Chapter 2
Dietary Restriction, Dietary Design and the Epigenetics of Aging and Longevity

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Abstract As the mechanisms of long-term control of gene expression, it would seem that the various aspects of epigenetics would be important for, even determinants of, aging and longevity. Yet few data connect these directly. Epigenetics changes with age; in particular DNA methylation and histone acetylation have been well studied. For humans, a DNA methylation based "epigenetic clock" has been developed to track the apparent chronological age of people, tissues, stem cells and cancers. Histone acetylation is important for maintaining cognitive memory in animals and restoration of histone acetylation improves memory in older animals. Several aspects of diet and metabolism affect epigenetics. These include the effects of glucose on histone acetylation and methylation, the effects of acetyl-coenzyme A and energy metabolism on histone acetylation, natural histone deacetylase inhibitors found in foods such as broccoli and garlic affecting histone acetylation and DNA methylation, and the effects of methyl metabolism and nutrients such as folate on DNA and histone methylation. Models of greatly extended longevity should be studied for epigenetics to test if epigenetics are preserved when longevity is extended and then studies to manipulate epigenetics in these models should be done to measure their effects on longevity.

Abbreviations

Ac	Acetyl group
AcCoA	Acetyl-coenzyme A
AGE	Advanced glycation end products
AMPK	AMP activated protein kinase
BHB	D-beta-hydroxybutyrate
CR	Calorie restriction
DCCT	Diabetes Control and Complications Trial
DIM	Diindolylmethane
DNMT	DNA methyltransferase

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B.P. Yu (ed.), *Nutrition, Exercise and Epigenetics: Ageing Interventions*, Healthy Ageing and Longevity 2, DOI 10.1007/978-3-319-14830-4_2

DR	Dietary restriction
EDIC	Epidemiology of Diabetes Intervention and Complications
ERV	Endogenous retrovirus
H3K4	H3 histone tail lysine 4
H3K9	H3 histone tail lysine 9
H4K12	H4 histone tail lysine 12
HAT	Histone acetyltransferase
HbA1c	Glycated hemoglobin used as a measure of long-term average blood glucose levels
HDAC	Histone deacetylase
HDACI	Histone deacetylase inhibitor
HERV-K	Human endogenous retrovirus virus K
HMT	Histone methyltransferase
IAP	Intracisternal A particle
iPSC	Induced pluripotent stem cell
L1	LINE1
LINE1	Long interspersed nuclear element 1
L1Md	An L1 sequence of mice
LSD1	Lysine-specific demethylase 1
LTR	Long terminal repeat
MS-275	Entinostat (an HDACI)
MuERV	Murine endogenous retrovirus
NFkB	Nuclear factor kappa-light chain enhancer of activated B cells
p65	Transcription factor p65 encoded by the RELA gene
RAGE	Receptor for advanced glycation end products
RTG	Yeast genes important in communication between the mitochondria and nucleus
SAH	*S*-adenosylhomocysteine
SAHA	Suberoylanilide hydroxamic acid
SAM	*S*-adenosylmethionine
Set7	Enzyme that methylates lysine residues (e.g. on histones)
TCA	Tricarboxylic acid (cycle) or Krebs cycle

2.1 Introduction

The idea that epigenetics needs to be intact to provide a "young" pattern of gene expression is an old one [1, 2]. We know that gene transcription profiles change with age and that dietary restriction (DR) can slow these changes [3]. Numerous studies show epigenetic change with age and it is regularly assumed that this epigenetic "drift" contributes to some or all of the functional decline and disease of aging [2, 4]. However, it is not at all clear what factors are driving epigenetic

change with aging and to what degree epigenetics controls longevity. In some models of extended longevity, developmental factors [5, 6], dietary factors (especially DR) [7–9] and specific genetic factors [5, 6, 10] clearly increase lifespan. Presumably epigenetics is maintained better in these models than in same chronological age controls, yet few data are available on this point. Further, if epigenetics is important for longevity, certain manipulations of epigenetics per se should extend lifespan, although this has not been demonstrated. However it is possible, even likely, that developmental, metabolic and other factors are controlling epigenetics as just one part of a lifespan extending process. Thus, we will look at various dietary and metabolic influences on epigenetics that may influence health and lifespan.

