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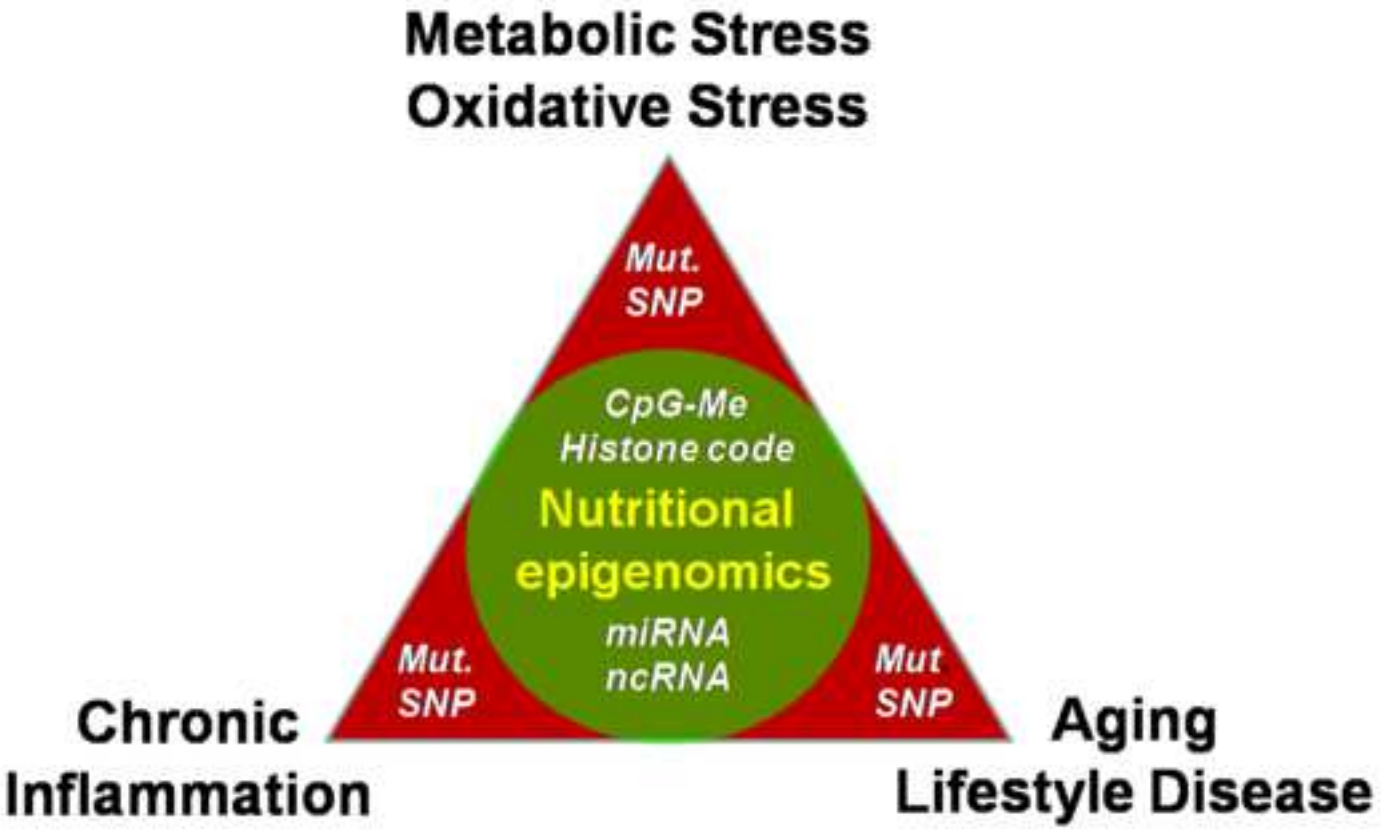

Nature or nurture: Let food be your epigenetic medicine in chronic inflammatory disorders

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Abstract:

Numerous clinical, physiopathological and epidemiological studies have underlined the detrimental or beneficial role of nutritional factors in complex inflammation related disorders such as allergy, asthma, obesity, type 2 diabetes, cardiovascular disease, rheumatoid arthritis and cancer. Today, nutritional research has shifted from alleviating nutrient deficiencies to chronic disease prevention. It is known that lifestyle, environmental conditions and nutritional compounds influence gene expression. Gene expression states are set by transcriptional activators and repressors and are often locked in by cell-heritable chromatin states. Only recently, it has been observed that the environmental conditions and daily diet can affect transgenerational gene expression via "reversible" heritable epigenetic mechanisms. Epigenetic changes in DNA methylation patterns at CpG sites (epimutations) or corrupt chromatin states of key inflammatory genes and noncoding RNAs, recently emerged as major governing factors in cancer, chronic inflammatory and metabolic disorders. Reciprocally, inflammation, metabolic stress and diet composition can also change activities of the epigenetic machinery and indirectly or directly change chromatin marks. This has recently launched re-exploration of anti-inflammatory bioactive food components for characterization of their effects on epigenome modifying enzymatic activities (acetylation, methylation, phosphorylation, ribosylation, oxidation, ubiquitination, sumoylation). This may allow to improve healthy aging by reversing disease prone epimutations involved in chronic inflammatory and metabolic disorders.

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Introduction

A large body of epidemiological and experimental data has demonstrated a direct link between chronic inflammation and complex diseases such as obesity, allergy, asthma, cardiovascular disease, type 2 diabetes, rheumatoid arthritis, bowel disease and several types of cancer. Nutrition, as the main aspect of the environment, is said to play a key role in some of this disparities, however, the molecular mechanisms involved still remain to be unraveled [1-3]. Genome-wide association studies have identified hundreds of genetic variants associated with complex human diseases and traits, and have provided valuable insights into their genetic architecture. However, most variants identified so far confer relatively small increments in risk, leaving many questions how the remaining 'missing' heritability can be explained, although polygenic disease traits may account for some of this limitations [4, 5]. Furthermore, genetics *per se* cannot explain the vast diversity of phenotypes. A substantial number of studies have shown that contstraint in the early life environment is associated with increased risk of cardiometabolic disease, affective disorders and cognitive decline, osteoporosis, allergy, inflammation and specific cancers. Furthermore, genetics *per se* cannot explain the vast diversity of phenotypes. The differences between identical twins and their different susceptibility to most diseases has recently been attributed to epigenetic changes which accumulate during life following exposure to different environmental conditions [6-8]. The contribution of epigenetic changes (epimutations) to human disease is probably underestimated. Epigenetics encompasses several extra-genetic processes such as DNA methylation (methylation of cytosines within CpG dinucleotides), histone tail modifications (including acetylation, phosphorylation, methylation, sumoylation, ribosylation and ubiquitination), noncoding RNA functions, regulation of polycomb group proteins and the epigenetic cofactor modifiers, all of which may alter gene expression but do not involve changes in the DNA sequence itself [9-13]. The combinatorial nature of DNA methylation and histone modifications significantly extends the information potential of the genetic code. In a large scale comparative study, authors concluded a lack of genetic factor in chronic obstructive pulmonary disorder (COPD), cardiovascular disease (CVD), rheumatoid arthritis and Crohn's disease, all typical examples of diseases with an important inflammatory component [14]. A recent survey of the global incidence of cancer shows that the age-adjusted cancer incidence in the Western world is above 300 cases per 100,000 population, whereas that in Asian countries is less than 100 cases per 100,000. Sedentary lifestyle, diet, obesity and metabolic syndrome have been named as the major contributors to this phenomena, which is further emphasized by the increase in cancer cases among immigrants from Asian to

Western countries [15, 16]. As such, a reasonable good fraction of cancer deaths maybe prevented by modifying the diet composition (i.e. content of fiber, fruit, vegetable, fat/oil, protein, spices, cereals, xenobiotics) and regular physical exercise [3, 17]. Abnormalities in DNA methylation, histone modifications, chromatin remodelling and microRNA (miR) patterns [12, 18, 19] are important hallmarks of inflammatory disease states and cancer [10, 12, 13, 20-22].

