From inflammaging to healthy aging by dietary lifestyle choices: is epigenetics the key to personalized nutrition?

Katarzyna Szarc vel Szic¹, Ken Declerck¹, Melita Vidaković² and Wim Vanden Berghe¹*

Abstract

The progressively older population in developed countries is reflected in an increase in the number of people suffering from age-related chronic inflammatory diseases such as metabolic syndrome, diabetes, heart and lung diseases, cancer, osteoporosis, arthritis, and dementia. The heterogeneity in biological aging, chronological age, and aging-associated disorders in humans have been ascribed to different genetic and environmental factors (i.e., diet, pollution, stress) that are closely linked to socioeconomic factors. The common denominator of these factors is the inflammatory response. Chronic low-grade systemic inflammation during physiological aging and immunosenescence are intertwined in the pathogenesis of premature aging also defined as ‘inflammaging’. The latter has been associated with frailty, morbidity, and mortality in elderly subjects. However, it is unknown to what extent inflammaging or longevity is controlled by epigenetic events in early life. Today, human diet is believed to have a major influence on both the development and prevention of age-related diseases. Most plant-derived dietary phytochemicals and macro- and micronutrients modulate oxidative stress and inflammatory signaling and regulate metabolic pathways and bioenergetics that can be translated into stable epigenetic patterns of gene expression. Therefore, diet interventions designed for healthy aging have become a hot topic in nutritional epigenomic research. Increasing evidence has revealed that complex interactions between food components and histone modifications, DNA methylation, non-coding RNA expression, and chromatin remodeling factors influence the inflammaging phenotype and as such may protect or predispose an individual to many age-related diseases. Remarkably, humans present a broad range of responses to similar dietary challenges due to both genetic and epigenetic modulations of the expression of target proteins and key genes involved in the metabolism and distribution of the dietary constituents. Here, we will summarize the epigenetic actions of dietary components, including phytochemicals, and macro- and micronutrients as well as metabolites, that can attenuate inflammaging. We will discuss the challenges facing personalized nutrition to translate highly variable interindividual epigenetic diet responses to potential individual health benefits/risks related to aging disease.

Keywords: Phytochemicals, Oxidative stress, Inflammation, Aging, Epigenetics, Metabolism, Personalized nutrition

Review

Since people of the twenty-first century live longer, the challenge will be to make these added years as healthy and productive as possible. Societal and medical advances have extended the life of humans. Despite its significance for the well-being of individuals and the population as a whole, aging is a poorly understood process. Among the hallmarks of aging are genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [1]. A large part of the aging phenotype is explained by an imbalance between inflammatory and anti-inflammatory networks [2,3]. Levels of inflammatory mediators typically increase with age even in the absence of acute infection or other physiologic stress. While levels are still in the sub-acute
range, this age-related chronic inflammation underlies many aging-related conditions. According to the oxidinflammaging theory, the aging process is a chronic smoldering oxidative and inflammatory stress that leads to the damage of cellular components, including proteins, lipids, and DNA, contributing to the age-related decline of physiological functions. This is especially evident in cells that regulate homeostasis, such as the nervous, endocrine, and immune systems. It explains their functional losses observed during aging, with a resulting increase in morbidity and mortality [4].

The progressive loss of physiological organismal and cellular integrity is the primary risk factor for major human pathologies, including metabolic syndrome, cancer, diabetes, cardiovascular disorders, and neurodegenerative diseases. Due to an imbalance between energy intake and expenditure, largely attributable to the increased availability of foods with high caloric content coupled with the adoption of a sedentary lifestyle, the continuing increase in obesity and metabolic disorders such as type 2 diabetes and accelerating aging population globally will remain the major contributors to cardiovascular mortality and aging disorders in the next 50 years. This emphasizes the importance of weight management and early intervention with regard to modifiable risk factors in overweight patients. To reduce the burden of cardiometabolic disorders and early onset of aging disorders, promoting exercise with a complementary diet, supplemented with bioactive phytochemicals, is expected to restore immune homeostasis and improve human health [5,6]. In the past couple of decades, evidence from prospective observational studies and clinical trials has converged to support the importance of individual nutrients, foods, and dietary patterns in the prevention and management of metabolic disorders [7-12]. With an emphasis on overall diet quality, several dietary patterns such as the Mediterranean diet, low glycemic index diet, moderately low carbohydrate intake, and vegetarian diets can be tailored to personal and cultural food preferences and appropriate calorie needs for weight control, diabetes prevention, and cardiometabolic management [11].

Although genome-wide association studies (GWAS) identified genetic variants that affect hundreds of genes related to energy metabolism involved in metabolic lifestyle diseases and aging, most variants identified so far confer relatively small increments in risk, leaving many questions about the remaining ‘missing’ heritability, although polygenic disease traits may account for some of these limitations [13-15]. In analogy to the reference human genome sequence which allowed GWAS studies, the NIH Roadmap Epigenomics Consortium generated today the largest collection of human epigenome sequences for epigenome-wide (EWAS) association studies [16]. From various epigenome-wide (EWAS) association studies, it has become clear that epigenetic changes in response to diet and environmental (stress) conditions complement genetic mutations and contribute to the development and progression of inflammaging diseases such as rheumatoid arthritis, metabolic disorders (obesity, type 2 diabetes), cardiovascular disease, and cancer [17-29]. For example, lifestyle factors and diet have a strong influence on the epigenetic regulation of key products of energy metabolism genes such as leptin (which is responsible for appetite control), insulin receptor (that plays a central role in glucose homeostasis), TNFα (considered as an adipokine because of its role in obesity-related inflammation and modulation of insulin response), and fatty acid synthase (catalyzing fatty acid synthesis) [30]. Accumulating evidence points to an epigenetic basis of the fetal origins of several adult metabolic disorders [31-35]. More particularly, some of the adverse epigenetic effects of lifestyle behaviors may be rooted in perturbations in utero during pregnancy and during early postnatal life which shape the metabolic phenotype, perhaps across generations, which affect lifelong disease risk [32,36-38].

This review will focus on the epigenetic aspects of ‘inflamming’ and whether there are windows of opportunity for nutri-epigenetic intervention with dietary lifestyle choices. Finally, challenges of personalized nutrition will be discussed to translate highly variable interindividual epigenetic diet responses to potential individual health benefits/risks related to diseases associated with aging.

### Epigenetics and aging

Striking links between organismal and cellular aging and epigenome alterations have recently been identified. Age-associated epigenetic changes involve alterations in DNA methylation patterns, posttranslational modification of histones, and chromatin remodeling [1,39]. In general, DNA is wrapped around nucleosomes, which are arranged as regularly spaced beads (147 bp DNA/nucleosome) along the DNA. Typically, nucleosomes consist of a histone (H) octamer of H2A/B, H3, and H4. The DNA bridging two adjacent nucleosomes is normally bound by the linker histone H1 and is termed linker DNA. While the core histones are bound relatively tightly to DNA, chromatin is largely maintained by the dynamic association with its architectural proteins (such as transcription cofactors and regulators, heterochromatin protein 1, and high mobility group (HMG) proteins). Before most activators of a gene access their DNA-binding sites, a transition from a condensed heterochromatin (‘solenoid-like fiber’) to a decondensed euchromatin (‘beads on a string’) structure appears to take place. Conversely, the acquisition of a more condensed heterochromatin structure is often associated with gene silencing.
The structural restriction of silenced chromatin on gene expression can be overcome by chromatin writer, reader, and eraser enzyme complexes that remodel nucleosomes along the DNA or reversibly modify histones (through posttranslational modifications, such as histone acetylation, phosphorylation, ubiquitylation, glycosylation, SUMOylation) and establish specific chromatin states involved in transcription [40-42]. Specific sets of histone modifications and/or variants are associated with genes that are actively transcribed or repressed, a phenomenon defined as the ‘histone code’ [40]. Based on coexisting histone marks and genome-wide ChIP-seq data available within the ENCODE consortium, principal component analysis has reduced the complexity of the histone code into different chromatin states that are associated with developmental and environmental cues [41-44].

DNA methylation is the best-known epigenetic mark [24,45,46]. It is catalyzed by two types of DNA methyltransferases (DNMTs): DNMT1 is a maintenance methyltransferase, whereas both DNMT3A and DNMT3B are de novo methyltransferases [47,48]. It is widely accepted that DNMT3A/B are mainly responsible for DNA methylation during development (differentiation) whereas DNMT1 maintains DNA methylation patterns during DNA replication (and cell division). The role of DNMT2 in DNA methylation is minor, its enzymology being largely directed to tRNA. DNA methylation is normally associated with gene inactivation, and it usually occurs in cytosine-phosphate-guanine (CpG) dinucleotides. Alternatively, DNA methylation of transcription factor binding sites which prevents the binding of repressor proteins can, paradoxically, induce gene activation. CpGs are normally methylated when scattered throughout the genome but are mostly unmethylated when clustered as CpG islands at the 5′ ends of many genes. Hypermethylation of CpG-rich promoters triggers local histone code modifications that result in a cellular camouflage mechanism which sequesters gene promoters away from transcription factors, causing stable silencing of gene expression. DNA methylation at CpG dinucleotides occurs upon transfer of S-adenosylmethionine (SAM) on cytosine by DNMTs. Recent results suggest that DNA methylation should be considered as a more dynamic and stochastic process, in which DNA methylation at each site is determined by the local activity of DNMTs, DNA demethylases, and DNA replication enzymes that are controlled by a dynamic network of chromatin marks [49] and signaling pathways [50,51]. For example, the inflammatory mediator prostaglandin E(2) (PGE(2)) has been shown to exert dynamic DNA methylation changes during cancer inflammation [52,53]. In mammalian cells, the fidelity of maintenance of methylation is 97% to 99.9% per mitosis, whereas de novo methylation is as high as 3% to 5% per mitosis, thus creating possibilities for dynamic epigenetic changes. Unavoidable errors may accumulate over time following long-term maintenance of epigenetic patterns or occurrence as a result of the accumulation of DNA lesions during aging in both nuclear and mitochondrial DNA caused by increased oxidative stress. Epigenetic errors could explain the stochastic differences in DNA methylation patterns reported in aging monozygotic twins [54,55]. Early studies described an age-associated global hypomethylation, concomitantly with hypermethylation of various tumor suppressor genes and Polycomb target genes [56]. Epigenetic changes accumulated throughout life may also result in the deterioration and reduced regeneration capacity of stem cells [57]. Although in most cases DNA methylation is a stable epigenetic mark, reduced levels of methylation are also observed during development. This net loss of methylation can either occur passively by replication in the absence of functional maintenance methylation pathways or, actively, by indirect removal of methylated cytosines. In mammals, a role for the 5-hydroxymethylcytosine (5-hmC) modification in DNA demethylation by ten-eleven translocation (TET) enzymes has been demonstrated as an intermediate in an active DNA demethylation pathway involving DNA repair and 5-hydroxymethylcytosine-specific DNA glycosylase activity [48,50,58].