2.2 Epigenetic Mechanisms

Epigenetics is the collection of heritable chromatin modifications, recursive RNA expression and other heritable factors outside of the DNA sequence itself that affect gene expression. Epigenetics also helps guide the health and development of plants and animals from fertilization and cell division through disease and aging. A broad range of factors affect epigenetics. Epigenetics is often reviewed [2, 11–16] and only a broad overview will be given here. Cancer epigenetics, in particular, has been well studied and helps inform aging and lifespan research.

DNA methylation

The dinucleotide CG (called CpG) in polymeric DNA is the main target of DNA methyltransferases (DNMTs) that methylate the 5 position of cytosines to form 5-methylcytosine [17]. The methyl group donor *S*-adenosylmethionine (SAM) is the other substrate in this reaction which ties DNA methylation to methyl metabolism. One product of this reaction is *S*-adenosylhomocysteine (SAH) which is an inhibitor of most methylation reactions but can be recycled back to SAM by methyl metabolism. The CpG sequence is a palindrome and one of the DNMTs, called DNMT1, copies the methylation pattern of a parental DNA strand onto the daughter strand during DNA replication in a process called maintenance methylation. Methylation of DNA also occurs de novo where unmethylated CpGs are methylated by DNMT1 (in a de novo role) and by DNMT3a and DNMT3b (dedicated de novo DNMTs). DNA methylation patterns can be inherited and propagate gene expression patterns in generations of cells and even in generations of animals [11, 18–20].

Generally, DNA methylation near transcription start sites silences gene expression [17, 21] by attracting methylated DNA binding proteins as well as preventing transcription factor access. Protein complexes that modify histones reinforce, or in some cases initiate, transcriptional silence. This can leave a gene silenced or in other cases it can "poise" a silenced region for rapid activation of gene expression [16].

DNA methylation is removed by base excision repair of 5-methylcytosine and/or by multiple steps of methyl group oxidation. Oxidized products, 5-hydroxymethylcytosine, 5-formylcytosine and 5-carboxycytosine are found in mammalian DNA and are thought to be intermediates in demethylation [22, 23]. DNA methylation patterns are extensively rewritten post-fertilization and in primordial germ cells, times when demethylation is prominent [22, 23].

Histone methylation

Histones, the major DNA binding proteins of chromatin, are methylated by SAM through the action of histone methyltransferases (HMTs) [16, 24]. Histone methylation can either promote or silence gene activity depending on which lysine and arginine sites in the histone sequence are methylated. HMTs, histone demethylases and methylated histone binding proteins are highly specific for the site (position) and the degree of methylation (number of methyls on an amino acid side chain). There are greater varieties and specificities of these enzymes and binding proteins for histone methylation than for respective enzymes and binding domains involved in histone acetylation and DNA methylation. As discussed elsewhere in this article, without adequate methyl metabolism and SAM both DNA methylation and histone methylation can be expected to drift. Histone methylation can direct both DNA methylation and histone acetylation and thus adequate methyl metabolism and SAM are particularly important for epigenetics.

Histone acetylation

Histones are also modified by acetylation of their lysines, which nearly always promotes gene activity. This depends on histone acetyltransferases (HATs), the acetyl donor acetyl-coenzyme A (AcCoA), and histone deacetylases (HDACs) [12]. There is a broad array of effects of diet and energy metabolism on histone acetylation [12, 25–28]. In addition, many foods contain compounds that are HDAC inhibitors (HDACIs) which tend to preserve histone acetylation and promote gene activation [29–33].

