DNA methylation, ageing and the influence of early life nutrition

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It is well established that genotype plays an important role in the ageing process. However, recent studies have suggested that epigenetic mechanisms may also influence the onset of ageing-associated diseases and longevity. Epigenetics is defined as processes that induce heritable changes in gene expression without a change in the DNA nucleotide sequence. The major epigenetic mechanisms are DNA methylation, histone modification and non-coding RNA. Such processes are involved in the regulation of tissue-specific gene expression, cell differentiation and genomic imprinting. However, epigenetic dysregulation is frequently seen with ageing. Relatively little is known about the factors that initiate such changes. However, there is emerging evidence that the early life environment, in particular nutrition, in early life can induce long-term changes in DNA methylation resulting in an altered susceptibility to a range of ageing-associated diseases. In this review, we will focus on the changes in DNA methylation that occur during ageing; their role in the ageing process and how early life nutrition can modulate DNA methylation and influence longevity. Understanding the mechanisms by which diet in early life can influence the epigenome will be crucial for the development of preventative and intervention strategies to increase well-being in later life.

Epigenetic mechanisms

Epigenetics literally means ‘on top’ of genetics and is defined as processes that induce heritable changes in gene expression without a change in the nucleotide sequence. The major epigenetic mechanisms are DNA methylation, histone modification and non-coding RNA. Here we will focus on DNA methylation but it is clear that there is substantial crosstalk between these epigenetic processes.

DNA methylation

Methylation is a common modification in mammalian genomes with the cytosine base being most frequently...
methylated to give rise to 5-methyl cytosine. The majority of methylated cytosines are found as part of a cytosine and guanine dinucleotide (CpG) where p denotes the intervening phosphate group. CpG dinucleotides are not distributed randomly through the genome but are found clustered at the 5' ends of genes in regions known as CpG islands(3). Hypermethylation of these CpG islands is associated with transcriptional repression, whereas hypomethylation of CpG islands is associated with transcriptional activation(10). DNA methylation induces transcriptional silencing by preventing the binding of transcription factors to the DNA or by recruiting methyl CpG-binding protein 2 to the DNA(9), which in turn, recruits histone-modifying complexes(10).

DNA methylation is essential for normal development; it is responsible for the asymmetrical silencing of imprinted genes(5), X-chromosome inactivation(6,9) and for the tissue-specific gene expression(8). DNA methylation patterns are largely established during development and early postnatal life. Following fertilisation, the methylation marks on the maternal and paternal genomes are largely erased, this is then followed by global de novo methylation just prior to blastocyst implantation when CpG mainly in repressive heterochromatin regions and in repetitive sequences are methylated(10,11). The methylation of tissue-specific genes occurs during embryogenesis and early postnatal life and is essential for cell specification. The de novo methylation of CpG dinucleotides is catalysed by the DNA methyltransferases (DNMT) 3a and 3b(12), and is maintained through mitosis by gene-specific methylation of hemi-methylated DNA by DNMT1(13).

DNA methylation works together with histone modifications to regulate gene expression. In a cell, DNA is wrapped around a core of eight histone proteins, which are subject to modifications including acetylation, methylation, ubiquitination, sumoylation and phosphorylation(14). The establishment of these marks on the histone tails is often referred to as the histone code, which leads to the binding of effector proteins that in turn bring about specific cellular processes. Histone acetylation is associated with transcriptional activity and an open chromatin state, and is brought about through histone acetyl transferases. Histone methylation of lysine (K) residues within the histone tail can either be an active or repressive mark depending on the specific lysine involved(15). Histone H3 K4 methylation is associated with gene activation, whereas histone H3 K9 methylation with gene silencing(16).