Of particular interest, reactive oxygen species (ROS) and oxidative stress may affect DNA demethylation by DNA oxidation or TET-mediated hydroxymethylation [59,60]. For example, age-related increase in levels of 5-hmC in the brain can be prevented by caloric restriction or upregulation of specific endogenous anti-oxidants [61,62]. Furthermore, nutrients like ascorbic acid can promote DNA demethylation via increased activity of TET enzymes [63,64]. In another remarkable study, loss of TET2 and 5-hmC was found to strongly correlate with smooth muscle cell plasticity and the degree of injury in different models of vascular and atherosclerotic disease, in which ROS are critically involved [65]. Alternatively, ROS can influence the methyline by formation of oxidized DNA lesions. Replacement of guanine to 8-hydroxy-2′-deoxy-guanosine (8-OHdG), one of the major DNA oxidative damage by-products, substantially diminishes the binding of methyl-CpG binding proteins and DNMTs and results in heritable epigenetic changes [66-68]. As such, it may be expected that oxidized DNA lesions formed by the hydroxylation of pyrimidines, including 5-methylcytosine (5-mC), interfere with epigenetic signals related to 5-hydroxymethylcytosine (5-hmC) due to their structural similarities [69,70]. Finally, in vitro studies suggest that glutathione (GSH) depletion by redox changes leads to global DNA hypomethylation, possibly through the depletion of SAM [71,72].
Tissues and cells of aging organisms also show age-associated changes in histone chromatin marks such as increased histone H4 lysine(K)16 acetylation, H4K20 trimethylation, or H3K4 trimethylation, as well as decreased H3K9 methylation [73-75]. Age-associated epigenomic changes could be driven by changes in expression of chromatin-modifying or -demodifying enzymes [75-77]. Of particular interest, deletion of components of histone methylation complexes (for H3K4 and for H3K27) extends longevity in nematodes and flies, respectively, and may involve the insulin/IGF-1 signaling pathway [78-81]. It is not yet clear whether aging is a cause or consequence following purely epigenetic changes or alterations affecting metabolic or signaling pathways outside of the nucleus. Importantly, since the activities of histone-modifying enzymes also depend on intracellular levels of essential metabolites (acetyl-coA, Fe, ketoglutarate, NAD+, S-adenosylmethionine), epigenetic changes are tightly linked to global cellular metabolism and energy levels [82-88] (Figure 1). Finally, ROS (such as •O₂, •OH, H₂O₂, NO, and ¹O₂) as well as reactive nitrogen intermediates such and NO and reactive nitrogen species (RNS), produced by neutrophils, macrophages, endothelial, and other cells, can indirectly modulate the activity of the epigenetic machinery. For example, ROS were demonstrated to modulate the activity of the Rph1 demethylase specifically at subtelomeres to remodel chromatin and extend lifespan [89].

Although epigenetic modifications previously were thought to be fixed during development and maintained over the lifetime, more recent research provides evidence that epigenetic mechanisms allow rapid adaptations to a changing environment and are responsive to signaling cascades [50,51]. Therefore, epigenetic mechanisms may exacerbate the epidemic of metabolic disease by first contributing to the development of obesity and type 2 diabetes and then passing modifications on to the subsequent generation via transgenerational inheritance [90]. Nevertheless, epigenetic mechanisms might also prevent the development of type 2 diabetes through nutritional intervention therapies [12,34,91,92]. Recent success of therapeutic intervention in chronic inflammatory diseases using epigenetic modifiers such as histone deacetylase (HDAC) and DNMT inhibitors has fuelled interest in methylome profiling of complex diseases [92-103].

---

**Figure 1** Metabolic pathways generate essential metabolites for chromatin- and DNA-modifying enzymes. NAD, acetyl-coenzyme A (Acetyl-coA), and 5-adenosylmethionine (SAM) are elemental for epigenetic control of transcription including methylation of DNA and posttranslational modifications of histones and non-histone chromatin factors (not shown). NAD contributes to transcriptional control mainly via the activity of the protein deacetylase sirtuin, which uses NAD as one of the substrates. Sirtuins are also important for maintaining the activity of the acetyl-coA acetyltransferases. Acetyl-coA is synthesized by acetyl-coA-synthetase (ACS) and ATP-citrate lyase that use acetate and citrate as the precursors, respectively. Citrate is an intermediate product of the TCA cycle. SAM is the methyl donor for DNA, RNA, histones, and non-histone protein methylation. 5-adenosylhomocysteine (SAH) generated in each round of methylation reaction is a potent inhibitor of methyltransferases and has to be cleared by SAH hydrolase (SAHH). NAD is an essential coenzyme for SAHH. Synthesis of methionine from homocysteine is achieved through extracting the methyl group from betaine, derived from choline, or 5-methyl-THF, a derivative of folate acid. Metabolism of phospholipids and folate acid may thus indirectly contribute to epigenetic regulation. Likewise, the abundance of NAD and citrate is linked to the cellular energy flux, e.g., the TCA cycle. Changes in the expression of certain genes may therefore be influenced significantly. Abbreviations used: Acetyl-coA, acetyl-coenzyme A; ACS, acetyl-coA-synthetase; AC-ACS acetylated-ACS; Ado, adenosine; HAT, histone acetyltransferase; Hcy homocysteine; MTases, methyltransferases; NAD, Nicotinamide adenine dinucleotide; ROS, reactive oxygen species, RNS, reactive nitrogen species, SAH, 5-adenosyl homocysteine; TCA, tricarboxylic cycle; THF, tetrahydrofolate.
Crosstalk of inflammation and energy metabolism fuel epigenetic plasticity

An increasing number of experimental and epidemiological evidence links multifaceted process of aging to systemic low-grade inflammation and disturbances in cellular metabolism and protein homeostasis [104-106]. An efficient autophagic flux, i.e., cellular mechanism for the degradation and recycling of cellular components, is essential for healthy aging and maintenance of cellular homeostasis and links inflammation to metabolic disorders (Figure 2). Autophagy negatively regulates inflammasome activation by maintaining mitochondrial homeostasis. Reciprocally, mitochondrial energy metabolites also regulate aging and autophagy through as-yet-elusive metabolic circuits [105]. Inflammation also profoundly affects the metabolic bioenergetic profile of target cells, promoting aerobic glycolysis, a process called the ‘Warburg effect’, first described in tumor cells [107]. Different cell conditions require flexible metabolic programs to support unique bioenergetic demands. Metabolic pathways rely on the dynamic balance between anabolic processes to support the synthesis of cellular building blocks and catabolic processes to ensure adequate bioenergetic resources. Beyond nutrient-sensing pathways which control gene transcription and intercellular/extracellular energetic status, nutrient-responsive metabolites, such as ATP, acetyl-CoA, UDP-N-acetylglucosamine (UDP-GlcNAc), and S-adenosyl methionine, mediate crosstalk between metabolism, cellular signaling, and the epigenetic control of transcription programs [108-116] (Figure 3). By operating as indicators of metabolic status, these metabolites serve as substrates for posttranslational modifications, including acetylation, glycosylation, methylation, and phosphorylation, which regulate the activity of metabolic enzymes, signaling pathways, and transcription factors. Because histone-modifying enzymes including kinases, acetyltransferases, and methyltransferases consume key metabolites, the metabolic state of a given cell will also be reflected in the chromatin modification patterns. In this respect, changes in nuclear acetyl-CoA or NAD+ levels affect histone acetylation patterns [88,114]. However, the specificity of chromatin changes also depends on the gene-specific recruitment of histone-modifying enzymes to specific chromosomal domains via their interaction with DNA-binding factors, ncRNAs [117-119]. Also, enzymes that use the same metabolite but modify different substrates, such as DNA or histone methyltransferases, may compete with each other leading to either one or the other methylation product. Furthermore, many nutrient metabolites have been shown to have a direct effect on gene expression patterns through binding to nuclear receptors that in turn affect the transcription of the gene they bind to [120]. Interestingly, even transient changes in the nutrition can have a long-lasting impact on gene expression patterns. Heritable ‘memory’ effects of metabolic disturbances have been demonstrated by the ablation of...
of key epigenetic enzymes such as SIRT1, HDAC6, and KDM3A in models of metabolic disorders [114,116]. These findings pave the way to the development of therapeutic strategies against epigenetic modifier enzymes for the treatment of metabolic and aging disorders [121-123]. Recent theories propose that mitochondria and energy metabolism play a major role in the regulation of health span through Krebs cycle intermediates that shape the epigenetic landscape of chromatin by regulating DNA and histone methylation during the aging process [124,125] (Figure 3B). Of particular interest, the histone variant MacroH2A1.1 but not MacroH2A1.2 was found to bind with high affinity to the SIRT1-metabolite O-acetyl ADP ribose. Upon its overexpression, it ameliorates glucose metabolism and reduces expression of lipidogenic genes and fatty acids [126]. In another study, genetic ablation of histone macro-H2A1 resulted in increased leanness, glucose tolerance, and energy expenditure in mice fed with a high-fat diet [127]. Major metabolic changes are also observed in cancers [72,88,128,129]. The ‘Warburg effect’ is accompanied by major alterations in gene expression profile whose causes are likely to be associated with specific chromatin-remodeling events [130-133]. Furthermore, mutated isoforms of the core metabolic enzymes isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH) result in accumulation of particular metabolites which inhibit TET enzymes responsible for oxidizing 5-mC, leading to pervasive DNA hypermethylation [111,134-136]. In analogy to ‘oncometabolites’ whose accumulation triggers aberrant signaling resulting in initiation of carcinogenesis, depletion of ‘gerometabolites’ was found to drive aging [137,138]. Altogether, the cellular metabolism is tightly regulated, and imbalance of energy intake and expenditure contribute to metabolic diseases, cardiovascular diseases, cancer, and other aging diseases. Dynamics and/or reversibility of epigenomic changes in response to altered metabolic states needs to be further investigated.