Chromatin non-coding RNAs

Some RNA molecules interact with chromatin to give a range of effects on gene expression. The X-inactive specific transcript and many other RNAs have important roles in epigenetics [34–37]. The expression of some genes encoding protein gene products are affected by small RNA genes that are embedded in the protein coding genes. Transcription of these small RNA coding regions can interfere with and slow the expression of the protein coding genes. Further, RNAs have a range of effects when binding to the chromatin or other nascent RNA transcripts. RNA expression is amenable to direct analysis by next generation sequencing [38].

2.3 Epigenetics with Aging

Epigenetics drifts and breaks down with aging and age-related disease [2, 4]. A fundamental issue in addressing epigenetics in aging is the paradoxical situation where the average DNA methylation over the genome declines with age (global

hypomethylation) concomitant with gradual, age-related DNA hypermethylation of some specific genes.

Early studies mainly showed global hypomethylation with age in animal tissues [39–42] and drift or hypomethylation with mammalian cells in vitro [43, 44]. Later studies of specific genes most often showed gradual DNA hypermethylation with age in normal tissues [45–47].

In a recent statistical and analytical *tour de force*, Steve Horvath [48] used publicly available datasets (from Illumina 27 and 450 K array platforms) covering large numbers of human genes, to show that age-related changes in DNA methylation are roughly half hypo- and half hypermethylation. Each data set contained DNA methylation values for over 21,000 CpGs from which Horvath identified an "epigenetic clock" based on 353 CpGs that closely correlate with a person's chronological age.

Horvath also showed that induced pluripotent stem cells (iPSCs, made from adult donor cells) have an age of zero and thus could be considered an example of age reversal at the epigenetic and cellular level. On the other end of the aging spectrum, some cancers showed an advanced age well beyond that of their host. This advanced age averaged 36 years (past that of the patient) demonstrating age acceleration at the epigenetic level. Age reversal in iPSCs and accelerated aging in cancer are not new ideas yet they are given greater strength and are quantified in Horvath's findings. Expressing the "age" of stem cells and cancer in terms of the "epigenetic clock" designed to track the age of normal human tissues at many ages could be a very useful tool. Among other applications, it seems that such an epigenetic tool could be a marker for the success of interventions into aging and lifespan. Testing this will require considerable research including development of epigenetic clocks in other species (such as mice) that can be used as models of extended lifespan.

The study of DNA methylation has presented many paradoxes over the years [49, 50]. One of these that occurs with aging, as mentioned above, is global hypomethylation concomitant with age-related gene specific hypermethylation [4, 25]. Interestingly, this same phenomenon occurs to an even larger degree in most cancers [4, 25]. However, this particular "DNA methylation paradox" is not a universal feature of human disease as has been recently shown with autoimmunity where mainly DNA hypomethylation occurs [51, 52]. In cancer and aging this concomitant DNA hypo- and hypermethylation may be driven, in part, by other aspects of epigenetics, especially histone acetylation.

While there are fewer studies of histone modification than DNA methylation with age, an increasing number of studies show changes in histone modifications with age [53–55]. Histone acetylation is particularly important here because some interventions can reverse these age-related changes [54, 56, 57]. Epigenetics is important not just for cell memory but for cognitive memory formation and learning [58].

To study memory in aged animals, Peleg et al. [54] measured hippocampus-dependent associative learning in mice at ages of 3, 8 and 16 months. Although all ages of mice performed similarly on many tests, old mice (16 months of age) did poorly in associative learning and a few other tests compared to younger mice.

In young mice, learning increased histone H4 lysine 12 acetylation (H4K12Ac) and changed the expression of 2,229 genes. In old mice H4K12Ac did not change significantly and only 6 genes were differentially expressed. Importantly, treatment with HDACIs increased H4K12Ac and improved learning in 16 month old mice.