Crosstalk between DNA methylation and histone modification clearly occurs. Methylated DNA is bound by methyl CpG-binding protein 2, which recruits both histone deacetylases, which remove acetyl groups from the histones(17), and histone methyl transferases, such as Suv39H1(16) which methylates K9 on histone H3, resulting in a closed chromatin structure and transcriptional silencing. Recent studies have also shown that DNMT1 can be recruited by a number of histone modifying enzymes such as histone deacetylases 1 and histone deacetylases 2, as well as the histone methyl transferase, enhancer of zeste homologue 2(20,21), suggesting that chromatin structure may also determine DNA methylation status.

DNA methylation, C1 metabolism and diet

Methyl groups for all biological methylation reactions including DNA methylation are primarily supplied from dietary methyl donors and cofactors via C1 metabolism(22). In this pathway, methionine is converted to S-adenosylmethionine, the universal methyl donor. After transferring the methyl group, S-adenosylmethionine is converted to S-adenosylhomocysteine, which is then converted to homocysteine. Homocysteine is then either recycled to methionine by the enzyme betaine homocysteine methyltransferase, which uses betaine or choline, or via a folate-dependent remethylation pathway, where 5-methyl tetrahydrofolate is reduced to 5,10-methylene tetrahydrofolate by 5,10-methylentetrahydrofolate reductase. This methyl group is then used by methionine synthase to convert homocysteine to methionine using vitamin B12 as the cofactor. This reliance on dietary sources of methyl donors and cofactors for DNA methylation reactions had led to the suggestion that nutrition may affect both the establishment and maintenance of DNA methylation patterns with long-term consequences for health. However, it is only recently that the full impact diet can have on DNA methylation and health has been realised and this will be discussed later in the review.

DNA methylation is dynamically regulated

DNA methylation was originally thought to be a very stable mark and once methylation marks were established during development, they were then stably maintained through the life-course. This premise was based on the thermodynamic stability of the methylation mark and the uncertainty of whether a biochemical mechanism existed by which the methyl group can be directly removed from 5-methylcytosine(23). Thus, it was assumed that DNA demethylation could only occur passively through a failure of the maintenance DNMT to copy the methylation mark during DNA replication. However, this concept has now been challenged, as there have been a number of studies, which have shown active demethylation. For instance, active demethylation has been observed on the paternal genomic DNA in the zygote upon fertilisation(11,24), on the synaptic plasticity gene reelin in the hippocampus upon contextual fear conditioning(24,25) and on the interferon gamma gene upon antigen exposure of memory CD8T cells(25). Moreover, a number of potential DNA demethylases have been discovered including ten–eleven translocation proteins(26,27), methyl-binding domain protein 2(28), methyl-binding domain protein 4(29), the DNA repair endonucleases XPG (Gadd45a)(30) and a G/T mismatch repair DNA glycosylase(31). These potential DNA demethylases function not by directly
removing the methyl group from cytosine but through multistep processes linked either to DNA repair mechanisms or through further modification of 5-methylcytosine.

**DNA methylation changes in the ageing cell**

Changes in DNA methylation patterns have been reported during ageing. Berdyshev *et al.* (32) first reported a global decrease in DNA methylation during ageing in the humpback salmon. Subsequently, a large number of studies in many different species including rat, mouse, cow, hamsters and human subjects have all shown a progressive loss of DNA methylation during ageing (37-35), primarily at repetitive sequences (33). The expression of DNMT have also been reported to change during ageing. Casillas *et al.* (36) found that while the expression of DNMT1 and DNMT3a decline during ageing, DNMT3b expression increases. As DNMT1 is the maintenance DNMT, a decrease in its expression during ageing is consistent with the increase in global hypomethylation seen in an ageing cell. However, alongside the increase in global hypomethylation observed during ageing, there is also an increase in gene-specific promoter hypermethylation. Examples of genes that are hypermethylated during ageing, include the oestrogen receptor (37), insulin-like growth factor-2 (IGF-2), tumour-suppressor candidate 3 and myogenic differentiation 1 (38), death-associated protein kinase, E-cadherin, alternative reading frame relative to p16 and tissue inhibitor of metalloproteinase 3 (39). The hypermethylation of gene promoters during ageing occurs more frequently at promoters associated with bivalent chromatin domains (37), promoters with both an activating H3 K4 methylation mark and a repressive H3 K27 trimethylation mark. Bivalent chromatin-associated promoters are generally found in developmental control genes, and they are also frequently hypermethylated in cancers (40).