Nutri-epigenomics: lifelong remodeling of our epigenomes by nutritional, phytochemical, and metabolic factors

Phytochemicals from plants appear to be crucial to achieve the correct relationship between man and nature - between dietary balance and health (Figure 4). Several polyphenolic compounds, such as resveratrol, tea catechins, and flavonoids, which are commonly found in vegetables, fruits, and plant-derived juices or beverages, exert well-evidenced cardioprotective, neuroprotective, chemopreventive, and anti-inflammatory properties, but, nevertheless, further clinical and epidemiological research is required. Classic proposed mechanisms for the health benefits of phytochemicals are the following: (1) direct antioxidant activity or increase in the expression of antioxidant proteins; (2) attenuation of endoplasmic reticulum stress signaling; (3) blockade of pro-inflammatory cytokines; (4) blockade of transcription factors related to metabolic diseases; (5) induction of metabolic genes expression; and (6) activation of transcription factors that antagonize inflammation [139]. Rather than the chemical conversion of food to energy and body matter of classic metabolism, food is now also a conditioning environment that shapes the activity of the (epi)genome and determines stress adaptive responses, energy metabolism, immune homeostasis, and the physiology of the body [91,140-143]. Human epidemiological studies and appropriately designed dietary

![Figure 3 Activity of chromatin modifying writer-eraser enzymes depends on available concentrations of cofactor metabolites and environmental signals. (A) Schematic representation of a nucleosome with extruding histone tails with residues that can be modified by various chromatin writer (i.e., DNA methyltransferase (DNMT), histone methyltransferase (HMT), histone acetylase (HAT), ubiquitin ligase (U), kinase (K), glycosylase (G)) or chromatin eraser enzymes (i.e., DNA hydroxymethylase (TET), demethylase (HDMT), deacetylase (HDAC), proteosome (P), phosphatase (PP)), resulting in dynamic histone methylation (Me), acetylation (Ac), ubiquitination (Ub), phosphorylation (P), and glycosylation (G). These histone modifications have been associated with changes in chromatin organization, gene activation, silencing, and several other nuclear functions (adapted from [338]). (B) Hypothetical model of a glycolytic-oxidative metabolic switch and its possible influence on epigenetic modifiers and the epigenetic landscape (adapted from [339]).](image-url)
interventions in animal models have provided considerable evidence to suggest that maternal nutritional imbalance and metabolic disturbances, during critical time windows of development, may have a persistent effect on the health of offspring and may even be transmitted to the next generation [22,144-149]. This has led to the hypothesis of 'fetal programming' and new term 'developmental origin of health and disease' (DOHaD) [35,150]. This hypothesis postulates that a nutritional or environmental mismatch between pre-natal (in utero gestation) and postnatal life (weaning, infancy, adult life), plays an important causative role in non-communicable diseases, including diabetes, cardiovascular disease, allergy, some forms of cancer, cognitive decline, and affective disorders [21,146,151-156]. The various non-Mendelian features of metabolic disease, cancer, or chronic inflammatory disorders, clinical differences between men and women or monozygotic twins, and fluctuations in the course of the disease are consistent with epigenetic mechanisms in the influence of fetal and/or lifelong nutrition or stochastic events on adult phenotype [22,144-149,157-159].

Thus, lifetime shapes the multitude of epigenomes not only within but also across generations [22,35,148,160-162]. Interest in transgenerational epigenetic effects of food components has initially been fuelled by observations in Agouti (A\(^{vy}\)/a) mice fed with a soy polyphenol genistein (GEN), which revealed changes in coat color, related to epigenetic changes in DNA methylation patterns in their offspring and protection against diabetes, obesity, and cancer across multiple generations [163-165]. However, some of these findings were contested in more recent studies with A\(^{vy}\)/a mice fed with soy protein isolate, containing comparable amounts of genistein [166]. In another study by Rosenfeld and colleagues, no association between a genistein-based diet and the so-called pseudoagouti, brown phenotype was revealed [167]. Also, only weak transgenerational effects could be observed with soy polyphenols in Daphnia Magna, despite the presence of functional DNMTs [168]. Nevertheless, the honeybee (Apis mellifera) is probably the clearest example of induction of alternative phenotypes and aging epigenotypes by nutrition in early life [169]. Female bees are genetic clones. However, queens are distinct from workers in their morphology, capacity to reproduce,
behavior, and longevity. The difference between the queen and worker castes lies in the exposure of the genetically identical larvae to royal jelly, an as yet incompletely defined mixture of proteins, amino acids, vitamins, fatty acids, steroids, hormones, lipids, and other nutrients [170-176].

Studies of human populations following famine have suggested that pathologies in later life are dependent on the timing of nutritional insult during pregnancy. Follow up of the Dutch Hunger Winter cohort showed that cardiovascular disease was more prevalent in offspring of mothers who were severely undernourished during the first trimester of their pregnancies in 1944 to 1945, as compared to those born to mothers whose pregnancies were more advanced at the time of nutritional insult [177-179]. Also, patern patterns of nutrition during the prepubertal growth period in children in Överkalix, in Sweden, during the nineteenth century are associated with differential risk of early cardiovascular death in their grandchildren [180,181]. Today, various epigenetic changes have already been characterized which are involved in atherogenesis [21,22,182-185]. Hypercholesterolemia, obesity, hyperhomocysteinemia, and high glucose are important cardiovascular disease risk factors which are implicated in enhanced inflammatory signaling, and long-lasting effects are driven by epigenetic reprogramming, which promote differentiation of monocytes/macrophages into more proatherogenic phenotypes [186-192]. Recent evidence suggests that the pathogenic role of hyperhomocysteinemia in vascular diseases might be mediated via adenosyl-homocystein (Hcy) accumulation and DNA methylation. Hcy competes with SAM (the methyl-group donor) for binding on DNMT, which may lead to passive loss of methylation in replicating DNA. High blood Hcy levels correlate with DNA hypomethylation and atherosclerosis and can lead to a 35% reduction in DNA methylation status of peripheral blood lymphocytes [193-196]. Similarly, insulin, glucose, folate, or flavanol-rich diets interfere with the methyl donor metabolism and the available pool of SAM, resulting in DNA methylation changes [196-199]. In contrast, very few studies have focused on impact of dietary methyl donors on histone methylation, which is also affected by alterations in SAM/S-adenosylhomocysteine (SAH) ratios [193,200]. As such, specific dietary classes of functional food maybe designed as therapeutic epigenetic modulators in lifestyle disease, such as metabolic disorders (diabetes), cardiovascular disease, asthma/COPD, and rheumatoid arthritis [91,142,143,201,202].

Epidemiologic and medical anthropological studies have indicated that flavanol-rich diets are inversely associated with cardiovascular risk [203-209]. Locus-specific DNA methylation changes, both hyper- and hypomethylation, have been demonstrated at the promoter of several genes involved in the pathogenesis of atherosclerosis, such as extracellular superoxide dismutase (SOD), hormone receptors (glucocorticoid receptor (GR), estrogen receptor (ER), peroxisomal proliferator-activated receptor (PPAR), arylhydrocarbon receptor (AhR), liver X receptor (LXR)), endothelial and inducible nitric oxide synthase (iNOS/eNOS), 15-lipoxygenase (LOX), fibroblast growth factor (FGF)2, hypoxia-inducible factor (HIF)1α, myc, insulin growth factor 1 (IGF1), and metalloproteases (MMPs) [189,210-213]. In a proatherogenic murine model, DNA-methylation polymorphisms preceded the appearance of histological signs of atherosclerosis [187,188]. Interestingly, involvement of the inducible JMJD3 demethylase was demonstrated to regulate monocyte/macrophage transdifferentiation programs, illustrating that developmental programs are plastic and monocyte lineage differentiation is susceptible to inflammatory pathways and oxidative stress [214]. A role for the JMJD1A demethylase was demonstrated in metabolic gene expression and oxidative resistance [215]. Furthermore, it was found that knockdown of the LSD1 demethylase affected monocyte adherence in a proatherogenic diabetic mouse model [216]. This suggests that LSD1 contributes to metabolic memory through long-term changes in gene expression via alterations in chromatin structure [217,218].

Poor maternal nutrition has also been associated with increased risk of type 2 diabetes over several generations in North American Indians [219,220]. Individuals with metabolic syndrome, obesity, type 2 diabetes, and cardiovascular disease may show a lifelong imbalance between energy intake and expenditure due to incorrect epigenetic programming during their early development as a result of placental insufficiency, inadequate maternal nutrition, metabolic disturbances, or neonatal medication [145,219-224].