Alzheimer's disease has been studied in mouse models using HDACIs [56]. Normal mice were compared with Alzheimer's mice after intraperitoneal HDACI injections. Normal mice were unaffected whereas the memory of Alzheimer's mice was significantly improved. More recent studies show that HDACIs can increase the expression of proteins that degrade, bind or transport amyloid beta-peptide thus reducing its contribution to cell death and Alzheimer's [57]. These studies show that HDACIs can reverse memory loss due to age-related dementia and Alzheimer's in mice.

In order to address the reduced effectiveness of some medications in the elderly, Montalvo-Ortiz et al. [59] studied the effectiveness of haloperidol in aged mice. They discovered that haloperidol efficacy was increased when mice were pretreated with the HDACIs valproate or entinostat (MS-275) and that this increased efficacy was correlated with increased histone acetylation of the c-fos promoter in the nucleus accumbens shell and prefrontal cortex. These combined HDACI and haloperidol treatments increased c-fos expression to levels comparable to those in young mice.

Some studies using cell culture and adult animals show that DNA methylation, histone acetylation and other epigenetic modifications can change over short periods (minutes or days) [58, 60]. With age there seems to be less epigenetic plasticity and flexibility and this leads to the age-related diminution of memory and other processes that require epigenetic change [2, 54, 55]. Several studies discussed here show improved memory in aged animals by use of HDACIs. This raises the very real possibility of using foods (such as broccoli, [32, 33]), supplements (such as butyrate, DIM or sulforaphane) or drugs (such as valproate or SAHA) to slow or reverse age-related memory loss and dementia. Other aspects of aging might also be improved by such treatments.

2.4 Dietary and Metabolic Factors Affecting Epigenetics

Dietary Restriction

Restricting the amount of food while avoiding malnutrition (dietary restriction or DR) or specifically restricting just the number of calories consumed (calorie restriction or CR) can extend lifespan and delay many symptoms of aging in a wide range of animals including yeast, nematodes, fruit flies, mice and rats [61, 62]. DR can also reduce or delay a number of age-related diseases, most notably cancer [63–66]. Although DR has not been shown to extend lifespan in humans, DR does improve glucose regulation and decrease body temperature and inflammation in humans and other mammals [62, 67–70]. Several signaling pathways are affected by DR, or may

mediate DR's effects. These include insulin, growth hormone, insulin-like growth factor-1 and intracellular pathways connected to mTOR activity [71–73]. DR also lowers the levels of a population of circulating micro RNAs that increase in amount with age in mice [38]. While DR probably affects most or all cells, some have argued that many, if not most, of DR's signaling effects and protective effects are mediated by the ventromedial hypothalamus [74]. This question of how DR exerts its effects is important. Does DR firstly act by broad metabolic change or firstly by altering central control by the ventromedial hypothalamus? The answer to this question affects where we should look for epigenetic change and other effects of DR and where we should look for other mechanisms that affect longevity. An important effect of DR is regulation of glucose levels [74]. Glucose in particular has been shown to affect epigenetics in several cell types and, at the whole body level, glucose causes what has been termed "glycemic memory" [13].

Glucose

Much of what we know about epigenetic changes effected by glucose comes from studies of diabetes. The results of these studies are also relevant to DR, diet (especially glycemic index), aging and longevity.

Well-regulated diabetes through intensive therapy (versus conventional therapy) seems to have lasting effects that extend well beyond particular periods of glucose control or specific treatment regimens [75–78]. The Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications study (EDIC) and the United Kingdom Prospective Diabetes Study indicate that periods of good glycemic control result in large health differences in diabetic subjects (types 1 and 2) many years later [76–80]. These include differences in vascular pathology as well as nephropathy and retinopathy. Several terms are used for this phenomenon including "glycemic memory", "hyperglycemic memory", "legacy effect" and "metabolic memory".