The most studied epigenetic lesion, which is DNA hypermethylation at the promoter region of many genes [20, 23], is proved to be responsible for silencing of more than 600 cancer-related genes and this number is still rising. They include tumour suppressor genes, as well as genes involved in the cell-cycle regulation, DNA repair, angiogenesis, metastasis and apoptosis [24]. On the other hand, global hypomethylation of the DNA is said to activate endoparasitic sequences and causes the global chromosome instability leading to various mutations and cancer progression [21]. Now, it is becoming clear that epigenetic changes complement genetic mutations and importantly drive the development and progression of various diseases ranging from allergy, asthma, rheumatoid arthritis, type 2 diabetes, obesity, bowel disease, cardiovascular disease and cancer [12, 13, 20, 21, 25-29]. Recent successes of therapeutic intervention in chronic inflammatory diseases using epigenetic modifiers such as histone deacetylase (HDAC) and DNA methyltransferase (DNMT) inhibitors has fuelled interest in exploring epigenomic maps of inflammatory disease states [30, 31]. Interestingly, emerging data demonstrate the direct influence of certain anti-inflammatory dietary factors (for example polyphenols, isothiocyanates, epicatechins) and micronutrients (for example folic acid, selenium) on heritable gene expression and DNA methylation or chromatin remodelling [32-40]. Because epigenetic changes are reversible, developing drugs that control epigenetic regulation now attract substantial research investment, including the development of functional foods or supplements as nutrition based epigenetic modulators which will be discussed in more detail below [2, 30, 41]

Extragenomic epigenetic information

The definition of 'epigenetics' evolved during the past 50 years into the current and common definition of 'heritable changes in gene function that cannot be explained by changes in DNA sequence, although some definitions have excluded heritability [42]. While "inheritance" and "heritability" strictly spoken, refer to intergenerational organismal phenomena, they are also widely used today for describing both molecular and phenotypic characteristics at the cellular level that are transmitted between mitotic cell division. Expression of our DNA genotype can

be twiddled by various volume knobs. Considerable cross-talk occurs between three main players in silencing: DNA methylation, histone modifications and noncoding RNAs. The chromatin template therefore serves as the major platform for epigenetic regulation in the form of DNA methylation, histone modifications and histone variants. More recently, an epigenetic role for RNA has also been demonstrated in normal situations as well as in disease [12]. Before most activators of a gene access their DNA-binding sites, a transition from a condensed ("solenoid-like fiber") to a decondensed ("beads on a string") chromatin structure appears to take place. Conversely, the acquisition of a more condensed chromatin structure is often associated with gene silencing [11]. This structural restriction of chromatin on gene expression can be overcome by chromatin remodeling cofactor complexes, which reversibly modify (acetylation, phosphorylation, ubiquitylation, glycosylation, sumoylation) on lysine, arginistine, serine or threonine residues of amino-terminal histone tails. In general, DNA is wrapped around nucleosomes, which are arranged as regularly spaced beads (146 bp DNA/nucleosome) along the DNA. Typically, nucleosomes consist of a histone octamer of histones (H)2A/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. Since the discovery of histone modifying enzymes, N-terminal histone tails protruding from nucleosomes were found to be 'velcro patches' for (de)acetylases (HDAC/HAT), (de)methylases (HMT/HDMT), ubiquitin ligases, small ubiquitin-related modifier (SUMO) ligases, kinases, phosphatases, ribosylases, which together establish specific histone modification patterns involved in transcription [11]. Specific sets of histone modifications and/or variants are associated with genes that are actively transcribed or are repressed, a phenomenon defined as the "histone code" [11]. Since the modifications do not involve underlying changes in nucleotide or amino acid sequences, they are “above the genome” and as such termed “epigenomic”. However, to establish specificity of epigenetic marks, histone modifying complexes have to be recruited to relevant genomic locations by DNA-binding proteins, RNAs or protein-RNA complexes that bind to their specific DNA sites as a consequence of their own binding specificities and cellular concentrations [43-46]. It cannot come from the enzymatic activities per se as neither DNMTs, nor enzymes which modify histones know which part of the genome needs to be tagged. Furthermore, there is now a large body of evidence showing that modifications of the histone tails provide signals ("binary switches") that are recognized by specific binding proteins, such as chromo-, bromo- or tudor-domains which in turn can influence gene expresion and other chromatin functions

[47-49]. The spatial and time-dependent combinations of histone modifications further increase the complexity of information contained in chromatin [11, 48, 49].

DNA methylation is the best-known epigenetic mark [20, 50]. It is catalyzed by two types of DNMTs: DNMT1 is a maintenance methyltransferase, whereas both DNMT3A and DNMT3B are *de novo* methyltransferases [51, 52]. 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 CpG dinucleotides. Alternatively, DNA methylation of transcription factor binding sites which prevents binding of repressor proteins, may paradoxically induce gene activation. CpGs are normally methylated when scattered throughout the genome, but are mostly unmethylated when they are clustered as CpG islands at 5' ends of many genes. Hypermethylation of CpG-rich promoters triggers local histone code modifications resulting in a cellular camouflage mechanism that sequesters gene promoters away from transcription factors and results in stable silencing of gene expression. DNA methylation at CpG dinucleotides occurs upon transfer of S-adenosylmethionine (SAM) on cytosine by DNMTs. Whereas DNMT3A/B are responsible for DNA methylation during development (differentiation), DNMT1 is in charge of maintaining DNA methylation patterns in DNA replication during cell division. In mammalian cells, the fidelity of maintenance of methylation is 97–99.9% per mitosis, whereas de novo methylation is as high as 3–5% per mitosis, thus creating possibilities for epigenetic changes. DNA methylation also regulates genomic imprinting [53], X-chromosome inactivation [54] and silencing of repetitive sequences [55]. Although in most cases DNA methylation is a stable epigenetic mark, reduced levels of methylation can also be observed during development. This net loss of methylation can either occur passively by replication in the absence of cuntional maintenance methylation pathways, or actively, by removing methylated cytosines. In plants active demethylation is achieved in plants by DNA glycosylase activity, probably in combination with the base excision repair pathway. In mammals, coupling of 5-methylcytosine deaminase and thymine DNA glycosylase activities maybe responsible for DNA demethylation. Alternatively, a role for the 5-hydroxymethylcytosine modification in mammalian DNA demethylation has also been proposed as an intermediate in an active DNA demethylation pathway involving DNA repair and 5-hydroxymethylcytosine-specific DNA glycosylase activity [52].