To investigate how DNA methylation may change over time, a number of groups have used longitudinal studies. Feinberg *et al.* (41), used a genome-wide screen to investigate about 4 million CpG sites over a 11-year time period and found 227 regions that showed extreme inter-individual variability (variably methylated regions) across the genome. These variable methylated regions fell into two groups: those that were dynamic and those that remained stable over the 11-year period. In a larger study, Bjornsson *et al.* (42), who measured the global DNA methylation levels in whole blood from 111 individuals (age 59–86 years) followed over 11 years and 127 individuals (age 5–72 years) followed over 16 years found that 8–10 % of individuals in both groups showed changes in methylation >20 % over an 11–16-year time span, which is consistent with the suggestion that there is an accumulation of epigenetic changes during ageing. The changes they observed showed familial clustering of both increased and decreased methylation. Because most family members did not share households during the time between sample collections, this suggests that genotype can influence the rate of change in methylation over time.

To examine the accumulation of epigenetic changes with age without the confounding influence of genetic background, a number of groups have used monozygotic twins to study variation in DNA methylation over time (43). Comparison of DNA methylation patterns in 3- and 50-year-old monozygotic (MZ) twin pairs found that while the genomic distribution of 5-methylcytosine showed significant overlap in the 3-year twin pairs, the distribution of DNA methylation marks were distinct in the 50-year twin pairs (44). Talens *et al.* (45) also found that variation in global DNA methylation levels in 460 individuals, which included 230 MZ pairs aged from 18 to 89 years increased proportionally with age. They also examined mean methylation and variation in DNA methylation across this age span in a number of candidate genes associated with common diseases. They found that while mean methylation differences between the young and the old age groups at these loci were relatively small, there was again an increase in variation of DNA methylation with age. However, there was a substantial difference in the stability of different CpG loci, the most pronounced increases in age-related variation in DNA methylation occurring at CpG sites associated with metabolic and homeostatic-related genes, such as IGF-2, corticotropin-releasing hormone and leptin. Bocklandt *et al.* (46), who measured DNA methylation in saliva samples of thirty-four pairs of identical twins, aged between 21 and 55 years, identified eighty-eight CpG sites near eighty genes where methylation was significantly correlated with age. Three CpG loci corresponding to the ectodysplasin A receptor-associated death domain, target of myb1 (L1), and neuronal pentaxin II genes were highly correlated in a linear manner with age over five decades (46) and using just two cytosines from these loci, they found that methylation at these loci explained 73 % of the variance in age, and was able to predict the age of an individual with an average accuracy of 5.2 years.

A number of studies have shown considerable epigenetic differences between both monozygotic and dizygotic twin pairs even at birth, which suggests that the intrauterine environment is a period of enhanced epigenetic sensitivity. Ollikainen and Craig (47), examined the methylation of four differentially methylated regions associated with the IGF-2/H19 locus in multiple tissues at birth and found that methylation discordance was present within twin pairs, with dizygotic pairs showing greater discordance than MZ pairs. Gordon *et al.* (48) using a genome-wide approach to screen for differences at individual CpG sites, also reported in MZ twins at birth, a wide range of within-pair methylation differences, but the discordance levels were in general lower than the dizygotic. Interestingly, within-pair methylation discordance increased with increasing distance from CpG islands (up to 4kb) in all tissues for both MZ and dizygotic pairs, with no evidence for a further increase at distances >4kb, suggesting that CpG islands may be under tighter epigenetic control than other regions of the genome.
Changes in histone posttranslational modifications during ageing