Basic research aimed at understanding hyperglycemic memory often includes cell culture studies and mouse studies comparing high and normal levels of glucose exposure. In particular, in vivo vascular endothelial cells (that line blood vessels) are exposed to high glucose levels from the blood. In vitro, high glucose causes upregulation of extracellular matrix protein expression and upregulation of proinflammatory pathways (e.g. NFkB expression) in vascular endothelial cells [13, 81].

El-Osta, Brownlee and coworkers studied how glucose levels affected gene expression and epigenetics in cultured bovine aortic endothelial cells [82, 83]. They found that when cells were switched from low to high glucose, the level of H3K4 monomethylation increased, and levels of H3K9 di- and trimethylation decreased, on the NFkB-p65 gene. They further showed that high glucose caused the preferential association of the Set7 HMT and the LSD1 histone demethylase on the NFkB-p65 gene and that these changes corresponded with NFkB-p65 transcription. Importantly, this pattern of histone modification, presence of Set7 and LSD1 and NFkB-p65 transcription persisted once glucose levels were returned to normal. This shows that the gene activating histone modifications and the enzymes likely

responsible for them remain with the active NFkB gene well past the period of hyperglycemia. In more recent work, El-Osta and colleagues used primary human aortic cells to show patterns of higher histone acetylation and gene transcription in several locations in the human genome due to transient high glucose [13].

Brasacchio et al. [83] used diabetic, formerly diabetic and control mice to show that several aspects of vascular damage persisted in the diabetic and formerly diabetic mice compared with controls. In similar comparisons, NFkB-p65, vascular adhesion molecule 1, and macrophage chemoattractant protein 1 were all upregulated in the aortas of diabetic and formerly diabetic mice compared with control mice. This indicates that the persistent effects observed in cell culture were also occurring in mice in vivo.

Blood lymphocytes and monocytes are also directly exposed to blood glucose and have been studied for epigenetics and gene expression with normo- and hyperglycemia. Miao et al. [84] did epigenetic studies of inflammation with high glucose in the human monocyte cell line THP-1. They also showed higher H3K9Ac of TNF-alpha and COX-2 promoters in peripheral monocytes of diabetic patients versus those of control subjects. They pointed out that this in vivo evidence provides at least one molecular mechanism by which high glucose and diabetes can promote the expression of inflammatory genes in peripheral monocytes.

Recently, Miao et al. [85] extended their earlier cell culture findings by studying patients treated with intensive versus conventional therapy from the DCCT and EDIC trials. Thirty subjects who received intensive treatment and maintained low glycated hemoglobin (HbA1c) levels in the DCCT and did not progress to retinopathy or nephropathy in the 10-year followup of the EDIC were compared with 30 subjects who received conventional treatment and maintained high HbA1c levels in the DCCT and did progress to retinopathy or nephropathy in the 10-year followup of the EDIC.

Using blood monocytes and lymphocytes and measuring H3K9Ac, H3K9 dimethylation and H3K4 trimethylation, Miao et al. found significantly more promoter regions of monocytes enriched in H3K9Ac in the conventional therapy subject group (high HbA1c in DCCT) compared to the intensive therapy group (low HbA1c in DCCT). Many of the top genes enriched in H3K9Ac were related to the NFkB inflammatory pathway or to diabetes complications. Combining data from the two groups, Miao et al. found that the recently measured H3K9Ac was significantly associated with the mean HbA1c levels measured many years earlier (during the DCCT and EDIC trials). This association was strong with a P value of less than 10^{-15}. These results indicate that past high glucose (as inferred by HbA1c) affects current gene expression (inferred by H3K9Ac) of inflammation and diabetes related genes. Further, this study provides in vivo human evidence for one likely epigenetic mechanism to explain metabolic or glycemic memory.