Although DNA methylation is the best-known epigenetic mark [51, 56, 57], DNA methylation does not act alone. It occurs in the context of nucleosome positioning and histone modifications [9, 58, 59]. For example, high resolution DNA methylation analysis has

revealed 10-base periodicities (i.e one helical turn) in the DNA methylation status of nucleosome-bound DNA and found that nucleosomal DNA was more highly methylated than flanking DNA [59]. These data revealed that nucleosome positioning influences DNA methylation patterning of promoters and intron-exon boundaries throughout the genome and that DNA methyltransferases preferentially target nucleosome-bound DNA. Whether nucleosome strings provide a combinatory histone code is a matter of debate [9, 11, 12, 48, 60-62], but in any event, histone modifications influence gene activity and regulation. For example, acetylation of lysines is generally associated with transcriptional activation whereas lysine methylation can dictate either activation (e.g. H3K4, H3K36, H3K79) or suppression (e.g. H3K9, H3K27 or H4K20). Specific histone modifications have been shown to be associated with DNA hypermethylation of CpG islands, including deacetylation of histones H3 and H4, loss of H3K4me, and gain of H3K9me3 and H3K27me3 [63, 64]. More importantly, specific histone modifications have been implicated in several diseases, such as cancer and CVD, while recently, evidence for modifications in allergic asthma and COPD is also emerging [21, 25, 65-68]. DNA methylation marks are recognized by DNA methyl-binding proteins (MBD) which can interact with corepressor-associated enzymes (i.e. HDACs, enhancer of zeste homologue (EZH)2, ...), thus further linking DNA methylation and chromatin regulation [43, 69]. Altogether, "histone code" may only become biologically meaningful at the level of the chromatin fiber ("chromatin regulatory code") which, upon integration of conformations of multiple nucleosomes, translates allosteric changes into specific gene (cluster) activities, in order to establish specific regulatory programs at the genome level [11, 70-72]. In analogy to allosteric control of enzymes, specific gene activity may be determined by the spatial organization (compartmentalization in discrete territories) and structural landscape (three-dimensional structure) of a gene locus, by altering the higher order structure of chromatin (cis mechanism) or by generating a binding platform for effector proteins (trans mechanisms) [70, 71, 73, 74].

There is good evidence that also noncoding RNAs regulate chromatin architecture [12, 75-80]. The term noncoding RNA (ncRNA) is commonly employed for RNA that does not encode a protein. Although it has been generally assumed that most genetic information is transacted by proteins, recent evidence suggests that the majority of the genomes of mammals and other complex organisms is in fact transcribed into ncRNAs, many of which are alternatively spliced and/or processed into smaller products. Besides tRNA and rRNA, these ncRNAs include long-noncodingRNAs (lncRNAs), microRNAs (miRNAs) and tinyRNAs (tiRNAs) as well as several other classes of, sometimes yet-to-be-discovered, small regulatory

RNAs such as snoRNAs [75-77]. These RNAs (including those derived from introns) appear to comprise a hidden layer of internal signals that control various levels of gene expression in physiology and development, including chromatin architecture/epigenetic memory, transcription (enhancer function), RNA splicing, editing, translation and turnover [81]. RNA regulatory networks may determine most of our complex characteristics and play a significant role in disease [81]. For example, miRNAs can change expression levels of the epigenetic machinery (DNMT, HDAC, sirtuin (SIRT), polycomb (Pc) proteins, etc.) by posttranscriptional gene regulation involving base pairing with 3'untranslated (UTR) regions in their target mRNAs resulting in mRNA degradation or inhibition of translation [12, 18, 19, 82]. Alternatively, long ncRNAs and tiRNAs can regulate gene expression and/or DNA methylation by promoter association [75, 76, 81]. DNA-methylation can thus also be RNA-directed [12, 83].

Inflammatory and metabolic stress fuel epigenetic plasticity

Inflammation is a fundamental adaptation to the loss of cellular and tissue homeostasis covering many important processes, including host defense, tissue remodeling and repair, and the regulation of metabolism. The complexity of the inflammatory response requires that its many functional programs are controlled coordinately in some situations but independently in others [84, 85]. This is achieved through multiple mechanisms that operate at different levels, including alterations in the composition of immune cells in tissues, changes in cell responsiveness to inflammatory stimuli, regulation of signaling pathways and epigenetic control of gene expression.

Cell-specific mechanisms operate at the level of different cell types, and include regulation of their recruitment and activation. The cellular component involves the movement of leukocytes from blood vessels into the inflamed tissue, while leukocytes are involved in the initiation and maintenance of inflammation [84, 86]. Macrophages participate in host defense, immunity and inflammatory responses, where they are potently activated resulting in the production of pro-inflammatory cytokines, oxygen and nitrogen species and eicosanoids. Acute inflammation is mediated by granulocytes or polymorphonuclear leucocytes, while chronic inflammation is mediated by mononuclear cells such as monocytes and macrophages which can be further stimulated to maintain inflammation through the action of an adaptive cascade involving dendritic cells, T- and B-lymphocytes and antibodies [84, 87-92]. Imbalances in control of haematopoesis and lineage differentiation of Th1, Th2 and Treg cells have a major impact on prevalence of sensitization to allergens and allergic diseases and has

reached epidemic proportions in Western societies [93-96]. Furthermore, tumors are typically infiltrated with immune cells and inflammation which impacts on most, if not all, stages of tumorigenesis [97-100]. Moreover, most cancers contain an inflammatory infiltrate that is hijacked by tumor cells to promote angiogenesis, tissue invasion and cell proliferation. What is more, overnutrition and obesity activate the immune system which at long-term switches to chronic inflammatory condition that is as fertile soil for cancer development [3, 101-106].

Signal-specific mechanisms operate at the level of pathways which for example activate the key transcription factor nuclear factor-κB (NFκB). Among all the mediators and cellular effectors of inflammation, NFκB is perhaps the central transcription factor, which regulates expression of more than 400 genes [107-109]. At the same time, it is responsible for many aspects of inflammatory disease and malignancy by inducing transcription of soluble mediators that amplify inflammation, angiogenesis and neoplastic cell proliferation, and affect progression to more aggressive disease states [97]. Members of the NFκB family of dimeric transcription factors (TF) regulate expression of a large number of genes involved in immune responses, inflammation, metabolic stress, cell survival, and cancer. NFκB family TF are rapidly activated in response to various stimuli, including cytokines, infectious agents, overnutrition (metabolic stress, endoplasmic reticulum stress) or danger signals (bacteria, viruses, chemicals, pathogen associated molecular patterns (PAMPs), danger associated molecular patterns (DAMPs), and radiation-induced DNA double-strand breaks. In nonstimulated cells, some NFκB TFs are bound to inhibitory (I)κB proteins and are thereby sequestered in the cytoplasm. Activation leads to phosphorylation of IκB proteins and their subsequent recognition by ubiquitinating enzymes. The resulting proteasomal degradation of IκB proteins liberates NFκB TF, which translocate to the nucleus to drive expression of target genes. Two protein kinases with a high degree of sequence similarity, IκB kinase (IKK)α and IKKβ, mediate phosphorylation of IκB proteins and represent a convergence point for most signal transduction pathways leading to NFκB activation. Most of the IKKα and IKKβ molecules in the cell are part of IKK complexes that also contain a regulatory subunit called IKKγ or NFκB-essential modulator (NEMO). Several years ago, two IKK-related kinases, called IKKε and TBK1 (TANK-binding kinase), were identified that exhibit structural similarity to IKKα and IKKβ [110]. Together, the IKKs and IKK-related kinases are instrumental for inducible activation of the host defense system and controlling metabolic stress [103, 105, 107, 111, 112]. Alternative to IKK, various additional kinases have been identified which modulate transcriptional nuclear activity of NFκB, including mitogen- and stress-activated protein kinase (MSK), protein kinase (PK)Ac, phosphoinositide 3-kinases

