulation of epigenetic processes.

One implication is that the level of methylation induced in early life sets the epigenetic background upon which changes associated with ageing operate and so variation in the epigenome induced during development may influence susceptibility to disease in later life (Waterland and Jirtle, 2004). As yet there are limited published human data linking maternal nutrition to induced epigenetic change in the offspring. A study of whole blood genomic DNA suggested that, compared with unexposed same-sex siblings, adults who were *in utero* during the Dutch Hunger Winter have hypomethylation of the differentially methylated region of the imprinted insulin-like growth factor-2 gene (*IGF2* DMR) (Heijmans et al., 2008). Although statistically significant, the mean level of methylation of exposed individuals was 52% compared to 49% in unexposed controls, with standard deviations of around 5% and thus the biological significance in terms of gene retulation is unclear. Preliminary evidence of an association of periconceptional famine exposure with altered methylation of the promoter regions of imprinted and non-imprinted genes implicated in growth and metabolic disease has come from the same group (Tobi et al., 2009). Among imprinted genes studied *INSIGF* was hypomethylated in exposed individuals and guanine nucleotide binding protein and *MEG3* were hypermethylated; among non-imprinted genes interleukin-10, leptin and *ATP* binding cassette *A1* were hypermethylated in exposed individuals. Interpretation of the findings is difficult as the maximum difference between exposed and unexposed individuals (6%) is similar to analytical error of the technique used (Ehrich et al., 2005). Further evidence for a small effect of maternal nutrition on epigenetic processes in the fetus has come from a study measuring 5 CpGs in the *IGF2* DMR: in children whose mothers did and did not take 400 μg of folic acid per day in the periconceptional period, whole blood methylation levels were 49.5% and 47.4%, respectively (Steegers-Theunissen et al., 2009). These changes are considerably smaller that those usually found in animal studies, which may reflect the specificity of the genomic and intergenic regions studied in the latter or the results of a more defined stimulus in such experiments. In all such studies it is important to recall that variance in outcome measures does not necessarily give evidence of plasticity (Lewontin, 1974).

Recently, we found that the epigenetic profile measured in umbilical cord tissue at birth can predict phenotype outcomes in later childhood independently of birthweight (Godfrey et al., 2009). In two independent cohorts, the epigenetic state of a single CpG site in the promoter region of the transcription factor *RXRA* was strongly related to childhood adiposity in both boys and girls; taking account of sex, *RXRA* promoter methylation explained over a fifth of the variance in childhood fat mass. This suggests that a far greater proportion of individual vulnerability to NCD may arise in development than has previously been considered.

4. Developmental epigenetic processes in animal models of NCD

In models where unbalanced maternal nutrition has been shown to alter cardiovascular function and metabolism in the offspring, feeding a protein restricted (PR) diet to rats during pregnancy induces hypomethylation of the PPARα and GR promoters and increased expression of the GR and PPARα in the liver of juvenile (Lillycrop et al., 2005) and day 80 adult (Burdge et al., 2007a) offspring. Hypomethylation of the GR promoter was associated with histone modifications which facilitate transcription; acetylation of histones H3 and H4 and methylation of histone H3 at lysine K4, while those that suppress gene expression were reduced or unchanged (Lillycrop et al., 2007). Although functionally consistent, the mechanistic relationship between GR hypomethylation and the associated histone changes is not known. These studies showed for the first time that, in contrast to modifying the maternal intake of nutrients directly involved 1-carbon metabolism (Lillycrop et al., 2005), stable changes to the epigenetic regulation of the expression of transcription factors can be induced in the offspring by modest changes to maternal macronutrient balance during pregnancy. Expression of PPARα and GR, and of their respective target genes, acyl-CoA oxidase and carnitine palmitoyltransferase-1, and PEPCK was increased in juvenile and adult offspring (Burdge et al., 2007a; Lillycrop et al., 2005, 2007). This is consistent with raised plasma β-hydroxybutyrate and glucose concentrations in the fasting offspring (Burdge et al., 2008).

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Sequencing analysis of the PPARα promoter showed that four specific CpGs were hypomethylated, and that two CpGs located within transcription factor response elements predicted the level of the transcript (Lillycrop et al., 2008). Thus the effects of the maternal PR diet on the offspring are targeted to specific CpGs. The mechanisms involved are not known but by regulating effects of transcription factors on expression they may have important effects on phenotype.