High glucose causes changes in patterns of gene expression that appear to be somewhat specific to cell type (although large data sets in each cell type to help define this have not been generated). In each case, however the gene expression patterns are one or more of prodiabetic, prohypertensive or proinflammatory and, at least in tissue culture experiments, these epigenetic and gene expression changes

happen quickly (within hours). Because these happen quickly we can ask what aspects of diabetes, inflammation and aging are due to these quick changes in gene expression and which are due to longer term effects of high glucose such as glycated proteins, advanced glycation end products (AGEs) and receptors for advanced glycation end products (RAGEs) [86]. Secondly, we can ask how persistent these changes are and would animals avoid these changes entirely if they were given a low glycemic index diet their whole lives with or without DR. Most rodent diets are made with a high proportion of grains and starches and probably have high glycemic indices [87]. Presumably there are conditions where these epigenetic changes can be partially or largely reversed (DR is a candidate). Conditions that lead to such reversal could be very useful in medicine.

Acetyl and energy metabolism and histone acetylation and methylation
A possible solution to the paradox of genome-wide declines of DNA methylation with age, concomitant with age-related DNA hypermethylation of specific genes, was proposed by Cooney [12, 25]. Similar proposals were made by Wallace et al. [27]. In these proposals, age-related (and cancer related) mitochondrial dysfunction (including the Warburg effect, [88] and other factors), limits AcCoA availability for histone acetylation. Limited histone acetylation limits gene activation resulting in the gradual silencing of genes. Genes not maintained in an active state become targets for DNA hypermethylation which promotes and maintains their silent state. This process may be reversible using diet, nutritional supplements or drugs [12] that improve the availability of AcCoA for histone acetylation and/or that inhibit HDACs to better maintain histone acetylation. For example, the essential nutrient, pantothenate, makes up part of AcCoA and thus pantothenate intake limits AcCoA levels.

To test some of these ideas, Friis et al. [28] studied mitochondrial dysfunction and AcCoA availability in relation to histone acetylation in yeast. They compared control yeast (with mitochondrial DNA) with yeast lacking mitochondrial DNA (rho-zero yeast) as a model of mitochondrial dysfunction. In their study histone acetylation in control yeast was not limited by the supply of AcCoA, however in rho-zero yeast both histone acetylation and AcCoA levels were low. As a workaround to rho-zero status, Friis et al. activated both the AMPK (Snf1) and RTG signaling pathways which increased the supply of AcCoA for HATs and increased histone acetylation.

As a workaround in mammals, Friis et al. suggested that nutritional interventions such as fasting or ketogenic diets might provide therapeutic benefit presumably through increasing histone acetylation and activating silenced genes. Mammalian cells lacking mitochondrial DNA also show increased gene silencing compared to the same cell lines with mitochondrial DNA [89].

Cells that are exposed to high glucose and/or develop mitochondrial dysfunction tend to rely on glycolysis for energy production [12, 25, 27]. Reliance on glycolysis can be expected to lower and change the balance of tricarboxylic acid (TCA) cycle intermediates. Increasingly these TCA cycle intermediates are being recognized as regulators of epigenetics [37]. Interestingly the influences are much more than metabolic with specific TCA cycle intermediates affecting the activities of enzymes

for epigenetic modifications [37, 90]. For example, Tsukada et al. [91] purified a JmjC domain-containing histone demethylase which demethylates histone H3 at lysine 36. Using the substrate alpha-ketoglutarate (2-oxoglutarate) and cofactor Fe2 +, this enzyme oxidizes the methyl group to generate formaldehyde and succinate. Subsequent work has identified additional dependencies between enzymes for epigenetics and TCA cycle intermediates. As reviewed by [37] and Salminen et al. [92], a picture is developing of histone and DNA demethylases using alpha-ketoglutarate as a substrate and being inhibited by their product, succinate and succinate's downstream product in the TCA cycle, fumarate.

Histone acetylation can be maintained by either (or both) increasing acetylation (HAT activity using AcCoA) or inhibiting histone deacetylation (inhibiting HDAC activity). Shimazu et al. [93] reported that d- beta-hydroxybutyrate (BHB, a ketone body) is a specific inhibitor of class I HDACs. BHB is an endogenous metabolite and metabolic conditions will affect its concentration. Shimazu et al. showed in mice that fasting, DR or exogenous BHB increased tissue histone acetylation. Inhibition of HDACs by BHB is another way that cellular metabolic status is coupled to transcriptional regulation.