PI3K and AKT [109, 113-116]. Furthermore, constitutive activity of NFκB/IKK has been observed in many cancer cells, inflammatory disorders, obesity and insulin resistance [102, 103, 105-108, 112, 117-119]. During obesity, the organism needs to adapt to and function under chronic exposure to high energy and nutrient intake. To cope with these challenges, the cell has developed the endoplasmic reticulum (ER) as a key nutrition sensor of cellular metabolic parameters (hyperglycemia, fatty acid overload, hypoglycemia, oxidative stress), which participates in viruatlly all anabolic and catabolic branches. Failure of the ER's adaptive capacity results in activation of the unfolded protein resonse (UPR), which intersects with many different inflammatory and stress signaling pathways at the crossroad of inflammation, cancer and metabolic disease [17, 105, 106].

Gene-specific mechanisms operate at the level of individual genes and gene subsets. Induction of inflammatory transcriptional responses is orchestrated by many transcription factors and extragenic noncoding RNAs acting on inflammatory enhancers consistent with the complexity of the response [120-124]. Controlled expression of cytokine genes is an essential component of an immune response and is crucial for homeostasis. In order to generate an appropriate response to metabolic stress or an infectious condition, the type of cytokine, as well as the cell type, dose range and the kinetics of its expression are of critical importance [125-127]. The NFκB family TF has a crucial role in rapid responses to metabolic stress and pathogens (innate immunity), as well as in development and differentiation of immune cells (acquired immunity). Although quite a number of genes contain NFκB-responsive elements in their regulatory regions, their expression pattern can significantly vary from both a kinetic and quantitative point of view [10, 84, 107, 112, 125, 128-131]. At the transcription level, selectivity is conferred by the expression of specific NFκB subunits and their respective posttranslational modifications, and by combinatorial interactions between NFκB and other transcription enhancer factors (for example interferon regulatory factor (IRF)3, activating transcription factor (ATF)3, cAMP response element-binding protein CREB, CCAAT-enhancer binding protein C/EBP, activator protein (AP)1 (i.e. jun, fos, Fra1), Sp1, Stat3, PU.1) [109, 121, 132]. In addition to NFκB, AP1 TF are closely involved in inflammatory disease and cancer invasive gene expression programs [133, 134]. Inflammatory transcription factors can be divided into different categories on the basis of their mode of activation and function [84]. Primary response transcription factors are constitutively expressed by many celltypes in the cytoplasm and are activated by signal-dependent posttranslational modifications, which involves their nuclear translocation, such as NFκB, IRF, CREB. This TF are mainly responsible for the primary phase of gene induction and integrate signals from

diverse signaling pathways which can amplify or terminate signal-dependent transcription factor activation. Another class TF requires de novo synthesis following inflammatory stimulation, for example C/EBPδ. Most are constitutively nuclear and regulate secondary waves of gene expression. A third class of constitutively nuclear TF are expressed in a cell type-specific and differentiation-dependent manner, such as Runx, PU.1, IRF8, AP1, C/EBP [121, 128]. They establish cell type-specific patterns of gene expression and are involved in chromatin remodelling during cell differentiation and organization of higher-order chromatin structure and chromosomal domains. The transcription factors of these TF categories do not act independently, but function coordinately to control the inflammatory transcriptional response. Upon combining datasets of expression profiling of inflammatory genes and *in silico* motif scanning of promoters of these genes they can define gene clusters that are coordinately regulated and the transcription factors that are likely to control their expression [10, 84, 107, 109, 112, 125, 128-131]. Since TF bind very poorly or not at all to nucleosomal DNA, their activation is coordinated to recruitment of ATP-dependent chromatin-remodeling factors (swith/sucrose non fermentable (SWI/SNF), Brahma (Brm), brahma-related gene, (Brg1)), histone-enzyme complexes such as kinases (IKK, MSK, ataxia telangiectasia mutated (ATM), AKT, PI3K), poly(ADP-ribose) polymerase (PARP), methylases (EZH2, coactivator-associated arginine methyltransferase (CARM)1, protein arginine methyltransferases (PRMT)), demethylases (lysine specific demethylase (LSD)1, Jumonji C family histone demethylase (JMJD)3), prolyl isomerase (PIN1), acetylases (p300, CREB binding protein (CBP), p300/CBP associated factor (p/CAF)), deacetylases (HDAC, SIRT) and DNMTs [10, 43, 107, 114, 135, 136]. Parallel posttranslational modifications (phosphorylation, acetylation, methylation, ribosylation, sumoylation, ubiquitination) of histone and non-histone TF and cofactor complexes allow formation of dynamic enhanceosome complexes which establish a distinct chromatin structure. These epigenetic settings are the ultimate integration sites of both environmental and differentiative inputs, determining proper expression of each inflammatory gene [10, 107, 131, 137, 138].

Further investigation of epigenetic regulation of inflammatory genes, revealed different different subclasses according to chromatin activation mode and gene expression profile [128, 139]. A major class of primary response genes is characterized by CpG-island promoters, which facilitate promiscuous induction from constitutively active chromatin without a requirement for SWI/SNF nucleosome remodeling complexes. The low nucleosome occupancy at promoters in this class can be attributed to the assembly of CpG-islands into unstable nucleosomes, which may lead to SWI/SNF independence. Another major class

consists of non-CpG-island promoters that assemble into stable nucleosomes, resulting in SWI/SNF dependence and the requirement for transcription factors that promote selective nucleosome remodeling. Some inflammatory stimuli such as TNF, exhibit a strong bias toward activation of SWI/SNF-independent CpG-island genes. In contrast interferon (IFN)β preferentially activates SWI/SNF-dependent non-CpG-island promoters. Interestingly, by activating a diverse set of transcription factors, Toll like receptors (TLR) induce both classes and others for an optimal response to PAMPs and DAMPs [128]. Remarkably, DNA methylation of IKK, IκB and RelB promoters [140-142] adds another regulatory control level which can act as transcription memory for repetitive pulsatile inflammatory exposures (endotoxin sensitization versus tolerance) [140, 143-146].

Chronic inflammatory disorders and epimutations: cause or consequence?