Changes in the abundance of histone proteins and histone modifications also occur during the ageing process. Levels of the histone proteins H3, H4 and H2A are greatly reduced in ageing cells (49,50). Reductions in histone H4 acetylation (51), histone H3 K9 methylation (52) and histone H3 K27 trimethylation (53) are also seen during ageing, whereas there is an increase in histone H4 K16 acetylation (52) and histone H4 K20 trimethylation (54,55). There is also a global decrease in heterochromatin (56) and an increase in senescence-associated heterochromatin foci (57). The expression of many of the enzymes that bring about these changes are also altered in the ageing cell. For instance, enhancer of zeste homologue 2, the catalytic subunit of the polycomb complex, which mediates H3 K27 methylation is decreased during ageing in a variety of cell types (53,58), while Sirtuin1, an NAD-dependent deacetylase that deacetylates both histones and protein substrates including p53 and PPARγ, coactivator 1 α is up-regulated (59–61). Such changes are reviewed elsewhere (62), although as there is crosstalk between DNA methylation and histone modifications, the changes in the histone code may signal a subsequent change in DNA methylation, as seen with the bivalent chromatin domains, which appear to be preferentially targeted for DNA hypermethylation during the ageing process.

The role of epigenetics in ageing-associated diseases

Studies to date do suggest there are loci-specific epigenetic changes within the genome as we age, but are these changes really causal or a consequence of the ageing process? Many of the changes seen in ageing cells are very similar to those observed in cancer cells, consistent with the idea that ageing is a major risk factor for the development of cancer. Global hypomethylation was one of the first epigenetic alterations to be found in human cancer (63). The loss of methylation occurs mainly in repetitive DNA sequences and the coding regions and introns of genes (64) and this increases as the cancer progresses (65). DNA hypomethylation may increase genomic instability, induce the reactivation of transposable elements, and the loss of imprinting (66), contributing to cancer progression and pathogenesis. However, alongside global hypomethylation, cancer cells also exhibit an increase in gene-specific hypermethylation of tumour suppressor genes (67). The pattern of gene-specific hypermethylation appears to be tumour type (68) and tumour stage-dependent (69). Hypermethylation can affect genes involved in the cell-cycle control, genome stability and repair, cell adhesion, apoptosis and angiogenesis. Hypermethylation, as in ageing cells, occurs more frequently at bivalent chromatin domain promoters (1). H3 K27 trimethylation, one of the marks of bivalent chromatin, is induced through the histone methyl transferase, enhancer of zeste homologue 2 and the polycomb complex, the presence of which has been reported to lead to the recruitment of DNMT and de novo methylation (70). In cancer, it has been suggested that the hypermethylation of bivalent genes leads to the silencing of genes required for differentiation, driving cell proliferation and self-renewal and increasing cancer risk (71). Thus, the hypermethylation of the bivalent promoters during ageing may act as an ‘epimutation’, contributing to the multiple mutations required for cancer development.

However, there are also marked differences between an ageing and cancer cell. In an ageing cell, the tumour suppressor gene p16INK4a (72–74). Polycomb proteins and the associated H3 K27 trimethylation mark normally blanket the p16INK4a gene locus, but levels of the polycomb protein enhancer of zeste homologue 2 and H3 K27 methylation decline in stressed and ageing cells, which leads to a loss of H3 K27 trimethylation at the p16INK4a locus and gene activation (75). This induction of p16INK4a during ageing promotes longevity in the short term by preventing the development of cancer. However, in the long term its induction may ultimately limit life span as p16INK4a expression drives the cell towards a senescence phenotype, restricting the regenerative capability and function of tissues and enhancing the ageing process. In contrast, in cancer cells, polycomb proteins are often up-regulated (76) and the p16INK4a gene is frequently hypermethylated and silenced (67).

Mechanisms of epigenetic change during ageing

The mechanism(s) by which DNA methylation changes accumulate in ageing cells is still poorly understood, but it has been proposed that ageing-associated changes in DNA methylation may be induced both by stochastic variation and environmental factors (Fig. 1).