Dietary HDACIs

Many HDACIs occur naturally in foods such as broccoli (sulforaphane and diindolylmethane) and garlic (allyl mercaptan). These are active against human cancer cells in vitro, against cancers in mice and are in clinical trials against cancer in humans (www.clinicaltrials.gov) [29–33]. HDACI activity in broccoli also appears to be active in young healthy people where eating broccoli sprouts decreased HDAC activity in peripheral white blood cells [29, 32, 94]. HDACIs from everyday foods may cause epigenetic change, possibly with a beneficial trend toward keeping some genes active that are otherwise silenced with cancer and aging. Potential benefits could include slowing or reversing dementia or slowing age- related decline [55] as discussed above in Sect. 2.3. A recent study shows that many genes (thousands of CpG DNA methylation sites) show changes in DNA methylation in normal and cancer human prostate cell lines when treated with sulforaphane or diindolylmethane [95]. Although the potential utility of naturally-occurring and pharmaceutical HDACIs is huge, much more research is needed before we will be able to use these effectively and predictably to prevent disease or affect aging.

Methyl metabolism provides SAM, the substrate for DNA and histone methylation

Diet and metabolism provide methyl groups for epigenetics and the availability of methyl groups to some degree influences the levels of DNA and histone methylation [12, 25, 27]. Further, the relative availability of the various modifying groups (methyl, acetyl, etc.) probably act to broadly influence epigenetics and gene activity [12, 25, 27]. In turn, epigenetics and gene expression affect cell differentiation and animal phenotype [12, 19, 20, 54, 96–98]. The methyl donor SAM is produced by methyl metabolism and is used by DNMTs and HMTs [99]. The product of these methylation reactions, SAH, inhibits DNMTs and probably HMTs [100–103].

SAM is produced from methionine and ATP and the methyl groups for methionine come via dietary methionine or from the recycling of SAH (and homocysteine) by methyl metabolism [25, 27].

Methyl metabolism, and the broader one-carbon metabolism, use folic acid and dietary folates, cobalamin (vitamin B12), zinc, methionine, *S*-methylmethionine, betaine and choline [104–106]. Folate, methionine, vitamin B_{12} and zinc are intermediates used for the transfer and transport of methyl groups in their roles as enzymatic cofactors [25, 27, 107–109]. All of these are obtained from the diet and, except for betaine and *S*-methylmethionine, all are essential nutrients.

2.5 Endogenous Retroviruses (ERVs) and Interspersed Repetitive Elements

Our DNA contains thousands of ERVs which are normal parts of our genomes [110, 111]. ERVs are inherited though the germline (Mendelian inheritance) but are thought to be derived from repeated retroviral infections of our germline cells in the evolutionary past [112]. Some well-studied ERVs include human endogenous retrovirus virus K (HERV-K) and, in mice, IAPs and MuERVs. Generally ERVs tend to be silent in healthy tissue and can remain fixed in the genome for many years and multiple generations [96, 113]. ERVs contain long terminal repeats (LTRs) that can drive viral transcription or that activate or interfere with expression of adjacent "host" genes. Nearby "host" genes can be over expressed, deregulated, silenced and otherwise dysregulated by ERVs [96, 114, 115]. Expression of ERV-encoded proteins, including reverse transcriptase, can cause ERV transposition and other processes that disrupt the genome (e.g. reverse transcription of "host" RNAs) [116]. Epigenetic silencing including DNA methylation of LTRs and many nutritional, metabolic and genetic factors can affect ERV expression [110, 117–120].