Since inflammatory gene expression dynamics is highly dependent on epigenetic control mechanisms [10, 84, 92, 120, 125, 137], we have compared chromatin organization in weak or strong inflammatory cancer cell types with inducible or constitutive interleukin (IL)6 gene expression patterns. Upon investigation of autocrine IL6 gene expression production in aggressive myeloma cells or metastatic breast cancer cells, we observed euchromatin-like properties and highly accessible chromatin at the IL6 gene promoter [133, 147]. Furthermore, recruitment of CBP/p300 acetylases and MSK kinase seems to prevent heterochromatinisation and recruitment of heterochromatin protein (HP)1 upon phosphacetylation of transcription factor and histone components [114, 115, 132, 133, 148] (See Figure 2). Interestingly, promoter binding activity of Sp1 and AP1 Fra1 are responsible for priming IL6 promoter chromatin relaxation, which further promotes binding of NFκB transcription factors and chromatin opening for maximal expression levels [133, 147]. Interestingly, complementation of low invasive cancer cells with Fra1 seems to convert the promoter chromatin architecture in a highly accessible chromatin configuration. Reciprocally, highly accessible chromatin in invasive cancer cells can be silenced with anti-inflammatory phytochemicals, or following silencing of AP1/NFκB transcription factors, demonstrating reversible epigenetic changes towards a less aggressive phenotype [133, 149, 150]. Along the same line, we and others observed DNA hypermethylation at the IL6 gene promoter in cancer cells with low NFκB/AP1 activity and inducible IL6 gene expression, as compared to DNA hypomethylation in cancer cells with hyperactivated NFκB/AP1 transcription factors and elevated constitutive IL6 gene expression ([151, 152] and Figure 2). Similarly, p53 knockout cells reveal defects in genomic imprinting and DNA methylation regulation [153] As such, this demonstrates that

inflammatory signaling and transcription factors are able to rewire epigenetic settings and amplify gene expression in an autocrine fashion [46, 154]. As another example, DNA methylation of the NFκB responsive element in the Fas (CD95, Apo-1, TNFRSF6) gene promoter, was found to silence its expression in metastatic prostate carcinoma [46, 155]. Surprisingly, depletion of NFκB can also trigger DNA demethylation and gene reactivation of the Fructose-1,6-biphosphatase-1 (FBP1) illustrating gene-specific epigenetic effects which may further depend on posttranslational NFκB modifications [136, 156].

Of special note, whereas studies with epigenetic drugs (azacytidin, suberoylanilide hydroxamic acid (SAHA)) frequently focus on reactivation of silenced tumor suppressor genes, these compounds also boost gene expression of inflammatory oncogenes such as IL6 which promote aggressive carcinogenesis, cancer stem cell proliferation, metastasis and hormone resistance [100, 157-164]. Furthermore, elevated IL6 gene expression is able to trigger epigenetic changes of tumor suppressor genes via regulation of DNMTs [165-168], microRNAs [158, 169, 170] and histone methyltransferases (Ezh2) [171]. This suggests that epigenetic regulators themselves and methylation of tumor suppressor genes are also susceptible to dynamic inflammatory control [158, 165, 169, 170, 172-175], which adds an extra level of complexity to the cancer-inflammation link.

Furthermore, besides epigenetic changes in neoplastic cells, inflammatory stimuli in the tumor microenvironment can also epigenetically reprogram tumor-associated immune cells, as demonstrated for the NFκB-dependent histone demethylase JMJD3 which determines cell fate and transdifferentiation of tumor-associated macrophages [120, 176]. Reports on epigenetic events in cancer are traditionally produced from analyses on "bulk" tumor samples, i.e. without distinction between neoplastic cells on one hand and the tumoral stroma on the other. The pro-inflammatory micro-environment that drives many tumor types is as such capable of triggering these epigenetic alterations within cancer progenitor cells, alterations which can substitute for genetic defects later in tumour progression [158, 177]. However, also tumor stromal components (which include bone-marrow-derived cells, tumor-associated macrophages) are a target of epigenetic events [92, 120, 149]. Similarly, in atherosclerotic plaques, interplay between monocytes, macrophages and vascular endothelium will trigger various epigenetic alterations in the different cell types in the plaque microenvironment [68, 178-185]. Besides inflammatory factors, the micro-environment also contains free radicals produced by neutrophils, macrophages, endothelial and other cells. Reactive Oxygen Species (ROS) such as $^{\bullet}O_2$, $^{\bullet}OH$, H_2O_2, NO and $^1O_2$ can injure cellular biomolecules such as nucleic acids, enzymes, carbohydrates, and lipid membranes, causing cellular and tissue damage,

which in turn augments the state of inflammation. In addition, reactive nitrogen intermediates such as NO and ROS, indirectly also modulate activity of epigenetic machinery which finally will affect chromatin dynamics in tumor-associated immune cells [186-190].

One of the key functional characteristics of macrophages is that they can be programmed to deal most effectively with a given kind of inciting stimulus. In the lung for example, resident alveolar macrophages are continuously encountering inhaled substances due to their exposed position in the alveolar lumen [93]. To avoid collateral damage to mucosal epithelium in response to harmless antigens, they are kept in a quiescent state, producing little inflammatory cytokines and displaying poor phagocytic activity. In the vessel wall, macrophages can scavenge large amounts of lipid, and differentiate into lipid-laden foamy cells [179]. As putative precursors for microglia and osteoclasts, monocytes may also be involved in the physiology of the central nervous system and in bone remodelling. Dendritic cells (DC) are also part of the monocytic phagocytic system and are the professional antigen presenting cells of the immune system that bridge innate and adaptive immunity [91]. DC cells come in many flavours and it is clear now that there are multiple pathways to develop DC from monocytes. The complexity of the monocytic phagocytic system requires that its many functional programmes are controlled coordinately in some situations, but separately in others. It is now clear that epigenetic mechanisms can lead to time-dependent and stimulus-specific alterations in the expresssion of functional modules [191]. Epigenetic modifications like histone modifications and CpG-island methylation in promotor regions of critical transcription factors (so called masterswitch transcription factors) of all of these functional programmes have been described and are controlled by microRNAs, DNMTs, HDAC, histone acetylases (HAT CBP/p300, p/CAF) histone lysine methylases (EZH2, CARM, PRMT) and demethylases (LSD1, JMJD3) [192, 193]. Emerging research indicates that epigenetic mechanisms that control the lineage development and polarization of monocytic phagocytic system and Th1, Th2 and Treg cells can be transmitted across multiple generations [84, 89, 194, 195]. Smoking, diesel exhaust, diet conditions, hygiene, dust mite, obesity seem have major influence on epigenetic programming of immune cell populations and inflammatory disease severity in asthma, allergy, rheumatoid arthritis, bowel disease [196-202]. Similarly, hypertension, obesity and lack of physical activity can have longlasting effects on epigenetic reprogramming of monocytes/macrophages and endothelial cells promoting differentiation into more proatherogenic phenotypes and increased risk of cardiovascular disease [68, 180, 182-185, 203].

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

Human epidemiological studies and appropriately designed dietary 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 [29, 32, 204-208]. This has led to the hypothesis of ‘‘fetal programming’’ and new term ‘‘developmental origin of health and disease’’ (DOHaD): common disorders, such as obesity, cardiovascular disease (CVD), diabetes, hypertension, asthma, cancer and even schizophrenia, take root in early nutrition during gestation and continues during lactation [28, 32, 209-214]. 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 [29, 32, 204-208, 215, 216]. Thus, lifetime shapes the multitude of epigenomes not only within, but also across generations [29, 207]. Interest in transgenerational epigenetic effects of food components has been fueled by observations in Agouti mice fed with a soy polyphenol diet, which revealed epigenetic changes in DNA methylation patterns in their offspring and protected against diabetes, obesity and cancer across multiple generations [217-219]. However, only weak transgenerational effects could be observed with soy polyphenols in *Daphnia Magna*, despite the presence of functional DNMTs [220]. Feeding pregnant mice with a diet rich in methyl donors altered DNA methylation at well defined CpG regions which led to decreased transcription of Runx3 and more sever asthma in offspring. Bronchial biopsies and alveolar macrophages of asthmatics revealed a disturbed epigenetic regulation of gene expression (increased HAT and decreased HDAC2 activity) [221]. Furthermore, the honeybee (*Apis mellifera*) is probably the clearest example of induction of alternative phenotypes and epigenotypes by nutrition in early life [222]. 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, lipids, and other nutrients [223-225].