Together, these results indicate that modest dietary protein restriction during pregnancy induces an altered phenotype through epigenetic changes in specific genes. Methylation of the GR and PPARα promoters was also reduced in the heart of the offspring (Lillycrop et al., 2006) and the PPARα promoter was hypomethylated in the whole umbilical cord (Burdge et al., 2007b). These findings are consistent with increased GR mRNA expression in a range of tissues from the offspring of rats fed a PR diet during pregnancy (Bertram et al., 2001). However, PPARα methylation does not differ between control and PR offspring in skeletal muscle, spleen and adipose tissue, indicating that the effects of the maternal diet are tissue specific (Lillycrop and Burdge – unpublished). Hypomethylation of the GR promoter has also been found in the offspring of mice fed a PR diet during pregnancy (Burdge et al., 2007b) which suggests that the effect of the PR diet may not be specific to one species.

The fundamental role of changes in the epigenetic regulation of transcription factor expression in altering the activity of pathways controlled by their target genes is underlined by the observation that although glucokinase expression was increased in the liver of the PR offspring, this was not accompanied by changes in the methylation status of the glucokinase promoter (Bogdarina et al., 2004). Since GR activity increases glucokinase expression through enhancement of insulin action (Printz et al., 1993), greater glucokinase expression in the PR offspring may have been due to increased GR activity as a result of hypomethylation of the GR promoter rather than a direct effect of prenatal under-nutrition on glucokinase.

The process by which environmental cues induce altered epigenetic regulation in the embryo remains unknown. Studies in liver from juvenile offspring have provided some insights into the underlying mechanisms. Feeding a PR diet to pregnant rats induced lower Dnmt1 expression and reduced binding of Dnmt1 at the GR promoter (Lillycrop et al., 2007). However, the expression of Dnmt3a, Dnmt3b and MBD-2, and binding of Dnmt3a at the GR promoter were unaltered (Lillycrop et al., 2007). This suggests that hypomethylation of the hepatic GR promoter in the offspring, and probably other genes including PPARα, is induced by reduced capacity to maintain patterns of cytosine methylation during mitosis rather than failure of methylation *de novo* or active demethylation (Burdge et al., 2007b; Lillycrop et al., 2007). This is consistent with lower MeCP2 binding and increased histone modifications which facilitate transcription at the GR promoter. Reduced Dnmt1 activity might be expected to result in global demethylation. However, studies *in vitro* show loss of Dnmt1 induced demethylation of only a subset of genes (Jackson-Grusby et al., 2001; Rhee et al., 2000). This indicates that Dnmt1 is targeted to specific genes, consistent with selective hypomethylation in the liver in the PR offspring (Lillycrop et al., 2005). Dnmt1 activity is also required for progression through mitosis (Milutinovic et al., 2003) and its expression is substantially reduced in non-proliferating cells (Suetake et al., 2001). Thus, suppression of Dnmt1 activity in the pre-implantation period could also account for the changes in the number of cell types during early embryonic development in this model (Kwong et al., 2000).

In contrast to the effects of maternal PR diet on the epigenetic regulation of hepatic genes in the offspring, a 70% reduction of total food intake during pregnancy in rats induced hypermethylation and lower PPARα and GR expression in the liver of 170 day old offspring (Gluckman et al., 2007a). One explanation may lie in the differences in severity of nutritional restriction between these two dietary regimens. If the induction of altered phenotypes is predictive, then it may be anticipated that induced changes in the epigenome would differ according to dietary regimen, in order to match the phenotype to the predicted future environment. Thus the maternal PR diet could be regarded as a moderate nutrient constraint which induces in the offspring increased capacity for using nutrient reserves for energy production. In contrast more severe global under-nutrition induces conservation of energy substrates. These interpretations are consistent with the phenotypes induced in the offspring (Gluckman et al., 2007a; Burdge et al., 2008, Vickers et al., 2000).

5. Interventions to prevent or reverse epigenetic changes and induced phenotypes

Identification of epigenetic mechanisms which underlie induction by unbalanced prenatal nutrition of increased later disease risk raises the possibility of nutritional interventions to prevent or reverse such processes. Attempts at such interventions have been tested in animal models using leptin (Vickers et al., 2005), growth factors (Stoffers et al., 2003) or nutrients involved in 1-carbon metabolism. Although these experiments have only reached the 'proof of principle' stage, they have identified possible benefits and pitfalls of relevance to preventing human disease.