Stochastic factors

Stochastic changes in DNA methylation have been proposed to explain some of the changes in DNA methylation seen during the ageing process. Stochastic changes are non-environmentally induced random changes in DNA methylation. These may arise for instance due to a lack of fidelity when the methylation mark from the parental strand is copied to the newly synthesised strand during the process of replication (77). This loss of epigenetic fidelity may well be accentuated during ageing as levels of DNMT1, the maintenance DNMT, has been reported to decline in ageing cells (78). This may lead to an increase in epigenetic heterogeneity within a cell population, and an increase in inter-cell gene expression differences within tissues during ageing (79). The accumulation of such epigenetic changes may ultimately lead to a decline in tissue function and eventual malfunction.
DNA methylation, ageing and the influence of early life nutrition

One of the best examples of how diet can alter phenotype and longevity through the altered methylation of DNA is seen in studies on the honeybee. Queen and worker bees are genetically identical, but differ in their morphology, reproductive capacity and life span, queen bees living 20-fold longer than worker bees. Maleszka (81) showed that if female larvae were incubated in the presence of Royal Jelly they developed into queen bees, whereas if the larvae were incubated in the absence of Royal Jelly they developed into sterile worker bees. However, silencing the expression of DNMT3 in the larvae increased the proportion of larvae developing into queen bees even in the absence of Royal Jelly. This shows that nutrition can profoundly affect phenotype and it does so through the altered methylation of DNA (82).

In rodents, alterations in maternal diet have also been shown to induce changes in DNA methylation in the offspring. In Agouti viable yellow mice, supplementation of the maternal diet with dietary methyl donors and cofactors (folic acid, vitamin B12, choline and betaine) shifted the coat colour of the offspring from yellow (agouti) to brown (pseudo-agouti) and this was associated with the increased methylation of the agouti gene (83).

Maternal diet can also alter the methylation of key metabolic genes within the offspring. For instance feeding rats a protein restricted diet during pregnancy induced the hypomethylation of the glucocorticoid receptor and PPAR-α promoters in the livers of juvenile and adult offspring, which was associated with an increase in glucocorticoid receptor and PPARα mRNA expression (84,85). Maternal protein restriction induced the hypomethylation of four specific CpG dinucleotides within the promoter of PPARα, two of which predicted the level of the mRNA transcript, in the juvenile offspring (86). As these CpG sites lie within transcription factor-binding sites, changes in the methylation status of these CpG induced during development may affect later transcriptional induction of PPARα by the specific stimuli and the capacity of the tissue to face the metabolic demand. In contrast to the effect of the maternal protein restricted diet, maternal dietary restriction during pregnancy induced the hypermethylation of glucocorticoid receptor and PPARα promoters and a decrease in glucocorticoid receptor and PPARα expression (87). Thus, the effects of maternal nutrition on the epigenome of the offspring depend upon the nature of the specific maternal nutrient challenge.

Similarly, alterations in paternal diet in rodents have been associated with altered DNA methylation in the offspring. Feeding fathers a low-protein diet prior to mating led to widespread changes in DNA methylation (10–20 %) in the liver of the low-protein offspring compared with controls, including an increase in methylation at an intergenic CpG island 50kb upstream of the PPARα gene (88). Ng et al. (89) have also shown that the IL-13 receptor α2 promoter was hypomethylated in female offspring after high-fat feeding the fathers.

**Environmental factors**

There is also increasing evidence that a number of environmental factors including nutrition, stress, placental insufficiency, endocrine disruptors and pollution can induce changes in the epigenome. These studies suggest that the epigenome is most susceptible to such factors during early life. Both human epidemiological and animal studies have shown that the early life environment is an important determinant of lifelong health (79). Such findings have led to the Developmental Origins of Adult Disease hypothesis, which suggests that environmental factors during early stages of development can result in long-lasting effects on metabolism and physiology, altering the risk of disease in later life (80). The environmental modulation of the epigenome in early life suggests a mechanism whereby early life environmental factors may be able to influence future health and longevity and indeed there is growing evidence that epigenetics processes are central to the mechanism by which the environment can influence future disease risk.