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 1944-1945, as compared to those born to mothers whose pregnancies were more advanced at the time of nutrional insult [226-228]. Also paternal 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 [229, 230]. Today, various different epigenetic changes have already been characterized which are involved in atherogenesis [28, 29, 65, 67, 231]. Hypercholesterolemia, obesity, hyperhomocysteinemia, high glucose are important CVD risk factors which are implicated in enhanced inflammatory signaling and long-lasting effects are driven by epigenetic reprogramming, promoting differentiation of monocytes/macrophages into more proatherogenic phenotypes [68, 181, 182, 232]. Recent evidence suggests that the pathogenetic role of hyperhomocysteinemia in vascular diseases might be mediated via Adenosyl-homocystein (Hcy) accumulation and DNA methylation. Hcy competes with S-adenosylmethionine (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 [233-236]. Similarly, insulin, glucose folate or flavanol-rich diets interfere with the methyldonor metabolism and the available pool of S-adenosylmethionine, resulting in DNA methylation changes [236-239]. In contrast, very few studies have focused on impact of dietary methyldonors on histone methylation, which is also affected by alterations in SAM/SAH ratios [233, 240]. 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, rheumatoid arthritis. Epidemiologic and medical anthropological studies have indicated that flavanol-rich diets are inversely associated with cardiovascular risk [241-246]. Locus-specific DNA methylation changes, both hyper- and hypomethylation, also occur at the promoter level of several genes involved in the pathogenesis of atherosclerosis, such as extracellular superoxide dismutase (SOD), hormone receptors (glucocorticoid receptor (GR), estrogen receptor (ER), peroxisome 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, insulator CCCTC binding factor (CTCF) and metalloproteases (MMPs) [68, 183, 247-249]. In a proatherogenic murine model, DNA-methylation polymorphisms preceded the appearance of histological signs of atherosclerosis [181, 182]. 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 [120]. A role for the JMJD1A demethylase was demonstrated in metabolic gene expression and obesity resistance [250]. Furthermore, it was found that knockdown of the LSD1 demethylase affected monocyte adherence in a proatherogenic diabetic mouse model [251]. This suggests that LSD1 contribute to metabolic memory through long-term changes in gene expression via alterations in chromatin structure [146, 252].

Poor maternal nutrition has also been associated with increased risk of type 2 diabetes mellitus over several generations in North American Indians [253, 254]. Individuals with metabolic syndrome, obesity and type II diabetes (T2D) CVD may show a lifelong imbalance between energy intake and energy expenditure due to incorrect epigenetic programming during their early development as a result of placental insufficiency, inadequate maternal nutrition, metabolic disturbances or neonatal medication [205, 253-258].

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 [259]. 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 [206]. 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) [28-30, 258-262]. 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 [6, 8]. 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) [38, 207, 211, 218, 219, 263, 264]. 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% [265, 266]. Alternatively, it can not be excluded that transgenerationally inherited nutritional effects may also depend on polycomb proteins [207, 267-269], miRNA profiles [12, 270] or epigenetic capacitor properties of hsp proteins [271-273].

A next challenge will be to determine which adverse epigenomic marks are reversible by specific diets, drugs or lifestyle changes [29, 32, 38, 259]. Numerous botanical species and plant parts contain a diverse array of polyphenolic phytochemicals which exert health-beneficial effects in man by its anti-inflammatory, anti-oxidant, phytohormone, cardio-protective, cancer preventive and anti-bacterial properties, by maintaining immune homeostasis (hormesis) [274, 275]. Phytochemicals have also succesfully been applied for regenerative medicine and cancer stem cell therapy [173, 276-280]. Oxidative stress and inflammatory damage plays 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 [97, 100, 281]. 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 lifestyle diseases [3, 100, 211]. Today, various nutritional natural compounds (including epigallocatechingallate, resveratrol, genistein, curcumin, isothiocyanates …) have been characterized which interfere with enzymatic activity of DNMT, Class I, II, IV HDAC, HAT and Class III HDAC sirtuins (SIRT) which modulate inflammatory responses and immunological senescence ([32-41, 213, 282] and references included, see Table 1). HDACs are zinc metalloproteins which rely on Zn^{2+} for their activity and are divided into 4 classes based on their homology with yeast HDACs. Class III HDACs, called sirtuins are zinc-independent but nicotinamide adenine dicnucleotide (NAD^{+})-dependent. Class I, II, IV HDAC inhibitors characteristically contain a Zn^{2+} chelating group consisting of a thiolate, thiol, hydroxamate, carboxylate, mercaptoamide, epoxide or ketone group. Natural HDAC inhibitors can be divided in following groups based on their chemical characteristics: carboxylates, organosulfides, isothiocyanates, hydroamates, cyclic tetrapeptides and macrocyclic depsipeptides [35]. In contrast to natural HDAC inhibitors, only few natural products (i.e. niacine, vitamin B3, dihydrocoumarin) 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 analogues 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 [283-287]. Of special note, 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" sheds a more realistic light on dietary studies, as longlife exposure at physiological concentrations can remodel the epigenome in a cumulative fashion by repetitive effects on the epigenetic machinery [241, 288-291]. 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 metabolisation [34, 35]. 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 that they induce are stable over time. Interestingly, even transient exposure to a specific dietary component can induce long-lasting epigenetic changes in the promoter of the NFκB subunit p65, which acts as a master switch in inflammatory gene expression [146]. Alternatively, compounds may chemically interfere with histone mark interacting effector domains (such as chromo-, bromo- or tudor domains) [47, 292, 293]. However, one should be careful with interpretation of *in vitro* compound screenings or cofactor activity assays based on peptide-protein interactions, as this may not always represent true targets *in vivo* [294, 295].

Besides specific interference of the diet with chromatin modifying enzymes and DNMTs at particular target genes, global epigenetic changes can also occur following biochemical metabolisation of dietary factors, which can deplete cellular pools of acetyl-CoA, NAD^+ and methyldonors, resulting in unbalanced DNA methylation and/or protein acetylation or methylation [282, 296, 297]. For example diets lacking in substrate or cofactors in methyldonormetabolism can contribute to DNA hypomethylation by impairing synthesis of SAM [234]. This methylation cycle is frequently cited to explain relations between diet and epigenetic changes [233, 298]. However, even without nutritional deficiency of methyl groups, impaired synthesis of SAM and perturbed DNA methylation can happen when the need for the synthesis of the detoxification enzyme glutathione transferase (GSH) synthesis

increases [299]. Diets or nutritional compounds which affect energy metabolism or mitochondrial respiration can have global epigenetic effects upon changes in NAD^+ availability and SIRT activity [300]. 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 epigenetic modulator phytochemicals which could reverse metabolic disease [297].