Methylation of DNA and histones are closely linked to pathways which supply methyl substrates for their respective methyltransferases (Tibbetts and Appling, 2010). For DNA methylation, methyl groups are primarily supplied from serine by the action of cytoplasmic serine hydroxymethyltransferase which transfers CH_3 to tetrahydrofolate (THF) to form 5,10-methylene THF which is reduced to 5-methyl THF by tetrahydrofolate reductase. This methyl group is used to convert homocysteine to methionine by methionine synthase with vitamin B_{12} as co-factor. Activated S-adenosylmethionine is the substrate for Dnmts which compete for CH_3 with phosphatidylethanolamine *N*-methyltransferase (PE *N*-MET) activity. PE *N*-MET uses 3 mol of CH_3 to synthesize 1 mol of phosphatidylcholine and in the liver is the major terminal reaction in 1-carbon metabolism. Betaine is an alternative substrate for remethylation of homocysteine which is catalyzed by betaine homocysteine methyltransferase. Glycine is used to generate serine as part of the mitochondrial folate cycle, which is, in turn, the substrate for cytoplasmic SHMT.

Supplementation of the maternal PR diet with glycine (Jackson et al., 2002) or folic acid (Torrens et al., 2006) has been shown to prevent the induction of hypertension and endothelial dysfunction in the offspring. Supplementation of the maternal PR diet with folic acid also prevented dyslipidaemia in the adult offspring (Burdge et al., 2008). In contrast, supplementation of the control diet with folic acid induced impaired endothelial dysfunction and dyslipidaemia in the offspring (Burdge et al., 2008; Torrens et al., 2006). Increasing the folic acid content of the PR diet prevented hypomethylation of the PPARα and GR promoters in the liver of the offspring (Schmalhausen, 1986). However, detailed analysis of the PPARα promoter showed that, although increased maternal folic acid intake prevented hypomethylation of the majority of CpG dinucleotides induced by the PR diet alone, two CpGs were hypermethylated (Lillycrop et al., 2008). Thus increasing maternal folic acid intake does not simply prevent the effects of the PR diet, but may induce subtle changes in gene regulation.

It is important to consider whether interventions after the neonatal period may be able to reverse the adverse effects of

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prenatal nutrition. In the maternal PR model a recent study investigated the effect of supplementing the diet of rats with folic acid during their juvenile-pubertal period (Burdge et al., 2009). In contrast to supplementation of the maternal PR diet with folic acid, supplementation during the juvenile-pubertal period induced impaired lipid homeostasis, including down-regulation of hepatic fatty acid β-oxidation, hepatosteatosis and increased weight gain. Adverse effects were seen irrespective of the maternal diet and were associated with altered methylation of specific genes, including hypermethylation of PPARα in the liver of the offspring. These findings suggest that the period between weaning and adulthood in rats represents another period of plasticity, possibly reflecting ongoing growth and development. This consistent with the view that puberty is one of four periods of increased instability of the epigenome; prenatal development, neonatal development, puberty and ageing (Dolinoy et al., 2007). Although the effects of folic acid supplementation on the offspring were deleterious, these findings do suggest that in principle it may be possible to reverse adverse effects of prenatal nutrition by nutritional interventions before adulthood.

Together, the findings of studies of folic acid supplementation during gestation or after weaning in rats using the maternal protein restriction model show that the outcomes of such interventions are complex. These are influenced by the timing of the intervention, and interactions between folic acid and the background diet cannot be easily predicted. Thus the design of supplementation regimens to reverse epigenetic effects in humans will need careful consideration of the timing and magnitude of the intervention.

6. Mechanisms for induced epigenetic change

The mechanism by which the nature of the future environment is transmitted to the embryo and fetus and the molecular events within the developing offspring which give rise to variations in epigenetic marks which underpin the induced phenotype are unclear. Since the effects of such signals can be detected as early as the blastocyst stage (Kwong et al., 2000), the signals must be in a form which can traverse the environment within the fallopian tube before implantation, or the uterine wall before the establishment of a functional placenta. The nature of the signals is not known, although circumstantial evidence suggests that corticosteroids may be involved (Langley-Evans, 1997). A further challenge is understanding the nature of the molecular changes which occur in response to the maternal signal that lead to epigenetic changes. Even more difficult to explain is the induction of epigenetic changes in post-mitotic cells in later life, for example induction of PPARα hypermethylation in juvenile rats fed a diet with increased folic acid content (Burdge et al., 2009). Szyf has suggested that DNA methylation is a dynamic process and that the level of methylation at a particular locus is the result of the equilibrium between the activities of DNA methyltransferases and the as yet unidentified demethylases, although there is considerable evidence for their existence (Syzf, 2007). Thus exposure to compounds which alter these activities may shift the equilibrium and so change the methylation status. While this provides a useful paradigm for induced change in DNA methylation at any stage of the life course, it does not explain differential variation between individual CpGs which underlies at least some of the induced changes in epigenotype and phenotype (Weaver et al., 2004; Lillycrop et al., 2007). However, as Dnmts can be targeted to specific DNA sequences by interactions with transcription factors or histone modifying complexes such as HDAC or EZH2 (Lillycrop et al., 2007), CpG-specific changes in methylation by this process may be possible.