**Nutritional modulation of the epigenome in early life**

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**Human studies of induced epigenetic change by maternal nutrition**

To date there is increasing evidence that early life nutrition can induce epigenetic alterations in human subjects. Heijmans et al. and Tobi et al. have reported DNA methylation differences in individuals who were periconceptually exposed to famine during the Dutch Hunger Winter (80,91). They found a decrease in the methylation of the imprinted IGF-2 gene and increases in the methylation of IL-10, leptin, ATP-binding cassette A1, guanine nucleotide-binding protein genes in genomic DNA isolated from whole blood cells from individuals.
who were exposed to famine in utero compared with unexposed same-sex siblings\textsuperscript{(91)}. Periconceptual folic acid supplementation (400 μg/d) has also been shown to alter the methylation of five CpG in the IGF-2 differentially methylated region in children from the folic-acid-supplemented mothers\textsuperscript{(92)}.

One implication from these human and animal studies is that perturbations in early life nutrition can induce changes in the epigenetic regulation of genes, which then persist throughout the life-course leading to alterations in metabolism and disease risk, suggesting that it may be possible to detect such epigenetic changes in early life and use these to predict later metabolic capacity and future disease risk. Recently, Godfrey et al.\textsuperscript{(93)} reported that epigenetic marks measured in umbilical cord tissue at birth can predict phenotypic outcomes in later childhood. In two independent cohorts, the epigenetic state of a single CpG site in the promoter region of the transcription factor, the retinoid X receptor α, was found to be strongly associated with childhood adiposity and future disease risk. Interestingly, calorie restriction during adulthood has also been reported to induce changes in DNA methylation. Interestingly, calorie restriction has been shown in many short-lived species to increase life span, and to delay a range of age-associated diseases in higher mammals\textsuperscript{(101,102)}. The precise mechanisms of calorie restriction-induced longevity are unclear and may involve a range of mechanisms\textsuperscript{(103)} including DNA methylation. For instance, calorie restriction has been associated with a decrease in H-ras and p16\textsuperscript{INK4a} methylation\textsuperscript{(104)} and an increase in DNMT1 activity\textsuperscript{(105,106)} potentially affecting/reversing the global hypomethylation seen in ageing cells.

\textbf{Future directions}

These studies show that DNA methylation is highly dynamic, and responsive to the environment. DNA methylation permits different phenotypes to be generated from a single genome, allowing an organism to adapt to its environment by modulating the expression of its genes and the processes that they control. The epigenome appears to be most susceptible to environmental factors in early life when the methylation marks are being established; it is also clear that the environment can alter DNA methylation even in adulthood, suggesting that these epigenetic processes function as part of a lifelong adaptation mechanism. However despite the fact that the epigenome is highly dynamic, it is at the same time strictly controlled ensuring tissue-specific and cell-specific gene expression. What makes one CpG stable and another susceptible to environmental influence is not known nor are the pathways leading from the nutritional cue to a DNA methylation change. However, it is likely that histone modifications as well as non-coding RNA may well be part of this response.

Ageing results in epigenetic changes induced by both environmental and stochastic factors. To date stochastic variation in DNA methylation has been difficult to study due to the lack of single-cell technology to investigate methylation changes at such a level, however with increasing technological advances this should become possible. It will be important to establish the cause and effect relationship between ageing and such epigenetic changes. What is the effect of accumulating stochastic epigenetic changes on tissue function? How does the environment influence such changes? If we can begin to answer some of these questions this will potentially allow the development of novel epigenetic-based preventative and intervention strategies to decrease ageing-associated diseases and increase well-being in later life.
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Conflicts of Interest

None.

Authorship

K. A. L. and G. C. B. wrote the initial draft. L. G. and S. H. provided corrections and comments. All authors have read and approved the final manuscript.

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