Conclusion

The phenotype of an individual is the result of complex gene-environment interactions in the current, past and ancestral environment, leading to lifelong remodelling of our epigenomes. In recent years, several studies have demonstrated that disruption of epigenetic mechanisms can alter immune function and and that epimutations not only contribute to various cancers but also to the development of diabetes, allergy, CVD and rheumatoid arthritis. Various replication-dependent and -independent epigenetic mechanisms are involved in developmental programming, lifelong recording of environmental changes and transmitting transgenerational effects. It is likely that understanding and manipulating the epigenome, a potentially reversible source of biological variation, has great potential in chemoprevention or stabilization of chronic inflammatory disorders. Much attention is currently focusing on modulating hyper/hypomethylation of key inflammatory genes by dietary factors as an effective approach to cure or protect against inflammatory disease [32-41, 213, 282]. In this respect, "Let food be your epigenetic medicine" could represent a novel interpretation of what Hippocrates said already 25 centuries ago. As such, it will be a challenge for future anti-inflammatory therapeutics and preventive cancer research to identify novel epigenetic targets which allow selective modulation of the inflammatory signaling network in the diseased tissue and/or microenvironment [275, 301-306]. Given several encouraging trials, prevention and therapy of age- and lifestyle-related diseases by individualised tailoring of optimal epigenetic diets or supplements are conceivable. However, these interventions will require intense efforts to unravel the complexity of these epigenetic, genetic and environment interactions. Another goal is to evaluate their potential reversibility with minimal side effects as diet components may reprogram malignant cells as well as the host immune system and HPA-axis depending on the bioavailability of the dietary compounds [32, 133, 149, 150, 289, 291] (See Figure 3). There is some concern that epigenetic therapy with dietary inhibitors of DNMT, HDAC, histon(de)methylases in longterm treatment setups may suffer from lack of specificity [283, 292, 294]. As such, the possible alternative is to combine nonselective

epigenetic therapies with more targeted approaches [46]. For example, combined treatment of specific transcription factor inhibitors and/or hormone receptor ligands with epigenetic drugs may trigger synergistic activities at subsets of inflammatory genes [43, 46, 307-309]. An excellent example of cooperation between a dietary vitamin A-derivative targeting a nuclear receptor and the HDAC inhibitor butyrate has been described in the treatment of acute promyelocytic leukemias [33]. Finally, microRNA and long ncRNA pathways also hold promise to join soon the arsenal of epigenetic combination therapies, as their target sequence specificity may bridge the gap between genetic and epigenetic changes [12, 79-81]. In conclusion, studies are revealing a dazzling complexity in the mechanisms leading to dynamic alterations of the epigenome and the need of combination therapies targeting different chromatin modifiers, to reverse disease prone epigenetic alterations to preserve healthy aging. Medical benefits of dietary compounds as epigenetic modulators, especially with respect to their chronic use as nutraceutical agents, will rely on our further understanding of their epigenetic effects during embryogenesis, early life, aging as well as through different generations.

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Figure 1

Interplay of inflammatory and metabolic stress pathways in nutritional epigenetic effects in lifestyle diseases. mut, mutation; SNP, single nucleotide polymorphism; miR, microRNA, ncRNA, noncoding RNA.

Figure 2

Working model illustrating crosstalk of inflammatory and metabolic stress pathways with epigenetic regulation in the nucleus. For example, transcription of the highly conserved IL6 gene promoter requires binding of activator protein AP1, CREB and nuclear factor NFκB transcription factors in response to various stimuli [310, 311], with strict stereospecific requirements for optimal cofactor recruitment, promoting a promoter enhanceosome model with multiple transcription factor/cofactor interactions, in which NFκB is the primary trigger for IL6 gene induction in response to TNF. Inflammatory stimuli (i.e. TNF, virus, bacteria) or metabolic stress (including oxidative stresss, endoplasmic reticulum (ER) stress or unfolded protein response (UPR) stress, for example during obesity or malnutrition) can activate the IKK-complex, responsible for IκB-phosphorylation, which allows NFκB to translocate to the nucleus, following degradation of IκB in the proteasome. IL6 gene expression also requires activation and recruitment of the mitogen- and stress-activated protein kinase-1 (MSK1) to elicit selective chromatin relaxation at the IL6 gene promoter, upon phosphorylation of NFκB p65 S276 and histone H3 S10, followed by further CBP/p300 recruitment and HAT-dependent acetylation of the IL6 promoter enhanceosome/chromatin environment [115]. Highly elevated expression levels of AP1 Fra1 and NFκB in ER-deficient tumor cells increase chromatin accessibility (DNA hypersensitive sites) in the proximal IL6 gene promoter. Of particular interest, dietary anti-inflammatory phytochemicals such as soy polyphenol genistein [149, 150, 274] and withanolide withaferin A [312] are able to silence the highly promiscuous IL6 promoter nucleosome configuration by lowering the cellular amounts of Fra1 and NFκB activity, concomitantly with decreased histone H3 phosphoacetylation levels and increased DNA methylation [133, 149, 150].

Figure 3.

Flowchart which summarizes the complex and multilayered regulation of nutritional epigenetic effects.

Table 1. Overview of nutritional epigenetic effects by dietary phytochemicals (summarized from [32-41, 213, 282] and references included). Suffix I, inhibitor; suffix a, activator, for example HDACi, HDAC inhibitor, or SIRTa, SIRT activator

Bioactive Phytochemical	Natural Source	Disease Target	Epigenetic mechanism	*In vitro / In vivo*	Target genes / microRNAs
3,3-diindolylmethane	Broccoli	Cancer	Decreased HDAC levels	*In vitro / in vivo*	COX2
6-methoxy-2E,9E-humuladien-8-one	Ginger	Cancer	HDACi	*In vitro*	
Allylmercaptan	Garlic	Cancer	HDACi	*In vitro/in vivo*	P21/WAF
Anacardic Acid	Cashew nuts	Cancer, Leukemia	HATi	*In vitro*	
Apigenin	Parsley, celery	Cancer	DNMTi	*In vitro*	
Betanin	Beetroot red	Cancer	DNMTi	*In vitro*	
Biochanin A	Soy	Cancer	DNMTi HDACi	*In vitro / in vivo* *Daphnia*	
Butyryc acid	Fermentation dietary fibers	Cancer	HDACi	*In vitro / In vivo*	
Caffeic acid	Coffea	Cancer Inflammation Energy metabolism	DNMTi HDACi	*In vitro*	RARβ, CDKN2A
Catechin	Green tea	Cancer Lymphocytes	DNMTi HATi	*In vitro*	RARβ
Chlorogenic acid	Coffea	Cancer	DNMTi HDACi	*In vitro*	RARβ, CDKN2A
Coumaric acid Cinnamic acid	Cinnamon	Cancer	DNMTi HDACi	*In vitro / in vivo*	
Coumarin analogues Dihydrocoumarin	Melilotus officinalis (Sweet clover)	Cancer, Leukemia,	SIRTi p53 acetylation	*In vitro*	
Curcumin	Turmeric (*Curcuma longa L.*)	Crohn's Disease, Ulcerative colitis Inflammatory disease Cancer, Leukemia Neurodegeneration Alzheimer Diabetes Heart Failure Epilepsy	DNMTi HATi HDACi	*In vitro / In vivo* *Plasmodium falciparum,* *Herpes Virus* *Mouse* *Rat*	GATA4, EOMES, GZMB, PRF1 Up: miR-22, miR-34a, miR-24, miR-181a, miR-21,miR-181b, miR-27a Down: miR-199a, miR-510, miR-196a, miR-7, miR-15b, miR-195, miR-374, miR-98
Cyanidin	Berries, Grapes	Cancer	DNMTi	*In vitro*	
Daidzein	Soy	Cancer	DNMTi SIRTa	*In vitro*	
Diallyl disulfide	Garlic	Inflammatory disease Cancer	HDACi	*In vitro / in vivo* *rat*	p21/WAF
Ellagic Acids	Berries	Cancer	DNMTi	*In vitro*	
Epicatechin	Apples, Cocoa, Green and black tea	Inflammatory disease, lymphocytes Cancer CVD	DNMTi HATi	*In vitro*	
Epicatechin gallate	Green tea	Cancer Lymphocytes	DNMTi HATi	*In vitro*	
Epigallocatechin	Green tea	Cancer Lymphocytes	DNMTi HATi	*In vitro*	
Epigallocatechin 3-gallate (EGCG)	Green tea	Inflammatory disease Parkinson Cancer, Leukemia CVD	DNMTi HDACi HMTi	*In vitro / In vivo* *Agouti* *Mouse/Human*	RARβ, MGMT, MLH1, CDKN2A, RECK, TERT, RXRα, CDX2, GSTP1, WIF1, NFkB, IL6, Bmi1, Ezh2, Suz12 Up : let-7, miR-16,