7. Transgenerational effects

A small number of studies have suggested that non-genomic transmission of induced phenotypes between generations may be an important mechanism in human disease (Gluckman et al., 2007b). Records from Överkalix in northern Sweden for individuals born in 1890, 1905 and 1920 have shown that diabetes mortality increased in men if the paternal grandfather was exposed to abundant nutrition during his pre-pubertal growth period (Kaati et al., 2002), an effect later extended to paternal grandmother/granddaughter pairs and transmitted in a gender-specific fashion (Pembrey et al., 2006). Poor maternal nutrition has also been associated with increased risk of type 2 diabetes mellitus over several generations in North American Indians (Benyshek et al., 2001), and individuals whose grandparents were *in utero* during the Dutch Hunger Winter had lower birth weight (Stein and Lumey, 2000). Exposure of pregnant women to diethylstilbestrol led to a marked increase in reproductive abnormalities and uterine fibroids (Baird and Newbold, 2005), an earlier menopause (Hatch et al., 2006), and breast (Palmer et al., 2006) and rare genital tract cancers in their children, and there is evidence of third-generational effects transmitted through the maternal line (Brouwers et al., 2006).

Emerging evidence from small animal models suggests that induced phenotypes can pass to more than one generation by a non-genomic mechanism. In rats, feeding a PR diet to the F_0 generation during pregnancy results in elevated blood pressure, endothelial dysfunction and insulin resistance in the F_1 and F_2 generations (Torrens et al., 2008; Martin et al., 2000; Zambrano et al., 2005), despite adequate nutrition during pregnancy in the F_1 generation. The adverse effects on glucose homeostasis of feeding a PR during pregnancy in the F_0 generation have been found in the offspring up to F_3 generation (Benyshek et al., 2006). The administration of dexamethasone to dams in late pregnancy induced increased expression of the glucocorticoid receptor (GR) and its target gene phosphoenolpyruvate carboxykinase (PEPCK) in the liver of the F_1 and F_2, but not F_3, offspring (Drake et al., 2005). These findings raise the important issue that assessment of true non-genomic transmission between generations requires studies which continue to at least the F_3 generation (Skinner, 2008). Transmission to the F_2 generation may represent either changes induced in the F_1 generation passing to the F_2 generation or because F_1 germ line cells, which give rise to the F_2 generation, may be affected directly by environmental cues from the grandmother. In the example described above loss of altered phenotype between the F_2 and F_3 generations suggests that the phenotype present in the F_2 generation may have resulted from exposure of the F_1 germ line to glucocorticoid.

There is substantial evidence for transgenerational epigenetic inheritance in non-mammalian species and its role in evolutionary biology has been reviewed (Gluckman et al., 2007b; Jablonka et al., 1995). Although epidemiological and experimental studies have shown transmission of induced phenotypes between generations, to date only one study has reported transmission of nutritionally induced epigenetic marks between generations. GR and PPARα promoters in 80 day old male grand-offspring of rats exposed to maternal PR diet during gestation were hypomethylated compared to controls, even though their dams received balanced nutrition throughout pregnancy (Burdge et al., 2007a). These findings imply that the female line is sufficient for transmission of such epigenetic information between generations, although other studies have shown transmission of phenotypes induced in the offspring by maternal exposure to dexamethasone in pregnancy through both male and female lines up to the F2, but not F3, generation (Drake et al., 2005). The tendency towards obesity in A^{vy} mice is

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exacerbated thorough successive generations (Waterland et al., 2008). Transmission of the obese phenotype was prevented by supplementation of females with a methyl donors and co-factors, although this was not associated with a change in the methylation status of the A^{vy} locus.