Recently, evidence emerged that also timing (preconception, pregnancy, lactation, neonatal life, early life, pre-/post-menopause, puberty) of various dietary exposures may be vitally important in determining health beneficial effects, as epigenetic plasticity changes continually from conception to death [225]. In principle, epigenetic changes occurring during embryonic development will have a much greater impact on the overall epigenetic status of the organism because, as they can be transmitted over consecutive mitotic divisions, alterations occurring in single embryonic stem cells will affect many more cells than those occurring in adult stem and/or somatic cells during postnatal development [147]. Epigenetic plasticity further also depends on other processes such as chromosomal instability, telomere shortening, metabolic cycles, mitochondrial deteriorations, and oscillatory, circadian, or seasonal rhythms of systemic hormone levels (hypothalamic-pituitary-adrenal (HPA) axis) [21,22,93,224-228]. In addition to epigenetic imprinting during crucial periods of development, stochastic or genetically and environmentally
triggered epigenomic changes (epimutations) occur day after day and accumulate over time, as maximal differences in DNA methylation profiles are observed in aged monozygotic twins with a history of non-shared environments [55,96]. Concerning nutritional transgenerational inheritance, there is increasing evidence in both plants and animals that, following nutritional intervention (caloric, iron and protein restriction, polyphenol-, folate-, micronutrient-, fat-, or carbohydrate-rich diet), maternal diabetes, during pregnancy, and lactation, can affect the following generation(s) [148,153,164,165,229-231]. Although it has long been thought that the epigenomic profile is wiped clean in the embryo shortly after fertilization, with the exception of imprinted genes, methylation clearing is not complete after fertilization and on a global DNA level is reduced to 10% [232,233] or converted into hydroxymethylcytosine [234]. Alternatively, it cannot be excluded that transgenerationally inherited nutritional effects may also depend on Polycomb proteins [148,235-237], miRNAs, or long noncoding RNAs [19,238-242]. Since hsp90 inhibitors trigger previously hidden morphological phenotypes in the next generation and for several generations thereafter, increasing evidence also supports a ‘capacitor’ role (i.e., storage of accumulated stress) of hsp90 in buffering transgenerational epigenetic variation during environmental or nutritional stress [243-245].

A next challenge will be to determine which adverse epigenomic marks are reversible by specific diets, drugs, or lifestyle changes [22,116,142,143,146,201,225,231]. Numerous botanical species and plant parts contain a diverse array of polyphenolic phytochemicals which exert health-beneficial effects in man by their anti-inflammatory, anti-oxidant, phytohormone, cardio-protective, cancer preventive, and anti-bacterial properties, by maintaining immune homeostasis (hormesis) [246,247]. Phytochemicals have also successfully been applied for regenerative medicine and cancer stem cell therapy [248-253]. Oxidative stress and inflammatory damage play an important role in epigenetic reprogramming of expression of cytokines, oncogenes, and tumor suppressor genes, thereby setting up a ground for chronic inflammatory diseases and carcinogenesis [254-256]. As such chemoprevention, the strategy to inhibit, retard, or even reverse the epigenetic stage of chronic inflammation is one of the most rational approaches to reduce the global burden of non-communicable aging diseases [30,153,256,257].

Today, various nutritional compounds (including epigallocatechin gallate, resveratrol, genistein, curcumin, isothiocyanates, witaferin A) have been characterized which interfere with enzymatic activity of chromatin writers, readers, or erasers such as DNMT, class I to IV histone deacetylases (HDACs), histone acetyl transferases (HATs), and class III HDAC sirtuins (SIRTs) which modulate inflammatory responses and immunological senescence ([91,140,141,145,231,258-269] and references included) (Figure 4). HDACs are zinc metalloproteins which rely on Zn$^{2+}$ for their activity and are divided into four classes based on their homology with yeast HDACs. Class III HDACs, called sirtuins, are zinc independent but nicotinamide adenine dinucleotide (NAD$^+$) dependent. Class I to IV HDAC inhibitors characteristically contain a Zn$^{2+}$ chelating group consisting of a thiolate, thiol, hydroxamate, carboxylate, mercaptoamide, epoxide, or keto group. Natural HDAC inhibitors can be divided in following groups based on their chemical characteristics: carboxylates, organosulfides, isothiocyanates, hydroxamates, cyclic tetrapeptides, and macrocyclic depsipeptides [261]. In contrast to natural HDAC inhibitors, only few natural products (i.e., nacin, dicyouromarin) have been identified as inhibitors of class III HDACs. Reciprocally, various natural flavonoids have been identified as activators of class III HDACs (SIRTs). Finally, turmeric and green tea have been identified as sources of natural inhibitors of p300/CBP HAT. Finally, DNMT inhibitors work mainly through one of the following mechanisms, either covalent trapping of DNMT through incorporation into DNA (i.e., nucleoside analogs decitabine, 5-azacytidine), non-covalent blocking of DNMT catalytic active site (i.e., EGCg, parthenolide), interruption of binding site of DNMT to DNA (i.e., procaine), degradation of DNMT (i.e., decitabine), or suppression of DNMT expression (i.e., miRNAs). Furthermore, a number of natural compounds act as multifunctional ligands by simultaneously acting on nuclear hormone receptors and changing activity of histone-modifying enzymes and DNMTs [270-274]. Although health-protective anti-oxidant or anti-inflammatory effects of dietary factors and extracts have frequently been demonstrated in in vitro experiments at concentrations which can never be achieved in vivo, ‘epigenetics’ might shed a more realistic light on dietary studies, as long life exposure at physiological concentrations could lead to remodeling of the epigenome in a cumulative fashion by repetitive effects on the epigenetic machinery [160,161,275]. Particular attention needs to be given to natural compounds which can trigger opposite effects on HDAC/HAT/DNMT or histone (de)methylase (H(D)MT) depending on the concentration- or cell type-specific metabolism [260,261]. It should also be stressed that it is not known whether all of them can be considered authentic epigenetic modifiers because it has not yet been demonstrated whether the epigenetic modifications which they induce are stable over time. Interestingly, even transient exposure to a specific dietary component can induce long-lasting epigenetic changes in inflammatory gene expression [218,276]. Alternatively, compounds may chemically interfere with histone mark interacting protein
structure motifs (such as chromo-, bromo-, or tudor domains) [277-279].

Besides specific interference of the diet with chromatin-modifying enzymes and DNMTs at particular target genes, global epigenetic changes can also occur following biochemical metabolization of dietary factors, which can deplete cellular pools of acetyl-CoA, NAD⁺, and methyl donors, resulting in unbalanced DNA methylation and/or protein acetylation or methylation [87,266,280]. For example, diets lacking in substrate or cofactors in methyl donor metabolism can contribute to DNA hypomethylation by impairing synthesis of SAM [194]. This methylation cycle is frequently cited to explain relations between diet and epigenetic changes [193,281]. However, even without nutritional deficiency of methyl groups, impaired synthesis of SAM and perturbed DNA methylation can happen when the need for glutathione (GSH) synthesis increases [282]. Diets or nutritional compounds which affect energy metabolism or mitochondrial respiration can have global epigenetic effects upon changes in NAD⁺ availability and SIRT activity [283]. Since SIRT activation has been linked to longevity (increased lifespan and healthy aging) and mimics a caloric restricted diet, SIRT activators such as resveratrol represent a major class of caloric mimetic phytochemicals which could reverse metabolic disease [280,284-286].

**Xenohormetic epigenetic effects of plant secondary metabolites across species: evolutionary role for stress adaptive responses in healthy aging and longevity**

The xenohormesis hypothesis proposes that under stressful conditions, plants synthesize phytochemicals (xenohormetins), which, when incorporated into the heterotroph diet, induce defense responses, leading to an extended lifespan and healthy aging and mimics a caloric restricted diet, SIRT activators such as resveratrol represent a major class of caloric mimetic phytochemicals which could reverse metabolic disease [280,284-286].

**Interindividual epigenetic variation in diet responses and challenges of personalized nutrition**

From clinical and diet intervention studies, it appears that individuals display different responses to pharmacological nutritional interventions, respectively, that result in variable benefits to particular treatments [143,289,290]. Similarly, considerable heterogeneity can be observed in biological aging and chronological age is not a reliable marker for healthy aging [291]. Heterogeneity in responsiveness can obscure associations between dietary intakes and health outcomes and bias the identification of the effects of bioactive phytochemicals in specific subpopulations.

Pharmacogenomic and -kinomic studies demonstrate that for some drugs and/or bioactive nutrients, individuals can be categorized into poor, intermediate, or extensive absorbers or metabolizers and dosing has to be personalized [102,143,160,161,203,292-295]. Various genetic single-nucleotide polymorphisms (SNPs) with known relevance to drug pharmacokinetics, such as detoxification enzymes and transporters, have already been compiled in online databases. For example, several genetic variants exist for genes encoding glutathione S-transferases (GSTs), which play major roles in the metabolism of glucosinolates and bioavailability of isothiocyanates that are present in cruciferous vegetables (broccoli) [296,297]. A significant interindividual variation has also been described for the LDL-cholesterol lowering response to plant sterol consumption, and it is associated with ABCG8 gene polymorphism [298].