Interspersed elements have some features of ERVs such as reverse transcriptase but lack LTRs. These include LINE-1 (L1) elements in humans and L1Md elements in mice. Like ERVs these elements are generally suppressed by DNA methylation [121]. Activation of L1 sequences involves H3K4 trimethylation and H3K9Ac and lower DNMT1 activity—all features of transcriptional activation [122].

ERV and LINE-1 activities are clearly increased, and may be causal, in some human cancers [123, 124]. ERV expression is increased in several autoimmune diseases of humans and mice [111, 125, 126]. ERV expression may be causal or an important mechanist step in autoimmunity. Toxic insult with benzo (a) pyrene [122] or trichloroethylene [127] can increase expression of LINEs and ERVs (respectively) in mice. Due to their high copy number (a few thousand IAPs and even more L1 sequences in the mouse genome), small increases in the expression of repeats could have huge effects if tens or hundreds of repeats per genome increase their

expression. Of course, large increases in expression of just a few repeats could have similar effects.

ERV and L1 hypomethylation and/or transcription have sometimes been associated with aging [128] and are part of the broad hypomethylation of DNA that occurs with aging [1, 41]. The roles of ERV and L1 activation in aging are unclear. At a minimum there is activation of ERVs, L1s and other repeats due to toxic insults, broad hypomethylation or other events that may accumulate over a lifetime [129]. Alternatively, activation of these sequences may play a more specific mechanistic role in aging and/or the induction of senescence [130].

2.6 Conclusions and Future Directions

It should be possible to design combinations of foods, dietary supplements and drugs to shift metabolism and epigenetics in a direction that would maintain healthy patterns of gene expression (i.e. to push patterns of gene expression away from aging and cancer). This dietary design might involve a combination of a low calorie, low glycemic index diet (to control glucose), leafy vegetables and quinoa (for folate, betaine, pantothenate), foods or supplements to supply TCA cycle intermediates. Others have proposed "epigenetic diets" for similar purposes [131, 132].

There are several nonexclusive approaches that are probably useful for designing diets for maintaining epigenetics. However all these approaches should be tested for efficacy.

- Diets designed to provide micronutrients for epigenetics such as an emphasis on foods high in micronutrients and low in calories [105] such as spinach and kale.
- Supplements of micronutrients such as pantothenate, folate, betaine etc.
- Diets and/or supplements high in HDACIs such as those from broccoli and garlic.
- Diets and/or supplements to increase BHB.
- Diets substituting other energy sources such as fats or citric acid cycle intermediates in place of readily digested starches and sugars that raise blood glucose.
- DR, fasting, low glycemic index diets (e.g. paleolithic), or ketogenic diets (e.g. 95 % fat, 5 % protein).

Glucose is clearly important in epigenetics. Even if other aspects of epigenetics are in a healthy range, high glucose will probably still lead to a diabetic pattern of gene expression. Just as certain minimum levels of micronutrients such as pantothenate, folate, betaine and/or choline are needed for the metabolism underlying epigenetics, low to normal glucose will be needed to keep epigenetics in a normal, nondiabetic state. Treatments that would prevent high glucose or prevent the adverse effects of high glucose could be especially valuable for medicine and longevity. Treatments that would reverse the epigenetic effects of transient or

repeated episodes of high glucose would be similarly valuable. Identification of such approaches could be very useful in medicine.

Horvath's epigenetic clock could be a very useful tool, along with yet to be developed epigenetic clocks for mice and other model organisms. Strategies for maintaining or changing epigenetics could be tested for their ability to change the epigenetic clock. Among other applications, it seems that such an epigenetic tool could be a preliminary marker for the success of interventions into aging and lifespan. Subsequent studies could determine if the changed epigenetic clock leads to changes in lifespan.

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http://www.springer.com/978-3-319-14829-8

Nutrition, Exercise and Epigenetics: Ageing Interventions

Yu, B.P. (Ed.)
2015, VIII, 278 p. 23 illus., 13 illus. in color., Hardcover
ISBN: 978-3-319-14829-8