The mechanism by which induced epigenetic marks are transmitted to subsequent generations is not known. Since the transmission was only to the F_2 generation, a direct effect of the diet fed to the F_0 dams on germ cells which gave rise to the F_2 offspring cannot be ruled out. Sequential transmission from F_1 to F_2, and possibly beyond, would involve induction in the germ line of altered epigenetic marks and such changes in DNA methylation would have to be preserved during genome-wide demethylation during fertilization, possibly by a similar mechanism to that which preserves the methylation of imprinted genes (Lane et al., 2003) and/or by targeted preservation of nucelosome structure as occurs for specific developmental genes during spermatogenesis (Hammoud et al., 2009). An alternative possibility is that prenatal nutritional constraint induces physical or physiological changes in the female which, in turn, restrict the intra-uterine environment in which her offspring develop. In this case, transmission of an altered phenotype between generations would involve induction of changes in gene methylation *de novo* in each generation. If so, the magnitude of the induced effect, epigenetic or phenotypic, might differ between generations. However, this is not supported by the similarity in the reduction in birth size and blood glucose concentration in the F_1 and F_2 generations born to rat dams exposed to dexamethasone in late gestation (Drake et al., 2005), or the degree of hypomethylation of the hepatic GR and PPARα in the F_1 and F_2 offspring of dams fed a PR diet in pregnancy (Burdge et al., 2007a). Furthermore, induced phenotypic traits would not be passed through the male line (Drake et al., 2005).

8. Relevance of epigenetic processes to the risk of adult disease

We now live much longer than our hominid ancestors. Thus, mechanisms selected for fitness advantage in our earlier evolution may no longer be advantageous, or may be advantageous in the young and disadvantageous in health terms in the elderly. Fitness and health are not identical (Gluckman et al., 2009). Non-genomic epigenetic processes of transmitting environmental information between generations may assist our survival as we moved across changing environments. They may also serve to buffer critical aspects of our development, especially the vulnerable period of weaning in infancy, against short-term environmental changes occurring between generations (Kuzawa, 1998). There are limits to the environment that the fetus can sense and use to adjust its development (Gluckman and Hanson, 2004a). Such processes were not 'designed' to deal with the massive mismatch between the relatively constrained fetal environment and the modern postnatal environment of high-energy intake and low energy expenditure (Gluckman and Hanson, 2006), and so disease risk is amplified by a greater mismatch between the pre-natally predicted and actual adult environments. As a result, societies in rapid economic transition are particularly vulnerable (Popkin, 2001; Bhargava et al., 2004; Prentice and Moore, 2005; Gluckman and Hanson, 2004b). Epigenetic and other non-genomic inheritance processes may have conferred survival advantage on evolving hominids; they now exacerbate risk of disease for several successive generations and play a major part in the current epidemics of metabolic and cardiovascular disease (Gluckman and Hanson, 2004b; Gluckman and Hanson, 2004c). Additionally, the possibility is now being explored that exposure to xenobiotics such as endocrine disruptors may have multigenerational effects through female and male lines by actions on similar epigenetic mechanisms (Anway et al., 2005).

Lastly, returning to our starting point of population studies, we must note that there is increasing evidence for the effects of maternal obesity, excessive pregnancy weight gain and gestational diabetes as risk factors for later metabolic and cardiovascular disease in the offspring (Forsen et al., 1997; Silverman et al., 1996; Gale et al., 2007; Crozier et al., 2010), a concept again supported by experimental studies in animals (Aerts and Van Assche, 2006). These effects contribute to the rising incidence of such disease in both developed and developing societies, especially the effects which are passed transgenerationally. The extent to which such risk of disease operates by epigenetic processes is not known, although there is recent evidence that the offspring of high fat-fed dams show changes in the pattern of micro-RNA expression, in particular those associated with IGF expression and methyltransferases (Zhang et al., 2009).

9. Conclusion

Variation in the expression of the genome leads to expression of novel phenotypes which have implications for understanding evolutionary biology and risk of disease. Epigenetic changes, in particular DNA methylation, provide a 'memory' of developmental plastic responses to early environment and are central to the generation of phenotypes and their stability throughout the life course. Their effects may only become manifest later in life, e.g. in terms of altered responses to environmental challenges. Further research is needed to determine whether measurement of epigenetic marks in early life could be used as biomarkers to identify individuals who have experienced environmental perturbations in development, and thus who are more likely to develop premature cardiovascular and metabolic disease or other NCD. Understanding these processes will provide a substantial step forward in biological research including the developmental origins of health and disease.

Uncited references

Galili et al., 2007; World Health Organization, 2008.

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