However, this is still insufficient to explain the large interindividual variations in therapeutic responses. In recent years, evidence that has accumulated suggests that epigenetic aberrations of key ADME genes (genes related to drug absorption, distribution, metabolism, and excretion)
involved in the metabolism and distribution of phytochemicals also contribute to interindividual variations in the nutritional response [102,299]. For example, hypermethylation of ADME gene promoters has been observed in cancer tissue, resulting in gene repression of various phase I and II enzymes, including CYP450s and UDP-glucuronosyltransferases, as well as ABC efflux transporters [300-302] (Figure 4). The introduction or removal of CpG dinucleotides at SNPs (CpG-SNPs, epimutations) may represent a potential mechanism through which SNPs affect gene function via epigenetic processes [31,303]. Conversely, epigenetic changes could increase susceptibility to genetic point mutations [304]. This indicates a complex interrelationship between genetic and epigenetic variations in different diet-related disease phenotypes [31,304-309]. Personalized nutrition is an increasingly recognized paradigm in nutrition research. Therefore, some population subgroups may gain more benefit than others from the consumption of plant foods and their bioactives. The further determination of environmental factors responsible for interindividual variations in the endocrine system, epigenetic profiles, and microbiome communities and the identification of ‘susceptibility profiles’ in response to plant bioactive consumption could lead to targeted dietary advice and use of functional foods customized for different population subgroups [143,310-312]. In contrast to prominent quantitative epigenetic changes at tumor suppressor genes (>60% increase of DNA methylation) associated with cancer, more subtle epigenetic changes are typically observed in cardiometabolic disorders (<20%) [312-320]. To reverse such subtle changes, several nutrients and bioactive food compounds may be preferred over toxic antineoplastic epigenetic drugs [91,121,142,143,321-327]. This will encourage the characterization of robust epigenetic dietary biomarkers and design of functional foods that could help to combat or prevent inflamming-related metabolic diseases.

Conclusions
The phenotype of an individual is the result of complex ongoing gene-environment interactions in the present, past, and ancestral environments, responsible for lifelong remodeling of our epigenomes. In recent years, several studies have demonstrated that disruption of epigenetic mechanisms can alter immune function and that epimutations not only contribute to certain cancers but also to lifestyle diseases such as type 2 diabetes, allergies, cardiovascular disease, and rheumatoid arthritis, as well as unhealthy aging. Various replication-dependent and -independent epigenetic mechanisms are involved in developmental programming, a lifelong intertwined process of monitoring and responding to environmental changes, and the transmission of transgenerational effects. It is likely that improved understanding of epigenetic processes will allow us to manipulate the epigenome which represents a reversible source of biological variation [328,329]. We believe that herein resides a great potential for chemoprevention, alleviation of chronic inflammatory disorders, and healthy aging. Much attention is currently focused on the modulation of hyper/hypomethylation of key inflammatory genes by dietary factors as an effective approach to chronic inflammatory disease management and general health benefits [146,155,231,259-266]. In this respect, ‘Let food be your epigenetic medicine’ could represent a novel interpretation of what Hippocrates said twenty-five centuries ago. As such, it will be a challenge for future nutritional research to identify novel epigenetic targets that promote healthy aging [247,330-335].

In conclusion, ‘inflamming’ disorders as well as dietary lifestyle reveal a dazzling complexity of epigenetic changes during lifetime. To prevent or to reverse adverse epigenetic alterations associated with multifactorial aging diseases, combinatorial therapeutic and/or nutritional approaches will be necessary to modulate different classes of chromatin modifiers. Future research needs to evaluate the optimal dose and exposure window during gestation in utero, post-natal early life, prepuberty, and adult life for specific dietary composition to elicit maximal epigenetic benefits against inflamming and improve the overall quality of life of the human population [35,309,324-327].

Abbreviations
5-hmc: 5-hydroxymethylcytosine; 5-mC: 5-methylcytosine; 8-OHdG: 8-hydroxy-2′-deoxy-guanosine; ADME: absorption, distribution, metabolism, excretion; AhR: arylhydrocarbon receptor; CpG: cytosine-phosphate-guanine; CTF: insulator CCCTC binding factor; DNMT: DNA methyltransferase; DOHD: developmental origin of health and disease; eNOS/nNOS: endothelial and inducible nitric oxide synthase; ER: estrogen receptor; FGF: fibroblast growth factor; FH: fumarate hydratase; GF: glucocorticoid receptor; GSH: glutathione; HAT: histone acetyl transferases; HDAC: histone deacetylate; HIF: hypoxia-inducible factor; HMT: histone methyltransferases; HPA: hypothalamic-pituitary-adrenal; IDH: isocitrate dehydrogenase; IGF: insulin growth factor; JMID: jumonji domain; KDM: lysine demethylase; LOX: lipoxygenase; LXR: liver X receptor; MMP: metalloproteases; ncRNAs: noncoding RNA; PDK: pyruvate dehydrogenase kinase; PGE2: prostaglandin E2; PPAR: peroxisome proliferator-activated receptor; RNS: reactive nitrogen species; ROS: reactive oxygen species; SAM: S-adenosylmethionine; SDH: succinate dehydrogenase; SIRT: sirtuin; SNP: single nucleotide polymorphism; SOD: superoxide dismutase; TET: ten-eleven translocation; UDP-GlcNAc: UDP-N-acetylglucosamine.

Competing interests
The authors declare that they have no competing interests.
Authors’ contributions
All authors contributed to the content. All authors read and approved the final manuscript.

Acknowledgements
This work has been supported by COST TD0905: Epigenetics from bench to bedside; COST CM1406: Epigenetic Chemical Biology; COST FA1403: Interindividual variation in response to consumption of plant food bioactives, and FWO research grants. MV wishes to recognize the assistance of the Serbian Ministry of Education, Science and Technological Development, Grant 173020 and bilateral project ‘Pavle Savic’ (451-03-3455/2013-09/12/02). We thank all lab members for helpful discussions.

Author details
1 Lab Protein Science, Proteomics and Epigenetic Signaling, Department of Biomedical Sciences, University Antwerp, Campus Drie Eiken, Universiteitsplein 1, 2610 Wilrijk, Belgium. 2 Department of Molecular Biology, Institute for Biological Research, University of Belgrade, Bulevar Despota Stefana 142, 11060 Belgrade, Serbia.

Received: 16 November 2014 Accepted: 9 March 2015

Published online: 25 March 2015

References
1. López-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013;153(6):1194–217.
2. Baylis D, Bantlett DP, Patel HP, Roberts HC. Understanding how we age: insights into inflamming. Longev Healthspan. 2012;1(18).
3. Franceschi C, Capri M, Monti D, Giunta S, Olivier F, Sovini F, et al. Inflamming and anti-inflamming: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. 2007;128(1):92–105.
4. De la Fuente M, Miquel J. An update of the oxidation-inflammation theory of aging: the involvement of the immune system in ox-inflamming. Curr Pharm Des. 2009;15(26):3003–26.
5. Ling C, Ronn T. Epigenetic adaptation to regular exercise in humans. Drug Discov Today. 2014;9(7):1015–8.
6. Denham J, O’Brien BJ, Marques FZ, Charchar FJ. Changes in the leucocyte methyline and its effect on cardiovascular related genes after exercise. J Applied Physiol. 2014. doi:10.1152/japplphysiol.00878.2014.
7. Santoro A, Pini E, Scurti M, Palmas G, Berendsen A, Brzozowska A, et al. Combating inflamming through a Mediterranean whole diet approach: the NU-AGE project’s conceptual framework and design. Mech Ageing Dev. 2014;136:137–13.
8. Zamora-Ros R, Forouhi NG, Sharp SJ, Gonzalez CA, Buijsse B, Guevara M, et al. Dietary intakes of individual flavanols and flavonols are inversely associated with incident type 2 diabetes in European populations. J Nutr. 2013;144(3):33–43.
9. Beaudoin C, Attig L, Vige A, Gabory A, Karimi M, Beauger A, et al. Dietary alleviation of maternal obesity and diabetes: increased resistance to insulin-induced obesity transcriptional and epigenetic signatures. PLoS One. 2013;8(6):e68616.
10. Berendsen A, Santoro A, Pini E, Cevenini E, Ostani R, Pietruszka B, et al. A parallel randomized trial on the effect of a healthful diet on inflamming and its consequences in European elderly people design of the NU-AGE dietary intervention study. Mech Ageing Dev. 2013;134(1–2):523–30.
11. Van Gaal LF, Maggioni AP. Overweight, obesity, and outcomes: fat mass and beyond. Lancet. 2014;383(9921):935–6.
12. Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: diet components and nutritional strategies. Lancet. 2014;383(9933):1999–2007.
13. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, et al. Finding the missing heritability of complex diseases. Nature. 2009;461(7265):743–7.
14. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008;456(7218):18–21.
15. Hinney A, Vogel CL, Hebebrand J. From monogenic to polygenic obesity: recent advances. Eur Child Adolesc Psychiatry. 2010;19(3):297–310.
16. Roadmap Epigenomics C, Kundaje A, Meuleman W, Ernst J, Bilenky M, Yan A, et al. Integrative analysis of 111 reference human epigenomes. Nature. 2015;518(7559):317–30.
17. Miller RL, Ho SM. Environmental epigenetics and asthma: current concepts and call for studies. Am J Respir Crit Care Med. 2008;177(6):567–73.
18. Villeneuve LM, Natarajan R. The role of epigenetics in the pathology of diabetic complications. Am J Physiol Renal Physiol. 2010;299(1):F14–25.
19. Gull S, Esteller M. DNA methylomes, histone codes and miRNAs: tying it all together. Int J Biochem Cell Biol. 2009;41(11):87–95.
20. Schwarz DA. Epigenetics and environmental lung disease. Proc Am Thorac Soc. 2010;7(2):123–5.
21. Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med. 2008;359(1):61–73.
22. Godfrey KM, Gluckman PD, Hanson MA. Developmental origins of metabolic disease: life course and intergenerational perspectives. Trends Endocrinol Metab. 2010;21(4):199–205.
23. Davalos V, Esteller M. MicroRNAs and cancer epigenetics: a macrorevolution. Curr Opin Oncol. 2010;22(1):33–45.
24. Esteller M. Cancer epigenomics: DNA methylomes and histone-modification maps. Nat Rev Genet. 2007;8(4):286–98.
25. Esteller M. Epigenetics in cancer. N Engl J Med. 2008;358(11):1148–59.
26. Paul DS, Beck S. Advances in epigenome-wide association studies for common diseases. Trends Mol Med. 2014;20(10):541–3.
27. Dick KJ, Nelson CP, Tsaprouni L, Sandling JK, Assi D, Wahl S, et al. DNA methyllyation and body-mass index: a genome-wide analysis. Lancet. 2014;383(9933):1990–8.
28. McAllister EJ, Dhurandhar NV, Keith SW, Anonne LJ, Barger J, Baskin M, et al. Ten putative contributors to the obesity epidemic. Crit Rev Food Sci Nutr. 2009;49(10):968–913.
29. Mill J, Heijmans BT. From promises to practical strategies in epigenetic epidemiology. Nat Rev Genet. 2013;14(8):585–94.
30. Milagro FI, Maniego ML, De Miguel C, Martinez JA. Dietary factors, epigenetic modifications and obesity outcomes: progresses and perspectives. Mol Aspects Med. 2013;34(4):782–812.
31. Teh AL, Pan H, Chen L, Ong ML, Dogsa S, Wong J, et al. The effect of genotype and in utero environment on interindividual variation in neonate DNA methylomes. Genome Res. 2014;24(7):1064–74.
32. Susiarjo M, Bartolomei MS. Epigenetics: you are what you eat, but what about your DNA? Science. 2014;345(6198):733–4.
33. Radford EJ, Ito M, Shi H, Corsh JA, Yamazawa K, Loganathan E, et al. In utero effects: in utero undernourishment perturbs the adult sperm methylome and intergenerational metabolism. Science. 2014;345(6198):1255903.
34. Lehnen H, Zechner U, Haaf T. Epigenetics of gestational diabetes mellitus and offspring health: the time for action is in early stages of life. Mol Hum Reprod. 2013;19(7):415–22.
35. Topol EJ. Individualized medicine from prewomb to tomb. Cell. 2014;157(1):51–53.
36. Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. Environ Health. 2012;11:42.
37. Adamo KB, Ferraro ZM, Brett KE. Can we modify the intrauterine environment to halt the intergenerational cycle of obesity? Int J Environ Res Public Health. 2013;10(4):1263–307.
38. Martinez D, Pentinat T, Ribó S, Daviaud C, Bloks Vincent W, Cebrià J, et al. In utero undernutrition in male mice programs liver lipid metabolism in the second-generation offspring involving altered lxra DNA methylation. Cell Metab. 2014;19(6):941–51.
39. Teschendorff AE, West J, Beck S. Age-associated epigenetic drift: implications, and a case of epigenetic drift? Hum Mol Genet. 2013;22(1):R97–15.
40. Chi P, Allis CD, Wang GG. Covalent histone modifications - miswritten, misinterpreted and mis-erased in human cancers. Nat Rev. 2010;10(7):457–69.
41. Ernst J, Kellis M. Discovery and characterization of chromatin states for systematic annotation of the human genome. Nat Biotechnol. 2010;28(8):817–25.
42. Ernst J, Khaledpour P, Mikkelsen TS, Shorey N, Ward LD, Epstein CB, et al. Mapping and analysis of chromatin state dynamics in nine human cell types. Nature. 2011;473(7345):43–9.
43. Zhu J, Adli M, Zou YJ, Verstappen G, Coyne M, Zhang X, et al. Genome-wide chromatin state transitions associated with developmental and environmenal cues. Cell. 2013;5(2):642–5.
44. Dunham I, Kundaje A, Aldred SR, Collins PJ, Davis CA, Doyle F, et al. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012;489(7414):57–74.
45. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev. 2002;16(11–12):21.