		Diabetes Energy metabolism			miR-18b, miR-20a, miR-25, miR-92, miR-93, miR-221, miR-320 Down: miR-10a, miR-18a, miR-19a, miR-26b, miR-29b, miR-34b, miR-98, miR-129, miR-181d
Equol	Soy	Cancer	HDACi	*In vitro / in vivo Drosophila*	
Fistein	Strawberies	Cancer Inflammatory disease	SIRTa	*In vitro*	
Flavone	Feijoa	Cancer	HDACi	*In vitro / in vivo Drosophila*	p16,p21,TRAIL
Folic Acid Folate	Leafy vegetables, Nuts, Sunflower seads	Inflammatory disease Asthma Cancer Obesity CVD	Induction of DNA methylation	*In vitro / In vivo*	Up : miR-10a, miR-10b, miR-9, miR-145, miR-30a-3p, miR-152, miR-122a, miR-125b Down: miR-200a, miR-496, miR-296, miR-30e-5p, miR-362, miR-339, miR-29c, miR-154, miR-10a
Galangin	Propolis	Cancer	DNMTi	*In vitro*	
Garcinol	Garcinia	Cancer HIV Leukemia Lymphocytes	DNMTi HATi	*In vitro*	Global downregulation gene expression
Genistein	Soy	Inflammatory disease Cancer	DNMTi HATi HDACi Increase DNA methylation Changed protein levels DNMTs, MBD1, MBD4, MeCP2	*In vitro / In vivo Agouti Daphnids*	RARβ, MGMT, CDKN2A, GSTP1, HMGN5, BTG3, TERT P21, p16,PTEN, CCLD, p53, FOXA3, SIRT1, BTG3, RARβ Up: miR-200b, miR-200c, let-7b, let-7c, let-7d, let-7e, miR-663, miR-146a, miR-374b Down: miR-34c, miR-376a, miR-196a, miR-320, miR-654, miR-34c, miR-196
Hesperidin	Citrus	Cancer	DNMTi	*In vitro*	
Isoliquiritigenin	Liquorice	Cancer	SIRTactivator	*In vitro / in vivo Drosophila*	
Isothiocyanate (6-Methylsulfinyl-hexylisothio-cyanate)	Broccoli, Japanese horseradish (Wasabi)	Anti-platelet effects Cancer	HDACi	*In vitro*	P21, GSTP1
Kaempferol	Apples, nuts, tea, onions	Cancer	SIRTa		
Luteolin	Parsley, celery	Cancer	DNMTi SIRTactivator	*In vitro / In vivo Drosophila*	
Lycopene	Tomatoes, Watermelon Apricots Pink guava Grapefruit, Rosehip	Cancer: Breast, Colon	DNMTi	*In vitro*	GSTP1, RARβ, HIN1
MCP30	Bitter melon seeds (Momordica charantia)	Cancer	HDACi	*In vitro*	
Myricetin	Berries	Cancer	DNMTi	*In vitro*	

Naringenin	Citrus	Cancer	DNMTi	*In vitro*	
Parthenolide	Feverfew (*Tanacetum parthenium*)	Arthritis Fever Lymphocytic leukemia Migraine	DNMTi HDAC depletion	*In vitro*	
Phloretin	Apples	Cancer	DNMTi	*In vitro*	
Piceatannol (Resveratrol metabolite)	Grapes, blueberries	Cancer	DNMTi SIRTa	*In vitro*	
Polyphenon B	Black and green tea	Cancer	Increased HDAC levels	*In vitro/in vivo* *Rat*	
Pomiferin	*Maclura pomifera*	Cancer	HDACi	*In vitro*	
Protocatechuric acid	Olives	Cancer	DNMTi	*In vitro*	
Quercetin	Citrus: Capers, Apples, Berries, Tea, Wine	Inflammatory disease Bowel inflammation Asthma Cancer CVD Pulmonary dysfunction	DNMTi HDACi SIRTactivator	*In vitro*	IL10, MIP2
Resveratrol	Grapes, Blueberries, Peanuts, Red wine	Inflammatory disease Cancer Leukemia CVD Neuroprotection	DNMTi HDACi SIRTa	*In vitro / In vivo* *Yeast* *Mouse* *Rat* *Drosophila*	TNF, IL8, RBP
Rosmarinic acid	Rosemary	Cancer	DNMTi	*In vitro*	
Retinoic Acid	Carrots, Spinach, Eggs	Cancer Leukemia	HDACi	*In vitro*	
S-allylmercapto-cysteine	Garlic	Cancer Leukemia	HDACi		
Sanguinarine	Opium poppy	Cancer	HMTi	*In vitro*	
Selenium	Careals, Nuts, Legumes, Fish, Shellfish,	Cancer	DNMITi Induction of DNA methylation	*In vitro*	
Silibinin	Milk thistle (*Silybum marianum*)	Cancer Liver protection Inflammatory disease	Increased histone acetylation SIRTa	*In vitro*	p21, p27, CASP3, CASP9
Sinapic acid	Sinapis (mustard)	Cancer	DNMTi	*In vitro*	
Sulforaphane	Broccoli	Inl Cancer	DNMTi HDACi Decreased DNMT levels	*In vitro / In vivo* *Mouse*	RARβ, HBD2, p21, BAX
Syringic acid	Red Grape	Cancer	DNMTi	*In vitro*	
Theophylline	Black and green tea	Immune cells Pulmonary inflammation Asthma, COPD Cancer	HDACa	*In vitro*	
Ursolic acid	Basil	Leukemia	HDAC inhibitor	*In vitro*	
Withaferin A	Ashwagandha (*Withania somnifera*)	Anti-angiogenic effects Inflammatory disease Rheumatoid arthritis Asthma Cancer Leukemia Neuroprotection	Inhibition histone acetylation Chromatin silencing	*In vitro*	

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