46. Schuberle D. Function and information content of DNA methylation. Nature. 2015;517(7534):621–6.

47. Jones PA, Liang G. Rethinking how DNA methylation patterns are maintained. Nat Rev Genet. 2008;10(11):805–11.

48. Law JA, Jacobsen SE. Establishing, maintaining and modifying DNA methylation patterns in plants and animals. Nat Rev Genet. 2010;11(3):204–20.

49. Guo X, Wang L, Li J, Ding Z, Xiao Y, Yin X, et al. Structural insight into autoinhibition and histone H3-induced activation of DNMT3A. Nature. 2015;517(7536):640–4.

50. Jeltsch A, Jurkowska RZ. New concepts in DNA methylation. Trends Biochem Sci. 2014;39(7):310–8.

51. Deplus R, Blanchon L, Rajavelu A, Bouakâa A, Defrance M, Luciani J, et al. Regulation of DNA methylation patterns by O2-mediated phosphorylation of DNMT3a. Cell Rep. 2014;8(3):743–53.

52. Huang SK, Scrucca AM, Donaghy J, McEachin RC, Fisher AS, Richardson BC, et al. Prostaglandin E2(2) increases fibroblast gene-specific and global DNA methylation via increased DNA methyltransferase expression. FASEB J. 2012;26(13):3703–14.

53. Xia D, Wang D, Kim SH, Katoh H, DuBois RN. Prostaglandin E2 promotes intestinal tumor growth via DNA methylation. Nat Med. 2012;18(2):224–6.

54. Hanum M, Guiney J, Zhao L, Zhang L, Hughes G, Sadda S, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. Mol Cell. 2013;49(2):359–67.

55. Forga MF, Ballester E, Paz MF, Rosero S, Setien F, Ballester ML, et al. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005;102(30):10604–9.

56. Maegawa S, Hinkel G, Kim HS, Shen L, Zhang L, Zhang J, et al. Widespread and tissue specific age-related DNA methylation changes in mice. Genome Res. 2010;20(3):332–40.

57. Oh J, Lee YD, Wagers AJ. Stem cell aging: mechanisms, regulators and therapeutic opportunities. Nat Med. 2014;20(8):870–80.

58. Delatte B, Deplus R, Fuks F. Playing TETris with DNA modifications. EMBO J. 2012;31(10):2249–54.

59. Wang L, Chia NC, Lu X, Ruden DM. Hypothesis: environmental regulation of the APE1 gene in the translocation-2 (TET2) is a master regulator of smooth muscle cell plasticity. Nucleic Acids Res. 2004;32(14):4100–8.

60. Wang L, Chia NC, Lu X, Ruden DM. Tet3 promotes blastocyst-like state in ES cells. Nature. 2013;500(7461):222–4.

61. Chang J, Zhang B, Heath H, Galjart N, Wang X, Milbrandt J. Nicotinamide adenine dinucleotide (NAD)-regulated DNA methylation alters CCCTC-binding factor (CTCF)/cohesin binding and transcription at the BDNF locus. Proc Natl Acad Sci U S A. 2010;107(50):21836–41.

62. Wallace DC. Bioenergetics and the epigenome: interface between the environment and genes in common diseases. Dev Disabil Res Rev. 2010;16(2):114–9.

63. Wallace DC. The epigenome and the mitochondrion: bioenergetics and the epigenetic link. J Cell Sci. 2010;123(Pt 22):3837–48.

64. Chang J, Zhang B, Heath H, Galjart N, Wang X, Milbrandt J. Nicotinamide adenine dinucleotide (NAD)-regulated DNA methylation alters CCCTC-binding factor (CTCF)/cohesin binding and transcription at the BDNF locus. Proc Natl Acad Sci U S A. 2010;107(50):21836–41.

65. Wallace DC. Bioenergetics and the epigenome: interface between the environment and genes in common diseases. Dev Disabil Res Rev. 2010;16(2):114–9.

66. Wallace DC. The epigenome and the mitochondrion: bioenergetics and the epigenetic link. J Cell Sci. 2010;123(Pt 22):3837–48.

67. Chang J, Zhang B, Heath H, Galjart N, Wang X, Milbrandt J. Nicotinamide adenine dinucleotide (NAD)-regulated DNA methylation alters CCCTC-binding factor (CTCF)/cohesin binding and transcription at the BDNF locus. Proc Natl Acad Sci U S A. 2010;107(50):21836–41.

68. Wallace DC. Bioenergetics and the epigenome: interface between the environment and genes in common diseases. Dev Disabil Res Rev. 2010;16(2):114–9.

69. Wallace DC. The epigenome and the mitochondrion: bioenergetics and the epigenetic link. J Cell Sci. 2010;123(Pt 22):3837–48.

70. Chang J, Zhang B, Heath H, Galjart N, Wang X, Milbrandt J. Nicotinamide adenine dinucleotide (NAD)-regulated DNA methylation alters CCCTC-binding factor (CTCF)/cohesin binding and transcription at the BDNF locus. Proc Natl Acad Sci U S A. 2010;107(50):21836–41.

71. Wallace DC. Bioenergetics and the epigenome: interface between the environment and genes in common diseases. Dev Disabil Res Rev. 2010;16(2):114–9.
local sequence features on the variation of DNA methylation in blood. Epigenetics. 2011;6(5):1908–19.

98. Tan Q, Christiansen L, Thomassen M, Kruse TA, Christensen K. Twins for epigenetic studies of human aging and development. Ageing Res Rev. 2013;12(1):182–7.

99. Zhao J, Forsberg CW, Goldberg J, Smith NL, Vaccarino V. MAAO promoter methylation and susceptibility to carotid atherosclerosis: role of familial factors in a monogygotic twin sample. BMC Med Genet. 2012;13:100.

100. Simo-Rualdals L, Esteller M. Targeting the histone orthography of cancer: drugs for writers, erasers and readers. Br J Pharmacol. 2014; doi:10.1111/bph.12844.

101. Helin K, Dhanak D. Chromatin proteins and modifications as drug targets. Nature. 2013;502(7472):480–8.

102. Ivanov M, Barragan I, Ingelman-Sundberg M. Epigenetic mechanisms of importance for drug treatment. Trends Pharmacol Sci. 2014;35(8):384–96.

103. Falkenberg K, Johnstone R. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014;13:763–91.

104. Eisenberg T, Schroeder S, Buttner S, Carmona-Gutierrez D, Pendl T, Katada S, Imhof A, Sassone-Corsi P. Connecting threads: epigenetics and tumour growth and metastasis: evidence that – epigenetics and tumour growth and metastasis: evidence that – histone macroH2A1.1 – driving process. Cell Signal. 2014;26(5):104.

105. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. Metabolic regulation of epigenetics. Cell Metab. 2012;16(1):14–20.

106. Figueroa ME, Abdel-Wahab O, Lu C, Ward PS, Patel J, Shih A, et al. Leukemic Polycomb/Trithorax response element. Nat Genet. 2014;46(9):973–8.

107. Thorburn AN, Macia L, Mackay CR. Diet, metabolites, and personalized medicine via metabolo-genomics. Cell Cycle. 2011;10(8):1271–9.

108. Teperino R, Schoonjans K, Auwerx J. Histone methyl transferases and inflammatory diseases. Immunity. 2014;40(6):833–42.

109. Bonuccelli G, Tsirigos A, Whitaker-Menezes D, Pavlides S, Pestell RG, Chiavarina B. Cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2012;11(2):146–59.

110. Martinez-Outschoorn UE, Prisco M, Ertel A, Tsirigos A, Lin Z, Pavlides S, et al. Nucleocytosolic depletion of the energy metabolite acetyl-coenzyme A drives oncogenesis. Cancer Cell. 2012;21(3):297–307.

111. Ordovas JM, Smith CE. Epigenetics and cardiovascular disease. Nat Rev Cardiol. 2010;7(9):510–9.

112. Salminen A, Kauppinen A, Hiltunen M, Kaarina J, Riekkinen O. Krebs cycle intermediates regulate DNA and histone methylation: epigenetic impact on the aging process. Ageing Res Rev. 2014;13(4):45–65.

113. Salminen A, Kaarina J, Hiltunen M, Kauppinen A. Krebs cycle dysfunction shapes epigenetic landscape of chromatin: novel insights into mitochondrial regulation of aging process. Cell Signal. 2014;26(7):1598–603.

114. Zuccaro G, Vignali D, Brugues A, Capellino F, et al. Genetic ablation of macrophiste H2A1.1 protects hepatocytes against lipid accumulation. Aging (Albany NY). 2014;6(1):35–47.

115. Zhang J, Wang X, Zhang J, Lian JK, Shi HY, Yang AS, et al. Warburg effect revisited: an epigenetic link between glycolysis and gastric carcinogenesis. Oncogene. 2010;29(4):492–502.

116. Rinn JL. lncRNAs: linking RNA to chromatin. Cold Spring Harb Perspect Biol. 2012;4(10):a006583.

117. Romagnolo DF, Zempleni J, Selmin OI. Nuclear receptors and epigenetic plasticity: implications for understanding human disease. Annu Rev Nutr. 2010;30:315–39.

118. Gallou-Kabani C, Vige A, Gross MS, Junien C. Nutri-epigenomics: lifelong remodelling of our epigenomes by nutritional and metabolic factors and beyond. Clin Chim Acta. 2007;453(1):321–7.

119. Gluckman PD, Hanson MA, Buklijas T. A conceptual framework for the developmental origins of health and disease. J Dev Orig Health Dis. 2010;1(1):16–18.
151. Anway MD, Cupp AS, Lutzcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science. 2005;308(5727):1466–9.
152. Anway MD, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors. Endocr Dev. 2006;17(1/6):Suppl5:43–9.
153. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. Nat Rev Genet. 2007;8(4):253–62.
154. Barker DJ, Martyn CN. The maternal and fetal origins of cardiovascular disease. J Epidemiol Community Health. 1992;46(1):8–11.
155. Jackson AA, BBerge GC, Lillycrop KA. Diet, nutrition and modulation of genomic expression in fetal origins of adult disease. World Rev Nutr Diet. 2010;101:56–72.
156. Chmuryzynska A. Fetal programming: link between early nutrition, DNA methylome, and complex diseases. Nutr Rev. 2010;68(2):87–98.
157. Kaminsky ZA, Tang T, Wang SC, Ptak C, Oh GH, Wong AH, et al. DNA methylation profiles in monozygotic and dizygotic twins. Nat Genet. 2009;41(2):240–5.
158. Petronis A. Epigenetics and twins: three variations on the theme. Trends Genet. 2006;22(7):347–50.
159. Castillo-Fernandez JE, Spector TD, Bell JT. Epigenetics of discordant monozygotic twins: implications for disease. Genome Med. 2014;6(7):160.
160. Li CC, Cropley JE, Cowley MJ, Press T, Martin DI, Suter CM. A sustained dietary change increases epigenetic variation in isogenic mice. PLoS Genet. 2011;7(4):e1001380.
161. Cropley JE, Dang TH, Martin DI, Suter CM. The penetrance of an epigenetic trait in mice is progressively yet reversibly increased by selection and environment. Proc Natl Acad Sci U S A. 2012;109(13):5347–51.
162. Pembrey M, Saffery R, Bygren LO. Human transgenerational responses to early-life experience potential impact on development, health and biomedical research. J Med Genet. 2014;51(9):563–72.
163. Dolinoy DC, Weidman JR, Waterland RA, Jirtle RL. Maternal genistein alters protein isolate reduces hepatosteatosis in yellow Avy/a mice without known effect on DNA methylation. Comparative Biochem Physiol Toxicol Pharmacol. 2010;151(3):278–85.
164. Gabor Miklos GL, Malezska R. Epigenomic communication systems in humans and honey bees: from molecules to behavior. Horm Behav. 2010;59(3):399–406.
165. Kucharski R, Malezska J, Forest S, Malezska R. Nutritional control of reproductive status in honeybees via DNA methylation. Science. 2008;319(5871):1827–30.
166. Malezska R. Epigenetic integration of environmental and genomic signals in honey bees: the critical interplay of nutritional, brain and reproductive networks. Epigenetics. 2008;3(4):188–92.
167. Forest S, Kucharski R, Pfitzkov Y, Lockett GA, Malezska R. Epigenetic regulation of the honey bee transcriptome: unravelling the nature of methylated genes. BMC Genomics. 2009;10:307.
168. Forest S, Kucharski R, Pelligrin M, Fung S, Jacobsen SE, Robinson GE, et al. DNA methylation dynamics, metabolic fluxes, gene splicing, and alternative phenotypes in honey bees. Proc Natl Acad Sci U S A. 2012;109(13):4968–73.
169. Kamakura M. Royaltacin induces queen differentiation in honeybees. Nature. 2011;473(7348):478–83.
170. Munich D, Ardam D, Nat. The curious case of aging plasticity in honey bee. FEBs Lett. 2010;584(12):2496–503.
171. Li X, Huang C, Xue Y. Contribution of lipids in honeybee (Apis mellifera) royal jelly to health. J Med Food. 2013;16(2):96–102.
172. Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJO. 2008;115(10):1243–9.
203. Manach C, Mazur A, Scalbert A. Polyphenols and prevention of cardiovascular diseases. Curr Opin Lipidol. 2005;16(1):177–84.

204. Fisher ND, Hollenberg NK. Aging and vascular responses to flavonoid-rich cocoa. J Hypertens. 2006;24(8):1375–80.

205. Sies H, Schewe T, Heiss C, Kelm M. Cacao polyphenols and inflammatory mediators. Am J Clin Nutr. 2005;81(1 Suppl):334S–51S.

206. Heiss C, Kleinebongard P, Oertel S, Scherer H, Sies H, et al. Acute consumption of flavanol-rich cocoa and the reversal of endothelial dysfunction in smokers. J Am Coll Cardiol. 2005;46(7):1276–83.

207. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006;5(6):493–506.

208. Bertelli AA, Das DK. Grapes, wines, resveratrol, and heart health. J Cardiovasc Pharmacol. 2005;46(5):468–76.

209. Chiva-Blanch G, Badimon L, Estruch R. Latest evidence of the effects of the Mediterranean diet in prevention of cardiovascular disease.Curr Atheroscler Rep. 2014;16(10):446.

210. Turunen MP, Aavik E, Yla-Herttuala S. Epigenetics and atherosclerosis. Biochim Biophys Acta. 2010;1801(10):1557–63.

211. van Straten EM, Bloks VW, Huijkman NC, Baller JF, Meer H, Lutjohann D, et al. Epigenetic malprogramming of the insulin receptor promoter due to inhibition of Polycomb-mediated gene silencing. Cell Metab. 2009;10(3):189–97.

212. Brasacchio D, Okabe J, Tikellis C, Balcerczyk A, George P, Baker EK, et al. Epigenetic changes caused by methylating agents cause the hypermethylation phenotype. Cancer Res. 2009;69(11):4355–61.

213. Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. J Nutr. 2005;135(6):1832–6.

214. De Santa F, Totaro MG, Prosperini E, Notarbartolo S, Testa G, Natoli G. G9a histone methyltransferase is essential for chromatin remodelling and gene silencing. Nature. 2004;430(7000):345–9.

215. Raghavan KK, Raghavan R, Chee MM, Dey SS, el-Sayed MA. Spatio-temporal methylome changes related to scale effect. Nucleic Acids Res. 2005;33(19):e190.

216. Reddy MA, Villeneuve LM, Wu X, Wen Z, Lanting L, Natarajan R. Role of the insulin-like growth factor (IGF) pathway in cardiovascular stress response of children at school age. Pediatrics. 2007;119(5):1439–46.
252. Bickford PC, Tan J, Shytle RD, Sanberg CD, El-Badry N, Sanberg PR. Nutraceuticals synergistically promote proliferation of human stem cells. Stem Cells Dev. 2006;15(1):118–23.

253. Zhou J, Zhang H, Gu P, Bai J, Margolick JB, Zhang Y. NF-kappaB pathway inhibitors preferentially inhibit breast cancer stem-like cells. Breast Cancer Res Treat. 2008;108(3):419–27.

254. Grivennikov SI, Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev. 2010;20(1):65–71.

255. Aggarwal BB. Inflammation, a silent killer in cancer is not so silent! Curr Opin Pharmacol. 2009;9(4):347–50.

256. Aggarwal BB, Gehlot P. Inflammation and cancer: how friendly is the relationship for cancer patients? Curr Opin Pharmacol. 2009;9(4):351–69.

257. Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, et al. Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25(9):2097–116.

258. Arasaratnam RP, Commune DM, Bradburn D, Mathers JC. A review of dietary factors and its influence on DNA methylation in colorectal carcinogenesis. Epigenetics. 2008;3(4):193–8.

259. Delage B, Dashwood RH. Dietary manipulation of histone structure and function. Annu Rev Nutr. 2008;28:347–66.

260. Link A, Balaguer F, Shen Y, Lozano JJ, Leung HC, Boland CR, et al. Clinical Epigenetics. 2015;7:33.

261. Hauser AT, Jung M. Targeting epigenetic mechanisms: potential of natural products in cancer chemoprevention. Planta Med. 2008;74(13):1593–601.

262. Vaquer A, Reinberg D. Calorie restriction and the exercise of chromatin. Annu Rev Nutr. 2008;28:347–64.

263. Kontogiorgis C, Bompou E, Ntella M, Vanden Berghe W. Natural products occurring regulators of histone acetylation/deacetylation. Curr Nutrit Food Sci. 2010;6:1–11.

264. Denison MS, Nagy SR. Activation of the aryl hydrocarbon receptor by xenoestrogens. Anticancer Res. 2010;30(3):815–20.

265. Vaquero A, Reinberg D. Calorie restriction and the exercise of chromatin. Annu Rev Nutr. 2008;28:347–64.

266. Grivennikov SI, Karin M. Inflammation and oncogenesis: a vicious connection. Curr Opin Genet Dev. 2010;20(1):65–71.

267. Vanden Berghe W, Ndlovu MN, Hoya-Arias R, Dijsselbloem N, Gerlo S, Haegeman G. Keeping up NF-kappaB appearances: epigenetic control of highly accessible chromatin and constitutive transcription across the interleukin-6 gene promoter in metastatic breast cancer cells. Mol Cell Biol. 2009;29(20):5488–504.

268. Vanden Berghe W, Sabbe L, Kalieeh M, Haegeman G, Heyninck K. Molecular insight in the multifunctional activities of Withaferin A. Biochem Pharmacol. 2006;72(9):1114–21.

269. Vanden Berghe W, Sabbe L, Kalieeh M, Haegeman G, Heyninck K. Molecular insight in the multifunctional activities of Withaferin A. Biochem Pharmacol. 2006;72(9):1114–21.

270. Fanger M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. J Nutr. 2007;137(1 Suppl):223S–8.

271. Suzuki T, Miyata N. Epigenetic control using natural products and synthetic molecules. Curr Med Chem. 2006;13(9):935–58.

272. Vaquero A, Reinberg D. Calorie restriction and the exercise of chromatin. Annu Rev Nutr. 2008;28:347–66.

273. Link A, Balaguer F, Goel A. Cancer chemoprevention by dietary polyphenols: promising role for epigenetics. Biochem Pharmacol. 2010;80(2):1712–72.

274. Folmer F, Orlikova B, Schnekenburger M, Dicato M, Diederich M. Naturally occurring modulators of histone acetylation/deacetylation. Curr Nutrit Food Sci. 2010;6:78–99.

275. Hauser AT, Jung M. Targeting epigenetic mechanisms: potential of natural products in cancer chemoprevention. Planta Med. 2008;74(13):1593–601.

276. Kontogiorgis C, Bompou E, Ntella M, Vanden Berghe W. Natural products from Mediterranean diet: from anti-inflammatory agents to dietary epigenetic modulators. Anti-Inflammatory & Anti-Allergy Agents Med Chem. 2010;6(1):1–24.

277. Fang M, Chen D, Yang CS. Dietary polyphenols may affect DNA methylation. J Nutr. 2007;137(1 Suppl):223S–8.
304. Bermingham EN, Albright AL, Volkov P, Almgren P, Ronn T, Ling C. Identification of CpG-SNPs associated with type 2 diabetes and differential DNA methylation in human pancreatic islets. Diabetologia. 2013;56(5):1036–46.

305. You JS, Jones PA. Cancer genetics and epigenetics: two sides of the same coin? Cancer Cell. 2012;22(1):19–20.

306. Heyn H. A symbiotic liaison between the genetic and epigenetic code. Front Genet. 2014;5:113.

307. Nilsson E, Jansson PA, Perflytje A, Volkov P, Pedersen M, Svensson MK, et al. Altered DNA methylation and differential expression of genes influencing metabolism and inflammation in adipose tissue from subjects with type 2 diabetes. Diabetes. 2014;63:926–76.

308. Heyn H, Sayoli S, Moutinho C, Vidal E, Sanchez-Mut JV, Stefansson OA, et al. Linkage of DNA methylation quantitative trait loci to human cancer risk. Cell Rep. 2014;7(2):331–8.

309. Loeffer M, Kreuz M, Haake A, Hasenclever D, Trautmann H, Arnold C, et al. Genomic and epigenomic co-evolution in follicular lymphomas. Leukemia. 2014;29(2):456–63.

310. Almouzni G, Altucci L, Amati B, Ashley N, Baulcombe D, Bejaoui N, et al. Relationship between genome and epigenome - challenges and requirements for future research. BMC Genomics. 2014;15:487.

311. Milenkovic D, Vanden Berghe W, Boby C, Leroux C, Deckert K, Szczalinski K, et al. Dietary flavonoids modulate the transcription of genes associated with cardiovascular pathology without changes in their DNA methylation state. PLoS One. 2014;9(4):e95527.

312. Moleres A, Campion J, Milagro FI, Marcos A, Campoy C, Garagori JM, et al. Differential DNA methylation patterns between high and low responders to a weight loss intervention in overweight or obese adolescents: the EVASONY study. FASEB J. 2013;27(6):5204–12.

313. Bouchard L, Rabasa-Lhoret R, Faraj M, Lavoie ME, Mill J, Perusse L, et al. Differential epigenomic and transcriptomic responses in subcutaneous adipose tissue between high and low responders to caloric restriction. Am J Clin Nutr. 2010;91(2):309–20.

314. Do Amaral CL, Milagro FI, Curi R, Martinez JA. DNA methylation pattern in overweight women under an energy-restricted diet supplemented with fish oil. Biomed Res Int. 2014;2014:675021.

315. Houde AA, Hivert MF, Bouchard L. Fetal epigenetic programming of adipokines. Adipocyte. 2013;2(1):41–6.

316. Desgagne V, Hivert MF, St-Pierre J, Guay SP, Baillargeon JP, Pèron P, et al. Epigenetic dysregulation of the IGF system in placenta of newborns exposed to maternal impaired glucose tolerance. Epigenomics. 2014;6(2):193–207.

317. Milagro FI, Campion J, Cordero P, Goyenechea E, Gomez-Urria AM, Abele I, et al. A dual epigenomic approach for the search of obesity biomarkers: DNA methylation in relation to diet-induced weight loss. FASEB J. 2011;25(4):1378–89.

318. Zierath JR, Barres RE. Nutritional status affects the epigenomic profile of peripheral blood cells. Epigenomics. 2011;3(3):259–60.

319. Wang X, Zhu H, Snieder H, Su S, Munn D, Harshfield GA, et al. Obesity related methylation changes in DNA of peripheral blood leukocytes. BMC Med. 2010;8:87.

320. Frank PW, Ling C. Epigenetics and obesity: the devil is in the details. BMC Med. 2010;8:88.

321. van Kampen E, Jamnison A, van Berkel TJ, van Eck M. Diet-induced (epigenetic) remodeling of epigenetic marks to modulate expression of selected target genes. Nucleic Acids Res. 2012;40(21):10596–613.

322. Paul AT, Gohil VM, Bhutani KK. Modulating TNF-alpha signaling with natural products. Drug Discov Today. 2006;11(15–16):725–32.

323. Ros JL, Recio MC, Escandell JM, Andujar I. Inhibition of transcription factors by plant-derived compounds and their implications in inflammation and cancer. Curr Pharm Des. 2009;15(11):1212–37.

324. Deorukhkar A, Krishnan S, Sethi G, Aggarwal BB. Back to basics: how natural products can provide the basis for new therapeutics. Expert Opin Investig Drugs. 2007;16(11):1753–73.

325. Khanina D, Sethi G, Ahn KS, Pandey MK, Kunnunummakara AB, Sung B, et al. Natural products as a gold mine for arthritis treatment. Curr Opin Pharmacol. 2007;7(3):344–51.

326. Bremner P, Heinrich M. Natural products as targeted modulators of the nuclear factor-kappaB pathway. J Pharm Pharmacol. 2002;54(4):453–72.

327. Karin M, Yamamoto Y, Wang QM. The IKK NF-kappa B system: a treasure trove for drug development. Nat Rev Drug Discov. 2004;3(11):17–26.

328. Tsai PC, Spector TD, Bell JT. Using epigenome-wide association scans of DNA methylation in age-related complex human traits. Epigenomics. 2012;4(5):511–26.

329. Murphy TM, Mill J. Epigenetics in health and disease: heralding the EWAS era. Lancet. 2014;383(9933):1952–4.

330. Szarc vel Szic K, Palagani A, Chandra Sekhar C, Diddens J, Vanden Berghe W. Connecting phytochemicals, epigenetics, and healthy aging: is metabolism the missing link? In: Rahman I, editor. Inflammation, advancing age and nutrition. Amsterdam: Elsevier; 2013. p. 111–24. ISBN 9780213708035.

331. Boonsanay V, Kim J, Braun T, Zhou Y. The emerging role of epigenetic modifiers linking cellular metabolism and gene activity in cardiac progenitor cells. Trends Cardiovasc Med. 2012;22(3):77–81.